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Diffusion Tensor-Based Fast Marching for Modeling Human Brain Connectivity Network

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Abstract

Diffusion tensor imaging (DTI) is an effective modality in studying the connectivity of the brain. To eliminate possible biases caused by fiber extraction approaches due to low spatial resolution of DTI and the number of fibers obtained, the fast marching (FM) algorithm based on the whole diffusion tensor information is proposed to model and study the brain connectivity network. Our observation is that the connectivity extracted from the whole tensor field would be more robust and reliable for constructing brain connectivity network using DTI data. To construct the connectivity network, in this paper, the arrival time map and the velocity map generated by the FM algorithm are combined to define the connectivity strength among different brain regions. The conventional fiber tracking-based and the proposed tensor-based FM connectivity methods are compared, and the results indicate that the connectivity features obtained using the FM-based method agree better with the neuromorphical studies of the human brain.

Keywords

diffusion tensor imaging; fast marching; brain connectivity analysis; fiber tracking; tractography

1. Introduction

One of the tasks of neuroscience is to understand inter-neuronal connectivity and interregional connectivity across the human brain [1]. Axons connecting about 100 billion neurons in the human brain and carrying signals to, from, and within the brain are the key factors to study brain network connectivity. However, no structural human brain networks have been mapped at the cellular resolution in vivo due to the limitation of current neuroimaging techniques. On the other hand, at the inter-regional connectivity level, through detecting the white matter neural bundles, we can study the connections among different neuroanatomical regions. Armed with the network system theory, along with recent advances in neuroimaging, increasing number of recent reports suggested that the brain behaves like a complex small-world network [2–7].

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In the literature, several anatomical networks of mammalian animals, such as cats and primates, have been constructed using morphology and systemic collection methods [8–10]. In these works, histological dissection and staining, degeneration and axonal tracing methods were used to construct cerebral white matter connections. Research on these networks showed that the two major features characterizing the organization of mammalian animal brain networks are cliquishness and cooperation: (1) brain evolutes to highly functional compartmentalization, which modularizes and accelerates high-level information processing; and (2) different functionally segregated regions are effectively connected together through neural fiber bundles to deal with complex tasks beyond the capability of individual compartments.

These advances of animal brain network analysis stimulate the research on human brain network. For example, neuroanatomical (or histological) methods [11,12] were used to analyze the structure of the white matter. However, neuroanatomical methods are time consuming, and the reliability is dependent on the skills and experience of individual researchers. It is further hampered by relatively lengthy post-mortem delays of the tissue and the scarceness of human brain tissue available for anatomical study. Moreover, we cannot conduct the patient-specific connectivity analysis in vivo using these post-mortem techniques.

With the aid of advanced brain imaging technologies, such as functional MRI (fMRI) [13,14], electroencephalography (EEG), magnetoencephalography (MEG) [15], or multielectrode array (MEA), different aspects of brain neural connectivity networks and their characteristics can be investigated with graph theory. However, the poor spatial resolution and task-dependence nature of these functional imaging technologies limit their power in studying the brain connectivity network as a whole.

Diffusion Tensor Imaging (DTI), a non-invasive neuromorphical imaging technique to obverse 3-D white matter architectures, can be used to detect network connectivity information about human brain at different time points and under different pathophysiological conditions [16–18]. Tractographic methods have been developed to reconstruct and visualize the neural fiber bundles in vivo [19,20]. In order to quantitatively study the brain connectivity network, fiber tracking results have been employed to define inter-region connectivity strength. [21] used the number of fibers between any two brain regions to measure the neuro connectivity strength, after applying an orientation density function (ODF)-based tractography method. [22] first utilized an iterative algorithm to find the most probable trajectory between any two nodes and then applied anatomical connection probabilities (ACP) to measure the connectivity strength between two brain regions. [23] constructed the popularity-based anatomical network from a large number of datasets, comprising a streamline-like tractography method and statistics-based nonparametric sign test.

These methods use the number of fibers or metrics derived from the extracted fiber bundles to measure the connectivity strength between neuroanatomical regions. Thus, the construction of human brain neuroconnectivity network is dependent on the results of fiber tracking, which might be biased by the assumptions of the tracking algorithm, low image spatial resolution, and the number of fibers obtained. For example, Fig. 1 shows that the fibers extracted from DTIStudio [24] only followed one direction in a known fiber crossing regions. In terms of network modeling, in [21,23] the brain network was treated as a binary network, which ignores the connectivity strength information among different brain regions. In [22], the binary network was extended to weighted network. However, only the lowest weight of arcs belonging to the most probable path was utilized as the connectivity strength measure, which is not reliable in eliminating image noise.

In summary, it is necessary to develop an alternate and robust method for brain connectivity analysis. Our rationale is that the connectivity extracted from the original tensor field could be more robust and suitable for analyzing DTI connectivity [25]. Previously, the methods in [26–28] applied the fast marching (FM) technique to derive connection paths between brain regions by using the principal eigenvectors of the tensors. In this paper, we extend the algorithm and model the connectivity between different anatomical regions by performing tensor-based FM using the whole tensor field rather than just the principal directions. The connectivity strength between two anatomical regions is then calculated based on the time map and velocity map generated by the FM algorithm.

In our approach, an elastic registration is first used to align a 3-D neuroanatomical atlas onto the DTI space to label various brain regions automatically. Then, an improved tensor-based FM algorithm is used to simulate the diffusion dynamics from one region to another so as to calculate the connectivity strength among different brain regions. The hypothesis is that faster diffusion along the tensors between anatomical regions indicates stronger white matters fiber bundle connectivity and vice versa. The connectivity strengths among sixtyeight selected anatomical regions overlapping the cortical surface and subcortical tissues are quantified to construct the brain connectivity network. Finally, topological analysis of the connectivity network is performed. Since no fiber tracking is necessary in this algorithm, we can eliminate the measurement errors by using tractography techniques. It is believed that the new measured region-to-region connectivity strength captures more global neural connectivity information and reflects the neuroanatomical connectivity network more realistically than conventional fiber tracking-based methods.

In the first experiment, the performance of the proposed tensor-based FM algorithm is evaluated on simulated tensor images. In the second experiment, the results of brain connectivity were compared between the fiber tracking-based method and the proposed approach using human brain data. Our experimental results indicate that the connectivity obtained from the proposed algorithm matches the neuroanatomical knowledge known in the literature better than the fiber tracking-based methods. Finally, we verified the small-world characteristics of the reconstructed neuroconnectivity network.

2. Method

2.1. The Analysis Framework of Neuro-connectivity Network

A schematic diagram of the proposed brain connectivity network analysis is illustrated in Fig. 2. This framework uses the FMRIB Software Library (FSL) FMRIB's Diffusion Toolbox (FDT) [29] for eddy current correction and the DTIStudio [24] for tensor calculation and channel image generation. It then employs the multi-channel DTI segmentation method in [30] to perform tissue segmentation based on DTI data. Afterwards, a high-dimensional registration method is adopted to register the brain atlas onto the DTI data [31,32]. The brain atlas used in our study is the Montreal Neurological Institute (MNI) atlas. In this way, we obtain a map of labeled WM and GM structures in the DTI space. An improved tensor-based FM algorithm [33] is used to simulate diffusion dynamics to get the connectivity strength among different brain regions. Based on the hypothesis that faster diffusion between brain regions indicates stronger white matter fiber bundle connectivity and vice versa, the connectivity strength among sixty-eight selected brain regions overlapping the cortical surface and the subcortical regions are quantified to construct the brain neuroanatomical connectivity network. Finally, topological analysis is performed on the brain connectivity network.

In the following subsections, after briefly introducing the tissue segmentation and anatomical region labeling, we present the FM algorithm for brain connectivity analysis.

2.2. Tissue Segmentation and Anatomical Region Labeling

The DTI segmentation algorithm in [30] is employed to segment the image into different tissue types. The idea is to classify the brain into two compartments by utilizing the tissue contrast existing in a single channel; for example, apparent diffusion coefficient (ADC) image can be used to separate cerebrospinal fluid (CSF) and non-CSF, while the fractional anisotropy (FA) image can be used to separate WM from non-WM tissues. Other channels, such as eigenvalues of the tensor, relative anisotropy (RA) and volume ratio (VR), can also be used for tissue segmentation. Finally, the STAPLE algorithm [34] is used to combine these two-class maps to obtain a complete segmentation of CSF, GM, and WM.

After segmenting DTI images, we employ a hierarchical warping method to register the atlas onto each subject image and automatically label the anatomical regions [31,32]. Fig. 3 shows an example of this procedure. Fig. 3 (a) is the FA image. Fig. 3 (b) provides the tissue segmentation map, and Fig. 3 (c) shows labeled neuroanatomical regions. In our work, sixty-eight regions overlapping the cortical surface and subcortical tissues are automatically labeled for constructing of the brain connectivity network.

2.3. Tensor-Based Fast Marching

In DTI images, the diffusivity of water molecules at a location is characterized by a tensor. Fig. 4 shows the principal directions of DTI overlaid on the color-coded FA map. Regular tractography method will follow the principal directions to extract fiber tracts. Thus, the brain connectivity strength dependent on the results of fiber tracking may not be stable in regions where fibers cross or branch out.

To remedy this problem, we hypothesize that the connectivity strength extracted from the original tensor field could be more robust and suitable for network analysis. Therefore, rather than performing fiber tracking along the principal directions, an improved FM algorithm is performed on the whole tensor field. Then, the connectivity strength among brain regions is calculated by combining the diffusion time map and velocity map. We will introduce how to get the time map and velocity map and the connectivity strength subsequently in detail.

As shown in Fig. 5, first the evolution of a front starts from the current voxel and marches according to the neighboring tensors. Suppose at a specified time point the evolving front comes to point i, the marching speed from i to another neighboring candidate point j outside the evolving front can be defined as,

$$\nu_{i \to j} = \eta \nu_i^{tensor}(\mathbf{r}) + (1 - \eta) \nu_{i \to j}^{tentual}(\mathbf{r}', \mathbf{r}), \tag{1}$$

where $v_i^{tensor}(\mathbf{r})$ is the major evolution speed calculated from the tensor at the current point *i*

toward point *j* along direction $\mathbf{r} : i \to j$, and $v_{i \to j}^{\text{inertia}}(\mathbf{r}', \mathbf{r})$ is the evolution speed of the previous marching step projected onto the current marching direction. In this work η is set to 0.9, so that 90% of the evolution speed is calculated from the current tensor.

$$v_i^{tensor}(\mathbf{r}) = w \mathbf{r}^T D_i \mathbf{r},\tag{2}$$

where D_i is the tensor at current point *i*, and *w* is the coefficient to eliminate fast evolution within cerebrospinal fluid (CSF) and gray matter (GM). Thus, *w* is calculated according to *FA* values as $w = 1/(1 + \exp(-\alpha \cdot (FA - \beta)))$. α and β are constants to control the effects of FA. α

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controls the slope of the Sigmoid function ($\alpha = 50$) and β is set as the FA threshold ($\beta = 0.3$). When the *FA* value is smaller than 0.3, it is more likely that the voxel is in CSF and GM.

The second term in Eq. (1) is the inertia term used to smooth the evolution procedure,

$$\nu_{i \to j}^{\text{inertia}}(\mathbf{r}', \mathbf{r}) = \nu'(\mathbf{r}' \cdot \mathbf{r}), \tag{3}$$

which reflects the projection of the previous speed v' onto the current direction. Fig. 6 illustrates the marching speed in one slice. To facility the observation, we project the 3D speed into X, Y and Z axis, corresponding to the Fig 6(a)–(c) respectively.

According to the FM method, the arrival time of the evolution front and the evolution speed are associated by the Eikonal equation [33],

$$|\nabla T|V=1. \tag{4}$$

 $\nabla \tau$ represents the gradient of the arrival time of the evolving surface, and ν denotes the speed of the marching front. Eq. (4) says that the gradient of arrival time surface is inversely proportional to the speed of the front. According to (Parker et al., 2002) the arrival time τ_j of the front at point *j* can be approximated as,

$$T_j = T_i + d(i, j) / \nu_{i \to j}. \tag{5}$$

 τ_i is the arrival time at point *i*, d(i, j) is the distance from point *i* to point *j*, and $v_{i \rightarrow j}$ is the marching speed determined in Eq. (1). For each neighboring point of *i* outside the evolving front, we calculate its arriving time using Eq. (5), and the one with the least arrival time is then updated as the new front point.

Fig. 7 shows an example of the diffusion time map calculated from a given voxel, where red indicates small arrival time, and yellow indicates large arrival time. It can be seen that the evolving front aligns well with the neural fibers, thus the time map can reflect the microstructure situation of tissues around the selected voxel.

With the tensor-based FM method, we not only obtain the arrival time map originating from a seed voxel or seed ROI, but also record the front evolutionary track, which shows how the evolving front advances to connect the target region from the initial region. Therefore, if the length of the track at voxel *i* is ι_i , the length of the track at voxel *j* will be,

$$L_j = L_i + |r_i| \,, \tag{6}$$

and the average speed along the track can be calculated as

$$V_j = L_j / T_j. \tag{7}$$

Fig. 8 shows an example of the resultant diffusion time map and velocity map using the tensor-based FM method. The green zone, indicated by the arrow, is the seed region where the FM algorithm starts. Here, the seed region is selected in the WM adjacent to the middle frontal gyrus. It can be clearly seen that the arrival time is smaller and the velocity is higher for regions connected to the seed region through fibers. For example the contralateral middle

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front gyrus and the ipsilateral occipital lobe are connected with the middle frontal gyrus through corpus callosum and association fibers, respectively. Thus the time maps on these regions are smaller, and the velocity values are larger. This observation inspires us that by combing the time map and velocity map carefully, we can measure the connectivity strength between two brain regions.

To calculate the network connectivity strength between two anatomical regions, we can set one as the seed region and calculate the average of the time map and the velocity map in another region as follows,

$$S_{M,S} = \frac{1}{N} \sum_{j \in M} V_j, \tag{8}$$

and

$$T_{M,S} = \frac{1}{N} \sum_{j \in M} T_j,$$
(9)

where *N* is the number of voxels in region *M*, v_j is the velocity of one voxel *j* in region *M*, r_j is the diffusion time of voxel j, and s stands for the seed ROI. Therefore, given a seed region, the average arrival time values and velocity values of other anatomical structures can be calculated. Next, we will describe how to construct a weighted connectivity network by simultaneously considering the average arrival time and velocity in Section 2.4.

2.4 Calculating the Neuro-Connectivity Matrix

The whole brain connectivity network can be constructed as follows:

Step 1: Set the ROI as one of the sixty-eight automatically labeled neuroanatomical regions (names are shown in Fig. 11);

Step 2: Set the ROI as the seed region and perform the proposed tensor-based FM algorithm toward the whole brain and generate the corresponding time and velocity maps.

Step 3: Calculate the average arrival times and the average velocities for all the other sixty-seven regions.

Step 4: Iterate step 2 and step 3 for all the sixty-eight regions. Therefore, for each brain image, we can get the matrices of the average time values and velocity values, respectively.

Fig. 9 provides an example of the results, where Fig. 9 (a) shows the matrix defined by the average time values, and Fig. 9 (b) shows the matrix using the average velocity values. Nevertheless, neither the matrix calculated from the average time values nor the one calculated from the average velocity values can be used to precisely define the connectivity strength among brain regions. The arrival time is dependent on not only the speed but also the distance, but in fact, the information transformation along white matter fibers might not be that sensitive to the length of fibers [35]. Also, evolving front can always grow from one region to another by crossing a "bridge" region, even there is no actual neural fiber, and the average velocity along that track might be large. Thus, we combine the diffusion time and velocity maps to define the neural connectivity strength. Our hypothesis is that the connectivity strength between two brain regions should be stronger if the average time is

3)

smaller and if the average velocity is larger. Therefore, the connectivity strength can be defined by combing time and velocity values as follows:

$$C_{m,n} = \frac{S_{m,n}}{1 + \exp(k(T_{m,n} - t))}.$$
(10)

Eq. (10) provides a new metric for measuring the connectivity strength through moderating the velocity value with arrival time. The purpose of this moderation is to remove those false positive connections caused by the "bridge" region because such connections usually have relatively large average time value. k and t control how time affects the strength. The sparsity of the connectivity network can also be adjusted by changing these parameters. In Section 3.2, we will give the definition of the degree of network sparsity in detail. It should be noted that, there is no biological evidence reported for Eq. (10), which is our attempt to create a more reasonable metric for connectivity strength metrics among brain regions through combining the time values and velocity values. Owing to the lack of convincing validation method, currently there has been no golden standard of connectivity network in the human brain.

3. Results

3.1 Phantom Studies

To evaluate the performance of the proposed algorithm, the simulated phantom dataset from the School of Psychology, Cardiff University, UK was used. The DWI images were simulated with the following parameters: matrix size $150 \times 150 \times 16$, 30 diffusion directions, b = $1000 \text{ s} / mm^2$, TE=90ms. Additional detailed information can be found from http://cubric.psych.cf.ac.uk/commondti/CommonDTIDataset/Common DTI Dataset-Welcome.html. Two kinds of datasets, the curve crossing and orthogonal crossing trajectories were used for this experiment. Fig. 10 shows the phantom data and the experiment results. Each seed ROI (red line in the first column) is composed with pixels in one circularity perpendicular to the simulated tracts. FM algorithm starts from the seed ROIs and the marching speed is calculated from the tensor information, as described in Eq. (1). The images in the second column show the evolution speed in the horizontal direction and in the third column display the evolution speed in the vertical direction. The fourth column provides the diffusion time map, and the fifth column represents the velocity map.

It can be seen from the results that for the crossing tracts with small angle in the first row, the marching front evolves towards two directions simultaneously after going through the crossing region. For the crossing with a large angle, such as orthogonal crossing tracts in the second row, the front wave can go through the crossing regions and keep the evolution direction. Because these two simulated datasets are corresponding to two common situations found in human neuroanatomy, such as fiber branching and crossing, we expect similar performance in dealing with real DTI datasets.

The problem with the fiber tracking-based methods is that the fiber tracts can only follow the principal directions such that it always follows one direction regardless of the crossing angles. The FM-based connectivity analysis calculates regional connectivity based on the whole tensor field and thus can overcome this problem.

3.2 Connectivity Matrix on Real Subject Data

The proposed human brain connectivity network construction method was also applied to five human brain DTI data. The DTI data was acquired on a Philips 1.5T Intera using 15-direction diffusion encoding, with b0=0 and b1=860 s/mm². One example of the

connectivity matrix is shown in Fig. 11, and the names of the sixty-eight brain regions are listed for reference. In this study, k is set as 20 and t as 0.5. From Fig. 11, we can see that the ipsilateral connectivity is notably stronger than the contralateral connectivity. To facilitate the observation of the connectivity map, the data of the second row and the 57^{th} row of the connectivity matrix, which are corresponding to left middle front lobe gyrus and left thalamus respectively, are selected and mapped onto the GM/WM (grey matter/white matter) surface. Fig. 12 and Fig. 13 illustrate the results. It can be seen from both figures that the regions with strong connections between the left middle front lobe gyrus and the associating tracts are: the contralateral front lobe (corpus callosum), the precentral gyrus, the ipsilateral front lobe (U-fiber connecting adjacent gyri), the temporal lobe (uncinate fasciculus), the precentral and postcentral gyrus (superior fronto-occipital fasciculus, superior longitudinal asciculus). Most of contralateral regions have strong connections with the left thalamus.

We compared our algorithm with the fiber tracking-based method. In [23], the authors first used DTIStudio to do the fiber tracking and then constructed the cortical neuroanatomical network. Here, we used the same method and the same tools to implement the fiber tracking with FA threshold set to 0.30 and angle turn threshold 70°. Based on the number of fibers between any two brain regions, the connectivity network is constructed, as shown in Fig. 14 (a). Totally, there are 764 connections, the sparsity degree of this connection matrix is 16.8% and is much scantier than the pathologically-confirmed sparsity degree of the known cat cortical network (30.1%) [8]. On the other hand, the sparsity degree of FM-based method is 33%. Here, the sparsity degree of a network is defined as:

$$d = \frac{1}{P(P-1)} \sum_{\substack{m,n \\ m \neq n}} C_{m,n},$$
(11)

where, $C_{m,n}$ is the connectivity strength of two brain regions and for unweighted network, $C_{m,n} \in \{0,1\}$ is the number of brain regions in the whole brain, and it is 68 in our research. m,n are the region indexes. We can see the sparsity degree calculated from the fiber tracking-based method is much smaller than that from the proposed method. The reason is that the conventional DTI-based tractography often fails to reveal those fiber tracts, which are lengthy or cross over to other main fiber tracts. For example, studies showed that the entire cortex is connected by the commissural fibers, but it is hard to find the commissural connections to the lateral areas of the hemispheres because there are massive projection fibers and long association fibers located lateral to the corpus callosum, which prevent the reconstruction tracking from penetrating these areas using conventional tractography methods [36].

To facilitate the observation of the connectivity situation based on the tractography method, the connectivity of the left middle front gyrus to other anatomic regions is mapped onto WM/GM surface, as shown in Fig. 14 (b–e). We can see that the regions with strong connections of the left middle front lobe are limited only on the contralateral frontal lobe, the ipsilateral frontal lobe and the superior temporal lobe. Compared with Fig. 12, it can be seen that only those connections with a massive tract, such as the corpus callosum, the uncinate fasciculus, et al., can be found with the tractography-based method, and lot of connections are missed. This indicates that the tractography-based method has limited ability to uncover the connectivity situation among the whole brain, and our FM based method can recover more connections than the tractography based method.

When it comes to parameters k and t in Eq. (10), the sparsity, as well as other characters of the network are heavily dependent on the choice of them. In this study, k is set as 20 and t as 0.5 so that the network sparsity is comparable with that of the cat. In order to show the effect of varying these parameters on the final connectivity network, Fig. 15 shows the sparsity of constructed network with different combinations of k and t around this setting. It can be seen that bigger k and t will generate a network with more connections among the anatomical regions.

To illustrate why the proposed algorithm is more suitable for connectivity analysis using DTI and more efficient to resolve the problems of fiber crossing and branching caused by partial volume effect (PVE), we also compared the results when only the principal vector is used in the FM, i.e., $v = \lambda \mathbf{e}$, where *e* is the principal eigenvector and λ is the largest eigenvalue. Fig. 16 illustrates the influence of different evolution speeds. It can be seen that the marching velocity generated from the whole tensors captures more authentically the neuro-connectivity as compared with the principal direction-based ones. Coming back to the results obtained in Fig. 12, the connectivity generated using the proposed algorithm is in consistent with the neuroanatomic results as in [37,38].

3.3 Characterization of Network Topological Structure

Many works have been done on the network structure analysis of the brain [4,22,39]. We calculated several network metrics to demonstrate the well-organized patterns of the human brain neuro-connectivity network, including clustering coefficient (CC) and characteristic path length (CL), using the brain connectivity toolbox (brain-connectivity-toolbox.net) [39]. A network would be considered to exhibit small-world characters, if the clustering

coefficient is much larger than that of the random network $(\gamma = \frac{CC^{real}}{CC^{rand}} \gg 1)$, and the characteristic path length is nearly equal to that of the random network $(\lambda = \frac{CL^{real}}{CL^{rand}} \sim 1)$ [39].

Namely, the small-worldness condition is that $\sigma = \frac{\gamma}{\lambda} > 1$ [40]. Fig. 17 shows the constructed connectivity matrix for all the five cases (Fig. 17(a–e)) with the proposed method, as well as the average connectivity matrix for them (Fig. 17(f)). Table 1 shows the network parameters, and average value of σ is 1.35, which demonstrate the small-worldness of the constructed human brain neuro-connectivity network. The results indicate the human brain behaves like one well-organized system with good local connectivity and effective interregion communication. It should be noted that the value of σ varies much in different studies. For example, in [6], it ranges from 1.30 to 2.18, and in [22], σ ranges from 1.37 to 2.04.

4. Discussion and Conclusion

Fast marching methods are commonly used to find the optimal or minimum cost track, and they also act as the basis for fiber tracking in DTI field [26,27]. Herein, we used this method to calculate the connectivity strength between any two brain regions. Since the marching procedure is based on the whole tensor field, not only the principal directions, the evolving front can always grow from one region into another by crossing a small unconnected region, and the average velocity along that track might be large. For example, Fig 6 (b) shows a strong connectivity between left middle frontal gyrus and right temporal lobe (green circle region) if we just use the velocity as the metrics of connectivity strength. Therefore, the velocity map only reflects one aspect of the connectivity. On the other hand, the diffusion time map also indicates how two regions are connected each other. Since the arrival time is an accumulated value along the evolving tracks, two connected regions with longer distance

can have relatively a larger average time. Thus, combining the time map and velocity map, we can get a reasonable calculation of the connectivity strength. This work is one preliminary attempt to create more reasonable connectivity strength metrics among brain regions through combining the time map and velocity map.

Although the proposed FM method can provide abundant information about the connectivity situation among brain regions and control the false-negative as much as possible, it is still likely to induce the false positive connection. Our next step is to evaluate the consistence of our method with specific known connectivity networks obtained from other image modalities, such as fMRI. DSI (diffusion spectrum imaging) [41], Q-ball image [42], and higher imaging resolution of DTI will also be investigated to help construct more comprehensive and robust neural connectivity networks. For example, for Q-ball image, multiple fiber directions within a single voxel can be inferred, and in this case the marching front evolves faster only along the tract directions, as opposed to evolving in all directions with similar speed, which would occur in fiber crossing regions with DTI. It is believed that such advantage of Q-ball imaging can help to reduce the false positive caused by the "bridge" regions using the DTI approach.

The parameters k and t in Eq.(10) are of great impact on the construction of network. Own to the poor knowledge of human brain connectivity information and the lack of gold stand of connectivity network, it is not trivial to optimize these parameters. But when applying the proposed method on neuropathology associated diseases and comparing them with normal controls, it would be possible to optimize the parameters in the feature selection and classification training stage in order to better separate patient data from the matched controls.

We used the Montreal Neurological Institute (MNI) atlas as a reference map for brain parcellation, and totally 68 brain regions were considered for the construction of the connectivity network. The accuracy of the brain parcellation algorithm certainly will have a large influence on the accuracy of white matter fiber network reconstruction. Although the hybrid volumetric and surface warping method used in this paper has reasonably good performance in parcellating human brains, improved brain parcellation and recognition algorithms in the future would further improve the quality and robustness of the reconstructed network, such as identifying more nodes in the network and enhancing the precision of the measurement of the connectivity strength via better segmentation and recognition of cortical structures following the cortical folding patterns [43].

In conclusion, we proposed a diffusion tensor-based FM approach to construction and analysis of the brain connectivity network. Given the relatively low resolution of DTI and limited ways to validate the tractography results, conventional fiber tracking-based connectivity analysis might be biased by the assumptions of fiber tracking, poor image resolution, and the incorrect number of fibers extracted. The proposed connectivity extracted from the original whole tensor field has been shown to be more robust and suitable for analyzing DTI connectivity than the conventional tractography-based method. The comparative experiments using both simulated and real human DTI data indicated that the neuromorphical studies of the human. The diffusion tensor-based FM algorithm can also be applied to investigate the brain connectivity between normal subjects and disease groups relating to abnormal network distribution, including autism spectrum and pervasive developmental disorders.

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Figure 1.

Illustration of the shortcoming of fiber tracking-based connectivity analysis. (a) T1-weighted image; (b) FA image; (c) three-directional color-coded FA images; (d) fiber tracking results; and (e–h) the respective enlarged images of (a–d). Fig. (e) illustrates the actual connectivity known from neuroanatomical studies [37,38], however, the fiber tracking method [20] mistakenly followed one direction in the fiber closing regions as shown in (h).

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Figure 2.

A schematic framework based on diffusion tensor-based fast marching for brain fiber connectivity analysis. After automatically segmenting DTI images and labeling the anatomical regions of an input data, the tensor-based fast marching algorithm is performed to determine the connectivity strength among different neuroanatomical regions. Brain connectivity network can be reconstructed for further statistical analysis.

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Figure 3.

An example of the tissue segmentation and anatomical region labeling results. (a) FA image; (b) tissue segmentation map; and (c) labeled anatomical brain regions.



Figure 4.

The principal vector color-coded by FA map. (a) The principal vector map color-coded by FA, and (b) the enlarged region of the rectangle box in (a). Red indicates large FA; and blue indicates small FA.





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(d)





Figure 6.

The speed map along each axis. (a) and (d) are the speed maps along x-axis (left-right) direction; (b) and (e) are the speed maps along y-axis (anterior-posterior) direction; (c) and (f) are the speed maps along z-axis (superior-inferior) direction. The top row illustrates the axial view while the bottom line shows the coronal view. Bright indicates large speed; and dark stands for small speed.



Figure 7.

The diffusion time map derived from a given seed voxel. (a) – (e) illustrate the evolution of the marching front (the boundary of the blue region) at different iterations from the seed point; arrow in (a) points to the seed point. It can be seen that the front moves quickly in the direction along the fibers; (f) the colored diffusion time map generated from the tensor-based fast marching algorithm. The color map shows the values of the arrival time at each voxel starting from the seed point.



Figure 8.

The diffusion time map and the velocity map for middle frontal gyrus. (a) Diffusion time map for axial view; (b) diffusion time map for coronal view; (c) velocity map for axial view; and (d) velocity map for coronal view. Yellow arrow points to the ROI.

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Figure 9.

(a) Connectivity maps calculated from the diffusion time maps; and (b) connectivity map calculated from the velocity maps. Label numbers are list in Fig. 11.

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(a)	(0)	(c)	(4)	(4)
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Figure 10.

Fast Marching-based brain connectivity analysis using phantom dataset. Two kinds of data are selected for the simulated experiments. (a)–(e): Curve crossing; (f)–(j): orthogonal crossing; In the first column, (a) and (f) show the FA maps of these two datasets under different projections; second column (b) and (g) display the speed maps in X-direction; third column (c) and (h) show the speed maps in Y-direction; fourth column (d) and (i) show diffusion time maps; and fifth column (e) and (j) illustrate velocity maps.

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CC Cingu.R Cingu.L Putamen.R Putamen L Thalamus.R Thalamus L Caudate R Caudate.L Brain_stem Insula.R Lingual.R Tem.Pole.R Infer.Tem.R Mid.Tem R Sup.Tem.R Parahipp.R Cuneus.R Uncus.R Lat.Occi.Tem.R Med.Occi.Tem.R Occi.Pole.R Inf.Occi.R Mid.Occi.R Sur.Occi.R Precuneus R Postcentral R Angular.R upramarginal R Sup Parietal R Supra Lat. Front-Orbital R Medial front-Orbital R Precentral.R Medial Front.R Inf.Front.R Middle.Front.R Super.Front.R Insula.L Lingual L Tem.Pole.L Infer, Tem L Mid.Tem.L Sup.Tem.L Parahipp.L Cuneus.L Uncus.L Lat.Occi.Tem.L Med.Occi.Tem.L Occi.Pole.L Inf.Occi L Mid.Occi.L Sur.Occi.L Precuneus L Postcentral L Angular L Supramarginal L Sup.Parietal L Lat.Front-Orbital L Medial front-Orbital L Precentral L Medial Front L Inf.Front.L Middle Front L



Figure 11.

A connectivity matrix calculated from both the diffusion time map and the velocity map on the 68 anatomatical regions of the cerebral cortex; the colorbar is same with Fig. 9.



Figure 12.

A connectivity map of the left middle frontal gyrus. (a) The blue ROI shows the left middle frontal lobe gyrus; (b–e), 3-D rendering of the connectivity map on the GM/WM surface.

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Figure 13.

A connectivity map of the left thalamus. (a) The blue ROI shows the left thalamus; (b–e), 3-D rendering of the connectivity map on the GM/WM surface;

	3 6

Figure14.

Results of fiber tracking-based connectivity analysis. (a) Connectivity matrix based on conventional tractography method; (b–e), 3-D rendering of the connectivity map on the GM/ WM surface. Yellow arrow points to the ROI.

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Figure 15.

Effect of network sparsity with different parameters k and t.



Figure 16.

Comparison between the results of the fast marching methods using the whole tensor and those of the principal direction-based fiber tracking. (a) Marching speed based on the whole tensor space, (b) marching speed (left-right) based on the principle vector space, (c) velocity map based on (a), and (d) velocity map based on (b). It can be seen that in the region where fibers cross (within the yellow circles), the fast marching goes through the region in (c), but not in (d). For (a) and (b), red indicates large speed; and blue indicates small speed; for (c) and (d), white indicates large velocity; and blue indicates small velocity.

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Figure 17.

Connectivity matrices for five cases (a–e); (f) is the average connectivity matrix of those five cases.

Table 1

Network properties of the human DTI data.

Case	сc	cL	λ	۲	σ	Sparsity
0	0.31	3 5 1	1 47	1.08	1 36	0.33
(1)	10.0	10.0	1.4/	1.00	00.1	<i>cc.</i> 0
(2)	0.31	3.38	1.42	1.07	1.33	0.34
(3)	0.29	3.50	1.40	1.03	1.36	0.34
(4)	0.31	3.45	1.43	1.08	1.33	0.35
(2)	0.32	3.47	1.48	1.07	1.39	0.34
Average	0.31 ± 0.01	3.46 ± 0.05	1.44 ± 0.03	1.07 ± 0.02	1.35 ± 0.03	0.34 ± 0.01