Detecting Changes of Functional Connectivity by Dynamic Graph Embedding Learning

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Abstract. Our current understandings reach the unanimous consensus that the brain functions and cognitive states are dynamically changing even in the resting state rather than remaining at a single constant state. Due to the low signal-to-noise ratio and high vertex-time dependency in BOLD (blood oxygen level dependent) signals, however, it is challenging to detect the dynamic behavior in connectivity without requiring prior knowledge of the experimental design. Like the Fourier bases in signal processing, each brain network can be summarized by a set of harmonic bases (Eigensystem) which are derived from its latent Laplacian matrix. In this regard, we propose to establish a subject-specific spectrum domain, where the learned orthogonal harmonic-Fourier bases allow us to detect the changes of functional connectivity more accurately than using the BOLD signals in an arbitrary sliding window. To do so, we first present a novel dynamic graph learning method to simultaneously estimate the intrinsic BOLD signals and learn the joint harmonic-Fourier bases for the underlying functional connectivity network. Then, we project the BOLD signals to the spectrum domain spanned by learned network harmonic and Fourier bases, forming the new system-level fluctuation patterns, called *dynamic graph embeddings*. We employ the classic clustering approach to identify the changes of functional connectivity using the novel dynamic graph embedding vectors. Our method has been evaluated on working memory task-based fMRI dataset and comparisons with state-of-the-art methods, where our joint harmonic-Fourier bases achieves higher accuracy in detecting multiple cognitive states.

Keywords: Brain state decoding · Graph learning · Functional dynamics

1 Introduction

Empirical studies and emerging evidences suggest that human brain is a complex network with very unique topological properties [16]. Different to the definition

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of structural network [3], functional connectivity (FC) is an essential statistical concept to characterize the topological relationship between spatially separated anatomical brain regions, which is usually estimated from the BOLD signals in a series of functional MRI images [8,17]. Although plenty of efforts focus on static functional brain networks by assuming FC remain stationary during a period of data collection (aka static FC), the interest is shifting to study the dynamic changes of FC (aka dynamic FC), which might provide more insight into the fundamental properties of brain networks [10,11,19].

In the past decade, there are mainly two branches of approaches for the characterization of function dynamic: (1) temporal change points model [6,18] and (2) sliding window technique [1,5,7]. Dynamic connectivity regression (DCR) method [6] is a typical example of temporal change points model, which first partitions the time course into intervals and then estimates connectivity networks within each interval using statistical inference. Dynamic connectivity detection method [18] further improved the DCR method by utilizing a sparse matrix estimation approach and a hypothesis testing procedure to detect change points. Although change points models provide a potentially powerful method for tracking dynamic FC, they are highly dependent on a greedy partitioning scheme for determining change points and the corresponding FC states. Compared to these statistical models, sliding window approach (SW) is computationally more efficient which essentially identify changes of FC based on the clustering result of FC matrices across sliding windows. However, SW is sensitive to the window size and external noise in BOLD signals, resulting in less replicable results [9,13].

Most of current state-of-the-art change detection methods use the attributes derived from BOLD signals. Due to the technical difficulty in imaging resolution and signal acquisition, the low signal-to-noise ratio in BOLD signals is the major difficulty in detecting FC changes [13]. Since brain functions are supported by the collaboration of multiple regions, functional network exhibits more connectivities than structural network. Such high node-to-node dependency in the network also challenges the accuracy of change detection. In this regard, we propose to find a new putative attribute descriptor to alleviate the noise and redundancy issue of directing using the observed BOLD signals by projecting the BOLD signals to a learned spectrum domain. As show in Fig. 1, we first propose a dynamic graph learning method to jointly (1) estimate a graph Laplacian matrix based on the intrinsic BOLD signals, and (2) smooth the BOLD signals more effectively in the context of the latent functional connectivities. Since the topology of functional network is largely governed by the harmonic bases derived from the underlying Laplacian matrix, we present a novel dynamic graph embedding (displayed in the middle of Fig. 1) to capture the fluctuation pattern at each time point using a set of orthogonal harmonic-Fourier bases for the individual network. We further integrate our dynamic graph embedding into a classic time series clustering method and automatically detect the changes of functional connectivity without knowing the experimental setup of fMRI studies. Experiments and comparison with state-of-the-art methods show that the proposed method can achieve significant performance improvement in identify changes of FC on task-based fMRI data involving working memory.

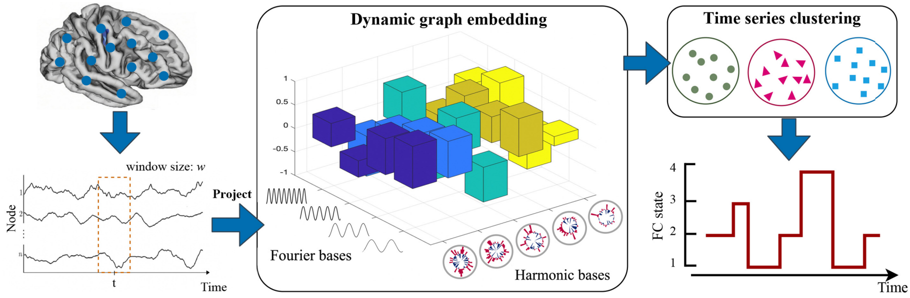


Fig. 1. The novel dynamic graph embedding (middle) is formed by projecting the BOLD signals in each sliding window into a spectrum domain which is spanned by learned joint Harmonic-Fourier bases. The new dynamic graph embeddings are used to replace BOLD signals in detecting the changes of functional network by time series clustering.

2 Methods

2.1 Estimating the Joint Harmonic-Fourier Bases

A brain network can be represented as a graph structure $G = (V, W)$, where V denotes the set of N nodes and $W = [w_{ij}]_{i,j=1}^{N}$ is the corresponding $N \times N$ weighted adjacency matrix of the functional network. Here, we use $L_G = D - W$ denotes the graph Laplacian matrix, where D is a diagonal matrix defined as $D_{ii} = \sum_{j=1}^{N} w_{ij}$. Supposing we have T acquisition time points, we can regard $x_t \in R^N$ as a signal on the graph G at acquisition time t. Then a $N \times T$ data matrix $X = [x_t]_{t=1,\ldots,T}$ is used to denote the whole-brain BOLD time course by concatenating each x_t along the time T.

Given the data matrix X, we opt to establish a subject-specific spectrum domain to capture dynamic functional fluctuation hidden behind BOLD signals X, which is spanned by the Fourier bases Φ_T in the temporal domain and network harmonic bases Φ_G in the graph spectrum domain. Although there are numerous solutions of Φ_T and Φ_G, we reckon the bases are governed by the joint Eigensystem that emerges dynamic fluctuation of self-organized FCs. Specifically, the time Laplacian matrix $L_T \in R^{T \times T}$ characterizes Eigensystem of temporal domain, where XL_T describes the second order temporal derivative of X, i.e., $XL_T|_t = 2x_t - x_{t-1} - x_{t+1}$ (change between forward difference $x_{t+1} - x_t$ and backward difference $x_t - x_{t-1}$). Since L_T is fixed and circulant ($x_{T+1} = x_1$), Eigen decomposition of $L_T = \Phi_T \Lambda_T \Phi_T^{\top}$ has the closed-form solution as the orthogonal Eigenvectors $\Phi_T(t,k) = [e^{-j(2\pi(k-1)/T)t}/\sqrt{T}]_{t,k=1,\ldots,T}$ and the diagonal Eigenvalue matrix $\Lambda_T(t,t) = \lambda_T(t) = 2(1 - cos(2\pi(t-1)/T))$. It is clear that the Fourier bases Φ_T of the temporal domain are exactly the classic Fourier waves. Similarly, the network harmonic bases Φ_G is the Eigenvectors after applying SVD (singular vector decomposition) on the latent L_G.

Thus, the good estimation of latent graph Laplacian matrix L_G becomes the backbone of our method. Although it is efficient to obtain L_G by constructing the function network based on the Pearson's correlation of any two rows in X, the substantial amount of external noise in X often undermines the reliability of function network. In light of this, we propose to learn the graph Laplacian matrix from X that can express the dynamic behaviors of functional connectivity. A better understanding of the network topology also allows us to remove the noise from X more effectively which eventually facilitates the graph learning.

First, we estimate the intrinsic BOLD signals $Y = [y_t]_{t=1,...,T}$ which is required to be close to the observed X. We use the l_2-norm $\|X - Y\|_F^2$ to measure the distance between X and Y. Then we estimate L_G from the intrinsic BOLD signals Y. The following three constraints are used to turn the ill-posed optimization problem into a well-posed objective function. **(1) Temporal smoothness on Y.** Since human cognition is not supposed to change rapidly in a short time period, it is reasonable to assume each BOLD time course is smooth along time by penalizing the large change between y_t^i and y_{t+1}^i, which can be quantified as $\|Y\|_{L_T} = tr(YL_TY^\top) = \sum_{i=1}^N \sum_{t=1}^T (y_{t+1}^i - y_t^i)^2$. **(2) Graph smoothness on Y.** Instead of treating each y_t as a data array, we underline y_t in the context of the latent functional network. Thus, the i^{th} node and j^{th} node should have similar signal y_t^i and y_t^j if there is a strong FC w_G^{ij} between these two nodes. Such graph smoothness can be quantified as $\|Y\|_{L_G} = tr(Y^\top L_G Y) = \sum_{t=1}^T \sum_{ij} w_{ij}(y_t^i - y_t^j)^2$. **(3) Regularization term on L_G.** To avoid trivial estimation of L_G, we require l_2-norm on L_G and the trace norm of L_G equals to the number of nodes in the network, which prevents L_G degenerate to all zeros. By integrating above terms, the overall energy function for estimating graph Laplacian matrix L_G becomes:

$$\arg\min_{Y,L_G} \|X - Y\|_F^2 + \mu_1 \|Y\|_{L_G} + \mu_2 \|Y\|_{L_T} + \eta \|L_G\|_F^2, \ s.t. \ tr(L_G) = N \quad (1)$$

where μ_1, μ_2 control the strength of temporal and graph smoothness, and η controls the L_2-norm constraint on the graph Laplacian matrix L_G.

To solve above optimization problem, an alternating optimization approach with two steps is employed.

Smooth Signals by Joint Filter. In this step, We optimize Y by fixing L_G and L_T. The objective function of Y becomes:

$$\arg\min_{Y} \|X - Y\|_F^2 + \mu_1 \cdot tr(Y^\top L_G Y) + \mu_2 \cdot tr(YL_TY^\top) \quad (2)$$

Since all three terms in Eq. (2) are quadratic, $\widehat{Y}$ has the following closed-form solutions:

$$vec(\widehat{Y}) = (\mu_1 I_T \otimes L_G + \mu_2 L_T \otimes I_G + I)^{-1} vec(X) \quad (3)$$

where $\otimes$ is the Kronecker product operator to unify L_T and L_G. Since L_G is symmetric, we decompose the graph Laplacian L_G into $L_G = \Phi_G \Lambda_G \Phi_G^\top$, where Φ_G and $\Lambda_G(n,n) = \lambda_G(n)$ are the eigenvectors and the corresponding eigenvalues of Laplacian L_G. In graph signal processing [15], graph Fourier transform of BOLD signals is defined as $GFT(X) = \Phi_G^\top X$, and the inverse transform is

$GFT^{-1}(X) = \Phi_G X$. Thus, Eq. (3) can be understood as filtering BOLD signals X on the temporal domain and graph spectrum domain as:

$$vec(\widehat{Y}) = h(L_G, L_T)vec(X) = \sum_{n=1,t=1}^{N,T} \Phi_J h(\lambda_G(n), \lambda_T(t))\Phi_J^\top vec(X) \qquad (4)$$

where $\Phi_J = \Phi_T \otimes \Phi_G$ describes the joint harmonic-Fourier bases of the smoothing kernel. $h(\lambda_G(n), \lambda_T(t)) = 1/(1 + \mu_1\lambda_G(n) + \mu_2\lambda_T(t))$ is the parameters to further characterize the shape of low-pass filter, where the inverse of Eigenvalues in Eq. (5) indicates the preference of suppressing the high frequency part of X.

Optimize the Graph Laplacian. By fixing Y, the optimization of L_G becomes minimizing $\mu_1 \|Y\|_{L_G} + \eta \|L_G\|_F^2$. This optimization task is convex and can be solved via Alternating Direction Method of Multipliers framework [4].

Given the learned graph Laplacian L_G, the orthogonal column vectors in Φ_G form the bases of the network harmonic domain. Therefore, the joint harmonic-Fourier bases Φ_J can be formed to capture the dynamic functional changes by combining the learned harmonic bases Φ_G and the Fourier bases Φ_T, as follows.

2.2 Dynamic Graph Embedding

First, we encode a set of functional networks along sliding windows into the dynamic graph J, as a multi-layer graph shown in the right of Fig. 2. It is clear that the dynamic graph J is essentially the periodically duplicated copy of graph G at each time t, where each node is connected to itself at time $t-1$ and $t+1$. Thus, the spectrum of dynamic graph L_J is defined as a Cartesian product of the time Laplacian L_T and graph Laplacian L_G, denoted as $L_J = L_T \otimes I_G + I_T \otimes L_G$. The Eigenvector of L_J can be derived by applying Eigen decomposition to L_J as: $\Phi_J = \Phi_T \otimes \Phi_G$, which is the Kronecker product of learned Φ_T and Φ_G in Sect. 2.1. Since Φ_J is orthogonal, it is straightforward to project the intrinsic BOLD signals data Y into the joint spectrum domain as:

$$F_Y = \Phi_J^\top vec(Y) = (\Phi_T \otimes \Phi_G)^\top Y = \Phi_G^\top Y \Phi_T \qquad (5)$$

Since F_Y characterizes the dynamics of functional network under the guidance of joint harmonic-Fourier bases, we further present the dynamic graph embedding vectors for the observed BOLD signals X in three steps. **(1)** Estimate the latent graph Laplacian matrix L_G and obtain the intrinsic BOLD signals Y by optimizing Eq. (1). **(2)** Construct joint harmonic-Fourier bases Φ_J. **(3)** For each time t, we construct a sliding window centered at t. Then we yield the dynamic graph embedding vector $F_Y(t)$ for the intrinsic BOLD signals $Y(t)$ within the sliding window by $F_Y(t) = \Phi_J^\top vec(Y(t))$ by Eq. (5).

Next, we consider these dynamic graph embedding vectors $\{F_Y(t)\}_{t=1}^T$ as the input to the classic spectral clustering method and cluster them into the predefined K clusters, where each cluster consists of very similar dynamic embedding vectors. Based on the clustering result, we automatically detect the changes of functional networks by examining the transition of cluster indexes along time.

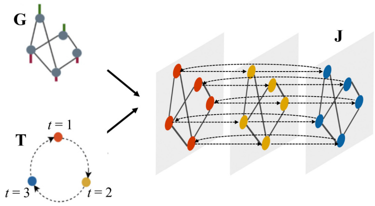


Fig. 2. The dynamic graph J is constructed by the Cartesian product of the graph G and the temporal domain denoted as a cycle graph T.

3 Experiments

In our experiment, we first evaluate the accuracy and robustness of detecting changes of functional networks using our proposed dynamic graph embeddings (dGE) in Sect. 3.1. We compare our method with two counterpart methods: (1) a recent dynamic brain state tracking method, i.e., sliding window correlation-based (SWC) method [1] which uses original BOLD signals as the input, and (2) our simplified method that only uses the learned harmonic bases Φ_G, denoted by (GE). The optimal parameters of μ and η are selected using cross validation strategy. The number of clusters K is determined by utilizing silhouette criteria for the task-based fMRI dataset [12]. In addition to change detection, we also evaluate the discriminative power of our dynamic graph embeddings in recognize different functional tasks in Sect. 3.2.

Data Description. In total 60 block-design working memory task-based fMRI data are selected from the HCP (Human Connectome Project) database [2]. The working memory task-based fMRI data consists of 2-back and 0-back task blocks of body, place, face and tools, as well as a fixation period. Each working memory data contains 393 scans, and are parcellated into 268 regions by the Shen 268 region atlas [14]. We specifically focus on 58 out of 268 brain regions that make up the attention and default mode network (DMN) areas of the brain since these regions are highly related to the working memory task.

3.1 Detection of Functional Connectivity Changes

Here, the performance of functional connectivity change detection on different methods is compared by using the same change detection method (classic clustering analysis method) but different embeddings (attributes). Since the SWC method slides rectangle window with 22 TRs across the fMRI data to extract functional connectivity embedding, in order to fairly compare the three methods, we use the same sliding rectangle window with 22 TRs to obtain corresponding embedding, then we perform the spectral clustering method on the obtained embedding to identify the changes of functional connectivity. Figure 3 (a) shows the detection results of functional connectivity changes on two randomly selected working memory task-based fMRI data obtained by feeding our dynamic graph embedding vectors into the clustering method, the change points (red triangle) we obtained are highly matched with the task event, that is, we are able to detect the beginning and end of each task. Figure 3 (b) shows the clustering accuracy results of all compared methods, our proposed method outperforms all other compared methods with an average accuracy of 0.771, compared to 0.734 by SWC and 0.663 by GE method. Meanwhile, in order to examine the sensitivity of sliding window size affects the performance of functional connectivity changes detection, we perform tests by varying the window size from 10 to 60 TRs. As shown in Fig. 3 (c), our proposed method (red curve) is more robustness to the selection of window size. Better performance of our method is attributed to the following two aspects. First, different from existing change detection methods that directly employ the attributes derived from noisy BOLD signals, the proposed method estimates the intrinsic BOLD signals in the context of the underlying functional connectivities, which alleviates the issue of detecting spurious changes caused by noise. Second, the joint harmonic-Fourier bases can better express the dynamic characteristics of functional connectivity than using the raw BOLD signals. As shown in the detection result in Fig. 3 (b), dGE achieves an improvement of 10.8% of clustering accuracy compared with the GE.

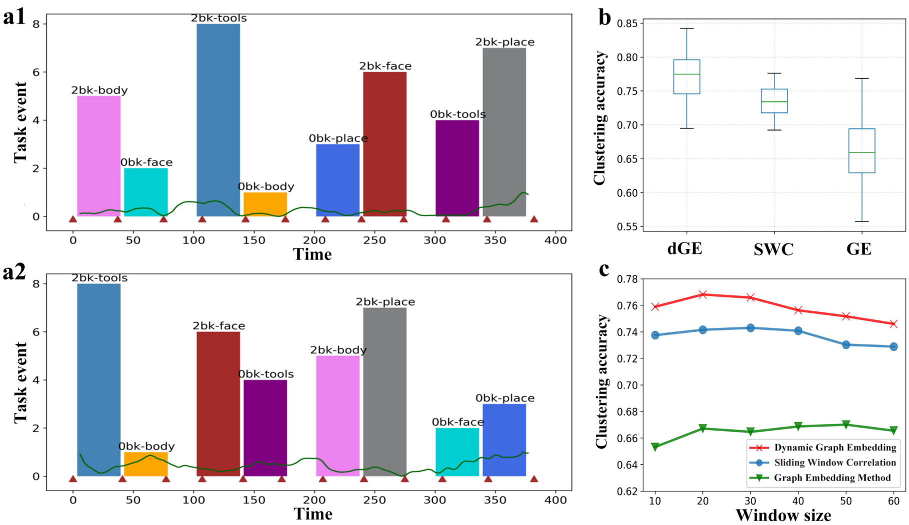
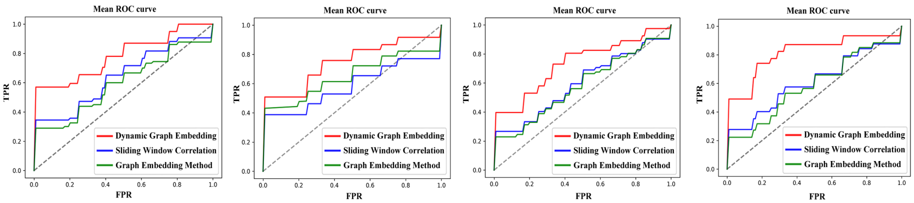


Fig. 3. Performance of detection of functional connectivity changes compared between the sliding window correlation (SWC) method, graph embedding method (GE) and our proposed method (dGE). (a) The detection performance of our proposed method on two random selected test data: the bar plots with different color represent different task events and the red triangles represent detected changes of functional connectivity. The green curve denotes the total energy of dynamic graph embedding. (b) Comparison of clustering accuracy using different embedding representation obtained from different methods. Each box shows a summary statistics of accuracy computed on 60 testing subjects. (c) Effect of the length of window size on the performance of detection of functional connectivity changes. (Color figure online)

3.2 The Performance of Classification on Different Task Events

We further investigate the classification ability of our graph embedding vectors for classifying 2-back task event versus 0-back task event in working memory task-based fMRI data. Since the ground truth of each task event are known in advance, we can obtain dynamic graph embedding of each task event by utilizing our proposed method on the subsequence of each task event in the time series of fMRI data, and utilize these embeddings to train the SVM for classifying 2-back task event and 0-back task event. In 10-fold cross validation strategy, the ROC curves of classifying 2-back task event versus 0-back task event involving body, place, face and tools are shown in Fig. 4. We can observe from the results that our classification results outperform the counterpart methods on classifying 2-back task event versus 0-back task event. The better classification ability shows that we get more discriminated embedding to distinguish changes between different back task events.



(a) ROC of body task events (b) ROC of place task events (c) ROC of face task events (d) ROC of tools task events

Fig. 4. ROC curves of 2-back versus 0-back task event classification involving body, place, face, and tools task events compared between the three methods.

4 Conclusion

In this paper, we proposed a dynamic graph embedding learning approach for detecting changes of functional connectivity. In this method, we first introduce a dynamic graph learning method to simultaneously estimate the intrinsic BOLD signals and estimate a set of harmonic bases based on the intrinsic BOLD signals. Given the learned harmonic bases, we then capture the dynamic graph embedding at each time point by using the joint harmonic-Fourier bases. Finally, a classic clustering method is utilized on the dynamic graph embedding vectors to detect changes of functional connectivity. We have evaluated our proposed method on working memory task-based fMRI dataset. The results show that the proposed method is effective to detect changes of functional connectivity.

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