SIMULATED ELECTROENCEPHALOGRAPHY (EEG) SOURCE LOCALIZATION USING INTEGRATED MEROMORPHIC APPROXIMATION

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A thesis submitted in fulfilment of the
requirements for the award of the degree of
Doctor of Philosophy (Mathematics)

Faculty of Science
Universiti Teknologi Malaysia

SEPTEMBER 2015

ACKNOWLEDGEMENTS

In preparing this thesis, I was in contact with many people, including researchers, academicians, and practitioners. They have contributed towards my understanding and thoughts. In particular, I wish to express my sincere appreciation to my main thesis supervisor, Professor Dr. Tahir Ahamd for encouragement, guidance, critics and friendship. I am also very thankful to my co-supervisors, Associate Professor Dr. Norma Alias for her guidance, advice and motivation. Without their continued support and interest, this thesis would not have been the same as presented here.

I am also indebted to Universiti Teknologi Malaysia (UTM) for funding my Ph.D. study. My fellow postgraduate students should also be recognised for their support. My sincere appreciation also extends to all my colleagues and others who have provided assistance on various occasions. Their views and tips are useful indeed. Unfortunately, it is not possible to list all of them in this limited space. And last, but certainly not least, I am grateful to all my family members.

ABSTRACT

Epilepsy is a chronic brain dysfunction in which neurons and neuronal network malfunction cause symptoms of a seizure. A seizure is an abnormal electrical discharge from the brain appearing at a small area of the brain. The seizure affected zone loses its normal task abilities and might react uncontrollably. Electroencephalography (EEG) is one of the useful instruments in diagnosing many brain disorders like epilepsy. This non-invasive modality is used to localize brain regions involved during the generation of epileptic discharges. At present, many quantitative methods for identifying and localizing the epileptogenic focus from EEG have been invented by scientists around the world. Under quasi-static assumptions, Maxwell’s equations governing the spatial behaviour of the electromagnetic fields lead to Partial Differential Equations (PDE) of elliptic type in domains of R^3. This thesis presents a new method based on integrated new EEG source detection, Cortical Brain Scanning (CBS) with meromorphic approximation to identify the sources on the brain scalp, which have highly abnormal activities when a patient is having a seizure attack. Boundary measurements for meromorphic approximation method are considered as isotropic and homogeneous in each layer (brain, skull, and scalp). The proposed method is applied on simulated and published EEG data obtained from epileptic patients. The method can enhance the localizations of sources in comparison to other methods, such as Low Resolution Brain Electromagnetic Tomography (LORETA), Minimum Norm Estimation (MNE), and Weight Minimum Norm Estimate (WMNE), coupled with meromorphic approximation. Standard validation metrics including Root Sum Square (RSS), Mean Square Error (MSE), and Receiver Operating Characteristic Curve (ROC) are used to verify the result. The proposed method produces promising results in enhancing the source of localization accuracy of epileptic foci.

ABSTRAK

Epilepsi adalah kegagalan fungsi otak yang kronik yang mana kegagalan neuron dan rangkaian neuron boleh menyebabkan gejala serangan sawan. Serangan sawan adalah keadaan di mana satu pelepasan elektrik yang tidak normal di kawasan kecil otak. Serangan sawan akan menyebabkan kehilangan keupayaan biasa dan mungkin berlaku tindak balas tanpa kawalan. Elektroensifalografi (EEG) adalah satu instrumen yang sangat berguna semasa mendiagnosis pelbagai gangguan otak, seperti epilepsi. Modaliti tidak ceroboh digunakan untuk mengenal pasti kawasan otak yang terlibat semasa serangan sawan. Pada masa ini, banyak kaedah kuantitatif untuk mengenal pasti dan mencari fokus sawan menggunakan EEG telah diciptakan oleh ahli sains serata dunia. Dengan andaian kuasi-statik, persamaan Maxwell di dalam pemodelan medan elektromagnetik menghasilkan Persamaan pembezaan Separa (PDE) jenis elliptik dalam domain R^3. Tesis ini memaparkan kaedah terbaharu EEG pengesan sumber bersepadu, Imbasan Otak Korteks (CBS) dengan anggaran meromorfik bagi mengenal pasti sumber di atas kulit kepala yang menunjukkan aktiviti abnormal tinggi apabila pesakit diserang sawan. Pengukuran sempadan bagi kaedah anggaran meromorfik diandaikan isotrofik dan seragam pada setiap lapisan (otak, tengkorak dan kulit kepala). Kaedah yang dicadangkan digunakan terhadap data yang disimulasikan dan data EEG yang diperolehi dari pesakit sawan. Kaedah ini boleh membantu meningkatkan pencarian lokasi sumber berbanding dengan kaedah lain seperti Tomografi Electromagnetic Otak Resolusi Rendah (LORETA), Jangkaan Norma Minimum (MNE), dan Jangkaan Norma Minimum Berpemberat (WMNE) serta dipadankan dengan anggaran meromorfik. Pengesahan metrik piawai termasuk hasiltambah kuasa dua punca (RSS), purata ralat kuasa dua (MSE) dan lengkung cirian operasi penerima (ROC) digunakan untuk menentusahkan keputusan yang terhasil. Kaedah yang dicadangkan telah berjaya meningkatkan keyakinan dalam penentuan lokasi fokus sawan.

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EEG	-	Electroencephalography
MRI	-	Magnetic Resonance Imaging
ROC	-	Receiver Operating Characteristic
SNR	-	Signal to Noise Ratio
RSS	-	Root Sum Square
MSE	-	Mean Square Error
AUC	-	Area Under the ROC Curve
MNE	-	Minimum Norm Estimation
LORETA	-	Low Resolution Brain Electromagnetic Tomography
WMNE	-	Weight Minimum Norm Estimate
CBS	-	Cortical Brain Scanning

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CHAPTER 1

INTRODUCTION

1.1 Introduction

Epilepsy is a chronic brain dysfunction in which neurons and neural network malfunction cause symptoms for a seizure. A seizure is an abnormal electrical discharge from the brain that appears at a small area of the brain. Seizure causes a loss of normal task ability and might occur uncontrollably. Clinical research in neurophysiology intends to understand the mechanisms leading to disorder of the abilities of the brain and central nervous system in order to improve diagnosis and propose new therapies. Electroencephalography (EEG) is mostly used in diagnosing epilepsy.

EEG is a valuable tool for diagnosing epilepsy as it records the electrical activity originating from the brain. Data extracted from records is highly effective for diagnostic procedure of epilepsy. The specific evaluation criteria have been defined by experts for recognizing the epileptogenic zone. Especially for patients with epilepsy, those who are not treated with medication will usually choose surgery to remove the epileptogenic zone. Hence the EEG plays a crucial role in localization of this region. Numerous techniques have been used to obtain critical information to determine source localization based on scalp-recorded EEG.

The motivation of this research, broadly stated, is to detect epileptogenic tissue of the brain using new EEG source localization method. The research seeks to identify a new approach to increase localization accuracy of EEG sources by combination of equivalent current dipoles model and distributed source model.

1.2 Background of the Research

A highly complex organ which is the core of human nervous system is called brain. It is made of a network of billions of neurons. There are electrical communications between these neurons through synaptic connections for human activities. Studying these communications is extremely beneficial for functional understanding of the brain. If the electrical activities (known as signals) generated by a cluster of cells are abnormal, epilepsy seizures will occur (Penfield and Jasper, 1954). The procedure of recording these electrical activities can be grouped into two categories: a) Invasive techniques (with surgery) and b) non-invasive techniques (without surgery).

EEG is a non-invasive technique that measures electrical activities at the surface of the head with millisecond temporal resolution. Hence, a series of sensors are placed at the surface or around the head at extremely close distance. In EEG for each human activity, large numbers of sources (neurons) are active. Each sensor measures a different combination of activities depending upon its distance from the sources. As these are non-invasive techniques, one has no idea about the sources and the mixing process that has taken place inside the head (Hämäläinen *et al.*, 1993). Many methods have been established to detect the epileptic foci, i.e. the location of the abnormal cells. This activity is called EEG source localization (Baillet, Mosher, *et al.*, 2001). Furthermore, several methods have been proposed for EEG source localization. These methods are formulated based on inverse and forward problems. Forward problems consist of the calculation of the potential difference between electrodes for a given distribution of the source in the brain. The mathematical translation of the forward problem is a Poisson differential equation (Sarvas, 1987). To solve the forward problem, i.e. to evaluate field quantities, several methods ranging from simple analytic approaches to numerical methods have been proposed (Hämäläinen *et al.*, 1993). Among the various methods, boundary element method

(BEM) has been applied most widely and is adopted in this work. In contrast, the inverse problem consists of estimating the source(s) that fits with the given potentials at the scalp electrodes. It is more difficult and complex to be solved than the forward problem. Two types of inverse source models have been proposed (Baillet, Mosher, *et al.*, 2001; Michel *et al.*, 2004) namely, Equivalent Current Dipoles (ECD) model (Koles, 1998; Scherg and Von Cramon, 1986), and Distributed source localization model (Dale and Sereno, 1993). The EEG inverse problem has endured different obstacles, such as high sensitivity to noise, complexity of verification, and ill-posed characteristics (Baillet, Mosher, *et al.*, 2001). Therefore, the evaluation of the inverse source models remains an open issue in this field in order to enhance the accuracy of finding the location of sources such as epileptic foci.

1.3 Statement of the Problem

To explore epileptic focus or epileptogenic tissue of the brain in a non-invasive way, several techniques based on EEG have been developed. These techniques were formulated based on the inverse problem and forward problem. There have been two common inverse methods: ECD model and Distributed source localization model. Both of the models have their own pros and cons. The most commonly used optimization algorithms for ECD model are deterministic and stochastic (Yang, 2014). Deterministic algorithms look for local peaks located closely to the starting points and usually utilize gradient information by distinguishing error functions. Levenberg-Marquardt algorithm (Dümpelmann *et al.*; Levenberg, 1944; Marquardt, 1963), Nelder-Mead downhill simplex searches, and conjugate gradient searches (Press, 2007) are the most widely used deterministic algorithms for ECD source localizations. If good initial starting points are assumed, the deterministic algorithms will be extraordinarily fast and robust. However, using gradient directions there is a large possibility that these algorithms will become trapped in local minima. On the other hand, different interacting sources must be observed and modelled via multiple dipoles in order to analyse the data from the cortex during a complicated task. Unless giving reasonably accurate initial locations, conventional deterministic algorithms are trapped in a local minima or even divergence. Therefore, a series of stochastic optimization algorithms have been used to deal with this difficulty. Most common algorithms are: Genetic Algorithms (Goldberg, 1989), Simulated Annealing (Kirkpatrick, 1984), Evolution Strategies (Hansen *et al*., 2013) Particle Swarm Optimization (Kennedy and Eberhart, 1995). ECD method not only has many good features explained earlier but also has some crucial restrictions as follows:

i. The number of dipoles should be determined through a general principle to work out the expected facts. Most of the time it is chosen with respect to the knowledge of the experiment which is considered, but it can also be determined more or less automatically using the residual error between the model and the data or by analysing the spectrum of the data. It is particularly challenging because of the absence of initial data.

ii. Eventual solutions highly depend on initial data of the ECDs (Uutela *et al*., 1998).

iii. Since anatomical information of the brain is not regarded by ECD models, there is high possibility of localizing outside the grey area of the cerebral cortex.

In contrast, the distributed source model not only assumes various dipole sources with fixed locations and/or orientations on the surface of cortex or in the whole volume of the brain, but also approximates their spatial parameters (moments) from the obtained information. The model requires neither a priori data on the number and locations of dipoles nor conjectures as to the shape or size of an activated area (Hämäläinen and Ilmoniemi ,1984). A fundamental study on the distributed source model yielded several different methods such as: Low resolution electrical tomography (LORETA), Minimum norm estimate (MNE), Weight minimum norm estimate (WMNE), and Focal underdetermined system solution (FOCUSS). This type of estimation is well suited to distribute source models where the dipole activity is extended over some areas of the brain (Pascual-Marqui, 1999). For improving the precision of ordinary algorithms, weighted minimum norm has been proposed (Gorodnitsky *et al*., 1995; Jeffs *et al*., 1987) which is typically applied to normalize lead field regarding source positions. LORETA proposed by Pascual-Marqui *et al*. (1994) functions as MNE, but it estimates deeper sources. This method has been extensively used, but it has a problem over unclear images because of the smooth effects of the Laplacian operator. Focal Underdetermined System Solution (FOCUSS) was planned by Gorodnitsky *et al*., 1995 to solve the underdetermined inverse problems more effectively and subsequently reorganize more focalized solutions and iterative focalization approaches. Although these techniques yielded better accuracy, they face the problem of omitting some small activations of the brain during the repetitive weighting procedures.

Early studies on the distributed source model showed regular voxel inside all areas of the cortical surface; however, it was accounted that the reorganization brings some undesired sources, known as phantom sources or spurious sources. Unfortunately, even using special reconstruction technique, there is no approach to omit those types of phantom sources.

As discussed above, each ECD model and distributed source model have important and unique advantages, but also significant limitations while detecting epileptogenic focus of the brain. This in turn affects the localization accuracy.

Meromorphic approximation has been categorized as ECD model. Previous studies related to Meromorphic approximation deal with ECD model presented by Clerc *et al*. (2012) without any consideration of distributed source model. Her research attention has not been directed toward integration of two models; hence this study gives more attention and focus in order to improve the accuracy of meromorphic approximation model by new EEG source localization.

Additionally, it seems that no research has yet addressed the integration of the meromorphic approximation model with distribution model in a holistic and comprehensive manner. Previous studies dealt with a subset of this problem, or considered individual model for localizing sources from exterior electromagnetic measurements.

Therefore this study intends to fill this gap in the literature by conducting a comprehensive and integrative study to localize the epileptogenic focus. It may be improved by integrating the previous models with some mathematical techniques.

1.4 The Research Objectives

The objectives of this research are as follows:

1. To prove mathematical model of the spatial behavior of dipole sources located inside the brain from quasi-static approximation of Maxwell equations.
2. To recognize the EEG source localization model (ECD model) by Meromorphic approximation technique in the complex plane.
3. To identify the origins of the errors in Meromorphic approximation method.
4. To propose new EEG source localization method based on integration of Meromorphic approximation with Cortical Brain Scanning (CBS) method.
5. To compare the new EEG source localization method with other methods based on Receiver Operator Characteristics (ROC), Root Sum Square (RSS), and Mean Square Error (MSE) criteria.

1.5 Significance of the Study

This study will enrich the collection of methods and approaches based on mathematical modelling of EEG source localization during epilepsy. One of the significant methods for localizing EEG sources is Meromorphic approximation. Despite the importance of this method, it has some drawbacks such as:

1. The spherical head model was applied, which is not based on the actual underlying brain anatomy.

2. It uses single time slice to solve the problem; hence, large noises at some time slices may reduce the localization accuracy.

The significance of this study is applying spatio-temporal dipole fit to improve the accuracy of source detection. The integration of the spatial and temporal domains represents a unique challenge because of the existence of anatomically distinct processing regions that communicate across several time scales. Furthermore, using realistic head modelling techniques for estimating EEG forward solutions instead of spherical head model was another strong point of this research.

This study is expected to contribute to the body of knowledge by providing new method for EEG source localization using integrated Meromorphic approximation. Furthermore, the main beneficiary of this research is the healthcare industry for patients suffering from epilepsy. Neurosurgeons may be able to gain more information on abnormal tissue prior to performing surgery on epilepsy patients.

1.6 Scope and Limitations of the Study

In this research, location of the sources will be carried out based on simulated EEG data. Realistic simulations were generated using EEG data obtained from a patient who suffered from focal epilepsy with focal sensory, secondarily generalized seizures since the age of eight years. EEG and Magnetic Resonance Imaging (MRI) data was acquired during one night of non-invasive telemetry recording at the Epilepsy Centre of University Hospital Freiburg in Germany. In addition, there are several limitations that should be considered when interpreting the findings for generalizability and transferability purposes.

First, the high computational cost of MRI is a limitation of forward model. It led to the consideration of a single case study.

The second limitation of the study was access to medical information of epileptic patient (EEG and MRI). It is not easy to access this information because of the high confidential level for physician and patient. Inevitably, free medical information from epileptic patients was used from (http://neuroimage.usc.edu/). Although data is free, it is real data obtained from epileptic patients with formal permission from relevant physicians.

The third limitation related to conductivity of head as it may influence the performance of inverse method that was not studied in this research. The conductivity values for each layer, namely scalp, skull, and brain (1:0.0125:1, or 0.33:0.0042:0.33) have been used for decades now. Inverse results in this study were obtained using (1:0.0125:1) conductivity values. These values were set as a default value for brainstorm software.

The forth limitation was the number of sources. In CBS method, process to scan neighbouring vertices requires considerable computation time especially when the number of sources were more than 5. Therefore, in this research, based on experience, 5 sources were considered.

1.7 Thesis Outline

This thesis is organized into 6 chapters as shown in Figure 1.1.

In the first Chapter, an overview of background, statement of the problem, objectives of the study, significance and scope of the study are outlined, respectively.

In Chapter 2, basic knowledge on epilepsy and seizure are explained. In addition, history of seizure prediction and the modality that has been extended for measuring the brain electromagnetic field exterior of the head is dealt with in this chapter. Various EEG source localization methods which have been used for imaging human brain functions in a non-invasive way are introduced. Some related basic knowledge of mathematics is presented in this chapter. In order to evaluate the performance of EEG source localization methods to localize sources regarding their ability, validation metrics as the assessment criteria are needed. These criteria encompass Mean Square Error (MSE), Receiver Operating Characteristic (ROC) curves, and Root Sum Square error (RSS) which are introduced in the rest of the chapter.

In Chapter 3, the basic simulation set-up and pre-processing procedures that will be used in analyzing EEG data were described. In addition, for localizing dipole sources located in the brain, a new approach, namely, integrated Cortical Brain Scanning (CBS) with Meromorphic approximation for inverse EEG problem was proposed. In chapter 4, the results of proposed method with appropriate discussion were explained.

In Chapter 5, the comparison of EEG localization methods used in this thesis with proposed method was presented. In addition, validation metrics are used to evaluate the accuracy of other EEG source localization methods with proposed method by evoking RSS, MSE, and ROC.

Finally, Chapter 6 provides a summary of the research. It also presents contributions of this study followed by suggestions for further researches.

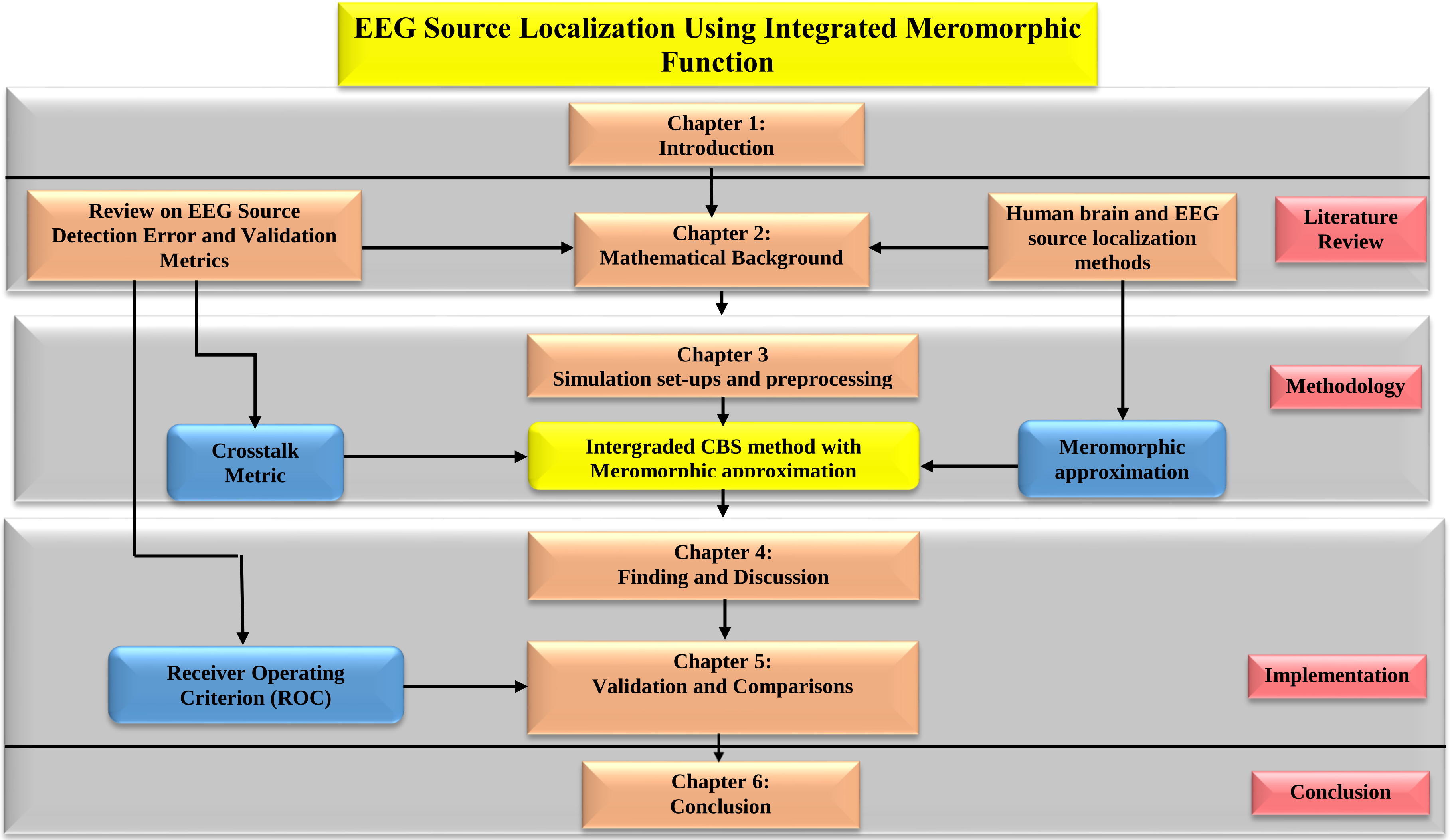

Figure 1.1 Outline of Thesis

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