Dynamical Systems for Epilepsy Prediction

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Abstract

Dynamical systems provide a unique framework to probe the inner mysteries of the brain, with simple foundations of differential equations leading to intricate results that can model complex, nonlinear behaviours. One such behaviour worth modelling is epilepsy, as its frequency is high among the most vulnerable people, its effects can have severe consequences, and its inner workings are not well understood. In this paper, we present an overview of the literature, including common dynamical systems that are used to model epilepsy and the various ways these models can be leveraged to predict the onset of epileptic seizures.

A. Abbreviations

AR	Autoregressive Model
CAS	Collective Almost Synchronization
CNN	Convolutional Neural Network
DNN	Deep Neural Network
DWT	Discrete Wavelet Transform
EMD	Empirical Mode Decomposition
FPR	False Positive Rate
HR	Hindmarsh-Rose
IMF	Intermediate Mode Function
LSTM	Long Short Term Memory
ML	Machine Learning
MLP	Multi-layer Perceptron
NMM	Neural Mass Model
NN	Neural Network
PCA	Principal Component Analysis
RLS	Recursive Least Square
RNN	Recurrent Neural Network
SNR	Signal-to-Noise Ratio
SVD	Singular Value Decomposition
SVM	Support Vector Machine
SWD	Signal Wavelet Decomposition

I. Introduction

A group of neuroscientists are given a microprocessor and told to investigate its inner workings as if it were a brain. They perform lesion studies, connectomic analysis, and examine the tuning curves and "local field potentials" of the transistors. The results were at best interesting but could provide no insight into the architectural organization of the processor (eg. the fetch-decode-execute cycle, or identifying the ALU), and at worst grossly misleading (eg. concluding a single transistor is responsible for playing a game from single-transistor lesion studies) [1]. The moral of the story: scientific discovery is a fundamentally model-centric process. Without a conceptual framework, meaningful insights become elusive no matter how much better the observational tools become.

Dynamical systems are one such framework that could provide the underlying premises for investigation in neuroscience. Compared to representational or connectionist frameworks[2], the salience of dynamical systems lies in their ability to model biophysical phenomena from single neurons up to the dynamics of an entire brain. Studying the brain as a dynamical system is not a new idea, and has been used since the development of the Hodgkin-Huxley neuron model [3]. But there has been a resurgence of such approaches in recent years [4].

To evaluate the effectiveness of dynamical systems as a modeling framework, we chose the problem of epilepsy characterization and prediction as a case study. The reasons are 3-fold: 1) epilepsy is a common neural disorder affecting an estimated 70 million people worldwide with serious symptoms that can result in injuries and even death [5][6][7], 2) seizure prediction presents significant challenges with its nonlinear and multidien dynamics, and 3) relevant research on seizure prediction and prevention is abundant.

Modeling provides many benefits for epilepsy research. The first is to gain insight into dynamics and answer questions such as: Are seizures predictable and to what extent are they predictable? What is the optimal time horizon for forecasting? What are the relevant biomarkers for prediction? These questions build up an understanding to enable forecasting, which is the second aspect. Furthermore, comprehensive computational models allow the simulation of neuromodulation techniques and evaluations of their efficacy. Arguably, dynamical systems have proven most worthy in the first aspect, contributing to localizing epileptic zones [8], presenting statistical evidence for the predictability of seizures [9], and identifying biomarkers associated with criticality [10]. However since there are more quantifiable and rigorous metrics for seizure prediction, this paper will focus on prediction techniques and provide a quantitative meta-analysis.

II. Background

A. A Brief Introduction of Dynamical Systems

A *dynamical system* is a set of differential equations with *states* that correspond to variables of a physical phenomenon that evolves in time. Such systems are characterized by qualitative features, most importantly, states when the derivative

is zero (*fixed points/equilibrium points*). These fixed points could either be *attractors*, which the system dynamic evolves towards over time, or *repellors/unstable attractors*, which the system tends to evolve away from. The set of fixed points can also form a continuous orbit, or a *limit cycle*. These *fixed points* are often plotted in a *phase space* plot, and a solution to this system is a trajectory in its phase space, found by following the instantaneous derivative at each point.

1) Bifurcation

In addition to variables, a dynamical system can also have parameters that do not vary with time. For example, in the Hodgkin-Huxley model of action potentials in a single neuron, membrane voltage, and injected current are variables, whereas maximum potassium/sodium conductance are parameters [3]. Variations of these parameters across their range of values prompt the study of *bifurcations*. In different bifurcations of the system, attractors may disappear, multiply, or merge into each other to form new attractors. Different configurations of attractors can lead to physical and qualitative differences in the system.

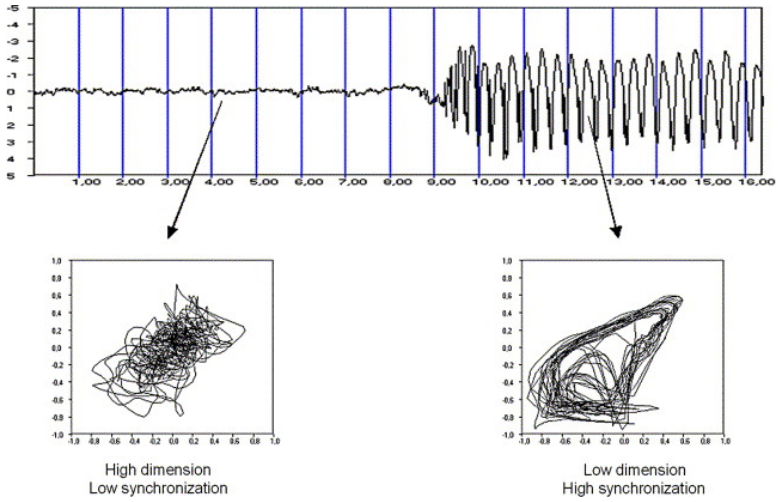

Fig. 1. An EEG time series showing the transition between inter-ictal (left) and ictal (right) dynamics and their associated attractor states below, indicating a bifurcation. The inter-ictal state attractor is high dimensional and reflects a low level of synchronization in the underlying neuronal networks, while the ictal state is low dimensional and reflects a high level of synchronization, demonstrating a clear qualitative change evoked by seizures [10]

2) Criticality

A *critical state* is a state where the system undergoes qualitative changes, for example, from oscillatory to non-oscillatory, from ordered to chaotic, and from asynchronous to synchronous. Interestingly, the point of criticality creates several favorable conditions for optimal computation, including maximizing the number of metastable states, the dynamic range, information transmission in terms of mutual information, and computational power in terms of input-output mappings [11]. It has been theorized that the brain operates in a *reverberating regime* near criticality and is capable of *self-organization* around the point of criticality [12], and that epilepsy also involves changes in criticality [10]. Parallels between critical behavior in epilepsy and, for instance, similar power-law relationships in earthquake dynamics also open up the floor for wide interdisciplinary collaboration [12].

B. A Brief Introduction of Epilepsy

Epileptic patients suffer from a lasting predisposition to spontaneous epileptic seizures [7]. Epilepsy is a common condition with a bimodal age distribution: infants less than 1 year old and adults above 50 are most likely to have epilepsy [7]. In addition to being a widespread condition, epilepsy can also be highly dangerous: Sudden death in epilepsy (SUDEP) is the leading cause of lost years of life after a stroke [13]. Along with SUDEP, other causes of premature death related to epilepsy include status epilepticus (seizures lasting longer than 5 minutes), accidents, drowning, and suicide [13]. Despite this, it is possible to treat and further recover from epilepsy [7][14].

There is an official definition of the specific diagnostic conditions for epilepsy. The International League Against Epilepsy (ILAE) provides the following official definition [14]:

Definition II.1. Epilepsy is defined as a disease of the brain where any of the following conditions are met:

1) Two or more unprovoked seizures, occurring more than 24 hours apart
2) One unprovoked seizure and a probability of further seizures with similar probabilities to general occurrence (i.e. $> 60\%$ over the next 10 years)
3) Diagnosis of an epilepsy syndrome

1) Brain States in Epilepsy

It is of interest to define when epileptiform activity begins in the brain, since the activity at the beginning and end of a seizure period may provide additional insight into the cause of the seizure [15]. Furthermore, a definition of the states of epilepsy enables a clear definition for states in a dynamical systems model or classes in a machine learning classifier. In general, an epileptic patient can either be in a seizure or in a normal state; therefore, the basic states of epilepsy are normal and *ictal* (referring to a seizure state) [15]. These states can be further divided into four types of states [16], with three ictal substates as shown in Table II-B1.

TABLE I
FOUR POSSIBLE STATES OF BRAIN DYNAMICS: BEFORE, DURING, AND AFTER A SEIZURE.

State Name	Definition	Symptoms/Physiology	Duration
inter-ictal	Between ictal (seizure) states, normal brain activity	N/A	N/A
pre-ictal	Windup prior to seizure starting	Muscle twitches, dysphoric symptoms (depression, irritability) [17]	Few min - 3 days [17][18]
ictal	Seizure state	Epileptic behaviour	30s - 30min [13][17]
post-ictal	Transition between end of ictal and beginning of inter-ictal state	Psychosis, potential mood changes [17]	0-120 hours [17]

C. Datasets

For verification of dynamical systems, as well as training of machine learning models, it is imperative to have large amounts of high quality data. In itself, acquisition of neurological data is a huge ongoing challenge. Commonly used invasive techniques such as intracranial EEG (iEEG), electrocorticography (ECoG), or stereoelectroencephalography (sEEG), can only be implemented in clinical settings at select hospitals with both the correct equipment and trained physicians [19]. As such, electroencephalography (EEG) appears to be a prime candidate for neurological data collection since it is significantly less costly, highly efficient, and non-invasive [20]. There is a large quantity of EEG data publicly available in the form of online datasets [21][22]. However, it is worth noting that EEG data presents some inherent challenges, namely that EEG data has low spatial resolution due to distance from the brain, and high sensitivity to noise [20].

In EEG, brain signals recorded across a given time window are captured with electrodes placed either on the scalp (EEG, sEEG), or from patients with implanted electrodes (iEEG) [16]. As EEG signals with seizure data requires data from epilepsy patients, publicly available datasets are provided which can be used for research without requiring access to a large number of patients. Using these datasets, performance of a given model can be properly benchmarked against other models [18]. A brief table of EEG datasets with epilepsy recordings is provided in Table II. General and pediatric populations refer to those with diagnosed epilepsy, whereas healthy correspond to baseline data recorded from healthy patients.

TABLE II
NOTABLE EPILEPSY EEG DATASETS

Dataset	n	Population	Sample Rate	Sample Duration	# Channels	Active	Public
CHB-MIT [23]	22	Pediatric (ages 3-22)	256hz	1-4 hrs	10-20*	Y	Y
Freiburg Dataset [24]	21	General (ages 10-50)	256hz	50 min-24 hrs	128	N	Y
EPILEPSIAE Project [25]	250	General	250-2.5khz	N/A	< 122	Y	N
Bonn Dataset [26]	10	General Healthy	173.61hz	12 hrs (avg)	10,12 (iEEG) 10-20* (EEG)	Y	Y
Bern Dataset [27]	5	General	512hz/1024hz	N/A	10-20*	Y	Y
Temple University (TUH) [28]	10874	General (ages 1-90)	250hz/other	15 hrs (avg)	20-31	Y	Y
Sienna Scalp EEG [29]	14	General (ages 20-71)	512hz	N/A	10-20*	Y	Y
Helsinki University [30]	70	Neonatal (32-45 weeks)	256hz	74min	10-20*	Y	Y

Note: n is the number of patients in each dataset. 10-20* refers to the international 10-20 system [31] for EEG electrode placements.

As shown in table II, the Bonn dataset contains iEEG data from 3 patients diagnosed with epilepsy, and scalp EEG data from 7 healthy baseline subjects [26]. The scalp EEG data from the Bonn dataset uses the international 10-20 system. Additionally, the Freiburg dataset [24] has recently been incorporated into the European Epilepsy Database (EPILEPSIAE Project) [25], and is therefore no longer actively available. All of the datasets in the table above were released after the year 2000, and correlates to a trend of data availability due to improvements in storage capacity, processing power, and information transmitability. As such, as more and more data is available, not only is quantity of datasets increasing, but also dataset size. The Temple University Hospital (TUH) dataset [28], released in 2014 and compromising 14 years of EEG data collection, has a cumulative disk size of over 330 GB. On the other hand, the CHB-MIT dataset, released in 2010, is only 42.6 GB large.

Lastly, we acknowledge that this is not a comprehensive list of epilepsy datasets used in dynamical systems or machine learning research. More comprehensive surveys of datasets exist, and can be found at [18][21][22].

III. Seizure Prediction

A. Problem Definition

One of the difficulties in managing epilepsy is the aspect of unpredictability: seizures are by definition sporadic and near impossible to predict. A system that can detect seizures early could have profound impacts on patient experience, since a significant number of accidents and injuries could be controlled and limited [32]. In this review, we follow the definition of Seizure Occurrence Period (SOP) provided by [33]: A SOP is an envelope of time where a seizure occurs, as shown in Figure 2. Then, we define a *prediction* system as one which can raise a flag or alarm *before* the SOP window. In other words, a prediction system should have a positive Seizure Prediction Horizon (SPH) duration. There is an additional subtask of seizure prediction called seizure *classification*, which is equivalent to seizure prediction with an SPH equal to zero and an ictal period overlapping with the SOP window. Classification is generally considered an easier subtask, and existing research is plentiful, especially in machine learning literature [18]. Therefore, we will only be presenting a review of techniques for early prediction of epilepsy in this paper.

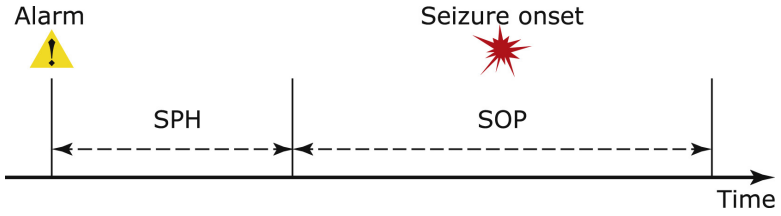

Fig. 2. Definition of Seizure Prediction Horizon (SPH) and Seizure Occurrence Period (SOP) [33]

B. SoDaPoP Search Strategy

In medicine, the PICO model is an effective and widely used search strategy to limit search scope when conducting reviews on existing literature [34]. However, PICO is more applicable to medical studies involving patients, where a clear intervention and control can be identified. As this study is focused on comparing epilepsy prediction models and systems, we adopt a different method to guide our literature search: SoDaPoP. A description of SoDaPoP, as well as the parameters for this review, are provided in Table III.

TABLE III
SoDaPoP: Source, Dataset, Population, Problem, Time

Category	Definition	This Review
Source	What type of data does the system use?	EEG (iEEG or scalp EEG)
Dataset	Where does the data come from?	Datasets, such as those in Table II
Population	Who is the primary recipient of data?	Human, no age restriction
Problem	What is the problem?	How are DS and ML models used for epilepsy prediction?
Time	What is the timeframe of the literature search?	Within last 20 years

Using SoDaPoP, we found and analyzed 17 papers.

C. Seizure Prediction

Methods for seizure prediction are extremely varied: EEG, ECG, accelerometry, and mattress-based sensors have all been previously used as data for seizure prediction [32]. Even trained canines have been applied to forecast a seizure [32]. As mentioned in Table III, we focus on the comparison of forecasting methods for human subjects based on EEG signals. The studies examined in this paper have SPH ranging from 5 seconds to 86 minutes.

In this section, we discuss in detail 3 types of seizure forecasting methodologies: (1) dynamical model-based prediction III-D, (2) linear/non-linear signal analysis methods III-F, and (3) data-centric or machine learning methods III-G. The first two are analytical methods focused on mathematical analysis, whereas (3) relies on large amounts of empirical data.

D. Dynamical Systems Models of Epilepsy

One of the most natural applications of dynamical systems is to build models at various scales - as mentioned previously, a set of differential equations lends itself well to describing how systems evolve through time. For example, neural mass models (NMMs), which represent aggregated clusters of neurons connected to other clusters of neurons, are some of the most commonly used dynamical systems models in neuroscience [35]. Some common models of epilepsy are analyzed below:

1) Epileptor Model

One of the most commonly used models is the epileptor by Jirsa et al, a series of differential and integral equations with five state variables [36]. These equations are:

$$\begin{aligned}
\dot{x_1} &= y_1 - f_1(x_1, x_2) - z + I_{rest1} \\
\dot{y_1} &= y_0 - 5x_1^2 - y_1 \\
\dot{z} &= \frac{1}{\tau_0}(4(x_1 - x_0) - z) \\
\dot{x_2} &= -y_2 + x_2 - x_2^3 + I_{rest2} + 0.002g(x_1) - 0.3(z - 3.5) \\
\dot{y_2} &= \frac{1}{\tau_2}(-y_2 + f_2(x_1, x_2)) \\
g(x_1) &= \int_{t_0}^{t} e^{-\gamma(t-\tau)} x_1(\tau) d\tau \\
f_1(x_1, x_2) &= \begin{cases} x_1^3 - 3x_1^2 & \text{if } x_1 < 0 \\ \left(x_2 - 0.6(z-4)^2\right) x_1 & \text{if } x_1 \geq 0 \end{cases} \\
f_2(x_1, x_2) &= \begin{cases} 0 & \text{if } x_2 < -0.25 \\ 6(x_2 + 0.25) & \text{if } x_2 \geq 0.25 \end{cases}
\end{aligned}$$

where $x_0 = -1.6$, $y_0 = 1$, $\tau_0 = 2857$, $\tau_2 = 10$, $I_{rest1} = 3.1$, $I_{rest2} = 0.45$, and $\gamma = 0.01$ [36]. In this model, the state variable pair (x_1, y_1) accounts for the oscillatory fast discharges, and (x_2, y_2) accounts for spike and wave events.

Both of these phenomena were proven to require at least two state variables to model in previous papers. Another variable z was introduced to model extracellular variations and was deemed the "slow permittivity variable" by the researchers. The output is $x_1 + x_2$, which resembles the local field potential of the brain described by the epileptor [36]. By using various canonical models and the properties observed from data collected in experiments, Jirsa et al. were able to piece together this dynamical system, which they then validated on various other seizure models [36].

Mathematical analysis

An advanced mathematical analysis has also been done on this model, which characterizes its properties such as attractors, bifurcation points, and behaviours at varying parameters [37]. For example, the full form of the equation for f_1 is

$$f_1(x_1, x_2) = \begin{cases} x_1^3 - 3x_1^2 & \text{if } x_1 < 0 \\ -\left(m - x_2 + 0.6(z-4)^2\right) x_1 & \text{if } x_1 \geq 0 \end{cases}$$

By using this form, we can vary the parameters m and x_0, which creates a parameter space that is broken up into 9 different areas as seen in Figure 2. Each of these areas consists of different numbers and types of stability points, which changes the dynamics of how the epileptor switches between ictal and interictal states [37].

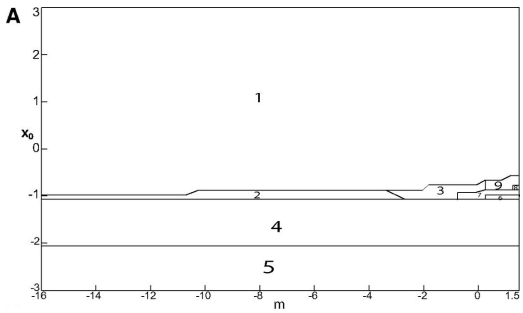

Fig. 3. Adapted from [37]. The equilibrium point is an unstable focus in area 1, a stable node in area 5, and a saddle in area 4. There are three equilibrium points in areas 2, 3, 6, 7, 8, and 9. In area 2, a stable node, a saddle, and an unstable focus coexist. In area 3, a stable focus, a saddle, and an unstable focus coexist. In area 6, three saddles coexist. In area 7, two saddles and one unstable focus coexist. In area 9, two unstable foci and one saddle coexist. In area 8, an unstable focus, an unstable node, and a saddle coexist. [37]

This switching is dependent on the location of the bifurcators in the phase space of various state variables. Specifically, at saddle points (found in areas 2, 3, 4, 6, 7, 8, and 9 of Figure 2), activity as modeled by the epileptor can transition from ictal to normal activity or vice versa [37]. These transitions are dependent on the ranges of z, and the exact boundaries are further dependent on the parameters m, x_0, and I_{rest2} [37]. Thus, the epileptor can not only account for and model changes within a patient's state, but also differences between patients and how that may affect the development of their brain activity.

As the activity of the brain through time can be modeled as trajectories through this phase space, the location of the bifurcators then influences where these trajectories converge into or diverge from - in other words, where the limit cycles are. These can be categorized as either stable limit cycles, or attractors, and saddle periodic orbits, which are repellors. Houssaini et al. also characterize a third limit cycle, a stable cycle with very small amplitude, deemed a "small limit cycle" [37].

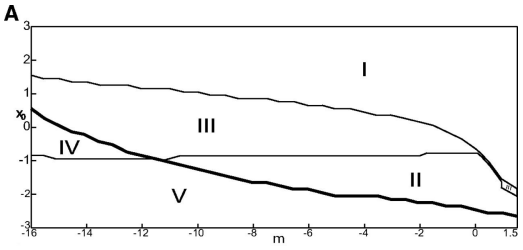

Fig. 4. Adapted from [37]. Attractor exists in area I and coexists with repellor in area II. Only small limit cycle exists in area IV, and coexists with attractor and repellor in area III. All three limit cycles disappear in area V [37].

Use in other models

This model has been used as the building block of other models for epilepsy prediction. For example, in conjunction with neural mass modeling, the epileptor was used to build a *Virtual Epileptic Patient* (VEP) — a personalized model of how an epileptic seizure can start and propagate through a patient's brain [38].

This VEP is an NMM based on a parcellation template, which is then fine-tuned using the patient's connectome. The individual nodes of this model are the epileptors, which are connected by their "slow permittivity variable". Specifically, the equation for the state variable z in each epileptor is modified such that it includes a K_{ij} term to denote the effects of node j on node i [38]:

$$\dot{z}_i = \frac{1}{\tau_0}\left(4(x_{i,1} - x_0) - z_i - \sum_{j=1}^{N} K_{ij} \cdot (x_{1,j} - x_{1,i})\right)$$

This research has been used to predict surgical outcomes for patients [38], and further expanded upon to include Bayesian criteria to predict the location of epileptogenic zones within patients [39]. Unfortunately, the authors were not able to find papers that used the epileptor to predict the onset time of seizures, although models such as the VEP and Bayesian VEP have been used to localize seizure locations and characterize its propagation [38] [39].

2) Physiological Neural Mass Models

While the epileptor model performs well in predicting brain states for epilepsy, one of its largest criticisms is that there is no physiological basis for its state variables. Thus, other scientists have used a different approach to modeling epilepsy: by starting from physiological phenomena found in populations of neurons and working from that phenomena to construct a model.

Canonical Model

The canonical physiological model is inspired by the organization of cortical cells in the thalamus, and consists of populations of pyramidal cells and interneurons that each affect the firing of the others [40]. With more research on cortical columns by Jansen et al, this model became the "Canonical" NMM [41] [42].

"Wendling-Class" Model

Adding to this model, Wendling et al. used observations of human epilepsy in the hippocampus to add onto the model as described in the figure below.

A series of five linear transfer functions is used to mathematically describe the interactions between these four

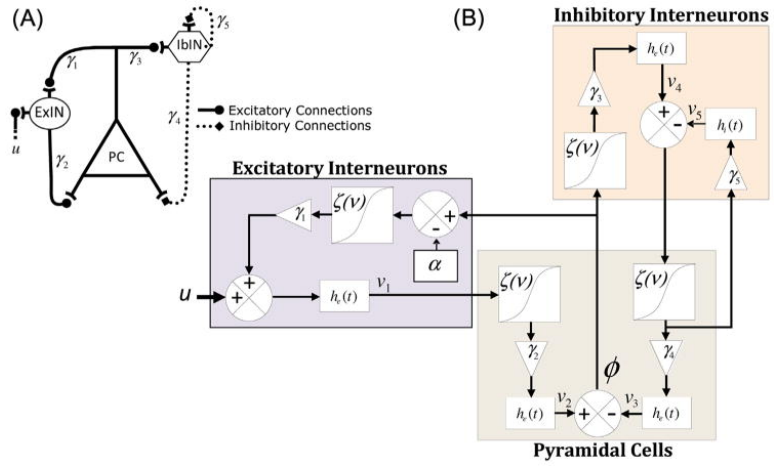

Fig. 5. Adapted from [41]. The modified model was built based on the incorporation of excitatory Pyramidal Cells (PC) receiving inputs from Excitatory InterNeurons (ExIN), Inhibitory InterNeurons (IbIN), and extrinsic input (u) coming from other cerebral regions. Each parameter corresponds to a physiological measurement [41].

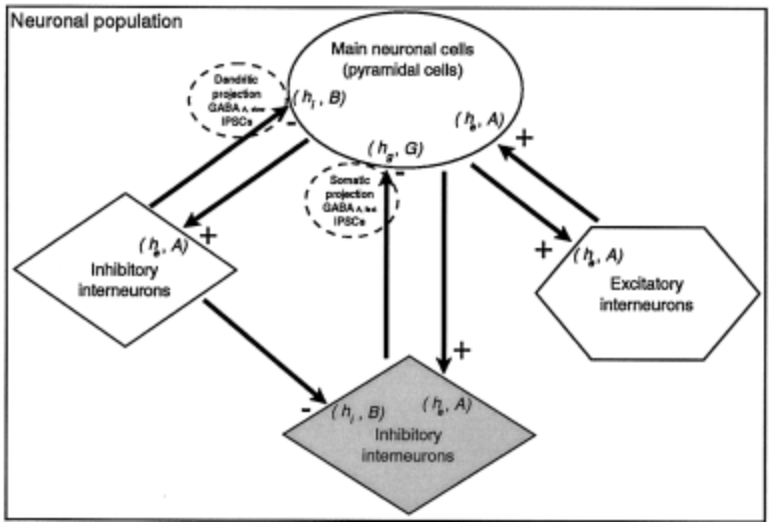

Fig. 6. Adapted from [43]. Structurally, the neuronal population is considered to be composed of four neuronal subsets: pyramidal cells, excitatory interneurons, dendritic-projecting interneurons with slow synaptic kinetics ($GABA_{A,\,slow}$) and somatic-projecting interneurons (grey rectangle) with faster synaptic kinetics ($GABA_{A,\,fast}$). Subset of pyramidal cells project to and receive feedback from subsets of interneurons. Dendritic interneurons project to somatic ones [43]

subpopulations of neurons, which then results in ten state variables and ten equations [43]:

$$
\begin{aligned}
\dot{y}_0(t) &= y_5(t) \\
\dot{y}_5(t) &= Aa\sigma[y_1(t) - y_2(t) - y_3(t)] - 2ay_5(t) - a^2 y_0(t) \\
\dot{y}_1(t) &= y_6(t) \\
\dot{y}_6(t) &= Aap(t) - C_2\sigma[C_1 y_0(t)] - 2ay_6(t) - a^2 y_1(t) \\
\dot{y}_2(t) &= y_7(t) \\
\dot{y}_7(t) &= BbC_4\sigma[C3y0(t)] - 2by_7(t) - b^2 y_2(t) \\
\dot{y}_3(t) &= y_8(t) \\
\dot{y}_8(t) &= GgC_7\sigma[C_5 y_0(t) - C_6 y_4(t)] - 2gy_8(t) - g^2 y_3(t) \\
\dot{y}_4(t) &= y_9(t) \\
\dot{y}_9(t) &= Bb\sigma[C_3 y_0(t)] - 2by_9(t) - b^2 y_4(t) \\
\sigma[v] &= \frac{2e_0}{1 + e^{r(v_0 - v)}}
\end{aligned}
$$

where A, B, G, a, b, g, C_1, C_2, C_3, C_4, C_5, C_6, C_7, e_0, and v_0 are various parameters corresponding to specific physiological constants such as synaptic gain, feedback time constants, and number of synaptic contacts. The output, a summated average of postsynaptic potentials on the pyramidal cells, resembles an EEG signal [43].

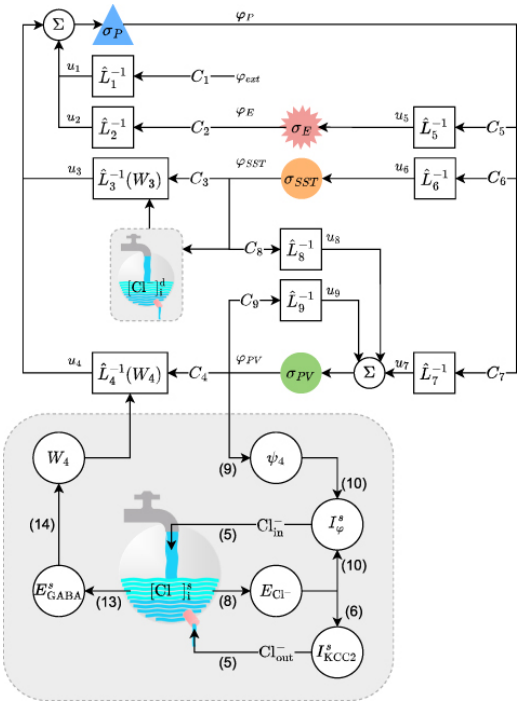

Fig. 7. Adapted from [44]. Diagram of the extended NMM equations. The grey box below represents the equations for chloride dynamics of the fast interneuron → pyramidal cell synapse. A similar model is used to describe the chloride dynamics of the slow interneuron → pyramidal cell synapse, located in the grey box in the middle of the diagram [44].

Like the epileptor, the "Wendling-Class" model can also be used both to create personalized models and to predict the results of various treatments. In a paper that could be seen as similar to the VEP for the epileptor, Lopez-Sola et al. were able to personalize the "Wendling-Class" model to patients through chloride accumulation dynamics [44]. External influences were also modeled as an input to the potential of the pyramidal cells; however, this was not used to link multiple "Wendling-Class" models together, rather, it was used to predict the effects of transcranial DC stimulation on epileptic events [44].

3) Other models

Hindmarsh-Rose

The Hindmarsh-Rose (HR) model of neural activity uses three equations to imitate the behaviour of spike bursts. The main variable, x, corresponds to membrane potential, while the other variables y and z account for additional ion transport activity [45]. The equations are as follows:

$$\dot{x} = y - ax^3 + bx^2 + I - z$$
$$\dot{y} = c - dx^2 - y$$
$$\dot{z} = r(s(x - x_1) - z)$$

where I is the current entering the neuron, a, b, c, and d represent fast ion channels and r represents slow ion channels [45].

Kuramoto Oscillators

Kuramoto oscillators are another, even simpler model that can be used to model neuronal activity, and how neurons affect each other. This model consists of a population of N oscillators, each with its own natural frequency [46]. These oscillators are also coupled with each other; this tends to synchronize them with each other [46]. The dynamics of this system are as follows:

$$\dot{\theta}_i = \omega_i + \sum_{j=1}^{N} K_{ij} \sin(\theta_j - \theta_i)$$

with ω_i being the natural frequency of the i^{th} oscillator and K_{ij} being some coupling constant between the i^{th} and j^{th} oscillator [46].

E. Model-Based Prediction

Despite the amount of literature around creating models for epilepsy, it was rather difficult to find any papers on using dynamical systems models to predict when epilepsy occurs. Most of the papers using models such as the epileptor or "Wendling-Class" models only attempted classification, localization, or control tasks [36] [38] [39] [44] [47] [48]. However, we were able to find two studies that did use dynamical systems to predict the onset of epilepsy, namely, Aarabi et al. using the canonical model [41], and Nguyen et al. using HR neurons and Kuramoto oscillators [49]. The results are summarized in the Table IV.

TABLE IV
DYNAMICAL SYSTEMS MODELS FOR EPILEPSY PREDICTION

Authors	Year	Model	Dataset	Results
Aarabi et al. [41]	2013	Canonical Model	Freiburg [24]	SPH: 10s Tuned for Max Sensitivity: SOP = 30min: Sensitivity: 87.07%, FPR: 0.2 SOP = 50min: Sensitivity: 92.6%, FPR: 0.15 Tuned for Max Specificity: SOP = 30 min: Sensitivity: 82.9%, FPR: 0.16 SOP = 50 min: Sensitivity: 90.05%, FPR: 0.12
Nguyen et al. [49]	2020	HR, KM	Bonn [26]	SPH: 5.67s Accuracy: 88.79%

1) Predictor Architectures

Canonical Model

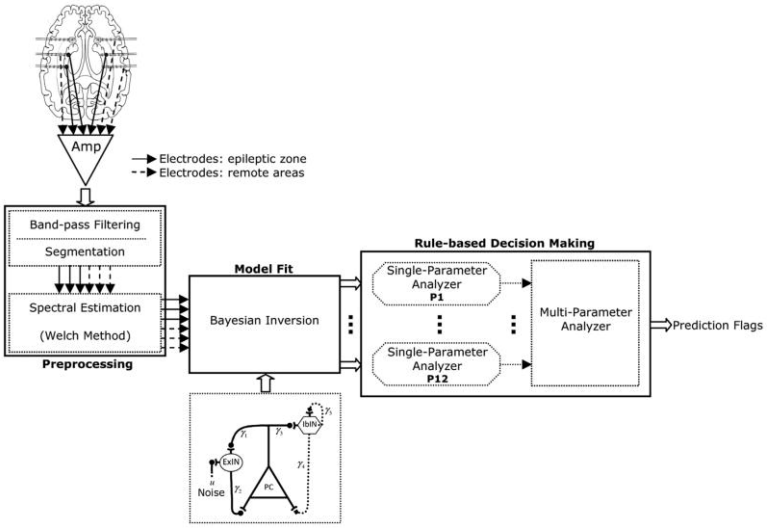

Fig. 8. Adapted from [41]. Schematic diagram of the model-based seizure prediction system [41].

The canonical model was used to characterize each of the individual electrodes, with no connections between the models. From each segment of time series data, parameters of the canonical model were estimated through the Bayesian inference method, and these values were then smoothed with a 5-minute backward-moving-average filter. Then, the result of this processing was fed to a rule-based decision model, which predicted whether a seizure would occur or not. The rule-based decision model was trained on the differences between ictal and interictal states, and were customized for each patient[41]. Figure 8, which was adapted from the original paper, summarizes the architecture.

Hindmarsh-Rose Neurons and Kuramoto Oscillators

Nguyen et al. tested the use of two models (HR neurons and Kuramoto oscillators) and two NMM topologies (random and small-world) to predict EEG data [49], which could then be fed into a classifier for epilepsy. The models were connected using a coupling strength parameter σ, which was tuned such that the system's behaviour fell into the collective almost synchronization (CAS) regime. This regime describes the emergence of complex properties from weak forms of synchronization [50]. In the brain, this would arise from the approximately constant local mean field experienced by individual neurons due to other neurons it is connected to [49] [50]. The equations for HR neurons

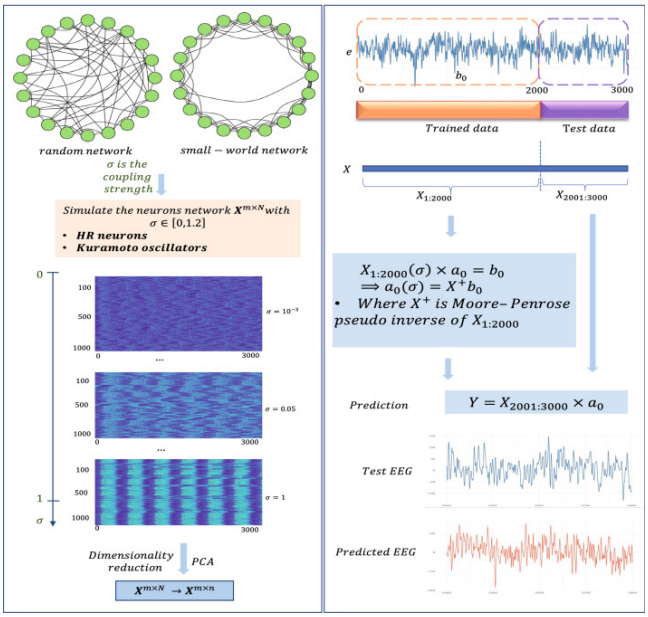

Fig. 9. Adapted from [49]. Overview of the model and method. Left: Dynamical networks with two types of topology: random and small-world networks. HR neurons or Kuramoto phase oscillators were used as a dynamical model. The coupling strength was selected to be [0, 1.2]. Data generated by the network were dimension reduced by singular value decomposition (SVD) analysis. Right: Datasets were divided into training data and test data. Then, the coupling strengths of the networks that produced the smallest fitting error were selected to generate the matrix X from which we calculated the predicted EEG signal (Y). [49].

under CAS are then

$$\dot{x_i} = y_i - ax_i^3 + bx_i^2 + I - z_i + \sigma \sum_{j=1}^{N} \mathbf{K}_{ij} H(x_j)$$
$$\dot{y_i} = c - dx_i^2 - y_i$$
$$\dot{z_i} = r(s(x_i - x_1) - z_i)$$

while those of the Kuramoto oscillators stay the same as connectivity is already accounted for in the model [49].

For each NMM, σ was then trained on the first $^2/_3$ of the data, and used to predict the last $^1/_3$ [49]. The architectures and methods are summarized by Figure 9.

F. Dynamical signal analysis methods

Seizure prediction is traditionally done with analysis techniques from statistics, signal processing, and information theory such as Fourier transform, wavelet transform, correlation, and statistical moments. To many in the field, applying dynamical systems is analogous to considering non-linear methods of analysis. That is to say, let our system be F and given two states x and y, it cannot be assumed that the summation of their future states $F(x) + F(y)$ is equivalent to $F(x + y)$. This implies that linear transformations such as Fourier transform and wavelet transform cannot be applied. The word ”dynamical” also implies not time-invariant. This means the time dependence of epileptic phenomena is built into dynamical models.

On a macroscopic level, some studies suggest epilepsy can be viewed as bifurcations to instability, ie. crossing of a critical point. Rather than thinking of seizure onset as a sequence of steps, there has been much evidence that it is analogous to a last straw (ie. perturbation) that tips a near-ictal system past the point of no return (ie. the critical point) [10] [51] [52] [53]. Other studies considered a 2-attractor system where one represents interictal dynamics and the other represents ictal dynamics [54], although this does not explain how the brain spontaneously recovers from seizures. ”The critical brain” hypothesis addresses this issue by theorizing that the brain operates in a self-organized reverberating regime around criticality [11] [12]. Some studies contend the idea that all types of epilepsy are predictable, and hypothesize the existence of a multistable system poised on the edge of unstable attractors, such that perturbations are impossible to predict [55] [56]. Building on top of all these theories, Saggio et al proposed a comprehensive taxonomy of seizure dynamotypes enumerating all 16 possible bifurcations based on onset and offset behavior [57].

Although there is no consensus on the correct paradigm, each of these models provides different insights and yields new metrics that can be examined as biomarkers for seizure prediction. Some examples of nonlinear metrics include:

1) Critical slowing down: the tendency for a system to take longer to return to equilibrium after perturbations, indicated by time series metrics (skewness, kurtosis, and coefficient of variation) and autoregressive features (variance and autocorrelation) [51] [52]
2) Distance to criticality: the margin between a state and its critical value [10] [53]
3) (Largest) Lyapunov exponent: [9]
4) Correlation dimension/fractal dimension: the real-valued dimension of a set of points, measuring how self-similar or fractal-like the signal is [9]
5) Local flow: a measure of determinism [9]
6) Loss of recurrence: measure of non-stationarity [9]
7) Entropy (algorithmic complexity, Shannon entropy): measure of the amount of information or unpredictability of a random variable [9] [58]
8) Non-linear similarity index: compares a sliding window with a fixed reference window using SVD and the cross-correlation integral [59] [60]

A comprehensive overview of quantitative results is presented in Table V.

TABLE V
DYNAMICAL SIGNAL PROCESSING METHODS FOR EPILEPSY PREDICTION

Authors	Year	Metrics	Dataset	Se	Sp	Acc	FPR	SPH (min)
Van Quyen et al. [61]	2001	similarity index	private, n=13	96%	-	-	-	-
Navarro et al. [62]	2002	similarity index	La Pitié-Salpêtrière Hospital, Paris, n=11	83%	-	-	0.31±0.20	7.54±1.15
Mormann et al. [9]	2004	CD, Lyapunov exponent, local flow, AC, loss of recurrence	private, n=5	95%	60%	-	-	-
Acharya et al. [63]	2009	CD, Hurst exponent, ApEn	Bonn [26]	98.33%	96.67%	93.33%		-
Liang et al. [58]	2010	ApEn	Bonn [26]	94.94%	99.09%	98.26%	-	-
Maturana et al. [10]	2020	critical slowing down (autocorrelation, variance, spike rate, synchronization indices)	iEEG dataset [64]	84±16%	-	-	-	2 to 4

Listed are signal processing methods of seizure prediction within the last 20 years. Se represents sensitivity, Sp specificity, Acc accuracy, FP/h false positives per hour, SPH seizure prediction horizon. ApEn is short for approximate entropy, CD is correlation dimension, AC is algorithmic complexity.

The following section examines in detail how one specific study applies analysis techniques from the field of dynamical systems to epilepsy forecasting.

1) Distance to criticality forecasting

In 2017, Chu et al. extracted the power spectral density of attractor dynamics in scalp EEG to forecast seizures with simple mathematical metrics [54]. The transition into the ictal period is seen as a critical transition from one attractor to another. The study derives a macroscopic view of dynamics before the transition from normal to epileptic seizure state. This paper models the critical transition to the ictal period as a stochastic Wiener process, similar to a random walk, as described by the stochastic differential equation:

$$\frac{dv(t)}{dt} = \big(v(t) - v_c\big)^2 + d + v_l \tag{1}$$

The dynamics of perturbations of an attractor can then be extracted with a linearization at v_a.

$$dv(t) = \big((v(t) - v_c)^2 + d + v_l\big)dt + \sigma dW \tag{2}$$

This is an Ornstein-Uhlenbeck process which is a Gaussian and Markov random process that is temporally homogeneous. Combining the power spectral density of an Ornstein-Uhlenbeck process with equation line 213, where $\Delta d = -d - v_l$ represents the distance to criticality, we get

$$S(w) = \frac{\sigma^2}{4(v_a - v_c)^2 + w^2} \tag{3}$$

The authors observed that, according to equation 3 and its graph 11, as states of the system approach criticality, the lower frequencies obtain a higher power spectral density, resulting in a slower recovery from perturbations similar to seizure dynamics. They then derived simple metrics from the power spectral density:

$$M1 = \frac{\sigma FC(v_\theta, v_\alpha, v_{\text{low}\beta})}{\sigma FC(v_\theta, v_\alpha, v_\beta, v_\gamma)} \tag{4}$$

where v_θ, v_α, and v_β represent theta, alpha, and beta waves respectively, and FC represents the Fourier coefficients of their attractors' power spectral density.

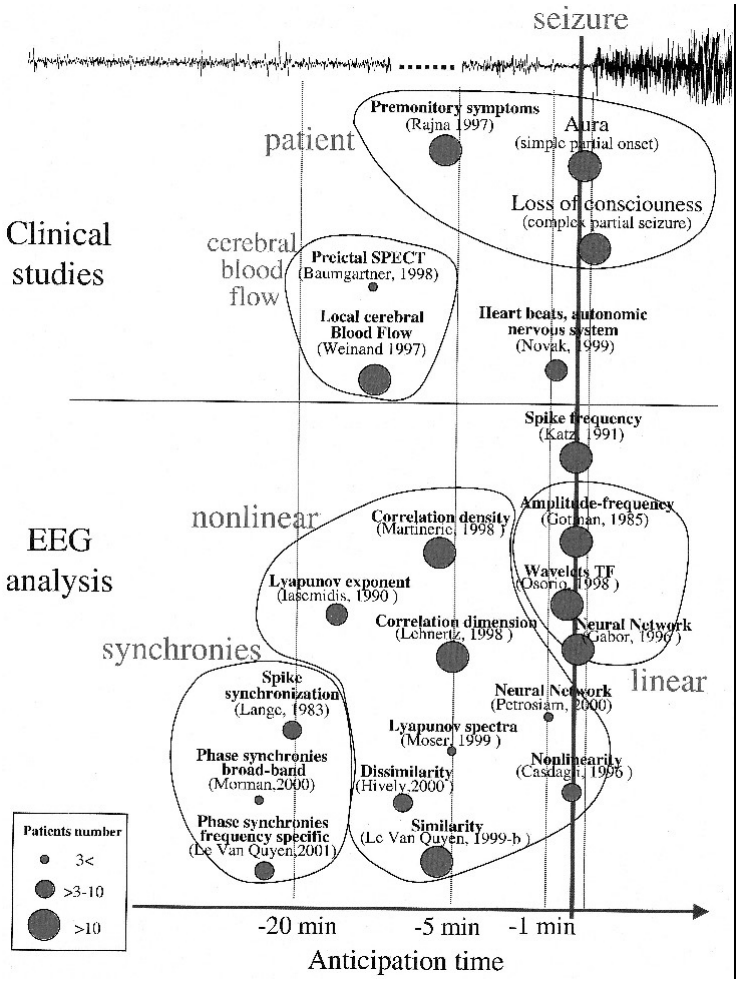

Fig. 10. A ”cartography” of seizure prediction metrics and their estimated prediction horizon (ie. ”anticipation time”) [61].

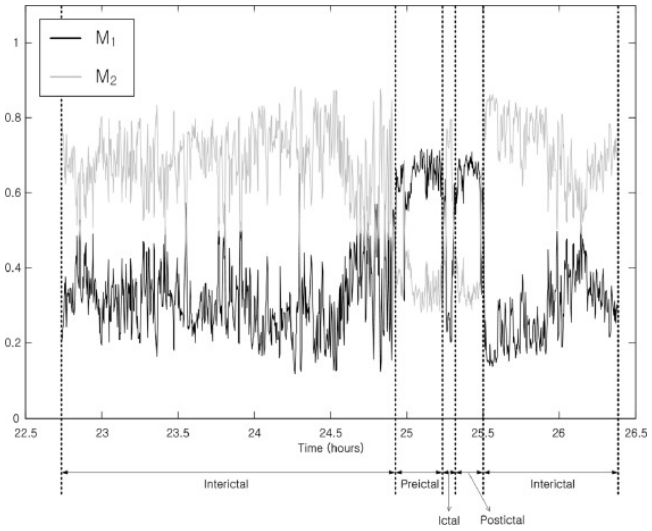

Fig. 11. Distance to bifurcation point vs the power spectral density of an attractor [54].

These metrics are evaluated over time and predict a seizure if 18 out of 25 consecutive samples from an EEG exceed a certain threshold.

Their method was evaluated on the CHB-MIT database with 13 selected cases, each containing three training seizures and more than one testing seizure. The EEG signals (sampled at 256 Hz) were measured from 23-26 channels in differential mode. The prediction horizon, which is the maximum time between a predicted seizure and an actual seizure for the prediction to be considered accurate, was chosen to be 86 min.

The predictor obtained a sensitivity of 86.67%, a false prediction rate of $0.367\ h^{-1}$, and an average prediction time of

45.3 min for the test dataset. The main advantage of this method is its simplicity in construction and computation. While other popular models such as SVMs and Hidden Markov Models have $O(m^2)$ and $O(mn^2)$ complexity respectively, the p-of-q analysis in this model yields $O(pq)$ and executes in constant time. This property, along with its decent performance, makes it a good choice for either preliminary diagnosis of seizures or as a feature that can be integrated into more complicated inference models. On the other hand, since seizures rely on perturbations near the bifurcation point to serve as triggers and such perturbations are stochastic, this method cannot conclude the exact time a seizure would happen, only that the system is at a state dangerously close to criticality.

G. Machine Learning Predictors

In the modern era, machine learning (ML) is applied to many problems where the underlying models and functions are unknown. In essence, ML seeks to create black box models which can learn representations to higher order functions. ML approaches work well even when the underlying function behaviour is unknown, as is the case for onset of an epileptic seizure. As such, significant research has been conducted on empirical (machine learning) models in epilepsy prediction [16][18][65][66]. These models focus on two main problems: epilepsy classification and the more challenging epilepsy prediction. The general workflow for these studies resembles 12, with varying amounts of stages. For example, a classification stage would end at the "classification" block, while a predictor or closed-loop neuromodulation system may end with decision-making and feedback respectively. Another common distinguishing factor between prediction systems and classification systems is the target epileptic state. Predictors generally focus on learning from the pre-ictal and inter-ictal states, whereas classifiers focus on the ictal and inter-ictal state [16].

Fig. 12. A block diagram of empirical models of epilepsy [66]

Unlike the models in III-D and III-F, which do not require any training to improve performance, ML models require training on data to learn accurate representations. In modern machine learning, especially in deep learning, having large quantities of relevant task-specific data is paramount to achieving good model performance. Even with the increased computation and data requirements, deep learning models prove their value by consistently outperforming traditional methods on both epilepsy prediction and epilepsy classification tasks [67]. The datasets mentioned in Table II provide the necessary data for research on ML, and are some of the most common datasets used [18]. Some notable model architectures are described below. A table with summarized results is shown in Table VI, with results entered in reverse chronological order (by year of publication).

1) SVM Models

One of the earliest SVM prediction models is Park et al [68]. Using the Freiburg dataset [24], they calculate spectral power for 9 bands in a 20s-long window of EEG data as the features for the SVM. A prediction from the SVM is provided every 10s. In addition to using raw iEEG data, Park et al also utilized bipolar (space-differential measurements) to reduce line noise and movement artifacts. To achieve this, they take recordings from neighbor electrodes and filter out common-mode noise in the recorded data. The SVM outputs also showed false positives (FP) and false negatives (FN) which tended to be sporadic in time, and thus Park et al used a second-order discrete-time Kalman filter to eliminate these fluctuations. Lastly, Park et al defined positive prediction as one where a seizure is guaranteed in the next 30 minutes. Using these values, we assume that they define SPH as zero, but SOP as 30 minutes. The SVM workflow from Park et al is shown in Figure 13.

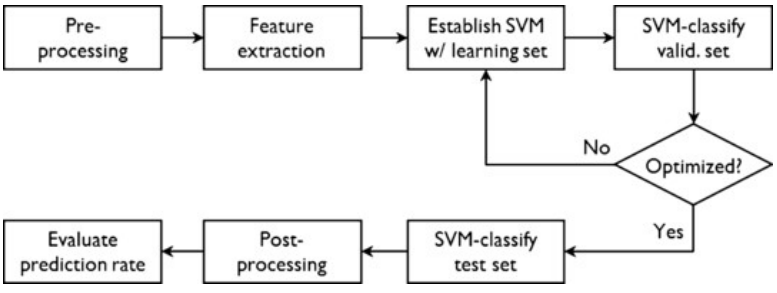

Fig. 13. A SVM based predictor [68]

Park et al were able to achieve a sensitivity of 93.8% and a FPR of $0.029/h$ when the SVM was trained on raw iEEG data. When bipolar preprocessing was used, they were able to achieve a higher sensitivity of 97.5%, and a FPR of $0.27/h$.

In 2017, Babak et al [69] utilized PCA as part of an SVM predictor. Their model first generates an embedding from raw EEG time series data, acquired from the Freiburg dataset [24]. The intent of this embedding is to characterize the nonlinear dynamics of the system. Then, a distribution of 64 fuzzy rules is generated based on the optimized Poincaré samples. The idea of the fuzzy rules is to generalize to the dynamics of sudden changes in synchronicity when neural cells enter an epileptic state. The authors conclude that only rules with significant variance encode the behaviour of a normal to ictal bifurcation, and thus use only the fuzzy rules with 90% of the total variance as inputs to the next stage of the pipeline [69]. At this point, Principle Component Analysis (PCA) is applied to reduce correlated variables and extract information. Finally, an SVM classifier is applied to generate inter-ictal versus ictal class predictions by taking the signed distance from x, the result of an observation, to either $+\infty$ or $-\infty$.

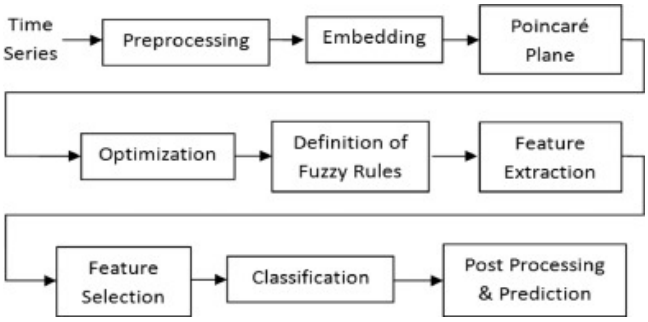

Fig. 14. A SVM based predictor, with Poincaré and PCA dimensionality reduction techniques [69]

Using this model, Babak et al were able to achieve sensitivity ranging from $0.918-0.966$, depending on a threshold of decision-making, set as -0.2,0,0.2. For a fair comparison to other models, we report these results when threshold is 0 since this represents a non-biased prediction towards either pre-ictal or inter-ictal. For this threshold, Babak et al. achieved a sensitivity of 92.9%, with an FPR of $0.06/h$. Additionally, a SPH of 31.1 minutes was reported.

Usman et al [70] implemented an SVM where EEG data is first decomposed using Empirical Mode Decomposition (EMD) to increase signal-to-noise (SNR) ratio. The process of EMD is akin to that of wavelet decomposition or Fourier transform, and involves decomposing a time-domain signal such as EEG, into oscillatory functions known as Intrinsic Mode Functions [70]. After pre-processing, the authors calculate both statistical and spectral moments as inputs to the SVM. A block diagram of the SVM model is shown in Figure 15.

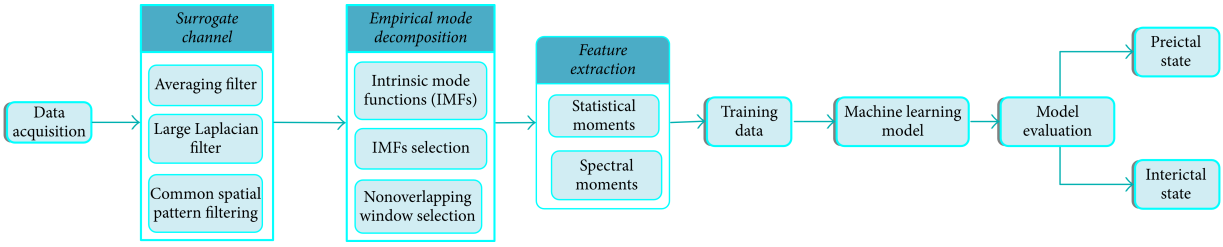

Fig. 15. A SVM based predictor using EMD [70]

For prediction, Usman et al classify between inter-ictal and pre-ictal states, where a pre-ictal state is defined as one containing three or more samples that are classified as pre-ictal. Since CHB-MIT is sampled at 256hz, a window of one second can be classified as pre-ictal if three or more samples (roughly 0.012 of a second) are classified as pre-ictal. Usman et al train their SVM on data from the CHB-MIT [23] dataset. They were able to achieve a prediction sensitivity of 92.23% and a specificity of 93.38%. Additionally, they report a SPH of 23.48 up to 33.46, depending on the EEG recording. On average, Usman et al report an SPH of 23.6 minutes.

2) CNN Models

Recently, Truong et al [33] implemented a Convolutional Neural Network (CNN) for seizure prediction. Using the CHB-MIT [23], Freiburg [24], and a Kaggle dataset from the American Epilepsy Society Seizure Prediction Challenge [71], Truong et al. designed a prediction model trained on inter-ictal and pre-ictal data. For data preprocessing, since pre-ictal data was sparse, Truong et al used a sliding window approach to generate more data. Additionally, a very specific definition for SPH and SOP is given, which is the definition we used in III-A: SPH was set as 5 min, and SOP was set as 30 min. As noted by the authors, CNN's commonly take 2D matrix data as inputs [72] such as visual data such as images or videos. By converting raw EEG signals into a 2D matrix feature using Short-time Fourier

Transforms (STFT) with an EEG window length of 30s, Truong et al. was able to apply a CNN to prediction on time-series (EEG) data. The CNN architecture, as shown in Figure 16, used 16 inputs each with a size of $n \times 5 \times 5$ kernels, where n is the number of EEG channels.

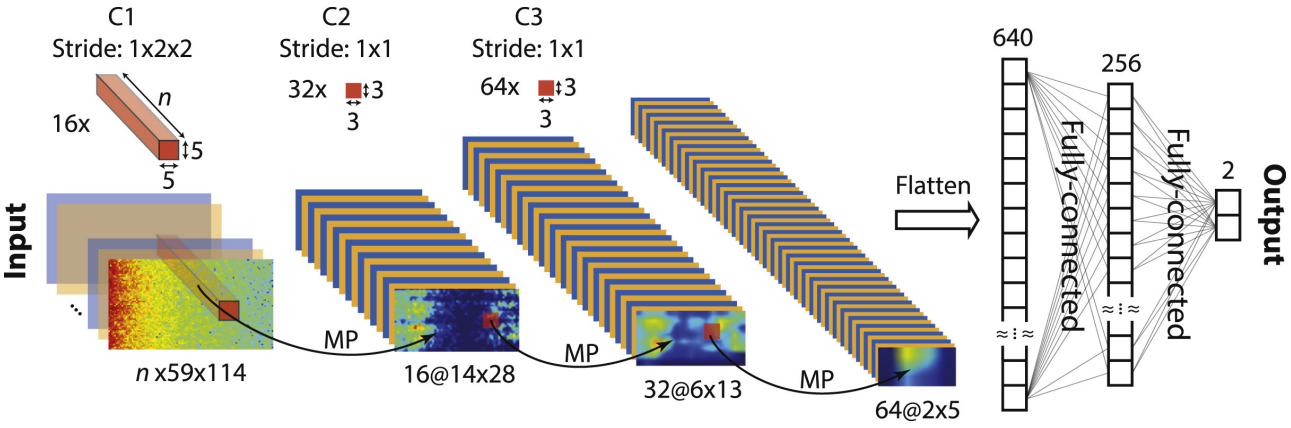

Fig. 16. A Convolutional Neural Network architecture for seizure prediction [33].

As an output classifier, Truong et al. used a $p - of - q$ method, where an alarm is set only if p predictions were positive out of q predictions. Using $p = 8$ and $q = 10$, an alarm is set if $240s$ of positive predictions occurred in the last $300s$. On the Freiburg dataset, a sensitivity of 81.4% is achieved (48 out of 59 seizures predicted successfully), with an FPR of $0.06/h$. On the CHB-MIT dataset, a similar result is achieved: 81.2% sensitivity with an FPR of $0.16/h$.

3) LSTM Models

Another deep learning model, Long Short-Term Memory (LSTM), has been applied to epilepsy prediction by Tsiouris et al [73]. The authors used the CHB-MIT dataset [23] and extracted the pre-ictal and inter-ictal components while discarding the ictal states. As LSTM models have not been applied to seizure prediction, Tsiouris et al tested three varying LSTM architectures, as shown in Figure 17.

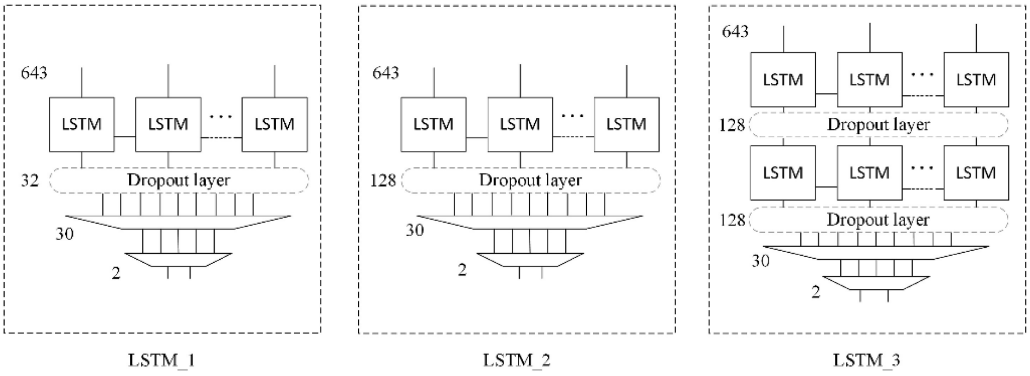

Fig. 17. Varying Long-Short Term Memory architectures for seizure prediction [73].

Each network has a fully connected layer and a final dense layer. Using a binary classifier, a one-hot encoded result is outputted, corresponding either to pre-ictal or inter-ictal prediction. By comparing classification accuracies across models, Tsiouris et al concluded that LSTM_3, with the dropout layer removed, performed the best. When testing the LSTM model, Tsiouris et al used four different pre-ictal window durations: 15min, 30min, 1 hour, and 2 hour. With the 15min window, the LSTM achieved 99.28% sensitivity and 99.28% specificity, with an FPR of $0.11/h$. For a 30min window, results rose to 99.38% sensitivity and 99.60% specificity, with an FPR of $0.06/h$. For the 1-hour window, they achieved 99.63% sensitivity and 99.78% specificity, with an FPR of $0.03/h$. Lastly, for the 2-hour pre-ictal window, Tsiouris et al achieved 99.84% sensitivity, specificity of 99.86%, and an FPR of $0.02/h$. Despite the superb performance, Tsiouris et al acknowledge that their model does not allow for evaluation of model SPH, since they require information from the entire pre-ictal window duration.

TABLE VI
DATA CENTRIC (ML) SYSTEMS FOR EPILEPSY PREDICTION

Authors	Year	Architecture	Dataset	Sensitivity	Specificity	FPR	SPH
Tsiouris et al. [73]	2018	LSTM DNN	CHB-MIT [23]	30min: 99.6% 120min: 99.86%	30min: 99.37% 120min: 99.84%	N/A	N/A
Truong et al. [33]	2018	CNN	CHB-MIT [23] Freiburg [24] Kaggle [71]	81.2% 81.4% 75%	N/A	$0.16/h$ $0.06/h$ $0.21/h$	5min
Usman et al. [70]	2017	SVM + EMD	CHB-MIT [23]	92.23%	93.38%	N/A	23.6min
Babak et al. [69]	2017	PCA + SVM	Freiburg [24]	92.9%	N/A	0.02	31.1min
Esmaeilpour et al. [74]	2017	DWT* + NN	Freiburg [24]	100%	97.1%	N/A	N/A
Zhang et al. [75]	2016	Spectral Power + SVM	Freiburg [24] CHB-MIT [23]	100% 98.68%	N/A	$0.0324/h$ $0.0465/h$	N/A
Behnam et al. [76]	2016	RLS + MLP	CHB-MIT [23]	97.27%	N/A	$0.00215/h$	N/A
Park et al. [68]	2011	SVM	Freiburg [24]	97.5%	N/A	$0.27/h$	0
Chisci et al. [77]	2010	AR + SVM	Freiburg [24]	100%	N/A	$0.412/h$	N/A

Note: False Positive Rate (FPR) is given as the ratio of false positives to total negatives per hour.

IV. DISCUSSION

1) Dynamical model-based methods

Compared to other methods of predicting epilepsy, dynamical systems models are unique and interesting. They are much more "white box" compared to other methods, as each of the parameters measured is physiologically informed, and the existence of model equations allows for mathematical analysis. Additionally, the parameters present in these systems of equations allow for flexibility, either by tuning through machine learning methods, or through personalization such as through the VEP or canonical model NMM. Unfortunately, not enough papers were found to allow for intra-method comparison, as many researchers studied other problems such as characterization and localization. When compared to other methods, dynamical systems models boast of high accuracies and relatively good SPH; however, there is still more room for improvements to architectures and methodologies, as compared to some purely machine learning methods, dynamical systems models still fall behind on these metrics.

2) Dynamical signal analysis methods

Although nonlinear dynamics analysis yields many sophisticated metrics that have been shown to be statistically significant [9], most such studies focus on the derivation of metrics and analyzing how metrics vary across time instead of getting higher performance on the task of prediction. Thus, there is an overall neglect of the selection of an equally sophisticated classifier. While Chu et al. uses a simple p-of-q prediction scheme [54], most other studies calculate or arbitrarily choose a threshold for positive predictions [59]. The advantage of these methods is their computational and cost efficiency, being able to carry out forecasting in real-time without consuming mass amounts of resources [54] [59].

For bifurcation-based methods, another difficulty lies in locating the underlying attractors of EEG signals [60]. Many of these metrics such as Lyapunov exponents and correlation dimension are predicated on the stationarity of the signal, so researchers have approximated stationary signals by segmenting EEG into smaller chunks. Similarity-based methods circumvent this problem [59] [62]. There is evidence that bivariate metrics operate on timescales of 240 min before seizure, which is much longer than univariate metrics of 5-30 min [9].

3) Data-Centric (Machine Learning) methods

The rigorous, analytical models produced by dynamical systems models or dynamical signal analysis require a white-box understanding of the underlying dynamics of the system at hand. With models like the [36], these dynamics are decently well understood for epilepsy. On the other hand, data-centric techniques like machine learning allow for a computational model to learn black box representations without the need to encode feature representations or design output classifiers. Machine learning predictors for epilepsy currently have excellent performance, with some deep learning techniques achieving above 99% sensitivity and false positive rates of < 0.1 per hour [73] [74]. However, there are drawbacks limiting the performance and development of deep learning models. Datasets such as CHB-MIT [23] and Freiburg [24] often do not provide sufficient data quantity and quality for deep learning models [69] [73]. Specifically, the lack of ideal data labeling and limited data quantity require predictors to have preprocessing steps [68] [69], or introduce data augmentation to increase data quantity [33] [73]. In some cases, these data augmentation techniques can be benign, but in others, they can hamper the ability of a predictor to generate predictions with positive SPH values [73].

4) General comments

Epilepsy prediction is a young field with its tractability being demonstrated only 20 years ago and still debated today [9] [78]. As seen from the meta-analysis and discussion provided above, although most studies are able to achieve impressive sensitivity, these results often come at the cost of specificity, suggesting a trend of heavy overfitting. The

specificity metrics are often non-standardized, ill-defined, or missing altogether. Furthermore, most studies evaluate with less than 100 patients, making the generalizability of these models debatable. Epilepsy is known to be a highly patient-specific disease, so one of the challenges is to make a forecasting model that is, if not generalizable, then at least easily adaptable to new patients. Patient-specific models such as VEP excel in this area, but in return require too much time to set up.

V. Future Work

The main direction that we see as promising for epilepsy prediction and neuroscience as a whole is the integration of dynamical systems with machine learning approaches. There are multiple ways in which they complement each other.

Dynamical systems provide a framework for ground analyses in biophysical foundations. But a tradeoff exists here where the more physiologically accurate the model is, the more unknown parameters it includes that must be determined, resulting in a parameter search space so large that the amount of arbitrary decisions made is comparable to a black box approach. Optimization techniques from artificial intelligence can be leveraged here to search for the right set of parameters more efficiently than a brute-force grid search. Mathematicians have also started using ML to find solutions to dynamical systems in favor of numerical methods [79].

As seen in Chu et al., even a simple p-of-q predictor can achieve above-chance performance by taking a bifurcation point of view [54]. Given the biomarkers discovered through nonlinear signal analysis, if these can be fed as features into a machine learning model, such as an LSTM, the performance of these neural networks should become even better. Combinations of biomarkers can also be easily explored without running into the curse of the dimensionality problem. There have been some studies that combine insights from dynamical system analysis with machine learning classifiers: Ghosh-Dastidar et al used standard deviation, correlation dimension, and largest Lyapunov exponent as features in a Levenberg-Marquardt backpropagation neural network (LMBPNN) and were able to achieve 96.7% accuracy on the Bonn dataset [80] [81]. On the same dataset, Sharma et al used radial basis functions in phase space representation with a Least-Squares SVM to obtain 98.67% accuracy [82], and Güler et al used Lyapunov exponent with RNN to achieve 96.75% [83]. However, all these studies dealt with the task of ictal/interictal state classification, which is a relatively easier problem than seizure prediction.

A third direction is the potential for a dynamical systems model to be used for control, whereas a black-box model would provide no opportunity for control. Cornelius et al presented a novel iterative approach that shows the benefit of considering bifurcations and attractors despite the complexity of nonlinear control [84]. The idea is to take advantage of the attractor dynamics so that the controller only needs to nudge the current state in the correct direction of the target state attractor, and let the system evolve there naturally.

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