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Epileptic Seizure Detection And Prediction From Electroencephalogram Using Neuro-Fuzzy Algorithms

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EPILEPTIC SEIZURE DETECTION AND PREDICTION FROM
ELECTROENCEPHALOGRAM USING NEURO-FUZZY ALGORITHMS

By

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Bachelor of Science, University of Dhaka
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for the degree of

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Grand Forks, North Dakota
May
2013

This dissertation, submitted by Ahmed Fazle Rabbi in partial fulfillment of the requirements for the Degree of Doctor of Philosophy from the University of North Dakota, has been read by the Faculty Advisory Committee under whom the work has been done, and is hereby approved.

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April 30, 2013
Date

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Title   Epileptic Seizure Detection and Prediction from Electroencephalogram
               using Neuro-Fuzzy Algorithms

Department   Electrical Engineering

Degree   Doctor of Philosophy

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                              Ahmed Fazle Rabbi
                              May 01, 2013

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ABSTRACT

This dissertation presents innovative approaches based on fuzzy logic in epileptic seizure **detection** and **prediction** from Electroencephalogram (EEG). The fuzzy rule-based algorithms were developed with the aim to improve quality of life of epilepsy patients by utilizing intelligent methods. An adaptive fuzzy logic system was developed to detect seizure onset in a patient specific way. Fuzzy if-then rules were developed to mimic the human reasoning and taking advantage of the combination in spatial-temporal domain. Fuzzy c-means clustering technique was utilized for optimizing the membership functions for varying patterns in the feature domain. In addition, application of the adaptive neuro-fuzzy inference system (ANFIS) is presented for efficient classification of several commonly arising artifacts from EEG. Finally, we present a neuro-fuzzy approach of seizure prediction by applying the ANFIS. Patient specific ANFIS classifier was constructed to forecast a seizure followed by postprocessing methods. Three nonlinear seizure predictive features were used to characterize changes prior to seizure. The nonlinear features used in this study were similarity index, phase synchronization, and nonlinear interdependence. The ANFIS classifier was constructed based on these features as inputs. Fuzzy if-then rules were generated by the ANFIS classifier using the complex relationship of feature space provided during training. In this dissertation, the application of the neuro-fuzzy algorithms in epilepsy diagnosis and treatment was demonstrated by applying the methods on different datasets. Several performance

measures such as detection delay, sensitivity and specificity were calculated and compared with results reported in literature. The proposed algorithms have potentials to be used in diagnostics and therapeutic applications as they can be implemented in an implantable medical device to detect a seizure, forecast a seizure, and initiate neurostimulation therapy for the purpose of seizure prevention or abortion.

CHAPTER I

1. INTRODUCTION

1.1. Background

The brain is the most complex organ of the human body and it is the center of the human nervous system. Neurons (nerve cells) are the biological building blocks of the brain. In a typical human brain, over 100 billion neurons are interconnected. The brain is responsible for controlling the body as well as for the executive functions, such as reasoning, thought, and planning. Interestingly, it is the most complex organ of the human body. Science, to date, does not understand the whole mechanism or how brain works. Electrophysilogy and hemodynamic response are the two techniques that have been used to study the activities of the brain [1]. Electrophysiological techniques are used for studying electrical properties of biological cells and tissues. It involves the measurement of voltages or electric current from a single ion channel to the whole organ, for example, brain [1]. In neuroscience and neuroengineering, the electrophysiological techniques widely used to measure the electrical activities of neurons are electroencephalogram (EEG) and magnetoencephalogram (MEG). Typically, electrophysiological measurements are performed by placing electrodes or sensors on the biological tissue [1], [2]. Functional activities, such as blood oxygen level of the brain also provide very useful and important insight into brain activities.

The functional neuroimaging techniques based on hemodynamic principles are functional Magnetic Resonance Imaging (fMRI), functional Near-Infrared Spectroscopy (fNIRS), and Positron Emission Tomography (PET). EEG is the recording of the brain's electrical activity which is caused by the firing of neurons. EEG has been primarily used as the most widely used tool in diagnosis of neurological disorders, such as epilepsy. It can be recorded in two ways: invasive and non-invasive as shown in Figure 1. Non-invasive EEG recording is done by placing electrodes or sensors on the scalp. In invasive EEG recording, subdural (strip or grid) electrodes are placed in surgical procedure on to the cortex whereas depth electrodes are used to record electrical activities from deep inside the brain. The standard protocol used to place the electrodes on scalp is known as the 10-20 international system [2], [3].

(a)   (b)
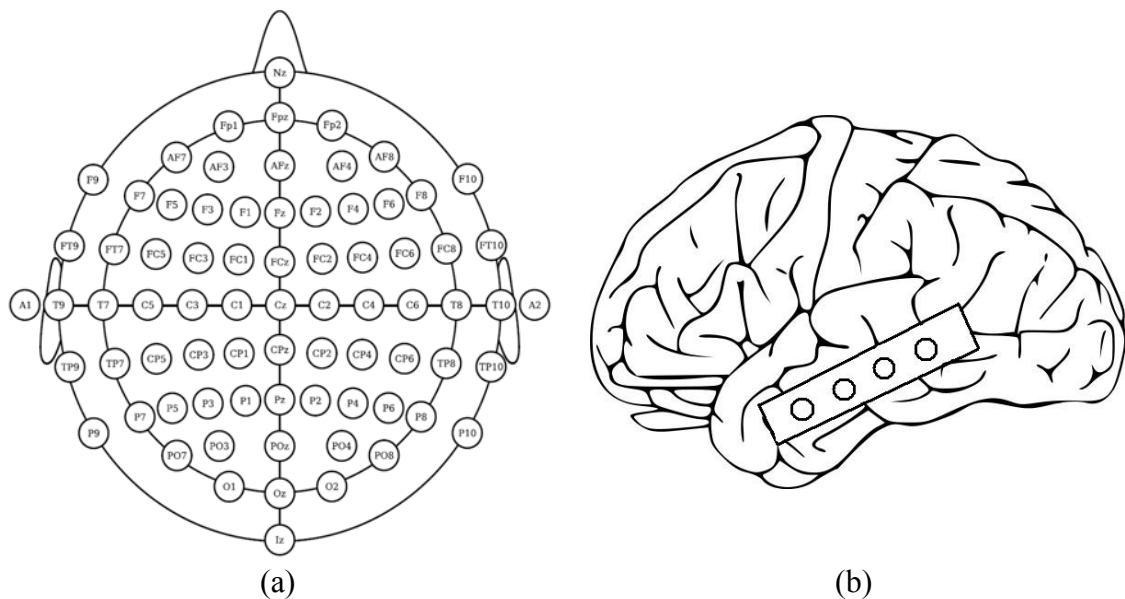
Figure 1. Non-invasive and invasive electrode placement patterns on brain: (a) The 10-20 international system for EEG scalp electrode placement [3] (b) implanted strip electrodes [4].

EEG sensors placed on scalp or on cortical surface records brain activities which is a combination of neural activities. The recorded signals can be saved in many formats. The amplitude values typically range in the order of hundred micro volts (μV) [5]. EEG

signals can be seen as an output of a complex nonlinear system. Therefore, advanced signal processing tools and techniques are required to analyze EEG. With the advancement of technology, EEG is now being used not only in medical devices (which includes implantable medical devices and neuroprosthetics) but also in brain computer interface (BCI) or human computer interface (HCI) applications targeted to assist disabled people controlling a wheel chair, virtual keyboard application, as well as consumer electronics market for various recreational applications. A new area, known as neuroergonomics, is of growing interest where the relationship of brain and body is studied in an operational environment [6], [7].

The brain is susceptible to damage and diseases. The most common neurological disorders are Alzheimer's disease, Epilepsy, Parkinson's disease, sleep disorders etc. Epilepsy is a chronic neurological disorder characterized by two or more recurrent seizures. It is prevalent in significant number of (approximately 1-3%) world's population. Epileptic seizures are due to the excessive firing of neural networks in the brain. The underlying mechanisms are described primarily as synchronous hyper excitability and hyper synchrony. However, the exact mechanism of how seizure generates remain largely unknown to date.

Monitoring of epilepsy patients is usually performed in a clinical setting on a continuous daily recording basis. As a result, huge EEG data is generated which is tedious and monotonous for epileptologists to visually inspect and analyze seizures in such long recordings. Therefore, an automatic seizure detection tool is of high demand. However, such a tool requires detecting seizures with high sensitivity and very low

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specificity to be considered for monitoring in clinical settings. An example of multi-channel EEG recordings is shown in Figure 2.
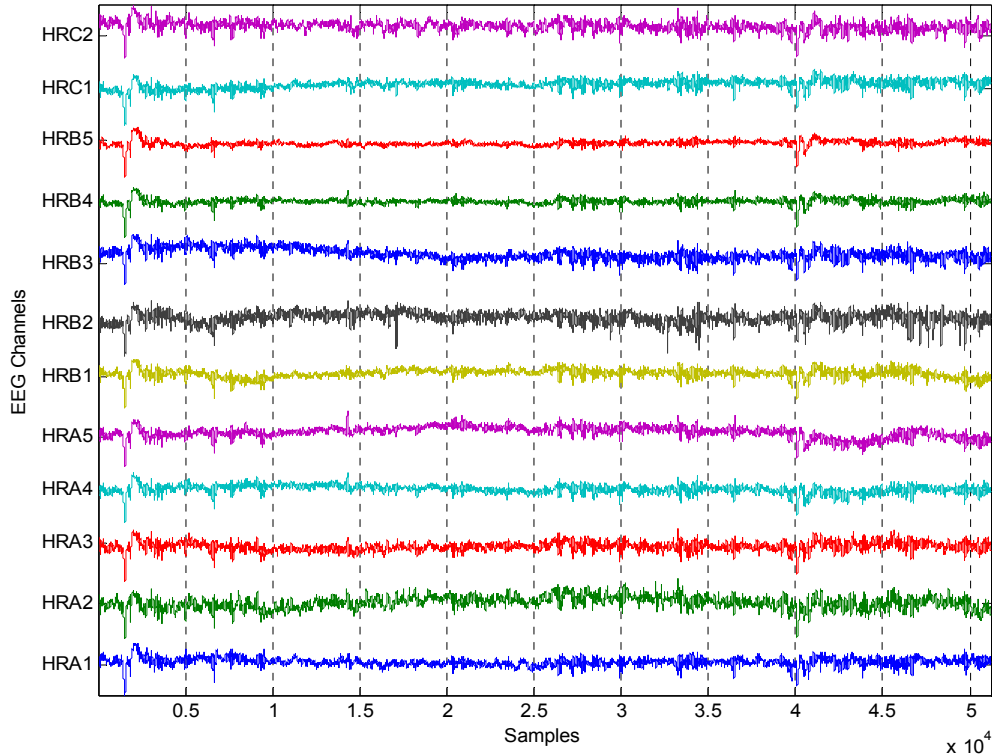
Figure 2. An example of multi-channel EEG recordings recorded using invasive electrodes.

The primary goal of the epilepsy treatment is to prevent the seizure activity as early as possible with as few side effects as possible. Available anti-seizure medications are used by doctors and clinicians in treating epilepsy patients. Often, the epilepsy patients have to undergo surgery in special cases where medications do not work effectively. For surgical procedure, EEG (along with fMRI and MEG) has been used to localize the seizure focus region to identify the brain region candidate for surgery. In recent days, much focus has been put into developing implementable medical devices for offering an alternate form of treatment to ensure better life for the epilepsy patients. With the advancement of bio-sensors and digital technology, it is now possible to design and develop such devices. These types of devices are capable of monitoring brain electrical

activities, stimulating the brain by electrical impulse to reduce the seizure frequency, and performing automatic drug delivery. Automatic seizure detection and prediction algorithms can be integrated in such a device.

1.2. Methods in EEG Signal Processing

EEG signal processing consists of several steps. These steps include preprocessing of signals for removing baseline shift, DC components, reducing noise and artifacts, characteristics feature extraction, classification using the features. In post-processing step, algorithms are optimized in achieving optimum performance in achieving specific goals. A typical block diagram of EEG signal processing pipeline, for both real-time and offline applications, are shown in Figure 3.

| EEG | → | Preprocessing | → | Feature Extraction | → | Classification | → | Postprocessing | → | Output |
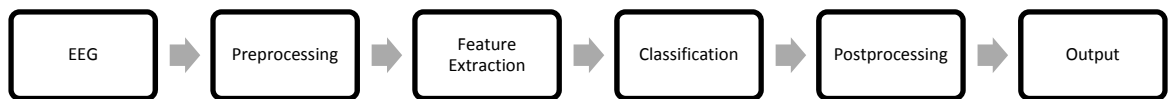
Figure 3. Typical steps in EEG signal processing

1.2.1. Preprocessing

EEG signal amplitudes are in the range of ten to several to hundred micro volts (µV) when measured on the scalp. Higher amplitude EEG (about 10 - 20 mV) can be obtained using subdural (grid or strip) electrodes. Moreover, EEG is a band limited signal having useful information in the range of 0.5 - 100+ Hz. Inherently, EEG recordings from the human brain are noisy and susceptible to numerous artifacts, such as eye blinks, eye movements, muscle activities, and movement related artifacts. Interference from power line could also appear as a 50/60 Hz peak in EEG. The artifacts and noise could severely contaminate EEG recordings and make analysis very challenging. These artifacts are extremely detrimental in EEG-based clinical and other applications, for example, BCIs.

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In preprocessing, EEG signals are investigated first to identify the presence of unwanted components. For further processing, these artifacts and noise components are required to be removed or reduced from the signals of interest. The artifacts rejection techniques include rejecting a portion of signal where the signal is badly corrupted with noise as well as by performing different available filtering operations on EEG segments.

Temporal and spectral threshold techniques are widely used in detecting artifacts with some degree of success [8]. In standard threshold of amplitudes values, a fixed threshold is applied to EEG signals. The signals under observation exceeding the predefined threshold are labeled as artifactual. Other techniques include computing time domain features relevant to artifacts and application of a threshold. The threshold in this case is determined after normalizing the feature values to zero mean and unity standard deviation to optimize the sensitivity and specificity of detection. However, spectral threshold methods reported to have better performance [8]. Wavelet denoising has been explored by few researchers for artifacts removal with limited success [9]. Application of the threshold-based techniques with independent component analysis (ICA) is now widely accepted in the neuroengineering scientific community to detect, isolate, and remove artifacts from data. The ICA-based techniques allow simple and reliable subtraction of independent components related to unwanted components [8]. It has been reported in literature that methods utilizing ICA algorithms yield better performance in dealing with most of the artifacts [8].

1.2.2. Feature Extraction

EEG signals can be characterized in time-, frequency-, spatial- or a combined domain, such as time-frequency domain. Multi-sensor EEG recordings provide intuitive

information related to complex spatio-temporal cortical activities. Depending on the type of problem statement or hypothesis under investigation feature extraction methods are chosen to characterize the EEG. As introduced earlier, we have to consider a few assumptions to analyze EEG signals in order to translate useful information. Nonlinearity of the head/brain physiology and nonstationary nature of the recorded electrical activity are to name a few. In most of EEG-based applications, it has been found that linear feature extraction algorithms are capable of extracting useful information. On the other hand, in some specific applications, such as diagnosis of neurological disorders, analysis of brain dynamics may provide very useful information. In such applications, dynamical analysis can characterize the nonlinearity of EEG, however, with the cost of high computing power requirement. In this research, a wide variety of feature extraction methods including the comparatively new areas of chaos theory and nonlinear dynamical analysis based feature extraction methods were exposed. Interesting behavior of these feature extraction methods were found in revealing changes in brain dynamics.

1.2.3. Classification

In analyzing EEG signals, the classification of a feature space is usually required for most of the applications. For example, maximum amplitude, a time-domain feature extracted from epileptic EEG may be useful to classify whether the portion of data under investigation is epileptic or not. The main objective of classification is to determine the boundary between two or more classes [5]. To date, many types of classification techniques have been developed, such as linear classifier to nonlinear classifier. In the context of EEG signal processing, the application of wide variety of classifier algorithms are found. In the last four to five decades, the area or artificial intelligence, machine

learning, and pattern recognition have witnessed development of many classifier algorithms and clustering techniques. These can further be divided into two broad categories, namely: supervised and unsupervised. Among those, linear discriminant analysis (LDA), artificial neural network (ANN), support vector machines (SVM), hidden Markov model (HMM), k-means clustering, and fuzzy logic to name a few are very popular and have been widely used in many applications. In this study, fuzzy logic based classification techniques have been explored and applied in epileptic seizure detection and prediction in EEG. The advantage of fuzzy logic is that it provides a way to mimic human (expert's) reasoning with significantly lower complexity relative to other classifiers, such as ANN and SVM.

1.3. Applications of EEG Signal Processing: Literature Review

1.3.1. Epileptic Seizure Detection

Epilepsy is the most common neurological disorder with prevalence in 1 - 3% world's population [10]-[12]. It is characterized by the occurrence of two or more unprovoked epileptic seizures which are due to abnormal rhythmic discharge of electrical activity of the brain [11]-[13]. A seizure is defined by sudden alteration of one or more neurological functions, such as motor, behavior, and/or autonomic functions. Epileptic seizures are episodic, rapidly evolving temporary events. Typically, the duration of an epileptic seizure event is less than a minute. Though the exact mechanism behind epileptic seizure generation and evolution is largely unknown to date, a seizure event can be described as the increased network excitation of the neural networks with synchronous discharge as well as variable propagation in the brain [10], [11]. In focal epilepsy, ictal

manifestations may localize in a specific brain region, whereas in generalized epilepsy the whole brain could be the candidate for seizure events to take place [1], [2].

EEG is the most widely used electrophysiological measure for diagnosis of neurological disorders, such as epilepsy in clinical settings. Long term monitoring of EEG is one of the most efficient ways for diagnosis of epilepsy by providing information about patterns of brain electrical activities, type and frequency of seizures, and seizure focus area [11]-[13]. In long term monitoring, ictal EEG recordings are usually correlated with the clinical manifestation of seizure. If the recording site is where the seizure focus is located, the changes in EEG can occur before the clinical manifestations [11], [12]. On the other hand, when electrodes are placed in remote location from the seizure focus site, the clinical manifestations may occur before any visual changes in EEG. Therefore, the placement of electrodes is a determining factor in seizure detection or early detection [12]. The clinical experts who monitor the long term EEG recordings usually look for earliest visually apparent changes in EEG to identify ictal onset [10]. An illustration of the different EEG states related to brain transition is shown in Figure 4 [14].
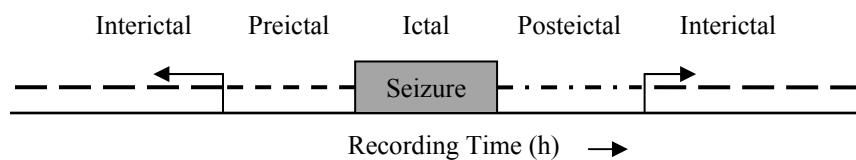
Figure 4. Illustration of the probable preictal, ictal, and postictal states relative to the interictal baseline in epilepsy EEG recording [14].

Seizure events are clinically termed as ictal event. Hypothetically, the state prior to seizure onset is termed as preictal. Similarly, the state following a seizure event is known as postictal. The baseline or regular EEG activities in between seizures are termed

as interictal. It is worth mentioning that these states may not be symmetrical. In seizure detection, correct classification of the ictal activities from the normal activities is the primary goal. In early detection or prediction, identification of the preictal state from the interictal baseline is the primary goal. An illustration of multichannel EEG recordings having recordings from two epileptic channels is shown in Figure 5.
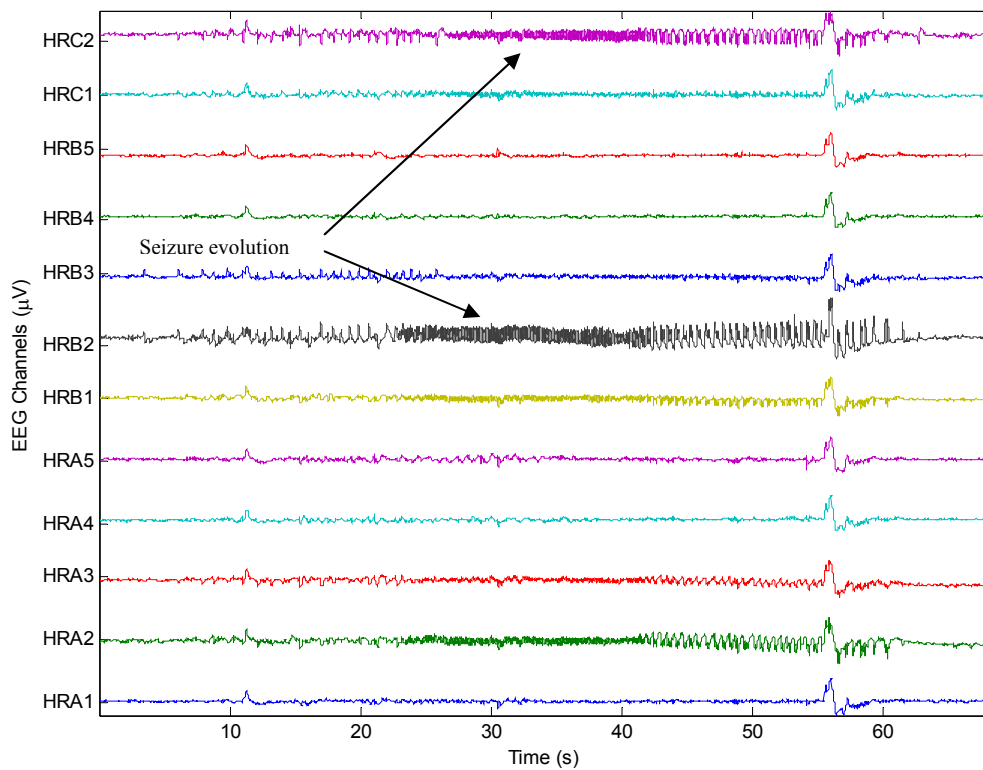
Figure 5. Multi-channel EEG recordings using invasive electrodes. Channels HRB2 and HRC2 are located in the epileptic region of the brain.

This information helps physician or caregiver to treat patients with the available medications. However, the visual inspection of long term EEG by clinicians is challenging as it is performed over several days to weeks due to the unknown nature of seizure occurrence. The visual inspection of this large amount of data to identify seizure (epilepsy diagnosis) is very time consuming and monotonous [12], [13], [15]. Therefore, an automatic seizure detection tool with high detection rate and considerably low false

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detection rate would have valuable application in clinical settings to help physicians and caregivers in epilepsy treatment [11]-[13], [15].

During a seizure event, increased abnormal synchronous firing occurs in the involved neural networks of the brain. The pattern and shape of ictal EEG varies according to the brain region as well as types of recordings (intracranial or scalp EEG). A detection algorithm should be able to identify these dynamic changes in EEG with high sensitivity. One of the most common patterns found in ictal EEG is periodic sharp activity (6 - 8 Hz activity of a mesial temporal lobe-onset seizure) [11], [12]. The ictal onset and offset is also characterized by relatively high complexity signals. However, the ictal initiation patterns may vary from patient to patient. Though the patterns in different patients may vary depending on the types of seizures, proximity of the recording electrodes to the seizure focus, types of recordings, the ictal onset patterns, and early evolution of brain dynamics in a given patient are of similar types. Therefore, the algorithm parameters can be tuned in a patient specific way to increase the sensitivity and specificity of detections [12], [13].

One of the applications of automatic seizure detection in clinical settings is to monitor patients and localize brain region for surgery. As for medically intractable focal epilepsies, brain tissue of seizure focus is candidate for surgery and the source localization information helps neurologists in surgical procedure. Moreover, to provide patients an alternative to currently available medication and surgical treatment, much focus has been put on early detection and prediction of epileptic seizure providing sufficient time of intervention prior to clinical onset, and ultimately preventing or controlling epilepsy [12]. Although the intervention time is crucial in designing a control

device, an early detection tool capable of detecting seizures several minutes prior to clinical seizure onset would help the patients in avoiding serious injuries by taking proper action or using available medications to reduce the intensity of seizure frequency [13], [15].

Significant progress has been made in automatic detection of epileptic seizure from intracranial EEG (iEEG) recordings over the last couple of decades [12], [13], [15]-[20]. Intracranial EEG is an invasive way of recording EEG where electrodes are placed onto the cortex or inside the brain. In both the types, surgical procedures are required. Gotman (1982) developed an automatic seizure detection method to detect various types of seizures in both surface and intracranial EEGs. It was based on decomposition of EEG into elementary waves and detecting paroxysmal bursts of rhythmic activities using relative amplitude, their duration, and rhythmicity [13]. Murro et al. (1991) developed a computerized method to detect complex partial seizures [15]. The method used three EEG features, relative amplitude, dominant frequency, and rhythmicity. Discriminant analysis was used for decision making [15]. In order to reasonably reduce the false alarm rate, Qu and Gotman (1995) developed a warning system based on template matching which relies on availability of one sample seizure for subsequent detections of similar seizures in scalp and intracerebral EEG recordings [18]. Following, Qu and Gotman (1997) proposed a patient-specific seizure onset detection system with high sensitivity and very low false positive rate [16]. Osorio et al. (1998) proposed an algorithm for real-time detection, quantitative analysis of seizures, and prediction of the clinical onsets [17]. Grewal and Gotman (2005) proposed an automatic warning system based on EEG data filtering in multiple bands, spectral feature extraction, Bayes' theorem, and spatial-

temporal analysis [19]. This system requires training and it is tunable in a patient specific way to optimize the performance [19]. In a different approach, Adeli et al. (2007) performed wavelet sub-band analysis as well as nonlinear analysis of EEG for detecting seizures and epilepsy [20]. They used correlation dimension and largest lyapunov exponent to quantify nonlinear dynamics of EEG [20]. From the same group, a novel wavelet-chaos-neural network methodology was proposed by Ghosh-Dastidar et al. (2007) [21]. Srinivasan et al. (2007) proposed a neural-network-based automatic seizure detection system using approximate entropy (ApEn) as the input feature [22]. Gardner et al. (2006) discussed a one-class support vector machine (SVM) novelty detection for seizures in iEEG by classifying short-time, energy-based statistics [23]. The detector was validated on a sample of 41 interictal and 29 ictal epochs and yielded 97.1% sensitivity, and mean detection latency of -7.58 seconds, but false positive rate (FPR) of 1.56 false positive per hour [23]. Chan et al. (2008) proposed a patient-specific algorithm for accurate measurement of seizure onset time detection [24]. The algorithm makes use of spectral and temporal features, and support vector machine as classifier [24]. Ghosh-Dastidar et al. (2009) presented a new supervised learning algorithm for Multi-Spiking Neural Networks (MuSpiNN) which was applied in seizure detection where they have demonstrated better accuracy of MuSpiNN over single-spiking Spiking Neural Network (SNN) model [25]. In a recent work, Zhang et al. (2010) proposed a novel incremental learning scheme based on nonlinear dimensionality reduction for automatic seizure onset detection [26]. Their study used continuous wavelet transform (CWT) for feature extraction and two stage decision making which makes use of nonlinear dimensionality reduction and incremental learning schemes [26].

Recently, much focus has been put in detection of seizures early in time or eventually predicting it. Interestingly, there have not been much significant works performed in the area of seizure detection or early detection based on fuzzy logic approaches. We realized this area requires careful investigation and innovative algorithms based on fuzzy logic might have useful application in epileptic seizure prediction. Subasi (2006) introduced the application of adaptive neuro-fuzzy inference system (ANFIS) for epileptic seizures detection and classification of epileptic patients from normal population [27]. This method combined the adaptive capabilities of artificial neural networks and qualitative approach of fuzzy logic. Relevant features were extracted using the wavelet transform [27]. Aarabi and Fazel-Rezai (2009) presented an automatic method which uses fuzzy rule-based system to detect seizures in iEEG [28]. Temporal, spectral, and complexity features extracted from iEEG were fed into two stage decision making system where they were spatial-temporally integrated. Intermediate decision making was performed in the first stage using rule-based fuzzy inference system [28]. Final decision was made using spatial combiner, feature combiner, and post-processor [28].

1.3.2. Epileptic Seizure Prediction

It is worth mentioning here that the boundary between early seizure detection and seizure prediction may be seen overlapping or blurry oftentimes. These two areas have two distinct objectives. In early seizure detection, an impending seizure is to be detected before onset from a few seconds to minutes. On the other hand, in seizure prediction, the hypothesis is that such an event could be detected in minutes to an hour or several hours before the event to take place. Thus the objective is to detect subtle changes in preictal

state corresponds to a seizure event to follow. These require correctly identifying the pre-ictal states and discriminate it from interictal states. The definitions of these states are mentioned here for clarity. The data recording between seizures are termed as interictal states and recording before a seizure is hypothesized as preictal state. The time when seizure is actually happening is known as ictal state. Similarly, the recordings immediate past seizure events are termed as postictal. The whole idea of seizure prediction comes from the hypothesis that in most of the seizures, (widely accepted for focal seizures and partially accepted for generalized seizures) there are changes in terms of clinical demonstrations as well as electroencephalographic changes (may not be visible to naked eyes) in some patients before a seizure actually takes place. Therefore, the changes in brain dynamics are considered as smooth transition rather than abrupt. Current available medications are incapable for nearly 30% of the patients. Moreover, due to the sudden nature of seizure attack, a device capable of predicting seizures early would have huge impact in improving the quality of patient's life and provide novel therapeutic treatment. To address this demand, last three decades witnessed a large number of seizure prediction algorithms were published and several patents were filed. However, almost all of these algorithms are retrospective in a sense that they fail in unselected or out of sample data and do not pass all the requirements to be considered in clinical applications.

Mormann et al. (2007) described the state of seizure prediction research emphasizing the need for rigorous statistical validation [29]. Several pitfalls of the current methods have been identified which require to be addressed properly and carefully in order to make further progress in this challenging area [29]. In this research, a large number of articles proposing seizure prediction algorithms were reviewed. The

literature on seizure prediction is very rich and most of the proposed methods fall in several major categories as threshold-based methods, clustering-based techniques, machine learning-based techniques, spatio-temporal combination of multiple seizure prediction methods, and rule-based methods. Most of the methods available in literature make use of a single characteristic measure, commonly known as seizure prediction method, and apply a thresholding procedure to trigger an alarm [30]. These include the application of both linear and nonlinear characteristic measures. Nonlinear methods are popular among many researchers. However, most of these methods are sensitive to noise which may lead to wrong findings [23], [24]. Therefore, the advantages of nonlinear feature extraction methods over linear methods are yet to be justified. The selection of test dataset is also critical because direct comparisons of different studies or approaches are difficult unless those are applied to the same dataset [19]. Proper statistical validation remains another major concern [24], [25].

To address one of these challenges, Feldwisch-Drentrup et al. (2010) described a method using logical "AND" and "OR" combinations in order to combine two epileptic seizure prediction methods [21]. The study showed improved performance for both the "AND"/"OR" combinations comparing to the performance of single method. The "AND" combination yielded better sensitivity comparing to the "OR" combination [21].

A patient-specific rule-based seizure prediction system was proposed by Aarabi et al. (2011) [31]. Six nonlinear features, both univariate and bivariate, were extracted from overlapping EEG segments of 10 seconds duration. Finally, the features were integrated spatio-temporally to predict seizures with high sensitivity [31]. This method yielded an average sensitivity of 96.5% with an average false prediction rate of 0.055/h for

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prediction horizon of 60 minutes. For prediction horizon of 30 minutes, their method yielded an average sensitivity of 90% with an average false positive rate of 0.06/h [31]. However, the presented results were for short sample size (two patients having 10 seizures) [31]. Discussing one of the most recent articles, a novel method of discriminating preictal state from interictal state was proposed by Gadhoumi et al. (2012) by utilizing high frequency analysis of EEG [32]. The method computed energy and entropy from selected preictal and interictal epochs using wavelet transform [32]. The two measures were plotted in features space revealing a dynamics referring to the brain dynamics [32]. A reference dynamics was defined and discriminant analysis was performed two classify the EEG epochs [32]. The method yielded over 80% of sensitivity with false prediction rates from 0.09/h to 0.7/h [32].

1.3.3. Challenges of Understanding Brain Mechanisms

EEGs, both invasive and non-invasive, are primarily being used as the tool for diagnosis of epilepsy. Novel treatment of epilepsy treatment, such as neuromodulation techniques are attracting great interest where the objective is to reduce the seizure frequency by an electrical pulse using a pacemaker like device. Feature extraction methods (characteristic measures) play a critical role in almost all seizure detection and prediction algorithms. The best choice of feature selection should be made based on the physiological phenomenon to be detected. Given the limited understanding of epilepsy, this is not a straightforward choice to make. Many feature extraction methods have been used so far with varying rate of success [33], [34].

A significant number of researchers agreed on the point that during a seizure event, many neurons fire at the same time. In other words, many neurons fire in

synchrony. In order to measure this 'synchronous firing of the neurons', various features have been used which measure the synchronous activity [34]-[36].

Often rhythmic discharges are visible in EEG during a seizure. Such discharges are identified as spikes (multiple spikes), described by Gotman (1982) [13]. These could be identified using morphological characteristics, such as amplitude, duration of the half waves. To study the rhythmic discharges many researchers have utilized frequency domain analysis based on frequency transform, time-frequency analysis, and wavelet transform. On the other hand, time-domain features are particularly popular among many researchers as temporal change in EEG is evident in seizure. These features represent the abnormal firing of the brain's neural networks. Furthermore, these features are significantly different than baseline EEG or interictal EEG. As the electrical activities recorded at the electrodes are the mixing of the potentials of brain fields, many researchers choose to use mathematical methods to decompose EEG signals into its constituent parts and analyze the signals [12], [37].

Finally, nonlinear dynamical analysis (chaos theory) based measures are particularly popular in seizure prediction [37]. Nonlinear measures are computed from EEG signals by utilizing time-delay embedding in space to reconstruct the phase space portrait [37]. The various nonlinear measures are then computed studying the properties of the reconstructed phase space trajectory [37].

The idea of early detection of epileptic seizure or prediction established with acceptance of the hypothesis that the changes in EEG started earlier in time before clinical manifestations in EEG. The assumption is that brain dynamics evolve smoothly

towards epileptic stage rather than abrupt. Therefore, nonlinear dynamics and chaos theory-based methods are particularly important in early detection or prediction study.

There are a number of reasons for which early detection or prediction of epileptic seizure remain a huge challenge to the scientific community. The exact underlying mechanism of seizure generation remains largely unknown [29], [30], [38]. From neuroengineering point of view, there is a lack of proper mathematical models of the brain, or brain circuits, which affects the understanding of neural diseases. Similarly, from neuroscience point of view, the understanding of the relationships among the neurons, the transmission of electrochemical signals (neurotransmitters, receptors) in the context of neural diseases, such as epilepsy is limited.

In the data driven approach, one idea could advance this field further is to study differences and similarities among different types of seizures. Different EEG databases could be used with various feature extraction methods in an aim to identify new diagnostic indicators or bio-markers. The success of the patient specific algorithms has to be transformed somehow to the development of non-patient specific algorithms.

The primary hypothesis inspiring the growing number of articles attempting early detection and/or seizure prediction in EEG is that the brain state transitions in focal epilepsies are smooth rather than abrupt. However, it is quite obvious that the predictive changes in EEG may vary in different types of epilepsy as well as in patients. The pathologies of underlying focal epilepsies may also vary. Obviously, better understanding of the complex spatio-temporal interactions between different brain regions is necessary.

Considering coupling in different brain regions, synchronization measures are likely the most sensitive features in detection preictal transitions in EEG. Moreover, previous researchers have reported that the bivariate features perform better over univariate features [39], [40]. Mormann et al. suggested that a combination of both univariate and bivariate features would be more appropriate in designing a reliable algorithm [38]. Therefore, an intelligent choice would be to use several bivariate features after proper investigation. Finally, a carefully designed decision making system, such as rule-based fuzzy inference system could be employed for identifying the preictal states from the interictal baseline. Evaluation of the proposed method should be done by statistical performance analysis in the form of sensitivity and false prediction rate per hour [29], [38].

CHAPTER II

2. ARTIFACTS DETECTION AND NOISE REDUCTION

2.1. Artifacts Detection

2.1.1. Background

Because of the low amplitude (~ 50 µV) EEG is susceptible to physiological and extra-physiological artifacts and noise as well as noise from environment. Typically EEG signal amplitude is in micro volts (µV) range and the frequency bandwidth of EEG range from zero to several hundred Hz. Fundamental EEG rhythms are below 100 Hz as described in chapter 1. Other physiological activities produce electrical activities in the low frequency region of EEG spectrum. Therefore, it not only records brain electrical activities but also other physiological activities, such as eye blinks, electrocardiogram, and muscle contractions. Electrical interference, for example, power line noise could appear as 50/60 Hz noise in EEG. In addition, electrode movements introduce movement related artifacts. Therefore, applications of EEG outside the controlled laboratory environment remain extremely challenging. Based on the characteristic properties of different types of artifacts and noise, it is possible to design filtering algorithms to reduce their effects. Before performing filtering or artifact rejection operations, it is required to investigate for the presence of artifactual components in a trial-like EEG segment under investigation.

2.1.2. Threshold-based Artifacts Detection

Typically, a threshold based detection is applied to EEG signals to detect a portion of signals having artifacts or not in both clinical and event-related research [8]. Artifactual EEG signals usually have higher potential comparing to background EEG activities. By applying a pre-defined upper bound of potential it is possible to detect portion of contaminated signals for rejection [8]. This simple technique, however, does not work in case the artifact's amplitude is less than the pre-defined threshold, for example, low amplitude eye blinks. Another type of common artifacts is produced by muscle activities having amplitude very close to background EEG activity but of higher frequency [8]. In detecting such high frequency artifacts, a standard threshold method can be applied to data spectra after transforming data to frequency domain [8].

In this study, several artifacts were encountered, such as saturation artifacts and electrode movement artifacts. Standard threshold based methods are applied to detect segments with artifacts and the detected segments were rejected from the analysis. The artifacts detection methods applied are discussed in details in the later chapter.

2.1.3. Machine Learning-based Artifacts Detection

Although threshold based techniques are widely used in clinical as well as event related potential (ERP) research, these are not highly reliable and efficient for all types of artifacts. The reason is that the morphology of the different movement related artifacts are of high variability. Threshold based methods utilize lower order statistical measurements, for example, maximum or minimum value. It is expected that higher order statistical measures as well as carefully extracted characteristics features are capable of

more reliable detection [8]. A similar threshold based procedure can be applied to these measures. In addition, many research groups are interested in developing machine learning based artifact detection algorithms in order to overcome the limitations of threshold based methods [41].

In this study, in addition to standard threshold based methods, application of a more sophisticated neuro-fuzzy based machine learning technique was proposed. Three different types of common artifacts which appear in EEG, eye blinks, muscle artifacts, and electrode movement/displacement artifacts were simulated. These artifacts were modeled and were added to regular (artifacts free) EEG to obtain semi-simulated artifactual EEG signals [42]. Finally, ANFIS classifiers were designed and applied to detect the presence of the artifacts in semi-simulated EEG data.

Three different types of artifacts commonly appear in EEG which could potentially contaminate EEG signals were modeled. These are eye blinks, muscle artifacts, and discontinuities in signals due to sensor displacement. The eye blinks were modeled by smoothing a low frequency sine wave using a moving average filter with window size of 37. This window size was chosen empirically to find the closest morphological shapes which resemble the eye blink activity. In order to model the muscle activities, random noise was band-pass filtered within 20 - 60 Hz [8]. Sampling frequency considered was 256 samples per second and two seconds or 512 sample points of artifacts as shown in Figure 6.

The normal EEG and the simulated artifacts were normalized to unity as shown in Figure 6. The modeled artifacts were linearly added to normal EEG in order to simulate

artifacts EEG [42]. The artifacts were scaled twice the amplitude of EEG to make sure
their dominant presence [9]. Semi-simulated EEG data corrupted with artifacts are shown
in Figure 7.
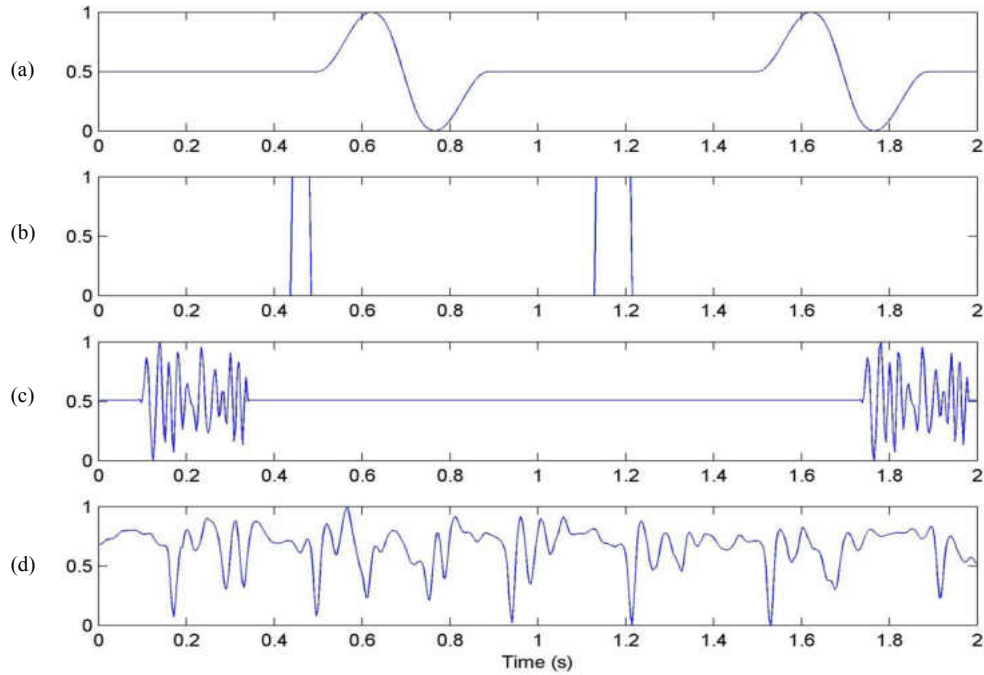
Figure 6. Modeled artifacts: (a) eye blinks, (b) movement related, (c) muscle activities; and (d)
normal EEG activity.
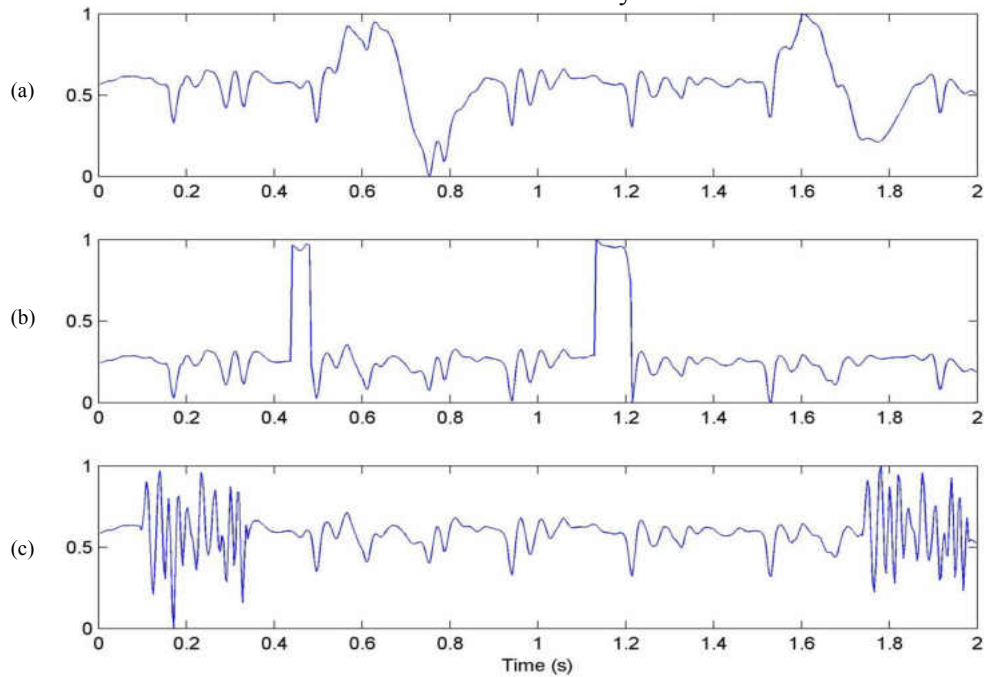
Figure 7. Semi-simulated EEG data affected by artifacts: (a) eye blinks artifacts, (b) sensor
motion artifacts, (c) muscle noise.

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The discrete wavelet transform (DWT) was used to extract features. Level four decomposition of artifacts EEG using discrete wavelet transform (DWT) was performed. Approximate and detail coefficients (cA1 - cA4 and cD1 - cD4) were computed. DWT actually performs sub-band decomposition of the original signals and the low frequency/high amplitude and high frequency/low amplitude patterns are localized in time-frequency domain. For dimensionality reduction, we computed three features: maximum value, standard deviation, and kurtosis of approximate coefficients (cA4 for eye blinks and electrode movement related artifacts, cA1 for muscle artifacts) [43].

ANFIS classifiers were designed to classify these artifacts correctly. The ANFIS is a Sugeno-type fuzzy inference system having neural-network adaptive learning capabilities [44], [45]. Therefore, it is more systematic to model ANFIS and it rely less on expert's knowledge. An ANFIS model was designed with three input and one output nodes. For each input feature three membership functions were defined: Low (L), Medium (M), and High (H) as shown in Figure 8. Figure 8 illustrates the initial Gaussian membership functions and Figure 9 shows the optimized membership functions after the training procedure.
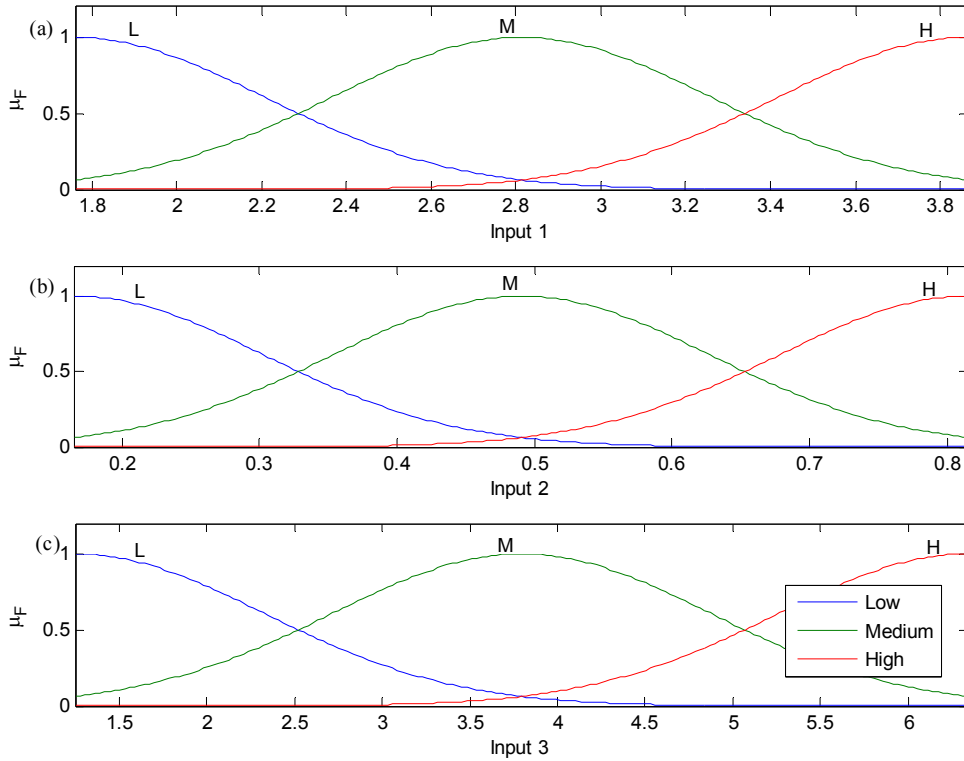
Figure 8. Initial Gaussian membership functions assigned to the feature inputs: (a) feature 1, (b) feature 2, and (c) feature 3. Three levels were assigned to the membership functions as low (L), medium (M), and high (H).
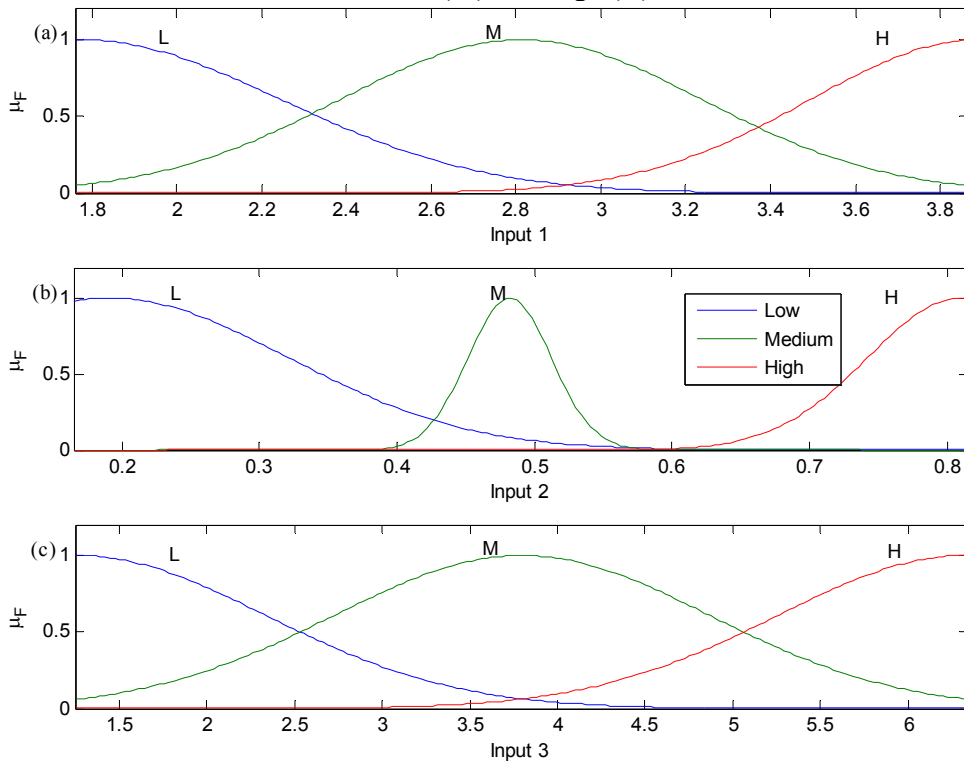
Figure 9. Optimized fuzzy input membership functions after training (a) feature 1, (b) feature 2, and (c) feature 3. Three levels were assigned as low (L), medium (M), and high (H).

The output node is assigned binary values for each class ('0' = regular; '1' = artifactual). The fuzzy if-then rules are defined as following.

$$If \ (x \ is \ A_i) and \ (y \ is \ B_i) and \ (z \ is \ C_i) then \ (f_i = p_i x + q_i y + r_i z + s_i) \qquad (1)$$

where x, y, and z are the inputs, A_i, B_i, and C_i are the fuzzy sets, and p_i, q_i, r_i, and s_i are the linear design parameters [44], [45]. The linear parameters are determined from the input patterns presented. These parameters were optimized during the training using least squares method. The ANFIS architecture is shown in Figure 10. The system required 27 fuzzy if-then rules.
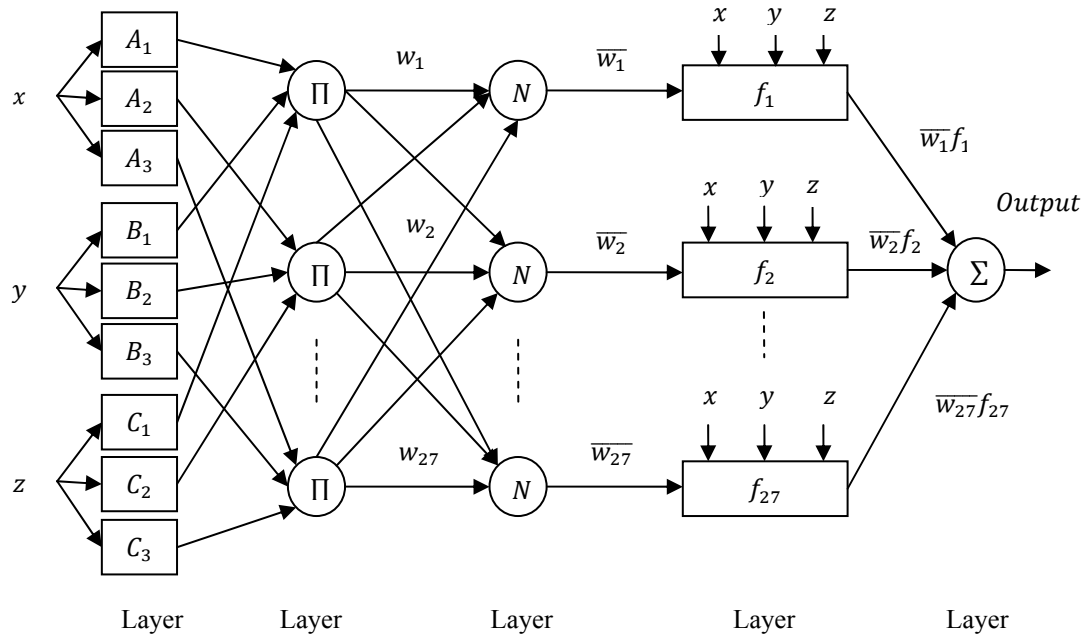
Figure 10. The ANFIS architecture designed for movement artifacts detection having three inputs with three membership functions. All the nodes in the middle layers 2, 3, and 4 were not shown.

Fuzzification of input variables was performed in the first layer and all the nodes of the first layer are adaptive nodes. The outputs of the first layer are the fuzzy membership grades of the inputs. The membership grade parameters are used to adaptively estimate the membership grades during training to better map the input/output

relationships. The second layer nodes perform product operation to calculate the firing strength of each rule using the following equation [43]-[45].

$$O_i^2 = w_i = \mu_{Ai}(x)\mu_{Bi}(y)\mu_{Ci}(z), i = 1,2,3 \tag{2}$$

The third layer is responsible for data normalization. In the fourth layer, each node has the following function:

$$O_i^4 = \overline{w_i}f_i = \overline{w_i}(p_i x + q_i y + r_i z + s_i) \tag{3}$$

where $\overline{w_i}$ is the output of the previous layer and $\{p_i, q_i, r_i, s_i\}$ is the first order polynomial parameter set [44], [45]. The polynomial parameters are for a first order Sugeno model [44], [45]. The fourth layer is also adaptive since the consequent parameters are modifiable. There would be a total of 27 nodes in each of the middle layers. The single node S in the final layer performs the summation of all incoming signals. The final output is given by the following equation.

$$O_i^5 = \sum_i \overline{w_i}f_i = \frac{\sum_i w_i f_i}{\sum_i w_i} \tag{4}$$

A total of 540 epochs (segments or windows) of EEG were generated with 180 epochs for each type of artifacts. Among those 160 epochs were normal EEG and 20 epochs were EEG affected by artifacts. The epochs were annotated as regular ("0") and artifactual ("1"). Further details on the datasets used are given in Appendix B.

Training and testing was performed using 10-fold cross validation technique [46]. During each fold the size of the training data sets were 162 epochs and test data sets were 18 epochs. The training was performed using a hybrid learning algorithm which combines the least squares method and the backpropagation gradient descent method.

Initially, gradient descent method was used to train the network. Finally, with trial and error it was found that hybrid learning algorithm is more efficient in adaptively estimating the fuzzy membership parameters.

2.1.4. Results and Discussion

An ANFIS classifier was generated for each type of artifacts and the performance of the ANFIS classifier is reported for test segments only in a 10-fold cross validation scenario. A threshold procedure was applied to evaluate the classifier's performance. The true positive ratio (TPR), false positive ratio (FPR), and detection accuracy (mean ± standard deviation) achieved are presented in Table 1. TPR was defined as the ratio of number of true positives divided by the number of one targets. Similarly, FPR was defined as the ratio of the false positives divided by the number of zero targets. Finally, accuracy was defined as the percentage of correct decisions being made.

Table 1. Accuracy, true positives rates, and false positives rates (mean ± standard deviation) in detection of artifacts using adaptive neuro-fuzzy inference system (ANFIS).

Artifacts type	TPR (%)	FPR (%)	Accuracy (%)
Eye blinks	85.56±11.62	42.73±1.94	96.67±3.88
Sensor motion	78.06±22.66	44.08±3.27	96.67±4.68
Muscle activities	79.95±14.74	44.00±1.15	90.56±6.44

The system yielded 97% accuracy for eye blinks and sensor motion artifacts. These are of similar characteristics having very low frequency and comparatively higher amplitude than baseline EEG. Specially, sensor motion artifacts could appear as several times larger amplitude than baseline EEG. They are easy to detect even applying a simple threshold. The accuracy was lower in case of detecting muscle noise. Significant spectral overlap with the baseline EEG makes it particularly difficult in detecting this type of noise

The classical fuzzy inference system suffers the drawback of relying too much on expert's knowledge and reasoning. Another drawback is that if offers no framework for optimization of the fuzzy membership grade parameters. One way to optimize the fuzzy membership function is by utilizing data mining techniques, such as fuzzy c-means clustering. The ANFIS overcomes this drawback by adopting neural learning capabilities. The membership function grades are optimized during the training process using gradient descent method [44]. The algorithms were implemented in MATLAB® (MATLAB® version 7.8 with wavelet toolbox and fuzzy logic toolbox).

2.2. Filtering of EEG for Noise Suppression and Artifacts Rejection

EEG is a band limited signals contains both transient and rhythmic activities. Filtering of EEG requires careful considerations of the source of noise and the information to be extracted from the signals. The signal to noise ratio (dB) should be high for extracting useful information. In this study, fourth order IIR (infinite impulse response) Butterworth bandpass filter was used to mitigate low frequency artifacts and high frequency noise. The filter cut-off frequencies were set at 0.5 Hz and 100 Hz. A second order IIR notch filter with cutoff 50 Hz (for EEG recorded in Europe) or 60 Hz (for EEG recorded in USA) was also used to suppress the power line noise.

2.3. Summary

In this chapter, an innovative approach based on adaptive neuro-fuzzy inference system (ANFIS) for detecting artifacts in EEG signals was proposed. Performance was evaluated on real EEG data. The algorithms yielded accuracies in the range from 90.56% to 96.67%. For muscle noise, the sensitivity and accuracy were the lowest. This was

expected since muscle noise is in the high frequency range of EEG band (20 - 60 Hz) and overlaps with the large bandwidth of regular EEG spectra. Therefore, detecting this type of noise is difficult and filtering and removing it is much more difficult. Spectral features were used to characterize the muscle noise. Other two types of artifacts due to eye blinks and sensor motion were relatively easy to characterize in feature domain. Similarly, those can be easily filtered out from EEG. The algorithms resulted in accuracies close to 97% for both of these artifacts. As for filtering of EEG, since the main objectives was to develop fuzzy logic based algorithms in artifacts detection, seizure detection and prediction, traditional digital filters were used to reduce the affects of artifacts and noise in EEG as described above.

CHAPTER III

3. EPILEPTIC SEIZURE ONSET DETECTION

3.1. Introduction

In the context of epilepsy, EEG waveforms recorded from patient's brain can be classified into two broad categories, epileptic and non-epileptic. Abnormal EEG activities associated with epilepsy can be classified as ictal (during seizures) or interictal (between seizures). When prediction of epileptic seizure is of primary interest, EEG activities before an impending seizure are termed as preictal hypothetically. For epileptic seizure detection, ictal patterns required to be differentiated from interictal baseline. This could be considered as a pattern recognition problem where classification of different patterns is the primary goal. Relevant features could be extracted from the EEG segments which later can be classified using different techniques. Similarly, to detect an epileptic seizure event earlier, the subtle changes in preictal state comparing to interictal baseline have to be detected. These changes in EEG are evident in various characteristics features. The feature extraction also helps in reducing the dimensionality of the data. In this research, wide varieties of characteristics features were studied. An adaptive rule-based fuzzy logic system was developed to detect seizure onset from iEEG recordings.

In this study, a fuzzy rule-based adaptive seizure onset detection method was presented. Fuzzy algorithms were applied in combining more than two methods (four in

this study) for seizure onset detection. We utilized fuzzy "AND" combination instead of logical "AND" combination to study the feasibility of this method in early detection. The fuzzy product implication was utilized to realize the "AND" combination using fuzzy inference mechanism. The results showed that this approach could be a promising solution to address some of the challenges in the area of early seizure detection and eventually in seizure prediction. The overall method consists of several steps, pre-processing, artifacts detection, feature extraction, decision making using fuzzy logic, and post-processing. Time domain, frequency domain, and entropy-based features were extracted from intracranial EEG (iEEG) segments. These features were combined using a set of fuzzy rules and another set of fuzzy rule was used to combine information spatially. Final decision was made by applying a threshold procedure to this spatial-temporal combination of multiple features. Artifacts detection algorithm was applied prior to feature extraction to identify segments corrupted with electrode movement and saturation artifacts as explained in the previous chapter. The information was stored to be used in post-processing step. False detections caused by artifacts and other activities were rejected in the post-processing step [47].

The iEEG recordings were obtained from the Freiburg Seizure Prediction EEG (FSPEEG) database [47]-[49]. The database contains iEEG data from 21 patients with medically intractable focal epilepsies. The details of the database including patient's information, seizure origin, seizure type, and average seizure duration are given in Table 2.

Table 2. Summary of the iEEG data selected for analysis, including patient number, total data length, gender, age, seizure type, seizure origin, the number of analyzed seizures, and average seizure duration per patient. Acronyms: SP-simple partial seizure, CP-complex partial seizure, GTC-generalized tonic-clonic seizure, F-female, M-male.

Patient	Data length (hour)	Gender F: Female M: Male	Age	Seizure Type	Seizure origin	Number of analyzed seizures	Average seizure duration (seconds)
1	2.48	F	15	SP	Frontal	3	15.10
2	5.16	M	38	SP,CP,GTC	Temporal	2	107.97
3	5.10	M	14	SP,CP	Frontal	4	88.67
4	5.87	F	26	SP,CP,GTC	Temporal	3	86.46
5	3.81	F	16	SP,CP,GTC	Frontal	2	14.72
6	4.13	F	31	CP,GTC	Temporo/Occipital	2	78.60
7	3.91	F	42	SP,CP,GTC	Temporal	2	70.71
8	3.49	F	32	SP,CP	Frontal	2	163.72
9	8.83	M	44	CP,GTC	Temporo/Occipital	5	113.02
11	4.92	F	10	SP,CP,GTC	Parietal	3	195.83
12	7.87	F	42	SP,CP,GTC	Temporal	4	55.06
13	3.92	F	22	SP,CP,GTC	Temporo-Occipital	2	158.30
14	4.91	F	41	CP,GTC	Fronto-Temporal	3	264.95
15	5.92	M	31	SP,CP,GTC	Temporal	2	202.39
16	9.83	F	50	SP,CP,GTC	Temporal	4	138.94
17	14.59	M	28	SP,CP,GTC	Temporal	5	86.16
18	1.96	F	25	SP,CP	Frontal	1	13.64
19	5.92	F	28	SP,CP,GTC	Frontal	2	15.32
20	6.87	M	33	SP,CP,GTC	Temporo-Parietal	3	122.51
21	2.96	M	13	SP,CP	Temporal	2	79.04
Total/ Average	112.45	7 M/13 F	29.9	-	-	56	103.56

In this study, we selected iEEG datasets obtained from 20 patients to evaluate the performance of the proposed method. The total length of the data analyzed was 112.45 hours and total numbers of analyzed seizures were 56 [47]. The sampling frequency of the data is 256 Hz. The database contains six channels with common reference, three located in the epileptogenic zone and three in remote locations [47]-[49]. A typical seizure evolution profile is shown in Figure 11 [47].
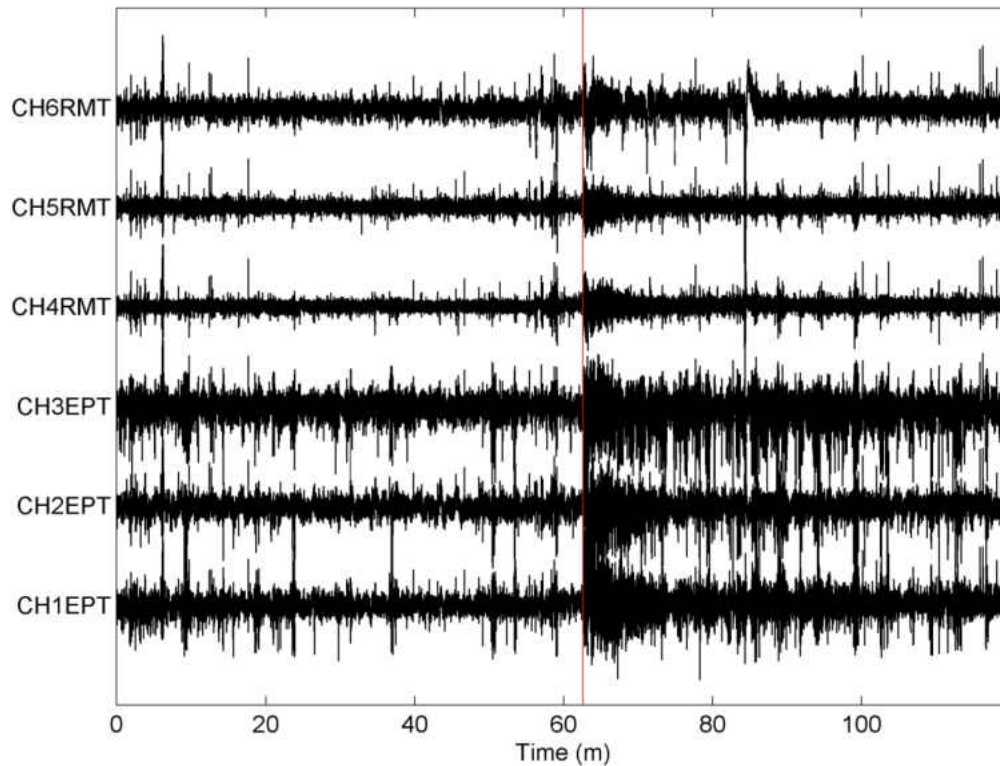
Figure 11. Typical seizure evolution profile in iEEG (patient 9 of FSPEEG database); seizure onset time is marked by red vertical line. Acronyms: CH1EPT-Epileptic channel 1, CH4RMT-Remote channel 4.

Although iEEG data are usually less corrupted with artifacts comparing to surface EEG, visual inspection confirmed the presence of saturation and electrode movement artifacts in some patients' data. The data files obtained from the FSPEEG database also provide some information on artifacts, mostly movement artifacts. Visual inspection was performed based on that information. An artifacts detection algorithm was implemented to identify the EEG segments corrupted with these two types of artifacts: saturation and electrode movement. Each segment with artifacts was marked and the information was stored in memory to be used later in the postprocessing step. The artifacts detection algorithm steps are discussed in the following section [47].

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3.2. Preprocessing

Although iEEG data are usually less corrupted with artifacts comparing to scalp EEG, visual inspection confirmed the presence of saturation and electrode movement artifacts in some patients' data. The data files obtained from the FSPEEG database also provided some information on artifacts, mostly movement artifacts and visual inspection was performed based on that information. We implemented an artifacts detection algorithm to identify the EEG segments corrupted with these two types of artifacts: saturation and electrode movement. Each segment with artifacts was marked and the information is stored in memory to be used later in the postprocessing step. The artifacts detection algorithm steps are discussed in following sub-sections [47].

3.2.1. Saturation Artifact

There were several cases of iEEGs corrupted with saturation artifacts. At the saturation time, iEEG signals have constant amplitude. The segments with saturation artifacts were identified by a derivative method. Every segment with zero derivatives was marked as segments with saturation artifacts [28]. A median filter of window size 5 was used to remove all single segment saturations [47]. This prevents false detection of artifacts in other EEG segments rather than in the region of saturation [47].

3.2.2. Sensor Motion Artifact

This type of artifact is usually caused by patient's head movement or displacement of the electrode box. This type of artifact is of high amplitude with an upstroke [28]. Analytical signal processing approach was utilized in order to detect envelope of iEEG segments using Hilbert transform [50]. Average absolute envelope (E_μ) was computed for each segment using the following equation.

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$$E_\mu = \frac{|H(x)|}{N} \tag{5}$$

where $|H(x)|$ is the absolute of the Hilbert transform [50] of iEEG segment and $N = 640$ is the number of samples in each iEEG segment. The segments with artifacts were identified from the other EEG segments by applying a predetermined threshold ($Th = 0.6$) after normalizing E_μ within the interval [0 1] [47]. Threshold estimation is crucial since it is important not to label a seizure segment as a segment with movement artifacts. The threshold was determined by setting up a condition. The condition is the average absolute envelope of a segment has to be greater than the maximum of average amplitude of seizure segment to be considered as segment with artifacts. Therefore, it was confirmed that no seizure activities were falsely rejected as movement artifacts [47].

3.2.3. Filtering

All iEEG segments were band-pass filtered between 0.5 Hz to 100 Hz using a 4th order IIR digital Butterworth filter to mitigate high frequency noise and low frequency artifacts. The iEEG segments were then notch filtered to remove 50 Hz power line noise. The notch filter cutoff frequency was set at 50 Hz since data analyzed were collected in a European hospital [47].

3.3. Feature Extraction

Time domain, frequency domain features and entropy-based features were extracted from iEEG segments. The four features used in this study were average amplitude, rhythmicity (coefficient of variation of amplitude), dominant frequency, and entropy. These features are known to contain the most discriminant information for

detecting seizure events [13], [15]-[19], [28]. Feature extraction methods are described briefly in the following sub-sections.

3.3.1. Average amplitude

Average amplitude (AVA) is a good measure for temporal evolution of partial seizures [13], [16], [28], [47], [51]. During partial seizures, iEEG signals show rhythmic activity with a repetition frequency between 3 and 30 Hz [28], [47], [51]. Therefore, to compute average amplitude, iEEG segments were first high pass filtered above 3 Hz to remove low-frequency noise [28]. Then, a peak detection algorithm based on the zero-crossings of the first derivative of iEEG signals was used to detect peaks [28]. The amplitudes of the peaks were computed by taking average of the amplitudes of their half waves. Finally, the AVA (μ_{amp}) was computed by taking the average of the amplitudes of the detected peaks [28], [47], [51].

3.3.2. Rhythmicity

Coefficient of variation of amplitude (CVA) is a measure of rhythmicity or regularities of ictal activities [28], [47], [52]. During seizure evolution, the regularity of the amplitude of EEG tends to increase slowly; this increase is characterized by the CVA [52]. In case of partial seizures, the signals exhibit strong rhythmic characteristics which likely to have regularity in amplitude [52]. The CVA quantifies the increased regularity observed during partial seizures [28], [47], [52]. The CVA is defined as the ratio of the standard deviation of absolute amplitude to the mean absolute amplitude as following [28], [47].

$$\delta_{cva} = \frac{A_{\sigma}}{A_{\mu}} \qquad (6)$$

where A_σ is the standard deviation and A_μ is the mean of each iEEG segment [28], [47], [52].

3.3.3. Entropy

Entropy is a measure of 'irregularity' or 'uncertainty' and was initially introduced by Shannon in 1948 [53]. The Shannon entropy (η) is computed as:

$$\eta = -\sum_k p_k log p_k \qquad (7)$$

where p_k are the probabilities of a datum in bin k [28], [47], [53]. Approximate entropy introduced by Pincus in 1991 is more appropriate to compute the entropy for short and noisy time series data [54]. A low value of the entropy indicates that the time series is deterministic, whereas, a high value indicates randomness. Therefore, a high value of entropy indicates the irregularities in the iEEG data. To compute approximate entropy, it is required to determine a run length and a tolerance window to measure the likelihood between runs of patterns [47], [54], [55]. The tolerance window, r and embedding dimension, m are the two important parameters. In this study, Sample Entropy which is a variant of approximate entropy to quantify entropy of iEEG was used considering its robustness over approximate entropy. Sample Entropy is the negative natural logarithm of an estimate of the conditional probability that segments of length m that match point wise within a tolerance, r also match at the next point [28], [47], [54], [55]. This measure is a useful tool for investigating dynamics of biomedical signals and other time series [47].

3.3.4. Dominant frequency

Dominant frequency (f_Δ) is defined as the peak with the maximum spectral power in the power spectrum of a signal [28]. This feature is particularly important in distinguishing ictal activities from interictal activities by quantizing the frequency signature information mostly found in partial seizures. This is characterized by a high frequency activity at seizure onsets and a low frequency activity at the end of the seizures [28], [47], [51]. In this study, parametric spectrum estimation method, autoregressive modeling (AR) approach, was used to estimate the spectral frequency band of the short iEEG segments [47]. The AR model order was chosen according to Akaike information criterion (20 in this study) [56]. The Burg method was used to for computing the AR coefficients for short iEEG segments [57]. Then, the spectral power of a given segment is estimated using these AR coefficients. For every spectral peak, the spectral frequency band was defined as [f_l and f_h] where f_l and f_h are frequencies at rising and falling slopes of the peak with half the amplitude of the peak [28]. The frequency of the peak with maximum spectral power is considered as the dominant frequency for the given segment [28], [47].

A typical epileptic seizure evolution profile along with revenant characteristic behaviors of the four extracted features as described above are shown in the following Figure 12 [47].
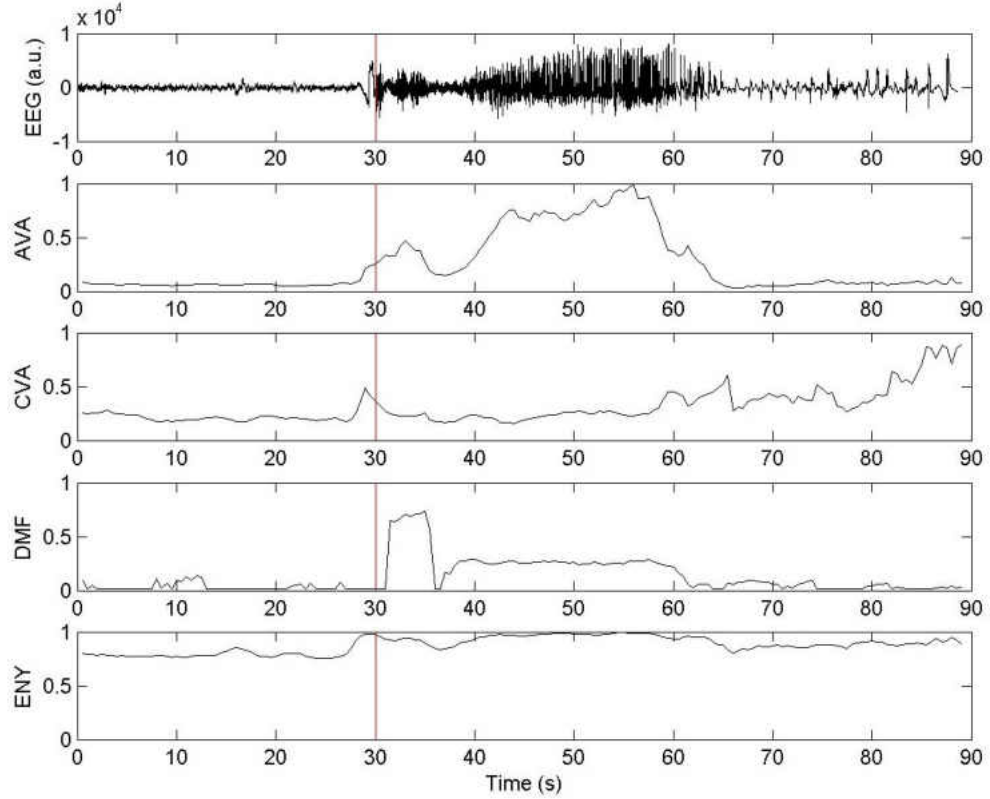
Figure 12. Seizure evolution profile: (a) top subplot: an example of a seizure evolution in iEEG (b) bottom four subplots: corresponding changes in characteristics features: average amplitude (AVA), coefficient of variation of amplitude (CVA), dominant frequency (DMF), and entropy (ENY). Seizure onset is marked by red vertical line. Early electrographic changes are visual in three of the four features.

3.4. Fuzzy Rule-based Detection

We designed a multi-stage fuzzy rule-based system for seizure onset detection. Decision making was performed in three steps [45], [47], [58]. We utilized the information obtained in spatial, temporal as well as feature domain to make the final decision [47]. Therefore, the fuzzy system was comprised of three sub-systems: (1) feature combiner, (2) spatial combiner, and (3) final decision making [47]. Figure 13 shows the block diagram of the overall system which includes pre-processing, feature extraction, fuzzy rule-based decision making, and post-processing [47].
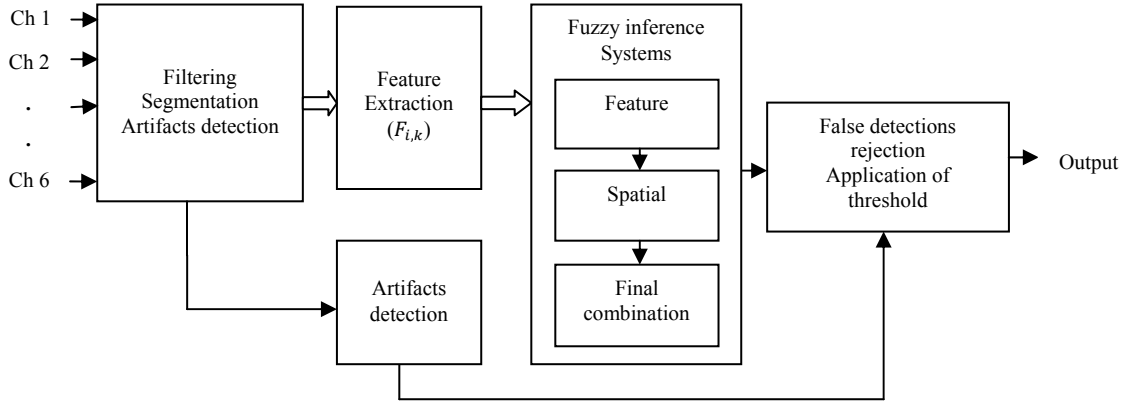
Figure 13. Block diagram of epileptic seizure onset detection system in iEEG. The system comprises of pre-processing, feature extraction, fuzzy rule-based decision making, and post-processing stages.

The features discussed above ($F_{i,k}$; $where\ i = 1,2,3,4\ and\ k = 1,2,\dots,6$) were used as the inputs to the first fuzzy sub-system which is adaptive in nature (feature combiner): Entropy (F_1: ENY), dominant frequency (F_2: DMF), average amplitude ($F3$: AVA), and coefficient variation of amplitude (F_4: CVA). The second fuzzy sub-system (spatial combiner) was used to select four specified channels and to combine the feature output from first fuzzy sub-system across channels. In final stage, another fuzzy sub-system was used followed by a threshold parameter in order to classify an EEG segment as "normal" or "seizure". The steps are discussed in detail in the following sub-sections [47].

The adaptive version of the fuzzy inference system was implemented as described in the previous section. Four features were combined using a carefully designed fuzzy inference system. Before fuzzifying the feature variables, they were normalized into the interval of [0 1] using a min-max normalization method. The triangular and trapezoidal membership functions were assigned to the fuzzy input and output variables. Assigning membership functions to the fuzzy input variables which are the features are extremely

important and critical [59]. We utilized fuzzy clustering to adaptively estimate the parameters for membership functions [59]. Fuzzy c-means clustering was applied to each of the feature to generate cluster center for two classes: "normal" and "seizure" [59]. Then cluster centers were used to generate the membership function by placing the fuzzy sets at the corresponding cluster centers. Two membership functions or fuzzy sets were considered for each of the four input features: low ($L: F_{i,k} < Th_h$) and high ($H: F_{i,k} > Th_l$) as shown in the Figure 14 (a). Th_l and Th_h were obtained from the corresponding cluster centers. This way membership functions were estimated adaptively based on the characteristics of the feature sets and the fuzzy system works adaptively. For the fuzzy output variable (OP_1), three levels were assigned as high ($H: OP_1 > Th_m$), medium ($M: Th_h > OP_1 > Th_l$) and low ($L: OP_1 < Th_m$) as shown in the Figure 14 (b). The values of threshold parameters chosen are $Th_l = 0.3$, $Th_m = 0.5$, and $Th_h = 0.7$. The OP_1 is the final feature after combining the four features [47]. We used the triangular and trapezoidal membership functions for the ease of their implementation [47]. Fuzzy logic has been utilized to combine this information obtained in feature domain using the first set of rules. The qualitative approach of fuzzy logic is specifically suitable to combine the four features and map them onto a final feature time series [47].
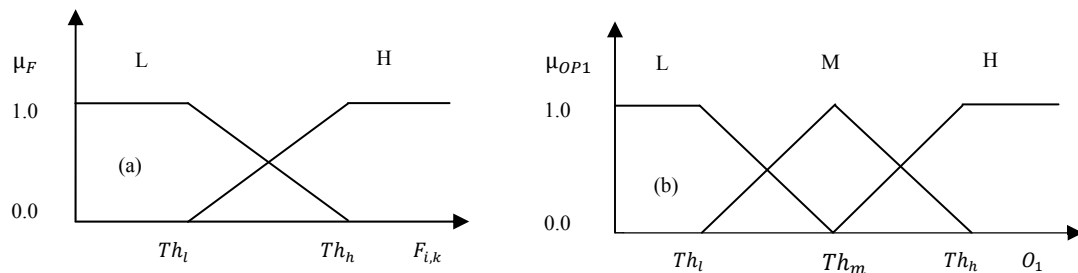
Figure 14. Triangular and trapezoidal membership grades assigned to the extracted features and the fuzzy output variables: (a) two membership grades, low (L) and high (H), were assigned for the membership functions of the feature inputs, (b) three membership grades, low (L), medium (M), and high (H), were assigned for the membership functions of output variable.

The fuzzy output variable (OP_1) will only be high "H" if and only if at least 3 feature input variables are high "H" and OP_1 will be medium "M" if two feature input is "H". For all other cases, the times OP_1 will be low "L" as shown in Table 3 [47]. The set of fuzzy rules for combining the features are listed in Table 3.

Table 3. Fuzzy rules for combining features.

F_1	F_2	F_3	F_4	OP_1
H	H	H	H	H
H	H	H	L	H
H	H	L	H	H
H	L	H	H	H
L	H	H	H	H
H	H	L	L	M
H	L	L	H	M
L	L	H	H	M
L	H	L	H	M
L	H	H	L	M
H	L	H	L	M
H	L	L	L	L
L	H	L	L	L
L	L	H	L	L
L	L	L	H	L
L	L	L	L	L

$F_{1\sim4}$= Feature 1 to Feature 4; OP_1= Output 1

The imprecise boundaries of interictal EEG and uncertainty associated with the features were addressed using this approach. To better explain, the behavior of rhythmicity alone may not hamper the performance of the overall system. More importantly, if any of the features is not able to detect subtle changes during seizure onset, a combination of the features using the fuzzy rules would be able to detect unless a seizure is missed due to non specific patterns. Similarly, spatial combination allows prioritizing the importance of in-focus channels due to their higher sensitivity to ictal activities [47].

For spatial combination, trapezoidal membership functions were assigned to the fuzzy inputs and output variable as shown in Figure 15. Two levels were considered for both the input (Ch_k where $k = 1, 2, ..., 4$) and output (OP_2) variables: low ($L: F_{i,k} < Th_h$) and high ($H: F_{i,k} > Th_l$) [47].
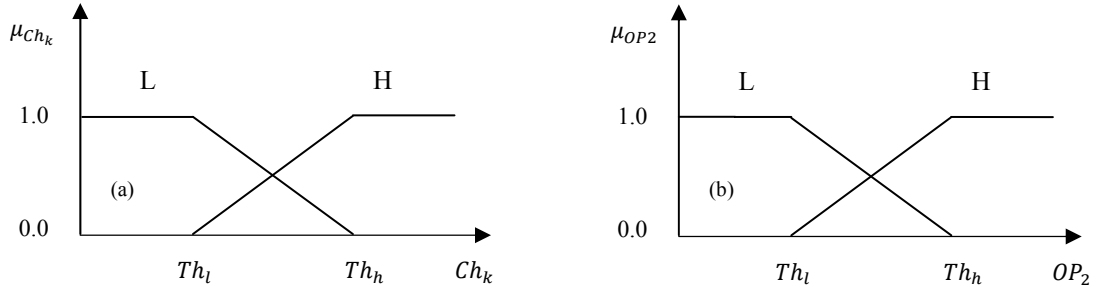
Figure 15. Trapezoidal membership grades assigned for combining across multiple channels to the extracted features. (a) Fuzzy input variable. (b) Fuzzy output variable. Two levels: high (H) and low (L) were considered.

Three channels in epileptogenic zone ($Ch_1, Ch_2, and \ Ch_3$) were combined with one channel chosen from remote area (Ch_4). These four channels were combined using another set of fuzzy rules based on expert's reasoning as given in Table 4. The criteria was set based on the information that the channels in seizure onset area is more sensitive in detecting changes in EEG comparing to those from remote area. It is expected that in-focus channels will detect earliest changes in EEG. In order to minimize the detection latency, we considered all three in-focus channels in drawing up the rules for spatial combination. However, there are interactions between different channels location in brain. Therefore, to have modularity of the detection algorithm we have also included one channel from the remote area [47]. The rules were set in such a way that the output will only be high when two or more channel inputs fall in high level. The set of fuzzy rules for combining the final feature output (OP_1) across channels are listed in Table 4.

Table 4. Fuzzy rules for combining channels.

Ch_1	Ch_2	Ch_3	Ch_4	OP_2
H	H	H	H	H
H	H	H	L	H
H	H	L	H	H
H	L	H	H	H
L	H	H	H	H
H	H	L	L	H
H	L	L	H	H
L	L	H	H	H
H	L	H	L	H
L	H	L	H	H
L	H	H	L	H
H	L	L	L	L
L	H	L	L	L
L	L	H	L	L
L	L	L	H	L
L	L	L	L	L

$Ch_{1\sim4}$= Channel 1 to Channel 4; OP_2= Output 2

The fuzzy rules were developed based on human (expert's) knowledge and reasoning. In clinical settings, epileptologists or EEG technologists identify seizure activities based on some criteria of the signals under investigations. They look into different morphological patterns, amplitude variation and/or frequency variation with respect to baseline activities. In addition, a decision is being made upon agreement of multiple people's opinion. The fuzzy rules were set to mimic human reasoning in detecting earliest change in EEG based on visual inspection. For feature patterns, higher probability assigned when three or more features fall in the same level. Similarly, medium probability was considered for two features in same level as combination of features for optimum performance was the primary objective. When only one feature level is high, the lowest probability was set. Similar ideas were implemented for spatial combination or the combination of the channels.

In final decision stage, averaging was performed for 5 consecutive segments using moving average method. Another fuzzy inference sub-system was utilized to combine channel combination (OP_2) and segment average (SA) information. This fuzzy system acts as a postprocessor. Taking average across segments were able to minimize shot length false detections. Four rules were defined based on human reasoning for mapping onto an alarm output space for preliminary decision making as shown in Table 5. The idea behind setting up the rules was, when output from previous system as well as segment average is high there is a high probability that the output will also be high. In case one of the inputs is high, medium probabilistic level was assigned for output. In the other scenario, when both the inputs are low, the output is assigned low fuzzy level. The Mamdani-minimum implication operator was used for fuzzy inference and centroid defuzzification method was used to defuzzify the fuzzy output (FOP) variables [45], [47], [58].

Table 5. Fuzzy rules for mapping onto an alarm output space.

OP_2	SA	SZ
H	H	H
H	L	M
L	H	M
L	L	L

OP_2= Output 2; SA = Segment average; SZ = Final output

Before making the final decisions, the system scans each iEEG segments for artifacts. In artifacts detection step, segments with artifacts were identified and the information was stored to be used in post-processing step. False detections caused by artifacts were filtered in this step. The iEEG segments corrupted with artifacts were assigned a value of '0' which leaves the probability of detection to zero too. Further analysis on false detections were carried on and false detection rates were labeled as

uninteresting and interesting [26]. In this study, the uninteresting false positives were mostly of short duration and caused due to residual artifacts and large amplitude rhythmic activities. These short length false detections were rejected by setting a minimum length detection criterion [28], [47].

A threshold procedure was applied for final decision making. Whenever the alarm 'SZ' crosses the threshold, a seizure event was detected. Each segment was assigned probability value of '0' for normal segment and '1' for seizure segment [47].

3.5. Performance Evaluation

3.4.1. Sensitivity

Since the objective of the system is to detect seizure onsets, sensitivity is an important statistical measure for event based performance evaluation. It measures the ability of a system to detect seizure onsets correctly. It is the measure of true positive rate and defined as the ratio of the number of correctly detected seizure onsets to the total number of seizures [22], [27], [47]. It is expressed in percentage as follows:

$$Sensitivity = \frac{TP}{TP + FN} \times 100 \tag{8}$$

where TP and FN are defined as follows [47]:

- True Positive (TP): The system detects a seizure that was annotated as seizure by the expert.
- False Negative (FN): The system misses a seizure that was annotated as seizure by the expert.

3.4.2. False Detection Rate

False detection rate (FDR/hour) is another important parameter for the system performance evaluation [28]. It was computed by counting the false positives and divided by the total data length analyzed in the experiment for a given patient [47]. To be successfully implementable in clinical settings, FDR should be considerably low so that neither the patient nor the caregivers have to wait too long under false alarms [47]. However, usually it is better to detect the onset patterns with longer detection latency rather than missing them [47].

3.4.3. Detection Latency

Detection latency or lag is the time delay between the system detected seizure onset and clinical seizure onset identified by experts [16]-[19], [28], [47]. Detection latency was computed as the difference between the clinical seizure onset (expert detected seizure) and system detected seizure onset [19], [28], [47]. For an automatic detection algorithm or in case of early detection, the detection delay time expected to be considerably low or negative for early detection [47]. FDR was presented as an alternative measure to specificity.

3.5. Results and Discussion

3.5.1. Changes in Characteristic Features

Before designing the fuzzy logic system, visual inspection was performed to identify the types of changes in characteristic features at the time of seizure onset as well as offset. In most cases, the values of average amplitude increase after a few seconds on seizure onset. The values of rhythmicity gradually increase during seizure onset followed

by a decrease to a minimum then return to the interictal baseline level few seconds prior to seizure offset. In case of partial seizures, frequency activity increases right after the seizure onset up to a peak then gradually decreases to a low frequency activity. Entropy values showed increase which reaches the maximum after a few seconds of seizure onset and fall down to interictal baseline at seizure offset. This means the complexity of signal increases during seizure. However, it does not increase to maximum right after the onset. In some patients, the electrographic changes are identified before clinical onset. Such a seizure evolution profile and the behavior of the characteristic features are shown in Figure 12 (for data obtained from patient 9) [47].

3.5.2. Threshold Estimation

A threshold procedure was applied to make the final decision and assigning probability value of '1' to ictal iEEG segment and '0' to normal iEEG segment. The threshold procedure was applied to preliminary results obtained at the output of the final fuzzy-subsystem where the spatio-temporal combination was performed. The threshold parameter was optimized in a patient specific way. The setting was optimized prioritizing higher sensitivity and lower false detection rate. It was determined by plotting the histogram of alarms generated for each patient. We used threshold values outside two standard deviations above mean. The range was 2 to 6 standard deviations above mean [47].

3.5.3. False Detections

The false positives less than 9.5 sec was rejected except for patient 18 where the minimum length criteria was lowered to 4 sec due to the unusual short length of one

seizure onset pattern. After rejecting unusual short length false positives, the system yielded average false detection rate of 0.26 per hour [47].

3.5.4. Performance Evaluation

A total of 112.45 hours of IEEG dataset having 56 seizures were used for system performance evaluation. The summary of the database used for testing of the algorithm is shown in Table 2 [47]. The results are given in Table 6. Out of 56 seizures analyzed, the system correctly detected 54 seizures whereas 2 seizures were missed. Therefore, the overall sensitivity achieved was 95.8%; the false detection rate was 0.26/hour and average detection latency was 15.8 seconds. Although, detection delays should be as low as possible, the obtained results are in the acceptable range and comparable to the other methods in literature. The results were compared in details with the other existing approaches in the later section 3.6. The data from patient no. 10 (of FSPEEG database) was not considered from in analysis due to the excessive presence of electrode movement artifacts [47].

Event based sensitivity is reported in percentage. A seizure onset is considered as an event to detect. The average detection latencies are listed in seconds. Short length false detections could also be reduced using a median filter or considering spatial criteria. The median filtering approach was tried but it has been seen that it falsely reject some true detections which are unusually of short lengths. Also, it affects the detection latency. To address this, we utilized a post-processor to minimize the uninteresting false detections which are significantly shorter in length then average seizure duration for each patient as described in post-processing section. The overall results are presented in Table 6 [47].

Table 6. Summary of the results: sensitivity in percentage, false detection rates per hour and average detection latencies in seconds.

Patient	No. of seizures	Data Length (h)	SEN (%)	FDR/h (uninteresting)	FDR/h (interesting)	Detection latency (s)
1	3	2.48	66.67	4.40	0.40	7.21
2	2	5.16	100.00	2.52	0.39	25.03
3	4	5.10	75.00	0.19	0.19	8.72
4	3	5.87	100.00	1.00	0.17	27.43
5	2	3.81	100.00	0.26	0.26	23.97
6	2	4.13	100.00	0.72	0.00	12.64
7	2	3.91	100.00	1.02	0.00	17.46
8	2	3.49	100.00	1.43	0.57	55.46
9	5	8.83	100.00	1.24	0.34	-24.92
11	3	4.92	100.00	1.01	0.40	-6.84
12	4	7.87	75.00	2.16	0.50	21.04
13	2	3.92	100.00	0.51	0.00	-37.69
14	3	4.91	100.00	0.61	0.20	40.14
15	2	5.92	100.00	0.00	0.00	27.37
16	4	9.83	100.00	3.86	1.01	5.64
17	5	14.59	100.00	0.06	0.00	23.52
18	1	1.96	100.00	1.02	0.00	0.31
19	2	5.92	100.00	0.33	0.00	1.33
20	3	6.87	100.00	0.43	0.14	27.07
21	2	2.96	100.00	4.72	0.67	61.42
Total/Average	56	112.45	95.83	1.37	0.26	15.81

Our method yielded average sensitivity of 95.8% with 0.26/h false detection rate. The average detection latency achieved is 15.80 seconds as shown in Table 6. The algorithm was developed in an unsupervised approach. We did not include the seizure free long-term interictal data for evaluation purpose since there is no training involved. Inclusion of long-term intracranial data could possibly lower the false detection rate and mimic the real-life application of a prospective seizure onset detection algorithm. The dataset we used were constructed from the "ictal" data files from Freiburg project which have seizures with at least 50 minutes of preictal data and postictal data with no specified duration. Therefore, the false detection rate per hour is little higher comparing to other methods in literature but reasonable considering the evaluation dataset [47].

3.5.5. Advantage and Motivation of Using Fuzzy Logic-based Approach

The motivation behind our fuzzy rule-based approach is that fuzzy logic uses a much simpler rule-based design using natural language. Clinical neurologists mostly look at different features of seizure onset patterns as well as different channels to identify a seizure correctly. This is however complex to model mathematically and implement in computer programs. Fuzzy logic, on the other hand, provides a simpler design of approximate reasoning which can mimic human reasoning efficiently. We have developed our method in such way to mimic the human reasoning in detecting seizure onset patterns. Furthermore, the system provides a possibility of lowering the detection latency by incorporating more sensitive features [47].

Fuzzy logic has been widely used in many signal processing and pattern recognition applications [34], [60]. Rule-base can be defined using expert's knowledge for decision making which are simpler to implement and modular as well. Increasing the number of rules one can increase the accuracy of the model. Processing speed can also be improved significantly with less complex mathematical analysis and modeling. Moreover, fuzzy logic is a useful method for nonlinear input-output mapping which is effective in seizure detection or early detection applications. Other popular methods, such as artificial neural networks and support vector machines require training and complex mathematical analysis. In this study, we utilized adaptive version of fuzzy logic system with a novel approach of combining information in feature as well as spatial and temporal domain. A comparison of performance of the adaptive fuzzy logic system is shown over conventional hard threshold-based methods and non-adaptive fuzzy system in Table 7. Non-adaptive fuzzy system is where the membership functions were generated in a

heuristic way. Adaptive fuzzy system clearly out-performs other methods by demonstrating better performance in terms of better sensitivity and significantly reduces false positive rates [47].

Table 7. Performance of adaptive fuzzy system over single method with conventional hard threshold and non-adaptive fuzzy system.

Method	SEN (%)	FDR/h
Feature 1 (hard threshold)	96.25	1.93
Feature 2 (hard threshold)	93.75	3.62
Feature 3 (hard threshold)	98.75	1.16
Feature 4 (hard threshold)	84.17	1.98
Non-adaptive Fuzzy system	91.49	0.35
Adaptive Fuzzy system	95.80	0.26

3.6. Summary

In the last several years, many algorithms for epilepsy and seizure detection have been developed with different degrees of success [2]-[61]. Here, we discussed briefly some of these methods providing a scope of comparison with our method. In a recent study, Zhang et al. (2010) proposed an automatic patient-specific method for seizure onset detection using a novel incremental learning scheme based on nonlinear dimensionality reduction. Feature sets were extracted using continuous wavelet transform (CWT) [16]. Considering computation time and resources, the choice of discrete wavelet transform might have been better. Their method was evaluated on iEEG recordings from 21 patients obtained from the Freiburg project with duration of 193.8 hour and 82 seizures. They have reported average sensitivity of 98.8% with 0.25/h interesting false positive rate and average median detection delay of 10.8 sec. Aarabi et al (2009) introduced a fuzzy rule-based system for epileptic seizure detection which yielded sensitivity of 98.7% and false detection rate of 0.27/h with detection delay of 11 sec [28]. In this paper, different thresholds were used for different patients and a post-processor

was utilized to reduce the false detections in two steps, first short-length detections (less than 5 sec) and artifacts were rejected [28]. Secondly, two consecutive detections were unified given they are less than a pre-defined minimum time interval (set to 30 sec) [18]. Chan et al. (2008) presented a novel patient-specific algorithm for seizure onset detection and accurate onset time determination. The algorithm extracts spectral and temporal features in five frequency bands within a sliding window and the feature windows were classified as containing or not containing a seizure onset using support vector machine (SVM) [14]. Support vector machine is a popular classification paradigm for epileptic seizure detection and prediction being used by many researchers in this area. In order to accurately localize the seizure onsets in time, the method makes use of clustering and regression analysis [14]. Therefore, their algorithm yielded precise detection in time as reported in five of the six patients, at least 90% of the latencies were less than 3 sec resulting median detection latency less than 100 ms with standard deviation less than 3 sec [14]. However, the method utilized user-adjustable parameters allow tuning to achieve high detection sensitivity, false positive rate and detection latencies. Standard cross-validation performance measures resulted sensitivities in the range of 80% to 98% and false positive rates from 0.12 - 2.8/h [14]. Gardner et al (2006) presented a detection latency which is negative in time (-7.58 sec); however, with a higher false detection rate of 1.56 false detections per hour [23]. The datasets used were selected from intracranial EEG recording of patients diagnosed with mesial temporal lobe epilepsy and described elsewhere [62]. Their system was evaluated on samples of 29 ictal and 41 interictal epochs and achieved 97.1% sensitivity [13]. Grewal and Gotman (2005) proposed an automatic warning system with high sensitivity and low false alarm rates for clinical use

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[19]. They used spectral features extracted from multiple bands, Bayes' theorem followed by spatio-temporal analysis [9]. The system required training and was tested on locally recorded datasets yielding 89.4% sensitivity with false detection rate of 0.22 per hour and mean detection latency of 17.1 sec with user tuning [9]. The datasets used for performance evaluation of the system were recorded at the Montreal Neurological Institute and Hospital [19].

The performance of our system is very much comparable to the other methods. It may not outperform the other methods in terms of all the performance measuring parameters. However, considering less mathematically complex design and lesser number of tuning parameters we have achieved similar results to other methods and in some cases better performance in terms of one or two performance measuring parameters [47].

In this chapter, adaptive fuzzy rule-based system was proposed for seizure onset detection from iEEG. Fuzzy rules were developed based on our knowledge and reasoning, obtained during visual inspection of data and features, for taking advantage of spatial-temporal combination of features and channels. To address the high inter-patient variability in feature space, we utilized fuzzy c-means clustering techniques for optimization of the fuzzy membership functions for features. Hence, adaptive fuzzy inference system was realized. The system yielded average sensitivity of 96% with 0.26 FDR/h, and detection latency of 15.81 sec. To summarize, more sensitive features are required for designing an early detection or prediction system.

CHAPTER IV

4. EPILEPTIC SEIZURE PREDICTION

4.1. Introduction

Epilepsy is one of the most common neurological disorders that affect approximately 3 million Americans according to the Epilepsy Foundation [63]. Every year approximately 200,000 new cases of epilepsy are diagnosed in the United States [63]. The estimated annual cost related to epilepsy and seizure is $17.6 billion [63]. Moreover, severe brain damage as well as death can be caused by uncontrolled seizure. Therefore, to improve the quality of life of epilepsy patient as well as minimizing the economical impact, new therapeutic solutions are of high demand. If it were possible to prevent or minimize seizure minutes to hour before clinical manifestations, the health risk could be minimized significantly by automatic drug delivery or issuing a warning to the patient. Development of such a warning device requires availability of a reliable and efficient prediction algorithm. Growing number of algorithms proposed in literature demonstrates the possibility of designing a seizure prediction algorithm. However, none of the algorithms were successful in predicting seizures when applied to unseen or out of sample EEG recording leaving the research area still open for improvement and experimentation.

In this study, fuzzy rule based algorithms were developed based on nonlinear features extracted from EEG as a first step towards developing a prediction algorithm. We have demonstrated the applicability of fuzzy logic based approaches in seizure prediction. Since Fuzzy logic can accommodate human reasoning and machine learning capabilities it has the potential to have application in solving this problem.

4.2. Seizure Prediction using Rule based Fuzzy Logic

4.2.1. Background

In the previous chapter, linear signal processing techniques along with adaptive fuzzy rule-based decision making system was applied in detecting epileptic seizure onset [47]. The detection delay was measured [47]. The combinations of multiple features using fuzzy logic based approaches were demonstrated. The combination showed improved performance over single feature extraction method. However, the features did not demonstrate enough sensitivity to be able to use in a prediction algorithm. To achieve the goal of prediction, sensitive feature extraction methods are required in identifying preictal states. During this study, a wide range of nonlinear dynamical systems based feature extraction methods were applied to EEG signals in attempt to quantify the pre-epileptic changes in EEG. EEG signals collected both from animal and human model were used [47], [64]. For decision making, fuzzy logic based approaches were utilized.

Chaos and fractal theory based nonlinear characteristic measures were applied to human invasive EEG recording in an attempt to predict seizures from EEG signals. A univariate feature, correlation dimension was computed after reconstructing a phase space trajectory from EEG signals. A fuzzy logic system was developed for decision

making which could be better described as a soft threshold method [65]. EEG data used in this study was obtained from the Freiburg Seizure Prediction EEG database as described in the previous chapter.

The concept of seizure prediction horizon (SPH) is important in prediction studies considering its importance in evaluating performance of a prospective algorithm. A prediction horizon is a hypothetical time window defined as a period in which a seizure event may occur. If an alarm predicting an impending seizure is issued in a predefined prediction horizon and if seizure event takes place within this horizon, it is termed as a true prediction. On the other hand, when an alarm does not follow a seizure, the prediction is false. In such scenario, there is a high probability of missing an impending seizure if the seizure occurs when the prediction horizon ends. This is termed as a missed seizure or false negative. Typical values of prediction horizon are found to be in the range of several minutes to hours in literature. Although, theoretically seizure prediction can be as long as an hour, this may not be convenient for patients as they have to wait the whole hour. Hence, shorter prediction horizons are desirable from both the point of view of patients and caregivers. However, shorter length of SPH might minimize the prediction probability. The probable scenarios in a prediction algorithm as well as the impact of SPH on performance of a prospective algorithm are illustrated in Figure 16.
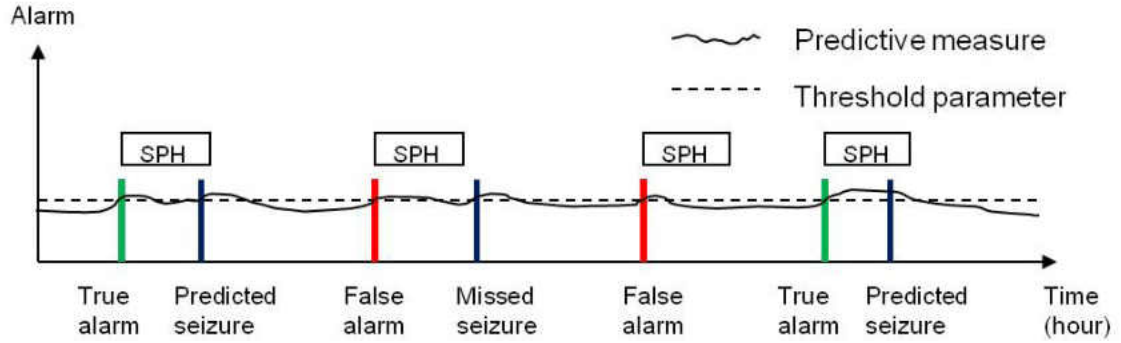
Figure 16. The concept of seizure prediction horizon and its impact on a prediction algorithm.

4.2.2. Preprocessing and Segmentation

In preprocessing step, EEG data was segmented using a moving window analysis technique. We chose 25 seconds of window length with 10 second overlap between the adjacent windows [65]. Data with such short lengths can be considered as quasi-stationary. This assumption is important considering the stationarity requirement of nonlinear analysis [29], [38]. An infinite impulse response (IIR) band-pass filter (4th order) with cut-off frequencies at 0.5 - 100 Hz was applied to reduce high frequency noise and low frequency artifacts [65]. Zero phase digital filtering was performed to keep phase information intact. Further, a notch filter with cut-off frequency at 50 Hz (European) was applied to reduce the power line interference [65].

4.2.3. Feature Extraction

In seizure detection, EEG data can be classified in two classes, epileptic (ictal) and non-epileptic (interictal or in between seizures). However, in seizure prediction problem, the widely accepted hypothesis is that there exists another state commonly termed preictal with significant overlap with ictal and interictal patterns. In this study, we hypothesized that identification of this preictal state is a pattern recognition problem.

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A. Phase Space Reconstruction: It is now widely accepted in the scientific community that the brain dynamics transition towards epileptic seizure is not an abrupt rather a smooth one. To study these changes in brain dynamics, phase space trajectory is reconstructed from EEG using Taken's theorem [66]. Nonlinear dynamical systems based measures quantify different properties of this state space trajectory which represent complex underlying brain dynamics. Figure 17 shows such trajectories reconstructed from normal and epileptic EEG segments showing the hypothetical state transitions.
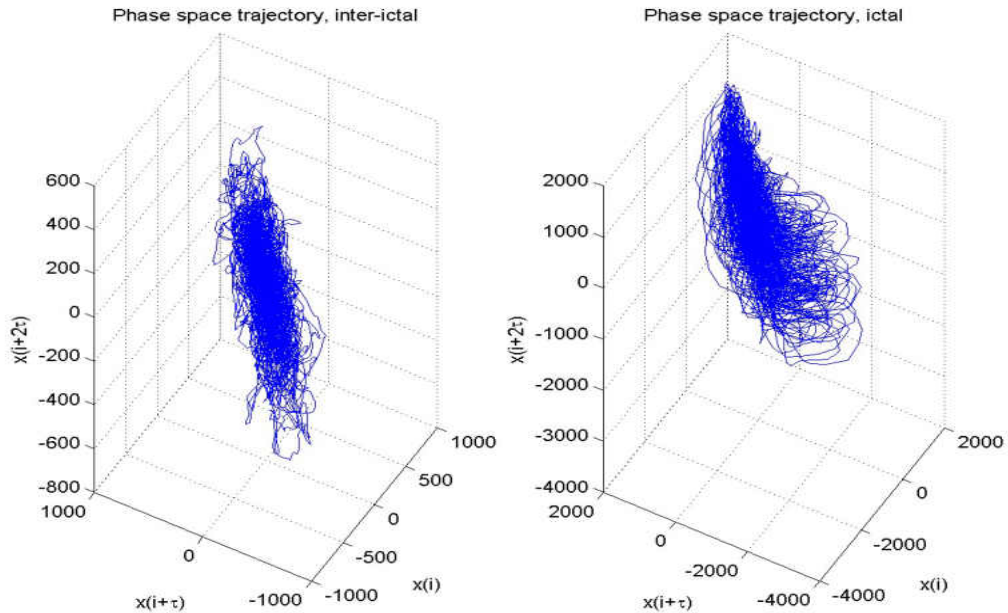
Figure 17. Reconstructed phase space trajectories from baseline EEG and ictal EEG.

B. Correlation Dimension Computation: In this study, correlation dimension was computed from iEEG segments [65], [67]. One of the main problems in estimating dimension from a chaotic time series, such as EEG time series is that the natural phenomena are usually corrupted by noise [65], [68]. These inaccuracies in measurement can be measurement noise and quantization noise resulted from the analog-to-digital

conversion [65], [68]. In some cases, experimental signals can also be corrupted by movement related artifacts and sensor displacement.

The classical Grassberger-Procaccia approach of estimating dimension may not be accurate in the case of noisy EEG segments [68]. We utilized a robust method of estimating dimension based on the assumption that the data are samples from a low dimensional attractor with noise components which are strictly bounded in amplitude [68]. The method first computes correlation integral [67]. The correlation integral or correlation sum is defined as the probability that two points or pairs of vectors in phase space are closer than a given radius, l [67], [68]. It is computed as following.

$$c(l) = \frac{2}{N(N-1)} \sum_{i=1}^{N} \sum_{j>1}^{N} \Theta(l - ||\vec{x_i} - \vec{x_j}||) \tag{9}$$

where $||.||$ indicates the Euclidean distance and Θ is is is the Heaviside step function as defined as following.

$$\Theta(s) = \begin{cases} 1 \ if \ s \geq 0 \\ 0 \ if \ s < 0 \end{cases} \tag{10}$$

Correlation integral has been found to follow a power law with, $c(l) = kl^D$ [65], [67]. Therefore, correlation dimension can be estimated as following [67].

$$D = lim_{l \to 0} \frac{\log{(c(l))}}{\log{(l)}} \tag{11}$$

In the case of noisy EEG, the scaling behavior might get corrupted by noise and the log-log plot will no longer show a linear part [65]. Hence, the dimension estimation could be flawed. The method proposed by Schouten et al. considers that there exists a trajectory that represents the true dynamics of the chaotic systems and close to the

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measured noise corrupted trajectory [65], [68]. The points of the noisy trajectory vectors

are assumed to be composed of noise free trajectory plus noise as described below [65],

[68].

$$z_{i,k} = x_{i,k} + \delta x_{i,k} \tag{12}$$

$$z_{j,k} = x_{j,k} + \delta x_{j,k} \tag{13}$$

where $z_{i,k}$ and $z_{j,k}$ are the elements of noisy trajectory and $x_{i,k}$ and $x_{j,k}$ are the elements in

the noise free part [65], [68]. The maximum norm distance between the noise-corrupted

vectors can be found from the following equation [65], [68].

$$l_z = lim_{m \to \infty} max_{0 \leq k \leq m-1} |z_{i,k} - z_{j,k}| = l_x + l_n \tag{14}$$

where l_z is the noise-corrupted distance, l_x is the noise free distance, and $l_n = \delta x_{max}$ is

the maximum noise distance [65], [68]. The power law can be re-written as following.

$$C(l_z | l_z > l_n) = k((l_z - l_n)^D \tag{15}$$

Furthermore, with the requirements that $C(l_z = l_0) = 0$ and $C(l_z = l_n) = 1$, we

can obtain [65], [68].

$$C(l_z) = \left(\frac{l_z - l_n}{l_0 - l_n}\right)^D, l_n \leq l_z \leq l_0 \tag{16}$$

Again, by normalizing all the distance measure with respect to the maximum

scaling distance, l_0, we can finally obtain [65], [68].

$$C(r) = \left(\frac{r - r_n}{1 - r_n}\right)^D, r_n \leq r \leq 1 \tag{17}$$

Finally, the correlation dimension can be estimated as following [65], [68].

$$D = \lim_{l \to 0} \frac{\log\left(c(r)\right)}{\log\left(r - r_n\right)} \tag{18}$$

Alternatively, the correlation dimension can be estimated using the maximum likelihood method as following [68].

$$D_{ML,n} = \left[\frac{-1}{M}\sum_{i=1}^{M} ln\left(\frac{r_i - r_n}{1 - r_n}\right)\right] \tag{19}$$

where $D_{ML,n}$ is the maximum likelihood dimension with $n \leq i \leq 1$ and M is the sample size of inter point distance, r_i [65], [68]. In practical cases, the parameter, D can be estimated from the non-linear least squares fit of the correlation integral function [66], [68]. We used the Levenberg-Marquardt least squares method to experimentally estimate dimension [65].

4.2.4. Rule-based Fuzzy Inference System

A fuzzy rule-based system was designed as an alternate to the crisp threshold based methods. Threshold parameter estimation is critical in prediction problem to achieve high sensitivity and specificity. The fuzzy rule-based system developed can be better described as a soft threshold method for detecting preictal changes in predictive features. The system was designed in such a way that each fuzzy system takes one feature as input and makes a decision based on the feature level and segment counts to generate predictive alarms. The fuzzy system utilizes expert's knowledge in the form of if-then rules for mapping of feature-segment input space onto an output alarm space. Although the exact behavior of correlation dimension prior to seizure onset is not defined, we considered that preictal segments exhibit significant change in dimension. This was the primary hypothesis in this study. The system counts the number of segments where the

feature level is below a specific level and uses this information to generate preliminary alarms [65]. The block diagram of the overall system is shown below in Figure 18 [65].
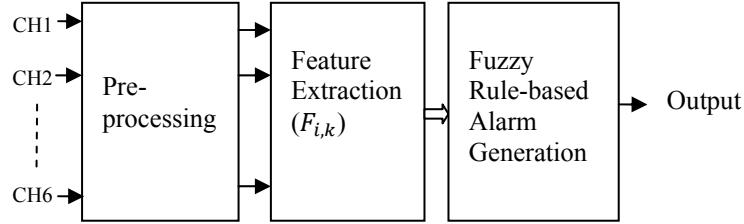

Figure 18. Block diagram of the fuzzy inference system designed based on changes in correlation dimension features.

The fuzzy inference system consists of several sub-systems work on single feature and single channel basis. Each sub-system works on a single channel basis having two input variables: the feature values ($F_{i,k}$) and the number of consecutive segments (N_{SEG}) with equal feature level [65]. Feature values ($F_{i,k}$) were normalized to zero mean and unity standard deviation before fuzzification of the input feature variables [65]. A seizure free reference window of length 215 sec was considered as baseline activities [65]. Statistical measures mean and standard deviation was computed from this reference window and used in normalization method [65]. Triangular and trapezoidal membership functions were used to fuzzify the input variables considering their ease of implementation [28], [65]. Two levels were considered for both the feature and segment count [65]. Low and high feature membership functions were defined as Low (L:$F_{i,k} < Th_c$), and High (H:$F_{i,k} > Th_c$) respectively. Similarly, low and high segment count membership function were defined as Low (L:$N_{SEG} < N_{Sc}$) and High (H:$N_{SEG} > N_{Sc}$) respectively. The parameters Th_c and N_{Sc} were chosen based on the statistical properties (mean $\pm$ standard deviation) of the feature vectors [65]. Similarly, two levels were assigned for fuzzy output variable as "SZ" for patterns referring to preictal changes and

"NS" patterns not referring to preictal changes [65]. The fuzzy if-then rules developed considering all the possible combinations of the input variables are given below [65].

If (F is L) and (SE is H) then (Output is SZ)
If (F is L) and (SE is L) then (Output is NS)
If (F is H) then (Output is NS)

where F stands for feature level, SE stands for segment level, L stands for low membership function, H stands for high membership function, SZ stands for higher probability of an impending seizure, and NS stands for lower probability of an impending seizure.

Mamdani min implication operator was used for fuzzy inference and centroid defuzzification was used for defuzzyfying the fuzzy output variable to crisp output [65]. The output for each segments was assigned a value within the range of [0 1] [65]. The output ($O_{i,k}$) results were the preliminary prediction results [65].

4.2.5. Postprocessing

A postprocessing method was applied to these primary results in order to generate final results. A temporal-spatial filter of size 5×6 (mask size) was applied to primary results and average was taken across this filtered channel sub-space data to generate the final alarm [65]. This filter size was chosen empirically in order to achieve the best results (highest true positive rate in percentage and lowest false prediction rate per hour). This required to be optimized in a patient specific way. This way, the information obtained in multiple channels (6 in this case) was combined spatial-temporally.

4.2.6. Results and Discussion

Two nonlinear features, correlation dimension (D_C) and maximum likelihood correlation dimension (D_{ML}) were extracted from intracranial EEG segments. Cubic spline curve fitting method was used for smoothing of the feature time series profile for decreasing trend of correlation dimension. The overall method was evaluated on EEG datasets obtained from 10 patients from the Freiburg seizure prediction EEG database (patient 10 - patient 19). The feature time series plot for data obtained from patient 14 (Freiburg Seizure Prediction EEG database) are shown in Figure 19 and Figure 20.
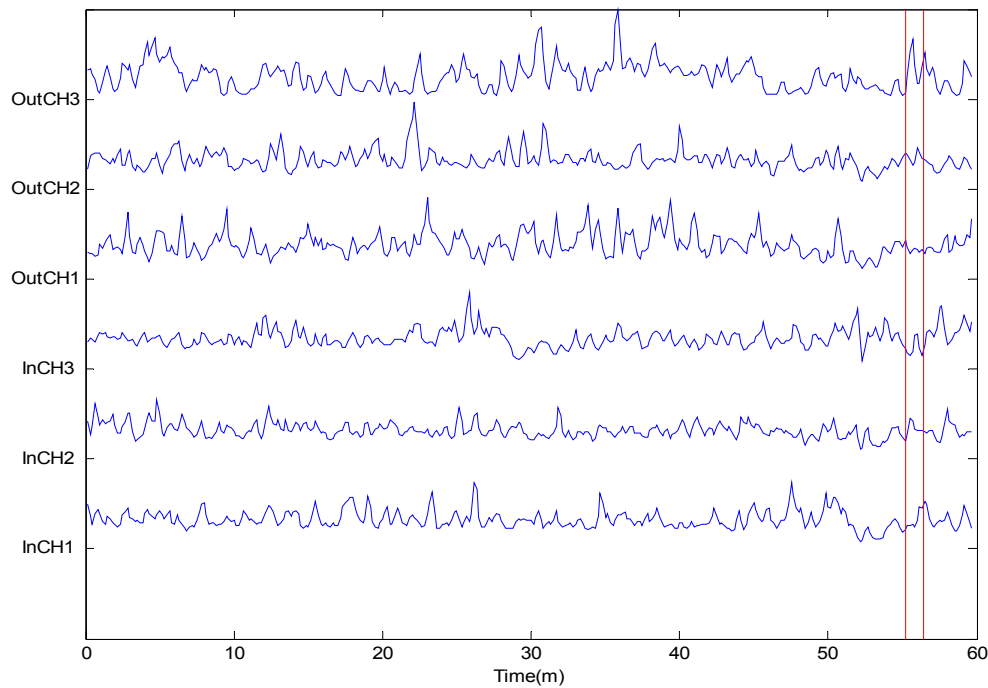

Figure 19. Correlation dimension characteristics feature profile. InCH and OutCH refer to the channels located in the epileptic zone and remote locations respectively. Seizure onset and offset times are marked by red vertical lines.
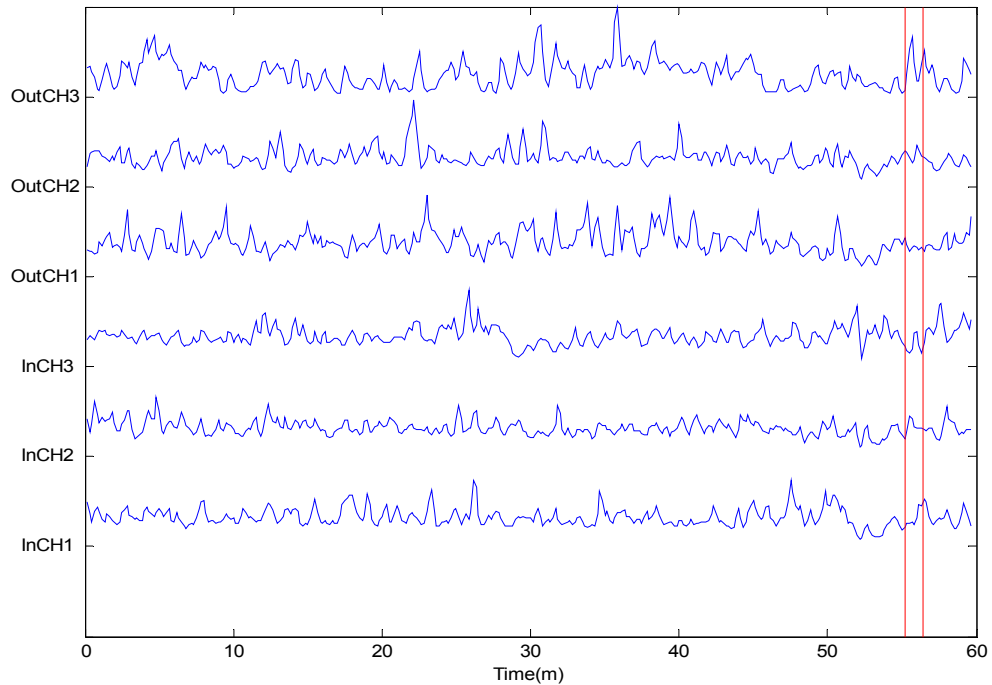
Figure 20. Maximum-likelihood characteristics feature profile. InCH and OutCH refer to the channels located in the epileptic zone and remote locations respectively. Seizure onset and offset times are marked by red vertical lines.

The fuzzy inference system takes one feature at a time as input and capable of making a seizure predictive decision. The output of the system after defuzzification provides the preliminary prediction results [65]. A post-processing method was applied before final decision making. A digital filter of size 5×6 was applied to the primary prediction results for reducing short length preliminary predictions across channels. Finally, average was taken across channels for issuing final alarms and a threshold procedure was applied. The threshold was optimized in a trial and error approach to maximize the performance (higher the prediction rate keeping the false prediction rate per hour least). The overall system makes use of spatial information in channels domain and temporal information in the feature domain. Exemplary prediction results obtained for feature 1 (correlation dimension) and feature 2 (maximum likelihood correlation dimension) are shown in Figure 21 and Figure 22 respectively.
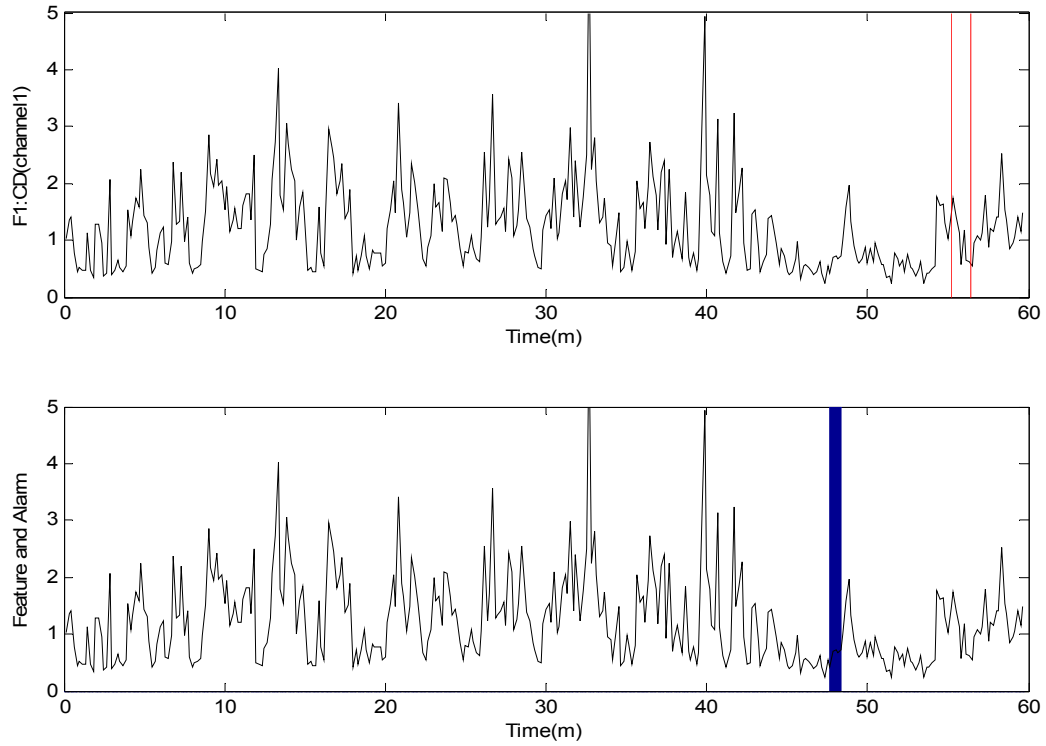
Figure 21. Correlation dimension feature profile and corresponding prediction alarms issued by the system. Seizure onset and offset times are marked by red vertical lines.
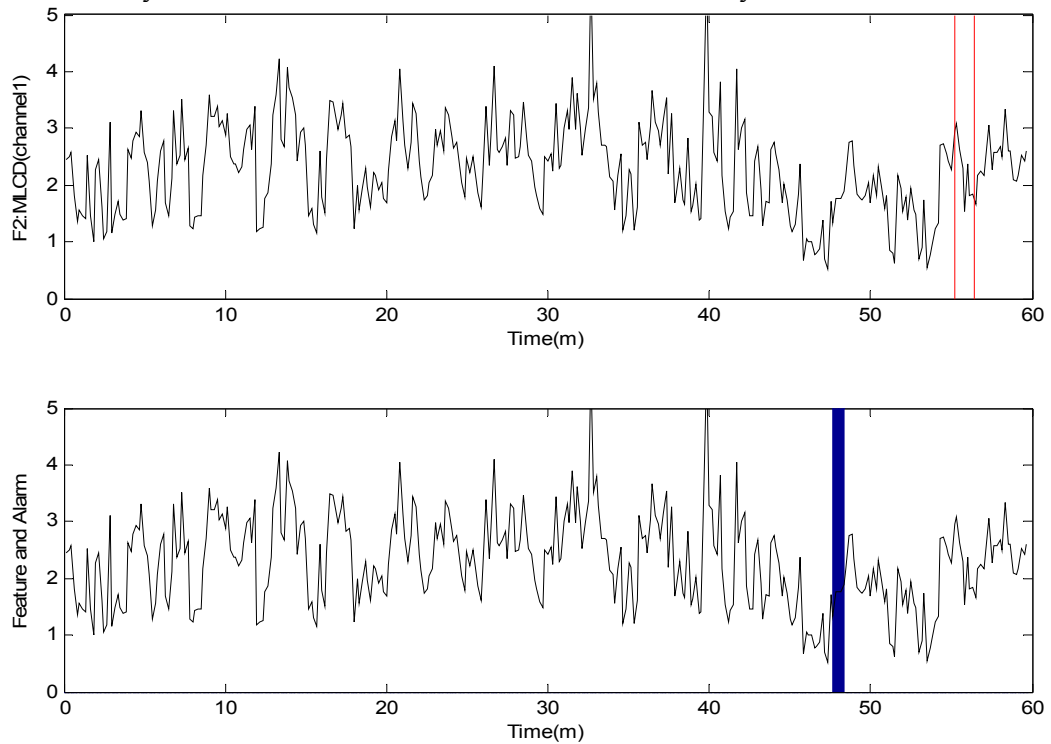

Figure 22. Maximum likelihood feature profile and corresponding prediction alarms issued by the system. Seizure onset and offset times are marked by red vertical lines.

The prediction results in terms of true positive rate in percentage and false prediction rate per hour for two different seizure prediction horizons are given in Table 8.

Table 8. Seizure prediction in terms of true positive rate (%) and false prediction rate (/h) results obtained from the data sets for maximum-likelihood correlation dimension as input feature and for two prediction horizon of 30 and 60 minutes.

Patient No.	Data length (h)	Seizure prediction horizon (min)			
		30		60	
		True positive (%)	False prediction rate (/h)	True positive (%)	False prediction rate (FPR/h)
10	4	50	0.5	100	0
11	1	0	1	100	0
12	1	100	0	100	0
13	1	100	0	100	0
14	2	50	1	100	0
15	1	100	2	100	0
16	2	0	1	100	0
17	1	100	0	100	0
18	1	100	0	100	0
19	2	50	0.5	100	0
Total/Average = 10	16	65	0.6	100	0

It is worth mentioning that the prediction results largely dependent on the sensitivity of the characteristic features in detecting subtle preictal changes. If the feature is not sensitive enough the system will most likely fail to produce desired results. Although decrease in dimension on or before seizure onset was reported [69], this claim was not confirmed rather challenged in other studies [70]. In this study, we also could not find a definite pattern of correlation dimension changes prior to a seizure. This raises the question whether the prediction results presented in Table 8 are reliable. The results demonstrated the role of prediction horizon lengths in predictions. Long prediction horizons can improve the prediction performance in expense of longer wait time. The prediction rate of 100% is unrealistic for the sudden and unpredictable nature of seizure occurrence. For shorter prediction horizon, the prediction rates of 65% with false

prediction rate of 0.6 per hour are more realistic. Therefore, we reproduced the common flaws found in current prediction algorithms tested on short or pre-selected data sets. Methods presented in later sections were focused on overcoming such flaws.

4.3. Recurrence Quantification Analysis of Rat EEG

4.3.1. Background

In the previous section, a fuzzy rule-based soft threshold method was proposed which can be applied to a seizure predictive feature for making prediction decision. The method was applied to correlation dimension, a nonlinear dynamical system based feature. However, the behavior of correlation dimension prior to seizure is unclear and the sensitivity of the same feature in detecting changes prior to an impending seizure is not proven yet [70]. On the other hand, one of the drawbacks of the nonlinear dynamical systems based features is their sensitivity to noise. Due to noise the reconstructed phase space trajectory from EEG signals may lead to wrong findings. To tackle this issue more robust data analysis methods are required. Therefore, we have applied a comparatively new method, Recurrence Quantification Analysis (RQA) proposed by Webber et al. and Marwan et al. [71]-[73]. The RQA based measures do not require the assumption of linearity, noiselessness, and stationarity which is advantageous considering their application in EEG signal processing. However, this method also requires the reconstruction of phase space trajectory using Taken's theorem [66]. Hence, the optimum choice of embedding dimension and time-delay parameters plays an important role in computation process [74]-[76].

In this study, RQA measures were applied in studying dynamical changes in EEG in an animal rodent model of epilepsy. Xioli Li et al. introduced the application of RQA measures in analyzing rat EEG for preictal changes [77]. Preictal changes identified by RQA measures were reported. In our study, RQA measures were applied to study the earliest pre-epileptic changes in rat's EEG collected in a rodent model of epilepsy [64]. EEG signal acquisition was performed from four adult rats. Three RQA measures, recurrence rate, determinism, and entropy were computed. A moving average filter was used to identify the decreasing trend towards status epilepticus.

4.3.2. Experiment

Epilepsy EEG data used in this experiment was collected from four adult Sprague-Dawley rats (each weighning 260 - 350 g.). Animals were housed individually in polypropylene cages at 22 ± 1 ºC. Food and water were provided ad libitum. To induce status epilepticus, Pilocarpine, a muscarinic cholinergic agonist, was used. Status epilepticus subsequently in due course of time results in chronic epilepsy. Each rat was injected with Scopolamine, an anticholinergic and antimuscarinic drug, half an hour prior to Pilocarpine injection. The purpose of Scopolamine injection was to suppress peripheral cholinergic effects. EEG data were collected with the sampling rate of 200 Hz from single channel where the electrode/sensor was placed in rat's brain in a surgical procedure [64].

The EEG recording prior to the Pilocarpine injection time was considered as the interictal baseline. Seizure start was identified by visual electropgraphic changes comparing to baseline activities by setting some criteria of amplitude and frequency change. The recording between the Pilocarpine injection and first electrographic change

was considered as preictal state hypothetically. The electrographic changes were became gradually dominant towards status epilepticus. Total lengths of 205 min of EEG recordings collecte from four adult rats were analyzed. The time lengths of each EEG recording data file and Pilocarpine injection time are given in Table 9 [64].

Table 9. Details on the EEG data collection experiments from rat.

Subject No.	Data length (min)	Injection Time (min)
1	40	11.93
2	50	9.98
3	35	11.63
4	80	12.31

4.3.3. Signal Processing

The raw EEG signals were first passed through a 4th order digital IIR Butterworth band pass filter to reduce high frequency noise and low frequency artifacts. The low pass cutoff frequency was set at 40 Hz while the high pass cutoff was at 0.5 Hz. Since the low pass cutoff was below power line frequency (60 Hz), a notch filter was not applied. For continuous computation of RQA measures, data was segmented using a moving window analysis technique. The length of each EEG window was 5 seconds with 50% overlap between the adjacent windows. Data were normalized to zero mean and unity standard deviation before RQA measure computation.

4.3.4. RQA Measures Computation

Recurrence of states is a fundamental property of chaotic systems or deterministic dynamical systems [71], [74]. Eckman et al. proposed a method to visualize the recurrence property in a phase space by using recurrence plot (RP) [78]. This method is the quantitative analysis of RP. The computation of recurrence matrix is given by

$$R(i,j) = \Theta(\varepsilon - ||\vec{x_i} - \vec{x_j}||) \tag{20}$$

where $\vec{x}$ is the reconstructed phase space array, $||.||$ indicates the Euclidean norm, ε is the predefined cutoff, and Θ is the Heaviside step function. Heaviside step function Θ is defined as follows:

$$\Theta(s) = \begin{cases} 1 \; if \; s \geq 0 \\ 0 \; if \; s \leq 0 \end{cases} \tag{21}$$

Three RQA measures, recurrence rate, determinism, and entropy were extracted from rat EEG data. These measures reveal important characteristics of the underlying dynamical systems, in this case epileptic brain. Recurrence rate quantifies the density of recurrence points in the phase space trajectory. Recurrence rate is computed by counting the black dots in the recurrence plot. Recurrence is computed as:

$$RR = \frac{1}{N^2} \sum_{i,j=1}^{N} R_{i,j} \tag{22}$$

In recurrence plot, deterministic behavior produces longer diagonals. On the other hand, stochastic behavior produces shorter diagonals. Determinism is defined by the ratio of the recurrence points on the diagonal structure to all the recurrence points. It is given by:

$$DET = \frac{\sum_{l=l_{min}}^{N} lP(l)}{\sum_{i,j}^{N} R_{i,j}} \tag{23}$$

where $P(l)$ is the frequency distribution of the lengths of the diagonal structures in the recurrence plot, l_{min} is the threshold which excludes the diagonal lines formed by the tangential motion of a phase space trajectory, and $R_{i,j}$ is all the recurrence points in the recurrence plot.

Entropy measures the complexity of the deterministic structure in a dynamical system [72]-[74]. The larger the entropy value, the more complex would be the deterministic structure [14]. The Shannon entropy that a diagonal line has exactly the length l is given by [72], [73], [77]:

$$ENTR = - \sum_{l=l_{min}}^{N} p(l) \ln p(l) \tag{24}$$

Embedding dimension, m and time delay, τ are two important parameters in computing these measures [73], [74], [77], [78]. In this study, two different sets of these parameters were considered and results were presented in the following section. The analysis was performed in MATLAB$^{\circledR}$ version 7.8.0.347 (R2009a) using the Cross Recurrence Plot (CRP) Toolbox [79].

4.3.5. Results and Discussion

The characteristics changes of RQA measures prior to and during seizure events were studied. The changes were identified as decreased value during ictal state from interictal baseline. As mentioned above, RQA measures were extracted with two sets of parameters: 1) embedding dimension, $m = 15$, time delay, $\tau = 11$, and radius of size of the neighborhood, $E = 1.5$; 2) embedding dimension, $m = 5$, time delay, $\tau = 5$, radius or size of the neighborhood, $E = 1.0$. Size of the neighborhood was chosen in units of the standard deviation σ of normalized EEG [64].

The results of the characteristics changes are illustrated in Figure 23 and Figure 24. The top subplot plot shows the EEG recording and bottom three subplots show the corresponding behavior of Recurrence Rate (RR), Determinism (DET), and Entropy

(ENTR) [64]. Decreased dynamics in terms of decreasing trends were found during start of the first electrographic seizure for average REC and DET [64]. Entropy values were found to be decreasing slightly before electrographic seizure start [64]. Steady decrease in all three features values was dominant towards status epilepticus [64]. Similar changes with slight variation were observed for the data obtained from the other three subjects [64].
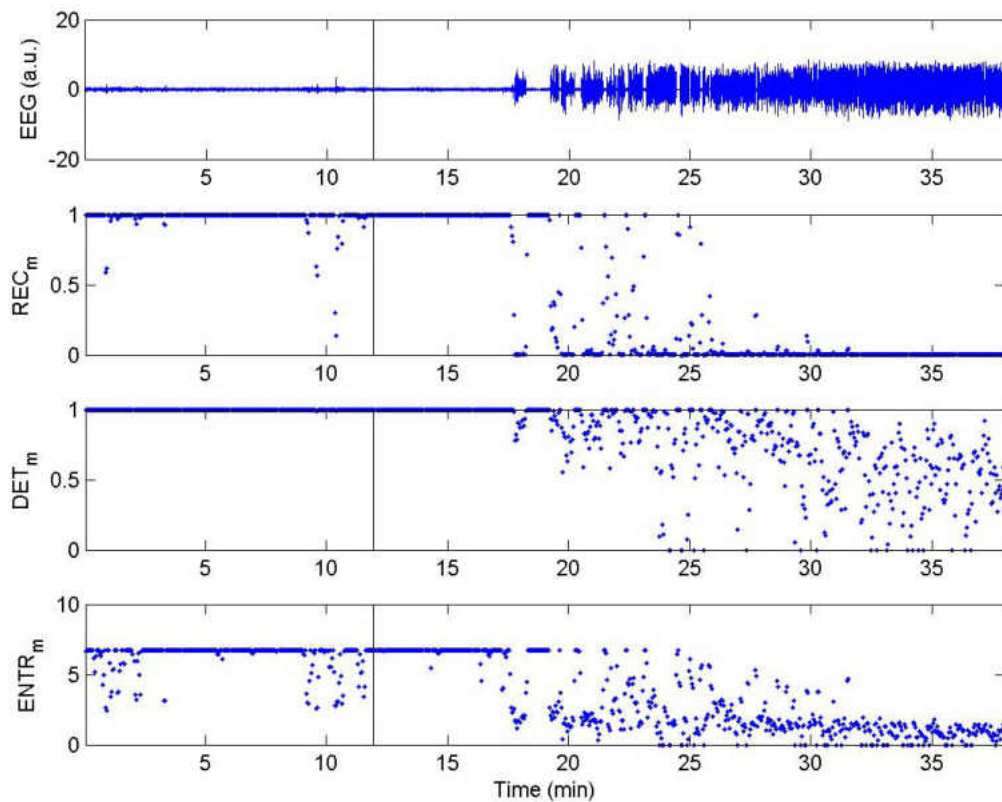

Figure 23. EEG data recorded from rat 1 and corresponding three average RQA measures for parameters, m = 15, τ = 11, and E = 1.5. The pilocarpine injection time is marked by the vertical line between 10 to 15 minutes.

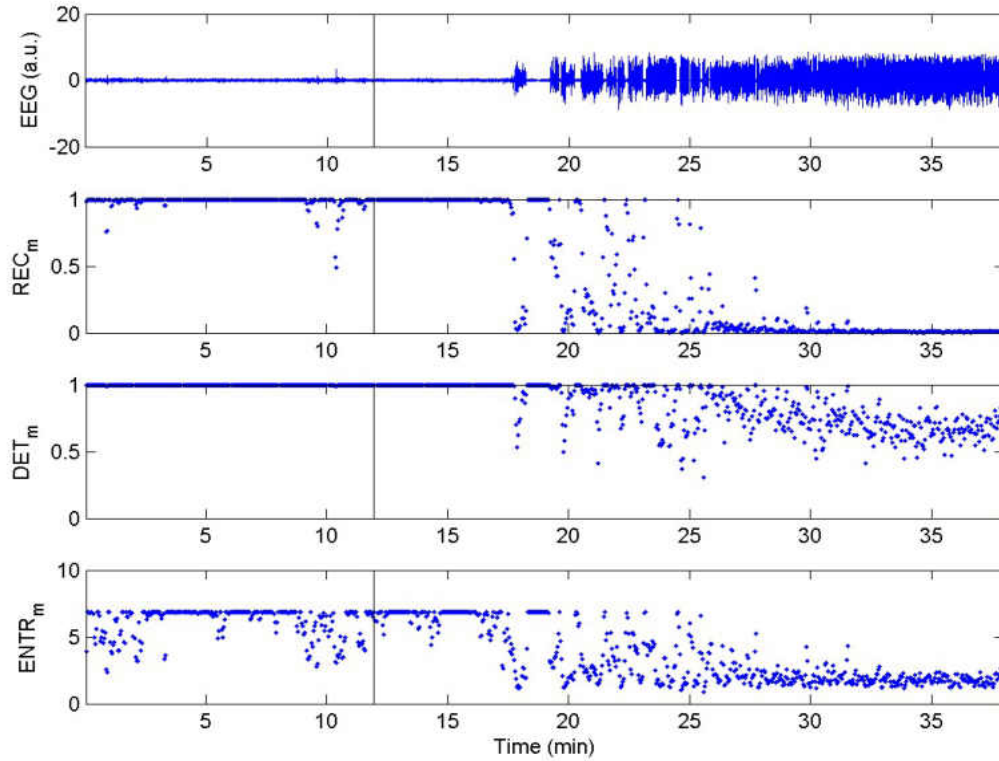Figure 24. EEG data recorded from rat 1 and corresponding three average RQA measures for parameters, m = 5, τ = 5, and E = 1.0. The pilocarpine injection time is marked by the vertical line between 10 to 15 minutes.

The characteristic feature time series profiles represent another problem of pattern recognition. The existence of two distinct classes is apparent in this case (subject 1) and the classes are linearly separable as shown in Figure 25. However, we could not find a smooth preictal transition in this pilocarpine induced rodent model of epilepsy. Li et al. reported their finding of significant decrease in RQA measures in pre-epileptic EEG [77]. In their experiment, they used bicuculline i.p. injection to induce epileptic seizures [77]. On the other hand, pilocarpine injection was used in our experiment to induce seizures and status epilepticus.
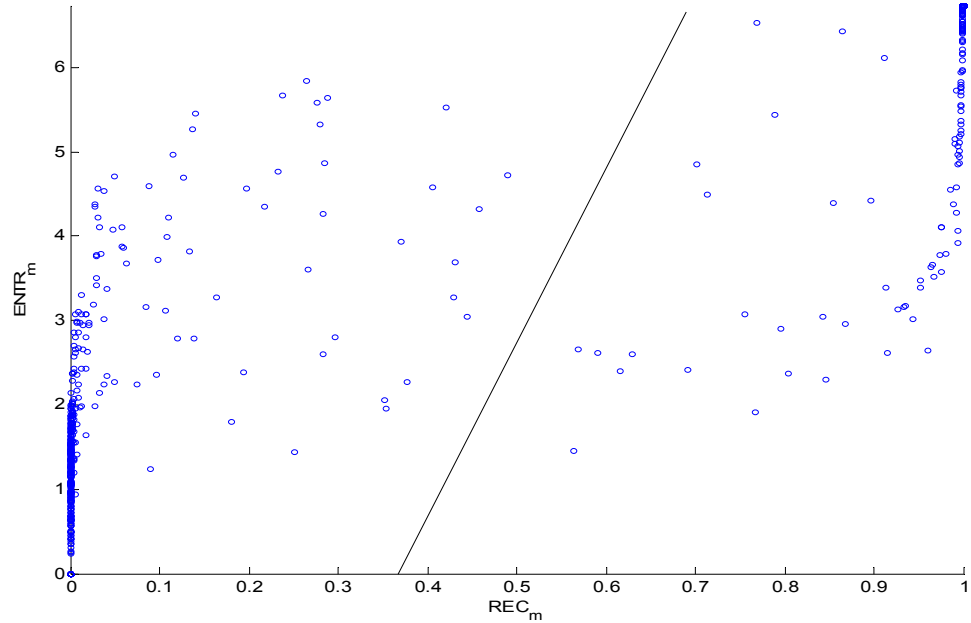
Figure 25. Linearly separable interictal and ictal classes revealed from the two RQA measures extracted from EEG data obtained from the rat 1.

In order to identify the trend in feature time series profile, a moving average filter with window size of 10 points was applied for smoothing. The trend identification, as illustrated in Figure 26, shows the gradual change in the RQA measures as EEG progress towards seizure. During status epilepticus, the feature values reach minimum.
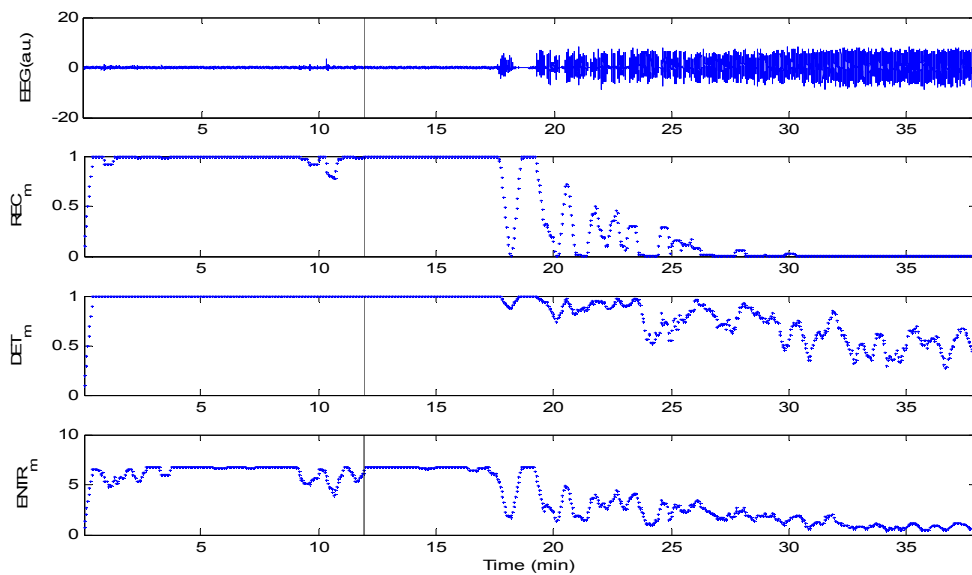

Figure 26. Trend identification of three RQA measures using a moving average filter.

This also facilitates application of a threshold procedure for decision making. Machine learning based methods can also be applied taking the features as inputs. Two sets of parameter values for delay time and embedding dimension were used for phase space reconstruction from EEG [64]. In practical applications, better results could be obtained while using optimum values of these parameters. The optimum embedding dimension can be found using false nearest neighbor method [66]-[68], [80]. Mutual information can provide optimum value of time delay for phase space reconstruction [66]-[68], [80].

4.4. Seizure Prediction Using Adaptive Neuro-Fuzzy Inference System

4.4.1. Background

The seizure prediction problem statement is introduced in previous sections. The importance of availability of a prospective seizure prediction algorithm is described. The current trend and past developments of research in this area has been discussed. There exist a large number of epileptic seizure prediction studies and/or algorithms leading to pacemaker like neurostimulation device in literature. These studies can be broadly classified in several categories. Firstly, most of the available algorithms apply a threshold based procedure on a single seizure prediction method or feature, such as phase synchronization [38]. In another approach, clustering based techniques were applied [34]. In machine learning based approaches, artificial neural network (ANN), support vector machine (SVM) have been used [81], [82]. These methods are capable of using multiple features extracted from EEG and require training in discriminating preictal state from interictal baseline. Recently, combining epileptic seizure prediction methods using Boolean "AND/OR" logic was proposed [83]. This method was shown having superior

performance over a single prediction method/feature based studies [83]. In another study, a patient-specific rule-based method was proposed taking advantage of spatial-temporal combination of multiple features [31]. All of these methods reported demonstrating limited degrees of varying success. The approach of combining multiple features could open new possibilities in seizure prediction.

Fuzzy logic based approaches could be very useful considering multiple features can be combined unlike Boolean logic which allows only combination of two features. Similarly, machine learning-based methods are also advantageous for having similar capabilities. Regardless of the choice of classifiers, the choice of features with significant sensitivity in identifying preictal states is another important point to consider. Both linear and nonlinear feature extraction methods are found in literature. Though the advantage of linear feature extraction methods over nonlinear ones are not clearly proven, seizure prediction studies are biased towards exciting computational aspects of nonlinear dynamical systems or chaos based features in detecting preictal transition states from EEG [29], [30]. The results of application of nonlinear methods in literature justify the applicability in detecting subtle and rather smooth transition of brain dynamics prior to a seizure [29], [31], [39], [47], [83], [84].

In this study, a seizure prediction algorithm using adaptive neuro-fuzzy inference system (ANFIS) is introduced building on the studies and results presented in the previous sections. The algorithm combines multiple nonlinear features, both univariate and bivariate. Univariate features are those extracted from single EEG channel whereas bivariate features are computed from two EEG channels. The ANFIS was trained to identify preictal state from interictal baseline [44], [45].

4.4.2. Methods and Materials

A. EEG Datasets: The EEG datasets used in this study were obtained from the European Epilepsy Database, one of the most comprehensive databases dedicated to epilepsy research [85], [86]. The database contains long-term continuous EEG recordings, both noninvasive and invasive, from 30 patients. The database is annotated by expert clinicians and provides comprehensive description of each of the patients' information, electrode montage descriptions, types of seizures, sub-clinical seizure activities etc [86]. Data obtained from one of the patients (patient id: FR_253) was selected for feature extraction, training, and testing of the ANFIS classifier. All 7 seven available seizures for this particular patient's data was analyzed. A total of 36 hours of data were used for feature extraction. Since, performance evaluation of the algorithm on long-term continuous data was primary objective, it was made sure that at least 3 hours or more preictal recordings were used for each of the analyzed seizure.

B. Preprocessing: Feature extraction was performed from continuous EEG using a sliding window analysis technique. The length of each window was 10 second with 50% overlap with the adjacent windows. This segmentation satisfies the criteria of stationary assumption in EEG analysis. Each of these segments can be considered as pseudo-stationary. A fourth order digital Butterworth IIR filter with cutoff frequencies at 0.5 - 100 Hz was applied to each of these segments to mitigate high frequency noise and low frequency artifacts. Moreover, a second order notch filter with cutoff frequency at 50 Hz was applied to reduce the affects of power line noise. Zero phase digital filters were used for both the filters. MATLAB® function *filtfilt* implements this zero phase filtering operation.

C. Feature Extraction: Univariate and bivariate nonlinear features were extracted from EEG. One univariate and two bivariate features were extracted from the two EEG channels located in the epileptic focus region. Univariate feature is typically computed from a single channel whereas bivariate features are computed from two EEG channels.

Dynamical Similarity Index (DSI) was the univariate feature we choose considering its sensitivity in detecting pre-epileptic changes as reported in previous studies [84]. This measure was applied to EEG signals successfully in identifying preictal state from interictal baseline [84]. In another study, this measure was applied to identify preictal state in rat EEG [87]. It was described by Le Van Quyen et al. in 1999 [84]. DSI quantifies the changes in dynamics of a test window relative to a constant reference window [84].

Bivariate features are well known for their sensitivity in detecting preictal changes [29]. Two bivariate features, phase synchronization and nonlinear interdependence, were extracted from two channels located in the epileptic focus region. Mean phase coherence measures the phase synchrony between two EEG channels [39]. Nonlinear interdependence measures the generalized synchrony or dependencies between two EEG channels or regions of the brain. Extremely low dependencies between regions generating epileptic patterns prior to seizure onset were reported [88]. Similarly, significant decrease in mean phase coherence before a seizure event was reported [39].

D. Application of ANFIS: ANFIS is a modified Sugeno type fuzzy inference system with added neural network learning capabilities proposed by Roger Jang in 1993 [44]. The ANFIS uses a hybrid learning algorithm for optimization which includes least

squares method and gradient descent backpropagation learning algorithm. The antecedent

or the premise part is linguistic in nature and perform the qualitative fuzzy reasoning in

the form of if-then rules. The consequent part is a linear function of the input variables. A

custom ANFIS architecture with four inputs F_1, F_2, F_3, and F_4 and one output O was used

in this study and shown in Figure 27. For simplicity, all the nodes in the three middle

layers (layer 2, layer 3, and layer 4) were not shown. The square nodes are adaptive in

nature whereas the circular nodes are fixed. The description of functions of each layer is

provided below. The fuzzy if-then rules for this ANFIS architecture are as follows:

$$If\ (F_1\ is\ A_i)\ and\ (F_2\ is\ B_i)\ and\ (F_3\ is\ C_i)\ and\ (F_4\ is\ D_i) \qquad (25)$$
$$then\ (f_i = p_iF_1 + q_iF_2 + r_iF_3 + s_iF_4 + t_i)$$

where F_1, F_2, F_3, and F_4 are the four feature inputs, A_i, B_i, C_i, and D_i are the fuzzy sets or

the sets defining membership functions, and p_i, q_i, r_i, s_i and t_i are the linear design

parameters. Both the membership functions and the linear parameters are adaptable and

optimized during training. The ANFIS architecture designed for seizure prediction with

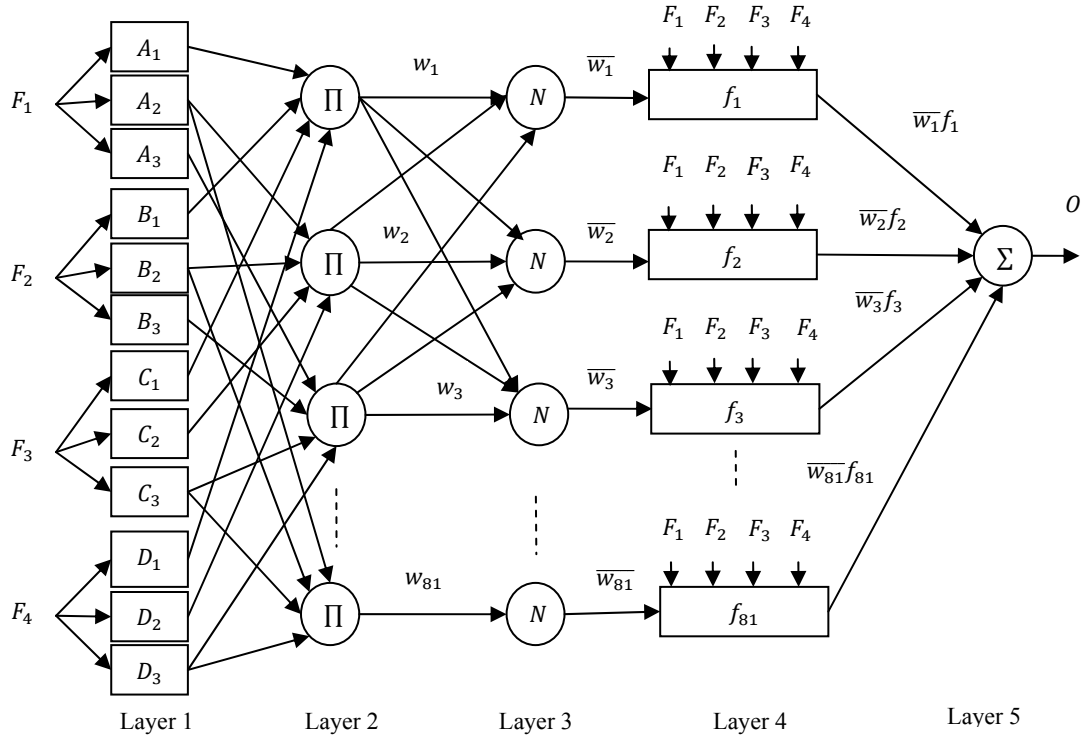four inputs and one output is illustrated in Figure 27.

Figure 27. ANFIS architecture with four inputs having three fuzzy membership functions and one output. For simplicity, not all the nodes and the connections of the middle layers (layer 2, layer 3, and layer 4) were shown. There would be a total 81 nodes in the middle layers.

Fuzzification of the input feature variables were performed in the first layer. Nodes in this layer are adaptive. Fuzzy input membership parameters were optimized during training using hybrid learning algorithm as described by Jang et al. [44]. The outputs of the first layer are the fuzzy membership grades of the input features are commonly referred as antecedent or premise parameters. Classical ANFIS model uses the bell-shaped membership functions. Since in previous studies trapezoidal and triangular functions were used in our study, Gaussian membership functions were used in this study. The nodes in the second layer, labeled $\prod$, performs the product implication operation (equivalent to logic operation "AND") on the incoming signals. This computes the firing strength of each rule as following.

$$w_i = \mu_{A_i}(F_1) \times \mu_{B_i}(F_2) \times \mu_{C_i}(F_3) \times \mu_{D_i}(F_4), i = 1, 2, \ldots, 81 \tag{26}$$

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The third layer is the normalization layer. The nodes in this layer computes the normalized firing strength of each as following.

$$\overline{w_i} = \frac{w_i}{w_1 + w_2 + \cdots + w_{81}}, i = 1, 2, \ldots, 81 \tag{27}$$

The nodes in the fourth layer are also adaptive and can be optimized for better input/output mapping. The nodes in this layer perform the following operation.

$$O_i^4 = \overline{w_i} f_i = \overline{w_i} \left(p_i F_1 + q_i F_2 + r_i F_3 + s_i F_4 + t_i \right) \tag{28}$$

where $\overline{w_i}$ is the output from the previous layer and $\{p_i, q_i, r_i, s_i, t_i\}$ is the first order polynomial set. Parameters in this layer are also referred as consequent parameters. These are linear functions of the input variables. Finally, the single node labeled $\sum$ in the output layer performs the aggregation or summation operation over all the incoming signals from the previous layer. The fuzzy output variable is the mapped output for the patterns presented at the inputs. The overall output computed as the summation of inputs is given below.

$$O_i^5 = \sum_i \overline{w_i} f_i = \frac{\sum_i w_i f_i}{\sum_i w_i}, i = 1, 2, \ldots, 81 \tag{29}$$

The consequent parameter and the premise parameters are updated using the hybrid learning algorithm. In the forward pass, the functional signals flow until the layer 4 and the consequent parameters are estimated using least squares method. Similarly, in backward pass, the error estimates propagate backward and the antecedent or premise parameters were updated using gradient descent method [44].

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Preparation of Training and Testing Datasets: A total of 36 hours of invasive EEG data having 7 seizures were used to evaluate the performance of the algorithm. The recordings were obtained from a patient's data within the European Epilepsy EEG database (patient id: FR_253). Data were divided in three sets, training, checking, and testing. The length of the training and checking data sets were 4.74 and 5 hours respectively with each having one seizure. Hence more than 3 hours of preictal recordings were available for training and checking against over fitting of the ANFIS model. Training was repeated until the checking error was in the acceptable range in a trial and error procedure. The ANFIS network was then tested on rest of the data set. The testing data set contained 5 seizures with total length of 26.12 hours. Hence, the algorithm was evaluated on out-of-sample data as well on long-term EEG recordings.

4.4.3. Results and Discussion

The temporal patterns of the feature time series profile for the testing data sets are shown in Figure 28 and Figure 29.
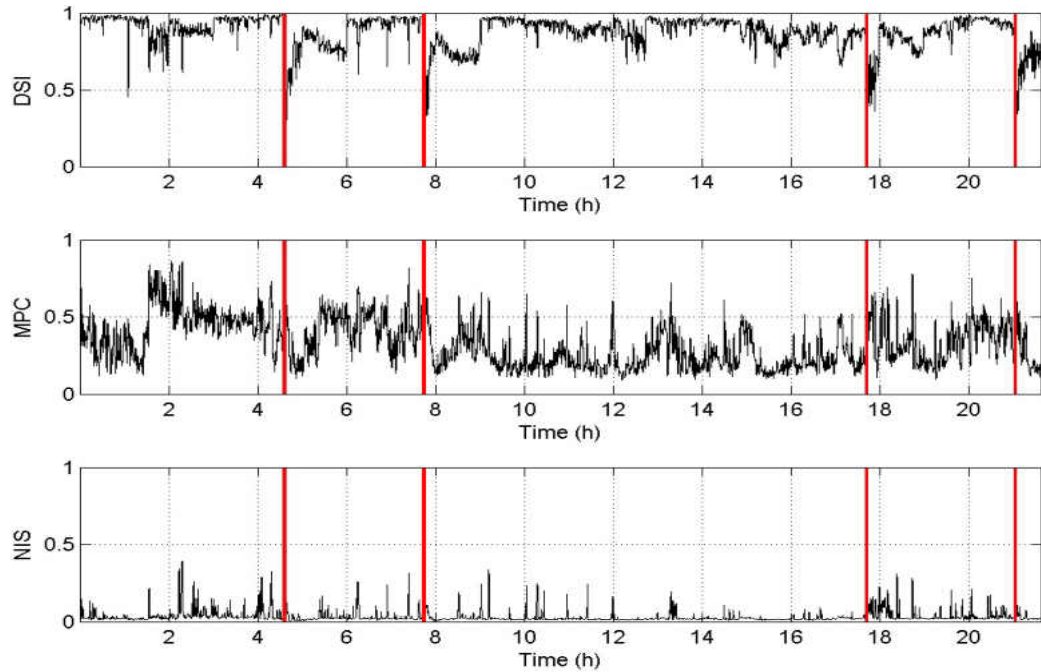
Figure 28. The temporal profile of the three features, dynamical similarity index (DSI), mean phase coherence (MPC), and nonlinear interdependence, S (NIS) extracted from 22 hours of test data. The start and stop time of the seizures are marked by red vertical lines.
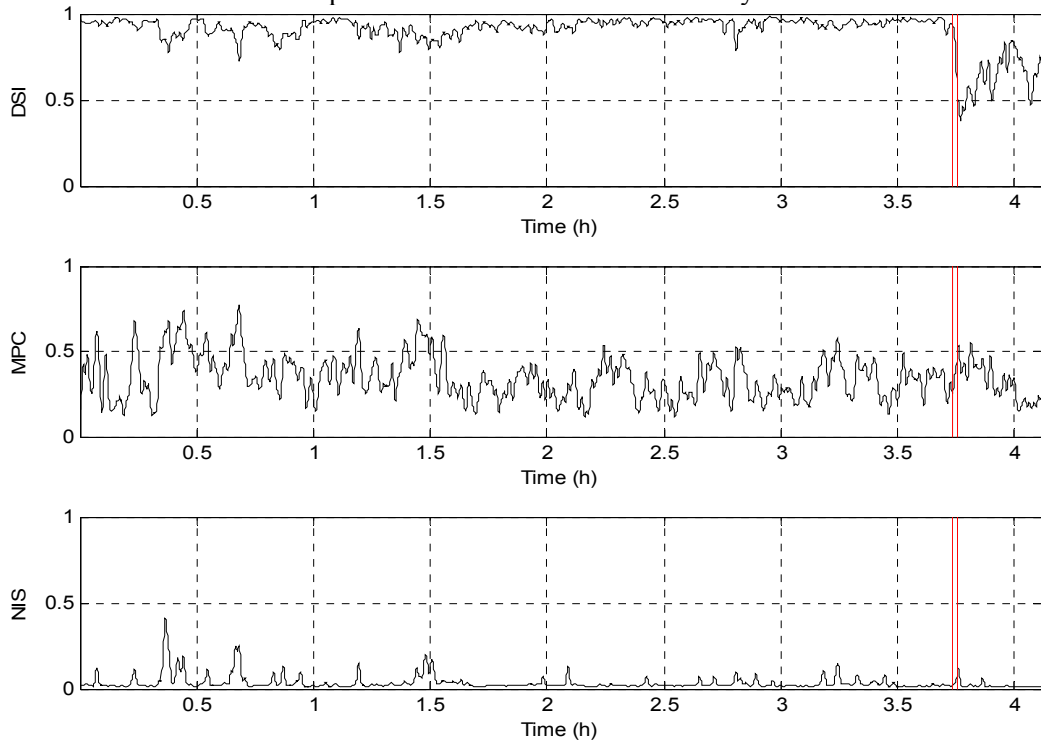

Figure 29. The temporal profile of the three features extracted from the rest 4.12 hours of continuous recording which constituted the testing dataset. The start and stop time of seizure are marked by vertical lines in red.

Gaussian membership functions were used to fuzzify the input feature variables. Three membership levels were assigned are low (L), medium (M), and high (H). These membership grades in the antecedent part play an important role in fuzzy logic based decision making. The membership functions were optimized during training using the backpropagation gradient descent learning method [44], [45]. The initial and final membership functions are shown in Figure 30 and Figure 31 respectively. This procedure should be repeated in every training and testing cycle. Also, it could be done in a patient specific way to optimize the algorithm in order to address the inter-patient variability.
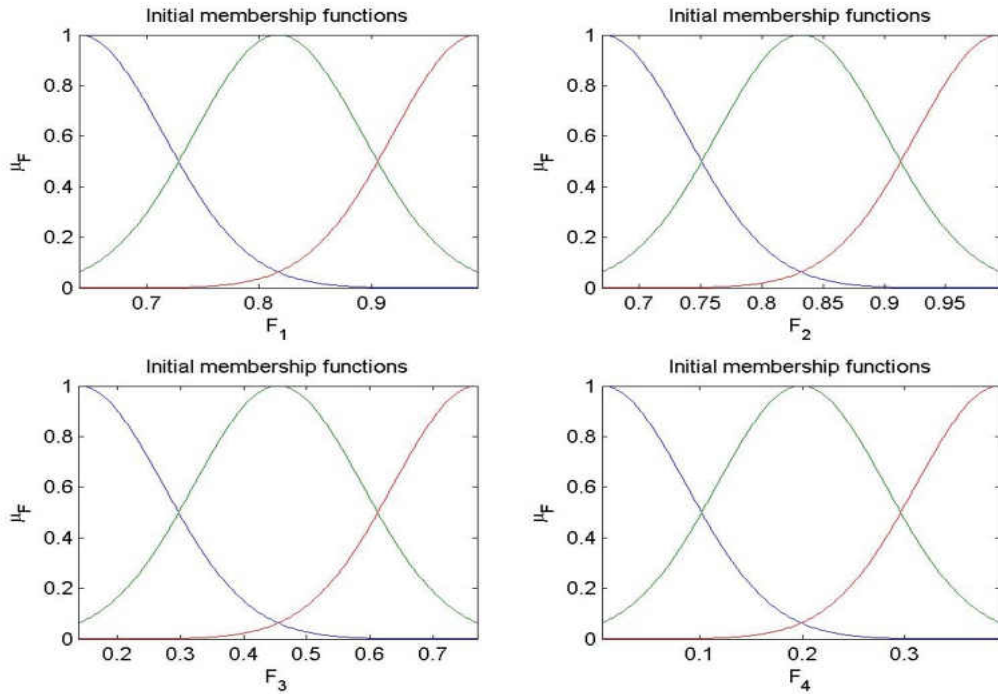
Figure 30. Initial membership functions assigned to the input feature variables.
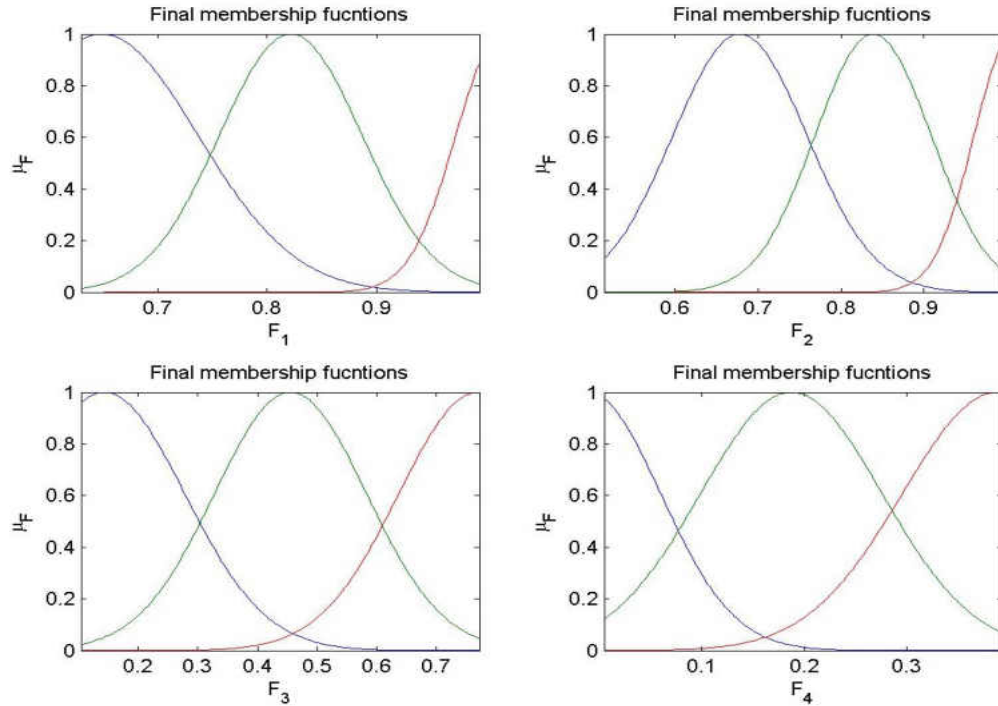
Figure 31. Final membership functions of the input variables after training. Three levels or sets were considered for fuzzification of the input variables: low, medium, and high.

A threshold procedure was applied to the final fuzzy output to convert it to a seizure predictive alarm space. This results in the primary alarm time series. The threshold was optimized for better sensitivity and lower false positive rate as it is better to forecast a seizure than to miss it within the prediction horizon. However, there exists a trade-off between these two parameters. The SPH was varied from 15 to 45 minutes with 15 minutes step size.

In post-processing step, the primary alarm time series was processed in a minute-by-minute basis. Short length predictions were minimized by setting up a criterion that the predictions with length less than 35 seconds duration would not be considered as true predictions. Also, within the prediction horizon when an alarm was issued, no further alarms were produced for the duration of the specified prediction horizon. When an alarm is followed by a seizure event, it is considered as a true positive and otherwise the alarm

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was considered as a false positive. Three different lengths of seizure prediction horizon were considered which yielded average sensitivity in the range of 20 - 80% with false prediction rate from 1.15 to 0.46 per hour. However, in longer prediction horizon the patient have to wait more or the intervention time is extended which might not be convenient for the patients and the caregivers. The results are shown in Table 10.

Table 10. Sensitivity and false prediction rate per hour with varying length of seizure prediction horizon for the testing data sets.

SPH (min)	Sensitivity (%)	FPR/h
15	20	1.15
30	40	0.73
45	80	0.46

The results demonstrated the applicability of ANFIS in epileptic seizure prediction. The algorithm was tested on unseen data or out of sample testing data. However, the threshold parameter was determined statistically by fitting a normal distribution from a reference window from the fuzzy output variable. In future, the algorithm will be tested against the dataset obtained from rest of the 29 patients' dataset from the European Epilepsy Database. Another important point to consider is if the algorithm is performing better than chance or not. To test this, the performance of the algorithm will be compared against a random predictor within the seizure prediction characteristic framework [49].

4.4. Summary

In this study, an innovative adaptive neuro-fuzzy inference system (ANFIS) based algorithm for seizure prediction was proposed. The performance of the algorithm was tested on long-term EEG recordings and promising results were found. The algorithm was designed in such a way that it could be trained for patterns from multiple prediction

characterizing features. If designed properly ANFIS or similar custom designed neuro-fuzzy algorithm would have the potential to be an effective alternative paradigm to other widely used machine learning algorithms, such as artificial neural network (ANN) and support vector machine (SVM). The advantages of ANFIS are that it is capable of utilizing human knowledge reasoning as well as machine learning capabilities. Also, ANFIS requires minimum training. The model overfitting can be avoided by finding optimum training epochs in a trial and error way as described in this study. In addition to a training data set, we utilized a checking data set as a safeguard against model overfitting. Performance of the algorithm was reported for the testing data sets only.

CHAPTER V

5. CONCLUSIONS AND FUTURE WORK

5.1. Summary

In this dissertation, two types of fuzzy logic-based algorithms were developed and applied in movement related artifacts detection, epileptic seizure onset detection, and seizure prediction from EEG signals. A number of relevant linear and nonlinear features or characteristics measures were extracted from both human and animal EEG recordings. Nonlinear dynamical systems-based measures were utilized in characterizing the changes in states transitions in brain waves. These characteristic features were then used to develop fuzzy rule-based and neuro-fuzzy algorithms for the above mentioned objectives. Performance analyses of the developed algorithms were presented.

Artifacts detection and noise reduction play an important role in EEG signal processing for both offline and real-time scenarios. A standard threshold based saturation and sensor movement related artifacts detection method was used in conjunction with the adaptive fuzzy inference system for seizure onset detection. This method was developed for iEEG which is less corrupted by artifacts. Hence, a simple threshold based method is good enough to reject those segments corrupted with electrode movement artifacts. Threshold based-methods are widely accepted due to the ease of implementation and effectiveness in practical applications. Although this method works for high-

amplitude and low-frequency artifacts, it may miss those artifacts which are of smaller amplitude than the predefined threshold value, for example, low amplitude eye blinks. In an experimental effort, ANFIS model was applied in artifacts detection from EEG. Wavelet transform was used for feature extraction and ANFIS was trained and tested in a 10-fold cross validation. The algorithms were found to be highly reliable in detecting the low frequency and high amplitude artifacts. Less accuracy was obtained for muscle noise detection. Spectral overlap of muscle noise makes it difficult to characterize it from normal EEG activities.

An adaptive fuzzy logic system was developed for seizure onset detection from iEEG. The primary objective was to study the applicability of fuzzy rule-based system in combining multiple features as well as taking advantage of spatial combination across channels or electrodes. Since clinicians visually inspect the changes in EEG in order to identify the seizure events, the system was designed in a way so that it could mimic human reasoning. Four widely used linear features were used in seizure onset detection from iEEG. The obtained results were comparable with other methods in literature and showed improvements in terms of some parameters. It was shown that the combination of multiple features were better than a single method in most of the cases. Also, the adaptive fuzzy system yielded better performance justifying the patient specific approach of seizure detection. In the proposed algorithm, fuzzy c-means clustering was utilized for fuzzy membership function optimization to realize the adaptive system. However, the features were not significantly sensitive in detecting changes earlier than onset. This resulted in detection delays in most of the cases. It is worth mentioning that in a very few cases, earlier changes were found as reported in Table 6.

In search for finding robust and sensitive features in identifying preictal changes, nonlinear dynamical systems-based characteristic measures were studied and applied to both human and animal EEG recordings. A fuzzy rule-based seizure prediction algorithm was developed based on changes in correlation dimension features. The limitations of this study were the evaluation datasets were short in length (1 hour) having a seizure event in each of the test set. This introduced a prior probability of predicting a seizure when the prediction horizon is an hour. To counter this, the performance of the system was evaluated on the same datasets with prediction horizon of 30 min. This actually reproduced the largely discussed controversy and/or drawbacks in seizure prediction. The high sensitivity found was actually unrealistic for the sudden and unpredictable nature of epileptic seizures. The algorithm used only one feature at a time (either correlation dimension or maximum likelihood correlation dimension). To add here, the behavior of correlation dimension changes prior to a seizure is not well defined rather controversial. A prospective seizure prediction algorithm should produce a probability estimate taking as multiple features as inputs within a time frame. We also studied recurrence quantification analysis (RQA), a recent approach which is known to be robust against noise. RQA measures were applied to characterize animal EEG data in a rodent model of epilepsy. RQA measures were revealed to be capable of differentiating epilepsy and status epilepticus from baseline EEG.

To achieve the goal of designing a prospective seizure prediction algorithm, a number of points were considered 1) the algorithm should be patient specific or tunable, 2) it should utilize both univariate and bivariate nonlinear features, thus increasing the probability of prediction, and 3) it should keep the complexity in minimal level. Though

several fuzzy logic-based approaches were studied, the ANFIS model was chosen for this attempt as it is one of the most advanced and reliable neuro-fuzzy algorithms available. An ANFIS classifier was trained to differentiate preictal patterns from interictal baseline and performance was reported for varying lengths of predefined seizure prediction horizons. The result was found to be very promising as presented in Table 10, but there are scopes of improvement.

5.2. Contributions

This dissertation describes several contributions in the domain of seizure detection and prediction. The specific contributions are outlined here.

- Development and Implementation of an innovative fuzzy rule-based adaptive system in seizure onset detection from iEEG. The algorithm was less complex yet showed comparable performance with the other available methods in literature. An article presenting the method and the results were published in a peer reviewed journal [47].

- Investigation of different nonlinear dynamical systems-based measures in characterizing EEG activities to find preictal changes with respect to interictal baseline [63]. Some of these features were later used to develop seizure prediction algorithms using neuro-fuzzy approaches. A fuzzy rule-based seizure prediction algorithm was proposed based on changes in correlation dimension [64].

- Finally, the application of ANFIS in seizure prediction was introduced. A prospective and innovative neuro-fuzzy seizure prediction algorithm was

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proposed. The algorithm makes use of one univariate and two bivariate features as described in chapter 4, section 4.4.2. The performance of the algorithm was presented with discussion on the effect of varying lengths of seizure prediction horizons. A paper describing the algorithm and the results were accepted for presentation in the 35th annual international conference of the IEEE Engineering in Medicine and Biology Society.

To conclude, the results obtained and discussion presented in this dissertation highlight the value of the application of neuro-fuzzy algorithms in epileptic seizure detection and prediction. The applicability of ANFIS was demonstrated in a complex problem like seizure prediction. The volume of fuzzy logic-based approaches in seizure prediction is very small in comparison to other methods in rich seizure prediction literature. These techniques have the potential to initiate a paradigm shift in artificial intelligence or machine learning research in medicine.

5.3. Future Work

In future, the performance of the neuro-fuzzy algorithm in seizure prediction needs to be analyzed against a random predictor within the seizure prediction characteristic framework [49]. The algorithm will be applied to the EEG recordings of the rest of the 29 patients data sets obtained from the European Epilepsy EEG database. This will provide more rigorous analysis of the performance of the algorithm and its applicability in clinical settings. False prediction rate per hour could be minimized by incorporating better post-processing methods. Another area could also be investigated is the subclinical seizures (SCS) and their impact on the performance of the prediction algorithms. It requires verification if the SCS patterns contribute in the false predictions.

APPENDICES

Appendix A

List of Abbreviations and Acronyms

ANFIS	Adaptive Neuro-Fuzzy Inference System
BCI	Brain-computer interface
CVA	Coefficient of variation of amplitude
CWT	Continuous wavelet transform
DWT	Discrete wavelet transform
EEG	Electroencephalogram
FDR	False detection rate
FIS	Fuzzy inference system
fMRI	Functional magnetic resonance imaging
FN	False negative
fNIRS	Functional near infrared spectroscopy
FP	False positive
FPR	False positive ratio
FPR	False prediction rate
HCI	Human-computer interaction
iEEG	Intracranial EEG
IIR	Infinite impulse response
MEG	Magnetoencephalogram
PET	Positron emission tomography
RQA	Recurrence quantification analysis
RR	Recurrence rate
SCS	Subclinical seizures
SPH	Seizure prediction horizon
TN	True negative
TP	True positive
TPR	True positive ratio

Appendix B

EEG Time Series

The EEG recordings used in Chapter 2 were obtained from the data set freely available for research by Andrzejak et al. (2001) [89]. The data set consists of 100 TXT-files consisting 4096 samples of EEG time series and were recorded in Europe. The data is available in ASCII code. MATLAB was used to read the data. 10 data files were used in this dissertation. Those are S001.txt - S010.txt. More detailed description of the EEG recordings has been provided by Andrzejak et al. (2001) [89]. Available from: http://epileptologie-bonn.de/cms/front_content.php?idcat=193&lang=3&changelang=3

Appendix C

Freiburg Seizure Prediction EEG Database

      This EEG database, known as FSPEEG in short, has been widely used by many research groups around the globe as a common platform for performance comparison among various types of seizure detection and/or prediction algorithms. The database contains invasive EEG recordings from 21 patients suffering from medically intractable focal epilepsy [49], [48], [90]. The data were recorded at the Epilepsy Center of the University Hospital of Freiburg. However, with the introduction of the new European Epilepsy EEG database, the FSPEEG database has been discontinued. Available at: http://epilepsy.uni-freiburg.de/freiburg-seizure-prediction-project/eeg-database.

Appendix D

The European Epilepsy Database

The European Epilepsy Database is one of the largest and most comprehensive databases available to date for epileptic seizure detection and prediction research. The database described in the previous section has been discontinued after the introduction of this new database. The database authority made available two packages of datasets from 30 patients each to the researchers. One of these packages was used in this study. Available at: http://epilepsy-database.eu/

The database was annotated by clinical experts and describes the necessary information required for the analysis which includes types of seizures, patient's information, seizure onset and offset times, EEG sensors name and location, sub-clinical seizures details etc. To manage all these information a local database was set in PC using PostgreSQL, an open source database. The information was available in tabular format. Two snapshots of the local database are provided which show the relational tables in the local database "epilepsy" and one of the tables named "seizure".
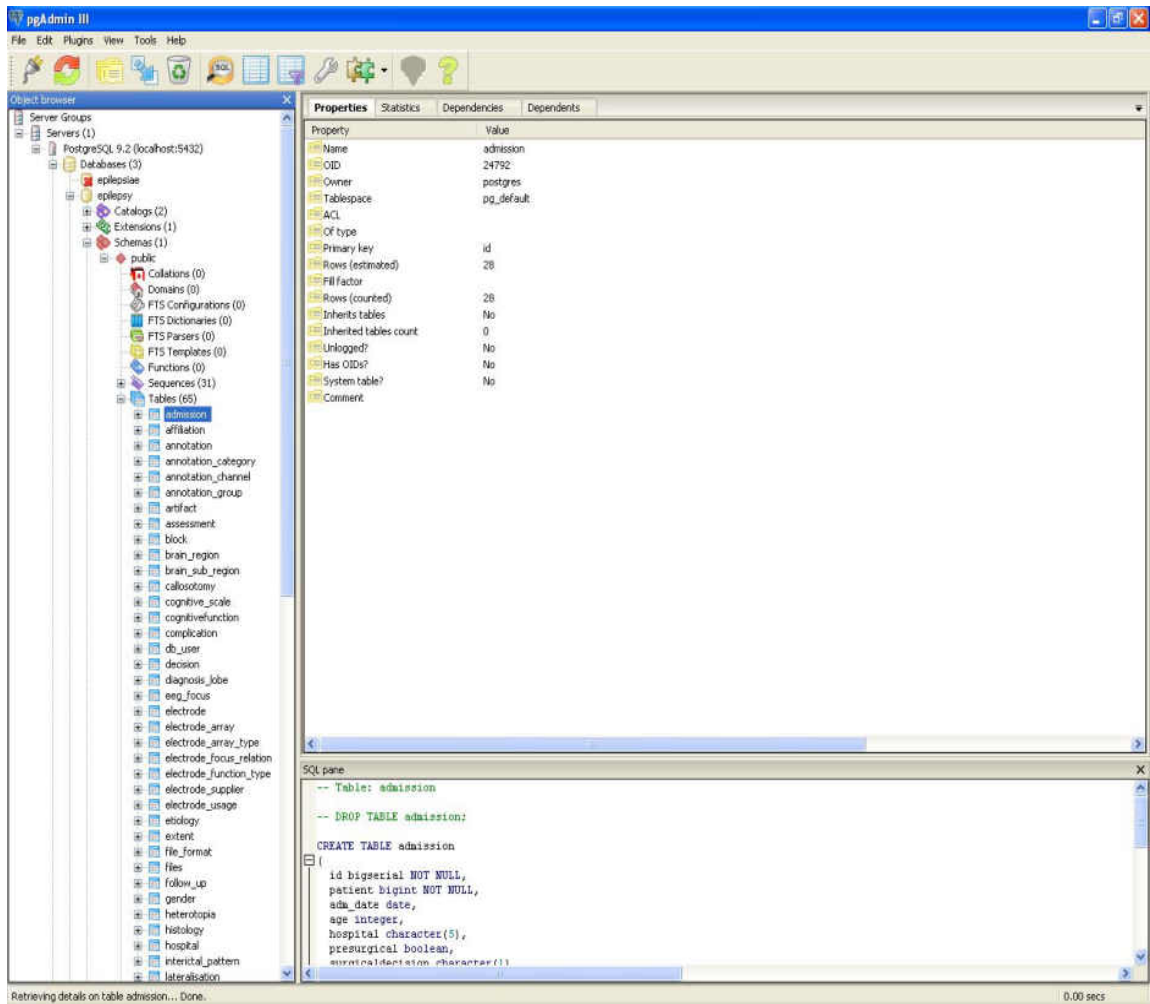
Figure D.1. A snapshot of the local database setup using the PostgreSQL software.

Figure D. 2. A snapshot of the table named "seizure" in the relational database named "epilepsy".

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