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Dynamical analysis of Parkinsonian state emulated by hybrid Izhikevich neuron models

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ABSTRACT

Computational models play a significant role in exploring novel theories to complement the findings of physiological experiments. Various computational models have been developed to reveal the mechanisms underlying brain functions. Particularly, in the development of therapies to modulate behavioral and pathological abnormalities, computational models provide the basic foundations to exhibit transitions between physiological and pathological conditions. Considering the significant roles of the intrinsic properties of the globus pallidus and the coupling connections between neurons in determining the firing patterns and the dynamical activities of the basal ganglia neuronal network, we propose a hypothesis that pathological behaviors under the Parkinsonian state may originate from combined effects of intrinsic properties of globus pallidus neurons and synaptic conductances in the whole neuronal network. In order to establish a computational efficient network model, hybrid Izhikevich neuron model is used due to its capacity of capturing the dynamical characteristics of the biological neuronal activities. Detailed analysis of the individual Izhikevich neuron model can assist in understanding the roles of model parameters, which then facilitates the establishment of the basal ganglia–thalamic network model, and contributes to a further exploration of the underlying mechanisms of the Parkinsonian state. Simulation results show that the hybrid Izhikevich neuron model is capable of capturing many of the dynamical properties of the basal ganglia–thalamic neuronal network, such as variations of the firing rates and emergence of synchronous oscillations under the Parkinsonian condition, despite the simplicity of the two-dimensional neuronal model. It may suggest that the computational efficient hybrid Izhikevich neuron model can be used to explore basal ganglia normal and abnormal functions. Especially it provides an efficient way of emulating the large-scale neuron network and potentially contributes to development of improved therapy for neurological disorders such as Parkinson's disease.

1. Introduction

Parkinson's disease (PD) is one of the most common progressive neurodegenerative disorder and is characterized by four primary motor symptoms: akinesia (poverty of voluntary movements), bradykinesia (slowness and impaired scaling of voluntary

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movement), muscle rigidity and resting tremor [1]. In PD, degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) of the midbrain leads to the emergence of pathological activities in the basal ganglia–thalamic neural loop [2,3]. Thus, the exploration of dynamical properties of the basal ganglia–thalamic neuronal network has attracted much attention [4–7]. Previous studies have reported that the neurophysiological hallmark of PD pathophysiology is excessive synchronous activity in the basal ganglia (BG) network [8–10] that consists of striatum, substantia nigra pars reticulate (SNr), SNc, subthalamic nucleus (STN) and globus pallidus (GP) (including the globus pallidus externa (GPe) and globus pallidus interna (GPi)). Moreover, as indicated by previous experimental studies, STN and GPe may constitute key substrates in the maintenance of pathological synchronous rhythms in Parkinsonian BG [11–14]. Modeling studies have also demonstrated that because of its reciprocal inhibitory–excitatory connections, the STN–GPe network can serve as a pacemaker for various rhythmic [15]. However, due to limitations of the preparations and the inability to measure the input signals of the neurons and their effects on outputs of the cells, theoretical predictions have rarely been validated experimentally, thus computational models are important for exploring these theoretical issues. For instance, Terman et al. developed a conductance-based computational neuronal network of STN and GPe, which illuminated the significant roles of coupling architecture of the network and associated synaptic conductances in modulating the firing patterns displayed by this reciprocal STN–GPe network. Their theoretical analysis and numerical simulation results showed that increased striatal input to, and weakened intrapallidal inhibition within, the reciprocal STN–GPe can switch the dynamical behavior of the circuit from irregular to rhythmic. It may explain the emergence of correlated oscillatory activity in the subthalamopallidal circuit after the loss of dopamine in the Parkinsonian condition [15]. Subsequently, they emphasized the BG's influence on the thalamus. Rhythmic inhibition from the output nucleus, GPi, to the thalamus destroys the ability of thalamocortical relay cells to respond to excitatory sensorimotor inputs. Rhythmic rebound bursts occur in the thalamocortical relay cells under the Parkinsonian states, due to the abnormality in deinactivation of the low-threshold calcium T-current in thalamocortical relay cells under pathological conditions [16]. Additionally, Humphries et al. presented a spiking neuron model of the BG circuitry to test a proposal about the centralized action selection function of the BG, which can resolve conflicts between multiple neural systems competing for access to the final common motor pathway. They found that the STN-GPe loop is functionally decoupled by tonic dopamine and thus does not show pacemaking activity under normal conditions, but recoupled by dopamine depletion to play a role as a pacemaker [17]. Moreover, Pirini et al. extended Rubin and Terman's network model by introducing a direct pathway of the BG system to investigate network effects of DBS for PD in different target sites based on a more complete BG network framework. Simulation results suggested that STN–DBS could functionally restore the thalamic relay activity, whereas GPe–DBS and GPi–DBS could functionally over-activate and inhibit it, respectively [18]. Besides, in order to further explore how patterns of basal ganglia population activity may affect the behavior of downstream thalamic neurons, Reitsma et al. studied pairs of model thalamocortical relay neurons receiving correlated inhibitory inputs from GPi. They observed that the bursting firing patterns seen in the Parkinsonian GPi allow for stronger transfer of correlations than do firing patterns found under normal conditions [19].

Given significant roles of computational model in the exploration of pathological activity patterns and mechanism of DBS, establishing more accurate models to capture the dynamical features of neurons within the basal ganglia–thalamic neural loop deserves our further efforts. Additionally, considering that innovative therapeutics that have been developed are mostly based on biophysical brain activity models, using mathematical models to describe and predict neural networks activity may be helpful for the further development of novel therapeutic approaches. For example, such computational models can be used to evaluate brain network responses to external stimulation signals [20].

In the functions studies of the subcortical structures of the BG network, the firing properties of individual neurons can be always characterized by various mathematical equations such as Hodgkin–Huxley equations [15,16,21]. However, such a detailed conductance-based model is difficult to be implemented in hardware due to its highly nonlinearity and complexity [22]. By reviewing and comparing twenty common neuro-computational properties of spiking and bursting ordinary differential equations (ODE) models, the Izhikevich model can generate a robust set of firing patterns with various preferences [23]. Particularly, from the viewpoint of biological plausibility and computational cost, the Izhikevich model exhibits its good performance in simulating the dynamical characteristics of the neurons with a strong computational efficiency [23]. Although these results originate from the comparison of large-scale simulations of cortical neural networks, the models can also be used for spiking and bursting neurons in other subcortical structures. Based on this, Thibeault et al. replicated above four physiological BG models by replacing the computationally expensive neuron models with hybrid Izhikevich neurons [12]. It suggests that applying hybrid Izhikevich models in physiologically inspired models of the BG can capture the normal or pathological physiological functions, especially in efficient large-scale network implementations in neuromorphic hardware. Although reproducing four published models of BG with efficient Izhikevich neuronal network is encouraging, more important things are exploring more accurate mechanism underlying the Parkinsonian state and designing the stimulation strategies to improve the pathological brain functions.

There is sufficient evidence that the emergence and transmission of synchronized oscillations in PD may potentially induce motor deficits; however, the underlying mechanism is still under controversy. Besides the cortical input to the BG system and the reciprocal subthalamopallidal circuit structure, the intrinsic properties of GP have been shown to be essential for the maintenance of these oscillations and play a major role in sculpting BG network activity [24]. Moreover, there is evidence showing that changes in strength of dopamine-modulated synapses can promote intermittent synchronous activity patterns [6,7]. Considering these characteristics displayed in the exploration of the mechanism of the Parkinsonian state, we propose a hypothesis that pathological behaviors may originate from combined effects of intrinsic properties of GP neurons [24] and synaptic conductances in the whole network [6,7]. On the basis of the efficient Izhikevich model, we aim to test our hypothesis