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EEG- AND MRI-BASED EPILEPSY SOURCE LOCALIZATION USING MULTIVARIATE EMPIRICAL MODE DECOMPOSITION AND INVERSE SOLUTION METHOD

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By

PEGAH KHOSROPANAH

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

April 2018

DEDICATION

Dedicated to

My dearest parents and sister
whose endless love and care supported me all through the way
and, to my lovely niece, Armita,
whose spirit encourage me to survive

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

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Chairman: Associate Professor Abd. Rahman Ramli, PhD
Faculty: Engineering

The only treatment for patients with medical refractory epilepsy is to resect the part of the cortex that is origin of epilepsy by surgery. An extensive pre-surgical evaluation is required to define the Epileptogenic Zone (EZ) accurately. There is a large variation of neuroimaging approaches that are utilized for pre-surgical evaluation depending on the protocol of each epilepsy surgery center. Although Electroencephalography (EEG)-based source localization (ESL) estimates the EZ more precisely than other techniques but, it is used rarely in surgery centers. The reason behind the low usage of this trustworthy technique is its requirement for technical expertise together with experts' supervision and lack of recommended guidelines for this technique. The accuracy of ESL depends on all the stages of data processing including: head model reconstruction, signal pre-processing and inverse solution. Therefore, a standardized algorithm with less supervision is desired to utilize ESL for pre-surgical evaluation. One of the factors that needs to be considered for the purpose of establishing an automated and standardized algorithm is eye blink artifact removal due to its morphological resemblance to epileptic discharges. Few studies considered eye blink artifact removal for purpose of epilepsy source localization studies and most of them used either visual inspection or computer-based approaches which still need of experts' supervision. Besides, non-stationary, non-linear and multivariate characteristics of EEG needs to be considered for choosing a proper processing method for extracting epileptic spikes' features. Nevertheless, patient's realistic head model is essential to obtain accurate source localization results. Although many inverse solutions exist but, the ones which do not require specialists' involvement with minimal error is desired. Standardized Low Resolution Tomography (sLORETA) and Weighted Minimum Norm (WMN) are linear distributed inverse solutions which lead up to zero localization error using noise-free EEG, state-of-the-art feature extractor and realistic head model. Therefore, in this study a coupled Multivariate Empirical Mode Decomposition (MEMD) with embedded automated artifact remover algorithm and inverse

solution method is proposed. To remove eye blink artifacts, the mother wavelet of Bior 3.3 was used due to its high morphological resemblance to eye blink and yet differentiable characteristic to epileptic spikes. Since MEMD method is a data-driven method which meets the criteria to be applied for EEG processing, therefore this method was employed to extract EEG epileptic spike features. In the current study, clinical dataset of 20 subjects were used to examine sLORETA and WMN fed by raw EEG signals and MEMD features on each patient's realistic head model. sLORETA in combination with MEMD feature after eye blink removal proved to be a reliable ESL algorithm with 100% accuracy. The results show significantly improved EZ localization results in comparison with similar works and capability of this algorithm to not only determine the epilepsy origin lobe, but also the exact focus on the lobe. The outcomes were validated using MRI references which are verified via post-surgical results. Therefore proposed algorithm has the advantages to localize EZ using ESL inexpensively and accurately which promotes usage of this valuable technique for epilepsy pre-surgical evaluation.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENEMPATAN SUMBER EPILEPSI BERASASKAN EEG- DAN MRI-MENGGUNAKAN KAEDAH MULIPERBEZAAN MOD EMPIRIKAL DAN PENYELESAIAN SONGSANG

Oleh

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Pengerusi: Profesor Madya Abd. Rahman Ramli, PhD
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Satu-satunya rawatan untuk pesakit sawan yang sembuh selepas dirawat adalah dengan cara membuang bahagian korteks yang merupakan punca sawan melalui kaedah pembedahan. Penilaian pra-pembedahan secara menyeluruh adalah diperlukan untuk mengenalpasti zon Epileptogenik (EZ) dengan tepat. Terdapat banyak pendekatan pengimejan neuro yang digunakan semasa pra-pembedahan bergantung kepada protokol yang digunapakai pada pusat pembedahan sawan berkenaan. Walaupun penentuan Electroencephalografi (EEG) berasaskan tempat punca (ESL) dapat menganggarkan EZ lebih tepat berbanding teknik lain tetapi ianya jarang digunakan di pusat pembedahan. Punca kaedah yang tepat ini kurang digunakan kerana ia memerlukan pakar teknikal serta penyeliaan pakar dan kurang garis panduan untuk kaedah ini. Ketepatan ESL bergantung kepada semua peringkat pemprosesan data termasuk pembentukan semula model kepala, prapemprosesan isyarat dan penyelesaian songsang. Oleh itu,algoritma piawai yang kurang penyeliaan adalah diperlukan untuk penilaian pra-pembedahan menggunakan kaedah ESL. Salah satu faktor yang perlu dipertimbangkan untuk tujuan membangunkan algoritma tanpa penyeliaan dan piawai adalah penyingkiran isyarat artifak kelipan mata yang disebabkan oleh persamaan morfologi dengan isyarat pelepasan sawan. Beberapa kajian mempertimbangkan penyingkiran isyarat kelipan mata untuk tujuan penentuan tempat punca sawan dan kebanyakannya menggunakan pemeriksaan secara visual atau pendekatan menggunakan komputer di mana penyeliaan pakar masih diperlukan. Selain itu, EEG yang tidak pegun, tidak linear dan berpelbagai pembolehubah perlu dipertimbangkan untuk memilih kaedah pemprosesan yang sesuai untuk mencari ciri denyutan sawan. Walau bagaimanapun, model realistik kepala pesakit adalah diperlukan untuk menentukan punca penyetempatan yang tepat. Walaupun terdapat banyak teknik songsang tetapi kaedah yang tidak memerlukan penyeliaan pakar lebih diperlukan. Kaedah Tomografi Beresolusi Rendah Piawai (sLORETA) dan Norma Berpemberat Minima (WMN) adalah kaedah songsang linear di mana ralat penyetempatan hampir sifar dengan menggunakan EEG

tanpa hingar. pencari ciri terkini dan model kepala realistik. Oleh itu, dalam kajian ini beberapa Mod Penguraian Muliperbezaan Empirikal (MEMD) dengan algoritma penyingkiran artifak tanpa pengawasan dan kaedah penyelesaian songsang dicadangkan. Untuk menyahkan isyarat artifak kelipan mata, gelombang induk Bior 3.3 digunakan kerana ia mempunyai persamaan morfologi yang tinggi dengan isyarat kelipan mata namun berbeza dengan isyarat denyutan sawan. Memandangkan kaedah MEMD adalah dipacu oleh data yang sama kriteria untuk pemprosesan EEG, oleh itu kaedah ini digunapakai untuk mencari ciri denyutan sawan EEG. Dalam kajian ini, 20 data klinikal digunakan untuk menguji sLORETA dan WMN menggunakan isyarat EEG tulen dan ciri MEMD pada ciri setiap model kepala pesakit. Gabungan kaedah sLORETA dengan ciri MEMD selepas isyarat kelipan mata disingkirkan membuktikan algoritma ESL boleh dipercayai dengan ketepatan 100%. Hasil kajian menunjukkan penyetempatan EZ yang lebih baik berbanding kaedah yang sama dan kemampuan algoritma ini bukan hanya menentukan lobus punca sawan, tetapi memfokus pada lobus dengan tepat. Hasil kajian disahkan menggunakan rujukan MRI yang disahkan dengan keputusan pasca pembedahan. Oleh itu, algoritma yang dicadangkan mempunyai kelebihan untuk menentukan tempat EZ mengggunakan ESL dengan lebih murah dan tepat di mana menggalakkan penggunaan kaedah ini untuk penilaian pra-pembedahan.

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I certify that a Thesis Examination Committee has met on 25 April 2018 to conduct the final examination of Pegah Khosropanah on his thesis entitled "EEG- and MRI-Based Epilepsy Source Localization using Multivariate Empirical Mode Decomposition and Inverse Solution Method" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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LIST OF ABBREVIATIONS

AC	Anterior Commissure
AED	Anti-Epileptic Drugs
BCI	Brain Computer Interface
BEM	Boundary Element Method
BOLD	Blood Oxygenation Level-Dependent
CSF	CerebroSpinal Fluid
CT	Computer Tomography
DBS	Deep Brain Stimulation
DICOM	Digital Imaging and Communications in Medicine
DIS	Distributed Inverse Solutions
DWT	Discrete Wavelet Transform
ECD	Equivalent Current Dipole
ECoG	Electrocorticography
EDF	European Data Format
EEG	Electroencephalography
EMD	Empirical Mode Decomposition
EOG	Electrooculargram
EPSP	Excitatory Post Synaptic Potential
FDM	Finite Difference Method
FEM	Finite Element Method
FINE	First principle vector
Flair	Fluid Attenuated Inversion Recovery
fMRI	functional Magnetic Resonance Imaging
FOCUSS	Focal Underdetermined System Solver
ICA	Independent Component Analysis
IED	Interictal epileptiform discharge
IH	Interhemispheric
IMF	Intrinsic Mode Function
IPSP	Inhebitory Post Synaptic Potential
KD	Ketogenic Diet
LORETA	Low Resolution Tomography
LPA	Left Pre-auricular
MEMD	Multivariate Empirical Mode Decomposition
MN	Minimum Norm
MRI	Magnetic Resonance Imaging
MTS	Mesial temporal sclerosis
MUSIC	Multiple Signal classification
NAS	Nasion
PC	Posterior Commissure
PCA	Principle Component Analysis
R-MUSIC	Recursive MUSIC
RAP-MUSIC	Recursively Applied and Projected MUSIC
RPA	Right Pre-auricular
SLF	Shrinking LORETA FOCUSS
sLORETA	standardized Low Resolution Tomography
SMA	Supplementary Motor Area
SNR	Signal to Noise Ratio
SSLF	Standardized Shrinking LORETA FOCUSS
TE	Time to Echo
TR	Repetition Time

VARETA	Variable Resolution Electrical Tomography
VNS	Vagus Nerve stimulation
WMN	weighted Minimum Norm
WROP	Weighted Resolution Optimization
WT	Wavelet Transform

CHAPTER 1

INTRODUCTION

1.1 Background

Epilepsy is the fourth common chronic brain disorder in humans and is the result of an excessive discharge of the group of neurons in the unprovoked brain. Patients with epilepsy often experience seizures throughout their lives, with different occurrence frequencies. The occurrences of seizures have a serious negative impact on the quality of a patient's life. During the seizures, the patients may hurt themselves, cause many types of accidents, or suffer brain damage. About 60% of these patients are stricken by focal epilepsy and 15% of focal epileptic patients can neither be treated nor controlled by medication. Usually in such a situation epilepsy surgery is prescribed to remove the part of the brain that is the origin of seizures. Therefore, accuracy of pre-surgical evaluation toward epilepsy source localization has a significant influence on post-surgical result. There are different neuroimaging (brain imaging) methods to directly or indirectly image the structure, function or pharmacology of the brain.

Non-invasive brain imaging techniques are utilized to better understand the electrophysiological, hemodynamic, metabolic, and neurochemical process of both normal and pathological brain functionality. These techniques are categorized into a multidisciplinary research field called functional brain imaging which includes Single Photon Emission Computer tomography (SPECT), Positron Emission Tomography (PET), functional Magnetic Resonance Imaging (fMRI), Magnetoencephalography (MEG) and electroencephalography (EEG).

Due to the fast propagation of the epileptic activities, the neuroimaging techniques with image-based output would display several hyper regions' activity; thus, a neuroimaging technique with high temporal resolution is needed to overcome this problem. EEG is the most utilized neuroimaging technique with high temporal resolution (about milliseconds) to record a subject's brain activities without being invasive, through the use of electrodes placed on the scalp. The origin of recorded EEG is the brain electromagnetic sources inside the brain, therefore EEG holds useful data of these electromagnetic sources' activities. This data is treasured to understand functionality of the brain, diagnosis and treatment of some brain disorders such as epilepsy. Using EEG to determine the source of epilepsy in the brain is called EEG-based source localization (ESL).

However, EEG signal contains not only signal of interest, but also background activity and artifacts. Eye blink artifact is one of the most important internal artifacts that may hugely deteriorate accuracy of EEG-based epilepsy source localization. Although there are a vast number of studies to remove eye blink artifact from healthy EEG, but few of them consider removing this artifact from epileptic EEG. Eye blink artifact removal is more complicated in epilepsy studies because of the morphological similarity between eye blink artifact and epileptic spikes. Therefore, the trustworthy method would be the one with high sensitivity of detecting eye blink artifact without distorting the EEG signal. For instance, an inaccurate method may falsely detect and remove epileptic spikes which is the signal of interest instead of the eye blink. Unfortunately, only few epileptic spike detection studies considered eye blink artifact removal from EEG and most of them implemented either visual inspection or computer-based methods which needs experts' supervision. These studies only evaluate eye blink artifact removal without evaluating epileptic EEG misrepresentation. Moreover, eye blink artifact removal in context of epileptic spike detection mostly was accomplished on frontal channels which is efficient for ultimate purpose of epilepsy type diagnosis but not for epilepsy source localization. However, eye blink activity can affect temporal lobe as well which would influence the results of source localization. Although eye blink artifact can drastically decrease the accuracy of epilepsy source localization results, but most relevant studies either did not take it into account or relied on experts' supervision which is prone to possible human error.

For recording EEG of an epileptic patient there are two periods known as ictal and inter-ictal. Ictal EEG refers to the brain activity signals recorded in the time of epileptic seizure and inter-ictal EEG is the one recorded between two seizures. Some studies used ictal EEGs for epilepsy source localization due to distinguishable epileptic activity with high amplitudes in that period. However, recording ictal EEG has some limitation such as timing and noisy recording. The frequency of the seizures among patients varies from once in a month to many times in a day. Additionally, inter-ictal epileptiform discharges (IEDs) are as informative as ictal recordings in scalp EEG for diagnosis and localization of epilepsy. Therefore, most studies including this study try to find more accurate epilepsy source localization algorithms using inter-ictal EEG which is recorded much easier.

EEG-based Source Localization (ESL) is accomplished in two main steps:

Firstly, a model which describes the relation between the sources inside the brain and scalp EEG is needed. The process of obtaining such a model in ESL is called solving the forward problem. Like any other modeling problems in science and engineering, this model needs to be as realistic as possible. Many studies have modeled the head as a concentric sphere to localize brain activities (Durka, 2003; Kybic et al., 2005; Liu et al., 2004), but in reality, the human head is not a layered sphere. To achieve a more accurate source localization result, a realistic head model with different compartments and related electrical conductivity is required to be constructed using techniques such as Magnetic Resonance Imaging (MRI). After modeling the head geometry, as a part of the forward solution, it is important to model the sources within the brain. Normally, active neurons are modeled as current dipoles. With head geometry, related compartment's conductivity, source model and electrode positions on the scalp, forward problem can be solved in order to obtain the lead field matrix. This matrix represents the relation between the sources and the scalp EEGs of each subject.

Secondly, finding the source of activity of interest based on forward solution which is called inverse solution. Unfortunately, in the case of using EEG, the inverse solution is ill-posed, meaning that there is no unique solution for source localization (number of sources are more than number of sensors). There are many inverse solutions which are assigned to two major categories: parametric and non-parametric, which will be explained in further detail in section 2.11. The accuracy of source localization using parametric methods highly depends on a prior assumption about location and number of sources, therefore implementing parametric methods needs neurological knowledge background. In contrary, since non-parametric methods consider all possible sources in the head model volume, thus utilizing these methods in order to find origin of activities do not require a prior knowledge of sources and reduce complexity of the process.

Furthermore, signal of interest needs to be expressed as its corresponding characteristics or features which may be time-domain features, frequency characteristics or time-frequency specs of a signal. The methods used to extract these specific characteristics of the signal of interest is called the feature extraction methods. Feature extracted noise-free EEG signal is needed for source localization studies. To achieve this, features of the epileptic signal needs to be separated from the background activities. Because if noise-free EEG without separation of the epileptic signal is fed to inverse solution, the localization results would be a wrong source which is the superposition of background and desired source activities. Since EEG is a signal with non-stationary, multivariate and non-linear characteristics, therefore the feature extraction method needs to be suitable for the nature of EEG signal. There are different approaches to extract features of the epileptic EEG such as time-domain, frequency-domain and time-frequency analysis and each of them has its own merits and disadvantages.

Although the accuracy of ESL is higher than conventional methods that are used for pre-surgical evaluation such as MEG, fMRI, Magnetic Resonance Imaging (MRI), PET and invasive EEG (iEEG), only few epilepsy surgery centers use this method to determine Epileptogenic Zone (EZ). Technical expertise along with specialist supervision requirement and lack of guidelines are among the reasons which reduce the usage of this method for pre-surgical evaluation. Furthermore, the accuracy of ESL can be influenced by many factors such as head model and electrode placements used in forward model, EEG signal noise and inverse solution itself. Therefore, recent studies tend to develop standardized algorithms of ESL which adopt proper methods on each step with less supervision for epilepsy pre-surgical evaluation process (Kaiboriboon et al., 2012).

1.2 Problem statement

ESL is one of the new and computer-based approaches to determine the origin of brain's activity. Although this method has the highest accuracy to localize EZ among other pre-surgical evaluation approaches, but only 38% of epilepsy surgery centers use this method due to lack of recommended guidelines and technical expertise and experts' supervision requirements (van Mierlo et al., 2017). Moreover, ESL accuracy highly depends on each step namely: forward modeling, signal processing and inverse solution (Zwoliński et al., 2010). Therefore, a small error in each stage of source localization would lead to mis-localization. Consequently, recent studies tend to develop standardized approaches which consider realistic methods with less experts' involvement in each step.

Nevertheless, eye blink is one of the most important artifacts that can influence epilepsy source localization results due to its similarity to epileptic spikes (Singh and Wagatsuma, 2017; Zeng et al., 2013). Most of the epilepsy source localization researches either did not consider removing eye blink artifacts or relied on experts' supervision which is time consuming, labor intensive and prone to human error.

Finally, based on the result of epilepsy source localization in intractable epilepsy, part of the brain that has no essential functionality is removed. Therefore, the accuracy of epilepsy localization is very important since it also affects the results after epilepsy surgery (van Mierlo et al., 2017). Thus, an automated and non-invasive system with high accuracy of localization is desirable.

1.3 Objectives

Based on literature review and observing the remaining gaps in neuroimaging research studies; in context of epilepsy source localization; these objectives have been defined to develop a standardized algorithm:

1. To evaluate patients' realistic head model reconstruction in forward solution

2. To implement automated eye blink artifact removal on all EEG channels

3. To investigate the performance of sLORETA and WMN in proposed algorithm

4. To examine the extracted features of epileptic activities using Multivariate

Empirical Mode Decomposition (MEMD) from EEG in proposed pipeline

5. To evaluate the estimated origin of epilepsy on MRIs using MRI references in which epileptogenic zones are marked by a neurologist.

1.4 Scope of work

The objectives of this study are accomplished by considering the following work scopes:

1. Epilepsy origin is localized with focus on using scalp and inter-ictal EEG.

2. A clinical dataset of 20 patients which suits the process and aims of this study is used for analysis and validation.

3. Forward model is reconstructed using Boundary Element Method (BEM) based on realistic head model of each patient using MRI.

4. Each individual's MRI is fed into FreeSurfer suite software to segment the inhomogeneous head compartments.

5. Eye blink artifacts are removed from EEG signal using wavelet method in the preprocessing stage.

6. Multivariate Empirical Mode Decomposition (MEMD) method is utilized for extracting epileptic features from EEG.

7. Two inverse solution algorithms including weighted Minimum Norm (WMN) and standardized Low-Resolution Tomography (sLORETA) are applied to the signal of interest using Brainstorm software in order to localize the epilepsy origin.

8. Performance of the proposed algorithm is verified by comparing the localization results with the MRI reference of each subject marked by a specialist and verified with post-surgical results.

1.5 Contributions

Based on objectives and results of this study, contributions of current work are as follows:

- Promote the usage of ESI method as pre-surgical evaluation toward epilepsy source localization in clinics and epilepsy surgery centres
- Minimize the experts involvement to save time and ease of implementation even with minimum neurological knowledge
- Utilizing realistic head model for each patient
- Automated eye blink removal from all epileptic EEG channels
- Utilizing MEMD method to extract epileptic features
- Using sLORETA and WMN along with noise-free, extracted epileptic features to minimize the source localization error

This pipeline can be used to develop an application or a web-based platform which produce a comprehensive report for surgeons to decide on each case. The proposed method not only is capable of determining EZ with high accuracy, but also it helps to save time and avoid human error with less need of neurologist supervision and technical expertise.

1.6 Thesis organization

Chapter one covers a brief background of epilepsy source localization, the scope of work, problem statement, objectives and finally thesis organization.

Chapter two delivers an outline of the methods applied to localize origin of focal epilepsy in the literature over the past two decades. Two major relevant steps to determine epileptogenic zone using non-invasive tools like EEG are: first, forward modeling that calculates estimated potential on the scalp from known sources including head and source modeling, and second, inverse solution that estimates the source of signal of interest including signal preprocessing/feature extraction step. Both are challenging problems, and significant research efforts have been directed towards accurate result.

Chapter three comprises the material and methods used in this study, comprising wavelet analysis, boundary element method (BEM), Multivariate Empirical Mode Decomposition (MEMD) and standardized Low-Resolution tomography (sLORETA).

Chapter four presents the results which are obtained by using the proposed method for epilepsy source localization.

Chapter five concludes the work.

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