neuron to take place. In contrast, an inhibitory synapse is a synaptic potential which makes a post-synaptic neuron less likely to generate an action potential. Several factors are available to a synaptic pathway to be created and chosen. One of these factors in the cellular-physical level is dendrite which is lengthened to approximately one meter (Tang and Thompson 2012; Gao et al. 2015). This fact can be considered in epilepsy study in terms of finding the source of origin of the synaptic pathway in which the seizure may start from a distance where the source presented from the surface. The result of the in vivo and in vitro studies demonstrates that the seizures may arise from the spread of cortical micro-domains and influence the regions which are located far than the Seizure Onset Zone (SOZ) (Netoff and Schiff 2002; Cymerblit-Sabba and Schiller 2012). In other words, the possibility of developing seizure is fed by a combination of various cortical sites flowing to SOZ (Bragin, Wilson, and Engel J. 2000), (Bikson et al. 2003).

TABLE 1. Different types of epilepsy

	Types of epilepsy		Description
(Jean Bancaud Olaf Henriksen 1981)	Partial	Simple	This follows with awareness of what occurs during seizure.
		Complex	In complex seizure, the patient is confronted by some impairments of awareness during the seizure. In some cases, it follows confusion, partially aware or zero awareness during the seizure.
		Secondary generalized	Secondary generalization of the seizure discharge may lead to the loss of consciousness which is caused by development of a complex partial seizure via alteration of consciousness.
		Generalized	Generalized seizures occur initially by the involvement of both hemispheres. The consciousness during generalized seizures may be impaired as a primary sign.
		Unclassified	Unclassified seizures included all seizures that cannot be classified due to insufficient or incomplete data. In some cases, seizures cannot be placed in the described categories because of not obeying those definitions.
(Fisher et al. 2017)	Focal		Partial in the primary classification becomes focal and focal to bilateral tonic–clonic seizure replaces secondarily generalized seizure. The awareness is considered as a classifier of focal seizures which means a person has consciousness of self and environment during the seizure. Focal seizures are characterized by one of the motor-onset or non-motor onset symptoms reflecting the prominent sign during the seizure.
	Aware Impaired Awareness		
	Motor onset Automatisms, Atonic, Clonic, Epileptic spasms, Hyperkinetic, Myoclonic, Tonic Nonmotor onset Autonomic, Cognitive, Emotional, Sensory		
	Focal to bilateral tonic-clonic		Individuals with generalized epilepsies may have a range of seizure types including absence, myoclonic, atonic, tonic, and tonic–clonic seizures. The diagnosis of generalized epilepsy is done assisted by clinical equipment by checking EEG signals in interictal status to find typical discharges. An absence is atypical for the reason of depicting slow onset or termination or significant changes supported by slow, generalized spike and wave on the EEG.
	Generalized		
	Motor Automatisms, Atonic, Clonic, Myoclonic, Myoclonic-tonic-clonic, Myoclonic-atonic, Atonic, Epileptic spasms Nonmotor (absence) Typical, Atypical, Myoclonic, Eyelid myoclonic		
	Unkonown Onset		The seizures of unknown onset contain some features led them to still be classified.
	Motor Tonic-clonic, Epileptic spasms Nonmotor (absence) Behavior arrest		
	Unclassified		A seizure may be unclassified due to the reasons; (a) definitions (b) degree of awareness which usually is not specified, (c) insufficient information or inability to place in other categories.

TABLE 2. Clinical causes, symptoms and risks in epilepsy

	Clinical causes	Symptoms	Risks
Issue	Head injury	Focal neurologic dysfunction	Stress
	Brain infection	Alteration of consciousness	Stress deprivation of fatigue
	Stroke	Dizziness	Insufficient food intake
	Tumour	Miscellaneous symptoms	Alcohol usage
	Unknown causes		Drug abuse
			Medication failure
Ref	(Beghi 2020)	(Walker, Hall, and Hurst 1990)	(van Campen et al. 2014; Gordon and Dooley 2015; Ena Lynn Suzi Lyons 2017)

ACTION POTENTIAL

Action potential is a phenomenon which occurs in the axon conditioned by the rapid fluctuation in membrane potential (Hodgkin and Huxley 1952), (Diaz-Casado et al. 2020), (Ito et al. 2020). In the axons, the velocity of action potential increases by sudden movement conduction influencing the ability of electrical signals to "Jump" (Sadock, Sadock, and Ruiz 2009). At nerve terminals, the wave of conducted action potential opens voltage-gated calcium channels. The influx of calcium promotes the release of a chemical neurotransmitter into the extracellular space where the neurotransmitter will affect a post neuron through specific protein receptors. Referring to (Grider and Glaubensklee 2020), an action potential can be summarized in three main stages; depolarization, repolarization and hyperpolarization. In general, depolarization of the neuronal membrane is the key to action potential manifestation (Bromfield, Cavazos, and Sirven 2006). It is a variation in membrane potential from -60 mV to +40 mV primarily caused by sodium influx while in normal body temperature, the equilibrium potential for sodium and potassium are +55 mV and -103 mV, respectively (Chen and Lui 2020). Figure 1 demonstrates this phenomenon by adding stimulus as a trigger for depolarization to be started and resting-state with -55 mv in membrane potential.
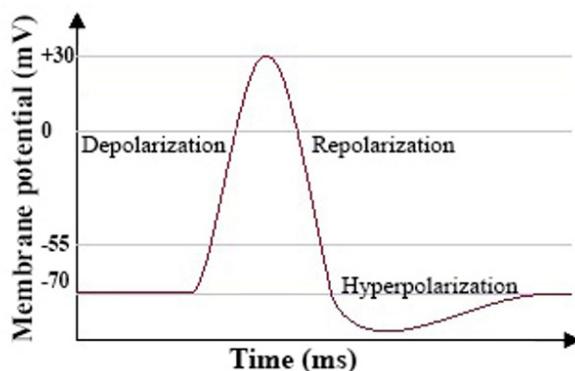

FIGURE 1. Action potential diagram ("CNX O" 2016).

ACTION POTENTIAL IN EPILEPSY

The action potential in epileptiform activity is similar to normal condition but with rapid repolarization followed by hyperpolarization as Paroxysmal Depolarization Shift (PDS) (Bromfield, Cavazos, and Sirven 2006). Epilepsy as a functional brain disorder is associated with excessive synchronization of large neural populations leading to a hypersynchronous state (Jiruska et al. 2013). In this regard, populations of bursting cells can synchronize their action potential firing in a normal brain to be exposed to pro-epileptic conditions (Foffani et al. 2007). High frequency signals resulting by action potential and hyper-synchronization of a cohort of neurons are two factors for seizure manifestation (Bromfield, Cavazos, and Sirven 2006). In detail, the presence of calcium ions ($Ca2+$) in the extracellular fluid would be more significant than sodium ($Na+$) (Rajakulendran and Hanna 2016). Calcium channels will be opened and PDS take place which notably is a broader phenomenon than a routine depolarization in normal action potential manifests. This occurrence causes an unbalance condition among the neurotransmitters; Gamma-Amino Butyric Acid (GABA); as the major inhibitory neurotransmitter, and glutamate (Werner and Covenas 2017). GABA is the major inhibitory neurotransmitter in contrast to the glutamate that is responsible for approximately 80% of brain synapses with fast excitatory (Sadock, Alcott, and Ruiz 1991). Furthermore, when an epileptic seizure occurs, glutamate (known as the major excitatory neurotransmitter) is released all along with the brain tissues and spinal cord. Glutamate in synaptic plasticity involves cognitive functions such as learning and memory (McEntee and Crook 1993). Synaptic plasticity is the ability of synapsis to be stronger or weak over time, in response to increases or decreases in their activity (Zhang et al. 2018). This cellular level information has been achieved using various tools and modalities in order to be applied in subsequent research. The next section presents what tools and methods are available to be applied in epilepsy studies and how researchers synchronize these methods with intracranial concepts.

BRAIN SIGNAL PROCESSING AND NEURONAL MODELLING

The major obstacle in brain signal processing is EEG low-resolution characteristics. Hence, the necessity to involve other methods that can provide strong and trustworthy conditions respecting to solve the EEG *forward* and *inverse* problems. Solving the problem using forward technique means how to be notified of the information of the neural system and the event from the consequences signals resulted by neural activities. Conversely, brain signal processing assisted researchers to consider relevant features and reduce targeting their purpose (here, seizure) to solve the inverse problem (Grech et al. 2008). The probable equations may result in enormous mathematical answers which increase the complexity of the problem. Neuronal modelling derived on mathematical equations and neural structure has attracted many researchers to apply it to solve various problems.

BRAIN SIGNAL PROCESSING

Neural activities flow charges transferring information towards destinations. The deflection of these functions is approached to scalp presenting as potential. The potential of this spot is differentiated from the potential of another spot (EEG reference) is presented under time series as signals of potential difference. These signals can be analyzed under two domains; time and frequency. Depending on what knowledge of signal behavior is under investigation, the algorithms and methods in each step of signal processing are different. Figure 2 shows the general steps of brain signal processing based on EEG which according to (Graimann, Allison, and Pfurtscheller 2010) includes acquisition, pre-processing, feature extraction, feature dimension reduction and classification.
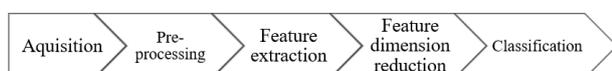

FIGURE 2. The steps of brain signal processing.

NEURONAL MODELLING

In definition, a model is defined as a designed system which is substantially similar to an actual system. To model a system, the system (here the brain) must be identified structurally. The physical structure of the brain presented by physiological concepts provides the condition to introduce a variety of neuronal models. A system is described based on the structures such as *mathematics*, *physics* or *electronic* models which are detailed by the function, evolution or the position of an event in the hierarchy as well

as parametric description (Malmivuo 1973). Regarding electrical neuronal modelling, the electronic circuits must be *designed* according to the primary concepts of physical brain structure as well as the electronic components. Next, the concept of *neuronal computing* which provides the condition for electronic circuits to behave as the actual system is applied.

The mathematical-based neuronal model illustrated by electronic characteristics describing the mechanism of the membrane has been introduced by Hodgkin and Huxley (HH). The model provides primary conditions that led the researches such as Lewis and Roy and Jansen to implement an electrical and digital computer-based membrane model based on HH's equations. The other aspect of brain physiological conditions related to neuron populations led *Lopes da Silva* and *Van Rotterdam* to present their neuronal model (Jaakko Malmivuo 1995). A few commonly explained models related to neuronal models are summarized in Table 3.

Neuronal simulators are machines towards solving the problems of the neuronal system supporting a range of models by providing a universal environment. The diversity of these machines is defined based on computational performance, code complexity for describing neuron models, user interface and user support, and integration with parallel high-performance computing platforms. NEURON and GEneral NEuronal Simulation System (GENESIS) as computer-modelling-based simulators refers to HH equations providing a powerful and flexible environment to implement biological models consisting of electrical and chemical components in a network of neurons (Kobayashi, Tsubo, and Shinomoto 2009). Table 4 introduces online-available neuronal simulators applied by researchers in epileptic study. A comparative study among GENESIS, NEURON and BRAIN determined in ModelDB database is vastly evaluated in (Tikidji-Hamburyan et al. 2017).

REVIEW OF OTHER RESEARCH WORKS RELATED TO EPILEPSY

Lots of theories have been proposed to explain what exactly epilepsy is. Although the paper covers a wide variety of such theories, it particularly focuses on general footsteps leading to the scenes of necessity to neuronal modelling under investigation. Based on the review of past papers, epilepsy study can be grouped into following three major perspectives; (a) Detection in epilepsy, (b) Prediction epileptic seizure and (c) Source localization to discover the zone where a seizure begins. Figure 3 illustrates these perspectives in addition to the detection of sub-branches including four items; (a) Epileptiform status detection, (b) Epileptic-type detection, (c) Epileptic marker detection and (d) Detection-surface localization which will be

explained in the next section. The role of brain signal processing methods and neuronal modelling will be described in each perspective.

TABLE 3. Summary of neuronal related models.

Models	Type	Descriptions
Hodgkin Huxley	Mathematical	The model presents how action potentials in neurons are initiated according to ionic mechanisms in axons. The model is a dynamic system which contains sets of nonlinear differential equations.
(Hodgkin and Huxley 1952)		
Hodgkin Katz	Mathematical	Known as Goldman equation presents the equation of reversal potential in synaptic coupling concentrated on ionic permeability.
(Hodking and Katz 1949)		
Lewis	Electrical	The model resents the conductance of sodium and potassium using electronic hardware such as discrete transistors, in the form of active filters representing the inside and outside of the cell membrane.
(Lewis 1966)		
Roy	Electrical	"Neurofet" introduced by Roy is based on the HH model but the analogous sort of Lewis model. The model consists of Field Effect Transistors (FET), amplifiers, capacitors and resistors. The goal was to create a simpler model rather than HH in the aspect of computational complexity.
(Roy 1972)		
Anderson	Computer-modelling	The model is based on Self-Oscillating Networks concentrated on the probability of firing of neurons.
(Andersen, Gillow, and Rudjord 1966)		
Lopes de Silva	Computer-modelling	Model is based on histological and biophysical data concentrated on Alpha-Rhythm obtained from the thalamus assumed by two types of neurons: thalamus-cortical relay neurons and interneurons. The model is based on post-synaptic potentials.
(Da Silva et al. 1974)		

...continued

Jansen	Mathematical	The HH mathematical-based model was used by Jansen in order to introduce single-column and double-column models obtained by the idea of cortical columns. Three interconnected neural populations including; one for pyramidal neurons and two for inhibitory and excitatory were considered. The rate of incoming spike to the amount of membrane potential is applied for each population using second-order differential and non-linear function.
(Jansen and Rit 1995)		

TABLE 4. Summary of neuronal simulators available in the market.

Sim	Description
GENESIS	GENESIS is a general-purpose simulation platform that was developed to support the simulation of neural systems ranging from subcellular components and biochemical reactions to complex models of single neurons, simulations of large networks, and system-level models. New model of chemical synapse can be implemented through external modules.
	(Van Drongelen et al. 2007; James M Bower 1998; "Genesis Simulation" 1994)
NEURON	The NEURON simulation environment is used in laboratories and classrooms around the world for building and using computational models of neurons and networks of neurons. NEURON requires code modification if the model developed for a single computer has to be mapped on a computational cluster.
	("NEURON," n.d.; N. T. C. Hines and L. 2006; M. L. Hines, Davison, and Muller 2009; M. L. Hines and Carnevale 2008; Migliore et al. 2006)
NEST	NEST can almost transparently map an existing model on a cluster or multicore computer. New model of chemical synapse cannot be implemented as an independent module. It can be applied through code modification.
	(Gewaltig and Diesmann 2007; Eppler et al. 2008; Plotnikov et al. 2016)
BRAIN	BRAIN can be done in script without writing modules. Coding in parallel mode is the weakest feature of BRAIN. There is no and limited supports for clustering and multicore computers in BRAIN, respectively.
	("BRAIN Simulation" 2013; Drewes, Zou, and Goodman 2009; Insel, Landis, and Collins 2013)

DETECTION, PREDICTION AND SOURCE LOCALIZATION

Previous papers present different aspects of epilepsy studies. Despite the substantial correlation, they can be divided into three promising branches to better address the scientific research. In the next subsections, the definitions of detection, prediction and source localization will be explained.

DETECTION

Detection is coupled by diagnosis in the medical system if a subject is considered as an epileptic or a non- epileptic person. As mentioned earlier, some specifications such as epileptiform discharges, exist for a subject to be considered as an epileptic person. Although in the majority of cases, the diagnosis is still under an epileptologists' responsibility, studies based on detection procedures attempted to decrease the human mistakes. According to Figure 3, detection can be further divided and summarized in four main approaches.
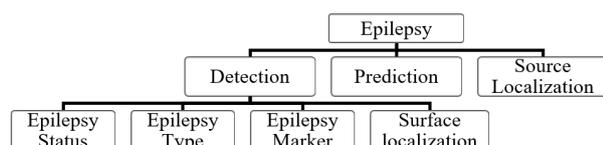

FIGURE 3. An overview of how many literature papers commonly categorize the descriptions of epilepsy.

EPILEPSY STATUS DETECTION

In some studies, the detection focus was to realize the differences between epileptiform status such as normal versus subjects in *interictal* versus subjects in *ictal* or in *pre-ictal* status. Figure 4 illustrates three different EEG sequences in three different statuses in epilepsy. Researchers worked on various datasets concentrating on different methods and techniques. The result and the methods considering the datasets are comparable. Classifying the features focused in three normal, interictal and ictal classes using brain signal processing methods in the frequency domain was investigated (Gajic et al. 2014). They announced that they achieved 99% accuracy in classification of the seizures and also claimed that their method can be used to diagnose in clinical settings involving noise. In another study, utilizing the same dataset with the concentration on feature selection. They applied Mutual Information (MI) to find the most relevant feature obtained by nonlinear dynamical analysis based on the Recurrence Quantification Analysis RQA method. The method resulted in 100% accuracy in classifying the three mentioned classes (Siddiqui, Islam, and Kabir 2019). Another study concentrated on analysis on the same dataset respecting making the comparison condition based on time span scales, fuzzy entropy and distribution entropy revealed 93% accuracy to classify the three mentioned classes following feature selection and training classifiers (Li et al. 2018). Another study achieved 98% of accuracy using wavelet in time-frequency domain to extract the features from statistical methods and approximate entropy. Principal Component Analysis (PCA) was used to extract the features which seemed redundant (Fathillah et al. 2018).

Distinguishing the epilepsy status such as ictal, pre-ictal and interictal led a study to apply Convolutional Neural Network (CNN) directly on raw EEG signals instead of manual feature extraction. The advantages of the approach are declared to produce faster diagnosis and continuous monitoring, decreasing the overall expenditure of medical treatment (Zhou et al. 2018). Whilst the other study concentrated on deep neural networks achieved significant result 99.07% accuracy in epilepsy detection considering three ictal normal and interictal status (Poomipat Boonyakitanont Apiwat Lek-uthai 2019).

EPILEPSY TYPE DETECTION

The detection process led some researchers to investigate the differences between the types of epileptic seizure. A study applied Support Vector Machine (SVM) to classify *generalized, focal* and *focal focused on tonic-clonic* seizure achieved the accuracies of 90.25% 97.83% and 91.4%, respectively for correct seizure classification (Saputro et al. 2019). To detect focal versus non-focal epilepsy, a study applied detection algorithms combining Flexible Analytic Wavelet Transform (FAWT) in time-frequency domain. The features were reduced and classified resulting in 94.80% accuracy in detection (You et al. 2020).
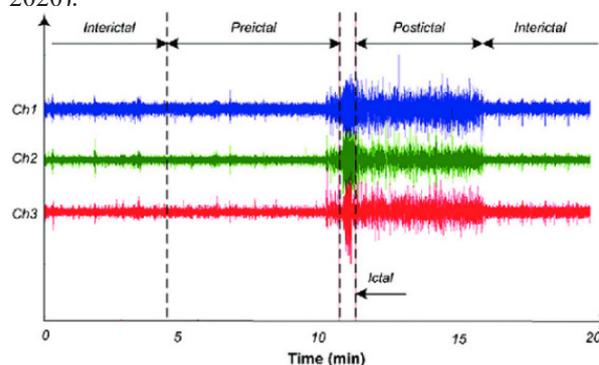

FIGURE 4. EEG in epilepsy during different status; Interictal, Pre-Ictal, Ictal and Postictal (Rasekhi et al. 2015).

EPILEPSY MARKER DETECTION

The golden technique for epilepsy confirmation is by visual detection of Interictal Epileptiform Discharge (IED) clarified by an epileptologist which identifies the presence of epileptiforms. A study worked exclusively on analyzing the spikes by focusing on frequency domain using statistical analysis achieved to 93.75% of accuracy to classify IED in two classes; spike-wave and sharp-wave (Juni Puspita G Soemarno 2017). Epileptiform discharges in focal and generalized epilepsy investigated using deep learning to detect IED (Tjepkema-Cloostermans, de Carvalho, and van Putten 2018). Whilst, the method was followed by video

monitoring to investigate eyelid myclonia as a unique type of generalized seizure in order to detect the focal frontal epileptiform discharges (Takahashi et al. 2015). Analyzing the spikes where the reliable methods are going to be used in clinical settings provides a complicated situation considering the substantial brain signal ratio to noise. To solve this problem, synched fMRI in resting time and EEG data was investigated (Omidvarnia et al. 2019). The focus of their study was to analyze the signal in the time domain in order to detect the sharp spikes and slow-spike-and-waves. However, these abnormalities are often not seen in all EEG recordings for those having epilepsy. Discovering and classifying different types of the EEG abnormalities (Figure 5), can be done using signal processing techniques. Note that, in the patients with normal EEG, discovering the clues comparing healthy EEG is one of the debated issues which can be investigated particularly by signal processing techniques. Figure 6 illustrates an example of one second EEG signal acquired from an epileptic patient compared to a healthy subject.
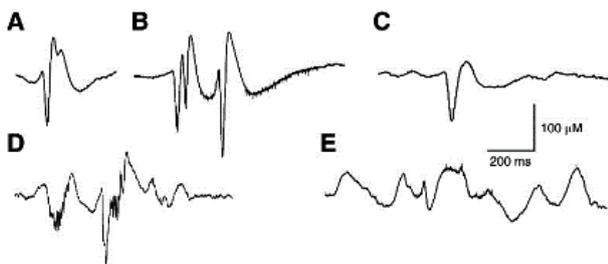

FIGURE 5. Different types of abnormalities in EEG. A) Inerictal spike; B) Group of interictal spikes; C) Sharp wave; D) Fast activity (brushes); E) Paroxysmal slow activity superimposed to slow spikes (Migliorelli Falcone, Mañanas Villanueva, and Alonso López 2017).
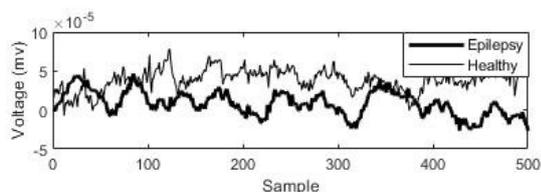

FIGURE 6. One second of raw EEG signal from epilepsy subject (bold line) and healthy subject (thick line).

DETECTION-SURFACE LOCALIZATION

Detection leads us to be informed of the region of the surface where epileptic signals are more activated; cautiously, the activated lobe. To speed up the decision procedure of epileptic analysis in multi-channel EEG signals, PCA was used to reduce the dimension of features (Murat Yildiz 2015). Linear Discriminant Analysis (LDA) classified the data in normal and seizure classes by 9 percent of better detection in comparison with non-using feature reduction

methods. Concentrating on localization the regions involved by seizure led a study to investigate temporal lobe epilepsy (Verhoeven et al. 2018). They first used signal processing methods in order to diagnose Temporal Lobe Epilepsy (TLE) from healthy subjects, then regionally investigated lateralized TLE. The features extracted in the frequency domain based on the frequency bands are then classified and achieved to 90.07% and 90.0% of accuracy for TLE and lateralize TLE detection, respectively.

PREDICTION

When does an epileptic seizure occur? By processing the EEG signal before onset and finding the dominant sign of stimulus, predicting the coming seizure can be done (Namazi et al. 2016). The claim has been investigated using visual stimulus and brain signal processing methods resulting in 25.76 seconds of prediction time. It presented that there is a direct relationship between visual stimulus and memory. A long-term neonatal investigation declared that the factor to do prediction is a combination between reducing synaptic strength and enhancing desynchronization (Zhang et al. 2018). In another study, the prediction was performed by modelling focused on pre-processing (Syed Muhammad Usman Muhammad Usman 2017). The research resulted in average time to 23.6 minutes concentrating on channel reduction; 23 to one single-channel. In this regard, Intrinsic Mode Functions (IMF) s were applied then selected in order to increase the ability of SVM to classify the features extracted from time and frequency domain.

SOURCE LOCALIZATION

The question is where epileptic seizure comes from? The most critical problem to answer this question refers to inaccessibility to intracranial in vivo. Hence, the majority of responsibilities are under medical doctors to conduct animal studies or using Electrocorticography (ECoG) in invasive research. In contrast, using non-invasive techniques plays a crucial role in epilepsy source localization which have been applied toward introducing neuronal models. In this case, the problem turns to mathematical problems; forward problem or inverse problem, which can be solved using particular techniques. The solutions which have been reflected in different mathematical-based simulators. Another method is to focus on a combination of synched non-invasive techniques for possible problem solution. In this regard, fMRI as a confirmation tool presenting intracranial activities led some researches to apply a simultaneous EEG-fMRI system to solve the source localization problem (Bagshaw et al. 2006; Wang, Gu, and Shen 2008).

In an *animal study*, a minimal model based on spikes responses was introduced (Kobayashi, Tsubo, and Shinomoto 2009). In this study, signal processing techniques were used to analyze the input fluctuated current. Membrane potential and spike threshold were two dynamic components for modelling. A time-scale of the signals related to Regular Spiking (RS), Intrinsically Bursting (IB) and Fast Spiking (FS) neurons were analyzed based on the proposed method for model individually. The relevant receptors including GABA were considered. The study concluded that high flexibility and low computational cost lead to a model of an actual brain for more examinations. Focusing on *invasive human research*, a study was one of the researches concerning on forest decision classifiers worked on ECoG data obtained from a single epileptic patient which focused on detection and localization (Siddiqui, Islam, and Kabir 2019). The purpose of *in vitro human study* on source localization led a study investigate on patients with glioma (a type of tumor that starts of glial cells) to be screened by "macroscropic" and "microscropic" techniques; multichannel Magnetoencephalography (MEG) and EEG, and patch-clamping, respectively (Patt et al. 2000). To find the source, the single suspicious segment from EEG was compared by Equivalent Current Dipole (ECD) and focused on the level of sodium in the tissues. The study raised the issue that the result did not strongly suggest that the cells related to glioma are directly involved in generating tumor-associated cells. In the *non-invasive study,* focal epileptic patients caused by lesion have been considered. The study worked on intracranial localization by Magnetic Resolution Imaging (MRI) and EEG. The study presented the pros and cons of the hypothesis considering the result of the clinical method (G A Worrell et al. 2000). A *case report study* investigated on source localization using EEG considering MEG data. For this reason, the data received from patients suffering from fronto-parietal "Opercular" epilepsy; where the spikes exhibited, were considered. According to the comparison of the results from EEG and MEG, the study emphasized on using MEG as a more beneficial method in localizing spikes in opercular epilepsy especially in the cases where EEG could not do the detection accuracy (Koren et al. 2018). Another *non-invasive study*, in order to overcome the inaccessibility of the brain, combined data obtained by high-density EEG and MEG was used and validated by input-criteria. The comparison among early-phase, mid-phase and late-phase by considering Electroencephalographic Source Localization (ESL), Magnetoencephalographic Source Localization (MSL) and combination of two previous methods Electroencephalographic-Magnetoencephalographic Source Localization (EMSL) were considered to compute the data obtained from patients in pre-surgery and during follow-up (Gregory A. Worrell et al. 2000). In some cases, it was needed to *reconstruct the real data* then accomplish the

research based on the functions that have been identified. In a study, the reconstruction procedure was done based on Enhanced Mode Decomposition (EMD) using IMF and the criteria of entropy. The study demonstrated that the proposed approach improves the data source reconstruction specifically epileptic seizure detection (Bueno-López et al. 2019). The idea from the presence of high-frequencies; as the biomarker in epileptic seizure genesis, led a study to use Tripolar Electroencephalography (tEEG) recording to distinguish high-frequencies from EEG routine frequencies in order to find the source of seizure onset (Chris Plummer, Simon J. Vogrin, William P Woods, Michael A Murphy, Mark J Cook 2019). Refer to (Bueno-López et al. 2019) for more information of tEEG.

A study in 2019 applied Multi-Resolution optimization of Cortical Potential Imaging (MR-CPI) based on Back Projection Cortical Potential Imaging (BP-CPI) to localize cortical activities (not relevant to epilepsy seizure). The proposed approach was estimated by the data obtained by Monte-Carlo simulator and real EEG. The result exhibited a good accuracy and may be considered for use as a clinical tool based on the level of complexity of computation and the reduction of estimation error (Haor et al. 2019). The GENESIS as is a powerful simulator for generating neural networks led another study to apply it able to produce 656 cells in the neocortical. The approach for neuronal models included different types of cells constituting ion channels and gap junctions. The journey of the investigation was around the influence of synapse weights in the cortical network leading to the seizure-like oscillations. They concluded that the distribution of seizure-like activity is caused by the weakness of excitatory connections in the neocortex, even though the strong excitatory connections are not the constant reason for seizure genesis (Van Drongelen et al. 2007).

DISCUSSION

A variety of fundamental challenges exist to explain what epilepsy is when an epileptic seizure occurs and where this seizure comes from. Although numerous investigations have been done to present reasonable justifications for each challenge, some of them still remained unanswered. EEG and fMRI as two powerful techniques promote epileptic investigations. Nowadays, technology provides a positive condition to speed up the process of analysis and solution. The conditions lead to introducing neuronal models inspired by the neural system due to the overcome the intracranial accessibility. In the present research, the studies have been explored which attempted on various aspects of epileptic studies concentrated on EEG, signal processing and neuronal modelling.

In this regard, the studies were categorized in three major perspectives despite correlations; (a) detection, which was focused by the majority of studies, (b) prediction, by answering to what relations exist between neurons respecting seizure occurs, and prediction using analyzing the signals obtained from transcranial, (c) source localization, strongly related to the specific zone where the seizure begins. The correlation signifies that the investigations to predict seizure onset or to discover SOZ require passing some steps earlier in the detection procedure. Detection is focused on different relevant algorithms in order to find epileptic status, different types of epilepsy, discovering epileptic markers such as epileptiforms as well as localizing the seizure according to signal processing on the surface. Various databases have been introduced to provide competitive conditions for better accuracy in each sub-branch of detection using brain signal processing. The review showed that the majority of epileptic studies belonged to detection applied brain signal processing techniques. Since the studies on epileptic brain signals restrictedly exhibit a consequent of neural system behavior, to respond what literally is occurring inside the brain, in vitro animal studies in neurophysiological level have been done (Toole et al. 2019). To the human, presenting a mathematical-based model of the neural system has been offered. The prediction argued according to two methodologies; prediction assisted by signal processing on the surface, and prediction by modelling via knowledge of intracranial (Jalilifar and Yadollahpour 2017) .

According to intracranial concepts, the neural system principally works based on the relation between sodium, potassium and chloride providing membrane potential difference following an action potential. Neurotransmitter which contain specific information lead specific chemical (s) to be released following the changes of charge into the membrane (Bromfield, Cavazos, and Sirven 2006). The changes of charges in neurons and population of neurons are reflected on the surface which conducts the detection studies to be done. The process of action potential inspired various types of models to become introduced based on different functions and parameters (Scharfman 2007).

In epileptic EEG signal studies, to detect the region where the seizure begins in its depth, a confirmation device such as fMRI is considered (Chaudhary et al. 2016). Practically, in some cases, the regions of seizure onset resulted by EEG and fMRI do not confirm each other. Then, surgery in these cases might be followed by observing seizure in follow up (Negishi et al. 2011). Physiologically, the cause may be due to gap junctions following the weakness of myelin of a membrane which must carry a neurotransmitter through a direct pathway to reach its destination (Nualart-Marti, Solsona, and Fields 2013). Jumping to adjacent

neural pathways destroy the balance of potential difference in the new pathway and leads charges to be piled towards seizure (Beenhakker and Huguenard 2009).

Alternatively, computer-based simulators lead some investigators to apply them to discover SOZ via introducing defined parameters (Baumgartner, Koren, and Rothmayer 2018). The simulators which directly are relevant to equations obtained from the relations of chemicals, lead to composing specific models ensuring to unique function (here, epileptic seizure as a function). The more information of the neurophysiological system promises a more accurate model to be introduced. The deficiency of neural relations information causes the limited epileptic investigation to be done on the seizure onset zone. Hence, the space for more investigations in localizing epileptic seizure onset promising to predict using neuronal modelling assisted by brain signal processing is open. As future investigations, analyzing brain signals can provide a proper condition in triggering procedure applied on case and control groups towards introducing a comparative model. Moreover, there are different types of non-invasive brain studies in the fields of learning, emotions and control movement; introduced particularly in BCI studies. The comparison between epilepsy as a case group and control group in these studies would conduct us to valuable achievements.

CONCLUSION

This paper presents epilepsy studies which focus on different aspects of epilepsy using clinical and mathematical methods and tools. The fundamental questions made us introduce a new categorization of previous studies classified in three perspectives; (a) Detection, (b) Prediction and (c) Source localization. In spite of strong correlation among these perspectives, the division was done due to following each study to a unique purpose. Hence, it is presented which algorithms and tools and using what methods; brain signal processing or neuronal modelling, have been applied in achieving what purpose of epileptic study.

The paper exhibited that brain signal processing technique has been applied extendedly in epileptic detection studies comparing applying the technique in prediction and source localization with restricted outputs. This does not mean that investigation on the responded issues has quite been terminated, conversely, to increase the resolution of results regarding reducing the computational complexities, the investigation is still under debate. It was illuminated that to overcome the deficiency of brain signal processing techniques in prediction and source localization, neuronal modelling would be a proper substitute. Modelling an epileptic brain as an alternative

solution leads the researcher to dominate the inability of prediction as well as finding the source location of seizure. In this paper in order to make a linkage between brain and model, the primary concepts of intracranial were presented. Furthermore, the primary procedure of modelling and well-known neuronal models was presented.

Neuronal modelling as the savior of epileptic studies is confronted with specific challenges. The challenges which are known as the most controversial crack in brain studies due to inaccessibility in vivo. The difficulties accurately refer to the same obstacles in which the source localization studies are faced with. To find SOZ, brain signal processing techniques can be applied in the phase of detection while for the rest of investigation, adequate knowledge of neurophysiological concepts play the pivotal role. Although the physical brain structure respecting medical science has been clarified, the relation between the constituted components is still debatable. In conclusion, it is strongly essential to do more investigation on various aspects of epilepsy to discover the rest of intracranial principles to increase human knowledge.

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DECLARATION OF COMPETING INTEREST

None

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