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Plausibility Tracking: A method to evaluate anatomical connectivity and microstructural properties along fiber pathways

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ABSTRACT

Diffusion MRI is a non-invasive method that potentially gives insight into the brain's white matter structure regarding the pathway of connections and properties of the axons.
Here, we propose a novel global tractography method named Plausibility Tracking that provides the most plausible pathway, modeled as a smooth spline curve, between two locations in the brain. Compared to other tractography methods, plausibility tracking combines the more complete connectivity pattern of probabilistic tractography with smooth tracks that are globally optimized using the fiber orientation density function and hence is relatively robust against local noise and error propagation. It has been tested on phantom and biological data and compared to other methods of tractography. Plausibility tracking provides reliable local directions all along the fiber pathways which makes it especially interesting for tract-based analysis in combination with direction dependent indices of diffusion MRI.
In order to demonstrate this potential of plausibility tracking, we propose a framework for the assessment and comparison of diffusion derived tissue properties. This framework comprises atlas-guided parameterization of tract representation and advanced bundle-specific indices describing fiber density, fiber spread and white matter complexity. We explore the new method using real data and show that it allows for a more specific interpretation of the white matter's microstructure compared to rotationally invariant indices derived from the diffusion tensor.

Introduction

Diffusion weighted magnetic resonance imaging (dMRI) is a non-invasive technique to evaluate microstructural properties of the brain. It is based on MRI sequences that measure the direction dependent diffusion of water molecules within biological tissue. Structures like cell membranes, myelin sheaths and filaments act as barriers that hinder or restrict this movement and lead to anisotropic diffusion profiles (Beaulieu, 2002). Depending on the type of tissue and the employed imaging protocol, the dMRI measurements are sensitive to particular aspects of the *diffusion propagator*, which gives the probability of a particle diffusing from one point to another within a certain time (for a detailed explanation refer, e.g., to Jones et al., 2013). Different local models for the diffusion propagator have been introduced, ranging from the simple diffusion tensor (Basser et al., 1994) to more sophisticated expressions that, to a certain extent, differentiate between the diffusion of different fiber bundles within one voxel (Aganj et al., 2010; Assaf et al., 2004; Behrens et al., 2007; Schultz and Seidel, 2008; Tuch, 2004; Wedeen et al., 2000; for a review see Alexander, 2005). Alternatively, explicit models of microstructural properties can be used, such as the *fiber orientation density function* (fODF) computed by *spherical deconvolution* (SD) (Dell'Acqua et al., 2007; Descoteaux et al., 2009; Kaden et al., 2008; Tournier et al., 2004, 2007) or various models for the axonal diameter distribution (Assaf et al., 2008; Zhang et al., 2011a,b).

For the most part, dMRI is used to characterize long-range white matter fiber tracts that connect cortical and subcortical gray matter areas. There are two principal approaches. First, one may map voxel-based indices derived from the local (i.e., voxel-wise) dMRI signal (Jones et al., 2005), which are sensitive to some aspects of the microstructural properties and spatial arrangement of nerve fibers as well as other white matter elements (e.g., oligodendrocytes). The by far most commonly used such index is the *fractional anisotropy* (FA)

Abbreviations: MRI, magnetic resonance imaging; dMRI, diffusion magnetic resonance imaging; fODF, fiber orientation density function; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; SD, spherical deconvolution; CSD, constrained spherical deconvolution; CHARMED, composite hindered and restricted model of diffusion; HARDI, high angular resolution diffusion imaging; FD, fiber density; AFD, angular fiber density; AFD_{max}, maximal angular fiber density; FS, fiber spread; GRAPPA, generalized auto calibrating partially parallel acquisitions; CC, corpus callosum; PFC, prefrontal cortex; BA45, Brodmann area 45; MC, motor cortex; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; CR, corona radiate; IFOF, inferior fronto-occipital fasciculus; ROI, region of interest; MAD, median absolute deviation; MNI, Montreal Neurological Institute.

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introduced by Basser and Pierpaoli (1996). Standard mapping methods include *voxel-based analysis* (VBA) (Ashburner and Friston, 2000) and *region* or *atlas-based analysis* (Faria et al., 2010; Snook et al., 2007). Second, diffusion tractography (Mori and van Zijl, 2002) interprets the local diffusion signal in terms of fiber directions and then integrates this information over voxels, thereby generating fiber pathways between different brain regions. Major types of tractography algorithms include *deterministic tractography* that always follows the most probable fiber direction (Descoteaux et al., 2009; Lazar et al., 2003; Malcolm et al., 2009; Mori and van Zijl, 2002; Tournier et al., 2012; for a review, see, Lenglet et al., 2009), *probabilistic tractography* estimating a distribution of possible pathways (Anwander et al., 2007; Behrens et al., 2003; Jeurissen et al., 2011; Kaden et al., 2007; Koch et al., 2002) and various *global tractography* methods (Jbabdi et al., 2007; Kreher et al., 2008).

While mapping of indices readily provides an overview on microstructural properties of the tissue (as far as the dMRI signal does provide this information – for a critical review, see Jones et al., 2013) – any assignment to connections between particular brain regions remains rather vague. Tractography, on the other hand, yields specific information on the existence and the course of fiber connections (again, within certain limits, see Jones et al., 2013), without yielding straightforward information on tissue properties other than fiber direction.

It is fairly obvious to look for combinations of both methods, that is, to map indices onto reconstructed fiber pathways, in order to achieve the best possible characterization of a connection. Such *tract-based analysis* (TBA) techniques have been proposed before and range from simple averaging of the FA over the fiber tract volume (Lebel et al., 2008) to more sophisticated parameterization along the tracts (e.g., Corouge et al., 2006).

However, there are several potential shortcomings in such algorithms. First, most of today's methods focus on rotationally invariant indices derived from the diffusion tensor (Basser et al., 1994), as they are fairly sensitive to changes and differences in tissue properties and relatively easy to handle. The downside of these and similar indices is that they are rather unspecific with respect to their possible underlying microstructural traits and that they disregard part of the information contained in modern *high angular resolution diffusion imaging* (HARDI) (Frank, 2002; Tuch, 2002). While there are a number of sophisticated approaches aiming at the estimation of specific microstructural traits, such as axonal density and axonal caliber, from dMRI (Alexander et al., 2010; Assaf et al., 2004, 2008; Zhang et al., 2011a,b), these usually require non-standard acquisition schemes that might not always fit into the routine of neuroscientific research and clinical practice. Recently, however, there have been some attempts to define more informative indices even on the basis of standard HARDI data (Dell'Acqua et al., 2013; Riffert et al., 2012; Savadjiev et al., 2013; Sotiropoulos et al., 2012; Zhang et al., 2012), estimating properties like fiber density, fiber spread and fiber arrangement complexity.

Second, most of the commonly used tractography algorithms, both probabilistic (Behrens et al., 2003) and deterministic (Mori and van Zijl, 2002), are sequential procedures that suffer from error accumulation and increasing uncertainty especially over longer distances (Jones, 2010). In particular, weaker pathways that are dominated by larger crossing bundles may be difficult to reconstruct. A promising alternative is the use of global tractography techniques that do not iteratively integrate the local diffusion information, but instead use other principles, such as self organization of small elements (Fillard et al., 2009; Kreher et al., 2008; Reisert et al., 2011), Hough transform (Aganj et al., 2011) and the solution of the Hamilton–Jacobi–Bellman equation (Melonakos et al., 2007; Pichon et al., 2005). A particularly insightful and promising approach involves parameterized (usually spline based) representations of pathways between predefined endpoints, which are then fitted to the diffusion data (Jbabdi et al., 2007; Tuch, 2002). For a comparison of deterministic, probabilistic and global tractography, see (Bastiani et al., 2012).

The third problem of many current TBA methods lies in the fact that all long-range fiber-tracts have crossings with other tracts. Even if the tractography technique used can disentangle these crossings without problems, the mapped indices are not a good representation of the properties of the tract of interest anymore. This is especially relevant, if the volume fraction of the tract of interest is small, that is, if the crossing fibers dominate the diffusion signal. On the other hand, modern local models of the diffusion propagator (for example, *constrained spherical deconvolution* ((CSD); Tournier et al., 2007) allow, within certain limits, for the disentanglement of the properties of multiple crossing fiber populations and thereby enable the definition of direction dependent and bundle specific indices (Raffelt et al., 2012; Riffert et al., 2012, under review; Sotiropoulos et al., 2012). In consequence, in each voxel several indices may be available and one can select the one that belongs to the tract of interest and assess how well it corresponds to that tract.

Based on the above considerations, we developed a new global tractography method called plausibility tracking and use it in a framework for the non-invasive characterization of white matter fiber connections in the human brain. This framework allows characterizing axonal connections with fiber bundle specific indices that potentially provide more specific information about the tissue microstructure than indices of the diffusion tensor, but requires reliable local directions all along the pathway, which are provided by our new tractography method. Plausibility tracking describes, according to the underlying dMRI data, the most plausible pathway between two defined regions in the brain. In contrast to many existing tractography methods, it provides a reliable local direction of the fiber bundle of interest in every location. This allows using direction dependent and population specific local indices to be mapped onto the tract. Our hypothesis is that these indices provide a more specific characterization of the tissue microstructure along pathways than it would be possible with rotationally invariant indices. In order to keep our framework applicable to standard clinical and scientific settings, we here restrict ourselves to indices computed from single shell HARDI data, but other more sophisticated indices may be easily incorporated. As a result, we can characterize a particular connection between gray matter areas by its most likely pathway and by local estimates of microstructural traits while minimizing contamination by unrelated fiber populations. Moreover, plausibility tracking offers a convenient way to assess the appropriateness, or plausibility, of an estimated tract in the light of the data.

The paper is organized as follows. In the chapter Materials and methods we describe in detail the novelties and implementation of our framework. The Results section is subdivided into validation of the proposed tractography method and an application example, featuring comparison of direction dependent indices along the *inferior longitudinal fasciculus* (ILF) between children and adults. Finally, the method and results are discussed in the last chapter.

Materials and methods

Our method consists of six steps: dMRI preprocessing, local modeling, computation of indices, plausibility tracking, mapping of indices onto the fiber bundles and statistical evaluation.

For the validation of plausibility tracking on human data and the tract-based analysis, we used data from nine children (five girls, mean age 7.0 years, stddev 1.1) and nine adults (five female, 27.8 years, stddev 2.7) previously presented by Brauer et al. (2011, 2013). The data were acquired on a Siemens 3 T Trio scanner with 1.7 mm isotropic voxel size, GRAPPA acceleration factor 2, 3×60 diffusion directions and a b-value of 1000 s/mm^2 and 21 images without diffusion weighting (b0 images). Anatomical images were acquired with T1 and T2 in 1 mm resolution. All subjects were right handed and healthy. Written informed consent was obtained from the participants in accordance with the ethical approval from the University of Leipzig. Children gave verbal assent prior to scanning and written consent was obtained from their parent or guardian. In order to minimize effects due to different brain sizes, we chose adults with relatively small heads. A *t*-test revealed no significant difference in brain size between children and adults ($p = 0.45$).