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Analysis of time-varying brain connectivity using nonparametric Bayesian model

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Abstract

The study of time-varying brain connectivity is essential for understanding the dynamic interactions between different brain regions, especially in the context of cognitive processes, neurological disorders, and brain network functioning. In this paper, we present a novel approach for analyzing effective brain connectivity using a nonparametric Bayesian model. Specifically, we apply a Hierarchical Dirichlet Process Auto-regressive Hidden Markov Model (HDP-AR-HMM) to capture the temporal evolution and structural patterns of connectivity between brain regions. The proposed model allows for flexible, data-driven clustering of brain states while incorporating both temporal dependencies and hidden states. We demonstrate the utility of this method in revealing the dynamic structure of brain networks and uncovering time-varying patterns of effective connectivity. Our approach is validated using Alzheimer fMRI data, showing that it the dynamic interaction among brain regions during a simple sensory-motor task experiment, providing new insights into the dynamic processes governing brain activity.

Keywords: Brain Connectivity; Time-varying Connectivity; Hierarchical Bayesian modeling; fMRI; HDP

1. Introduction

Examining the causal relation among brain regions, also known as effective connectivity, during a cognitive task is a challenging work in the field of neuroscience [1]. Methods from previous studies have focused on estimating the causal relation based on neuroimaging data such as functional Magnetic Resonance Image (fMRI) [1, 3], and ElectroEncephaloGraphy (EEG) [5]. Dynamic Causal Model (DCM) [6] is based on a nonlinear input-state-output system and comprises a bi-linear approximation in order to model the interaction at a neural level. Another study, Structure Equation Modeling (SEM) [7], decomposes interregional covariances of fMRI time-series to find interactions among brain regions.Besides, several methods have been proposed using Vector AutoRegressive (VAR) [2, 3] and the Granger causality to identify the directed influence among activated brain areas. The VAR models temporal effects across different regions and characterizes the dependencies in terms of the historical influence one variable has on another. In general, the gap these approaches reveal is that they tend to assume the data are stationary, while most neuroimaging data are non-stationary. Actually, the connectivity changes over time and the rule of these changes is unknown. To overcome this limitation, a common approach is to use a sliding time window method [8] which assumes stationarity within a window, thus makes it possible for the time-varying connectivity estimation. But how to select the window length is a nontrivial task. Dynamic Bayesian Network (DBN) has been used to learn the time-dependent interactions among brain areas [9]. By averaging all the data from a group, these methods assume that every subject within the group has the same connectivity structure. Adaptive AutoRegressive (AAR) model has been applied to estimate the time-varying connectivity in EEG [4]. However, in this method, finding optimal parameter values such as model order and

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updating coefficients is nontrivial and the method also assumes that all the subjects have the same connectivity structure.

In neuroimaging applications, it is commonly required to estimate the connectivity shared by a group of subjects or to find the different connectivity between groups. At the same time, group analysis also needs to find specific features of individual subjects [10]. In [9], they took the average of the fMRI time series of all the subjects and assumed that the estimated connectivity represented for all the population. But in some cases, this approach could enhance the signal-to-noise ratio [10]. Another study estimates a connectivity network for each individual subject and then performs group analysis on these individual estimated connectivity networks [11]. However, this method may not help to draw comprehensive group data for correct inferences about statistically significant disparities among groups [10].

To address this issue, we propose the use of a nonparametric Bayesian method, specially employing multiple Hierarchical Dirichlet Process-Autoregressive-Hidden Markov Models (HDP-AR-HMM) [12] for time-varying connectivity analysis that applies to group fMRI data. HDP-AR-HMM is an extension of switching VAR process with an infinite dynamical mode. The AR model parameters which capture the relationship among brain regions can be changed and modulated by a hidden Markov chain, in which the number of states can be learned from the data. The HDP-AR-HMM has been used in econometric [12] and target tracking [13], but to our best knowledge, has not been applied to fMRI data.

HDP-AR-HMM can be used to estimate the time-varying connectivity from multiple subjects by combining all subjects using the same set of transition and dynamic parameters. But this approach assumes that all subjects share the same set of features and switch among them in the same way. Thus it does not represent the variability across subjects in terms of individual selection of subset of features or their different ways of switching. This problem has been dealt with in [14], where dynamic behaviors are shared across objects using Beta processes. Hence the variability was captured by using subsets of low-lever features precisely sampled to a specific object. The method focuses on capturing separate variations considered as unique features for a specific object. Compared to this method, ours goes further by trying to discover the global connectivity shared across subjects while allowing for subject specific variability. We integrate multiple HDP-AR-HMMs, each HDP-AR-HMM corresponding to one subject. The base distributions of each HDP-AR-HMM are shared via HDP to encourage the common connectivity patterns shared among subjects. This allows us to simultaneously learn the common time-varying connectivity of a group of individuals without ignoring individual specificness.

The rest of the paper is organized as follows. In section 2, we review the background of Hierarchical Dirichlet Process, the Hierarchical Dirichlet Process Autoregressive-Hidden Markov model and describe the developed HDP-AR-HMM for group analysis. In section 3, we present and discuss the experimental results. Finally, session 4 is conclusive.

2. Proposed Method

2.1. Hierarchical Dirichlet Process

Dirichlet process (DP) denoted by $DP(\gamma, H)$, provides a distribution on discrete measure. γ is a concentration parameter and H is the base measure on a measure space θ. Sethuraman [15] shows that $G_0 \sim DP(\gamma, H)$, a sample drawn from the DP, is a discrete distribution by the following stick-breaking construction.

$$G_0 \sim \sum_{k=1}^{\infty} \beta_k \delta_{\theta_k}, \quad \beta_k = \beta'_l \prod_{l=1}^{k-1} (1 - \beta'_l), \quad \beta'_k \sim Beta(1, \gamma), \quad \theta_k \sim H \tag{1}$$

The set of atoms θ_k drawn from base measure H and β represent a set of weights satisfied $\sum_{k=1}^{\infty} \beta_k = 1$ and denoted by $\beta \sim GEM(\gamma)$. δ_{θ_k} is a probability measure concentrated at θ_k.

DP is often used as a prior distribution for a mixture model with unbounded number of components, resulting in a DP mixture model. To generate the observations, let $z_i \sim \beta$ and draw $y_i \sim F(\theta_{z_i})$. Data points sharing the same parameter θ_k are clustered together under the mixture model.

Hierarchical Dirichlet process (HDP) [16] extends the DP to model groups of data, some of which are related, such that data from one group may be shared with data from another. In HDP, a global measure G_0 is drawn from $DP(\gamma, H)$, and then a set of specific measures G_j is drawn from $DP(\alpha, G_0)$ with base measure G_0 for each group:

$$G_0 \sim DP(\gamma, H) \quad (2)$$
$$G_j \sim DP(\alpha, G_0) \quad (3)$$

The common base measure G_0varies around the prior H where the amount of variability is determined by γ. Moreover, the discreteness of G_0 guarantees that the G_j will reuse the same set of shared mixture components defined in G_0but with different proportions [16]:

$$G_0 \sim \sum_{k=1}^{\infty} \beta_k \delta_{\theta_k}, \ \ \beta \sim GEM(\gamma), \ \ \theta_k \sim H \quad (4)$$

$$G_j \sim \sum_{k=1}^{\infty} \pi_k \delta_{\theta_k}, \ \ \pi_j \sim DP(\alpha, \beta) \quad (5)$$

Given G_j, the data samples y_{ji}, in each group j are drawn from $y_{ji} \sim F(\theta_{z_{ji}})$, where $z_{ji} \sim \pi_j$

2.2. Time-varying connectivity analysis with HDP-AR-HMM

HDP-AR-HMM is an extension of switching VAR process with an infinite dynamical mode. VAR models quantify the linear interdependence among regions in the system [2]. The weights in the coefficient matrix measure the influence that each region exerts on others. A pair of independent regions leads to a weight of zero whereas a pair of dependent ones results in a nonzero magnitude. The advantage of this model is that the parameters of VAR process, including coefficients and noise covariance, are modulated by hidden Markov chain. Thus this model can switch between states or modes, each of which has its own set of parameters. Hence the overall parameters are time-variant.

In HDP-AR-HMM, to model the transition to an unknown number of states, an infinite mixture is required. Here, β is the prior on the transition matrix, formulated as a stick-breaking construction (4). We consider the rows of the state transition matrix as multiple groups and each state as the index of components. Therefore, the transition vector associated with state j is represented by π_j (5), each HDP group distribution π_j is a state specific transition distribution. Let $y_{1\ldots T}$ be the observation sequence corresponding to hidden states $z_{1\ldots T}$. Given that the previous state z_{t-1}, z_t is generated from $Mult(\pi_{z_{t-1}})$, then the observation y_t will be generated from the distribution $F(\theta_{z_t})$. In this model, the observations are modeled as conditionally VAR.

$$z_t \sim \pi_{z_{t-1}}, y_t = \sum_{l=1}^{p} A_l^{\pi_{z_t}} y_{t-1} + e_t(z_t) \quad (6)$$

where A_i is a coefficients matrix and $e_t \sim N(0, \Sigma)$ is Gaussian noise

By sampling π_j as in (5) each row of the transition matrix is drawn from the same DP and thus the HDP does not differentiate between self-transitions and transitions to other states. However, when modeling fMRI time series exhibit state persistence and we would like to incorporate this feature into the prior in order to rule out unrealistic high dynamics in the state sequence. To address this problem, [17] has considered the sticky HDP-HMM where π_j is distributed as follows:

$$\pi_j \sim DP(\alpha + k, \frac{\alpha\beta + k\delta_j}{\alpha + k}) \quad (7)$$

An amount k is added to j^{th} component of β , which leads to an increased probability of self-transitions.

Given the transition matrix π_k, dynamic parameters $(A_i^k, \sum^k)$, and the observation $y_{1\ldots T}$, sample the state sequence by using a variant of the forward-backward procedure.

Sample the dynamic parameters $(A_i^k, \sum^k)$, from the posterior given conjugate prior of the matrix-normal inverse-Wishart and sample the transition matrix π_k given the state sequences $z_{1\ldots T}$ and observations $y_{1\ldots T}$

Since the VAR coefficients and covariance matrix of HDP-AR-HMM characterize the influence each region has upon them, they are exploited to the study of time-varying brain connectivity (locally invariant). Specially, we employ the ideas from the Partial Directed Coherence (PDC) [18] to represent the effective connectivity among brain regions in the

concept of Granger causality. In order to define the PDC, we need to take the Fourier transformation of the VAR coefficients:

$$A(f) = I - \sum_{r=1}^{p} A(r)exp - ifr \tag{8}$$

Then the PDC from ROI j to ROI i is defined as

$$PDC_{i \leftarrow j} = \frac{|A_{ij}(f)|}{\sqrt{\sum_{l=1}^{K} |A_{lj}(f)|^2}} \tag{9}$$

If there are multiple subjects and we would like to estimate the common connectivity patterns which are shared among subjects. HDP-AR-HMM can be used in which all subjects are combined with the same set of transition and dynamic parameters. However this approach assumes that all subjects share the same set of features and switch among them in the same way and not consider the variability across subjects. Thus our work focuses on modeling multiple subjects and capturing the subject-specific from a shared set of connectivity patterns.

2.3. Group time-varying connectivity analysis with multi HDP-AR-HMM

Our method builds on HDP-AR-HMM to learn the common connectivity patterns from a group of subjects while allowing for subject specific variability in terms of individual selection from a shared set of features. For this purpose, we integrate a multiple HDP-AR-HMM using HDP, such that the connectivity patterns are shared across subjects. The graphical model of the multiple HDP-AR-HMM is shown in Fig. 1:

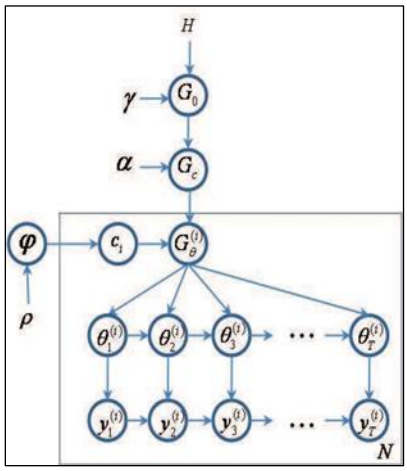

Figure 1 Multiple HDP-AR-HMM

In our model, a global random measure G_0 is distributed as Dirichlet process $G_0 \sim DP(\gamma, H)$ and is represented in the form of stick-breaking according to (4): $G_0 \sim \sum_{k=1}^{\infty} \beta_k \delta_{\theta_k}$, $\beta \sim GEM(\gamma)$, $\theta_k \sim H$. Here, G_0 is used as a prior distribution over all models. All the subjects are grouped and each group s has a random probability measure $G_s \sim DP(\alpha_0, G_0)$. Similar, the form of Gs is: $G_s \sim \sum_{k=1}^{\infty} \beta_{jk} \delta_{\theta_k}$, $\beta_j \sim DP(\alpha_0, \beta_0)$. For each subject i, a label s_i is indicated that $G_0^{(i)} = G_{s_i}$. A subject i choose G_{s_i} as the base probability measure and draws its own transition probability $G_j^{(i)}$ from Dirichlet process $G_j^{(i)} \sim DP(\alpha, G_{s_i})$.

The generative model is:

$$\varphi = GEM(\rho) \tag{10}$$
$$c_i = Mult(\varphi) \tag{11}$$
$$\beta = GEM(\gamma) \tag{12}$$
$$\pi_{kc} = DP(\alpha, \beta) \tag{13}$$
$$\pi_j^{(i)} = DP(\alpha_0, \pi_{c_i}) \tag{14}$$
$$z_t^{(i)} = Mult(\pi_{c_i}{}_{t-1}^{(i)}) \tag{15}$$

$$y_t^{(i)} = \sum_{l=1}^{p} A_{l,z_t}^{(i)} y_{t-l}^{(i)} + e_t^{(i)}(z_t^{(i)}) \tag{16}$$

3. Experimental Results

3.1. FMRI data

The data used in this method is from Washington University [21]: thirteen subjects with very mild to AD condition were scanned during a simple Sensory-motor experiment. During the task, subjects are required to respond with a button press with their right index fingers to a stimulus onset. The visual stimulus was a flash186 ing checkerboard which was presented for 1.5 sec in single or in pairs with a 5.36 sec gap between presentations. The raw data were received from the fMRI Data Center at Dartmouth College and were preprocessed using SPM5 [20]. Images were motion corrected and normalized to coordinates of Talairach and Tournoux [19]. They are also smoothed with a 4mm Gaussian kernel to decrease spatial noise.

We apply group independent component analysis (ICA) (Calhoun and Adali, 2006) on the group of subjects from Washington University (Buckner et al., 2000) to extract the activation areas. Recent studies showed that ICA can be used to separate fMRI data into meaningful components, classified as task-related, transiently task-related and motion-related (Calhoun et al., 2003). The sensory-motor experiment suggests that the regions of interest (ROIs) are those associated with visual processing and motor response. In this analysis, the number of components is selected using the minimum description length (MDL) criteria (Rissanen, 1978). The number of components extracted from the data is 24. From this configuration, we use two PCA reduction steps and the Infomax algorithm (Bell and Sejnowski, 1995) to decompose data into temporal and spatial components. We created a brain mask consisting of these regions using the Brodmann template. After applying ICA, an activation map consisting of voxels whose spatial map shows the highest correlation with the mask was selected. The ROIs identified were the primary motor cortex (PMC, BA4, 1267 voxels), the supplementary motor area (SMA, BA6, 3601 voxels), the primary visual cortex (PVC, BA17, 1137 voxels), and the extrastriate visual cortical cortex (EVC, BA18 and BA19, 5949 voxels) as shown in Figure 2.

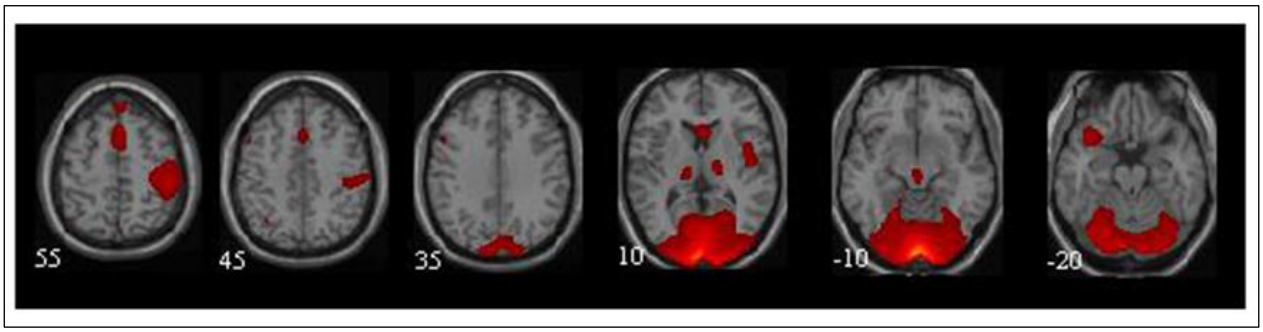

Figure 2 Activated voxels obtained by ICA on the group of 13 subjects

Time series was extracted from each ROI and the intensity of voxels appears in wide ranges because not every voxel in the ROI are strongly activated. Figure 3 shows the average of time series extracted from each ROI.

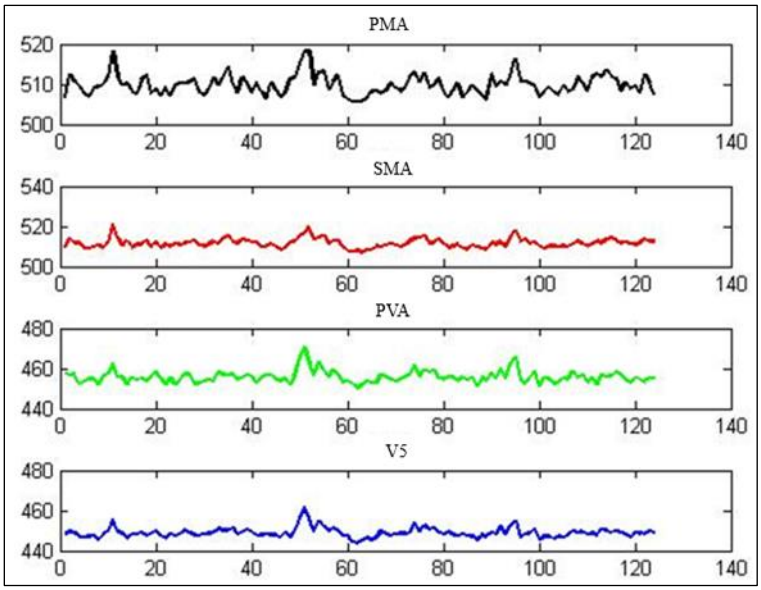

Figure 3 The averaged time series from 4 ROIs

The fMRI time series of each ROI of each subject was applied to the multiple HDP-AR-HMMs. The optimal model order was selected by using Akaike Information Criterion (AIC) and the model order was 4 for all subjects. Fig. 4 shows the feature matrix which indicates the underlined states of each subject and the state shared across the subjects. In this figure, each subject has a different sub AR model modulated by the states and there is only one sub AR model shared among the subjects. Therefore, it is very important to employ a flexible framework like multiple HDP-AR-HMMs in modeling. This is advantageous over mAR-HMM [24] which requires a prior number of the states. The common AR coefficient was used as input to the PDC to calculate the connectivity among ROIs. In Fig. 5, results of the partial directed coherence analysis for four ROIs are shown. The spectra of the processes are given on the diagonal. Partial directed coherence detects the causal influences in PVC→PMC, PVC→SMA, PVC→V5, V5→PVC and PMC→PVC is significant at the corresponding oscillation frequencies. The corresponding 5%−significance levels are indicated by dot lines.

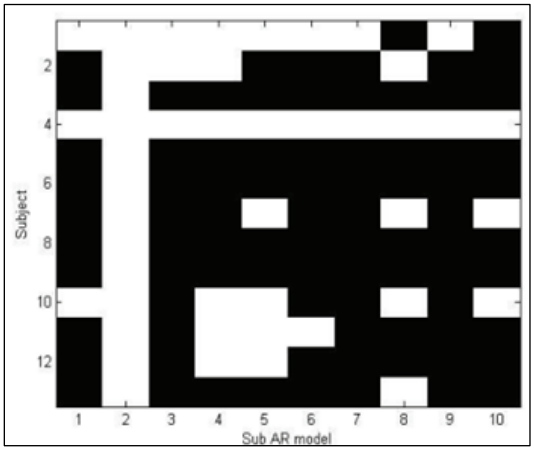

Figure 4 Feature matrix**.**

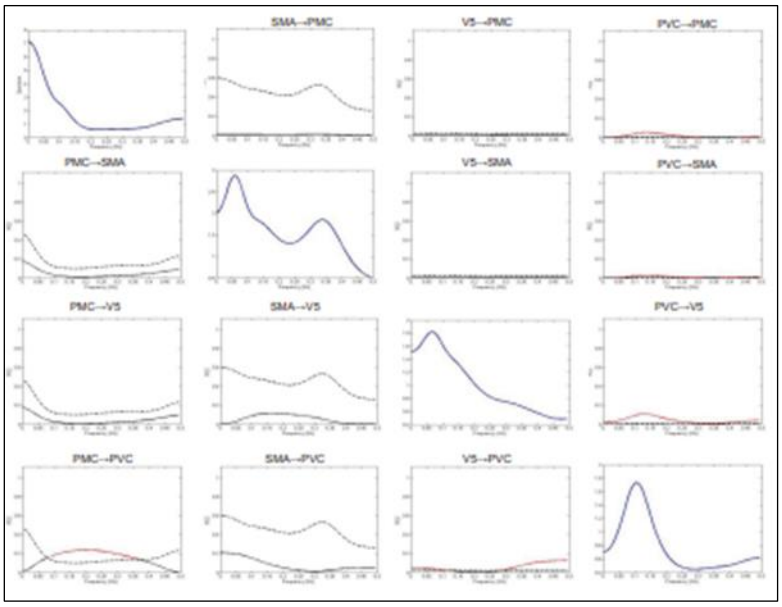

Figure 5 Partial Directed Coherence, which measure the influence of ROI ***j*** on to ROI ***i***.

4. Conclusion

In this paper, we proposed non-parametric framework for group time-varying connectivity analysis and demonstrated how the shared dynamic parameter can be used to identify the time-varying connectivity among brain regions. In this approach, each subject is modeled by an HDP-AR-HMM, which solves the problem of non-stationary fMRI. By adding an additional level making use the master DP to link the multiple HDP-AR-HMMs, we allow all models to share the common states and the transition characteristic of multiple subjects to be combined. This approach is able to identify the common connectivity among subjects based on shared dynamic parameter, which is firmly supported by the results on synthetic data and real fMRI data. Thus this approach can serve as a useful tool for exploring the time-varying connectivity among brain regions from multiple subjects.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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