



Original Research

Ultra-Local Model Control of Parkinson's Patients Based on Machine Learning

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ABSTRACT

Parkinson's disease (PD) is one of the most privileged neurodegenerative, which has had an upward trend in recent decades. The most important complications of PD are tremor, rigidity, and slow movement. A surgery method namely Deep brain stimulation (DBS) plays a vital role in the treatment of advanced Parkinson's patients. In the past decades, stimulating one nucleus of basal ganglia including Globus pallidus internal (GPi) or Subthalamic nucleus (STN) without any feedback (open-loop manner) has had a common strategy, which leads to several different side-effects like muscle tonic and forgetfulness. In the present paper, two nuclei of BG are stimulated in a closed-loop structure (feedback signal) to reduce the entrance electric field intensity to the brain, and in addition to shrinking hand tremor in Parkinson's patients. For this purpose, an ultra-local model (ULM) control based on a deep deterministic policy gradient (DDPG) is designed to stimulate the STN and a conventional feedback controller is considered for stimulating GPi. In this method, the coefficients of the ULM are adaptively assumed as the control objective parameters, which are designed by the critic and actor neural networks (NNs) of DDPG. To demonstrate the effectiveness and suitability of the suggested approach is compared to state-of-the-art strategies such as ULM, SMC, and PI controllers.

Keywords: Parkinson's Disease, Deep Brain Stimulation, Basal Ganglia, Hand Tremor, Ultra-local Model

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INTRODUCTION

Over the past few decades, Parkinson's disease (PD) is constantly rising, and millions of people suffer from neurological disorders (1, 2). PD is due to decreasing and destroying dopamine in the substantia nigra (SN) that occurs in the basal ganglia (BG). The most important Medications of PD are hand tremor, slow movements (bradykinesia), and dystonia. BG consists of five nuclei with two distinct functions (excitatory and inhibitory) and two main internal loops (direct and indirect) (3, 4). Since sensors play a vital role in treat PD, several kinds of research have been developed for measuring and assessing PD's signal. A vast number of methodologies such as gyroscope or accelerometers (5, 6), electromyography (EMG) (7), and radar technology (8) have been adopted to detect and assess the actions of the patients during disorder prosses.

Up to now, several different methods have been introduced for treating PD, which drug therapy and neurological surgeries have known as the main methods to reduce the symptoms of PD. Drug therapy like levodopa used for early stages and neurological surgeries is used for patients with severe symptoms. Deep Brain Stimulation (DBS) has known as an effective therapy to reduce and control the complications of PD (9). In this method, DBS sends electrical signals to the nuclei of BG such as globus pallidus internal (GPi), subthalamic nucleus (STN), and ventralis intermediate (VIM) (10) through electrodes that implemented in the brain (11, 12). Stimulating an area like GPi or STN in the form of open-loop and without any feedback has been common in the past decades. Studies have shown that high field intensity due to the stimulation single area of BG leads to several different side-effects such as tonic muscles and speech disorder (13). Recently, researchers have introduced closed-loop intelligence strategies to tackle side-effects and also to shrink hand tremor in advanced Parkinson's patients. To this end, diverse controllers like adaptive controller (4), feedback linearization controller (14), the backstepping controller (15), adaptive SMC (16), and single input interval type-2 fuzzy logic (SIT2-FL) (17) have been developed to stimulate GPi and STN at the same time.

Designing a controller procedure for nonlinear systems can be divided into two types: *i*) model-based controller *ii*) model-free controller. For having acceptable performance in a model-based manner, the exact dynamic model of a specific system should be identified in an offline manner. Because of the uncertainties and unknown disturbance of environmental designing controller in the nonlinear dynamic systems faces many difficulties. Recently, owing to the simplicity and acceptable success in nonlinear systems, the ultra-local model (ULM) has received increasing attention among the various fields and approaches. In the ULM structure, a controller namely proportional integrator (PI) is considered, and besides an extant state observer (ESO) is embedded to reject disturbances and uncertainties (18, 19). Since the performance of the controller is linked to the parameters, meta-heuristic algorithms like genetic and sine-cosine play a crucial role in the quality of the controller. Despite the extensive applications and common in the huge number of fields, the aforementioned algorithms suffer from disadvantages such as weak learning and compatibility issues.

For this purpose, an intelligent algorithm called reinforcement learning (RL) has been introduced that has attracted the attention of the researcher (20-22). In this type unlike the other methods of machine learning such as supervised and unsupervised learning that act based on labeled and unlabeled data, respectively, learn based on interaction an agent and environment and it finds the best position with high reward. Moreover, RL has known as an effective method for addressing the limitation of real-time optimization strategies and acceptable performance in complicated systems by merging deep neural networks (NNs) (23). Recently, two advanced structures called deep Q-network (DQN) and deep deterministic policy gradient (DDPG) are introduced to act in the discrete and continuous action spaces, respectively. For this purpose, DQN by using a deep neural network (DNN) learns the best way to maximize the reward of the structure. But this method in the continuous action spaces has a wide range of challenges (24). While DDPG has the potential to work in continuous spaces and also has the potential to produce continuous control signals (25, 26).

The main contribution of the present paper is as follows:

- i*) Two distinct controllers called ultra-local model (ULM) and conventional feedback controller are employed to stimulate two separate areas of BG (STN & GPi), respectively, for decreasing the field intensity and reducing hand tremor.

- ii) To increase the quality and effectiveness of the controller, the coefficients of the controller should be tuned precisely. Because of this, the parameters of the controller are tuned by the learning ability of the DDPG.
- iii) To indicate the suitability of the suggested structure, the suggested strategy is examined under noise and robustness tests.

DYNAMIC FORMULATION OF BG

The overall structure of the dorsal part of BG is illustrated in Fig. 1, which includes five main nuclei (GPi, globus pallidus external (GPe), STN, Striatum, and substantia nigra (SN)) and different neurotransmitter namely gamma-aminobutyric acid (GABA) with inhibitory function, glutamate (with excitatory function), and dopamine (with multiplex function (excitatory/inhibitory) (27). As depicted in Fig. 1, the function of the neurotransmitters follows: i) by increasing neurotransmitter GABA is transmitted from the striatum to the GPe and also it is transmitted from the striatum to SN with decrease neurotransmitter ii) with the increase of neurotransmitter manner glutamate is transmitted from STN to the globus pallidus iii) by decreasing neurotransmitter Dopamine is transmitted from SNc to the striatum (9).

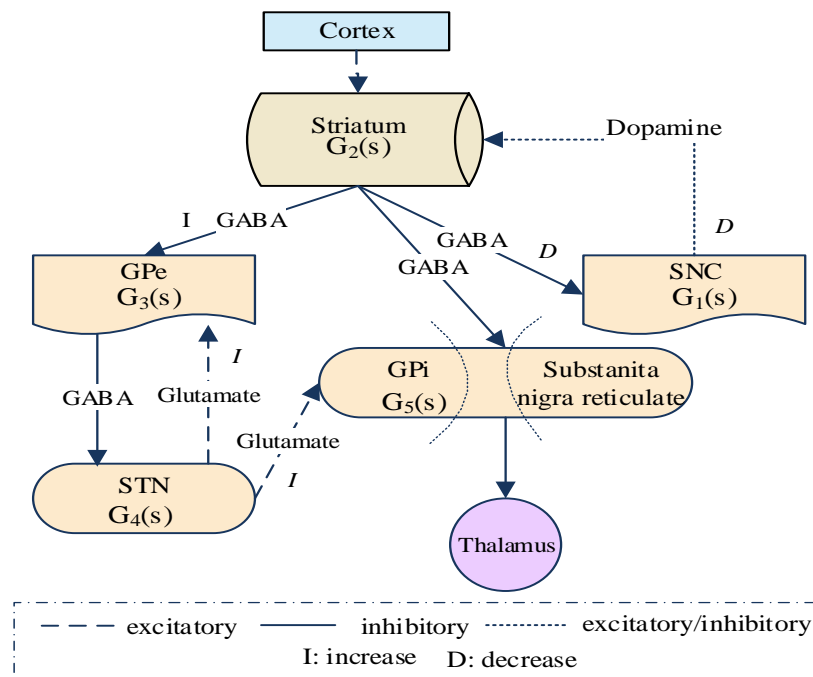


Fig. 1. The overall structure of the BG

In Fig. 2, the striatum and the STN are the input of BG, while the output of BG consists of the GPi and the SNr. In the input layer, the striatum and the STN receive the excitatory signals from all layers of the cortex and the motor areas of the frontal lobe, respectively. The output layer sends inhibitory signals to the motor areas in the brainstem and Thalamus. Excitatory and inhibitory signals traveled from the STN and the striatum to the GPe, whereas the GPe sends inhibitory signals to the STN, GPi, and SNr. SNc plays a role as a fundamental part of the concentration of the dopamine-containing neurons.

In (9), the mathematical model of the system is exploited according to the clinical data and neurophysiological model of BG, which considered each nucleus as a separate transfer function and addition change the rate of neurotransmitters are assumed as gain between the transfer functions. The overall structure of the dynamic system for each nucleus and neurotransmitters is furnished in Table 1. Moreover, the mathematical system of BG follows:

$$\left\{ \begin{array}{l} G_1(s): SNco(t) = \mathcal{L}\{sign(A(t))\} \\ A(S) = \frac{-10}{s+40} gSO_2(s) \\ G_2(s): SO_1(S) = \frac{1}{s+30} SNco(s) \\ SO_2(S) = \frac{10}{s(s+30)} SNco(s) \\ G_3(s): GPO(S) = \frac{10}{s+10} \left(-\frac{k}{g} SO_1(S) + \frac{5}{g} STNo_1(S) \right) \\ G_4(s): STNo_1(S) = g \times \frac{-0.1}{s+40} GPO(s) \\ STNo_2(S) = g \times \frac{-1}{s+40} GPO(s) \\ G_5(s): OUT(S) = \frac{200}{s+10} \left(\frac{1}{g} STNo_2(S) - gSO_2(s) \right) \end{array} \right. \quad (1)$$

According to the mathematical model, the output of the *SNc* with excitatory/inhibitory function is depicted by *SNco*. Additionally, the outputs of the striatum with inhibitory role illustrated by *SO₁* and *SO₂*. *GPO* is considered as the output of *GPI* with inhibitory function. The outputs of the *STN* with excitatory function are described by *STNo₁* and *STNo₂*. Finally, the output of *GPI* with inhibitory function is considered as an output of the system (9).

Transfer Function	Nucleus
G_1	<i>SNc</i>
G_2	<i>Striatum</i>
G_3	<i>GPe</i>
G_4	<i>STN</i>
G_5	<i>GPI</i>
$0.1 < k < 1$	GABA neurotransmitter
$1 < g < 10$	Decrease neurotransmitter
$1/g$	Increase neurotransmitter

Table 1: Descriptions of various components of the BG

As shown in Table I, g and k represent the different levels of the tremors in the PD patients, which $k=1$ and $g=10$ expressed the disease condition and the health condition is described by $k=0.1$ and $g=1$. The state-space system through inverse Laplace has introduced in (4, 15), which *SO₁* and *SO₂* are depicted by x_1 and x_2 , respectively. x_3 is the *STNo₁*, and *GPO* and *SNco* are represented by x_4 and x_6 , respectively. In the end, the output of the *GPI* (tremor) illustrates by x_5 . The overall structure of the BG based on state-space equations with two distinct controllers (ULM based on DDPG is employed to the *STN* and *GPI* was controlled by conventional feedback controller) is illustrated in Fig. 2. The state-space equations are formulated as:

$$\begin{cases} \dot{x}_1 = -30x_1 + \text{sign}(x_6) \\ \dot{x}_2 = 10kx_1 \\ \dot{x}_3 = -40x_3 - 0.1x_4 \\ \dot{x}_4 = -10k^2x_1 + 50kx_3 - 10x_4 \\ \dot{x}_5 = -200g + \left(\frac{200}{g}\right)x_3 - 10x_5 \\ \dot{x}_6 = -10gx_2 - 40x_6 \end{cases} \quad (2)$$

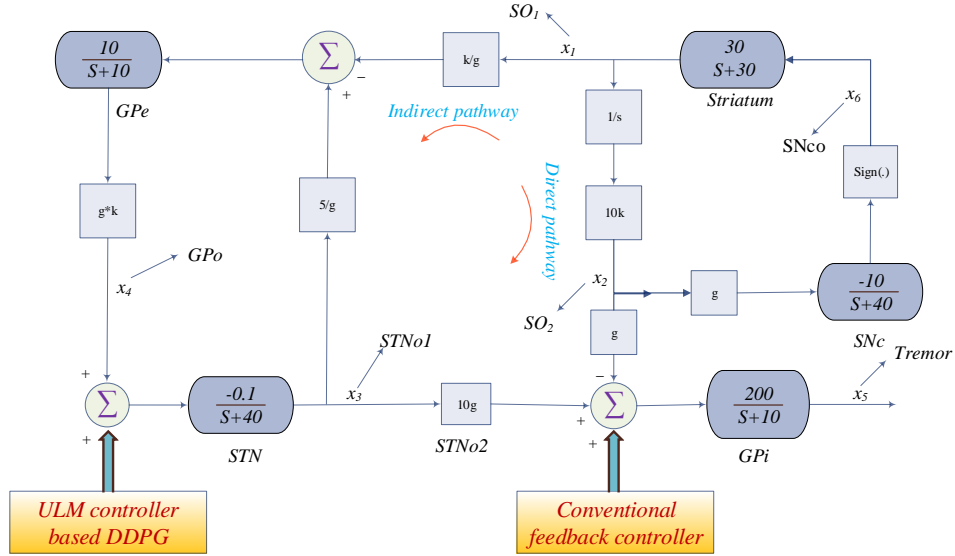


Fig. 2. Dynamic model of the BG with two distinct controllers

METHODOLOGY

In the present paper, a closed-loop strategy is established to reduce hand tremor and decreases the side-effects due to the high electric field intensity (9, 15). For this perspective, two spots of the BG (STN & GPi) are simultaneously stimulated by two distinct controllers including ULM based on DDPG and conventional feedback controller with the aim of reducing the applied electric field intensity to the brain and consequently removing the side-effects and decreasing the hand tremor. Moreover, feedback is considered to tune the parameters of the controller based on the level of the hand tremor off PD patients.

A. Fundamental of the ULM controller

The nonlinear dynamic model of ULM with a single input/output is as follows:

$$y^n = F + \bar{\alpha}.u \quad (3)$$

where n denotes the derivative order of the output y . u and $\bar{\alpha}$ represent the control signal and the input gain, respectively. Finally, F describes dynamic uncertainties. It should be noted that if F and $\bar{\alpha}$ being clear, the control signal of the intelligent proportional integrator derivative (iPID) can be formulated as:

$$u = \frac{1}{\bar{\alpha}}(-\hat{F} + \dot{y}^* + k_p(e) + k_i \int (e)dt + k_d \frac{de}{dt}) \quad (4)$$

Where \dot{y} denotes the predesignate reference and e represents the error of area control. \hat{F} describes the estimation of F . The proportional, integrator, and derivative gains represented by k_p , k_i , and k_d , respectively, in which the desired quality of the controller is linked to the proper tuning of these. In the purposed controller, an extant state observer (ESO) is considered for estimating the unfamiliar dynamics of the system \hat{F} . The structure of the ESO follows:

$$ESO = \begin{cases} \bar{e}_1 = z_1 - y \\ \dot{z}_1 = z_2 - \beta_1 \bar{e}_1 + \alpha U_i \\ \dot{z}_2 = -\beta_2 |\bar{e}_1|^{\frac{1}{2}} \text{sign}(\bar{e}_1) \\ \hat{F} = z_2 \end{cases} \quad (5)$$

In the ESO structure, the estimated error and estimated produced by ESO represented by \bar{e}_1 and \dot{z}_2 , respectively. β_1 and β_2 express the constant terms and the intermediate parameters are shown by z_1 and z_2 . The overall scheme of the ULM strategy with ESO is shown in Fig. 3.

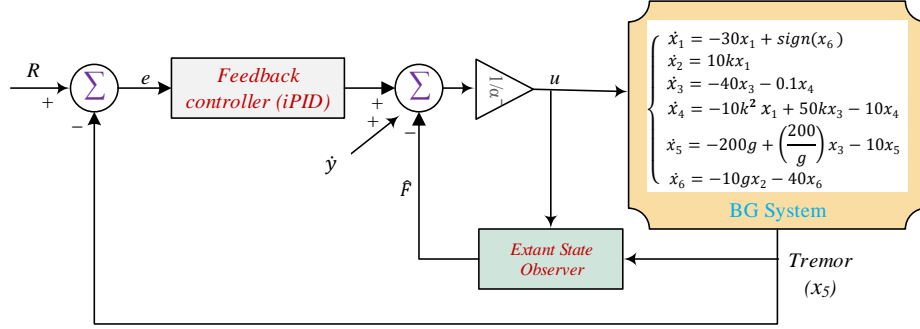


Fig. 3. The architecture of the ULM controller

B. Theory of the Deep Reinforcement Learning

B.1 RL Strategy

Lately, an intelligence type of machine learning namely reinforcement learning (RL) has been introduced that works in the infinite Markov decision trend (iMDP) way. For this purpose, RL agent given that the policy $\pi(a_t|s_t)$ tries to find the top action a_t for the running state in the environment s_t of the action space A . Afterward, the agent acts based on the rewards r_t for each action and then decide to alter the state of the environment from s_t to s_{t+1} and repeats this trend with the aim of maximizing discounted reward to each state and then follows this process until when attaining to the final state. The discount reward for each state can be formulated as:

$$R_t = \sum_{k=0}^{\infty} \gamma^k r_{t+k} \quad (6)$$

Where the discount factor describes by $\gamma \in (0,1]$.

B.2 The strategy of Deep Q-Network

Q -learning is known as an important algorithm that plays a vital role in developing a model-free approach. The update equation of the Q -learning algorithm can be computed as:

$$Q(s_t, a_t) \leftarrow Q(s_t, a_t) + \lambda [r_t + \gamma \max_a Q(s_{t+1}, a) - Q(s_t, a_t)] \quad (7)$$

The learning rate and discount factor are described by $\lambda \in (0,1]$ and $\gamma \in (0,1]$. This algorithm faces huge difficulty in the high dimensional and continuous spaces including violent output oscillation in the real system. To improve the quality of the Q -learning and also for solving the restriction of that algorithm in the complex spaces in particular continuous space and high dimension, an advanced algorithm called deep Q -learning (DQN) has introduced, which uses a deep neural network (DNN) as an approximator to select the optimal control signal in the action space via estimating the value function of each discrete action. The Q -value function, $Q(s, a, \theta^Q)$, is estimated by the network that learns the value function with the weight θ^Q and the target network described by θ^{Q^-} , follows the way that gives the adaptive target during the backup process. The DQN algorithm can work well in discrete spaces and faces difficulties in continuous spaces. For this purpose, an advanced algorithm namely deep deterministic policy gradient (DDPG) has been introduced

for working in continuous spaces and producing continuous control signals. The structure of the RL theory is illustrated in Fig.4.

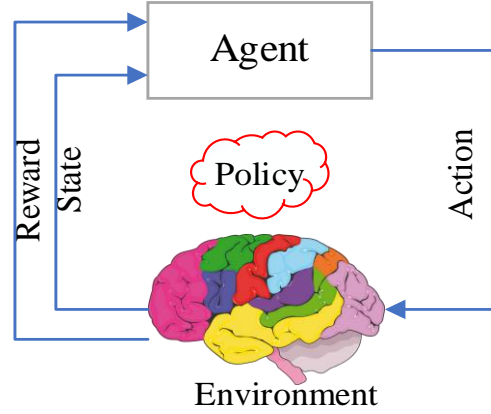


Fig. 4: The strategy of the RL algorithm

B.3. The fundamental of Deep deterministic policy gradient (DDPG)

In the DDPG structure, the algorithm attempts to provide stable and robust learning by using two diverse actor and critic NNs with continuous action, which is combined with reply memory and Q-target approach. In this method, the Q-value function and the current policy $\mu(s|\theta^\mu)$ predict by critic network $Q(s, a|\theta^Q)$ based weights θ^Q and actor-network with weight θ^μ . Lose function $L(\theta)$ for training the critic NN follows:

$$L(\theta^Q) = E_{(s,a)} \left[(Q(s_t, a_t|\theta^Q) - y_t)^2 \right] \quad (8)$$

$$y_t = r_t(s_t, a_t) + \gamma Q(s_{t+1}, \mu(s_t|\theta^\mu) | \theta^Q) \quad (9)$$

Thus, the gradients function for the actor coefficients can be calculated as:

$$\nabla_{\theta^\mu} J^{\theta^\mu} \approx \mathbb{E}_{s_t \sim \rho^\beta} \left[\nabla_a Q(s, a|\theta^Q) |_{a=\mu^\theta(s)} \nabla_{\theta^\mu} \mu(s|\theta^\mu) \right] \quad (10)$$

where the discounted rate distribution and special policy for the running policy are expressed by ρ and β . Additionally, two further neural networks namely target network $Q'(s, a|\theta^{Q'})$ and $\mu'(s|\theta^{\mu'})$ are added to apply to the DDPG to tackle the divergence issue and computing of the target rate (28, 29). Additionally, for training the supplementary networks to follow the main networks, two separate soft updates are adopted that the soft updates equations can be computed as:

$$\begin{aligned} \theta^{Q'} &\leftarrow \tau \theta^Q + (1 - \tau) \theta^{Q'} \\ \theta^{\mu'} &\leftarrow \tau \theta^\mu + (1 - \tau) \theta^{\mu'} \\ \tau &\ll 1 \end{aligned} \quad (11)$$

To construct an exploratory actor, an exploration noise \mathcal{N} given that the Ornstein-Uhlenbeck (OU) process is appended to the basic actor policy.

$$a_t = \mu(s_t|\theta^\mu) + \mathcal{N} \quad (12)$$

The process of the DDPG algorithm is drawn in Fig. 5.

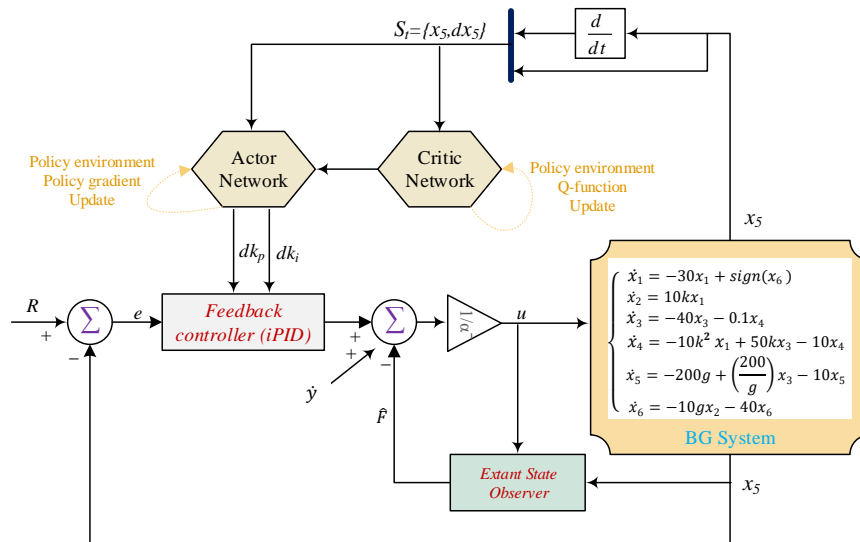


Fig. 6. The structure of the ULM based DDPG algorithm

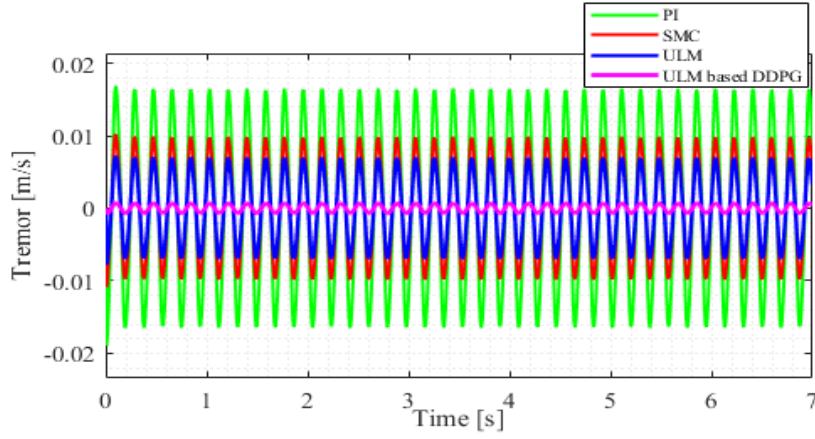
SIMULATION RESULTS

In this section, the BG system was analyzed by employing two distinct purposed controllers: *i*) ULM controller

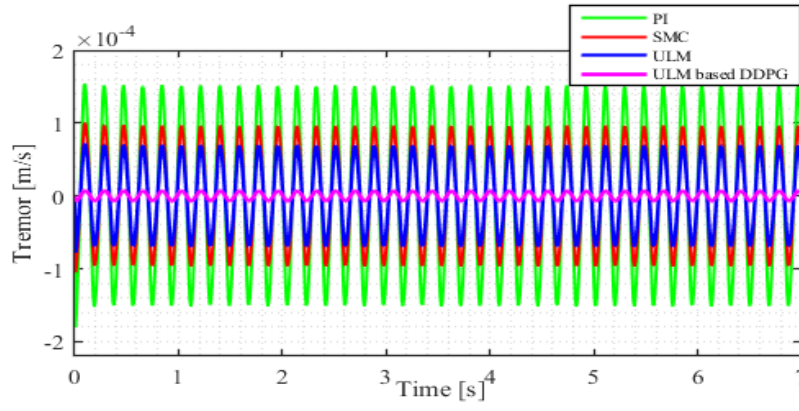
is established to employ the STN nuclei, additionally, an advanced tuner algorithm called DDPG is developed for setting the iPI parameters *ii*) the conventional feedback controller is adopted to control the GPi spot. . To investigate the applicability of the suggested approach, the outcomes of the BG system under three typical scenarios including nominal condition, variations of system parameters, and imposing noise are considered. Moreover, to demonstrate the merit and the effectiveness of the purposed strategy, the mentioned scheme is examined with ULM controller, SMC controller, PI controller that are employed to the STN nucleus. For a fair comparison, the conventional feedback controller with similar configurations ($K_p = 20$ and $K_i = 12$) is fixed in all the examinations. Here, K_p and K_i describe the proportional and derivative gains of the conventional feedback controller.

Case 1: Analysis of the system under health and disease conditions

In this case, the BG model with the purposed system (closed-loop strategy) is executed in the health condition with $k = 0.1/g = 1$ and disease condition with $k = 1/g = 10$. Resulting of the BG system under health conditions and disease conditions with the application of ULM based DDPG, ULM, SMC, and PI controllers are illustrated in Fig. 7(a) and Fig. 7(b), respectively. According to the sub-figures of Fig. 7, it is obvious that the performance of the BG system in the health/disease situations (suppressing hand tremor) with the purposed strategy (ULM based DDPG) is superior compared to other designed controllers. Thus, the first goal of the designing controller for Parkinson's patients will be confirmed.



(a)



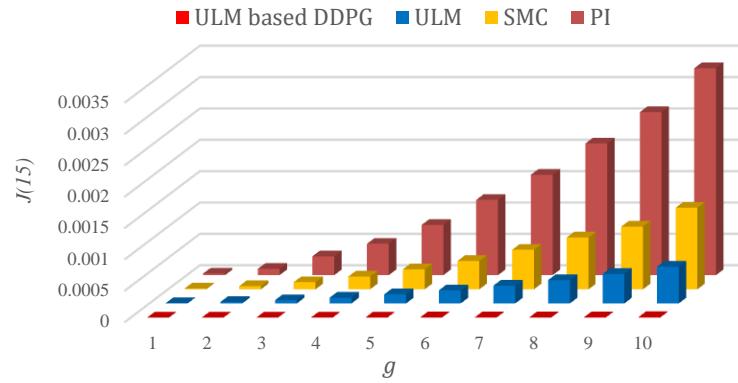
(b)

Fig. 7. Tremor output a) disease condition b) health condition

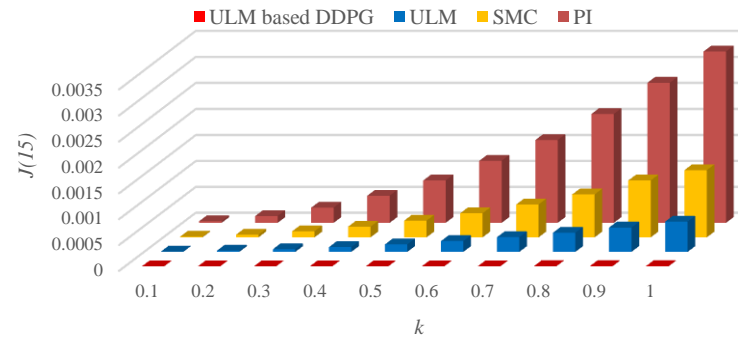
Case 2: Analysis of the robustness and control output index

To evaluate the robustness of the BG system with the purposed scheme, a performance index according to Eq. (15) is defined, which the parameters of the BG model (k and g) have changed in the following way: k from 1 to 0.1 and g from 10 to 1. Furthermore, to verify the second aims of the controller designing for the BG system (reducing electric field intensity to the brain), an index namely Control Output Index (COI) that is considered as root mean square (RMS) of the controller behaviors has introduced. The robustness and COI analysis are drawn in Fig. 8 and Fig. 9, respectively. From Fig. 8 and Fig. 9, it is seen that the suggested strategy has a valuable performance under both examinations.

$$J = \int_0^{\infty} t \cdot tremor^2 \cdot dt \quad (15)$$

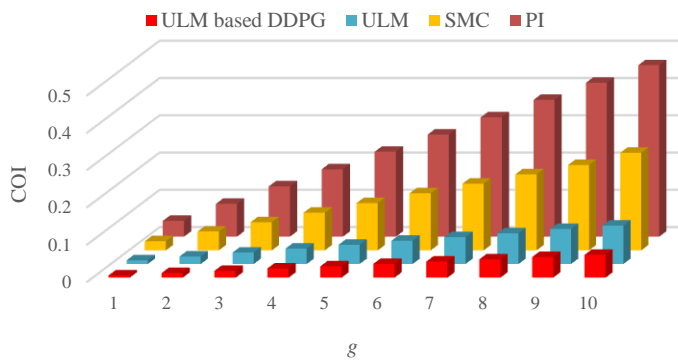


(a)

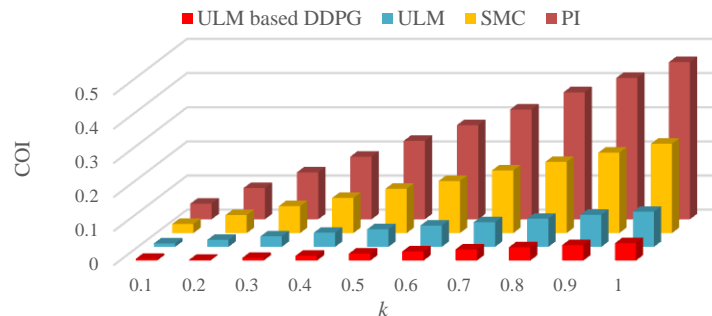


(b)

Fig. 8. Variation of performance index ($J(15)$) according to a) variation of g , and b) variation of k .



(a)



(b)

Fig. 9. Variations of COI according to a) changes of g , and b) changes of k .

Case 3: Noise analysis

In this case, to further investigate the purposed controller, three different noises low noise (with variance 0.001), high noise (with variance 0.01), and very high noise (with variance 0.1) are employed in the BG system. The output of the system under various noise analyses is depicted in Fig. 10. Additionally, for the quantitative evaluation, the result of the performance index based on Eq. (15) for the mentioned applications in the presence of distinct noises is furnished in Table 2.

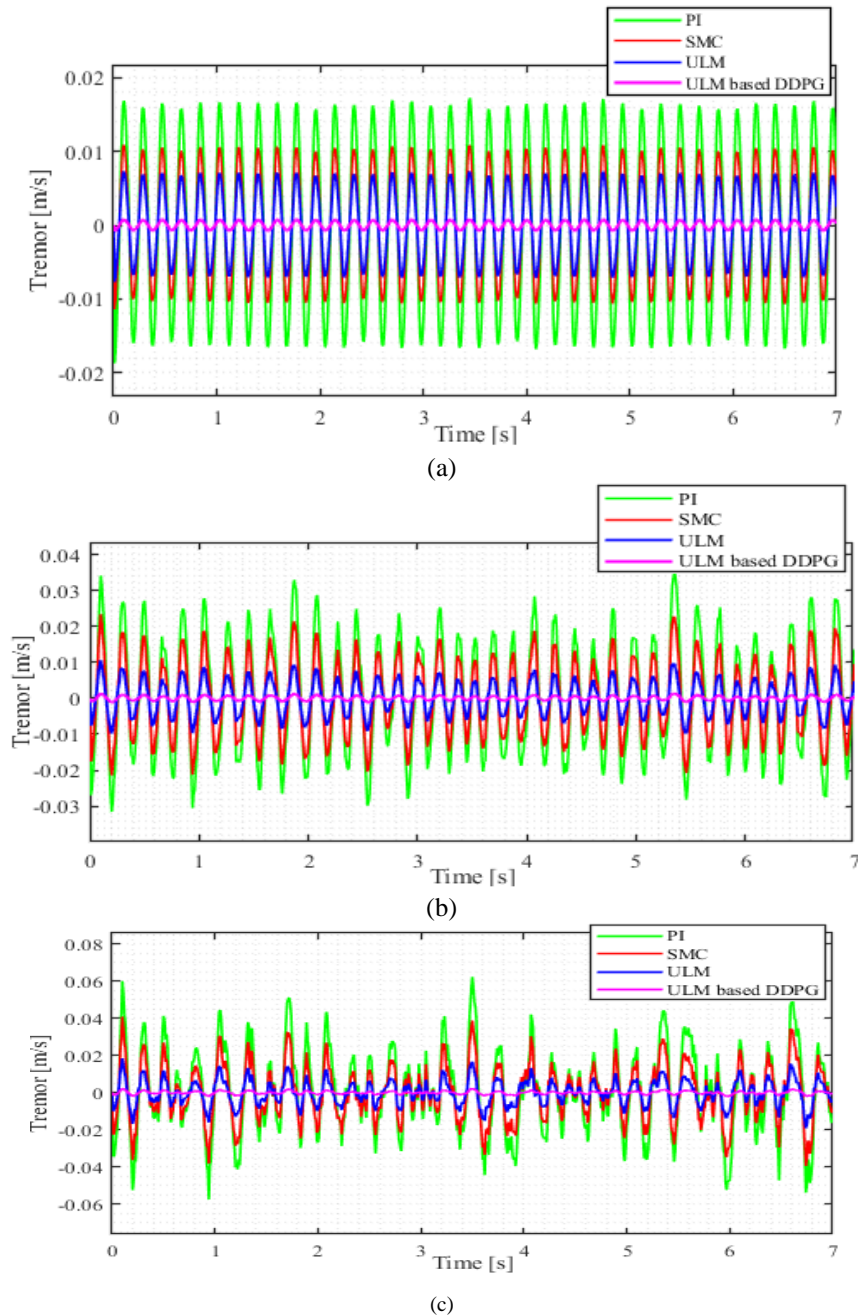


Fig. 10. Tremor output in the presence noises a) low noise (variance 0.001) b) high noise (0.01) c) very high noise (variance 0.1).

Controller	Performance Index		
	Low	High	Very High
ULM based DDPG controller	6.3927e-06	7.9718e-06	1.6711e-05
ULM controller	5.8196e-04	0.0053	0.0237
SMC controller	0.0013	0.034	0.402
PI controller	0.0043	0.0113	0.1394

Table 2: Result of the performance index

DISCUSSION

In recent decades, Parkinson's disease is counted as a second CNS disease and the common medications are hand and head tremor, rigidity, and bradykinesia. The methods of therapy for Parkinson's patients are divided into drug therapy (Levodopa) and surgery (DBS). The drug therapy method is used for the initial stage of the disease, while DBS can be effective for Parkinson's patients in the acute stage.

In the current work a model of BG, which is discussed in Section 2, is considered to simulate hand tremor in Parkinson's patients (9, 15). Conventional methods (stimulate one nucleus of BG) lead to a wide range of side-effects including visual problems, speech disorder, and apathy resulting in high field intensity to the brain (4). For this purpose, in the recent literacy stimulating two nuclei of BG (GPi & STN) has been studied and different methodologies have been developed to reduce complaints of DBS such as SMC (4), backstepping (15), PID (30), SIT2-FLC (17), and adaptive control (4). According to (4, 15, 17, 30), it is clear that stimulating two areas of BG at the same time is more suitable and plays a crucial role in reducing side-effects and hand tremor. Designing a model-based controller for the nonlinear dynamics due to uncertainties, unfamiliar disturbances and the exact dynamic model of the system under study faces many challenges. Because of these cases, a model-free controller called ULM is designed to control GPi and STN, simultaneously. The mentioned controller is constructed of a PI controller and ESO for rejection the disturbances and uncertainties. Since the quality of the controller is linked to proper adjustment of the coefficients, several meta-heuristic optimization algorithms like IJAYA (17), Sine-Cosine (31), and harmony search and cuckoo (HSC) (30) have introduced for carefully tuning the controller's parameters. However, the aforementioned algorithms face many difficulties in practical including poor learning and compatibility issues (28). For this purpose, a type of machine learning namely DDPG is developed to adaptively set the coefficients of the PI controller. Additionally, two NNs (actor & critic) have been added to the DDPG for increasing the care and speed of the parameters tuning.

CONCLUSION

The main contributions of the present paper are suppressing the hand tremor and reducing the entrance electric field intensity to the brain. To do this, a model-free controller based on the ULM controller is established for applying to the STN spot as a nucleus of the BG system, which was considered as a test-system for investigating the DBS system. Given that the performance of the ULM controller is linked to the iPI parameters, a DDPG algorithm that is based on the actor-critic network is adopted to automatically adjust the coefficients of the controller. Furthermore, the GPi part was controlled by a conventional feedback controller. To demonstrate the supremacy of the suggested architecture, it has been compared with state-of-the-art methodologies such as ULM, SMC, and PI controllers under various scenarios. As illustrated in the simulation results, the suggested controller (ULM based DDPG) has superior performance is able to effectively alleviate the tremor deviations and outperform other considered methods. In addition, when the system is subjected to parametric variations and various noises, a higher level of robustness is achieved by the suggested control methodology than the other three controllers.

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چکیده فارسی

کنترل لرزش دست بیماران پارکینسونی از طریق کنترل کننده ULM مبتنی بر ماشین لیرنینگ

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بیماری پارکینسون یکی از شایع ترین اختلالات عصبی دهه های اخیر بوده است. مهمترین عوارض اختلال پارکینسونی لرزش، سفتی عضلات است. تحریک عمیق مغز (DBS) نقش حیاتی در درمان بیماران پیشرفته پارکینسون ایفا می کند. در مقاله حاضر، دو هسته از بازال گانگلیا در یک ساختار حلقه بسته تحریک می شوند تا شدت میدان الکتریکی ورودی به مغز را کاهش دهند و علاوه بر این لرزش دست در بیماران پارکینسونی را به میزان مطلوبی کاهش دهد. برای این منظور، یک کنترل کننده (ULM) مبتنی بر ماشین لیرنینگ برای تحریک هسته ساب تالامیک و یک کنترل کننده بازخورد معمولی برای تحریک گلبوس پالیدوس داخلی در نظر گرفته شده است. در این روش، ضرایب کنترلر ULM توسط شبکه های عصبی منتقد و بازیگر تنظیم شده است. برای نشان دادن مناسب بودن روش پیشنهادی با روش های پیشرفته دیگر مانند ULM، مد لغزشی و بازخوردی مرسوم مقایسه می شود.

واژه های کلیدی: اختلال پارکینسونی، تحریک عمیق مغزی، لرزش دست، کنترل کننده تطبیقی، ماشین لیرنینگ