Track density imaging using diffusion tensor imaging data from 1.5 T MRI scanner

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Abstract: Superresolution track density imaging (TDI) has recently been developed for achieving high resolution track density maps from low-resolution diffusion images acquired at 3 T. But, the utility of the approach is still unclear when applied to diffusion tensor imaging (DTI) data acquired at lower 1.5 T magnetic field strength and thus its advantages or disadvantages awaits for exploration. We implemented an algorithm to generate track density maps of human white matter using streamline tracking and tested its performance with data acquired from two healthy volunteers at 1.5 Tesla. The effects of number of diffusion directions and seed selections on the quality of the reconstructed TDI maps were investigated under a variety of settings. The results were visually evaluated by an anatomist and a radiologist, and statistically characterized using gray level cooccurrence Matrices (GLCM). Producing high-quality maps with improved resolution required increasing the number of seeds per voxel. Statistical implications were consistent with visual inspection. Low signal-to-noise ratio in DTI data intrinsically yielded low SNR in the final TD map. Accurately defining the diffusion and thus fiber orientation within a voxel necessitated increasing the number of diffusion encoding directions. Our data suggests that TDI image with DTI data acquired at 1.5 T is possible using right trade-offs in data acquisition and processing and has the capability of delineating the substructures of the brain.

Key words: Diffusion tensor imaging, track density imaging, superresolution, tractography

1. Introduction

Developing new approaches for better delineation of brain structures with in vivo imaging is an active area of research in neuroscience. Efforts are focused on understanding the underlying physical principles, producing new MR contrast mechanisms, improving image quality and increasing the spatial resolution of images [1–6]. Track density imaging (TDI) has been introduced as a means of visualizing the density of neuronal axonal fiber tracts in white matter. In the application of the method described here (Figure 1: Detailed Flowchart), diffusion weighted magnetic resonance (MR) images constitute the core data from which diffusion tensor images are derived and fiber tractography is constructed. The number of tracks per voxel are counted and mapped spatially as a TD image.

Diffusion images are typically acquired at low spatial resolution for achieving signal-to-noise ratio (SNR) sufficient enough to overcome the signal loss from diffusion weighting. Thus, the resulting TD images are affected

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by low SNR. This issue has recently been addressed with the introduction of the superresolution approach [7]. The superresolution property inherent to the method allows mining the extra (long-range) information provided by the fiber-tracking and thus producing TD images at subvoxel resolution without compromising the integrity of the original diffusion data.

The past studies have successfully demonstrated the utility of the super resolution property with specific diffusion data acquired using MR scanners operating at magnetic field strength of 3 T and above [8–15]. However, the MR systems currently installed in most clinics operate at 1.5 T. The diffusion data acquired at this field suffer greater losses in SNR and resolution. Investigating the merits of superresolution TD imaging as applied to such routine clinical data was the primary aim of this study. Under different settings, protocols concerning the acquisition or post-processing of the diffusion data were examined for achieving optimal quality in TD images. In particular, the effects of the critical parameters; diffusion encoding directions, superresolution voxel size, and seed locations, on the consistency and characteristics of TD images were analyzed by using both qualitative and quantitative performance measures that included gray level cooccurrence matrix (GLCM), contrast, entropy, and energy.

![Figure 1. Schematic overview of the TD algorithm implemented in this study.](image)

Fiber tracking is an important step of the TD image reconstruction process. In the past, several algorithms have been proposed for fiber tracking. In this study, we implemented streamline fiber tracking based on a deterministic procedure [16–19]. Details of the algorithm are described in the next section.

2. Materials and methods

2.1. MRI acquisition

This study was approved by the local Human Research Ethics Committee. Two healthy volunteers were scanned using 1.5 T Siemens Aera MRI system. The MR protocol consisted of a 3D high-resolution Magnetization Prepared Rapid Acquisition with Gradient-Echo (MPRAGE) sequence (sagittal orientation, voxel size 1 mm × 1 mm × 1 mm, TR/TE=1900 / 2.57 ms, and flip angle 15°) and a 2D single-shot EPI-based twice-refocused diffusion weighted sequence (axial orientation, 55 contiguous slices, 2.5 mm × 2.5 mm × 2.5 mm isotropic voxel size, 230 mm × 230 mm field of view (FOV), 92 × 92 imaging matrix, b-value = 0 or 1000 s/mm², and number of signal averages = 3). A b=0 s/mm² volume was acquired before each average acquisition. The DWI acquisition was repeated for four different sets of diffusion encoding: 6, 12, 30, or 64 directions. The total scan time was about 30 min for the 64 directions.
2.2. Fiber tracking

Fiber tractography process consisted of two steps: the first step was to calculate and diagonalize the diffusion tensor and the second step was to reconstruct the fibers. Elimination of motion and Eddy current artefacts and the diffusion tensor calculations were performed using DTI-Studio software package (Version 3.0.3; Johns Hopkins University, Baltimore, MD, USA) [20]. Each component of the diffusion tensor was skull stripped to eliminate regions except brain. Then, the tensor for each voxel was diagonalized to acquire eigenvalues and eigenvectors that yielded the main diffusion direction with diffusivity information. The eigenvalues were also utilized to calculate gray-scale and color-coded fractional anisotropy (FA) maps. The second step was fiber reconstruction. A number of seed points were embedded in the voxel and per each point, FA value was calculated. FA value was required to be larger than 0.15 in order to initiate fibers from the white matter part of the brain. Fiber tracking was carried out with streamline fiber tracking algorithm implemented in-house based on a deterministic procedure using Mathematica 9 (student edition) on a 2.60 GHz Intel Xeon E5-2670 CPU [19, 21]. Fiber propagation was performed by using the fourth-order Runge-Kutta method with 0.1 step-sizes explained in detail below. The propagation process was ended when the angle between the successive fiber parts was greater than 45°. Other fiber termination criteria were FA being less than 0.15 and fibers being shorter than half of the voxel size [19]. Streamline fiber tracking algorithms utilize local main diffusion eigenvector field \( \vec{E}(\vec{r}_n) \) to reconstruct the fiber tracks. Initiating from a starting point \( (\vec{r}_0) \) to a terminating point, subsequent points \( (\vec{r}_n) \) that define the curve can be formulated as follows [19]:

\[
\vec{r}_{n+1} = \vec{r}_n + h\vec{V}_{n+1},
\]

where \( h \) is the step size parameter (which is defined as 0.1 in this work) and \( \vec{V}_{n+1} \) is the main diffusion vector direction the track will follow. Fourth-order Runge-Kutta method was utilized to define \( \vec{V}_{n+1} \). Method is advantageous for controlling errors encountered at each step by tailoring the step size and for generating smooth and accurate results. The definition of the initial values \( (\vec{r}_0, \vec{V}_0) \) was required to originate the fiber track. Tri-linear interpolation was employed on tensor data. Details of the method can be found in [19]. Following streamline-based fiber tracking algorithm [19], tracks were reconstructed for different number of seeds per voxel: 1, 3, and 9 seeds per voxel corresponding to 32,000, 100,000, and 300,000 fiber tracks, respectively. In studies utilizing deterministic processes such as the fiber assignment by continuous tracking (FACT), seed points were placed in the center of the voxel which further provided one fiber track under certain conditions. In the probabilistic approach, seeding is generally performed randomly such that coordinates of the seed points change from voxel to voxel. This approach does not yield equal distribution of seed points for each voxel [22–24]. Here, we employed a deterministic approach that the coordinates of seed points were defined equally per each voxel as one in the center and the others were spread almost equidistantly. The demonstration of the seed points within a voxel is shown in Figure 2.

2.3. Simulation study

Prior to fiber-tracking process on real DT data, we tested our in-house tracking algorithm on simulated tensor data. The tensors were predefined positive-definite and symmetric pretending as a real DT. Visualization of the results was realized by vector fields, i.e. the three eigenvectors or solely the main eigenvector having the largest eigenvalue or ellipsoids. In this case, we defined discrete and nondiscrete seed points to initiate the fiber tracking. The generated fiber tracts were compared to the simulated vector fields so as to test the accuracy of
the tracking algorithm. Following the experimental testing, fiber tracking algorithm was applied to the human DT data.

2.4. Track-density imaging

Track-density images were generated following the fiber reconstruction steps indicated above. In order to calculate the track-density values, whole brain fiber-tractography was carried out with different seed numbers per voxel, i.e. 1, 3, and 9. The track-density value in each voxel in the whole brain was then calculated using the number of fiber tracts and the voxel size information. Based on the track density, TD images were reconstructed. Density values represented the number of fibers that either initiated in the related voxel or traversed the related voxel. The reconstructed voxel size was either the same as or smaller than the actual voxel size. Using smaller voxel size would have a positive effect on image resolution. In our study, we improved the linear resolution by five-times along each axis making 125-times per voxel. Schematic overview of the algorithm was demonstrated in Figure 1.

2.5. Statistical properties of TD images

In order to define pattern-related properties of track-density images and assure visual inspection done by a radiologist and an anatomist quantitatively, second ordered statistical analyses were performed by the use of gray level cooccurrence matrices (GLCM) on cropped regions of TDI images [25]. The analysis was done on cropped images to mainly focus on white matter and to save computation time at the same time. Contrast, energy, and entropy properties were calculated for TD images as follows:

Energy,
\[ \sum i \sum j P[i,j]^2, \]  

Entropy,
\[ -\sum i \sum j P[i,j] \log P[i,j], \]  

Contrast,
\[ \sum i \sum j(i-j)^2 P[i,j], \]  

where \( P[i,j] \) shows the joint probability occurrence function matrix. The matrix defines the probability of alteration from gray level i to j between pixels with distance \( d \) and angle \( \theta \). In this study, we set \( d = 1 \) and \( \theta = 0^\circ, 45^\circ, 90^\circ, \) and \( 135^\circ \).

As one of the statistical properties obtained by GLCM analysis, contrast represents local differentiation of intensity values of the image. It utilizes intensity difference between a pixel and its neighboring pixels. As the
difference rises, contrast increases. The contrast of single-valued images is zero due to the absence of intensity difference. Energy is an indication of homogeneity and is known as an angular second moment. Energy of a single-valued image is one. Lastly, entropy shows the distribution of energy in the image. The more energy decreases, the more entropy increases intrinsically [25]. In this regard, we sought statistical trends in contrast, energy, and entropy measures of TD maps obtained at different resolutions with constant seed numbers.

3. Results

TD maps for the two subjects were generated successfully using superresolution of TD imaging. The results from both subjects were consistent with each other. Figure 3 shows TD images for one subject at increasing resolution from left to right, with increasing track numbers from top to bottom for the same image slice of brain. The isotropic resolutions of the maps from left to right were 2.5 mm (original DWI resolution), 1.25 mm, and 0.5 mm, respectively. DWI, ADC, and color-coded FA map at the original resolution was also accompanied at the top row for comparison. TD image clearly delineated the white matter. These images could be at either coarse resolution, i.e. same with the original image, or higher resolution based on the final grid size. As the resolution increased, the details of white matter were better visible.

A close inspection of TD images generated at 2.5 mm and 0.5 mm isotropic resolutions (Figure 4) demonstrated that the higher resolution attained with the approach contributed to better delineation of the anatomical information (the genu of the corpus callosum pointed by the red arrow on Figure 4). It is of note that the yellow arrow indicates a signal loss artifact caused by deterministic tensor tractography. The tensor model causes this on regions where fibers are crossing or merging.

![Figure 3. High resolution images obtained by TD imaging, using 64 diffusion-direction DWI data. First row: DWI image, ADC image and color-coded FA map, respectively. Second row: axial whole-brain track density maps sequentially at 2.5 mm, 1.25 mm and 0.5 mm isotropic voxel size generated with one seed per voxel (approximately 32,000 fiber tracks). Third row: axial whole-brain track density maps sequentially at 2.5 mm, 1.25 mm and 0.5 mm isotropic voxel size generated with three seeds per voxel (approximately 100,000 fiber tracks). Fourth row: axial whole-brain track density maps sequentially at 2.5 mm, 1.25 mm and 0.5 mm isotropic voxel size generated with 9 seeds per voxel (approximately 300,000 fiber tracks).]
Figure 4. Track density maps generated with nine seeds per voxel (approximately 300,000 fiber tracks) at (a) 2.5 mm isotropic resolution (original image resolution), (b) 0.5 mm isotropic resolution. The red arrows indicate the genu of the corpus callosum and the yellow arrows indicate an intrinsic artifact caused by deterministic approach at fiber crossing areas.

Figure 5 shows the effect of the number of seeds per voxel. The images were achieved at 0.5 mm isotropic resolution, i.e. 125 times smaller than the original isotropic voxel resolution. To accentuate the contribution of the seed numbers in the image quality, we compared the TD maps produced with one seed per voxel with TD images obtained by 9 seeds per voxel in Figure 5. The results showed that increment in the seed number per voxel led to apparent visual improvements in the sense that the continuity information of structures was provided with meaningful coherence in terms of anatomical composition of the brain.

Figure 6 demonstrates the consequences of employing different number of diffusion gradient encoding directions on TD maps. The maps were generated at 0.5 mm isotropic resolution. Scanning with increased number of diffusion directions provided extended data to better characterize the real diffusion within a voxel and hence increased the information content of the map.

In this study, second ordered statistical properties (contrast, energy, entropy) of TD maps were calculated for different seed numbers and different resolutions. The cropped regions chosen for this analysis are shown in Figure 7. The results of the analysis were confirmed for the accuracy via visual inspection by a radiologist and anatomist of at least 8 year experience. Table shows that as the resolution increased contrast and entropy measures from TD images decreased. However the increase in resolution resulted in increase in the energy measures.
Figure 6. Track density maps generated with three seeds per voxel (approximately 100,000 fiber tracks) at 0.5 mm isotropic resolution from DWI images scanned with (a) 6 DWI-directions, (b) 64 DWI-directions.

Figure 7. The cropped regions for TD images generated with nine seeds per voxel (approximately 300,000 fiber tracks) for statistical analyses at (a) 2.5 mm isotropic resolution, (b) 1.25 mm isotropic resolution, (c) 0.5 mm isotropic resolution.

Table. Statistical properties of the track density maps.

<table>
<thead>
<tr>
<th>Number of seeds per voxel</th>
<th>Property</th>
<th>2.5 mm × 2.5 mm</th>
<th>1.25 mm × 1.25 mm</th>
<th>0.5 mm × 0.5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>One seed</td>
<td>Contrast</td>
<td>0.4572</td>
<td>0.2104</td>
<td>0.1471</td>
</tr>
<tr>
<td></td>
<td>Energy</td>
<td>0.2827</td>
<td>0.4887</td>
<td>0.6967</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>5.3363</td>
<td>3.7614</td>
<td>1.8225</td>
</tr>
<tr>
<td>Three seeds</td>
<td>Contrast</td>
<td>0.4500</td>
<td>0.1870</td>
<td>0.1119</td>
</tr>
<tr>
<td></td>
<td>Energy</td>
<td>0.2779</td>
<td>0.4518</td>
<td>0.6899</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>5.4106</td>
<td>4.6711</td>
<td>2.9454</td>
</tr>
<tr>
<td>Nine seeds</td>
<td>Contrast</td>
<td>0.4278</td>
<td>0.1769</td>
<td>0.0724</td>
</tr>
<tr>
<td></td>
<td>Energy</td>
<td>0.2961</td>
<td>0.4703</td>
<td>0.7700</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>5.3285</td>
<td>4.6922</td>
<td>3.8310</td>
</tr>
</tbody>
</table>

4. Discussion
In this study, we implemented an algorithm to calculate TD images at higher resolution based on streamline fiber tracking and achieved a significant resolution improvement on diffusion tensor images obtained at 1.5 T MRI scanner. We measured that the accuracy and reliability of TD maps depend on parameters such as the number of seeds per voxel used in fiber tracking algorithm, number of diffusion directions in the DWI protocol, and final voxel size of the reconstructed TD images. Increasing the number of seeds and number of diffusion
weighting directions led to improvements in the delineation of brain structures on the TD images. The finer distinction of brain structures was obtained with the smallest final voxel size and the highest number of seeds per voxel. These results were consistent with the findings at 3 Tesla [7]. We observed that statistical properties of the TD images showed overall consistency with visual investigation where contrast and entropy measures of TD images decreased but energy measure increased at higher resolution.

The accurate fiber tracking is an important step in obtaining a TDI map. We used a streamline fiber tracking method with fourth-order Runge-Kutta for track propagation and a deterministic approach. When compared with the literature that utilized probabilistic fiber tracking [7], we qualitatively observed that our TD images based on deterministic fiber-tracking algorithm seemed to serve lower quality than the ones based on probabilistic fiber tracking. TD images based on deterministic fiber tracking suffered from an artifact appearing as dark streak lines specifically on regions where fibers are crossing or merging (Figure 4, yellow arrow). These artifacts were mainly caused by the use of diffusion tensor model [16]. Diffusion tensor provides a single orientation in a voxel, thus gives a false representation in case of a crossing fiber within a voxel. Calamante et al. used constrained spherical deconvolution (CSD) method to resolve crossing-fibers [7, 26]. If tensor model is insisted, probabilistic tractography approach can be a better choice for TDI.

In our study, we enhanced the resolution of TD images from 2.5 mm to 0.5 mm along the three dimensions. We observed that enhancement of resolution results in deterioration of GLCM contrast measure compared to the map at original resolution if same number of tracks are used (Table). This could be because the track density per voxel in the final map decreases as the voxel size gets smaller, i.e. the fibers within the original voxel split into subvoxels. The GLCM analysis also showed that when same number of fiber tracks was used, the enhancement of resolution made an improving effect on energy, but a decreasing effect on entropy similar to contrast. We note that contrary to our results, improving both the resolution and the contrast would be possible if a substantial number of tracks is generated as shown by Calamante et al. [7].

We also observed that in case of insufficient number of fibers, continuity information could not be provided and, thus the anatomically true brain structure cannot be reconstructed at high resolution TD images (Figure 5). This observation suggests the use of a higher number of fibers and hereby a higher number of seed points within a voxel.

TD imaging has potential to be useful in clinics such as better delineation of white matter lesions and tumors at high resolution for investigation before surgical treatment [27–29]. The details shown by the high-resolution TD images are not visible on standard DTI maps such as FA [11]. The best result is assumed also at 1.5 T when the highest number of seeds is used for the smallest voxel size (Figure 3). Thus, TD represents a value for a semiquantitative parameter based on the imaging protocol and tractography method.

This study has some limitations. We present data only from two volunteers. We used Mathematica 9 (Student Edition) as the programming platform to reconstruct TD images. This was not a good choice considering the intrinsic computational nature of the method. Without any parallelization, the total computation time for 0.5 mm × 0.5 mm × 0.5 mm TD image using 9 seeds was 7 days on a 2.60 GHz Intel Xeon E5-2670 CPU. This outcome suggested the use of more effective programming languages such as C++ or faster software packages such as MRTrix (Brain Research Institute, Melbourne, Australia, http://www.brain.org.au/software/) as reported in reference [7].

Based on our experience, a quality TD image necessitates high number of diffusion directions. Figure 6 shows two TD images that were obtained with different number of diffusion directions while everything else was same in two DWI protocols. One could argue that SNR was different between two DWI acquisitions since
more images were acquired in the acquisition with larger number of diffusion directions. We admit this as a limitation. However it could safely be claimed that more number of diffusion directions contribute in the better quality of TD images. We note that larger number of diffusion directions extends the scan time (about 30 min for 64 directions in our study). To prevent unbearably long scan times particularly for the 64 directions, the number of signal averages (NSA) could be set small. However this results in low SNR. Thus, data acquisition with sufficient SNR and large number of diffusion directions necessitates an optimum protocol at 1.5 T. During reconstruction of TDI images, employing more number of seeds per voxel is a good strategy if deterministic approach is preferred. This will cause long computation time but can be compensated if modest improvement in the resolution of the TD image is expected. We conclude that the reconstruction of TD images at 1.5 T field strength is possible using right trade-offs in data acquisition and processing. The TDI maps at 1.5 T have the capability of delineating the substructures of the brain.

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