Technical Note

Robust intra-individual estimation of structural connectivity by Principal Component Analysis

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**Abstract**

Fiber tractography based on diffusion-weighted MRI provides a non-invasive characterization of the structural connectivity of the human brain at the macroscopic level. Quantification of structural connectivity strength is challenging and mainly reduced to “streamline counting” methods. These are however highly dependent on the topology of the connectome and the particular specifications for seeding and filtering, which limits their intra-subject reproducibility across repeated measurements and, in consequence, also confines their validity. Here we propose a novel method for increasing the intra-subject reproducibility of quantitative estimates of structural connectivity strength. To this end, the connectome is described by a large matrix in positional-orientational space and reduced by Principal Component Analysis to obtain the main connectivity “modes”. It was found that the proposed method is quite robust to structural variability of the data.

1. Introduction

Diffusion magnetic resonance imaging (dMRI) is a non-invasive method for investigating the microstructure of the human brain in vivo (Basser et al., 1994). Based on dMRI, fiber tracking algorithms allow for the macroscopic characterization of the structural connectivity between different brain regions (Basser et al., 2000).

A variety of different fiber tracking approaches exist to infer structural connectivity such as deterministic (Mori et al., 1999; Tournier et al., 2010a), probabilistic (Behrens et al., 2007; Berman et al., 2008; Parker et al., 2003), and global algorithms (Kreher et al., 2008; Mangin et al., 2013; Reisert et al., 2011). Tracts in terms of fiber bundles reflecting the connectivity between specific brain regions are commonly determined by dividing the gray matter (GM) into regions of interest (ROIs) that are used as seeds or a priori constraints for the selection of connecting streamlines. Architectonic and template-based atlases provide the most simple way to obtain GM parcellations (Caspers et al., 2013) that can be registered with individual subjects to ensure that ROIs are matched with respect to data size, geometry and location. Generalizations to parcellation-based ideas represent the cortex continuously on the two-sphere (Moyer et al., 2017). However, the anatomical variability of cortical structures, undefined positions of fiber terminals and the variability in fiber topology, like the sudden of streamline due to insufficient resolution, are problems that are inherent to the common “streamline counting” ideas and challenge common ROI-based approaches on structural connectivity (Sotiropoulos and Zalesk, 2019). For example, in Petrov et al. (2017) a good overview and evaluation of the common brain connectivity construction pipelines can be found. The choice of the most appropriate analysis method for fiber tracking is still an object of discussion (Jones and Cercignani, 2010; O’Donnell et al., 2013; Sotiropoulos and Zalesk, 2019).

Quantification of structural connectivity strength constitutes another challenge. Streamlines resulting from fiber tracking describe trajectories of anatomical fiber bundles at the macroscopic level, but do not correspond directly to individual axons at the microscopic level (Beckmann et al., 2009; Jbabdi and Johansen-Berg, 2011; Jones et al., 2013). For the majority of algorithms the inference of structural connectivity strength is reduced to simple “streamline counting” procedures, which are highly dependent on the topology of the the connectome (Soro et al., 2005) considered. The topology can however be highly variable owing to reasons such as poor resolution, outliers and masking, just to name a few (see Sotiropoulos and Zalesk, 2019; Zalesk et al., 2016; Zalesk et al., 2009 for overview). This, in turn, directly affects the reproducibility of quantitative estimates of structural connectivity strength as only ma-
In this work we propose a novel method that overcomes several limitations of the common ROI-based “streamline counting” procedures approached described above. We will see that it can substantially increase the intra-subject reproducibility of quantitative estimates of structural connectivity strength. The proposed idea shares similarities with clustering approaches, which are applied in the context of automatic tract segmentation (Siless et al., 2011; Brun et al., 2004; O’Donnell et al., 2006; O’Donnell and Westin, 2007; Zhang et al., 2018; Zhang and Laidlaw, 2005). Fiber clustering links streamlines to tracts (or fiber bundles) based on similar trajectories and anatomical positions but without any reference to a priori specified brain regions. These methods focus mostly on anatomy of fiber tracts, but not on built connections. Here we concentrate on ROI-based methods, since they allow to investigate connectivity between cortical regions and also enable graphical analysis of the brain networks. In our approach the connectome is described by a huge density matrix (≈ 10^7 × 10^9) in position-orientation space, which is the basis for the commonly ROI-based approaches. We reduce it by Principal Component Analysis (PCA) to obtain the main “modes” of connectivity\(^1\). The intuition behind this idea is that the found major singular vectors can be interpreted as the superposition of the Tract Orientation Distributions (TODs) (O’hollander et al., 2014), of the major tracts, no matter how the configuration of underlying fiber reconstruction looks like. In the context of fiber clustering the similarity may also be interpreted as similarities between vectors representing cluster memberships. The approach of embedding fibers in an ‘ambient’ space, which is part of the proposed idea, was also presented in Durrleman et al. (2011), where the embedding is used for the metrification of the space of fiber bundles. Also in Reisert et al. (2013) an embedding in a TOD-like space is used to derive quantitative estimates for fiber densities.

In the remainder we will specify the details of the proposed method and will demonstrate its performance on simulated phantom data and in vivo data of 26 subjects who underwent two repeated dMRI measurements. Results reveal that our PCA approach is more robust to breaks within continuous streamlines than commonly applied “streamline counting”. Analyses of intra-class correlation coefficients (ICCs) further show a stronger robustness of the proposed method to the structural variability of the data in terms of a substantially increased intra-subject reproducibility of estimates of structural connectivity strength across separate dMRI measurements.

2. Methods

2.1. Fiber density matrix and fiber features

Suppose a given set of streamlines \( F \) coming from some whole brain tractography algorithm, then its corresponding fiber density matrix \( M \) is defined as

\[
M_{(v,d),f} = \delta(f \text{ passes through } (v,d))
\]

where \( \delta \) is indicator function, \( f \in F \) is a streamline and \( v \) is a voxel visited by \( f \), \( d \) is the direction (tangent) of the fiber in this voxel.

The obtained density matrix \( M \) represents the full information of the set of streamlines \( F \), i.e. under rather mild assumptions (the tangent of \( f \) is continuous) we are able to reconstruct all streamlines from \( M \).

Note that \( M^T M \) defines a similarity metric in fiber space (here \( M^T \) denotes the transpose matrix). Correspondingly, \( MM^T \) defines a similarity metric in position/orientation space. We will see below that our approach relies on a spectral decomposition of \( MM^T \). Note the similarity to spectral clustering (see e.g. O’Donnell et al., 2006; Zhang et al., 2018), where the decomposition of the matrix \( MM^T \) is used for the clustering of fibers into bundles. Indeed, the spectrum of \( MM^T \) and \( M^T M \) are identical, so the approaches are deeply interlinked, but with completely different purpose. The matrix \( M^T M \) is indeed the common similarity metric, when streamline counting approaches are used. Our approach is based on the idea that the major singular values of the matrix \( M \) induce a more stable connectivity measure than the ordinary streamline counting idea.

In general, to obtain the “Feature Connectivity Matrix” (FCM), we find reduced density matrix \( T \) using right-singular vectors of density matrix \( M \) and calculate the correlation between \( T_i \) and \( T_j \) for each pair of ROIs \( i \) and \( j \) (Fig. 1).

Now, let \( V_i \) and \( V_j \) be two ROIs and \((V_i)\), the indicator function, which is one, if the voxel \( v \) is contained in \( V_i \), otherwise zero. With this, and the definition of \( M \) we approximate the “ordinary” connectivity \( CM_{ij} \),

\[ CM_{ij} = \sum_{v \in V_i} \sum_{d \in d} (V_i)_v M_{(v,d),f} M_{(v,d'),f'} (V_j)_v \]

(2)

The kernel matrix is just the product \( K = M M^T \) and defines the induced similarity metric. Now, we approximate this similarity \( K \) by

\[ CM_{ij} = \sum_{v \in V_i} \sum_{d \in d} (V_i)_v K_{(v,d),f} (V_j)_v = : FCM_{ij} \]

(3)

where \( K_{(v,d),f} \) is the matrix obtained when restricting to the \( numC \) largest eigenvectors of \( K \). We call the new connectivity measure “Feature Connectivity Matrix”, as we will see later, it can be computed as an inner product in a certain features space. To evaluate this, we write \( K_{(v,d),f} = \sum_{j} M_{(v,d),f} P_{f,f'} M_{(v,d'),f'} \)

(5)

where \( P \) is the projector onto the subspace spanned by the \( numC \) largest eigenvectors of \( K \). If the singular value decomposition of \( M \) is

\[ M_{(v,d),f} = \sum_{k=1}^{numC} \epsilon_k G_{k,(v,d)} W_{f,k} \]

(6)

where \( G \) and \( W \) are the left-singular and right-singular vectors of matrix \( M \). Then the projector is

\[ P_{f,f'} = \sum_{k=1}^{numC} W_{f,k} W_{f',k} \]

(7)

With this we can compute \( FCM_{ij} \) by first computing

\[ T_{d,k} = \sum_{i \in V_i} \sum_{f \in F} M_{(v,d),f} W_{f,k} \]

(8)

where the outer sum runs over all voxels in ROI \( V_i \), such that \( T_{d,k} \) constitutes a ROI specific descriptor of the connectivity relationships. Note that the descriptor still depends on the directionality \( d \) of the fibers within the ROI. Now, the inner-product of the descriptors give the connectivity

\[ FCM_{ij} = \sum_{k=1}^{numC} T_{d,k}^T T_{d',k} \]

(9)

So, \( FCM \) can be computed by a simple inner-product in a certain low-dimensional feature space. The intuition behind the idea, that \( FCM \)’s lead to more robust connectivity, is based on the observation that the major singular vectors \( G_{k,(v,d)} \) when interpreted as tract orientation distributions (TOD), are superpositions of the TODs of the major tracts, no matter how the actual topology of the underlying tractography is

\[ \text{The term "modes" is in the context of eigen analysis associated with the different eigenvectors, or also "eigenmodes".} \]
Calculation of density matrix $M$ ($\sim 10^7 \times 10^5$) (1)

Singular Value Decomposition of $M$ for $numC$ largest eigenvectors (7)

Calculation of Feature Connectivity Matrix $FCM$ (10)

Calculation of reduced density matrix $T$ ($\sim N_p \times numC$) for ROI $V_i$ and fibers $F_i$ passing through $V_i$ (8)

$$= \sum_{k=1}^{numC} \left( \sum_d T_{d,k}^i \right) \left( \sum_d T_{d,k}^j \right)$$

We found in experiments, that, indeed coefficients $a > 1$ can be beneficial in terms of robustness and quality of reproducibility, however an important property is also lost: if $A$, $B$ and $C$ are disjunct ROIs, one expects to have: $FCM_{A,B,C} = FCM_{A,C} + FCM_{B,C}$. It holds for $a = 1$, but not for $a > 1$. Nevertheless, we used power coefficient $a = 2$ in all experiments with simulated data and $a = 1$ for in vivo data. Higher values of $a$ allow the reduction of “background noise” in obtained connectivity matrices. Since the connectivity matrices for simulated data are quite sparse, higher values of $a$ can improve obtained results.

2.2. Normalization

Since values in $FCM$ change between 0 and 1, and c-values in $CM$ indicate the number of fibers, we normalized both $CM$ and $FCM$ in some experiments by the row/columns sums, i.e.

$$C_{ij} = \frac{CM_{ij}}{\sqrt{\sum_i C_{ij}^2 \sum_j C_{ij}^2}}$$

where $C$ is one of connectivity matrices.

2.3. Implementation

To compute $FCM$ the directional index has to be discretized by $d$. We found, that 32 or 64 directions were enough to obtain adequate results. To compute the projection operators $W_{ijkl}$ we computed the eigendecomposition of $J_{ijkl} = \sum_{k,l} M_{ijkl} M_{ijkl}^\top$ by using MATLAB’s eigs function. The function eigs requires the application of the matrix $J$, which involves the repeated application of the matrix $M$, normalized over the fiber densities along the position/orientation direction and normalized over the fiber length along the fiber direction.

3. Data

3.1. Simulated data

Phantom data was simulated using Phantomas software (Caruyer et al., 2014) using known ground-truth geometry of testing set from the 2nd reconstruction HARDI challenge (Fig. 3a). The phantom consists 20 fiber bundles and includes 40 seed regions. Images were corrupted by Rician noise with SNR 10, 30, 50. Voxel size 1 mm$^3$ isotropic; 74 gradient directions with b-factor $b = 2000$ s/mm$^2$ were used to simulate the data.

3.2. In vivo data

To investigate intra-subject reliability 26 healthy subjects were scanned twice on a Siemens TIM TRIO, 6/8 partial Fourier, TR=10,900 ms, TE=107 ms; b-factor $b = 1000$ s/mm$^2$ with 61 gradient direction and an isotropic resolution 1 mm$^3$. The data was reconstructed with adaptive combine (Walsh et al., 2000) such that the noise distribution is close to Rician. Additionally, T1-weighted images were segmented using SPM into white matter, gray matter and CSF. A threshold of 0.5 was used to estimate the area of reconstruction for white matter.

(Fig. 2). This is actually similar to spectral clustering, where the same observation can be made, and is used to cluster streamlines. Note that in the above derivations the directional index $d$ could have already been traced out at a quite early stage. Even the matrix $M$ could have been defined by $M_{ijkl} = \delta(f \text{ passes through } i)$ completely disregarding the orientation. Disregarding $d$ would actually lead to a much smaller problem, and hence, smaller running times. However, we found that there are higher order similarities, which prohibit this, and which are beneficial as we will see later. That is, one can easily generalize the introduced connectivity measure by

$$FCM_{ij} = \sum_{k=1}^{numC} \sum_{d,d'} (T_{d,k}^i T_{d',k}^j)^a$$

Fig. 1. Main steps of the method.

Fig. 2. Visualization of the top singular vectors for a subsection of the phantom. Top: the original tract orientation distribution (TOD). Bottom rows: the singular vectors $G_{k,i,j}$ corresponding to the first four $k = 1, \ldots, 4$ are visualized. Left: the voxel-wise normalized orientation distributions. Right: the corresponding mean values of $G_k$ for each voxel, blue color indicates negative values, red color indicates positive values.
3.3. Fiber tracking algorithms

Results from three fiber tracking algorithms were used to obtain connectivity matrices:

1. Global Tracking (GT) (Reisert et al., 2011). Parameters of reconstruction were set according to “dense” suggestion: width = 0.5 mm, length = 1.5 mm, weight = 0.01 for simulated data and width = 1 mm, length = 3 mm, weight = 0.055 for in vivo data.

2. Model-free global tractography (mGT) (Konopleva et al., 2018). We used length = 2 mm for simulated data and length = 2 mm with over-sampling factor 2 for in vivo data. Maximal SH order \( l_{\text{max}} = 6 \) for all datasets.

3. Constrained Spherical Deconvolution (CSD) (Tournier et al., 2007) followed by probabilistic streamline tractography by 2nd order integration (iFOD2) (Tournier et al., 2010b). All parameters were set by default – step size 0.5 of the voxel size, angle threshold 45°, seed points were distributed uniformly within the white matter mask.

4. Results

4.1. Parameters evaluation

First, we investigated the influence of the number of Principal Components \( \text{numC} \) and the power coefficient \( a \) (formula (10)) on the obtained connectivity matrices using simulated and in vivo data. For simulated data we compared obtained connectivity matrices with ground truth connectivity matrix using chi-squared similarity measure (Fig. 3b):

\[
W = \exp\left(-\frac{\chi^2}{a}\right) \quad \text{with} \quad \chi^2 = \frac{1}{2} \sum_{ij} (c_1(i,j) - c_2(i,j))^2 \left(\frac{c_1(i,j) + c_2(i,j)}{2}\right)
\]

(12)

\( c_1 \) and \( c_2 \) are the connection values from compared matrices, we set \( a = 0.1 \) in our experiments. It should be noted, that matrices should be normalized before comparison.

Obtained similarity values for different \( \text{numC} \) and \( a \) are shown in Fig. 3. We found lower similarity values for streamline algorithm iFOD2. It can be explained by higher number of false fibers in results and also “curly” fibers, since the proposed method accounts for directional distribution of fiber segments. Figs. 3 and 4 demonstrate the influence of the described parameters on obtained connectivity matrices. It can be seen, that the power coefficient \( a \) just reduces the “noise” in background: low \( c \)-values get even lower and high \( c \)-values just remain high. The increase of \( \text{numC} \) emphasizes trajectories that are built of coherent fibers, whereas connections built by less homogeneous bundles get weaker. Fig. 4 c shows an example: fibers with different directions inside a bundle (connecting 39th and 40th ROIs) get weaker with increasing of \( \text{numC} \). We also investigated the global behavior of the obtained FCMS \( c \)-values for different \( \text{numC} \) and \( a \) settings (Fig. 5). The \( c \)-values were divided into three groups by their median values. It can be seen, that in all settings high \( c \)-values remain high, but low \( c \)-values get lower with the increasing of \( \text{numC} \). With increasing of power coefficient \( a \) groups of \( c \)-values get more separable.

The spherical-shaped phantom has a rather simplified structure in comparison to the real human brain. Thus, we also evaluated the influence of the above parameters on results obtained from in vivo data. We investigated the connectivity between 90 areas defined by the AAL atlas (Tzourio-Mazoyer et al., 2002). The AAL atlas was registered to the subject’s space, normalization and deformation were performed using SPM. The first 45 ROIs belong to the right hemisphere, another 45 ROIs belong to the left hemisphere.

For analysis we considered the connection density as the proportion of existing connections in the connectivity matrix relative to all possible connections that can be formed. For binarization we used a threshold of 0.05 for all obtained FCMS. The connection density can be calculated as follows (Connectivity, 2016):

\[
k = \frac{2E}{N(N-1)}
\]

(13)

where \( E \) – is the number of nonzero elements in connectivity matrix, \( N \) – is the number of nodes.

Fig. 6 (top row) shows the obtained connectivity density for different feature space dimensions \( \text{numC} \) and different values for the power coefficient \( a \). It can be seen, that the density decreases with increasing \( \text{numC} \), since \( c \)-values are getting lower (see Fig. 7). The same was observed for simulated data.

The reproducibility of the connectivity estimates is also an important aspect. Therefore, the intraclass correlation coefficient (ICC) for each \( c \)-value was computed for both CM and FCMS. If \( c_1 \) and \( c_2 \) are the \( c \)-values for scan 1 and scan 2 of a certain subject, then the ICC is calculated as follows:

\[
\text{ICC}(c) = \frac{\langle c_1 - \bar{c}\rangle^2 + \langle c_2 - \bar{c}\rangle^2}{\langle c - \bar{c}\rangle^2}
\]

where \( \langle c \rangle \) denotes the expectation value over the whole group of subjects, and \( \bar{c} = \langle c_1 + c_2 \rangle / 2 \). In order to exclude the influence of connectivity density on the obtained results, mean and median values were calculated only for nonzero ICC values.

The obtained median ICC values (see Fig. 6) were more or less on the same level for all features space dimensions. Fig. 7 shows obtained average FCMS. We found, that with an increase of the feature space dimension \( \text{numC} \) a lower number of \( c \)-values remain high. Which seems quite reasonable, since with an increase of \( \text{numC} \), the set of characteristics used to calculate the correlation between ROIs is also increased. Accordingly, an increase in \( \text{numC} \) leads to the identification of areas connected by the most homogeneous fiber bundles. The coefficient \( a \), in turn, only affects the degree of weighting of \( c \)-values. An increase in \( a \) leads to an even greater decrease for low \( c \)-values. Thus, the patterns found in experiments with simulated data were also revealed for data in vivo.
Fig. 4. (a) c-Values depending on features space dimension (numC) for connections between ROIs 25–26 (region a) and ROIs 39–40 (region b). (b) FCM for iFOD2 reconstruction, SNR 30, numC = 100, a = 2. Region a indicates connection between ROIs 25 and 26, region b indicates connection between ROIs 39 and 40. This figure illustrates how numC and a influence obtained connectivity matrices – whereas a just reduces the “noise” in background, increasing of numC leads to c-values decrease of less homogeneous connections (c).

Fig. 5. The change of FCM c-values, divided into three groups by their median values. High c-values remain more or less high, whereas low c-values get lower with increasing of numC.
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Fig. 6. Obtained connectivity density (top row) and median ICC values for different features space dimension \(numC\) and power coefficient \(a\).

Fig. 7. Average \(FCMs\) obtained for different features space dimension \(numC\) and power coefficient \(a\) (mfGT, SNR 30).

By varying the features space dimension (\(numC\)) we can determine the amount of the specificity of the connectivity information obtained. A high number of components only recovers highly coherent bundles, while a lower number let survive also more chaotically organized tracts. In case of simulated data we found that there was no significant improvement for \(numC\) values higher than 50. However, due to the simple structure of the phantom, there are only 20 fiber bundles and 40 seed regions, it seems more reasonable to use larger \(numC\) for in vivo data. The power coefficient \(a\) in formula 11 influences the “sharpness” of \(c\)-values distribution. Values higher than 1 allow reduce the number of low \(c\)-values, but they lead to a lost of the linearity in formula 11. In the remainder of the work we will show experimental results for \(numC = 80\) and \(a = 2\) for simulated data and \(a = 1\) for in vivo data.

4.2. Simulated data results

We compared the chi-similarity metrics for both \(CMs\) and \(FCMs\) (see Fig. 8). The obtained similarity values are shown in Table 1. It can
connectivities can be thresholded to obtain also binary connectivity matrices. To compare with the ground truth we used the f1-score\(^2\). Fig. 10 shows the f1-score for \(CM\) (dashed line) and \(FCM\) (solid line) with different thresholds. It can be seen, that scores differ significantly for broken FT results.

4.3. In vivo data

Similar to Reisert (2015) logarithmic scaling was used to obtain comparable contrast of connectivity matrices: 

\[
\epsilon_{\text{log}}(i, j) = \log(1 + c(i, j)),
\]

where \(t\) is the 30% quantile of \(c\)-values over all regions. Fig. 11 shows the average connectivity matrices in logarithmic scale. For connectivity matrices, shown on this figure we did not used any threshold.

Fig. 12 (top row) shows individual ICC values for each \(c\)-value for \(CMs\) and \(FCM\) for mfGT. To investigate the robustness of connectivity matrices against artificial breaks of fibers, broken FT results were created for each FT algorithm – all fibers were broken at fixed position relative to their length. We obtained connectivity between different ROIs after that. We show here the results for fibers, broken at 0.7 of their length. Obtained ICC values for each individual \(c\)-value for broken mfGT results are shown in Fig. 12 (bottom row). ICC values reduced for both \(CM\) and \(FCM\) in most cases, but ICCs are still higher for \(FCM\) than \(CM\). Table 2 shows mean and median ICCs for all FT algorithms, ICC values for broken FT results are shown in parenthesis. While ICCs for \(FCM\) for original and broken FT results are close, there is a significant difference in ICCs for \(CMs\).

5. Discussion

The proposed method performs topologically robust connectivity estimation using tract density features. The idea is to describe the connectome by a huge density matrix in position-orientation space. We used

\[
\text{f1-score} = \frac{2 \times \text{precision} \times \text{recall}}{\text{precision} + \text{recall}}.
\]

be seen, that there was no significant difference in similarity values for both methods. But \(FCM\)s seem more robust to noise – whereas there was a decrease in similarity values with decrease of SNR for \(CMs\) (up to 8% for iFOD2), similarity values for \(FCM\)s remain the same.

Further, we investigated the robustness of the proposed method against artificial breakage of fibers to show the robustness of the proposed method against the topology of the underlying streamline configuration. All streamlines were cut at a fixed position relative to their length. Here we show results for fibers, broken at 0.7 of their length. It was found, that there was no dependency between obtained results and the position of the breaks. We also investigated the robustness of the method for fibers broken at random points. But, in this case, significant changes in fiber length distribution affected the obtained results. Fig. 9 shows end points maps overlaid with FA maps for mfGT results before (a) and after (b) breakage. It was found, that whereas there were no true connections on \(CMs\) for broken fibers, \(FCM\)s remained the same. Example of \(CM\) and \(FCM\) for broken mfGT results are shown in Fig. 9c–d. Similarity values for broken FT results are shown in parenthesis in Table 1.

The \(\chi^2\)-metric takes the absolute values of the connectivities into account. To get an agreement measure, which is more independent of the absolute values (the ground truth is actually a binary matrix), the

| SNR 50 | SNR 30 | SNR 10 |
|--------|--------|--------|
| GT     | \(CM\) | \(FCM\) | \(CM\) | \(FCM\) | \(CM\) | \(FCM\) |
| 0.69   | 0.05   | 0.46   | 0.44   | 0.40   | 0.35   |
| (0.12) | (0.05) | (0.05) | (0.05) | (0.05) | (0.05) |

Table 1

Similarity between obtained and ground-truth connectivity matrices for different FT algorithms and SNR levels, similarity for broken FT results are indicated in parenthesis.

Fig. 8. Obtained \(FCM\)s and \(CM\)s for simulated phantom, SNR = 30.

2 If \(GC_{ij}\) is the ground truth and \(C_{ij}\) is the predicted binary connectivity matrix, we computed the precision \(p = \sum_{i,j} GC_{ij} C_{ij} / \sum_{i,j} C_{ij}\), the recall \(r = \sum_{i,j} GC_{ij} C_{ij} / \sum_{i,j} GC_{ij}\) and finally the f1-score by \(2 \times \text{precision} \times \text{recall} / (\text{precision} + \text{recall})\).
Fig. 9. End points map for initial (a) and broken (b) mfGT results overlaid with FA map of phantom, SNR 30; (c) CM for broken mfGT results; (d) FCM for broken mfGT results. There are no true connections in CM for broken FT results, but FCM remains the same.

Fig. 10. f1-score for different threshold value for initial (a) and broken (b) FT results, f1-scores for FCM are shown with solid line, f1-scores for CM are shown with dashed line. Obviously for broken fibers CM fails completely.

Fig. 11. In vivo data results. Average FCM for GT, mfGT and iFOD2 (upper row) in logarithmic scale; Average CM for GT, mfGT and iFOD2 (lower row) in logarithmic scale. There are more “strong” connected, but also “weak” connected areas on FCMs.
Table 2
Mean and median ICC values for $CM$ and $FCM$ for different approaches, values for broken FT results are indicated in parenthesis.

|       | GT | mFGT | $iFOD2$ |
|-------|----|------|---------|
| Mean ICC | $CM$ | 0.41 | 0.46 | 0.46 |
|       | $FCM$ | 0.57 | 0.43 | 0.44 |
|       | Median ICC | 0.41 | 0.47 | 0.49 |
|       | $CM$ | 0.65 | 0.46 | 0.48 |
|       | $FCM$ | 0.52 | 0.18 | 0.12 |
|       | $iFOD2$ | 0.26 | 0.16 | 0.18 |

Principal Component Analysis to obtain the major components of this matrix, which correspond to the main underlying tract orientation distributions.

First, we investigated the dependency of the results on the number of principal components and the value of the power coefficient $a$ in formula (11) for simulated and in vivo data. For simulated data we investigated the similarity between the estimated and ground-truth connectivity matrices. It was found, that similarity values increase in case of global FT algorithms up to $numC = 50$ and then remain stable (see Fig. 3). The situation was different for $iFOD2$, since there were a lot of false bundles in the reconstruction. The similarity was low for all investigated values of $numC$. It was found, that the power coefficient $a$ influences the weighting of the $c$-values: during increase of $numC$ only connections built by fibers with similar trajectories remain high, connections built by less homogeneous bundles become weaker (Fig. 4). This can be explained by the fact, that by increasing of $numC$ we increase the number of features or “characteristics” that we use to calculate the correlation. Similar tendencies were observed for in vivo data.

Since the reproducibility of the connectivity results is an actual challenge today (e.g. Buchanan et al., 2014; Prčkovska et al., 2016) 26 subjects were scanned twice to evaluate robustness of the proposed method with the original “fiber counting” method. It was found, that the ICC values were higher in most of the cases for $FCM$ (see Fig. 12 and Table 1). We also calculated the connectivity density of the obtained matrices depending on $numC$. We found that the connectivity density decreases with an increase of $numC$, but ICC values remain more or less on the same level for $a = 1$.

To show the robustness against topological changes we artificially broke fibers. It was found that although $CM$s were ruined after the breaking procedure, there were no changes in $FCM$s. This was also confirmed by the similarity values indicated in parenthesis in Table 1. There were no significant changes in mean and median ICC values for all FT algorithms (see Table 2). An improvement in ICC values for $FCM$s for all FT algorithms in comparison with $CM$s was up to 20% (for mFGT results).

In general, a connectivity estimation method, not dependent on the topology of the connectome, can be potentially used to generate scanner-independent large-scale normative data for clinical applications. In this work we proposed a method to increase the robustness and intra-subject reproducibility of structural connectivity measures, which was demonstrated in experiments with simulated and in vivo data.

Data and code availability statement

The data and code used in the study will be available on request. The data and code sharing adopted by the authors comply with the requirements of the Medical Center, University of Freiburg, and comply with ethics of the Medical Center, University of Freiburg.

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