Published in final edited form as:

Neuroimage. 2011 August 1; 57(3): 825–838. doi:10.1016/j.neuroimage.2011.05.056.

Clustering method for estimating principal diffusion directions

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Abstract

Diffusion tensor magnetic resonance imaging (DTMRI) is a non-invasive tool for the investigation of white matter structure within the brain. However, the traditional tensor model is unable to characterize anisotropies of orders higher than two in heterogeneous areas containing more than one fiber population. To resolve this issue, high angular resolution diffusion imaging (HARDI) with a large number of diffusion encoding gradients is used along with reconstruction methods such as Q-ball. Using HARDI data, the fiber orientation distribution function (ODF) on the unit sphere is calculated and used to extract the principal diffusion directions (PDDs). Fast and accurate estimation of PDDs is a prerequisite for tracking algorithms that deal with fiber crossings. In this paper, the PDDs are defined as the directions around which the ODF data is concentrated. Estimates of the PDDs based on this definition are less sensitive to noise in comparison with the previous approaches. A clustering approach to estimate the PDDs is proposed which is an extension of fuzzy c-means clustering developed for orientation of points on a sphere. MDL (Minimum description length) principle is proposed to estimate the number of PDDs. Using both simulated and real diffusion data, the proposed method has been evaluated and compared with some previous protocols. Experimental results show that the proposed clustering algorithm is more accurate, more resistant to noise, and faster than some of techniques currently being utilized.

Keywords

Principal diffusion directions; Fuzzy c-means; Minimum description length; Fiber orientation distribution function

Introduction

Diffusion of water molecules is conventionally investigated using diffusion tensor magnetic resonance imaging (DTMRI) that uses a symmetric positive definite matrix (tensor) to model the diffusion behavior. Under Gaussian diffusion condition, this model characterizes the diffusion behavior very well (Basser et al., 1994a, 1994b); however, it fails to model anisotropies of orders higher than two in the heterogeneous tissues containing more than one fiber population. Diffusion behavior can be evaluated more accurately if the probability density function (PDF) of the molecular displacement over diffusion time is determined

from which desirable diffusion indices such as mean diffusivity, second order tensor (and related anisotropies), fourth order kurtosis, and even higher order statistics can be extracted. Estimation of the diffusion PDF conventionally involves diffusion spectrum imaging (DSI), a modified q -space imaging method that resolves intra-voxel diffusion heterogeneity by measuring diffusion spectra (Wedeen et al., 2000). This method is clinically impractical because it takes a long time to acquire the required data.

To address the time complexity, high angular resolution diffusion imaging (HARDI) and orientation distribution function (ODF) have been introduced as alternatives to DSI and diffusion PDF, respectively (Tuch et al., 2002). The ODF requires taking more than 50 measurements of HARDI, each corresponding to a specific gradient direction. The ODF maintains information about the orientation of the diffusivity by integrating over the radial component of the PDF in the spherical domain. The ODF may be estimated using the Funk–Radon transform, closely approaching the true ODF under certain conditions (Tuch, 2004). Descoteaux et al. estimated the ODF by a linear combination of the spherical harmonic coefficients that describe the diffusion signal within a voxel (Descoteaux et al., 2007).

In previous work (Jansons and Alexander, 2003; Tournier et al., 2004; Bloy and Verma, 2008; Ghosh et al., 2008), principal diffusion directions (PDDs) are defined as the directions of the ODF local maxima. Several methods have been proposed to find the PDDs from ODF based on this definition. Jansons and Alexander assumed a symmetry on the ODF with respect to the position vector x (Jansons and Alexander, 2003). That means the ODF peaks appear in equal and opposite pairs. In their method, for each spherical point s on the sphere S , the set M is defined as follows:

$$M = \{x \in S : ODF(x) = \max_{s \in T(x)} ODF(s)\} \quad (1)$$

$$T(x) = \{s \in S : |s - x| < \rho\} \cup \{s \in S : |s + x| < \rho\} \quad (2)$$

where ρ is a constant. The set M contains the candidate PDDs. Starting at each member of M , the estimates are refined by searching for local maxima using the Powell's method, a general method for estimation of the local minima without taking derivatives (Press et al., 2007). Finally, tiny ODF peaks smaller than the ODF mean are discarded. In Tournier et al. (2004) and Sakaie and Lowe (2007), the same strategies are adopted, except for the Powell's method which is replaced by spherical Newton's method and sequential quadratic programming (constraint spherical Newton's method) (Cottle et al., 2009), respectively. The problem of all these methods is the likelihood of getting trapped in small local maxima. In Descoteaux (2008), assuming that the PDDs are the local maxima of the normalized ODF projected on a tessellated sphere with a fine mesh, the finite difference method is applied to the sphere in order to obtain the PDDs. In this method, if the ODF value for a point is above all of its neighbors and above 0.5, the point will be reserved as a local maximum.

Thresholding is required in order to diminish minor peaks. The method, subsequently, is dependent on the threshold value. Plus, this method is very sensitive to the mesh grid size. Frey et al. (2008) take derivative of the ODF smoothed by a Gaussian kernel to get the local maxima. Applying such kernel, which is used to diminish noise, may degrade the angular resolution of the PDDs. In Bloy and Verma (2008), the ODF is represented by a symmetric tensor constrained to the sphere resulting in a homogeneous polynomial representation. The idea takes advantage of such representation to take analytic derivatives and find the stationary points of the ODF instead of the maxima. These stationary points are then classified into primary maxima (PDDs), secondary maxima, minima and saddle points. In Ghosh et al. (2008), the stationary points are found by using Lagrange multipliers and applying the combination of subdivision methods and generalized normal form algorithms to

the resulting polynomial system. The stationary points are then sorted and thresholded to extract the PDDs. In this paper, we refer to this technique Poly-Tensor method. One of the main problems of the Bloy's and Ghosh's methods is that classifying stationary points in order to get the PDDs may become erroneous in noisy data condition. In our previous work, we determined the first principal direction as the gradient direction in which the ODF is maximum and sorted the other gradient directions based on their angular distances from this principal direction (Nazem-Zadeh et al., 2011). We then estimated the envelope of the resulting 1D profile using a moving maximum filter whose output peaks are the remaining principal diffusion directions. This method is sensitive to noise. We refer to this technique as Angular-Distance method. Using finite difference method, Camino software package (Cook et al., 2006) locates local maxima by ascertaining all points at which the function is larger than all other points within a fixed search radius. It then removes duplicates and tiny peaks with function values smaller than a pre-specified threshold (Descoteaux et al., 2007). This procedure is both inaccurate and time-consuming. In addition, the number of PDDs is restricted to three for estimation and two for visualization. For DTI data with dimensions $128 \times 128 \times 56$, it takes almost a week to find up to three PDDs for each voxel, using a commonly used personal computer (Core 2Duo CPU, E8400@ 3.00 GHz, 3.00 GHz, and 8 GB RAM).

All of the above methods define the PDDs as the directions in which the ODF data is locally maximal. The PDDs, based on this definition, are sensitive to noise. In addition, some of the methods post-process the results by discarding tiny ODF detected peaks. Depending on the kernel width, this may lead to discarding important diffusivity information. In this paper, the PDDs are defined as the directions around which the ODF data is concentrated (clustered). Estimates of the PDDs based on this definition are less sensitive to noise in comparison with the previous approaches. They may be related to clustering principles whereby a set of data points is considered as potential PDDs and examined to determine whether they properly represent the ODF data. In other words, they are examined to determine whether they minimize the overall distance of the data points from the cluster centers. Unfortunately, this approach involves an exhaustive search which is very time-consuming when there are more than two PDDs. To reduce the computational complexity, we propose an iterative algorithm based on fuzzy c-means clustering (Dunn, 1973; Bezdek, 1981) in which the cluster centers and memberships are iteratively updated. Our proposed algorithm benefits from good features of the fuzzy c-means algorithm and is sufficiently accurate for practical purposes. It transforms the original 3D cluster data into a 2D format and thus simplifies computation. The 2D data points contain co-latitudes and co-longitudes of the spherical angles.

The ODF can be considered as a convolution of complex fiber structure, denoted by fODF (fiber ODF), and the ODF response to a single fiber (ODF kernel). Therefore, fODF can be calculated by deconvolution of the ODF with the ODF kernel (Descoteaux et al., 2007; Tournier et al., 2004). The fODF has more distinct lobes and thus is more appropriate for locating the PDDs. Hence, we apply our algorithm to the fODF.

Starting with two cluster centers and using the spherical law of cosines, the proposed approach calculates the arc (geodesic) distances between points on the sphere and the cluster centers. The membership values and centers of the clusters are updated iteratively until convergence is achieved. To automatically determine the number of clusters, this number is increased by two and the resulting data representation is evaluated based on the minimum description length (MDL) criterion (Rissanen, 1989). Applications of the proposed method to simulated and clinical data show that our algorithm is more accurate, and easier to implement than current methods in the literature, especially when the signal-to-noise ratio (SNR) is low.

Materials and methods

Spherical deconvolution

Expansion of a function on a sphere using spherical harmonics is a generalization of Fourier series in the spherical coordinates (Mousa et al., 2006). The diffusion signal at any point of the unit sphere can be estimated using the spherical harmonic coefficients (SHCs) according to the equations:

$$S(\theta, \varphi) = \sum_{j=1}^N c_j Y_j(\theta, \varphi) \quad (3)$$

where S is the diffusion measurement, $\theta \in [0, \pi]$ and $\varphi \in [0, 2\pi]$ are co-latitude and co-longitude spherical angles, N is the total number of coefficients, c_j is the j th SHC, and the corresponding harmonic $Y_j(\theta, \varphi)$ is the non-singular separated solution for the Laplace equation on the surface of the sphere (see Appendix 1). In our previous work (Nazem-Zadeh et al., 2010), we investigated the characteristics of the SHC through simulations. The 8th order SHCs can represent diffusion profiles with a maximum of four major distinct peaks in each voxel (Descoteaux et al., 2006).

In Q-ball imaging, ODF data are computed from HARDI measurements distributed on a hemisphere using a Funk–Radon transform (FRT) (Descoteaux et al., 2007). Using the spherical harmonics, computation of ODF is simplified to a linear relationship (Descoteaux et al., 2007; Hess et al., 2006):

$$\text{ODF}(\theta, \varphi) = \sum_{j=1}^N \underbrace{2\pi P_{l(j)}^0(0) c_j}_{d_j} Y_j(\theta, \varphi) \quad (4)$$

where d_j s are the coefficients describing ODF(θ, φ), $P_{l(j)}^0(0)$ is a zero-order Legendre polynomial characterizing the degree of $l(j)$ associated with the j th element of the spherical harmonic basis (point zero) (Descoteaux et al., 2007).

The ODF can be considered the convolution of complex fiber structure (called fiber ODF or fODF in recent papers) with the ODF response to a single fiber (ODF kernel). Therefore, one may deconvolve the ODF with the ODF kernel to get the desired complex fiber structure (Descoteaux et al., 2007; Tournier et al., 2004). The fODF can be linearly calculated from the SHCs of the diffusion measurements within each voxel by the equation:

$$\text{fODF}(\theta, \varphi) = \sum_{j=1}^N \underbrace{2\pi P_{l(j)}^0(0) c_j / f_j}_{e_j} Y_j(\theta, \varphi) \quad (5)$$

where e_j s are the coefficients describing fODF and f_j is calculated using the Funk–Henke formula (see Appendix 1). As has been shown where the fODF obtained by this process has more distinct lobes and offers improved angular resolution and fiber detection compared to the standard ODF (Tournier et al., 2004), we use fODF in our clustering algorithm as explained above.

Clustering problem

We propose a novel clustering algorithm to estimate the principal diffusion directions of the fODF data. As stated above, fODF is obtained by deconvolution of the ODF with the ODF kernel (Tournier et al., 2004; Descoteaux et al., 2007) and the resulting data are used to

estimate the PDDs. By PDDs we do not mean the directions that generate the highest ODF values, but rather the directions around which most of the ODF points are concentrated.

For illustrating the problem, consider a three-cluster profile of fODF data points distributed in 3D space with cluster directions S_1 , S_2 and S_3 (Fig. 1). The Euclidean distance between a data point P_i and a cluster center (direction) S_j (distance between a point and a line) is calculated as:

$$d(P_i, S_j) = \sqrt{\|P_i\|^2 - |P_i \cdot S_j|^2 / \|S_j\|^2}. \quad (6)$$

We define the distance of P_i to the profile of all data points (the set of all data points) as the minimum of distances to the cluster directions. For example, in Fig. 1A, since P_i is closer to S_3 , it is classified to the cluster whose main direction is S_3 and hence, its distance to the profile of whole data points is its distance to S_3 .

The overall distance is defined by the summation of the distances of all points to the profile of all data points. At certain specific orientations (S_{j^*} , S_{k^*} , ...), the overall distance of the data points is minimal. In the three-cluster case:

$$S_{j^*}, S_{k^*}, S_{m^*} = \operatorname{argmin}_{j,k,m} \sum_{i=1}^N d^2(P_i, S_j, S_k, S_m) = \operatorname{argmin}_{j,k,m} \sum_{i=1}^N \left[\|P_i\|^2 - \max \left\{ |P_i \cdot S_j|^2 / \|S_j\|^2, |P_i \cdot S_k|^2 / \|S_k\|^2, |P_i \cdot S_m|^2 / \|S_m\|^2 \right\} \right].$$

These directions may be considered as PDDs which have low sensitivity to noise. One may consider each possible combination of data points as a set of PDD candidates and evaluate their representation of the fODF data in terms of minimizing overall distance. We refer to this as the “Search-All” method, however, increasing the number of clusters renders the search very time consuming. Here, we introduce an iterative algorithm in the spherical domain based on the fuzzy c-means clustering algorithm (Dunn, 1973; Bezdek, 1981), called, hereafter, Sph-FCM. The fuzzy c-means algorithm has been proven more accurate than K-means algorithm in clustering, as it takes into account the membership of each point to each cluster. As all measurements are made on a sphere, we perform the clustering algorithm in the spherical domain concentrating on orientation of fODF.

For visualization of fODF data, the unit radius of the spherical coordinate of each point may be replaced by its fODF value as shown in Fig. 1A. In this representation, we deal with points in 3D space. Fig. 1B, alternatively, shows the use of hot colors in visualizing the fODF value on the sphere. We are interested in a clustering method which simply exploits the points on the sphere and their fODF values and returns the PDDs. Therefore, the search domain is the space of co-latitude and co-longitude spherical angles of the points.

We introduce an on-sphere version of fuzzy c-means clustering in which cluster centers are updated based on formulas derived in the spherical domain. The proposed clustering technique has worked very well for this application and is data-driven. Moreover, the technique favors rounded clusters, which is mostly the case in practice. Note that using the fuzzy c-means clustering in the 3D spatial domain does not generate an analytic solution for the derivatives in updating cluster centers (directions) with the definition of distance in Eq. (6). Using the spherical law of cosines, the geodesic distance between each point x_i on the sphere and the cluster center μ_j is calculated as:

$$d(x_i, \mu_j) = \arccos \left\{ \cos \theta_{x_i} \cos \theta_{\mu_j} + \sin \theta_{x_i} \sin \theta_{\mu_j} \cos (\varphi_{x_i} - \varphi_{\mu_j}) \right\} \quad (8)$$

where $\theta_{x_j, \mu_{x_j}}$ and $\theta_{\mu_j, \mu_{\mu_j}}$ are the co-latitude and co-longitude spherical angles of the data point x_j and the cluster center μ_j , respectively. Note that here the cluster centers are considered points on the sphere, in contrast to the previous 3D spatial domain where each cluster center is a direction around which the data is distributed. With this definition, an analytic solution for the derivatives in updating the cluster centers and cluster memberships in fuzzy c-means clustering algorithm can be achieved. Since points with higher fODF value should have higher weight in determining the PDDs, we define the cost function of the fuzzy c-means clustering algorithm as follows:

$$L = \sum_{i=1}^N \sum_{j=1}^{N_c} fODF(x_i) \cdot U^m(\mu_j | x_i) \cdot d(x_i, \mu_j) \quad (9)$$

where N is the number of data points, N_c is the number of clusters, $U(\mu_j | x_i)$ is the membership of the data point x_i in the cluster whose center is μ_j , and m is its power (a constant). Informally, the goal is to find the cluster centers μ_j and membership values $U(\mu_j | x_i)$ such that for each cluster, its data points (or equivalently data points with higher membership values to that cluster) are overall close to the cluster center. The factor $d(x_i, \mu_j)$ in Eq. (8) measures how close a data point is to the cluster center and weights the cost function to minimize the overall distance of the data points of each cluster to their cluster center. For a μ_j located at the center of the cluster, the values of $d(x_i, \mu_j)$ are overall lower for data points x_i belonging to cluster j and that makes L smaller. Data points x_i which do not belong to cluster j , are relatively more distant from the cluster center μ_j and thus their membership function $U(\mu_j | x_i)$ is smaller which reduces the effect of their higher value of $d(x_i, \mu_j)$. The $fODF(x_i)$ causes the points with higher fODF to have higher weights in determining the cluster centers. Thus the cluster centers will tend to be close to the points with higher fODF values when the above cost function is minimized. Note that unlike Eq. (7), the cost function in Eq. (9) uses the distance $d(x_i, \mu_j)$ instead of its square $d^2(x_i, \mu_j)$ since based on the definition of distance in Eq. (8) we are able to derive an analytic solution for the derivatives in updating cluster centers, thus the square of distance is not required.

To minimize the cost function with respect to memberships and cluster centers, we should have:

$$\frac{\partial L}{\partial U(\mu_k | x_i)} = 0, \frac{\partial L}{\partial \varphi_{\mu_k}} = 0, \frac{\partial L}{\partial \theta_{\mu_k}} = 0. \quad (10)$$

The above equations generate the following relationships (see the Appendix 2 for details):

$$U(\mu_k | x_i) = \frac{\left\{ \frac{1}{d(x_i, \mu_k)} \right\}^{m-1}}{\sum_{j=1}^{N_c} \left\{ \frac{1}{d(x_i, \mu_j)} \right\}^{m-1}} \quad (11)$$

$$\varphi_{\mu_k} = q_k \pi + \tan^{-1} \frac{\sum_{i=1}^N \frac{fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot \sin \theta_{x_i} \cdot \sin \varphi_{x_i}}{\sin d(x_i, \mu_k)}}{\sum_{i=1}^N \frac{fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot \sin \theta_{x_i} \cdot \cos \varphi_{x_i}}{\sin d(x_i, \mu_k)}} \quad (12)$$

$$\theta_{\mu_k} = q'_k \pi + \tan^{-1} \frac{\sum_{i=1}^N \frac{fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot \sin \theta_{x_i} \cdot \cos(\varphi_{x_i} - \varphi_{\mu_k})}{\sin d(x_i, \mu_k)}}{\sum_{i=1}^N \frac{fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot \cos \theta_{x_i}}{\sin d(x_i, \mu_k)}} \quad (13)$$

where q_k, q'_k are integers. Depending on the choice of q_k and q'_k , the resulting φ_{μ_k} and θ_{μ_k} may maximize or minimize the cost function. For each cluster center, we choose appropriate values of q_k and q'_k that minimize L .

Minimum description length

Choosing the right number of clusters is crucial for any algorithm; choosing a wrong number will result in a poor outcome as demonstrated in Fig. 2, in which selection of two or four clusters rather than three; the final extracted PDDs (red lines) deviates from the actual directions (blue lines) around which the diffusion signal is simulated. Alexander et al. proposed a method for selecting the number of clusters that estimates the order of non-Gaussian diffusion (Alexander et al., 2002) by determining the truncation level of the SHC coefficients used in the diffusion signal logarithm by means of ANOVA (Armitage, 1971). They use incomplete beta probability statistics in Camino (Voxelclassify function) instead of the F -test proposed originally (Cook et al., 2006). In our comparative experiments, we have implemented Alexander's original method as well as the method used in Camino. A problem with these methods is that their statistical thresholds are not sufficient to obtain a good classification of the diffusion orders as we show in the Results section.

We estimate the optimal number of clusters from the data distribution based on the minimum description length (MDL) criterion (Rissanen, 1989). This criterion has been previously used in vector quantization as the minimization of the length of the description for the data S is transferred to a receiver without error (Bischof et al., 1999). A set of reference vector A is specified around which the data points are distributed. The data S is divided into inliers I , i.e., data points clustered around the reference vectors A , and outliers O . Thus, $S = I + O$. The inliers I are coded by the reference vectors and transferred. The outliers O are identified and not coded by the reference vectors. Using the reference vectors A , the length of encoding S is then given by:

$$L(S(A)) = L(A) + L(I(A)) + L(\in I_A) + L(O) \quad (14)$$

where $L(A)$ is the length of encoding the reference vectors A , $L(I(A))$ is the length of encoding the index of A to which the vectors in I are assigned, $L(\in I_A)$ is the length of encoding the residual errors, and $L(O)$ is the length of encoding the outliers. Therefore, our goal is to minimize the cost of encoding S using A to determine outliers and the number of clusters (Bischof et al., 1999).

Considering the ODF is antipodally symmetric and each pair of diffusion lobes repeats reciprocally, we consider two centers for each pair. We start with two cluster centers and raise the number of clusters by two until increasing the clusters no longer lowers the transfer cost. The PDD estimation algorithm is updated based on the number of clusters we obtain using the MDL.

Proposed algorithm

The proposed algorithm is summarized in Fig. 3. Starting with two cluster centers, the arc distance between each point and the cluster centers are calculated and the cluster centers and memberships updated accordingly. The procedure is repeated until the difference between two consecutive cluster centers is negligible. The final cluster centers are considered the

principal diffusion directions. Next, we increase the number of clusters by two and evaluate its effect on the data representation using MDL. If it is beneficial, the algorithm continues with the new number of clusters; otherwise, it stops and the previous number of clusters is taken as final.

As mentioned before, the 8th order SHC can represent diffusion profiles that have a maximum of four major distinct peaks (Descoteaux et al., 2006). However for real MRI data, practically, it is preferred to restrict the number of PDDs to three.

Experimental results and discussion

Simulated data

We used multi-tensor model to generate simulated data (Jansons and Alexander, 2003; Descoteaux et al., 2007). For a given b -factor, noise level and encoding direction i , we generate the diffusion-weighted signal

$$S(u) = \sum_{j=1}^N \alpha_j e^{-bu^T D_j u} + \text{noise} \quad (15)$$

where u is the vector of gradient direction, N is number of fibers, α_j is the proportion of the j th fiber, D_j is the j th tensor profile with eigenvalues $[1700, 300, 300] \times 10^{-6} \text{ mm}^2/\text{s}$, noise is generated with Gaussian probability distribution function with a standard deviation of σ , producing a S diffusion signal with $\text{SNR} = 1/\sigma$. Assuming some directions as actual PDDs, we calculated each tensor with its main axis being one assumed direction. Simulated diffusion signals with different b -values (500–2000) and SNRs (12–100) and varying numbers of gradient directions were generated. Different crossing configurations were implemented by positioning two, three, and four fibers at different crossing angles.

There are different parameters that affect the estimation of PDDs, including: 1 — The diffusion signal simulation parameters (number of crossing profiles, number of diffusion gradients, gradient schemes, and SNR), 2 — ODF calculation parameters (r : regularization parameter of linear reconstruction, number of ODF interpolation points, l_{max} : maximum order of spherical harmonics; see Appendix 1), 3 — fODF modeling parameter (e_2/e_1 ; see Appendix 1), and 4 — Sph-FCM method parameters (m : membership power, DIFF_C : minimum difference between the cluster centers in successive iterations for algorithm termination, and η : quantification factor for the MDL framework) (Bischof et al., 1999). We found this set of parameters optimal for our PDD estimation framework in the sense of accuracy and speed: $e_2/e_1 = 0.3$, $m = 1.2$, $\text{DIFF_C} = 0.01$, $r = 10^{-4}$, $\eta = 0.012$, $l_{\text{max}} = 8$.

Plus, we found that for the SNR values higher than 20, b -value = 1500 s/mm^2 , and 55 diffusion gradient directions, and for crossing angles larger than 45° , the ODF retained the major peaks, each oriented co-linearly with the main axis of an individual diffusion tensor. Therefore, this number of diffusion gradient directions proved to be adequate for a reasonable reconstruction of diffusivity at an angular resolution of about 45° . Using fODF instead of ODF, we were able to reduce the number of diffusion gradients to 35. However, the consequences of applying ODF kernel to the algorithm, especially in areas where the ODF kernel with constant ratio of e_2/e_1 is invalid, must be acknowledged (see Appendix 1). Fig. 4 represents the reconstructed ODF and estimated PDDs from a diffusion profile with an angular resolution of 45° and a SNR of 30 for three and four major peaks.

For comparison, we applied the five protocols discussed in this paper, namely: a) and b) our two proposed methods, Sph-FCM and Search-All (as the optimal solution based on the proposed definition of PDDs); c) the Camino software package method; d) Angular-

Distance technique (Nazem-Zadeh et al., 2011), and e) Poly-Tensor method (Ghosh et al., 2008). By averaging over 50 repetitions, we calculated the similarity between the actual PDDs (the main axes of the tensors used in diffusion signal simulation in Eq. (15)) and those extracted using each method over a wide range of SNRs (12, 16, 20, 24, 28, 32, 36, 40, 44, 50, 60, 70, 80, 100) and using diffusion profiles with three and four major peaks. We define the following similarity measure which incorporates both the accuracy of each estimated PDD as well as the estimated number of PDDs:

$$\text{Similarity} = \min \left\{ \frac{N_a}{N_e}, \frac{N_e}{N_a} \right\} \cdot \prod_{i=1}^{\min\{N_a, N_e\}} PDD_e(i) \cdot PDD_a(i) \quad (16)$$

where $PDD_a(i)$ is i th actual PDD and $PDD_e(i)$ is the closest estimated PDD to $PDD_a(i)$. N_a is the number of actual PDDs and N_e is the estimated number of PDDs by a given method. Since the estimated PDDs and the number of PDDs may be different in different trials (with different added noise), we repeated the algorithm 50 times for each SNR value and averaged them.

As shown in Fig. 5 as expected, the Search-All method was superior among all methods, whereas Camino was inferior in terms of similarity between actual and extracted PDDs as well as the estimated number of PDDs. The Search-All method is more robust to noise and works slightly better than Sph-FCM at low SNRs. With close performance to the Search-All method, our proposed Sph-FCM method is significantly more accurate than the Poly-Tensor, Angular-Distance and Camino methods in low SNRs, while in high SNRs both Sph-FCM and Poly-Tensor methods perform similarly and result in high similarity as defined by Eq. (16). The inferiority of Poly-Tensor method compared to Sph-FCM is due to the fact that fitting high order tensor to a noisy measurement leads to inaccuracy in the PDDs detection. Note that the total error in the simulations combines the estimation error (due to ODF approximation by the SHCs) and detection error (i.e., deviation from the PDDs based on definition).

Based on the MDL criterion, our proposed methods (Sph-FCM, Search-All) correctly estimate the number of PDDs for almost all SNRs especially for the SNRs higher than 28. Among the other methods, the Poly-Tensor shows good performance especially for the SNRs higher than 50.

Real data

HARDI data for a normal subject was acquired using a GE Signa Excite 3 T MRI scanner at Henry Ford Hospital (Detroit, MI, USA) with 55 diffusion gradient directions with b -value=1500 s/mm² and six B0 references. The imaging in-plane pixel and matrix size were 0.975 × 0.975 mm² and 256 × 256, respectively, with a slice thickness of 2.5 mm. These values were originally 1.95 × 1.95 mm² and 128 × 128 but were automatically interpolated to 256 × 256 #x000D7; 6 by the E console.

To evaluate Camino in the estimation of number of clusters, we implemented and applied the method described in Alexander et al. (2002) and the method implemented by Camino. The problem with both methods is that their statistical thresholding is not appropriate to obtain a good classification of non-Gaussian diffusion order. For instance, in most crossings between the corona radiata, superior longitudinal fasciculus (SLF) and corpus callosum, diffusion with an order of four or more is expected, whereas within the corpus callosum, prolate diffusion of order two should predominate. However, by changing the F -test statistical thresholds in order to assign an order of four to the crossing, an order of four is assigned to the corpus callosum as well.

To improve inter-plane resolution, we further interpolated diffusion data to a voxel size of $0.975 \times 0.975 \times 0.98 \text{ mm}^3$ and matrix size of $256 \times 256 \times 144$. The proposed method takes about 24 h to find up to three PDDs for each voxel using a PC with Intel Core 2Due CPU (E8400@ 3.00 GHz, 3.00 GHz) and 8 GB RAM and using a MATLAB Executable-MEX file that is dynamically linked to the function produced from visual C++ 2008 source code in Windows Vista 64 bit. However, when we restored the data to their original size ($128 \times 128 \times 56$), the computation time was decreased to less than three hours which can be considered feasible in the clinical settings, especially compared to the Camino method which takes about one week to find up to three PDDs for each voxel using the same machine.

Fig. 6 shows color-coded fractional anisotropy (FA) in the coronal plane at the intersection of the corpus callosum, superior corona radiata (internal capsule of cortico-spinal tract), and SLF with PDDs extracted by Camino in the crossing area (Fig. 6B).

Figs. 7 and 8 represent the same crossing area in Fig. 6A with PDDs estimated by the Poly-Tensor and the proposed Sph-FCM method, respectively. Note that Camino did not resolve the crossings between these fiber tracts, while the Poly-Tensor (partly) and the proposed Sph-FCM methods were successful in resolving the fibers in the crossing areas. As illustrated in these figures, the Poly-Tensor method underestimates the number of clusters.

Fig. 9 illustrates the intersection of the SLF and arcuate fasciculi. Note that Camino, as a HARDI-based method, again was unable to resolve the crossings between these fiber tracts, whereas the proposed Sph-FCM method was able to resolve this crossing in this intersection in Fig. 10. Although the SLF crosses the arcuate fasciculi, one can zoom in on the image and track one of the PDDs parallel to the main axis of the SLF from the occipital to the frontal lobe. In addition, note the smooth transition from the main PDD of the SLF to the inferior longitudinal fasciculus (ILF), rarely detectable by other methods.

Fig. 11 shows a tractography reconstruction of the corpus callosum and the cortico-spinal tract up to the corona radiata, cingulum and SLF using up to three PDDs as estimated by our proposed method in sagittal, axial, and coronal views, respectively. The FACT algorithm (Mori and van Zijl, 2002) has been modified to deal with more than one PDD and used to reconstruct the fiber tracts with an FA threshold of 0.01 and a maximum 25° angle of successive trajectories. When the trajectory reaches a voxel with more than one PDD, it adopts the most co-linear direction. Then, by removing the most co-linear and maintaining the other directions, we consider the current voxel as a new ROI (region of interest) point. Thus, the modified FACT algorithm is capable of dealing with the branching fibers. As in the crossing between these fiber tracts, our tracking algorithm is capable of resolving each tract using the PDDs extracted by the proposed method.

Discussion

In this paper, for estimating the fiber ODF, we used spherical deconvolution method as it is still being used in the literature (Leergaard et al., 2010). Although different ODF reconstruction methods have been proposed in the literature, there is no specific one preferred in general over others. Tristan-Vega et al. (2009) proposed a probabilistic method for computing the orientation probability density function, and demonstrated improved results in better resolving fiber crossings over Q-ball reconstruction using spherical harmonics. Compared to Q-ball method that does not assume any kind of underlying model, they assume slow variation of the apparent distribution function, which would be a restriction especially for very noisy images with low SNR. Plus, they may suffer from some computational imperfections which need a post-processing on the results. In Aganj et al. (2010), a new technique is proposed for correcting the definition of the ODF resulting in a

dimensionless and normalized expression. They showed an improvement in performance of their proposed ODF on simulated as well as HARDI data. However, in addition to the calculation complexity, they made some approximations, simplifications and assumptions which may not be valid in every diffusivity condition. In another theoretical work, Barnett (2009) showed that the interpretation of the approximated ODF described by Tuch (2004) is not valid. Instead, he derived another ODF expression from Q-ball imaging and claimed that it is more accurate. However, he demonstrated that for large b values, the ODF derived from their proposed method and the ODF described by Tuch's approach to same values and therefore reveal same representation of diffusion profiles. Therefore, using b -value=1500 s/ mm^2 in our data acquisition makes the ODF estimation error very small.

We chose 755 reconstruction points for ODF which have been recommended in Tuch (2004). This number of ODF points is large enough to achieve a high level of accuracy. We found out that further increase of this number does not improve the PDD estimation accuracy. However, this is not a rigid choice and we could have chosen a smaller number. Also since we are interested in estimating up to three PDDs in the crossing areas, we could set $l_{max}=6$. However, setting $l_{max}=8$ along with small regularization parameter ($r=10^{-4}$) would generate sharper ODF/fODF profile making it easier to estimate PDDs using the proposed clustering method.

We used fuzzy c-means algorithm to extract the PDDs. Although this is an old technique, it has worked very well for this application. There are other techniques that could be used but some of them with better convergence, such as Expectation Maximization, are based on a specific model of the clusters which may not be an appropriate assumption in this particular application.

Conclusions

In this paper, we have proposed an iterative clustering algorithm in the spherical domain for estimation of the PPDs. The proposed algorithm is based on fuzzy c-means clustering and benefits from the stability of the fuzzy c-means algorithm (Dunn, 1973; Bezdek, 1981). In this framework, the clustering process in 3D Cartesian space is transformed into 2D in spherical space, simplifying computation. Since fODF has more distinct lobes than ODF and thus is more appropriate for locating PDDs, we applied the proposed algorithm to the fODF. Also, we used the MDL criterion to estimate the number of clusters, which we found to be superior to some other methods proposed in the literature. By applying our method to the simulated data, we showed that it is both more accurate than the traditional methods, especially at low SNRs. Furthermore, we showed that the proposed method is applicable to tracking the fibers in the crossing regions of the human brain. We were able to resolve crossing in the corpus callosum, cortico-spinal tract extending to the corona radiata, cingulum, and SLF using our algorithm.

Acknowledgments

This work was supported in part by Iran National Science Foundation (INSF).

Appendix 1. Spherical deconvolution

Expansion of a function on a sphere using spherical harmonics is a generalization of Fourier series in the spherical coordinates (Mousa et al., 2006). The diffusion signal at any point of the unit sphere can be estimated using the spherical harmonic coefficients (SHCs) according to the equations:

$$S(\theta, \varphi) = \sum_{j=1}^N c_j Y_j(\theta, \varphi) \quad (\text{A1-1})$$

$$Y_j(\theta, \varphi) = \begin{cases} \sqrt{2}(-1)^m Y_l^m(\theta, \varphi) e^{-im\varphi} \cos m\varphi & ; -l \leq m < 0 \\ Y_l^0(\theta, \varphi) & ; m=0 \\ \sqrt{2}(-1)^m Y_l^m(\theta, \varphi) e^{-im\varphi} \sin m\varphi & ; 0 \leq m < l \end{cases} \quad (\text{A1-2})$$

$$Y_l^m(\theta, \varphi) = \sqrt{\frac{2l+1}{4\pi} \frac{(l-m)!}{(l+m)!}} P_l^m(\cos \theta) e^{im\varphi} \quad (\text{A1-3})$$

where $j = j(l, m) = (l^2 + l + 2)/2 + m$, S is the diffusion measurement, $\theta \in [0, \pi]$ and $\varphi \in [0, 2\pi]$ are co-latitude and co-longitude spherical angles, N is the total number of coefficients, c_j is the j th SHC, and the corresponding harmonic $Y_j(\theta, \varphi)$ is the non-singular separated solution for the Laplace equation on the surface of the sphere. If we write Eq. (A1-1) in matrix form, we will have $S = YC$, where S is the vector containing diffusion signal for every encoding gradient direction; Y is a matrix with each row representing a set of spherical harmonics for θ and φ of one measurement point; and C is the vector of SH coefficients. C can be calculated by:

$$C = (B^T B + rL)^{-1} B^T S \quad (\text{A1-4})$$

where r is regularization weight and L is a diagonal matrix containing entities $l_j^2(l_j+1)^2$ (l_j is the order associated with the j th coefficient) (Descoteaux et al., 2007).

In Q-ball imaging, ODF data are computed from HARDI measurements distributed on a hemisphere using a Funk–Radon transform (FRT) (Descoteaux et al., 2007). Using the spherical harmonics representation in (A1-1)–(A1-3), computation of ODF is simplified to a linear relationship (Descoteaux et al., 2007; Hess et al., 2006):

$$\text{ODF}(\theta, \varphi) = \sum_{j=1}^N \underbrace{2\pi P_{l(j)}^0(0) c_j}_{d_j} Y_j(\theta, \varphi) \quad (\text{A1-5})$$

where d_j s are the coefficients describing $\text{ODF}(\theta, \varphi)$, and $P_{l(j)}^0(0)$ is a zero-order Legendre polynomial characterizing the degree of $l(j)$ associated with the j th element of the spherical harmonic basis (point zero) (Descoteaux et al., 2007). The computed ODF values can reveal major diffusion directions within a voxel up to some angular resolutions. The ODF can be considered the convolution of complex fiber structure (called fiber ODF or fODF in recent papers) with the ODF response to a single fiber (ODF kernel). Therefore, one may deconvolve the ODF with the ODF kernel to get the desired complex fiber structure (Descoteaux et al., 2007; Tournier et al., 2004). The fODF can be linearly calculated from the SHCs of the diffusion measurements within each voxel by the equation:

$$\text{fODF}(\theta, \varphi) = \sum_{j=1}^N \underbrace{2\pi P_{l(j)}^0(0) c_j / f_i}_{e_j} Y_j(\theta, \varphi) \quad (\text{A1-6})$$

where e_j s are the coefficients describing fODF and f_i is calculated using the Funk–Henke formula:

$$f_i = 2\pi \int_{-1}^1 P_{l(j)}^0(t) R(t) dt. \quad (\text{A1} - 7)$$

The ODF kernel may be chosen as (Descoteaux et al., 2007):

$$R(t) = \frac{1}{z \sqrt{\left(\frac{e_2}{e_1} - 1\right) t^2 + 1}}, Z = \int_{-1}^1 \left(\frac{1}{\sqrt{\left(\frac{e_2}{e_1} - 1\right) t^2 + 1}} \right) dt \quad (\text{A1} - 8)$$

where e_1 and e_2 are the presumed first and second eigen-values of the tensor assigned to the profile of a single fiber response (Descoteaux et al., 2007). As has been shown where the fODF obtained by this process has more distinct lobes and offers improved angular resolution and fiber detection compared to the standard ODF (Tournier et al., 2004), we use fODF in our clustering algorithm as explained above. Note that we regularize the fODF indirectly through the calculation of c_j in Eq. (A1-4) (Descoteaux et al., 2007).

Appendix 2. Updating memberships and cluster centers

By minimizing the cost function with respect to the parameters (memberships and cluster centers), we find the following relationships:

$$\begin{aligned} \frac{\partial L}{\partial \varphi_{\mu_k}} = 0 &\Rightarrow \sum_{i=1}^N fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot \frac{\partial d(x_i, \mu_k)}{\partial \varphi_{\mu_k}} \\ &= 0 \Rightarrow \sum_{i=1}^N \frac{fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot (\sin \theta_{x_i} \cdot \sin \theta_{\mu_k} \cdot \sin(\varphi_{x_i} - \varphi_{\mu_k}))}{\sqrt{1 - [\cos \theta_{x_i} \cdot \cos \theta_{\mu_k} + \sin \theta_{x_i} \cdot \sin \theta_{\mu_k} \cdot \cos(\varphi_{x_i} - \varphi_{\mu_k})]^2}} \\ &= 0 \Rightarrow \sum_{i=1}^N \frac{fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot \sin \theta_{x_i} \cdot (\sin \varphi_{x_i} \cos \varphi_{\mu_k} - \cos \varphi_{x_i} \sin \varphi_{\mu_k})}{\sin d(x_i, \mu_k)} \quad (\text{A2} - 1) \\ &= 0 \Rightarrow \varphi_{\mu_k} \\ &= q_k \pi + \tan^{-1} \frac{\sum_{i=1}^N \frac{fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot \sin \theta_{x_i} \cdot \sin \varphi_{x_i}}{\sin d(x_i, \mu_k)}}{\sum_{i=1}^N \frac{fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot \sin \theta_{x_i} \cdot \cos \varphi_{x_i}}{\sin d(x_i, \mu_k)}} \end{aligned}$$

$$\begin{aligned} \frac{\partial L}{\partial \theta_{\mu_k}} = 0 &\Rightarrow \sum_{i=1}^N fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot \frac{\partial d(x_i, \mu_k)}{\partial \theta_{\mu_k}} \\ &= 0 \Rightarrow \sum_{i=1}^N \frac{fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot (-\cos \theta_{x_i} \cdot \sin \theta_{\mu_k} + \sin \theta_{x_i} \cdot \cos \theta_{\mu_k} \cdot \cos(\varphi_{x_i} - \varphi_{\mu_k}))}{\sqrt{1 - [\cos \theta_{x_i} \cdot \cos \theta_{\mu_k} + \sin \theta_{x_i} \cdot \sin \theta_{\mu_k} \cdot \cos(\varphi_{x_i} - \varphi_{\mu_k})]^2}} \quad (\text{A2} - 2) \\ &= 0 \Rightarrow \theta_{\mu_k} \\ &= q'_k \pi + \tan^{-1} \frac{\sum_{i=1}^N \frac{fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot \sin \theta_{x_i} \cdot \cos(\varphi_{x_i} - \varphi_{\mu_k})}{\sin d(x_i, \mu_k)}}{\sum_{i=1}^N \frac{fODF(x_i) \cdot U^m(\mu_k | x_i) \cdot \cos \theta_{x_i}}{\sin d(x_i, \mu_k)}} \end{aligned}$$

$$\frac{\partial L}{\partial U(\mu_k|x_i)}=0 \Rightarrow U(\mu_k|x_i)=\frac{\left\{\frac{1}{d(x_i,\mu_k)}\right\}^{m-1}}{\sum_{j=1}^{N_c}\left\{\frac{1}{d(x_i,\mu_j)}\right\}^{m-1}}. \quad (\text{A2}-3)$$

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Fig. 1.

(A) Illustration of the distance of a fODF data point P_i (distributed in 3D) from cluster directions S_1 , S_2 and S_3 in the “Search-All” method. Here, P_i is closer to S_3 and thus is classified in the cluster whose main direction is S_3 . Also, its distance to the whole profile is defined as its distance to S_3 . Note that for visualization of fODF data, the unit radius of the spherical coordinate of each point may be replaced by its fODF value. (B) The use of hot colors in visualizing the fODF value on the sphere.

Fig. 2. Deviation of extracted PDDs (in red) from 3 main directions (in blue) around which the diffusion signal is simulated when the number of clusters is wrong. (A): 1 cluster, (B): 2 clusters, and (C): 4 clusters (axial plane).

1. Calculate fODF of diffusion signal for each voxel.
2. Start with two cluster centers.
3. Repeat until the stopping criterion is met.
 - a. Calculate the arc distance between fODF points and the cluster centers using spherical law of cosines in equation [8].
 - b. Update the memberships and the centers of the clusters using equations [11]-[13].
4. Increase the number of clusters by two and repeat Step 3.
5. If MDL decreases, accept the new number of clusters and continue the algorithm in Step 4. Otherwise, stop.

Fig. 3.

The proposed algorithm for clustering fODF data points.

Fig. 4. Reconstructed ODF and estimated PDDs from diffusion profile with angular resolution 45° and SNR=30 in 3D and axial plane. (A) Three major peaks, (B) four major peaks.

Fig. 5. Similarity measure between the actual PDDs and extracted PDDs (left) and the number of PDDs estimated using different methods with SNR = [12, 16, 20, 24, 28, 32, 36, 40, 44, 50, 60, 70, 80, 100] for diffusion profiles with four (top row) and three (bottom row) major peaks. The algorithm was repeated 50 times for each SNR value and the results are averaged of different trials. Note that the two proposed methods (Sph-FCM and Search-All) are superior to the Poly-Tensor, Angular-Distance and Camino methods.

Fig. 6. Intersection of corpus-callosum, corona radiata, and superior longitudinal fasciculus tracts with PDDs estimated by Camino. Note that the crossings between these fiber tracts are not resolved.

Fig. 7.
Intersection of corpus-callosum, corona radiata, and superior longitudinal fasciculus tracts
with up to three PDDs estimated by the Poly-Tensor method.

Fig. 8.
Intersection of corpus-callosum, corona radiata, and superior longitudinal fasciculus tracts
with up to three PDDs estimated by the proposed method.

Fig. 9. Intersection of superior longitudinal fasciculus (SLF) and arcuate fasciculi with PDDs estimated by Camino. Note that the crossings between these fiber tracts are not resolved.

Fig. 10.

Intersection of superior longitudinal fasciculus (SLF) and arcuate fasciculi with up to three PDDs estimated by the proposed method. Although crossing with arcuate fasciculus, one can zoom on the image and track one of PDDs parallel to the main axis of SLF from occipital to frontal lobes, which cannot be resolved by tensor-based PDDs finding algorithms and non-accurate HARDI-based algorithms like Camino. In addition, note the smooth transition of this main PDD of SLF to the inferior longitudinal fasciculus (ILF) which is rarely detectable in other methods.

Fig. 11. Reconstruction of corpus-callosum (red), cortico-spinal tract up to corona radiata (blue), cingulum (green) and superior longitudinal fasciculus (yellow) tracts using up to three PDDs estimated by the proposed method in (A) sagittal, (B) axial, (C) coronal views. Note that in the crossing area between these fiber tracts, the tracking algorithm is capable of resolving each fiber tracts using PDDs extracted by the proposed method.