A MULTI-SUBJECT, DYNAMIC BAYESIAN NETWORKS (DBNS) FRAMEWORK FOR BRAIN EFFECTIVE CONNECTIVITY

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ABSTRACT

As dynamic connectivity is shown essential for normal brain function and is disrupted in disease, it is critical to develop models for inferring brain effective connectivity from non-invasive (e.g., fMRI) data. Increasingly, (dynamic) Bayesian network (BNs) have been suggested for this purpose due to their flexibility and suitability. However, ultimately extrapolating BN results from one subject to an entire population first requires methods meaningfully addressing inter-subject, within-group variability. Here we explore two group analysis approaches in fMRI using DBNs: one is to construct a group network based on a common structure assumption across individuals, and the other is to identify significant structure features by examining DBNs individually-trained. By investigating real fMRI data from Parkinsons Disease (PD) and normal subjects performing a motor task at three progressive levels of difficulty, we noted that both methods detected statistically significant, biologically plausible connectivity between task-related region-of-interest (ROIs) that differed between the PD and normal subjects. However, the second approach was more sensitive, finding more features that were also consistent with prior neuroscience knowledge. Determining highly reproducible DBN nodes/edges across subjects seems promising for inferring altered functional connectivity within a group.

Index Terms— effective connectivity, dynamic Bayesian networks, inter-subject variability, fMRI

1. INTRODUCTION

Effective brain connectivity, the neural influence that one brain region exerts over another, is important for brain function, and its impairment may be associated with neurodegenerative diseases such as Alzheimers or PD. Some mathematical methods such as structural equation modeling (SEM), multivariate autoregressive modeling and dynamic causal modeling (DCM) have been proposed for effective connectivity using functional magnetic resonance imaging (fMRI) data. DCM is the only approach to date that attempts to explicitly model the "neuronal" and "hemodynamic" levels, but the stability of the parameters specifying the relation between the neuronal and hemodynamical levels, especially in older or diseased subjects remains to be established. Recently, (dynamic) Bayesian networks (BN) have been proposed to discover brain connectivity in fMRI [1, 2, 3]. The BN approach is attractive due to its solid bases in statistics. The generality of the DBN framework is that DCM can be regarded as one particular case of DBN, where each ROI's "neuronal activity" is represented by a hidden node, the observed nodes (i.e. the BOLD fMRI signal in a ROI) represent the "hemodynamic level" of the model.

Our previous work on DBNs have showed connectivity in PD may be altered given data from a single subject [3]. However, ultimately extrapolating BN results from one subject to an entire population (e.g. patients with Parkinsons disease) first requires methods to meaningfully integrate results from several subjects and rigorously compare BNs across different populations. This inter-subject variability, a common and critical problem in many biomedical studies, remains a challenging problem. One study assumed that averaging the fMRI time series over all subjects is an effective representation of the study population [1], another suggested applying the same model to all subjects and hence treating a group of subjects' data as being from the same subject [4], and another applied analysis to only a single subject [5]. These approaches may fail to distinguish connectivity patterns which are truly robust across individuals, as they may be sensitive to outliers. Goncalves [6] have demonstrated the difficulty of interpreting fMRI data when intersubject variability is large. Nevertheless inter-subject variability has been successfully dealt with in positron emission tomography (PET) studies [7], suggesting it is possible and important to address in fMRI studies.

Employing large, multi-subject SEM networks was proposed to address inter-subject variability [8], where all subjects were modeled with fully connected SEMs. The basic idea was to infer differences across subjects by comparing two models: one that allowed inter-subject variability and another that did not. In the former one, the parameters of each connection are allowed to be different across subjects, but in the latter one they are not allowed. With this approach, all subjects are assumed sharing a common structure, (in this case a fully connected graph), and inter-subject variability is accommodated by different parameter values across subjects. An alternative approach for dealing with inter-subject variability is to estimate the connectivity for each subject individually [2, 6], allowing not only different parameters cross subjects but also different connectivity structures. Since there is no apparent statistical reason why one approach should necessarily be superior to another, in this paper, we investigate both approaches, utilizing real fMRI data from PD study, with an important distinction: instead of arbitrarily assuming fully connected networks for each subject as done previously [8], we learn the common structure from the data utilizing dynamic Bayesian network modeling.

The paper is organized as follows. We describe the DBN framework for brain effective connectivity and group analysis in Section 2. A case study using fMRI data from normal and PD subjects is discussed in Section 3. Finally, we give conclusions.

2. METHODS

In this section, we present the DBN-based framework for inferring effective connectivity between brain regions based on fMRI data. The fMRI data from multiple regions are regarded as a vector-valued stochastic process $X_t = \{x_t^1, ..., x_t^i, ..., x_t^M\}^T$, with x_t^i represent-

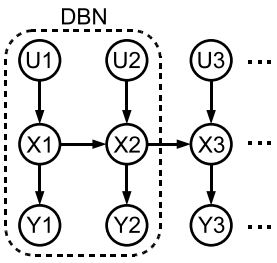
ing the i^{th} region at time t and M being the total number of regions. A DBN is learned to model X_t, representing the connectivity between regions. To deal with the issue of inter-subject variability, we then investigate group analysis by inferring DBN representative of multiple subjects within a given group.

2.1. Dynamic Bayesian Networks

A dynamic Bayesian network (DBN) [9] is a graphical model for stochastic process. The term "dynamic" means that the Bayesian network models a dynamic system, but not that the model itself changes overtime. A first order Markov process is a good example of DBN (see Fig. 1). The Markov process can be fully specified by the initial distribution $P(Z_1)$ and the transition distribution $P(Z_{t+1}|Z_t)$ where Z_t is the state variable at time t. A directed graph with arrows from Z_t to Z_{t+1} (t = 1, 2, ...) can represent the temporal dependence relationships. Since the same transition distribution repeats, the graph can be simplified as just an arrow from Z_1 to Z_2 and the two nodes. If Z_t is a vector composed of random variables, for example, Z_t=[U_t, X_t, Y_t]^T as in Fig. 1, the dependence relationships can be represented more exactly by expanding the nodes Z_1 and Z_2 to the their elements and by replacing the arrow from Z_1 to Z_2 with arrows from nodes at time t=1 to those at time t=2. Meanwhile, arrows between nodes at the same time points can be added to represent the dependence relationships within them, in addition to the temporal dependences. The expanded directed graph must satisfy two contrains: first, there is not any arrow from time t to $t+1$; second, there is not any cycle. Either a conditional or an unconditional probability distributions is associated with a node, describing how it depends on its parent nodes or its unconditional distribution if it does not have any parent nodes. The joint probability of an observed process is the multiplication of the conditional or unconditional probabilities of all the nodes.

We can model fMRI signals from multiple regions with a DBN by regarding them as a vector-valued Markov process. Though DBNs can also represent Markov processes of higher orders, we strict ourselves to the first order Markov processes in this study. Moreover, we assume all the conditional or unconditional distributions associated with the DBN follow Gaussian distributions. Applied to fMRI signals, a DBN can not only represent the temporal dependence between brain regions, but also the assoication at the same time point.

Brain connectivity, *i.e.* the structure of a DBN, is learned from fMRI data according to the maximum *a posteriori* (MAP) criterion, *i.e.* to choose the most probable structure after observing the data. More specifically, we choose the structure with the largest Bayesian information criterion (BIC) [10] score which is defined in Eq. (1)



Z_t = [U_t, X_t, Y_t]^T is a first order Markov process with dependence relationships specified as in the figure; X_t is a Markov process whose transition distribution $P(X_t|X_{t-1}, U_t)$ varies according to the input U_t. Arrows from X_{t-1} and U_t to X_t are associated with the transition distribution. Y_t is the output observation at time t. The arrow from X_t to Y_t is associated with the distribution $P(Y_t|X_t)$. Such a process can be represented by the first two time-slices circled by dots [9].

Fig. 1. An example of dynamic Bayesian networks

where N means the sample size of data X and K means the number of the free parameters θ of the model S.

$$\mathrm{BIC}(S) = \sup_{\theta} \log P(X|S,\theta) - 0.5K \log N \quad (1)$$

Since the selected brain regions in this study were all activated by the input task, we set a constrain in the structure, that there must be at least a path from the input task to every ROI. We had relaxed the constrain to that there must be a path from the input to at least a ROI, but the results showed that all the structures learned under the relaxed contrain satisfy the more rigorous one, which supports that our constrain is reasonable.

2.2. Inter-subject variability

In addressing the issue of inter-subject variability, as it is difficult to specify, a priori, which approach will be superior for our population, we employ two approaches: one is the individual-structure approach, and the other is the common-structure approach.

For the individual-structure approach, a DBN is learned for each subject independently according to the maximum *a posteriori* (MAP) criterion. As a result, a group of subjects will have a group of DBN structures. Robust connections in a group are extracted by picking out those whose appearance across subjects is higher than a threshold, for example, above 50%. Features distinguishing one group from another can be detected by simply compare the two robust structures, or more elaborately comparing the two groups of structures as in [11]. We compared the existence of pathways from one region to another but not direct connections, because biomedical knowledge usually only hints that there are pathways for neural signals to be transmitted from one region to another, but not necessarily that the signals are directly transmitted (i.e. one step path). The comparison procedure is as follows. First, a subject's connectivity structure where an arrow means a direct connection, are converted to a "path" graph where an arrow means the existence of a path. Then the appearance frequencies of "path" connections in two groups of subjects are compared with statistical tests, such as the t-test or Fisher's exact test. Finally, the effect of multiple testing is adjusted if multiple "path" connections are tested.

For the common structure approach, regions from different subjects are assumed to be unconnected, a common connectivity structure between ROIs is imposed for every subject in the same group, and inter-subject variability is accounted for by adjusting the parameters for each subject. Correspondingly, a common structure's BIC score for the whole group is the sum of its BIC scores for each individual subject, as Eq. (2) where G is a group of subjects and g is a subject in the group.

$$BIC(S|G) = \sum_{g \in G} BIC(S|g) \quad (2)$$

The structure with the largest group BIC score is selected as the common structure of the group. Comparison between two groups are performed directly on their common structures via simple topology assessment, e.g. comparing the nodes/edges/subnets.

3. FMRI CASE STUDY

3.1. fMRI Data Collection and Preprocessing

Seven healthy subjects and five PD patients were recruited. By using a pressure-responsive squeeze bulb as the response device, connected electronically to a computer, subjects were asked to squeeze

Connection	Count	p value
R_SMA → R_M1	4/7 vs 4/5	p_o = 0.576, p_a = 0.924
R_M1 → L_CER	6/7 vs 0/5	p_o = 0.015, p_a = 0.044 *
R_SMA → L_CER	4/7 vs 4/5	p_o = 0.576, p_a = 0.924

Table 1. Comparison of the appearance frequencies. The counts are in the form of "No. of appearances / No. of subjects". p_o and p_a are the orignal p value and the adjusted p value respectively. p_o was calculated with Fisher's exact test. The effect of multiptle comparisons was adjusted with Sidak correction: p_a=1 - $(1-p_o)^n$ where n (n=3) is the number comparisons.

Group	Fig. 2 Only	Fig. 3 Only	Both Figures
Control	1	5	8
PD	1	7	6
Both	2	12	14

Table 2. Appearances of the Connections in Figs. 2 and 3. The direction of the connections were ignored.

the bulb with their left hands to control, on the computer screen, the height of a vertical bar to match a target bar which will move up and down in a sinusoidal fashion. This task were repeated at three levels of difficulty by increasing the target frequency: slow, medium and maximum, in the order of six sessions: maximum, slow, medium, slow, maximum and medium. Each speed session lasted for 20sec and followed by a resting period of 23 sec. Six regions of interest (ROIs) were studied here: the left and the right supplementary motor areas (SMA), the left and the right cerebellear hemisphers (CER), and the left and the right primary motor cortices (M1).

All fMRI data were acquired with a 3.0 Tesla Philips scanner. Functional images were scanned using a dynamics sense protocol with a EPI factor of 39, and a TR of 1985.40 msec. Each slice was scanned at 80 by 80 resolution, 3mm slice thickness with a 1mm slice gap, reconstructed to 128 x 128 and then resliced back to 80 by 80 with Amira. Slices were collected in interleaved fashion. A total of 130 volumes were collected for each 260sec. run. High-resolution T1 weighted anatomical images (3D SPGR, TR=8.24ms, TE EPI: 30ms, TE TFE: 3.8ms, flip angle=8, voxel dimensions $1.0 \times 1.0 \times 1.0$mm), were acquired for co-registration of functional images. All fMRI data were corrected for motionwere and corrected for acquisition delays associated with the different slices within a volume. ROIs were manually drawn on the high-resolution structural images using published atlases as a guide and then were co-registered to functional images.

The time series of each ROI is typically the mean time series of all the voxels within an ROI, or perhaps the mean of the voxels within an ROI which appear modulated by the behavioral task above a specified statistical threshold . In this study, each ROI fMRI time-series was obtained by averaging the time-series of all voxels within the anatomically-defined region.

3.2. Results and Discussions

In the proposed DBN framework, the fMRI signals of the six brain regions were considered as the state variables, and the behavior signal of squeezing was considered as the input variable "Freq". We studied the performance of the proposed approach by examining the fMRI data collected above. Our purpose was to reveal brain connectivity features by DBN-based group analysis which were significantly different between the control and PD subjects.

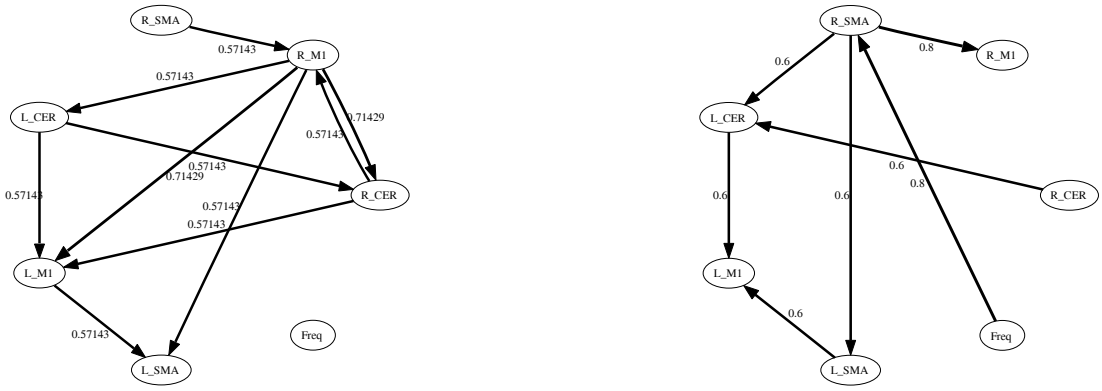
We first investigated the individual structure approach. To get insight into the connectivity difference between healthy and PD status, we compared the learned DBNs when performing the same tasks. Fig. 2 shows the "average" network, indicating the frequency of each connection's appearance in the two groups with only frequencies higher than 50% shown. The results were not highly consistent within the groups, with few frequencies exceeding 80%. Since the sample size (control = 7, PD =5) could not support a large scale of multiple hypothesis testing, we predefined three connections of interest (R_SMA → R_M1, R_M1 → L_CER and R_SMA → L_CER) and compared whether they appeared more frequently in one group than in the other. These connections were selected because using the left hand typically activates the left SMA and M1 and the right cerebellum. The SMA is typically considered "upstream" in the motor pathway and would expect to influence M1. The connection R_M1 → L_CER appeared significantly more frequently (p value = 0.044) in the control group than in PD group, as shown in Table 1. This suggests an alteration of the typical functional connectivity in PD. The cerebellum is believed to receive "corrollary discharges" from M1, in order to predict the sensory consequences of a movement. This result suggest that PD subjects may have impairement in the development of corollary discharges, despite the fact that the main pathology is in the basal ganglia, not the cerebellum.

Further, we investigated the common structure approach. The common structures of the control group and the PD group are shown in Fig. 3. It was noted that some connections appeared only in the control group but not in the PD group, for example: R_SMA → R_CER and L_CER, and R_M1 → L_M1. Some appeared only in the PD group but not in the control group, for example: R_SMA → L_SMA, L_M1 → L_CER and Freq → R_SMA, L_CER and L_M1. The result that the pathway from R_M1 → L_CER appeared only in the control group was consistent with the individual structure approach (see Table 1). The altered connectivity with the Left and Right SMA between normal and PD subjects may reflect the mesial prefrontal dopaminergic pathway involvement in PD. We noted that the increase in the task frequency, while restricted to M1 in normal subjects, is distributed over a much more widespread area in PD subjects, possibly reflecting compensatory mechanisms.

Among the sixteen connections (with their direction ignored) in Fig. 2, forteen also appeared in Fig. 3, which suggests that the common structure approach is highly sensitive to inter-subject robust connections. Among the twenty six connections (with their direction ignored) in Fig. 3, twelve, nearly a half, did not appear in Fig. 2 (see Table 2), which means that the common structure approach has a high error rate in detecting robust connections. The high sensitivity was gained by losing accuracy.

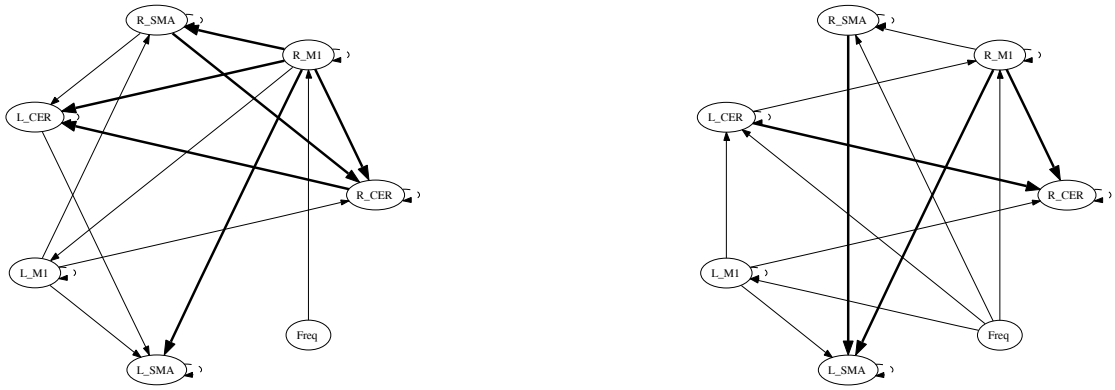
4. CONCLUSIONS

We have presented a multi-subject, dynamic Bayesian network (DBN) framework for inferring brain effective connectivity in fMRI. The feasibility and effectiveness of the proposed framework is demonstrated by an fMRI case study involving PD subjects performing motor tasks. The connectivity differences between the PD group and the control group suggest that changes in connectivity may be a sensitive marker for Parkinsons disease severity and provide insights into the underlying mechanisms of PD. Comparisons between the individual structure approach and the common structure approach suggest that it may not be valid to assume that different subjects with a given group share the same brain connectivity structure. Rather, inter-subject variability may well be pronounced and should not be regarded as random, well-behaved, and uninteresting. Within the



Control PD

Fig. 2. Connection's Appearance Frequencies. Only those whose frequencies are higher than 50% are shown. No matter a connection is from time $t-1$ to t or is within time t, it is considered as a connection from one region to another.



Control PD

Fig. 3. Common Structures of the two groups. Thick solid arrows are connections not only with time t but also from time t to $t+1$; narrow solid arrows are connections only within time t; dashed arrows are connections only from time t to $t+1$.

proposed DBN framework, future work will focus on improving the common structure approach. Specifically by using the common structure as a "prototype", we will detect significant structure features across subjects by comparing a model that allows a feature (e.g. one edge) for inter-subject variability with one that does not.

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