ADAPTIVE NONLINEAR MULTIVARIATE BRAIN CONNECTIVITY ANALYSIS OF MOTOR IMAGERY MOVEMENTS USING GRAPH THEORY

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To my wife Najmeh, for her endless support, encouragement, love and patience
and to my lovely parents and sister

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ABSTRACT

Recent studies on motor imagery (MI)-based brain computer interaction (BCI) reported that the interaction of spatially separated brain areas in forms of functional or effective connectivity leads to a better insight of brain neural patterns during MI movements and can provide useful features for BCIs. However, existing studies suffer from unrealistic assumptions or technical weaknesses for processing brain signals, such as stationarity, linearity and bivariate analysis framework. Besides, volume conduction effect as a critical challenge in this area and the role of subcortical regions in connectivity analysis have not been considered and studied well. In this thesis, the neurophysiological connectivity patterns of healthy human brain during different MI movements are deeply investigated. At first, an adaptive nonlinear multivariate state-space model known as dual extended Kalman filter is proposed for connectivity pattern estimation. Several frequency domain functional and effective connectivity estimators are developed for nonlinear non-stationary signals. Evaluation results show superior parameter tracking performance and hence more accurate connectivity analysis by the proposed model. Secondly, source-space time-varying nonlinear multivariate brain connectivity during feet, left hand, right hand and tongue MI movements is investigated in a broad frequency range by using the developed connectivity estimators. Results reveal the similarities and the differences between MI tasks in terms of involved regions, density of interactions, distribution of interactions, functional connections and information flows. Finally, organizational principles of brain networks of MI movements measured by all considered connectivity estimators are extensively explored by graph theoretical approach where the local and global graph structures are quantified by computing different graph indexes. Results report statistical significant differences between and within the MI tasks by using the graph indexes extracted from the networks formed particularly by normalized partial directed coherence. This delivers promising distinctive features of the MI tasks for non-invasive BCI applications.

ABSTRAK

Kajian terkini mengenai interaksi antara otak dan komputer (BCI) berasaskan imaginasi motor (MI) melaporkan bahawa, interaksi antara bahagian otak yang berasingan dalam bentuk kesalinghubungan secara berfungsi atau berkesan dapat memberikan gambaran yang lebih baik bagi corak neural otak berhubung semasa pegerakan MI, dan dapat menghasilkan ciri-ciri yang berguna untuk sistem BCI. Walau bagaimanapun, kajian sedia ada bergantung kepada andaian yang tidak realistik atau mempunyai kelemahan dari segi teknikal bagi pemprosesan isyarat otak seperti sifat kepegunan, kelinearan dan rangka kerja analisis bivariat. Di samping itu, kesan isipadu konduksi adalah cabaran yang kritikal dalam bidang kajian ini dan peranan bahagian subkortikal dalam analisis kesalinghubungan tidak dipertimbangkan dan dikaji dengan baik. Dalam tesis ini, corak kesalinghubungan neurofisiologi bagi otak manusia yang sihat semasa pergerakan MI yang berlainan dikaji secara mendalam. Pada mulanya, suatu model mudah suai tidak linear multivariat ruang-keadaan yang dikenali sebagai lanjutan penapis Kalman duaan dicadangkan untuk menganggar bentuk kesalinghubungan. Beberapa penganggar kesalinghubungan berfungsi dan berkesan berdomain frekuensi dibangunkan untuk isyarat tidak linear tidak pegun. Keputusan penilaian menunjukkan prestasi pengesanan parameter yang lebih baik dan analisis kesalinghubungan lebih tepat diperolehi daripada model yang telah diusulkan. Yang kedua, sumber-ruang pada masa yang berbeza-beza dengan model multivariat tidak linear, kesalinghubungan otak semasa pergerakkan MI kaki, tangan kiri, tangan kanan dan lidah dikaji dalam julat frekuensi yang luas dengan menggunakan penganggar kesalinghubungan yang telah dibangunkan. Keputusan mendedahkan persamaan dan perbezaan di antara tugas-tugas MI dari segi bahagian yang terlibat, ketumpatan interaksi, taburan interaksi, hubungan berfungsi dan aliran maklumat. Akhir sekali, prinsip organisasi jaringan otak semasa pergerakkan MI diukur dengan semua penganggar kesalinghubungan yang telah diambil-kira, serta dikaji secara meluas dengan pendekatan teori graf di mana, struktur lokal dan global graf diukur dengan mengira perbezaan indeks graf. Keputusan melaporkan perbezaan yang signifikan secara statistik antara tugas-tugas MI dengan menggunakan indeks graf diekstrak daripada jaringan yang terbentuk terutamanya oleh separa koheren berarah yang dinormalkan. Ini memberikan ciri-ciri tersendiri yang baik bagi tugas MI untuk aplikasi BCI yang tidak invasif.

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LIST OF ABBREVIATIONS

AMI	-	adjacency matrix image
AMVAR	-	adaptive multivariate autoregressive
AR	-	autoregressive
BCI	-	brain computer interface
BCM	-	brain connectome maps
BEM	-	boundary element head model
BP	-	band power
BSS	-	blind source separation
BVAR	-	bivariate autoregressive
CAR	-	common average reference
CC	-	correlation coefficient
CCD	-	cortical current density
CMI	-	cross mutual information
Coh	-	coherence
CSP	-	common spatial pattern
CSWBVAR	-	combined short-window bivariate autoregressive
DCM	-	dynamic causal modeling
DEKF	-	dual extended Kalman filter
DIPFIT	-	dipole fitting
DTI	-	diffusion tensor imaging
DTF	-	directed transfer function
dDTF	-	direct DTF
ECOGs	-	electrocorticograms
EEG	-	electroencephalography
EKF	-	extended Kalman filter

EMDPL	-	empirical mode decomposition phase locking
ERD	-	event-related desynchronization
ERP	-	event related potential
ERS	-	event-related synchronization
FDA	-	Fisher discriminant analysis
ffDTF	-	full frequency DTF
FFT	-	fast fourier transform
fMRI	-	functional magnetic resonance imaging
GC	-	granger causality
GPDC	-	generalized PDC
GT	-	graph theory
HMMs	-	hidden Markov models
HQ	-	Hannan-Quinn criterion
ICA	-	independent component analysis
iCoh	-	imagery coherence
ICs	-	independent components
i.i.d.	-	independent identically distributed
Infomax	-	information maximization
KF	-	Kalman filter
LDA	-	linear discriminant analysis
LH	-	left hand
LHF	-	left hand finger
LMSE	-	log mean square error
LRM	-	linear regression model
LS	-	least-squares
M1	-	primary motor area
MEG	-	magnetoencephalography
MI	-	motor imagery
MNI	-	Montreal Neurological Institute
MSC	-	magnitude squared coherence
MSP	-	most significant pairs
MVAR	-	multivariate autoregressive
NC	-	new causality

NIRS	-	near infrared spectroscopy
NLR	-	nonlinear regressive
nPDC	-	normalized partial directed coherence
PCA	-	principal component analysis
pCoh	-	partial coherence
PDC	-	partial directed coherence
PDCF	-	PDC factor
PET	-	positron emission tomography
PLI	-	phase lag index
PLV	-	phase locking value
PS	-	phase synchronization
PSD	-	power spectral density
PSR	-	phase synchrony rate
RH	-	right hand
RHF	-	right hand finger
RIM	-	robust interdependence measure
ROIs	-	region of interests
RV	-	residual variance
SFFS	-	sequential floating forward feature selection
SL/LF	-	surface laplacian filter
SM1	-	primary sensorimotor area
SMA	-	supplementary motor area
SOBI	-	second order blind identification
SSM	-	state space model
SST	-	statistical significant test
SVM	-	support vector machine
TA	-	topographical analysis
TE	-	transfer entropy
TF	-	time-frequency
TVAR	-	time-varying autoregressive
TV-MVAR	-	time-varying multivariate autoregressive
VAR	-	vector autoregressive
VC	-	volume conduction

WPLI	-	Weighted phase lag index

LIST OF SYMBOLS

$\mathbf{K}_x(t)$	-	state's Kalman gain in DEKF
$\hat{a}_{ti}$	-	i^{th} AR coefficient estimate at time t in LMSE
T_1	-	preparation phase in the experiment
$\hat{x}(t)$	-	estimated state vector in DEKF
T_2	-	imagination phase in the experiment
$d_{ij}^{\rightarrow}$	-	shortest directed path length from i to j
$S(f)$	-	spectral density matrix of the process
$Y(f)$	-	$M \times M$ spectral matrix of the multivariate process
Σ	-	time-varying estimation error covariance matrix
a_t	-	true value at time t in LMSE
$E_{glob}^{\rightarrow}$	-	weighted local efficiency
$E_{loc}^{\rightarrow}$	-	weighted local efficiency
$\mathbf{P}_{\hat{x}}(t\|t)$	-	covariance of $P\big(x(t)\|y(1:t)\big)$
$\hat{a}(t)$	-	estimated parameter vector in DEKF
$\pi_{ij}(f)$	-	$nPDC$ from j to i
H	-	Hermitian operator
$iCoh_{ij}(f)$	-	imagery part of the $Coh\,/\,iCoh$
s_n	-	n independent components
T	-	length of time-series
(i,j)	-	link between nodes i and j where $(i,j \in N)$
$Coh_{ij}(f)$	-	magnitude squared Coherency/ Coh

$V(f)$	-	matrix of random sinusoidal shocks
$\hat{x}(t\|t)$	-	mean of $P(x(t)\|y(1:t))$
$\hat{x}(t\|t-1)$	-	mean of $P(x(t)\|y(1:t-1))$
k_i^w	-	number of links connected to node i in the weighted network
l	-	number of links in the network
$v_y(t)$	-	observation white noise with covariance matrix $\mathbf{R}_y$
$P(x(t)\|y(1:t-1))$	-	one-step ahead prediction density
$\mathbf{P}_{\hat{a}}$	-	parameter estimation error covariance matrix in DEKF
$P_{ij}(f)$	-	partial $Coh\,/\,pCoh$
$g_{i\leftrightarrow j}^w$	-	shortest weighted path between nodes i and j
$\hat{\mathbf{w}}_t$	-	stationary process posteriori estimate in parameter estimation
s_i^{in}	-	sum of inward link weights
$a(t)$	-	time-varying parameter of DEKF
$x(t)$	-	time-varying state of DEKF
$A(f)^{-1} = H(f)$	-	time-varying transfer function
$\mathbf{K}_t^{\mathbf{w}}$	-	weight filter gain
E_{glob}^w	-	weighted global efficiency
E_{loc}^w	-	weighted global efficiency
$\mathbf{v}_t$ / $v(t)$	-	*i.i.d.* Gaussian observation noise
$\alpha(t)$ and $\beta(t)$	-	intensity of the parameters' influences in simulation
$\mathbf{c}_{ki}$	-	attenuation coefficient
$\mathbf{v}_k(t)$	-	bipolar voltage difference recorded in channel k
$E(x(t)\|y(1:t))$	-	conditional mean
a_{ij}	-	connection status between i and j

$\mathbf{P}_{\hat{x}}(t\|t-1)$	-	covariance of $P(x(t)\|y(1:t-1))$
$\mathbf{d}_t$	-	desired output in parameter estimation
$\mathbf{r}$	-	dipole location
$\mathbf{m}$	-	dipole moment
$\mathbf{o}$	-	dipole orientation
$\mathbf{S}$	-	dipole source potential matrix
$g_{i\to j}$	-	directed shortest path from i to j
$\mathbf{e}_k$	-	electrode k
$\mathbf{P}_{\mathbf{w}_t}$	-	error covariance posteriori estimate in parameter estimation
$\mathbf{P}_{\mathbf{w}_t}^{-}$	-	error covariance priori estimate in parameter estimation
$P(x(t)\|y(1:t))$	-	filtering density
$\mathbf{w}_t$	-	*i.i.d.* Gaussian state noise in state estimation / stationary process in parameter estimation
$\Delta\mathbf{W}$	-	infomax learning rule
$\mathbf{P}_0$	-	initial error covariance
$\mathbf{P}_{\mathbf{w}_0}$	-	initial error covariance in parameter estimation
$\hat{\mathbf{x}}_0$	-	initial state
μ_0	-	initial state mean
Σ_0	-	initial state variance
$\hat{\mathbf{w}}_0$	-	initial stationary process in parameter estimation
$\mathbf{G}_t$	-	Kalman gain
x_N	-	linear mixture of signals
$\ln\|\tilde{\Sigma}(p)\|$	-	logarithm of the determinant of the estimated noise covariance matrix
f	-	map from weight to length
$\mathbf{e}_t$	-	model error in parameter estimation
$p(\mathbf{s})$	-	multivariate probability density function of vector $\mathbf{s}$
$I(\mathbf{x})$	-	mutual information of the observed vector $\mathbf{x}$

$\mathbf{h}(t,\mathbf{x}_t)$	-	nonlinear measurement matrix
$\mathbf{f}(t,\mathbf{x}_t)$	-	nonlinear transition matrix function
R	-	observation noise covariance matrix
$\mathbf{K}_a$	-	parameter’s Kalman gain in DEKF
$\mathbf{G}(\mathbf{x}_t,\mathbf{w})$	-	parameterized nonlinear function
$\mathbf{p}_k(t)$	-	potential at the electrode k
$\mathbf{p}_r(t)$	-	potential at the reference electrode
$p(\mathbf{x})$	-	probability density function of vector $\mathbf{x}$
$\mathbf{r}_t$	-	process noise in parameter estimation
$\mathbf{x}$	-	random vector with elements $x_1,\ldots,x_N$
$\mathbf{s}$	-	random vector with elements $s_1,\ldots,s_n$
$\mathbf{p}_k$	-	scalp potential
$\mathbf{P}$	-	scalp potential matrix
L	-	set of all links in the network
N	-	set of all nodes in the network
d_{ij}^{w}	-	shortest weighted path length between nodes i and j
$\mathbf{s}_i$	-	source i
Q	-	state noise variance
$\mathbf{x}_t$	-	state of the system in state estimation / known input in parameter estimation
$\mathbf{P}_t$	-	state posteriori covariance matrix
$\hat{\mathbf{x}}_t$	-	state posteriori estimate matrix
$\mathbf{P}_t^-$	-	state priori covariance matrix
$\hat{\mathbf{x}}_t^-$	-	state priori estimate matrix
$v_a(t)$	-	state white noise with covariance matrix $\mathbf{R}_a$ for parameter estimation
$v_x(t)$	-	state white noise with covariance matrix $\mathbf{R}_x$ for state estimation
l^w	-	sum of all weights in the network

s_i^{out}	-	sum of outward link weights
s_i^{w}	-	sum of weights of links connected to node i
$C_{ij}(f)$	-	time-varying Coherency
$a_{ij}^{k}(t)$	-	time-varying linear interactions between signal i and signal j at the delay k
k_i^{in}	-	total number of connections incoming to node i in the directed network
k_i^{out}	-	total number of connections outgoing from node i in the directed network
NT	-	total number of datapoints
$\mathbf{F}_{t+1,\mathrm{t}}$	-	transition matrix
$\mathbf{u}$	-	unmixed signals
$\mathbf{H}_t$	-	vector of past p observation
$y_t / y(t)$	-	recorded signals (measurement) / time-series
$A_{kt} / A_k(t)$	-	time-varying model coefficients
$\mathbf{A}$	-	mixing matrix in ICA
$\mathbf{C}$	-	geometrical weighting coefficients
g	-	network density
M	-	number of channels
p	-	order of MVAR model
R	-	realizations in LMSE
u	-	the node under investigation
v	-	neighbors of node under investigation
$\mathbf{W}$	-	linear mapping matrix

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CHAPTER 1

INTRODUCTION

1.1 Overview

1.1.1 Brain Computer Interface

Brain computer interface (BCI) is a state-of-the-art technology that translates neuronal activities into user commands. This topic was introduced over 40 years ago [1] however it has considerably developed recently and there is a continuous increase in the number of research groups focusing on this area [2, 3]. It provides a communication and control channel between the brain and external environment which does not depend on the brain's normal output pathways of peripheral nerves and muscles so that it offers an effective assistance to individuals with motor disabilities [3]. BCIs are of great value to the rehabilitation engineering and assistive technology where the use of prosthetics, robots and other devices fully controllable by mental intentions have become a reality [4]. These systems have a direct positive influence on the life quality of the disabled and also offer new modes of human machine interaction for both disabled and healthy users such as music generation [5] or computer game control [6]. Nowadays, more complex devices including orthoses, prostheses, robotic arm and mobile robots [7-12] can be controlled by modern BCI systems.

Generally, BCIs measure neurophysiologic signals, process them and produce control signals that reflect the user's intent. BCIs can be categorized based on measuring brain neural activities through different neuroimaging techniques among which electroencephalographic (EEG)-based BCI is very well established and accepted for practical applications as well as clinical and research settings for decades. This is because EEG equipment is inexpensive, lightweight, portable, non-invasive with minimal clinical risks, user friendly and comparatively easy to apply [13, 14]. It can provide signals with high temporal and low spatial resolution with limited frequency range [15]. However, spatial resolution can be increased by means of more electrodes and the existent frequency range is enough for BCI purposes.

EEG-based BCI systems detect the existence of particular patterns in a person's ongoing brain activity that relates to the person's intention to start control and then translate these patterns into meaningful control commands. Figure 1.1 illustrates an EEG-based system components and steps.

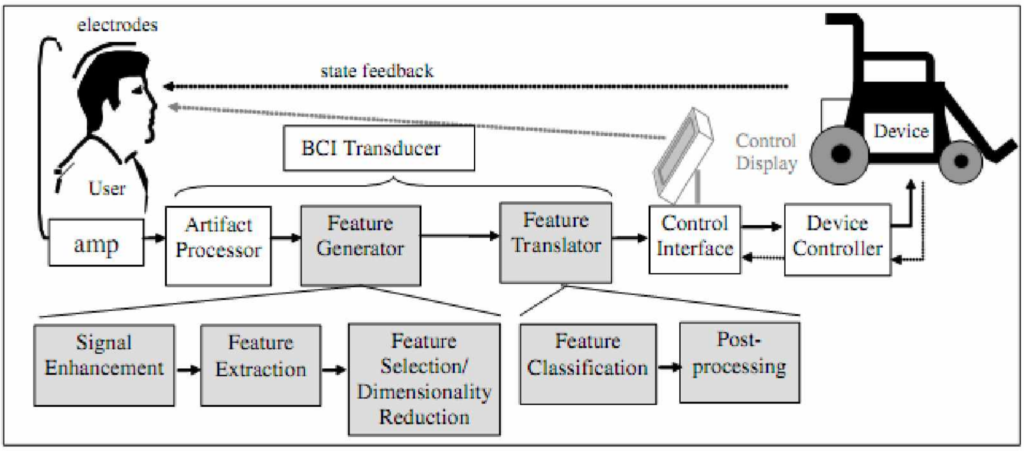

Figure 1.1 A typical EEG-based BCI components [16].

In the depicted system, the user's brain activity is recorded by the electrodes placed on the head via an electrode cap. Then, the signals transmit from electrodes to the biosignal amplifier to convert the brain signals from analog to digital format. After that, the digital signals are processed in a computer in the following steps. Artifacts are removed from attained signals after they have been amplified to increase the signal-to-noise ratio. In order to generate the most prominent signal values known as features, signal enhancement, feature extraction and feature selection techniques are considered. Feature translator aims to transform the provided features into logical control signals commonly in the two stages of classification and post-processing. The former targets to distinguish different patterns and classifies them into separate groups while the latter aims to reduce the number of error activations of the system.

In BCI systems, electrophysiological sources refer to the neurological mechanisms or processes employed by a BCI user to generate control signals. Current BCIs are grouped into seven major categories based on the neuromechanisms and recording technology they use [16]. These are sensorimotor rhythms, P300 evoked potentials, visual evoked potentials, slow cortical potentials, activity of neural cell, response to mental tasks and multiple neuromechanisms. BCI based on sensorimotor rhythms is known as Motor Imagery (MI) BCI, a type of endogenous EEG-based BCI which is much more suitable for BCI [15] and is focused in this thesis.

1.1.2 Motor Imagery-based BCI

Imagination of doing something is an important cognitive process that occurs throughout lifespan. MI which refers to the act of imagining a specific action without actually executing it, has fascinated scientists from a wide range of domains including sport sciences, psychology, neuroscience and neural engineering. MI has been defined as the conscious mental simulation of actions involving brain's motor representations similar to when actually perform movements [17]. This has led to the suggestion that MI and motor execution rely on similar neural structures and processes [17-20]. Moving a limb or the imagination of limb movement changes the brain activity in the cortex and results in different EEG patterns [21]. The BCIs based on MI are known as MI-BCI where each mental task is associated with one of the commands to the external device. In MI-BCI, subjects are asked to haptically imagine movements of certain limbs, e.g., the left or the right hand. Then, in order to produce the commands, the operator switches voluntarily between corresponding mental tasks in either synchronous (cue-paced) or asynchronous (self-paced) mode.

Brain oscillations are typically categorized according to the specific frequency bands: delta is < 4 Hz, theta is 4-7 Hz, alpha is 8-15 Hz, beta is 16-30 Hz and gamma is > 30 Hz. Alpha activity recorded from sensorimotor (somatosensory and motor) areas is also called mu activity. Increase/decrease of oscillatory activity in a specific frequency band is called event-related synchronization/desynchronization (ERS/ERD). Previous studies have indicated that when the subject performs or even imagines limb movement, specific frequency components of EEG such as the mu and central beta rhythms are (de)synchronized over the contralateral (ipsilateral) sensorimotor area [21-23]. Besides, depending on the part of the body imagined to be moved, the amplitude of multichannel EEG recordings exhibits distinctive spatial patterns [24]. Therefore, most of early studies on MI-BCI have employed features of single channels for movement pattern discrimination such as amplitude values like autoregressive (AR) model coefficients, frequency based features like quantification of ERS/ERD using band power (BP) and time–frequency maps of cortical activity at specific regions [25].

1.1.3 Challenges and Limitations of Conventional MI-based BCI

Although promising results and achievements have been reported in the literature by using the mentioned EEG features, yet there remain many challenges and barriers to use this technology easily and effectively for the intended beneficiaries i.e. those who require an alternative means of communication/control such as people with neuromuscular deficiencies due to disease, spinal cord injury or brain damage. It has been shown that the motor imagery responsive frequency bands are not consistent for inter- and intra-subjects [26] which indicates the instability of such BCIs. ERD/ERS analysis for different subjects has proven to be complex since it occurs in different parts of the cortex, at different frequencies and during different time intervals which leads to difficulty when extracting features for classification [27]. As EEG data is often of low amplitude and noisy, there is no consistency in the patterns among different subjects and the arising patterns can change within a session for the same subject [27].

It has been reported that activity invoked by imagination of limb movements is located on contralateral side of somatosensory cortex and only few electrodes have been employed (C3, C4, Cz) to capture the corresponding EEG patterns in such areas [28, 29]. However, other studies showed that somatosensory stimuli suppressed mu rhythms at both the contralateral and the ipsilateral somatosensory cortex [30, 31]. In addition, the positions of ERDs are not necessarily beneath electrodes C3 and C4 [32]. Several EEG studies also further confirmed the notion that MI can activate primary sensorimotor areas [33-35]. Other researchers have tended to show that during the performance of cognitive tasks many different parts of the brain are activated and communicate with one another, thus making it difficult to isolate one or two regions where the activity takes place [36]. For instance, it has been demonstrated that the supplementary motor area (SMA), prefrontal area, premotor cortex, cerebellum and basal ganglia are activated during both movement execution and imagination [37-41]. Moreover, the role of primary motor cortex has been widely reported in numerous brain imaging studies explored by EEG [33-35, 42-48], functional magnetic resonance imaging (fMRI) [49-69], magnetoencephalography (MEG) [34, 70], positron emission tomography (PET) [71-73] and near infrared spectroscopy (NIRS) [74, 75].

Another observed limitation is that foot movement imagery invokes activity over Cz and a distinction between left and right foot movement is not possible because the corresponding cortical areas are too close [15]. Similarly, ERD/ERS patterns of individual fingers cannot be discriminated [15]. It was concluded that to produce detectable patterns, the cortical areas involved have to be large enough so that the resulting activity is sufficiently prominent compared to the remaining EEG. Hand areas, foot areas and the tongue area are comparatively large and topographically different. Therefore, current MI-based BCIs are limited in imagination of only four movements: left hand, right hand, feet and tongue [76].

However, a flexible and applicable BCI requires more control commands.

Study evidences on stroke patients revealed their ability to perform MI despite chronic or severe motor impairments [77-79], but patients with lesions in the parietal and frontal cortices have difficulty in performing MI [79, 80]. These studies showed that the portion of the brain that is responsible for generating ERD/ERS in MI-BCI could be compromised. Hence, the issue remains as whether stroke patients are practically capable of operating MI-BCI effectively. Although some promising findings have shown the reliability of MI-BCI in stroke rehabilitation [81-85], there is a lack of long-term evidence to support its clinical relevance. Besides, no successful communication has been established through BCI with a completely locked-in subject. Therefore, the most challenging part in MI-based BCI researches is during the communication with such patients, for which the reason is still unknown. Cognitive deficits in completely locked-in patients cannot be ruled out at present as the cause of this failure. It may be from abnormal brain activities in patients with severe disabilities alike in late stages of amyotrophic lateral sclerosis [86]. It is possible that intentionally induced BP changes in the electric field of the brain reduce in these subjects [87].

One of the most possible and inevitable reasons of aforementioned weaknesses and limitations of MI-based BCI is the use of temporal-spectral MI EEG features from individual channels for discriminating different MI patterns as they may not provide enough information. Consequently, a better understanding of brain neural dynamic patterns behavior is essential for providing more useful and informative features for BCIs. It is well known that the execution of even simple motor and/or cognitive tasks by the brain requires the participation of multiple cortical regions which are mutually interconnected and exchange information via plastic long-range synapses [88]. Hence, knowledge of brain connectivity has become an essential aspect of modern neuroscience especially for understanding how the brain realizes its basic functions and what the role of different regions is. Accordingly, it is expected that different cognitive tasks like MI of different limbs are associated with different connectivity patterns among brain regions. Therefore, a promising approach for solving the mentioned limitations is to consider the relationships among inter-channels/sources brain signals by measuring connectivity of spatially distributed regions during MI movements. These connectivity patterns can be detected from EEG recordings and thus offer a new type of feature space for inferring a subject's intention. This research proposes source-space adaptive nonlinear multivariate brain connectivity analysis during MI movements by Dual Extended Kalman Filter (DEKF) method. Moreover, significant information from the estimated brain neural network during different MI movements is extracted by means of graph theoretical approach.

1.2 Background of Problems

The human brain performs its sensory and cognitive functions by dynamically employing highly complex and interlaced neuronal networks. In BCI context, better understanding of these network functions may open insight into neurophysiological mechanisms of different motor tasks and may deliver more efficient features to enhance the system performance. In this regard, several studies have performed MI brain connectivity analysis to be used for BCI (review is provided in Chapter 2).

One of the most critical challenges of brain connectivity analysis is volume conduction (VC) effect (completely explained in Chapter 2) which can give rise to spurious instantaneous correlations between scalp EEG signals and potentially lead to misinterpretation of sensor-space EEG analysis [89]. In this regard, literature shows that (refer to Table 2.1) some studies did not take into account the possible VC effects which might lead the authors to misinterpretation in brain connectivity analysis [28, 90-102].

The most conventional way of estimating the brain connectivity is by evaluating the phase relations by a pair-wise (bivariate) estimation of coherence or covariance. The direction of EEG propagation was estimated using a two-channel AR model [103]. The concept of Granger causality (GC) [104] was applied to determine the propagation of EEG activity between two channels at a time [105, 106]. Bivariate GC formulates the problem in such a way that if a time series $X_2(t)$ contains information in past terms that helps in the prediction of $X_1(t)$, and this information is contained in no other time series used in the predictor, then $X_2(t)$ is said to cause $X_1(t)$. It has been shown that bivariate methods for the assessment of directionality are likely to give misleading results, no matter if they are based on phases of bivariate coherence or bivariate GC measure [107]. When two or three sources are acting simultaneously, which is a quite common situation, dense and disorganized structure of connections is obtained, similar to random structure. Therefore, the results reported by most of previous studies on MI brain connectivity analysis might be violated by this issue. Accordingly, multivariate measures derived from multivariate autoregressive (MVAR) modeling of multichannel EEG signals have been proposed. In this case, not only one but some time series, vector $Y(t)$, contain information in past terms that helps in the prediction of time series $X(t)$, then $Y(t)$ is said to cause $X(t)$. MVAR models have been widely applied for neurophysiological connectivity analysis, [108-112] and can be used to obtain several different measures of connectivity [113-116]. Although this technique has been proved as a superior method to estimate connectivity measures compared to bivariate methods [107]; it only captures the linear interactions among time series. However, many crucial neural processes like EEG have nonlinear characteristics (e.g. the regulation of voltage-gated ion channels corresponds to a steep nonlinear step-function relating membrane potential to current flow) [117]. In order to interpret the amount of transmission of nonlinear information among brain regions and its functional role, it is important to consider the physiological basis of the signal, which is likely to be nonlinear. So, nonlinear brain connectivity analysis may reveal the hidden interactions and provide complementary information of brain neural network during different motor tasks. However, most of MI-BCI studies have just investigated the linear brain connectivity. There are a few approaches that have applied phase locking value (PLV) index to measure the nonlinear interactions [24, 28, 90, 94, 95, 102, 118, 119] however they have other limitations such as unrealistic assumptions (e.g. stationarity of EEG signals) and methodological defect (e.g. bivariate analysis). Moreover, PLV is a phase-based connectivity estimator; while it has been widely reported that frequency-based estimators are more efficient for the analysis of EEG data since the activity of neural populations is often best expressed in this domain [120, 121].

A significant drawback of conventional MVAR is that the connectivity measures are fixed with time and computed from MVAR models with constant coefficients fitted over the entire time-course, assuming brain as static or stationary process. This shortcoming has been observed in some of previous studies on MI brain connectivity analysis [28, 90, 97, 100-102, 118, 119, 122]. However, an important property of brain is its dynamic (time-variant) behavior during any task therefore analyzing brain connectivity within a static (time-invariant) framework or stationarity assumption is incompatible with the well-known dynamical condition-dependent nature of brain activity and leads to misinterpretation of the results. A number of algorithms have been proposed for fitting MVAR models to non-stationary signals, known as adaptive MVAR (AMVAR) or time-varying MVAR (TV-MVAR). In modern neuroscience, the most popular approaches include segmentation (overlapping sliding-window) [123, 124] and state space approaches [125, 126]. Segmentation-based AMVAR models apply a sliding window of length W from the multivariate dataset with length T, and fit a MVAR model to this data. Then, the window by a quantity Q is incremented and the procedure is repeated until the start of the window is greater than $T-W$. This technique has been recently utilized for single-trial connectivity estimation for classification of two MI tasks in BCI [127]. Although this technique produces MVAR coefficient matrices that describe the evolution of the MVAR process across time, the local stationarity of each window is still assumed and this may not be able to detect rapid parameter changes of brain activity. State space models (SSMs) on the other hand are the AMVAR models where the AR coefficients vary instantaneously with time. SSM provides a general framework for analyzing deterministic and stochastic dynamical systems that are measured or observed through a stochastic process. Although this is a powerful technique for dealing with non-stationarity of neurophysiological signals, there are very limited studies [128, 129] of applying SSMs for brain connectivity analysis in the literature and there is no study of using SSMs for brain connectivity analysis during MI movements. The SSM consists of two components: (1) state equation which models the dynamics of the hidden states $\{x_t\}$ where t is the discrete time index, typically following a Markov process and (2) observation equation which describes the mapping of the hidden states to the observations $\{y_t\}$. In SSMs, conventionally, the estimators of the TV-AR coefficients are obtained sequentially in time using Kalman filter (KF), which is an optimal algorithm in mean-square sense for inferring linear Gaussian systems. This technique assumes linear model for connectivity analysis which is inappropriate for the complex real processes that typically exhibit nonlinearity. When the model is nonlinear, the KF cannot be applied directly and requires a linearization of the nonlinear model at each time step. This algorithm is called the extended Kalman filter (EKF), and effectively approximates the nonlinear function with a time-varying linear one. Nonlinear SSM poses the dual estimation problem [130] that can be solved by dual Kalman estimation, known as DEKF. This technique has been recently employed to investigate the newborn brain neural connectivity during sleep [131].

Different types of functional and effective connectivity measures were considered to analyze the brain network in the literature. Most of these approaches only studied the mechanisms of functionally related of spatially distinct neuronal groups during particular tasks known as couplings which are measured by functional connectivity measures either in phase or frequency domain. Literature shows that effective connectivity analysis has not been studied well yet on different MI movements.

Conventional brain connectivity-based MI-BCI studies have been focused to discriminate different MIs by considering the connectivity measures as feature sets and employing machine learning algorithms for classification. However, a deep study of organization principals of brain networks which can reveal interesting characteristics and differences of various MI movements has been neglected. Recently, graph theoretical approach as an efficient tool in modern neuroscience has enabled the researchers to explore many important statistical properties underlying the topological organization of the human brain while performing different motor tasks. This powerful mathematical framework can be used to characterize and compare the brain network of different MI tasks.

Almost all studies in the literature have investigated the brain connectivity only among different sensors at scalp or regions at cerebral cortex while the roles of subcortical regions as well as deep brain structures have been neglected. However, it has been shown that cerebellum and basal ganglia [132, 133] are activated during both movement execution and imagery.

To the best of author's knowledge, there are no studies on applying adaptive nonlinear state-space models estimated by DEKF and graph theoretical approach for source-space brain connectivity analysis during different MI tasks in BCI context.

1.3 Statement of Problems

The problems of the research are summarized as follows:

1) There are very few studies on brain connectivity analysis during MI tasks in BCI context. In this regards, differences of brain neural network among several MI tasks particularly in form of effective connectivity has not been well investigated yet.

2) Existing studies either at sensor or source level examined the brain connectivity only among different regions at cerebral cortex and the roles of subcortical regions as well as deep brain structures have been neglected.

3) Volume conduction effect as one of the most challenging problems in EEG-based MI brain connectivity analysis has not been taken into account in several previous studies.

4) Existing studies on frequency-dependent connectivity analysis have assumed inappropriate linear static interaction among brain regions. Some researches applied short-time window-based AMVAR approach to deal with EEG non-stationarity; however, this method assumes that the signals are locally stationary in short time intervals and therefore they are limited in tracking rapid parameter changes and cannot provide high resolution time-frequency connectivity representations.

5) Several existing studies have estimated brain connectivity in bivariate (pair-wise) framework which suffers the estimation of spurious functional links.

6) A deep study of organization principals of brain networks which can reveal interesting characteristics and differences of various MI movements has been neglected.

1.4 Research Hypothesis

The main hypotheses of this research are as follows:

1) Nonlinear SSM-based TV-MVAR is a superior model for estimating dynamic connectivity for detecting neurophysiological nonlinear interactions and rapid parameter changes.

2) A better understanding of the brain mechanisms during MI tasks using DEKF and nonlinear connectivity estimators across time and frequency should reveal (1) the neurophysiological properties of brain (2) the time-varying connectivity pattern (3) the similarities and the differences within MI tasks and (4) the unique connections of each MI task.

3) Local and global graph indexes can reveal different properties underlying the brain topological organization during different MI tasks which should provide a clearer picture of similarities and (statistical significant) differences.

1.5 Objectives

In this research, a better understanding of the underlying mechanisms involved in different MI tasks that requires the knowledge of how the co-activated brain regions interact with each other is explored. The main objective of this thesis is to investigate the neurophysiological pattern of healthy human brain during different MI movements by taking into account the brain dynamic nonlinear functional/effective interactions in frequency domain. Besides, topological organization of the estimated brain networks is quantified and studied using graph theoretical approach. This includes the following sub-objectives:

1) To evaluate the robustness of DEKF for detecting nonlinear interactions and tracking fast parameter changes. And to develop several frequency-based non-linear connectivity estimators.

2) To recover and localize the MIs source signals for studying brain neurophysiological behavior by estimating dynamic nonlinear brain interactions using DEKF and the developed connectivity estimators within a broad frequency range.

3) To construct and characterize the estimated brain network of each MI task using graph theoretical approach to reveal the similarities and (statistical significant) differences within MI tasks.

1.6 Scope

The scope of this research is given as follows:

1) Using only a nonlinear AMVAR model in SSM framework for estimating the time-varying interactions.
2) Dataset of healthy subjects containing four MI movements, feet, left hand, right hand and tongue is used.

3) Source space analysis is considered for MI brain connectivity analysis.

4) Equivalent current dipoles corresponding to source signals are localized by DIPFIT technique.

5) Brain interactions are estimated by three functional and one effective connectivity estimators Coherence, imagery Coherence, partial Coherence and normalized partial directed Coherence.

6) Brain connectomes are characterized by graph indexes degree, strength, density and efficiency in order to study brain underlying organization.

7) All processing steps including stimulations and EEG signal analysis are carried out offline.

1.7 Significance of Study

BCI systems are of great value to the rehabilitation engineering and assistive technology, prosthetics, robots and other devices for people with neuromuscular deficiencies due to disease, spinal cord injury or brain damage. MI-based BCI needs to detect the correct brain patterns of different MI tasks and transform them to the interested control commands. Brain connectivity analysis is a promising approach to provide more clear patterns of each motor function and deliver more efficient and accurate BCIs. Estimating true brain connectivity requires a complete mathematical model that can reflect the realistic behavior of brain activity such as non-stationarity and nonlinearity. This research proposes a robust nonlinear AMVAR model in state space framework to carefully study brain network by estimating functional and effective connectivity measures during different MI tasks. Moreover, graph theoretical approach is implemented to characterize the brain networks topology to explore the brain organization during MI tasks and find significant differences among them.

1.8 Research Contributions

The main objective of this thesis is to investigate the neurophysiological pattern of healthy human brain during different MI movements by taking into account the brain dynamic nonlinear functional/effective interactions in frequency domain and applying graph theoretical approach to quantify the estimated brain networks and reveal the significant within MI tasks. Therefore, the current research targets to develop the frequency domain multivariate adaptive nonlinear brain connectivity estimators in SSM framework for MI brain source connectivity analysis in conjunction with graph theoretical approach. So, the following contributions are achieved.

i. DEKF has proven as a superior method to study time-varying nonlinear modeling of neurological signals.

ii. Four frequency domain brain connectivity estimators *Coh, iCoh, pCoh* and *nPDC* are developed for studying any non-stationary and nonlinear neurophysiological data.

iii. For the first time, brain source signals of four different MI tasks are reconstructed and localized for studying nonlinear dynamic brain connectomes using DEKF and the developed connectivity estimators within a broad frequency range.

iv. For the first time, the brain networks of four MI tasks are constructed and characterized using graph theory to identify the similarities and (statistical significant) differences within all tasks.

1.9 Outline of the Thesis

Chapter 1 introduces the research study including introductory materials (research overview, background of problems, statement of problems, research hypothesis, objectives, scope, significance of study and contributions of the research). Chapter 2 provides a comprehensive literature review related to this research. Chapter 3 proposes an adaptive nonlinear multivariate state-space model, dual extended Kalman filter, for connectivity pattern estimation. Besides, time-varying nonlinear frequency domain connectivity estimators are computed. Chapter 4 deeply investigates time-varying nonlinear multivariate brain connectivity for studying couplings and information flows among the brain regions during four different motor imagery tasks. In Chapter 5, organizational principles of brain networks of different MI movements are extensively explored by graph theoretical approach. Chapter 6 concludes the thesis and presents the possible future directions.

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