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Exploring action potential initiation in neurons exposed to DC electric fields through dynamical analysis of conductance-based model

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ABSTRACT

Noninvasive direct current (DC) electric stimulation of central nervous system is today a promising therapeutic option to alleviate the symptoms of a number of neurological disorders. Despite widespread use of this noninvasive brain modulation technique, a generalizable explanation of its biophysical basis has not been described which seriously restricts its application and development. This paper investigated the dynamical behaviors of Hodgkin's three classes of neurons exposed to DC electric field based on a conductance-based neuron model. With phase plane and bifurcation analysis, the different responses of each class of neuron to the same stimulation are shown to derive from distinct spike initiating dynamics. Under the effects of negative DC electric field, class 1 neuron generates repetitive spike through a saddle-node on invariant circle (SNIC) bifurcation, while it ceases this repetitive behavior through a Hopf bifurcation; Class 2 neuron generates repetitive spike through a Hopf bifurcation, meanwhile it ceases this repetitive behavior also by a Hopf bifurcation; Class 3 neuron can generate single spike through a quasi-separatrix-crossing (QSC) at first, then it generates repetitive spike through a Hopf bifurcation, while it ceases this repetitive behavior through a SNIC bifurcation. Furthermore, three classes of neurons' spiking frequency f–electric field E (f–E) curves all have parabolic shape. Our results highlight the effects of external DC electric field on neuronal activity from the biophysical modeling point of view. It can contribute to the application and development of noninvasive DC brain modulation technique.

1. Introduction

Noninvasive brain stimulation recently has been widely used to study brain-behavior relations and treat a variety of neurologic and psychiatric disorders [1]. One of the most well-known examples of neuromodulation is the use of static DC electrical stimulation such as transcranial direct current stimulation (tDCS) of the central nervous system (CNS). In tDCS, a weak direct current is applied to the human cortex by means of a pair of relatively large electrode pads positioned on the scalp [2]. By means of tDCS, a DC electric field can be induced to stimulate the corresponding brain issue directly. Preliminary positive results of tDCS have shown that it can change cortical excitability [2] and modulate plasticity in neuropsychiatric diseases [3], otherwise it can induce beneficial effects in working memory, cognitive function and motor rehabilitation [4,5]. Therapeutic utility of tDCS has been claimed in the literature for many neuropsychiatric disorders, such as major depression

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[6], schizophrenia [7], Parkinson's disease [8] and epilepsy [9]; treatment of aphasia after stroke [10], and pain syndromes, such as those caused by traumatic spinal cord injury, fibromyalgia, and cancer pain [3]. Animal studies suggest that anodal tDCS, via an extracellular negative sink, causes a depolarization of the resting-membrane potential and increases the firing rates of many perpendicularly oriented cortical neurons in the tissue under the electrode. Cathodal stimulation has the opposite effect, causing a hyperpolarisation of the resting-membrane potential and a decrease in firing rates [11,12]. However, the precise mechanism underlying neuronal excitation by tDCS is still unclear. Furthermore, there is lack of theoretical research and mechanism analysis about how applied DC electric field induced by tDCS affects neuronal activity so far.

1977, Mackey and Glass proposed the concept of *dynamical disease*, stating that abnormal dynamics occur when control parameters of the physiological system are out of range [13]. In other words, the dynamics of neuronal system are closely related to their function, and perturbation of control parameters governing the dynamics of the system could cause qualitatively different dynamics, and thus affect the corresponding function. It is found that many neuropsychiatric diseases, such as Parkinson's disease, Alzheimer's disease, depression and obsessive–compulsive disorders are related to neural abnormal spiking rhythm [14,15]. Devos and Lefebvre proposed to explain the benefits of neuromodulation by external stimulus is that the impaired neural rhythms originating the symptoms are re-organized by the stimulus toward normal physiological rhythms [16]. This proposal is partly supported by several experimental results which showed that DBS and TMS could prevent the abnormal neural rhythms [17,18]. So to investigate how neuromodulation techniques modulate the dynamics and further improve the function of neuronal system, spiking patterns of single neuron and their dynamical explanations of spike initiation need to be studied.

Exploring how DC electric field affects brain function and modulates neuronal activity has always been drawing a plenty of researchers' attentions. Experimental studies found that applied electric field or current can change many neuronal systems' excitability, such as turtle cerebellum [19], guinea-pig hippocampal cells [20], pyramidal cell [21] and so on. 1996, Gluckman et al. observed that external DC electric field around brain issue can suppress seizures temporarily [22]. Then, Durand and Bikson found that uniform DC electric fields and localized electric field induced by electric stimulation have the same effective to control the epileptiform abnormal neuronal activity of brain slice [23]. After that, Bikson with his partner explored the effects of extracellular uniform DC electric fields on neuronal excitability in rat hippocampal slices. They found uniform DC electric fields can altered the thresholds of action potentials evoked by orthodromic stimulation; large electric fields could trigger neuronal firing and epileptiform activity, and induce long-term (>1 s) changes in neuronal excitability [24]. Further, Akiyama et al. using optical imaging and patch-clamp recordings, showed that CA1 pyramidal neurons indeed exhibit the characteristic membrane polarization profiles in response to DC electric fields, and investigated the mechanism underlying the profiles [25]. However, it is difficult to integrate these findings into a unified framework, since results give priority to experimental study and are not always reproducible among studies.

Apart from above experimental studies, there are also plenty of theoretical investigations with regard to the dynamical behaviors of neuron exposed to external electric field. For instance, Park et al. explored the effects of applied electric fields on neuronal synchronization with a two-compartment model [26]. Kotnik and Miklavcic built a second-order model of membrane electric field induced by alternating external electric fields and analyzed the effects of electric field's parameter on neural cell and their membrane [27]. In our previous studies, we have investigated neuronal dynamical behaviors exposed to extremely low frequency (ELF) sinusoidal electric fields by different neuron models [28–30]. It has been shown neuron can exhibit period-n, bursting and chaotic spiking patterns under the effects of external periodic electric field. There is a rich bifurcation structure including period-doubling bifurcation, phase-locking alternated with chaos and inverse period-adding bifurcation without chaos, appearing in the transition of different firing patterns. In addition, different control methods have been recently introduced to the control of neuron spiking behaviors under external current stimulus, such as phase feedback control [31,32], internal model control [33] and linear proportional-integral control [34]. Our earlier researches also used several control strategies, such as H_∞ variable universe adaptive fuzzy control [35] and adaptive neural network H_∞ control [36], for synchronizations of Hodgkin-Huxley neurons exposed to ELF electric fields. However, most of above studies are mainly focus on periodic electric field, there is still lack of dynamical analysis about neurons exposed to static DC electric field. The underlying mechanisms of the interaction between electric field and neuron activity are still unknown.

In this paper, we addressed the question of DC electric field exposure effects on brain activity and function from the biophysical modeling point of view. First, we presented a single neuron model during exposure to DC electric field based on a two-dimensional model proposed by Prescott et al. [37]. Second, we studied the spiking properties of Hodgkin's three classes of neurons [38] under the effects of different DC electric fields. Finally, we analyzed the spike initiating dynamics for different neurons from a dynamical systems point of view. Our results could provide a new insight into the mechanism of non-invasive brain stimulation techniques.

2. Material and Methods

2.1. Effects of external DC electric field on neuronal membrane potential

In brain tissue, different ions are present both in extra- and intra-cellular medium, with different concentrations. This differential of ionic concentrations between the extra- and intra-cellular mediums originates the membrane potential $V(t)$ of the cell [38]. The electrical activity in neurons is sustained and propagated via ionic currents through neuron