ISSN: 2754-4737

Journal of Neurology Research Reviews & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

A Review of Epileptic Seizure Prediction: Physiological Mechanism and Data Based Attempts

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ABSTRACT

Epilepsy is a chronic brain disorder and epileptic patients encounter recurrent seizures caused by abnormally synchronous electrical activity in parts of the brain. Over 50 million people spread across the world have epilepsy amongst whom approximately 30% suffer from refractory epilepsy which cannot be controlled by existing treatment protocols. For all epileptic sufferers, the thought that their next seizure could come at any time is agonizing and traumatic. However, if seizures could be predicted reliably, associated dangers and inconveniences will be greatly mitigated. Although the epileptic seizure prediction challenge has been tackled headlong by researchers through different modelling methods the problem of prediction has not yet been satisfactorily solved. In this paper, a systematic literature review of prominent epileptic seizure prediction attempts was carried out. We focus majorly on the two predominant classes of modelling attempts used: physiological mechanism and data based. The review underscores the richness and utility of the diverse modeling strategies as well as the gainful contribution of researchers in the field of epilepsy. It shows that meaningful progress has been made towards discovering the exact mechanism of seizure generation and realization of reliable and consistent seizure prediction algorithm.

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Received: May 08, 2021; **Accepted:** May 14, 2021; **Published:** May 20, 2021

Keywords: Epilepsy, Seizure Prediction, Physiological Mechanism & Data Based Attempts

Introduction

Epilepsy is a chronic brain disorder that constitutes a considerable public health concernment. It affects more than 50 million people worldwide [1]. The prevalence of the disease is notably high in developing countries principally, Latin America and several African countries such as Liberia, Nigeria and the United Republic of Tanzania [2]. The hallmark of epilepsy is recurrent and spontaneous seizures which are caused by parts of the brain eliciting abnormally synchronous electrical activity. Epileptic seizures not only obstruct smooth and normal living but also induce physical and mental damage.

Generally, the cause of epilepsy can be grouped into three scopious categories: genetic, cryptogenic and others (head trauma, brain tumors etc.). Pundits believe that genetic predisposition coupled with environmental circumstances contribute to epilepsy in some patients. The affected genes are majorly those that regulate the excitability of nerve cells in the brain [3]. In most of epileptic cases, correct diagnosis can be made and treatment in the form of routine use of anti-epileptic drugs (AEDs) are prescribed. But there are issues concerning the side effects of anti-epileptic drugs. Also, quite a number of epileptic patients suffer from intractable epilepsy and often need surgical measures which involve excision of parts of brain tissue. Aside the fact that surgery might result in neurological disability, epileptic seizure occurrences have been observed in quite a number of sufferers who had resection [4]. Summarily, there are certain side effects associated with AEDs and refractory epilepsy has challenged all existing treatment methods therefore, alternative therapeutic strategies for epilepsy are presently being considered.

Epileptic seizure prediction constitutes an excellent alternative therapeutic strategy because of the following reasons. For patients with intractable seizures, a timely seizure prediction will give room for adequate preparation in order to guide against life threatening injuries or sudden deaths during seizure events. Additionally, side effects associated with dosage will be greatly reduced in patients placed on AEDs as the drugs would forthwith be applied only when required. Furthermore, some emerging alternative therapeutic strategies such as optogenetics drug perfusion, neuro-stimulation and focal cooling depend on devices whose animation is triggered by reliable seizure prediction algorithm [4, 5].

Following the pioneering efforts of Viglione and colleagues which were aimed at predicting epileptic seizures, many other studies have been conducted but to date this problem has not been satisfactorily solved [6, 7]. To this end, the International Workshop on Seizure Prediction (IWSP) is held. Biennially, the IWSPs forum assemble an international interdisciplinary group of epileptologists, engineers, physicists, mathematicians, neurosurgeons and neuroscientists with the goal of developing engineering-based epilepsy treatments [8].

Since seizures come and go, the epileptic brain system is believed to make transitions into and out of seizures. Researchers, have therefore referred to epilepsy as a dynamical disease and thus need to be studied from dynamical systems point of view [9, 10]. Making predictions about dynamical systems involve modelling the time dependent behaviour of the system and so deterministic

and nondeterministic methods of modeling the time dependent behaviour of dynamical systems have been applied in epilepsy research.

In the deterministic approach complete knowledge of the system (epileptic brain) is assumed. This assumption allows us to translate phenomenon occurring in the system into mathematical equations which can be solved and used to study the dynamics of the systems through simulation. Deterministic modelers propose to make use of the dynamic (physiological) mechanism underlying seizure generation to predict seizures. Consequently, deterministic modelers have come up with quite a number of physiologically based mathematical models which have been used to study mechanism leading to seizure in the brain [4]. Despite these modelling efforts, the exact mechanism of seizure generation in the brain is still unknown.

In the nondeterministic approach, incomplete knowledge of the system is assumed. This method is often used when the system under consideration is very complex and intricate [11]. Accurate mathematical models describing the phenomenon occurring in such systems is very difficult; what is usually done is to analyze some measurements taken from the system's behaviour over time. Such analysis may give great insight into the global dynamical properties of the system. Currently, nondeterministic modelers are leveraging the wide availability of computing and storage devices which surfaced around the tail end of the 20th century, advances in biomedical signal processing and data mining techniques to obtain and analyze electroencephalogram (EEG) data of epileptic patients in order to track seizure dynamics [11].

However, following decades of huge efforts by nondeterministic modelers to achieve activity (EEG) data, the problem of prediction still persists. Many seizure prediction algorithms utilizing different signal processing and data mining techniques have been proposed but to date no algorithm has been able to meet the required standard for clinical applications [12-17].

This paper presents a review of prominent published works on epileptic seizure prediction by researchers in the deterministic and nondeterministic modelling approaches. Research activities in the two areas were carefully analyzed with the intent of guiding future research works. The rest of the paper is arranged as follows: section 2 gives a brief physiological and technical background on the subject matter. In sections 3 and 4 mechanism based and data based attempts at seizure prediction are reviewed respectively. Lastly, section 5 contains conclusions from the review process and suggested future directions.

Physiological and Technical Background

In this section we present relevant definitions, meanings and explanations of the physiological and technical concepts explored in this review. Important concepts in the mechanism-based approach to epileptic seizure prediction are discussed in section 2.1 while those related to the data based approach are discussed in section 2.2.

Concepts in Mechanism Based Seizure Prediction

The Brain and Electrical Activity of Neuron (Nerve Cell)

The brain happens to be the most complex organ in the body. It consists of three major parts: the cerebrum, cerebellum and brain stem. The cerebrum largely consists of the paired cerebral hemispheres which are composed of a thin shell of grey matter known as the cerebral cortex. The cerebral hemispheres divide into four lobes – frontal lobe, parietal lobe, occipital lobe and the temporal lobe (Figure 1a). Slicing the cerebrum reveals subcortical structures including the hippocampus, amygdala, thalamus and hypothalamus. The hippocampus is responsible for the formation of new memories and recollection of personal experiences. The amygdala takes care of all manners of emotional response. The thalamus is often described as the gateway to the cortex because almost all ascending pathways synapse in a thalamic nucleus in order to reach the cerebral cortex. Finally, the hypothalamus caters for the maintenance of constant internal environment (homeostasis)

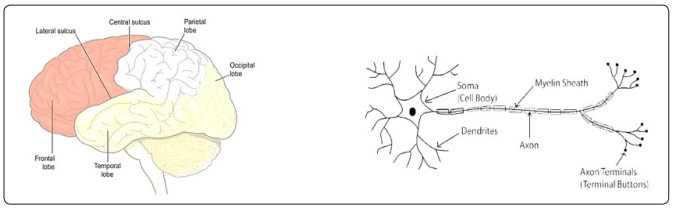

Figure 1: Schematic representation of (a) the four lobes of the cerebral hemisphere (b) the neuron Reproduced from [18]

The Neuron

The nerve cells (neurons) constitute major building blocks of the brain. They are seen as the central processing units of the brain. They consist of three major parts, namely dendrites, soma and axon (Figure 1b). The soma, which is seen as the centre of convergence of various incoming signals encloses the nucleus and other organelles. Signals from other cells are received through the dendrite. The synapse is the point of connection between nerve cells where electrical signals get converted to chemical signals (neurotransmitters). A neuron that is sending signals is called presynaptic while the one receiving is the postsynaptic neuron. Furthermore, inhibitory neurons transmit inhibitory signals which tend to reduce the chances of the postsynaptic neurons to also send signals to other cells while excitatory neurons send excitatory signals which tend to increase the chances of the postsynaptic neurons to also send out signals. The axon is a long extension of the soma that is used by the postsynaptic neuron to transmit signals to other neurons.

Action Potentials

Glutamate is considered to be a major excitatory neurotransmitter while Gamma-aminobutyric acid (GABA) is the prominent inhibitory neurotransmitter in the brain [18]. The binding of these chemical messengers to receptors (Alpha-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA) receptor and the N-methyl-D-aspartate (NMDA) receptor are prominent excitatory receptors while γ – aminobutyric acid (GABA) receptor is the major inhibitory receptor) in the postsynaptic neuron results in the opening of ion-channels on the cell membrane and subsequently change in the membrane potential. Excitatory neurotransmitters cause the ion-channels to allow the flow of sodium ions (Na+) into the cell from the extracellular space following which an excitatory postsynaptic potential (EPSP) is generated locally. This results in what is referred to as depolarization (i.e. the cell becomes more positive than its resting (steady state) potential of approximately -70 mV). When depolarization crosses a certain threshold, the cell fires action potentials (i.e. signal sent to other neurons). Otherwise, when the neurotransmitters are inhibitory in nature, the ion-channels will permit the flow of potassium ions (K+) out of the cell generating a local inhibitory postsynaptic potential (IPSP). This makes the cell more negative and less likely to fire action potential. A phenomenon called hyperpolarization.

Astrocytes

Astrocytes (shown in Figure 2) are process-bearing cells having a stellate morphology and they are the main support cells of the central nervous system (CNS). Astrocytic processes have specialized structures called end-feet that make contact with neurons and capillaries. The interaction between neurons and astrocytes is largely due to homeostasis and energy metabolism. Astrocytes contribute to homeostasis (i.e. helping to maintain a constant internal environment for neurons) by removing excess ions and neurotransmitters from the extracellular fluid. For instance, with the aid of glutamine synthetase enzyme glutamate is metabolized to glutamine by astrocytes. Furthermore, ammonia, which constitute a nitrogenous waste product of metabolism is also detoxified in the process by providing the amine group of glutamine. The glutamine is then taken up from the extracellular fluid by neurons and get hydrolyzed by the mitochondrial enzyme glutaminase thereby, converting it back to glutamate. Astrocytes are also very much involved in brain energy metabolism. Not only do astrocytes store a modest amount of glycogen but also take up glucose and pre-digest it to lactate. The lactate gets.

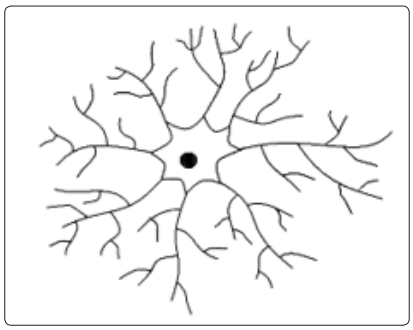

Figure 2: Schematic representation of the astrocyte [18]

exported to the extracellular compartment where it is consumed by neurons as their main source of energy.

EEG Signals

Electroencephalography (EEG) is the recording of the electrical activity of the brain. The electroencephalogram represents the variation in time and space of summed extracellular potential simultaneously arising at the synapses of cortical pyramidal neurons (Gloor, 1985). EEG signals can be recorded both in an invasive or non-invasive manner. When the recording is carried out invasively, electrodes are placed in direct contact with the brain tissue. EEG signal obtained in this manner is referred to as intracranial EEG (iEEG). On the other hand, in non-invasive recording, electrodes are placed in strategic locations on the scalp. This type of signal is referred to as scalp EEG (sEEG) (shown in Figure 3). Although sEEG is inexpensive and easy to obtain it is susceptible to noise and cannot provide localized electrical activity of the brain. On the contrary, iEEG has high signal to noise ratio and provides localized recording of brain activity.

Epilepsy Classification

The commonest way of classifying epilepsy is by distinguishing between focal (partial) and generalized epilepsies [19]. The onset of the seizure is localized in one hem- isphere of the brain for focal epilepsy and involves both hemispheres for generalized epilepsy. Temporal lobe epilepsy (TLE) and generalized absence epilepsy (GAE) are popular types of focal and generalized epilepsies respectively. Temporal lobe seizure has its onset in the region of the brain called temporal lobe and it is convulsive in nature while generalized absence epilepsy causes brief loss of consciousness.

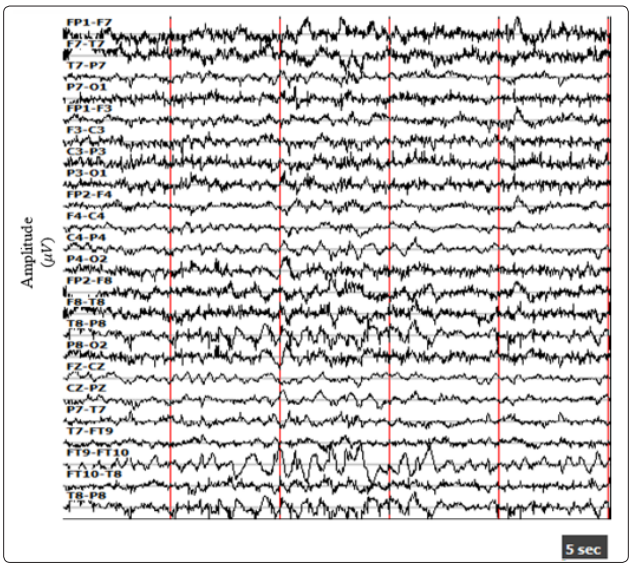

Figure 3: Typical Scalp E EG recording [20]

Dynamical Systems

Dynamical system can be described as a system that evolves in time (i.e. values of the variables describing the state of the system depend on time). They can exhibit different kinds of interesting properties but particularly, the existence, stability and characteristics of asymptotic solutions (e.g. fixed points and cycles) of dynamical systems are typically quite sensitive to variations of the parameters in the model. Specifically, the system can undergo sudden changes in the number or in the stability of its fixed points or limit cycles when continuously varying the parameters. These sudden changes are termed bifurcations.

Concepts in Data Based seizure prediction

Data Based Seizure Prediction Workflow

In other to extract useful information from the acquired suitable EEG data of epileptic patients, data is preprocessed to remove noise and other unwanted contaminants in the EEG signals. The data is then separated into normal and pre-seizure segments following an assumption of a desired pre-seizure period. Next, data in the normal and pre-seizure segment is divided in overlapping or non-overlapping temporal windows of length L and for each interval i (i=1,….,N,with N=M/L, where M is the length of the whole time series to be analyzed) a sample of all EEG features (measures believed to exhibit different temporal trends during interictal and preictal brain states) considered is extracted and formed into feature vectors. Many time domain, frequency domain and time-frequency domain EEG features have been engineered and used for seizure prediction. Time-frequency EEG analysis specifically, the wavelet transform has the advantage of simultaneous localization of EEG events in time and frequency domains. In biomedical signals, components with high frequency that are closely spaced in time are commonly mixed with components with low frequency. The wavelet transform (WT) is considered appropriate for the analysis of such signals due to its multiresolution capabilities [21]. A richer time-frequency analysis derived from wavelet transform is the wavelet packet transform. The feature vectors are then divided into three sets: the training, validating and test sets each of which will contain certain fraction of normal and pre-seizure EEG feature vectors. Next, artificial intelligence is used to learn the decision boundary between feature vectors belonging to normal and pre-seizure brain states by designing and evaluating a classification algorithm. The trained classifier can then be used to make predictions about new EEG feature vectors [11].

Classifier Design

A classifier is a system trained to identify feature vectors belonging to different categorical data instances (classes). The classifier is often trained through supervised learning techniques in which the classifier is trained based on a set of input variables and a correct output variable and tries to find an approximate map the takes the input variables to the known output variable. The trained model is then optimized through validation techniques in order to produce an accurate prediction on unseen data. The primary outcome of this process is finding a model that generalizes the data based on a particular training-set, and using the constructed model to make predictions on the target value of unseen data [11].

Hyperparameters Optimization (Tuning)

Classification algorithms are extremely powerful. But they have a lot of tunable hyperparameters associated with them and figuring out the best configuration for these hyperparameters in order to get the best out of the system is extremely non-intuitive. We can formalize the search for parameters of a learning model via well-defined mathematical functions. These functions, commonly referred to as cost functions, take in a specific set of model parameters and return a score indicating how well we would accomplish a given learning task using that choice of parameters. A high value indicates a choice of parameters that would give poor performance, while the opposite holds for a set of parameters providing a low value. Because a low value corresponds to a high performing model, we will always look to minimize cost functions in order to find the ideal parameters of their associated learning models. As the study of computational methods for minimizing formal mathematical functions, the tools of numerical optimization therefore play a fundamental role in classification algorithm.

Physiological Mechanism Based Attempts at Seizure Prediction

Understanding the circumstances behind spontaneous seizure generation in the human brain has been an unresolved issue. Therefore, the primary aim of researchers engaged in the study of epilepsy is to comprehend the fundamental mechanisms of seizure generation as this will enable prediction and possibly, elimination or prevention of epileptic seizures. The mechanism of seizure generation can either be studied in the laboratory using animal models or on the computer through computational models. Computational models refer to mathematical models that need the processing leverage of computer for their analysis. Mathematical equations describing the evolution of complex dynamical systems are usually nonlinear as a result they are difficult to solve analytically. Computational models are preferred over animal models for a number of reasons. Firstly, computational models are not subject to both environmental impediments and procedural bottlenecks that are usually encountered in the laboratory. Secondly, experiments and parameter dependencies can be run easily on the model by just varying mathematical structure of the model or parameter values. Obviously one needs to first come up with a physiologically based mathematical description of neuronal activities. Computational studies on the model may then reveal conditions necessary for normal, pathological (epileptic) and transitional activities as observed on EEG recording of epileptic patients. This task can be carried out at the microscopic or macroscopic level depending on the research question being asked and level of simplification desired by the modeler. On the microscopic level the attention is on individual neurons however, on the macroscopic level, neuronal assemblage or population is targeted. Microscopic models are detailed in nature as such they contain tremendous amount of physiological parameters making them require very huge computational resources. Furthermore, since epilepsy is said to be associated with synchronization of many cortical areas these models are less attractive for examining network level effects. The macroscopic modelling approach was conceived due to the consideration that many brain functions such as sensory information processing or pattern recognition result from large-scale activity in population of neurons [22]. Therefore, attention of greater percentage of researchers has since shifted to population models of epilepsy [23].

Population Models

There are a number of factors supporting the appropriateness of simplification offered by considering population models of neural activities. Firstly, the observed conduct of detailed neuronal system is usually confined to a proportionately low dimensional sub space of its huge state space [24]. Secondly, lots of variables vary over time line much smaller or longer than time line of interest therefore, such variables can be considered as constant parameters [25]. Lastly, many of the variables may exhibit strong correlation and can be regarded as a single variable [23]. Two variants of the population models exist in literature. The neural field model and the neural mass model. Neural field models refer to models accounting for both spatial and temporal activities of neuronal population while in neural mass model the attention is only on the temporal component. Most researchers consider neural mass models for the following reasons. Epilepsy is thought to be a dynamical disorder of the brain whose hallmark is hyper-synchronous neural activity across areas of the cortex [26] thus spatial dependencies can be securely neglected. In addition, the types or families of neurons involved in the modelling are relatively small making the dimensionality of the system sufficiently small for rapid computer analysis.

Neural Mass Modeling Framework

The fundamental motive in neural mass modeling is to describe or model the mean firing activities of assemblage of neuronal populations. This can be seen as a simplification of the idea behind modelling at the macroscopic scale which is to lower the degrees of freedom in a dynamical system such as a large population of neurons to a distribution function which represents the probabilistic evolution of neuronal states in the population at a given time [27].

In neural mass modeling, only the first moment of the distribution function (equivalent to the center of mass) is considered thus representing the mean firing rate of the neuronal population. Consequently, the mean membrane potential, $v^p(t)$ of a subpopulation p of neurons within the network is obtained by convolving incoming signal with an impulse response function of the configuration:

$$irf^{p}(\mathrm{t}) = Grte\ -rt \qquad \text{Equ. 1}$$

where and are parameters controlling the rise time and amplitude of the mean membrane potential of the subpopulation in response to inputs. Input to a subpopulation could be from the subpopulation itself or from other subpopulations in the network and is usually configured to be a sigmoidal function $s(v^p(\mathrm{t}))$. Early neural population models were developed in order to simulate normal real EEG signals and they describe interactions between excitatory and inhibitory neuronal sub populations. However, several neural mass models have also been built to recreate and interpret epileptiforms. Epileptiforms are electrical activity of the brain observed in the course of epileptic phenomena. They are not only seen during seizure episodes but also in many abnormal transient events outside seizures such as interictal spikes and high-frequency oscillations in partial epilepsies.

Interictal epileptic spikes are commonly seen in human partial epilepsies and most experimental models of focal epilepsy [22]. In epileptogenesis (study of the structural and functional changes leading a normal brain network to produce recurring epileptic seizures) quite a number of experimental investigations have also observed the appearance of solitary or isolated epileptic spikes in the latent period. Two main types of interictal spikes have been distinguished type 1, a spike succeeded by an enduring wave; and type 2, a spike without wave. Presented the first attempt to study interictal spikes in a neural mass model (NMM) [28-31]. Their model represents a local neuronal population consisting three subpopulations of neurons (two excitatory subpopulations and one inhibitory subpopulation). These subpopulations are interconnected via positive and negative feedback loops and model equations featured linear dynamic and nonlinear static elements. The analysis of model behavior showed that instability (emergence of limit cycles) in the neural network can occur as a result of noise input level in the system. A proposition arising from authors observations was that epileptic spikes are instituted in a population of neurons that runs near instability and that spikes may be interpreted as a borderline phenomenon between normal background and epileptic activities. Variation in glutamatergic and GABAergic drives were studied in pilocarpine model of Temporal lobe epilepsy during epileptogenesis using a neural mass model of the CA1 hippocampal area [32, 33]. Using recordings observed 3 days (early stage), 10 days (late stage) after injection and at chronic stage (characterized by recurrent spontaneous seizures), conditions necessary to reproduce the observed interictal spikes (in terms of morphology and occurrence frequency) were obtained from comprehensive simulations where model parameters (excitatory postsynaptic potential (EPSP) and inhibitory postsynaptic potential (IPSP) amplitude, rise and decay time constants) were varied at the soma and dendrites of the pyramidal cell subpopulation. It was found out that a rise in glutamatergic/GABAergic drive ratio constitute a sufficient condition for the emergence of epileptic spikes and that this ratio equally impacts the frequentness of the spikes.

The neural mass model has again provided the opportunity to explain the rise in interictal spike frequency seen during epileptogenesis and its morphological characteristics in the kainite model of epilepsy. In this work, the authors developed signal processing methodology to automatically detect and differentiate epileptic spikes over a period of thirty days [34]. How the shape of epileptic spikes changes as a function of time were first characterized and then recreated in a neural mass model. Consequently, some key parameters controlling the morphology of epileptic spikes could then be obtained. In the results it was shown that rise in frequency of epileptic spikes stems from graduated diminution of GABAergic inhibition. Based on this finding, an innovative electrophysiological marker computed from local field potentials was proposed. The marker provides information about the progression of epilepsy after initial insult. In focal epilepsy, seizures are often heralded by the appearance of very fast waves typically, 70 to 120 Hz [35, 36]. Fast oscillations have been noticed at onset of seizure in temporal lobe epilepsy in the hippocampus, amygdala and entorhinal cortex brain areas. However, these oscillations are usually associated with a lower frequency range, specifically 20-40 Hz in comparison to fast oscillations observed in the neocortex [37]. Furthermore, in temporal lobe epilepsy, a sizable number of investigations have suggested that fast activity at seizure onset may stem from synchronous activity of GABAergic cells [37-39]. Supported by in vivo and in vitro recordings, came up with the hypothesis that high frequency oscillations are generated by networks of pyramidal neurons coupled by gap junctions The physiological mechanisms underlying the emergence of high frequency oscillations, specifically oscillations above 80 Hz usually observed in intracranial EEG recordings at the onset of neocortical seizures has been studied using a neural mass model [40, 41]. The proposed model has two neural subpopulations representing pyramidal neurons and the interneurons. The interneurons target the peri-somatic region of the pyramidal neurons where fast GABAergic currents are mediated. Through model simulations the authors accurately replicated the chirp-like fast discharges with frequency in the range 70-110 Hz while keeping physiological values of rise and decay times of the average glutamatergic excitatory postsynaptic potential and GABAergic inhibitory excitatory postsynaptic potential. The model equally suggested in line with previous experimental work that mutual inhibition was a key factor for the generation of high frequency oscillations at seizure onset [18].

Came up with an adaptation of the neural mass model proposed by Jansen & Rit (1995). The new model was able to produce rapid activity seen at seizure onset in temporal lobe epilepsy [42]. Customarily, a development of spikes with high amplitude and a low frequency is first encountered. This activity is then followed by waves of low amplitude and high frequency commonly referred to as low voltage rapid discharges. The maximum frequencies contained in the high-frequency signals belong to the band 30-100 Hz and are always emerging from epileptogenic regions of the brain. decided to split up the local inhibitory population (Jansen & Rit (1995) into a fast and slow inhibitory populations [42]. Therefore, the model consists of pyramidal, local excitatory and fast and slow local inhibitory neural subpopulations. All local neural subpopulations receive excitatory input from the pyramidal cells. The pyramidal cells in return receive excitatory input from the local excitatory cells and from sources external to the neural population. Furthermore, the pyramidal neural subpopulation receives inhibitory input from the fast and slow local inhibitory cells. Lastly, slow inhibitory cells interact in a feedforward only manner with the fast inhibitory cells through an inhibitory projection.

Spike-wave (or "spike-and-wave") discharges are a regular, symmetrical and generalized pattern seen in the EEG, customarily during generalized absence seizures [43]. Experimental and clinical investigations have given much insight into some basic mechanisms of spike-wave discharges. However, the mechanisms that are responsible for the spontaneous transition between normal ongoing activity and paroxysmal SWD activity are not completely resolved. Typically, issues like thalamocortical versus cortical mechanisms of SWD generation or role of GABAa versus GABAb are still being debated. Over the years, giving explanations to these issues, among others, have been approached by the use neural mass modelling. [44] aimed at finding out the mechanisms responsible for transitions from normal EEG activity to pathological spike wave discharges observed during generalized absence seizure. They constructed an extended version of the neural mass model of da Silva (1974) for the study. The new model has two modules namely cortical and thalamic modules that are mutually interconnected. This model was based on the experimental findings that favour interactions between cell populations in the cortical and the thalamic areas of the brain over interactions only between cell populations in the cortical area as the source of GAE. Another feature of the model is that interaction between subpopulations were modeled through excitatory and inhibitory mediating synapses. Although the model produced outputs that resemble those seen in the EEG as well as spontaneous transitions to epileptic activities (quasi sinusoidal

waveform), the model failed to produce the characteristic spike wave discharges which are the electrographic correlate of GAE [6, 45, 47, 56]. The authors concluded that random fluctuations in control parameters and/or dynamical variables can lead to sudden onset epileptic EEG activity. A blend of the Jansen & Rit (1995) model and the models was developed by [42, 48]. This model has three populations like the Jansen & Rit (1995) model however, they modeled a fast and slow inhibitory connection from inhibitory cells to the pyramidal cells instead of only one inhibitory connection. Their target was to model in a better manner than did Wendling et al (2002) the inhibitory process which was discovered through experimental studies to have a varying time course. used the model to simulate epileptic spike wave EEG activity in a broad region of the brain [42, 48]. The model was also capable of producing oscillations with a frequency slightly lower than 15Hz. These oscillations are comparable with the alpha rhythms in the Jansen & Rit (1995) model. Furthermore, this model was also able to generate poly SWD (multiple spikes followed by a slow wave) and other complex behaviours. related at a neuronal mass level, electrophysiological patterns regularly noticed during the transition from normal activity to epileptic activity in human temporal lobe epilepsy to mechanism involved in seizure generation using computational model of EEG activity earlier developed by [42, 49]. EEG data of five patients with temporal lobe epilepsy recorded during normal brain activity, just before seizure onset, at seizure onset and during seizure activity) were used to identify three important parameters of the model which are related to excitation, fast somatic and slow dendritic inhibitions. The joint temporal dynamics of the identified parameters across the mentioned evolving brain states was then studied in order to infer physiologically based preictal changes which could be used to predict epileptic seizures. They observed that during pre-onset activity, a rising dendritic inhibition make up for a steadily increasing excitation up to a fatal drop at seizure onset when faster oscillations are observed. These faster oscillations were then rationalized by the model feedback loop between pyramidal cell subpopulation and interneuron subpopulation targeting their peri-somatic region.

Carried out a comprehensive model-based seizure prediction study using a modified version of the model proposed by Jansen and Rit (1995). The model comprises pyramidal neurons, excitatory and inhibitory interneurons described through state equations and was used to simulate on a macro-scale the dynamics of intracranial EEG data during transition from normal brain activity to temporal lobe epileptic seizure activity [50]. By fitting the model to the power spectral density obtained from real intracranial EEG signals recordings of twenty-one patients suffering from refractory epileptic seizures, twelve model parameters were estimated and integrated based on the information gathered by tracking changes in model parameters before to seizures. The novel prediction method was evaluated using test dataset of each patient and it achieved average sensitivities of 92.6% and 87.07% with average false prediction rate of 0.15/h and 0.2/h using maximum SOP of 50 and 30 min and a minimum SPH of 10s respectively. The author concluded that the spatio-temporal changes observed in the parameters implied patient-specific pre-seizure precursors that could be used to predict seizures. Unlike who studied the temporal trend of parameters relating to excitation and inhibition as seizure develops, studied the temporal dynamics in the population to population synaptic connection strength parameters. Unifying the neural mass model of Jansen and Rit (1995) with a large database of human epileptic seizure EEG recordings through model inversion, they observed a very high stereotyped trend of evolution for individual patient, different sub-groups of seizure onset mechanisms within patients and dissimilar offset mechanisms for short and long seizure events [49, 51].

Neuron Astrocyte Interaction

Many experimental findings have pointed to the fact that astrocyte cells play crucial roles in modulating neural activity. Specifically, observed the presence of GABA and glutamate transporters in both neural and astrocyte compartments. Predominantly, high affinity astrocytic glutamate and GABA transporters are expressed in areas proximate to synaptic terminals, raising the discussion of the functional relevance of uptake of neurotransmitters by astrocytes in the regulation of synaptic transmission on one hand and pattern of neural excitability on the other hand with respect to brain pathophysiology [52]. observed that astrocyte cells can be activated by transmitters from presynaptic neurons. The activated astrocyte cell in turn releases gliotransmitters that can immediately stimulate the postsynaptic cell and can also feed back to the presynaptic terminal [53]. In 2005, Voltra and Meldolesi studied this glial stimulation and concluded that neuronal excitability and synaptic transmission by astrocytes is mediated by glutamate release while inhibitory effects are mediated by ATP (Adenosine Triphosphate) and its derivatives. They also hinted that another form of astrocytic excitation exist that is independent of neuronal input. This is described as spontaneous excitation [54]. Summarily, amid neural activity, glutamate release by the presynaptic neurons is taken up by astrocytes and brought into the glutamate-glutamine cycle [55, 56]. The uptake of glutamate by astrocytes and its consumption into the glutamine circle is the major pathway after glutamate is released in the extracellular space. Also, contribution of GABA to neuron-astrocyte interactions is almost as important as glutamate contribution due to multiple mechanisms including GABA uptake. These are involved in the inhibitory GABAergic interneurons [57]. However, consumption of GABA and glutamate are considered as a secondary mechanism compared with their uptake by neurons and astrocytes [58, 59]. There exist a number of published models for neuron-astrocyte interactions at the cellular scale and subcellular [60-63].

The output of such models can only be compared to intracranial (surface or depth) EEG data which are very expensive and scarce. Furthermore, scaling these models up to the population level which gives output comparable to cheap and popular scalp EEG data is computationally expensive and almost mathematically intractable. On the other hand, population scale models are known to be low dimensional and their output is comparable to scalp EEG data. Blanchard et al., (2016) developed a neuron-astrocyte mass model that links local field potential signal to cerebral blood flow dynamics. The model which is based on the neural mass model of Jansen and Rit (1995) also integrates astrocytic recycling of glutamate and GABA. This neuron- astrocyte mass model was later used by to do a theoretical study of the role of glia activity in neuronal hyper excitability [64].

Owing to the important role that astrocytes play in regulating the activities of neurons and the bi-directional relationship between astrocytes and neurons, it is important to study predictability of epileptic seizure using population models of neuron-astrocytes interaction. In a novel contribution to the field of epileptic seizure prediction, developed neuron astrocyte population models to propose possible pathophysiological mechanisms to temporal lobe and generalized absence seizure generation in the brain [65]. The models incorporated explicit biophysical parameters which are defined at the macroscopic level and relate to the activities in the neural and astrocytes compartments and feedforward and feedback interplay between them. The models were developed

in line with the physiological basis consistent with experimental and theoretical works of (neural compartments) and (astrocyte compartment) [42, 64, 66]. Through bifurcation analysis, two model parameters: the extrinsic input into the models, P and ratio of inhibitory to excitatory neurotransmitters fed back from the astrocyte compartment into the neural compartment, γ were identified as leading model parameters influencing the behaviour of the models. The neuron-astrocyte population models generated different types of activities comparable to wave patterns seen in normal and epileptic real EEG signals. The models equally displayed spontaneous transitions from one activity type to the other simply by varying parameter γ. The simulated transitions demonstrated the importance of neurotransmitters (GABA and glutamate) feedbacks in the regulation of brain activities. Since the feedbacks depend on the extracellular neurotransmitters concentrations, regulation of neurotransmitters in the extracellular space is also very germane. For instance, the outcome of one of the simulations carried out in the study is shown in Figure 4a. It presents the effect of flooding the extracellular space with GABA during a seizure event. Suppose there is a deficiency in glutamate but not GABA uptake process by astrocytes leading to accumulation of glutamate in the extracellular space and consequently resulting in the reduction of PY cell subpopulation excitability threshold which finally leads to seizure. To simulate this, the TLE model was started in a seizure mode and at time t=25s the extracellular GABA concentration ($gab_{c,e}$ (t))was increased instantaneously. It is observed that right after the increase the seizure activity disappears but as soon as the GABA concentration goes back gradually to its original level (i.e. after rapid uptake by astrocytes) seizure activities re-emerges. The uptake of GABA by astrocytes enabled the increased GABA concentration in the extracellular space go back to its original level supporting the re-emergence of seizure activity. What if there is also a deficiency in this GABA uptake process? Once again, the model is started in the seizure activity mode (Figure 4b). Possibly, in the seizure activity mode the astrocytic GABA uptake rate (i.e. $gab_{e,a}$ (t)) maintains extracellular GABA concentration at a level that cannot neutralize the excitatory effect of glutamate concentration and consequently stopping seizure activities. At time t=40s the maximum rate of GABA uptake by astrocyte (V_{ma})was set to zero and left at that value until t=80s when the value was raised again. It is observed that extracellular GABA concentration begins to increase as soon as V_{ma} was set to zero. Possibly, this enabled $gab_{c,e}$ (t) reach a level where it can neutralize the excitatory effect of extracellular glutamate and finally suppressing seizure activity. The increase in $gab_{c,e}$) (t) persists until V_{ma} was raised instantaneously, at this moment $gab_{c,e}$(t) begins to drop until it reaches its original level when seizure activity re-emerges.

Finally, activity maps obtained from simulation experiments using Simulink block diagrams of the neuron – astrocyte population models gave regions associated with normal, pre-seizure and epileptic activities in the P, γ plane. There is a transitory region associated with the TLE model. This vital observation might be pointing to the fact that TLE events may be easily detectable or predictable while GAE might not be. Using the activity map for GAE the authors predicted that seizure activity will develop in an epileptic brain network if parameter P varies within the range [10 16] and there is a decline in the value of parameter γ from 2.5 to

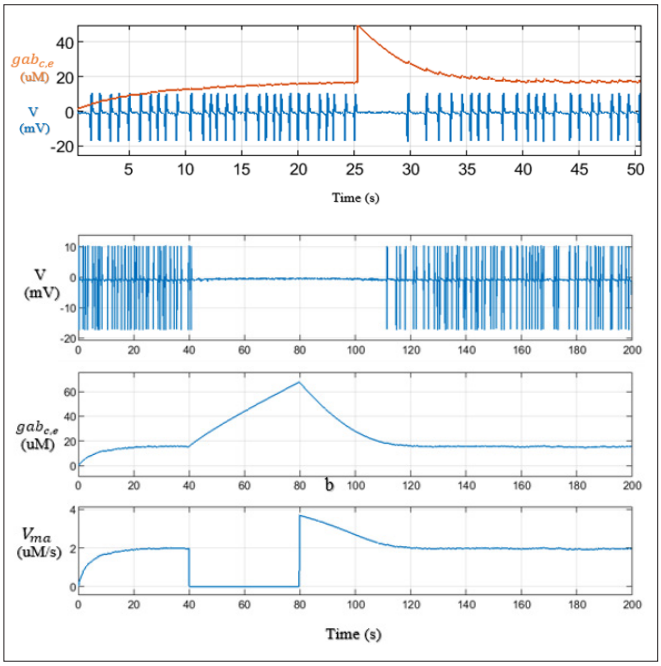

Figure 4: Simulation of effects of deficiency in astrocytic (a) glutamate uptake process (b) GABA and glutamate uptake processes from the extracellular space (Reproduced from Agboola et al., 2017)

2.3. For TLE however, they predicted that keeping the value of parameter P in the range [60 120] and allowing parameter γ decrease slowly from 4 to 1.3 will first lead an epileptic brain into a transitory or pre-seizure activity before finally plunging it into an epileptic activity. These observed seizure onset mechanisms have an important significance for seizure prediction. It can be used to track preictal changes (especially in TLE) for seizure prediction and control, if methods for quantifying and controlling the values of these parameters reliably inside the brain are devised.

Data Based Attempts at Seizure Prediction

It was around early seventies when the first attempt at predicting epileptic seizure occurrence through EEG data analysis was made. With the very optimistic results obtained from early studies, there seemed that a breakthrough was imminent but unfortunately, more than forty years down the line the road that leads to reliably predicting epileptic seizures through EEG analysis is still chronicled as long and winding [11, 67, 68]. The major faults found in most of the early studies were purely methodical, for instance they were not subjected to rigorous statistical test. They were also not applied to long-term continuous EEG data exemplifying situations close to the real conditions. These factors among other suggested ones made it impossible to evaluate the clinical validity of the proposed methods. Summarily, the guidelines put forward by as requirements for a practical prediction method can be summarized as follows: (1) The prediction power of a seizure prediction algorithm should be demonstrated through prospective randomized controlled tests using long- term, continuous and blinded EEG recordings. (2) Test dataset must be independent from the training dataset used for model optimization. (3) The efficacy of the algorithm should be expressed in terms of sensitivity and specificity on the test dataset. (4) Since an average frequency of 3.6 seizures per day or 0.15 seizures per hour are observed during epilepsy monitoring, false prediction rates (FPR) which is a measure of specificity greater than 0.15/h should be questioned and (5) In addition to predicting seizures, if an algorithm is designed to trigger interventional devices in other to abort seizure, the minimum intervention time

(IT) which is defined as the minimum interval between a prediction alarm and the start of the seizure prediction horizon (SPH) or seizure occurrence period (SOP) must serve as an additional constraint when assessing the seizure prediction performance of the algorithm. The SOP is the time window following the IT during which seizure is expected to occur. A prediction alarm not followed by seizure event within the SOP should be regarded as a false alarm [11, 15, 69, 70].

The major task in predicting seizures through EEG data is to show that certain measures or features derived from the EEG exhibit high but inverse correlation with normal and pre-seizure brain states. As a result, many EEG features have been engineered and used for seizure prediction. Generally, EEG features can be categorized based on type of analysis (i.e. linear, nonlinear) or the type of domain (i.e. time, frequency and time-frequency). They can also be categorized as being univariate or bivariate/multivariate. Univariate features monitor changes in EEG signal coming from a single recording channel while bivariate/multivariate features monitor relationship between changes in two/more EEG recording channels.

A nonlinear univariate feature named Lyapunov exponent was used by for seizure prediction [12]. This feature is conceptually the most fundamental clue to deterministic chaos that measures the exponential divergence of close paths (trajectories) in the reconstructed phase plane of the dynamical system (epileptic brain). The authors used dynamic threshold crossing to track the pre-seizure change in the temporal profile of the feature and demonstrated the prediction power of their seizure prediction algorithm using 2100 hour long intracranial Gainsville EEG database of 10 patients containing a total of 130 seizure segments. Using an SOP of 30 minutes, the proposed method was reported to achieve an average sensitivity, false prediction rate and mean seizure warning time of 80%, 0.56/hr and 13.3 minutes respectively. The seizure prediction method was statistically validated using random and periodical predictors. investigated six types of bivariate features known in literature namely cross correlation, nonlinear interdependence, short-term Lyapunov exponent, phase- locking synchrony, coherence and entropy of phase difference [71]. Cross correlation is a linear time domain measure of dependence between two spatially distant EEG signals. Nonlinear interdependence is a nonlinear time domain measure of the distance in state-space between the trajectories of two EEG channels. Phase-locking synchrony, coherence and entropy of phase difference are time-frequency based features which are based on phase synchrony. Following feature extraction, feature selection algorithms were applied to identify features with desirable seizure prediction power. A pattern classification method for tracking the pre-seizure state was adopted which led to the design of classification algorithms. Three classification algorithms namely logistic regression, support vector machine and convolutional neural network were tested. The Freiburg Seizure Prediction EEG database (FSPEEG) was used to demonstrate the performance of the proposed method. The FSPEEG was proposed as an EEG database made available for free download. The database contains intracranial EEG data from 21 patients suffering from refractory focal epilepsy. The authors reported that for individual patient, 100% sensitivity was achieved on average 60 minutes before the onset with no false alarm using at least one method. The seizure time surrogates method was used to validate the prediction result. The mean phase coherence feature has also been used for seizure prediction (Kuhlman et al., 2010) [8, 72]. Mean phase coherence is a bivariate feature that measures the degree of phase synchronization between signals. Some authors have reported a significant drop in the mean phase coherence in the pre-seizure brain state while both increase and decrease was reported several hours to the onset of seizure (Qu yen et al., 2005) [73-75]. By applying both fixed and dynamic threshold crossing method to track pre-seizure state in six patients with EEG data spanning 596.7h and containing 73 seizure segments in the FSPEEG database, was able to achieve a best sensitivity for each patient ranging from 50 to 88% while the corresponding false prediction rates ranged from 0.64 to 4.69/h. The statistical validation method used are Poisson process predictor and alarm time surrogates [8]. Spectral power which represents a univariate EEG feature was combined with the support vector machine classifier to study seizure prediction in 18 patients [21]. The patients whose EEG spanned a total of 433.2h and contains 80 seizure segments were also drawn from the FSPEEG database. The output of the classifier was smoothed using a Kalman filter to remove isolated false positives. Using seizure occurrence period of 30 min which was equal to the assumed 33 preictal period, the group reported an average sensitivity and false prediction rate of 98.3% and 0.29/h respectively across 18 patients. Investigated the rate of epileptic spikes in intracranial EEG as a measure for seizure prediction [14]. The feature used is the spiking rate and the pre-seizure tracking method is threshold crossing. The whole 21 patients in the FSPEEG database was used for the study. Evaluated using IT of 10s, the algorithm recorded 56% sensitivity and an FPR of 0.15/h for SOP of 30min and 72.7% sensitivity and a FPR of 0.11/h for SOP of 50 min. The reported results were proven to be above chance level with the use of a random predictor. Utilizing the same feature and the same database as adopted a threshold crossing method to track pre-seizure signatures [8, 16]. A random predictor was reportedly used as their statistical validation method. Using a cross-validation scheme on the entire dataset, the authors assessed the performance of their method and reported that the levels of performance recorded were on average greater than those of a chance predictor. For a maximum FPR of 0.15/h, the average sensitivity varied between 25 and 70% while the SOP varied between 2 and 40 min respectively and the IT was fixed at 10 min.

Unlike the FPSEEG database which is commercially available to only epilepsy research groups the Children Hospital Boston and Massachusetts Institute of Technology (CHB-MIT) scalp EEG database is freely accessible to all researchers in the field of epilepsy. The CHB-MIT database consists of scalp EEG (sEEG) recordings of 23 patients suffering from intractable epileptic seizures. The EEG data can be accessed through the PhysioNet website: http://physionet.org /physiobank/database/chbmit/. Quite a number of research works on epileptic seizure prediction have utilized the CHB- MIT database for instance, through the analysis of positive zero-crossing intervals in scalp EEG, Shahidi (2013) proposed a seizure prediction algorithm that uses novel measures of similarity and dissimilarity hinged on a variational Bayesian Gaussian mixture model. The proposed algorithm was evaluated using approximately 561 h of CHB-MIT scalp EEG data containing a total of 86 seizure segments and belonging to 20 epilepsy patients. A high sensitivity of 88.34% was claimed to have been achieved with FPR of 0.155/h and an average prediction time of 22.5 min on the test dataset. The method was further tested against a Poisson-based chance predictor. In the same vein, the power of Phase/amplitude Lock Values (PLV/ALV) which is a bivariate measure as a pre-seizure marker through the threshold crossing scheme was demonstrated using ten patients chosen from the CHB-MIT scalp EEG database [76]. Depending on the type of EEG

preprocessing method employed the authors reported sensitivity values ranging from 33 to 100% for each patient. Features based on short time Fourier transform and Convolutional Neural Networks (CNNs) classifier was applied on different intracranial (FSPEEG) and scalp (CHB-MIT) electroencephalogram (EEG) datasets to propose a generalized retrospective and patient-specific seizure prediction algorithm. 30-second EEG windows with 50% overlap was 35 used to track temporal and spectral patterns for pre-seizure state identification [78]. This method achieved average sensitivity and FPR of 89.8% and 0.17/h respectively on FSPEEG dataset, and average sensitivity and FPR of 89.1% and 0.09/h on the CHB-MIT dataset. A patient-specific epileptic seizure predication scheme relying on common spatial pattern- (CSP) based feature extraction and linear discriminant analysis classifier has also been proposed [77]. A leave-one-out cross-validation strategy was adopted in the seizure prediction experiments carried out on the scalp EEG recording in the CHB-MIT database. Result from experiments reveal that the proposed predictor can achieve an average sensitivity, false prediction rate and prediction time of 89%, 0.39/h, and 68.71 min respectively using a 120-minute prediction horizon.

From the foregoing it is noticed that a lot of research works have been published showing various level of conformity to the seizure prediction guidelines [11]. They have utilized several time, frequency and time-frequency domain techniques either in a linear or nonlinear fashion and classification algorithms. Although, results reported in these studies appear so promising, attempts made at continually reproducing them in different settings have been unsuccessful. There seems not to be that magical single or group of features that will always predict each seizure of individual patients. This consideration suggests the need to explore and exploit new mathematical tools for EEG data analysis for seizure prediction. Since the EEG features mostly utilized are engineered (i.e. hand crafted) based on domain knowledge, a new way of distilling these features in other to automatically obtain new set of features that will further entangle hidden discriminatory properties between normal (baseline) and pre-seizure EEG data should be experimented.

Unsupervised representation learning consists of set of methods that map input features (engineered or low-level features) to new output features (high-level features) without any information about class labels (i.e. pre-seizure or normal) of data. The new features which could arise from either "under complete" or "over complete" learnings can lead to improved classification accuracy as extensively proved that if adequately tuned, very simple unsupervised learning algorithm could uncover representations of the data that enables even basic classification algorithms, such as a linear support vector machine, to achieve excellent performances. In addition, feature learning algorithms have been shown to improve computer vision (image recognition or classification) tasks and speech recognition tasks in recent studies [78-82].

In a recently published seizure prediction method, a hyperparameters optimization procedure (Bayesian optimization) was employed to adaptively choose between reconstruction independent component analysis (RICA) and sparse filtering (SF) which respectively, represent linear and nonlinear unsupervised representation learning methods for obtaining useful representations of several frequency domain low-level features (normalized logarithmic wavelet packet coefficients energy ratios (NLWPCER) extracted from long term scalp EEG recordings of patients suffering from refractory epileptic seizures [83]. The NLWPCER measures the ratio of wavelet packet coefficients energy of relevant EEG spectral bands i.e. delta (δ), theta (θ), alpha (α) and beta (β) whose frequency ranges are 0 – 4 Hz, 4 – 8 Hz, 8 – 15 Hz and15 – 30 Hz respectively across the bands and between EEG channels (i.e. bivariate EEG feature). EEG data window of 5seconds without overlap was used in the extraction of the NLWPCER features. For each data window in all channels, full wavelet packet decomposition was implemented, then normalized logarithmic wavelet packet coefficient energy (NLWPCE) was extracted for each relevant decomposition nodes. This feature reveals the cross energy information not just between two EEG channels but also between EEG frequency bands across channels. The seizure prediction algorithm employed a simple binary support vector machine classifier with regularized output. Prospective evaluation of the proposed seizure prediction algorithm showed that the algorithm correctly predicted 38 out of 43 test seizures with an average of one false prediction every 12 hours. These results were validated by the authors using an analytical random predictor. In addition, the consistency of unsupervised representation learning was verified by comparing prediction results obtained with and without the use of representation learning. Six different experimental schemes (A - F) were carried out. In schemes A, C & E different sets of engineered features were extracted and used for seizure prediction across all patients. Schemes B, D & F consisted extracting engineered features as in schemes A, C and E respectively but with additional adaptive representation learning before being used for seizure prediction. Furthermore, one of the issues in seizure prediction studies bordered on variability of predictive onset times obtained from different seizure prediction algorithms. The predictive onset times reported in several works do vary largely from the order of a few seconds to several hours. Consequently, it has been theorized that seizure prediction parameters particularly seizure onset prediction times exhibit high sensitivity to the theoretical methodology employed for seizure prediction. The authors studied this phenomenon in their proposed seizure prediction method by observing the trends of average prediction times achieved for experimental schemes A - F across prediction schemes and patients.

Conclusion and Future Direction

Epileptic seizure events are complex and diverse in nature and so are the neurophysiological mechanisms underlying their occurrence. The epileptic seizure prediction challenge has been tackled over the years through deterministic (mechanism - based) and nondeterministic (data based) dynamical systems modelling methods. Although no satisfactory resolution appears to have been found, significant progress has been made in both areas. At least, through computational modelling of neural population activities, it is now known that sequence of changes in certain parameters controlling synaptic interactions between subpopulations of neurons can lead to seizure generation. Therefore, seizure could be predicted if these parameters are properly tracked and controlled. Bistability/multistability properties have also been discovered in some classes of epileptic behaviour where seizures can also be induced by simple fluctuations in the system. Efforts made so far in predicting seizure occurrence through EEG analysis are confirming the presence of the pre-seizure brain state so much so that today, the main problem has gone beyond proving the feasibility of seizure prediction through EEG but perhaps more about the reproducibility of seizure prediction performance. Through computational modelling of neuron-astrocyte population interactions studies have shown that changes in parameters associated with the astrocyte population activities can also cause transitions from normal to epileptic activities and seizure suppression. Therefore, proper monitoring and control of activities of both neural and astrocyte population in the brain may offer more effective way of seizure prediction and suppression. Future

investigation on the neuron- astrocyte population models that may give more insight into the seizure generating mechanisms include unifying the models through model inversion techniques with long term intracranial or surface EEG data of epileptic patients. This may offer simpler and clearer neurophysiological paths connecting interictal to ictal brain states. It is noticed that in the data based approach to seizure prediction, a great deal of effort has been invested over characteristic EEG features that are always indicative of the preictal brain state. In fact, feature extraction step has been described as the most difficult steps in the seizure prediction workflow (Ning and Michael, 2014). Feature engineering has been the traditional approach to EEG feature extraction for seizure prediction. The major drawbacks of feature engineering are that it is error prone, tedious, time consuming and dependent on domain knowledge. Feature learning or representation learning is an automated feature extraction scheme that improves upon the standard workflow by automatically extracting meaningful and useful features from raw data. In particular, deep learning models such as deep convolutional neural networks (CNNs) nowadays provide state-of-the-art solutions to many problems in computer vision or image classification, speech recognition, natural language processing, etc. These models can learn data representation at different levels of abstraction and extract complex features from input raw data. Accordingly, deep learning networks have recently gained attention in several EEG classification tasks such as emotion recognition motor imagery mental workload, seizure detection, event related potential and sleep stage scoring [84-89]. Results showed that deep learning networks performed very well on these tasks and hopefully it will also impact seizure prediction problem positively. Notwithstanding, deep learning networks have their own disadvantages as well. For instance, they require large number of labeled learning data and computational needs owing to the large number of hyperparameters to be learned in the network. In addition, features derived through CNNs can be difficult to interpret. Interestingly, a technique which addresses the challenges of deep learning networks was proposed. This technique which is called group invariant scattering has an even greater potential to impact the field of epileptic seizure prediction from EEG data analysis [90]. The scheme utilizes multi-layered network of fixed wavelet kernel based transform. It is common knowledge that physiological signals often exhibit certain variabilities that are not useful for classification task. Shifting and stretching in time and transposition in frequency are examples of such variabilities. Since characteristics desired for any given classification task are usually not known, scatter transform circumvents this problem by creating representations of the raw signal that are invariant to variabilities that do not impact the class of the signals but preserve as much information in the data. This permits us to keep other variabilities that are useful in determining the class of the signals. An immediate advantage of this new method is that it allows us to construct classification models and hence prediction models that do not require much training data [91]. Although the theoretical framework for scattering transform was developed some years back, computational methods that allow its smooth implementation are just getting popular. By comparing the mode of predictions from these two modelling methods, it seems the data based method offers a more practicable and convenient way of predicting epileptic seizures while the mechanism based method is better suited for the understanding of the pathophysiological mechanisms underlying seizure occurrence. This line of reasoning is further consolidated, judging by the way seizure predictions were inferred for GAE and TLE models which rely on monitoring changes in certain physiological parameters in the epileptic brain network. Although the data based prediction scheme is straightforward and simple, the mechanism based models can be very important and helpful in providing useful insight into the possibility or otherwise of predicting epileptic seizures through data based modelling. For example, geometries of two different attractors (normal and epileptic attractors) in the state space of a physiological mechanism-based model of epilepsy were compared in the normal and pathological topologies. In the normal topology, the attractors are well separated so that little random activities cannot shift the brain out of its normal attractor into the epileptic attractor [24]. On the other hand, the normal and epileptic attractors are not well separated in the pathological topology so that any slight random activity will cause the brain to shift from the normal attractor into the epileptic attractor. The results from this mechanism based study have remarkable implication for the data based modelling which include: (i) stochastic seizure causation which might imply no pre-seizure state for some seizures, (ii) seizure prediction from EEG might not be possible in all kinds of seizures and (iii) epileptic seizures possess seizure and patient dependent characteristics. Finally, an avenue that will offer a realistic intersection of the two modelling methods will be in the realm of closed loop epileptic seizure control strategies specifically, through brain stimulation protocols or drug infusion processes. A reliable and consistent seizure prediction algorithm derived through data based modelling can be used to predict an impending epileptic seizure while stimulation protocols (i.e. frequency and amplitude of stimulation)/drug infusion parameters learnt from the use of mechanism based models via in silico experiments is triggered in order to abort an impending seizure [92, 94].

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