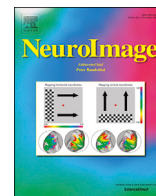




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## Spatio-temporal modeling of connectome-scale brain network interactions via time-evolving graphs

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### ABSTRACT

Many recent literature studies have revealed interesting dynamics patterns of functional brain networks derived from fMRI data. However, it has been rarely explored how functional networks spatially overlap (or interact) and how such connectome-scale network interactions temporally evolve. To explore these unanswered questions, this paper presents a novel framework for spatio-temporal modeling of connectome-scale functional brain network interactions via two main effective computational methodologies. First, to integrate, pool and compare brain networks across individuals and their cognitive states under task performances, we designed a novel group-wise dictionary learning scheme to derive connectome-scale consistent brain network templates that can be used to define the common reference space of brain network interactions. Second, the temporal dynamics of spatial network interactions is modeled by a weighted time-evolving graph, and then a data-driven unsupervised learning algorithm based on the dynamic behavioral mixed-membership model (DBMM) is adopted to identify behavioral patterns of brain networks during the temporal evolution process of spatial overlaps/interactions. Experimental results on the Human Connectome Project (HCP) task fMRI data showed that our methods can reveal meaningful, diverse behavior patterns of connectome-scale network interactions. In particular, those networks' behavior patterns are distinct across HCP tasks such as motor, working memory, language and social tasks, and their dynamics well correspond to the temporal changes of specific task designs. In general, our framework offers a new approach to characterizing human brain function by quantitative description for the temporal evolution of spatial overlaps/interactions of connectome-scale brain networks in a standard reference space.

### Introduction

Recently, increasing evidence from neuroscience research has suggested that functional brain networks are intrinsically dynamic on multiple timescales. Even in the resting state, the brain undergoes dynamical changes of functional connectivity (Chang and Glover, 2010; Smith et al., 2012; Majeed et al., 2011; Gilbert and Sigman, 2007; Ekman et al., 2012; Zhang et al., 2013, 2014; Keilholz, 2014; Li et al., 2014). Thus, computational modeling and characterization of time-dependent functional connectome dynamics and elucidating the fundamental temporal attributes of these connectome-scale interactions are of great importance to better understand the brain's function. In the literature, a variety of approaches have been proposed to examine the dynamics of functional brain connectivities, such as ROI-based methods (e.g. Zhu et al., 2016; Li et al., 2014; Zhang et al., 2013, 2014; Ou et al., 2014; Kucyi et al., 2015;

Shakil et al., 2016; Xu et al., 2016b; Thompson and Fransson, 2015; Kennis et al., 2016) and independent component analysis (ICA) based methods (e.g., Calhoun et al., 2001; Kiviniemi et al., 2009; Damoiseaux et al., 2006; Allen et al., 2014). In these approaches, the time series of pre-selected ROIs or brain network components extracted from ICA are employed to model temporal brain dynamics. For instance, based on the ROIs defined by the Dense Individualized and Common Connectivity-based Cortical Landmarks (DICCCL) (Zhu et al., 2013), functional connectomes based on resting-state fMRI data have been divided into temporally quasi-stable segments via a sliding time window approach. Then, dictionary learning and sparse representation were used to identify common and different functional connectomes across healthy controls and PTSD patients (Li et al., 2014) and to differentiate the brain's functional status into task-free or task performance states (Zhang et al., 2013).

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Despite that previous studies have revealed interesting dynamics patterns of functional brain networks themselves, however, it has been rarely explored how functional networks *spatially overlap or interact* with each other, and it has been largely unknown how such connectome-scale network interactions temporally evolve. In the neuroscience field, a variety of recent studies suggested that spatial overlap of functional networks derived from fMRI data is a fundamental organizational principle of the human brain (e.g., Fuster, 2009; Harris and Mrcsic-Flogel, 2013; Xu et al., 2016a). In general, the fMRI signal of each voxel reflects a highly heterogeneous mixture of functional activities of the entire neuronal assembly of multiple cell types in the voxel. In addition to the heterogeneity of neuronal activities, the convergent and divergent axonal projections in the brain and heterogeneous activities of intermixed neurons in the same brain region or voxel demonstrate that cortical microcircuits are not independent and segregated in space, but they rather overlap and interdigitate with each other (Harris and Mrcsic-Flogel, 2013; Xu et al., 2016a). For instance, researchers have explicitly examined the extensive overlaps of large-scale functional networks in the brain (Hermansen et al., 2007; Fuster, 2009; Fuster and Bressler, 2015). Several research groups have reported that task-evoked networks, such as in emotion, gambling, language and motor tasks, have large overlaps with each other (e.g., Hermansen et al., 2007; Fuster, 2009; Fuster and Bressler, 2015; Xu et al., 2016a). Thus, development of effective computational methods that can faithfully reconstruct and model the spatial overlap patterns of connectome-scale functional networks is of significant importance.

Recently, in order to effectively decompose the fMRI signals into spatially overlapping network components, we developed and validated a computational framework of sparse representations of whole-brain fMRI signals (Lv et al., 2015a, 2015b) and applied it to the HCP (Human Connectome Project) fMRI data (Q1 release) (Barch et al., 2013). The basic idea of our framework is to aggregate all of the hundreds of thousands of fMRI signals within the whole brain of one subject into a big data matrix (e.g., a quarter million voxels  $\times$  one thousand time points), which is subsequently factorized into an over-complete dictionary basis matrix (each atom representing a functional network) and a reference weight matrix (representing this network's spatial volumetric distribution) via an efficient online dictionary learning algorithm (Mairal et al., 2010). Then, the time series of each over-complete basis dictionary represents the functional activities of a brain network and its corresponding reference weight vector stands for the spatial map of this brain network. A particularly important characteristic of this framework is that the reference weight matrix naturally reveals the spatial overlap and interaction patterns among those reconstructed brain networks. Our extensive experiments (Lv et al., 2015a, 2015b) demonstrate that this novel methodology can effectively and robustly uncover connectome-scale functional networks, including both task-evoked networks (TENs) and resting-state networks (RSNs) from task-based fMRI (tfMRI) data that can be well-characterized and interpreted in spatial and temporal domains. Extensive experiments also demonstrated the superiority of this methodology over other popular fMRI data modeling methods such as ICA and GLM (general linear model) (Lv et al., 2015a, 2015b). Experimental results on the HCP Q1 data show that these well-characterized networks are quite reproducible across different tasks and individuals and they exhibit substantial spatial overlap with each other, thus forming the Holistic Atlases of Functional Networks and Interactions (HAFNI) (Lv et al., 2015a, 2015b). This computational framework of sparse representation of whole-brain fMRI data provides a solid foundation to investigate the temporal dynamics of connectome-scale network interactions derived by sparse dictionary learning algorithms in this paper.

To leverage the dictionary learning and HAFNI methods' superiority in reconstructing spatially overlapping functional networks while significantly advancing them towards modeling *temporal brain dynamics*, this paper presents a novel framework for spatio-temporal modeling of connectome-scale functional brain network interactions via two main

effective computational schemes. First, we designed a novel group-wise dictionary learning framework to derive connectome-scale consistent brain network templates that can be used to define the common reference space of brain networks and their interactions across fMRI scans and across different brains, in order to integrate, pool and compare these corresponding brain networks across individuals and their cognitive states under task performances. Second, the temporal dynamics of spatial network overlaps or interactions is computationally modeled by a weighted time-evolving graph, and then a data-driven unsupervised learning algorithm based on the dynamic behavioral mixed-membership model (DBMM) (Rossi et al., 2013) is adopted to identify behavioral patterns of brain networks during the temporal evolution processes of spatial overlaps/interactions. Extensive experimental results on four different HCP task fMRI datasets showed that our methods can effectively reveal meaningful, diverse behavior patterns of connectome-scale network interactions. In particular, those networks' behavior patterns are distinct across four HCP tasks including motor, working memory, language and social tasks, and their dynamics well correspond to the temporal changes of specific task designs. In general, our framework offers a new approach to characterizing human brain function by quantitative description for the temporal evolution of spatial overlaps/interactions of connectome-scale brain networks in a standard reference space.

## Materials and methods

### Overview

As shown in Fig. 1, the computational pipeline of the proposed framework consists of five main steps. In the first step, the whole-brain tfMRI time series of each subject are segmented into multiple overlapped sliding windows (Agcaoglu et al., 2016; Li et al., 2014), in order to capture the temporal dynamics of functional brain networks. Then, the tfMRI data in each window from each subject in HCP Q1 release are temporally concatenated to obtain corresponding group-wise tfMRI time series segments. In the second step, based on the temporally concatenated sparse coding (Lv et al., 2016), we extract the group-wise local temporal dynamics and the corresponding spatial profiles of functional brain networks at the same time, represented by the dictionary and the sparse weighting coefficients, respectively. In the third step, an affinity propagation (AP)-based hierarchical clustering method is proposed to generate the common group-wise functional networks (GFNs) from the spatial maps (or network components) learned in the second step. In the fourth step, spatio-temporal dynamics of functional interactions among brain networks is modeled by a weighted time-evolving graph that incorporates connectivity relationships of the brain networks into a hierarchical structure, where each layer describes the spatial interactions among the GFNs in each sliding window and the sequence of layers represents dynamic change of the network interactions over time. At last, the behavioral roles of each GFN are identified by the effective DBMM-based role detection algorithm (Rossi et al., 2013), to model and characterize its spatio-temporal dynamic behaviors.

For the detailed description of the proposed methods in this paper, the following definitions and notations are used.

$s_i (i = 1, 2, \dots, m_j)$  The  $i$ -th sliding window.

$|s_i|$  The size of  $s_i$ .

$X_i (i = 1, 2, \dots, m_j)$  Concatenated input matrix for  $s_i$ .

$D_i = [d_1, d_2, \dots, d_p], (i = 1, 2, \dots, m_j)$  Dictionary.

$d_q (q = 1, 2, \dots, p)$  Atom in the dictionary.

$\alpha_i (i = 1, 2, \dots, m_j)$  Coefficient matrix.

$GFN_j$  The  $j$ -th group-wise functional network.

$FNC_{k,p}$  The  $p$ -th functional network component occurring in  $s_k$ .

$TEG = (V, E)$  Time-evolving graph with vertex set  $V$  and edge set  $E$ .

$e_k^{ij}$  Edge between the vertices  $GFN_i$  and  $GFN_j$  in the  $k$ -th layer of  $TEG$

$w_k^{ij}$  Weight of the edge  $e_k^{ij}$ .

$F_k \in \mathbb{R}^{N \times f} (k = 1, 2, \dots, M)$  Feature matrix of the  $k$ -th layer of  $TEG$ .

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