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Model-based iterative learning control of Parkinsonian state in thalamic relay neuron

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ABSTRACT

Although the beneficial effects of chronic deep brain stimulation on Parkinson's disease motor symptoms are now largely confirmed, the underlying mechanisms behind deep brain stimulation remain unclear and under debate. Hence, the selection of stimulation parameters is full of challenges. Additionally, due to the complexity of neural system, together with omnipresent noises, the accurate model of thalamic relay neuron is unknown. Thus, the iterative learning control of the thalamic relay neuron's Parkinsonian state based on various variables is presented. Combining the iterative learning control with typical proportional–integral control algorithm, a novel and efficient control strategy is proposed, which does not require any particular knowledge on the detailed physiological characteristics of cortico-basal ganglia-thalamocortical loop and can automatically adjust the stimulation parameters. Simulation results demonstrate the feasibility of the proposed control strategy to restore the fidelity of thalamic relay in the Parkinsonian condition. Furthermore, through changing the important parameter—the maximum ionic conductance densities of low-threshold calcium current, the dominant characteristic of the proposed method which is independent of the accurate model can be further verified.

1. Introduction

The basal ganglia (BG) is a set of small subcortical nervous system nuclei, including the striatum, the internal segment of the globuspallidus (GPi), the external segment of the globuspallidus (GPe), the subthalamic nucleus (STN), and substantianigra, which is further separated in pars compacta (SNc) and pars reticula (SNr). The primary 'input' components of the BG are the striatum and STN, which can receive the neural information from the cerebral cortex. Moreover, GPi and SNr are the main 'output' nuclei of the BG, projecting to frontal cortex via the thalamus [1–3]. Numerous experiments have demonstrated that there is evidence linking the BG to an extensive range of processes, including perception [4], mental task [5], learning [6], etc. Simultaneously, dysfunction of the BG is associated with the movement disorders such as Parkinson's disease (PD) and Huntington's chorea [7].

PD is a neurodegenerative disease that can gradually destroy the dopaminergic neurons in the SNc [8,9]. This dopaminergic deficiency leads to a cascade of functional changes in BG system, which is ultimately responsible for the development of the cardinal features of PD [10,11]. The neurological manifestations of PD include four key signs: tremor, rigidity (stiffness), bradykinesia (slowness of movement) and postural instability [12]. The essential pathophysiological characteristic of the PD

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is abnormally synchronized, rhythmic, and burst-like firing activity in the STN and GPi [13–16]. Since GPi, the output nuclei of the BG, becomes overactive, excessive inhibition of thalamus and brainstem motor systems is induced. The resulting effect of this inhibition is that thalamic cells cannot respond faithfully to incoming sensorimotor signals [17–20].

In modern times, deep brain stimulation (DBS) has emerged as a mainstay in the surgical treatment of PD [21]. DBS provides high frequency (>100 Hz) electrical square pulse trains to selected targets inside the patient's brain through surgically implanted electrodes [22]. So far, there are three main targets for treating movement disorders using DBS: the thalamus, STN and GPi [23]. Numerous researches have demonstrated DBS of the thalamus to be an effective therapy for debilitating tremor associated with essential tremor and tremor-predominant PD [24]. Although the beneficial effects of chronic DBS on PD motor symptoms are now largely confirmed, the underlying mechanisms behind DBS remain unclear and under debate [25,26]. The therapeutic effects of DBS are highly dependent on stimulation parameters, such as pulse width, frequency and amplitude. However, the stimulation parameters are determined empirically in clinical settings, and the process of device tuning is time consuming and tedious, presenting a burden for clinicians [22,27]. For these reasons, the objective of this work is to develop a closed-loop control scheme that automatically adjusts the stimulation parameters based on various feedback signals (fast variable and slow variable).

Previous microelectrode, single-unit recording studies demonstrated that oscillatory interaction within and between BG nuclei is very often accompanied by synchronization at Parkinsonian rest tremor frequencies (3–10 Hz). These oscillations have a profound influence on thalamic projections and then impair the thalamic relaying of cortical input by generating rebound action potentials [28]. Thalamic relay fidelity is correlated with the efficacy of symptom alleviation in PD, thereby serves as a valid proxy for treatment effectiveness [29]. Under the appropriate DBS input, pathological rhythms of thalamic neuron can be replaced by reliable firing activity, and then some symptoms of PD can be alleviated. Various computational models have been proposed for understanding and development of DBS therapy, due to the restrictions on human experiments. In the present paper, we develop a thalamic relay neuron model, regarding DBS as an external electric field applied on thalamic neuron.

Based on the pioneering study of control theory, various modern control methods have been developed to control the spiking behavior of neuronal systems in recent years [30–32]. However, because of the complexity of neural system, together with the lack of precise mechanism, there are so many uncertainties and blind spots, such as ionic channel noise, external environmental noise and non-model dynamics, etc. Therefore, the performances of many control methods are disappointing. In recent decades, iterative learning control (ILC) which was originally introduced in 1984 by Arimoto et al. [33] has drawn much attention because of its simple control structure and remarkable tracking performance for the processes that are repetitive in nature [34]. The system using ILC is capable of reducing the tracking error to zero as the iterations increase toward infinity; hence it improves the control performance by an extreme simple self-tuning process. As compared with the other advanced control algorithm, ILC exhibits a great deal of merits. On the one hand, it takes full advantage of the repetitiveness in the control process; on the other hand, the control implementation is quite simple in the sense that accurate system model and the knowledge of model parameters are not needed. More detailed surveys for different kinds of ILC can be found in [35,36].

Accordingly, in this paper, a combined ILC and proportional–integral (PI) closed-loop control strategy is designed, where ILC can greatly improve the PI control performance of this high nonlinear neural system. Various control implements based on different feedback signals are compared. One feedback signal is common membrane potential of thalamic relay neuron, another is the gating variable of its unmeasurable T-type Ca^{2+} current. According to the fast or slow evolution of these variables, the membrane potential is called fast variable, while gating variable of T-type Ca^{2+} current is regarded as slow variable. Since ion exchange is the indispensable foundation of neuron firing behavior, both fast variable and slow variable can reflect the dynamic evolution behaviors of neuron. However, it is worth noting that although slow variable has a distinct advantage of its slow change, it cannot be measured directly in actual physical experiments. Luckily, recent advances in Kalman filtering to estimate system state and parameters in nonlinear systems have offered the potential solution [37,38]. In this paper, the nonlinear method of unscented Kalman filtering (UKF) is adopted to estimate the unobserved slow variable from membrane potential containing unknown noises. Thus, from the view point of a practical implementation, the proposed control strategy is effective via the measure and stimulation electrodes applying to the target sites [39]. The remainder of the paper is organized as follows. In Section 2, after presenting the computational model of thalamic relay neuron, the dynamic characteristics of thalamic neuron in the normal state and in the Parkinsonian state are given, respectively. Then, the basic structure of the combined control strategy based on the ILC and PI control law is introduced. Section 3 displays the control results of both slow and fast variables feedback control. Finally, conclusions are presented in Section 4.

2. Methods

2.1. Model of thalamic relay neuron

In the Parkinsonian conditions, especially when the tremor is dominated, the relay reliability of the thalamic neurons may decrease drastically. Thus, the model used in this paper is modified from the whole cortico-basal ganglia-thalamocortical model developed by Rubin and Terman [40,41], where external characteristic of the thalamic nucleus is primarily focused onto reveal the mechanism of thalamic nucleus DBS. As illustrated in Fig. 1(A), the BG is comprised of striatum, STN, GPe