Estimation of Fiber Orientation and Spin Density Distribution by Diffusion Deconvolution

Fang-Cheng Yeh\(^1\), Van Jay Wedeen\(^2\), and Wen-Yih Isaac Tseng\(^3,4,*\)

\(^1\)Department of Biomedical Engineering, Carnegie Mellon University, Pennsylvania, USA;

\(^2\)Department of Radiology, MGH Martinos Center for Biomedical Imaging, Harvard Medical School, Charlestown, Massachusetts, USA;

\(^3\)Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan;

\(^4\)Center for Optoelectronic Biomedicine, National Taiwan University College of Medicine, Taipei, Taiwan;

Running title: Diffusion Deconvolution

*Correspondence to:

Wen-Yih Isaac Tseng, M.D., Ph.D.,

Center for Optoelectronic Biomedicine

National Taiwan University College of Medicine

No. 1, Sec 1, Jen-Ai Rd., Taipei, Taiwan 100

Tel: +886-2-2312-3456 ext. 88758

Fax: +886-2-2392-6922

Email: wytseng@ntu.edu.tw
Abstract

A diffusion deconvolution method is proposed to apply deconvolution to the diffusion orientation distribution function (dODF) and calculate the fiber orientation distribution function (fODF), which is defined as the orientation distribution of the fiber spin density. The dODF can be obtained from q-space imaging methods such as q-ball imaging (QBI), diffusion spectrum imaging (DSI), and generalized q-sampling imaging (GQI), and thus the method can be applied to various diffusion sampling schemes. A phantom study was conducted to compare the angular resolution of the fODF with the dODF, and the in vivo datasets were acquired using single-shell, two-shell, and grid sampling schemes, which were then reconstructed by QBI, GQI, and DSI, respectively. The phantom study showed that the fODF significantly improved the angular resolution over the dODF at 45- and 60-degree crossing angles. The in vivo study showed consistent fODF regardless of the applied sampling schemes and reconstruction methods, and the ability to resolve crossing fibers was improved in reduced sampling condition. The fiber spin density obtained from deconvolution showed a higher contrast-to-noise ratio than the fractional anisotropy (FA) mapping, and further application on tractography showed that the fiber spin density can be used to determine the termination of fiber tracts. In conclusion, the proposed deconvolution method is generally applicable to different q-space imaging methods. The calculated fODF improves the angular resolution and also provides a quantitative index of fiber spin density to refine fiber tracking.

Key words: diffusion MRI; diffusion deconvolution; fiber ODF; fiber spin density
1. Introduction

Diffusion MR imaging is a non-invasive imaging technique capable of revealing microstructural characteristics of the human brain (Basser and Pierpaoli, 1996; Moseley et al., 1993). The diffusion MR signals can be reconstructed by diffusion tensor imaging (DTI) to obtain the diffusion tensor, which implies the underlying axonal fiber orientation and microstructural integrity based on the principal orientations and principal magnitudes, respectively (Basser et al., 1994; Basser and Pierpaoli, 1996; Pierpaoli and Basser, 1996; Pierpaoli et al., 1996). The principal orientations, which are the eigenvectors obtained from the diffusion tensors, allow tracking of axonal fiber tracts and reveal the white matter connections between cortical areas (Basser et al., 2000; Behrens et al., 2003; Mori et al., 1999). However, due to inherent limitations of the tensor model, DTI cannot resolve complex structures such as crossing or branching fiber patterns (Alexander et al., 2001; Wiegell et al., 2000). To overcome this problem, several reconstruction methods have been proposed, and they can be categorized into model-free and model-based approaches. These reconstruction methods usually have their own applicable diffusion sampling schemes, which may include a single-shell scheme, also known as high angular resolution diffusion imaging (HARDI)(Tuch et al., 2002); a multiple-shell scheme (Khachaturian et al., 2007; Wu and Alexander, 2007); and a grid scheme, also as known as the Cartesian sampling scheme used by diffusion spectrum imaging (DSI)(Wedeen et al., 2005).

The model-free approaches, or the q-space imaging methods, are based on the Fourier relation between the diffusion MR signals and the underlying diffusion propagator (Callaghan, 1993). Based on the data acquired by the HARDI scheme, Tuch proposed q-ball imaging (QBI) to estimate the diffusion orientation distribution functions (dODF) of the diffusion propagators by using the Funk-Radon transform (Tuch, 2004). Using a grid sampling scheme, Wedeen et al.
(2005) proposed diffusion spectrum imaging (DSI), which calculates dODF by applying the Fourier transform to the diffusion MR signals and conducting radial integration. To further extend the applicability of q-space imaging methods, Yeh et al. (2010) proposed generalized q-sampling imaging (GQI), which could be applied to balanced sampling schemes such as single-shell, multi-shell, and grid sampling schemes, with accuracy comparable to QBI and DSI. Although q-space imaging methods such as QBI, DSI, and GQI are able to resolve crossing fibers, they still require higher b-values or hundreds of sampling directions to attain satisfactory angular resolution (Cho et al., 2008; Kuo et al., 2008), which may limit its application to clinical studies.

Instead of using model-free methods, several studies have shown that model-based methods can characterize crossing fibers (Jansons and Alexander, 2003; Lazar et al., 2008; Özarslan and Mareci, 2003; Özarslan et al., 2006), model the diffusion pattern (Assaf and Basser, 2005; Jensen et al., 2005), or obtain the fiber distribution (Alexander, 2005; Tournier et al., 2004). To estimate the fiber orientation distribution, Tournier et al. (2004) estimated the signal response pattern of a fiber bundle, termed the response function, and used it to perform deconvolution on the diffusion MR signals. The deconvolution resulted in a fiber orientation distribution (FOD), which was shown to have better angular resolution than q-ball imaging (Tournier et al., 2008). Other deconvolution methods based on constraint optimization or regularization methods have also been proposed, aiming to handle the negativity condition (Kaden et al., 2008; Tournier et al., 2007) or the background corruption problem (Dell'acqua et al., 2009). However, unlike the model-free methods, which are able to make use of different sampling schemes, the current model-based methods are limited to single-shell diffusion acquisition, though some studies have suggested the benefit of using multiple b-values (Aganj et al., 2010; Correia et al., 2009;
Khachaturian et al., 2007; Wu and Alexander, 2007; Yeh et al., 2009). To meet this need, it is desirable to have a reconstruction method that applies deconvolution to dODFs, thereby combining the strengths of both q-space imaging and deconvolution methods. One attempt was proposed by a recent study, which applied a deconvolution approach to DSI and restored the dODF (Canales-Rodriguez et al., 2010). However, the restored dODF is still the diffusion distribution, and it could be further deconvolved by the response function to obtain the fiber distribution. In another approach, Descoteaux et al. (2009) applied the spherical deconvolution concept to the analytical q-ball solution and calculated the fiber ODF (fODF), which was claimed to have better accuracy than the FOD obtained from the spherical deconvolution. However, that method could be applied only to images acquired by the single-shell sampling scheme, and not to data acquired by other sampling schemes.

To provide a deconvolution method applicable to q-space imaging methods such as DSI, QBI, and GQI, we propose a mixed diffusion model and define the fODF as the orientation distribution of the fiber spin density. This deconvolution method, named diffusion deconvolution, can be applied to dODFs obtained from QBI, DSI, or GQI, and is thus equally applicable to single-shell, grid, and multiple-shell sampling schemes. To examine the performance of diffusion deconvolution, we conducted a phantom study to compare the angular resolution of the fODF with the dODF. To examine the consistency of the deconvolution under different q-space reconstruction methods and sampling schemes, we conducted an in vivo study by acquiring q-space data with single-shell, two-shell, and grid sampling schemes, which were then reconstructed by QBI, GQI, and DSI, respectively. To demonstrate the potential usefulness of the fiber spin density, it was compared with the fractional anisotropy (FA) obtained from DTI analysis. The application of the fiber spin density on tractography was also demonstrated in
comparison with the conventional approach.

2. Material and methods

2.1 Mixed diffusion model

Q-space imaging methods are based on the Fourier transform relation between q-space signals and the probability density function, or the diffusion average propagator (Callaghan, 1993). The dODF derived from the diffusion average propagator can be viewed as a linear combination of multiple dODF components, each of which corresponds to a constituent fiber population. This linear combination can be described as a mixed diffusion model: the overall dODF $\psi_d$ is the summation of the component dODFs $\psi_i$ plus a background isotropic dODF $\psi_0$.

$$\psi_d = \sum \frac{n_i}{n} \psi_i + \frac{n_0}{n} \psi_0$$

(1)

where $n$ is the total amount of the spins in the voxel of interest, $n_i$ is the amount of the spins associated with the component dODF $\psi_i$, and $n_0$ the amount of the spins in the background diffusion. All the component dODFs should satisfy the requirements that the distribution value is non-negative and all dODFs should add up to one. In our implementation, the dODF is represented by a vector with finite dimensions; specifically, the sampling directions of the dODF are defined by the vertices of a 6-fold tessellated icosahedron, resulting in a vector with 362 dimensions. Since dODF is assumed to be symmetric about the origin, the ODF vector can be represented by one half of the dimensions (181 directions).

The proposed mixed diffusion model is based on two assumptions. First, the exchange of the
spins between constituent fiber populations is negligible. Second, the background diffusion is isotropic, and all the anisotropic diffusion comes from the spins of the constituent fibers.

Comparing the mixed diffusion model with other fiber composition models, it is of note that spherical deconvolution (Tournier et al., 2004) modeled the fiber composition in terms of volume fractions to estimate the FOD, whereas we used fractions of spin quantity, $\frac{n_i}{n}$ and $\frac{n_0}{n}$, because the signal intensity of diffusion MR is in proportion to the amount of the spins. Another difference is that we included the isotropic component $\frac{n_0}{n}\psi_0$ in the model to consider the background diffusion.

Without loss of generality, a unit volume can be assigned to the imaging voxel, and this reformulates Eq. (1) in terms of the spin density.

$$\rho \psi_d = \sum \rho_i \psi_i + \rho_0 \psi_0$$

(2)

where $\rho$ is the spin density of the voxel of interest, $\rho_i$ is the fiber spin density associated with the component dODF $\psi_i$, and $\rho_0$ is the spin density of the background diffusion. To simplify the model, the component dODFs $\psi_i$ are assumed to share a common characteristic dODF $\psi_c$, and thus each of the dODFs $\psi_i$ can be replaced by the characteristic dODF $\psi_c$ oriented at the respective fiber orientation. Furthermore, since the fiber spin density $\rho_i$ can be viewed as an orientation function, we defined the fODF as the distribution of the fiber spin density, i.e.

$$\psi_f(\hat{u}) = \rho_f$$

Having introduced the characteristic dODF and the definition of fODF, Eq. (2) can be reformulated to a convolution form.
\[ \rho \psi_d = \psi_f \otimes \psi_c + \rho_0 \psi_0 \]  

(3)

where \( \psi_f \otimes \psi_c \) stands for the convolution between the fODF and the characteristic dODF. Numerically, this convolution can be calculated by a simple matrix multiplication: \( A \psi_f \), where \( A \) is a 181-by-181 convolution matrix, and the column vectors of \( A \) are the characteristic dODF \( \psi_c \) oriented at 181 orientations.

2.2 Fiber profile and convolution matrix

To calculate the convolution matrix \( A \), the characteristic dODF \( \psi_c \) (Fig. 1a) is first converted to a one-dimensional fiber profile \( f(\theta) \), where \( \theta \in [0, \frac{\pi}{2}] \) is the angle to the fiber orientation. A fiber profile function converted from the dODF only has discrete data points as shown in Fig. 1b, and further regression is needed to obtain a continuous profile function. This can be done by kernel regression, formulated as follows:

\[ f(\theta) = \frac{1}{Z} \sum \psi_c(\hat{u}) \exp\left(-\frac{(\theta - \cos^{-1}|\hat{u} \cdot \hat{\alpha}|)^2}{2\sigma^2}\right) \]  

(4)

where \( \hat{\alpha} \) is the fiber orientation of the characteristic fiber dODF, \( \sigma \) is the standard deviation for the Gaussian radial basis kernel, \( Z \) is the normalizing factor equal to

\[ \sum \exp\left(-\frac{(\theta - \cos^{-1}|\hat{u} \cdot \hat{\alpha}|)^2}{2\sigma^2}\right), \]  

and the unit vector \( \hat{u} \) iterates through 181 ODF sampling directions. From our experience, \( \sigma \) can be determined by the angular resolution of an ODF. In this study, we used \( \sigma = 9 \) degrees to get a continuous fiber profile function, which is demonstrated in Fig. 1c. Based on the kernel regression result of the fiber profile \( f(\theta) \), the 181-by-181 convolution matrix \( A \) can be calculated using the following equation:
\[ A(i, j) = f(\cos^{-1}|\hat{u}_i \cdot \hat{u}_j|) \]  \hspace{1cm} (5)

where \( \hat{u} \) is the 181 sampling directions of the orientation function. Since the convolution of an isotropic ODF is also isotropic, it is obvious that

\[ A\psi_0 = \hat{\lambda}_0\psi_0 \]  \hspace{1cm} (6)

where \( \hat{\lambda}_0 \) is a constant value.

In this study, the characteristic dODF \( \psi_c \) was selected from the voxel having the highest anisotropy. This strategy is similar to those of other deconvolution methods used to select the response function (Descoteaux et al., 2009; Tournier et al., 2004). However, one should note that the characteristic dODFs taken from different locations of the white matter may be different, as shown in our preliminary analysis of the \textit{in vivo} study (Fig. 1d). This difference in the fiber profile functions could produce false peaks in fODF, a phenomenon that has to be handled by applying additional regularization or constraint optimization.

2.3 Fiber ODF estimation

Eq. (6) and Eq. (3) can be combined to estimate the fODF:

\[ \psi_f + \frac{\rho_0}{\hat{\lambda}_0} \psi_0 = \rho A^{-1}\psi_d \]  \hspace{1cm} (7)
Eq. (7) indicates that the estimation of the fODF is an inverse problem, and a straightforward way to estimate the fODF is to multiply the inverse matrix of the convolution matrix $\mathbf{A}$ to the dODF. However, this inverse problem is often ill-conditioned, and small noise in the input results in significant noise in the output, which is not favorable. In practice, the poor signal-to-noise ratio of diffusion weighted images can cause significant noise in dODF, and the deconvolution matrix $\mathbf{A}$ may not be accurate due to the variety of the characteristic dODF. All these factors will result in spiky fODF after the deconvolution. To deal with this problem, additional regularization can be conducted by using Tikhonov’s regularization:

$$\hat{\mathbf{\psi}}_f + \frac{\hat{\rho}_0}{\lambda_0} \mathbf{\psi}_o = \rho \hat{\mathbf{A}} \mathbf{\psi}_d$$

(8)

where $\hat{\mathbf{A}} = (\mathbf{A}^\dagger \mathbf{A} + \alpha \mathbf{I})^{-1} \mathbf{A}^\dagger$ and $\alpha$ is the control parameter for the regularization and $\mathbf{I}$ the identity matrix. To estimate $\frac{\hat{\rho}_0}{\lambda_0} \mathbf{\psi}_o$, we further applied the sparsity feature of an fODF: for any fODF, there is at least one orientation having no fiber population. Therefore, the minimum value of the fODF should be zero, i.e. $\min(\hat{\mathbf{\psi}}_f) = 0$, and the isotropic component $\frac{\hat{\rho}_0}{\lambda_0} \mathbf{\psi}_o$ could be estimated by $\min(\rho \hat{\mathbf{A}} \mathbf{\psi}_d)$. The final deconvolution computation is formulated as follows:

$$\hat{\mathbf{\psi}}_f = \rho \hat{\mathbf{A}} \mathbf{\psi}_d - \min\left(\rho \hat{\mathbf{A}} \mathbf{\psi}_d\right)$$

(9)

In implementation, one should note that the $\min$ function may return a negative value, and in this study, we handled it by replacing the negative values with zero. Although better constraint optimization methods could be used to get more accurate results (Dell'acqua et al., 2009;
Tournier et al., 2007), we use only Tikhonov’s regularization to demonstrate the results of our deconvolution model.

2.4 Spin density

The calculation of fODF requires the estimation of the dODF $\psi_d$ and the corresponding overall spin density $\rho$. To obtain the overall spin density, one could acquire multiple EPI b0 images with different TEs and a long fixed TR to correct for the $T_2$ effect. The calculated overall spin density is then multiplied by the dODF, resulting in the term $\rho \psi_d$. This term is named the spin distribution function (SDF) in the GQI method (Yeh et al., 2010). To further give the SDF a unified value, as proposed by the GQI method, free water diffusion is invoked as a reference and $\rho \psi_d = 1$ is assigned for the free water. In brain imaging, one can use the cerebrospinal fluid in the ventricles to equate the free water and use it as the reference. A more accurate approach is to include a pure water tube in the scan to calibrate the free water diffusion. This approach provides a way to measure the spin density on a relative scale.

2.5 Regularization parameter

The regularization parameter $\alpha$ in Tikhonov regularization controls the penalty against the fluctuated values of the fODF, thereby offering a way to reduce the spiky appearance and smooth the contour of the fODF. Higher values of $\alpha$ reduce the fluctuation of the fODF, but they may also smooth out small crossing fibers, causing decreased sensitivity to subtle connections. On the other hand, lower values of $\alpha$ may result in a spiky fODF, which is not accurate in terms of its specificity. To reach a balance between the sensitivity and specificity, we devised an approach to estimate the error in fODF sensitivity and specificity, which were further used to determine the regularization parameter $\alpha$. To estimate the error in sensitivity, a voxel known to have one fiber
population (e.g. the corpus callosum at the mid-sagittal plane) was used to calculate the corresponding fODF. The sensitivity error was estimated by the ratio between the second largest and largest local maximum on the fODF. To estimate the error in specificity, a voxel with free water diffusion (or cerebrospinal fluid as a compromised approach) was selected. Since an ideal fODF of a free water diffusion voxel should have values equal to 0, the specificity error was thus estimated by the ratio between the mean value of the free water fODF and the maximum of the one-fiber fODF. The optimal $\alpha$ was then determined by balancing the sensitivity and specificity error. In our in vivo study, we chose a value of $\alpha$ with both sensitivity and specificity error within 5%~10% to reach an adequate balance.

2.6 Applications in deterministic fiber tracking

The fiber spin density $\rho_i$ offered by the fODF can be used in fiber tracking to get a more robust tracking result. Deterministic fiber tracking often uses the FA or generalized FA (GFA) (Tuch, 2004) threshold as a stopping criterion to determine the termination of the fiber tracking (Wedeen et al., 2008), but these anisotropy indices are not specific to each fiber population in a voxel. To provide a better termination for fiber tracking, the fiber spin density can be used to decide the extent of the fiber tracts. In implementation, the fiber orientations were first obtained by searching for the local maxima on fODF. The spin densities of the local maxima were checked to determine whether they were greater than a predefined value, i.e. $\hat{\psi}_i(\hat{\alpha}) > \rho_{\theta}$, where $\hat{\alpha}$ is the orientation the local maxima and $\rho_{\theta}$ is a predefined threshold for the fODF value. The local maxima with fiber spin densities lower than $\rho_{\theta}$ were discarded, and the remaining fiber orientations were then used for fiber tracking.

2.7 Phantom study
We performed diffusion MRI scan on a diffusion phantom, which was created by using silica capillary tubes with an inner diameter of 20 μm and an outer diameter of 90 μm (Polymicro Technologies, Phoenix, Arizona, USA). These tubes were aligned in two placeholders, and the relative orientations were set to 30, 45, 60, or 90 degrees to simulate a crossing fiber pattern. For each crossing angle setting, one placeholder was placed vertically, and another one crossed it at the assigned crossing angle. The whole phantom was immersed in water and vibrated to remove air bubbles, as described in a phantom validation study (Tournier et al., 2008). The phantom was scanned in a 9.4 Tesla Bruker spectrometer (Bruker Companies, Ettlingen, Germany) with 2D-FT stimulated-echo high angular resolution diffusion-weighted imaging (HARDI). TR/TE = 1900/13.8 ms, matrix size = 32 × 32 × 1, FOV = 25 mm × 25 mm, slice thickness = 3.6 mm, the diffusion time = 100ms, the diffusion gradient duration = 3 ms, b-value = 4000 s/mm² and NEX = 4. T₂-weighted images were also acquired to measure the exact crossing angles of the phantom. The angles were measured by calibrating the inner angle between the inner borders of the vertically-placed placeholder and the crossing placeholder. The measured inner angles on the left and right side were averaged to get a more accurate estimation. For crossing angles originally arranged at 30°, 45°, 60°, and 90°, the measured crossing angles were 27°, 45°, 63°, and 90°, respectively. The dODF was calculated by the analytical QBI solution (Descoteaux et al., 2007) with a spherical harmonic order of 8 and a regularization factor of 0.006, as recommended by the original work. The fiber orientations were determined by the peaks on the dODFs. To obtain the fODFs from the dODFs, the fiber profiles were estimated using the single fiber component, and the deconvolution was conducted by using a regularization parameter of 0.4, which had 7.62% error in sensitivity and 3.98 % error in specificity. Both the QBI reconstruction and deconvolution were conducted in DSI Studio (http://dsi-studio.labsolver.org/). The performance was evaluated by the angular error between the resolved fiber orientations and the orientation of
2.8 In vivo study

A 25-year-old healthy male subject without any known neurological disease received a diffusion scan on a 3T MRI system (TIM Trio, Siemens, Erlangen, Germany) after informed consent was obtained, in accordance with the regulations of the institute. The scan was performed using a 12-channel head coil and a single-shot twice-refocused echo planar imaging (EPI) diffusion pulse sequence. On the same subject, QBI, DSI, and GQI sampling schemes were acquired consecutively under the same spatial parameters: the field of view = 240 mm × 240 mm, matrix size = 96 × 96, slice thickness = 2.5 mm (no gap), and the number of the slices was 40 to cover the cerebral cortex, resulting in voxel size = 2.5 mm × 2.5 mm × 2.5 mm. For QBI, the number of gradient directions = 252, b-value = 4000 sec/mm$^2$ and TR / TE = 7200 ms / 133 ms, resulting in a scanning time of approximately 30 minutes. For DSI, number of gradient directions = 202, maximum b-value = 4000 sec/mm$^2$ and TR / TE = 7200 ms / 144 ms, resulting in a scanning time of approximately 25 minutes. For GQI, the sampling scheme included two DTI datasets acquired by the built-in DTI b-table. One DTI dataset had 64 gradient directions, b-value = 3000 sec/mm$^2$, and TR / TE = 6300 ms / 121 ms. The other one had 30 gradient directions, b-value=1500 sec/mm$^2$, and TR / TE = 5500 ms / 101 ms. The total scanning time for GQI was approximately 10 minutes. The b0 images with TR/TE = 5500 / 101 ms, 6300 / 121 ms, 7200 / 133 ms, and 7200 / 144 ms were used to estimate the T$_2$ values (the T$_1$ effect is ignored) and calculate the overall spin density.

The image reconstruction, including QBI, DSI, and GQI, was performed in DSI Studio. The QBI reconstruction algorithm and parameters were the same as those of the phantom study. The DSI
reconstruction was implemented as proposed by an optimization study (Kuo et al., 2008), and a Hanning filter of 17 in width was applied to the q-space data to smooth the dODF. The GQI reconstruction was implemented with a diffusion sampling length ratio of 1.25 to cover more than 80% of the diffusion pattern, as suggested in the GQI study (Yeh et al., 2010). To obtain the fODFs from the dODFs, the single fiber profiles were estimated from the dODFs having the highest GFA value, and the deconvolution was conducted using a regularization parameter of 7. The resulting errors in sensitivity of the deconvolution were 10.85% in QBI, 5.97% in DSI, and 9.23% in GQI, whereas the errors in specificity were 4.82% in QBI, 3.24% in DSI, and 6.15% in GQI. The qualitative comparison between dODF and fODF was conducted in the centrum semiovale region, a region where the anatomical evidence suggests three-way crossing of the corticospinal tract, corpus callosum, and superior longitudinal fasciculus. The resolved fiber orientations were further separated into major and minor fibers. The major fiber orientation was determined by orientation of the global maximum on an ODF, whereas the minor fiber orientation was determined by orientation of the second largest local maximum. In general, the major fiber presents the main fiber bundle, while the minor fiber presents crossing fiber or branching fiber. By separating the major and minor fibers, we could separately evaluate the effect of deconvolution on them, thereby obtaining a more specific performance evaluation.

2.9 Deterministic fiber tracking

The in vivo DSI scan was further used to evaluate the application of fiber spin density on fiber tracking. The conventional approach was proposed by Wedeen et al. (2008), who suggested the use of an anisotropy threshold (e.g. FA or GFA) to determine the extent of the fiber tracts. The comparison between fiber spin density and GFA was conducted under the same fiber orientation information, and the termination of the tractography was determined using two different quantity
measures. For each voxel, the fiber orientations with the quantity measures (fiber spin density or GFA) below a predefined threshold were discarded. To generate the tractography, we adopted the same modified streamline fiber tracking method used in the DSI tractography study (Wedeen et al., 2008). A ball-like seeding region was placed near the left supramarginal gyrus (Fig. 9), and a total number of 20,000 seeding points were placed uniformly within the seeding region. The propagation direction was calculated by trilinear interpolation, which interpolated the fiber orientations from the 8 nearby voxels. In cases of multiple fibers being resolved within a voxel, the fiber orientation nearest to the current propagation direction was selected for interpolation. The propagation step size was 1.25 mm, which was the half of the pixel dimension, and the maximum allowable turning angle was 60 degrees. The termination condition was met if the current position had no fiber orientation, or the current turning angle was greater than the angular threshold.

To assign comparable thresholds between the spin density and GFA, the thresholds were determined by inspecting their thresholding coverage on the white matter. A value of 0.0022 was determined for the fiber spin density, whereas a threshold of 0.6 was determined for GFA. The fiber tracking was conducted in DSI Studio, and only association fibers passing through the left supramarginal gyrus were selected for further qualitative evaluation.

3. Results

3.1 Phantom study

The resolved fiber orientations of the 30°, 45°, 60°, and 90° crossing phantoms are shown in Fig. 2, where the inset figures illustrate the dODFs and fODFs selected from the crossing regions. As shown in the figure, the fODF resolved fibers crossing at 45°, 60° and 90°, whereas the dODF
resolved only fibers crossing at $60^\circ$ and $90^\circ$. The improvement of fODF at $45^\circ$ could be explained by the sharper contour of the fODFs shown in the inset figure. The quantitative analysis of the angular error at different crossing angles is shown in Fig. 3. While dODF and fODF both achieved perfect performance at $90^\circ$ crossing, fODF outperformed dODF in resolving fibers crossing at $45^\circ$ and $60^\circ$. This analysis result is consistent with the qualitative comparison on the ODF contours and peak orientations.

3.2 In vivo study

The dODF and fODF reconstructed by DSI, QBI, and GQI are shown in Fig. 4, which presents the axial slice at the right centrum semiovale, a crossing region occupied by the corticospinal tract, corpus callosum, and superior longitudinal fasciculus. The ODFs are rendered with directional colors and normalized (min/max = 0/1) to the same size to facilitate comparison. As shown in Fig. 4, the fODFs of all the three q-space methods present sharper contours than those of the dODFs, and the peak orientations were readily identified on fODF.

The resolved orientations of major fiber population and minor fiber population are shown in Figs. 5 and 6, respectively. In these figures, the fibers passing horizontally (red) are corpus callosum, and the fibers passing vertically (green) are superior longitudinal fascicules. In Fig. 5, all three imaging settings show consistent major fiber orientations in both fODFs and dODFs, and the difference in major fiber orientations is subtle. The dODF seemed to have accurate resolution of major fibers, and the deconvolution did not show obvious improvement. In Fig. 6, however, the dODFs failed to identify several minor fibers in the GQI, which only had 96 diffusion samplings. After the deconvolution, all three imaging settings presented consistent minor fiber orientations. The results suggest that the fODF can provide better resolving power in detecting minor fiber
orientations, and the improvement is particularly obvious in scans with reduced diffusion samplings.

To examine the fiber spin density, the fODFs without normalization are shown in Fig. 7, a coronal view of the left centrum semiovale. The fODFs are rendered with directional colors, and the sizes of the fODFs are presented according to the fiber spin density of the fODFs. The fODFs in the middle of the corpus callosum show higher fiber spin density, which could be explained by the high packing density of the fibers in this region. The size of the fODF gradually decreases as the fibers approach gray matter, suggesting that the fiber tracts spread out as they enter the gray matter. The fODFs in all three imaging settings showed consistent fiber spin density and fiber orientations regardless of the reconstruction methods and the sampling schemes being applied.

The mapping of the fiber spin density along the major fiber is presented in Fig. 8a, for comparison with the mapping of the fractional anisotropy (FA) in Fig. 8b. The images are shown in the axial view at the level of the corpus callosum. Both images were obtained from the same DSI dataset. To facilitate comparison, the intensities of the images were individually scaled by their relative contrasts (min/max = 0/255). The FA was calculated by DTI analysis, while the fiber spin density along the major fiber was the maximum value of the fODF. From Figs. 8a and 8b, a grossly similar contrast pattern between these two quantitative indices can be observed, but the FA mapping shows a higher noise level than the fiber spin density mapping. This is particularly obvious in the background region, where the fiber spin density shows lower intensity and the FA presents a much noisier pattern.

3.3 Deterministic fiber tracking
The result of the tractography comparison is shown in Figs. 9a and 9b, where the termination criterion of the tractography was respectively set by the fiber spin density and the GFA. The oval seeding region at the angular gyrus is presented by a yellow region, and only the anterior-posterior fiber tracts passing through the seeding region are presented. Relative positions of the fibers to the whole brain are shown in the pictures to the left. A comparison of Fig. 9a and 9b shows that the fiber tracts using fiber spin density are more coherent, and the termination locations are more definite. In contrast, the fibers using GFA threshold present incoherent tracts and termination locations. Figure 9c further illustrates the details of the annotated region in Fig. 9a, whereas Fig 9d illustrates the same region with the cortical surface rendered from high-resolution T1-weighted structure images. As shown in Fig. 9c, the fiber tracts branch into several fiber bundles as they reach the cortex area. Further examination of Fig. 9d shows that the fiber bundles indicated by the arrows bulge into the gyrus and terminate at the cerebral cortex, which is consistent with current understanding of the anatomy.

4. Discussion

In this study, we propose a method called diffusion deconvolution to obtain the fODF from the dODF, thereby improving the resolving power of crossing fibers and also offering an index of the fiber spin density of the resolved fiber populations. The phantom study showed that in comparison with the dODFs, the fODF achieved significant improvement in resolving fibers crossing at 45° and 60°. The improvement could be explained by the sharper contours of the fODFs, which enabled better resolution of the peaks. In the \textit{in vivo} study, we applied the proposed deconvolution method to the dODFs reconstructed by different q-space imaging methods, including QBI, DSI, and GQI, based on the shell, grid, and two-shell diffusion sampling schemes, respectively. The results showed that the fODFs offered consistent fiber
orientations regardless of the reconstruction methods and diffusion sampling schemes, implying the robustness of the proposed method in different imaging settings. Moreover, the fODFs presented contours sharper than those of the dODFs, thereby allowing easier identification of the crossing fiber patterns. Further qualitative analysis showed that the detection of the major fibers did not show obvious improvement. This may be due to the fact that the major fibers resolved on dODFs already offer accurate orientations and further deconvolution may not achieve significant improvement. On the other hand, for the minor fibers, namely the branching or crossing fibers superimposed on a main trunk, the analysis showed that the sharpened contour led to different levels of improvement in the detection power. This improvement was most obvious in the GQI, which was applied to the 96-direction dataset in this study. In contrast, 203-point DSI applied to a grid dataset already presented reasonable resolving power in the dODFs, and the improvement contributed by deconvolution seemed to be limited. This observation suggests that the deconvolution may be applied on a reduced sampling dataset to improve the angular resolution, and thus it may prevent a lengthy scanning time. Such a feature is potentially useful in clinical studies that only allow a limited scan time for patients.

In addition to the angular resolution, the fiber spin density offered by the fODF presented less background noise in comparison with the FA, an improvement that could be explained by the low spin density of the background. Moreover, we observed a gradually decreasing pattern of the spin density as the fibers approached the gray matter. This observation could be explained by the anatomical knowledge that the fiber bundles branch off and become less dense as they approach the gray matter. This observation leads us to speculate that the fiber spin density may be related to the axonal number of a fiber population; however, further tissue-based study is required to examine this claim.
The tractography comparison study showed that fiber tracts determined by the fiber spin density had more coherent tracts and more definite termination locations, and the termination locations matched the gyral folding rendered from the high-resolution structure images. These qualitative examinations suggest that the fiber spin density could replace the roles of FA or GFA in determining the tract termination, since it has less noise and is specific to the resolved fiber population.

The proposed deconvolution method has some properties in common with the existing deconvolution approaches. The general deconvolution concept is similar, and the fiber profile function estimated in this study is comparable to the response function used in spherical deconvolution. Furthermore, like other deconvolution methods, the proposed method still needs to handle the problem of ill-conditioning and the negative components, which requires additional regularization or constraint optimization. Despite the commonality, our method has some unique features that are worth mentioning. First, the deconvolution proposed in this study is applied to the dODF, not to spherical harmonic parameters. This approach decouples the deconvolution process from the reconstruction process of the dODF, allowing the deconvolution of dODF to be applied to all q-space imaging methods. The applicability to grid, single-shell, and multi-shell encoding schemes further opens up the possibility of comparing the performance among these schemes. Second, the fODF obtained in our study is the distribution of the fiber spin density, whereas the FOD in spherical deconvolution is the distribution of the fiber volume fraction. The FOD model implicitly assumes that signal intensity is in proportion to the fractional volume, neglecting the fact that the spin density is not uniform across voxels. This assumption results in an overestimation of the volume fraction in areas that contain high spin density, such as the
periventricular region, making the FOD prone to a partial volume effect, which was pointed out as the corruption effect in a deconvolution study (Dell'acqua et al., 2009). In contrast, the mixed diffusion model used in this study includes the isotropic background component, which also models the partial volume condition. Thus the estimated fiber spin density is free from the partial volume effect and can be used in quantitative analysis to investigate fiber populations. This feature also benefits fiber tracking, since the termination of the fiber tracts can be more accurately determined using the spin density threshold, as shown in our fiber tracking result.

There are still limitations to our deconvolution method. In our study, we found that while the deconvolution improves the sensitivity to crossing and branching fibers, it does not simultaneously guarantee good specificity. Even if a higher regularization is applied, it also indiscriminately removes some subtle fiber connections. The best trade-off between sensitivity and specificity is hard to determine and requires repeated adjustment of the parameters to obtain a better result. Moreover, the phantom validation is in fact an over-simplified scenario as compared with living brain tissue. The diverse axonal diameters and heterogeneous cell components in the human brain may result in different fiber profiles, subjecting the deconvolution method to more errors in the in vivo application. This can be observed, as we have to use higher regularization parameters (7) in the in vivo studies as opposed to the lower parameters (0.4) in the phantom study to achieve the comparable error percentage (5~10%).

Furthermore, the regularization method we used could not handle the negative value condition, which can be better handled by using constraint optimization. Also, $L_1$-regularization can be used to maximize the sparsity in fODF instead of using Tikhonov regularization, which is an $L_2$-regularization. This may reduce the cost in regularization and increase the accuracy in optimization. Another limitation of this study is the estimation of the overall spin density. While
it is true that we could correct the T₂ shine-through effect by acquiring multiple b₀ images with different TEs or additional proton density maps, we did not consider that different TEs have different scales of distortion, which makes the estimation inaccurate in areas with large distortion. Meanwhile, other factors such as B₁ inhomogeneity and susceptibility artifacts can further complicate the problem. Lastly, due to the fact that the actual fiber orientations could not be accessed in the *in vivo* study, our study largely depends on qualitative inspection and requires further validation using cadaver subjects. Furthermore, though we conducted the *in vivo* images using difference diffusion sampling schemes to demonstrate the applicability, only one subject was recruited in the study. Additional studies are still needed to confirm the accuracy of our method.

**Acknowledgements**

We thank Dr. Ching-Po Lin and Dr. Kuan-Hung Cho for providing the data of the phantom study and technical assistance in the image acquisition at National Yang-Ming University. This work was supported in part by the National Science Council, Taiwan (NSC98-2752-M-002-005-PAE, NSC99-2321-B-002-037, and NSC99-3112-B-002-030).

**References**


imaging (DSI) tractography of crossing fibers. Neuroimage 41, 1267-1277.
Yeh, F.C., Wedeen, V.J., Tseng, W.Y., 2009. Dataset-independent reconstruction of high angular
resolution diffusion sampling schemes by generalized q-space imaging. Proceedings 17th
Scientific Meeting, International Society for Magnetic Resonance in Medicine, Honolulu, p.
3545.
Imaging 29, 1626-1635.
Fig. 1. (a) The characteristic diffusion ODF and (b) its one dimensional fiber profile directly converted from the diffusion ODF. (c) The continuous fiber profile estimated by kernel regression. (d) The continuous fiber profiles estimated from the preliminary in vivo data.

Fig. 2. The fiber orientations on the diffusion ODF (dODF) and fiber ODF (fODF) obtained from the 30°, 45°, 60°, and 90° crossing phantoms. The dODF and fODF selected from the central portion of each crossing area are shown in the inset figures. Compared with the dODFs, the fODFs show sharper contours in all crossing settings. The difference in angular resolution can also be observed at 45° crossing, where the fODFs resolve two fiber orientations but the dODFs present only one orientation.

Fig. 3. The angular error of the resolved fibers on diffusion ODF (dODF) and fiber ODF (fODF) obtained from the 45°, 60°, and 90° crossing phantoms. At 45° and 60° crossing, the fODF group shows significant lower angular errors (P <0.01) than the dODF group. At 90° crossing, both dODF and fODF can resolve crossing pattern accurately.

Fig. 4. The diffusion ODF (dODF) and fiber ODF (fODF) obtained from QBI, DSI, and GQI, applied to shell, grid, and two-shell sampling schemes, respectively. The ODFs are selected from the same region and normalized to the same size to facilitate comparison. In all three imaging settings, the fODFs present consistent contours regardless of the different diffusion schemes and reconstruction methods applied. In addition, the fODFs show sharper contours and more definite peak orientations than the dODFs.

Fig. 5. The resolved major fiber orientations from the same diffusion ODF (dODF) and fiber ODF (fODF) presented in Fig. 5. The major fiber orientations, which reveal the orientations of the main fiber bundles, are defined by the orientations of the global maximum on the ODFs. The fiber orientations on dODFs are similar to those on the fODFs, and the fODFs do not provide obvious improvement in resolving the major fibers.

Fig. 6. The resolved minor fiber orientations from the diffusion ODF (dODF) and fiber ODF (fODF) presented in Fig. 5. The minor fiber orientations, which reveal the orientation of a branch or a superimposed crossing, are defined by the second largest local maximum on the ODFs. Some minor orientations cannot be resolved on the dODFs, especially the ones in GQI, which has only 96 diffusion samplings. On the contrary, the fODFs show obvious improvement in recovering the minor fiber orientations.
Fig. 7. The fiber ODF (fODF) of QBI, DSI, and GQI in the coronal view of the central semiovale region, whose location is shown by the yellow slack to the left of the figure. The fODFs are rendered by directional colors, and their sizes are presented according to their fiber spin density. The compact fiber structure of the corpus callosum can be revealed by the larger fODFs, and the fODFs gradually fade out as fibers approach the gray matter. Consistent results in the fODF contour and size are also observed even though the deconvolution is applied to different reconstruction methods and sampling schemes.

Fig. 8. The axial view at the colossal level – (a) the fiber spin density of the major fiber population obtained from fODF, and (b) the fractional anisotropy (FA). Both maps are obtained from the same dataset and presented in the contrast of min/max = 0/255. Although both maps show a similar contrast pattern between the gray matter and white matter, their difference in noise level can be observed in the background. It is easier to identify the gray-white junction on the fiber spin density mapping.

Fig. 9. The tractography generated from two different termination criteria: (a) the fiber spin density and (b) the generalized fractional anisotropy (GFA). The annotated region in (a) is further illustrated in (c) and (d), which respectively shows the termination location in detail and the corresponding cortical surface generated from high-resolution $T_1$-weighted images. The oval seeding region near the supramarginal gyrus is presented in yellow, and only the anterior-posterior fiber tracts passing through the seeding region are presented. Tracking using the fiber spin density presents more definite pathways and terminations than that using the GFA. The termination locations also match the gyral folding rendered from $T_1$-weighted images (arrows) and thus provide definite cortical connection, which is consistent with the cortical anatomy revealed by structure images.