Research Paper:
Optimal Canceling of the Physiological Tremor for Rehabilitation in Parkinson's Disease

Behnam Faraji[1], Zahra Esfahani[2], Kourosh Rouhollahi[3], Davood Khezri[4*]

1. Department of Electrical and Biomedical Engineering, Faculty of Biomedical Engineering, University College of Rouzbahan, Sari, Iran.
2. Department of Electrical Engineering, University of Alborg, Alborg, Denmark.
3. Department of Mathematics, Faculty of Applied Mathematics, Yazd University, Yazd, Iran.
4. Department of Sport Biomechanics and Technology, Sport Science Research Institute, Tehran, Iran.

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ABSTRACT

Introduction: This study was conducted to control hand tremors and decrease adverse effects due to the high field intensity in advanced Parkinson's disease. We aimed at concurrently controlling two areas of Basal Ganglia (BG) in a closed-loop strategy.

Methods: In the present research, two nuclei of BG, namely subthalamic nucleus and globus pallidus internal were simultaneously controlled. Furthermore, to enhance the feasibility of the suggested control strategy, the coefficients of the controller were determined using a hybrid version of the harmony search and cuckoo optimization algorithm.

Results: The advantages of the applied method include decreasing hand tremors and applied electric field intensity to the brain; consequently, it leads to reducing adverse effects, such as muscle contraction and speech disorders. Moreover, the purposed controller has achieved superior performance against changing the parameters of the model (robustness analysis) and under noise tests, compared to other conventional controllers, such as Proportional Integrator (PI) and Proportional Derivative (PD).

Conclusion: The employed approach provided an effective strategy to reduce hand tremors. It also decreased the delivered high field intensity to the brain; consequently, it reduced adverse effects, such as memory loss and speech disorders. It is important to ascertain the superior performance of the suggested closed-loop control scheme in different conditions and levels of tremor. Such a function was examined in terms of robustness against the variation of parameters and uncertainties. We also obtained time domain outcomes, i.e., compared with the state-of-the-art approaches.

*** Corresponding Author:**
Davood Khezri, PhD.
Address: *Department of Sport Biomechanics and Technology, Sport Science Research Institute, Tehran, Iran.*
Tel: *+98 (912) 0549811*
E-mail: *davidkhezry@gmail.com*

Introduction

Parkinson's Disease (PD) is a progressive neurological condition of the Central Nervous System (CNS) [1]. Dopamine (DA) is a regulator function of Basal Ganglia (BG). Such a condition usually occurs due to a loss of dopaminergic neurons in the substantial nigra pars compacta of the brain [2, 3]. The destruction of dopamine appears in a region of the brain, called BG. BG is composed of 5 main nuclei, which include an excitatory and an inhibitory function in the thalamus [4-7]. Neural signals from the striatum to the thalamus are transmitted through two pathways (direct & indirect). The imbalance in the two pathways can produce tremors with a frequency of 4-6 Hz.

Over the past decade, Deep Brain Stimulation (DBS) has been an effective solution for treating patients with PD who strongly resist pharmacotherapy [5, 8]. DBS provides a high electrical frequency (130-185 Hz) to different parts of the BG, where electrodes are put in the nuclei of BG, including the Subthalamic Nucleus (STN), Globus Pallidus internal (GPi), and Ventralis Intermediate (VIM) [9]. Although DBS is among the effective therapies in PD, the exact mechanism of DBS in suppressing hand tremors remains undiscovered [10].

In previous research, the open-loop control methods (without feedback signal) were widely adopted in the context of DBS. However, the open-loop DBS techniques resulted in continuous and high field intensity. Accordingly, it generated various adverse effects, such as anxiety, apathy, cognitive impairment, dysphagia, and impulse control disorders. Because of the availability and feasibility of tremor measurement, the closed-loop DBS strategies [11-13] are preferred in the environments subjected to some uncertainties and measurement noises. Various control methodologies (with feedback signal), such as adaptive [14], backstepping [15], and intelligent single input interval type-2 fuzzy logic (iSIT2-FL) [16] have signified the closed-loop strategy as a more appropriate method for reducing the intensity of the electrical field and the destructive effects of DBS. A suitable solution to address the adverse effects of DBS is to simultaneously stimulate two nuclei of BG [15, 17].

The model-based DBS control strategies have suggested excellent performance in reducing hand tremors among patients with PD; however, the need for the mathematical model of a plant in the design of such robust controllers limits their applicability. To reduce the complexity of the control design and overcome the necessity for model identification, some model-free controllers, such as a Neural Network (NN) [18], Machine Learning [19], and fuzzy expert [20, 21] systems were presented for treating patients with PD. Additionally, in the area of artificial intelligence, some meta-heuristic techniques, such as Bacteria Foraging (BF) [22], Sine-Cosine Algorithm (SCA) [23], and Grey Wolf Optimizer (GWO) [24] have been introduced to design a controller. The optimization techniques based on Proportional Integral Derivative (PID) controllers and their variants were successfully applied to the nonlinear power plant [25], robotic [26], fuel cell system [27], and so on.

In the present study, a PID controller based on simultaneous stimulation of two distinct nuclei of BG was designed to reduce hand tremors and additional pulse inputted to the brain. The efficiency of the PID controller-based DBS system highly relies on the controller gains; thus, implementing meta-heuristic mechanisms with high exploration/exploitation capabilities for the fine-tuning of these gains can ameliorate the system performance. Accordingly, a hybrid combination of harmony search and cuckoo optimization algorithm, entitled HSCOA, was adopted for determining the PID controller coefficients. The present work is summarized as follows:

(i). Two distinct controllers based on the stimulation of two sections of BG, STN, and GPi were optimally designed concurrently.

(ii). The quality of the closed-loop DBS controller depends on the PID controller gains; therefore, a hybrid meta-heuristic mechanism based on HSCOA was established to adjust the controller coefficients in an optimal scheme.

(iii). To prove the suitability of the suggested optimal closed-loop controller, a different range of noises was applied to the concerned BG model.

(iv). Robustness analysis includes changes in the critical parameters of the BG system (k & g). The same analysis was performed to investigate the suggested controller in various ranges of tremors. In this analysis, the terms k and g varied within the range of 0.1 1 and 1 10, respectively.

The dynamic model of BG

BG is composed of 5 main nuclei, including the striatum, GPe, GPi, STN, and SN. BG receives signals from all layers through striatum and STN (striatum & STN are the inputs) [18]. Besides, its outputs include GPi and SNr, as illustrated in Figure 1. Moreover, BG has various neurotransmitters; DA, Gamma-Aminobutyric Acid (GABA), and Glutamate. The role of each section in the BG follows [7, 16]:

● By decreasing the neurotransmitter DA (excitatory/inhibitory function) is transmitted from SNc to the striatum.

● By decreasing and increasing the neurotransmitter GABA (Inhibitory) is transmitted from the striatum to SN and from the striatum to GPe, respectively.

● By increasing the neurotransmitter glutamate (excitatory) is transmitted from STN to GP.

Based on the previously-reported mathematical model [19], each nucleus of BG is considered as a transfer function. Thus, 5 transfer functions, including G1, G2, G3, G4, and G5 were considered for SNc, striatum, GPe, STN, and GPi, respectively. Furthermore, various regions were considered for changing the gain of neuro-transmitters. Accordingly, concerning the g ($1\leq g \leq 10$) and k ($0.1\leq k \leq 1$) rates, g=10 and k=1 represent the condition of disorder, g=1 and k=0.1 represent the health condition. Besides, the term 1/g rate illustrates the change of neurotransmitters (increasing & decreasing). The proposed BG model structure follows [20] (Equation 1-5):

1. $G_1(s){:}SNco(t)=L\{sign(A(t))\}$

$$A(S)=\frac{-10}{s+40}\,gSo_2(s)$$

2. $G_2(s){:}\ So_1(S)=\frac{1}{s+30}\,SNco(s)$

$$So_2(S)=10\frac{10}{s(s+30)}\,SNco(s)$$

3. $G_3(s){:}GPo(S)=\frac{10}{s+10}\left(-\frac{k}{g}\,So_1(S)+\frac{5}{g}\,STNo_1(S)\right)$

4. $G_4(s){:}STNo_1(S)=g\times\frac{-0.1}{s+40}\,GPo(s)$

$$STNo_2\,(S)=g\times\frac{-1}{s+40}\,GPo(s)$$

5. $G_5(s){:}OUT(S)=\frac{200}{s+10}\,(1/g\ STNo_2(S)\ -g\ So_2(s))$

Based on the state-space model of the inverse Laplace transform, the dynamic equations of the system are as follows [14, 17, 16] (Equation 6):

$$6.\ \begin{cases}\dot{x}_1=-30x_1+sign(x_6)\\ \dot{x}_2=10kx_1\\ \dot{x}_3=-40x_3-0.1x_4\\ \dot{x}_4=-10k^2x_1+50kx_3-10x_4\\ \dot{x}_5=-200g+(\frac{200}{g})\,x_3-10x_5\\ \dot{x}_6=-10gx_2-40x_6\end{cases}$$

, where $x_1,x_1,\dots,x_6$ represents the state variables.

Design of the controller

In this work, the aim of designing the closed-loop DBS control strategy was to suppress the hand tremor and reduce its adverse effects in patients with DP. For this purpose, two optimal PID controllers were simultaneously designed and applied to two targets of GPi and STN [17]. The simultaneous stimulation of two BG nucleus decreased the energy inputted to the brain and the range of stimulation in the recovery condition. Thus, two controllers were used; the controller u1 and controller u2 were applied to STN (direct pathway) and the GPi (indirect pathway), respectively.

The block diagram of the BG model along with two input controllers is illustrated in Figure 2. As mentioned, this model has excitatory and inhibitory functions. To simplify and reduce the intensity of the applied field, each function is controlled separately.

The PID controller is among the most frequent examples of a feedback control algorithm. It is widely adopted in various control applications due to its design flexibility and structural simplicity. Moreover, such controllers provide simplified modeling, require little effort, and less expertise for development, i.e., valuable issues from the perspective of practical engineering. The transfer function of a typical PID controller structure is defined in the form of $G_c=K_p+K_i/s+K_ds$, where , K_p, K_i, and K_d represent the controller gains. According to the definition of the PID controller structure, the overall closed-loop controller for the BG system is illustrated in Figure 3.

Optimization algorithm and objective function

A. HSCOA hybrid algorithm

Finding novel heuristic methodologies to solve the realistic optimization problem is currently a popular subject among researchers. Among the heuristic mecha-

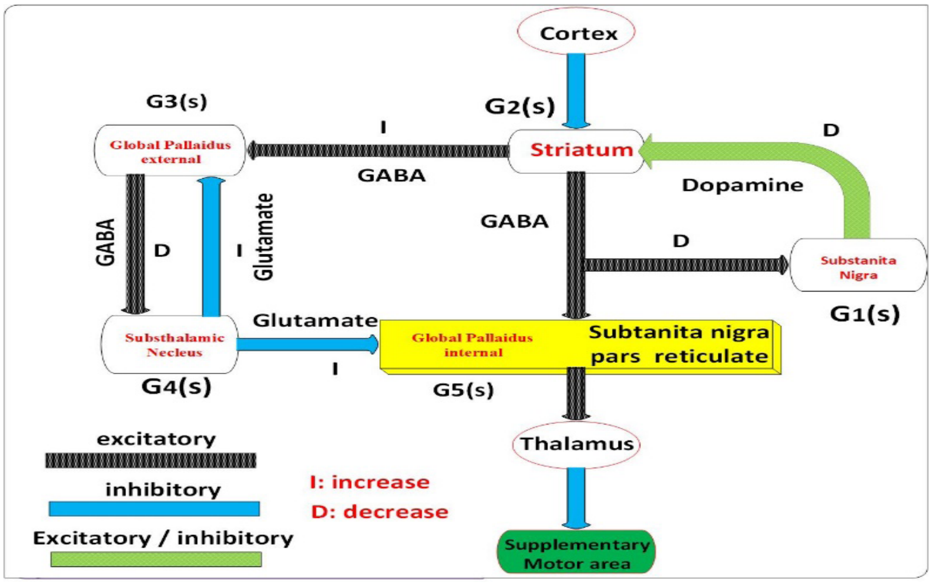

Figure 1. The overall structure model of BG [7, 14]

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nisms, the HS algorithm is one of the most popular ones with high adaptability to solve a wide range of control problems [28-30]. However, the dependency of HS on its control parameters as well as some inherent obstacles reduce its feasibility and global search ability in some sophisticated problems. To address the shortcomings of the HS, a modified version of the COA algorithm is incorporated into the HS algorithm. Accordingly, some modifications are initially introduced for the COA algorithm, then the modified algorithm is effectively combined with the HS algorithm (Figure 4).

A.1 Overview of the original HS

The HS is a population-based algorithm, i.e., inspired based on the musician's attempts to improve their instrument pieces to finding the desired harmonies. The evaluation procedure of HS is characterized based on three steps. These measures include initialization [a random population of search agents is generated and stored in the Harmony Memory (HM)], search agent (harmony) improvement (the improvisation of search agents: Based on an improvisation mechanism of HS, a new search agent is created in the decision space), and selection (the evaluation procedure will be iteratively repeated until the defined termination condition is satisfied) [31].

The computational process under the aforesaid steps of the HS is summarized in Algorithm 1. In this algorithm, HMCR, HMS, PAR, and BW represent the HM consideration rate, the size of HM, pitch adjusting rate, and distance bandwidth.

A.2 COA and Its Modifications

A.2.1 Overview of the original COA

The egg-laying scheme presented by Rajabioun is called Cuckoo Optimization Algorithm (COA) [32], i.e., inspired from specific egg-laying. The COA is initialized by a collection of one-dimensional vectors, called "habitat", in the deceive space. According to the egg-laying scheme, numerous eggs are randomly dedicated to each search agent (or cuckoo) to explore the space around the cuckoos. To realize this local search scheme, an Egg-Laying Radius (ELR) is defined per search agent, given as (Equation 7):

7. $ELR_i=\alpha\times(NE_i/T.NE)\times(var^{max}-var^{min})$

where α is an integer, $T.NE$ and NE_i are the whole number of eggs and the number of dedicated eggs to the i^{th} cuckoo; the minimum and maximum bounds of the design variables are represented by , var^{min} andvar^{max} , respectively.

Based on relevant ELR to the cuckoo's eggs in the host bird's nest, the profit will be assessed and only the fittest eggs are retained. When the cuckoo chicks become mature enough, they migrate toward new habitat (with the best profit among whole cuckoos). The immigration mechanism to generate new habitat is as per below (Equation 8):

8. $x_{i,j}^{new}=x_{i,j}^{old}+\varphi\times(x_j^{best}-{}_{xi,j}^{old}$

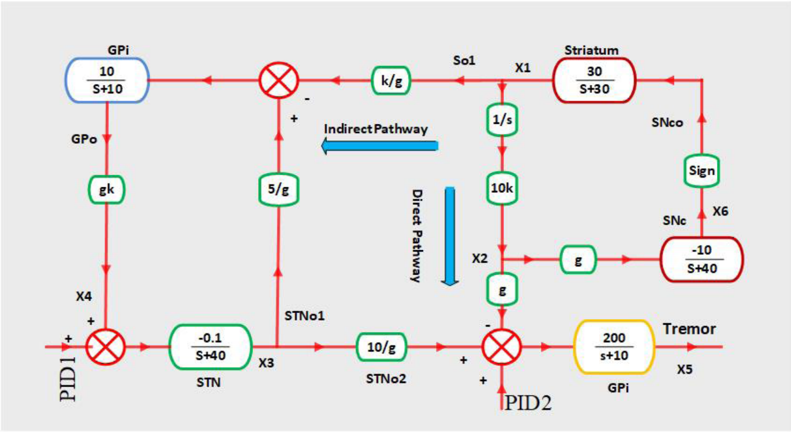

Figure 2. The dynamic Model of BG with two distinct controllers [14]

j={1,2,....N}

where the index of the best and current habitat is expressed by the best and old, respectively. φ is division parameter and ϕ is determined by (Equation 9):

9. $\varphi=MC\times rand\ (0,1)$

where the MC is the motion factor.

A.2.2 Modified Egg-Laying and Migration Mechanism

In this sub-section, an alternative scheme of the stochastic allocation to enhance the efficiency of the egg-laying mechanism is presented to offer a stronger local search. For the egg-laying modification, the search agents are ranked from high-profit to low-profit. Then, a Fitness Rank (FR) is allocated to each of the individuals. To perform this modification, the profit of cuckoo is classified based on their profit (from high to low). The modified allocation is defined as (Equation 10):

10. $NEi=NE^{min} + floor\ ((\frac{FR_i}{current\ population\ size})) \times (NE^{max} - NE^{min}))$

where the lowest and highest number of eggs are represented by NE^{min} and NE^{max}, respectively.

Next, the chaos theory is incorporated into the immigration scheme to ameliorate global search and accelerate algorithm convergence. For this purpose, the coefficient φ in the migration movement is chaotically obtained, given as (Equation 11)

11. $\varphi=\varphi_l+z_n\times(\varphi_u-\varphi_l)$

where φ_l and φ_u are respectively the lower and upper bounds for φ.

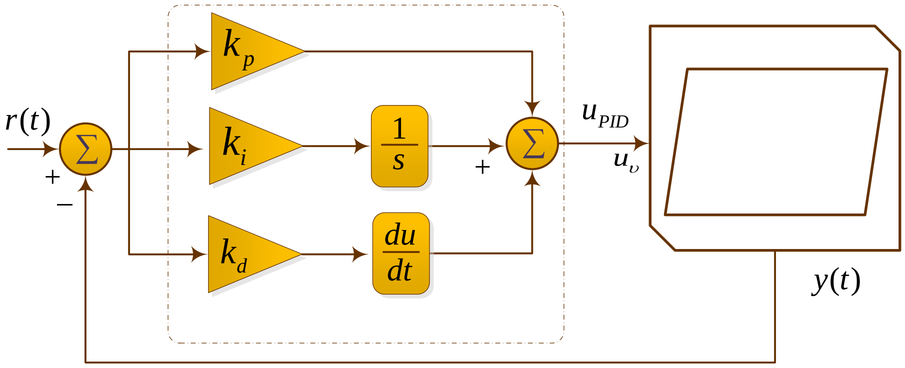

Figure 3. The structure of the closed-loop control strategy for the BG model

A

Algorithm 1. The Pseudo code of the ***HS***

$\boldsymbol{for}\ j = 1{:}\,N\ do$
% memory consideration
$\boldsymbol{if}\ rand\ (0.1) \leq HMCR\ then$
$x_j^{new} = x_{r.j} \qquad \boldsymbol{r} \in (\mathbf{1.2}.,,, ,,,.HMS)$
% pitch adjustment
$\boldsymbol{if}\ rand\ (0.1) \leq PAR\ then$
$x_j^{new} = x_j^{new} \pm rand\ (0.1) \times BW$
$\boldsymbol{end\ if}$
$\boldsymbol{else}$
% random selection
$x_j^{new} = var_j^{min} + rand\ (0.1) \times (var_j^{max} - var_j^{min})$
$\boldsymbol{end\ if}$
$\boldsymbol{end\ for}$

B

The Pseudo code of the ***HSCOA***

Set the algorithm parameters: HMS, $NHMS$, PAR^{min}, PAR^{max}, NE^{min}, NE^{max}, α, φ_i, φ_h, Max_Gen
Randomly initialize the HM in the size HMS
Evaluate the fitness for all the HM solutions
$\boldsymbol{While}\ Gen \leq Max\_Gen$ **do**
Calculate $PAR(Gen)$ according to Eq. (7)
Sort the fitness of the HM solutions and find their corresponding fitness rank
$\boldsymbol{for}\ i = 1{:}\,HMS$ **do**
% determine how many local harmonies should be allocated to the ith solution
$NEi = NE^{min} + floor\big((FR_i/NHMS) \times (NE^{max} - NE^{min})\big)$ % $Eq, (11)$
% compute the egg-lying radius of the solutions stored in the HM
$ELR_i = \alpha \times (NE_i/T, NE) \times (var^{max} - var^{min})$ % see Eq. (8)
Generate local harmonies around the HM solutions based upon relative ELR
Perform bound constraints repairing
$\boldsymbol{end\ for}$
Add all the local harmonies to the HM
Keep HMS number of the better HM solutions and eliminate the remaining solutions
$\boldsymbol{for}\ i = 1{:}\,NHMS$ **do**
$\boldsymbol{for}\ \boldsymbol{j} = \mathbf{1}{:}\,\boldsymbol{N}$ **do**
% memory consideration
$\boldsymbol{if}$ rand (0, 1) $\leq HMCR$ **then**
$x_{i.j}^{nhm} = x_{r.j} \qquad \boldsymbol{r} \in (\mathbf{1.2}.,,, ,,,.HMS)$
% modified pitch adjustment
$\boldsymbol{if}$ rand (0, 1) $\leq PAR(Gen)$
Generate chaotic sequence φ by the logistic map according to Eq. (13)
$x = x_{i.j}^{nhm} + \varphi \times (x_j^{best} - x_{i.j}^{nhm})$
Perform bound constraints repairing
$\boldsymbol{end\ if}$
$\boldsymbol{else}$
% random selection
$x = var_j^{min} + rand\ (0.1) \times (var_j^{max} - var_j^{min})$
$\boldsymbol{end\ if}$
$\boldsymbol{end\ for}$
$\boldsymbol{end\ for}$
% update the HM
$\boldsymbol{for}\ i = 1{:}\,NHMS$ **do**
$\boldsymbol{if}\ f(x^{nhm}) < f(x^{wrost})$ **then**
$x^{wrost} = x^{nhm}$
$\boldsymbol{end\ if}$
$\boldsymbol{end\ for}$
Record the best harmony x^{best} in the HM
Gen= Gen + 1
$\boldsymbol{end\ while}$

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Figure 4. COA and its modifications; Overview of the original COA; B. Objective Function.

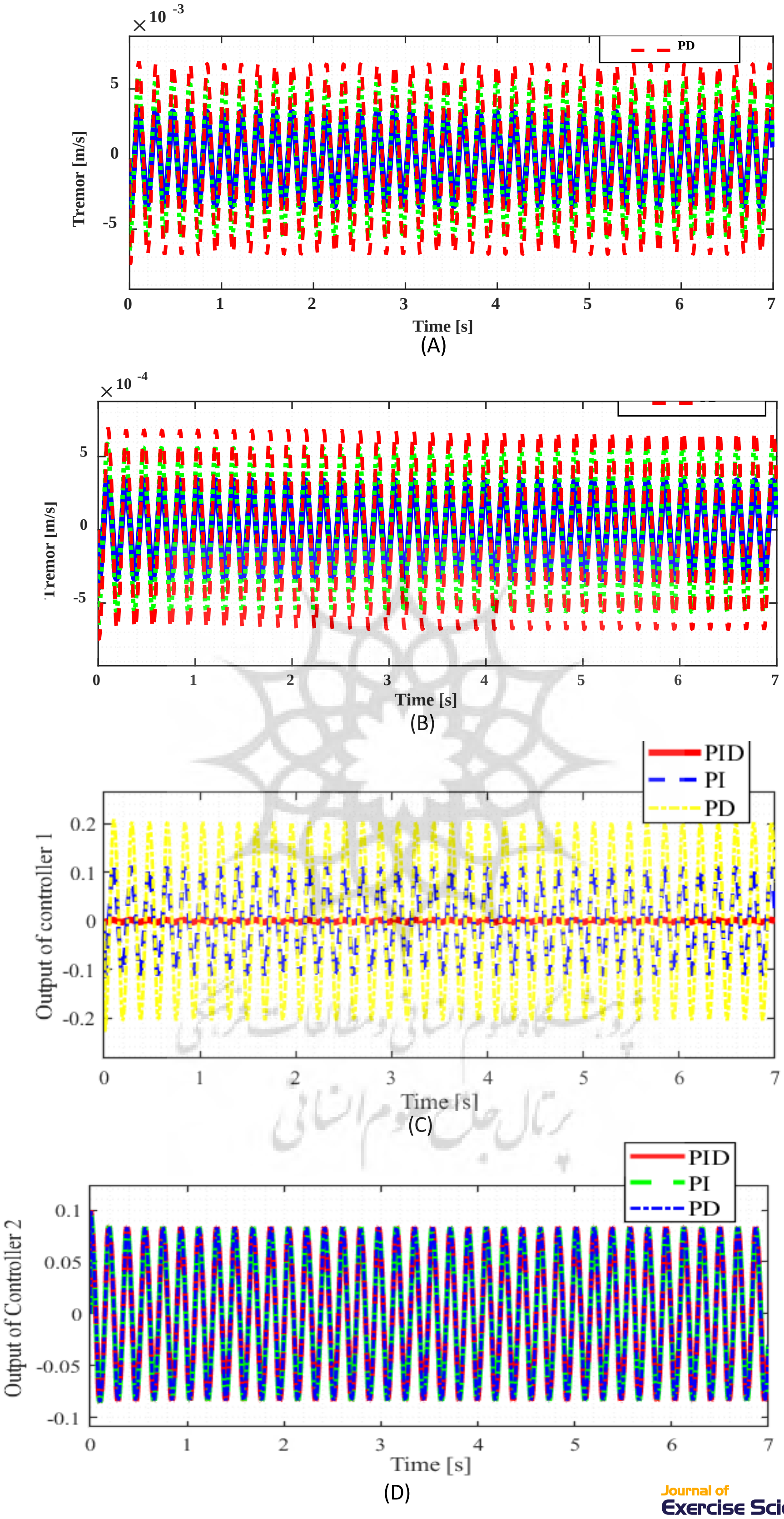

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Figure 5. The response of PID controllers

A. Disease condition; B. Health condition; C. Output of controller 1 in the disease condition; D. Output of controller 2 in the disease condition.

Table 1. The performance indexes corresponding to the PID, PI, and PD controllers designed by HSCOA

Controller	COI	TR
PD	0.155	0.0047
PI	0.0968	0.0038
PID	0.0599	0.0024

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A.3 Combination of COA and HS

A.3.1 Egg-Laying As Local Search

To refine solutions in the evolving process of HS, the egg-laying scheme of COA is adopted as a local search. First, the ELR is computed for each search agent of HS. Then, some local search agent is dedicated to the HM agents according to its related ELR and the locally-produced search agents will be added to the HM.

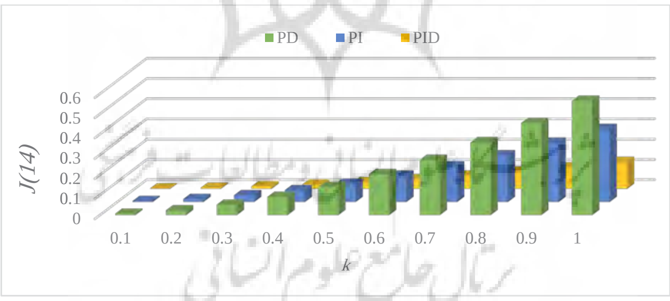
A.3.2 COA immigration mechanism under condition parallel improvisation strategy

To enrich the exploitation process of HS, the pitch adjustment procedure is accomplished by the COA immigration mechanism. In this process, the BW coefficient is omitted and the information of the best search agents is configured to the new elements. Next, a pre-defined search agent, namely New HMS (NHMS), and in the parallel scheme, is evolved at each generation. Besides, based on Equation 12, the PAR parameter is linearly increased to improve the efficiency of the hybrid algorithm by an egg-laying mechanism [33].

12. $PAR(Gen)=PAR^{min}+(\frac{PAR^{min}-PAR^{max}}{Max\_Gen})\times Gen$

A.3.3 Bound constraints repairing

A typical scheme of bound repairing is applied to constraint the individuals to the bounds of the decisive space. The mechanism is realized by the following formula [33] (Equation 13):



(a)

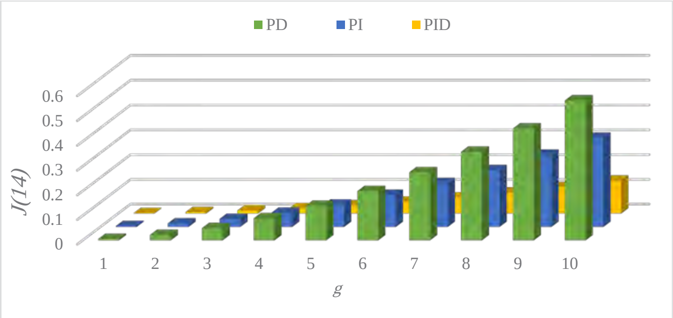


Figure 6. Changes in the objective function J (14)

A. Variation of k; B. Variation of g

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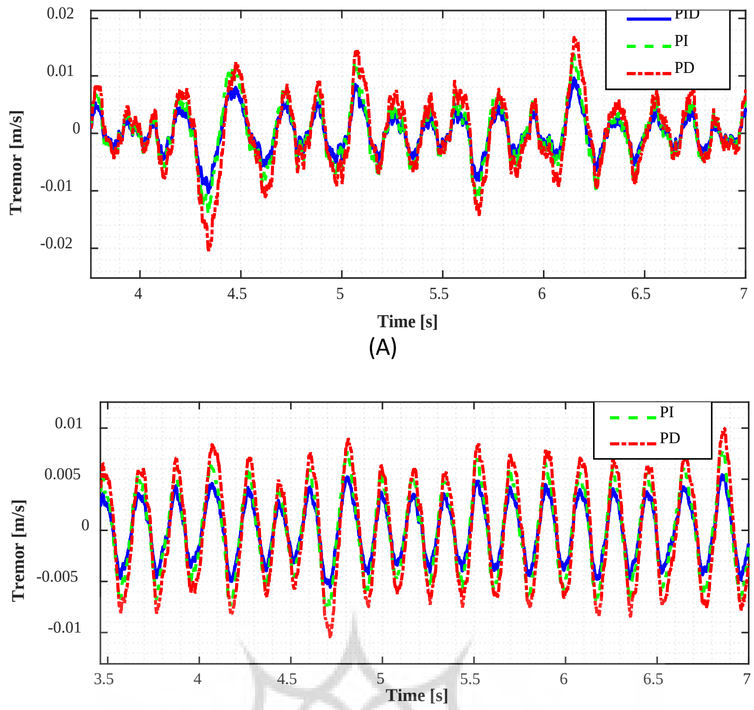

(A)

(B)

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Figure 7. The performance of designed closed-loop DBS controllers in the presence of noise in disease condition a) low noise (with the variance of 0.001) b) high noise (with the variance of 0.01)

$$13.\quad \begin{cases} x_{i,j}=\{var_j^{min} & if x_{ij} var_j^{min} \\ var_j^{max} & if x_{ij}>var_j^{max} \end{cases}$$

The pseudo-code of the combined HSCOA scheme is illustrated in Algorithm 2 [28].

B. Objective function

Based on Figure 2, the output of the system is tremor. As presented in the literature [11, 12], tremor is more suitable for the use of the feedback strategy in a closed-loop structure. This is because the measurement of tremors is easy and needs no prediction. Thus, the objective function based on the output of the system is formulated as below (Equation 14):

$$14.\ J=\int_0^{\infty} t.tremor^2.dt$$

Based on J (14), the baseline coefficients of PID to control two sections of BG are optimized by the HSCOA algorithm under the following constraints (Equation 15):

$$15.\ k_{p.min}) \leq k_p \leq k_{p.max}$$

$$k_{i.min}) \leq k_i \leq k_{i.max}$$

$$k_{d.min} \leq k_d \leq k_{d.max}$$

where, $k_{pid.min}$ and $k_{pid.max}$ indicate the maximum and minimum gains of controller coefficients, respectively, i.e., selected in the range of 0-10.

Simulation and result

In this part, the BG model (described in section II), is simulated (in MATLAB/SIMULINK) by PID controllers. To implement a more-efficient closed-loop strategy, the controller coefficients are determined by the hybrid algorithm of HSCOA. Three scenarios are considered to evaluate the efficiency of suggested optimal controllers. In addition, to perform the superiority of the suggested scheme, the simulation outcomes are compared with the performance of state-of-the-art methodologies, like PI and PD.

Scenario I: Controller Performance in both conditions (health & disease) and the analysis of the produced electrical field in both controllers

Figure 5A and b show the simulation of evaluating the performance of the suggested controller scheme at health (g=10, k=0.1) and disease (g=10, k=1) states. As it is shown, the frequency is constant in both conditions while the amplitude is notably changed. Evaluating the suggested optimal controller in terms of field intensity generation by controllers is depicted in Figure 5C and Figure 5B. Based on Figure 5C and Figure 5D by adopting the optimal PID-based HSCOA, the electrical field intensity presented to the brain is much better than other methods; it means a reduction occurs in the side effects. Besides, the results of controllers concerning Control Output Index (COI) and Tremor Ratio (TR) are presented in Table 1. From the quantitative analysis, the superior outcomes of tremor performance indices are achieved, compared with other methods, such as PI and PD.

Scenario II: Robustness analysis

In this scenario, to evaluate the robustness of the PID controller based HSCOA, k and g, as the critical components of the BG plant, are varied. The effect of the variations of k and g on the amplitude of the output tremor for the different controllers is illustrated in Figure 6A and B, respectively. Based on Figure 6A and B, the PID controller-based HSCOA is quite robust against the variation of k from 0.1 to 1 and g from 1 to 10. Thus, the suggested controller provides a higher degree of robustness, compared with PI and PD controllers based on HSCOA.

III. The Noise analysis

In this section, to assess the performance, the suggested strategy under noise situation is tested by two Gaussian noise; (i) low noise with a variance of 0.001, (ii) high noise with a variance of 0.01, i.e., applied in two distinct paths as (i) the input of direct pathway, (ii) the input of indirect pathway. The performance of designed controllers with Gaussian noise is displayed in Figure 7.

Discussion

Hand tremor in PD has been a considerable and important topic in recent years. The Deep Brain Stimulation (DBS) method used in recent decades is among the most effective and common methods for reducing hand tremors in PD. A prevalent method in previous studies was stimulating one area of the brain (BG), which led to complications, such as speech impairment, amnesia, and forgetfulness due to the high field intensity of stimulation of a single area. In this study, a BG model was adopted as a test-system for developing the DBS control mechanism. Besides, a new control structure was designed for decreasing two indices; i) hand tremor ii) the extent of delivered energy during stimulation. For this purpose, two separate optimal PID controllers were optimally designed by employing HSCOA for the simultaneous stimulation of GPi and SNc areas of the brain. The results of the BG simulation revealed that with the help of the designed PID controller based on HSCOA, the speed and amplitude of tremor control and the energy delivered to the brain were significantly improved, compared to the PI and PD controllers. Moreover, some parameters of the BG model are varied to ascertain the feasibility and robustness of the designed optimal controllers. Finally, a noise analysis was conducted by applying various degrees of noise to the BG model. The time-domain simulation outcomes of the BG system prove the supremacy of the suggested optimal controller, compared to other controllers (PI & PD) against the severe condition of parameter variation and noise analysis. Hand tremors and produced electric field intensity by controllers have conflicting design specifications; thus, future work is recommended to focus on the find trade-off optimal solutions in the design of the established controller. For this purpose, establishing adaptive controllers using machine learning and neural networks is suggested to reduce the terms of hand tremor and electric field intensity in a multi-objective manner.

Conclusion

The employed approach provided an effective strategy to reduce hand tremors. It also decreased the delivered high field intensity to the brain; consequently, it reduced adverse effects, such as memory loss and speech disorders. It is important to ascertain the superior performance of the suggested closed-loop control scheme in different conditions and levels of tremor. Such a function was examined in terms of robustness against the variation of parameters and uncertainties. We also obtained time domain outcomes, i.e., compared with the state-of-the-art approaches.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors have contributed equally to this article.

Conflict of interest

The authors declared no conflict of interest.

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