FDR-Controlled Network Modeling and Analysis of fMRI and sEMG Signals

by

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Abstract

Neural recording technologies such as functional magnetic resonance imaging (fMRI) and surface electroencephalography (sEMG) provide great potential to studying the underlying neural systems and the related diseases. A broad range of statistical methods have been developed to model interactions between neural components. In this thesis, a false discovery rate (FDR)-controlled exploratory group modeling approach is introduced to model interaction/cooperation between neural components.

Group network modeling for comparison between populations is of great common interest in biomedical signal processing, particularly when there might be considerable heterogeneity within one or more groups, such as disease populations. A group-level network modeling process, the group PC_{fdr} algorithm with taking into account inter-subject variances, is proposed. The group PC_{fdr} algorithm combines group inference with a graphical modeling approach for discovering statistically significant structure connectivity. Simulation results demonstrate that the group PC_{fdr} algorithm can accurately recover the underlying group network structures and robustly control the FDR at user-specified levels.

To further extract informative features and compare the connectivity patterns across groups at the network level, network analysis methods including graph theoretical analysis, lesion and perturbation analysis are applied to examine the inferred networks. It can provide great potential to investigate the connectivity patterns as well as the particular changes associated with certain disease states.

The proposed network modeling and analysis approach is applied to fMRI data collected from control and Parkinson’s Disease (PD) groups. The network analysis results of the PD groups before and after L-dopa medication support the hypothesis
that PD subjects could be ameliorated by the medication. In addition, based on the comparison between PD subtypes, we observe that the learned brain effective networks across PD subtypes display different connectivity patterns.

In another sEMG study in low back pain, significant findings of muscle coordination networks are found to be associated with low back pain. The results indicate that the networks representing the normal group clearly exhibit globally symmetrical patterns between the left and right sEMG channels, while the connections between sEMG channels for the patient group are more likely to cluster locally and the learned group networks show the loss of global symmetrical patterns.
Preface

This thesis is based on two submitted journal papers:


The research was initiated by Dr. Z. Jane Wang and the majority of the research, including literature survey, model design, algorithm implementation, numerical simulations, statistical data analysis and paper writing, was conducted by the author of this thesis, with suggestions from Dr. Z. Jane Wang and Dr. Martin J. McKeown. Dr. Junning Li helped a lot on the methods part in Chapter 2. Dr. Martin J. McKeown helped greatly on data collection, result interpretation and paper revision in Chapter 3. Dr. Z. Jane Wang helped greatly on revisions of the journal manuscripts. The descriptions of the real data in Chapters 3 and 4 were originally written by Samantha J. Palmer and Dr. Yong Hu respectively.
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## Glossary

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<td>AIC</td>
<td>Akaike information criterion</td>
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<tr>
<td>BIC</td>
<td>Bayesian information criterion</td>
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<td>BN</td>
<td>Bayesian Network</td>
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<tr>
<td>BOLD</td>
<td>Blood-oxygen-level dependence</td>
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<td>DAG</td>
<td>Directed Acyclic Graph</td>
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<td>ECG</td>
<td>Electrocardiography</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>FDR</td>
<td>False discovery rate</td>
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<td>FMRI</td>
<td>Functional magnetic resonance imaging</td>
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<td>KL-DIVERGENCE</td>
<td>Kullback Leibler divergence</td>
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<td>L-DOPA</td>
<td>Levodopa</td>
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<td>LBP</td>
<td>Low Back Pain</td>
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<td>MAP</td>
<td>Maximum a posteriori</td>
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<td>PD</td>
<td>Parkinson’s Disease</td>
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Chapter 1

Introduction

1.1 Motivation

Investigating the functions and mechanisms of human bodies has a long history in the development of neuroscience. Thousands of years ago, the ancient Egyptians already described the cases of brain damage in “The Edwin Smith Surgical Papyrus” which was considered as the oldest medical document in the history of mankind [60]. From then on, people have never stopped exploring the knowledge about human bodies and huge progress has been made in this field over the years. Modern neuroscience covers a broad range of topics such as cellular neuroscience, neurology, neuroimaging and cognitive neuroscience; moreover, it becomes one interdisciplinary area including biology, chemistry, physics, medicine, engineering, computer science, psychology, etc.

Despite the progress made in neuroscience, lots of enigmas still involve human bodies and lots of areas deserve further exploring. The development of neural recording technologies inspires the neuroscience research. In particular, the non-invasive nature of some modern neural recording technologies makes it practical to easily investigate the activities in vivo to study the neural systems, and to understand the underlying mechanisms of some neurological disorders. Some of the most popular neural recording technologies are listed in Table 1.1. Electrocardiography (ECG) is used to measure the electrical activity of the heart by the surface electrodes attached to the skin; Electromyography (EMG) is one primary method for...
measuring muscle activities by detecting the electrical signals produced by muscle contractions; as one popular method to measure the brain activity generated by changes in the electrical charge of thousands of neurons of the cerebral cortex, surface Electroencephalography (EEG) is the recording of electrical activity along the scalp; the advances of the brain mapping technologies including CT (Computed tomography), PET (Positron emission tomography) and fMRI (Functional magnetic resonance imaging) allow the researchers to better explore and understand brain activity and function.

With the development of neural recording technologies, there has been great growth in the number of simultaneously recorded channels [83]. Stevenson and Kording conducted a meta-analysis on previous 56 studies and they found that about every 7 years, the number of simultaneously recorded neurons became doubled [83]. These advances in data collection technologies also affect data analysis approaches. The traditional methods usually focus on a single channel analysis such as amplitude and spectrum estimation. However, modern recording technologies can generate large datasets collecting from multi-channels and thus pose a great challenge on traditional analysis methods. To tackle with this challenging issue, more suitable mathematical methods have been developed to extract information from the large scale datasets. In particular, investigating the interactions between different neural components is receiving increasing research attention.

Studying the interactions between different neural components is important to
understand the organizations and functions of certain neural systems. It is clear that the neural components do not act individually, but interact with each other depending on the particular cognitive tasks. To study which neural components involve in the interactions and how they interact with each other can help us better understand the functions of the neural systems. What is more, researchers are also interested in finding out whether some conditions such as a disease, medication, and physical therapy could alter certain interactions between neural components.

Studying the interaction between different neural components can also provide great potential to investigate the related diseases. For instance, the depletion of the dopamine, a neurotransmitter between cells, can result in Parkinson’s Disease (PD). It is of great interest to investigate the impact of PD on different brain regions and the alternations of interactions between these brain regions of interest in PD. As another example in our study, abnormal back muscle contraction coordination was shown to be related to the chronic Low Back Pain (LBP). The network analysis of lumbar region muscle coordination activity allows the visualization of the muscle coordination activity and the extraction of particular interaction patterns associated with LBP by comparing the networks of control subjects and patients with LBP.

In particular, since biomedical research typically studies a group of subjects rather than focusing on an individual subject, group analysis plays an important role in statistical analysis of neural recording data. For instance, group modeling of brain effective connectivity for comparison between populations is a challenging topic of great importance, particularly when there might be considerable heterogeneity within the groups. Also, for patients with LBP, we want to extract the group-common interaction patterns of lumbar region muscles shared by the patient group.

In this study, we plan to develop a group-level network modeling and analysis framework to investigate the interactions between neural components from fMRI or sEMG data. Moreover, we attempt to extract the group-common features shared by a certain population.
1.2 Background of fMRI and Brain Connectivity

fMRI is one recently developed neuroimaging technology for measuring the brain activities by detecting the changes of the blood oxygenation. Around 1948, Seymour Kety and Carl Schmidt proved that the oxygen metabolism and blood flow in the brain are regulated by the brain activities [44]. In the 1990s, Seiji Ogawa demonstrated the potential to visualize brain activities by the magnetic resonance imaging with contrast dependent on the blood oxygen levels [63]. The underlying mechanism of fMRI is shown in Fig. 1.1. When a brain region becomes active, the blood flow to this area is increasing. More oxygen is delivered to the neurons by haemoglobin which could exhibit different magnetic properties during oxygenation to deoxygenation. When oxygenated, haemoglobin is diamagnetic. However, when deoxygenated, it is paramagnetic. The magnetic property of haemoglobin makes it possible to measure the brain functions via MR signal of blood.

Figure 1.1: (a) BOLD signal mechanism for fMRI. (b) Oxyhaemoglobin and deoxyhaemoglobin blood flow during rest and activation. The figure (b) is from [1].
Several advantages of fMRI make it become one popular brain mapping technology in the cognitive neuroscience: It measures brain functions non-invasively with a relatively good spatial resolution; Various statistical methods developed for fMRI data allow its wide use for studying brain functions; fMRI measures brain activity by recording all regions of the brain instead of being constrained by the cortical surface. Despite all those benefits offered by fMRI, its temporal resolution is relatively low with the order of several seconds. It is hard to measure the differences of the BOLD responses within a short period. Opposed to fMRI, EEG has high temporal resolution but poor spatial resolution. Some studies has combined fMRI with EEG as complementary tools to achieve high spatial resolution as well as high temporal resolution [66].

fMRI has been used widely in the clinical and biomedical applications. One common use of fMRI in clinic is to diagnose neurological disorders such as Parkinson’s Disease (PD), Alzheimer’s Disease (AD), Autism and so on. It is helpful to study the underlying changes of the brain in the conditions of those disorders using fMRI. Human brain is considered as one of the most complex systems and attracts many efforts to study its structure and functions, where fMRI is shown to be a powerful research tool. Based on the data collected from multiple brain regions, it was possible to investigate the interactions between those brain regions or neurons using fMRI. As a result, brain connectivity modeling using fMRI has been attracting increasing research attention during the last decade. There are three kinds of brain connectivity: structural brain connectivity, functional brain connectivity and effective brain connectivity [38].

Structural brain connectivity usually refers to anatomical or physical connections. A lot of structural connectivity studies have been conducted based on datasets collected from the mammals such as rat, cat and monkey, while the data describing human brain structural is relatively few [77]. The diffusion imaging technology advances the progress in the structural connectivity analysis. Some network features are found to be shared by the structural brain networks. For instance, the studies demonstrated that the structural brain networks were neither randomly connected nor completely linked across the cerebral cortical areas, but showed an intricate organization [77].

Functional and effective connectivity are usually derived from the fMRI map-
ping. Functional brain connectivity describes the statistical dependences between different brain regions based on the correlation or coherence. The correlation threshold (CT) is one popular method applied to the fMRI data to estimate the relationships between two components. In the case that the correlation coefficient between two components is higher than the threshold, then the two are considered to be functional linked with each other [21]. Structural equation models (SEM) and Dynamic Causal Modeling (DCM) are linear models for connectivity analysis in neuroimaging which offer great potential for both confirmatory and exploratory modeling. Graph theoretical analysis of functional brain connectivity can extract the connectivity patterns for evaluating the brain functioning and organizations [19].

Effective brain connectivity studies the causal relationships between different brain regions. Many mathematical models have been proposed in the literature to model brain effective connectivity. For instance, Granger causality was employed to learn the directed interactions between brain neurons during the cognitive task [18]. Li etc. used (Dynamic) Bayesian Network to model the effective brain connectivity and demonstrated that the Bayesian Network is a good representation of the causal relationships between different brain regions [51].

1.3 Background of sEMG and Multichannel Analysis

Electromyography is one primary method of measuring muscle activities by detecting the electrical signals produced by muscle contractions. Motor Unit (MU) is the most fundamental functional unit of a muscle which is comprised by a motor neuron and a number of muscle fibers it innervates [81]. When a motor unit fires, the electrical pulse is propagated from the axon of the motor neuron to its terminal branches which connect to the muscle fibers at the neuromuscular junction (See Fig. 1.2). As the electrical pulse reaches the neuromuscular junction, the innervated muscle fibers accumulate the action potentials (AP) and thus trigger the contraction of the MU. The sum of APs from the muscle fibers in a contracting MU is the motor unit action potential (MUAP) which is the building block of the EMG signals [24]. A number of factors such as the number of MUs and the contraction rate can affect the shape of the recorded EMG signals.
Two types of EMG have been used to measure the muscle activities: the needle EMG and the surface EMG. Needle EMG acquires signals by inserting the needle electrode through the skin into the muscle tissue. It can record the muscle activities precisely on a single muscle fiber. In general, needle EMG is performed to observe and diagnose the disorders of peripheral nervous system and muscles in clinic. Surface EMG measures the electrical activity signals of muscles by placing the electrodes on the skin surface along the muscles. Different from needle EMG which is able to detect each individual MUAP, the recorded activities of sEMG are the summation of several active MUs. sEMG is often used to monitor the activity of a large group of muscles simultaneously to acquire the spatial information about muscles.

The non-invasive nature of sEMG allows it to be widely used in various settings and applications. In clinic, it can be used for evaluation and diagnosis of neuromuscular diseases such as low back pain. To evaluate the functional status of skeletal muscles, sEMG can be used as an assistive technology in neuromuscular
training and rehabilitation. Using sEMG signals in the prosthetic devices control has been attracting great interest during the recent years. Another promising application of sEMG is muscle computer interface. By decoding the muscle signals, sEMG sensors can be used to control the computer or other equipments without touching the input devices which is especially more convenient for disabled people. In Chapter 4 of this thesis, we will focus on network modeling and analysis of sEMG signals to investigate the muscle connectivity patterns in low back pain.

The recorded sEMG signals are continuous waveforms whose properties depend on a number of factors such as anatomical and physiological properties of the muscles, the layout of the electrodes and the quality of the contact between the electrode and the skin. The amplitude of sEMG usually varies from the uV level to the low mV level depending on the observed muscles [33]. The acquisition process of sEMG begins with using the electrodes placed on the skin surface to measure the electrical currents. After amplifying the signals, analog band pass filtering is applied to remove the DC offset, baseline drift and high frequency noise. Then the analog signals are converted to digital signals by A/D sampling. A more detailed description of the sEMG acquisition process could refer to [33]. There are mainly two sources of noise introduced into the sEMG acquisition process: One is ambient noise which is generated by the electromagnetic devices with a wide range of frequency components. The other is transducer noise which is introduced by the electrode to skin junction. In measuring sEMG signals, one important criterion is to maximize the signal to noise ratio. The detailed information about factors and sources of noise in the sEMG acquisition could be found in [25].

Depending on different applications, a number of statistical methods have been developed to model and analyze sEMG signals. The traditional methods usually focus on the single variable analysis to estimate the amplitude and frequency information of the sEMG signals such as the Root Mean Square (RMS) and Mean Frequency (MNF). RMS is defined as the square root of the arithmetic mean of the squares of the sEMG signal within a window which is used to estimate the amplitude of the sEMG signals over a period,

\[ RMS(i) = \sqrt{\frac{1}{n} \sum_{k=i}^{i+n} x^2(k)} \]  

(1.1)
where \( x(k) \) means the sEMG signal sample at time \( k \) and \( n \) means the width of the time window. The time series of RMS is produced by shifting the time window with a fixed step size. RMS measures the power of sEMG signals which is associated with other important factors such as onset time of muscle activations and the force produced by muscle. In general, RMS is considered as one traditional simple measurement of single channel sEMG signals.

Fast Fourier transform (FFT) is often applied to decompose the signals into different frequency components for frequency spectrum analysis which can provide useful information of the sEMG signals. MNF is usually used to characterize the frequency spectrum of sEMG signals [24],

\[
    f_m = \frac{\sum_{i=1}^{N} f_i P_i}{\sum_{i=1}^{N} P_i}
\]

where \( N \) represents the index of the highest frequency component, \( i \) indicates the \( i \)-th component, and \( P \) means the power spectrum. Since FFT is more suitable for the stationary signals, while the sEMG is considered as non-stationary process, other methods such as wavelet transform and short-time Fourier transform were proposed to analyze the time-varying sEMG signals [43].

More sophisticated methods have been developed to analyze multichannel sEMG signals. Among them, as an extension on the univariate autoregressive model (AR), multivariate autoregressive model (mAR) is one popular model to study the linear relationships between sEMG variables,

\[
    X(i) = \sum_{p=1}^{P} A_p X(i - p) + e(i)
\]

where \( X(i) \) denotes the column vector of multi-channel sEMG signals at time \( k \), \( A_p \) is the regression matrix at time lag \( p \) and the vector \( e(i) \) means the noise term which is generally assumed to be Gaussian distributed. mAR has been applied to a wide range of neuroimaging data including EMG, EEG, fMRI, etc. [6, 35, 39]. Due to the nonstationary nature of sEMG signals, the variants of regular AR models such as autoregressive integrated moving average models (ARIMA) were proposed to better describe sEMG signals [72].

The linear decomposition methods including Principal component analysis (PCA),
Independent component analysis (ICA) are widely used matrix factorization methods for studying sEMG signals [85]. These methods are operated on the assumption that multichannel sEMG signals are generated by a set of unknown underlying sources, and the objective is to distinguish the sources by projecting multichannel sEMG signals to a subspace. PCA is a statistical transformation method to uncover the observed correlated variables into a set of independent components, and it is one form of factor analysis. ICA is used for the separation of independent underlying sources from the observed multichannel sEMG signals.

1.4 Research Objectives and Methodology

The technical objective of this thesis is to efficiently and accurately model the interactions between neural components such as different brain regions of interest (ROIs) represented by fMRI signals or muscles represented by sEMG signals. Particularly, since biomedical research typically studies a group of subjects rather than focusing on an individual subject, we plan to tackle the group analysis concern and develop a group-level network modeling and analysis framework. With the real applications to the PD study using fMRI and the LBP study using sEMG, we want to visualize the interactions between ROIs and sEMG channels respectively and extract more informative information at the network level. In the application to fMRI data collected from control and Parkinson Disease (PD) groups before and after L-dopa medication, we want to investigate the features of the detected connections associated with the PD disease and examine the effect of L-dopa medication. In the application to sEMG data, we attempt to compare the lumbar muscle coordination patterns between people with and without low back pain.

In order to achieve the above objectives, we propose a FDR-controlled graphical network modeling and analysis framework in this thesis:

- Network Modeling

  Network modeling using fMRI or sEMG data to study the interactions between different components has been attracting increasing attention in the area of biomedical signal processing. In this thesis, with controlling over false discovery rate to assume the overall accuracy of the learned network connections, we propose a group-level network modeling process, group
PC\textsubscript{fdr} algorithm, for inferring conditional dependence/independence between variables (e.g. ROIs or different muscles). Taking into account inter-subject variances, the proposed group PC\textsubscript{fdr} algorithm combines group inference with a graphical modeling approach for discovering statistically significant connectivity. Simulation results demonstrate that the proposed group PC\textsubscript{fdr} method can accurately recover the underlying group network structures and robustly control the false discovery rate (FDR) at user-specified levels.

- **Network Analysis**

To characterize the features of the inferred connectivity networks, we employ network analysis approach including the graph theoretical analysis, lesion and perturbation analysis to identify key nodes and extract unique connectivity patterns. The network measures such as global efficiency, clustering coefficient, graph modules and symmetric pattern scores are used to describe the connectivity patterns, and the lesion and perturbation analysis are used to model the different importance of each node variable. This network analysis serves as the feature extraction tool for better understanding of the network properties.

The organization of the remainder thesis is as follows. In Chapter 2, the subject level and group level PC\textsubscript{fdr} algorithms are described in detail for inferring the connectivity networks using neural signals. Then the network analysis including graph theoretical analysis, lesion and perturbation analysis is described to further extract informative features from the learned networks. Chapter 3 contains two applications to real fMRI data. Applying the network modeling and analysis methods to the data collected from normal and PD groups before and after medication, the analysis on network level supports the hypothesis that PD subjects could be ameliorated by L-dopa medication. With another application to control group and PD groups with and without trembling symptoms, different connectivity patterns are identified to be associated with PD subtypes. Chapter 4 reports one sEMG application to low back pain. Ten healthy subjects and eleven LBP patients were asked to perform the flexion-extension task, and the sEMG signals were recorded during the task. We apply two level PC\textsubscript{fdr} algorithms to infer the activity coordination network between lumbar muscles and perform the network analysis to compare the
lumbar muscle coordination patterns between subjects with and without LBP. Distinguishing symmetric connectivity patterns are noted between two groups. The conclusions are given in Chapter 5 along with suggestions for future work.
Chapter 2

Method

2.1 Introduction

Modeling the interactions between neural components, such as inferring the brain effective connectivity network using fMRI data or learning the muscle contraction coordination activity using sEMG data, is crucial in understanding the neural systems and the related disorders. Compared with traditional methods which mainly focus on the amplitude, spectrum and correlation analysis for the single variable estimation, network modeling allows the visualization of the interaction relationships between multiple node variables (e.g. ROIs) and the extraction of more informative features of the neural activities. In this thesis, a network modeling, especially the group-level network modeling, and network analysis framework are introduced to investigate the interactions between neural components.

Modeling brain effective connectivity

Various mathematical models have been developed for modeling brain effective connectivity, such as Structural Equation Modeling [56], Dynamic Causal Models [31], and Dynamic Bayesian Networks [51]. As biomedical research typically studies a group of subjects rather than focusing on an individual subject, group analysis plays an important role in statistical analysis of biomedical data. However, compared with various choices of group-level methods for functional-connectivity analysis [32, 90], research into group-level effective-connectivity analysis is rela-
tively less well studied, likely because it needs to handle not only the variances and correlations across subjects, but also complicated structures of brain connectivity networks.

A theoretically elegant and feasible method for group-level exploratory analysis of effective connectivity must include both efficiency of searching through a large number of candidate connectivity networks, and accuracy of the learned networks. In contrast to confirmatory studies that usually involve verification of just a few pre-selected models, exploratory studies must search through a huge number of possible models to find one or a few that are best supported by data. Thus, efficiency of the search strategy becomes important, especially since the number of possible network structures increases super-exponentially to the number of brain regions of interest (ROIs) involved. For example, with just seven ROIs, there are more than a billion possible network structures.

Besides efficiency, accuracy is another important criterion for an exploratory method. “How many of the connections inferred from data are actually true?”, “how many true connections can be detected?” and “how many non-existing connections are falsely reported?” are questions that must be answered. Therefore, error control is a crucial point in the design of reliable methods for discovering connectivity. The False discovery rate (FDR) [13] in the context of learning network structures, defined as the expected ratio of spurious connections to all learned connections, is a suitable error-rate criterion.

Currently, most group-level methods for network modeling fail to satisfactorily address the aforementioned concerns. A common practice is first to learn connectivity networks individually for each subject, and then perform group analysis on the subject-level networks. While this approach allows enough freedom for inter-subject variability, the group-level and the subject-level models are not well integrated. Another common practice is to make inference from pooled group data. This approach ignores inter-subject variability, and is suitable only when the group is relatively homogeneous. Bayesian model selection [82] proposed by Stephan, Penny, etc. in 2009 elegantly handles inter-subject variability and error control, but its current design cannot efficiently handle a large number of networks, making it more suitable for confirmatory, rather than exploratory research.

Therefore in this study, we propose a group-level exploratory method for infer-
ring connectivity between neural components, which utilizes both efficient search strategy and control over false discovery rate. This method is a combination of the PC\textsubscript{fdr} algorithm [49] proposed by Li and Wang in 2009 and the mixed-effect model, a widely used method for handling inter-subject variability. The original version of the PC\textsubscript{fdr} algorithm [49] was proved to be capable of efficiently discovering network structures with the FDR being robustly controlled at pre-specified levels, such as the conventional value of 5%. In the proposed group-level method, we bring the advantages of the PC\textsubscript{fdr} algorithm to the group level by embedding mixed-effect models into it. To the best of our knowledge, this is the first group-level exploratory method for brain effective connectivity analysis that attempts to jointly address efficiency, accuracy and inter-subject variability. Our simulations demonstrate that the proposed group-level PC\textsubscript{fdr} algorithm is able to robustly discover group-level network structures, yielding results more trustful than simply pooling together the data from different subjects.

**Network analysis**

Based on the inferred connectivity networks, the next step is to extract useful information for evaluating the network properties which traditionally depend on empirical observations. However, empirical evaluation suffers from the subjective analysis which may lead to inconsistence. One more trustful method arised recently is graph theoretical approach that was originated from graph theory. It serves as the feature extraction tool for better understanding of brain functions at the network level. Prior studies of network analysis have been applied to large scale brain structural, functional or effective connectivity networks to explore common features of brain organizations [19]. One of the most significant features is small-world topology which describes brain networks with low wiring cost but high efficiency [10]. The hierarchical modular organization of the brain connectivity networks has been discussed in the recent papers [78]. Some other graph measures such as centrality, motif and clustering have been applied to brain networks and give significant findings of the brain organizations [76] [68].

The information of brain structures and functions extracted by network analysis is also insightful when investigating brain connectivity impairments and disorders.
such as Alzheimer’s Disease, Parkinson’s Disease and etc. [34]. The simulation study of cortical networks reveals the robustness of the brain networks against local damage and demonstrates the importance of various regions [42]. In another study, comparing the human brain structure and functional networks in health and disease, the authors found the changes of the connectivity patterns in disease [11]. Applying graph theoretical analysis to resting-state brain networks in Alzheimer’s disease and control subjects, Stam etc. showed the loss of the network connectivity; in particular, they further demonstrated the loss of “small-world” topology in AD [79] [80]. Similarly, Huang etc. suggested that Parkinson Disease may lead to progressive changes of brain activities at key regions [41]. The perturbation analysis is our attempt to model the evolution of the connectivity networks by adding the noise to the nodes or connections through simulations.

**Studying the muscle contraction coordination connectivity**

The Bayesian network modeling is also suitable for inferring muscle contraction coordination networks. The basic idea is to infer the interactions between the sEMG channels by detecting conditional dependence/independence between muscle activities, i.e. whether the activities of two sEMG channels are associated given other sEMG channels. We have argued that Bayesian network may be particularly suitable for modeling muscle coordination networks [50]. The subject-level and group-level network modeling and network analysis methods can be extended to study muscle coordination connectivity networks.

### 2.2 Network Modeling

In this section, we first introduce the Bayesian Network (BN) in brief, and then focus on the proposed group PC_fdr algorithm, an exploratory group level modeling approach for multichannel neural recording signals. The simulation part serves to verify the proposed group modeling method and compare it with the single subject PC_fdr algorithm. The notations used in this section are listed below in Table 2.1.
Table 2.1: The notations used in the method section

<table>
<thead>
<tr>
<th>Notations</th>
<th>Explanations</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAG</td>
<td>directed acyclic graph</td>
</tr>
<tr>
<td>$G$</td>
<td>a directed graph</td>
</tr>
<tr>
<td>$G^*$</td>
<td>the skeleton of a directed graph</td>
</tr>
<tr>
<td>$a, b, \cdots$</td>
<td>vertices</td>
</tr>
<tr>
<td>$A, B, \cdots$</td>
<td>vertex set</td>
</tr>
<tr>
<td>$X_a, X_A, \cdots$</td>
<td>variables associated with a vertex or a vertex set</td>
</tr>
<tr>
<td>$a \perp b</td>
<td>C$</td>
</tr>
<tr>
<td>$X_a \perp X_b</td>
<td>X_C$</td>
</tr>
<tr>
<td>$\text{Adj}(a, G)$</td>
<td>vertices adjacent to $a$ in a directed graph $G$</td>
</tr>
<tr>
<td>$\text{Adj}(a, G^*)$</td>
<td>vertices adjacent to $a$ in the skeleton graph $G^*$</td>
</tr>
</tbody>
</table>

2.2.1 Bayesian Network

Graphical models usually represent their variables as vertices and variable-wise relationships as edges which can be used for the causal inference. BN, also known as belief network, is one type of graphical models where a Directed Acyclic Graph (DAG) encodes a set of conditional dependence/independence relationships among random variables with Bayes’ rules [47].

One important concept in BN is d-separation (see Spirtes, 2001, page 36)[75]. Suppose $a$ and $b$ are vertices, $C$ is the vertex set in graph $G$, and there exists intermediate vertices $m$, then $a$ is said to be d-separated from $b$ by vertex set $C$ if and only if at least one of the following holds:

1. presence of the path $a \rightarrow m \rightarrow b$, and $m \in C$,
2. presence of the path $a \leftarrow m \leftarrow b$, and $m \in C$,
3. presence of the path $i \leftarrow m \rightarrow b$, and $m \in C$,
4. presence of the path $i \rightarrow m \leftarrow b$, and $m \notin C$.

With the concept of d-separation, DAG encodes a set of conditional dependence/independence relationships according to directed Markov property which is defined as follows: if $A$, $B$ and $C$ are three disjoint vertex sets, and $A$ is d-
separated by \( C \) from \( B \), then \( X_A \) and \( X_B \) are conditionally independent given \( X_C \), that is, \( P(X_A, X_B | X_C) = P(X_A | X_C)P(X_B | X_C) \) (See Lauritzen, 1996, pages 46-53) [47].

Moreover, a BN is the representation of joint distribution over random variables \( X = [X_1, X_2, \cdots, X_n] \) which can be factorized as,

\[
P(X) = \prod_{i=1}^{n} P(X_i | pa(X_i))
\]

where \( pa(X_i) \) is the parents set of \( X_i \), that is the vertex set directly pointing to \( X_i \). For instance, in Fig. 2.1, the joint probability distribution can be factorized as follows:

\[
P(X) = \prod_{i=1}^{5} P(X_i | pa(X_i))
\]

\[
= P(X_1)P(X_2 | X_1)P(X_3 | X_2)P(X_4 | X_2)P(X_5 | X_3, X_4)
\]

**Figure 2.1:** The illustration of a BN. The joint probability distribution can be factorized as: \( P(X) = P(X_1)P(X_2 | X_1)P(X_3 | X_2)P(X_4 | X_2)P(X_5 | X_3, X_4) \).

BNs can be used to represent the probabilistic relationships for the multichannel neural signals. For instance, when analyzing brain effective connectivity, we use vertices to denote brain ROIs, and edges to denote connections between ROIs. The network structure of most types of graphical models is associated with mathematical meaning, i.e. encoding conditional-independence relationships among variables. Usually, if a model is faithful, then a connection between nodes \( a \) and \( b \) implies that the variables associated with \( a \) and \( b \) are conditionally dependent given any other variables. This can be a good statistical interpretation of brain effective connectivity.

The first step for learning a BN is the structure learning which aims to select
the probably DAG from the candidates by the Maximum a posteriori (MAP) criterion. The implementation of MAP approach can be realized by selecting the largest Bayesian information criterion (BIC) or Akaike information criterion (AIC). The second step is the parameters estimation according to the maximum likelihood criterion. In practice, for simplicity, a Gaussian BN is usually used to model the continuous multichannel biomedical signals by Markov Chain Monte Carlo (MCMC) approach. A more detailed description of BN learning can be found in [50].

2.2.2 FDR-Controlled Exploratory Group Modeling

The PC algorithm, named after Peter Spirtes and Clark Glymour, is one computationally efficient and asymptotically reliable Bayesian network-learning algorithm which infers the interactions between the node variables by detecting the conditional dependence/independence relationships between the nodes [75]. The pseudo-code of PC algorithm is given in Table 2.2, with Step 6 (a).

The PC algorithm gains its efficiency by incrementally shrinking the size of \( \text{Adj}(a,G^*) \) to avoid exhaustively testing all conditional independence relationships. Its search depth \( d \) represents the number of conditional variables which begins with zero. The searching is initial with the completely connected graph \( G \) and search depth \( d = 0 \). At each loop, for all the subsets of conditional variables \( C \) with cardinality equal to \( d \), testing the hypothesis of conditional independence of any possible neighbor vertices \( a \) and \( b \) given subset \( C \). Once \( C \) is found to disconnect \( a \) and \( b \), then remove the connection between them and update the neighbors of vertices. At the end of each loop, increase the search depth \( d \) with the step of size one. In this way, the PC algorithm could efficiently recover the structure of the graph. The operation procedure of the PC algorithm is shown in Fig. 2.2.

Different from the PC algorithm which controls the type I error rate individually for each connection during the conditional independence testing, the \( \text{PC}_{\text{fdr}} \) algorithm developed by Li and Wang is capable of asymptotically controlling the False Discovery Rate (FDR) under pre-specified levels [49]. (Interested readers may refer to [49] for a complete proof.) The FDR is defined as the expected ratio of falsely discovered positive hypothesis to all those discovered, which is one of the important error control criteria for multiple testing (see Table 2.4). Compared
Table 2.2: PC algorithm in [75], \( \text{PC}_{\text{fdr}} \) algorithm in [49] and the proposed group-level method

1: Form the complete undirected graph \( G^* \), and set search depth \( d = 0 \).
2: \textbf{repeat}
3: \quad \textbf{repeat}
4: \quad \quad Select an ordered pair of variable vertices \( a \) and \( b \) such that they are adjacent in \( G^* \) and \( \text{Adj}(a, G^*) \backslash b \) has at least \( d \) vertices in it.
5: \quad \quad \textbf{for} vertex subset \( C \subseteq \text{Adj}(a, G^*) \backslash b \), and \( |C| = d \) \textbf{do}
6: \quad \quad \quad (a) test hypothesis \( X_a \perp X_b | X_C \) and calculate the p-value for edge \( a - b \) at the \textbf{subject level}. Control the Type I error rate to decide which edges should be removed from \( G^* \), and then remove them, or
7: \quad \quad \quad (b) test hypothesis \( X_a \perp X_b | X_C \) and calculate the p-value for edge \( a - b \) at the \textbf{subject level}. Input edge p-values to an \textbf{FDR-control} procedure to decide which edges should be removed from \( G^* \), and then remove them, or
8: \quad \quad \quad (c) test hypothesis \( X_a \perp X_b | X_C \) and calculate the p-value for edge \( a - b \) at the \textbf{group level}. Input edge p-values to an \textbf{FDR-control} procedure to decide which edges should be removed from \( G^* \), and then remove them.
9: \quad \quad \textbf{end for}
10: \quad \textbf{update} \( G^* \).
11: \quad \textbf{if} the edge between \( a \) and \( b \) is removed \textbf{then}
12: \quad \quad Break loop at step 5
13: \quad \textbf{end if}
14: \textbf{end repeat}
15: \textbf{until} all existing edges have been tested.
16: \( d = d + 1 \).
17: \textbf{until} Cannot find a triple \( (a, b, C) \) for step 5.

Step 6(a) is for the PC algorithm in [75]; Step 6(b) is for the \( \text{PC}_{\text{fdr}} \) method in [49]; step 6(c) is for the proposed group \( \text{PC}_{\text{fdr}} \) method.

Table 2.3: The notations for the results of multiple testing

<table>
<thead>
<tr>
<th>Truth</th>
<th>Testing Results</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>True Negative (TN)</td>
<td>False Positive (FP)</td>
<td>T1</td>
</tr>
<tr>
<td>Positive</td>
<td>False Negative (FN)</td>
<td>True Positive (TP)</td>
<td>T2</td>
</tr>
<tr>
<td>Total</td>
<td>R1</td>
<td>R2</td>
<td></td>
</tr>
</tbody>
</table>

20
with the traditional type I and type II error rate control, FDR is more reasonable in some real applications such as bioinformatics and neuroimaging since it directly related with the uncertainty of the discovered positive results. The pseudo-code of PC_{fdr} algorithm is shown in Table 2.2 with Step 6.

One crucial step is the hypothesis testing of conditional independence at Step 6. The PC_{fdr} is the extension based on the original PC algorithm by substituting the FDR procedure for the type I error control. For the group-level methods, mixed-effect models can be embedded into Step 6 for group analysis. In this section, we will extend the PC_{fdr} algorithm from single subject level to the group-level with mixed-effect models. It is our first attempt to the graphical group network

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**Figure 2.2**: The operation procedure of the PC algorithm. This figure was modified based on one figure from [75].
Table 2.4: Error control criteria for multiple testing

<table>
<thead>
<tr>
<th>Types of Error Rate Control</th>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Discovery Rate</td>
<td>FDR</td>
<td>$E(\frac{FP}{R2})$</td>
</tr>
<tr>
<td>Type I Error Rate (False Positive Rate)</td>
<td>$\alpha$</td>
<td>$E(\frac{FP}{T1})$</td>
</tr>
<tr>
<td>Type II Error Rate (False Negative Rate)</td>
<td>$\beta$</td>
<td>$E(\frac{FN}{T2})$</td>
</tr>
<tr>
<td>Specificity (True Negative Rate)</td>
<td>$1 - \alpha$</td>
<td>$E(\frac{TN}{T1})$</td>
</tr>
<tr>
<td>Sensitivity (True Positive Rate)</td>
<td>$1 - \beta$</td>
<td>$E(\frac{TP}{T2})$</td>
</tr>
<tr>
<td>Family Wise Error Rate</td>
<td>FWER</td>
<td>$P(FP \geq 1)$</td>
</tr>
</tbody>
</table>

Related notations for the results of multiple testing are recorded in Table 2.3.

modeling.

Suppose we have $m$ subjects in a group. For subject $i$, the conditional independence between the activities of two brain regions $a$ and $b$ given other regions $C$ can be measured with the partial correlation coefficient between $X_a(i)$ and $X_b(i)$ given $X_C(i)$, denoted as $r_{ab|C}(i)$. Index $i$ indicates that these variables are for subject $i$. By definition, the partial correlation coefficient $r_{ab|C}(i)$ is the correlation coefficient between the residuals of projecting $X_a(i)$ and $X_b(i)$ onto $X_C(i)$. In practice, it can be estimated as

$$
\hat{r}_{ab|C}(i) = \frac{\text{Cov}[Y_{a|C}(i), Y_{b|C}(i)]}{\sqrt{\text{Var}[Y_{a|C}(i)] \text{Var}[Y_{b|C}(i)]}},
$$

(2.3)

where

$$
\beta_{a|C}(i) = \arg \min_{\beta} |X_a(i) - X_C(i)\beta|^2
$$

(2.4)

$$
\beta_{b|C}(i) = \arg \min_{\beta} |X_b(i) - X_C(i)\beta|^2
$$

(2.5)

$$
Y_{a|C}(i) = X_a(i) - X_C(i)\beta_{a|C}(i)
$$

(2.6)

$$
Y_{b|C}(i) = X_b(i) - X_C(i)\beta_{b|C}(i).
$$

(2.7)

Alternatively, we can also use Fisher’s $z$-transformation of the partial correlation coefficient $r$ to measure conditional independence. The $z$-transformation is
defined as
\[ z = Z(r) = \frac{1}{2} \ln \left( \frac{1+r}{1-r} \right). \tag{2.8} \]

As we are interested in discovering the group-level conditional-independence relationships, a group-level model should be introduced for \( r_{ab|C(i)} \) or \( z_{ab|C(i)} \). In the remaining part of this section, in order to focus on the group-subject relationship, we omit the subscript “\( ab|C \)”, and simply use index “\( i \)” to emphasize that a variable is associated with a subject. Here we assume that
\[ z_i = z_g + e_i \tag{2.9} \]
where \( e_i \) follows a Gaussian distribution \( N(0, \sigma^2_g) \). Consequently, the group-level test of conditional independence is to verify whether the null hypotheses \( z_g = 0 \) is true or not.

Because \( z_i \) is unknown, and can only be estimated, the inference of \( z_g \) should be conducted with \( \hat{z}_i = Z(\hat{r}_i) \). If \( X_a(i), X_b(i) \) and \( X_C(i) \) jointly follow a multivariate Gaussian distribution, then \( \hat{z}_i \) asymptotically follows a Gaussian distribution \( N(z_i, \sigma^2_i) \) with \( \sigma^2_i = 1/(N_i - p - 3) \), where \( N_i \) means the sample size of subject \( i \)'s data and \( p \) means the number of variables in \( X_C(i) \). Therefore, based on Eq. (2.9), we have
\[ \hat{z}_i = z_g + e_i + e_i, \tag{2.10} \]
where \( e_i \) follows \( N(0, \sigma^2_i) \), and \( e_i \) follows \( N(0, \sigma^2_g) \).

This is a mixed-effect model where \( e_i \) denotes the within-subject randomness and \( e_i \) denotes the inter-subject variability. At the group level, \( \hat{z}_i \) follows a Gaussian distribution \( N(z_g, \sigma^2_i + \sigma^2_g) \). Note that unlike regular mixed-effect models, the within-subject variance \( \sigma^2_i \) in this model is known, since \( N_i \) and \( p \) are known given the data \( X(i) \). In general, \( \sigma^2_i \) is not necessarily equal to \( \sigma^2_j \) for \( i \neq j \), and the inference of \( z_g \) should be conducted in the manner of mixed-models, such as estimating \( \sigma^2_g \) with the Restricted Maximum Likelihood (ReML) approach. If the sample size of each subject’s data is the same, then we have \( \sigma^2_i = \sigma^2_j \). In this balanced case, which is typical in practice and the case of the fMRI application in this paper, we can simply apply a t-test to \( \hat{z}_i \) to verify the null hypothesis \( z_g = 0 \). This t-test for balanced cases was what we employed in our simulation study and
when we analyzed the fMRI data. Replacing the within-subject hypothesis test at Step 6(a) of the single version PC_{fdr} algorithm with the test of $z_g = 0$, we extend the single-subject version of the algorithm to its group-level version. Balance testing mostly simplifies the estimation process and the simulation results prove this method could still control the FDR at the user specified error rate level.

2.2.3 Simulation

The simulation in this section serves two purposes: First, to verify whether the proposed group PC_{fdr} algorithm can control the FDR at the specified level; second, to compare its performance with that of pooling data together and then learning connectivity using the single-subject version of the PC_{fdr} algorithm in [49].

The simulation is conducted as follows. First, a connectivity network is generated as the group-level model. Subject-level networks are then derived from the group-level model by randomly adding or deleting connections. Third, subject-specific data are generated according to subject networks. Forth, the two group-level network learning methods, i.e., the proposed group PC_{fdr} algorithm and the single-subject version PC_{fdr} method of pooling all subject data approach, are applied to the simulated data. Finally, the outputs of the algorithms are compared with the group-level network to evaluate their accuracy. This procedure is repeated several times to yield a reliable assessment.

The data generation process is as follows.

1. Randomly generate a directed acyclic graph (DAG) as the group-level network, and associate each connection with a coefficient. The DAG is generated by randomly connecting nodes with edges, and then orienting the edges according to a random order of the nodes. The connection coefficients are assigned with random samples from the uniform distribution $U(\beta_1, \beta_2)$.

2. A subject-level network is derived from the group-level network by randomly adding and deleting connections. For each of the connections already in the group network, delete with probability 0.05. For each of the connections not existing in the group network, add with probability 0.01, and derive its connection coefficient by randomly sampling from the uniform distribution $U(\beta_1, \beta_2)$.

3. Given a subject-level network, the subject-specific data is generated from
a Gaussian Bayesian network, with the additional Gaussian noise following the standard Gaussian distribution $N(0, 1)$.

Figure 2.3: (a) Group-level network, with 20 nodes and an average of two connections per node. (b) FDR results (with standard deviation) of group-level PC$_{fdr}$ algorithm and the single-subject version PC$_{fdr}$ of pooling all subject data together. (c) Type I error rate (with standard deviation) of group-level PC$_{fdr}$ algorithm and the single-subject version PC$_{fdr}$ of pooling all subject data together. (d) The power (with standard deviation) of group-level PC$_{fdr}$ algorithm and the single-subject version PC$_{fdr}$ of pooling all subject data together. The x-axis represents the generating distribution $U(\beta_1, \beta_2)$ for connection coefficients.
Figure 2.4: (a) Group-level network, with 15 nodes and an average of two connections per node. (b) FDR results (with standard deviation) of group-level PC_{fdr} algorithm and pooling all subject data together. (c) Type I error rate (with standard deviation) of group-level PC_{fdr} algorithm and pooling all subject data together. (d) The power (with standard deviation) of group-level PC_{fdr} algorithm and pooling all subject data together. The x-axis is the number of subject.
Figure 2.5: (a) Group-level network, with 20 nodes and an average of two connections per node. (b) FDR results (with standard deviation) of the group-level PC_{fdr} algorithm and the single-subject version PC_{fdr} of pooling all subject data together. (c) Type I error rate (with standard deviation) of group-level PC_{fdr} algorithm and the single-subject version PC_{fdr} of pooling all subject data together. (d) The power (with standard deviation) of group-level PC_{fdr} algorithm and the single-subject version PC_{fdr} of pooling all subject data together. The x-axis is the number of subject.
In the first simulation example, we test the performance of the algorithms with different strength of the connection coefficients between node variables. In this example, the group-level network is the DAG in Figure 2.3(a). From this model, thirty subject-level models are derived, and for each subject, data with three hundred samples are simulated. To test the performance of the algorithms as a function of the connection strength, we increase the generating distribution of connection coefficients gradually from $U(0.2,0.3)$ to $U(0.7,0.8)$. At the network learning stage, we set the target FDR to be 5%. For reliable assessment, this procedure is repeated fifty times. Figure 2.3(b)(c)(d) show the FDR, type I error rate and the power estimated from the fifty repetitive runs respectively. It shows that the proposed group PC$_{fdr}$ algorithm can steadily control the FDR below the desired level and can accurately make the inference on the group level. On the other hand, if all subjects data are simply pooled together for network learning using the single-subject version of the PC$_{fdr}$ algorithm, the FDR will fail to be controlled at the user-specified level, but is higher than 0.4.

In the second simulation example, we test the performance of the algorithms when the number of subjects changes. In this example, the group-level network is the DAG in Figure 2.4(a) Figure 2.5(a), and the number of subjects increases from eight to thirty. At the network learning stage, we set the target FDR to be 5%. This procedure is repeated for fifty times. Figure 2.4(b) and Figure 2.5(b) show the FDR results estimated from the repetitive runs. It is clear that in this example, the proposed group PC$_{fdr}$ algorithm is able to steadily curb the FDR below the specified level. The power estimated in Figure 2.4(d) and Figure 2.5(d) gradually increase as the number of subjects increase. On the other hand, the approach of pooling data together fails to control the FDR, and its FDR does not decrease as the number of subject increases, probably due to the increasing heterogeneity within the group.

The simulation results show that the proposed group PC$_{fdr}$ algorithm can accurately discover the group level connectivity from the individual subjects and control the FDR below the user-specified level. From the empirical observation, with the increasing of the degree of the network, the power estimated from the group PC$_{fdr}$ method will decrease which demonstrates group PC$_{fdr}$ method may achieve better performance in making inference on sparse networks.
2.3 Network Analysis

2.3.1 Graph Theoretical Analysis

Graph theoretical analysis can be used to extract both local and global features of the networks, and it was originated from graph theory. Back to 1735, the city Konigsberg was on both sides of the Pregel River, and there were seven bridges that connected two islands in the city. Some were curious how to walk across the city through seven bridges once and only once, and named it Seven Bridges of Konigsberg problem. Later, Leonhard Euler proved there was no solution for Seven Bridges of Konigsberg problem which laid the foundations of graph theory [14].

The modern graph theoretical analysis was inspired by the discovery of the small world property and scale free topology at the end of 20th century [8, 89]. The scale free model describes the preferential attachments of the growth networks where the new added connections are more likely to attach those vertices with high degrees (the degree of a node in the undirected graph is defined as the total number of edges connected with this node). A large class of real networks display scale free property such as World Wide Web and collaboration networks of movie actors [8, 9]. One previous study demonstrated that large scale brain functional connectivity networks have the scale free property [26].

Small world networks were first described by Duncan J. Watts and Steven H. Strogatz. In their model, the network is started with the ring lattice and each node only connects to their four nearest neighbors. Then they rewire the connection randomly with probability $P$ ranging from 0 to 1. By increasing the value of $P$, the network will change from a regular network to a completely random network [89].

To investigate the properties of the whole range networks, two independent structure features, clustering coefficient $C$ and characteristic path $L$, can be applied. Suppose in a binary undirected graph, the total number of the vertices is $N$, the degree of node $i$ is $k_i$, and the number of existing edges between the neighbors of node $i$ is $t_i$, then the clustering coefficient of node $i$ is defined as the ratio of $t_i$ to the maximum number of edges between the neighbors of node $i$. The clustering coefficient of the graph is obtained by averaging $C_i$ [89].
The characteristic path $L$ is defined as the average of the shortest path length between any nodes in the graph [89],

$$L = \frac{1}{N(N-1)} \sum_{i \neq j \in N} d_{ij}$$

(2.12)

where $d_{ij}$ means the shortest path length between node $i$ and node $j$.

According to the clustering coefficient $C$ and the characteristic path $L$, regular networks have long $L$ and high $C$, and random network has short $L$ and small $C$. For the networks with a small randomness $P$, it was found that they have short $L$ but high $C$ and called small world networks. Those neither regular nor completely random networks are of great interest. Previous studies suggested that a number of real world networks are small world networks, including social networks, metabolic networks and brain networks [5, 10, 87]. However, analysis of characteristic path requires that all the nodes in the graph are connected directly or indirectly with each other. In our case, we investigate the moderate size networks and most are sparse with some disconnected vertices. Therefore, we use global efficiency instead of characteristic path to analyze the structure features of the networks. Global efficiency $E$ describes communication efficiency of the whole graph [46], defined as the average inverse shortest path:

$$E = \frac{1}{N(N-1)} \sum_{i \neq j} d_{ij}^{-1}$$

(2.13)

Compared with characteristic path, global efficiency is generally more meaningful when dealing with disconnected graphs in which infinite distance leads to zero efficiency [68]. A shorter characteristic path $L$ usually corresponds to a higher global efficiency. In the following, we will compare the sEMG connectivity networks in two groups with the random networks in terms of global efficiency and clustering coefficient. The comparison could describe the network types of the normal and patient groups.

Another measure used in our study is modularity. Many networks including so-
cial networks, gen regulatory networks and computer networks can be divided into several modules within each module the nodes are densely clustered, and various functions can be associated with different modules. Modularity is used to describe how well the modules are divided [62]. Suppose the number of nonoverlapping modules in a graph is \( M \), \( r_{uu} \) is the fraction of the edges within modules \( u \), and \( r_{uv} \) is the fraction of all edges that connect nodes in module \( u \) with nodes in module \( v \) [61], then the modularity is defined as,

\[
Q = \sum_{u \in M} \left[ r_{uu} - \left( \sum_{v \in M, u \neq v} r_{uv} \right)^2 \right] \tag{2.14}
\]

By maximizing the modularity function, we can find the best division of sEMG networks. In real applications, a modularity value larger than about 0.3 shows significant substructures [61]. The comparison of the normal and patient groups in module division can provide us new insights into the network symmetry.

For a graph, the centrality measures can be used to distinguish different importance levels of the nodes or edges. The central regions often play key roles in the information flow and exert significant impact on other regions. There are various measures of centrality to identify the central regions such as degree, betweenness [30], and closeness [12]. The betweenness centrality is designed for measuring the node importance,

\[
b_i = \frac{1}{(N-1)(N-2)} \sum_{k \neq i \neq j} \frac{\rho_{kj}(i)}{\rho_{kj}} \tag{2.15}
\]

where \( \rho_{kj} \) is the number of the shortest path between node \( k \) and node \( j \), \( \rho_{kj}(i) \) denotes the number of shortest path go through node \( i \) between node \( k \) and node \( j \). A higher betweenness value \( b_i \) means that more shortest paths go through node \( i \), indicating that node \( i \) has higher impact on the information flow of the graph.

The “hub and authority” method was first proposed by Kleinberg to identify importance pages in World Wide Web (WWW)[45]. Considering the WWW as large scale directed graphs, it provides an effective method to evaluate the pages by calculating the authority and hub values. The HA value of one node is related to the structure of its neighbors, where a high HA value usually means that more important nodes are connected with it. The authority value of node \( i \) is the sum of
the hub values of the nodes pointing to node $i$ and the hub value of node $i$ is the sum of authority values of those nodes pointed by node $i$ [15]:

$$h_i = \sum_j S_{ij} a_j, \quad (2.16)$$

$$a_i = \sum_j S_{ji} h_j, \quad (2.17)$$

where $S$ represents the binary connectivity matrix with the entry $S_{ij}$ denoting the connection from node $i$ to node $j$ (if there is no connection between them, $S_{ij} = 0$). In the matrix form, the HA values can be iteratively calculated as

$$\begin{bmatrix} H \\ A \end{bmatrix}_{k+1} = \begin{bmatrix} 0 & S \\ S^T & 0 \end{bmatrix} \begin{bmatrix} H \\ A \end{bmatrix}_k \quad k = 1, 2, 3, \cdots \quad (2.18)$$

Eq. (2.18) can be further represented as

$$Z_{k+1} = MZ_k, \quad k = 1, 2, 3, \cdots \quad (2.19)$$

where $Z = \begin{bmatrix} H \\ A \end{bmatrix}, M = \begin{bmatrix} 0 & S \\ S^T & 0 \end{bmatrix}$. With the initial values $Z_0$ and the normalized $Z_k$ at each step,

$$Z_{k+1} = \frac{MZ_k}{\|MZ_k\|_2}, \quad k = 1, 2, 3, \cdots \quad (2.20)$$

it has been proved that the odd subsequences and even subsequences of $Z_k$ do converge, and the even limit vector $Z_{\text{even}}$ with initial values $[1, 1, \cdots]^T$ has the largest possible 1-norm [15]. Similar to [15], we set the initial values as $Z_0 = [1, 1, \cdots]^T$ and use the even convergence $Z_{\text{even}}$. For the undirected graphs, $S = S^T$, as a result, the hub value is equal to the authority value. In this case, we use the vector HA to denote the hub and authority value in our network analysis.

### 2.3.2 Lesion and Perturbation Analysis

Lesion and perturbation analysis can be used to study the networks in various aspects such as robustness, response to the impairments and detecting the hub regions
Here we measure the effect of ROI lesion by inactivating individual nodes in the network and calculating the global efficiency of the lesion networks. The comparison between the original value and the value after lesion represents the importance of the corresponding region. A larger difference between original graph and the lesion graph without node $i$ represents a higher impact of node $i$ on the network.

The perturbation analysis attempts to model the evolvement of the network. After adding the noise to the connectivity network, we want to investigate the changes associated with the perturbation. The perturbation analysis has been conducted for Gaussian Bayesian networks using Kullback Leibler divergence (KL-DIVERGENCE) in previous study [59]. Gaussian BN is often used to model continuous multichannel biomedical signals in order to learn the interactions between different neural components. Here, we apply the KL-divergence to the inferred Gaussian BN to evaluate the impact of each connection and each node under the perturbation. Moreover, we want to compare the similarity or dissimilarity of the inferred networks between different groups under the perturbation.

The Gaussian BN is one type of BNs with the random variables $X = [X_1, X_2, \cdots, X_n]$ following multivariate normal distribution $N(\mu, \Sigma)$. The joint density distribution of a Gaussian BN can be factorized as:

$$f(X) = (2\pi)^{-n/2} |\Sigma|^{-1/2} \exp(-\frac{1}{2} (X - \mu)' \Sigma^{-1} (X - \mu)) \quad (2.21)$$

where $\mu$ is the mean vector and $\Sigma$ is the covariance matrix.

In a Gaussian BN, each variable $X_i$ can be denoted as:

$$X_i = \mu_i + (\sum_{i \neq j} \beta_{ji} X_j) + \epsilon_i \quad (2.22)$$

where $\beta_{ji}$ is the connection coefficient from node $j$ to node $i$ (e.g. $\beta_{ji} = 0$ if there is no connection from node $j$ to node $i$), and $\epsilon_i \sim (0, \sigma_i^2)$. $\sigma_i^2$ means the conditional variance of $X_i$ given its parents,

$$X_i | pa(X_i) \sim N(\mu_i + \sum_{i \neq j} \beta_{ji} X_j, \sigma_i^2). \quad (2.23)$$
Suppose that we add noise to the mean value $\mu$ or $\Sigma$ to get $\mu^*$ or $\Sigma^*$, then we can use KL-divergence to measure the changes \[59\],

$$
KL(f^*(X), f(X)) = \int f(X) \log \frac{f(X)}{f^*(X)}
$$

$$
= \frac{1}{2} \left( \ln \frac{\Sigma^*}{\Sigma} + tr(\Sigma \Sigma^{-1}) + (\mu - \mu^*)' \Sigma^{-1} (\mu - \mu^*) - dim(X) \right).
$$

(2.24)

Moreover, the perturbation analysis can also be conducted on each connection in the Gaussian BN using KL-divergence \[84\]. Suppose $D$ is the diagonal matrix with the diagonal elements being the conditional variances $\epsilon_i^2$'s; $S$ is the connectivity matrix, and the element $S_{ij} = \beta_{ij}$ is the connection coefficient from node $i$ to node $j$; $I$ means the identity matrix. Then the covariance matrix $\Sigma$ can be denoted as \[71\],

$$
\Sigma = [(I - S)^{-1}]^T D (I - S)^{-1}.
$$

(2.25)

We then can substitute $\Sigma$ with $S$ and $D$ to the $KL(f^*(X), f(X))$ measure. To summarize, we could add noise to the mean vector $\mu$ to analyze the perturbation effect on each node as well as on each connection by changing the matrix $S$:

- With adding noise $\delta$ to the mean vector, i.e. $\mu^* = \mu + \delta$, the KL measure is simplified as

$$
KL(f^*(X), f(X)) = \frac{1}{2} (\delta' \Sigma^{-1} \delta).
$$

(2.26)

- With adding noise $\Delta$ to the connectivity matrix $S^* = S + \Delta$, the KL measure is simplified as

$$
KL(f^*(X), f(X)) = \frac{1}{2} [tr(\Sigma K), K = (S - S^*)^D^{-1} (S - S^*)'].
$$

(2.27)

2.4 Conclusion

We introduce a framework of network modeling and analysis to study the interactions between neural components. The group PC$_{fdr}$ algorithm is proposed for inferring connectivity networks at the group-level, with inter-subject variances being taken into consideration. As a combination of the PC$_{fdr}$ algorithm and mixed-
effect models, the proposed method takes advantage of the error control ability of the PC\textsubscript{fdr} algorithm and the capability of handling inter-subject variances of mixed-effect models. Our simulation results show that the proposed method is able to accurately discover the underlying group network and steadily control the false discovery rate at the user-specified level. The proposed method is shown to be much more reliable than simply pooling together the data from all subjects.

One limitation of the proposed group PC\textsubscript{fdr} algorithm is the requirement of a sufficient number of subjects. Our simulation results show that the number of subjects should be at least around 10 to achieve a good performance. While in many biomedical applications, data collection is time consuming and the number of subjects could be small which may restrict the employment of the proposed group PC\textsubscript{fdr} algorithm. Also, from our empirical observations, the proposed group PC\textsubscript{fdr} method is more suitable for sparse network inference, since increasing the density of the group network may lead to the decrease of the detection power. However, it is worth emphasizing that, compared with various choices of methods for single-subject analysis, the options for group-level analysis of brain effective connectivity are considerably fewer. The proposed method represents a practical attempt to fill the gap between exploratory group analysis and brain effective-connectivity inference, and it is our first attempt on group level modeling. Developing a more theoretically rigorous algorithm is one of our future directions.

At the network level, the network analysis approach based on graph theoretical analysis, lesion and perturbation analysis represents a powerful tool to investigate the connectivity patterns and to extract more informative features from the neural recording signals. To sum up, the proposed network modeling and analysis approach can help us better study the functions of neural systems and understand the interactions between neural components.
Chapter 3

fMRI Studies in Parkinson’s Disease

3.1 Introduction

Functional magnetic resonance imaging (fMRI) is a popular non-invasive neuroimaging technology that measures relative alterations in deoxygenated hemoglobin as a result of ongoing brain activity. Due to fMRI’s wide availability and the growing recognition of the importance of connectivity in normal and disease brain states, many efforts have been made in the area of brain connectivity network modeling and analysis. More specifically, a lot of studies have been conducted on studying neurological disorders such as Parkinson’s Disease using fMRI signals.

PD was first clearly described by James Parkinson. In 1817, he published a monograph entitled “An essay on the shaking palsy” in order to draw the medical professions’ attention to this movement disorder which was then named as Parkinson’s disease [48]. From then on, generations of physicians, neurologists and scientists began to explore the cause, diagnosis and treatment of PD. PD affects all ethnicities, and its prevalence is estimated at 0.3% of the whole population in industrialized countries [69]. It is one of the most common chronic neurodegenerative disorders which is characterized by muscle rigidity, rest tremor, bradykinesia. Besides those symptoms, autonomic dysfunction and the cognitive and psychiatric changes often accompany with PD [69]. The high prevalence and serious conse-
quences of PD have enormous impact on the population.

The underlying pathology associated with PD is the depletion of dopamine-producing neurons in the pars compacta region of substantia nigra [53]. Dopamine serves as the neurotransmitter that carries signals between nerve cells in the brain. At the early course of the disease, the symptoms such as resting tremor usually appear asymmetrically on one side of the body [69]. The presence of intraneuronal Lewy bodies and the Lewy neurites is the pathological hallmark of the disease [16]. When around 80% of striatal dopamine are lost, the clinical signs of the illness are in general evident [27]. Though the etiology of PD is still unclear, multiple factors may be related to it such as aging, genetic risk and environment influence [69].

The record shows that the occurrence of PD is increasing with age. For instance, the prevalence of PD for the people aged 65 years and older increases to 1-2%, and the prevalence for the people aged over 85 years old is as high as 3-5% [3]. The role of genetic factors in the cause of PD is supported by recent research on family studies and twin studies [88]. The environment influences are also considered as one important factor in most PD cases, though the environment observations are not consistent in different surveys [88].

The most widely used pharmacological treatment for PD has been Levodopa (L-DOPA) medication which can convert into dopamine reaching the brain after oral administration. Other treatments such as surgical intervention, deep brain stimulation and rehabilitation are also used to slow the disease progression and relieve the symptoms [69].

The diagnosis of Parkinson’s disease heavily depends on the medical history and clinical symptoms. However, since no lab test clearly identifies PD, diagnosing PD from other parkinsonian diseases at a sufficiently accurate level is still challenging [3]. As one of the non-invasive neuroimaging technologies, Functional magnetic resonance imaging (FMRI) has been widely used for studying the brain activities in PD, and providing useful information for the PD diagnosis and treatment effectiveness evaluation [17, 55, 70]. Previous study suggested that PD may lead to disrupted interactions between brain regions and alternations of connectivity patterns [41]. Modeling and comparing brain connectivity network patterns in health and disease states could provide more insights into the connectivity abnormalities in PD [11].
Here, we apply network modeling and analysis to investigate the connectivity patterns and interactions between different brain regions of interest (ROIs) using fMRI data. Two datasets are investigated in this study. In the first one, the control subjects and patients before and after L-dopa medication are compared at the group level. The moderately sized brain effective connectivity networks are learned to extract the connectivity changes in Parkinson’s Disease and study the effect of the L-dopa medication on PD. In the second case, the normal and PD groups with and without trembling symptoms are studied to investigate particular connectivity features associated with different PD subtypes.

### 3.2 Experiment 1

In this section, the moderate-size brain effective connectivity networks for the PD groups before and after L-dopa medication as well as for the control group are learned by the group PC <sub>fdr</sub> method and further analyzed by different network measures. Based on the learned networks, we found evidences likely supporting the hypothesis of compensatory recruitment in PD, and the network analysis results show the effect of L-dopa medication on PD subjects.

#### 3.2.1 fMRI Datasets

All the experiments were approved by the University of British Columbia ethics committee. The fMRI data were collected from 9 health people as the control subjects and 10 mild to moderately affected PD patients before and after L-dopa medication. Ten recruited patients had typical Parkinsonism symptoms with no other neurological or psychiatric conditions. The patients who used antidepressants, sleeping tablets or dopamine blocking agents were also excluded. The mean duration of the symptoms for patients was more than 5 years, and all of them showed bradykinesia to some extent.

The subjects were asked to perform the bulb squeezing task. They viewed a computer screen via a projection mirror built into the head coil while lying on their back in the functional magnetic resonance scanner. A MR-compatible rubber squeeze bulb which connected to a pressure transducer outside the scanner room was used in the experiment. Subjects were instructed to squeeze the bulb with their
right hand to control the width of an inflatable ring which was shown as a horizontal black bar in the screen (Fig. 3.1). Adding pressure to the bulb increased the width of the bar and releasing pressure from the bulb decreased the width of the bar. As a result, the subjects had to change the pressure on the bulb in order to control the horizontal bar within the white undulating pathway without touching the sides. The maximum voluntary contraction (MVC) was measured for each subject at the beginning of the experiment and the bulb squeezing movements were scaled, so that each subject had to squeeze the bulb at 5-15% of maximal force to accomplish the task.

Figure 3.1: The bulb squeezing task. Squeezing a pressure-responsive bulb to control the width of the horizontal black bar in order to keep the ends on the white.

12 ROIs were chosen for network modeling analysis, as listed in Table 3.1. Before analysis, in addition to standard preprocessing operations, the data were preprocessed by motion correction [52]. A detailed description of the fMRI data collection and experiment design can be found in [51].

3.2.2 Methods
We apply the group PC$_{fdr}$ algorithm to the normal and patient groups to infer the effective brain connectivity networks. Based on the learned connectivity networks, network measures in terms of density, global efficiency, modularity and HA value
Table 3.1: 12 brain ROIs studied in experiment 1. In the abbreviations, “l” and “r” stand for “left” and “right” respectively.

<table>
<thead>
<tr>
<th>Brain ROI</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>left/right cerebellar hemispheres</td>
<td>l/r CER</td>
</tr>
<tr>
<td>left/right globus pallidus</td>
<td>l/r GLP</td>
</tr>
<tr>
<td>left/right Putamen</td>
<td>l/r Put</td>
</tr>
<tr>
<td>left/right supplementary motor area</td>
<td>l/r SMA</td>
</tr>
<tr>
<td>left/right thalamus</td>
<td>l/r THA</td>
</tr>
<tr>
<td>left/right primary motor cortex</td>
<td>l/r M1</td>
</tr>
</tbody>
</table>

are applied to compare the connectivity patterns of the two groups. The lesion analysis is finally applied to quantify the changes in terms of global efficiency associated with the impairment of each ROI. The lesion analysis also displays the different importance of different brain regions on the information flow in the entire connectivity network.

3.2.3 Results

The connectivity networks learned by the group PC<sub>fdr</sub> algorithm for the normal group and the PD groups before and after medication are compared in Figure 3.2, with the target FDR being 5%. We note that the connection from the lCER to the rTHA, part of the cerebellothalamocortical loop, as well as the connection from the lM1 to the rGLP are lost in the PD groups. In addition, the connectivity between the ISMA and the ITHA to the hand used in the task, part of the expected striatothalamocortical loop, is lost in PD before medication group, while this connectivity is re-established in the PD after medication group. We also note new connections in the PD group, including the one between the ITHA and the rCER in the PD before medication group, the one between the ISMA and lPut and the one between the rSMA and rPut in the PD after medication group. Though a thorough future investigation is needed, we feel that these new connections detected by the proposed method may represent compensatory recruitment in PD.

In order to calculate the statistical significance of a measure difference between the normal and the PD group, we learn the connectivity networks for each group.
Figure 3.2: (a) Learned effective connections for the normal group. (b) Learned effective connections for the PD group before medication. (c) Learned effective connections for the PD group after medication.

by employing the leave-one-out-validation approach. We then calculate different network measures to compare the connectivity features of brain effective connectivity networks in different states. As shown in Fig. 3.3, density, global efficiency
Figure 3.3: Network comparisons across the normal and PD groups. Here the investigated network measures include density, global efficiency and modularity. “Normal” denotes the control group, “Ppre” denotes the PD group before medication and “Ppost” denotes the PD group after medication.

and modularity are used to measure the global features of the networks. “Normal” stands for the healthy group, “Ppre” and “Ppost” stand for the PD groups before and after medication respectively. We note from Fig. 3.3 that the normal group has higher global efficiency than that of PD groups, meaning that the information spread ability is more efficient in the connectivity networks of normal control subjects. Moreover, compared with the PD group before L-dopa medication, the network measures of the PD group after medication are more similar to that of the normal group. This observation indicates that the L-dopa medication has positive effect on the PD disease and ameliorates PD to some extent.

The local features of the network in terms of betweenness centrality and HA value can be used to represent different importance of each brain region. The results in Fig 3.4 show that some common ROIs such as rSMA and lPut are important in all three groups, while rCER has less impact on the information transformation.
Figure 3.4: (a) Betweenness centrality measures of the normal group and the PD groups before and after medication. (b) HA value measures of the normal group and the PD groups before and after medication.

The rGLP region plays different roles in different connectivity networks where it displays high importance in the network representing the normal group and less importance in the connectivity network of the PD group before medication. Moreover, in the PD after medication group, the global efficiency and HA value of rGLP
Figure 3.5: Effect of a single region lesion on the brain effective connectivity, measured by the global efficiency after inactivation of the particular ROI. “Original” denotes the original connectivity network without any region lesion. -lCER denotes the removal of the region lCER from the original network.

region become higher than those in the PD before medication group. Similar observation is found in the ICER region. In Fig 3.5, the lesion effects are shown for the normal group and the PD groups before and after medication. In general, removal of the regions from the connectivity network has negative impact on the global efficiency of the network. Similar to the results in Fig 3.4, the rSMA and rPut regions are especially important since inactivation of each of these regions leads to a great decreasing in the global efficiency.

The network modeling and analysis results reported here demonstrate that the brain connectivity patterns are different in the normal and PD states, and the observations of the network features in the control group and the PD groups before and after medication show that the L-dopa medication generally has a positive impact on PD subjects. The proposed network modeling and analysis approach is a powerful tool to describe the interactions between brain ROIs and extract brain connectivity features at the network level, and it can provide complementary information for the brain activities in the normal and PD states.
Table 3.2: 16 brain ROIs studied in experiment 2. In the abbreviations, “l” and “r” stand for “left” and “right” respectively.

<table>
<thead>
<tr>
<th>Brain ROI</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>left/right primary motor cortex</td>
<td>l/r PMC</td>
</tr>
<tr>
<td>left/right pre-motor cortex</td>
<td>l/r PreMC</td>
</tr>
<tr>
<td>left/right supplementary motor area</td>
<td>l/r SMA</td>
</tr>
<tr>
<td>left/right somatomotor cortex</td>
<td>l/r SMC</td>
</tr>
<tr>
<td>left/right thalamus</td>
<td>l/r THA</td>
</tr>
<tr>
<td>left/right basal ganglia</td>
<td>l/r BG</td>
</tr>
<tr>
<td>left/right cerebellar hemisphere</td>
<td>l/r CH</td>
</tr>
<tr>
<td>left/right Putamen</td>
<td>l/r Put</td>
</tr>
</tbody>
</table>

3.3 Experiment 2

In this section, we want to investigate different connectivity patterns across disease subtypes in Parkinson’s Disease. The PD patients with and without trembling symptom as well as control subjects are recruited in our study. The brain connectivity networks are learned for each subject and the network measures are calculated accordingly to extract the connectivity features across the groups. The lesion and perturbation analysis are also applied in this study.

3.3.1 fMRI Datasets

All the experiments were approved by the local institutional ethics committee. fMRI data were collected from 16 healthy people, 9 PD patients without trembling symptom and 15 PD patients with trembling symptom. All of them were required to perform the internally guided (IG) and externally guided (EG) tasks with their left hands. The IG task is to sequentially tap the fingers in the order of the index, middle, ring and little fingers. The EG task is to tap the fingers following the hands on the screen. In this experiment, 16 ROIs were chosen for the network analysis as shown in Table 3.2.
3.3.2 Methods
The connectivity network structure is learned by the PC$_{fdr}$ algorithm [49] and the strength coefficients of the connections are further computed by Bayesian Network learning method [51]. We assume that the connectivity networks within one group have the same network structure but different connectivity coefficients. Based on the learned connectivity networks, network measures including density, global efficiency, reachability and modularity are applied to extract and compare different connectivity patterns across the groups. The lesion analysis is used to measure the impairment and different importance of each ROI. Finally, the perturbation analysis is applied. The perturbation analysis is our attempt to model the evolvement of the connectivity networks by adding noise to the nodes or connections. In particular, in our study, we want to add noise to the connectivity networks in PD, and then compare the changed networks with that of the normal group.

3.3.3 Results
The connectivity networks are learned by the PC$_{fdr}$ algorithm and the Bayesian network modeling method for the PD patients with and without trembling symptom, with the target FDR being 5%. Within each group, each subject is assumed to have the same connectivity structure but different connectivity coefficients. Based on the inferred networks, network measures in terms of density, global efficiency, reachability and modularity are compared in Fig. 3.6. From Fig. 3.6 we note that the connectivity networks for control subjects display higher global efficiency than that of PD groups in both EG and IG tasks, which is consistent with our previous observations. Another important observation is that, compared with the PD subjects without trembling symptom, the connectivity features of PD subjects with trembling symptom are more similar to that of the normal subjects. In the following, for simplicity, PDAR denotes the PD without trembling symptom group and PDT denotes the PD with trembling symptom group.

The reported network measures provide basic comparisons across the normal group and different PD subtypes. To further measure the importance of each brain ROI, the lesion analysis is applied to each group connectivity network and the results are shown in Fig. 3.7. It is obvious that the connectivity network representing
Figure 3.6: (a) Network comparisons across the groups for the EG task. (b) Network comparisons across the groups for the IG task. Network measures reported here include density, global efficiency, reachability and modularity. NA denotes the control group, PDAR denotes the PD group without trembling symptom and PDT denotes the PD group with trembling symptom. LExt denotes the EG task by left hand and LInt denotes the IG task by left hand.
the normal group always has higher global efficiency in inactivation of individual brain ROIs compared with the PD groups. From the results, we can see that different brain ROIs have different importance across the groups. For instance, in Fig. 3.7(a), in the normal and PDT groups, rSMA is especially important since removal of this region leads to a great decreasing in the global efficiency, however, in the PDAR group, rSMA is less important than some other ROIs such as lPreMC. Similar observations could also be noted in Fig. 3.7(a). These results reveal that different connectivity patterns are associated with the normal and PD subtype groups.

In our study, we want to use perturbation analysis to model the evolvement of the connectivity networks. For the PD connectivity networks, we add perturbation to the connections by removing individual connection from the network, and then compare the changed network with the normal group one. With the perturbation analysis, we attempt to provide some insights into the question "how to make the PD connectivity network becomes more similar to the normal connectivity network". In Fig. 3.8, we note that for the EG task, the original value (without perturbation) of KL-divergence between PDT and normal groups is a bit smaller than that between the PDAR and normal groups, which indicates that the PDT group might be more similar to the normal group. The changes of the KL-divergence after removing certain individual connections demonstrate the development of the connectivity networks of the PD groups. For both the PDAR and PDT groups, after removing the connectivity between lTHA and lSMA, the KL-divergence becomes smaller, meaning that the connectivity networks are closer to the connectivity network of the normal group. In addition, the KL-divergence increases after removing some connections such as the connectivity between rPMC and rSMC and the connectivity between rTHA and lTHA. Similar results are also noted in the IG task as shown in Fig. 3.9. These results together shed some light on the evolvement of the connectivity networks which might be useful to the diagnosis and treatment of PD in the future.
Figure 3.7: (a) Effect of a single region lesion on the brain effective connectivity for the EG task. (b) Effect of a single region lesion on the brain effective connectivity for the IG task. Corresponding global efficiency values are calculated after inactivation of individual ROIs. Here “Original” means the original connectivity network without lesion. -lPMC means the removal of the region lPMC from the original network.
Figure 3.8: (a) The perturbation analysis on the PD group without trembling symptom for EG task. (b) The perturbation analysis on the PD group with trembling symptom for EG task. “Original” means the original connectivity network without perturbation.
Figure 3.9: (a) The perturbation analysis on the PD group without trembling symptom for the IG task. (b) The perturbation analysis on the PD group with trembling symptom for the IG task.
3.4 Conclusion

We applied the network modeling and analysis approach to investigate moderate-size brain effective connectivity networks in different states. The first fMRI study is conducted on the PD groups before and after medication as well as the control group. The results show that the normal and PD groups display different connectivity patterns. The comparison results support the hypothesis that L-dopa has a positive impact on the PD subjects, and the identified connections are likely related to compensatory recruitment in PD.

The second fMRI study focuses on the network comparisons between the normal group and the PD groups with and without trembling symptom. The network analysis results demonstrate that the connectivity networks representing the PD group with trembling symptom are much closer to the normal connectivity networks. The perturbation analysis attempts to model the evolvement of the connectivity networks. The results on perturbation analysis may shed some light on effective diagnosis and treatment of PD.
Chapter 4

sEMG Study in Low Back Pain

4.1 Introduction

Low back pain (LBP) is one of the most common musculoskeletal problems which could result in activity limitations, loss of work ability and even disability. It is estimated that 75-80% of adults can be affected by LBP at some point at least once in their life [7]. A five years study showed that in most cases, LBP is usually continuous with periodic recurrences after the initial episode [37]. It is suggested that the LBP is one of the most frequent causes for people’s seeking medical care services in the US [7]. Similarly, data from western countries demonstrated that the LBP is one of the leading causes of absence from work [28]. Moreover, one study based on a local survey in North Carolina showed that the prevalence of LBP is still increasing [29].

The high prevalence and widespread of low back pain has enormous impact on the entire population. A broad range of studies have been conducted on the LBP patients for accurate diagnosis and effective treatment of LBP. Various interventions have been developed for low back pain. One widely used therapy for LBP is physical exercise. It has been shown that physical exercise as one effective treatment of LBP can help on function improvement, pain intensity decrease and return-to-normal-activities [86]. In particular, with increasing exercise intensity and self-motivation, the treatment effects appear to be more effective [73]. However, there still lacks of the universal comparison and assessment of intervention
results of various exercise types and intensities. Hayden et al. suggested in their systematic review that the exercise therapy should be designed individually for each patient with close supervision [36]. Other therapeutic interventions for LBP include medicine, surgery, acupuncture and so on [91].

However, no universally accepted standard methods for measuring the results of various therapies are available yet, and the effectiveness of different interventions is still in debating. The recent advances of neuroimaging technologies can provide complementary information for the diagnosis and treatment of LBP. It is recommended that the clinicians perform the diagnostic imaging such as Radiography, Magnetic Resonance Imaging or Computed Tomography on the LBP patients with serious underlying conditions [23]. As one of the non-invasive neuroimaging technologies, surface electromyography (sEMG) has been widely used for measuring the muscular activities of patients with low back pain, and can provide useful information for the LBP diagnosis and treatment effectiveness evaluation [20, 54, 65]. Compared with the needle EMG, the non-invasive nature of the sEMG makes it practical in recording global information from several muscles simultaneously, and thus sEMG is used to investigate lumbar muscle coordination and can provide new perspectives for the diagnosis and treatment of LBP.

Previous research in studying lumbar muscle coordination using sEMG signals has been focused on learning coordination of muscular contractions by employing conventional amplitude, spectrum and correlation analysis. By calculating the pairwise correlations between the right and left corresponding muscles using sEMG, Lu et al. found that a significant risk factor for LBP is abnormal back muscle contraction coordination during motions [54]. Roy et al. proposed that the low back pain is associated with the left side to right side imbalance of the sEMG signals by analyzing the corresponding spectral and amplitude parameters [67]. Our recent study using root mean square (RMS) dynamic topography of sEMG signals also revealed the asymmetric or disorganized patterns associated with the LBP patients [40]. In light of previous studies on lumbar muscle activities, the measurement of muscle contraction coordination shows a potential tool to distinguish low back pain from normal healthy, even further to evaluate severity of pain and to assess progress of pain relief.

In the sEMG literature, although not been investigated specifically in LBP
study yet, in addition to the traditional amplitude and frequency analysis, a number of different statistical methods have been proposed for inferring muscle coordination activities using sEMG signals such as Principle Component Analysis (PCA) and linear Independent Component Analysis (ICA) [57, 58]. Such linear decomposition based methods are operated on the assumption that multichannel sEMG signals are generated by a set of underlying unknown source signals, and thus interactions between muscles (or sEMG channels) can be implicitly revealed through the extracted underlying sources by projecting multichannel sEMG signals to a particular subspace. Different from P/ICA approaches, we recently proposed directly inferring the meaningful interactions between muscles instead of using the underlying latent variables as in P/ICA, including a Multivariate Autoregressive (mAR) modeling approach [22] and a Bayesian network modeling approach [50]. Bayesian network is a popular type of graphical models where a directed acyclic graph (DAG) encodes a set of (conditional) dependence/independence relationships among random variables (e.g. sEMG channels). Our basic idea was to infer the interactions between the sEMG channels by detecting conditional dependence/independence between muscle activities, i.e. whether the activities of two sEMG channels are associated given other sEMG channels. We have argued that BN may be particularly suited for modeling muscle coordination networks [50].

Further inspired by recent theoretical PC_{fdr} work on controlling the false discovery rate of the learned connections in Bayesian networks [49], in this paper, we will study muscle coordination activities in LBP by employing two level PC_{fdr} algorithms to model the coordination network between sEMG channels and by employing graph theoretical analysis of networks to measure the trunk muscle coordination activities in LBP. Particularly, to investigate the left side to right side imbalance of the sEMG activities in LBP, we define three types of symmetry connections and use the corresponding scores to characterize the learned sEMG networks. It is worth mentioning that, though being relatively new in sEMG analysis (especially being new in LBP study), the network modeling and analysis, as a powerful tool to extract interaction information from the nonstructural data, has been successfully used in economics, sociology and neurosystems such as brain effective connectivity modeling using fMRI [4].

The objective of this study is to develop a new test of lumbar myoelectrical
activities using the sEMG coordination network analysis approach, visualizing the lumbar myoelectrical activities during flexion-extension task and capturing the features of the networks in normal and patient groups to propose a new method to low back pain diagnosis and monitoring. The constructed networks for normal and patient groups clearly display different sEMG coordination activity patterns, and in particular, they exhibit distinguishing symmetry patterns. The network analysis results provide a global comparison and evaluation of the lumbar muscular activities. It is potential to apply the network analysis in the clinical diagnosis and rehabilitation assessment of LBP in the future work. The contributions of this paper are summarized as follows:

- We introduce the network modeling with error rate controlled for sEMG signals to study coordination networks between sEMG channels.
- We propose new symmetry scores for the learned sEMG networks to characterize symmetric patterns and to investigate the particular symmetry patterns associated with the lumbar muscles in low back pain.
- We explore sEMG network analysis in terms of symmetric patterns, global efficiency, clustering coefficient and graph modules.
- We apply the proposed network modeling and analysis approach to a real sEMG study in LBP. Control subjects and patients with LBP can be clearly distinguished by the network features and symmetric patterns.

The remainder of this section is organized as follows. In Section 4.2, the real sEMG datasets for healthy control subjects and patients with LBP are described, and data analysis methods are introduced in detail. Two level results of sEMG data are discussed in Section 4.3. In Section 4.4, we present the discussion and conclusions of this paper.
4.2 Methods and Materials

4.2.1 sEMG Datasets

All the experiments were approved by the local institutional ethics committee. The sEMG data were collected from 10 healthy male subjects and eleven male patients with chronic low back pain. All recruited patients don’t have spinal deficits, or any other back surgeries. The durations of the low back pain for all patients were more than 3 months without any related organic findings which need the surgical interventions.

All subjects were required to perform the flexion-extension task during the sEMG recording. The subjects bent their trunk forward up to 30 degrees, measured by the protractor, and they maintained the bending posture for 4 seconds, then they returned to the standing posture, as shown in Fig. 4.1. The flexion-extension task was repeated twice by each subject with at least two-minute rest between each attempt upon the patients’ request.

The sEMG signals were collected by a surface electrode-array which was applied to the low back muscles evenly in the lumbar region. As shown in the electrode placement (Fig. 4.2(a)), sixteen active electrodes were used together with three reference electrodes along the posteromedian furrow, and the two ground electrodes were placed at the left and right upper corners respectively. The sixteen-channel sEMG signals were amplified by a factor of 2000, band-pass filtered at
Figure 4.2: (a) The sEMG electrode array placement. (b) The sEMG electrode array alignment in the lumbar region.

15-950Hz, and then sampled at 2000Hz by an NI data acquisition card (DAQ6063, National Instruments Inc., Austin, Texas, USA). During the experiment, considering the impact of the temperature on the muscle conduction velocity and contractility, we maintained a constant temperature to eliminate the temperature effect.

In general, the maximum voluntary contraction (MVC) method is used to normalize the sEMG signals [74]. However, since the LBP patients usually have weaker back muscles than normal subjects, it’s hard for them to perform the MVC tasks. As a result, in this study, we used the lumbar muscle activities during sit-
ting and standing to normalize the sEMG signals. The root mean square (RMS) value during sitting and standing was calculated as the reference for performing the sEMG normalization.

4.2.2 Methods

sEMG is a semistochastic process whose properties depend on a number of factors such as anatomical and physiological properties of the muscles. Here we model the sEMG signals by error-rate-controlled Bayesian networks to directly represent the interactions/coordination between muscles. We use the single subject level and group level PC$_{fdr}$ algorithm to model the connectivity between the sEMG channels. Based on the inferred connectivity networks, the network measures in terms of density, global efficiency, clustering coefficient and group modules are applied to extract the connectivity patterns at the network level. The details of the network modeling and analysis methods are introduced in Chapter. 2.

In addition to the network measures introduced in Chapter. 2, we propose the symmetry measure particularly for our sEMG study. Here, the sixteen sEMG channels are symmetrically located in the left and right lumbar regions. Each channel in the left side has the corresponding symmetric channel in the right side. In order to investigate the symmetry of the networks in normal and LBP patient group, we define three types of symmetric coordination patterns in the sEMG networks and hence calculate the symmetry scores for the two groups. As illustrated in Fig. 4.3 in a network of twelve channels with unique labels, the first type of symmetry refers to the edges connecting the pairs of symmetric channels in the left and right sides, e.g. the edge $L_1 - R_1$. These symmetric connections indicate the pair-wise sEMG coordination in the left and right sides. The first type of symmetry represents individual sEMG channel symmetry in the left and right sides. The second type of symmetry refers to the pairs of cross-side symmetric connections, e.g. the pair of the symmetric edges $L_5 - R_4$ and $R_5 - L_4$. The 2nd type of symmetry represents inter-side connection symmetry in the left and right sides. The third type refers to the pairs of intra-side symmetric connections, e.g. the pair of the symmetric edges $L_1 - L_4$ and $R_1 - R_4$. The first two types of coordination symmetry describe the global (cross-side) symmetry of the networks, while the last type shows the
local structure symmetry. Correspondingly, we can define three types of symmetry scores as the corresponding ratios of the number of certain types of connections over the total number of connections in the network:

\[ \text{Symm}1 = \frac{1}{M} \sum_{i} e_{L_iR_i}, \quad (4.1) \]
\[ \text{Symm}2 = \frac{2}{M} \sum_{i \neq j} e_{L_iR_j} e_{R_iL_j}, \quad (4.2) \]
\[ \text{Symm}3 = \frac{2}{M} \sum_{i \neq j} e_{L_iL_j} e_{R_iR_j}, \quad (4.3) \]

where \( M \) means the total number of edges in the graph, \( e_{L_iR_i} = 1 \) means the presence of the connection from the node \( L_i \) to the node \( R_i \) and \( e_{L_iR_i} = 0 \) means the absence of the connection, and \( e_{L_iR_j}, e_{L_iL_j}, \text{and } e_{R_iL_j} \) are similarly defined.

The different symmetry patterns reveal different muscle synergies and coordination during the task. We will use the symmetry scores to quantify the symmetry properties of the learned sEMG networks and compare them between normal and patient groups.

### 4.3 Results

We first learn the sEMG connectivity networks at the subject level. The corresponding network analysis can reveal the similarity within the group and the dissimilarity between the groups. We then model the networks and perform network analysis at the group level to compare normal and LBP patient groups. We note significant differences in the network patterns of the two groups, and the results from the subject and the group levels are consistent.

#### 4.3.1 Subject Level Analysis

Applying the subject level PC\_fdr algorithm to the sEMG signals of each subject, we control the FDR as 0.01 and learn the sEMG networks respectively. Fig. 4.4 shows one example of the learned sEMG connectivity network from a normal subject (Fig. 4.4(a)) and one example from a subject with LBP (Fig. 4.4(b)). Though
Figure 4.3: Example of three types of symmetric connections. The red solid lines represent the first type symmetric connections, the black broken dotted lines represent the second type symmetric connections, and the blue dashed lines represent the third type symmetric connections. The number of total edges in the graph is $M = 11$, and the corresponding three types of symmetric scores are calculated, defined as the ratio of the edge in a particular type of symmetric connections over the total number of edges in the graph.

From the networks in Fig. 4.4 and similar networks for other individual subjects (which are omitted here due to space limit), it is obvious that, for the normal subjects, most of the connections are between the pairs of symmetric channels in the left and the right sides, i.e. the first type of symmetric connections. For instance, in Fig. 4.4(a), we note that all 8 symmetric pair connections $L1−R1$, $L2−R2$, $L3−R3$, $L4−R4$, $L5−R5$, $L6−R6$, $L7−R7$, $L8−R8$ are learned. Observations from Fig. 4.4(a) suggest that the muscle coordination of normal subjects during the task is dominated by cross-side connections. However, the patient network in Fig. 4.4(b) lacks of such globally symmetric connectivity patterns, while it is more dominated by the local connections within the same side though we do observe the left-right symmetry between the connections (i.e. the 3rd type of symmetric connections).

To quantify the symmetry patterns of muscle coordination in the normal and
Figure 4.4: (a) The learned connectivity network between sEMG channels for one healthy subject, the total number of connections in this network is 19. (b) The learned connectivity network between sEMG channels for one patient subject, the total number of connections in this network is 28.

Patient subjects during the flexion-extension task, we compare the three types of symmetry scores in Fig. 4.5. From the bar figures, we can see that the sEMG coordination patterns for the normal and patient subjects are statistically significantly different. For the normal subjects, the scores of first two types of symmetric connections are significantly greater than that of the patient subjects. Such obvious symmetric patterns found in the normal subjects indicate that the left and right muscles in the lumbar regions, in particular the pairs of symmetric muscles, are interactive and thus generate efficient global coordination. For the patient subjects, the synergy/coordination from the left to the right side is significantly weaker. The connections are most locally connected within the same side and they only preserve the third type of symmetry patterns. Previous studies have assessed that the left to right imbalance is associated with the low back pain [67], which is consistent with our network analysis results that the normal subjects recruit global symmetry connections from the whole lumbar region while the patient subjects mainly recruit local connections. By investigating the individual subject networks, we also note a larger inter-subject variability in the patient group (e.g. different local connections
To investigate different network features for the normal and patient subjects, we also compare network measures in terms of network density, global efficiency, modularity and clustering coefficient, as shown in Fig. 4.6. All the four measures between normal and patient subjects are significantly different (the corresponding P-value for the four measures are 0.0015, 0.000076, 0.00073 and 0.0104). From the network analysis perspective, a possible explanation is as follows: because of the weaker muscle functions of the patients with LBP, more connections between local muscles are recruited to compensate the weaken muscle functions, and the denser connections lead to the increase of the communication ability of the muscles. In other words, for the patient subjects, the information spread ability improvement is at the expense of increasing the local connections. The modularity shows that the
networks of normal subjects can be better divided into the sub-communities, as be shown at the group level analysis too.

In order to better understand the network patterns of the normal and patient subjects, we further compare global efficiency and clustering coefficient measures with that of the random networks to investigate the network types. For each subject, we generate fifty random networks having the same degree distribution and calculate their global efficiencies and clustering coefficients. As shown in Fig. 4.7, for the normal subjects, the average global efficiency is smaller than that of the random networks (Fig. 4.7(a)) and the average clustering coefficient is significantly larger than that of the random networks (Fig. 4.7(b)). As discussed in the method part, this observation indicates that the normal sEMG networks are different from random networks, and probably closer to the ordered networks characterized by lower global efficiency and higher clustering coefficient.

Compared with the normal subjects, both global efficiency and clustering coefficient of the patient networks are closer to those of random networks (Fig. 4.8). This observation suggests that the patient subject networks are closer to the random networks and probably have the small world property to some extent. One
Figure 4.7: (a) The comparison between normal connectivity networks and random networks in terms of global efficiency. (b) The comparison between normal connectivity networks and random networks in terms of clustering coefficient. The errorbars stand for the standard deviations.

possible explanation for the phenomena is the following: The muscles in the normal subjects can work interactively and those interactions between muscles exhibit the ordered patterns (e.g. type 1 symmetry pattern), while for the patient subjects, to compensate the missing interactions between two side lumbar regions, the new connections in the local regions are randomly recruited to compensate the muscle functions during the task. The randomness of the connections for the patient subjects results in the network small-worldness [89]. In summary, the comparisons with the random networks demonstrate that the normal and patient sEMG networks belong to different network categories. These observations confirm the differences of sEMG coordination patterns between the normal and patient subjects. A more precise conclusion will need a large-scale database support.

4.3.2 Group Level Analysis

The subject level analysis reveals some features of the sEMG networks of the control subjects and patients with LBP. However, even within the same group, considerable heterogeneity may exist and thus requires performing efficient group analysis to infer the underlying group-common network patterns. In this paper, we apply the group PC_{fdr} algorithm to make the inference at the group level, with the FDR
Figure 4.8: (a) The comparison between patient connectivity networks and random networks in terms of global efficiency. (b) The comparison between patient connectivity networks and random networks in terms of clustering coefficient. The errorbars stand for the standard deviations.

being controlled at 0.05. In Fig. 4.9(a)(b), the learned group level sEMG networks are shown. Compared with the subject-level networks, the group-level networks are sparser since only those significant connections within the group are learned, indicating statistically group-common connections. Since the inter-subject variability is taken care by the group analysis, the learned group-level networks are easier to interpret.

The symmetry patterns are also investigated in the group networks. We note that the normal group network is dominated by the left to right symmetric connections especially the first type of symmetric connections, while most connections in the patient group network are the third type of symmetric connections restricted to the local neighbors. In Fig. 4.10, the comparison of the connection types at the group level is displayed. Similar to the subject level analysis, for the normal group, the scores of first two types of connections are much greater than those of patient group and a much smaller score of the third type of symmetric connections is observed in the normal group network. Actually compared with the subject-level analysis, such observations are even much more apparent.

We believe that different symmetry patterns are associated with different muscle coordination synergies. The symmetric muscles in the left and right lumbar regions tend to work pair-wise together in the normal state while the muscles tend
Figure 4.9: (a) The learned connectivity network for the normal group, the total number of connections in this network is 15. (b) The learned connectivity network for the patient group, the total number of connections in this network is 17.

to interactive locally in LBP state. We further study the optimal module divisions to investigate different community structures for the two groups. As shown in Fig. 4.11, within each of the divided modules, the involved sEMG channels (thus the corresponding muscles) are highly symmetric from the left to right sides in the normal group. All the symmetric sEMG channels in the left and right sides are divided into the same community, indicating that the two side muscles coordinate closely and perform the task together. The modules are quite different for the patient group. We note that the modules generally are constrained locally within one side and the neighbor sEMG channels coordinate together during the task. However interesting, we note the symmetric pattern between the modules, e.g. one module in the left side has a symmetric module in the right side. The subject and group level analysis provides some consistent insights into the sEMG coordination networks: the normal group network displays the global symmetric patterns characterized by the 1st and 2nd types of symmetry patterns and the network structure properties are closer to that of the ordered networks. For the patient group, the connections are mostly interactive in the local region only within one side, though high-level connection symmetry is observed, as characterized by the 3rd type of symmetry connections.
Figure 4.10: (a) The first type symmetry scores of both group connectivity networks. (b) The second type symmetry scores of both group connectivity networks. (c) The third type symmetry scores of both group connectivity networks.

Basically the low back pain in the lumbar region leads to the inter-side connection imbalances. Also, it is noted that local connections are recruited with certain randomness in the patient sEMG networks to compensate the weaker functions of the muscles, and this may lead to somehow small-worldness of the networks.

4.4 Conclusion

This paper proposes an error-rate-controlled network modeling and network analysis framework using the sEMG signals during flexion-extension to infer and visualize the lumbar muscle coordination activities of the subjects with and without low back pain. By comparing different sEMG networks of the two groups, the proposed method provides a new perspective to investigate muscle coordination patterns associated with low back pain. Both subject-level and group-level analysis
are provided in this paper. The subject level analysis reveals connection features (e.g. network types) of normal and patient subjects and shows the inter-subject variability observed in subjects within the same group. The group level analysis can infer the group-common muscle coordination patterns by statistically addressing the heterogeneity within the groups.

Our real sEMG study in LBP shows that the coordination network properties and the symmetry patterns are significantly different between the normal group and the patient group. Based on the network measures, the normal networks are closer to the ordered networks, while a higher degree of randomness is observed in the patient networks. The different muscle functioning may result in different network types, and the different network types may account for different properties of the learned networks. The symmetry analysis results in our study are consistent with previous findings by using other methods such as the frequency analysis and the dynamic topography analysis [40, 67]. The normal group displays type-1 and type-2 symmetry patterns. In other words, the symmetric muscles in both sides are acting interactively during performing the task. While for the patients with LBP, the networks mainly exhibit type-3 symmetry patterns where the connections are constrained locally in one side. These results suggest that the weaker muscle functions associated with the LBP may result from the deficiency of the coordination
of trunk muscles in both sides of the body.

We would like to clarify that the sEMG channels in this study do not exactly represent specific trunk muscles, and thus as a result, the connectivity network between the sEMG channels is not exactly equal to the muscle coordination network or muscle coordination synergy. In LBP study with using the sEMG array, the non-invasive nature of sEMG makes it possible to collect the information of muscle activities globally, but also makes it difficult to distinguish different muscles within one region. Several sEMG channels around one region may stand for one single muscle. Considering the symmetric layout of the channels, we believe that our results could represent the inter-activities between the symmetric muscles at the left and right sides of the lumbar region. The results represent the overall performance of the lumbar region muscles during the flexion-extension task.

The proposed network analysis characterizes the activity behaviors of the lumbar region muscles and their interactions at the network level. Since significant differences are found between the normal and the patient subjects, in the future work, it is possible to use the network measures and symmetry scores for the diagnosis of LBP. Previous studies have used some methods such as spatial distribution of the root mean square (RMS), spectral electromyography parameters to distinguish healthy and patient subjects [64, 65]. The network type and asymmetric patterns associated with LBP are also of great interest. For instance, investigating the mechanism of these changes from the normal to the patient group may make great progress in clinical treatments. Another direction is to use the proposed network modeling method to investigate different cross-talks of muscles under pain.
Chapter 5

Conclusion and Future Work

5.1 Conclusion and Contribution

In this thesis, we presented an error-rate-controlled graphical network modeling framework for inferring interactions between the neural components using biomedical signals such as fMRI and sEMG. As a complementary tool to the physical and anatomical analysis, the graphical network analysis approach allows the visualization and the extraction of more informative features from the multi-channel neural signals.

In Chapter 2, we explored group network modeling for multi-channel signals. Group modeling of connectivity networks for comparisons between populations is a challenging topic, particularly when there might be considerable heterogeneity within one or more groups, such as disease populations. We proposed a group-level exploratory modeling process, the group PC_{fdr} algorithm, for inferring connectivity between multi-channel signals. Taking into account inter-subject variances, the proposed group PC_{fdr} algorithm combines group inference with a graphical modeling approach for discovering statistically significant connectivity. Simulation results demonstrated that the group PC_{fdr} method can accurately recover the underlying group network structures and robustly control the false discovery rate (FDR) at user-specified levels. Based on the inferred connectivity networks, graphical network analysis is used to extract the features at the network level based on the chosen application-dependent network measures. The lesion and perturbation
analysis can be treated as complementary methods to analyze the importance of each individual node and connection.

In Chapter 3, we examined real fMRI studies in PD, where the fMRI data were collected from control and PD subjects before and after L-dopa medication. The results on the learned brain connectivity networks provide significant insights into the relationship between the brain connectivity and the PD disease. The detected connections are likely related to compensatory recruitment in PD, and the analysis at the network level supports the hypothesis that PD subjects could be ameliorated by L-dopa medication. In another fMRI application to the control group and the PD groups with and without trembling symptoms, the results indicate that the brain networks across PD subtypes display different connectivity patterns.

Chapter 4 focused on the graphical network modeling and analysis of sEMG data in a LBP study. Ten healthy subjects and eleven LBP patients were asked to perform the flexion-extension task, and the sEMG signals were recorded. The subject-level and the group-level PC$_{fdr}$ algorithms were applied to learn the sEMG coordination networks with the error-rate being controlled. The network features were further characterized in terms of network symmetry, global efficiency, clustering coefficient and graph modules. The results indicated that the networks representing the normal group are much closer to the ordered networks and clearly exhibit globally symmetric patterns between the left and right sEMG channels. While the coordination activities between sEMG channels for the patient group are more likely to cluster locally and the group network shows the loss of global symmetric patterns.

5.2 Future Work

In this thesis, since group analysis is of great importance in many biomedical applications where people often are interested in extracting group-common features from the populations, we extend the single subject level PC$_{fdr}$ algorithm to the group level. However, it is just our first attempt to the group level network modeling and several limitations are still associated with the current group PC$_{fdr}$ algorithm. The simulation results show that the performance of our group PC$_{fdr}$ method is subject to the number of subjects. However, in many biomedical applications,
data collection is really time-consuming. What is more, the observations from the simulation results indicate the group $\text{PC}_{\text{fdr}}$ method is more suitable for sparse network inference, while increasing the density of the group network may lead to the decrease of the detection power. To conquer these limitations, developing a more theoretically rigorous group level network modeling algorithm is our goal in the future work.

PD is one of the most common movement disorders. Studying brain effective connectivity using fMRI data could provide better understanding of the underlying brain function in PD, and the network analysis could provide more scientific interpretations of the involved brain connections. One possible application in the future is to use the network modeling and analysis approach for early diagnosis of PD and for quantizing the severity of PD.

Using network modeling and analysis to characterize coordination interactions between lumbar region muscles provides great potential to study muscle activities in low back pain. In the future work, we may apply the proposed network modeling and analysis approach to classify the LBP patients from the normal subjects. Another direction is to use the proposed network modeling method to investigate different cross-talks of muscles under pain.
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