Neural Networks 98 (2018) 283–295

Contents lists available at ScienceDirect

Neural Networks

journal homepage: www.elsevier.com/locate/neunet

Nonlinear predictive control for adaptive adjustments of deep brain stimulation parameters in basal ganglia–thalamic network

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ARTICLE INFO

Article history:
Received 14 February 2017
Received in revised form 5 September 2017
Accepted 1 December 2017
Available online 7 December 2017

Keywords:
Parkinson's disease
Closed-loop stimulation
Parameter adjustment
Volterra model
Nonlinear predictive control

ABSTRACT

The efficacy of deep brain stimulation (DBS) for Parkinson's disease (PD) depends in part on the post-operative programming of stimulation parameters. Closed-loop stimulation is one method to realize the frequent adjustment of stimulation parameters. This paper introduced the nonlinear predictive control method into the online adjustment of DBS amplitude and frequency. This approach was tested in a computational model of basal ganglia–thalamic network. The autoregressive Volterra model was used to identify the process model based on physiological data. Simulation results illustrated the efficiency of closed-loop stimulation methods (amplitude adjustment and frequency adjustment) in improving the relay reliability of thalamic neurons compared with the PD state. Besides, compared with the 130Hz constant DBS the closed-loop stimulation methods can significantly reduce the energy consumption. Through the analysis of inter-spike-intervals (ISIs) distribution of basal ganglia neurons, the evoked network activity by the closed-loop frequency adjustment stimulation was closer to the normal state.

1. Introduction

Deep brain stimulation (DBS) is an adjustable and reversible surgical treatment for Parkinson's disease (PD), which is usually used for patients who do not respond well to medication (Bronstein et al., 2011; Castrioto et al., 2011; Halpern et al., 2007; Krack et al., 2003). The stimulation parameters used for DBS are tuned for each patient using a time consuming trial-and-error process. Then the selected regular short-duration (60–180 μs), high-frequency (130–185 Hz) pulses are used to alleviate the motor symptoms. The efficacy of DBS is strongly dependent on the stimulation parameters (Kuncel, Cooper, Wolgamuth, & Grill, 2007; Kuncel & Grill, 2004; Rizzone et al., 2001). Currently, the stimulation parameters are adjusted intermittently every 3–12 months by neurologists while remain unchanged between clinical visits (Deuschl et al., 2006; Hickey & Stacy, 2016). Unfortunately, the therapeutic window of such constant stimulation is sometimes limited by strong side effects. Reprogramming stimulation parameters have been shown to reverse the adverse effects (Frankemolle et al., 2010; Lee et al., 2010; Moro, Poon, Lozano, Saint-Cyr, & Lang, 2006).

Although studies are carried out to investigate the relationship between stimulation parameters and the clinical effectiveness of DBS (Heldman et al., 2016; Kuncel et al., 2007; Rizzone et al., 2001), the parameter setting for different patients and follow-up adjustments are still not standardized. Temporal pattern of stimulation and closed-loop modulation of stimulation parameters are deemed as two stimulation waveform related therapeutic innovations (Rossi et al., 2016). Some studies prove that temporal patterns of DBS are less effective than regular DBS in reducing symptoms in rats (McConnell, So, & Grill, 2016), tremor (Birdno, Kuncel, Dorval, Turner, & Grill, 2008; Birdno et al., 2011) and bradykinesia in patients (Dorval, Kuncel, Birdno, Turner, & Grill, 2010). However, these studies offer important insights into how DBS works: the efficacy of high-frequency DBS is correlated with its ability to regulate neuronal firing patterns within the basal ganglia. Also, some studies demonstrate that the non-regular patterns of stimulation are more effective than regular stimulation (Baker, Zhang, & Vitek, 2011; Brocker et al., 2017, 2013). The differences in findings may attribute to differences in stimulation targets (STN, GPi and Vim) or methods of evaluation (Baker et al., 2011).

Closed-loop DBS consists of closed-loop, real-time adjustment of stimulation parameters according to the patient's clinical status, which can tailor the therapy to individual patients' needs (Beuter, Lefaucheur, & Modolo, 2014; Carron, Chaillet, Filipchuk, Pasillas-Lépine, & Hammond, 2013; Gorzelic, Schiff, & Sinha, 2013; Hebb et al., 2014; Holt, Wilson, Shinn, Moehlis, & Netoff, 2016; Little et al., 2016, 2013; Liu et al., 2013, 2015; Modolo, Beuter, Thomas, & Legros, 2012; Rosin et al., 2011; Santaniello, Fiengo,

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https://doi.org/10.1016/j.neunet.2017.12.001
0893-6080/

Glielmo, & Grill, 2011; Su et al., 2015; Tinkhauser et al., 2017). Rosin et al. use the spike time recorded in the primary motor cortex to control the open time of stimulation delivered to the GPi and prove these patterns are superior in alleviating akinesia than standard DBS in MPTP-treated monkeys (Rosin et al., 2011). Little et al. use the beta oscillation power of the STN local field potentials (LFPs) to control the on and off time of stimulation signal in PD patients, which can realize a 56% reduction in stimulation time than standard DBS (Little et al., 2013). These two stimulation strategies belong to the on-demand control from the control-theory perspectives. Another type of stimulation strategy called adaptive stimulation is realized through the real-time modulation of DBS amplitude or frequency parameter and mainly carried out on computational models. The traditional proportional–integral–derivative (PID) methodology (Liu et al., 2013), the generalized minimum variance control law, the adaptive control (Su et al., 2015) and variable universe fuzzy control algorithm (Liu et al., 2015) are studied to calculate the online stimulation waveforms. Although these studies are very promising, the optimal closed-loop stimulation method is still not discovered and the different action mechanisms between regular DBS and closed-loop stimulation need to be explored.

These studies motivated our current study. The nonlinear predictive control algorithm was used to realize the online adjustment of stimulation parameters, and then we attempted to explain the difference between regular DBS and closed-loop modulated stimulation from the distribution of BG neurons' inter-spike-intervals (ISIs). This paper was organized as follows. The introduction of the computational model and selection of feedback signal were given in Section 2. In Section 3, the identification of the AR-Volterra model using the input–output data was described. The control framework was introduced in Section 4. Computer simulation results were presented in Section 5. Finally, the discussion and conclusion were given in Section 6.

2. Computational model of the basal ganglia–thalamic network

We used the basal ganglia–thalamic network model (BG model) developed by Rosa et al. to test the efficacy of the proposed stimulation method in reducing the mean energy consumption and preserved efficacy (So, Kent, and Grill, 2012). The model is modified from the Rubin and Terman model (RT model) (Rubin & Terman, 2004). Compared with the original RT model, Rosa et al. change the ionic currents in each neuron and the topological structure of the network to make the model activity closer to experimental data. This model includes the subthalamic nucleus (STN), the globus pallidus internal (GPi), the globus pallidus external (GPe), and the thalamus (TH). The number of each nucleus is 10. Each GPe (GPi) neuron receives excitatory inputs from two STN neurons and inhibitory inputs from two GPe neurons. Each STN neuron receives inhibitory inputs from two GPe neurons. Each GPi neuron projects to a single TH neuron. The network and connectivity patterns of individual neurons were illustrated in Fig. 1.

2.1. Simulation of the network activity under normal and pathological states

Positive constant bias currents (I_{app}) are applied to each neuron to represent the net synaptic inputs from other brain regions. The pathological changes induced by the death of dopaminergic neurons in the substantia nigra compact (SNc) are modeled by the decrease of bias currents to STN, GPe and GPi neurons. As proposed

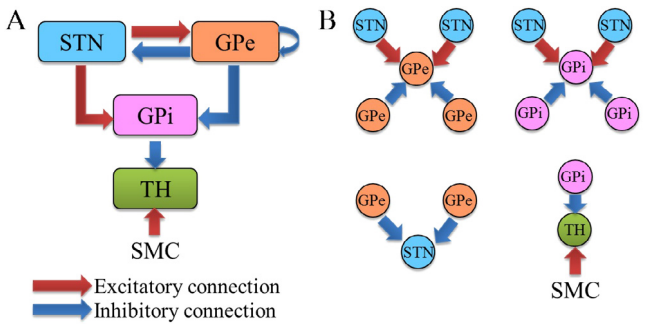

Fig. 1. (A) The network layout of the BG model. (B) Topology connections among neurons.

by Rosa Q. (So et al., 2012), the Hodgkin–Huxley type equations are used to model the membrane dynamics of STN, GPe, GPi and TH neurons which are as follows,

$$\begin{aligned}
C_m\frac{dv_{STN}}{dt} &= -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{GPe\to STN} \\
&\quad + I_{app_STN} + I_{dbs} \\
C_m\frac{dv_{GPe}}{dt} &= -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{STN\to GPe} \\
&\quad + I_{GPe\to GPe} + I_{app_GPe} \\
C_m\frac{dv_{GPi}}{dt} &= -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{STN\to GPi} \\
&\quad + I_{GPe\to GPi} + I_{app_GPi} \\
C_m\frac{dv_{TH}}{dt} &= -I_L - I_{Na} - I_K - I_T - I_{GPi\to TH} + I_{SMC}
\end{aligned} \tag{1}$$

here v_i, $i \in \{STN, GPe, GPi, TH\}$ are the membrane potentials of single STN, GPe, GPi, and TH neuron respectively, $C_m = 1\ \mu F/cm^2$ is the membrane capacitance. $I_L, I_{Na}, I_K, I_T, I_{Ca}, I_{AHP}$ are the leak current, the sodium current, the potassium current, the low-threshold calcium current, the high-threshold Ca^{2+} current, and the after hyper polarization K^+ current, separately. $I_{\alpha\to\beta}$ describes the synaptic current from structure α to β:

$$I_{\alpha\to\beta} = g_{\alpha\to\beta}s_\alpha\left(v_\beta - E_{\alpha\to\beta}\right) \tag{2}$$

where α represents the pre-synaptic neuron and β represents the post-synaptic neuron, $\alpha \in \{GPe, STN, GPi\}$ and $\beta \in \{STN, GPe, GPi, TH\}$ .s_α is the synaptic variable of the pre-synaptic neuron, $g_{\alpha\to\beta}$ is the maximal synaptic conductance and $E_{\alpha\to\beta}$ is the synaptic reversal potential. $I_{app\_i}, i \in \{STN, GPe, GPi\}$ represent the bias currents applied to the STN, GPe, and GPi neuron respectively, which are the sensitive parameters modified to change the model states, and the values for different states are given in Table 1. I_{SMC} is the excitatory monophasic current pulse applied to the TH neurons from the sensorimotor cortex (SMC), which is modeled as a series of monophasic current pulses as follows,

$$\begin{aligned}
I_{SMC} &= i_{SMC}H\left(\sin\left(2\pi t/\rho_{SMC}\right)\right) \\
&\quad \cdot\left[1 - H\left(\sin\left(2\pi\ (t+\delta_{SMC})\right)/\rho_{SMC}\right)\right]
\end{aligned} \tag{3}$$

where $i_{SMC} = 3.5\ \mu A/cm^2$ is the amplitude of the pulse, $\delta_{SMC} = 5$ ms is the duration. In order to model the non-regular nature of SMC input, the frequency of the pulse $1/\rho_{SMC}$ is drawn from a gamma distribution with an average rate of 14 Hz and a coefficient of variation of 0.2 (So et al., 2012). The stimulation pulse delivered to STN I_{dbs} is modeled as follows,

$$I_{dbs} = i_d H\left(\sin\left(2\pi t/\rho_d\right)\right)\cdot\left[1 - H\left(\sin\left(2\pi\ (t+\delta_d)\right)/\rho_d\right)\right]. \tag{4}$$