Quantitative analysis of epileptic and meditation EEG signals

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**NANYANG
TECHNOLOGICAL
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**QUANTITATIVE ANALYSIS OF EPILEPTIC AND
MEDITATION EEG SIGNALS**

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SCHOOL OF ELECTRICAL AND ELECTRONIC ENGINEERING

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List of Acronyms

AdaBoost	A daptive B oosting
BhPr	Bh ramari Pr anayama
BSS	B lind S ignal S eparation
CT	C omputed T omography
DT	D ecision T ree
DTW	D ynamic T ime W arping
ECG	E lectro c ardiogram
ECoG	E lectro c orticography
ED	E uclidean D istance
EEG	E lectro e ncephalography
EMG	E lectro m yography
FDG	F luoro d eoxy g lucose
GUI	G raphical U ser I nterface
HF	H igh F requency
HFO	H igh F requency O scillation
ICA	I ndependent C omponent A nalysis
IFSECN	I nternational F ederation of S ocieties for E lectroencephalography and C linical N europhysiology
kNN	k - N earest N eighbors
LDA	L inear D iscriminant A nalysis
MEG	M agneto e ncephalography
MGH	M assachusetts G eneral H ospital
MRI	M agnetic R esonance I maging

NB	Naive Bayes
NIH	National Institutes of Health
NLEO	Non-linear Energy Operator
PCA	Principal Component Analysis
PET	Positron Emission Tomography
PGW	Paroxysmal Gamma Wave
ROC	Receiver Operating Characteristics
RP	Relative Power
stereo-EEG	stereotactical Electroencephalography
SES	Stochastic Event Synchrony
sNLEO	smoothed Non-linear Energy Operator
SPET	Single Photon Emission Tomography
SOZ	Seizure Onset Zone
SVM	Support Vector Machine
TM	Transcendental Meditation
UCR	University of California Riverside
2D	2 Dimensional
3D	3 Dimensional

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Summary

Electroencephalography (EEG) refers to the recording of the brain's spontaneous electrical activity over a period of time. EEG remains the primary test to diagnose brain disorders such as epilepsy, sleep disorders, coma, encephalopathies, and brain death, which cause abnormalities in EEG readings. In this thesis, novel signal processing methods are developed for quantitative EEG analysis. We demonstrate that brief interictal intracranial EEG can be used to delineate the seizure onset zone (SOZ) for patients with epilepsy. Unlike traditional methods based on single EEG features, multiple features are applied to localize the SOZ in this thesis. An automated system is also developed for detecting high frequency oscillations (ripples and fast ripples) in epileptiform EEG. Moreover, in order to assist EEG interpretation and improve the efficiency of the neurologists, we develop a novel system that dramatically accelerates the process of acquiring expert-annotated EEG records based on template matching under Dynamic Time Warping. Last but not least, we also develop an automated system for paroxysmal gamma wave (PGW) extraction in scalp EEG recordings of meditation practitioners. We have better insights about the brain activity during meditation through PGW-related analysis.

In this thesis, we consider three applications of EEG analysis:

- Application 1: To localize the SOZ in the brain of epilepsy patients
- Application 2: To accelerate the annotation of epileptiform spikes
- Application 3: To study the brain activity during meditation

Both Applications 1 and 2 are related to EEG recordings of patients with epilepsy, but in different EEG data types, intracranial and scalp EEG, respectively. On the other hand, in Application 3 we analyze the scalp EEG recorded from the meditation practitioners. The common EEG pattern that joins three applications together is a special waveform named “spike”. It is also known as “interictal discharges” or “paroxysmal gamma waves (PGWs)” under different applications. Interictal spikes are the key diagnostic biomarker for epilepsy, predicting seizure recurrence, and allowing a physician to make a confident diagnosis of epilepsy and to prescribe appropriate treatment. On the other hand, the PGWs found in meditation EEG can be characterized by distinct high-frequency biphasic patterns, with a sharp peak closed to an interictal spike. Strong EEG activity has been observed in Bhramari Pranayama meditators, exhibiting frequent PGWs in active brain regions.

However, visual inspection and manual extraction of spikes (or PGWs) is tedious, time-consuming and subjective, relying on experts who are in short supply. As a result, there is a great need for automated systems for spike detection. To this end, we have developed and utilized spike detection algorithms for each application, emphasizing on different aspects to cater different needs.

◇ ***Application 1: To localize the SOZ in the brain of epilepsy patients***

Application 1 applies quantitative EEG analysis to localize the SOZ for patients with intractable focal epilepsy. Successful treatment of intractable focal epilepsy requires proper localization of SOZ. In current clinical practice, this is achieved through a combination of imaging modalities, clinical history and, ultimately, interpretations of electroencephalogram (EEG) recordings. In an effort to utilize brief recordings of neural activity that do not contain seizure activity and to improve consistency and incorporate quantitative methods, we have developed automated techniques that delineate SOZ from short intracranial EEG recordings. Analysis of interictal recordings obtained from stereotactically placed depth electrodes (stereo-EEG) from 14 patients with pharmacologically intractable epilepsy shows that stereo-EEG features such as slowing, high-frequency oscillations and interictal spikes are highly

correlated with SOZ. A binary classification scheme is also constructed employing the adaptive boosting method.

◇ ***Application 2: To accelerate the annotation of epileptiform spikes***

Interictal spikes are the key diagnostic biomarker for epilepsy. However, EEG interpretation such as spike detection relies on experts who are in short supply. There is a great need for automated pattern recognition systems to assist with interpretation. Furthermore, attempts to develop such systems have been limited by insufficient expert-annotated data. To address these issues, in Application 2, we develop a system named *NeuroBrowser* for EEG review and rapid waveform annotation. At the core of *NeuroBrowser* lies a new algorithm that performs ultrafast template matching under Dynamic Time Warping, which substantially accelerates the task of annotating waveforms.

◇ ***Application 3: To study the brain activity during meditation***

We consider scalp EEG of meditation practitioners to understand the brain activity during meditation. The PGWs found in meditation EEG can be characterized by distinct high-frequency biphasic patterns, with a sharp peak closed to an interictal spike. In a recent study, strong EEG activity has been observed in the left temporal lobe of Bhramari Pranayama (BhPr) meditators, with more frequent PGWs. We apply similar detection techniques developed for spike detection to extract PGWs in the context of meditation EEG. The algorithm is able to identify multiple sources in the brain that generate PGWs. In the meantime, sources associated with different types of PGWs can be distinguished. The effectiveness of this procedure is assessed on seven subjects possessing different degrees of expertise in practicing BhPr. Both power and PGW density are investigated for each subject, revealing brain activities during BhPr meditation. Moreover, we also study the synchrony between PGW sequences, constructing functional connectivity patterns in the brain.

Chapter 1

Introduction

Electroencephalography (EEG) refers to the recording of the brain's spontaneous electrical activity over a period of time. It measures voltage fluctuations resulting from ionic current in the neurons of the brain (Niedermeyer and da Silva, 2005). EEG can be subdivided into different types based on the electrode configuration. Scalp EEG is a noninvasive procedure that EEG is recorded by electrodes placed on the human scalp. Electrocorticography (ECoG) is an invasive procedure using electrodes placed directly on the exposed surface of the brain to record electrical activity from the cerebral cortex. Stereotactical EEG (stereo-EEG) is also invasive, with depth electrodes placed penetrating the brain tissue to reach deeper cortex structures. EEG remains the primary test to diagnose brain disorders such as epilepsy, sleep disorders, coma, encephalopathies, and brain death, which cause abnormalities in EEG readings (Abou-Khalil and Misulis, 2005). Intracranial EEG (ECoG and stereo-EEG) may become necessary when conventional imaging modalities (MRI, CT, PET, SPECT) and non-invasive scalp EEG are ambiguous or eloquent cortex needs to be defined. Despite limited spatial resolution, EEG continues to be a valuable tool for both research and clinical diagnosis.

EEG recordings are used extensively in neuroscience, cognitive science, cognitive psychology, neurolinguistics and psychophysiological research. For instance, EEG

remains the primary test for epilepsy. The key factor to the success of epilepsy surgical resections is the proper localization of the seizure onset zones (SOZs). Great attempts have been made to localize SOZ through quantitative EEG analysis. Extensive EEG studies are available either using scalp EEG (De Vos et al., 2007; Saab and Gotman, 2005; Staljanse et al., 2015a), or surface intracranial EEG (ECoG) (Foldvary et al., 2001; Greiner et al., 2016; Sun et al., 2015). On the other hand, the majority of the EEG studies focus on ictal EEG (Pellegrino et al., 2016; Staljanse et al., 2015a,b), or explore the correlation between a single EEG feature and SOZ such as interictal spikes (Engel, 2013; Wasade et al., 2015), high-frequency oscillations (Akiyama et al., 2011; Andrade-Valenca et al., 2011; Jacobs et al., 2016), and slowing (Dauwels et al., 2011; Roebuck, 2012). While all of these features show promise in delineation of SOZs, none appear to be sufficient in doing so. To address such problems, in Chapter 2, we demonstrate that brief interictal intracranial stereo-EEG can be used to localize SOZs. Multiple stereo-EEG features such as ripples, fast ripples, interictal spikes, and slowing are incorporated in a classification scheme. We also carried out multi-scale analysis by grouping neighboring contacts of the same electrode. Moreover, leave one patient out crossvalidation was performed with all possible combinations of EEG features, and all possible group sizes.

EEG feature extraction/detection is one of the hottest topics in quantitative EEG analysis. For instance, as classical seizure bio-markers, spike detection is very important in epilepsy study. However, spikes are difficult to detect in an automated manner due to the large variability of spike waveforms within and between patients among other factors. Great attempts have been made to detect interictal spikes by general classifications such as mimetic, linear predictive and template based methods. Many current spike detection algorithms apply multiple methods with various emphases such as the local context, morphology, the field of the spike, artifact rejection, and larger context (Wilson and Emerson, 2002). Unfortunately, these methods have not been validated on a large dataset and consequently are not

universally accepted. The most critical hurdle to developing an effective algorithm for interictal spike detection is the lack of a sufficiently large database of expert-annotated spike waveforms. To address such problems, in Chapter 3, we have developed an integrated system to accelerate the process of acquiring expert-annotated EEG records. It includes a graphical user interface designed for EEG review and rapid waveform annotation via template matching under Dynamic Time Warping. We also developed automated detection systems to detect other EEG events such as high frequency oscillations in epileptiform EEG, and paroxysmal gamma waves in meditation EEG, which will be discussed in detail in Chapter 2 and Chapter 4, respectively.

Artifact reduction is also crucial in EEG analysis, which is considered as the very first step. Artifacts are defined as signals that are captured by EEG electrodes but originate from non-cerebral activities. EEG recordings are almost always contaminated by artifacts. Common EEG artifacts include biological artifacts, such as eye-induced artifacts (eye blinks, eye movements and extra-ocular muscle activity), EKG (cardiac) artifacts, and EMG (muscle activation)-induced artifacts. In addition, there are also environmental artifacts such as electrode failure, electrode pops, loose contact, and power-line interference. Source separation algorithms such as independent component analysis (ICA) have been used to reduce or remove EEG artifacts (Delorme and Makeig, 2004; Delorme et al., 2007; Viola et al., 2009). The principle behind is to remix those components that result in clean EEG by nullifying the weights of unwanted components. Digital filters such as band-pass (or low-pass, high-pass, band-stop) filter and notch filter can be used to remove the artifacts of a particular frequency or frequency band. Other techniques such as Surface Laplacian has been proved effective in eliminating muscle artifacts (Fitzgibbon et al., 2014, 2013). In this thesis, digital filters are widely applied to remove artifacts such as power-line interference and EEG baseline drifts. Specifically, in Chapter 4, we have developed a system consisting of analysis techniques such as principal component analysis, blind signal separation, and automated paroxysmal gamma wave extraction

to remove the artifacts in meditation EEG.

Contributions

In this thesis, we develop various novel EEG processing methods for different EEG applications. The main contribution of Chapter 2 is to demonstrate that brief segments of interictal stereo-EEG can be used to localize SOZs. To our best knowledge, there are very few studies considering brief segments of stereo-EEG alone to localize SOZs, as investigated in our study. In Chapter 2, we present an automated binary classification system based on multiple stereo-EEG features that is able to delineate SOZs, whereas only single EEG features are considered in most EEG studies in this field (Andrade-Valença et al., 2012; Jacobs et al., 2016; Warren et al., 2010). We demonstrate that EEG features including interictal spikes, high-frequency oscillations, and slowing, are highly correlated with SOZ, which is in agreement with the literature (Andrade-Valença et al., 2012; Jacobs et al., 2016). Moreover, we have tested all possible combinations of multiple EEG features, and identified the combination with the best localization accuracy. Compared to single EEG features in the literature, features combinations improved the overall localization performance. In addition, the proposed system yields more reliable results for subjects with temporal SOZs compared to those with extra-temporal SOZs. These results demonstrate that not only does stereo-EEG have great potential in localizing SOZs, but that a rigorous, quantitative heuristic can be employed which can move significant clinical decisions from the subjective to objective.

Last but not least, extractions of EEG events such as spikes, ripples, and fast ripples were performed manually in most literature (Andrade-Valença et al., 2012; Jacobs et al., 2016), while it is automated detection in our study. For instance, we propose a novel detection method for high frequency oscillations (HFOs) in Chapter 2, and compare its performance with two other detection methods (Lévesque et al., 2011; Salami et al., 2012; Staba et al., 2002). The benchmark experiment was conducted

on a channel of 1-hour EEG with 108 HFOs consistently labeled by two experts. Compared to the other two methods, the proposed HFO detector achieves the highest sensitivity (97.22%), and very low false positive rate (4/hour); although slightly more computationally complex, it still runs very fast (1 sec to analyze 1 hour EEG with hundreds of HFOs).

In addition, as we aim to establish a binary classification scheme for localization, we also conduct benchmark comparison among six commonly used classifiers, including the support vector machines (SVMs) (Cristianini and Shawe-Taylor, 2000; Friedman et al., 2001), decision trees (DT) (Dietterich, 2000; Quinlan, 1986), linear discriminant analysis (LDA) (Izenman, 2013), the k -nearest neighbors (kNN) (Riley et al., 2009), the naive Bayes (NB) (Murphy, 2006; Zhang, 2004), and the adaptive boosting (AdaBoost) method (Freund and Schapire, 1995). We have tested the six classifiers on 50 EEG records, and assessed their performance by 5-fold crossvalidation. The AdaBoost outperforms the other classifiers with the lowest classification error, which as a result chosen as our classifier to conduct further analysis in Chapter 2.

The main contribution of Chapter 3 is the development of an integrated system that dramatically accelerates the process of acquiring expert-annotated EEG records. This system, named *NeuroBrowser*, includes a graphical user interface designed for EEG review and rapid waveform annotation via template matching under Dynamic Time Warping. Our experimental results show that *NeuroBrowser* is able to save EEG experts an average of approximately 70% of time spent on annotating interictal epileptiform spikes, relative to the “gold standard” conventional unassisted annotation in clinical practice. Neurologists have used *NeuroBrowser* to extract 35,000+ spikes from 303 patient EEG recordings. To our knowledge this represents the largest annotated database of spikes in existence, which is crucial in developing automated spike detection methods.

The main contribution of Chapter 4 is the development of an automated system for PGW extraction and source localization. Specifically, we analyze scalp

EEG recordings from subjects practicing a yoga type meditation called Bhramari Pranayama (BhPr), focusing on breath control. To best of our knowledge, there are very few studies analyzing EEG from this type of meditation. We further compare the proposed automated PGW detector with two other detection methods (Acir et al., 2005; Borghi et al., 2007; Liu et al., 2013). The benchmark experiment was conducted on a channel of 15-sec humming EEG with 2050 non-PGW samples and 200 PGWs, consistently labeled by two experts. Compared to the other two methods (M_1 : 99.6% sensitive, 82.1% specific, 83.6% accurate; M_2 : 79.7% sensitive, 97.8% specific, 96.2% accurate), the proposed HFO detector achieves a balanced performance, high in both sensitivity (97.1%), specificity (95.8%), and accuracy (95.9%). By applying this PGW detector, we are able to have better insights about the brain activity during meditation through PGW-related events, such as PGW density, power analysis, and pairwise synchrony of PGW sequences.

Chapter 2

Localization of Seizure Onset Zones using Interictal Intracranial Stereo-EEG

2.1 Introduction

Successful treatment of intractable focal epilepsy requires proper localization of seizure onset zone (SOZ). In current clinical practice, this is achieved through a combination of imaging modalities, clinical history and, ultimately, interpretations of electroencephalogram (EEG) recordings. For patients with intractable focal epilepsy, it is often necessary to perform intracranial EEG monitoring as well. These data, particular the recordings of seizure initiations, are then utilized to approximate the region of brain tissue that can be safely excised and produce seizure freedom. These approaches relay tremendously on clinician experience and subjective judgments. In an effort to utilize brief recordings of neural activity that do not contain seizure activity and to improve consistency and incorporate quantitative methods, we have developed automated techniques that delineate SOZ from short intracranial EEG recordings. Analysis of interictal recordings obtained from stereotactically

placed depth electrodes (stereo-EEG) from 14 patients with pharmacologically intractable epilepsy shows that stereo-EEG features such as slowing, high-frequency oscillations and interictal spikes are highly correlated with SOZ. A binary classification scheme was constructed employing an adaptive boosting method. stereo-EEG feature values are used first to narrow the range of suspected SOZ region. Each individual contact of those suspected electrodes is further checked, and ranked according to the likelihood it is inside SOZ. With proper choice of threshold, the final decisions are made to delineate SOZs in terms of individual contacts with 74% accuracy, 82% sensitivity, and 73% specificity on average compared to the clinically determined SOZ.

2.2 Background

Epilepsy is a group of brain disorders, affecting 65 million people worldwide (WHO, 2014). Medication remains the primary treatment for epilepsy. Only 70% of patients, however, are successfully treated with anti-epileptic drugs. Furthermore, the side effects of medications can be substantial. Surgical therapy might be beneficial to those intractable patients who respond poorly to drug treatments, providing seizure reduction or even cure. One of the key factors to the success of surgical resections is the proper localization of SOZ, as defined by those electrodes with first electrographic changes evaluated by experienced electroencephalographers. In current clinical practice, neurologists combine multiple medical modalities such as MRI, SPECT, and EEG to localize SOZs (Jayakar et al., 1991). When these methods are ambiguous or eloquent cortex needs to be defined, then intracranial monitoring may be required. In that instance SOZ is often defined as those electrodes with first electrographic changes evaluated by experienced electroencephalographers; ictal EEG containing seizures is therefore necessary for this determination and may require multiple-days or even weeks of hospitalized stay for the patient.

Great efforts have been made in the study of localization of SOZ. There are many

attempts utilizing medical imaging modalities such as MRI (Lee et al., 2014; Smith et al., 2015), PET (Juhász et al., 2003; Van den Broeck et al., 2014), and SPECT (Baumgartner et al., 1998; So et al., 2015), or combinations (Shin et al., 2015; So, 2000) to localize SOZ. Extensive EEG studies are also available either using scalp EEG (De Vos et al., 2007; Staljanse et al., 2015a), or surface intracranial EEG (Foldvary et al., 2001; Greiner et al., 2016; Sun et al., 2015). The majority of the EEG studies focus on using ictal EEG (Pellegrino et al., 2016; Staljanse et al., 2015a,b), or explore the correlation between a single EEG feature and SOZ. For instance, interictal discharges or spikes are a classical seizure bio-marker, often correlated with SOZ (Engel, 2013; Wasade et al., 2015). However, spikes were also often observed in channels outside SOZ. It has been discussed whether the localization, number, and multifocality of spikes seen in scalp and intracranial EEG have a predictive value for seizure outcome after surgery, which remains a matter of debate in epilepsy studies (Bautista et al., 1999; Holmes et al., 2000; Hufnagel et al., 2000). High-frequency oscillations are a relatively new EEG pattern that is believed to correlate to SOZ (Akiyama et al., 2011; Andrade-Valenca et al., 2011; Jacobs et al., 2016). Relative power, particularly at lower frequencies, has been explored as well because signals recorded from damaged cortex often appear to be “slower”, with more power at low frequencies (Dauwels et al., 2011; Roebuck, 2012). While all of these features show promise in delineation of SOZ, none appear to be sufficient in doing so and none are used in an automated fashion to help guide surgical resection. Epilepsy is a disorder characterized by heterogeneity in seizure patterns, etiology, lobe of involvement, etc. It is naive to think that a localization approach using only one or a few features could work for all patients. Furthermore, most research utilizes relatively long recordings, often in order to capture seizure activity. Methods to reduce the duration of intracranial data needed could greatly alter the landscape for patient care.

The main contribution of Chapter 2 is to demonstrate that brief interictal intracranial EEG can be used to localize SOZ; instead of ictal EEG, clinicians may rely

on brief interictal data to delineate SOZ. Multiple stereo-EEG features such as ripples, fast ripples, interictal spikes, and slowing are incorporated to localize SOZ. We also carried out multi-scale analysis by grouping neighboring contacts of the same electrode. In order to validate the performance, leave one patient out crossvalidation was performed with all possible combinations of EEG features, and all possible group sizes. We are able to delineate SOZ at the scale of electrodes with 83% accuracy, 85% sensitivity, and 83% specificity on average, and at the scale of individual contacts with 74% accuracy, 82% sensitivity, and 73% specificity on average.

2.2.1 Literature Review

2.2.1.1 EEG Studies on Localization of SOZ

Most studies on localization of SOZ consider the correlation between a single EEG feature and SOZ. In this section, we briefly review three studies in this field (Andrade-Valença et al., 2012; Jacobs et al., 2016; Warren et al., 2010), as listed in Table 2.1.

Table 2.1: EEG studies on localization of SOZ.

	EEG type	EEG feature	Remarks
Study 1 (Andrade-Valença et al., 2012)	stereo-EEG	spikes	91% sensitive, 30% specific, 44% accurate
		ripples	91% sensitive, 42% specific, 54% accurate
		fast ripples	66% sensitive, 80% specific, 76% accurate
Study 2 (Jacobs et al., 2016)	stereo-EEG	HFOs	Significantly higher rates of HFOs in SOZ
		spike-related HF power	Spike-related HF power fails to identify SOZ The rate of HFOs identifies SOZ the best
Study 3 (Warren et al., 2010)	ECoG	linear cross-correlation mean phase coherence	lower between SOZ to other regions lower between SOZ to other regions

A. SOZ Localization Study 1 (Andrade-Valença et al., 2012)

In (Andrade-Valença et al., 2012), Andrade-Valença et al. analyze the relationship between HFOs-generating regions and SOZ in epileptic patients without a visible lesion on MRI. Intracerebral EEGs were recorded in 17 patients with intractable focal seizures and normal MRIs. The rates of interictal HFOs and spikes inside and

outside the SOZ are analyzed as well as the specificity, sensitivity and accuracy of HFOs and spikes to determine the SOZ.

The mean rate of spikes, ripples and fast ripples is higher in the SOZ than in the non-SOZ channels. In regard to the identification of SOZ, Andrade-Valenca et al. build a simple system to identify the SOZ based on each feature by counting the channels with occurrence of such feature (i.e., threshold at 0). Concretely, the sensitivity is computed as $[\text{SOZ channels with feature } x / (\text{SOZ channels with feature } x + \text{SOZ channels without feature } x)] \times 100$, similarly for the computation of specificity and accuracy. As a result, the sensitivity is 91% for spikes, 91% for ripples and 66% for fast ripples, the specificity is 30% for spikes, 42% for ripples and 80% for fast ripples, and the accuracy is 44% for spikes, 54% for ripples and 76% for fast ripples.

HFOs are less sensitive but much more specific and accurate than spikes to delineate the SOZ. However, this study did not consider automated classification of the SOZ based on multiple EEG features, whereas our study explores this topic.

B. SOZ Localization Study 2 (Jacobs et al., 2016)

In (Jacobs et al., 2016), Jacobs et al. analyze how well the rate of HFOs and spike-related high frequency (HF) power changes are correlated with SOZ. The data set consists of 583 channels (68 in the SOZ) sampled from 14 patients who underwent intracranial EEG recording. All events (spikes, HFOs) are manually extracted.

Study 2 investigates whether the rate of visually-marked HFOs and spike-related HF power changes differ between SOZ and non-SOZ channels. Significantly higher rates of HFOs are found in SOZ than non-SOZ (ripples: $19.20 \pm 36.79/\text{min}$ vs. $6.29 \pm 18.72/\text{min}$, $p < 0.001$; fast ripples: $6.95 \pm 29.24/\text{min}$ vs. $0.31 \pm 3.10/\text{min}$, $p < 0.001$). Spikes are significantly more frequent in areas of SOZ ($14.93 \pm 21.59/\text{min}$) than non-SOZ ($3.69 \pm 8.43/\text{min}$, $p < 0.001$). The degree of spike-related HF power augmentation fails to differ between SOZ and non-SOZ, whereas that of post-spike HF power attenuation is significantly more severe in SOZ, compared to non-SOZ.

With regard to the identification of SOZ channels, Jacobs et al. observe a large variability between patients for different feature, i.e. , each feature identifies SOZ most indicatively just for a small subset of patients. None of the measures is helpful to identify the SOZ even in three patients. There is no numerical results available directly related to localization accuracy. Instead, Jacobs et al. study the correlation of each feature with the post-surgical outcome. Concretely, the percentage of feature values (total rates, channel portions etc.) in surgically removed region are calculated and compared for patients with seizure-free outcome (Engel 1), vs. those with remaining seizures (Engel 2—4).

Similar to Study 1, this study still investigates the correlation of SOZ with single EEG features, without automated classification of the SOZ based on multiple EEG features, whereas our study explores this topic. In addition, the extraction of the events (ripples, fast ripples, and spikes) is performed manually, whereas it is automated detection in our study.

C. SOZ Localization Study 3 (Warren et al., 2010)

In (Warren et al., 2010), Warren et al. investigate neuronal synchrony in intracranial EEG recordings from four patients with medically resistant partial epilepsy and two control subjects with intractable facial pain. Neuronal synchrony can be altered and in epilepsy may play an important role in the generation of seizures. Linear cross-correlation and mean phase coherence of local field potentials (LFPs) are commonly applied measures of neuronal synchrony and have been studied extensively in epileptic brain. Synchrony measures are computed on four sub-groups of EEG recordings including: SOZ, non-SOZ, bridging (between SOZ and non-SOZ), and control. For both epilepsy and control patients, average LFP synchrony decreases with increasing inter-electrode distance. Results in epilepsy patients show lower LFP synchrony between seizure-generating brain regions and other brain regions. This relative isolation of seizure-generating brain underlies the paradoxical finding that control patients without epilepsy have greater average LFP synchrony than patients

with epilepsy. In patients with focal epilepsy, the region of epileptic brain generating seizures is functionally isolated from surrounding brain regions. This functional isolation may contribute to spontaneous seizure generation and may represent a clinically useful electrophysiological signature for mapping epileptic brain.

Statistical comparisons of features are performed by means of the nonparametric Mann-Whitney test. Boxplots and p -values are applied to evaluate the significance of each feature in distinguishing the four groups of EEG (SOZ, non-SOZ, bridging (between SOZ and non-SOZ)). However, no algorithms nor numerical results are provided for the problem of localization of SOZ, in contrast to our study.

As illustrated in previous sections, most of the EEG studies on localization of SOZ only consider the correlation between the SOZ and single EEG features (spikes, HFOs, or synchrony). No numerical results are presented directly related to localization accuracy in both Studies 2 and 3, while Study 1 build a simple system to localize SOZ by counting the channels with occurrence of a particular feature, without implementing binary classification to localize the SOZ, based on each feature and their combinations. In contrast, we have tested all possible feature combinations in a binary classification scheme. Last but not least, the extraction of the events (ripples, fast ripples, and spikes) is performed manually in Studies 1 and 2, while it is automated in our study.

2.2.1.2 Automated Methods in HFO Detection

In this Chapter, we propose an automated detector for high frequency oscillation (HFO) detections. To validate the performance of this proposed detector, we compare our automated method (labeled as M_3) to two other automated methods (labeled as M_1 and M_2), and to visual analysis, during the interictal period of a sample EEG trace from a patient with epilepsy. The first method (method M_1) (Lévesque et al., 2011; Salami et al., 2012; Staba et al., 2002) detects HFOs by means of the average of the normalized period, the second method (method

M_2) (Salami et al., 2012) detects HFOs by leveraging on the average of the normalized period in 1 sec windows, while our proposed method (method M_3) utilizes the envelope of the normalized period, and recursively detects HFOs (see Section 2.2.4.2).

A. Automated Method M_1

The first method M_1 is commonly applied to detect HFOs during interictal periods (Bragin et al., 2004; Lévesque et al., 2011; Salami et al., 2012; Staba et al., 2002). The filtered traces in each frequency band are normalized by their own average and standard deviation (SD):

$$\text{Normalized EEG} = \frac{\text{Raw}(\text{EEG}) - \text{Avg}(\text{EEG})}{\text{SD}(\text{EEG})}, \quad (2.1)$$

where the EEG waveform reaches a standard threshold, with three consecutive cycles (Bragin et al., 2004; Lévesque et al., 2011) higher than 3 SD above the background mean, the waveform is considered to be an HFO. Moreover, the time lag between two consecutive cycles is between 5 and 12.5 ms for ripples, and between 2 and 4 ms for fast ripples. Figure 2.1 shows a sample trace with HFOs detected by method M_1 .

B. Automated Method M_2

In the method proposed in (Salami et al., 2012), Salami et al. divide the EEG traces first in 1 sec segments. Every 1 sec segment is then normalized by its root mean square (RMS) value:

$$\text{Normalized 1-sec EEG} = \frac{\text{1-sec EEG}}{\text{RMS(1-sec EEG)}}. \quad (2.2)$$

After normalization, oscillations with 3 consecutive cycles with amplitude above 4

Figure 2.1: A sample interictal trace (normalized) is filtered by a bandpass filter at [80–200Hz]. The markers indicate the onset points of the detected HFOs by three automated methods (method M_1 ($\circ$), method M_2 ($\square$), and the proposed method M_3 (∇)); HFOs detected by visual inspection are marked by red dashed rectangles.

SD of the background mean are detected as HFOs. As in method M_1 , the time lag between two consecutive cycles is between 5 and 12.5 ms for ripples, and between 2 and 4 ms for fast ripples. Figure 2.1 also shows the HFOs detected by method M_2 .

C. Benchmark for HFO Detection

To compare the performance of these three automated methods, we have selected a sample EEG trace from a single EEG channel lasting 1 hour. Before applying the three HFO detectors, the EEG signal was bandpass filtered at 80–200Hz. The ground truth was obtained by visual inspection. Specifically, two experts manually annotated the HFO events in the EEG signal. Only those HFO events that were consistently marked by both experts are retained (see Table 2.2).

Table 2.2: The number of HFOs labeled by each of the two experts. The HFO events consistently labeled by both experts are considered as the ground truth.

	HFO count
Rater 1	109
Rater 2	126
Both Raters 1 and 2	108

We evaluate the performance of each detection method by the following metrics: sensitivity, false positive rate, and computational time.. The sensitivity quantifies how accurate the positive events (HFOs) are detected:

$$\text{sensitivity} = \frac{\text{True Positives}}{\text{Total number of Positives}} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}}. \quad (2.3)$$

We also investigate the number of “false positives” (also known as “false alarms”), which is defined as events labeled as HFOs by the automated method but not considered as HFOs by at least one of the experts.

2.3 Materials and Methods

2.3.1 Patient Characteristics and Recording Parameters

14 patients with epilepsy (Table 2.3) with long-standing pharmaco-resistant complex partial seizures had depth electrode implantation at Massachusetts General Hospital. Patients were selected who were known to have seizures with focal SOZ and typical complex partial events often with secondary generalization. All recordings were performed using a standard clinical recording system (Xltek a subsidiary of Natus Medical Inc, Oakville, Canada) with a 500 Hz sampling rate. Analysis of the data from these patients was performed retrospectively under protocols monitored by the local Institutional Review Boards according to NIH guidelines. The position of the electrodes was selected exclusively for clinical reasons. Depth electrodes with multiple contacts (6 or 8) penetrating the brain were placed in order to confirm the hypothesized seizure focus, and locate epileptogenic tissue in relation to essential cortex, thus directing surgical treatment.

Although not as easily amenable to 2D analysis as surface electrodes are, depth electrodes are increasingly used in clinical practice and have the advantage of being

Table 2.3: Characterization of 14 patients with pharmacologically intractable epilepsy participated in this study.

Patient	Age at onset and surgery		Sex	Electrode	Etiology	Clinical seizure onset zones	Resection area(s)		Outcome
1	17	29	M	Bilateral	Post traumatic Epilepsy	Right mesial temporal	Right	anterior temporal	Seizure free
2	21	28	M	Bilateral	Temporal lobe Epilepsy	Bilateral temporal	None		Continued medical management
3	17	45	F	Left	Temporal lobe epilepsy	Left temporal	None		Continued medical management
4	43	45	M	Bilateral	Post-traumatic temporal lobe epilepsy	Bilateral temporal	Right	anterior temporal	Seizure free
5	59	65	F	Bilateral	Temporal lobe Epilepsy	Right subfrontal and left temporal	None		medical management
6	-	49	M	Bilateral	Unknown	Right posterior and dorsal frontal	None		-
7	07	23	F	Bilateral	Unknown	Left posterior frontal and cingulate	Left frontal corticectomy		Seizure free
8	10	27	F	Bilateral	Cortical dysplasia	Left pre-motor	-		-
9	-	31	F	Right	-	Right temporal	-		-
10	8 months	24	F	Bilateral	Orbitofrontal cortical dysplasia	Left orbital frontal	Left frontal		Significantly improved, but with 1-2 seizure per year
11	-	40	M	Bilateral	-	Right temporal and orbital frontal	-		-
12	-	25	F	Bilateral	-	Right temporal	-		-
13	31	41	F	Right	-	Right temporal	-		-
14	42	46	M	Bilateral	Unknown	Left temporal	Left	temporal lobe	Seizure-free over one year.

able to be placed directly into deep structures (e.g. hippocampus and amygdala). Furthermore, by being directly in the brain tissue, they avoid spread pattern and distortions which may be present for recordings done from the pial surface due to unfavorable angles and intervening tissue (Wheless et al., 2009). As a result, we focused on patients implanted with depth electrodes, i.e., stereo-EEG to delineate SOZs. Platinum alloy electrodes are arranged in 6 or 8 contact arrays along the shaft of a depth electrode with 2.5mm length and 5mm center-center spacing (Ad-tech biomedical, Racine, Wisconsin).

2.3.2 Data Preprocessing

Of the entire record, usually spanning several days, blocks of data lasting 1 hour long and separated from seizure activity by at least 24 hours both before and after were selected as representatives of interictal information. Blocks of both awake and sleep periods were selected for 13 patients except one patient with only a single stereo-EEG

record. Before feature extraction, each stereo-EEG signal was z-normalized (mean subtracted, divided by standard deviation). The data was high-pass filtered at 1Hz cutoff frequency, and a 60 Hz notch filter was applied to remove the power-line interference. stereo-EEG channels which were corrupted by significant artifact (as assessed visually) were excluded. We utilized 2 different referential montages, including local common average referential (average of local contacts of the same array subtracted), and global common average referential (average of all the contacts of the same patient subtracted).

One significant difficulty for a study of this type is the determination of a “ground truth”. In this case we relied on a determination of SOZ as performed by a group of clinical electroencephalographers independent from this research and then used for clinical decision making, including which area to resect. Their judgment of electrodes involved in the SOZ was made based on examination of the raw stereo-EEG recordings (ictal and interictal).

2.3.3 Traditional Classifiers

In order to select the proper classifier that suits our data analysis, we have applied six commonly used classifiers, including the support vector machines (SVMs) (Cristianini and Shawe-Taylor, 2000; Friedman et al., 2001), decision trees (DT) (Dietterich, 2000; Quinlan, 1986), linear discriminant analysis (LDA) (Izenman, 2013), the k -nearest neighbors (kNN) (Riley et al., 2009), the naive Bayes (NB) (Murphy, 2006; Zhang, 2004), and the adaptive boosting (AdaBoost) method (Freund and Schapire, 1995).

We tested the six classifiers on 50 EEG records, and assessed their performance by 5-fold crossvalidation. Before discussing the results for the six classifiers, we briefly review each of these classifiers in Sections 2.3.3.1 to 2.3.3.6.

2.3.3.1 Support Vector Machines (SVM)

In binary classification, a support vector machine (SVM) (Cristianini and Shawe-Taylor, 2000; Friedman et al., 2001) classifies data by finding the best hyperplane that separates all data points of one class from those of the other class. The best hyperplane for an SVM means the one with the largest margin between the two classes, with margin the maximal width of the slab parallel to the hyperplane that has no interior data points. The support vectors are the data points that are closest to the separating hyperplane; these points are on the boundary of the slab. Figure 2.2 illustrates these definitions, with “+” indicating data points of type 1 (positive class), and “−” indicating data points of type −1 (negative class).

Figure 2.2: SVM definitions.

Mathematically, following the discussions in (Cristianini and Shawe-Taylor, 2000; Friedman et al., 2001), the data for training is a set of points (vectors) x_j along with their categories y_j . For some dimension d , the $x_j \in R^d$, and $y_j = \pm 1$. The equation of a hyperplane is given by:

$$f(x) = x'\beta + b = 0, \quad (2.4)$$

where $\beta \in R^d$ and b is a real number. The following formulation defines the best

separating hyperplane (i.e., the decision boundary): Find β and b that minimize $\|\beta\|$ such that for all data points (x_j, y_j) ,

$$y_j f(x_j) \geq 1. \quad (2.5)$$

The support vectors are the x_j on the boundary, those for which $y_j f(x_j) = 1$. For mathematical convenience, the classification is usually formulated as an equivalent problem of minimizing $\|\beta\|$. To find the optimal solution $(\hat{\beta}, \hat{b})$, we multiply each constraint by positive Lagrange multipliers α_j , and include these terms into the objective function:

$$L_P = \frac{1}{2} \beta' \beta - \sum_j \alpha_j (y_j (x_j' \beta + b) - 1), \quad (2.6)$$

where we search for stationary points of L_P over β and b . Setting the gradient of L_P to 0, we obtain

$$\beta = \sum_j \alpha_j y_j x_j, \quad \sum_j \alpha_j y_j = 0, \quad (2.7)$$

and substituting these expressions into L_P , we obtain the dual L_D :

$$L_D = \sum_j \alpha_j - \frac{1}{2} \sum_j \sum_k \alpha_j \alpha_k y_j y_k x_j' x_k, \quad (2.8)$$

which is maximized over $\alpha_j \geq 0$. In general, many α_j are 0 at the maximum. The nonzero α_j in the solution to the dual problem define the hyperplane, as seen in Equation 2.7, which determines β as the sum of $\alpha_j y_j x_j$. The data points x_j corresponding to nonzero α_j are referred to as support vectors. The derivative of L_D with respect to a nonzero α_j is 0 at the optimum. This gives $y_j f(x_j) - 1 = 0$. In particular, this leads to the value of b at the solution, by taking any j with nonzero α_j . Eventually, the optimal solution $(\hat{\beta}, \hat{b})$ enables classification of a sample z as follows:

$$\text{class}(z) = \text{sign}(z' \hat{\beta} + \hat{b}) = \text{sign}(\hat{f}(z)), \quad (2.9)$$

with $\hat{f}(z)$ the classification score.

2.3.3.1 Decision Trees (DT)

Decision trees (Dietterich, 2000; Quinlan, 1986), or “classification trees” and “regression trees”, predict responses to data. To predict a response, one needs to follow the decisions in the tree from the root node down to a leaf node. The leaf node contains the response. Classification trees give responses that are nominal, such as “true” or “false”. Regression trees give numeric responses. Each step in a prediction involves checking the value of one predictor (variable). For example, Figure 2.3 depicts a simple classification tree.

Figure 2.3: A simple decision tree.

This tree predicts classifications based on two predictors (features), x_1 and x_2 . To predict, one starts at the top node, represented by a diamond ($\diamond$). The first decision is whether x_1 is smaller than 0.5. If so, one follows the left branch, leading to a leaf node with label “0”. Consequently, the data is labeled as “0”. If, however, x_1 exceeds 0.5, one needs to follow the right branch to the lower-right diamond node. At this node, it is verified whether x_2 is smaller than 0.5. If so, one needs to follow the left branch to see that the tree classifies the data as label “0”. If not, one takes the right branch to see that the tree classifies the data as label “1”.

In this study, we apply decision tree with binary splits for classification. To create decision trees, we examine all possible binary splits on every predictor (feature). We select a split that maximizes the impurity gain ΔI at node t :

$$\Delta I = P(T)i_t - P(T_L)i_{t_L} - P(T_R)i_{t_R}, \quad (2.10)$$

where $P(T) = \sum_{j \in T} w_j$ is the estimate of probability that a sample is in node t , with w_j the weight of sample j , T the set of all sample indices in node t ; without specifying any priors, $w_j = 1/n$, with n the sample size. The impurity of the node t is quantified by the Gini's Diversity Index (gdi) (Jost, 2006):

$$i_t = 1 - \sum_k p^2(k), \quad (2.11)$$

with $k \in \{\text{type 0, type 1}\}$ the binary class labels, $p(k)$ the fraction of class k samples in node t . The lower the value of i_t , the purer the samples in node t ($i_t = 0$ for a pure node with all samples belonging to the same class). The subscripts R and L represent the right and left child nodes after the binary split at node t .

We repeat the same procedure recursively for the two child nodes. We stop splitting when any of the following holds:

- The node is pure, containing only samples from the same class.
- There are less than L_1 samples to split in this node.
- If any further split imposed on this node will produce child node with less than L_2 samples.
- The algorithm exceeds L_3 nodes (number of splits).

L_1 , L_2 , and L_3 are user defined parameters to limit the size of the decision tree (here we apply $L_1 = 1, L_2 = 10, L_3 = n - 1$, with n the size of training samples).

2.3.3.3 Linear Discriminant Analysis (LDA)

In discriminant analysis, it is assumed that different classes generate data based on different Gaussian distributions. Each class (Y) generates data (X) via a multivariate normal distribution. In linear discriminant analysis (Izenman, 2013), the covariance matrix is identical for each class, whereas the means are different. With these assumptions, we infer the means by computing the sample means of each class. Then we infer the covariance by first subtracting the sample mean of each class from the observations of that class, and taking the empirical covariance matrix of the result.

Classification with LDA is carried out by minimizing the expected classification cost:

$$\hat{y} = \arg \min_{y=1,\dots,K} \sum_{k=1}^K \hat{P}(k|x) C(y|k), \quad (2.12)$$

where $\hat{y}$ is the predicted classification, and K is the number of classes ($K = 2$ for binary classification). The posterior probability $\hat{P}(k|x)$ of class k for sample x is defined as:

$$\hat{P}(k|x) = \frac{1}{(2\pi|\Sigma_k|)^{0.5}} \exp\left(-\frac{1}{2}(x - \mu_k)^T \Sigma_k^{-1} (x - \mu_k)\right), \quad (2.13)$$

with μ_k , Σ_k the mean and covariance of class k . $C(y|k)$ is the cost of classifying a sample as y when its true class is k , $C(y|k) = 1$ if $y \neq k$, and $C(y|k) = 0$ if $y = k$.

2.3.3.4 Classification Using k -Nearest Neighbors(kNN)

The kNN (Riley et al., 2009)-based classification are widely used as benchmark learning rules. The relative simplicity of the kNN makes it easy to compare with the results from other classification techniques. The kNN has been used in various areas such as bioinformatics, image processing and data compression, document retrieval, computer vision, multimedia database, and marketing data analysis.

To predict the label of a sample x_{new} , kNN classifier first finds the k points $X_k = \{x_1, x_2, \dots, x_k\}$ in the training set X_{train} that are nearest to x_{new} according to the distance measure, and also the k corresponding labels $Y_k = \{y_1, y_2, \dots, y_k\}$ in Y_{train} of those k nearest points. After that, kNN classifier assigns the classification label y_{new} that has smallest expected misclassification cost among the values in Y_k . As binary classification it is in this study, the labels only take two values “1”, or “0”. Therefore, kNN classifier just assigns the classification label with a higher fraction in Y_k . In this study, we apply Euclidean distance as the distance measure, and set $k = 3$ neighbors.

2.3.3.5 Naive Bayes

Naive Bayes (Murphy, 2006; Zhang, 2004) is a classification algorithm that applies density estimation. The algorithm leverages Bayes theorem, and “naively” assumes that the predictors (features) are conditionally independent. Though the assumption is usually violated in practice, naive Bayes classifiers tend to yield posterior distributions that are robust to biased class density estimates (Friedman et al., 2001).

The naive Bayes classifier estimates the parameters of a probability distribution from the training data, assuming predictors are conditionally independent in each class. The naive Bayes algorithm classifies a sample by estimating the posterior probability for each class, and then assigns the sample to the class yielding the maximum posterior probability. Concretely, the posterior probability according to Bayes rule is defined as:

$$\hat{P}(Y = k | X_1, \dots, X_P) = \frac{\pi(Y = k) \prod_{j=1}^P P(X_j | Y = k)}{\sum_{k=1}^K \pi(Y = k) \prod_{j=1}^P P(X_j | Y = k)}, \quad (2.14)$$

with Y the random variable corresponding to the class index of a sample, $X_1, \dots, X_P$ the random predictors of a sample, $\pi(Y = k)$ the prior probability that a class index is k .

2.3.3.6 Adaptive Boosting

Ensembles of classifiers such as adaptive boosting (AdaBoost) are commonly used in data-mining problems with different contexts (Bifet et al., 2009; Shan et al., 2005; Sun et al., 2007). When tackling classification problems of non-stationary concepts, ensembles of classifiers have several advantages over single classifier methods: they are easy to scale and parallelize, they can adapt to change quickly by pruning under-performing parts of the ensemble, and therefore they usually generate more accurate concept descriptions.

AdaBoost is a general method for generating a strong classifier out of a pool of weak classifiers (Freund and Schapire, 1995). The weak classifiers are trained sequentially, and for classifier with index m , AdaBoost computes the weighted classification error:

$$\varepsilon_m = \sum_{n=1}^N d_n^{(m)} \mathcal{I}(y_n \neq h_m(x_n)), \quad (2.15)$$

with x_n denoting the observation, y_n the desired label, h_m the prediction, $\mathcal{I}$ the indicator function, and $d_n^{(m)}$ the weight of observation. AdaBoost then increases the weights for misclassified observations while reducing the weights of correctly classified ones. AdaBoost computes prediction for new data with the score function defined as:

$$f(x) = \sum_{m=1}^M \alpha_m h_m(x), \quad (2.16)$$

where $\alpha_m = 0.5 \log \frac{1-\varepsilon_m}{\varepsilon_m}$ are the weights of the weak predictions. Training of AdaBoost can be viewed as stage-wise minimization of the exponential loss:

$$\sum_{n=1}^N w_n \exp(-y_n f(x_n)), \quad (2.17)$$

with w_n denoting the normalized observation weights, $f(x)$ the predicted classification score for new data.

2.3.4 Interictal Stereo-EEG Features

2.2.4.1 EEG slowing

EEG signals recorded from damaged cortex often seem to be “slower”, i.e., containing more power at low frequencies (Dauwels et al., 2011; Roebuck, 2012). Relative power (RP) is used to quantify this slowing effect by computing the power in the frequency band 1-8Hz, normalized by the total power:

$$RP = \frac{\text{Power}_{[1 \text{ } 8\text{Hz}]}}{\text{Power}_{[1 \text{ } 250\text{Hz}]}}. \quad (2.18)$$

2.2.4.2 High frequency oscillations

High Frequency Oscillations (HFOs) are particular patterns recorded from intracranial electrodes in patients with intractable epilepsy (Akiyama et al., 2011; Andrade-Valenca et al., 2011; Jacobs et al., 2012, 2016; Zelmann et al., 2009). According to the frequency range, HFOs are further divided into 3 subcategories, referred to as ripples (80-200Hz), fast ripples (200-500Hz) and very fast ripples (>500Hz). HFOs can be characterized by oscillations of at least 4 cycles, with a typical duration of 80-100ms for ripples, and 30-50ms for fast ripples. HFOs are believed to be associated with SOZ, with higher rates of HFOs observed in SOZ from interictal intracranial EEG (Andrade-Valenca et al., 2011; Jacobs et al., 2016). Due to the relatively low sampling rate (500Hz), only ripples (80-150Hz) and fast ripples (>200Hz), as shown in Figure 2.4 are of our interest. The HFO detector consists of 3 major techniques:

- **Envelope detection via Hilbert Transform**

The envelope $\hat{x}$ (see Figure 2.5) of a given time series x can be obtained by

Figure 2.4: Interictal stereo-EEG and epileptic-related stereo-EEG features; panels from top to bottom illustrate: raw stereo-EEG, interictal spikes, ripples, and fast ripples extracted from the same segment of stereo-EEG recorded by a depth electrode located in the vicinity of SOZ.

Hilbert Transform (Hahn, 1996):

$$\hat{x}(t) = |x(t) + i(\frac{1}{\pi}P \int_{-\infty}^{\infty} \frac{x(\tau)}{t - \tau} d\tau)|. \quad (2.19)$$

Morphological features such as amplitude and duration are extracted from the envelope $\hat{x}$.

- **Decision making upon amplitude and duration**

According to the definition in (Jacobs et al., 2008), only waveforms with amplitude larger than β ($\beta=5$ for ripples, and $\beta=3$ for fast ripples) multiples of the standard deviation σ_n of the current input signal x_n , and duration within 80-100ms (or 30-50ms), are considered as ripples (or fast ripples).

- **Iterative Process**

The detection process is made iterative as shown in Figure 2.5, such that HFOs newly detected in current stage are removed from the previous input signal x_n , to initiate the new loop of detection. The iteration stops when there are no more HFOs newly detected. Iterations can help to reduce the false negatives due to small-amplitude HFOs. By removing HFOs iteratively, the remaining signal left eventually is the baseline (without HFOs).

Figure 2.5: Block diagram of the proposed HFO detector.

2.2.4.3 Interictal spikes

Interictal spikes are brief morphologically defined events with duration <200 ms, that are paroxysmal and clearly distinguishable from the background, characterized by abrupt changes in polarity and “sharp contours” (see Figure 2.4); they are often observed in EEG of patients with epilepsy (Engel, 2013; Gastaut and Broughton, 1972; Wasade et al., 2015).

Interictal spikes are highly correlated with epilepsy and may potentially be used for diagnostic purpose (Engel, 2013; Sammaritano et al., 1991; Staley et al., 2005). In order to detect the interictal spikes at each stereo-EEG channel, we apply the non-linear energy operator (NLEO), commonly used to estimate the energy content of a

linear oscillator in AM-FM modulation. Due to its accentuation of high frequencies and computational efficiency, NLEO is believed to be an effective spike detector in biomedical signal processing (Mukhopadhyay and Ray, 1998). The NLEO of discrete-time series $x(n)$ is defined as:

$$\Psi(x) = x^2(n) - x(n+1)x(n-1). \quad (2.20)$$

The output of the NLEO is further smoothed by a Gaussian kernel, in order to reduce noise and interference. At last, a hard threshold is applied, where the threshold value is equal to 5 times the mean of the smoothed NLEO output $\tilde{\Psi}(x)$ (Maragos et al., 1993). Consequently, only sufficiently large peaks associated with local maxima are retained, corresponding to rising flanks of spikes (see Figure 2.6).

Figure 2.6: Interictal spike detection by smoothed NLEO.

All features vary considerably across patients, consequently, normalization is needed. We normalize each EEG record separately. Concretely, we first compute the average and standard deviation of each feature within the EEG record (e.g., average number of spikes at different stereo-EEG channels and the corresponding standard deviation), and then we normalize the features by subtracting this record-wise mean and dividing by this record-wise standard deviation.

2.3.5 Multi-scale Analysis: from Individual Channels to Depth Electrodes

2.3.5.1 Analysis of channel groups

Each depth electrode has multiple (6 or 8) contacts/channels, linearly arranged along the electrode. The stereo-EEG signals can be analyzed at the level of the individual channels. Alternatively, it is meaningful to average the signals or features at each depth electrode, across its 6-8 channels, and analyze each depth electrode in terms of average statistics. It is also possible to consider an intermediate scenario, where certain groups of channels are averaged. Concretely, we group neighboring contacts by applying a moving window; the group average is calculated, and is assigned to the central contact of the group. More precisely, we define a window centered at the channel of interest c_i , containing the channel c_i and the r adjacent channels in both directions along the same electrode (see Figure 2.7). The value of r ranges from 0 (individual contact) to $G-1$ (electrode average), where G is the number of contacts at the depth electrode ($G=6$ or 8). Therefore, the values of r are associated with different levels of spatial resolution. Each feature is averaged across the channels inside the window. The average value is signed to the central contact c_i :

$$\bar{f}_i^r = \frac{1}{2r+1} \sum_{k=i-r}^{i+r} f_k. \quad (2.21)$$

with f_k the feature value of contact c_k and $\bar{f}_i^r$ the feature value of contact c_i after smoothing. The SOZ region is smoothed similarly: if at least one of the channels inside the window is located inside SOZ (“positive” channel(s)), the central contact of the window is considered as positive as well.

Figure 2.7: Analysis of channel groups: feature values of an electrode with 8 channels c_1 – c_8 are color-coded, and smoothed by a sliding window defined by width r . For the 4th contact c_4 , the smoothing window at each r value is highlighted in red dotted lines, illustrating the calculation of feature value $\bar{f}_4^r$ of c_4 after smoothing.

2.3.5.2 Decision making: From depth electrodes to individual channels

Detecting SOZ on the level of individual channels is challenging. It is far easier instead to detect the electrodes that are located inside SOZ. To facilitate the detection on the level of individual channels, we first try to detect the electrodes that are located inside SOZ. Then we investigate these electrodes more closely, and examine the stereo-EEG features at the contacts of these electrodes. More precisely, the individual contacts are ranked according to the cumulative density of the contact-wise classification scores. If the cumulative density is above a carefully chosen threshold, the corresponding channel is considered to be lying inside SOZ. As will be explained in the next section, this multi-scale decision making process substantially improves the capability to automatically delineate the seizure focus on the level of individual channels.

2.4 Results

2.4.1 Comparison with the State of Art

2.4.1.1 Benchmark of Classifiers

In order to select the proper classifier that suits our data the best, we conduct benchmark comparisons among six commonly used classifiers including SVM, kNN, DT, LDA, NB, and Adaboost (see Section 2.3.3.1–2.3.3.6). We extract four EEG features (ripple, fast ripple, spike, and slowing on global common average montage) from each channel of all 50 EEG records. We conduct 5-fold cross-validation and compute the average classification error for each classifier as comparison criterion. The average classification loss (or error) for 5-fold cross-validation on six classifiers are list in Table 2.4.

Table 2.4: Benchmark of six classification models.

Classification Loss	
AdaBoost	0.0949
SVM	0.0978
LDA	0.0971
kNN	0.1255
NB	0.1258
DT	0.1350

As shown in Table 2.4, the AdaBoost outperforms the other classifiers with the lowest classification loss. Therefore, in this Chapter, adaptive boosting (AdaBoost) is chosen as our classifier to conduct further analysis.

2.4.1.2 Benchmark Comparison of HFO Detectors

As mentioned in Section 2.2.1.2, we have selected a sample EEG trace to compare our proposed HFO detector M_3 , with two other automated HFO detection methods M_1 and M_2 . The EEG trace contains a single EEG channel lasting 1 hour in ripple

frequency band (80–200Hz). The ground truth was obtained by visual inspection. Specifically, two experts manually annotated the HFO events in the EEG signal. Only those HFO events that were consistently marked by both experts are retained.

Table 2.5: HFO detection results on a sample EEG trace using three automated methods $M_1 - M_3$. As the duration of the given EEG trace is 1 hour, the first four metrics HFO count, true positive (T.P.) count, false negative (F.N.) count, and false positive (F.P.) count also represent the rate values per hour.

	M_1	M_2	M_3 (proposed)	Visual (G.T.)
HFO count	124	5	109	108
T.P.	90	5	105	-
F.N.	18	103	3	-
F.P.	34	0	4	-
Sensitivity	83.33%	4.63%	97.22%	-
Running time	0.0835 sec	0.0864 sec	1.1828 sec	-

Performance metrics such as sensitivity, false positive rate, and running time cost for each method are listed in Table 2.5. The values of the parameters of methods M_1 and M_2 were set as in the literature (Lévesque et al., 2011; Salami et al., 2012; Staba et al., 2002) (see Section 2.2.1.2). As shown in Table 2.5, the proposed HFO detector outperforms the other two methods with the highest sensitivity of 97.22%, and lowest false negative rate at 3/hour. Although method M_2 has the best false positive rate (0), its sensitivity is too low at only 5%, probably due to the high threshold (4 SD above BG mean) set on the amplitude detection. On the other hand, the false positive rate of the proposed HFO detector M_3 is only 4/hour, which is the 2nd best among the three methods. Last but not least, the proposed HFO detector is only slightly more computationally complex than the other two methods; it takes about 1 sec to analyze 1 hour of EEG with 100+ HFOs.

2.4.1.3 Comparison with Existing Methods for Localization of SOZ

As mentioned earlier, most EEG studies explore the correlation between a single EEG feature and SOZ, addressing the problem in a limited manner. In contrast,

here we have investigated multiple EEG features including slowing, ripples, fast ripples, and interictal spikes, and their combinations.

In order to compare our approach with existing methods (Andrade-Valença et al., 2012; Jacobs et al., 2016; Warren et al., 2010), we consider the following criteria: (A) individual feature statistical analysis (mean, SD and p value for Mann-Whitney U-test), in order to check the significance of each EEG feature; (B) Localization by means of binary classification. Concretely, all possible combinations of EEG features are investigated, including single EEG features as in the existing literature (Andrade-Valença et al., 2012; Jacobs et al., 2016). We generate the receiver operating characteristic (ROC) curves, and rank each feature combination according to the classification accuracy, while keeping the sensitivity at 85%. In this way, we can compare our proposed approach to the existing methods, which are built based on single EEG features.

A. Stereo-EEG Feature Statistics

Compared to stereo-EEG signals outside SOZ, stereo-EEG signals inside SOZ exhibit higher interictal spikes rate, ripples rate, and fast ripples rate, and they contain more power at low frequencies. The results are summarized in Table 2.6, and are in agreement with other EEG studies (Andrade-Valença et al., 2012; Jacobs et al., 2016).

Some of our datasets are corrupted with significant common electrocardiogram (EKG) artifacts. We apply the common averaging referential montages to get rid of those artifacts. Synchrony computed in such circumstance is trivial in characterizing SOZ. Therefore, we exclude the synchrony measures in this thesis. In addition, the features vary considerably across patients. To this end, we applied record-wise normalization, as explained in the previous section. We subtract the mean and divide the standard deviation from each feature for a given record. The boxplots for each feature are shown in Figure 2.8. Significant differences ($p \ll 0.05$) can be

Table 2.6: Statistic analysis of stereo-EEG features (unnormalized) for channels inside (“SOZ”, $N_1 = 315$) and outside (“non-SOZ”, $N_2 = 2,825$) the SOZ, with p values computed for the Mann-Whitney U-test; and the average classification results for each stereo-EEG feature at 85% sensitivity.

Feature	SOZ mean $\pm$ std	non-SOZ mean $\pm$ std	p value	Specificity	Accuracy
slowing ₁	0.78 $\pm$ 0.16	0.77 $\pm$ 0.17	4.3E-02	1.6%	10.7%
slowing ₂	0.80 $\pm$ 0.15	0.78 $\pm$ 0.16	3.5E-03	1.8%	11.0%
spike ₁	187.1 $\pm$ 154.4	102.6 $\pm$ 112.6	8.0E-32	16.3%	23.9%
spike ₂	169.6 $\pm$ 147.7	98.6 $\pm$ 106.0	1.8E-27	32.9%	38.3%
ripples ₁	265.4 $\pm$ 275.6	140.5 $\pm$ 246.6	1.5E-29	24.3%	31.9%
ripples ₂	275.8 $\pm$ 255.6	120.1 $\pm$ 184.3	8.4E-40	35.6%	40.9%
fast ripples ₁	163.7 $\pm$ 181.9	87.1 $\pm$ 183.6	2.4E-30	27.5%	33.7%
fast ripples ₂	146.6 $\pm$ 156.6	80.1 $\pm$ 145.6	1.4E-29	12.1%	20.4%

1: on local common average referencing montage

2: on global common average referencing montage

Figure 2.8: Boxplots of (normalized) contact-wise stereo-EEG features, with red boxes and “+” referring to electrodes inside the seizure focus, blue boxes and “−” referring to channels outside the focus (“normal”), and indices “1” and “2” referring to local common average and global common average montage, respectively.

observed for each stereo-EEG feature, indicating that slowing, high frequency oscillations (ripples and fast ripples) and interictal spikes are highly correlated to SOZ. More concretely, stereo-EEG channels inside SOZ contain more energy in the low-

frequency band, and are consistently exhibiting more high frequency oscillations and spikes compared to others.

To investigate the correlation of SOZ with each single feature as in existing literature (Andrade-Valença et al., 2012; Jacobs et al., 2016), we perform leave-one-patient-out classification based on each single feature. The classification specificity and accuracy are listed in Table 2.6, while keeping sensitivity at 85%. As listed in Table 2.6, the ripple rates perform the best (40.9% accuracy) compared to other features. The conclusion is similar to that in (Andrade-Valença et al., 2012; Jacobs et al., 2016), where HFO rates provide the most indicative identification of SOZ. However, 40.9% accuracy is still considered inadequate for localizing SOZ. Is it possible to improve the accuracy? Why not try classification on multiple feature combinations? We will explore this idea in the following section.

B. Feature Selection for Different Spatial Resolutions

In order to select the feature combination with the best localization results, we have tested all possible feature combinations starting from $d = 1$ feature, to $d = 8$ features, from the pool of features. As there are 4 features on 2 referential montages, altogether there are 8 features and ${}^1C_8 + {}^2C_8 + \dots + {}^8C_8 = 255$ different feature combinations.

On the other hand, we are also interested in the impact of spatial resolution on the classification performance. Therefore, we group adjacent contacts on the same electrode in a window with width r , and average the corresponding EEG features, as explained in Section 2.3.5. For each r value, all possible combinations of stereo-EEG features were tested with leave-one-patient-out validation.

The receiver operating characteristic (ROC) curve is a graphical plot that illustrates the performance of a binary classifier as its discrimination threshold is varied; it is generated by plotting the sensitivity against the false positive rate at various threshold settings. The ROC curve is obtained for all possible combinations of features

Figure 2.9: Receiver operating characteristic (ROC) curves for all possible combinations of features. Classifiers are ranked according to specificity while the sensitivity is kept at 85%; the larger the specificity, the better the performance.

and for the values of window size $r = 0, 1, \dots, G - 1$. As illustrated in Figure 2.9, there are $255 \times 8 = 2040$ different classifiers and corresponding ROCs. In order to select the optimal classifier, we set the sensitivity at 85% (see dotted horizontal red line in Figure 2.9), and rank each classifier according to its specificity (or accuracy). For each window size r , there are multiple $({}^dC_8)$ options available for each d -feature combination for binary classification. Due to space constraints, only the classifier with the highest average specificity is shown in Figure 2.10 for each (r, d) combination.

As shown in both Table 2.6 and Figure 2.10, for single EEG features, channel-wise detection ($r = 0$) only yields 41% accuracy at best (ripple rate on global CAR). Single stereo-EEG features ($d = 1$) are not adequate to localize SOZ. The accuracy is less than 60% when the smoothing window is small ($r < 4$). The specificity is less than 50%, indicating over half of the stereo-EEG channels outside SOZ are

Figure 2.10: Average performance: accuracy (top panel), and specificity (bottom panel) for each (r, d) combination, while the sensitivity is kept at 85%. For each d -feature combination, only the classifier with the largest average specificity is selected.

wrongly classified as lying inside SOZ. The highest classification accuracy for a single feature ($d = 1$) occurs at the maximum degree of smoothing with $r = 7$ (contact-average) with 73.95% accuracy and 72.83% specificity on average.

With more stereo-EEG features (increasing d), the average accuracy and specificity improve. However, it deteriorates gradually for larger d values, probably due to overfitting. The best performance for each window size r occurs when d takes values between 2 and 4. On the other hand, the larger the window size r , the better the classification, regardless how many features are used.

Among all possible (r, d) combinations, the best performance occurs at contact average $r=7$, using $d=3$ stereo-EEG features (fast ripples on local common average, spike and slowing on global common average), with 85.0% sensitivity, 75.86% specificity, and 78.12% accuracy on average. The classification results for each individual stereo-EEG are shown in Figure 2.11.

Figure 2.11: Individual stereo-EEG classification metrics: accuracy (top), sensitivity (middle) and specificity (bottom), from the optimal classifier selected the highest average specificity in Figure 2.10, when $r=7$ and $d=3$ (fast ripples on local common average, spikes and slowing on global common average). The status of stereo-EEG record is indicated by the edge of the bar: either asleep (dashed line) or awake (solid line). Alternative red and blue colors are used to distinguish stereo-EEG of adjacent patients.

Although the contact average data along the electrode ($r=7$) can provide us a localization accuracy of 78.12%, there is hardly any structural information attached, i. e., how deep/far along the electrode (brain tissue associated) is suspected, as all the contacts of the same shaft have the same classification. On the other hand, the contact-wise ($r=0$) data can offer the best spatial resolution, but the performance

is only 61.97% average accuracy. As illustrated in Figure 2.11, the system fails for a small group of stereo-EEG, with low sensitivity (such as P5–7, P10 and P11). We further analyze those stereo-EEG recordings to investigate the possible causes. As will be explained in the next section, a priori stereo-EEG rejection is conducted before training the classifiers, consequently improving the overall performance.

2.4.2 A Priori Rejection of Stereo-EEG Recordings

We observe low sensitivity for certain stereo-EEG recordings, indicating the system has missed most of the channels in SOZ. In order to investigate the reason of failure, we carefully examine each stereo-EEG, feature values, and the corresponding clinical report that was generated independently from this study. There are various possible sources contributing to such cases (see Figure 2.12): (i) poor feature quality when the classic stereo-EEG signatures fail to characterize SOZ. For instance, active interictal spikes and HFOs are observed in channels outside SOZ; (ii) significantly large artifacts interfered with the stereo-EEG data.

In order to purify the train datasets and consequentially improve the classification, we carefully reject a few stereo-EEG segments before training the classifier. The clinical report is of the most priority to follow during this priori rejection process: a stereo-EEG record is rejected, only if it is with known odd interictal spike events and/or significantly large artifacts that is indicated explicitly in the clinical report.

As listed in Table 3.3, we have found 8 stereo-EEG segments from 3 subjects that satisfy the above rejection criteria. Please note that stereo-EEG feature values are listed here only as the evidence from quantitative stereo-EEG analysis, to validate and support the statement in the clinical report. None of them are used to reject any stereo-EEG recordings during this prior rejection process. The clinical report generated independently from this study is the only truth to follow. For instance, stereo-EEG segments from subject P5 are rejected due to odd interictal spike events

Table 2.7: stereo-EEG recordings rejected during priori classification rejection.

	Cause of rejection	
	Clinical report	Automated stereo-EEG analysis
All 4 records of P5	Active interictal spikes found in left frontal lobe electrodes that are outside SOZ	stereo-EEG features (*SOZ/**non-SOZ) - interictal spikes: 52.1/103.5 (ICAR), 98.6/120.3 (gCAR) - ripples: 56.9/82.3 (ICAR), 86.0/99.8 (gCAR) - fast ripples: 23.7/23.0 (ICAR), 32.3/29.5 (gCAR)
All 3 records of P10	Rhythmic slowing onsets and active interictal spikes found in left temporal lobe electrodes that are outside SOZ	stereo-EEG features (*SOZ/**non-SOZ) - interictal spikes: 19.0/490.3 (ICAR), 23.7/445.8 (gCAR) - ripples: 62.3/1357.5 (ICAR), 45.0/1358.2 (gCAR) - fast ripples: 20.3/1181.6 (ICAR), 96.7/1090.0 (gCAR)
One record of P11	Significantly large recording artifacts	-

ICAR: local common average montage. gCAR: global common average montage

* the average of channels inside SOZ

** the average of abnormal channels outside SOZ mentioned in the clinical report

mentioned in the clinical report. Active interictal spikes are found in left frontal lobe electrodes of P5 stereo-EEG outside SOZ (see Figure 2.12 (top panel)), while the true SOZ electrodes are in the right subfrontal and the left temporal lobe. The statement in clinical report can be further confirmed by our quantitative stereo-EEG analysis, which estimates the rates of events for channels in/outside SOZ. From the numerical results, the rate of interictal spikes in those normal electrodes is >100 /hour, while it is only ~ 50 /hour on average for SOZ electrodes. Similar situation applies to stereo-EEG recordings of subject P10, from whose clinical report active interictal spikes are found in left temporal lobe electrodes outside SOZ, while the true SOZ is the left orbital frontal lobe.

Furthermore, HFOs (ripples and fast ripples) often occur frequently during interictal spikes which may reflect pathological hypersynchronous events (Jacobs et al., 2008). For those channels with high spike rates, normally the rates of ripples and fast ripples are high as well. As shown in Figure 2.12 (middle panel), the rate of ripples of a normal channel outside SOZ is 1988/hour, which is much higher than the average rate of SOZ channels, 62.3/hour. In such cases, the stereo-EEG features fail to characterize SOZ, which forms a paradox to the existing conventional argument that both interictal spikes and HFOs are supposed to be prominent in SOZ. In

Figure 2.12: Evidence from qualitative stereo-EEG analysis to support statement found in clinical report about EEG abnormalities: a channel of P5 outside SOZ with active interictal spikes (top), a channel of P10 outside SOZ with active ripples (middle), and a channel from P11 with significantly large noise (bottom).

addition, significantly large artifacts can be observed from the data of one stereo-EEG recording of subject P11 (see Figure 2.12 (bottom panel)), which is obviously rational to get rejected.

With priori rejection of stereo-EEG, as shown in Figure 2.13, the average performance is improved for each (r, d) combination compared to those before rejection in Figure 2.10. Similar patterns can be observed that the larger the window size r , the better the performance will be. Adding features does not always guarantee performance improvement. For each window size r value, the best performance still occurs with a relatively small number ($d=2$ to 4) of stereo-EEG features. The highest average specificity is from contact-average ($r=7$) with $d=3$ features (fast ripple

Figure 2.13: Average performance with prior stereo-EEG rejection: accuracy (top panel), and specificity (bottom panel) for each (r, d) combination, with the sensitivity of each combination being kept at 85%. For each d number of features, only the combination with the largest specificity is listed.

on local common average, spike and fast ripple on global common average), with 83.23% average accuracy.

2.4.3 Localization by Integrating both Contact-average and Contact-wise Data

Detecting SOZ on the level of individual channels is challenging. As shown in Figure 2.13, the contact-wise ($r=0$) data achieves 69.98% average accuracy at the most, while it is 83.23% for contact-average data ($r=7$). To facilitate the detection on the level of individual channels, we first try to detect the electrodes that are located in SOZ with the contact-average data ($r=7$). Then we investigate these electrodes more closely, and examine the stereo-EEG features at the contacts ($r=0$) of these electrodes. More precisely, the individual contacts are ranked according

to the cumulative density (see Figure 2.15) of the contact-wise classification scores. If the cumulative density is above a carefully chosen threshold, the corresponding channel is considered to be lying in SOZ.

Figure 2.14: Individual stereo-EEG classification metrics: accuracy (top), sensitivity (middle) and specificity (bottom) on the level of individual channels with $r=0$ and $d=3$ features (fast ripples on local common average, spikes and fast ripples on global common average), after applying the contact-average ($r=7$) data to narrow the searching range electrode-wisely first.

More precisely, the individual channels are ranked according to the cumulative density of the channel-wise predicted classification scores. In binary classification, given a sample x , the final decision (either “positive” or “negative”) is made by imposing

a threshold γ on the predicted classification scores $f(x)$ (see (2.3) in Section 2.3.3). If $f(x)$ is larger than γ , sample x is classified as “positive”; otherwise sample x is classified as “negative”. In other words, the larger the value of $f(x)$, the more likely sample x will be classified as “positive”, i.e., “inside SOZ” in our case. As a result, we apply the cumulative density of the channel-wise predicted classification scores $f(x)$ to estimate the likelihood that a channel is inside SOZ. We further set a threshold θ on the cumulative density. If the cumulative density is above θ , the corresponding channel is considered to be lying inside SOZ. We choose the values of θ and γ that correspond to an average sensitivity of approximately 80% ($\theta=0.996$ and $\gamma=0.012$). After incorporating contact-average data, the classification results for each individual stereo-EEG on the level of individual channels are shown in Figure 2.14. This multi-scale decision making process substantially improves the capability to automatically delineate SOZ on the level of individual channels. The localization accuracy on the level of individual channels is improved from 61.97% to 73.81% on average.

We further divide the subjects by anatomic location of SOZ into 2 groups: temporal SOZ and extra-temporal SOZ. For subjects with temporal SOZ (30 stereo-EEG from 9 subjects P1-4, P9, P11-14), the average performance is 74.92% accuracy, 92.08% sensitivity and 72.96% specificity. Among those 30 stereo-EEG recordings, except for 4 (one each from P2 and P11, and two from P9), the sensitivity is 100% for the remaining 26 records. On the other hand, for extra-temporal group subjects (10 stereo-EEG from 3 subjects P6-8), the average performance is 70.25% accuracy, 49.00% sensitivity and 73.17% specificity. There are 3 out of 10 stereo-EEG recordings having 100% sensitivity; 2 subjects (P6 and P8) with multiple stereo-EEG records having average sensitivity $>60\%$, and it is only 13.33% sensitivity on average for P7 (with 2 stereo-EEG having 0% sensitivity). In addition, our results seem to be similar for stereo-EEG recorded when the patient was awake (74.02% accuracy, 79.83% sensitivity, and 72.87% specificity) or asleep (73.62% accuracy, 83.64% sensitivity, and 73.13% specificity).

Figure 2.15: Cumulative density estimation by the percentage cumulative histogram of the contact-wise classification scores.

For each patient, the color-encoded fuzzy likelihood values (i. e., before thresholding) of each depth contact are displayed on MRI brains, as shown in Figures 2.16, 2.17, 2.18, and 2.19, with the clinical-determined “ground truth” displayed on the left-hand-side most panel. Please note these figures are approximations since it is impossible to show the accurate locations of multiple electrodes on a single brain slice. For simplicity, the 3D position of each contact is projected onto the 2D brain slice selected from the MRI.

Figure 2.16: Color-encoded likelihood scores (i.e. before thresholding) of each contact for patients P1, P2, and P3, with the clinical-determined “ground truth” displayed on the left-hand-side most panels in red.

Figure 2.17: Color-encoded likelihood scores (i.e. before thresholding) of each contact for patients P4, P6, and P7, with the clinical-determined “ground truth” displayed on the left-hand-side most panels in red.

Figure 2.18: Color-encoded likelihood scores (i.e. before thresholding) of each contact for patients P8, P9, and P12, with the clinical-determined “ground truth” displayed on the left-hand-side most panels in red.

Figure 2.19: Color-encoded likelihood scores (i.e. before thresholding) of each contact for patients P11, P13, and P14, with the clinical-determined “ground truth” displayed on the left-hand-side most panels in red.

2.5 Summary

In Chapter 2, we have incorporated multiple features as recorded in brief blocks of intracranial depth electrode data (stereo-EEG) to localize SOZ of 14 patients with epilepsy. A binary classification scheme is established employing an adaptive boosting method, and tested via leave-one-patient-out crossvalidation with all possible combinations of stereo-EEG features. A method for rejecting likely outliers is imposed; and a multi-scale analysis of stereo-EEG is used to provide a probabilistic weighting for each stereo-EEG channel involvement in SOZ. Ultimately, the likelihood of a certain stereo-EEG channel being in SOZ is estimated using the cumulative density of the contact-wise classification scores.

◇ *Stereo-EEG features: Single or multiple?*

In this thesis, 4 different stereo-EEG features: slowing, ripples, fast ripples, and interictal spikes are analyzed on 2 referential montages (local and global common average referential montage). Analysis of 50 stereo-EEG records from 14 patients with epilepsy shows that all these stereo-EEG features are highly correlated with SOZ: for channels inside SOZ, they have more power in low frequency band, fire constantly more high frequency oscillations (both ripples and fast ripples), and interictal spikes. Significant differences can be observed in each EEG feature ($p \ll 0.05$). Our results illustrate that the localizing evidence derived from interictal EEG abnormality may provide valuable additional diagnostic information, identifying a likely SOZ.

The majority of feature-related localization studies under EEG explore the correlation between a single EEG feature with SOZ, addressing the problem in a limited manner. For instance, separate qualitative analysis of ripples, fast ripples, and spikes are conducted in (Andrade-Valença et al., 2012) to localize SOZ. The mean rate of spikes, ripples and fast ripples is higher in the SOZ than in the non-SOZ channels. In addition, HFOs are much more accurate than spikes to delineate the SOZ. A similar study (Jacobs et al., 2016) considers rates of HFOs and spike-related

HF power changes, to study their impact on characterizing the SOZs. The rates of HFOs provide the most informative identification of SOZ. Interictal spikes are the key diagnostic biomarker for epilepsy. The presence of spikes predicts seizure recurrence (van Donselaar et al., 1992), and allows a physician to make a confident diagnosis of epilepsy and to prescribe appropriate treatment (Fountain and Freeman, 2006; Pillai and Sperling, 2006; van Donselaar et al., 1992). It has been proposed that quantitative analysis of interictal spikes might be useful for delineation of SOZ (Andrade-Valenca et al., 2011; Hufnagel et al., 2000). There are also studies (Schevon et al., 2007; Warren et al., 2010) focusing on neuronal synchrony in localizing SOZ. However, some of our datasets are corrupted with significant common electrocardiogram (EKG) artifacts. We apply the common averaging referential montages to get rid of those artifacts. Therefore, synchrony is under-estimated to certain degree. Synchrony computed in such circumstance is trivial in characterizing SOZ. That is why we exclude the synchrony measures in this thesis.

Although all these literatures mentioned above could reveal the value of a certain EEG feature in interpreting SOZ, and compared with one another, none of these studies have combined multiple features or even tested all possible combinations. While in this study, we have the chance to test any possible combination of multiple features and identify the combination with the best accuracy. Our results show that multiple features can improve the overall localization performance compared to each single EEG feature. However, adding features does not always guarantee improved performance; the performance gradually starts deteriorating from a certain number of stereo-EEG features (see Figures 2.10 and 2.13), probably due to over-fitting (Dauwels et al., 2011; Duda et al., 2012).

◇ *Anatomy locations: Temporal or extra-temporal?*

According to the anatomy locations of SOZ, subjects can be subdivided into two groups: temporal SOZ and extra-temporal SOZ. The proposed system works better on subjects with temporal SOZs compared to those with extra-temporal SOZs. For

subjects with temporal SOZs (30 stereo-EEG from 9 subjects), the average performance is 92.08% sensitivity and 72.96% specificity, while for extra-temporal SOZ group subjects (10 stereo-EEG from 3 subjects), the average performance is 49.00% sensitivity and 73.17% specificity. This might be explained as certain EEG SOZ features associated with the anatomic location and its connections independent of the pathology. The variety of those stereo-EEG features might be more characteristic for temporal than extra-temporal SOZs. The existence of such differences suggests that the underlying anatomy may in part determine such stereo-EEG features.

Localization of temporal SOZs is more accurate than extra-temporal SOZs has also been reported with other imaging modalities. There is a study (Lee et al., 2003) trying to determine SOZ by fluorodeoxyglucose (FDG) PET and subtraction ictal SPECT. Their results illustrate that FDG-PET and subtraction SPECT had localizing value for temporal SOZs, while so little for extra-temporal SOZs. Another study (Spencer et al., 1992) analyzed the frequency and morphological characteristics of the initial EEG manifestations of spontaneous seizures, and found out different features may correlate to different anatomy locations. Studies in (Foldvary et al., 2001; Lee et al., 2000) also proposed that the correlation between certain features and SOZs are distinguishable for different anatomic locations.

In addition, our results seem to be similar for stereo-EEG recorded when the patient was awake (74.02% accuracy, 79.83% sensitivity, and 72.87% specificity) or asleep (73.62% accuracy, 83.64% sensitivity, and 73.13% specificity). The status of stereo-EEG seems to have little influence on the classification, which is in agreement with (Lieb et al., 1980).

◇ *Relevance of Brief Stereo-EEG Analysis for Localizing SOZ*

Most research studies investigate relatively long recordings, often in order to capture seizure activity. Methods to reduce the duration of intracranial data needed could greatly alter the landscape for patient care. In this study, we demonstrate that brief interictal intracranial stereo-EEG (one hour) can be used to localize SOZ. From

our numerical results on 14 patients, we are able to delineate SOZ (channel-wise) with 82% sensitivity, 73% specificity, and 74% accuracy on average, compared to the clinically determined SOZ.

Chapter 3

Rapid Annotation of Interictal Epileptiform Discharges via Template Matching under Dynamic Time Warping

3.1 Introduction

EEG interpretation relies on experts who are in short supply. There is a great need for automated pattern recognition systems to assist with interpretation. However, attempts to develop such systems have been limited by insufficient expert-annotated data. To address these issues, we developed a system named *NeuroBrowser* for EEG review and rapid waveform annotation. At the core of *NeuroBrowser* lies a new algorithm that performs ultrafast template matching under Dynamic Time Warping, which substantially accelerates the task of annotating waveforms. Our results demonstrate that, *NeuroBrowser* can reduce the time required for annotation of interictal epileptiform discharges by EEG experts by 20 – 90%, with an average of approximately 70%. While the algorithm is currently tailored to the annotation of

interictal epileptiform discharges, it can be readily generalized to other waveforms and signal types.

3.2 Background

Electroencephalography (EEG) is the primary diagnostic test for epilepsy. EEG involves recording of the brain’s electrical activity from sensors placed on the scalp; it is a measure of voltage fluctuations resulting from the ionic current flow within the neurons of the brain. EEG provides a continuous measure of cortical function with excellent temporal resolution.

Significant efforts (manpower, money, and time) are spent on interpreting EEG data for clinical purposes. Approximately 10-25 million EEG tests are performed annually worldwide (Encyclopedia of Surgery, 2014). The duration of EEG recordings ranges from 30 minutes to several weeks. While in current clinical practice, visual inspection and manual annotation are still the gold standard for interpreting EEG, this process is tedious and ultimately subjective. For instance, the agreement rate for interictal discharges has been found to be as low as 60% between electroencephalographers for certain cases (Wilson and Emerson, 2002). Moreover, experienced electroencephalographers are in short supply (Racette et al., 2014). Therefore, a great need exists for automated systems for EEG interpretation.

The finding of primary importance for the diagnosis for epilepsy is the presence of interictal epileptiform discharges, also known as “spikes” and “sharp waves”, hereafter referred to collectively simply as “spikes(s)”. The International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) describes spikes as a subcategory of “epileptiform pattern”, in turn defined as “distinctive waves or complexes, distinguished from background activity, and resembling those recorded in a proportion of human subjects suffering from epileptic disorders...” (Chatrian et al., 1974). Automated spike detection would be faster, less

Figure 3.1: 200 interictal epileptiform spikes chosen at random from the database of 35,000+ spikes of 303 patients. Clearly a large variety exists in the morphology of the spikes.

expensive, more objective, and potentially more accurate. Automated spike detection would enable wider availability of EEG diagnostics and more rapid referral to qualified physicians who can provide further medical investigation and interventions. However, spikes are difficult to detect in an automated manner due to the large variability of spike waveforms within and between patients (see Figure 3.1) among other factors.

Figure 3.2: Interictal epileptiform spikes: each row presents 10 spikes (blue) extracted using a spike template (red) from the EEG recording of one out of 15 patients. For each patient, the spikes have morphology similar to the template.

Great attempts have been made to detect spikes by general classifications such

as mimetic, linear predictive and template based methods. Many current spike detection algorithms apply multiple methods with various emphases such as the local context, morphology, the field of the spike, artifact rejection, and larger context (Wilson and Emerson, 2002). Unfortunately, these methods have not been validated on a large dataset and consequently are not universally accepted. The most critical hurdle to developing an effective algorithm for spike detection is the lack of a sufficiently large database of expert-annotated spike waveforms. To date, no algorithmic approach has overcome these challenges to yield expert-level detection of spikes primarily due to: (i) the intense labor and expense required to gather a sufficiently large and diverse collection of examples of spikes as training examples; and (ii) the lack of rigorous validation on large numbers of prospectively collected EEG, leading to physician mistrust of and failure to adopt published algorithms. A review study (Wilson and Emerson, 2002) has compared a list of various spike detection methods.

The brute-force approach to generating such a database is to manually annotate numerous EEG records. However, exhaustive manual annotation of spikes is prohibitively time-consuming, especially for EEG recordings with large numbers of spikes (up to thousands per hour). The time and labor required severely limits the willingness of EEG experts to help establish a large database of annotated spikes. At present, no technology exists to enable rapid waveform annotation in EEG recordings.

The main contribution of Chapter 3 is that we developed a novel system that dramatically accelerates the process of acquiring expert-annotated EEG records. This system, named *NeuroBrowser*, includes a graphical user interface designed for EEG review and rapid waveform annotation. The algorithm underlying *NeuroBrowser* is based on the observation that, within the same patient, spikes typically share a similar morphology (as shown in Figures. 3.2 and 3.3).

With suitable choice of similarity measure and spike templates, it is possible to extract many more similar candidate waveforms from the same EEG record in less

Figure 3.3: Dynamic Time Warping distance of spikes (red) and background EEG (blue) extracted from the EEG recordings of 15 patients. The histograms are normalized to sum to one. The X -axis corresponds to the DTW distance. The Y -axis shows the normalized counts.

time. Rather than annotating one spike at the time, groups of spikes (typically 10-100 spikes) can be annotated by template matching, accelerating the annotation process. *NeuroBrowser* includes a fully functional EEG viewer plus a custom-built algorithm for template matching to enable rapid waveform annotation. In our first attempt (Jing et al., 2014), we applied the Euclidean Distance (ED) as the similarity measure. However, the ED is sensitive to small variations in waveforms, and

often fails to “match” waveforms that share strong morphological similarity, limiting annotation speed. In order to improve the performance, we consider a more powerful similarity measure: Dynamic Time Warping (DTW) (Berndt and Clifford, 1994; Keogh and Ratanamahatana, 2005; Müller, 2007). Specifically, a modification of the *Trillion* algorithm from the UCR (University of California, Riverside) suite (Rakthanmanon et al., 2012) is employed here for rapid similarity search under DTW. Annotation speed is improved drastically as a result.

A related system (hereafter referred to collectively simply as the “*Self-Adapting System*”) has been proposed in (Lodder and van Putten, 2014), which also integrates the concept of template matching together with user assessment to iteratively refine the detection results while populating the database of templates. The *Self-Adapting System* is not dependent on user-selected templates in the actual application, while for *NeuroBrowser*, the user does need to define a specific template for the EEG recording at hand. Rather than a specific template, the detection in *Self-Adapting System* is made based on the similarities in detected transients in naive EEGs that are subsequently compared to templates collected from other recordings. During user assessment, the system only shows the top 10 candidate spikes to the user that have the best agreement with any of the templates in the database. After that, the system learns from the user, as he/she agrees, disagrees or is uncertain about the 10 candidates presented. In addition, correlation is used as the similarity measure in *Self-Adapting System*, and the candidate spikes are assessed by the user one at a time. By contrast, we achieve much faster assessment by a variety of strategies, including preprocessing, DTW, and clustering of spikes.

Our experimental results show that *NeuroBrowser* is able to save EEG experts an average of approximately 70% of the time spent on annotating spikes, relative to conventional unassisted annotation. We have already extracted 35,000+ spikes from 303 patient EEG recordings. To our knowledge this represents the largest annotated database of spikes in existence. While the algorithm is currently tailored to annotation of spikes in scalp EEG recordings, the concepts can be easily generalized to

other waveforms and signal types.

3.3 Materials and Methods

3.3.1 Clinical EEG Data

We consider EEG data from 303 patients with known epilepsy at Massachusetts General Hospital. Each recording lasts approximately 30 minutes and is recorded from 19 scalp electrodes arranged according to the standard international 10-20 system (see Figure 3.4a). All EEG records were down-sampled to 128Hz. This step reduces computational complexity without compromising the ability to visually identify spikes. A digital high-pass filter with cutoff frequency of 0.1Hz and a notch filter at 60Hz were applied to remove artifacts such as baseline drift and power-line interference.

3.3.2 Rapid Waveform Annotation

NeuroBrowser utilizes fast matching to user-selected templates to enable rapid waveform annotation. *NeuroBrowser*'s template matching algorithm is based on Dynamic Time Warping (DTW) as a similarity measure. While DTW is traditionally considered too computationally intensive for real-time applications, we overcome this challenge by taking advantage of a recent breakthrough, the *Trillion* algorithm, that enables ultra-fast DTW-based similarity search. An implementation of the *Trillion* algorithm is publicly available in the UCR suite (Rakthanmanon et al., 2012).

In this Chapter we used a custom-modified version of the core *Trillion* algorithm. *NeuroBrowser* is semi-automated as illustrated in Figure 4.2, in the sense that users are actively involved in 2 types of tasks: (i) the user needs to provide templates for DTW-based matching; (ii) the user needs to accept or reject the suggested

Figure 3.4: Epileptiform EEG: (a) electrodes placed according to the 10-20 system on a 2-dimensional human scalp (top-view); (b) 9 seconds sample from a 19-channel EEG of a subject with epilepsy. Spikes are highlighted in red.

matches. More specifically, the user is required to determine whether the suggested waveforms are indeed spikes. Several strategies have been implemented in *NeuroBrowser* to further improve the efficiency of the matching procedure, as we explain in the following sections.

Figure 3.5: The block diagram of the *NeuroBrowser* system.

3.2.2.1 Template matching via DTW

We begin by defining the data type of interest, time series: A time series T is an ordered list of data points of length N : $T = t_1, t_2, \dots, t_N$. While the source data T is one long time series, we ultimately wish to compare it to shorter segments called subsequences: A subsequence $T_{i,n}$ of a time series T is a shorter time series starts from position i with a length of n , i.e., $T_{i,n} = t_i, t_{i+1}, \dots, t_{i+n-1}$, $1 \leq i \leq N-n+1$. Where there is no ambiguity, we may refer to subsequence $T_{i,n}$ as X , that matches to a “Template” Q of length n . The Euclidean distance (ED) between Q and X , with the same length n , is defined as:

$$\text{ED}(Q, X) = \sqrt{\sum_{i=1}^n (q_i - x_i)^2}. \quad (1)$$

In our first approach (Jing et al., 2014), we applied the ED as a similarity measure for

template matching. The ED is based on a simple one-to-one alignment of waveforms that can be computed rapidly. However, a major problem with ED is the high sensitivity to small variations in the morphology of the waveforms. As illustrated in Figure 3.6a, ED fails to emphasize the essential morphological features of a spike such as the sharp contour. This leads to false recommendations where, relative to a given spike template Q , the non-spike X_1 is ranked closer in similarity than the spike X_2 . Consequently the non-spike X_1 must be rejected by the user and the spike X_2 must be annotated manually at a later stage, slowing down the annotation process. While additional enhancements are able to compensate (Jing et al., 2014), these limitations of ED-based template matching ultimately motivated us to further improve the method by moving to DTW-based similarity search.

Figure 3.6: Matching by means of ED and DTW: (a) Matching according to ED: non-spike X_1 is more similar to spike template Q than spike X_2 . (b) Matching according to DTW: spike X_2 is more similar to spike template Q than non-spike X_1 . Therefore, DTW is a more suitable similarity measure for matching spike templates.

To improve the performance, we replace ED by the Dynamic Time Warping (DTW) similarity measure. DTW permits non-linear distortion of the time axis to achieve better waveform alignments (see Figure 3.6b). In DTW, segments of a time series are aligned with segments of another time series, effectively allowing for matching similar waveforms in spite of small local dilations and stretches of the time axis. DTW first became popular in the speech recognition community, where it has been used to determine whether two speech waveforms represent the same underlying spoken phrase (Sakoe and Chiba, 1978). Since then it has been adopted in many other areas, becoming the similarity metric of choice in many time series analysis applications (Keogh and Pazzani, 2000).

To align 2 time series $Q = q_1, q_2, \dots, q_n$ and $X = x_1, x_2, \dots, x_n$, a warping matrix $D \in \mathbb{R}^{n^2}$ is constructed whose entries $D_{i,j}$ are the following:

$$D_{i,j}(Q, X) = |q_i - x_j| + \min(D_{i-1,j}, D_{i-1,j-1}, D_{i,j-1}). \quad (3.1)$$

The optimal warping path (the path marked by blue squares in Figure 3.7b) is obtained within the region constrained by the Sakoe-Chiba Band (Sakoe and Chiba, 1978) with a width of R (typically set to 10% of the signal's length), i.e., the pair of black lines parallel to the diagonal as shown in Figure 3.7b.

3.2.2.2 The UCR suite: Rapid similarity search under DTW

Similarity search is the core subroutine of the majority of time series data mining algorithms. Consequently, the time cost for similarity search is the most common computational bottleneck for virtually all time series data mining algorithms. In spite of dozens of alternatives, there is increasing empirical evidence that the classic DTW measure is the most similarity measure suitable in many domains (Ding et al., 2008).

Although DTW yields good matches, it is computationally expensive and thus con-

Figure 3.7: (a) Alignments between two time series by means of ED and DTW, respectively; (b) DTW matrix with the optimal warping path (solid blue squares) obtained by applying the Sakoe-Chiba band with a width of R .

ventionally slow (Alon et al., 2009; Chadwick et al., 2011). The UCR suite draws on four ideas to massively reduce the computational complexity and increase the speed of DTW. As a result, DTW can now be applied to massive datasets, including the EEG data in this Chapter. The four key ideas in the UCR suite to substantially reduce the computational complexity of DTW are:

◇ ***Early abandoning z-normalization***

A classic technique to speed up sequential search with an expensive distance measure such as DTW is to use a cheap-to-compute lower bound to prune off unpromising candidates (Ding et al., 2008; Keogh et al., 2009). The idea here is to interleave early abandoning calculations of the lower bound with online z-normalization to optimize the normalization step. In other words, as we incrementally compute the z-normalization, we can also incrementally compute the lower bound of the same data point. Thus, if we can abandon this computation early, we have pruned not only the distance calculation, but also the normalization steps.

In similarity search of a short query $Q \in \mathbb{R}^{1 \times m}$ in a long time series $T \in \mathbb{R}^{1 \times M}$ and $m \ll M$, one needs to scan over T with a sliding window of length m , moving at a single point (with $m - 1$ points overlap) each time to extract the subsequence X , and compare it to the query Q . Each subsequence X needs to be z-normalized first before it is compared to the query Q , by subtracting the mean, and dividing the standard deviation. Rather than computing the mean μ (or standard deviation σ) with conventional method $\mu = \frac{1}{m} \sum_{i=k-m+1}^k x_i$ (or $\sigma = \frac{1}{m} \sum_{i=k-m+1}^k x_i^2 - \mu^2$) consisting of m additions of x_i (or x_i^2), μ can be obtained by keeping two running sums of the long time series, which have a lag of exactly m values. The computational cost can be reduced from $O(n^2)$ to $O(n)$. The standard deviation σ of the subsequence X can be similarly computed. The formulas are given below for clarity:

$$\mu = \frac{1}{m} \left(\sum_{i=1}^k x_i - \sum_{i=1}^{k-m} x_i \right), \quad \sigma^2 = \frac{1}{m} \left(\sum_{i=1}^k x_i^2 - \sum_{i=1}^{k-m} x_i^2 \right) - \mu^2. \quad (3.2)$$

Online normalization enables early abandoning of the distance computation of the lower bound in addition to the normalization. A high-level outline of the algorithm is shown in Table 3.1, where the online normalization in line 11 allows the early abandoning of the distance computation in addition to the normalization; X can be seen as a circular buffer to store the current subsequence being compared with the query Q .

◇ *Reordering early abandoning*

Instead of the conventional left-to-right ordering to incrementally compute the distance, the UCR suite utilizes a universal optimal ordering. Figure 3.8a shows the conventional left-to-right ordering, in which the early abandoning calculation proceeds. In this case, nine calculations were performed before the accumulated distance exceeded the threshold, and therefore we could abandon. In contrast, a different ordering is shown in Figure 3.8b, which was able to abandon earlier with just five calculations.

Table 3.1: Subsequence search with online z-normalization (Rakthanmanon et al., 2012).

Algorithm Similarity Search	
Procedure $[nn] = \text{SimilaritySearch}(T, Q)$	
1	$\text{best-so-far} \leftarrow \infty, \text{count} \leftarrow 0$
2	$Q \leftarrow \text{z-normalize}(Q)$
3	while !next(T)
4	$i \leftarrow \text{mod}(\text{count}, m)$
5	$X[i] \leftarrow \text{next}(T)$
6	$ex \leftarrow ex + X[i], ex2 \leftarrow ex2 + X[i]^2$
7	if $\text{count} \geq m-1$
8	$\mu \leftarrow ex/m, \sigma \leftarrow \text{sqrt}(ex2/m - \mu^2)$
9	$j \leftarrow 0, \text{dist} \leftarrow 0$
10	while $j < m$ and $\text{dist} < \text{best-so-far}$
11	$\text{dist} \leftarrow \text{dist} + (Q[j] - (X[\text{mod}(i+1+j, m)] - \mu) / \sigma)^2$
12	$j \leftarrow j + 1$
13	if $\text{dist} < \text{best-so-far}$
14	$\text{best-so-far} \leftarrow \text{dist}, nn \leftarrow \text{count}$
15	$ex \leftarrow ex - X[\text{mod}(i+1, m)]$
16	$ex2 \leftarrow ex2 - X[\text{mod}(i+1, m)]^2$
17	$\text{count} \leftarrow \text{count} + 1$

Figure 3.8: (a) Standard early abandon ordering from left to right, with 9 computations required before exceeding the best-so-far; (b) Different ordering allows abandon after just 5 calculations (Rakthanmanon et al., 2012).

It is conjectured that the universal optimal ordering is to sort the indices based on the absolute values of the z-normalized Q . The intuition behind this idea is that the value at Q_i will be compared to many X_i values during a search. However, for subsequence search with z-normalized candidates, the distribution of many X_i values

will be approximately Gaussian, with a mean of zero. Thus, sections of the query that are farthest from the zero mean will tend to have the largest contributions to the distance measure. This universal optimal ordering was validated by comparing it with the empirically determined optimal ordering, yielding a correlation value of 0.999.

◇ *Reversing the query/data role in lower bound computation*

Usually, lower bounds are applied to build an envelope around the query Q , as illustrated in Figure 3.9a. However, as discussed in the next section, envelopes can also be formed around the candidate C (see Figure 3.9b), in a “just-in-time” fashion, to handle the scenario where all other bounds fail to further prune the candidate waveform. This removes the space overhead and, as we will see, the time overhead pays for itself by pruning more full DTW calculations.

Figure 3.9: (a) Lower bound computed based on envelopes U and L around the query Q . (b) Reversing the roles of Q and X such that the envelopes U and L are built around the candidate X (Rakthanmanon et al., 2012).

◇ *Cascading lower bounds*

An efficient strategy to speed up time series similarity search is to use lower bounds to admissibly prune off unpromising candidates. This has led to a flurry of investigations on lower bounds, with at least eighteen proposed lower bounds for DTW (Ding et al., 2008; Keogh et al., 2009; Kim et al., 2001; Sakurai et al., 2005; Yi et al., 1998; Zhang and Glass, 2011; Zinke and Mayer, 2006). The UCR suite applies all of

these lower bounds in cascade. The algorithm first considers the $O(1)$ lower bound $LB_{Kim}FL$, which is a weak but fast-to-compute lower bound that prunes many candidates. If a candidate is not pruned at this stage, the $O(n)$ lower bound $LB_{Keogh}EQ$ is considered. If we complete this lower bound without exceeding the best-so-far, we reverse the query/data role and compute lower bound $LB_{Keogh}EC$. If this bound does not allow pruning, we start the early abandoning calculation of DTW.

3.2.2.3 Further efforts to improve time efficiency

Besides fast DTW template matching, multiple strategies are employed to further improve the time efficiency of template matching. First, while the *Trillion* algorithm available in the UCR suite finds the single best match to any given query waveform, *NeuroBrowser* uses a custom-modified version of *Trillion* (coded by author TR), which returns the top K matches. Second, we preprocess EEGs by down-sampling to 128Hz in order to reduce the computational complexity. This step was based on observations (of the authors MBW and SSC) that visual recognition of spikes in scalp EEG is uncompromised by subsampling to this level. Furthermore, DTW similarity search is limited to the same channel/electrode where the expert-selected spike template is located, based on the observation that within any given patient spikes with similar morphology tend to occur in the same spatial location. In addition, we carry out the following operations to improve time efficiency (in the flowchart in Figure 3.10):

Figure 3.10: Flowchart of the proposed algorithm for rapid waveform annotation.

◇ *Overlap scan*

We carry out post-processing steps to remove overlaps from waveform matches. The output from our customized version of the *Trillion* algorithm is a list of the top K similar waveforms, ranked according to their DTW values relative to a given template. However, there are typically numerous candidates with large overlaps, resulting from the fact that the UCR suite applies a sliding window when extracting waveform candidates. The sliding window has a length of n and moves 1 data point each time along the time series $X = x_1, x_2, \dots, x_N$, with n being the length of the template, and N the length of the input EEG X . For instance, if the n -point candidate $X_m = x_m, x_{m+1}, \dots, x_{m+n-1}$ has a high ranking in the list, it is very likely to find $X_{m\pm 1}$ also in the list with similar rankings. To remove candidates with large overlaps, the list of waveforms is scanned from top to bottom. For each candidate, once it is found to have more than 32 data points (half of the window length) overlapping with any candidate possessing a higher ranking, it is discarded

from the list.

We set the value of DTW parameter K to be 1,000 at first. The overlap scan stops when there are $h = 60$ candidates with less than 32-point overlaps. If there are less than 60 candidates after scanning the list of all $K = 1,000$ waveforms, we discard these $K = 1,000$ waveforms from the input EEG. We then select the next 1,000 DTW-based candidates and repeat the overlap scan to identify more candidates. Ultimately, this process yields at most 60 candidates with less than 32-point overlap, ready to be passed to the user for assessment.

Threshold on feature V_{pp}

As the *Trillion* algorithm also utilizes z-normalization, low amplitude spike candidates are often detected. However, these low amplitude spikes are often determined to be false detections by EEG experts. To eliminate those low amplitude false detections, the peak-to-trough value V_{pp} (see Figure 3.11) is extracted from all 60 candidates after the overlap scan. A threshold is applied such that we only keep candidates with V_{pp} greater than the threshold, which takes the value of $\gamma(V_{pp})_{\min}$, with $\gamma = 95\%$, and $(V_{pp})_{\min}$ the minimum peak-to-trough voltage obtained from existing annotated spikes.

Figure 3.11: The peak-to-trough value V_{pp} of a spike.

Please note that the values of the parameters K , h , and γ were selected by the neurologists for the purpose of convenience and easy implementation, which are also customizable.

◇ *User input to harvest spikes*

The remaining candidates are grouped into clusters of 10 waveforms each (see Figures 3.13 and 3.14), according to the characteristic V_{pp} . The user can then assess the waveforms in the different clusters. The user is given the option to accept an entire cluster at once as true spikes or, if some of the candidates in a cluster are not considered true spikes, the user can mark them accordingly.

3.4 The *NeuroBrowser* System

The current implementation of *NeuroBrowser* includes a MATLAB-based graphical user interface (GUI) designed for review of scalp EEG and rapid waveform annotation. *NeuroBrowser* consists of an EEG viewer, and three modules for providing candidate spikes to the user and collecting assessments from the user.

Figure 3.12: Screenshot of the viewer GUI of *NeuroBrowser*. The EEG recordings are displayed with existing markers if any. Spikes are labeled in red with pink background. Manual annotation can easily be done by left clicking on the target (right clicking to un-select). The current manually selected template is labeled in red with yellow background.

3.4.1 EEG Viewer

As the name suggests, *NeuroBrowser* allows the user to display and navigate through EEG recordings (Figure 3.12). *NeuroBrowser* offers various options to navigate rapidly along the time axis and to vary the display window duration. One can move forward and backward at a fixed step of 5 seconds (with inter-frame overlap) or 10 seconds (without overlap). One can also apply the time slider at the bottom of the GUI to swiftly-shift to any time point. An option is available for the user to navigate by spike events, such that the nearest spike annotated in time (“previous” or “next”) is displayed in the center of the screen.

The gold standard for interpreting EEG in clinical practice is expert visual inspection. To support annotation, we have integrated functions for manual annotation into the EEG viewer. Selection/deletion of waveforms can be easily done by left/right clicking. Montage swap buttons enable easy switching among the three most commonly used referential schemes, i.e., mono-polar, common-average, and bipolar montage, catering to the needs of neurophysiologists to display EEG in different formats.

The main algorithm for rapid waveform annotation is activated by clicking the button labeled “Auto-Template Match”. *NeuroBrowser* utilizes the most recently annotated spike as the template, and executes the *Trillion* algorithm for rapid DTW searching. After processing the results (Figure 3.10), the top 60 similar candidate waveforms are identified and ready for user assessment. In this assessment, the user is required to indicate which of these candidates are true spikes. Finally, spikes approved by the user are automatically indicated in the EEG by colored bars.

3.4.2 Modules for User Input Collection

To display the candidate spikes identified by DTW-based matching, and to collect assessments from the user, *NeuroBrowser* utilizes three sub-GUIs, as illustrated in Figures 3.13, 3.14, and 3.15. One sub-GUI shows the top 60 candidate waveforms in clusters (see Figure 3.13). The candidates are sorted into 6 clusters, according to the peak-to-trough value V_{pp} , with 10 waveforms per cluster. The waveforms in each cluster are overlaid, since these waveforms are usually very similar. The user can assess the waveforms cluster-by-cluster at a glance, and potentially accept an entire cluster as true spikes.

Figure 3.13: Module for displaying candidate spikes and collecting user input, where the top 60 candidate waveforms are displayed in clusters. The waveforms in each cluster are overlaid, since these waveforms are usually very similar.

If the user wishes to see the waveforms in a cluster in more detail, *NeuroBrowser* allows the user to expand a cluster as shown in Figure 3.14, providing a list of

the individual waveforms with detailed information to support the assessments, including both temporal and spatial coordinates, and 10s of context EEG. Another module displays the current spike density on a topographic map (see Figure 3.15), showing the brain regions that exhibit spikes.

Figure 3.14: Expanded list of candidate waveforms from a single cluster.

Figure 3.15: Spike density visualized on a topographic map.

3.5 Annotation Experiments

We conducted annotation experiments to assess how much the *NeuroBrowser* system speeds up spike annotation. Two clinical neurophysiologists from MGH and one EEG expert from NTU were asked to annotate 5 EEG records under 2 different scenarios: (i) manual annotation, and (ii) annotation assisted by *NeuroBrowser*. The time needed for exhaustively annotating all spikes in each EEG was recorded, and summarized in Table 3.2. As can be seen from Table 3.2, on average *NeuroBrowser* is able to reduce the time spent on annotating spikes by approximately 70%.

Table 3.2: Annotation experiments.

EEG	User	Spike number		Time cost [min]		Efficiency measures	
		Manual	DTW-TM	Manual	DTW-TM	Time saved [%]	Speed-up [%]
S1	Expert1	833	890	53.2	8.3	84.4%	640.6%
	Expert2	947	1048	23.0	12.0	47.7%	191.2%
	Expert3	940	934	38.0	5.5	85.6%	692.2%
S2	Expert1	390	388	58	11.3	80.6%	515.5%
	Expert2	800	737	23.3	17.4	25.4%	134.0%
	Expert3	383	391	22.7	4.8	79.0%	475.3%
S3	Expert1	182	179	15.4	6.8	55.8%	226.5%
	Expert2	183	177	17.9	13.4	25.3%	133.8%
	Expert3	159	173	15.4	3.7	75.8%	413.7%
S4	Expert1	1689	1719	108.4	11.5	89.4%	940.2%
	Expert2	1582	1601	26.9	5.5	79.6%	491.2%
	Expert3	1802	1777	61.8	5.5	91.1%	1122.3%
S5	Expert1	292	301	18.9	3.4	81.3%	535.3%
	Expert2	850	874	23.0	10.8	53.2%	213.5%
	Expert3	304	323	17.5	1.2	93.1%	1447.1%
Average						69.8%	554.8%

Though the time savings achievable with *NeuroBrowser* is our focus, the existence of significant variability among experts in the number of spikes detected for the case in Table 3.2 deserves comment. This variability is expected as different experts may have different thresholds for choosing the spikes. As mentioned above, the inter-rater agreement is imperfect (Wilson and Emerson, 2002). Due to the lack of a universal definition, spike detection is ultimately to some extent subjective and dependent on experience. The agreement rate for spikes can be only around 60% between electroencephalographers (well-trained) for certain cases (Wilson and Emerson, 2002). Nevertheless, in clinical practice, the exact number of spikes turns

to be rarely important. In the majority of cases, physicians are most concerned with whether or not spikes are present/absent in a given patient's EEG. This determination is critical to making a confident diagnosis of epilepsy and to prescribing appropriate treatment (Fountain and Freeman, 2006; Pillai and Sperling, 2006; van Donselaar et al., 1992).

We apply 4 different measures (see Figure 3.16) to assess manual vs. semi-automated annotation for these 5 subjects: (i) total time for annotation, (ii) the number of clicks required for acquiring spikes, (iii) the number of spikes obtained from each application of template matching, and (iv) precision (a.k.a. acceptance rate) for each application of template matching.

NeuroBrowser dramatically improves annotation speed for each EEG record compared to manual annotation. To illustrate how this time saving is realized, detailed performance curves are shown in Figure 3.16 for one of the three expert annotators. Figure 3.16a shows substantially less time is required in all 5 cases to perform a complete annotation. As can be seen from Figure 3.16b, the curves for manual annotation are all linear and overlapping with a constant increment at one spike per click. By contrast, semi-automated annotation with *NeuroBrowser* requires much fewer user operations to annotate the same number of spikes. Rather than one spike at a time, *NeuroBrowser* enables spike annotation in batches.

As shown in Figures 3.16c and 3.16d, at the beginning of the annotation the precision is 100% for each application of template matching; this means that all 60 candidate spikes are accepted by the user. Performance starts to deteriorate when the EEG record is almost entirely annotated, since then only a few unannotated spikes remain in the EEG recording. As a result, not all recommendations are true spikes, leading to smaller spike increment and lower precision. Nevertheless, the precision does not drop below 65%, and hence performance remains acceptable.

Figure 3.16: Illustration of time savings of semi-automated annotation on 5 EEG recordings, based on one expert-EEG rater’s annotations: (a) time vs. number of spikes; (b) number of clicks vs. number of spikes; (c) number of spikes vs. number of DTW template matching performed; and (d) precision vs. number of DTW template matching performed.

3.6 Summary

In Chapter 3, we have developed *NeuroBrowser*, an integrated system for rapid waveform annotation. As demonstrated in our numerical results, in comparison with the “gold standard” conventional manual EEG annotation, *NeuroBrowser* is able to save EEG experts approximately 70% on average of the time spent in annotating spikes. Currently, no semi-automated software exists on the market for substantially speeding up the annotation of clinical EEG recordings. Past attempts to create automated spike detection systems have failed primarily due to the intense labor and costs required to gather a sufficiently large and diverse collection of spikes as training

examples, and the lack of rigorous validation on large numbers of prospectively collected EEGs, leading to physician mistrust of and failure to adopt published algorithms. That is probably why visual inspection and manual annotation remain the “gold standard” in clinical practice.

NeuroBrowser employs a suite of signal processing algorithms to enable semiautomated EEG analysis. A core component of *NeuroBrowser* is the Trillion algorithm, which enables, ultrafast template matching under Dynamic Time Warping (Rakthanmanon et al., 2012). The insensitivity of DTW-based similarity search to small dilations and stretches of the time axis, characteristic of variation in many natural signals, allows highly reliable retrieval of waveforms similar to a user-selected example waveform. While the algorithm is currently tailored to annotation of spikes, it can easily be generalized to other waveforms and signal types.

Epileptiform spikes are the key diagnostic biomarker for epilepsy. The presence of spikes predicts seizure recurrence (van Donselaar et al., 1992), and allows a physician to make a confident diagnosis of epilepsy and to prescribe appropriate treatment (Fountain and Freeman, 2006; Pillai and Sperling, 2006; van Donselaar et al., 1992). In practice, physicians detect spikes by visually inspecting 10 – 20 second-long of an EEG signal at a time. EEGs are frequently misinterpreted by neurologists without specialized neurophysiology training (the majority of neurologists interpreting EEGs) (Benbadis, 2007). The difficulty is due to: (i) the wide variety of morphologies of spikes (Figure 3.1), and (ii) the similarity of spikes to waves that are part of the normal background activity and to artifacts, e.g., potentials from muscle, eyes, and the heart. Consequently, many patients go undiagnosed and untreated, or are misdiagnosed by unqualified practitioners, leading to inappropriate medical interventions and avoidable suffering.

Great attempts have been made to detect spikes by general classifications such as mimetic, linear predictive and template based methods. Many current spike detection algorithms apply multiple methods with various emphases such as the local context, morphology, the field of the spike, artifact rejection, and larger context (Wilson

Table 3.3: Spike detection methods.

Literature	Year	Patient number	Spike count
1. (Gotman and Gloor, 1976)	1976	93	>605 ^a
2. (Gotman et al., 1979)	1979	34	>1394 ^a
3. (Guedes De Oliveira et al., 1983)	1983	5/5 ^b	Unknown
4. (Faure, 1985)	1985	Unknown	Unknown
5. (Davey et al., 1989)	1989	1	23
6. (Witte et al., 1991)	1991	1	50
7. (Gabor and Seyal, 1992)	1992	5	752
8. (Gotman and Wang, 1992)	1992	20	Unknown
9. (Hostetler et al., 1992)	1992	5	1393
10. (Sankar and Natour, 1992)	1992	11	Unknown
11. (Pietilä et al., 1994)	1994	6	Unknown
12. (Webber et al., 1994)	1994	10	927
13. (Senhadji et al., 1995)	1995	1? ^c	982
14. (Feucht et al., 1997)	1997	3	1509
15. (Özdamar and Kalayci, 1998)	1998	5	n.a. ^d
16. (Park et al., 1997)	1998	32	n.a. ^d
17. (Dümpelmann and Elger, 1999)	1999	7	2329
18. (Hellmann, 1999)	1999	10	n.a. ^d
19. (Ramabhadran et al., 1999)	1999	6/18	? ^c /982
20. (Wilson et al., 1999)	1999	50	1952
21. (Black et al., 2000)	2000	521	Unknown
22. (Goelz et al., 2000)	2000	11	298
23. (Ko and Chung, 2000)	2000	20	n.a. ^d
24. (Acir and Güzelis, 2004)	2004	18/7	Unknown/139
25. (Xu et al., 2007)	2007	12	957
26. (Oikonomou et al., 2007)	2007	13	333
27. (Ji et al., 2011)	2011	17	>780
28. (Liu et al., 2013)	2013	12	142
29. (Lodder and van Putten, 2014)	2014	8	2,973

^a Total number of spikes not known. Algorithm detections reviewed after processing.

^b N/N format is applied when both training and test sets exist.

^c A “?” after a value denotes uncertainty.

^d The “n.a.” values indicate that the data was presented in a non-standard manner that precluded comparison.

and Emerson, 2002).

Unfortunately, none of them are universally accepted or tested on a significantly large dataset of patents and spikes. To date, no algorithmic approach has overcome these challenges to yield expert-level detection of spikes primarily due to: (i) the

intense labor and expense required to gather a sufficiently large and diverse collection of examples of spikes as training examples; and (ii) the lack of rigorous validation on large numbers of prospectively collected EEGs, leading to physician mistrust of and failure to adopt published algorithms. A review study (Wilson and Emerson, 2002) has compared a list of various spike detection methods. As illustrated in Table 3.3, the largest number of patients that were used to validate the related literature is 521 patients in (Black et al., 2000), however with the total spike count unknown, while in this thesis we have constructed a huge database of 35,000+ spikes from 303 patients. On the other hand, among all these methods with a known spike count, the spike count ranges from 23 – 2,973, which is far less than our number 35,000+. To our knowledge, this is the largest database of expert-annotated spike waveforms established to date. A large database of this type is crucial for training fully automated systems for complex and transient waveform analysis. With this database in hand, we are working to project in the future to develop a general-purpose spike detector.

Chapter 4

Study of Paroxysmal Gamma Waves in Bhramari Pranayama Meditation EEG

4.1 Introduction

Meditation is a fascinating topic that is still relatively poorly understood. In a recent study, strong EEG activity has been observed in the left temporal lobe of Bhramari Pranayama (BhPr) meditators, with more frequent paroxysmal gamma waves (PGWs). In this Chapter, we have applied a procedure to extract PGWs from meditation EEG in an automated fashion. The algorithm is able to identify multiple sources in the brain that generate PGWs. In the meantime, sources associated with different types of PGWs can be distinguished. The effectiveness of this procedure is assessed on seven subjects possessing different degrees of expertise in practicing BhPr. Both power and PGW density were investigated for each subject, revealing brain activities during BhPr meditation. Moreover, we also study the synchrony between PGW sequences, constructing functional connectivity patterns in the brain. Specifically, three synchrony measures: Stochastic Event Syn-

chrony (SES), Schreiber Similarity Measure, and Van Rossum Distance are applied to quantitatively assess the synchrony of pairs of PGW sequences.

4.2 Background

Meditation refers to a broad variety of practices upon training attention and awareness, so as to bring mental processes under greater voluntary control. Practitioners could benefit a lot from meditation practices. For instance, meditation decreases depression, reduces stress and anxiety in general, and helps regulate mood and anxiety disorders (Arias et al., 2006; Davidson and Lutz, 2008; Goyal et al., 2014). Meditation also increases grey matter concentration in areas of the brain involved in learning and memory, regulating emotions, sense of self, and having perspective (Hölzel et al., 2011; Luders et al., 2009). There are various types of meditation techniques, such as Transcendental meditation, Buddhist meditation, and Yoga meditation. Bhramari Pranayama (BhPr) is a yoga type meditation focusing on breath control, with alternative long exhalation periods and short inhalation periods. BhPr may help to ease up the hormonal imbalance manifestation, such as hypertension, anxiety, and abnormal blood pressure (Pandey et al., 2010).

Despite around 50 years of study, the psychophysiological properties and personality traits of meditation still have not been adequately studied (Takahashi et al., 2005; Vialatte et al., 2009). To understand the cortical process and psychophysiological properties of meditation, neuroimaging studies have been carried out to investigate the brain activity during meditation. Several fMRI studies demonstrated that the temporal lobes are active during meditation (Hölzel et al., 2008, 2007; Lazar et al., 2000). EEG studies on meditation have revealed enhanced alpha band activity (Banquet, 1973; Cahn and Polich, 2006; Travis and Wallace, 1999). Active events in gamma band EEG during meditation has also been reported (Lehmann et al., 2001; Lutz et al., 2004; Vialatte et al., 2009); in particular, subjects exhibit more frequent paroxysmal gamma waves (PGWs) in active brain regions. In other

words, PGW can serve as an effective indicator of brain activity during meditation.

The combination of the PGW density distribution during meditation, together with the brain functional mapping may help us to have a better insight of the brain activity during meditation. However, comprehensive PGW marking is subjective, tedious and time-consuming. Earlier studies on meditation EEG have reported enhanced long-range EEG coherence, suggesting stronger coordination of brain activity. For instance, studies of Transcendental meditation (TM) demonstrated enhanced EEG coherence during TM meditation, along with synchronized alpha power in the frontal cortex (Dillbeck et al., 1981; Hebert et al., 2005; Travis and Wallace, 1999). High-amplitude gamma-band oscillations and long-range phase-synchrony were observed as well in the EEG of long-term Buddhist meditators (Davidson and Lutz, 2008; Lutz et al., 2004).

The main contribution of Chapter 4 is the system (Vázquez et al., 2013) developed to extract and sort PGWs from BhPr EEG in an automated fashion. The proposed procedure consists of techniques such as principal component analysis, blind signal separation, and K-means clustering. It is able to identify multiple sources that generate PGWs, and associate sources and so brain regions with different types of PGWs. The proposed method could potentially be generalized to PGWs detection in other contexts, e.g., EEG of other types of meditation; or even epileptiform EEG, as PGW has a shape very similar to that of an inter-ictal spike, which remains a challenging topic in epilepsy study.

We also conducted power analysis of BhPr EEG in different frequency bands to understand the brain activity during BhPr meditation. Furthermore, we explored synchrony in the gamma band between PGWs occurring in different brain regions, leading to functional connectivity patterns in the brain during BhPr meditation. Concretely, we apply multiple synchrony measures: Stochastic Event Synchrony (SES) (Dauwels et al., 2009), Van Rossum Distance (van Rossum, 2001) and Schreiber synchrony (Schreiber et al., 2003) to quantitatively assess the synchrony of pairs of PGW sequences extracted from BhPr EEG.

From our preliminary results, strong EEG activity can be observed in left temporal lobe of BhPr meditator. For each subject, the power and PGW distribution during exhalation periods is stable, while it is far less consistent during inhalation periods. We also identified two different stereotypes of PGWs associated with different brain regions, via unsupervised PGW sorting using K-Means clustering. Moreover, strong local connections can be observed in the temporal lobes for each subject, in addition to long-range inter-hemispheric connections for all three synchrony measures. Consistent connectivity patterns are present in each breathing episode, and visually stable for all three measures. The enhanced synchrony also can be found during meditation sessions.

4.3 Materials and Methods

4.3.1 Bhramari Pranayama Scalp EEG

We consider scalp EEG recorded from seven subjects possessing different degrees of expertise in practicing BhPr: one beginner “*B*” having no experience before, five intermediate subjects “ I_1-I_5 ” trained for a month, and one expert “*E*” trained for 4⁺ months. Scalp EEG was recorded during BhPr sessions, in which each subject performed multiple breathing episodes. During each exhalation period, the subjects would produce a typical sound like a humming bee.

As shown in Figure 4.1b, an ambient sound signal was recorded simultaneously, which allows one to differentiate each breathing period (either exhalation or inhalation). Resting EEG for each subject was also recorded as the control group, during which the subject breathed normally. The EEG recordings were recorded in an electrically shielded room using the standard Biosemi system with 128 active electrodes (as shown in Figure 4.1a). The sampling rate was 2048Hz for all the subjects, except 1024Hz for I_1 . A digital band-pass filter between 15Hz and 85Hz was applied to extract EEG contents of interest. A band-stop filter between 45Hz

Figure 4.1: Scalp EEG (in blue): (a) electrodes placed according to the 10-20 system on a 2-dimensional human scalp (top-view); (b) Ambient sound signal (in black) recorded during BhPr meditation, with high amplitude segments (“h”) corresponding to exhalation periods, and low amplitude segments (“s”) corresponding to inhalation periods.

and 55Hz were applied to remove the power-line interference.

4.3.2 Automated Paroxysmal Gamma Wave Detection

The schematic of the proposed system for artifacts removal and PGW extraction is depicted in Figure 4.2. Principal component analysis (PCA) (Lindsay, 2002) is the first step to deduce the dimensions of the 128-channel EEG data. Blind signal separation (BSS) (Cardoso, 1998) is applied to identify the sources from the EEG with reduced dimensions after PCA. A PGW detector is applied to estimate the PGW rate for each source. Source selection is carried out such that only sources with significant large PGW rate are retained. Finally, the selected sources are back-projected in sensor domain, to reconstruct the 128-channel EEG.

Figure 4.2: Schematics of the proposed procedure for artifacts removal and PGW extraction.

4.2.2.1 Principal Component Analysis

Principal component analysis (PCA) (Lindsay, 2002) is a technique for pattern recognition in high-dimensional data. One major assumption is that the scalp EEG is somehow “redundant”, full of artifacts and irrelevant information. PCA is therefore applied to reduce the dimensions of the data, while preserving the essential patterns. Mathematically, let $Z \in \mathbb{R}^{N \times M}$ denote the N -channel EEG recordings,

where M is the number of samples in each channel. The importance of each eigenvector of the covariance matrix R of Z can be quantified by its associated eigenvalue: the larger the eigenvalue, the more relevant the corresponding eigenvector in interpreting the data. If we denote the eigenvalues of R as $\lambda_1, \lambda_2, \dots, \lambda_N$ (descending order), and the corresponding eigenvectors as $u_1, u_2, \dots, u_N$, the original data Z can be compressed by retaining the top L ($L \ll N$) dimensions. The compressed data $Y \in \mathbb{R}^{L \times M}$ can be obtained as:

$$Y = \begin{bmatrix} u_1 & u_2 & \cdots & u_L \end{bmatrix}^T Z. \quad (4.1)$$

L is constrained by a parameter $\zeta \in (0, 1]$ (we choose $\zeta = 0.95$):

$$\frac{\sum_{i=1}^L \lambda_i}{\sum_{i=1}^N \lambda_i} \geq \zeta, \quad (4.2)$$

4.2.2.2 Blind Signal Separation

Blind signal separation (BSS) (Cardoso, 1998) is a method for source reconstruction from multi-sensor recordings. The word “blind” stresses the fact that the sources are hidden/unobserved, while little information is available about the mixture (Cardoso, 1998). We assume that the compressed data Y , resulting from PCA, is a linear combination of independent sources $X \in \mathbb{R}^{L \times M}$ located under the scalp:

$$Y = AX + N, \quad (4.3)$$

where $A \in \mathbb{R}^{L \times L}$ is the mixing matrix and $N \in \mathbb{R}^{L \times M}$ is the i.i.d. Gaussian noise. We aim at reconstructing the sources X from the observation Y :

$$X = WY, \quad (4.4)$$

where the unknown weight matrix $W \in \mathbb{R}^{L \times L}$ can be identified by one of the BSS methods “Second Order Blind Identification” (SOBI) (Belouchrani et al., 1997) as:

$$\hat{W} = \hat{U}^H [(\lambda_1 - \hat{\sigma}^2)^{-0.5} u_1, \dots, (\lambda_L - \hat{\sigma}^2)^{-0.5} u_L]^H, \quad (4.5)$$

where $\hat{\sigma}^2$ represents the estimated noise variance, computed using resting EEG. The unitary matrix $\hat{U}$ is obtained as joint diagonalizer of the sample estimates.

4.2.2.3 Paroxysmal Gamma Wave Detection

The paroxysmal gamma waves (PGWs) in meditation EEG (see Figure 4.3) can be characterized by distinct high-frequency biphasic patterns, with a sharp peak closed to a neural spike (Vialatte et al., 2009). The large amplitude voltage transients occur at sustained fast rhythms of 10–30 Hz. Manual extraction of PGWs is tedious and time-consuming. To address such problems, we have proposed an automated PGW detector, which exploits morphological aspects of PGWs, as illustrated in Figure 4.3.

The following conditions are evaluated for PGW detection:

- The main peak value V_{p1} should to be larger than multiples of the standard deviation of the signal, i.e. $V_{p1} > \alpha \sigma_x$, with σ_x being the standard deviation of the entire signal and α a scalar.
- The presence of second peak is constrained by the ratio of peak-to-peak values such that: $\rho_1 V_{pp1} \leq V_{pp2} \leq \rho_2 V_{pp1}$, with $\rho_1 < \rho_2 < 1$.
- The trough should be lower than the onset: $V_{on} > V_{tr}$.
- The duration T of the PGW should be smaller than a constant τ .

For each channel (either sensor or source domain), the parameters $(\alpha, \rho_{1,2}, \tau)$ are obtained from 60 true PGW samples extracted from that channel. For each PGW

Figure 4.3: Morphological parameters of a PGW.

sample with index k ($k = 1, 2, \dots, 60$) at channel i , we compute the parameters $\alpha^{i,k}$, $\rho_1^{i,k}$, $\rho_2^{i,k}$ and $\tau^{i,k}$. Extreme values are assigned to each parameter to further extract PGWs remained in that channel, i.e., $\alpha_i = \min_k \alpha^{i,k}$, $\rho_{1,i} = \min_k \rho_1^{i,k}$, $\rho_{2,i} = \max_k \rho_2^{i,k}$ and $\tau_i = \max_k \tau^{i,k}$,

Once all PGWs have been extracted, we apply an unsupervised classifier, specifically binary K-means (Faber, 1994) to sort the PGWs into different clusters. For simplicity, only 2 clusters are applied, with three features extracted for clustering: timing of the main peak T_{p1} and the main trough T_{tr} , and the slope of the rising flank of the main peak.

4.2.2.4 PGW Sources Selection and Back Projection

Sources with a total number of PGWs below a certain percentile Q_λ are discarded, i.e., only sources with significant large number of PGWs are selected. In addition, sources with PGW rate below a certain threshold v are removed as well. In our numerical analysis, we set $Q_\lambda=80^{th}$ and $v=10$ PGWs/sec as in (Vialatte et al., 2009) analyzing the same set of data. After source selection, remaining sources are back-projected in sensor domain. EEG features such as PGW density, power, and synchrony could be extracted afterwards, and visualized on topographic maps, supported by EEGLAB (Delorme and Makeig, 2004).

4.3.3 Power Analysis

EEG can be described in terms of rhythmic activity and transients. The rhythmic activity is divided into bands by frequency. Rhythmic activity within a certain frequency range was noted to have a certain distribution over the scalp or a certain biological significance (Table 4.1). Waveforms are subdivided into bandwidths known as Delta, Theta, Alpha, Beta and Gamma to signify the majority of the EEG used in clinical practice (Tatum, 2014).

We are only interested in Beta and Gamma bands of the “clean” or reconstructed EEG in Section 4.3.2, as the rest EEG bands were attenuated by the digital band-pass filter between 15Hz and 85Hz applied when extracting the PGWs. Digital filters were applied to further split EEG in different frequency bands. Given a time series $x(n), n = 1, 2, \dots, N$, the absolute power can be computed as:

$$P_x^{(i)} = \frac{1}{N} \sum_{n=1}^N x^2(n), \quad (4.6)$$

with $i \in \{Beta, Gamma\}$ representing the EEG band of interest.

Table 4.1: Comparison of EEG bands (Deuschl and Eisen, 1999; Kanayama et al., 2007; Kirmizi-Alsan et al., 2006; Kisley and Cornwell, 2006).

Band	Frequency (Hz)	Location	Bio-significance
Delta	<4	-frontally in adults -posteriorly in children	-adult slow-wave sleep -in babies -continuous-attention tasks
Theta	4–8	-locations not related to task at hand	-higher in children -idling -inhibition of elicited responses
Alpha	8–14	-posterior regions -central sites at rest	-relaxed/reflecting -closing the eyes -inhibition control
Beta	15–30	-frontally	-active calm, intense, stressed, mild obsessive -active thinking, focus, hi alerts, anxious
Gamma	30+	-Somatosensory cortex	-cross-modal sensory processing -short-term memory matching of recognized objects, sounds, or tactile sensations

4.3.4 Synchrony Measures

Synchrony is a hot topic in neuroscience. It is widely debated that the synchronous firing of neurons plays a role in cognition (Varela et al., 2001) and even in consciousness (Singer, 2001). The synchronous firing paradigm has also attracted substantial attention in both the experimental and the theoretical neuroscience literature (Dauwels et al., 2009). In this Chapter, we have applied three synchrony measures: two classical measures Van Rossum Distance (van Rossum, 2001) and Schreiber Similarity (Schreiber et al., 2003), and a novel method Stochastic Even Synchrony (SES), to quantitatively assess the synchrony between PGW sequences extracted from BhPr EEG.

4.2.4.1 Stochastic Event Synchrony

The Stochastic Event Synchrony (SES) method (Dauwels et al., 2009) quantifies the synchrony of pairs of point processes. We consider each PGW as an event (or point), so that PGW sequences extracted from meditation EEG can be viewed as point processes. The idea behind SES is to align the given point processes: the

better the alignment, the more similar the point processes are considered. Unlike classical synchrony measures, SES quantifies the alignment of two point processes using multiple parameters: time delay δ_t , variance of the time jitter s_t , and fraction of coincident events γ . SES captures two different aspects of synchrony: timing precision and reliability, quantified by s_t and γ , respectively.

Figure 4.4: A symmetric procedure to generate a pair of point process x and x' .

the (event) timing jitter, and γ is the percentage of coincident events:

$$\gamma \triangleq \frac{n_{co} + n'_{co}}{n + n'}, \quad (4.7)$$

with n and n' the total number of events in x and x' , respectively, and n_{co} and n'_{co} the total number of coincident events in x and x' , respectively.

The SES parameters are computed by performing inference in a probabilistic model. As shown in Figure 4.4, a hidden point process v of length ℓ is generated, with events v_k mutually independent and uniformly distributed in $[0, T_0]$. The point process z and z' are obtained by shifting v over $\pm 0.5\delta_t$, respectively, and slightly perturbing the timing with variance $0.5s_t$. Finally, x and x' are derived from z and z' by deleting events with probability p_d .

This procedure amounts to the statistical model:

$$p(x, x', b, b', v, \delta_t, s_t, l) = p(x|b, v, \delta_t, s_t)p(x'|b', v, \delta_t, s_t) \cdot p(b|b', l)p(v|l)p(l)p(\delta_t)p(s_t), \quad (4.8)$$

where b and b' are binary strings indicating the events in x and x' are coincident/paired ($b_k = 1$ if x_k is non-coincident, $b_k = 0$ otherwise; likewise for b'_k). The length ℓ has a geometric prior $p(l) = (1 - \lambda)\lambda^l$ with $\lambda \in (0, 1)$, and $p(v|l) = T_0^{-l}$. The prior on the binary strings b and b' is given by

$$p(b, b'|l) = (1 - p_s)^{n+n'} p_s^{2l-n-n'} = (1 - p_s)^{n+n'} p^{n_{non-co}^{tot}}, \quad (4.9)$$

with $n_{non-co}^{tot} = n_{non-co} + n'_{non-co} = 2l - n - n'$ the total number of non-coincident events in x and x' , $n_{non-co} = \sum_{k=1}^n b_k = l - n'$ the number of non-coincident events in x , and likewise n'_{non-co} the number of non-coincident events in x' . The conditional

distributions in x and x' are equal to:

$$p(x|b, v, \delta_t, s_t) = \prod_{k=1}^n (\mathcal{N}(x_k - v_{i_k}; -\frac{\delta_t}{2}, \frac{s_t}{2}))^{1-b_k}, \quad (4.10)$$

$$p(x'|b', v, \delta_t, s_t) = \prod_{k=1}^n (\mathcal{N}(x'_k - v_{i'_k}; -\frac{\delta_t}{2}, \frac{s_t}{2}))^{1-b'_k}, \quad (4.11)$$

where v_{i_k} is the event in v that corresponds to x_k (likewise $v_{i'_k}$), and $\mathcal{N}(x; \mu, s)$ is a univariate Gaussian distribution with mean μ and variance s .

Eventually, marginalizing Eqn. (4.8) w.r.t. v results in the model:

$$p(x, x', b, b', v, \delta_t, s_t, \ell) \propto \beta^{n_{non-co}^{tot}} \prod_{k=1}^{n_{co}^{tot}} \mathcal{N}(x'_{j_k} - x_{j_k}; \delta_t, s_t), \quad (4.12)$$

with $(x_{j_k}, x'_{j'_k})$ pairs of coincident events, $n_{co}^{tot} = n + n' - \ell$ the total number of coincident event pairs, and $\beta = p_s \sqrt{\frac{\lambda}{T_0}}$.

The variables in that model are inferred by cyclic maximization: with initialization $\hat{\delta}_t^{(0)}$ and $\hat{s}_t^{(0)}$, the update rules are:

$$(\hat{j}^{i+1}, \hat{j}'^{i+1}) = \underset{b, b'}{\operatorname{argmax}} p(x, x', j, j', \hat{\delta}_t^{(i)}, \hat{s}_t^{(i)}) \quad (4.13)$$

$$(\hat{\delta}_t^{(i+1)}, \hat{s}_t^{(i+1)}) = \underset{\delta_t, s_t}{\operatorname{argmax}} p(x, x', \hat{j}^{i+1}, \hat{j}'^{i+1}, \delta_t, s_t). \quad (4.14)$$

The update rule Eqn. (4.13) amounts to the empirical mean and variance, computed over the coincident events. The update rule Eqn. (4.14) can readily be carried out by applying the Viterbi algorithm (dynamic programming) on an appropriate trellis (with the pairs of coincident events $(x_{j_k}, x'_{j'_k})$ as states), or equivalently, by applying the max-product algorithm on a suitable factor graph; the procedure is similar to

Dynamic Time Warping.

Figure 4.5: Van Rossum Distance and Schreiber Similarity. From top to bottom: Two point processes x and x' , exponential convolutions, Euclidian difference, Gaussian convolution and normalized point-wise multiplication.

4.2.4.2 Van Rossum Distance

In the approach of (van Rossum, 2001), the two point processes are converted into continuous time series (as shown in Figure 4.5). In particular, each event of x is convolved with an exponential function $\exp(t - x_k/\tau_R)$ (with $t > x_k$), resulting in the time series $s(t)$. Likewise each event of x' is convolved with this exponential function, leading to the time series $s'(t)$. From the time series $s(t)$ and $s'(t)$, the Van Rossum Distance (van Rossum, 2001) is computed as:

$$D_R(\sigma_S) = \frac{1}{\tau_R} \int_t [s(t) - s'(t)]^2 dt, \quad (4.15)$$

Note that $D_R = 0$ if and only if x and x' are identical. The timescale of this distance measure is determined by the time constant τ_R .

4.2.4.3 Schreiber Similarity

In the approach proposed in (Schreiber et al., 2003), the two point processes x and x' are first convolved with a filter, resulting in time series $s(t)$ and $s'(t)$ (as shown in Figure 4.5). The filter is gaussian with a certain width τ_S . Next the pairwise correlation between the time series $s(t)$ and $s'(t)$ is computed:

$$S_S(\sigma_S) = \frac{\int_t s(t)s'(t)dt}{\sqrt{\int_t s^2(t)dt}\sqrt{\int_t s'^2(t)dt}}. \quad (4.16)$$

Note that the width τ_S of the filter defines the timescale of interaction between the two point processes. We also point out that if and only if x and x' are identical do we have $S_S = 1$.

4.4 Results and Discussions

4.4.1 Benchmark of PGW Detection Methods

In this Chapter, we proposed an automated PGW detector. To validate the performance of this proposed detector, we have compared our automated method (named as M_3) to two other automated methods (named as M_1 and M_2), using a 15 sec humming period of a sample EEG trace from one subject practicing BhPr meditation. The first method (method M_1) (Borghi et al., 2007; Hidden and O'Boyle, 1979; Lüscher et al., 1983) detects PGWs by a two-threshold procedure with additional low-pass filtering for trough detection. The second method M_2 (Acir et al., 2005; Liu et al., 2013) computes morphological features and feeds them into an adaptive boosting classifier for detecting PGWs. Our proposed method M_3 detects PGWs

utilizing a morphological filter (see Section 4.2.2.3).

A. Automated PGW detector M_1

The two-threshold method is similar to conventional spike sorting algorithms (Hidden and O’Boyle, 1979; Lüscher et al., 1983). The PGW detection algorithm M_1 determines the peak and trough of the PGW, as illustrated in Figure 4.6. Two thresholds are used for the detection of a PGW: a positive threshold (D), set to detect the PGW peak, and a negative one (C), of lower amplitude (approximately 1/2 of the first threshold), employed for the detection of the PGW trough. If the trough follows the peak within a certain time period, the EEG waveform is considered to be a PGW. Importantly, M_1 applies an extra low-pass filter for trough detection in EEG with high noise level (see Figure 4.6).

Figure 4.6: (Left) Block diagram of the method implementation M_1 . (Right) Sample signals for the two-threshold scheme with low-pass filtering. Signal names refer to the block diagram, with dashed lines in (a) and (b) representing the threshold values (Borghi et al., 2007).

B. Automated PGW Detector M_2

In method M_2 (Acir et al., 2005; Liu et al., 2013), specific points of the PGW are defined, as illustrated in Figure 4.7. Six features are extracted for subsequent

classification by the adaptive boosting method. The calculations and descriptions of these features are listed in Table 4.2.

Figure 4.7: Feature points in method M_2 (Liu et al., 2013).

Table 4.2: Six PGW features analyzed in method M_2 .

Feature	Calculation	Description
T_{AP}	$t_P - t_A$	Duration of the rising flank of the peak of PGW
T_{PB}	$t_B - t_P$	Duration of the falling flank of the peak of PGW
V_{AP}	$V_P - V_A$	Amplitude of the rising flank of the peak of PGW
V_{PB}	$V_P - V_B$	Amplitude of the falling flank of the peak of PGW
Slope_{AP}	V_{AP}/T_{AP}	Slope of the rising flank of the peak of PGW
Slope_{PB}	$-V_{PB}/T_{PB}$	Slope of the falling flank of the peak of PGW

C. Benchmark of PGW Detectors

We selected an EEG signal from a single channel of 15 sec from the humming period of a subject practising BhPr meditation. The ground truth was obtained by visual inspection. Specifically, two experts manually extracted PGW events in the EEG signal. Only PGW events that were consistently marked by both experts are retained. The non-PGW waveforms are extracted by applying a sliding waveform window of fixed length (20 ms), with 20% overlap. As a result, there are $N_+ = 200$ PGWs, and $N_- = 2050$ non-PGW samples in this EEG trace for the benchmark comparison. Sensitivity, specificity, and classification accuracy are computed to validate the performance the PGW detectors.

We conduct 5-fold cross-validation to validate the performance of each method. Concretely, for methods M_1 and M_3 , the threshold values are inferred from the extreme values of the corresponding features of the training data (4 folds). For instance, the minimum peak voltage of training PGWs is identified and considered as the threshold for the peak detection in M_1 and M_3 . For method M_2 , the adaptive classifier is trained by the features extracted from the training data (4 folds). The detection metrics (sensitivity, specificity, and accuracy) are computed on the test data (the 5th fold). We repeat the same procedure for all 5 folds, and summarize the results in Table 4.3.

Table 4.3: Benchmark comparison of three PGW detectors (sensitivity [%], specificity [%], and accuracy [%]) using three automated methods $M_1 - M_3$, on a 15-sec EEG trace ($N_+ = 200$, $N_- = 2050$).

		M_1	M_2	M_3 (proposed)
Fold 1	sensitivity	100	73.2	92.7
	specificity	82.2	98.5	95.6
	accuracy	83.8	96.2	95.3
Fold 2	sensitivity	100	72.7	100
	specificity	81.3	97.1	94.2
	accuracy	82.7	95.3	94.7
Fold 3	sensitivity	100	75.6	97.6
	specificity	82.9	98.8	96.8
	accuracy	84.4	96.7	96.9
Fold 4	sensitivity	100	92.5	97.5
	specificity	82.7	97.8	97.1
	accuracy	84.2	97.3	97.1
Fold 5	sensitivity	97.8	84.4	97.8
	specificity	81.5	96.8	95.1
	accuracy	83.1	95.6	95.3
Average	sensitivity	99.6	79.7	97.1
	specificity	82.1	97.8	95.8
	accuracy	83.6	96.2	95.9

As shown in Table 4.3, although method M_1 achieves the highest average sensitivity of 99.6%, its specificity and accuracy are the lowest of all (82.1%, and 83.6%). In

other words, the number of false positives is quite high for M_1 : approximately 170 non-PGW segments are wrongly classified as PGWs by M_1 . By contrast, for method M_2 , the average specificity and accuracy are high (97.8%, and 96.2%). However, the average sensitivity is only 79.7%, losing nearly 20% of total PGWs. In comparison to these two methods, the proposed PGW detector M_3 achieves relatively high sensitivity and specificity of 97.1% and 95.8%, respectively. As the validation dataset is skewed with $N_- \gg N_+$, the overall classification accuracy is more “sensitive” to the negative class (i.e., specificity). Therefore, the average accuracy of M_3 (95.9%) is slightly lower than that of M_2 (96.2%).

4.4.2 Power Analysis under Various EEG Bands

To investigate the brain activity during BhPr meditation, absolute power is computed for each breathing episode on EEG after removing artifacts by the proposed system in Section 4.3.2. To incorporate the control condition, the resting EEG are divided into multiple segments with fixed length of 5s for each subject, which serve as the control group. EEG contents are further split into Beta and Gamma band by digital filters. Apart from these two bands, absolute power is computed for the entire band between 15Hz and 85Hz (Beta+Gamma). Topographic maps are used to display the power pattern distribution on the scalp. The absolute power of each EEG band is shown in Fig .4.8, Fig .4.9, Fig .4.10, and Fig .4.11.

The absolute power distribution pattern is relatively stable for exhalation (or “humming”) periods, during which the humming sound was made. For each subject, the left temporal lobe (region associated with T3, T5 electrodes) is more active with high absolute power values during exhalation periods. On the other hand, the distribution pattern during inhalation (or “silent”) periods is visually less stable compared to exhalation periods. As for the control condition the resting EEG, although the pattern is stable for the majority of the subjects (except “ I_1 ”), the active regions are different from those during exhalation periods.

Figure 4.8: Normalized absolute power topographic maps for subject B and I_1 : there are three panels for each subject representing three EEG bands “Gamma+Beta”, “Gamma”, and “Beta”, respectively; on each panel, topographic maps are arranged in three rows, for three successive exhalation periods (top “H”), three successive inhalation periods (middle “S”), and three successive control periods (bottom “C”).

Figure 4.9: Normalized absolute power topographic maps for subject I_2 and I_3 : there are three panels for each subject representing three EEG bands “Gamma+Beta”, “Gamma”, and “Beta”, respectively; on each panel, topographic maps are arranged in three rows, for three successive exhalation periods (top “H”), three successive inhalation periods (middle “S”), and three successive control periods (bottom “C”).

Figure 4.10: Normalized absolute power topographic maps for subject I_4 and I_5 : there are three panels for each subject representing three EEG bands “Gamma+Beta”, “Gamma”, and “Beta”, respectively; on each panel, topographic maps are arranged in three rows, for three successive exhalation periods (top “H”), three successive inhalation periods (middle “S”), and three successive control periods (bottom “C”).

Figure 4.11: Normalized absolute power topographic maps for subject *E*: there are three panels for each subject representing three EEG bands “Gamma+Beta”, “Gamma”, and “Beta”, respectively; on each panel, topographic maps are arranged in three rows, for three successive exhalation periods (top “H”), three successive inhalation periods (middle “S”), and three successive control periods (bottom “C”).

We have three different groups of subjects divided in terms of the degree of expertise in practicing BhPr meditation, labeled with B, I, and E, respectively. In order to investigate the impact of the degree of expertise on brain activity during BhPr meditation. The mean and standard deviation of the power strength in each group are listed in Table 4.4. There are two states for each subject: “meditate” and “control”. The measures of state “meditate” are obtained by averaging the powers among each breathing episode of both exhalation and inhalation periods, while the measures of state “control” are obtained by averaging the powers among each episode of the resting EEG. As there are multiple subjects in group I, we take the average among those subjects. Boxplots of absolute power are shown in Figure 4.12, with the p -values computed for Mann-Whitney test in Table 4.5.

Table 4.4: The mean and standard deviation of absolute power.

		Gamma+Beta	Gamma	Beta
Beginner	meditate	0.91±1.67	0.58±1.16	0.29±0.44
	control	1.01±1.75	0.60±1.15	0.36±0.56
Intermediate	meditate	2.02±2.35	1.28±1.61	0.65±0.65
	control	1.87±1.94	1.24±1.38	0.55±0.50
Expert	meditate	2.58±2.99	1.80±2.26	0.69±0.67
	control	1.90±3.14	1.45±2.42	0.36±0.57

As shown in Table 4.4, the mean power values drop slightly for the Beginner during BhPr meditation, compared to control condition no matter in which EEG band. On the contrary, there is an increment for the group of more experienced subjects I and E, respectively. Moreover, the increment is more significant for E than I. If we consider only the meditation states on for each group of subjects, the mean power value increases as the degree of expertise increases, i.e., $\bar{P}_B < \bar{P}_I < \bar{P}_E$. In the meantime, the standard deviation also increases along the degree of expertise, which can be visualized from the heights of the boxplots as well shown in Figure 4.12. For each group of subjects, the mean power of Gamma band is higher than that of Beta band, while the entire frequency band (Gamma+Beta) obviously has the highest power than either band on its own.

(a) Gamma+Beta

(b) Gamma

(c) Beta

Figure 4.12: Boxplots of absolute power for each subject during meditation (subscript “M”, in red), and control condition (subscript “C”, in blue) for three groups of subjects B, I and E, distinguished by degree of expertise in practising BhPr meditation.

Table 4.5: The p -values computed for Mann-Whitney test for absolute power between meditation and resting state for each group of subject ($X_M - X_C$, $X \in \{B, I, E\}$), and between meditation states of different groups ($X_M - Y_M$, $X, Y \in \{B, I, E\}$).

	$B_M - B_C$	$I_M - I_C$	$E_M - E_C$	$B_M - I_M$	$I_M - E_M$	$B_M - E_M$
Gamma+Beta	0.47	0.71	7.8E-10	1.1E-9	3.6E-2	5.8E-19
Gamma	0.11	8.4E-6	4.6E-7	1.3E-8	4.1E-4	4.7E-20
Beta	0.83	3.8E-6	1.9E-17	2.2E-11	0.46	1.5E-16

As shown in Table 4.5 and Figure 4.12, it is hard to differentiate the meditation states from the control condition for the Beginner for all three EEG bands. In both Gamma and Beta band, there exist significant differences between meditation and control condition for more experienced subjects I and E. Moreover, the difference is more significant for Expert E than Intermediates I. In other words, it is easier to distinguish the meditation from the resting state for subject with a higher degree of expertise in practicing BhPr meditation, i.e., $p_{B,C} \gg p_{I,C} \gg p_{E,C}$ (except for Gamma+Beta band where $p_{B,C} < p_{I,C}$). If we consider only the meditation states on for each group of subjects, there exist significant differences among each group in all three EEG bands, with $p < 5\%$ (except Beta band, between B and I).

4.4.3 PGW Density Distribution

From the power analysis in Section 4.3.2, we observe a common active brain region, the left temporal lobe, for each subject during the exhalation periods with a stable distribution pattern. We further apply the proposed PGW detector on the reconstructed EEG and extract all the PGWs. The PGW density distribution is visualized on topographic maps as shown in Figures 4.13 and 4.14.

Figure 4.13: PGW density visualized on topographic maps for subject I_1 - I_5 : for each subject the topographic maps are arranged in three rows, for three successive exhalation periods (top “H”), three successive inhalation periods (middle “S”), and three successive control periods (bottom “C”).

Figure 4.14: PGW density visualized on topographic maps for subject *B* and *E*: for each subject the topographic maps are arranged in three rows, for three successive exhalation periods (top “H”), three successive inhalation periods (middle “S”), and three successive control periods (bottom “C”).

As shown in Figures 4.13 and 4.14, the PGW density distribution is similar to that of the absolute power in Figures 4.8 to 4.11, indicating that PGW is highly correlated to active brain regions. The distribution pattern is visually less stable for inhalation periods. Although for certain cases, the pattern is relatively stable during the control condition resting EEG, the active regions are different from those during exhalation periods. Similar brain regions are active during exhalation periods of BhPr meditation: for each subject left temporal lobe is active with high PGW rate, which is in agreement with the hypothesis in (Hölzel et al., 2007; Lazar et al., 2000) suggesting that meditation is associated with an activation of the left temporal lobe.

Temporal lobes are often functional-associated with emotional responses and memory. Our results may provide some insights about how the subjects may benefit from meditation, as such brain regions are kept enhanced in activation during each breathing control along the practice of BhPr meditation. As mentioned earlier, the PGW density distribution during exhalation periods is quite stable, while it is visibly less stable during inhalation periods. In other words, the enhanced activation of certain brain regions takes place most probably during exhalation periods rather

than inhalation periods.

(a)

(b)

Figure 4.15: PGW sorting by K-means clustering: (a) PGWs in feature domain, and (b) overlaid PGWs and random individual PGW samples for each cluster.

Figure 4.16: PGW density distribution visualized on topographic maps. For each subject an exhalation period is analyzed, and the topographic maps are arranged in 4 columns (from left to right): PGW density distribution from the raw data (column 1), from reconstructed EEG without PGW clustering (column 2), from reconstructed EEG based on cluster 1 PGWs (column 3), and from reconstructed EEG based on cluster 2 PGWs (column 4).

In addition, K-means clustering is applied to sort the PGWs extracted from multiple sources. For simplicity, only two clusters are applied, with three features extracted for clustering: timing of the main peak T_{p1} and the main trough T_{tr} , and the slope of the rising flank of the main peak. As shown in Figure 4.15, these two clusters

are displayed in a 3-dimensional feature domain, with sample PGWs illustrated from each cluster. Comparing to PGWs in cluster 1, the main peaks of PGWs from cluster 2 come later, smoother and have smaller rising slopes. The topographic maps of PGW density distribution for different clusters are shown in Figure 4.16. The brain regions associated to the two clusters are mostly non-overlapping, suggesting that different regions of the brain might generate different types of PGWs during meditation. Cluster 1 has a dominant PGW rate at $\sim 10\text{--}20$ PGWs/sec, while it is <5 PGWs/sec for cluster 2, which also reflects on the topographic maps that the distribution pattern associated with cluster 1 is very similar to that without clustering.

4.4.4 Synchrony Analysis of PGWs

Three synchrony measures Stochastic Event Synchrony (SES) (Dauwels et al., 2009), Schreiber Similarity (SS) (Schreiber et al., 2003), and Van Rossum Distance (VRD) (van Rossum, 2001) are used to study the pairwise synchrony of the PGW sequences extracted from BhPr EEG. To reveal the brain connectivity networks, only connections with significantly large strength are retained. In addition, we also consider the impact of the channel-wise PGW count in this selection process to discard channel pairs with small contributions in generating PGWs. Eventually, only connections with strength greater than 20^{th} percentile, and the associated pair of channels with PGW count greater than the 90^{th} percentile of all the channels are retained. Moreover, for SES method, one extra condition is considered about the timing jitter for validity of SES: $\sigma_t < 0.1\bar{T}_{iei}$, with $\bar{T}_{iei}$ denoting the average inter-event interval.

Figure 4.17: Brain connectivity networks from three synchrony measures for subject *B* and I_1 – I_3 : SES (“Syn 1”), SS (“Syn 2”), and VRD (“Syn 3”), with the power distribution pattern as the reference indicating brain activities. For each subject, the linked topographic maps are arranged in 3 rows representing three successive exhalation periods H_1 – H_3 .

Figure 4.18: Brain connectivity networks from three synchrony measures for subject I_4 , I_5 and E : SES (“Syn 1”), SS (“Syn 2”), and VRD (“Syn 3”), with the power distribution pattern as the reference indicating brain activities. For each subject, the linked topographic maps are arranged in 3 rows representing three successive exhalation periods H_1 – H_3 .

We apply the same set of rules to each subject, and only considered three successive exhalation periods, during which the majority of the brain activation occurred. The strength of the connections for each measure is defined by γ , S_S , and $-D_R$ (see Section 4.3.4), respectively, which are color-coded. In addition, the pattern of the PGW density distribution is displayed in the background of each brain connectivity map in order to visualize the active brain regions correspondingly. To avoid confusions, only colorless contours of the PGW density distribution are shown here.

As shown in Figures 4.17 and 4.18, consistent patterns of connections are present during each exhalation period. Similar patterns can be observed for three synchrony measures. Strong local synchrony can be found in temporal lobes for each subject among channels with high PGW density. In addition, long-range connections between distinct active brain regions also can be found in each subject with moderate strength. For illustration, using SES results from subject Beginner, both PGW sequences extracted from local and distant pairs of channels are shown in Figure 4.19. Both local and long-range connections between different brain regions suggest better brain coordination and more effective brain activations during meditation.

Figure 4.19: SES brain connection network (left) and EEG (right) with extracted PGW sequences from a pair of (a) adjacent channels Ch. 119 and Ch. 123 with $\gamma=97.3\%$; and (b) distant channels Ch. 41 and Ch. 123 with $\gamma=79.6\%$.

Another concern is about the change of synchrony patterns during meditation sessions along time. Enhanced synchrony can be observed from Figures 4.17 and 4.18 along successive breathing episodes. Especially for subject Beginner and Expert, one can visualize the enhanced synchrony from weak to strong, with gradually growing connectivity network and long-range connections. The effect is not that obvious for Intermediate subjects.

4.5 Summary

In Chapter 4, we have proposed an automated procedure to extract paroxysmal gamma waves (PGWs) in scalp EEG recordings of subjects practicing Bhramari Pranayama (BhPr) meditation. We investigated the effectiveness of the proposed method on seven subjects possessing different degrees of expertise in practicing BhPr meditation. Power analysis was carried out to investigate the active brain regions during BhPr meditation. It is found that the power distribution is stable during exhalation (or “humming”) periods, during which the humming sound was made. For each subject, the left temporal lobe (region associated with T3, T5 electrodes) is more active with high absolute power values. On the other hand, the distribution pattern during inhalation (or “silent”) periods is visually less stable compared to exhalation periods. We also included control condition, i. e., the resting EEG, and find out that the active regions are distinguishable from those during exhalation periods. Compared to the control condition, there is an increment in the mean power during BhPr meditation. The amount of increment is correlated with the degree of expertise of practicing BhPr meditation: the higher the degree of expertise, the higher the increment of mean power. Moreover, there exist significant differences in power values for groups of subjects possessing different degree of expertise. The mean power drops as the expertise decreases.

The resulting PGW density distributions agree well with the power analysis: strong PGW related EEG activity can be observed in each subject. The distribution pattern is visually less stable for inhalation periods. Although for certain cases, the pattern is relatively stable during the control condition resting EEG, the active regions are different from those during exhalation periods. Similar brain regions are active during exhalation periods of BhPr meditation: for each subject left temporal lobe is active with high PGW rate, which is in agreement with the hypothesis in (Hölzel et al., 2007; Lazar et al., 2000) suggesting that meditation is associated with an activation of the left temporal lobe. Temporal lobes are often functional-associated with emotional responses and memory. As mentioned earlier, the PGW

density distribution during exhalation periods is quite stable, while it is visibly less stable during inhalation periods. In other words, the enhanced activation of certain brain regions takes place most probably during exhalation periods rather than inhalation periods. We also identified two different types of PGWs associated with different brain regions, with PGW sorting using K-Means clustering.

We further investigated the synchrony of pairwise PGW sequences extracted from the EEG during successive exhalation periods of BhPr meditation. To quantify the synchrony, three different measures were used: Stochastic Event Synchrony (SES), Schreiber Similarity Measure, and Van Rossum Distance, to pairs of PGW sequences extracted from the BhPr EEG. Strong local synchrony can be observed in the temporal lobes for each subject, in addition to long-range inter-hemispheric connections, suggesting better brain coordination and more effective brain activations. Consistent connectivity patterns are present in each breathing episode, and visually stable for all three measures. The enhanced synchrony can be found during meditation sessions especially for subject Beginner and Expert.

Chapter 5

Conclusion

Electroencephalography (EEG) continues to be a valuable tool for both research and clinical diagnosis. In this thesis, we have investigated applications of quantitative EEG analyses under three different scenarios to solve real life problems:

- Application 1: To localize SOZ in the brain of epilepsy patients
- Application 2: To accelerate the annotation of epileptiform spikes
- Application 3: To study the brain activity during meditation

5.1 Localization of Seizure Onset Zones using Interictal Intracranial Stereo-EEG

In Chapter 2, we have incorporated multiple stereo-EEG features such as slowing, ripples, fast ripples, and interictal spikes, as recorded in brief blocks of intracranial depth electrode data (stereo-EEG) to localize the seizure onset zones (SOZ) of patients with epilepsy. Analysis of 50 stereo-EEG records from 14 patients shows that all these stereo-EEG features are highly correlated with SOZ. A binary classification scheme is established employing an adaptive boosting method, and tested

via leave-one-patient-out crossvalidation with all possible combinations of stereo-EEG features. Our results show that multiple features can improve the overall localization performance compared to each single EEG feature. However, adding features does not always guarantee improved performance; the performance gradually starts deteriorating from a certain number of stereo-EEG features, probably due to over-fitting. In addition, a method for rejecting likely outliers is imposed; and a multi-scale analysis of stereo-EEG is used to provide a probabilistic weighting for each stereo-EEG channel involvement in SOZ. Ultimately, the likelihood of a certain stereo-EEG channel being in SOZ is estimated using the cumulative density of the contact-wise classification scores. The proposed system works better on subjects with temporal SOZs compared to those with extra-temporal SOZs. In addition, our results are similar for stereo-EEG recorded when the patient was awake or asleep, therefore the status of stereo-EEG seems to have little influence on the classification.

5.2 Rapid Annotation of Interictal Epileptiform Discharges via Template Matching under Dynamic Time Warping

In Chapter 3, we have developed *NeuroBrowser*, an integrated system for EEG review and rapid waveform annotation. *NeuroBrowser* employs a suite of signal processing algorithms to enable semi-automated EEG analysis. A core component of *NeuroBrowser* is the Trillion algorithm, which enables ultrafast template matching under Dynamic Time Warping. The insensitivity of DTW-based similarity search to small dilations and stretches of the time axis, characteristic of variation in many natural signals, allows highly reliable retrieval of waveforms similar to a user-selected example waveform.

As demonstrated in our numerical results, in comparison with conventional manual EEG annotation, *NeuroBrowser* is able to save EEG experts up to 90% of the time

spent in annotating interictal epileptiform spikes. Currently, no semi-automated software exists on the market for substantially speeding up the annotation of clinical EEG recordings in populating high-quality databases of expert-annotated waveforms. A large database of this type is crucial for training fully automated systems for complex and transient waveform analysis. Past attempts to create automated spike detection systems have failed primarily due to the intense labor and costs required to gather a sufficiently large and diverse collection of spikes as training examples, and the lack of rigorous validation on large numbers of prospectively collected EEGs, leading to physician mistrust of and failure to adopt published algorithms. With *NeuroBrowser*, we have extracted 35,000+ spikes from 303 patients. To our knowledge, this is the largest database of expert-annotated spike waveforms established to date. While the algorithm is currently tailored to annotation of spikes, it can easily be generalized to other waveforms and signal types.

5.3 Study of Paroxysmal Gamma Waves in Bhramari Pranayama Meditation EEG

In Chapter 4, we have proposed an automated procedure to extract paroxysmal gamma waves (PGWs) in scalp EEG recordings of subjects practicing Bhramari Pranayama (BhPr) meditation. We have investigated the effectiveness of the proposed method on seven subjects possessing different degrees of expertise in practicing BhPr meditation.

Power analysis has been carried out to investigate the active brain regions during BhPr meditation, and shows that the power distribution is stable during exhalation periods. For each subject, the left temporal lobe is more active with high absolute power values. On the other hand, the distribution pattern during inhalation periods is visually less stable compared to exhalation periods. We also included control condition, and find out that the active regions are distinguishable from those during

exhalation periods. Compared to the control condition, there is an increment in the mean power during meditation. The amount of increment is correlated with the degree of expertise of practicing BhPr meditation: the higher the degree of expertise, the higher the increment of mean power. Moreover, there exist significant differences in power values for groups of subjects possessing different degree of expertise. The mean power drops as the expertise decreases.

The resulting PGW density distributions agree well with the power analysis: strong PGW related EEG activity can be observed in each subject. The distribution pattern is visually less stable for inhalation periods. Although for certain cases, the pattern is relatively stable during the control condition resting EEG, the active regions are different from those during exhalation periods. Similar brain regions are active during exhalation periods of BhPr meditation: for each subject left temporal lobe is active with high PGW rate, which is in agreement with the hypothesis suggesting that meditation is associated with an activation of the left temporal lobe. Temporal lobes are often functional-associated with emotional responses and memory. The PGW density distribution during exhalation periods is quite stable, while it is visibly less stable during inhalation periods. We have also identified two different types of PGWs associated with different brain regions, with PGW sorting using K-Means clustering.

We further investigate the synchrony of pairwise PGW sequences extracted from the EEG during successive exhalation periods of BhPr meditation. To quantify the synchrony, three different measures were used: Stochastic Event Synchrony (SES), Schreiber Similarity Measure, and Van Rossum Distance, to pairs of PGW sequences extracted from the BhPr EEG. Strong local synchrony can be observed in the temporal lobes for each subject, in addition to long-range inter-hemispheric connections, suggesting better brain coordination and more effective brain activations. Consistent connectivity patterns are present in each breathing episode, and visually stable for all three measures. The enhanced synchrony can be found during meditation sessions especially for subject Beginner and Expert.

5.4 Future Work

In Chapter 2, we have presented an automated system that is able to delineate SOZ from interictal stereo-EEG recordings, by exploiting various electrophysiological signatures such as slowing, interictal spikes, and high frequency oscillations (both ripples and fast ripples). Further refinement of the algorithm and, perhaps, incorporation of other stereo-EEG features such as synchrony, entropy measures are needed. However, the overall capability of the approach indicates a pathway forward to greater automation in determination of a resection zone for epilepsy and methods for decreasing the duration, and therefore, risk and cost, associated with intracranial investigations for epilepsy. It is also possible that we can incorporate short-term intra-operative recordings, ECoG (by surface electrodes) as well as non-invasive recordings (e.g. high-density EEG and/or MEG) into our algorithm. Demonstrating that an accurate SOZ prediction could be obtained from these modalities might eventually obviate the need for semi-chronic invasive recordings. It is also possible to incorporate quantitative EEG analysis with other methodologies such as imaging modalities (MRI, PET, or SPET), computational epilepsy modeling to localize SOZ. We can also consider the ictal data and develop approaches for seizure detection and artifact removal.

In Chapter 3, we developed *NeuroBrowser*, an integrated system for rapid waveform annotation that is specifically designed for interictal discharges. We have already extracted 35,000+ interictal discharges from 303 patients. To our knowledge, this is the largest database of expert-annotated interictal discharges established to date. A large database of this type is crucial for training fully automated systems for complex and transient waveform analysis. As future work, we will apply unsupervised learning to automatically identify groups of virtually identical interictal discharges from each EEG. Exemplars will be extracted from each group constructing the set training data without redundancy. We will leverage the training data to develop a general purpose automated interictal discharge detection algorithm. To cope with

the wide between-patient variability inherent in these EEG data, our approach to classifier development will be based on the concept of classifier ensembles and cascades, i. e., building up a sophisticated classifier out of many simpler classifiers. We hypothesize that a cascade of differentiated classifiers for progressive background rejection can overcome the between-patient variability of interictal discharges to achieve expert-level interictal discharge detection. This method is similar to boosting, where a strong algorithm emerges from an ensemble of weak classifiers. Background waveforms are rejected partially at each step while reserving all or nearly all valid interictal discharges. Classifier cascades have the advantage of being able to deal with extreme pattern variability (no single classifier in the cascade is expected to do all the work), and exceptional computational efficiency (“easy” parts of the data are processed/rejected very quickly; more sophisticated and computationally intensive classification algorithms are reserved only for the residual difficult cases).

In Chapter 4, we have investigated the brain activity through PGW-related events in Bhramari Pranayama meditation EEG. In future work, we will extend the study to have a larger number of subjects from various degrees of expertise in practicing the Bhramari Pranayama meditation. We plan to apply multi-dimensional stochastic event synchrony on PGW sequences, which may provide additional insights into the synchrony measure. In addition to Beta and Gamma band, we can also consider other EEG frequency bands such as Delta, Theta, and Alpha band activity. Another topic of our interest is “cross frequency coupling”. Recent studies have demonstrated that oscillations in various frequency bands occur simultaneously and can interact with each other. For instance, the phase of low frequency oscillations modulates the amplitude of higher frequency oscillations, which is called phase-amplitude cross frequency coupling and the best-known example occurs in the rodent hippocampus between the Theta phase and Gamma amplitude. Phase-amplitude cross frequency coupling has been implicated in cognitive processes including both working memory and long-term spatial memory. The link of cross frequency coupling with learning

and memory is further strengthened by experimental protocols for the induction of synaptic plasticity. These findings have led credence to the idea that phase-amplitude cross frequency coupling may be the most predictive neurophysiological marker for cognition yet found.

List of Publications

Journals and Articles:

- J. Jing, J. Dauwels, and S. S. Cash. “Automated Localization of Seizure Onset Zones using Interictal Intracranial EEG” (Submitted to *Journal of Clinical Neurophysiology* in May 2016).
- J. Jing, J. Dauwels, T. Rakthanmanon, E. Keogh, S. S. Cash, and M. B. Westover. “Rapid Annotation of Interictal Epileptiform Discharges via Template Matching under Dynamic Time Warping” (Accepted by *Journal of Neuroscience Methods* in February 2016, with DOI:10.1016/j.jneumeth.2016.02.025).

Conference Papers:

- M. Vazquez, J. Jing, J. Dauwels, and F. B. Vialatte (2013, May). “Automated Detection of Paroxysmal gamma Waves in Meditation EEG”. *In Acoustics, Speech and Signal Processing (ICASSP), 2013 IEEE International Conference*, on (pp. 1192-1196). IEEE.
- J. Jing, J. Dauwels, and S. S. Cash (2014, Aug). “Automated Localization of the Seizure Focus using Interictal Intracranial EEG”. *Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE*, on (pp. 4439-4442). IEEE.
- J. Jing, J. Dauwels, S. S. Cash, and M. B. Westover (2014, August). “SpikeGUI: Software for Rapid Interictal Discharge Annotation via Template Matching

and Online Machine Learning”. *Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE*, on (pp. 4435-4438). IEEE.

- J. Jing, J. Dauwels, F. B. Vialatte, and A. Cichocki (2014, May). “Synchrony Analysis Of Paroxysmal Gamma Waves In Meditation EEG”. *In Acoustics, Speech and Signal Processing (ICASSP), 2014 IEEE International Conference*, on (pp. 4703-4707). IEEE.
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- J. Thomas, J. Jing, J. Dauwels, S. S. Cash, and M. B. Westover (2016, March). “Clustering of Interictal Spikes by Dynamic Time Warping and Affinity Propagation”. *In Acoustics, Speech and Signal Processing (ICASSP), 2016 IEEE International Conference*, on (pp. 749-753). IEEE.
- A. R. Johansen, J. Jing, T. Maszczyk, J. Dauwels, S. S. Cash, and M. B. Westover (2016, March). “Epileptiform Spike Detection via Convolutional Neural Networks”. *In Acoustics, Speech and Signal Processing (ICASSP), 2016 IEEE International Conference*, on (pp. 754-758). IEEE.

Intellectual Properties:

- PCT of “NeuroBrowser” filed with the US Patent Office in August 2015, with Serial No. PCT/US15/45886.
- Provisional patent for “NeuroBrowser” filed with the US Patent Office in August 2014, with Serial No. 62039070.

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