Estimation of diffusion properties in three-way fiber crossings without overfitting

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Abstract
Diffusion-weighted magnetic resonance imaging permits assessment of the structural integrity of the brain’s white matter. This requires unbiased and precise quantification of diffusion properties. We aim to estimate such properties in simple and complex fiber geometries up to three-way fiber crossings using rank-2 tensor model selection. A maximum a-posteriori (MAP) estimator is employed to determine the parameters of a constrained triple tensor model. A prior is imposed on the parameters to avoid the degeneracy of the model estimation. This prior maximizes the divergence between the three tensor’s principal orientations. A new model selection approach quantifies the extent to which the candidate models are appropriate, i.e. a single-, dual- or triple-tensor model. The model selection precludes overfitting to the data. It is based on the goodness of fit and information complexity measured by the total Kullback-Leibler divergence (ICOMP-TKLD). The proposed framework is compared to maximum likelihood estimation on phantom data of three-way fiber crossings. It is also compared to the ball-and-stick approach from the FMRIB Software Library (FSL) on experimental data. The spread in the estimated parameters reduces significantly due to the prior. The fractional anisotropy (FA) could be precisely estimated with MAP down to an angle of approximately 40° between the three fibers. Furthermore, volume fractions between 0.2 and 0.8 could be reliably estimated. The configurations inferred by our method corresponded to the anticipated neuro-anatomy both in single fibers and in three-way fiber crossings. The main difference with FSL was in single
fiber regions. Here, ICOMP-TKLD predominantly inferred a single fiber configuration, as preferred, whereas FSL mostly selected dual or triple order ball-and-stick models. The prior of our MAP estimator enhances the precision of the parameter estimation, without introducing a bias. Additionally, our model selection effectively balances the trade-off between the goodness of fit and information complexity. The proposed framework can enhance the sensitivity of statistical analysis of diffusion tensor MRI.

Keywords: diffusion MRI, multi-tensor models, model selection, maximum a posteriori estimation, maximum likelihood

(Some figures may appear in colour only in the online journal)

I. Introduction

Diffusion-weighted magnetic resonance imaging (DW-MRI) is a unique tool for assessing the integrity of white matter (WM) in vivo (Le Bihan 2003) (Horsfield and Jones 2002) (Mori et al 1999). Essentially, it provides a way to measure the 3D diffusion profile of water in the brain. Classically, a single rank-2 diffusion tensor, estimated from a series of DW images, is used to model the local diffusion of water molecules: hence the name Diffusion Tensor Imaging (DTI) (Basser, Mattiello and LeBihan 1994) (Le Bihan et al 2001). Typically, properties are derived from such a tensor by invariants like the fractional anisotropy (FA) (Basser and Jones 2002).

However, it is widely known that a single rank-2 tensor as applied in classical DTI cannot accurately characterize complex fiber structures such as crossings and bifurcations (Basser, Mattiello and LeBihan 1994). There is an ongoing debate on how to best characterize the orientation and diffusion properties in these configurations (Behrens et al 2007) (Caan et al 2010). This is relevant since accurate orientation and diffusion estimation has led to promising applications in brain mapping (Assaf and Pasternak 2008) and detection of pathologies (Douaud et al 2011). Many approaches such as the ball-and-stick model (essentially a rank-1 tensor model) (Behrens et al 2007), spherical deconvolution (Jeurissen et al 2011) (Dell’Acqua et al 2013), diffusion spectrum imaging (Wedeen et al 2005), the composite hindered and restricted model of diffusion (CHARMED) (Assaf et al 2004) (Assaf and Basser 2005) and diffusion kurtosis imaging DKI (Jensen et al 2005) enable a more sophisticated characterization of the diffusion in order to achieve a better reconstruction, particularly of the principal fiber orientations. A potential advantage of the multi-tensor model is in that it asserts a Gaussian diffusion partitioned over multiple compartments. As such, an intuitive physical interpretation can be attributed to the parameters of the dual tensor model (as with the conventional, single tensor model). Furthermore, notice also that the full diffusion shape is captured by such tensors and not only the diffusion along single directions (as in the ball-and-stick model).

Recently, the existence of three-way crossings has been reported (Sotiropoulos et al 2013). Although the full diffusion shape of two-way fiber crossings has been characterized by a single rank-4 tensor model (Özarslan and Mareci 2003) (Minati et al 2007) and a dual rank-2 tensor model (Caan et al 2010) (Schultz, Westin and Kindlmann 2010), there is no literature doing the same for voxels with triple-way crossing fibers as revealed in (Jeurissen et al 2011) (Sotiropoulos et al 2013). Essentially, two issues hamper estimating the full diffusion shape of three-way fiber crossings by means of a high-rank tensor model:
I. Unbiased estimation of a triple tensor model requires high-quality DW-MRI data and proper constraints on the parameters to be estimated, i.e. the degrees of freedom (DOF) embedded in the data should support the large number of parameters to be estimated; II. Fitting dual or triple tensor models to voxels comprising a simpler fiber structure will inevitably cause unreliable estimates as a result of overfitting. Therefore, a proper model should be selected based on the available data from a voxel.

Several model selection methods were introduced in the field of DW-MRI. Automatic relevance determination (ARD) aims to eliminate the redundant parameters in a complex model, such that a simplified model yields a better description of the data (Neal 1995). Behrens (Behrens et al 2007) adopted ARD for assessing the appropriate number of fiber orientations in each voxel for fiber tracking. ARD methods assume a prior distribution for the model parameters. A Gaussian distribution is a straightforward choice for a prior (Neal 1995). Previous ARD approaches (Behrens et al 2007) (Jbabdi et al 2012) (Nummenmaa et al 2007) involved marginalization (integration) over the hyper-parameters to get a prior for each parameter separately. Such a prior is likely to be suboptimal for individual voxels since potential correlations between parameters are ignored. Alternatively, model selection techniques related to constrained spherical deconvolution (CSD) (Tournier et al 2004), the Bayesian information criterion (BIC) (Freidlin et al 2007), and the generalization-error (Scherrer, Taquet and Warfield 2013) were used. A potential drawback of model selection in CSD is that the model selection criterion is not implicitly defined, so that it requires tuning of a threshold. A limitation of the BIC is that it is not determined by the data itself, but through non-estimated factors such as the number of parameters and the sample size. Finally, a restriction of the generalization-error method (Scherrer, Taquet and Warfield 2013) is that it is a non-local model selection technique. To our knowledge, model selection methods have not been studied especially for rank-2 triple tensor models.

To address the aforementioned challenges, we need (1) to extend the range of rank-2 tensor models to triple-tensor estimation and simultaneously achieve a high accuracy and precision by incorporating suitable priors and imposing appropriate constraints; and (2) to select the right model for a given set of diffusion measurements per voxel.

This paper introduces a maximum a-posteriori estimator to characterize diffusion profiles particularly in voxels comprising three-way crossing fiber bundles. The proposed model selection method selects from the single-, dual- and triple-tensor models the most suitable representation given the data. This data-adaptive model selection framework, which compares the competing models by a measure of information complexity based on the total Kullback-Leibler divergence, dubbed ICOMP-TKLD (see below), is an explicit model selection approach. The whole framework will be validated on DW-MRI data from the Human Connectome Project (HCP) (Van Essen et al 2013) (Van Essen et al 2012) and data from an ongoing study into the effects of HIV on the brain (Su et al 2014). Moreover, the performance of the proposed framework will be compared to a state-of-the-art approach (Behrens et al 2007) (Jbabdi et al 2012).

I.A. Significance

The aim of the proposed framework is to achieve unbiased estimation of diffusion properties in white matter structures throughout the brain. In particular, our work targets to improve neuroimaging research by providing the estimation of diffusion properties along fiber bundles, which cross multiple other structures along theirs tract. Specifically, the properties extracted from the fitted diffusion model may facilitate a more sensitive detection of WM changes, e.g. related to aging or disease processes.
II. Method and materials

We will first present the triple-tensor model and its constrained parameterization for estimating diffusion profiles in three-way fiber crossings. Second, we will introduce a prior, which is required to solve this ill-posed inverse problem. Third, we describe the posterior probability function that is optimized to obtain an unbiased fit of the triple-tensor model. Fourth, we introduce the structure-adaptive model selection method that balances the goodness of fit and a new measure for information complexity named ICOMP-TKLD.

II.A. Triple-tensor model

We assume that the diffusion in a single fiber bundle is mono-exponential and can be described by an anisotropic Gaussian profile. Accordingly, the measured DW signal $S_j$ in voxels comprising a three-way fiber crossing is modeled by a weighted sum of three anisotropic, Gaussian basis functions:

$$S_j = S_0 \left( \sum_{i=1,2,3} f_i \exp(-b_j g_i^T D_i g_i) \right). \tag{1}$$

In (1) $S_j$ is the signal predicted by the triple-tensor model; $S_0$ is the signal without diffusion weighting; $b_j$ is the amount of diffusion weighting in gradient direction $g_j$, $b_j$ is selected from a vector $b$ whose length $n_b$ equals the number of unique $b$-values; $D_1$, $D_2$, and $D_3$ are three positive definite rank-2 tensors (i.e. $3 \times 3$ matrices), which independently describe the diffusion profile of a fiber; $f_i$ quantifies the volume fraction of each fiber bundle, with the constraint: $f_1 + f_2 + f_3 = 1$. For the single and dual tensor model we limit ourselves to one respectively two anisotropic compartments.

II.B. Constraints

In this paper, the tensor $D_i$ is parameterized by a diagonal eigenvalue-matrix $E_i$ and eigenvector-matrix $V_i$: $D_i = V_i^T E_i V_i$. The diffusion perpendicular to the fiber orientation is assumed to be isotropic. Accordingly, we model the diffusivities by an axial and a radial diffusivity, denoted by $\lambda_{i//}$ and $\lambda_{i\perp}$ respectively. Now $E_i$ yields:

$$E_i = \text{diag}(\lambda_{i//}, \lambda_{i\perp}, \lambda_{i\perp}) \text{ with } i \in \{1, 2, 3\}. \tag{2}$$

As tensor $D_i$ must be symmetric positive-definite, non-negativity of the diffusivities is enforced by adopting exponential mappings $\exp(\cdot)$ as in (Caan et al 2010); additionally, to impose that diffusion along a fiber is faster than perpendicular to it, i.e. $\lambda_{i//} > \lambda_{i\perp}$, we further constrain the diffusivity parameters by

$$\lambda_{i//} = c_{i//}\lambda_{\text{free}}, \tag{3}$$

with

$$\lambda_{i\perp} = c_{i\perp}\lambda_{i//}, \tag{4}$$

where $\lambda_{\text{free}}$ represents the approximated diffusivity of free water at body temperature and the coefficients $c_{i//}$ and $c_{i\perp}$ are positive fractions ranging between 0 and 1.

Additionally, we expect that the variance of the estimated parameters is significantly reduced by constraining the axial diffusivity of all tensor compartments to be equal, as was
previously reported for the dual-tensor case (Caan et al 2010), i.e. \( \lambda_{ii} = \lambda_{2i} = \lambda_{3i} \) so that \( c_{1i} = c_{12} = c_{13} \). The benefit of this constraint will be demonstrated in the experiment section.

It is assumed that the orientation of each fiber is aligned with the first principal eigenvector of the corresponding tensor in model (1), i.e. \( \mathbf{v}_{1,i} \) in the matrix \( \mathbf{V} = \begin{bmatrix} \mathbf{v}_{1,i} & \mathbf{v}_{2,i} & \mathbf{v}_{3,i} \end{bmatrix} \). We use spherical coordinates to represent \( \mathbf{v}_{1,i} \) uniquely by its zenith angle \( \theta_{1,i} \) and azimuth angle \( \phi_{1,i} \):

\[
\mathbf{v}_{1,i} = \begin{bmatrix} \cos(\phi_{1,i}) \sin(\theta_{1,i}) & \sin(\phi_{1,i}) \sin(\theta_{1,i}) & \cos(\theta_{1,i}) \end{bmatrix}^T.
\]

The other two eigenvectors, i.e. \( \mathbf{v}_{2,i} \) and \( \mathbf{v}_{3,i} \), are defined in the plane perpendicular to \( \mathbf{v}_{1,i} \). Volume fractions of tensor compartments are defined in the range \( 0 \leq f_i < 1 \) by means of an error function \( \text{erf}() \):

\[
\int_{-\infty}^{x} \frac{2}{\sqrt{\pi}} \exp(-t^2) dt \quad \text{mapping of } \{ f_i \} \in [0,1] \text{ to } [0,1].
\]

In summary, the \( i \)th fiber in a three-way crossing will be characterized the parameters \( \{ \lambda_{ii}, \lambda_{1,i}, \theta_{1,i}, \phi_{1,i} \} \). Employing the aforementioned parameterization, the complete DW-signal is described by a 16D parameter vector \( \Theta \):

\[
\Theta = \begin{bmatrix} S_0, c_{11}, c_{21}, c_{12}, c_{22}, c_{13}, c_{23}, \
\theta_1, \theta_2, \theta_3, \phi_1, \phi_2, \phi_3, f_1, f_2, f_3 \end{bmatrix}.
\]

However, with the constraint that \( c_{11} = c_{12} = c_{13} \) (i.e. \( \lambda_{ii} = \lambda_{2i} = \lambda_{3i} \)) and \( f_3 = 1 - f_1 - f_2 \), 13 DOFs need to be estimated.

II.C. Priors on the parameters of the triple tensor model

The number of parameters to be estimated in the triple-tensor model is large, and correlations between some of these parameters lead to high variances in the estimated parameters. Therefore, imposing a prior on a subset of the parameters is needed to facilitate precise estimation. In (Caan et al 2010), we demonstrated that the performance of estimation got worse as the angle between two tensors decreased below 45 degrees. Accordingly, the prior applied by us is given by

\[
p(v_{1,1}, v_{1,2}, v_{1,3}) = \prod_{i,j=1}^{3} \exp(-|v_{1,i} \cdot v_{1,j}|^3),
\]

in which \( v_{1,i} \cdot v_{1,j} \) represents the inner product between the principal eigenvectors of \( \mathbf{D}_i \) and \( \mathbf{D}_j \). The prior (8) essentially states that a relatively large divergence between any pair of fibers is more likely than a configuration in which they make a small angle. This is reasonable, since complex models with a small divergence between any pair of fibers will not survive the model selection step anyway (see below). No restrictions will be imposed on the other parameters, i.e. these priors are given by uniform distributions: \( p(S_0) = p(\lambda_{ii}) = p(\lambda_{1,i}) = U(0, \infty), f_i = U(0, 1) \). The complete multivariate prior for parameter vector \( \Theta \) is given by

\[
p(\Theta) = p(v_{1,1}, v_{1,2}, v_{1,3})p(f_1)p(\Delta \lambda_{ii})p(\Delta \lambda_{1,i})p(S_0).
\]
II.D. Maximum a-posteriori (MAP) estimator

The probability density function (PDF) of a measured diffusion weighted image (DWI) signal \( \tilde{S}_j \) is a non-central \( \chi \)-distribution (Brion et al. 2011):

\[
p(\tilde{S}_j|S, \sigma, n) = \frac{\tilde{S}_j}{\sigma^n} \left( \frac{\tilde{S}_j}{\sigma} \right)^{n-1} \exp \left( -\frac{\tilde{S}_j^2 + S_j^2}{2\sigma^2} \right) I_{n-1} \left( \frac{\tilde{S}_j S_j}{\sigma^2} \right),
\]

where \( n \) determines the rank of the \( \chi \)-distribution. The value of \( n \) depends on the DWI reconstruction protocol: for ‘GRAPPA’ (Griswold et al. 2002), \( n \) is assigned by the number of receiver coils involved, whereas for ‘SENSE’ (Pruessmann et al. 1999), \( n = 1 \), i.e. the non-central \( \chi \)-distribution degenerates to the Rician distribution. \( I_{n-1}(\cdot) \) denotes the \( (n-1)^{th} \) order modified Bessel function of the first kind.

II.D.1. Likelihood function. The DWIs are independent; therefore the joint PDF \( p(\tilde{S} | \Theta) \) of the signal profile \( \tilde{S} \) is given by the product of the marginal distributions, i.e. the likelihood function becomes

\[
p(\tilde{S} | \Theta) = \prod_{j=1}^{N} p(\tilde{S}_j | S_j, \sigma).
\]

Posterior distribution: Combining the likelihood function (11) and the prior (9) in Bayes’ rule yields the posterior distribution of parameter vector \( \Theta \)

\[
p(\Theta | \tilde{S}) \propto p(\tilde{S} | \Theta) p(\Theta).
\]

The parameter values can be estimated by maximizing (12), yielding the maximum a-posteriori (MAP) estimate

\[
\hat{\Theta} = \arg \max_{\Theta} \ln(p(\Theta | \tilde{S})).
\]

We use Levenberg-Marquardt optimization to solve (13) (Moré 1978). Therefore, the triple-tensor model is initialized multiple times based on an initial single-tensor fit: \( \lambda_{ij} = \lambda_{ij} + c_i \cdot N(0, 1) \) (i.e. \( c_i = \lambda_{free}/\lambda_{ij} \)) and \( \lambda_{ij} = \lambda_{ij} + \lambda_{ij} \cdot N(0, 1) \) (i.e. \( c_i = \lambda_{ij}/\lambda_{ij} \)). Furthermore, the zenith and azimuth angles are initialized randomly and \( f_i = 1/3 \). Ultimately, we select the parameters corresponding to the maximum a-posteriori probability of all these fits.

Unfortunately, simply applying the triple-tensor model to all voxels yields massive overfitting, since only a small fraction of them comprises triple-way fiber crossings. Therefore, we fit single-, dual-, and triple-tensor models followed by model selection based on the total Kullback-Leibler divergence (ICOMP-TKLD) to select the ‘best’ model for each voxel.

II.E. Model selection: ICOMP-TKLD

Model selection methods evaluate the appropriateness of competing models. Typically, these methods assess each model by balancing a measure for goodness-of-fit (e.g. residual energy) with a measure for model complexity. First, we briefly review the standardly used ICOMP criterion (Bozdogan 2000), which is based on the conventional Kullback-Leibler divergence (KLD), and show its shortcomings in evaluating nested rank-2 tensor models. Second, we
present our ICOMP-TKLD technique, which employs the total Kullback-Leibler divergence (TKLD) (Vemuri et al 2011) to assess the information complexity of each model, and show that this solves the problems associated with TKLD.

II.E.1. Information complexity (ICOMP). ICOMP quantifies a model’s complexity not simply by the number of parameter in the model such as the Akaike information criterion (AIC) (Akaike 1976), but as the degree of interdependence among the parameters (Bozdogan 2000). Therefore, it employs the Kullback-Leibler divergence (Kullback and Leibler 1951) between the joint PDF and the product of the marginal PDF’s of the parameters to measure the model complexity. For a model in which the parameters are totally independent, proper scaling of the parameters can be achieved such that the complexity, i.e. the KLD, is zero. This accords with one’s intuition that a nested model may be expanded as long as parameters are not ‘superfluous’ with respect to the data. ICOMP quantifies an overall criterion for a model in two terms: the first denoting the residual energy that remains after ML or MAP estimation and the second expressing the complexity:

\[ \text{ICOMP}(\Theta_i) = -2 \ln(L(\hat{\Theta}_i|\hat{S})) + 2C_i(\Gamma^{-1}(\hat{\Theta}_i)), \quad (14) \]

where

\[ C_i(\Gamma^{-1}) = \frac{1}{2} \sum_{j} \log(\varepsilon_j^2) - \frac{1}{2} \log(|\Gamma^{-1}|), \quad (15) \]

with \( C_i(\Gamma^{-1}) \) being the KLD defined as

\[ C_0(\Gamma^{-1}) = \frac{1}{2} \sum_{j=1}^{k_i} \log(\varepsilon_j^2) - \frac{1}{2} \log(|\Gamma^{-1}|), \quad (16) \]

and the Fisher information matrix given by

\[ I = -E_S \left\{ \frac{\partial^2 \ln(p(S|\Theta, \sigma))}{\partial \Theta \partial \Theta^T} \right\}. \quad (17) \]

Here, \( \Theta_i \) denotes the estimated parameter vector of respectively the single-, dual- and triple-tensor models; \( \Gamma^{-1} \) represents the inverse of the Fisher information matrix. Furthermore, \( \varepsilon_j^2 \) denotes the \( j \)-th diagonal element of \( \Gamma^{-1} \) and \( k_i \) the number of parameters to be estimated in model \( i \). However, the KLD \( C_0(\Gamma^{-1}) \) is a coordinate dependent measure, so that mere changes in the parameterization (i.e. coordinate system) of a model already yield a different KLD. To overcome this issue, equation (15) calculates \( C_i(\Gamma^{-1}) \) by maximizing the KLD over all possible orthogonal transforms (denoted by \( T \)). As such, the measure of complexity becomes coordinate independent. The closed-form expression for \( C_i(\Gamma^{-1}) \) is the theoretically maximum measure of complexity for a given covariance matrix \( \Gamma^{-1} \). Finally, \text{ICOMP} (14) is evaluated for all models and the model with the smallest value is selected as the appropriate model for the given data.

Unfortunately, the maximum KLD is not necessarily a fair measure to compare competing models, because the maximum KLD for the different diffusion-tensor models will generally occur for different orthogonal transformations, i.e. different ‘choices’ of the coordinate system. This is a disadvantage for complex models, whose larger number of parameters increases the chance of finding an unfavorable orthogonal transformation.
II.E.2. ICOMP-TKLD. The concept of total Kullback-Leibler divergence (TKLD) was proposed in (Vemuri et al 2011) as a rotation-invariant divergence for a completely different application than ours. It measures the orthogonal distance (Vemuri et al 2011) between two distributions. Compared to the original KLD, TKLD can be viewed as a weighted KLD:

\[ C_{\text{tot}}(I^{-1}) = \frac{C_0(I^{-1})}{\sqrt{1 + \left\| \nabla f(q) \right\|^2}}, \]  

where the numerator \( C_0(I^{-1}) \) is the KLD (defined in (16)) between two PDFs and the denominator is the weighting of the KLD in which \( f(q) \) is a convex function defined as \( f(q) = \int q \log q \) and \( q = N(\Theta, I^{-1}) \) is the approximate joint posterior PDF of \( \Theta \). Vemuri (Vemuri et al 2011) has derived that \( \int \nabla f(q)^2 = \int (1 + \log q)^2 q \).

In (15), the theoretical maximum value of KLD was employed to obtain a measure of complexity that was invariant to a rotation of the coordinate system. As such the KLD of the more complicated model is potentially penalized more, so that its ICOMP measure will be non-comparable to that of the simpler model. Replacing the theoretical maximum KLD, i.e. \( C_0(I^{-1}) \) in (14) by TKLD solves this:

\[ \text{ICOMP}_{\text{TKLD}}(\Theta) = -2 \ln(L(\Theta; \bar{S})) + 2C_{\text{tot}}(I^{-1}(\Theta)), \]  

with \( C_{\text{tot}}(I^{-1}(\Theta)) \) as defined in equation (17).

Summarizing, ICOMP-TKLD is a model selection criterion that balances the goodness-of-fit and the model complexity. A more complex model, with more parameters, will always yield a better fit than a simpler model, i.e. yielding a smaller misfit term \( -2 \ln(L(\Theta; \bar{S})) \). On the other hand, a more complex model will simultaneously yield a larger value for the complexity term. \( C(I^{-1}(\Theta)) \) The increase of the complexity term is larger if the additional parameters are not needed to model the data. Now, the single, dual and triple-tensor models are all fit to the data and the model with the lowest ICOMP-TKLD, i.e. the optimal balance between goodness-of-fit and model complexity, is eventually selected.

III. Experiments and results

The proposed MAP estimate and the ICOMP-TKLD model selection were tested on simulated data and on experimental data. The performance of ICOMP-TKLD was compared with a state-of-the-art model-order selection technique for complex fiber geometries (bedpostx in toolbox FSL). Specifically, we applied our framework to estimate the FA on both simple and complex fiber geometries along the corpus callosum. Finally, we applied our framework to a neuroimaging case study involving tract-based spatial statistics (TBSS) analysis.

III.A. Three-way crossings: a simulation study

We simulated data of three-way crossings by means of (1) with varying divergence between the fibers to determine the angular resolution of the model estimation. Therefore, we considered fiber-1 to cross a plane spanned by fiber-2 and fiber-3; the angle between the orientation of fiber-1 and this plane was set to different angles: 90°, 60°; furthermore, the divergence between fiber-2 and fiber-3 varied from 0° to 90°. For each configuration, we first generated the noise-free DWI data, i.e. the signal \( S_j \) was calculated via equation (1) for each gradient.
direction $j$, while arbitrarily setting $S_0 = 1$. Subsequently, noise polluted DWI data $\tilde{S}_j$ was generated by drawing from a Rician distribution with expectation value $\tilde{S}_j$ and standard deviation $1/25$ (so that SNR = 25) for each gradient direction. This was repeated 500 times to have 500 independent noisy realizations of the DWI data $\tilde{S}_j$ for each configuration of fibers. The diffusion parameters were set as defined in table 1. As such, the FA’s of the fibers were: $FA_1 = 0.7$, $FA_2 = 0.8$, $FA_3 = 0.9$. Furthermore, a scan protocol was emulated comprising 92 gradient directions for each of the three $b$-values (1000, 2000 and 3000 mm$^{-2}$ s), homogeneously distributed over the surface of a sphere as in (Caan et al 2010). The parameters of the triple-tensor model were estimated by maximizing a posterior probability (12) (MAP) and the maximum likelihood estimation (11) (MLE). We did not apply model selection at this stage. The estimated tensors were labeled based on the orientation similarity to the ground truth. Therefore, we computed for each of six labeling permutations the similarity to the ground truth. This similarity was defined as the sum of the absolute values of the inner products between an eigenvector of the estimated tensor ($v_{i,est}$) and an eigenvector of the ground truth ($v_{i,GT}$), i.e. $\sum_{i=1}^{3} |v_{i,GT} \cdot v_{i,est}|$. The combination that returned the highest value was taken as the final labeling.

### III.A.1. Estimated fractional anisotropy in three-way fiber crossings

Figure 1 shows line plots of the estimated FA (vertically) as a function of the angular divergence between fiber-2 and fiber-3 (horizontally) based on the proposed MAP approach (red) and MLE (Caan et al 2010) (blue). The top, middle and bottom graphs depict FA of the first, second and third tensor, respectively. The left, middle and right graphs represent different angles that tensor-1 makes with the plane spanned by tensors 2 and 3: 90°, 60°. It can be observed that the spread in the estimations by MLE is generally much larger than those of MAP. Furthermore, it may be noticed that the FA of the second tensor is precisely estimated down to an angle of approximately 40° with the third tensor. Below this angle there is large spread in both the MLE and MAP estimates. The small spread that can be observed in the FA estimation of the third tensor is due to a biased estimation and labeling errors that may occur for small angular divergences between the fibers. In previous work on MLE of the dual tensor model applied to two-way fiber crossings (Caan et al 2010) we also noticed a biased, high FA value for small angular divergence. As a two- or three-tensor model is fit to data from a single tract, the estimated FA of the tensor along the tract tends to become positively biased. This is because a nearly isotropic component can be transferred to one of the additional tensors, which effectively sharpens the tensor.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
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</thead>
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<tr>
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<td>}$</td>
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<tr>
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<td>Radial diffusivity of fiber-1</td>
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<td>$\lambda_{2,\perp}$</td>
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<tr>
<td>$\lambda_{3,</td>
<td></td>
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<tr>
<td>$\lambda_{3,\perp}$</td>
<td>Radial diffusivity of fiber-3</td>
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<td>$f_1$</td>
<td>Volume fraction of fiber-1</td>
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</tr>
<tr>
<td>$f_2$</td>
<td>Volume fraction of fiber-2</td>
<td>0.3</td>
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that is aligned with the tract. We observed such a bias both with MLE and MAP. Below we will show that the dual and triple tensor models tends not to survive the model selection for these configurations.

**Figure 1.** Statistics of compartment-specific FA estimation in three-way fiber crossings. Each graph depicts FA (from top to bottom FA1, FA2 and FA3) as a function of the angular divergence between fiber-2 and fiber-3, estimated by respectively MAP (red) and MLE (blue). The shaded region around each line indicates the interval bounded by the 25 and 75 percentiles of the estimated values. The left and right graphs represent different angles that fiber-1 makes with respect to the plane spanned by fibers 2 and 3: 90° respectively 60°. For each configuration 500 noisy realizations were synthesized with SNR = 25.
III.A.2. Estimated fiber orientation in three-way fiber crossings. Figure 2 (a) and (b) present line plots of the estimated angular divergence between fiber-2 and fiber-3 based on the proposed MAP approach (red) and MLE (blue). This orientation divergence was calculated by \((\hat{v}_{12}, \hat{v}_{13}) = \text{acos}(\hat{v}_{12} \cdot \hat{v}_{13})/|\hat{v}_{12}| |\hat{v}_{13}|\), in which \(\hat{v}_{12}\) and \(\hat{v}_{13}\) are the largest principal eigenvectors of estimated tensor-2 and tensor-3 (after sorting). Clearly, the estimation of the angular divergence of both MAP and MLE demonstrates a large spread below 40°. However, above 40° the spread of the MAP estimation is small and the median estimated divergence shows a nice linear relation with the imposed divergence. Alternatively, the spread of MLE is somewhat larger in this range. Figures 2 (a) and (b) demonstrate that the MAP estimation of the angular divergence is precise down to 40°, just like the MAP estimation of FA. Figures 2 (c) and (d) show scatterplots of projected orientations estimated by means of the MAP approach for 500 noisy realizations of two configurations in which tensor-1 makes an angle of either 90° or 60° with the plane spanned by the first principal eigenvectors of tensor-2 and tensor-3 while the angle between tensor-2 and tensor-3 remains fixed at 90°. Essentially, these figures confirm the small spread that is also observed in the corresponding line plots of figures 2 (a) and (b) (see the 90° result in each plot).

III.A.3. Estimated volume fraction in three-way fiber crossings. To assess the influence of compartment size, we simulated three-way crossings by means of (1) while varying the volume fractions of the underlying fibers. For simplicity the three fibers were taken perpendicular to each other. Furthermore, the volume fraction of fiber-1 (i.e. \(f_1\)) was varied from 0 to 1 and the volume fractions of fiber-2 and fiber-3 were taken equal, i.e. \(f_2 = f_3 = (1 - f_1)/2\). Thus, \(f_1 = 0\) corresponds to a two-way crossing and \(f_1 = 1\) represents a single-fiber case. The other parameters were the same as in the previous experiment: SNR = 25, 92 gradient directions for each of the three \(b\)-values, diffusivities see table 1. Notice that 500 noisy realizations were generated for each configuration.

Figure 3 shows the estimated volume fraction (figures 3 (a)–(c)) and FA (figures 3(d)–(f)) based on MAP estimation (red) and MLE (blue). The top, middle and bottom images represent the parameters estimated for tensors \(-1, -2\) and \(-3\), respectively. Again MLE generally yields a larger spread in its estimations than MAP. The FA of tensor-1 is precisely estimated for volume fractions larger than 0.2 (top right). The FA estimation of tensor-2 and tensor-3 are precise for volume fractions of tensor \(-1\) up to 0.7 (middle/bottom right). Observe that this corresponds to volume fractions of 0.15 for each of the other tensors. The volume fraction of the tensor-1 is precise also at small volume fractions, but becomes biased below 0.1 (top left). On the other side it becomes no longer precise for volume fractions of 0.7 and higher. Notice that with increasing volume fraction of fiber-1 (and consequently decreasing volume fractions of the other two fibers) the configuration tends to resemble a single fiber structure, but that the uncertainty and sometimes the bias of the estimated parameters increase.

Summarizing, MAP clearly outperforms MLE in estimating the parameters of the triple-tensor model. However, the reliability of triple-tensor estimation by MAP reduces with decreasing divergence and volume fraction. Observe that the three-way crossing becomes a two-way crossing with decreasing divergence between the second and third tensor. Furthermore, it becomes a single fiber with decreasing volume fraction of the second and third tensor and the simultaneous increase in volume fraction of the first tensor. Consequently, the model has more degrees of freedom than is supported by the (noisy) data, irrespective whether MLE or MAP is used for parameter estimation. Therefore, different parameter settings yield the same fit, which reduces the reliability of the triple tensor estimation. A better signal to noise ratio (SNR) allows for improved estimation of the triple tensor model down to a lower angle.
between the simulated fibers and also with a lower volume fraction. However, the current setting of the SNR is representative for our clinical data.


We applied the proposed ICOMP-TKLD model selection to the data from the previous experiments. The most computationally expensive step is the calculation of the Fisher information matrix. We used an algorithmic speed-up by Poot (Poot 2010), in which the (inverse) Fisher information matrix for Rice distributed measurements is efficiently computed by numerical integration and tabulation.

As such, figure 4 collates the performance of the proposed ICOMP-TKLD model selection approach. Figure 4(a) shows the percentage of cases the triple-tensor model was selected as a function of the angle between fiber-2 and fiber-3 on the data from figure 1. Likewise,
Figure 4(b) depicts the same percentage as a function of the volume fraction of fiber-1 on the data from figure 3. Figure 4(a) demonstrates that the success rate of triple-tensor model selection decreases significantly as the divergence between the two fibers is smaller than 40°, which corresponds with the lower precision of the estimated parameters in figures 1 and 2. Furthermore, figure 4(b) shows that the triple-tensor model is particularly preferred when...
III.B. Validation of model selection on brain data

The proposed model selection framework for single-, dual-, and triple-tensor models was applied to DTI data of the Human Connectome Project (HCP) (Van Essen et al. 2012) (Van Essen et al. 2013) and DTI data of an ongoing study into the effects of HIV on the brain (Su et al. 2014). The HCP data is an open-access dataset intended for characterization of brain connectivity and function and their relationship to behavior (Van Essen et al. 2012, 2013) (Sotiropoulos et al. 2013). The relevant acquisition parameters of the HCP dataset were: three $b$-values 1000, 2000 and 3000 s mm$^{-2}$, 288 gradient directions, TE/TR 89.5/5520 ms, voxel size $1.25 \times 1.25 \times 1.25$ mm$^3$. Similarly, the relevant acquisition parameters for the HIV data were: two $b$-values, i.e. 1000 and 2000 s mm$^{-2}$, 130 gradient directions, voxel size $2.0 \times 2.0 \times 2.0$ mm$^3$.

III.B.1. Comparison of model-order selection. Figures 5(a) and (d) show images of a randomly selected subject from the HCP dataset and the HIV dataset, respectively. The left sub-images in figures 5(a) and (d) reflect the principal directions of single tensor fits to the data: red denotes left-right, blue top-bottom, and green front-back. The right sub-images display the FA derived from single tensor fits and the overlay depicts the probabilistic tractography outcome of FSL-PROBTRACKX (FSLVm6_64). Notice that the ROI’s contain among others a single fiber region (the center of the corpus callosum) and a triple tensor region (as reported previously (Zeki 1993) (Mori et al. 2004)). Figures 5(b) and (e) depicts the model selection and fiber-orientation estimation results from FSL (by means of the command ‘bedpostx’ (Behrens et al. 2007) (Jbabdi et al. 2012) (Sotiropoulos et al. 2013)) on these data. The number of line segments quantifies the number of fiber bundles in a voxel, while the color of each line segment indicates the orientation of the fiber (red for

Figure 4. (a) Estimated probability of selecting the triple-tensor model selection as a function of the angle between fiber-2 and fiber-3 on the data from figure 1 by MAP (red) and MLE (blue). The different line styles reflect different orientations of fiber-1 with respect to the plane spanned by fibers 2 and 3. (b) Estimated probability of selecting the triple-tensor model selection as a function of the volume fraction of fiber-1 on the data from figure 3 by MAP (red) and MLE (blue).
left to right, green for front to back, and blue for bottom to top). Much in the same way figures 5(c) and (f) demonstrate the model selection and MAP estimation by the proposed framework.
The consistency of the model selection was explored by registering 10 subjects from the two datasets using FNIRT registration (Andersson, Smith and Jenkinson 2008). Subsequently, we determined the average number of fibers in each voxel of the region of interest. Figure 6 shows this number in a false color representation. The main difference between the results of FSL and that of the proposed framework is in the central part of the Corpus Callosum (CC). Here, ICOMP-TKLD predominantly infers a single fiber configuration as preferred, whereas FSL mostly selects dual or triple ball-and-stick models. The proposed framework gives comparable inference to FSL in the region supposedly containing crossing fibers. Thus, figures 5(c) and (f) and figure 6 essentially convey that the proposed method yields improved adaptation to the underlying structures compared to the FSL technique particularly in ‘simpler’ structures.

III.B.2. Influence of model selection on fractional anisotropy of Corpus Callosum. Figure 7 shows the estimated FA along the Genu of the Corpus Callosum (GCC) in one subject from the HCP dataset. The graph corresponds to the voxels in the yellow box (see inset) highlighted by the red-colored tractography outcome. The FA along the tract was estimated by: (A) the proposed single-, dual- and triple-tensor model selection framework (red); (B) a simplified version of this framework that focused on single- or dual-tensor models only, thus not considering three-way crossings (blue); (C) a conventional single tensor fit (green). The former, multi tensor methods require selection of the tensor compartment that corresponds to the GCC since the labels assigned to the compartments are random. To solve this, the FA belonging to CC was selected based on ‘front evolution’ (25). In front evolution, the estimated tensor of one compartment is randomly chosen as the reference tensor. Then, the tensor of a neighborhood voxel with the smallest Frobenius norm to the reference tensor receives the same label. After processing all neighbors of the current front, these neighbors become the new reference tensors for the next iteration. The solid lines in the figure denote the median value of the estimated FA value perpendicular to the tract. Furthermore, the shaded areas comprise the 25 and 75 percentiles of the local distributions of estimated FA values.

The figure illustrates how estimation of the FA along a tract is influenced by the model choice. We hypothesize that the large fluctuations of the single tensor approach is caused by space-variant partial volume effects, c.q. the mixing with neighboring structures. Clearly, only the estimation by the proposed framework (red) is without large fluctuations. This outcome accords with one’s intuition that the FA should vary smoothly along a tract. Essentially, the stable estimation signifies that the confounding influence of partial volume effects are effectively dealt with by our framework.

III.B.3. A case study into the influence of handedness using TBSS. The application and potential benefit brought by our framework will be demonstrated by a small case study into the influence of handedness on brain structure using TBSS. The handedness of subjects from the HCP dataset is quantified on a scale from –100 to 100 (left-handed to right-handed) by the handedness inventory of Schachtar et al (Schachter, Ransil and Geschwind 1987). We included the 12 most left-handed and the 12 most right-handed female subjects from the HCP dataset. The handedness of the selected subjects ranged from –100 to −30 in the left-handed group and from 80 to 95 for the right-handed group.

All data was registered to the MNI152 standard space using the version of FNIRT that is implemented in FSL (version 5.0.7) (Jenkinson et al 2012). Subsequently, differences between the left and right brain were analyzed in relation to the handedness. Therefore, we used the TBSS symmetry test. We performed this test with the classical TBSS technique (Smith et al 2006), i.e. based on single tensor data, as well as the extended TBSS (Jbabdi et al 2012)
method for the one/dual/triple tensor models. Compared to the classical TBSS method, the extended TBSS technique (Jbabdi, Behrens and Smith 2010) employs ‘front evolution’ to avoid swapping of the tensor components, i.e. so that corresponding tensor components are properly compared.

Figure 8 shows the outcome of testing whether one or more of the left brain’s FAs or the left brain’s volume fractions is significantly greater than the corresponding parameter in the right brain. The top images focus on the left-handed subjects, the bottom images on the right-handed subjects. The first column shows the classical TBSS outcome (based on a single tensor); the second column visualizes the extended TBSS outcome for the volume fractions of FSL’s ball-and-stick model; the third and fourth columns display the extended TBSS outcome for FAs respectively volume fractions estimated by the proposed three-tensor approach. Notice that in such a comparison TBSS imposes symmetry of the data. Therefore significant differences are indicated only on the right brain’s skeleton.

It can be clearly seen that the classical TBSS analysis and the TBSS analysis of FSL’s volume fraction find little differences in both groups. Instead, the TBSS analysis of the triple-tensor FA and volume fraction yields substantially more significant differences. Furthermore, it can be observed that the classical DTI differences are identifiable in either the triple-tensor’s

*Figure 6.* The average number of fibers inferred in spatially aligned ROIs of 10 subjects from the HCP dataset (a,b) and control group of HIV (CHIV) dataset (c,d). Note that the ROI supposedly contains a three fiber crossing, as in figure5; subjects were registered using fsirt (Andersson, Smith and Jenkinson 2008).
Finally, slightly more differences were found in the right-handed group than in the group of left-handers. This outcome essentially confirms previous results (see e.g. (Büchel et al 2004)).

To our opinion, the outcome signifies how the proposed method can enhance the sensitivity of statistical analysis of experimental brain data. We believe that the enhanced sensitivity is due to a more accurate and precise estimation of FA and volume fraction in fiber crossings.

IV. Discussion and conclusion

We developed a framework for adaptive estimation of diffusion properties particularly for three-way fiber crossings. A MAP estimator involving a mild prior was used to estimate the parameters of a triple-tensor model. The prior precluded the degeneracy of the model estimation. A new model selection technique quantified the extent to which candidate models were appropriate, i.e. single-, dual- or triple-tensor model. As such, overfitting was circumvented. The model selection employed the total Kullback-Leibler divergence (Vemuri et al 2011) to assess the information complexity (Bozdogan 2000) (ICOMP-TKLD), thereby avoiding problems related to the choice of coordinate system. It balanced the trade-off between the goodness of fit and the complexity brought by the order of the diffusion model. The model selection used the Cramer–Rao lowest bound of variance, so that it implicitly adapts to the data acquisition protocol. The model selection approach requires that three models are fit to the data. Actually, any model selection method taking the goodness of fit into account has to do so. Alternatively, automatic relevance determination methods, such as described in (Behrens et al 2007), eliminate redundant parameters automatically. However, such approaches are also very time consuming due to the implementation using a Monte Carlo Markov Chain. In this work
we apply the method described in (Poot 2010) to compute the (inverse) Fisher information matrix. This greatly alleviates the computation task, after the fits have been performed.

The proposed technique extends previous work, which aimed to reconstruct fiber orientations in three-way crossings (Jeurissen et al 2011) (Sotiropoulos et al 2013). A crucial difference is that we employ a rank-2 tensor model, whereas the previous works concerned non-parametric (Jeurissen et al 2011) or ball-and-stick models (Sotiropoulos et al 2013). In other words, we recover the full diffusion shape in different types of structures.

The proposed MAP estimation was compared to MLE using phantom data of three-way fiber crossings. The experiments showed that the prior helps to improve the precision of the triple-tensor model, without introducing a bias in the estimated diffusivities. The spread in the parameters from MLE was generally much larger than those from MAP estimation. The FA of the third tensor could be precisely estimated with MAP down to an angle of approximately 40° with the second tensor. Furthermore, the volume fractions and FAs could be accurately and precisely estimated if the volume fraction of the first tensor was between 0.2 and 0.7. At the latter boundary (0.7), the volume fractions of the remaining two tensors were merely 0.15.

The proposed framework was also compared with the ball-and-stick modeling approach from FSL using experimental brain data, acquired with two different protocols. The configurations inferred by our method corresponded to the anticipated neuro-anatomy, both in the single fiber and in the triple-crossing regions. The main difference with FSL was observed in a single fiber region. Here, ICOMP-TKLD predominantly inferred a single fiber configuration, as preferred, whereas FSL mostly selected dual or triple ball-and-stick models. The different performance is due to ICOMP-TKLD’s model selection. FSL’s model selection method is done in a Bayesian way, merely by adding a prior to the parameter estimation. Finally, a TBSS

![Figure 8. FSL-TBSS outcome testing whether the brain’s FA or volume fraction in the left hemisphere is significantly larger than in the right hemisphere. Results of a group of predominantly left-handed subjects (top row) and predominantly right-handed subjects (bottom row). The first column shows the classical TBSS outcome for FA; the second column visualizes the outcome of the extended TBSS framework for the volume fraction of FSL’s ball-and-stick model; similarly, the third and fourth columns show the extended TBSS outcome for FA respectively volume fraction generated with the proposed triple-tensor framework. The green lines denote the white matter’s skeleton; the red points indicate clusters of significant difference.](image-url)
experiment showed the enhanced sensitivity of statistical analysis using the proposed method. An obvious limitation of the TBSS experiment is that there is no ground truth available. Still, we believe that the outcome by our method is more plausible than the outcome by FSL as it confirms previous results (Büchel et al 2004). Also, we found that the proposed method yields improved adaptation to the underlying structures compared to the FSL technique (see figures 5 and 6). The ensuing larger variability of FSL might be at the basis of the observed reduced sensitivity.

There are a few limitations of our approach. Firstly, we assume a mono-exponential decay along the eigenvectors of the three compartments up to $b = 3000 \text{ s mm}^{-2}$. Measuring at higher $b$-values will certainly introduce sensitivity to compartments such as the myelin sheet (Peled 2006) with severely restricted and hindered diffusion (Assaf and Basser 2005). In the latter case, the Gaussian diffusion assumption is no longer valid. We considered investigating non-Gaussian diffusion beyond the scope of our current work.

Secondly, our framework focused on single, dual- and triple-tensor models to characterize the full diffusion profile. There might exist four-way crossings or even more complicated fiber structures, although we did not find papers reporting about such configurations. In (Caan et al 2010) we showed that estimating a dual rank-2 tensor model already requires HARDI at two $b$-values, data of sufficient SNR, and some model restrictions. The latter is needed to ensure stability as the number of model parameters may approach or even surpass the number of degrees of freedom present in the data. Presently, the modeling was extended to triple-way crossings by employing several sophisticated concepts. Fitting a quadruple rank-2 tensor model to voxels with a four-way-crossing will be even more challenging. Developing for estimation of the diffusion properties in four-way-crossing fiber bundles will remain an important challenge for future research.

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