STATE-SPACE MODELING AND ESTIMATION FOR MULTIVARIATE BRAIN SIGNALS

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Dedicated to my beloved Emak, Abah,
sisters, brother
and friends.

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ABSTRACT

Brain signals are derived from underlying dynamic processes and interactions between populations of neurons in the brain. These signals are typically measured from distinct regions, in the forms of multivariate time series signals and exhibit non-stationarity. To analyze these multi-dimensional data with the latent dynamics, efficient statistical methods are needed. Conventional analyses of brain signals use stationary techniques and focus on analyzing a single dimensional signal, without taking into consideration the coherence between signals. Other conventional model is the discrete-state hidden Markov model (HMM) where the evolution of hidden states is characterized by a discrete Markov chain. These limitations can be overcome by modeling the signals using state-space model (SSM), that model the signals continuously and further estimate the interdependence between the brain signals. This thesis developed SSM based formulations for autoregressive models to estimate the underlying dynamics of brain activity based on measured signals from different regions. The hidden state and model estimations were performed by Kalman filter and maximum likelihood estimation based on the expectation maximization (EM) algorithm. Adaptive dynamic model time-varying autoregressive (TV-AR) was formulated into SSM, for the application of multi-channel electroencephalography (EEG) classification, where accuracy obtained was better than the conventional HMM. This research generalized the TV-AR to multivariate model to capture the dynamic integration of brain signals. Dynamic multivariate time-varying vector autoregressive (TV-VAR) model was used to investigate the dynamics of causal effects of one region has on another, which is known as effective connectivity. This model was applied to motor-imagery EEG and motor-task functional magnetic resonance imaging (fMRI) data, where the results showed that the effective connectivity changes over time. These changing connectivity structures were found to reflect the behavior of underlying brain states. To detect the state-related change of brain activities based on effective connectivity, this thesis further developed a novel unified framework based on the switching vector autoregressive (SVAR) model. The framework was applied to simulation signals, epileptic EEG and motor-task fMRI. The results showed that the novel framework is able to simultaneously capture both slow and abrupt changes of effective connectivity according to the brain states. In conclusion, the developed SSM based approaches were effective for modeling the non-stationarity and connectivity in brain signals.

ABSTRAK

Isyarat otak berasal dari proses dinamik asas dan interaksi antara populasi neuron dalam otak. Isyarat ini biasanya diukur dari kawasan yang berbeza, dalam bentuk isyarat multivariat siri masa dan mempamerkan sifat tidak statik. Untuk menganalisis multi-dimensi data dengan dinamik terpendam, kaedah statistik yang cekap diperlukan. Analisis isyarat otak lazimnya menggunakan teknik tidak dinamik dan fokus pada satu dimensi, tanpa mengambil kira hubungan di antara isyarat tersebut. Model konvensional lain ialah diskret *hidden Markov model* (HMM), di mana evolusi bagi keadaan tersembunyi dicirikan dengan rantaian diskret Markov. Kelemahan ini boleh diatasi dengan memodelkan isyarat menggunakan *state-space model* (SSM), yang memodelkan isyarat secara berterusan dan juga menganggarkan saling-kebergantungan antara isyarat otak. Tesis ini membangunkan formulasi berasaskan SSM bagi model-model autoregresif untuk menganggar dinamik asas aktiviti otak berdasarkan isyarat yang diukur dari kawasan otak yang berlainan. Anggaran bagi model dan keadaan yang tersembunyi telah menggunakan penapis Kalman dan kebarangkalian maksimum dianggarkan berdasarkan algoritma pengoptimuman jangkaan (EM). Model adaptif dinamik *time-varying autoregressive* (TV-AR) telah diformulasikan ke dalam SSM, untuk aplikasi pengklasifikasian multi-saluran *electroencephalogram* (EEG), dimana ketepatan klasifikasi yang diperolehi lebih baik daripada konvensional HMM. Kajian ini menggeneralisasikan model TV-AR kepada multivariat untuk tujuan merakam integrasi dinamik bagi isyarat otak. Model multivariat dinamik *time-varying vector autoregressive* (TV-VAR) digunakan bagi mengkaji kesan suatu kawasan otak terhadap kawasan lain yang dikenali sebagai sambungan efektif. Model ini digunakan untuk menganalisis data motor-imaginasi EEG dan motor-kerja *functional magnetic resonance imaging* (fMRI), di mana keputusan mendapati bahawa sambungan efektif berubah dari masa ke semasa. Struktur sambungan yang berubah-ubah adalah mencerminkan keadaan sebenar otak. Untuk mengesan perubahan yang berkaitan dengan keadaan otak berdasarkan sambungan efektif, kajian ini seterusnya telah membina satu penyatuan rangka-kerja baru berdasarkan model *switching vector autoregressive*. Rangka-kerja ini diaplikasi ke atas simulasi data, epilepsi EEG dan motor-kerja fMRI. Dapatan kajian menunjukkan bahawa rangka-kerja baru ini dapat merekodkan perubahan yang perlahan dan mendadak pada sambungan efektif berdasarkan keadaan otak. Kesimpulannya, pendekatan berasaskan SSM yang dibangunkan adalah efektif bagi memodelkan sifat tidak statik dan sambungan bagi isyarat otak.

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LIST OF ABBREVIATIONS

ACg	–	anterior cingulate gyrus
AD	–	Alzheimers disease
AFNI	–	analysis of functional neuroimages
AIC	–	Akaike information criterion
amPFC	–	anterior medial prefrontal cortex
AP	–	action potential
ApC	–	anterior precuneus
AR	–	autoregressive
BCI	–	brain computer interface
BOLD	–	blood oxygenation level dependent
CNS	–	central nervous system
CT	–	computerized tomography
DBN	–	dynamic Bayesian network
DCD	–	dynamic connectivity detection
DCM	–	dynamic causal modeling
DCR	–	dynamic connectivity regression
dDTF	–	direct directed transfer function
DMN	–	default mode network
dmPFC	–	dorsomedial prefrontal cortex
DNA	–	deoxyribonucleic acid
DTF	–	directed transfer function
ECG	–	electrocardiogram
ECoG	–	electrocorticography
EEG	–	electroencephalography
EM	–	expectation maximization
EP	–	evoked potential
ERD	–	event-related desynchronization
ERP	–	event-related potential

ERS	–	event-related synchronization
FFT	–	fast Fourier transform
fMRI	–	functional magnetic resonance imaging
GC	–	Granger causality
GCM	–	Granger causality model
GLASSO	–	graphical least absolute shrinkage and selection operator
HMM	–	hidden Markov model
HRF	–	hemodynamic response function
i.i.d.	–	independent and identically distributed
ICA	–	independent component analysis
iEEG	–	intra-cranial electroencephalography
KF	–	Kalman filter
kNN	–	k-nearest-neighbor
KS	–	Kalman smoother
LDA	–	linear discriminant analysis
LDM	–	linear dynamic model
LEP	–	laser-evoked potential
LLM	–	local level model
LM1	–	left primary motor
LPM	–	left premotor cortex
LS	–	least-square
LSE	–	least square estimation
LSM	–	left sensory-motor cortex
M1	–	primary motor cortex
MA	–	moving average
MEG	–	magnetoencephalography
ML	–	maximum likelihood
MSE	–	mean-squared error
MTL	–	medial temporal lobe
MVAR	–	multivariate autoregressive
NIRS	–	near-infrared spectroscopy
NMR	–	nuclear magnetic resonance
PCA	–	principle component analysis
PCC	–	posterior cingulate cortex
PCG	–	phonocardiographic

PDC	–	partial directed coherence
PET	–	positron emission tomography
PET	–	positron emission transmission
PMd	–	dorsal premotor cortex
PPG	–	photoplethysmography
RLS	–	recursive least square
ROI	–	region of interest
ROIs	–	region of interests
RPM	–	right premotor cortex
RpM1	–	right premotor cortex
RSM	–	right sensory-motor cortex
RTS	–	Rauch-Tung-Striebel
sDTF	–	short-time directed transfer function
SEM	–	structural equation modeling
SKF	–	switching Kalman filter
SKS	–	switching Kalman smoother
SLDS	–	switching linear dynamic system
SLDS	–	switching linear dynamical system
SMA	–	supplementary motor area
SNR	–	signal-to-noise ratio
SPM	–	statistical parametric mapping
SSM	–	state space model
SSM	–	state-space model
SSSM	–	switching state-space model
STFT	–	short-time frequency transform
SVAR	–	switching vector autoregressive
SVM	–	support vector machine
TFD	–	time-frequency distribution
TV-AR	–	time-varying autoregressive
TV-DTF	–	time-varying directed transfer function
TV-MVAR	–	time-varying multivariate autoregressive
TV-PDC	–	time-varying partial directed coherence
TV-VAR	–	time-varying vector autoregressive
TV-VAR	–	time-varying vector autoregressive
VAR	–	vector autoregressive

VAR	–	vector autoregressive
VC	–	volume conduction
WHO	–	World Health Organization

LIST OF SYMBOLS

$\mathbf{A}$	-	state transition matrix
$\mathbf{A}_{[S_t]}$	-	switching state transition matrix
$\mathbf{B}$	-	constraint matrix
$\widehat{\mathbf{b}}$	-	estimated LSE
$\mathbf{b}$	-	least square estimator
$\mathbf{C}$	-	observation transition matrix
$\mathbf{C}_{[S_t]}$	-	switching observation transition matrix
d	-	dimension of state variable $\mathbf{x}_t$
D	-	the number of tested coefficients
$\mathbf{E}$	-	collection of noise terms at all time points
$\mathbf{e}_t$	-	prediction error
$\mathbf{I}_N$	-	$N \times N$ identity matrix
$\mathbf{J}_t$	-	smoother gain
$j = 1, \ldots, K$	-	switch states
$\mathbf{K}_t$	-	Kalman gain
$k = 1, 2, \ldots$	-	iteration number of expectation maximization
$L_Y(\boldsymbol{\Theta})$	-	log-likelihood
$\mathbf{M}_{t\mid\tau}(j)$	-	probability of switching state at j
$\mathbf{M}_{t-1,t\mid\tau}(i,j)$	-	probability of switching state at (i, j)
N	-	total number of features/nodes/channels, $n = 1, \ldots, N$
$N(\mathbf{0}, \mathbf{Q})$	-	Gaussian distribution with mean, $\mathbf{0}$, covariance matrix, $\mathbf{Q}$
$N(0, \sigma_w^2)$	-	Gaussian distribution with mean, 0 and variance, σ_w^2
$\mathbf{P}_{\mathbf{e}_t}$	-	covariance of prediction error
$\mathbf{P}_{0\mid 0}$	-	covariance of initial state
$\mathbf{P}_{t,t-1\mid T}$	-	cross-covariance of $p(\mathbf{x}_t\mid\mathbf{Y}_{1:T})$
$\mathbf{P}_{t\mid t}$	-	covariance of $p(\mathbf{x}_t\mid\mathbf{Y}_{1:t})$
$\mathbf{P}_{t\mid T}$	-	covariance of $p(\mathbf{x}_t\mid\mathbf{Y}_{1:T})$
$\mathbf{P}_{t\mid t-1}$	-	covariance of $p(\mathbf{x}_t\mid\mathbf{Y}_{1:t-1})$
$P(S_t\mid\mathbf{Y}_{1:T})$	-	discrete state probability

p	-	model order
$p(\mathbf{x}_t\vert\mathbf{Y}_{1:t})$	-	filtering density
$p(\mathbf{x}_t\vert\mathbf{Y}_{1:T})$	-	smoothing density
$p(\mathbf{x}_t\vert\mathbf{Y}_{1:t-1})$	-	one-step-ahead prediction density
$\mathbf{Q}$	-	state covariance matrix
$\mathbf{Q}_{[S_t]}$	-	switching state covariance matrix
$\mathcal{Q}$	-	expected log-likelihood
$q(\mathbf{x}_t\vert\mathbf{x}_{t-1})$	-	state density
$\mathbf{R}$	-	observation covariance matrix
$\widehat{\mathbf{R}}$	-	estimated VAR covariance noise
$\mathbf{R}_{[S_t]}$	-	switching observation covariance matrix
$r(\mathbf{y}_t\vert\mathbf{x}_t)$	-	observation density
$\mathbf{S}_{t,t-1\vert T}$	-	expectation quantity for $(\mathbf{x}_t\mathbf{x}'_{t-1}\vert\mathbf{Y}_{1:T})$
$\mathbf{S}_{t\vert T}$	-	expectation of
$\mathbf{S}_{t\vert T}$	-	expectation quantity for $(\mathbf{x}_t\mathbf{x}'_t\vert\mathbf{Y}_{1:T})$
$\hat{S}_t^{KM}$	-	estimated state by K-means
$\hat{S}_t^{SKF}$	-	estimated state by switching Kalman filter
$\hat{S}_t^{SKS}$	-	estimated state by switching Kalman smoother
$S_{t+1} = k$	-	future switching state
$S_{t-1} = i$	-	previous switching state
$S_t = j$	-	current switching state
S_t	-	hidden switch state
T	-	total number of time samples, $t = 1, \ldots, T$
$\mathbf{U}$	-	matrix of previous observations
$\mathbf{v}_t$	-	observation noise
$\mathbf{w}_t$	-	state noise
$\mathbf{X}_{1:T}$	-	hidden state vectors sequence
$\mathbf{x}_0$	-	initial state
$\hat{\mathbf{x}}_{0\vert 0}$	-	mean of initial state
$\mathbf{x}_t$	-	hidden state vector
$\hat{\mathbf{x}}_{t\vert t}$	-	mean of $p(\mathbf{x}_t\vert\mathbf{Y}_{1:t})$
$\hat{\mathbf{x}}_{t\vert T}$	-	mean of $p(\mathbf{x}_t\vert\mathbf{Y}_{1:T})$
$\hat{\mathbf{x}}_{t\vert t-1}$	-	mean of $p(\mathbf{x}_t\vert\mathbf{Y}_{1:t-1})$
$\mathbf{Y}_{1:T}$	-	observation vectors sequence
$\mathbf{Y}_{1:t-1}$	-	previous observation vectors

$\mathbf{y}_t$	-	observation vector
Z	-	transition matrix of discrete Markov process
z_{ij}	-	transition coefficient
α	-	the significance level
$\boldsymbol{\beta}$	-	VAR coefficients matrices
$\widehat{\boldsymbol{\beta}}$	-	estimated VAR coefficients matrices
$\delta_{ij}(t,f)$	-	TV-DTF coefficients
$\boldsymbol{\Gamma}$	-	LSE covariance matrix
$\widehat{\boldsymbol{\Gamma}}$	-	estimated LSE covariance matrix
$\widehat{\boldsymbol{\Gamma}}_{kk}$	-	k-th diagonal entry of $\widehat{\boldsymbol{\Gamma}}$
$\boldsymbol{\Theta}$	-	model parameter
ℓ	-	time lag
$\pi_{ij}(t,f)$	-	TV-PDC coefficients
σ_v^2	-	observation noise variance
σ_w^2	-	state noise variance
$\boldsymbol{\Phi}_{\ell t}$	-	TV-VAR coefficient matrix
$\boldsymbol{\Phi}_{\ell,[S_t]}$	-	SVAR coefficients
$\boldsymbol{\Phi}_{\ell}$	-	VAR coefficient matrix
$\hat{\boldsymbol{\Phi}}_j^{EM}$	-	effective connectivity matrix with EM algorithms
$\hat{\boldsymbol{\Phi}}_j^{LS-KM}$	-	estimated effective connectivity matrix by K-means
$\hat{\boldsymbol{\Phi}}_j^{LS-SKF}$	-	effective connectivity matrix by SKF
$\hat{\boldsymbol{\Phi}}_j^{LS-SKS}$	-	effective connectivity matrix by SKS
$\boldsymbol{\Phi}(t,f)$	-	time frequency coefficients of TV-VAR
$\{\phi_{t,\ell}\}$	-	TV-AR coefficient

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CHAPTER 1

INTRODUCTION

1.1 Introduction

The human brain is a part of the central nervous system that functions to control the whole human body activities. Electrical activities generated in the brain are originated from neuronal activation in the cerebral cortex during the synaptic process which is typically measured by electroencephalogram (EEG) or magnetoencephalography (MEG). Another modality such as functional magnetic resonance imaging (fMRI) is used to measure and record the hemodynamic activity of the brain. The data of these modalities are often in the form of time series that contains information on the dynamic brain activities which is very useful for monitoring and diagnosing various brain diseases. The data are also present in multi-dimensional recording such as multichannel EEG signals from scalp electrodes of different locations or multiple fMRI time series from different voxels or region of interests (ROIs). The dimension of the data is determined by the number of channels or brain regions.

The locations of the electrode placement for EEG typically follow international 10-20 systems. Instead of channel, fMRI analysis used region of interest (ROI) to define an interest region with specific functionality which consists of a number of 3D voxels stack together. However, some of the important information of the dynamic brain activities is latent and could not be directly observed from the recording. Moreover, the EEG signals for instances, have low amplitudes and are typically obscured by various background noises and artifacts where it can be physiological and technical origin. In addition, causality effects that one region has on another needs to be analyzed from the observed signals in order to learn the underlying physiological process of the brain during specific conditions. Thus, the challenge is to develop reliable and computationally efficient multivariate modeling approach with dynamic properties for better modeling and analyzing the multidimensional dynamical brain signals in presence of noise.

This thesis proposes a novel approach based on the state-space modeling to model the dynamics of multivariate neuronal signal in time series with application to EEG and fMRI data. The state-space models is a statistical modeling method which is widely applied in various studies especially in time series analysis, such as speech signals, biomedical signals, deoxyribonucleic acid (DNA) sequences, and financial time series. The models are capable to track, predict and forecast complex underlying dynamic phenomena. Thus, this could be well-suited for analyzing and learning the hidden dynamic of the brain. This thesis proposes a family of state-space models based on autoregressive (AR) process, to address some important signal processing problem in neurosciences for example multi-channel classification of EEG signal, non-stationary multivariate modeling for effective connectivity and state-related changes estimation in EEG and fMRI data.

1.2 Background of Problems

Biomedical signal processing has played an important role in advance medical and clinical diagnostic. Brain signal is a type of biomedical signal that originates from the physiological activity of the brain. According to World Health Organization (WHO), neurological disorders such as epilepsy, dementia, cerebrovascular disease and others constitute 12% of 100,000 total deaths globally until 2030 which are classified as one of the greatest threats to public health [1]. These diseases can be detected early and accurately by diagnostic modalities such as EEG, computerized tomography (CT), positron emission transmission (PET) and fMRI. This may helps to reduce mortality and disability, enhance rehabilitation and prevent relapses and recurrence of the illness [1].

EEG has very good temporal resolution (milisecond) which is efficient in detecting temporal changes because of the capablity of measuring the instantaneous response of the neuroral signal. However, it has a low spatial resolution with maximum number of 10-10 system electrode is 128 channels [2]. In contrary, other functional neuroimaging data such as fMRI has the best spatial resolution with optimal voxel size $(1.5 \times 1.5 \times 1.5)mm^3$ [3] but low in temporal resolution (appoximately two frames/second [4]). This data do not directly measure the neural activity, but only capture local changes in metabolism and blood oxygenation flow in the brain

[5]. The challenge is to develop an advanced analysis of these brain signals for better understanding of the underlying neurological processes as well as diagnosing neurological diseases.

Neuroimaging modalities produced multi-dimensional recording data. This thesis refer multi-dimensional recording as the number of channel or signal measured. Let's denote the measured time series as $\mathbf{Y}_t = [\mathbf{Y}_{1t}, \ldots, \mathbf{Y}_{Nt}]$ where time, $t = 1, \ldots, T$ and N dimension signals. EEG for instance, has a number of channel up to 256 commercially [6], furthermore [2] has proposed 5% system electrode that can produce a number of channel locations up to 345. Some may be interested in studying certain area of the brain for specific task and response for example motor task (channel C3, C4 and CZ) [7], mental task or decision making (channel F3, F4, P3 and P4) [4], visual response (O1, O2 and Oz) [8] and others. Most of these studies addressed a specific response that includes a multi-channel EEG recording. fMRI time series also a multi-dimensional data with a good spatial resolution. fMRI recorded in 3-D image elements named voxels with size $1.5mm \times 1.5mm \times 1.5mm$ [3], where the whole-brain imaging could achieved thousands number of voxels. It poses a challenge to analyzed such multi-dimensional data. Usually, fMRI analysis is focused on combined region of interest (ROI) with specialized functionality for example default-mode, cognitive-control, visual and somatomotor [9].

The importance of multi-dimensional analysis is that one could tell how the brain regions are inter-connected and inter-dependent to one another. It is called brain connectivity analysis. There are two types of connectivity; 1) functional connectivity: defined as statistical dependencies among spatially different brain regions [10], 2) effective connectivity: defined as causal effect of one region has on another or it always refered as directed connectivity [11]. The study has important role in understanding brain process and diseases. Connectivity analysis showed inter-regional connectivity disrupted in patients with schizophrenia [12], low causality connection between seizure foci and across other brain regions during ictal [13], and different connectivity pattern for healthy and stroke patients in motor area [14]. Based on stated studies, brain connectivity analysis could give advantages in solving neurosciences problems. Complex multivariate approach is required to model dependency between signals.

Common signal analysis studies use univariate method for example autoregressive modeling [15–17] to infer the dynamic of physiological system. This method has superior performance in estimating single-trial signal compared to conventional fast Fourier transform, short-time Fourier transform and wavelet transform [18–22] by offered better time-frequency resolutions. The limitation of univariate autoregressive is the process includes only correlation in time precedence of a signal, while the correlation between regions is ignored [23, 24]. The inter-regional could not be assessed directly from univariate models. The alternative to this problem is the generalization of univariate model to multivriate modeling [25]. Using mutivariate model, the inter-regionals correlation could give additional information to discriminate between brain conditions where the models or methods can measure the synchronization between coupling regions and the coherency among them [26–31]. The state-of-the-art of multivariate analysis method independent component analysis (ICA) is frequently used to analyze multivariate EEG and fMRI time series [32–34]. This method is an advantage for task-free of neuronal data set (i.e. resting-state fMRI) [34]. However, the main drawback of this multivariate method is that it only assesses the spatial correlation, while the temporal correlations were ignored which leads to results misinterpretation. Thus, it is obviously not suitable for task-related or highly non-stationary time series signals.

Human brain signals are generally derived from physiological process of underlying biological systems interaction [35]. These physiological signals generally exhibit in non-stationary form by changing over time in term of amplitude, spectrum and connectivity [4,16,18,33,36,37]. Non-stationarity of the signal in EEG for instance could be frequently induced by task and stimulus, transition of ictal conditions, event-related potential (ERP) and evoked potential (EP) [4, 38–40]. Many studies have proven the non-stationarity in single-trial EEG through synchronization and de-synchronization of spectrum assessment [19, 41–43] and also in multivariate signals analysis where the frequency content changing over the time recording [44, 45].

Current studies of non-stationary EEG signals use short-time windowing analysis for example short-time fourier transform and wavelet transform by assuming piece-wise stationary of the signals [24, 44, 46–48]. Selection to the size of window frame is a limitation to the methods. To achieved good temporal resolution small-window frame need to be applied. However, it would be a destructive to the frequency content of the signals [19, 20]. The result will be reversed when large-window frame is applied. This effect is known as spectral leakage problem [20, 22]. An alternative to this piece-wise stationary analysis is time-varying autoregressive (TV-AR) model as proposed in [15, 16, 19]. These studies successfully addressed non-stationary of underlying brain signal which capable to capture or estimate abrupt changes of the time series data. However, this solution is only limited to a single trial-brain signal which is unreliable for multi-dimensional time series. Another advanced non-stationary signal analysis is time-frequency distribution (TFD) technique [49, 50]. The TFD is a frequency component based method that has been proposed to improve the time-frequency resolution estimation in various biomedical signals analysis [51–53]. However, this method estimates trial-by-trial or channel-by-channel time-frequency component of the signals where the spatial correlation of brain regions are not measured.

Non-stationarity of brain signals was further demonstared in recent studies on brain connectivity analysis which has discovered the functional connectivity patterns changing over time, especially for task-related time series data [54–56]. Even in resting-state or task-free fMRI, researchers have found the evolving of functional connectivity [57, 58]. The evolving of effective connectivity is actually found earlier across task-related in [59–61]. These studies as a result motivate to analyze and quantify the temporal dynamic in connectivity pattern over time. To date, the commonly used approach to infer dynamic causality network is multivariate autoregressive (MVAR) model [62, 63]. MVAR is the most reliable modeling method to model a dynamic system however, in most effective connectivity analysis assumed the inter-regional integration is stationary with manually determined time frame [45, 64]. This condition would be easy for known simulation framework, but it is rather difficult to segregate the brain-conditions in resting-state data. Implementation of complex multivariate autoregressive model with non-stationary assumption is necessary to solve this important problem.

The importance of effective connectivity analysis is the ability of the integration to explain the observed dependencies which is functional dependency [10]. For example, direction and degree of influence among brain regions. In addition, important study of non-stationary or dynamic effective connectivity is enabled the understanding of underlying neurophysiological process especially functional integration changes for example, as given in paragraph 4. The dynamic changes in effective connectivity can be use detect state-related transition as previusly studied in functional connectivity analysis [9, 65–68] which is still limited in term of the number of studies for effective connectivity.

In clinical application, EEG is one of the neuroimaging modalities that can provide low cost screening yet valuable information. The problem is, recorded EEG signals are contaminated by artifacts from various sources for example line interference, environment, cardiac activity and muscle artifacts [69]. These noises have to be removed to avoid misinterpretation of the neurophysiolocigal processes. An alternative to this problem is using ICA which based on rejection and reconstruction methods [70–72]. However, the limitation of this methods is the requirement of a sufficient amount of data to get a reliable result, otherwise the result will not be meaningful [73]. Furthermore, the stationarity assumption of the artifacts and brain activity through time would violate the dynamic nature of brain signals.

Another problem to EEG recording is volume conduction where electrophysiological signals that are captured by scalp EEG is not direct from source the neuron firing [42, 74, 75]. In other words, distance between scalp electrode and neuron activity could cause this confound effect. As an alternative, a method, that can incorporate with these noise and artifacts and the confound effect is needed. Multivariate estimation based methods can be solution to this problem by allowing multiple brain regions to be analyzed at a time which minimized signal normalization and avoid multiple comparison [76, 77]. This is important to quantify the actual characteristic of the signals which can help to achieve a good result and proceed to the next clinical decision procedures.

1.3 Statement of Problems

The problems that will be addressed in this research are summarized into three main issues as follows:

a) Brain signals such as multi-channel EEG and ROI-wise fMRI time series are often measured from distinct brain areas and presented in a multi-dimensional time series data form. Identifying the effective connectivity of brain network requires analyzing the dependence between these multi-dimensional brain signals. The challenge in analyzing brain networks is to develop multivariate approach for modeling, estimation and inference of the dependence of these signals.

b) Multivariate neuronal signals are non-stationary, where the dependence structure between signals evolves over time. This is illuminated by recent neuroscience studies which showed the dynamic changes in brain connectivity networks. Current non-stationary analysis tools focus on the non-stationary of single signal, and neglect the time-evolving dependence between signals. There are two main challenges in analyzing the non-stationary in multivariate brain signals

(i) Brain signals exhibit depends on brain states or activity regimes, with smooth changes within a regime but abrupt change in transition between regimes. Current windowing-based analysis is unable to capture both smooth and abrupt changes simultaneously.

(ii) The dynamics of the brain connectivity are hidden by the signals measurement and obscured by noise.

The motivation is to develop advanced non-stationary analysis methods for modeling and estimating these complex changes in the connectivity between multi-dimensional brain signals.

c) Brain signals are typically obscured by various types of noise and artifacts of physiological and instrumental origin. For example, multi-channel EEG are affected by the confounding effect of volume conduction, where the measured signals are not directly measurement of neuronal activity but superposition of neuronal sources. The challenge is to recover the underlying structure of the noising signals.

1.4 Objectives of the Research

The objectives of this research study are as follows:

a) To propose a class of vector autoregressive (VAR) models and associated estimation procedures for analyzing inter-dependence between multi-dimensional brain signals with application to identify reliable brain connectivity networks with direction (effective connectivity).

b) To propose extension of the stationary case to non-stationary VAR models for analyzing changes in dependence between brain signals with applications to time-varying brain connectivity.

(i) To apply time-varying VAR models to capture instantaneous changes in effective connectivity.

(ii) To propose a new estimation framework to capture state-related changes in effective connectivity.

c) To formulate the above non-stationary VAR models into state-space formulation with expectation-maximization estimation, to allows sequential and online estimation of latent dynamics brain connectivity between brain signals and to alleviate the confounding noise effects for multi-dimensional signals.

d) To apply the above proposed methods to multi-channel EEG and ROIs-wise fMRI time series to solve variety of problems in neuroscience studies.

1.5 Scope of the Research

The scope of this study are as follows:

a) Time series modeling based on state-space methods and its estimations for brain signals will includes these general steps;

(i) The underlying (hidden state) parameter estimation are solved analytically using closed form Kalman filter (KF)

(ii) The model parameter estimated using maximum likelihood (ML) approach which a proposed expectation-maximization (EM) algorithms

b) Linear dynamic models for multi-channel EEG with application to classification of motor imagery EEG signals.

c) This study also embarks on dynamic multivariate modeling of VAR variants

(i) Application of stationary VAR model with least square estimation (LSE).

(ii) Application of TV-VAR model TV-VAR(p),

(iii) Formulation of SVAR model SVAR(p),

for effective connectivity estimation of brain signals.

d) Effective connectivity estimation and analysis includes

(i) Identifying causal connectivity pattern during motor imagery movement of EEG data for healthy subjects.

(ii) Differentiate the connectivity patterns of fMRI for stroke and healthy subjects during motor task functions.

(iii) Detection of epileptic seizure event of EEG data based on dynamic effective connectivity.

e) Formulating data-driven simulation of VAR time series to validate the proposed novel framework.

f) Databases

(i) Motor imagery data are obtained from online database of Brain Computer Interface Competition 2003 (dataset IIIa)

(ii) The motor-task fMRI data were collected by Dr. Steven C. Cramer from University of California, Irvine, that consist of two groups of subjects which are healthy subjects and stroke patients.

(iii) EEG data set were recorded from a patient of Dr. Malow (neurologist at the University of Michigan) during epileptic seizure monitoring.

1.6 Contribution of the Study

This study proposes novel methods based on state-space modeling for analyzing dynamic changes in multivariate brain signals, with potential applications to solve important neuroscience problems such as identifying the directed connectivity of the brain networks. To the best of our knowledge, this study is among the few to apply the state-space methods for modeling and estimating dynamic effective connectivity from brain signals. Specifically, the research contributions are given follows:

a) This thesis introducing linear dynamic state-space models based classifier for multi-channel EEG. Two types of dynamic classifiers which are LLM and TV-AR is introduced in this thesis. The estimation problem of the models solved by EM algorithms. The proposed methods were applied to BCI data classification.

b) Developing novel framework for analyzing non-stationary multivariate brain signals, with potential applications to solve important neuroscience problems;

(i) Identifying time-evolving connectivity with the direction (effective connectivity) of brain signals by using TV-VAR model. The estimation of dynamic effective connectivity was solved based on state-space formulation with Kalman algorithms as the hidden states estimator and expectation maximization as the iterative model parameters estimator. The proposed method is applied for identifying time-frequency evolving brain connectivity of motor-imagery EEG data (healthy) and motor-task fMRI data (healthy and stroke subjects).

(ii) Detecting state-related changes associated with underlying physiological brain conditions. To detect the state-related changes, this thesis proposed a unified framework based on SVAR modeling and estimation. The framework contains initialization connectivity estimation by TV-VAR process and K-mean clustering, and then refined the state-related changes by switching Kalman filter (SKF) and EM algorithms. This framework was applied to detect the epileptic seizure on-set and off-set of EEG data and motor-task of fMRI data.

c) This study also embarks on dynamic multivariate modeling of VAR variants. Application of time-invariant vector autoregressive (VAR) model, time-varying VAR model and formulation of Switching-VAR model for effective connectivity estimation of brain signals.

d) Formulating multivariate AR models to state-space modeling with its parameters estimations based on Kalman algorithms and expectation-maximization algorithm. The contribution of this thesis is summarized in Table 1.1.

Table 1.1: Summary of Contributions of this thesis.

<table>
<tr><th colspan="4">This Thesis, 2017</th></tr>
<tr><th rowspan="2">Method</th><th colspan="2">Parameter Estimation</th><th rowspan="2">Application</th></tr>
<tr><th>State</th><th>Model</th></tr>
<tr><td>LLM & TV-AR</td><td rowspan="2">KF and KS</td><td rowspan="3">EM algorithm</td><td>Dynamic classifier for BCI dataset. Motor imagery EEG</td></tr>
<tr><td>TV-VAR</td><td>Rapid changes estimation in effective connectivity of motor imagery EEG, motor task stroke and healthy fMRI and epileptic seizure EEG data</td></tr>
<tr><td>SVAR</td><td>SKF and SKS</td><td>State-related changes detection (slow & abrupt) for motor-task stroke and healthy fMRI and epileptic seizure EEG data</td></tr>
<tr><td>VAR</td><td colspan="2">Least square estimator (LSE)</td><td>Effective connectivity in localized stable brain state</td></tr>
</table>

1.7 Thesis Organization

The thesis organization includes the introduction chapter that is contains of the background, statement of problems, objectives, scopes and contribution of the study. The second chapter provides a comprehensive literature study of the brain signals analysis, state-space modeling and multivariate analysis. The third chapter proposes of multi-channel EEG classification using state-space models. In the fourth chapter, this thesis proposes the time-varying vector autoregressive modeling for dynamic effective connectivity analysis. In the fifth chapter, this thesis proposes the estimation framework for state-related changes in effective brain connectivity. The final chapter of this thesis contain the conclusions and the possible future directions.

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