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Review

Computational models of epilepsy

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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.

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

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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 seizure [5] 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:

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

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, $I = 35\ \mu A/cm^2$), 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 analysis [18] 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 $j = 1 \cdots 8$ of such trajectories. The set of all the