Closed-loop Controller Based on Reference Signal Tracking for Absence Seizures

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Closed-loop controller based on reference signal tracking for absence seizures

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Abstract

Deep brain stimulation (DBS) targeting thalamus reticular nucleus (TRN) brain regions has been proven to play an irreplaceable role in the treatment of absence seizures. Compared with open-loop DBS, closed-loop DBS has been recognized by researchers for its advantages of significantly inhibiting seizures and having fewer side effects. However, due to the complexity of the nervous system, the mechanism of DBS control epilepsy is still unclear, which hinders the study of closed-loop DBS. In our study, based on the biophysical model jointly constituted by cortical, thalamic, and basal ganglia, we selected the 2-4 Hz spike and wave discharges (SWDs) of the cortical region as a biomarker for response to absence epilepsy, and the mean firing rate (MFR) of substantia nigra pars reticulata (SNr) was used as a reference signal for modulation of closed-loop DBS. Moreover, to obtain the linear relationship between the stimulus and the response, we adopted an algorithm that combines controlled auto-regressive (CAR) and recursive least squares (RLS), and we built a proportional integral (PI) controller to make the DBS stimulus parameters self-update to control the seizures. The numerical simulation results show that the closed-loop DBS controllers based on frequency modulation and amplitude modulation respectively not only successfully track the firing

rate (FR) of SNr, but also significantly destroy the SWDs of cerebral cortex and restore it to the other two normal discharge modes.

1 Introduction

Absence epilepsy has been widely studied for its unique pathogenesis¹⁻², including the main frequency of 2-4 Hz SWDs in electroencephalogram (EEG)³⁻⁴, sudden and temporary loss of consciousness⁵, and widespread seizures in the adolescent years⁶⁻⁷. Previous studies have suggested that the thalamus plays a crucial role in epileptic seizures and that abnormal feedback from the thalamus to the cerebral cortex is responsible for the appearance of SWDs⁸⁻⁹. Subsequently, electrophysiological records in the cerebral cortex and thalamus of epileptic patients also demonstrated the existence of the corticothalamic system¹⁰⁻¹¹, and the corresponding biophysical model was established¹²⁻¹³. The basal ganglia, as the information processing unit of the brain, directly or indirectly participates in the information transmission between the cortex and the thalamus¹⁴⁻¹⁵. Clinical studies have shown that damage to basal ganglia can lead to various brain disorders, including epilepsy¹⁶, cognitive impairment, and Parkinson's disease¹⁷⁻¹⁸. The basal ganglia are composed of subthalamic nucleus (STN), globus pallidus internal (GPi), globus pallidus external (GPe), and substantia nigra pars reticulata (SNr), of which the most important output nucleus is SNr neurons. Moreover, experimental studies on SNr in rodent models suggested that SNr plays an important role in the control of absence epilepsy¹⁹⁻²⁰. Therefore, given that underlying mechanism of SNr in the brain is not clear, further research on SNr is necessary.

Slow oscillations of 0.1-0.2 Hz in the human brain are traveling waves that can trigger the thalamic spindles and periodically sweep across the cerebral cortex²¹. Spindles, which are associated with slow oscillations, can be observed in the electroencephalogram (EEG) in deep sleep²².

Furthermore, experimental records showed that sleep spindles disappear when the transmission between TRN and specific relay nucleus (SRN) is disrupted²³⁻²⁴. Therefore, researchers believe that TRN can act as a pacemaker of the spindles, and that the slow oscillation of different brain regions can also be regulated by TRN²⁵⁻²⁶. In recent years, more and more biophysical models have been established to study TRN. Fan et al. achieved the interconversion between spindles and SWDs in the cerebral cortex by applying DBS stimulation to TRN²⁷. Wang et al. investigated the mechanism of external stimulation on TRN in the cortical thalamic model²⁸. These studies have stimulated our enthusiasm to study the underlying mechanism of DBS stimulation on TRN.

There are many ways to treat epilepsy and the traditional methods are drug therapy or surgical removal²⁹⁻³⁰. Although these methods have a certain control effect on the absence epilepsy, the risks of surgery and the side effects of drugs should not be ignored³¹⁻³². DBS stimulation may be an alternative treatment for epilepsy in some patients with drug immunity³³. DBS stimulation, which uses implanted electrodes to send electrical pulses to specific areas of the brain, has been shown to significantly reduce the onset of absence seizures³⁴⁻³⁵. However, when we build DBS stimulation, we need to take into account many constraints such as battery life, stimulation intensity, and dynamic changes of the system³⁶⁻³⁷. In recent years, closed-loop DBS stimulation has received more attention than traditional open-loop DBS stimulation³⁸. Closed-loop DBS is a control method that adaptively adjusts parameters and optimizes battery utilization³⁹. The design of the closed-loop DBS stimulus controller is mainly about the selection of biomarkers reflecting the absence epileptic state and the selection of reference signals adapting to the dynamic changes of the system⁴⁰⁻⁴¹. Specifically, when the epilepsy marker changes, which means the seizure, the reference signal triggers our preset value, and then the closed-loop controller automatically updates the DBS

parameters to control the seizure³⁴. From a dynamic point of view, the nervous system is multi-stable during epileptic seizures, and the closed-loop DBS controller serves to pull the cortical state back to the normal attraction basin⁴²⁻⁴³. Based on the above discussion, it is necessary to research deeply by combining absence epilepsy with closed-loop DBS controller.

The rest of the paper is organized as follows. In Section II, the absence seizures model was introduced, the relation of stimulus-response was established through CAR model and RLS method and the PI controller was designed according to the parameters obtained by Routh-Hurwitz stability criterion. In Section III, the results of numerical simulation were illustrated. In Section IV, the conclusion was given.

2 Model and measure

In this section, we selected the absence epilepsy model composed of cerebral cortex, thalamus, and basal ganglion as the carrier of DBS stimulation and the experimental platform for the generation of absence epilepsy data⁴⁴⁻⁴⁵. Then, considering the importance of SNr in basal ganglia and its high correlation with other neurological diseases, we selected the MFR of SNr as a reference signal, and identified the linear relationship between the DBS stimulus parameters and the FR of SNr. Finally, we constructed a closed-loop controller using a linear CAR model and Routh-Hurwitz stability criterion to control absence epilepsy.

2.1 Introduction of absence seizures model

The basal ganglia-cortical-thalamic network proposed by Chen et al. extends the basal ganglia based on the cortical-thalamic model⁴⁵⁻⁴⁶. Based on this model, we can successfully achieve the transformation of SWDs to spindle oscillations in the cerebral cortex. As shown in Fig. 1, the whole

network model can be divided into three categories according to color, namely cerebral cortex (orange), thalamus (blue) and basal ganglia (green), each of which can be divided into different sub-modules. For example, the cerebral cortex is made up of two orange rectangles, called inhibitory interneurons (II) and excitatory pyramidal neurons (EPN). The different submodules are connected by projections: excitatory projections mediated by glutamate (purple arrow solid line), inhibitory projections mediated by GABA_A (blue arrow solid line), and inhibitory projections mediated by GABA_B (blue arrow dot line).

Figure 1. Structural diagram of a computational model for absent epilepsy. Nine neuron groups are shown as follows, STN = subthalamic nucleus; GPe = globus pallidus external; SNr = substantia nigra pars reticulata; D₂ = striatal D₂ neurons; D₁ = striatal D₁ neurons; SRN = specific relay nuclei; TRN = thalamic reticular nucleus; II = inhibitory interneurons; EPN = excitatory pyramidal neurons. The excitatory projections are represented by purple arrow solid line. The blue lines represent inhibitory projections, where the solid and dot lines represent GABA_A-mediated and GABA_B-mediated, respectively.

The biophysical model of absence epilepsy is shown as follows⁴⁶:

$$X''(t) = \alpha\beta(C_1 Y_1(t) - Y_2(t)) - (\alpha + \beta)X'(t), \quad (1)$$

$$\phi_e''(t) = \gamma_e^2 [-\phi_e(t) + F(V_{EPN})] - 2\gamma_e \phi_e'(t), \quad (2)$$

$$F[V_i(r, t)] = \frac{Q_i^{max}}{1 + \exp[-\frac{\pi}{\sqrt{3}} \frac{(V_i(r, t) - \theta_i)}{\sigma}]}, \quad (3)$$

$$\text{where } X(t) = [V_{EPN}(t), V_{D_1}(t), V_{D_2}(t), V_{SNr}(t), V_{GPe}(t), V_{STN}(t), V_{TRN}(t), V_{SRN}(t)]^T,$$

$$Y_1(t) = \begin{bmatrix} \phi_e, F(V_{EPN}), F(V_{D_1}), F(V_{D_2}), F(V_{SNr}), F(V_{GPe}), \\ F(V_{STN}), F(V_{TRN}), F(V_{TRN}(t - \tau)), F(V_{SRN}) \end{bmatrix}^T, \quad (4)$$

$$Y_2(t) = [V_{EPN}(t), V_{D_1}(t), V_{D_2}(t), V_{SNr}(t), V_{GPe}(t), V_{STN}(t), V_{TRN}(t), V_{SRN}(t) - \phi_n]^T, \quad (5)$$

$$C_1 = \begin{bmatrix} v_{EPNEPN} & v_{EPNII} & 0 & 0 & 0 & 0 & 0 & (0,0) & v_{EPNSRN} \\ v_{D_1EPN} & 0 & v_{D_1D_1} & 0 & 0 & 0 & 0 & (0,0) & v_{D_1SRN} \\ v_{D_2EPN} & 0 & 0 & v_{D_2D_2} & 0 & 0 & 0 & (0,0) & v_{GPeSRN} \\ 0 & 0 & v_{SNrD_1} & 0 & 0 & v_{SNrGPe} & v_{SNrSTN} & (0,0) & 0 \\ 0 & 0 & 0 & v_{GPeD_2} & 0 & v_{GPeGPe} & v_{GPeSTN} & (0,0) & 0 \\ v_{STNEPN} & 0 & 0 & 0 & 0 & v_{STNGPe} & 0 & (0,0) & 0 \\ v_{TRNEPN} & 0 & 0 & 0 & v_{TRNSNr} & 0 & 0 & (0,0) & v_{TRNSRN} \\ v_{SRNEPN} & 0 & 0 & 0 & v_{SRNSNr} & 0 & 0 & (v_{SRN,TRN}^A, v_{SRN,TRN}^B) & 0 \end{bmatrix}, \quad (6)$$

where α is synaptodendritic decay time constant, and β is synaptodendritic rise time constant.

γ_e denotes cortical damping rate, and $i \in [EPN, II, TRN, SRN, D_1, D_2, SNr, GPe, STN]$ represents one of nine groups of neurons. r indicates the spatial position, σ represents the threshold variability of firing rate, θ_i represents the mean firing threshold, and Q_i^{max} indicates the maximum firing rate. ϕ_e denotes cortical excitatory axonal field. τ and ϕ_n are represent the GABA_B delay and the constant nonspecific subthalamic input onto SRN. $v_{i,j}$ indicates coupling strength from i to j , $i, j \in [EPN, II, TRN, SRN, D_1, D_2, SNr, GPe, STN]$. The other parameters are shown in Table 1.

Table1 Parameter interpretation

Parameter	Interpretation	Standard value
v_{TRNSNr}	Coupling strength SNr-TRN	0.035 mV s
v_{SRNSNr}	Coupling strength SNr-SRN	0.035 mV s
v_{STNEPN}	Coupling strength EPN-STN	0.1 mV s
v_{SRNEPN}	Coupling strength EPN-SRN	2.2 mV s
v_{EPNSRN}	Coupling strength SRN-EPN	1.8 mV s
v_{STNGPe}	Coupling strength GPe-STN	0.04 mV s
v_{GPeSTN}	Coupling strength STN-GPe	0.45 mV s
v_{GPeGPe}	Coupling strength GPe-GPe	0.075 mV s
v_{GPeD_2}	Coupling strength D ₂ -GPe	0.3 mV s
v_{SNrGPe}	Coupling strength GPe-SNr	0.03 mV s
v_{SNrD_1}	Coupling strength D ₁ -SNr	0.1 mV s
v_{D_2SRN}	Coupling strength D ₂ -SRN	0.05 mV s
$v_{D_2D_2}$	Coupling strength D ₂ -D ₂	0.3 mV s
v_{D_2EPN}	Coupling strength EPN-D ₂	0.7 mV s
v_{D_1SRN}	Coupling strength SRN-D ₁	0.1 mV s
$v_{D_1D_1}$	Coupling strength D ₁ -D ₁	0.2 mV s
v_{D_1EPN}	Coupling strength EPN-D ₁	1 mV s
v_{TRNSRN}	Coupling strength SRN-TRN	0.5 mV s
v_{TRNEPN}	Coupling strength EPN-TRN	0.05 mV s
v_{EPNII}	Coupling strength II-EPN	1.8 mV s
v_{EPNEPN}	Coupling strength EPN-EPN	1 mV s

2.2 Establishment of stimulus-response relation

The design diagram of the closed-loop DBS controller is illustrated in Fig. 2A. We selected the firing rate of SNr as the reference signal $r(m)$. Then, we input the difference between $r(m)$ and expected MFR $r_{rs}(m)$ into the PI controller to obtain the DBS stimulus parameter $s(m)$. Finally, we obtained DBS stimulation for the control of absence epilepsy. Since absence epilepsy is highly nonlinear, direct use of PI controller is not appropriate. Fig. 2B shows the linear system of a closed-loop DBS controller, which is used to describe the linear relationship between DBS stimulus parameter and the MFR of SNr. The CAR model is calculated as follows⁴⁷:

$$\left(1 + a_1 z^{-1} + a_2 z^{-2} + \dots + a_{n_a} z^{-n_a}\right) r(m) = \left(b_0 + b_1 z^{-1} + b_2 z^{-2} + \dots + b_{n_b} z^{-n_b}\right) s(m) + \varepsilon(m), \quad (7)$$

where z , $r(m)$, and $s(m)$ are the lag operator, output signal, and input signal, respectively. n_a , $\varepsilon(m)$, and n_b are the order of output, error, and the order of input, respectively.

Figure 2. (A) The closed loop DBS controller. First, The MFR of SNr is calculated from the absence epilepsy model and used as feedback signals $r(m)$. Then, the difference between the expected MFR $r_{rs}(m)$ and $r(m)$ is used as input to the PI controller to calculate the frequency or amplitude of DBS stimulate $s(m)$. Finally, the DBS stimulus current input to the absence epilepsy model is constructed. (B) Linear system of closed-loop DBS controller.

As we know, the CAR model describes a linear relationship between stimulus and responses and relies heavily on input and output data. Therefore, to extract more information from the relationship between DBS parameters and MFR of SNr, we let DBS parameters change randomly

in a certain range. For example, Fig. 3A and Fig. 3B respectively show the discharge of DBS current during 4-6 s, and we change the frequency and amplitude of current respectively every 0.2 seconds. In addition, we also consider the influence of time window bin on the control accuracy of closed-loop DBS. As shown in Fig. 3C, we plotted the box diagram of MFR of SNr as a function of the time window bin. The simulation results show that when the time window bin is 0.2 s, the MFR of SNr measured each time is scattered, which means that the time window bin of 0.2 s is sensitive to the changes of the system.

Figure 3. (A) The DBS current with different frequency. The duration of each current is 0.2 s, and the current frequency is between 20 Hz and 100 Hz. (B) The DBS current with different amplitude. The duration of each current is 0.2 s, and the current amplitude is between 1 mA and 4 mA. (C) The box figure of MFR of SNr plotted as a function of time window bin (60 trials).

The RLS method is used to estimate CAR model parameters a_1, a_2, K, a_{n_a} and b_1, b_2, K, b_{n_b} .

The least square form of the CAR model is shown as follows^[47]:

$$\begin{aligned} r(m) = & -a_1 r(m-1) - a_2 r(m-2) - \dots - a_{n_a} r(m-n_a) \\ & + b_0 s(m) + b_1 s(m-1) + b_2 s(m-2) + \dots + b_{n_b} s(m-n_b) + \varepsilon(m), \\ = & \varphi^T(m) \theta + \varepsilon(m) \end{aligned} \quad (8)$$

where $\varphi(m) = [-r(m-1), -r(m-2), \dots, -r(m-n_a), s(m), s(m-1), \dots, s(m-n_b)]^T$ is composed of past input and output data and current input data. $\theta = [a_1, a_2, \dots, a_{n_a}, b_0, b_1, \dots, b_{n_b}]^T$ can be estimated by the following equation:

$$\begin{cases} \hat{\theta}(m) = \hat{\theta}(m-1) + K(m) \left[y(m) - \varphi^T(m) \hat{\theta}(m-1) \right] \\ K(m) = \frac{P(m-1) \varphi(m)}{1 + \varphi^T(m) P(m-1) \varphi(m)} \\ P(m) = [I - K(m) \varphi^T(m)] P(m-1) \end{cases} \quad (9)$$

Fig. 4 shows the performance of CAR model tracking dynamically changing FR of SNr when $n_a = 2$ and $n_b = 2$. We periodically change the DBS parameters from 1s and start tracking the FR of SNr using the CAR model. When the input of CAR model is the frequency and amplitude of DBS current respectively, the corresponding performance of CAR model in model training is illustrated in Fig. 4A1 and Fig. 4B1 respectively. Fig. 4A2 and Fig. 4B2 show the parameter estimation process of CAR model and the fitting of test data is shown in Fig. 4A3 and Fig. 4B3 respectively. As we can see in Fig. 4, the CAR model performs well in training and testing, even though the order of the CAR model is relatively low. We should be more interested in the stability than the fitting accuracy of CAR model. Therefore, the CAR model in this paper is expressed as follows:

$$r(m) = -a_1 r(m-1) - a_2 r(m-2) + b_0 s(m) + b_1 s(m-1) + b_2 s(m-2). \quad (10)$$

Figure 4. The performance of CAR models in model training (A1), parameter estimation (A2), and model testing

(A3) when input of CAR model is DBS current frequency. The performance of CAR models in model training (B1), parameter estimation (B2), and model testing (B3) when input of CAR model is DBS current amplitude.

2.3 Design of closed-loop controller

The system replacing the absence epilepsy model with CAR model is shown in Fig. 2B and the structure of PI controller is as follows:

$$s(m) = s(m-1) + k_p [e(m) - e(m-1)] + k_i e(m), \quad (11)$$

where k_p and k_i are computed by the Routh-Hurwitz stability criterion, which is introduced by the following equations.

The forward transfer function of the system in Fig. 2B is as follows:

$$\begin{aligned} G(z) &= \frac{R(z)}{E(z)} = \frac{R(z)}{S(z)} \cdot \frac{S(z)}{E(z)} = \frac{b_0 z^2 + b_1 z + b_2}{z^2 + a_1 z + a_2} \cdot \frac{(k_p + k_i)z - k_p}{z - 1} \\ &= \frac{b_0(k_p + k_i)z^3 + [b_1(k_p + k_i) - b_0 k_p]z^2 + [b_2(k_p + k_i) - b_1 k_p]z - b_2 k_p}{z^3 + (a_1 - 1)z^2 + (a_2 - a_1)z - a_2}. \end{aligned} \quad (12)$$

The closed-loop transfer function is

$$T(z) = \frac{G(z)}{1 + G(z)}. \quad (13)$$

The characteristic equation of this system is

$$\begin{aligned} D(z) = 1 + G(z) &= [1 + b_0(k_p + k_i)]z^3 + [(a_1 - 1) + b_1(k_p + k_i) - b_0 k_p]z^2 \\ &+ [(a_2 - a_1) + b_2(k_p + k_i) - b_1 k_p]z - b_2 k_p - a_2 = 0, \end{aligned} \quad (14)$$

substituted z with w , where $z = \frac{w+1}{w-1}$, we get

$$D(w) = m_3 \left(\frac{w+1}{w-1} \right)^3 + m_2 \left(\frac{w+1}{w-1} \right)^2 + m_1 \left(\frac{w+1}{w-1} \right) + m_0 = 0, \quad (15)$$

where:

$$\begin{cases} m_3 = 1 + b_0(k_p + k_i), \\ m_2 = (a_1 - 1) + b_1(k_p + k_i) - b_0 k_p, \\ m_1 = (a_2 - a_1) + b_2(k_p + k_i) - b_1 k_p, \\ m_0 = -b_2 k_p - a_2. \end{cases} \quad (16)$$

Then, multiplying both sides of Equation by $(w-1)^3$, we get

$$(w-1)^3 D(w) = n_3 w^3 + n_2 w^2 + n_1 w + n_0 = 0, \quad (17)$$

where:

$$\begin{cases} n_3 = m_0 + m_1 + m_2 + m_3, \\ n_2 = -3m_0 - m_1 + m_2 + 3m_3, \\ n_1 = 3m_0 - m_1 - m_2 + 3m_3, \\ n_0 = -m_0 + m_1 - m_2 + m_3. \end{cases} \quad (18)$$

Based on the Routh-Hurwitz stability criterion, the stability of this system is equivalent to

$n_i(k_p, k_i) > 0 (i = 0, 1, 2, 3)$, and the corresponding subset of feasible solutions is k_p and $k_i > 0$.

To sum up, we designed two types of closed-loop DBS controllers, one of which is based on frequency modulation (BoFM). We limit the frequency to 20-100 Hz, and the BoFM controller is shown as follows:

$$s(m) = \begin{cases} 20 & s(m) < 20 \\ s(m-1) + 5 * [e(m) - e(m-1)] + 0.3125 * e(m) & 20 \leq s(m) \leq 100. \\ 100 & s(m) > 100 \end{cases} \quad (19)$$

The other is a closed-loop DBS controller based on amplitude modulation (BoAM). We limit the amplitude to 1-4 mA, and the BoAM controller is shown as follows:

$$s(m) = \begin{cases} 1 & s(m) < 1 \\ s(m-1) + 0.3 * [e(m) - e(m-1)] + 0.01875 * e(m) & 1 \leq s(m) \leq 4. \\ 4 & s(m) > 4 \end{cases} \quad (20)$$

3 Results

3.1 Dynamics of SNr firing rate induced by open loop DBS

Figure 5. State (left) and dominant frequency (right) diagrams of the cerebral cortex in absence epilepsy model.

The initial state and dominant frequency are shown in (A) and (B) respectively, while the state and dominant frequency with DBS stimulation is shown in (C) and (D) respectively. Different color regions in (A) represent different discharge states and are marked by different symbols: saturation state (green filled square), SWDs oscillation state (red filled circle), simple oscillation state (yellow filled diamond), low firing state (blue filled pentagram).

Our model successfully demonstrated the dynamic transition from SWDs firing to normal firing state by changing the inhibitory coupling strength $-v_{SRNTRN}$ and GABA_B delay τ . As shown in Fig. 5A, when the time delay is fixed at $\tau = 49$ ms, the firing state of the cerebral cortex first change from saturation state to SWDs state, and then from SWDs state to normal simple oscillation state with the increase of coupling strength $-v_{SRNTRN}$. Finally, the firing state of the cerebral cortex changes to low firing state due to the high inhibition of SRN by TRN. Correspondingly, transition

in the main frequency of the cerebral cortex is shown in Fig. 5B. Moreover, when we add appropriate DBS stimulation to the absence epilepsy model, all firing regions of the cerebral cortex are inhibited. As shown in Fig. 5C, under the effect of DBS, the four firing states of the cerebral cortex are inhibited to the low firing state in the $(\tau, -v_{SRNTRN})$ panel. Correspondingly, the main frequency of cortical electrical activity also decreases to 0 Hz in Fig. 5D.

Figure 6. The four main kinds of firing activities (right) of the cerebral cortex and the corresponding firing rate (left) of the SNr. The firing activities of (A2), (B2), (C2) and (D2) correspond to saturation state, SWDs state, simple oscillation state and low firing state respectively. and (A1), (B1), (C1) and (D1) show the firing rate of SNr in these four states.

As we can see, Fig. 6 clearly shows the four different firing states of the cerebral cortex and the corresponding firing rate of the SNr. Compared with the more stable firing rates such as

saturation state and low firing state, the mean firing rates of SWDs oscillating state and simple oscillating state are constantly changing, which brings us difficulties in designing the closed-loop controller with MFR as reference signal in the next section. For simplicity, we calculated the mean firing rate of four firing activity and find that the mean firing rate of SNr is arranged from high to low in the order of saturation state, SWDs oscillation state, simple oscillation state, and low firing state. Therefore, we chose the average value of firing rates of simple oscillation and low oscillation respectively as the expected firing rates of the closed-loop DBS controller, which are $r_{rs} = 27.7884$ Hz and $r_{rs} = 28.4144$ Hz, respectively.

Figure 7. The firing rate of SNr when the frequency of DBS stimulation is 20 Hz (A1), 40 Hz (B1), and 60 Hz (C1).

The firing activity of cerebral cortex when the frequency of DBS stimulation is 20 Hz (A2), 40 Hz (B2), and 60 Hz (C2).

It has been known from Fig. 5C that DBS stimulation current can inhibit the firing activity of

cerebral cortex, therefore we also want to research whether DBS stimulation current can also control the firing rate of SNr. For this purpose, we investigated the effects of frequency and amplitude of DBS stimulation on MFR of SNr. As shown in Fig. 7, when the frequency of DBS stimulation increases from 20 Hz to 40 Hz, the cortical firing activity changes from SWDs oscillation state to simple oscillation state, and the amplitude of the firing rate oscillation of SNr decreases. At the same time, we found a similar situation when the amplitude of DBS stimulus increased. As shown in Fig. 8A1 and Fig. 8B1, as the amplitude of DBS stimulation increases from 1 mA to 3 mA, the amplitude of the firing rate of SNr decreases significantly. Correspondingly, the transition of cortical action potential is shown in Fig. 8A2 and Fig. 8B2. In addition, an interesting phenomenon is that we detected simple oscillations of 60 Hz with very low amplitude in the low firing state suppressed by DBS stimulation in Fig. 7C1, Fig. 7C2, Fig. 8C1, and Fig. 8C2. This may be due to the introduction of artificial high-frequency electrical stimulation in the absence epilepsy model.

Figure 8. The firing rate of SNr when the amplitude of DBS stimulation is 1 mA (A1), 3 mA (B1), and 4 Hz (C1).

The firing activity of cerebral cortex when the amplitude of DBS stimulation is 1 mA (A2), 3 mA (B2), and 4 mA (C2).

To test whether the above results can be generalized to a larger parameter range, we extended the frequency and amplitude ranges to $[20, 100]$ Hz and $[1, 4]$ mA respectively. As shown in Fig. 9A1, the mean firing rate of SNr increases to a peak at Freq2 and then decreases slowly with increasing frequency. Combined with Fig. 9A1 and Fig. 9A2, it is found that the mean firing rate of SNr when the firing activity is in simple oscillation state is higher than that when the firing activity is in SWDs oscillation state. The same situation can be observed in Fig. 9B1 and Fig. 9B2. Therefore, it can be concluded that when DBS stimulation intensity increases, including the frequency or amplitude of DBS stimulation, the mean firing rate of SNR increases to a peak at the transition point from simple oscillation state to low discharge state, and then slowly decreases.

Figure 9. The mean firing rate (A1) of SNr and the firing state (A2) of cerebral cortex with the increase of DBS stimulation frequency. The mean firing rate (B1) of SNr and the firing state (B2) of cerebral cortex with the increase

of DBS stimulation amplitude. The states 1,0, and 2 represent SWDs oscillation state, simple oscillation state, and low firing state respectively.

3.2 Efficacy of BoFM closed-loop control strategy

After the analysis in the previous section, we known that the increase of DBS stimulation intensity will decrease the amplitude of SNr firing rate, which constitutes the theoretical basis for our design of closed-loop DBS controller. In this section, we will focus on the control effect of absence epilepsy under the BoFM strategy. As shown in Fig. 10, we designed a closed-loop controller based on BoFM control strategy for the purpose of controlling the state of cortical discharge activity. Meanwhile, considering the influence of expected firing rate on DBS control results, we selected the mean firing rate of SNr under the condition of cortical low firing state as the expected firing rate, and we applied closed-loop DBS control at 1 s. As shown in Fig. 10B, the cortical firing activity realized the transition from SWDs oscillation state to simple oscillation state at $T1=1.20825$ s, and from simple oscillation state to low firing state at $T2=1.66255$ s. The variations of SNr firing rate and closed-loop DBS current are shown in Fig. 10A and Fig. 10C, respectively.

Figure 10. Variations of firing rate of SNr (A), firing activity of cerebral cortex (B), and the current of closed-loop DBS (C) during the closed-loop DBS control when the expected firing rate is 27.7884 Hz.

Moreover, we also selected the mean firing rate of SNr under the condition of cortical simple oscillation state as the expected firing rate to study the control effects of cortical activity. As shown in Fig. 11B and Fig. 11A, the cortical firing activity realized the transition from SWDs oscillation state to simple oscillation state at $T_1=1.1772$ s, and the firing rate of SNr was inhibited at the same time. Compared with Fig. 10B, the cortical firing activity in Fig. 11B did not switch to a low firing state but presented a simple oscillation state. The reason may be that we increase the expected firing rate of the closed-loop controller. Compared with Fig. 11C and Fig. 10C, The DBS current in Fig. 11C is sparser than that in Fig. 10C, which means that the power consumption of the closed-loop DBS current is inversely proportional to the value of the expected firing rate. In addition, an interesting finding is that the response time ($T_1=1.1772$ s) of simple oscillation in Fig. 11B is smaller than the response time ($T_1=1.20825$ s) of simple oscillation in Fig. 10B.

Figure 11. Variations of firing rate of SNr (A), firing activity of cerebral cortex (B), and the current of closed-loop DBS (C) during the closed-loop DBS control when the expected firing rate is 28.4144 Hz.

3.3 Efficacy of BoAM closed-loop control strategy

In the previous section, we successfully implemented the closed-loop control under the BoFM strategy, and we found that under the BoFM strategy, the control effect induced by different expected rate of fire is different. Considering the influence of DBS amplitude on SNr firing rate, we will focus on the control effect of absence epilepsy under the BoAM strategy in this section.

Figure 12. Variations of firing rate of SNr (A), firing activity of cerebral cortex (B), and the current of closed-loop DBS (C) during the closed-loop DBS control when the expected firing rate is 27.7884 Hz.

Like Fig. 10B, when the expected firing rate is 27.7884 Hz, we realize the transition from SWDs oscillation state to low firing state under the BoAM strategy. As shown in Fig. 12B, the simple oscillation state appeared at time $T1=1.19885$ s, and the low firing state appeared at time $T2=4.8032$ s. Meanwhile, the discharge rate of SNr also underwent two conversions, as shown in Fig. 12A. However, the response time T2 of low discharge state under BoAM strategy is much larger than that under BoFM strategy. Moreover, the amplitude of the closed-loop control BDS current under the BoAM strategy rises from 1mA to nearly 4mA and gradually remains stable in Fig. 12C.

We also analyze the control of cortical firing activity when the expected firing rate is 28.4144 Hz, which is the mean firing rate of SNr when the cortex is in simple oscillation state. As shown in Fig. 13B and Fig. 13A, when the expected firing rate is 28.4144 Hz, the cortical firing activity changes from SWDs oscillation state to simple oscillation state at time $T_1=1.19885$ s, and the firing rate of SNr is inhibited at the same time. The response times of simple oscillations are similar in Fig. 12B and Fig. 13B, which is different from we concluded in the previous section. In addition, we find that the amplitude of closed-loop DBS current in Fig. 13C is chaotic, which is different from Fig. 12C. However, like the conclusion in the previous section, the DBS current in Fig. 13C is sparser than that in Fig. 12C, which means that the DBS current in Fig. 13C consumes less power than that in Fig. 12C.

Figure 13. Variations of firing rate of SNr (A), firing activity of cerebral cortex (B), and the current of closed-loop DBS (C) during the closed-loop DBS control when the expected firing rate is 28.4144 Hz.

4 Conclusion

In this paper, we successfully achieved the conversion of SWDs oscillating state to other firing

state in the cerebral cortex using a closed-loop DBS controller based on a model of absence epilepsy involving cerebral cortex, thalamus, and basal ganglia. The mean firing rate of SNr is selected as a reference signal, and the cortical firing activity is selected as a biomarker reflecting the epileptic state. The CAR model and the Routh-Hurwitz stability criterion are introduced to determine the coefficients of the PI controller. Moreover, we chose the average value of firing rates of simple oscillation and low oscillation respectively as the expected firing rates of the closed-loop DBS controller, which are $r_{rs} = 27.7884$ Hz and $r_{rs} = 28.4144$ Hz, respectively.

According to the numerical results, the intensity of the open-loop DBS current, including the amplitude or frequency of the DBS current, will reduce the amplitude of the SNr firing rate. With the increase of current intensity, the mean firing rate of SNr increase firstly and then decrease, and the firing activity of cerebral cortex change from SWDs oscillation state to simple oscillation state and finally kick to low firing state. Therefore, we designed closed-loop controllers based on BoFM strategy and BoAM strategy, respectively. The closed-loop controllers with two control strategies can achieve the desired control effect under different expected firing rates. By adjusting the expected firing rate from 27.7884 Hz to 28.4144 Hz, the final firing state under the closed-loop control is transformed from low firing state to simple oscillation state. Meanwhile, the power consumption of closed-loop DBS current decreases with the increase of expected firing rate. In addition, an interesting phenomenon is that the response time of low firing state under BoAM strategy is much larger than that under BoFM strategy when the expected firing rate is 27.7884 Hz, we hope that the research can provide reference and help for the treatment and prevention of epilepsy patients.

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Author Contributions

H. Z. and Y. Chai conceived the idea; Y. Chen collected the data; H. Z. performed the calculations and conducted the numerical analyses; Y. X. prepared figures and illustrations; Y. Chai supervised the overall study; H. Z., Y. Chen, Y. X., and Y. Chai jointly wrote the manuscript.

Data Availability

The data used to support the findings of this study are included within the article.

Competing financial interests

The authors declare no competing financial interests.