Group-Wise Functional Community Detection through Joint Laplacian Diagonalization

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Abstract. There is a growing conviction that the understanding of the brain function can come through a deeper knowledge of the network connectivity between different brain areas. Resting state Functional Magnetic Resonance Imaging (rs-fMRI) is becoming one of the most important imaging modality widely used to understand network functionality. However, due to the variability at subject scale, mapping common networks across individuals is by now a real challenge.

In this work we present a novel approach to group-wise community detection, i.e. identification of functional coherent sub-graphs across multiple subjects. This approach is based on a joint diagonalization of two or more graph Laplacians, aiming at finding a common eigenspace across individuals, over which clustering in fewer dimension can then be applied. This allows to identify common sub-networks across different graphs.

We applied our method to rs-fMRI dataset of mouse brain finding most important sub-networks recently described in literature.

Keywords: Joint Diagonalization, fMRI, Laplacian, Spectral Clustering, Community Detection.

1 Introduction

Many studies on functional Magnetic Resonance Imaging (fMRI) have demonstrated temporal correlations in the blood oxygen level-dependent signal of widely separated brain regions. These temporal correlations among distinct time series are usually interpreted in terms of functional connectivity, i.e. functional relationships among the brain areas. This connectivity is usually described by graphs, where brain regions are nodes and functional correlation between them are weighted edges [1,2,3]. The advent of this graphical interpretation of brain, often called connectomics, has changed the way to study brain functions [4]. It is in fact common practice to exploit graph theory tools to characterize the brain functions with this graph-based perspective. In particular one of the endeavor in connectomics is to detect the community structure of the functional networks, defined in terms of network's static topology as opposed to a more dynamical

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definition [5]. Even more, the characterization of such functional connectivity across multiple subjects, in order to detect group-wise sub-networks, is still an open problem gathering increasing interest in the neuroscience community.

Group-wise characterization of brain dynamics usually passes through the construction of an average graph over which connectivity indexes are computed to describe a general brain organization [6]. However, these analyses are affected by some issues related to the underlying univariate approach, such as the graph thresholding in the multiple comparison framework, common practice adopted on complex network in order to differentiate "possibly false" connections from "true" connections [7]. Moreover, the average graph could be a limited and not fully representative statistic.

Although such approach is widely used, the above issues can be addressed by advanced multivariate methods, characterizing cross-subject brain networks. Indeed, tools for multi-subject community detection are becoming essential to map networks across individuals [8], regardless the modality adopted (fMRI, DTI, EEG and MEG).

In machine learning terms, community detection means graph partitioning or clustering. However, despite multi-modal investigation of connectomics is gathering interest in the research community, still few approaches have been proposed based on learning methods and clustering techniques. For example, group fMRI clustering based on a probabilistic framework was proposed to manage both group-wise and individual networks [9]. Similarly, Normalized Cut was also applied on group fMRI clustering [10]. Both method work at the voxel level with whole-brain coverage but the results are conditioned by the choice of clusters number or by the cut off threshold, which is substantially different across subjects. A co-training learning method, based on multi-view spectral clustering was applied to extract networks between subjects and from different modalities (fMRI-DTI) [11]. This approach finds an agreement across multiple graphs to extract common sub-networks but the results vary according to the number of iterations and to the number of selected eigenvectors. Moreover, the criteria adopted to stop learning do not guarantee the convergence of the method.

We are therefore proposing a novel approach to identify brain functional communities across multiple subjects. Our approach searches for a common eigenspace for multiple graph Laplacians via joint diagonalization allowing a further spectral clustering in fewer dimensions [13]. The idea of using graph Laplacian operator – an approximation of the Laplace-Beltrami operator defined on the Riemannian manifold – within the joint diagonalization framework is also addressed in [12], where some theoretical studies and validation of properties on artificial data have been reported.

We adopted joint diagonalization through generalized Jacobi angles proposed by Cardoso and Souloumiac [14] since it always converges to a unique solution. We applied our algorithm on a real dataset finding results in line with the literature.

2 Material and Method

2.1 fMRI Mouse Dataset

All experiments were carried out in accordance with Italian regulations governing animal welfare and protection. MRI experiments were performed on male C57Bl6/J mice (n=10). The procedure employed for rs-fMRI has been recently described in [15]. Briefly, mice were anesthetized with isoflurane (5%), intubated, and artificially ventilated. Resting state-fMRI time series were acquired using controlled halothane anesthesia (0.7%). All experiments were performed using a 7.0 Tesla MRI scanner using a single-shot EPI sequence with TR/TE 1000/15 ms, matrix 100 × 87, field of view 2.3 × 2 cm^2, 16 coronal slices, slice thickness 0.75 mm an NT=360.

Rs-fMRI time series were pre-processed (registered, motion regressed, band-pass filtered 0.1- 0.01 Hz and smoothed) as recently described in [15]. ROI masks corresponding to 50 cortical areas were selected from a mouse brain atlas [15], and mean time series were computed for each area. Pairwise correlation coefficients (Fisher's z-transformed) were finally computed from the rs-fMRI means for each pair of ROIs generating an adjacency matrix.

2.2 Spectral Clustering

Spectral clustering determines a graph partitioning based on the eigenspace of the adjacency matrix [13,16]. Specifically, it takes into account the properties of graph Laplacians to cluster similarity graphs using fewer dimensions.

Let $G = (V, E)$ be an undirected graph with similarity matrix W having non-negative weights $w_{ij} \geq 0$. Given this adjacency matrix, graph Laplacian can be computed in different ways. We used the Normalized Symmetric Laplacian [16] defined as follow:

$$L = D^{-\frac{1}{2}}(D - W)D^{-\frac{1}{2}} \tag{1}$$

where $D = \text{diag}\,(\sum_j w_{ij})$ is the degree matrix of W.

The Laplacian is a symmetric and positive semi-definite matrix and it can be decomposed through eigenspace decomposition, so it admits $L = U\Lambda U'$, with $U'U = I$, where $U = (u_1, ..., u_n)$ is the eigenspace matrix and Λ is a diagonal matrix of the corresponding eigenvalues $0 = \lambda_1 \leq ..... \leq \lambda_n$, which are always positive and the first λ is zero. Due to this general rule and to other mathematical attributes, Laplacians are often used in combination with spectral methods.

In particular, spectral clustering partitions a graph using a subspace U_k of the eigenmatrix U, using only the first k eigenvectors associated with the first k smallest eigenvalues. Actually, the first k smallest eigenvalues hold the most important information to cluster the nodes of a similarity graph. In the ideal case, the multiplicity K of the eigenvalues 0 (number of $\lambda_i = 0$) equal the number of connected components in the graph. As a general rule, however, when $K = 1$, the number of clusters can be set using the spectral gap on the eigenvalues ordered in ascending way. Once k is defined, usually k-means algorithm is used to partition the graph using the rows of U_k.

2.3 Multi-subject Functional Community Detection

In our case, we have a set $\mathcal{W} = \{W_i | \, i = 1...N\}$ of N real $n \times n$ adjacency matrices where each element w_{ij} is the mean pairwise correlation coefficient (Fisher's z-transformed). A Laplacian matrix L_i is therefore built for each W_i. This means we have a different Laplacian for each different graph, which can result into different clusterings. Hence, starting from a set of graph Laplacians, the main idea is to build a common eigenspace across multiple-graphs. This would allow to perform the clustering on a common space describing the entire graph population.

If Laplacians have the same size and they commute pairwise ($L_i L_j = L_j L_i$ $\forall \; i, j = 1....N$) they are jointly diagonalizable. Basically, we are looking for an eigenspace V such that:

$$V' L_i V = \Lambda_i \quad \forall i \tag{2}$$

where Λ_i are diagonals made by the eigenvalues for each Laplacian L_i.

However, in a real scenario, due to differences between subjects and to the presence of noise in the data, the Laplacians rarely commute. As a consequence the Laplacians are not jointly diagonalizable and the common eigenspace can be only approximated. The problem can therefore be formulated as an optimization problem solving:

$$\min_{V} \sum_{i=1}^{N} \mathbf{off} \; (V' L_i V) \; , \quad V'V = I \tag{3}$$

where $\mathbf{off}(A) = \sum_{i \neq j} |a_{ij}|^2$. In order to find the joint eigenspace, we applied the generalized Jacobi angles algorithm proposed by Cardoso et al. [14]. The joint diagonalization can be achieved building a matrix as a product of plane rotation globally applied to all matrices L_i.

The approximate diagonalized Laplacians are therefore obtained by the following equation:

$$\tilde{L}_i = V \; \text{Diag} \; (V' L_i V) \; V' \tag{4}$$

where Diag(A) sets to zero off-diagonal elements of corresponding matrix.

Due to the behavior of the algorithm, the eigenspace V is not guaranteed to be ordered according to the eigenvalues. Indeed, the joint eigenspace has different eigenvalues for each different Laplacian. Hence, matrix V needs to be sorted in order to cluster using the k smallest eigenvectors. To obtain an eigenvectors ranking we introduced a statistical estimation of the eigenvalues cross-subjects, averaging and then sorting in ascending way the eigenvalues Λ_i as:

$$\tilde{\mathbf{\Lambda}} = \text{sort} \; \left(\frac{1}{N} \sum_{i=1}^{N} \Lambda_i \right) \tag{5}$$

This allowed us to draw a unique solution for the problem such that the columns of V were reordered according $\tilde{\mathbf{\Lambda}}$ (from the smallest to the biggest one).

Algorithm 1. Joint Diagonalization of Graph Laplacians

Data: Similarity matrix for each Subject: W_i
Result: Joint Eigensapce V, Assignments to k clusters
Initialization $L_i = D_i^{-\frac{1}{2}}(D_i - W_i)\ D_i^{-\frac{1}{2}}$
Joint Diagonalization: $\min \sum_{i=1}^{N} \mathbf{off}\ (V' L_i V)\ , \quad V'V = I$
for $i = 1$ *to* N **do**
  $\Lambda_i = V' L_i V$
$\tilde{\mathbf{\Lambda}} = \text{sort}\ \left(\frac{1}{N} \sum_{i=1}^{N} \Lambda_i\right)$
k-means applied to the first k columns of V according to $\tilde{\mathbf{\Lambda}}$

3 Results

We applied the proposed algorithm to our rs-fMRI dataset of 10 healthy mice described in section 2.1. To ease the data interpretation, we thresholded functional correlations to focus our attention only on positive values. As an example, in Fig. 1 are depicted the graph matrices of 3 subjects. For each functional graph, the Normalized Symmetric Laplacian has been computed following Eq. 1 and the joint diagonalization has been applied finding the joint eigenspace V.

In Fig. 2 are depicted the ordered eigenvectors and corresponding eigenvalues. Notice the spectral gap between the first 4 eigenvalues. This indicates that there are 4 connected components, i.e. clusters. For this reason we decided to perform spectral clustering on V using $k = 3$ and $k = 4$.

The algorithm produced inter-hemispheric sub-networks related to common functional community already shown in literature. Fig. 3 shows group-wise common functional community determined by our approach. Each of these networks is associated to known brain processes and can be related to well-characterized functional network modules of the human brain (default-mode, visual hippocampal, sensory-motor, and basal ganglia respectively [17]). We also qualitatively compared our results on mouse brain with the results obtained using a method frequently adopted known as Louvain modularity algorithm [18], finding the same functional communities recently described in [19].

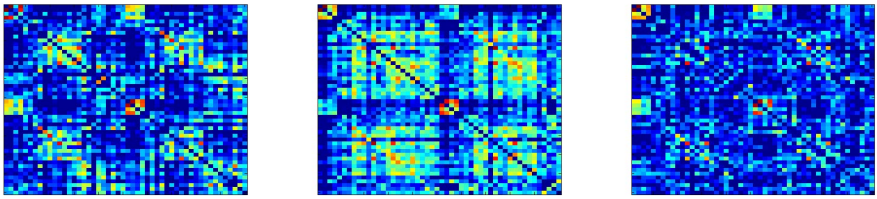

Fig. 1. Overview of functional graphs across subjects. Mean pairwise correlation coefficients are between [0-1] (Blue = 0, Red = 1)

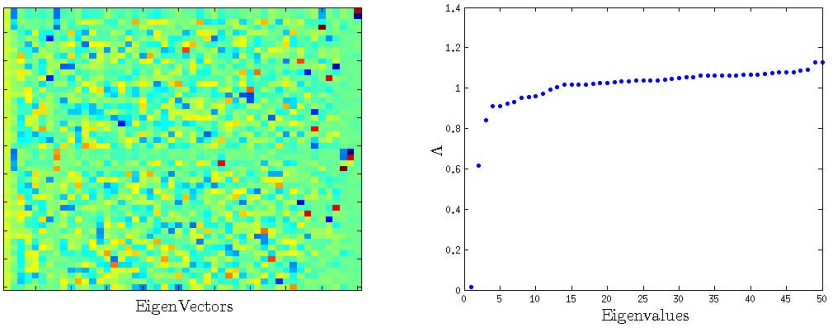

Fig. 2. Left: Joint Eigenbase V sorted according to smallest joint approximate eigenvalues. Right: Average joint eigenvalues $\tilde{\mathbf{\Lambda}}$ sorted in ascending order

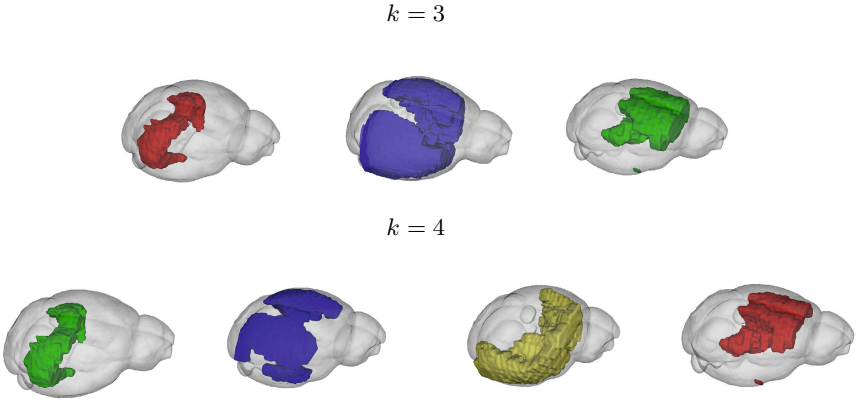

Fig. 3. Top: Group wise fMRI community observed with $k = 3$ shows Hippocampal formation, Parietal and perihippocampal cortices and Corticofrontal and thalamic areas. Bottom: Group wise fMRI community observed with $k = 4$ shows Hippocampus, Parietal somatosensory cortices, Basal ganglia and basolateral cortical areas, and Corticofrontal and thalamic areas

We also evaluated a similar method proposed by Chen et al. [11] and discussed in Section 1. Applying Chen algorithm to our data, we actually observed a good agreement between modified similarity graphs. However, at the end of the iterative process, we were obtaining a different eigenspace for each different similarity graph. As a result their method does not entirely answer the group-wise variability issue. In particular, although the method aims at converging all graphs to a unique representation, it produces different clustering results for each subject, making difficult the identification of common sub-network. Conversely our approach gives back a unique graph representation that well approximates inter-subject graph similarities.

4 Discussion

In this paper, we presented a novel approach to explore functional sub-networks across subjects. The joint diagonalization method, which is mathematically sound, permits to analyze a large number of subjects simultaneously, mapping all connectomes to a unique subspace able to describe the common group-wise sub-networks that delineates a population. Experimental results have shown that our approach is robust since the eigenspace does not significantly change when changing the set of matrices. Moreover, the only source of variability is related to the number of clusters we search for, but this number can be suggested by the data itself.

Other approaches better approximating the joint eigenbase [20] could be explored in the future to minimize the influence of approximation on the eigenvalues. This framework can be also extended to multi-modal network analysis (e.g., functional and structural data) in order to carry out the relationships between two or more views.

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