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Design of adaptive neuro sliding mode controller for anesthesia drug delivery based on biogeography based optimization

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Abstract
Monitoring depth of anesthesia (DOA) is a significant point in general anesthesia (GA). It can be obtained from the assessment of the drug dose carefully and preciously. As a benefit of drug delivery automation, closed-loop method will present several advantages. It may prevent excessive dose amount or less needed dose and the controlled feedback system can decrease the cost of the healthcare by reducing the patient recovery period. This paper addresses the use of adaptive sliding mode controllers (ASMC) for calculating the depth of anesthesia by administrating a dose of propofol drug and measure patient state according to the monitoring device the bispectral index (BIS). In this study, we suggest a simple nonlinear control strategy consists of an ASMC combined with single neuron self-tune neural controller. It is used for maintaining DOA and reducing the effect of the nonlinear element. The adaptive controller uses the BIS value measured as a reference tracking value and propofol dose rate as a control signal. The parameters of the controller are tuned using a procedure based on the biogeography-based optimization (BBO) algorithm. The results indicate that including adaptive parts of the controller and tune its gains needed by BBO algorithm may enable optimal and stable performance for controller for all patients. It also provides fast reach to the induction phase and stay in a stable value in maintenance phase, which reflects the efficient response of the suggested controller if it compared to other nonlinear controllers. It is also justified by the results obtained that the suggested controller gives a very good response.

Keywords
Depth of anesthesia (DOA), Pharmacokinetics/pharmacodynamics model (PKPD), Adaptive sliding mode control (ASMC), Bispectral index (BIS), Biogeography based optimization (BBO).

1.Introduction
General anesthesia ensures an adequate level of DOA to the patients during medical surgery. DOA can be assessed by doctors manually by regulating the anesthetic dose (propofol) to gain a fully loss of awareness. The suitable anesthesia level can be obtained depending on experience, on the known value of doses and on the clinical signs appeared on a patient during surgery like the blood pressure, irregular rate of the heart, excessive sweating, unstable respiration and the expression on his face, closed-loop method can be used for automated the specified infusion rate of the drug during general anesthesia. It can provide considerable features and advantages.

Due to these benefits the burdens of the anesthesiologist may reduce and, consequently, the mistakes that happen due to confusion or tiredness are also minimized. The closed-loop method will also enhance the safety of patient due to persistent monitoring of the DOA and finally decreases the infusion rate of the drug. Also, this will reflect in the health of patients by reducing the recovery stage of the GA step and decrease any complications may happen after surgery [1].

The GA is divided into: pre-operation, induction and maintenance and finally the emergence phase. The induction phase of anesthesia, is the time of managing the drugs and loss of awareness, in which the patient state will be changed from a perfect consciousness state to the unsteady level of anesthesia, always reached in 15 minutes. This phase is fast and it is extremely sensitive. The medical steps

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of surgery happen in the maintenance phase of anesthesia. This phase very significant to controlling a suitable DOA and to fix harmful effects. Once the surgery is finished, given drug will stop and the emergence phase of anesthesia will start. In the final step, the patient will transfer from the hypnosis state to the awake state [2].

The high differences between patients and the Shortfall of a prime experience in the medical methods leads to a high uncertainty case in which it induces to work with robust control. In which the design of controller is built in a way that it can modify all cases not only nominal one, but all the cases will differ by a suitable range, caused by known values (robust stability). It can work perfectly, but must guarantee a minimum competence in set point tracking and robustness to disturbance (robust performance) [3].

In recent years, different methods and approaches have been presented by researchers to analyze monitoring of the depth of anesthesia [4–9]. In [4] PID controllers are used for the estimating of the rate of propofol and monitoring the depth of anesthesia, tuning of PID gains has been founded by genetic algorithm. In [5] the authors present a method of the closed - loop system depends on an open-loop system and Kalman filter. A use of Eleveld's PK model was suggested as the initial condition model in the proposed closed-loop control algorithm, while inter- and intra-individual variables were used for realistic measurement generation.

While in [6] a nonlinear design method is presented by using the SMC method for calculating the infusion rate, all the cases give better values as compared with the desired value within the acceptable range for surgery. Also, in [7] extended prediction, self-adaptive control (EPSAC) method has been used. Hereafter, a closed loop method has been maintained with a suitable sampling time and chose a suitable value of a prediction horizon in the EPSAC algorithm.

In [8] a computer-controlled predictive control strategy (EPSAC) and a computer-controlled Bayesian rule-based optimized control strategy (BAYES) are adopted for the performance of regulatory closed loops in anesthesia process, and finally in [9] a positive state observer is designed for the implementation of a control scheme proposed for the automatic administration in order to track a desired level for the BIS. The objective of this paper is to estimate the dose rate for the anesthesia drug for the patients during general anesthesia in the medical surgery by suggest a proposed ASMC to controlling of the DOA, by making a hybrid between a single neuron PID controller and an adaptive hyperbolic function and use also the linearization method that adopted by [10] for fixing the nonlinearity of the patient PK/PD model, then BBO tuning algorithm is used for tuning the gains of the proposed controller to find an optimal wanted dose rate.

2.The patient mathematical model

The drug distribution in the patient's body is represented by a structure consists of two important parts. The first part called pharmacokinetics part translates related drug distribution to the dose rates inside patient's body during surgery, while the second part called pharmacodynamic part which translates the relation of the drug concentration in the most important part of the body (blood) and the response (effect) during surgery in the two parts the dose rate seemed to be regular. The parameter or variables used in the PKPD model have been explained in *Table 1* [10] and the pharmacological model is shown in *Figure 1*.

Table 1 Variables of patient model [10]

Symbols	Meaning
u(t)	Infusion rate
X1	Rate of drug in blood
X2	Rate of drug in fat part
X3	Rate of drug in muscle part
Xe	Flow of drug in effect side part
Ce	Effect side drug rate
K10	Elimination rate constant
K1e	Effect side rate
Ke0	Effect side elimination rate
Kij	Drug transfer rate from j^{th} part to the i^{th} part

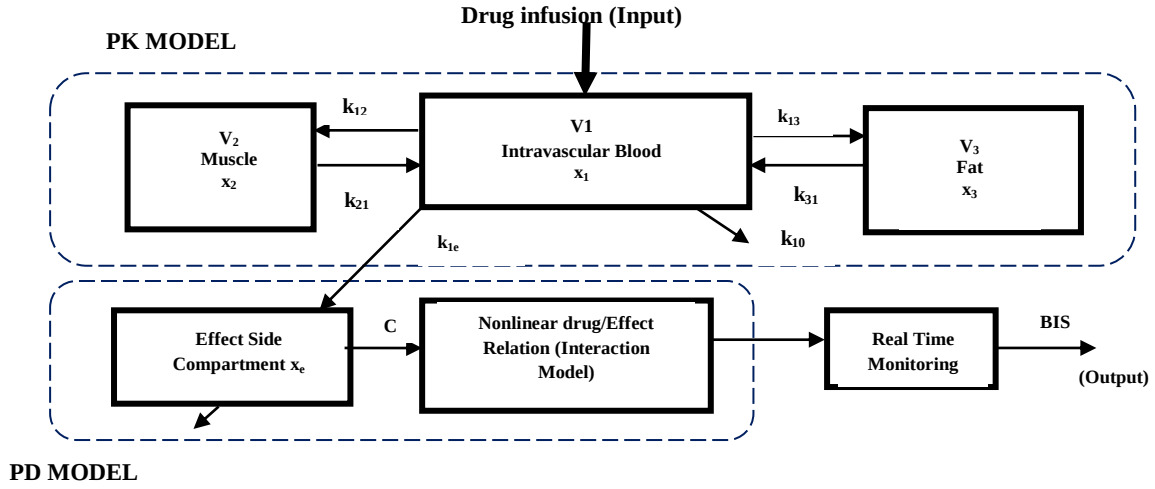

Figure 1 Patient mathematical model

The Equations that explain the PK part model are represented by the following relations:

$$x_1'(t) = -[K_{10} + K_{12} + K_{13}].x_1(t) + K_{21}.x_2(t) + K_{13}.x_3(t) + u(t) \quad (1)$$

$$x_2'(t) = K_{12}.x_1(t) - K_{21}.x_2(t) \quad (2)$$

$$x_3'(t) = K_{13}.x_1(t) - K_{31}.x_3(t) \quad (3)$$

The PD part model equation as shown below in Equation 4:

$$x_e'(t) = -K_{e0}.x_e(t) + K_{1e}.x_1'(t) \quad (4)$$

Applying Laplace transform on Equations 1, 2, 3 and 4, we obtain the input and output relationship as shown in Equations 5, 6, 7 and 8:

$$sX_1(s) = -[K_{10} + K_{12} + K_{13}].X_1(s) + K_{21}.X_2(s) + K_{13}.X_3(t) + u(s) \quad (5)$$

$$sX_2(t) = K_{12}.X_1(s) - K_{21}.X_2(s) \quad (6)$$

$$sX_3(t) = K_{13}.X_1(s) - K_{31}.X_3(s) \quad (7)$$

$$sX_e(t) = -K_{e0}.X_e(s) + K_{1e}.X_1(s) \quad (8)$$

Then solving Equations 5, 6, 7 and 8 to find the final relations as indicated below in Equations 9 and 10:

$$PK(s) = \frac{X_1(s)}{U(s)} = \frac{b_2s^2 + b_1s + b_0}{a_3s^3 + a_2s^2 + a_1s + a_0} \quad (9)$$

Where b2=1, b1 = $K_{21} + K_{31}$, $b_0 = K_{21}.K_{31}$, $a_3 = 1$, $a_2 = (K_{10} + K_{12} + K_{13} + K_{31})$, $a_1 = (K_{10}.K_{21} + K_{10}.K_{31} + K_{12}.K_{31} + K_{13}.K_{21} + K_{31}K_{21})$, $a_0 = K_{10}.K_{21}.K_{31}$.

Parameters used in PK Equation above are calculated according to Schnider model as explained in Appendix A.

$$PD(s) = \frac{K_{e0}}{(s+K_{e0})} \quad (10)$$

Finally, patient model is shown in Equation 11 [6]:

$$\text{Patient Model} = \frac{b_2s^2 + b_1s + b_0}{a_3s^3 + a_2s^2 + a_1s + a_0} * \frac{K_{e0}}{(s+K_{e0})} \quad (11)$$

BIS device or monitoring tool is explain the patient's hypnosis level of, it have a known index for measuring DOA starting from 0 to 100. Its value from 0 to 100. Zero indicates that there is no encephalic activity, and 100 indicate that the patient is completely awake and not take any drug dose. During surgery, the specified BIS value must be 50 and should stay in a range from 40 to 60, to reach to the suitable anesthetized state. The BIS parameter has a relation with drug effect concentration C_e by a nonlinear equation as shown in Equations 12 called hill equation or the Sigmoid E_{max} curve:

$$BIS(t) = E_0 - E_{max} \frac{C_e(t)^\gamma}{C_e(t)^\gamma + EC_{50}{}^\gamma} \quad (12)$$

Where E_0 represents the patient state without taking any drug, since it is equal to 100, E_{max} describes the full effect value measured due to the dose rate, EC50 is the dose rate at half full effect and reflects the dose response on patient state and γ explains the steepness of the equation. The final relation will be the hill inverse equation as shown in Equation 13 [10]:

$$C_e(t) = EC_{50}.\left(\frac{E_0 - BIS(t)}{E_{max} - E0 + BIS(t)}\right)^{1/\gamma} \quad (13)$$

All the relations above converted the patient model into system has an input value u(t) and output value related to BIS value measured, now the system is

completely prepared to be controlled by the proposed controller.

Biogeography-based optimization

Biogeography-based optimization (BBO) algorithm is depending on distribution of habitat biogeography. In this algorithm, the result is comparable to a habitat and the parts are comparable to suitability index variables (SIVs). The object function of any result be compared with the wealth of habitat or habitat suitability index (HSI). The most important variables in BBO are migration and mutation variables. The first one is explained as exploitation parameter is maintained for enhancing the existing habitats depending on the values of their immigration and emigration. In fact, the migration parameter develops the indigent habitats. Mutation parameter is a significant parameter because it raises variety to drive this optimization method to isolate local optimums then after that discovers the seeking field. This parameter can alter the random modifications of the SIVs of a habitat depending on the prime probability of existence P_i. The mutation rate m_i is shown in Equation 14:

$$m_i = m_{max}(1 - \frac{P_i}{P_{max}}) \quad (14)$$

Where m_{max} is defined by user and P_{max} is the maximum value of P_i [11].

In a simple BBO algorithm, the immigration and emigration parameters will be calculated by Equation 15 and 16 below:

$$\lambda_j = \mathrm{I}(1 - \frac{k_J}{n}) \quad (15)$$

$$u_j = \mathrm{E}(\frac{k_J}{n}) \quad (16)$$

where λ_j indicates the immigration value at j^{th} individual(island) , u_j explains the emigration value at j^{th} individual(island), I explains maximum possible of immigration value and finally E explains maximum possible of emigration value [12]. The flowchart of applying BBO algorithm on controller has been shown in *Figure 2*.

The proposed controller schemes

The block diagram for proposed controller scheme is shown in *Figure 3*. It consists of the sliding mode control (SMC) combine with single self-tune neural network. In addition to use the inverse hill function with feedback connection the desired reference signal has been used also.

This function used as an exact linearization method to avoid the nonlinearity caused by hill equation in the considered model.

The following subsection explains the details about the proposed controller parts:

Sliding mode controller part

The function of proposed controller is to adopt a neuro SMC to prove and achieve desired response despite of the inter-intra patient's variability. It ensures the limit values for the parameters using closed-loop method, and reach to the best final value of set point signal. The essential idea of using the SMC is to move the system response from any initial state to the sliding surface (i.e. reaching phase). The system is then stayed on this surface for all future values of time (sliding phase). The main benefit gained by using the SMC is its low sensibility to plant disturbances and uncertainties. It is one of the best and effective robust controllers can be adopted efficiently in nonlinear plants or systems. To do these points mentioned, the sliding function Equation 17 has been used.

$$s(t) = \lambda_1 \dot{e}(t) + \lambda_2 e(t) \quad (17)$$

Where $e(t)$ is the error which and is equal to:

$$e(t) = x(t) - x_d(t) \quad (18)$$

For keeping $s(t)$ reach zero value, and make the system state trajectory stay in a sliding surface, $s(t)$ 0, outside the boundary specified for sliding surface. Then the stability analysis is done by using the Lyapunov function candidate:

$$V = \frac{1}{2} S(t)^{\mathrm{T}}.\mathrm{S(t)} \geq 0 \quad (19)$$

It depends on the time derivative for the above Equation 19. The reaching condition (sliding condition) is obtained by Equation 20:

$$S(t)^{\mathrm{T}}.\mathrm{S(t)} \leq -\eta\ |\mathrm{S(t)}| \quad (20)$$

Where Ƞ is a positive constant that guarantees the system, response hits the sliding surface in a finite time [13].

Single self-tune neural network

A single neuron PID controller is combined with a neural network have a structure of delta learning method and it is supervised type which is shown in *Figure 4.*

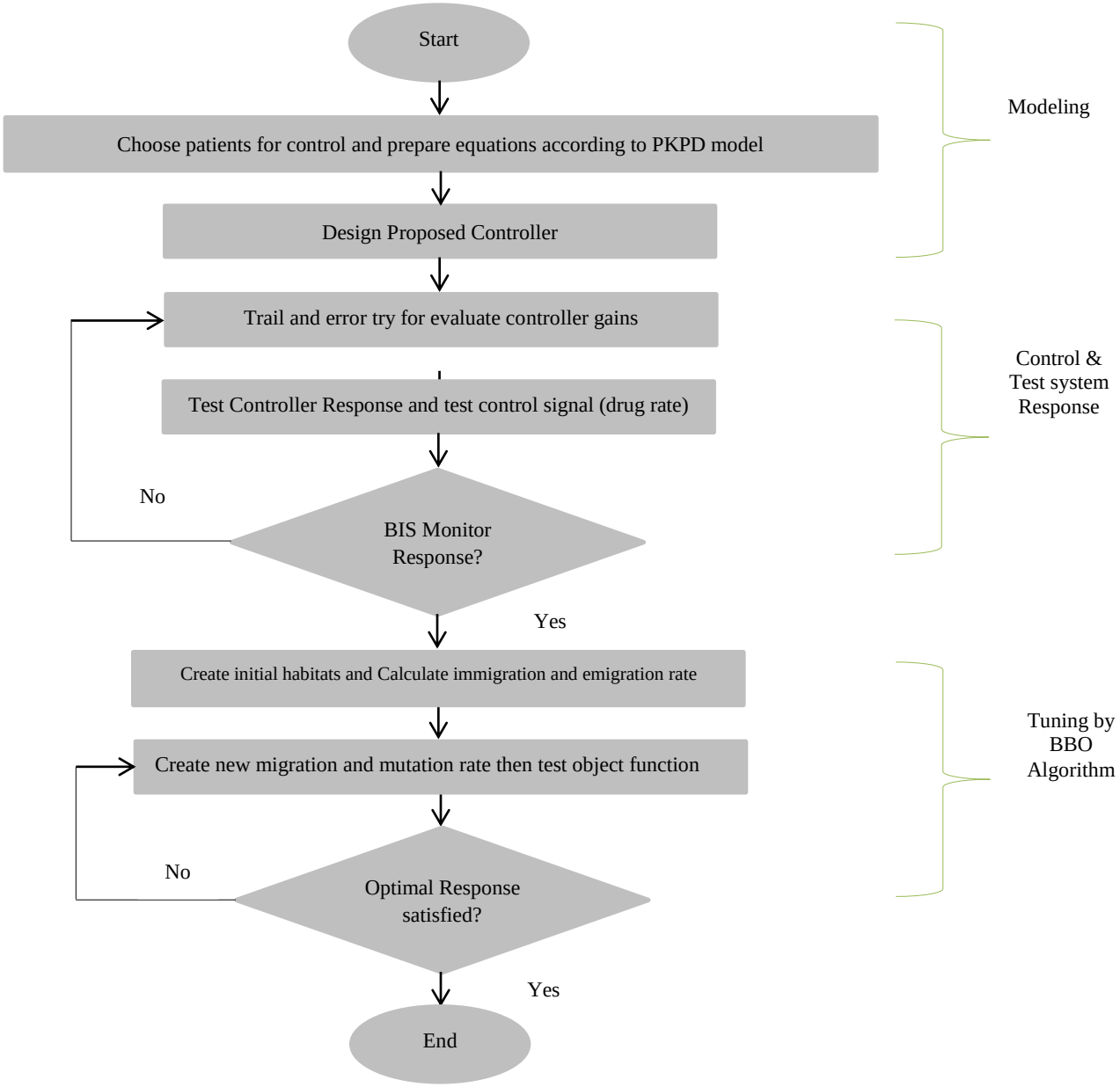

Figure 2 Flowchart of the applying BBO algorithm on system

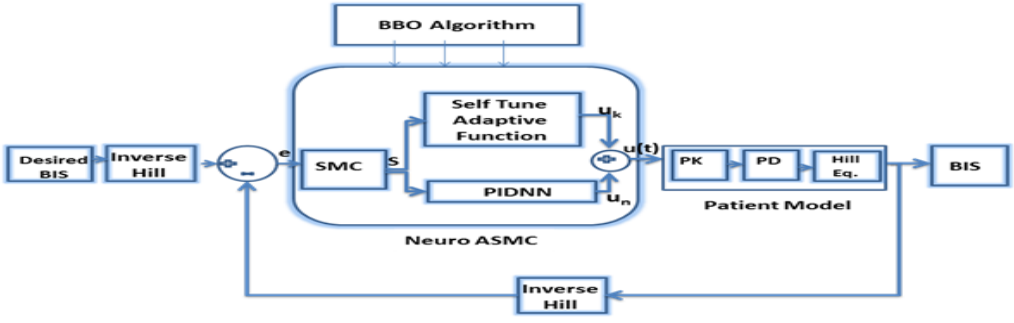

Figure 3 Proposed Neuro ASMC controller

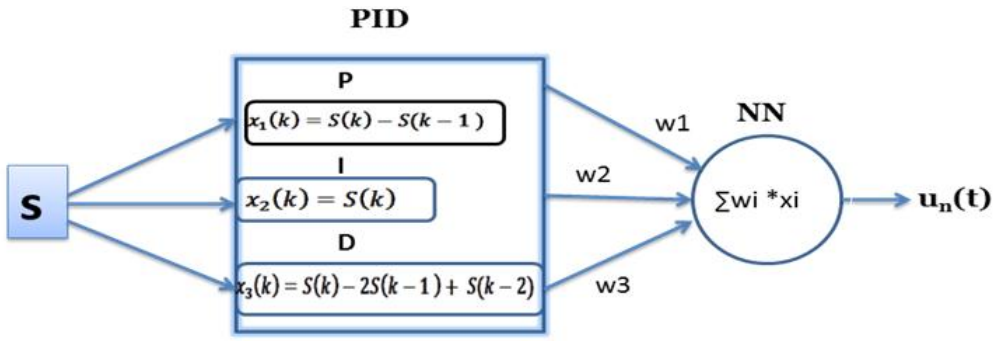

Figure 4 Single self-tune neural network

As shown in *Figure 4* the sliding function is representing the input to the neural network. The weights of the neural network are [w_1, w_2, w_3], representing the self-tune controller gain values, [x_1(k), x_2(k), x_3(k)] are the error corresponding to PID controller proportional error, integral error and the derivative error which is shown below in Equations 21, 22 and 23.

$x_1(k) = S(k) - S(k-1)$ (21)

$x_2(k) = S(k)$ (22)

$x_3(k) = S(k) - 2S(k-1) + S(k-2)$ (23)

The final Equation 24 is shown below:

$u(k) = u(k-1) + K \sum_{i=1}^{3} (w_i(k).x_i(k))$ (24)

K is a gain variable used to adjust the system response.

The new weights after updating is shown in Equations 25, 26 and 27 [14].

$w1(k) = w1(k-1) + \eta_p S(k-1)u(k-1)$ (25)

$w2(k) = w2(k-1) + \eta_I S(k-1)u(k-1)$ (26)

$w3(k) = w3(k-1) + \eta_D S(k-1)u(k-1)$ (27)

Combine sliding controller with the single self-tune neural network

As shown in *Figure 3* and *Figure 5*, the sliding function s is the input of the single neural network, and the suggested neuro SMC control low indicated in Equation 28.

$u = u_n * u_k$ (28)

Where u_k will be the self tune adaptive function and u_n will be the output of PID Neural network (PIDNN), u_k is an absolute of a tangent hyperbolic function as shown in Equation 29.

$u_k = abs(\tanh(k * S))$ (29)

3.Simulation results

To start simulation and analysis for maintaining proposed controller for monitoring and controlling the DOA, it must know in which region the controller work since the GA consists of three regions. The first one is the pre-operation in which the patient is awake and in full awareness, the second region is the induction and maintenance in which patient is in a conscious state (BIS indicate 100) after that start to be in a mid-hypnotic level (BIS reads of 40-60). This stage must be better monitored and controlled to ensure the surgery steps safety and finally the recovery phase in which the patient's body may extract the anesthetic drug uniformly to recover its consciousness. Since from above declaration the adaptive proposed controller may work in the second phase and consider the BIS reading is the controllable value that must be tracked as a set point and with the help of the closed loop scheme (optimized feedback). The adaptive gain function may ensure the robustness of the controller to be in stable action despite of any disturbances until reach to recovery phase with stable steps. Now for modeling the human body to be controlled, a PKPD model is chosen because it is acceptable for pharmakacology field to translate drug effect and its relation to the characteristics of the human body like (height, weight, age, gender) in which it is influenced directly on the rate of the anesthetic drug (is considered as control signal). PK part is considered to describe the dose distribution of the human body, by explaining the dose transfer and distribution in the blood while the other PD part explain the relation between dose concentration and noticed signs during surgery appeared clinical signs and electroencephalogram (EEG) shown monitor. There is also a nonlinear relation that describes the connection between the dose concentration and its effect; pharmacodynamic model has adopted the famed and known relation hill equation. The simulation and analysis were done in five cases as indicated below in *Table 2* [1]:

Table 2 Characteristic of patients [1]

PAT.	Age	Height	Weight	Sex	EC50	E0	Emax	Γ
1	28	164	52	F	8.44	91.2	80.7	4.1
2	50	163	83	F	6.44	95.9	102	2.18
3	28	164	60	M	4.93	94.7	85.3	2.46
4	43	163	59	F	12.1	90.2	147	2.42
5	37	187	75	M	8.02	92	104	2.1

The proposed ASMC is maintained to track the specified BIS index value (i.e. 50). It is also saving constraints and robust enough to reject any disturbances may happen. At starting the medical operation, the patient was completely awake state i.e. BIS=100 and after the drug dose will start increasing until BIS monitor read value of 50 as shown in *Figure 5*.

The drug input rate has been calculated and tuned in an optimized and adaptive gain of the proposed controller as explained in *Figure 6*. For ensuring that the wanted value will reach, it is shown that the drug dose calculated by the controller satisfied the specific constraints, but there is a very small steady state error appeared as shown in *Figure 7*.

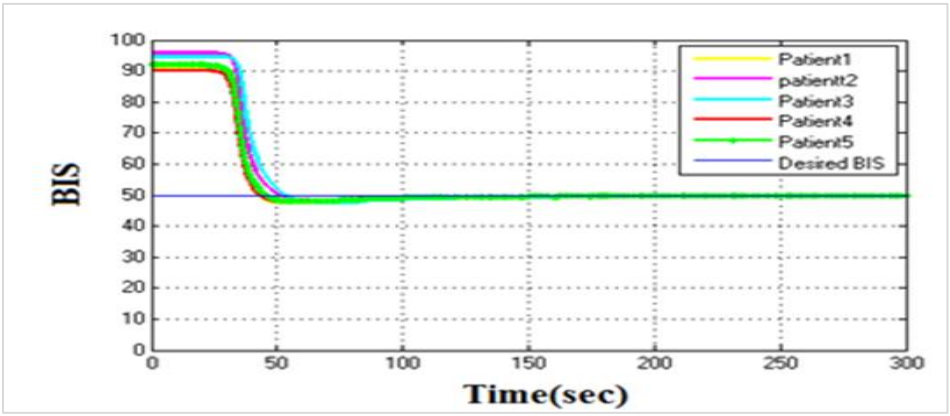

Figure 5 BIS reading t for all 5 patients

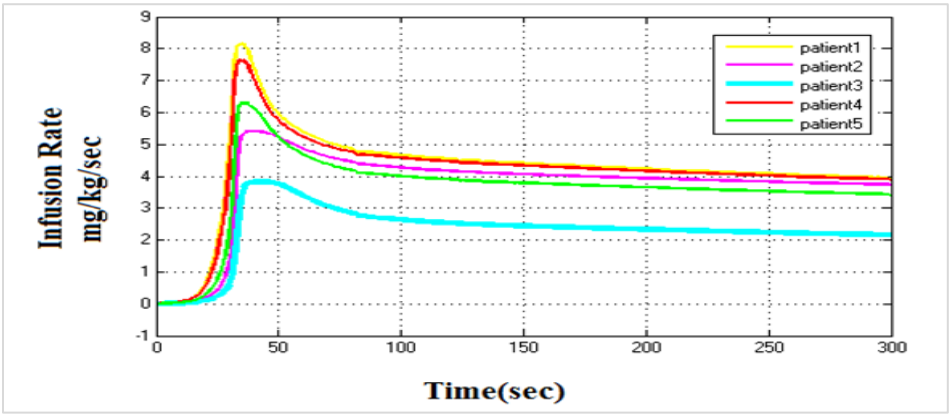

Figure 6 Drug infusions for all 5 patients

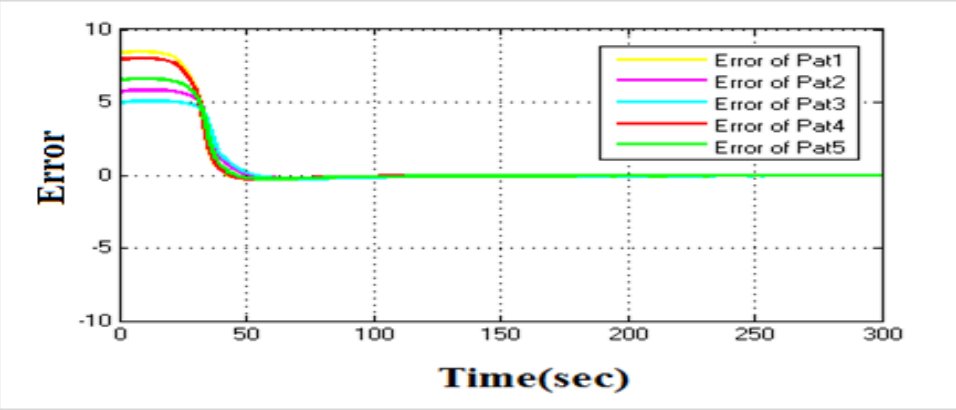

Figure 7 Error Estimated for all 5 patients

For tuning the proposed controller parameters (λ_1, λ_2) BBO algorithm is used, firstly the BBO algorithm produces an initial result in search field. Every initial solution can be assumed as a candidate solution for the controller. In this work, the number of population size is assumed to be 40 and the mutation probability is equal to 0.01 as shown in *Table 3*. Then after a number of iterations run optimal values of the gains is calculated to obtain the best response. These optimal values of all variables are gained from decreasing the integral time absolute error (ITAE) cost function based on the Equation 30.

$$ITAE = \int t|\, e|\, d \qquad (30)$$

Table 3 BBO variables

BBO Variables	The selected value
Generation limit	10
Population size	40
Mutation probability	0.01
Number of elites	2
Min. domain	0
Max. domain	3

4.Discussion

The response of the proposed controller obtained in this study was compared with the other studies. In fact, the same patient model and the same propofol drug used for controlling the action in [4, 6] while in [5, 9] used two drug propofol and regimental. But if analyzing the controlling action for the induction and maintenance phase, induction period will start from the starting of the surgery till reach 50 seconds. It is shown in *Figure 5*, but in [4], it will start from the starting till at approximately two and half minute it mean after 150 seconds and in [6] start from starting to approximately 80 seconds while in [7] reach to five minutes and then the maintenance phase will start after that till finishing the surgery for all [4, 6, 7, 9]. The varying in the induction phase period for patients will affected by many parameters like age, weight, gender and height. These parameters also affected on the infusion rate for each patient as we see in drug rate, more drug dose as shown also in [4, 6, 9] while in [8] the rate for the two-drug used was changed always with time. This mean that it needs good monitoring from the doctors responsible of anesthesia process then when the patient is stable and entered in the hypnosis level. The rate has specified preciously but also each patient have its own dose rate depending on its real characteristics and his health status as shown in *Figure 6*. Finally, if we look to the curve of the error, we see that error bonded value was acceptable for medical surgery as appeared also in [4]. Its overcome by using derivative action in designing their controller but in [6] its measured in between 5 in which it is also acceptable values but in [9] a big error value appeared in the BIS signal. It is related to dose minimizing, so that "false" high BIS values will appeared, then an additional dose will give immediately, also a lower BIS value was noticed and it appeared due to some interruptions may happens because of some medical factors but in [5] an estimation with Kalman filter were used to decrease the error value appeared.

SMC was tracking the set point value and the closed-loop feedback scheme completely enhances the performance of the anesthesia step in the surgery. The SMC and the adaptive gain chosen control the system to reach to the wanted value of BIS index in a little period of time. The most essential matters of using the PKPD model and the proposed SMC is the considerable and good focusing on the high inter and intra-patient variability, responses according to the hypnotic agent besides these two reasons also the model parameter related to human body real

characteristics. These issues are considered as important issues for the proposed ASMC to deal with when controlling the DOA.

5.Conclusions and future work

Controlling the DOA of patients during surgery has been an active scope of study for several decades. Design an adaptive neuro SMC for automating the drug delivery of anesthetic drug has been considered in this paper. It is utilized to assess the monitoring of DOA by dividing the controller into a number of nonlinear subsystems, and then due to this the complexity of controller design is minimized. The suggested SMC calculates various amounts of drug dose for all the patients, according to the difference in their characteristics like age, weight, height, gender and finally provides the suitable values of DOA. This indicates that the proposed controller gives good results and efficient response despite of the intra and inter-patient variability also the stability driven from closed-loop control scheme and tuning the controller gains according to interpatient variability enhance the system efficiency. This leads to a stable behavior and efficient estimating of propofol administration and also resulting to reach to a suitable and adequate BIS reading and finally ensures the ability to induce the patients in an acceptable clinical period. In the future other optimization algorithms like genetic algorithm technique or differential evaluation technique also may be applied on a microcontroller or on FPGA kit and try to build an embedded controller to automate all the controller parts as one chip or a separate device. The input for the proposed controller will be fed from patient characteristics and the output will be displayed, and can also be suggested to be either off line or on line operation, which is also be a valuable researching field in the future.

Appendix

When we say that the parameters used in PK equations above are calculated according to Schnider model, it means that the equations have been written as indicated below:

$V_1 = 4.27\ [l], V_2 = 18.9 - 0.391.(age - 53)\ [l], V_3 = 238\ [l]$ (1)

$C_{l1} = 1.89 + 0.456(weight - 77) - 0.0681(lbm - 59) + 0.264(height - 177)[\ l/min]$ (2)

$C_{l2} = 1.29 - 0.024(age - 53)[\ l/min], C_{l3} = 0.836[\ l/min]$ (3)

$K_{10} = C_{l1}\ /\ V_1\ min^{-1}, K_{12} = C_{l2}\ /\ V_1\ min^{-1}, K_{13} = C_{l3}\ /\ V_1\ min^{-1}$ (4)

$K_{21} = C_{l2}/\ V_2\ min^{-1}, K_{31} = C_{l3}/\ V_3\ \ min^{-1}, K_{e0} = 0.456\ min^{-1}$(5)

The C_{l1} is the rate that extracted from the body, and C_{l2} and C_{l3} are the rates that extracted from central compartment to other compartments by distribution. The lean body mass (lbm) for men (M) and women (F) are calculated as shown below:

$$lbm_{\_M} = 1.1\ .weight - 128\ \frac{weight^2}{height^2} \quad (6)$$

$$lbm_{\_F} = 1.07\ .weight - 148\ \frac{weight^2}{height^2} \quad (7)$$

All these equations were regarded when we use the most famous model Schnider model and choose the propofol drug to be estimated.

Acknowledgment

None.

Conflicts of interest

The authors have no conflicts of interest to declare.

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