FUNCTIONAL CONNECTIVITY STATES OF THE BRAIN USING RESTRICTED BOLTZMANN MACHINES

Zeynep Kahraman

Dept. of Electrical and Electronics Engineering, Boğaziçi University, Istanbul 34342, TR zeynep.kahraman@boun.edu.tr

ABSTRACT

Recent work on resting-state functional magnetic resonance imaging (rs-fMRI) suggests that functional connectivity (FC) is dynamic. A variety of machine learning and signal processing tools have been applied to the study of dynamic functional connectivity networks (dFCNs) of the brain, by identifying a small number of network states that describe the dynamics of connectivity during rest. Recently, deep learning (DL) methods have been applied to neuroimaging data for learning generative models. In this paper, we employ the restricted Boltzmann machine (RBM), to learn FC states from resting-state dFCNs. Unlike previous applications of DL to neuroimaging data that focus on feature extraction based on the voxel level activation data, the current work employs RBM to learn connectivity patterns, where the input to RBMs are a collection of windowed covariances across time and subjects. The extracted FC states are evaluated based on their occurrence rate as well as modularity.

Index Terms— rs-fMRI, dFCN, RBM, functional connectivity states

1. INTRODUCTION

Assessment of functional connectivity from resting-state fMRI has contributed significantly to the understanding of functional integration and segregation of the brain. Correlations between intrinsic low-frequency oscillations have led to the identification of a number of intrinsic connectivity networks such as the default-mode network, ventral and dorsal attention networks and salience network [1]. Until recently most studies of FC has been limited by an assumption of spatial and temporal stationarity throughout the scan. Recent studies have demonstrated that dynamics of FC are prominent during resting state [2]. Understanding the time-varying nature of FC provides new understanding of the FC differences found in neuropsychiatric diseases.

In recent years, multiple data-driven and model-based approaches have been developed to assess FC dynamics such as independent component analysis (ICA), principal component Selin Aviyente

Dept. of Electrical and Computer Engineering, Michigan State University, MI 48824, USA aviyente@egr.msu.edu

analysis (PCA) [3], tensor decomposition along with clustering methods such as k-means [4, 5]. These methods learn connectivity patterns directly from data, decompose multisubject resting state data into functionally homogenous networks (FC network states), and capture inter-subject variability.

In this paper, we propose a deep learning inspired approach to extract these concise connectivity patterns from dFCNs of the brain across time and subjects. In particular, we propose a restricted Boltzmann machine (RBM) network architecture to learn the network states from input variables that correspond to windowed covariance matrices. RBMs have been previously used in the context of neuroimaging for identifying intrinsic networks (IN) and have been compared to ICA in terms of the INs extracted [6-8]. Previous work has shown that the RBM structure is similar to a matrix factorization, where the weights of the mixing matrix are directly learned from the data. In this setting, each visible variable corresponds to a single voxel and each hidden variable corresponds to an IN or latent factor. Unlike prior work, in this paper we develop a RBM based framework to learn FC states rather than INs. Therefore, in our setting each visible variable corresponds to a pair of FC values across time and subjects, where the FC values are computed using a sliding window approach with the connectivity matrix estimated as the inverse of the precision matrix obtained from graphical LASSO (glasso). The hidden units in this case are the FC states and the weights refer to the mapping between the observed connectivity networks and a given state. The current work also differs from prior work on FC extraction in that the network states are directly learned from connectivity without any prior assumptions about the number of states or the nature of the dynamics unlike in [5,9]

2. BACKGROUND

2.1. Graphical LASSO

When the number of variables is larger than the number of samples, the estimation of an accurate and stable covariance matrix is difficult, as it may become rank-deficient, i.e. singular. For this reason, penalized likelihood methods are used for estimating a sparse precision matrix, i.e. the inverse of covariance matrix. A commonly used method is Graphical LASSO [10] which proposes a fast solution for this problem with L1-penalty forcing the relation between conditionally independent regions to be zero for a sparser undirected graphical model.

Let Θ and S be the precision and sample covariance matrices of the data, respectively. For a fixed penalty ρ , the problem is to maximize the log-likelihood function given by:

$$\ell(\Theta) = \log \det \Theta - \operatorname{tr}(S\Theta) - \rho ||\Theta - \operatorname{diag}(\Theta)||_1, \quad (1)$$

where tr is the trace operator and $||.||_1$ is the absolute sum of the matrix elements. In order to prevent underfitting, the optimum value of the regularization parameter ρ is determined by cross-validation.

2.2. Restricted Boltzmann Machine

A Boltzmann machine [11] is an energy-based model with known visible variables v and unknown hidden variables h, representing a stochastic undirectional graphical model, also known as Markov random field. Due to the computational complexity resulting from the large number of connectivities, the topology is 'restricted' where linking between same sorts is not allowed.

The goal of DL is to find the parameter set $\theta = \{W, a, b\}$ describing the stochastic model for the data, where W represents the symmetric visible-hidden interactions, a and b correspond to the biases for the visible and hidden units, respectively. The negative log-likelihood of the joint probability distribution of hidden and visible variables, given by:

$$\log(p(x_n)) = \log(\sum_{h} e^{-E(x_n, \boldsymbol{h})}) - \log(Z)$$
 (2)

is minimized for each data point x_n with normalizing factor Z and the energy function $E(\boldsymbol{v}, \boldsymbol{h})$ defined as, $E(\boldsymbol{v}, \boldsymbol{h}) = -\boldsymbol{v}^T W \boldsymbol{h} - \boldsymbol{a}^T \boldsymbol{v} - \boldsymbol{b}^T \boldsymbol{h}$.

In order to apply stochastic gradient descent algorithm, the model distribution must be known beforehand. For this purpose, Monte Carlo approximation is helpful to estimate the distribution from a limited number of samples.

3. METHODS

3.1. Dynamic Functional Connectivity Networks

Most work on constructing dynamic functional connectivity networks relies on sliding window correlation [9], [12]. In this approach, for each subject s = 1, ..., S, each time-series $x_r(t)$ from a ROI r = 1, ..., R is windowed with a tapering window, resulting in $x_r(t_w)$ and the connectivity is calculated as the correlation within each window w = 1, ..., W, i.e. $dFCN(s, w, r_1, r_2) = corr(x_{r1}(t_w), x_{r2}(t_w))$.

Due to the short-length of the window compared to the number of ROIs, the resulting covariance estimate is biased. In order to address this problem, we propose to use glasso to estimate sparse precision matrices of windowed covariances. To determine the regularization parameter ρ , for a sequence of ρ 's (preferably, between 0.001 and the largest off-diagonal value of windows' sample covariances), $\ell_{sw}(\Theta_{\rho,w})$ given in equation (1) is calculated in a cross-validation framework, where $\Theta_{\rho,w}$ is the precision matrix of a randomly selected window estimated from gLASSO for each ρ and S is the sample covariance computed from the remaining signal. This process is repeated for all the windows of a given subject s, consequently the optimum ρ_{opt} is determined as the one maximizing the mean of these log-likelihood values ℓ_{sw} . Finally, the covariance for each window is estimated as the inverse of the precision matrices resulting from gLASSO with ρ_{opt} .

The estimated covariance matrices are then Fisher transformed to stabilize the variance across all connectivities with the same correlation. In conclusion, dynamic FC of rs-fMRI is constructed as an array $dFCN \in \mathbb{R}^{S \times W \times R \times R}$.

3.2. Gaussian-Bernoulli RBM

To extract 'FC states', defined in [9] as patterns of consistent FC across time and subjects, restricted Boltzmann machines with different number of hidden units are evaluated. The number of units nHid represents the number of assumed FC states at resting-state. First, the upper triangular part of the connectivity matrix within each window is vectorized to a vector of length $\binom{R}{2}$. These vectors are then cascaded to form the matrix $P \in \mathbb{R}^{S \cdot W \times \binom{R}{2}}$. These time-varying connectivity vectors form the input layer of RBM (similar to [6].).

Since the conventional RBM, which is also called BB-RBM (Bernoulli-Bernoulli RBM) requires the input to be a binary variable, we use the *Gaussian-Bernoulli RBM (GB-RBM)* to deal with real-valued data as the input to its visible units [13]. Each column of the connectivity matrix P corresponds to the connectivities of a pair of ROIs varying with time. For computational efficiency, the input is assumed to be sampled from a zero-mean, unity-variance Gaussian distribution. In order to obtain a $\mathcal{N}(0, 1)$ distribution, we normalize each column of the matrix P, which corresponds to each pair. With the assumption that visible unit v_i is a sample from a Gaussian distribution centered around a_i with std σ_i , the energy function $E(\boldsymbol{v}, \boldsymbol{h})$ of GB-RBM is given by:

$$E(\boldsymbol{v},\boldsymbol{h}) = -\sum_{i,j} \frac{v_i}{\sigma_i} W_{ij} h_j - \sum_i \frac{(a_i - v_i)^2}{\sigma_i^2} - \sum_j b_j h_j.$$
(3)

The difference of GB-RBM from BB-RBM is that [14] the sampling of the visible unit from the hidden unit is done by using a Gaussian distribution;

$$p(v_i = v | \boldsymbol{h}) = \mathcal{N}(\boldsymbol{v} | a_i + \sum_j w_{ij}, \sigma_i^2).$$
(4)

During gradient update weights are divided by the variance, which does not have any impact on the result, since the variance σ_i^2 is initially assumed to be 1. In order to generate positive and negative weights, hyperbolic tangent function is used for the activation of hidden units.

Once the feature vectors of length $\binom{R}{2}$ are extracted from RBM, they are converted into adjacency matrices corresponding to FC networks of *nHid* states. FC matrices of all windows and across all subjects are clustered into one of these states, using the Manhattan distance function. Percentage of occurrences, which is the ratio of the number of times a particular state occurs to the total number of windows, is calculated for each state of an RBM result with fixed *nHid*.

4. RESULTS

4.1. Data and preprocessing

In this paper, we study the Bangor rs-fMRI dataset from the 1000 Functional Connectomes Project [15]. BOLD responses from 20 healthy subjects (males, ages 19-38) were collected with a 3T scanner while the subjects were at rest with their eyes open. A total of 34 slices were acquired at a TR of 2s, resulting in 265 time points. All pre-processing was carried with CONN toolbox [16]. As part of the pre-processing, images were spatially normalized to MNI space and corrected for slice timing and motion, and spatial convolution with 8mm FWHM Gaussian kernel. Regions of interest (ROIs) were obtained with the automated anatomical labeling (AAL) atlas, resulting in R = 90 ROIs. Finally, time series were band-pass filtered between 0.008-0.09 Hz. Regional time-series signals were computed by averaging BOLD signals of all the voxels within each region. Finally, these average time series signals have been z-scored, minimizing possible bias in subsequent variance-based data reduction steps.

4.2. Optimal dynamic FCNs

Once the time-series for all the ROIs are obtained, they are windowed with a tapered window which is created by convolving a rectangular window (width = 22TRs) with a Gaussian with σ = 3TRs. This window is slid in steps of 1TR along time, resulting in W = 233 windows for each subject. The covariance matrices of these windowed signals are computed by gLASSO after the optimal regularization parameter ρ_{opt} is determined through cross-validation for each subject separately. ρ_{opt} was found to be between 0.033 and 0.068 with a mean of 0.05 and a standard deviation of 0.012 across all subjects.

4.3. RBM results

The vectorized dFCNs after Fisher transformation are the input of RBM, resulting in 'FC states' as features. RBMs [17] were constructed with $\binom{90}{2} = 4005$ Gaussian visible units,



Fig. 1. Analysis to determine the L1-parameter and nHid: (a) The ratio of the maximum weight for each feature to the overall maximum weight is plotted with respect to the feature index for RBMs with different nHid; (b) Variance of occurrences with respect to the number of hidden units and for different L1-parameters; (c) Histogram of the weights of different states from RBMs with nHid = 6 and varying weight decay rate.

corresponding to each pair of ROIs and one hidden layer with varying nHid, ranging from 2 to 32. We searched in this range, since previous work on dFCNs found 8-10 consistent FC states across subjects and time. The learning rate was fixed at 0.001, which is the scaling factor of the gradient update at each 'epoch'. As the simplest version, contrastive divergence with 1 step of chain was preferred for the alternating Gibbs sampling. For full convergence of the parameters, RBMs were trained during 100 epochs with a minibatch size of 5.

To find the optimum weight decay rate, histogram of the weights for all the state networks after applying RBM with varying $L1 \in [0.02 : 0.125]$ was analyzed. As observed in Fig.1(c), there is not any significant change to the sparsity of the weights after weight decay rate of 0.075 (represented in yellow). To determine nHid, the ratio of maximum absolute weight of each feature to the maximum absolute weight overall was computed for RBMs trained with varying nHid. In Fig.1(a), each line represents an RBM with

different nHid and the ratios are sorted in descending order. This ratio drops off significantly around 6 hidden units, indicating that increasing the number of features after 6 will not result in a significant change in representing the data. Moreover, if L1-norm of each feature were to be plotted in descending order, it would also show a decay after the 6th feature. Fig.1(b) shows the variance of occurrences for RBMs with nHid = 2 : 16. As the variance of occurrences decreases, the percentage of occurrences is more uniformly distributed across the hidden units. Fig.1(b) shows this variance stabilizes after 6 hidden units, consistent with the results presented above.

4.4. FC states

Fig.3 illustrates the FC states extracted using RBM with 6 hidden units and a weight decay regularization parameter of 0.075. States are ordered based on their corresponding occurrence percentages (range 11.5-21.8% with mean and deviation $16.7\%\pm3.3\%$.). The observed functional connectivity states are evaluated with respect to the well-known restingstate networks including AN (auditory network), SMN (somatomotor network), SCN (subcortical network), VN (visual network), CCN (cognitive control network), DMN (default mode network) and BiN (bilateral limbic network) [18].

In State1 and State3, DMN is the dominant network and is anti-correlated with sensorimotor regions AN, VN and SMN as well as within itself. At State1, some frontal regions of CCN, are included to form an expanding module with DMN. These dynamic and anti-correlated networks are consistent with previous literature [19]. State2 illustrates the anti-correlation of CCN with the rest of the network, and a module consisting of CCN with SMN, AN and SCN. In State5 and State6, the correlations of sensorimotor regions with each other are salient, where as the subnetworks AN and SMN are highly connected in State5. State4 summarizes the connectivity of VN within itself as well as the interactions with cognitive regions of the brain.

In the first three states, as most of the connectivity values are negative, resulting in a large negative modularity value. Moreover, the number of optimal modules is n = 2 for the first 4 states, indicating that each state is a representation of two distinct pairs of subnetworks. Fig.2 shows the state transitions as a function of time for two subjects, which have similar patterns. FC stays at State1 for long periods, and the duration of other states, especially State6, are shorter. Clearly, this is observed through the occurrence percentage of each state.

5. CONCLUSION

In this article, we examined FC states of rs-fMRI scans by extracting them as features of dFCN using a restricted Boltzmann machine. The obtained states summarize the dominant interactions between and within functional subnetworks. DMN is found to be as one of the prominent subnetworks during resting state similar to previous work in [18, 19]. Furthermore, sensorimotor regions are highly connected, due to perpetual sensing. FC states obtained by RBM are highly modular and representative of the patterns in dFCN. In terms of future work, this research can be extended by using a deep belief network.



Fig. 2. State transitions of Subject2 and Subject8.



Fig. 3. FC network states resulting from RBM with nHid = 6 and weight decay L1-parameter 0.075. For each state, occurrence percentages, modularity index (Q) and the optimal number of modules n calculated by Brain Connectivity Toolbox [20] are given.

6. REFERENCES

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