Multiple Subject Analysis of Functional Brain Network Communities Through Co-regularized Spectral Clustering

Alp Ozdemir[1], Arash Golibagh Mahyari[1], Edward M. Bernat[2] and Selin Aviyente[1]

Abstract— **In recent years, the human brain has been characterized as a complex network composed of segregated modules linked by short path lengths. In order to understand the organization of the network, it is important to determine these modules underlying the functional brain networks. However, the study of these modules is confounded by the fact that most neurophysiological studies consist of data collected from multiple subjects. Typically, this problem is addressed by either averaging the data across subjects which omits the variability across subjects or using consensus clustering methods which treats all subjects equally irrespective of outliers in the data. In this paper, we adapt a recently introduced co-regularized multi-view spectral clustering approach to address these problems. The proposed framework is applied to EEG data collected during a study of error-related negativity (ERN) to better understand the functional networks involved in cognitive control and to compare between the network structure between error and correct responses.**

I. INTRODUCTION

Functional connectivity is defined as the statistical dependency between spatially remote neurophysiological events and is the key to understanding how the coordinated and integrated activity of the human brain takes place. Synchronization of neuronal oscillations has been suggested as one plausible mechanism in the interaction of spatially distributed neural populations and has been quantified using phase synchrony measures.

Recently, research in the area of complex networks, in particular graph theoretic measures, has been used to characterize the relationship between the topology and the function of the brain [1]. The bivariate relationships between neuronal populations are represented as graphs where the nodes correspond to the individual sites and the edges correspond to the strength of the interaction quantified by functional connectivity measures.

One important property of complex networks is modular structure. A module is composed of a densely connected set of nodes with sparse connections between modules in the network. It is hypothesized that the modular structure of complex biological networks is indicative of robustness [2] and contributes to functionality by compartmentalizing specific functions within certain cortical regions.

Identification of functional modules or communities in the brain has been originally addressed using multivariate data analysis approaches such as Principle Component Analysis (PCA) and Independent Component Analysis (ICA) which put non-physiological constraints in the obtained components such as orthogonality and independence. Recently, methods from spectral analysis of graphs [3], unsupervised learning algorithms such as k-means, have been used for graph clustering by mapping the functional connections to a multi-dimensional subspace defined by a set of eigenvectors. A key challenge in identifying modular organization of brain networks is determining a common structure across multiple subjects. Current work either focuses on obtaining the community structure for the average connectivity network or on analyzing each subject individually and obtaining a common modular structure using a consensus clustering method. Averaging neglects the variance across subjects. Consensus clustering, on the other hand, combines individual clusterings into a single map weighing each clustering equally and does not allow for iterative refinement of the cluster structure. Recently, clustering methods which exploit information from multiple views of the data have been proposed in machine learning and signal processing literature. These approaches show that a spectral clustering framework which generates clusters that are consistent across different views of the same data produce clusters that are more accurate than the ones obtained through the individual views or through averaging [4].

In this paper, we adapt this multiview clustering approach to develop a framework for identifying functional connectivity modules across subjects. First, we introduce a graph similarity metric to assign weights to different subjects. Then, we introduce an iterative algorithm for determining the best cluster structure across subjects using a co-regularization framework. Finally, we present the application of this framework to both simulated networks and real data obtained from a study of error-related negativity (ERN) from electroencephalogram (EEG) data.

II. BACKGROUND

A. Time-Varying Phase Synchrony Measure

In this paper, we quantify the connectivity between brain regions using a recent phase synchrony measure based on RID-Rihaczek distribution [5], which has been shown to be more robust to noise and to provide better resolution as discussed in [5].

First, we quantify the time varying phase of a signal as: $\Phi_i(t,\omega) = \arg\left[\frac{C_i(t,\omega)}{|C_i(t,\omega)|}\right]$ where $C_i(t,\omega)$ is the complex

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[1] A. Ozdemir, A. G. Mahyari and S. Aviyente are with the Department of Electrical and Computer Engineering, Michigan State University, East Lansing, MI 48824, USA aviyente@egr.msu.edu

[2]E. Bernat is with the Department of Psychology, University of Maryland, College Park, MD, USA

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RID-Rihaczek distribution [1]:

$$C_i(t,\omega) = \int\int \underbrace{\exp\left(-\frac{(\theta\tau)^2}{\sigma}\right)}_{\text{Choi-Williams kernel}} \underbrace{\exp(j\frac{\theta\tau}{2})}_{\text{Rihaczek kernel}} A_i(\theta,\tau) e^{-j(\theta t+\tau\omega)} d\tau d\theta \tag{1}$$

and $A_i(\theta,\tau) = \int s_i(u+\frac{\tau}{2}) s_i^*(u-\frac{\tau}{2}) e^{j\theta u} du$ is the ambiguity function of $\boldsymbol{s_i}$. The phase synchrony between nodes i and j at time t and frequency ω is computed using 'Phase Locking Value' (PLV):

$$PLV_{i,j}(t,\omega) = \frac{1}{L}\left|\sum_{k=1}^{L} \exp\left(j\Phi_{1,2}^k(t,\omega)\right)\right| \tag{2}$$

where L is the number of trials and $\Phi_{i,j}^k(t,\omega) = |\Phi_i(t,\omega) - \Phi_j(t,\omega)|$ is the phase difference estimate between the two nodes for the k^{th} trial.

From this measure, we can construct a time sequence of graphs $\{\boldsymbol{G}(t)\}_{t=1,2,...,T}$ where $\boldsymbol{G}(t)$ is an $N \times N$ weighted and undirected graph corresponding to the functional connectivity network at time t for a fixed frequency or frequency band, T is the total number of time points and N is the number of nodes within the network. The time-varying edge values are quantified by the average PLV within a frequency band and at a certain time as:

$$\boldsymbol{G}_{i,j}(t) = \frac{1}{\Omega}\sum_{\omega=\omega_a}^{\omega_b} PLV_{i,j}(t,\omega) \tag{3}$$

where $\boldsymbol{G}_{i,j}(t) \in [0,1]$ represents the connectivity strength between the nodes i and j within the frequency band of interest, $[\omega_a, \omega_b]$, and Ω is the number of frequency bins in that band.

We can extend this representation across multiple subjects with $\{\boldsymbol{G}^s(t)\}$ as the time varying graph for the s^{th} subject and use the tensor $\mathcal{X} \in \mathbb{R}^{N\times N\times T\times S}$ to describe the time varying functional connectivity networks across all subjects.

B. Spectral Clustering

The goal of graph clustering or partitioning is to detect the community structure in the graph by maximizing the within cluster connectivity strength while minimizing the between cluster connectivity. Since linear clustering algorithms like K-means are not capable of handling non-linear data, non-linear algorithms such as kernel K-means and spectral clustering algorithms have been preferred [3], [6].

Let $\mathbf{W} \in \mathbb{R}^{\mathbf{N}\times\mathbf{N}}$ be the adjacency matrix for a weighted and undirected graph with $\mathbf{N}$ nodes, standard spectral clustering solves the following relaxed minimization problem:

$$\min_{\mathbf{U}\in\mathbb{R}^{\mathbf{N}\times\mathbf{k}}} tr(\mathbf{U}^\top \mathcal{L}\mathbf{U}) \text{ subject to } \mathbf{U}^\top\mathbf{U} = \mathbf{I}, \tag{4}$$

where $\mathcal{L}$ is the normalized Laplacian defined as $\mathcal{L} = \mathbf{I} - \mathbf{D}^{-1/2}\mathbf{W}\mathbf{D}^{-1/2}$ and $\mathbf{D}$ is the degree matrix. The solution to this optimization problem is to choose $\mathbf{U}$ such that its columns are the k eigenvectors corresponding to the smallest k eigenvalues of $\mathcal{L}$. Applying k-means to the eigenvector matrix ($\mathbf{U}$) provides the cluster structure for the graph $\mathbf{W}$.

[1]The details of the RID-Rihaczek distribution and the corresponding synchrony measure are given in [5].

C. Modularity

Modularity is a commonly used metric to quantify the quality of the partitioning [7]. For a weighted undirected graph, modularity is defined as: $Q = \frac{1}{2m}\sum_{ij}\left(\mathbf{W}_{ij} - \frac{d_i d_j}{2m}\right)\delta(i,j)$, where d_i is the degree of the $i^{th}node$, m is the sum of the edge weights in the graph ($m = \frac{1}{2}\sum_{ij}\mathbf{W}_{ij}$) and $\delta(i,j) = 1$ if nodes i and j are in the same cluster.

III. Methods

A. Tensor-Tensor Projection

In this paper, we are interested in summarizing the common cluster structure across all subjects for a given time interval of interest. For a given subject S_0, connectivity across time can be represented as a 3-way tensor $\mathcal{X}_{S_0} \in \mathbb{R}^{N\times N\times T_0}$. We first summarize the information across time using the full Tucker decomposition [8] as $\mathcal{X}_{S_0} = \mathcal{C}_{S_0} \times_1 \mathbf{V}_{S_0}^{(1)} \times_2 \mathbf{V}_{S_0}^{(2)} \times_3 \mathbf{V}_{S_0}^{(3)} + \mathcal{E}_{S_0}$ where $\mathcal{C}_{S_0} \in \mathbb{R}^{N\times N\times T_0}$ is the core tensor, and $\mathbf{V}_{S_0}^{(1)} \in \mathbb{R}^{N\times N}$, $\mathbf{V}_{S_0}^{(2)} \in \mathbb{R}^{N\times N}$, $\mathbf{V}_{S_0}^{(3)} \in \mathbb{R}^{T_0\times T_0}$ are the unitary projection matrices, $\mathcal{E}_{S_0} \in \mathbb{R}^{N\times N\times T}$ is the residual error, and $\times_k$ is the product of a tensor and a matrix along mode-*k*.

In order to summarize the time information, the 3-way tensor $\mathcal{X}_{S_0}$ is projected to the singular vector $\mathbf{v}_l^{(3)}$ corresponding to the l^{th} largest singular value of the time mode, $\hat{\mathcal{X}}_{S_0} = \mathcal{X}_{S_0} \times_3 \mathbf{v}_l^{(3)}$. The value of l is usually equal to 1 but may change depending on the data.

B. Multiple Subject Clustering

Once the time compressed connectivity graphs are constructed for each subject, the goal is to identify the common modular structure across subjects. To achieve this goal, we adapted centroid-based co-regularization approach for multi-view data clustering to multiple graph clustering [4].

In centroid based co-regularization approach, it is desired to extract the common clustering structure obtained from the centroid eigenvector matrix $\mathbf{U}_\pi$ by minimizing the disagreement between the eigenvectors of the individual graphs, i.e. subjects, while still minimizing the cost function of spectral clustering, i.e. $tr(\mathbf{U}_i^\top \mathcal{L}\mathbf{U}_i)$, for each graph. Let $\{\mathbf{W}_1, ..., \mathbf{W}_S\}$ be a set of connectivity matrices for the S subjects and $\{\mathbf{U}_1, ..., \mathbf{U}_S\}$ be the corresponding eigenvector matrices in $\mathbb{R}^{N\times k}$ which minimize the optimization problem in equation (4). Clustering disagreement between each $\mathbf{U}_i$ and the centroid $\mathbf{U}_\pi$ is measured as the difference between the normalized similarity matrices of the eigenvectors

$$D(\mathbf{U}_i, \mathbf{U}_\pi) = \left\| \frac{\mathbf{U}_i\mathbf{U}_i^\top}{\| \mathbf{U}_i\mathbf{U}_i^\top \|_F^2} - \frac{\mathbf{U}_\pi\mathbf{U}_\pi^\top}{\| \mathbf{U}_\pi\mathbf{U}_\pi^\top \|_F^2} \right\|_F^2, \tag{5}$$

where $\| \circ \|_F$ is the Frobenius norm. Reducing the disagreement between $\mathbf{U}_i$ and $\mathbf{U}_\pi$ in equation 5 is similar to finding $\mathbf{U}_\pi$ which maximizes $tr(\mathbf{U}_i\mathbf{U}_i^\top\mathbf{U}_\pi\mathbf{U}_\pi^\top)$.

If we combine the objective of spectral clustering given in equation 4 while minimizing the disagreement terms, we obtain the following joint optimization problem.

$$\min_{\mathbf{U}_1,\ldots,\mathbf{U}_n,\mathbf{U}_\pi\in\mathbb{R}^{N\times k}} \sum_{i=1}^{S} tr(\mathbf{U}_i^\top \mathcal{L}_i \mathbf{U}_i) - \sum_{i=1}^{S} \lambda_i tr(\mathbf{U}_i \mathbf{U}_i^\top \mathbf{U}_\pi \mathbf{U}_\pi^\top) \tag{6}$$

where λ_i's are the weights of each regularization term and $\sum_{i=1}^{S} \lambda_i = 1$.

After initializing $\mathbf{U}_\pi$ as the average of $\mathbf{U}_i$'s , the problem can be solved iteratively by applying the following two steps.

1) Fix $\mathbf{U}_\pi$ and solve the following optimization problem:

$$\min_{\mathbf{U}_1,\ldots,\mathbf{U}_n\in\mathbb{R}^{N\times k}} \sum_{i=1}^{S} tr(\mathbf{U}_i^\top (\mathcal{L}_i - \lambda_i \mathbf{U}_\pi \mathbf{U}_\pi^\top)\mathbf{U}_i). \tag{7}$$

Determining each U_i is equivalent to finding the k eigenvectors corresponding to the smallest k eigenvalues of the modified Laplacian $\hat{\mathcal{L}}_i = \mathcal{L}_i - \lambda_i \mathbf{U}_\pi \mathbf{U}_\pi^\top$.

2) Fix $\mathbf{U}_i$'s and solve the following optimization problem

$$\max_{\mathbf{U}_\pi\in\mathbb{R}^{N\times k}} \sum_{i=1}^{S} \lambda_i tr(\mathbf{U}_i \mathbf{U}_i^\top \mathbf{U}_\pi \mathbf{U}_\pi^\top). \tag{8}$$

By using the circular property of the trace function, equation (8) can be represented as $\max_{\mathbf{U}_\pi\in\mathbb{R}^{N\times k}} tr(\mathbf{U}_\pi^\top (\sum_{i=1}^{S} \lambda_i \mathbf{U}_i \mathbf{U}_i^\top)\mathbf{U}_\pi)$, which is equivalent to finding the k eigenvectors corresponding to the largest k eigenvalues of $\sum_{i=1}^{n} \lambda_i \mathbf{U}_i \mathbf{U}_i^\top$.

After $\mathbf{U}_\pi$ converges, applying k-means on $\mathbf{U}_\pi$ will yield the common clustering structure.

C. Choice of the Regularization Parameters

The regularization parameters λ_i's penalize the spectral clustering objective by considering the cluster disagreements between each U_i and U_π. In this paper, we use the cosine similarity between the connectivity graphs of pairs of subjects to determine λ_i's. The cosine similarity is computed as: $\mathbf{\Phi}_{ij} = \frac{\langle \mathcal{L}_i, \mathcal{L}_j \rangle}{\|\mathcal{L}_i\|_2 \|\mathcal{L}_j\|_2}$; $i, j = 1, 2, ..., S$, where $\mathcal{L}_i$ is the normalized Laplacian matrix of the i^{th} subject and $\langle \circ, \circ \rangle$ is the inner product. λ_i is then defined as the normalized total similarity of the subject with all other subjects: $\lambda_i = \frac{\boldsymbol{\psi}(i)}{\|\boldsymbol{\psi}\|_2}$, where $\boldsymbol{\psi}(i) = \sum_{j=1}^{N} \mathbf{\Phi}_{ij}$. This parameter indicates how much the subject's connectivity network is consistent with other subjects.

IV. Results

A. Simulated Data

Performance of the co-regularized spectral clustering algorithm was first evaluated on three sets of simulations and was compared to the performance of the spectral clustering algorithm applied to the average of the input graphs. In a real data set, it is very common to have outliers that may affect the performance of the whole analysis. For this reason, we consider a collection of 10 networks where a subgroup of the networks are outliers. Weighted, undirected and fully connected graphs with 64 nodes were created and target graphs were constructed with 3 modules consisting of 16, 32 and 16 nodes respectively. Intra-cluster edge values were selected from a truncated Gaussian distribution in the range of $[0, 1]$ with $\mu_{intra} = 0.6$ and $\sigma_{intra} = 0.1$ while the inter-cluster edge values were taken from the same distribution with $\mu_{inter} = 0.3$ and $\sigma_{inter} = 0.2$. On the other hand, the outlier graphs were constructed with two equal size modules. Intra-cluster edge values were selected from a truncated Gaussian distribution in the range of $[0, 1]$ with $\mu_{intra} = 0.8$ and $\sigma_{intra} = 0.1$ while the inter-cluster edge weights were selected from a truncated Gaussian distribution with $\mu_{inter} = 0.1$ and $\sigma_{inter} = 0.2$.

The performance of the original spectral clustering applied to the average graph and the co-regularized spectral clustering algorithm were quantified by the average adjusted mutual information (AMI) score [9] over 100 simulations. Set of 10 graphs which consist of both the target and outlier graphs were partitioned into $k = 2, 3.., 10$ clusters and the k which maximizes the average modularity metric was selected. Table-I shows the results of three different simulations without any outliers, with 1 and 2 outliers. In all cases, regularization parameters were selected to be equal. As seen in Table-I, both algorithms were able to discover the true partition when there were no outliers. However, when outliers exist, applying spectral clustering to the average of the graphs is less robust than the proposed multi-graph clustering approach indicated by the lower AMI scores.

B. EEG Data

The proposed framework is applied to a set of EEG data containing the error-related negativity (ERN). The ERN is a brain potential response that occurs following performance errors in a speeded reaction time task usually 25-75 ms after the response [10]. Previous work [11] indicates that there is increased coordination between the lateral prefrontal cortex (lPFC) and medial prefrontal cortex (mPFC) within the theta frequency band (4-8 Hz) and ERN time window. EEG data from 63-channels was collected in accordance with the 10/20 system on a Neuroscan Synamps2 system (Neuroscan, Inc.) sampled at 128 Hz from 91 subjects. A speeded-response flanker task was employed, and response-locked averages were computed for each subject. All EEG epochs were converted to current source density (CSD) using published methods [12]. In this paper, we constructed tensors corresponding to time-varying graphs in the theta band and the time interval corresponding to 25-125 ms after

TABLE I
Clustering performance of Co-regularized Spectral Clustering Algorithm and The Averaging Method on simulated networks

Method	AMI scores of Simulations (mean ± std)		
	0/10 outlier	1/10 outlier	2/10 outliers
Co-Reg SC	1 ± 0	1 ± 0	1 ± 0
SC on Average	1 ± 0	0.9729 ± 0.0923	0.8288 ± 0.1235

the response for each subject for both correct (CRN) and error (ERN) responses.

C. Module Identification for ERN and CRN

First, Tucker decomposition was applied to tensors $\mathcal{X} \in \mathbb{R}^{63\times63\times14\times91}$ obtained for both response types. The time interval corresponding to 25-125 ms after the response with 14 samples was projected to obtain connectivity matrices for each subject. Then, the proposed clustering approach was used to identify cluster structure of the brain during the error and correct responses. Co-regularization parameters were specified as described in section III-C (Fig. 1) and the optimal cluster number k was determined as 5 for the ERN data and 4 for the CRN data based on the modularity metric. The clusters for ERN (Fig. 2a) are more localized whereas the clusters for CRN are more spread out. In particular, for the ERN there is a separation between the right and left lPFC and the mPFC as these regions are key in the processing of an error response.

Average inter cluster edge values for each cluster pairs were computed for each subject and response type and the resulting distributions were compared using Wilcoxon signed-rank test. For ERN, the synchronization between the right frontal cluster and the central cluster has been found to be significantly higher than all of the other connectivity values of the right frontal cluster ($p < 0.05$). In addition, the synchronization between the central and the frontal clusters was higher than all the other connectivity values during the correct response ($p < 0.05$).

V. CONCLUSIONS

In this paper, we have introduced a new framework for finding the common cluster structure of functional brain connectivity graphs across multiple subjects. Unlike previous work in the area which either considers the clustering structure of the average connectivity network or voting based consensus clustering, the proposed framework adapts co-regularized multi-view spectral clustering approach [4] for finding a common cluster structure across subjects such that the dissimilarity between the clustering structures for individual subjects is minimized while the separability between the different clusters is maximized. Moreover, in the proposed framework we introduced a way of assigning weights to different subjects such that the subjects that are the least similar to the group are deemphasized. The robustness and accuracy of the proposed framework is illustrated through simulated networks. Finally, the proposed approach is applied to functional connectivity networks constructed from multichannel EEG data where the connectivity is quantified through phase synchrony. The resulting clusters for ERN and CRN illustrate that there is increased specialization of brain regions for the error response especially in the right and left lPFC and mPFC.

Future work will consider extensions to the current approach in terms of choosing different similarity measures in the cost function and different approaches to choosing the regularization parameters. The application of this clustering approach to dynamic connectivity networks will also be considered.

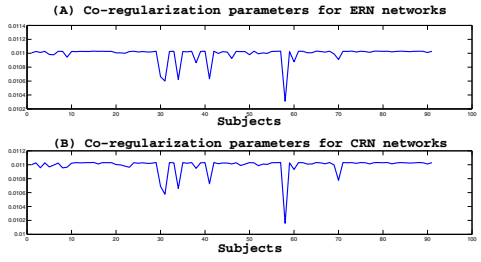
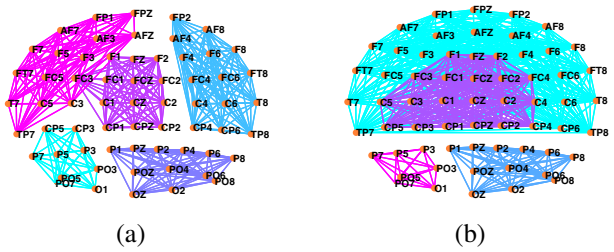


Fig. 1. Co-regularization parameters for ERN networks (A) and CRN networks (B)



(a) (b)

Fig. 2. (a) Clusters for ERN data obtained by Centroid-Based Co-regularization Algorithm, $k = 5$ (b) Clusters for CRN data obtained by Centroid-Based Co-regularization Algorithm, $k = 4$

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