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Informed constrained spherical deconvolution (iCSD)

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ABSTRACT

Diffusion-weighted (DW) magnetic resonance imaging (MRI) is a noninvasive imaging method, which can be used to investigate neural tracts in the white matter (WM) of the brain. However, the voxel sizes used in DW-MRI are relatively large, making DW-MRI prone to significant partial volume effects (PVE). These PVEs can be caused both by complex (e.g. crossing) WM fiber configurations and non-WM tissue, such as gray matter (GM) and cerebrospinal fluid. High angular resolution diffusion imaging methods have been developed to correctly characterize complex WM fiber configurations, but significant non-WM PVEs are also present in a large proportion of WM voxels.

In constrained spherical deconvolution (CSD), the full fiber orientation distribution function (fODF) is deconvolved from clinically feasible DW data using a response function (RF) representing the signal of a single coherently oriented population of fibers. Non-WM PVEs cause a loss of precision in the detected fiber orientations and an emergence of false peaks in CSD, more prominently in voxels with GM PVEs. We propose a method, *informed* CSD (iCSD), to improve the estimation of fODFs under non-WM PVEs by modifying the RF to account for non-WM PVEs locally. In practice, the RF is modified based on tissue fractions estimated from high-resolution anatomical data.

Results from simulation and in-vivo bootstrapping experiments demonstrate a significant improvement in the precision of the identified fiber orientations and in the number of false peaks detected under GM PVEs. Probabilistic whole brain tractography shows fiber density is increased in the major WM tracts and decreased in subcortical GM regions. The iCSD method significantly improves the fiber orientation estimation at the WM-GM interface, which is especially important in connectomics, where the connectivity between GM regions is analyzed.

1. Introduction

Diffusion-weighted (DW[1]) magnetic resonance imaging (MRI) is a noninvasive imaging method to investigate tissue microstructure via the measurement of the displacement of water molecules (Stejskal and Tanner, 1965; Jones, 2010). Diffusion in white matter (WM) neural tracts is anisotropic, larger parallel to the tract than perpendicular to it. This property can be exploited to extract fiber orientations from DW data and investigate neural tracts in the brain WM using fiber tractography algorithms (Conturo et al., 1999; Basser et al., 2000; Mori and van Zijl, 2002; Jones, 2008; Tournier et al., 2010; Jeurissen et al., 2011).

The image resolution in DW-MRI is relatively low, with voxel sizes typically larger than $2 \times 2 \times 2$ mm^3. Thus, significant partial volume effects (PVE) are present in the measured DW signal (Alexander et al., 2001; Vos et al., 2011). These PVEs may be caused by complex WM fiber configurations, such as crossing tracts (Vos et al., 2011; Jeurissen et al., 2013), or several tissue types present in a voxel (Pasternak et al., 2009; Metzler-Baddeley et al., 2012b; Roine et al., 2014).

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[1] **Abbreviations**: ACT: anatomically constrained tractography, CI: confidence interval, CSD: constrained spherical deconvolution, CSF: cerebrospinal fluid, DTI: diffusion tensor imaging, DSI: diffusion spectrum imaging, DW: diffusion-weighted, EPI: echo-planar imaging, FA: fractional anisotropy, fODF: fiber orientation distribution function, FOV: field of view, FWE: free water elimination, GM: gray matter, HARDI: high angular resolution diffusion imaging, iCSD: informed constrained spherical deconvolution, MD: mean diffusivity, MPRAGE: magnetization-prepared rapid gradient-echo, MRI: magnetic resonance imaging, NEX: number of excitations, PVE: partial volume effect, RF: response function, SH: spherical harmonics, SNR: signal-to-noise ratio, TDI: tract-density imaging, VF: volume fraction, WM: white matter.

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Currently, the most common method to analyze DW-MRI data is diffusion tensor imaging (DTI) (Basser et al., 1994b; Basser et al., 1994a; Jones and Leemans, 2011; Tournier et al., 2011). However, its shortcoming is the inability to identify complex fiber configurations (Alexander et al., 2001; Frank, 2001; Frank, 2002), present in 60–90% of WM voxels (Jeurissen et al., 2013). To overcome this, high angular resolution diffusion imaging (HARDI) (Tuch et al., 2002; Jansons and Alexander, 2003; Tournier et al., 2004; Tuch, 2004; Anderson, 2005; Alexander, 2005; Hosey et al., 2005; Tournier et al., 2007; Dell'Acqua et al., 2007; Descoteaux et al., 2007; Behrens et al., 2007; Descoteaux et al., 2009; Daducci et al., 2014) and methods based on diffusion spectrum imaging (DSI) (Wedeen et al., 2005; Wedeen et al., 2008; Canales-Rodríguez et al., 2010) have been developed.

However, although able to identify complex fiber configurations, many of the HARDI methods do not account for PVEs caused by non-WM tissue, such as gray matter (GM) and cerebrospinal fluid (CSF) (Dell'Acqua et al., 2010; Metzler-Baddeley et al., 2012b; Roine et al., 2014). In our previous study, we reported that significant PVEs with non-WM tissue were present in 35–50% of WM voxels, of which the vast majority was with GM (Roine et al., 2014). This indicates that the non-WM PVEs are nearly as common as complex fiber configurations within a voxel, and thus taking them into account is important.

Diffusion in non-WM tissue is mostly isotropic within the resolution of DW-MRI (Dell'Acqua et al., 2010). Isotropic non-WM PVEs have been shown to affect DTI (Alexander et al., 2001; Pasternak et al., 2009; Metzler-Baddeley et al., 2012b) and constrained spherical deconvolution (CSD) (Tournier et al., 2007; Roine et al., 2014). Pasternak et al. (2009) used constrained optimization of a bi-tensor model for free water elimination (FWE) in DTI, showing increased fractional anisotropy (FA) and mean diffusivity (MD). Metzler-Baddeley et al. (2012b) used FWE to correct for CSF-contamination in tensor-derived measures in CSD-based tractography and showed that diffusivity measures were more sensitive to PVEs than anisotropy measures. However, FWE-based approaches are not suitable for GM-contaminated regions. Roine et al. (2014) showed that in CSD, the precision of the identified fiber orientations decreased and the number of spurious false peaks increased, when isotropic non-WM volume fraction (VF) increased. These effects were most prominent with GM, which may cause significant consequences when studying the connectivity between GM regions.

In HARDI methods, few methods account for non-WM PVEs. To the authors' knowledge, the ball and stick model is one of the few methods that directly includes an isotropic compartment and has been extended into multiple fiber orientations (Behrens et al., 2003; Behrens et al., 2007; Schultz et al., 2010; Jbabdi et al., 2012). In addition, a method based on total variation and sparse deconvolution has been developed to address the isotropic partial volume effects in q-ball imaging (Tuch, 2004; Zhou et al., 2014). In another study, isotropic non-WM PVEs were dampened through adaptive regularization in the iterative Richardson-Lucy deconvolution algorithm (Dell'Acqua et al., 2010). This method reduced the number of spurious false peaks, but is limited in that it reports large isotropic fODFs in regions without WM fibers.

CSD is currently one of the most used, clinically feasible and readily available HARDI methods (Tournier et al., 2012; Leemans et al., 2009; Metzler-Baddeley et al., 2012a; Emsell et al., 2013; Farquharson et al., 2013; Forde et al., 2013; Kristo et al., 2013; McGrath et al., 2013a; McGrath et al., 2013b; Reijmer et al., 2013b; Reijmer et al., 2013a; Thompson et al., 2014; Roine et al., 2015). In CSD, the fiber orientation distribution function (fODF) is estimated from clinically feasible DW data by deconvolving the data with a kernel constructed from a response function (RF) representing a single coherently oriented population of fibers (Tournier et al., 2004; Tournier et al., 2007). However, the non-WM PVEs have not previously been taken into account in CSD.

In this paper, we propose a novel method, *informed* CSD (iCSD), where the traditional RF representing a single fiber orientation in pure WM regions is modified to account for isotropic diffusion from GM and CSF. In practice, this can be done by using VFs estimated from high-resolution anatomical data. We evaluate the performance of the proposed method in comparison to the original CSD with comprehensive simulations. In addition, experiments on real DW data are performed to confirm the simulation results.

2. Material and methods

We propose a novel method to improve the fiber orientation estimation with CSD under non-WM PVEs. The performance of the method is evaluated with simulations and in-vivo experiments.

2.1. Fiber orientation estimation with CSD

In CSD, the full fODF is deconvolved from the DW signal using a kernel constructed from the RF representing a single coherently oriented population of WM fibers (Tournier et al., 2004). During the deconvolution procedure, to be able to reliably solve the ill-posed problem, constraints are imposed to suppress negative peaks in the fODF (Tournier et al., 2007; Tournier et al., 2008). The RF is the DW signal of an ideal fiber population perfectly aligned along the z-axis. In practice, it can be estimated from real data by recursive calibration (Tax et al., 2014) or by selecting voxels with high FA, (e.g. FA >0.7), aligning their principal eigenvectors along the z-axis, and then averaging their spherical harmonics (SH) decompositions (Tournier et al., 2004).

2.2. Informed CSD (iCSD)

In WM regions with non-WM PVEs, the use of the single traditional RF estimated from pure WM voxels is not accurate. Therefore, we propose a novel method, iCSD, which exploits the VFs estimated from high-resolution T1-weighted data to account for local non-WM PVEs in CSD. In iCSD, the RF corresponding to a single coherently oriented population of fibers is adapted to the local tissue composition. This anatomically-informed RF is estimated by linearly combining the DW signal from the WM RF with the isotropic RFs from GM or CSF tissue, assuming no exchange between the compartments, as shown in Fig. 1. Thus, the RF in iCSD becomes:

$$\mathbf{r}_{\mathrm{iCSD}} = f_{\mathrm{wm}}\mathbf{r}_{\mathrm{wm}} + f_{\mathrm{gm}}\mathbf{r}_{\mathrm{gm}} + f_{\mathrm{csf}}\mathbf{r}_{\mathrm{csf}}, \tag{1}$$

where $\mathbf{r}_{\mathrm{iCSD}}$ is the iCSD RF, $\mathbf{r}_{\mathrm{wm}}$ is the single-fiber RF from pure WM tissue (as in CSD), f_{wm}, f_{gm} and f_{csf} are the VFs of WM, GM and CSF tissue and $\mathbf{r}_{\mathrm{gm}}$ and $\mathbf{r}_{\mathrm{csf}}$ are the isotropic GM and CSF responses, respectively.

After the deconvolution with the iCSD RF, the resulting fODF is proportional to the WM volume in the voxel. However, as the fODF was extracted from the voxels with different tissue types, a scaling factor of f_{wm} should be used to scale the amplitudes of the fODF to be proportional to the total volume of the voxel.

2.3. Simulated DW data

The WM signal was simulated for two crossing WM fiber configurations with equal weight, FA, and MD. The orientation of the first fiber bundle was randomly selected, after which the orientation of the second fiber bundle was calculated in spherical coordinates with a predefined crossing angle.

Then, the DW signal was simulated separately for different tissue types, and the resulting signals were combined assuming no

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