



Review

Computational models of epilepsy

Roxana A. Stefanescu^b, R.G. Shivakeshavan^a, Sachin S. Talathi^{a,b,c,*}^a Department of Biomedical Engineering, University of Florida, Gainesville, FL 32611, United States^b Department of Pediatrics, Division of Neurology, University of Florida, Gainesville, FL 32610, United States^c Department of Neuroscience, University of Florida, Gainesville, FL 32610, United States

ARTICLE INFO

Article history:

Received 11 March 2012

Received in revised form 29 August 2012

Accepted 29 August 2012

Keywords:

Epilepsy

Computational modeling

Dynamical systems theory

Deterministic models

Non-deterministic models

Macro vs. micro models

Electrical stimulation therapy

Light stimulation therapy

ABSTRACT

Purpose: Approximately 30% of epilepsy patients suffer from medically refractory epilepsy, in which seizures can not controlled by the use of anti-epileptic drugs (AEDs). Understanding the mechanisms underlying these forms of drug-resistant epileptic seizures and the development of alternative effective treatment strategies are fundamental challenges for modern epilepsy research. In this context, computational modeling has gained prominence as an important tool for tackling the complexity of the epileptic phenomenon. In this review article, we present a survey of computational models of epilepsy from the point of view that epilepsy is a dynamical brain disease that is primarily characterized by unprovoked spontaneous epileptic seizures.

Method: We introduce key concepts from the mathematical theory of dynamical systems, such as multi-stability and bifurcations, and explain how these concepts aid in our understanding of the brain mechanisms involved in the emergence of epileptic seizures.

Results: We present a literature survey of the different computational modeling approaches that are used in the study of epilepsy. Special emphasis is placed on highlighting the fine balance between the degree of model simplification and the extent of biological realism that modelers seek in order to address relevant questions. In this context, we discuss three specific examples from published literature, which exemplify different approaches used for developing computational models of epilepsy. We further explore the potential of recently developed optogenetics tools to provide novel avenue for seizure control.

Conclusion: We conclude with a discussion on the utility of computational models for the development of new epilepsy treatment protocols.

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1. Introduction

Epilepsy is a neurological disease that affects people all around the world and of all socioeconomic groups. The condition is primarily a disorder characterized by spontaneously occurring seizures. These seizures not only disrupt normal living but can also cause mental and physical damage, and in extreme cases, even death. Methods to treat epilepsy include medication, brain stimulation, surgery, dietary therapy or various combinations of the above, directed toward the primary goal of eliminating or suppressing seizures.¹ For many epileptic patients, seizures are well controlled with anti-epileptic drugs (AEDs). However, approximately 30% of epileptic patients suffer from medically refractory epilepsy. These patients continue to exhibit seizures despite treatment with a maximally tolerated dose of a AED, alone

or in combination with at least one adjuvant medication.² This has motivated clinicians and researchers alike to investigate the mechanisms of seizures in refractory epilepsy using techniques from many scientific disciplines, including molecular biology, genetics, neurophysiology, neuroanatomy, brain imaging and computer modeling.

There is a growing awareness within the epilepsy research community that epilepsy is a heterogeneous syndrome characterized by cognitive, behavioral and emotional co-morbidities.³ The etiology of refractory epilepsy and its effects on cerebral function is so diverse and complex that it is a formidable task to conceive of a single framework in which to characterize all of the pathophysiological changes that define epilepsy at the genetic, molecular, cellular and neuronal network levels. It may, therefore, be difficult to understand how computational models can aid in unraveling the complexity of epilepsy.

From a reductionist point of view, epilepsy is fundamentally a seizure disorder and the control or elimination of seizures remains a key treatment objective. Therefore, a strong case can be made for computational modeling as a means of obtaining new insights into

* Corresponding author at: Department of Pediatrics, Division of Neurology, University of Florida, Gainesville, FL 32610, United States.

E-mail address: talathi@ufl.edu (S.S. Talathi).

the pathogenesis and treatment of epileptic seizures. Indeed, computational models have been successfully employed to gain insights into and generate novel hypotheses related to the cellular and network level brain mechanisms of epileptic seizures,⁴ as a tool to guide the prediction of an impending epileptic seizure⁵ and as a tool to guide strategies for therapy by surgical, pharmacological and electrical stimulation techniques.⁶

Computational models provide a unique framework in which data from experimental findings can be integrated in order to develop new hypotheses, which in turn can guide future experiments. Models provide an excellent avenue for relating variables across multiple levels of analysis, thereby offering the opportunity to establish links between the hierarchy of brain networks involved in the origin and spread of epileptic seizures. Another significant advantage of modeling is that experiments that are more challenging to perform can be easily simulated. This is particularly valuable in the study of epilepsy. For instance, it is relatively easy to mimic lesions in a computational model, which can enable the study of the underlying mechanisms of lesion-evoked seizures. There are few practical barriers (the availability of computational resources and the relevant modeling framework appropriate to the question of interest) and no ethical barriers to conducting a large number of exploratory virtual experiments. This allows researchers to perform systematic investigations in order to extract the most relevant information, which can be further verified in an experimental laboratory setting. As a result, the emergence of a wide variety of computational models of epilepsy has been witnessed over the last decade.

In this paper, we present a brief survey of computational modeling approaches in modern epilepsy research. There is an abundance of valuable literature on the computational modeling of epilepsy, and as a result, in recent years, a number of excellent review articles on this topic have been published.^{7–10} The focus of these review articles varies from a brief survey of different levels and types of models in literature,^{7,8} to a review of specific classes of epilepsy models,⁹ to a recent survey on computational modeling literature in epilepsy relevant to experimental neurologists.¹⁰ To the best of our knowledge, no single review article providing a broad overview of computational models for epilepsy has been published, although there is an entire book dedicated to the subject,¹¹ which encompasses an introduction to basic dynamical systems theory, the primary “workhorse” of most computational models for epilepsy. The present review also covers new ground in that we present a comprehensive discussion of three specific examples from the published literature, which exemplify distinct approaches involving computational models of epilepsy.

We begin by first introducing basic concepts from the mathematical theory of dynamical systems in support of the idea that epilepsy can be primarily understood as a dynamical disease.^{12,13} We then review some of the commonly adopted modeling frameworks used to develop computational models of epilepsy, with special emphasis on case examples from the recent literature. Rather than presenting an exhaustive list of all publications about modeling in epilepsy, our goal is to summarize key results from selective case examples to highlight the importance and relevance of different modeling frameworks. We then present a brief survey of computational models that attempt to capture the inherent variability in recorded brain activity, and identify how the source of this variability can influence the excitability of an epileptic brain. We follow this presentation by a review of the utility of computational models for developing novel epilepsy treatment protocols. We discuss classical and novel directions, including the possibilities offered by optogenetics,¹⁴ a novel technology that aims to control neural activity by means of light stimulation. We present some preliminary results from our group using light stimulation-based

feedback control strategies to regulate pathological brain activity. We conclude with a discussion on the future prospects of computational models for developing novel therapeutic protocols for epilepsy.

2. Understanding the dynamical characteristics of epilepsy

2.1. Basic introduction to dynamical systems theory

From a dynamical systems point of view, the brain can be considered as a multi-dimensional dynamical system, defined by an independent set of system variables, such as neuronal membrane potentials, which evolve in time following a set of deterministic equations and system parameters that either do not evolve in time (for example, the maximal conductance of the ion channels on the neuronal membrane) or whose evolution happens on a much slower time scale relative to the evolution of the system variables (for example, structural changes in brain networks following injury).

In order to illustrate the key concepts of dynamical systems that are essential to understanding the notion of epilepsy as a dynamical (time evolving) disease, we consider a generic example of a two-dimensional neuron model described by a set of ordinary differential equations (ODEs) as follows:

$$\begin{aligned}\frac{dv}{dt} &= F_1(v, w, p) \\ \frac{dw}{dt} &= F_2(v, w, p)\end{aligned}\quad (1)$$

where v and w are the system variables, typically representing the voltage of the neuronal membrane and the gate variable for an ion channel on the cell membrane respectively. The system parameters are represented by the variable p , which is a collection of the internal parameters of the model neuron, such as the ion channel conductance and reversal potential and the external parameters that are under the control of an experimenter, such as the current I injected into the neuron. A number of choices for F_1 and F_2 have been proposed in the literature to mimic neuronal dynamics.^{15,16} For the purpose of this discussion, we choose to implement the Morris–Lecar (ML) model.¹⁷

Perhaps the most important concept in dynamical systems is the *fixed point* equilibrium state, defined in the model described above as the set of values v_s, w_s for which the following constraints are satisfied $F_1(v_s, w_s, p) = 0$ and $F_2(v_s, w_s, p) = 0$. In the phase space of the system (the space spanned by the system's variables, see Fig. 1), the fixed points can be easily found at the intersection of the curves $F_1(v, w, p) = 0$ (pink curve in Fig. 1a and b) and $F_2(v, w, p) = 0$ (orange curve in Fig. 1a and b) referred to as the *nullclines* of the system. In the example shown in Fig. 1a (in the presence of an externally injected current, $I = 35 \mu\text{A}/\text{cm}^2$), we find three fixed point equilibrium states (labeled as black, cyan and red dots).

Stability is an important concept in dynamical systems theory. The experimentally observable equilibrium state of the given physical system that the dynamical model emulates (in this case, the membrane potential of the neuron) always corresponds to the stable equilibrium state. For the model considered in Eq. 1, stability analysis¹⁸ shows that there is one stable fixed point (black dot in Fig. 1a) and two unstable fixed points (cyan and red dot in Fig. 1a). When starting from different initial conditions $\{v_j(0), w_j(0)\}$ the dynamical system will evolve in the phase space, towards the stable fixed point equilibrium state and away from the unstable fixed points. For this reason, the stable fixed points are also called *attractors* while the unstable fixed points are called *repellers*. We exemplify this behavior in Fig. 1 (blue curves) by plotting a set of $j = 1 \dots 8$ of such trajectories. The set of all the

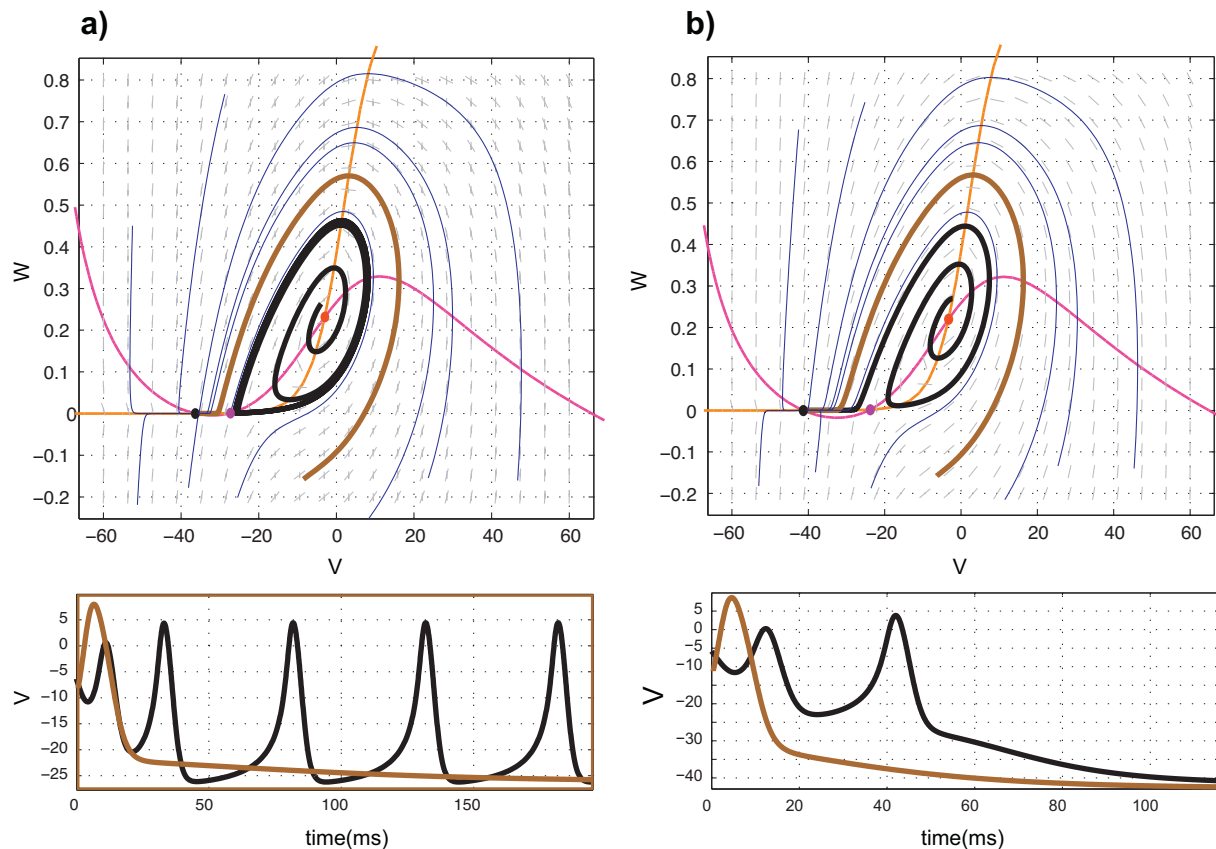


Fig. 1. a) Phase space representation of neuronal dynamics is shown when $I = 35 \mu\text{A}/\text{cm}^2$. Several dynamical quantities are exemplified: the nullclines, the stable (black dot) and unstable fixed equilibrium points (brown and red dots) and trajectories representing the time evolution of neuron model system variables. Two examples trajectories are emphasized: a trajectory evolving towards the limit cycle (black curve) and the second trajectory evolving towards the fixed point attractor (brown curve). The voltage time series associated with these trajectories are displayed in the panel below. b) Phase space representation of neuronal dynamics is shown when $I = 30 \mu\text{A}/\text{cm}^2$. Some features presented in a) change via a bifurcation generated by the changes in the system parameter I . The limit cycle is no longer an attractor in the phase space; All trajectories evolve towards the only stable fixed point attractor in the network. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

initial conditions from which the trajectories evolve to a given fixed point attractor defines the *basin of attraction* for that attractor. As stated earlier, the stable fixed point equilibrium represents the resting state of the neurons membrane potential. In addition to fixed point equilibrium states, the system may exhibit other types of attractors. For instance, in Fig. 1a we also see trajectories that move away from the fixed point repeller and merge into a closed-loop trajectory (shown in black in Fig. 1a), which is referred to as the *limit cycle* attractor. Limit cycles correspond to a scenario where the neuron is in a periodic spiking state. In general, the number and complexity of the attractors that can inhabit the phase space of a dynamical system depends greatly on the dimensionality of the system, its parameters and the degree of nonlinearity.

Another important concept in dynamical systems is the notion of *multi-stability*. Multiple attractors can reside in the phase space at the same time and depending on the initial conditions, the dynamical system can evolve to any one of these attractors. For the example considered here, the dynamical system has two attractors: one stable fixed point and one limit cycle. A simple computational principle following from the existence of the two stable attractors is that the neuron can switch from a resting state to a periodically spiking state via an appropriately timed current pulse that moves the dynamics of the neuron in the phase space from a point closer to the fixed point attractor to a point closer to the limit cycle attractor and vice-versa.

Finally, a very important concept in dynamical systems is the notion of *bifurcation*. Bifurcation designates a qualitative change in the dynamical behavior of the system associated with modifications in the system parameters. In Fig. 1b, we show the phase space of the model neuron when the amount of injected current in the neuron is decreased ($I = 30 \mu\text{A}/\text{cm}^2$). We see a qualitative difference in the system dynamics as compared to the case considered in Fig. 1a. This observation suggests that for a particular value of the system parameter $I = I'$, where $30 < I' < 35$ there is a bifurcation in the system dynamics. For the case $I = 30 \mu\text{A}/\text{cm}^2$, the system still exhibits three fixed point equilibrium states, but there is only one attractor instead (the limit cycle is lost). All of the trajectories evolve towards the fixed point attractor. In this case, the neuron is not able to generate periodic spiking behavior.

The key concepts from dynamical systems theory introduced here through the specific example of a ML model neuron are common to a large variety of neural network models. In the following section, we will explore how these ideas can facilitate our understanding of epilepsy as a dynamical brain disorder.

2.2. Epilepsy as a dynamical disease

Epilepsy is considered a time-evolving or a “dynamical” disease.^{12,13} Most acquired epilepsies, those that are not a result of known genetic defects, result from a precipitating brain injury. This injury can occur through a multitude of factors ranging from

an incidence of oxygen deprivation at birth to stroke and infections such as meningitis and encephalitis to head trauma or an acute brain injury that induces status epilepticus (SE). The transition of a brain into a spontaneously seizing state can occur within minutes following brain injury or may not occur until several months or years after the injury.³ The concept of a “latent” or “silent” period is usually used to describe this transition. Seizures are temporal events, usually not life threatening by themselves, that typically last several tens of seconds and end abruptly. Life threatening seizures such as SE can last up to several hours in absence of any intervention. This kind of temporal evolution pattern involving multiple time scale processes is also observed in other systems, for example in earthquakes and weather patterns and has been the object of mathematical and computational analysis for the last several decades.

The concepts introduced above regarding dynamical systems theory enable us to better understand some aspects of the complex temporal patterns of epileptic brain activity, specifically, the transition of an epileptic brain from a non-seizing state to a seizing state. The basic idea is to view the evolving brain as transitioning from one attractor state to another in a multi-stable dynamical landscape as a result of changes in system parameters (bifurcation) or perturbations induced in the system. For example, these transitions could be mediated by various modulatory mechanisms that are active in the brain or by triggers originating outside of the central nervous system (for instance light induced seizures). Based on this view, different dynamical models for the brain networks that are susceptible to epileptic seizures have been proposed. Lopez da Silva et al.,¹² have proposed three distinct dynamical models to account for a broad spectrum of epilepsies. Their first model suggests that the attractors for the “normal” (non-seizing) and the “pathological” (seizing) brain states are very close in the phase space of the dynamical system representing an epileptic brain as opposed to a healthy non-epileptic brain. As a result, random fluctuations in some of the system parameters are sufficient to induce a transition to the pathological seizing state. In this scenario, seizure occurrence may not be predictable. In the later two models, the authors propose that these attractors are further away from each other, such that random fluctuations in the system parameters cannot trigger a seizure. Rather, the dynamics of an epileptic brain are characterized by unstable system parameters that are very sensitive to endogenous and/or exogenous factors. These parameters may gradually evolve in time in such a way that the basins of attraction corresponding to the non-seizing and seizing brain attractors get closer in the phase space, and any random fluctuation can then facilitate the transition to seizures. It is plausible that the gradual evolution of the system parameters is detectable by the analysis of EEG signals, which may in turn offer ways to anticipate and design appropriate treatments protocols for evading an impending seizure.

3. Modeling attempts in epilepsy

A key question for any modeler is what trade off can be made to simplify the process of model development, while maintaining a certain degree of biological realism relevant to the questions of interest? Based on the level of simplification, several classes of models become available. In the following paragraphs, we will discuss models of epilepsy that follow two of the most commonly employed criteria of simplification: (a) the type of the model (i.e., deterministic vs. non-deterministic) and (b) the spatial scale of the model (i.e., micro vs. macro).

3.1. Deterministic models

Deterministic models are usually presented in the form of a system of ODEs (of the form given in Eq. 1). These models assume

that the time evolution of the system variables is completely governed by the set of ODEs. In other words, if the initial conditions and the system parameters are specified, one can evaluate the state of the system at any time in the future. Due to the high degree of structural and temporal complexity in an epileptic brain, many deterministic models of epilepsy aim to represent the dynamics of an epileptic brain by limiting their analysis to a given spatial scale of resolution. Micro-scale models are typically confined to neuronal networks within a given brain region, such as the hippocampus and aim to preserve the biophysical reality of neuronal dynamics. In contrast, macro-scale models attempt to model the averaged activity an ensemble of neural populations, involving multiple brain regions at the expense of the biophysical realism of the underlying networks.

3.1.1. Micro-scale models

On a micro-scale, modelers are concerned with questions related to the dynamical behavior of individual neurons including the neuronal ion channels, neuronal morphology (dendritic tree, axonal arborization) and interaction between neurons and their local environment. Neuronal networks are constructed using deterministic models of neurons, many of which are based on the Hodgkin–Huxley framework.¹⁹ Network dynamics are inferred from the activity of individual neurons and the interactions between the neurons in the network. In many instances, the spatial structure of the neuron is ignored. Instead the neuron is considered as an uni-compartment system represented by the soma. At the single neuron level, the focus is on changes in the kinetic properties of the ion channels (channelopathy) that comprise the neuronal membrane. For example, computational models of a single hippocampal pyramidal neurons have examined the role of I_h current up-regulation as a potential source of pro-excitability in epileptic hippocampal networks.^{20,21} At the network level, the focus is on the neuronal network topology and the synaptic interactions between the neurons in the network and their surrounding environment.

Other micro-scale models focus on the role of neuronal morphology and the contributions of morphology to the increased excitability of epileptic brain networks. Compartmental modeling represents the most general framework for constructing anatomically realistic representation of neurons.^{22,23} In a compartmental model, a neuron is divided into small segments, or compartments, each of which is described by an ODE. This approach represents the highest level of detail for constructing detailed model neurons while preserving complex neuronal morphology. Compartmental models of hippocampal pyramidal neurons have been constructed with the number of compartments ranging from a few^{24,25} to several hundred.^{26,27} As explained later in this section, such multi-compartmental models have been employed in several applications to investigate the contribution of the spatial extent of pyramidal cells to enhanced excitability in epileptic brain networks.

The above approach of conductance-based compartmental modeling can become computationally expensive, especially in simulated networks comprised of thousands of neuronal units. In order to tackle the issue of computational complexity, various simplified neuronal models have been made available. These models are specifically designed to reduce the complexity of the system to be modeled, i.e., to reduce the number of ODEs required to model a neuron, while still replicating the important dynamical characteristics observed under varying experimental conditions. The Moris–Lecar,^{28,29} Hindmarsh–Rose³⁰ and FitzHugh–Nagumo³¹ models are some of the most prominent neuron models that fall under this category and have been used to investigate the dynamics of epileptic brain networks.

3.1.2. Macro-scale models

On a macro-scale, an attempt is made to model the dynamics of neuronal populations rather than the membrane potential dynamics of individual neurons. Macroscopic models aim to inform us about the dynamics resulting from the interactions between multiple brain regions such as the cortex, the thalamus and the brain stem. Given that many experimental techniques that measure epileptic brain activity, including EEG and field potential recordings, employ large populations of neurons across multiple brain regions, models on this scale are suitable for direct comparison with experimental data. Wilson and Cowan pioneered the macro-scale modeling framework in a series of theoretical papers in the 1970s.^{32,33} The basic idea of macro-scale modeling is to reduce the degrees of freedom in a dynamical system representative of a large population of neurons to a distribution function describing the probabilistic evolution of neuronal states in the population at a given time.³⁴ A simplification of this approach that has gained prominence in the field of computational neuroscience^{35–38} involves a further reduction by considering only the first moment of the distribution function (equivalent to the center of mass), representing the mean firing rate of the neuronal population. These simplified models are known as neural mass models.³⁹ In general, neural mass models are constructed by representing the expected depolarization $v(t)$ in a subpopulation of neurons in the network as the convolution of the input signal with an impulse response function of the form $h_X(t) = Aae^{-at}$ (X represents the neuronal subpopulation type, see Fig. 3). The constant a controls the rise time of the mean voltage in response to inputs and the constant A scales the amplitude of the mean voltage. The input is commonly construed to be the mean firing rate, $r(t)$, of the same neuronal ensemble, or a different ensemble, and is the sigmoidal function $s(v(t))$ of the mean voltage of the neuronal ensemble (see Fig. 2). A schematic for modeling the firing activity of a neuronal subpopulation using a neural mass model described above is shown in Fig. 2.

The simplest neural mass model constructed within this framework include interactions between single subpopulations of excitatory and inhibitory neurons as shown in Fig. 3. The constants C_1 and C_2 account for the total number of synapses between the two neural populations. An extension of this approach has been implemented in the Jason–Ritt model³⁵ to explain alpha rhythm generation within cortical columns, in Wendling et al.³⁶ to explain fast epileptic activity by means of impaired GABAergic dendritic inhibition and, more recently, as the basis of a generative model (using model parameters estimated from empirical data using Bayesian procedures) for event related potentials.⁴⁰

3.2. Case examples

In this section, we present case examples of deterministic models of epilepsy from published literature. Our objective is to



Fig. 2. Schematic block diagram representation of the mean field neural population model. The linear transfer function block converts average presynaptic firing rate of neural population $r(t)$ to average postsynaptic membrane potential (PSP) $v(t)$. Note that the operation of this block for the specific form of impulse response function $h_X(t) = Aae^{-at}$ can be described in terms of a second order ODE as $\frac{d^2v(t)}{dt^2} + 2a\frac{dv(t)}{dt} + a^2v(t) = Aar(t)$. The nonlinear sigmoidal function block converts the mean PSP $v(t)$ into the mean postsynaptic spiking rate $s(v(t))$ of neural population. The most commonly used analytical form for the sigmoid function block is given as: $s(v(t)) = \frac{e_0}{1 + \exp(r(v_0 - v(t)))}$, where the parameter e_0 corresponds to the maximum firing rate of the family of neurons in the neuronal ensemble, v_0 is a measure for the excitability of the neuronal ensemble and r is the slope of sigmoid at v_0 .

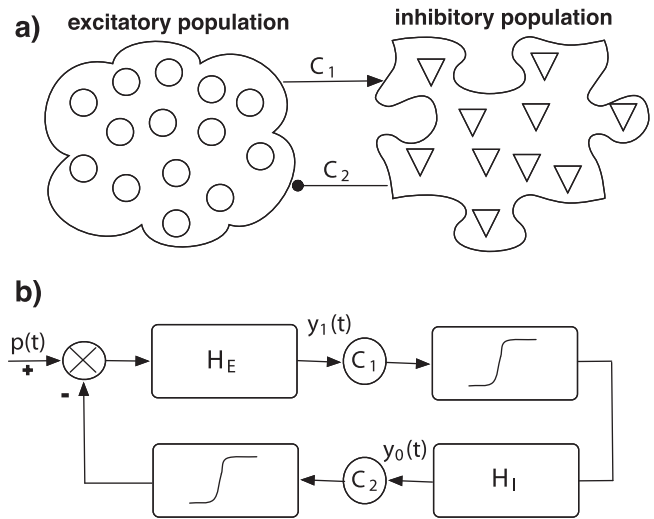


Fig. 3. (a) Schematic diagram of two interacting neural populations. (b) The neural mass representation of the interaction: $y_0(t)$ and $y_1(t)$ represent the average postsynaptic membrane potentials (PSPs) of the inhibitory and excitatory neuronal populations respectively. The transfer functions for the excitatory and inhibitory blocks are given by $h_E(t) = Aae^{-at}$ and $h_I(t) = Bbe^{-at}$ respectively. The parameters (A,a) and (B,b) model the maximal PSP amplitudes and the time constants of the excitatory and inhibitory transfer function blocks respectively. $p(t)$ represents the pulse density of neighboring or distant neural populations that synapse onto the excitatory neural population block, and can be modeled as an arbitrary function including Gaussian white noise. The interaction between the two neural population blocks can be modeled using a set of two second order ODEs as: $\frac{d^2y_0(t)}{dt^2} + 2b\frac{dy_0(t)}{dt} + b^2y_0(t) = Bbs(C_1y_1(t))$ and $\frac{d^2y_1(t)}{dt^2} + 2a\frac{dy_1(t)}{dt} + a^2y_1(t) = Aa[p(t) - s(C_2y_0(t))]$, where s is a sigmoid function of the form given in Fig. 2 caption.

highlight the utility of deterministic modeling framework to address pertinent questions in epilepsy. The case examples are chosen to represent the micro- and macro-modeling frameworks in computational models of epilepsy and to demonstrate how the choice of modeling hierarchy is governed by the question that the study attempts to address.

3.2.1. First case example

The first example is from the work of Ullah et al.⁴¹ This example demonstrates the utility for micro-scale models to address questions related to the influence of surrounding environment (glia dynamics and extracellular potassium concentration) on the excitability of neuronal networks. The modeling framework in this study is based on a generic micro-scale neuronal network model of excitatory and inhibitory Hodgkin–Huxley neurons that are modified to explicitly model the concentration gradients of intra- and extra-cellular potassium ions.

The authors investigate the conditions under which persistent neural activity, defined as spatially restricted sustained firing activity in neuronal networks in response to a brief input stimulus, can transition to seizure-like activity, defined as the condition in which the spatially restricted neural activity spreads to the entire network. The authors focus on the role for extracellular space and glia in modulating the excitatory–inhibitory balance in the network, which in turn influence the spread of persistent network activity. From a dynamical systems point of view, the state of persistent neural activity within the network can be viewed as a high dimensional stable attractor involving a subset of spiking neurons in the network. The transition of the network to a seizure like state where the neural activity spreads to the entire network can be viewed in terms of a bifurcation of the network to a new stable high dimensional attractor involving spiking activity of all neurons in the network.

The authors first demonstrate that in the presence of weak stimulation, under the conditions of excitatory–inhibitory balance and normal glia function, the network maintains spatially restricted persistent neural activity. The authors then investigate the influence of extracellular $[K^+]$ on the network activity. They demonstrate that an increase in extracellular $[K^+]$ narrows the region in the excitatory–inhibitory coupling strength parameter space, in which the network can exhibit stable persistent neural activity. Furthermore, they show that there is an increase in the overall excitation in the network making the network more prone to exhibit seizure-like activity. These results are consistent with experimental findings of Rutecki et al.⁴² where the authors show that raising extracellular $[K^+]$, increased the rate of spontaneous epileptiform discharges in *in vitro* hippocampal slices. Furthermore, in support of these findings, Vincent et al.⁴³ have recently showed that by changing the concentration of extracellular potassium in a rodent hippocampal slice preparation, the slice is prone to spontaneously transition to and from seizure-like states to regular activity.

The authors use the above findings to then investigate the contrasting experimental findings related to the glial contribution to epilepsy. It has been shown by Oberheim et al.⁴⁴ that the $[Ca^{2+}]$ dependent glutamate release from glial cells appear to synchronize the activity of adjacent neurons through simultaneous non-synaptic slow inward neuronal currents. The synchronized neuronal activity is then manifested in the form of epileptic seizures. However, Fellin et al.⁴⁵ reported that the glutamate release by glia is not necessary for the generation of epileptic activity in hippocampal slices. The authors use their neuronal network model to identify conditions under which the glutamate release by glial cells would cause their network to exhibit seizure like activity. In their model they mimic the effect of glia induced perturbations by transiently increasing the strength of excitatory–excitatory synaptic coupling throughout the network from a given baseline value. Using this approach they show that the glia induced perturbations are dependent on the baseline level of excitatory–excitatory synaptic strength in the network, with higher baseline value resulting in higher likelihood for the network to generate seizure like activity in response to glia induced perturbations. Based on these findings the authors suggest that the experimental findings of Oberheim et al.⁴⁴ and Felin et al.⁴⁵ can be explained in terms of different levels of baseline excitation under which the effect of glia induced perturbations were experimentally studied.

3.2.2. Second case example

The second example is the work by Santhakumar et al.⁴⁶ which demonstrates the utility for biophysically realistic multi-compartmental neuronal network models in investigating the impact of changes in neuronal morphology such as cell-sprouting on the excitability of neuronal networks.

The authors study the impact of mossy cell loss and mossy fiber sprouting on post traumatic excitability in the dentate gyrus (DG) subfield of the hippocampus. They construct a detailed representation of the DG network using multi-compartmental models for dentate granule cells, mossy and basket cells and the hilar perforant-path associated cells. The authors use these detailed neuronal models to investigate excitability of two specific DG-network architectures: a nontopographic network in which the postsynaptic targets of each cell in the network are selected at random from a pool of potential target neurons while maintaining the cell type specific levels of incoming and outgoing connections and a topographic network in which the neurons are distributed in a ring structure and the network connectivity is designed to incorporate axonal arborization of each cell type observed in the biological hippocampus.

Detailed simulation studies by the authors showed that increasing the degree of mossy fiber sprouting in a non-topographic network resulted in propagation of activity from the directly activated granule cells to the other cells in the network. The degree of this propagation was proportional to the degree of the mossy cells sprouting and failed to sustain for longer periods of time. In contrast, in a topographic network, increased mossy fiber sprouting resulted in faster propagation of neural activity to the entire network, which eventually translates into self-sustained seizure-like network activity. From a dynamical systems point of view, a modification in the parameter that controls the degree of mossy fiber sprouting in the topographic DG network induces a bifurcation i.e., a qualitative change in the dynamical behavior of the network, corresponding to the emergence of a seizure like network activity. This regime of network behavior was observed to be robust against a number of network parameters including synaptic conduction delay and synaptic strength. The study concludes by suggesting that the restricted topography of sprouted mossy fibers (which have been reported in experimental studies⁴⁷) may play a central role in determining the spread of network activity in the DG.

3.2.3. Third case example

The third example is the study by Suffczynski et al.⁵⁴, demonstrating the utility of macro-scale models to study mechanisms for epilepsy that involve multiple brain regions of interest.

The authors investigate whether normal sleep-spindle activity and the pathological spike-wave discharges observed in patients suffering from absence epileptic seizures share a common underlying network mechanism, both emerging from interactions between the cortex and the thalamus. The authors adopted a macro-scale modeling framework in their study. Specifically, they constructed neural mass models for the cortex and the thalamus in order to capture the mean field activity of sub-populations of neurons resulting from interactions between these regions. They subject their cortico-thalamic network to 3 distinct inputs: direct cortical input, sensory input (received by the thalamo-cortical (TC) cells) and a third input received by the reticular thalamic cells.

For a reference set of parameters, they show that the model exhibits bistable dynamical characteristics with a fixed point attractor coexisting with a limit cycle attractor. They suggest that the normal sleep-spindle oscillations corresponds to noise induced fluctuations in the network dynamics around a fixed point stable attractor, whereas pathological spike-wave discharges correspond to the network dynamics evolving on a limit cycle attractor in the network. Systematic bifurcation analysis of the network dynamics using the strength of cortical input P_{ex} as the system parameter showed that the network dynamics transitions from a fixed point attractor to limit cycle attractor when the strength of cortical input exceeds a critical threshold P_{ex}^{bif} . Subsequently, as P_{ex} is gradually decreased, the network transitions to a fixed point attractor for yet another value for $P_{ex} = P_{ex}^*$ that satisfies the condition $P_{ex}^* < P_{ex}^{bif}$. This analysis suggests that for values of cortical input $P_{ex}^* < P_{ex} < P_{ex}^{bif}$, the network exhibits bistable attractors and depending on the initial conditions and the noise in the network, the network can evolve to either a normal fixed point attractor or to a pathological limit cycle attractor. The authors conclude that this finding has strong implications in the sense that random nature of the occurrence of noise induced paroxysmal spike wave discharges renders them impossible to predict.

The authors also investigate the possibility of controlling the pathological spike-wave activity. They first show that a well timed external stimulus pulse of 40 Hz applied as cortical input for 10 ms causes the network to exhibit pathological spike-wave oscillations. They further show that a counter stimulus of the same intensity

applied at a specific phase of the spike-wave oscillations can destroy this activity and restore the network to normal sleep-spindle state. These findings have potential applications in open-loop control strategies, which will be discussed in Section 4.

3.2.4. Concluding remarks

We note that multi-compartment conductance based neuron models have been used extensively to investigate mechanisms involved in epilepsy. Most notable are the classical modeling studies by Traub and collaborators using a 19 compartment model for hippocampal CA1 pyramidal cells. Following a series of combined experimental/theoretical investigations^{48–51} the authors conclude that gap junctions between the axons of pyramidal neurons may play a critical role in inducing epileptic seizures with focal hippocampal origin. In other studies,⁵² the authors have found that enhanced NMDA conductance can explain epileptiform activity observed in conditions of low extracellular $[Mg^{2+}]$ in hippocampal slices. A similar modeling approach was recently taken by Morgan and Soltesz⁵³, where the authors show that the presence of highly interconnected neurons (hubs) play a critical role in increasing the overall excitability of brain networks such as the DG making it prone to sustained seizure-like network activity. These examples demonstrate the utility for micro-scale multi-compartmental modeling to generate mechanistic hypotheses such as gap junction coupling and hub networks, which then provide guidelines for specific experimentations.

We also note that in all the case examples presented above, enhanced excitability is a key factor that can drive a given network to exhibit abnormal epileptiform activity. However, recently there have been indications that higher degree of excitation relative to inhibition may not be a necessary condition for the manifestation of epileptiform state.⁵⁵ An interesting study was conducted by Drongelen et al.⁵⁶ in which the authors systematically investigated the implications for this idea in a computational model of epileptic cortical network. Guided by an earlier study by Vreeswijk et al.⁵⁷, where the authors show that dependent on the time scale of synaptic interactions, inhibition can play a significant role in enhanced synchrony in neuronal networks, the authors show that their cortical network model can exhibit emergent epileptiform activity in conditions of weak excitatory synapses. The authors have further confirmed the prediction of their model findings in mouse neocortical slices, by showing that a pharmacological reduction of excitatory synaptic transmission elicits sudden onset of repetitive epileptiform bursting behavior in the network.

3.3. Non-deterministic models

The discussion thus far has focused on deterministic dynamical models of epilepsy, which are the primary workhorse of computational epilepsy modeling.^{8,9} There is yet another category of computational models of epilepsy that falls under the umbrella of non-deterministic models. These models aim to capture the inherent variability of the recorded brain activity. The source of this variability is primarily from “noise” in the brain. Noise appear across multiple spatial and temporal scales, ranging from molecular noise in gene expression to synaptic noise resulting from the probabilistic nature of neurotransmitter release, all the way up to noise in the firing activity of neuronal networks across the whole brain.⁵⁸ To address the contribution of these random factors to the observed dynamics associated with epilepsy, two broad categories of models have been used: stochastic models and statistical models.

3.3.1. Stochastic models

Stochastic models attempt to model the evolution of the system of random variable in time. Random variable refers to an

experimentally observable quantity such as the EEG signal, that under repeated observations under identical circumstances do not yield the same outcome. In other words, there is no deterministic regularity in the observed outcomes. The basic idea underlying stochastic modeling framework is to consider a family of random variables $x(t, \omega)$, where the variable t represents time and the variable ω defines a set of all possible outcomes for x . This system of random variables evolving in time represents a stochastic process. For fixed ω , we get an instance of the stochastic process $x(t)$ that evolves in time representing a *sample function*. For fixed t , the stochastic process $x(\omega)$ represents a family of random variables called the *ensemble*.

An example of a stochastic process relevant to the study of epilepsy is an EEG signal recorded on scalp electrodes. Since each scalp electrode picks up the mean electrical activity from a finite region of brain surface (filtered by the skull, which separates the electrodes from the cortical neuronal circuitry), each electrode will record a different time course of electrical activity. The magnitude of the recorded electrical activity on a given EEG electrode $x(t)$ represents a random variable. At a given time t_1 , there is a family of n random variables $\{x_1(t_1), x_2(t_1), \dots, x_n(t_1)\}$ (corresponding to n electrode channels). At another time t_2 , there is another set of random variables $\{x_1(t_2), x_2(t_2), \dots, x_n(t_2)\}$. The set of n records simultaneously observed at a given time represents the ensemble. In general, the statistical properties of the stochastic process are evaluated based on such an ensemble and, hence, they may or may not remain the same as time progresses. In this context, it is critically important to understand what is the probability distribution of the ensemble and how it changes over time; a formal description of these characteristics constitutes a stochastic model.

Most stochastic models are formulated using stochastic differential equations (SDEs), the common form of which is the *Langevin equation*, consisting of ODEs describing the deterministic portion of the time evolution of random variables and an additive noise term representing the stochastic process. A second and popular formulation for stochastic modeling is the *Fokker–Plank equation*, which is a partial differential equation that describes the time evolution of the probability distribution of an ensemble of random variables. In the following paragraph, we will briefly discuss examples from the literature that apply stochastic modeling to epilepsy research.

Studies using SDE formulations of neural models with an additive noise term have revealed important functions for noise in establishing conditions that favor seizure-like activity in cortical networks.⁵⁹ For example, at the macroscopic level, simulation studies using models of cortical networks have demonstrated that noise facilitates the occurrence of traveling waves, which then promote local oscillatory coupling and recruitment of the surrounding neural populations,⁶⁰ critical mechanisms in the initiation and development of epileptic seizures. At the microscopic level, fluctuations in ion channel proteins resulting in probabilistic gating behavior have been shown to place limits on the wiring density of the brain,⁶¹ and, as a result, play an important role in regulating the excitability of neuronal networks.⁶² These findings have paved novel ways for investigating the effects of ion channel mutations associated with epilepsy.^{63,64} Finally, stochastic models using the Fokker–Plank formalism have recently been applied to obtain improved characterizations of epileptic brain dynamics using EEG,⁶⁵ which have implications for better identifying of the epileptogenic foci, an important consideration in resective surgery for epilepsy.

3.3.2. Statistical models

At the basic level, statistical models attempt to identify functional relationship between random variables. Similar to the

stochastic modeling approach discussed above, the relevance of statistical models stems from the underlying assumption that the observed brain dynamics (for example, EEG recordings) are generated by a high dimensional dynamical system with a low signal to noise ratio.⁶⁶ As not all system variables are observable, the idea is to treat the observed dynamics as a stochastic process and devise statistical rules that govern the time evolution of the observed brain activity. A classical example of a statistical model is the autoregressive (AR) model, which represents a class of linear predictive models in which the future outcome of the observed variable is predicted based on a linear combination of past outcomes and an independent identically distributed random variable. AR models have been applied to seizure detection and prediction problems.^{67,68} Advanced techniques from statistical learning theory such as support vector machines⁶⁹ and artificial neural networks,⁷⁰ have been employed to enhance the efficacy of AR models for seizure detection and prediction. Other statistical models that have found applications in epilepsy research include generalized linear models (GLM), which are an extension of linear regression models and are used to evaluate the prevalence of cognitive co-morbidities in epilepsy⁷¹ and structural equation models (SEM), a class of multivariate regression models that are used for causal interpretation of qualitative observational data, for instance, to evaluate the relationship between physical and psychosocial factors and the quality of life among adults with epilepsy.⁷² SEMs have also been applied to study how the attitude of children towards epilepsy influence their psychological adjustment to the disease.⁷³

Yet another class of statistical models referred to as Markov chain models and hidden Markov models has found significant application in epilepsy research. The basic idea underlying the utility of these models is that there are multiple attractor states within the brain. The transition between these attractor states is assumed to follow the Markov property, namely that the transition of the brain to any future attractor state is only dependent on the present attractor state of the brain. Based on this assumption, a probabilistic rule is identified that transitions the brain across various attractor states. This modeling approach has found applications in both seizure prediction⁷⁴ and in the assessment of statistical model based seizure prediction algorithms.⁷⁵

4. Applications of computational models for epilepsy therapy

Following the discussion presented above on the various computational modeling approaches to epilepsy, one might be left with the impression that deterministic-dynamical models are more appropriate for probing at the cellular and network mechanisms implicated in epilepsy, whereas non-deterministic stochastic or statistical models are geared toward practical applications, with a focus on predicting the timing of seizure recurrence. While this is true to a certain extent, efforts are currently underway within the community of computational epilepsy researchers to bridge these two somewhat distinct modeling approaches. The drive in this direction is due in part to the recent emergence of control engineering applications for the treatment of epilepsy.^{76,77} Efficient controller design and implementation requires both an excellent ability to predict an impending seizure as well as a precise understanding of the mechanisms involved in seizure generation in order to develop control protocols that will result in a long-term seizure-free status.

In the following sections, we will discuss some of the recent advances in modeling efforts that aim to bridge deterministic and non-deterministic modeling approaches in order to develop novel treatment protocols for epilepsy with specific emphasis on the utility of brain stimulation techniques for seizure control.

4.1. Electrical stimulation

There is a general consensus within the epilepsy community that despite pharmacological and surgical advances in the treatment of epilepsy, many patients still suffer from uncontrolled epileptic seizures. As a result, there is a need for new therapeutic approaches.⁷⁸ To this end, a growing body of clinical research indicates that controlling seizures may be possible through direct (deep brain) and indirect (vagal nerve) electrical stimulation.⁷⁹ The initial success of electrical stimulation has propelled further research aimed towards improving the efficacy of this form of treatment. In particular, the focus has been on determining the most appropriate brain structures for stimulation and finding the most effective stimulation protocols for aborting epileptic seizures. For example, it is not yet clear why high and low frequency electrical stimulations have contrasting effects on different seizure models and structures.^{80,81} Computational models offer the potential to address some of these questions via systematic exploration through testing various electrical stimulation protocols across multiple brain regions.

The work of Tass and collaborators represents a step in this direction. Using an abstract network model of coupled oscillators, the authors propose a novel electrical stimulation protocol to suppress seizure-like synchronous activity in the network. They hypothesize that effective electrical stimulation protocols allow the network to unlearn the abnormal synchronized regime associated with epileptic seizures by means of synaptic plasticity mechanisms.⁸² Following this hypothesis, they show that high frequency pulse trains of electrical stimuli applied in a coordinated fashion at different locations in the oscillator network are able to suppress the synchrony of the network. Furthermore, the robust suppression of neural synchrony was maintained using a closed-loop feedback signal that controlled the timing of the stimulus train and the width of the applied stimulus pulses. The authors further investigated the effects of delayed feedback stimulation on maintaining a desynchronized network.⁸³ An important consideration of these research findings from the point of view of applications for seizure control is that the stimulation parameters are dynamically modulated depending on the state of brain activity without the need for time-consuming calibration of the stimulation parameters. The findings from the above theoretical investigations were recently validated in an experimental study,⁸⁴ in which it was shown that sustained neural desynchronization was maintained in epileptic hippocampal brain tissue via multisite, coordinated feedback electrical stimulation. Together, these studies offer a glimpse of the potential for computational models to aid in the design and implementation of novel electrical stimulation protocols that are highly effective in suppressing, or even eliminating, epileptic seizures.

Recently, clinical trials have been conducted to determine the efficacy of a closed-loop electrical stimulation approach for seizure control.^{85,86} In this approach, an online time series based statistical measure is employed to identify signatures of seizure or pre-seizure epileptic activity in the patients EEG signal. Following the successful detection of abnormal brain activity, a train of electrical stimulation pulses is delivered in order to suppress the occurrence of an impending epileptic seizure. The success of this approach not only depends on the specific stimulation protocol, but more importantly, depends on the detection and classification accuracy of the time series measure used to detect abnormal brain activity. From this perspective, advances in models that can predict seizures are expected to play an important role in enhancing the efficacy of closed-loop stimulation protocols.

4.2. New direction: light stimulation for seizure control

Optogenetics is an emerging technology that leverages techniques from molecular biology, virology and genetic engineering to selectively express light sensitive ion channels in the membranes of either excitatory or inhibitory neurons.¹⁴ Light is used to specifically excite [using algae protein channelrhodopsin-2 (ChR2)] or suppress [using the light driven chloride pump halorhodopsin from archaea *Natronomonas pharaonis* (NpHR)] impulse activity in neurons with a high degree of spatial and temporal resolution.⁸⁷ As a result, this technique holds tremendous potential for use in the fine external control of activity states

in neuronal networks.⁸⁸ Furthermore, the kinetics of the light activated ion channels are well understood^{89,90} and are amenable to mathematical modeling.⁹¹ These models can be integrated into the Hodgkin Huxley conductance-based neuron models,⁹² which provide a natural framework that is suitable for computational modeling studies of the effects of light stimulation on brain network activity.

Our research has recently focused on the question of how to leverage the temporal and spatial precision of light stimulation to achieve robust suppression of pathological neural synchrony in brain networks? Here, we will present results demonstrating the success of light stimulation based feedback controllers in achieving

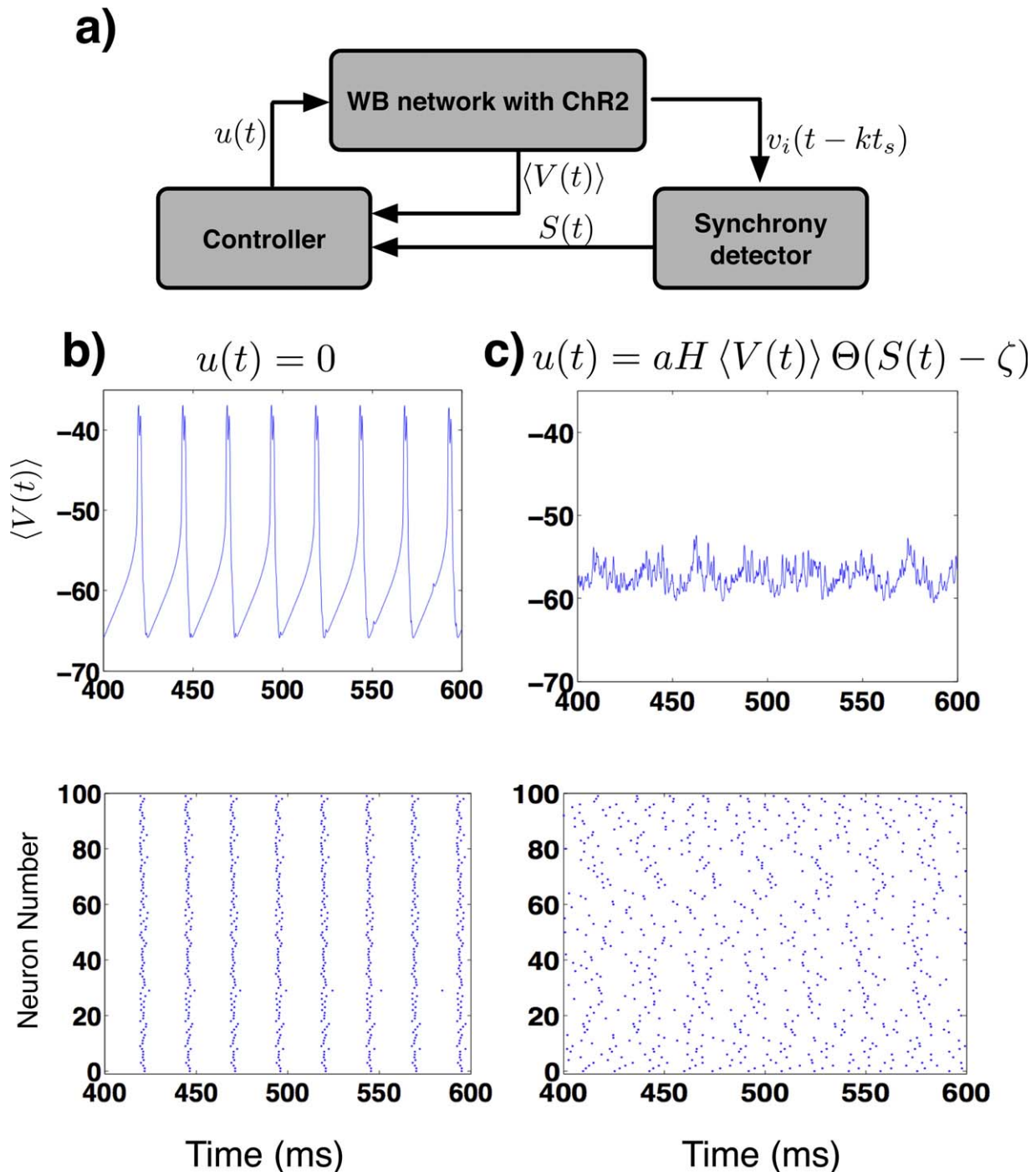


Fig. 4. (a) Schematic of the closed-loop control architecture. (b) The mean field network activity (top) and the raster plot of neuronal spiking (bottom) in absence of control. (c) The response of the network when the closed loop controller is active. Light intensity, $I = 0.01 \text{ mW/mm}^2$.

neural de-synchronization in a Wang–Buzsaki (WB) neuronal network of 100 all-to-all coupled identically firing interneurons.⁹³ A WB network was chosen as the ideal template for this study as it is a classical model that is used to study neural synchrony in a biophysically realistic neuronal network. We modified the WB-network such that the membrane dynamics of each neuron in the network involved an additional ion channel, the light sensitive protein ChR2. We further assumed that the neurons in the network were arranged in a circle in a 2-dimensional Euclidean space. Neural synchrony was quantified using a synchrony metric, $S(t)$, that has been well-characterized in the literature.⁹⁴ In the absence of light stimulation, the WB network exhibits robust neural synchrony.⁹³ The stable synchronous firing state of the network is shown in Fig. 4b. We then tested the following linear proportional feedback controller using light stimulation with low intensity such that light itself did not evoke an action potential in a given neuron in the network:

$$u(t) = aH\langle V(t) \rangle \Theta(S(t) - \zeta) \quad (2)$$

where Θ is the heaviside step function and a , T and ζ are the control parameters and

$$\langle V(t) \rangle = (100T)^{-1} \int_{t-T}^t du \sum_{i=1}^{100} v_i(u) \quad (3)$$

The light intensity was set at a nominal value of $H = 0.01$ mW/mm². The schematic of the closed-loop control architecture is shown in Fig. 4a and in Fig. 4c, we present an example of successful closed loop control (suppression) of neural synchrony using the above linear proportional feedback controller. This proof-of-principle example illustrates the potential for a weak light intensity stimulation based feedback controller to suppress neural synchrony. We envision that in the future multi-disciplinary collaborative efforts between scientists with expertise in clinical epilepsy, molecular biology, computational modeling and control engineering will pave the way for the development of control systems and algorithms specifically designed to suppress pathological neural synchrony such as epileptic seizures originating in focal brain, using novel optogenetic stimulation protocols.

5. Discussion

The premise of this review is that epilepsy is a dynamical disease. Motivated by this idea, we have attempted to provide to the uninitiated reader a brief introduction to the framework of dynamical systems. We present examples from the recent literature to demonstrate how concepts from dynamical systems are used to formulate computational models on both micro- and macro-scales that can be used to explore various mechanisms of epilepsy. We also present a brief discussion on computational models of epilepsy that fall under the general category of non-deterministic models. These models are primarily focused on addressing practical questions related to the predictive nature of seizure occurrence and the methods aimed at assessing the performance of computational models for seizure prediction. We have also explored some applications that have great potential for providing novel avenues for epilepsy treatment. In particular, we discuss recent progress in electrical stimulation based treatment protocols and also present preliminary results on the utility of light stimulation based protocols for controlling pathological brain activity.

As evident from the multiple case examples presented in this review, there are currently many well known mechanisms that can contribute to epileptic seizures and many computational models that explain how these mechanisms mediate the enhanced brain

excitability that leads to epileptic seizures. Despite these advances, developing effective treatment protocols for patients suffering from refractory epilepsy has proven to be difficult. The primary reason for this undesirable situation is the vast complexity of the human brain and the epileptic syndrome. Most models, while not simple, are only able to capture a small portion of this complexity. However, we believe that the future is promising. Several investigations over the last 20 years focused on understanding the biology of the human brain have led to a wealth of data, such as the human genome project, the Allen Brain atlas, the human proteomics database and the brain connectome. It is expected that future efforts to model epilepsy will make use of these datasets to improve upon the existing models, address gaps in our knowledge, generate new predictions and possibly provide avenues for new and effective treatment strategies.

Recent advancements in computer technology, including the availability of super computers (such as the Blue Gene/P super computer at the Argonne National Laboratory), and new computational methods (such as distributed parallel computing architecture) now provide the necessary tools for scientists to use computational strategies to reverse engineer the brain (for example, the Blue Brain Project at Ecole Poly-technique Federale de Lausanne), in the hope of obtaining a better understanding of normal and abnormal brain function. Furthermore, advances in experimental technologies, such as optogenetics, are making it possible for us to achieve precise control of brain function at the level of individual neurons, thereby providing a novel means to target and remotely control the brain networks that are susceptible to epileptic seizures. In this context, there are reasons to believe that more efficient treatment strategies for epilepsy are on the horizon.

In summary, in this review we presented a brief survey of the utility of computational models for the treatment of epilepsy. Our goal was to increase awareness of computational modeling as one of the many tools at the disposal of epilepsy researchers, which may facilitate the development of novel solutions to the challenging problems of epilepsy and seizure control. Furthermore, we hope that this review will encourage active collaborations between experimental and computational researchers that will ultimately result in more efficient treatment protocols for epilepsy.

Acknowledgements

SST would like to acknowledge kind support from the Wilder Center of Excellence for Epilepsy Research and the Childrens Miracle Network. We acknowledge the feedback from Paul Carney for his insights into the readability of the manuscript for a clinical audience. We also thank Jason Coleman and the editor for their feedback on English language edits for our manuscript. Finally, we thank the anonymous reviewers for their critical feedback, which helped us to significantly improve the manuscript.

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