Rev Bras Anestesiol. 2017;67(2):122–130

Sociedade Brasileira de Anestesiologia

REVISTA BRASILEIRA DE ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br

SCIENTIFIC ARTICLE

# Regulation of hypnosis in Propofol anesthesia administration based on non-linear control strategy

**Muhammad Ilyas**[a], **Ali Khaqan**[a], **Jamshed Iqbal**[b,*], **Raja Ali Riaz**[a]

[a] *COMSATS Institute of Information Technology, Department of Electrical Engineering, Chak Shahzad, Pakistan*
[b] *National University of Computer and Emerging Sciences (FAST-NU), Department of Electrical Engineering, Islamabad, Pakistan*

Received 28 May 2015; accepted 17 August 2015
Available online 11 May 2016

**KEYWORDS**
Closed-loop anesthesia;
Modern control;
Biocontrol;
Pharmacodynamics;
Pharmacokinetics

**Abstract** Continuous adjustment of Propofol in manual delivery of anesthesia for conducting a surgical procedure overburdens the workload of an anesthetist who is working in a multi-tasking scenario. Going beyond manual administration and Target Controlled Infusion, closed-loop control of Propofol infusion has the potential to offer several benefits in terms of handling perturbations and reducing the effect of inter-patient variability. This paper proposes a closed-loop automated drug administration approach to control Depth Of Hypnosis in anesthesia. In contrast with most of the existing research on anesthesia control which makes use of linear control strategies or their improved variants, the novelty of the present research lies in applying robust control strategy i.e. Sliding Mode Control to accurately control drug infusion. Based on the derived patient's model, the designed controller uses measurements from EEG to regulate DOH on Bispectral Index by controlling infusion rate of Propofol. The performance of the controller is investigated and characterized with real dataset of 8 patients undergoing surgery. Results of this *in silico* study indicate that for all the patients, with 0% overshoot observed, the steady state error lies in between ±5. Clinically, this implies that in all the cases, without any overdose, the controller maintains the desired DOH level for smooth conduction of surgical procedures.


* Corresponding author.
*E-mail:* jamshed.iqbal@nu.edu.pk (J. Iqbal).

http://dx.doi.org/10.1016/j.bjane.2015.08.011

**PALAVRAS-CHAVE**
Anestesia de circuito fechado;
Controle moderno;
Biocontrole;
Farmacodinâmica;
Farmacocinética

**Controle da hipnose na administração de propofol com base na estratégia de controle não linear**

**Resumo** O ajuste contínuo de propofol na administração manual de anestesia para a realização de um procedimento cirúrgico onera a carga de trabalho de anestesiologistas que trabalham em ambiente multitarefa. Indo além da administração manual e da infusão alvo-controlada (IAC), o controle de circuito fechado da infusão de propofol tem o potencial de oferecer vários benefícios em termos de manejo das perturbações e reduzir o efeito da variabilidade interpaciente. Este artigo propõe uma abordagem para a administração automatizada de drogas em circuito fechado para controlar a profundidade da hipnose (PDH) em anestesia. Em contraste com a maioria das pesquisas existentes sobre o controle da anestesia que usam estratégias de controle linear ou de suas variantes melhoradas, a novidade da presente pesquisa reside na aplicação de uma estratégia de controle robusto; isto é, o Controle por Modos Deslizantes (CMD) para controlar com precisão a infusão da droga. Com base no modelo derivado do paciente, o controlador projetado usa as medições do EEG para regular a PDH no Bispectral Index (BIS), controlando a taxa de infusão de propofol. O desempenho do controlador é investigado e caracterizado com um conjunto de dados reais de oito pacientes submetidos à cirurgia. Os resultados deste estudo in silico indicam que, para todos os pacientes, com 0% de excesso observado, o erro de estado estacionário fica entre $\pm 5$. Clinicamente, isso implica que em todos os casos, sem qualquer sobredosagem, o controlador mantém o nível desejado de PDH para a condução tranquila dos procedimentos cirúrgicos.


## Introduction

Thanks to technological advancements, the benefits offered by modern medicine have totally transformed the concept of clinical surgery. Nowadays, surgical procedures can be performed with much ease and comfort. This incredible milestone has been achieved only through the research outcomes in modern anesthesia. Prior to the discovery of anesthesia, surgery has to be conducted extremely fast. Historically, trivial techniques like application of cold, compression of nerve or reduction in cerebral perfusion were employed to keep patient unconscious.[1] Undoubtedly, invention of inhalation gases in 1840 by Hickman was a pivotal step toward discovery of anesthesia to finally permit conduction of invasive surgeries. The first procedure of anesthesia, based on diethyl ether, was performed in 1842 by C.W. Long. This new revolutionary concept was later on termed as anesthesia meaning lack of esthesia i.e. sense.

Anesthesia is intensively used particularly in medical domain in many applications including surgical operation with incision, dental surgery and intensive care.[2] The primary objective of anesthesia is to offer painless feelings to a patient under operation by driving him/her into unconscious state without memory. The overall functional scenario of anesthesia can be categorized into three temporal phase in sequence: induction, maintenance and emergence. During the first phase, the objective is to bring a patient to a reference Depth of Hypnosis (DOH). It is then necessary to administer the anesthetic drug in order to maintain an adequate DOH. For induction and maintenance of anesthesia, commonly used intravenously administered anesthetic drug is Propofol.[3] During emergence phase in post-surgery activities, vaporizer and other infusion devices are turned off so as to enable patients to awake fast.

During general anesthesia, Propofol is usually used together with fast acting opioids e.g. remifentanil to have a synergistic effect.[4] Under-dosing of anesthetic drugs may lead to insufficient analgesia or awareness. On the other hand, it is dangerous for patients to have excessive amount of drug. Thus careful management of the intravenous drug delivery is the key factor behind successful anesthesia practice. It is desirous to access the depth of anesthesia together with automatic and interactive drug administration with little human intervention so as to adjust drug dosage accordingly for balancing the anesthetic state, autonomic function and response to noxious stimuli.

The procedures to administer intravenous drug delivery have been evolved from simple manual delivery and computer-assisted automated Target Controlled Infusion (TCI) to more sophisticated Closed-Loop ANesthesia (CLAN). Traditionally, hypnotic drug delivery rates in intravenous anesthesia are manually controlled by an anesthetist. Doses are principally decided based on patient demographics, qualitatively measured signs (e.g. presence of certain reflexes, movement) and quantitatively measured signals (e.g. oxygen saturation, blood pressure, heart rate). The dosage scheme is then tuned by hit and trial to optimize anesthesia and to evade toxicity. TCI, also known as Computer Assisted Continuous Infusion (CACI),[5] relies on population-based pharmacokinetic (PK) and pharmacodynamic (PD) models[6] for calculating an adequate infusion profile to achieve the reference drug concentration set by the anesthesiologist. Given the past and present infusion rates, these models can predict the time evolution

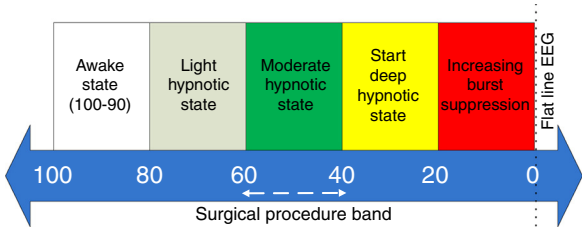


**Figure 1** BIS scaling band to indicate DOH level.

of plasma concentration. This prediction is then used to track the reference concentration thus devising an open loop control paradigm. Instead of adjusting the infusion rate, the anesthetist manipulates the reference concentration, both reactively and proactively, using commercially available infusion pumps. TCI systems suffer from drawbacks of sensitivity to model non-linearities and disturbances since there is no feedback of measurement on drug effect. These drawbacks can be addressed by closing the control loop through DOH measurement, which is given by EEG-based monitors e.g. Bispectral Index (BIS).[7] The value of BIS is mapped to the DOH level of a patient based on the scaling band shown in Fig. 1. The value of 100–90 corresponds to a fully awake state while level of 90–60 and 60–40 indicate light and moderate hypnosis levels respectively.[8] The moderate level represents the surgical procedure band in which general surgery is performed by clinical professionals. Level beyond deep hypnotic state (40–20) is quite dangerous.[9]

In a CLAN system, drug effect is measured in real time and is compared with the reference DOH to obtain an error signal. Based on which, the system subsequently adjusts a drug infusion rate. A CLAN system offers several benefits in comparison with a TCI system including automatic handling of perturbations, precise control of drug infusion rate, minimizing the effect of patient variability and reducing the need of anesthetist intervention.

Trend to realize a CLAN system has been based on trivial or linear control approaches.[10] Dong[2] proposed a CLAN system for total intravenous anesthesia based on Proportional, Integral, Derivative (PID) controller. With BIS as sensory feedback and Digital Signal Processing (DSP) based supervisory system, the realized system was tested on 21 healthy volunteers and 15 patients undergoing surgery. Except for the 2 patients, satisfactory clinical results were obtained. Another study[11] based on PID control investigated the control performance with 10 patients undergoing elective hip or knee surgery. The median absolute performance error was found to be 8%. The control strategy was able to provide adequate anesthesia in 9 patients with oscillatory response recorded in BIS values for 3 patients. Other prominent studies reporting PID control of anesthesia include.[12,13] Comparing conventional PID with Linear Model Predictive Control (LMPC), it is reported in Ref. 14 that the later approach outperforms in terms of robustness to intra and inter-patient dynamics and handling disturbances, constraints and measurement noise. Recent studies[15–18] aim to improve linear approaches by properly tuning the controllers to achieve sufficient robustness margins for identifiable uncertainties. However, for control laws based on the linear approaches, the model of a patient, exhibiting a non-linear behavior, is linearized. Such approximation achieves good control performance only if the difference between the predicted and actual closed-loop systems is small for the designed controller.[19] The traditional PID controller cannot handle disturbances like blood pressure changes, neural muscular blockade and heart rate variability[10] and may result in oscillatory behavior during clinical trials. Also for wide acceptance of a CLAN system by clinical professionals and regulatory bodies, guarantees of robust stability and performance are must. Employing a non-linear and robust control strategy is therefore need of the hour in clinical anesthesia.

This research is aimed at unleashing the potential of a sophisticated control strategy i.e. Sliding Mode Control (SMC) to manage Propofol anesthesia infusion rate. The paper is organized as follows: Section II derives patient model. Section III explains the design details of SMC while Section IV presents results based on clinical parameters of actual patients. Finally Section V comments on conclusion.

## Patient model

The dynamics of the hypnotic drug is categorized in its pharmacokinetics (PK) and pharmacodynamics (PD) parameters. The PK parameter is used to govern the behavior of the infused drug in the body over time including its distribution, metabolism, absorption and clearance[20] while the PD parameter represents the drug concentration in the blood and the corresponding impact caused at the effect site.[21]

On the basis of blood flow in different organs, medical literature divides human body into various compartments.[22] Compartmental model represents a basic kinetic approach to describe drug absorption, distribution and elimination.[23] Relating plasma drug levels to PD parameters, this model is intensively used in various biomedical and biotechnical applications because of their inherent flexibility and simplicity. The integrated PKPD structure follows compartmental modeling. In the present study, a three compartment PK model with an additional effect compartment has been adopted owing to its sufficient precision and computational efficiency.[24] Centred on a primary compartment (intravascular blood) with volume $V_1$, a rapid peripheral compartment (muscle) and a slow peripheral compartment (fat), with volumes $V_2$ and $V_3$ respectively, are connected to the primary compartment. Thus distribution and elimination of the drug between primary and peripheral compartments take place with weighted rate constants $k_{12}$, $k_{21}$, $k_{13}$, $k_{31}$ as depicted in Fig. 2. At any time, the change in concentration of drug in primary compartment is related to the drug moved to and from the rapid and slow peripheral compartments. The induction and clearance of the drug takes place through the primary compartment. The drug eliminates from this compartment in an exponential fashion.[17] At the effect side (brain), the concentration of the drug is measured through the cortical activity in the brain measured through the modified form of EEG signal.[25] The extracted information can then be mapped to Depth Of Hypnosis (DOH) so as to analyze patient's suitability for surgical procedures.

Table 1 shows the nomenclature for derivation of patient model.

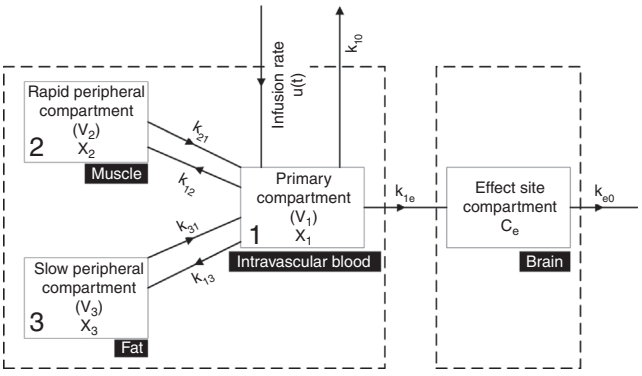


**Figure 2** Block diagram of PK and PD models.

To derive the PK model, state equations corresponding to the three compartments can be written as (1)–(3)

$$\dot{x}_1(t) = -k_{10}x_1(t) - k_{12}x_1(t) - k_{13}x_1(t) + k_{21}x_2(t) + k_{31}x_3(t) + u(t) \tag{1}$$

$$\dot{x}_2(t) = -k_{12}x_1(t) - k_{21}x_2(t) \tag{2}$$

$$\dot{x}_3(t) = -k_{13}x_1(t) - k_{31}x_3(t) \tag{3}$$

Laplace transform of (1)–(3) yields (4)–(6)

$$sX_1(s) = -(k_{10} + K_{12} + K_{13})X_1(s) + k_{21}X_2(s) + k_{31}X_{13}(s) + \mu(t) \tag{4}$$

$$sX_2(s) = k_{12}X_1(s) - k_{21}X_2(s) \tag{5}$$

$$sX_{23}(s) = k_{13}X_1(s) - k_{31}X_3(s) \tag{6}$$

Solving (4)–(6), the input–output relationship can be written as (7)

$$D_p(s) = \frac{X_1(s)}{U(s)} = \frac{(s^2 + s(k_{21} + k_{31}) + k_{21}k_{31})}{(s^3 + s^2(k_{10} + k_{12} + k_{21} + k_{13} + k_{31}) + s(k_{10}k_{21} + k_{10}k_{31} + k_{13}k_{21} + k_{31}k_{21}) + (k_{10}k_{21}k_{31}))} \tag{7}$$

where $D_p(s)$ is the rate of drug absorption/metabolism within the body defined as disposition rate. Rewriting (7), the general form of PK model is obtained as

$$D_p(s) = \frac{X_1(s)}{U(s)} = \frac{b_2s^2 + b_1s + b_0}{a_3s^3 + a_2s^2 + a_1s + a_0} \tag{8}$$

where $b_2 = 1$, $b_1 = \kappa_{21} + \kappa_{31}$, $b_0 = \kappa_{21}\kappa_{31}$, $a_3 = 1$, $a_2 = (\kappa_{10} + \kappa_{12} + \kappa_{13} + \kappa_{31})$, $a_1 = \kappa_{10}\kappa_{21} + \kappa_{10}\kappa_{31} + \kappa_{12}\kappa_{31} + \kappa_{13}\kappa_{21} + \kappa_{31}\kappa_{21}$, $a_0 = \kappa_{10}\kappa_{21}\kappa_{31}$

The PD model indicating level of consciousness relates concentration of the drug in plasma to the effect site concentration and can be derived based on the state Eq. (9)

$$\dot{x}_e(t) = k_{1e}x_1(t) - k_{e0}x_e(t) \tag{9}$$

Applying Laplace transform on (9)

$$sX_e(s) = k_{1e}X_1(s) - k_{e0}X_e(s) \tag{10}$$

**Table 1** Nomenclature.

| Symbol | Unit | Name |
|---|---|---|
| $u(t)$ | mg seg$^{-1}$ | Infusion rate |
| $k_{10}$ | seg$^{-1}$ | Elimination rate constant |
| $x_1$ | mg | Amount of drug in primary compartment |
| $x_2$ | mg | Amount of drug in rapid peripheral compartment |
| $x_3$ | mg | Amount of drug in slow peripheral compartment |
| $x_e$ | mg | Flow of hypnotic agent in effect site |
| $k_{1e}$ | s$^{-1}$ | Rate constant at effect site |
| $k_{e0}$ | seg$^{-1}$ | Elimination rate constant at effect site |
| $C_e$ | mg L$^{-1}$ | Effect site concentration |
| $E_0$ | – | Awake stage (100–90) |
| $E_{max}$ | – | Maximum effect achieved by drug infusion |
| $C_{50}$ | mg L$^{-1}$ | Drug concentration at half of the maximum effect |
| $\gamma$ | – | Sigmoid curve slope parameter |

Considering $k_{1e}$ and $k_{e0}$ are equal because of its negligible volume of the effect site compartment, the disposition rate at the effect side is given by (11)

$$D_e(s) = \frac{X_e(s)}{X_1(s)} = \frac{k_{e0}}{(s + k_{e0})} \tag{11}$$

Based on the cascaded nature of PK and PD models, the overall patient model can finally be written as

$$H_p(s) = \frac{k_{e0}}{(s + X_{e0})} * \frac{b_2s^2 + b_1s + b_0}{a_3s^3 + a_2s^2 + a_1s + a_0} \tag{12}$$

BIS is related with anesthetic effect site concentration $C_e(t)^{\gamma}$ through nonlinear sigmoid model i.e.

$$\text{BIS}(t) = E_0 - E_{max} * \frac{C_e(t)^{\gamma}}{C_e(t)^{\gamma} + C_{50}^{\gamma}} \tag{13}$$

where $C_e(t)$ can be computed by integrating (14)

$$\dot{C}_e(t) = -0.1068x_1 + 0.456C_e \tag{14}$$

## Control design

The overall closed-loop system in the present study mainly consists of SMC and cascaded PK-PD model. The output of this model is fed to the sigmoid function also known as Hill function, which maps the output on BIS scale. The value of BIS is used as a feedback to the controller. Fig. 3 presents the block diagram of the overall feedback control system used

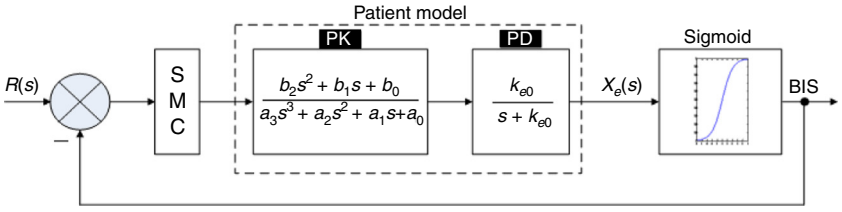


**Figure 3** Block diagram of overall closed-loop system.

to achieve the desired DOH during surgical procedures. The overall objective in the control design is to minimize steady state error so as to maintain DOH level within acceptable range for surgery.

The control law is based on SMC, which is one of the most effective robust control techniques for highly nonlinear systems operating in uncertain environments subjected to disturbances. SMC involves defining a sliding surface typically a linear hyper-surface. The fundamental concept[26] behind SMC is to drive the system dynamics from any initial state to the sliding surface (i.e. reaching phase). The system is then maintained on this surface for all future values of time (sliding phase). The major benefit offered by SMC is its low sensitivity to plant disturbances and uncertainties.[27]

To design SMC, considering the sliding surface given by (15)

$$\sigma = a_1x_1 + a_2x_2 + a_3x_3 + a_4x_e \tag{15}$$

or

$$\dot{\sigma} = a_1\dot{x}_1 + a_2\dot{x}_2 + a_3\dot{x}_3 + a_4\dot{x}_e \tag{16}$$

where $a_1$, $a_2$, $a_3$, $a_4$ are tuning parameters of the controller. With $a_1 = 1$, values of other parameters are chosen in a way that 0 becomes Hurwitz monic polynomial. This condition ensures reduction in order of the system which can be represented with $n-1$ states. Such a system demonstrates insensitivity to matched uncertainties. Substituting the state equations, (16) can be re-written as,

$$\begin{aligned}\dot{\sigma} = {} & a_1[(-k_{10} - k_{12} - k_{13})x_1(t) + k_{21}x_2(t) + k_{31}x_3(t) + u(t)] \\ & + a_2[k_{12}x_1(t) - k_{21}x_2(t)] + a_3[k_{13}x_1(t) - k_{31}x_3(t)] \\ & + a_4[k_{1e}x_1(t) - k_{e0}x_e(t)]\end{aligned} \tag{17}$$

The overall control law ($u$) consists of equivalent control ($u_{eq}$) and discontinuous control ($u_{disc}$) i.e.

$$u = u_{eq} + u_{disc} \tag{18}$$

The equivalent control forces the system dynamics to move to the sliding surface and depends on the states of the system and state parameters. It makes the derivative of sliding manifold equal to zero and can be computed by putting $\sigma = 0$ along the system dynamics (17). Thus,

$$\begin{aligned}u_{eq} = {} & -[(-k_{10} - k_{12} - k_{13})x_1(t) + k_{21}x_2(t) + k_{31}x_3(t)] \\ & - a_2[k_{12}x_1(t) - k_{21}x_2(t)] - a_3[k_{13}x_1(t) - k_{31}x_3(t)] \\ & - a_4[k_{1e}1(t) - k_{e0}x_e(t)]\end{aligned} \tag{19}$$

Presence of disturbances or uncertainties may lead $\sigma \neq 0$. Discontinuous control handles such disturbances and depends on gain and signum function, which exhibits switching behavior. Thus,

$$u_{disc} = -k\,\mathrm{sign}(\sigma) \tag{20}$$

where $k \in R^{n\times n}$ is the discontinuity gain matrix. Mathematically,

$$\mathrm{sign}(\sigma) = \begin{bmatrix} 1 \text{ for } \sigma > 0 \\ -1 \text{ for } \sigma < 0 \end{bmatrix} \tag{21}$$

To investigate and characterize the performance of the designed controller, clinical data including characteristic variables of eight patients is presented in Table 2.[8]

Based on the patient's attributes, clinical parameters computed using Schnider three compartmental model for Propofol are given below:

$$V_1 = 4.27[l]$$

$$AV_2 = 18.9 - 0.391(Age - 53)[l]$$

$$AV_3 = 238[l]$$

**Table 2** Clinical dataset showing patients' attributes.

| Patient | Age years | Height ($H$), cm | Weight ($W$), kg | Gender | $C_{50}$ | $E_0$ | $E_{max}$ | $\gamma$ |
|---|---|---|---|---|---|---|---|---|
| 1 | 40 | 163 | 54 | F | 6.33 | 98.80 | 94.10 | 2.24 |
| 2 | 36 | 163 | 50 | F | 6.76 | 98.60 | 86.00 | 4.29 |
| 3 | 34 | 172 | 58 | F | 4.95 | 96.20 | 90.80 | 1.84 |
| 4 | 28 | 164 | 60 | M | 4.96 | 94.70 | 85.30 | 2.46 |
| 5 | 37 | 187 | 75 | M | 8.02 | 92.00 | 104.00 | 2.10 |
| 6 | 42 | 179 | 78 | M | 4.82 | 91.80 | 77.90 | 1.85 |
| 7 | 38 | 174 | 80 | F | 6.56 | 95.50 | 76.40 | 4.12 |
| 8 | 43 | 163 | 59 | F | 12.10 | 90.20 | 147.00 | 2.42 |

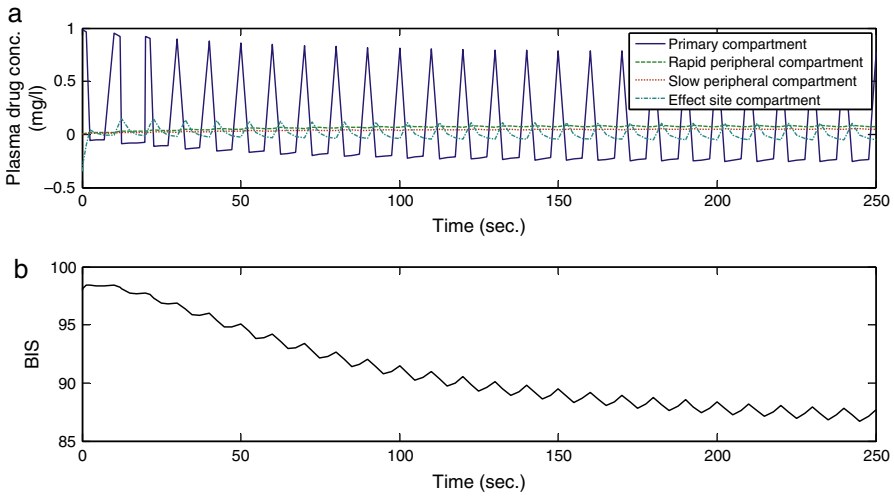


**Figure 4** Controller-less administration of anesthetic agent in patient 6: (a) drug concentration in various compartments and (b) output profile.

$$C_{l1} = 1.89 + 0.0456(W - 77) - 0.0681(\text{LBM} - 59) + 0.0264(H - 177)$$

$$C_{l2} = 1.29 - 0.24(\text{Age} - 53)$$

$$C_{l3} = 0.836$$

where Lean Body Mass (LBM) is a function of patient's gender, height and weight. For male and female, it is respectively given as

$$\text{LBM} = 1.1 * W - 128 * \frac{W^2}{H^2}$$

$$\text{LBM} = 1.07 * W - 148 * \frac{W^2}{H^2}\pi r^2$$

The rate constants $k_{10}$, $k_{12}$, $k_{13}$, $k_{21}$, $k_{31}$ depend on weight, height, age, gender of the patient and are given as:

$$k_{10} = \frac{C_{l1}}{V_1}$$

$$k_{12} = \frac{C_{l2}}{V_1}$$

$$k_{13} = \frac{C_{l3}}{V_1}$$

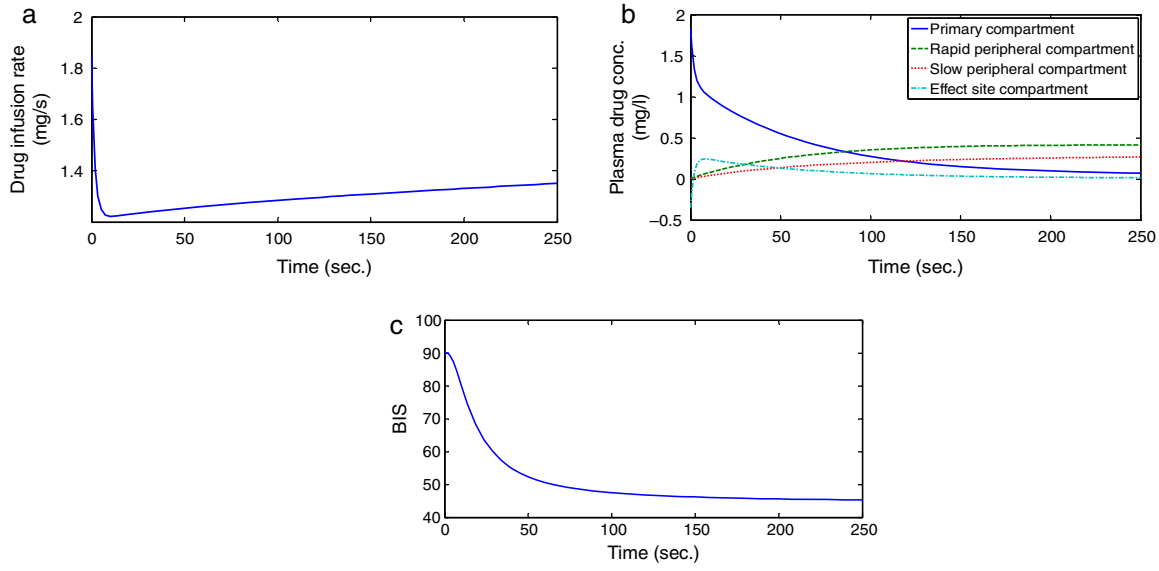


**Figure 5** SMC based closed-loop control of anesthetic agent in patient 6: (a) control input, (b) plasma drug concentration in various compartments, and (c) output profile.

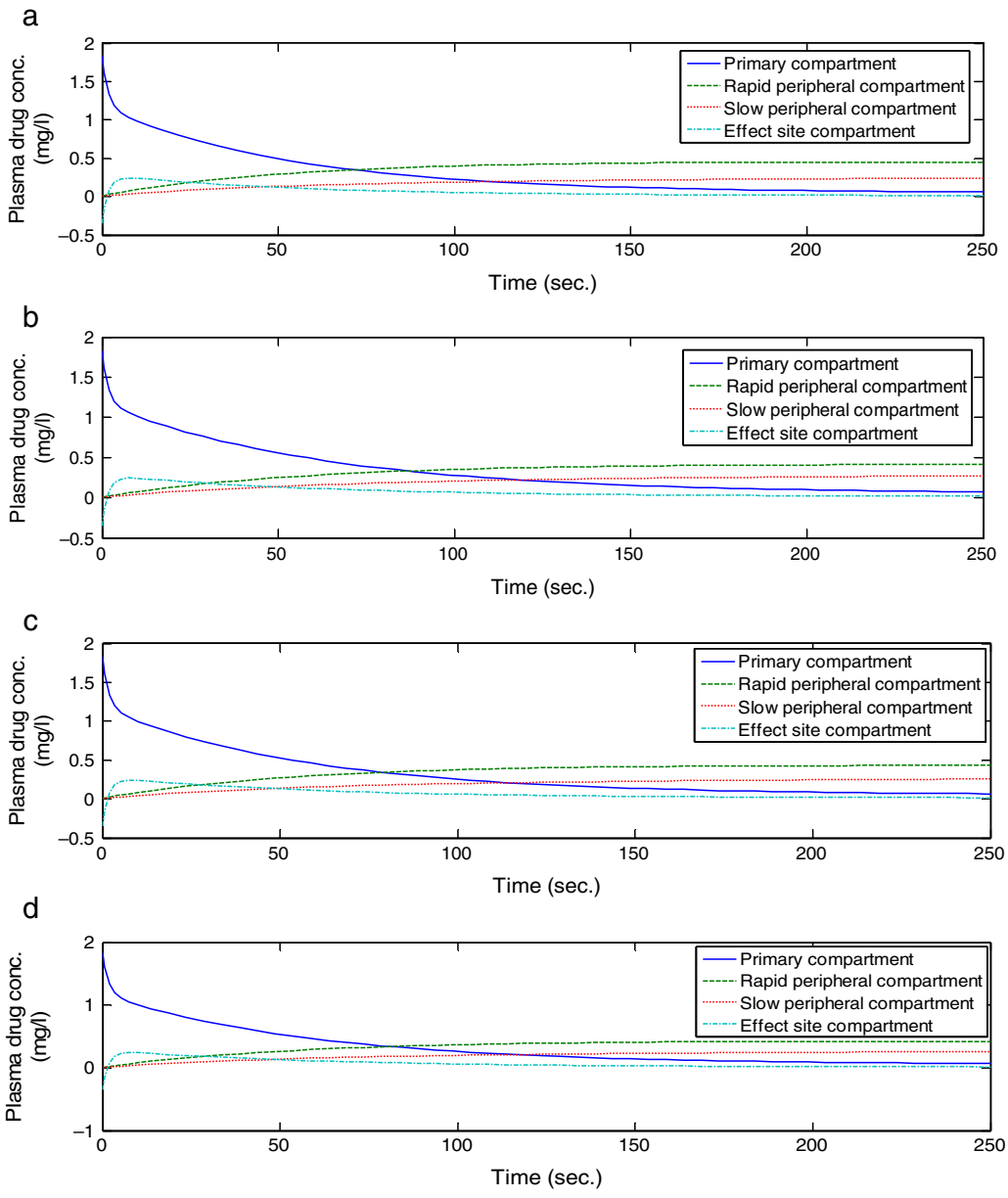


**Figure 6** Plasma drug concentration in (a) patient 4, (b) patient 8, (c) patient 2, and (d) patient 7.

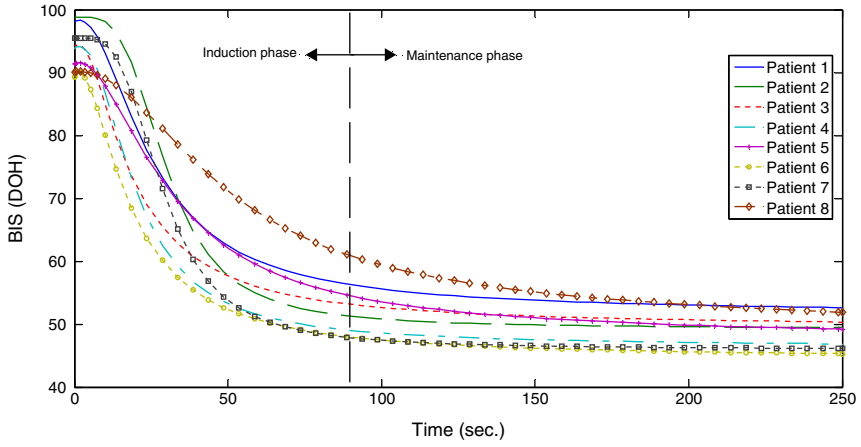


**Figure 7** Simulation results for BIS value for various patients showing that there is no overdose.

$$k_{21} = \frac{C_{l2}}{V_2}$$

$$k_{31} = \frac{C_{l3}}{V_3}$$

## Results and discussion

The trivial scheme of anesthetic agent administration simply consists of a controller-less paradigm. With such a scheme, Fig. 4A presents plasma drug concentration in various compartments while Fig. 4B shows the output profile in the form of BIS signal. BIS values are still far away from the desired DOH level which is required for the general surgery. It is observed from these results that manipulating anesthesia without a dedicated controller in the loop can be quite risky and may not be suitable in many operational scenarios. Using this scheme, the accuracy and precision of the drug delivery to a patient during surgery is totally dependent on the anesthesiologist experience. The critical response of this controller becomes more problematic and crucial especially in case of children and cardiac patients.

Employing a robust controller in a closed-loop fashion completely changes the response. Fig. 5A presents the controlled drug infusion level using SMC technique for patient 6. Plasma drug concentration in the compartments of the PKPD structure is illustrated in Fig. 5B, where the rate of change of drug concentration with respect to time in all the four compartments of the body after the drug infusion is shown. Initially the drug concentration is maximum in the primary compartment. But as the drug moves between primary and peripheral compartments, its level decays exponentially in the primary compartment and rises in the peripheral compartments. This flow of drug in the compartments is represented through the use of rate constants. The output of BIS indicator is plotted in Fig. 5C. It clearly shows that the presence of the controller with a closed-loop feedback system dramatically improves performance of anesthesia process. The output converges to the required level of BIS for surgery within seconds. The controller then maintains this DOH level

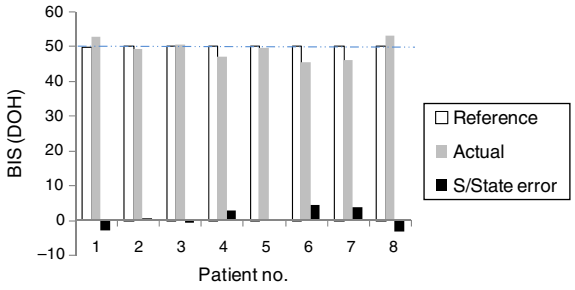


**Figure 8** Steady state error showing that DOH is under desired range.

so as to assist anesthesiologist in ensuring safer region of operation.

Plasma drug concentration in various compartments is a function of factors including patients' age. Lesser the age of a patient, faster is the metabolism/elimination of the drug. As an example, compare the drug concentration of patients 4 and 8 illustrated in Fig. 6A and B respectively. It is evident that patient 4 being comparatively younger demonstrates fast metabolism of the drug occurring in primary compartment than patient 8. Comparison of young and old patients discloses that the concentration in rapid peripheral compartment increases substantially due to the fast flow of Propofol from primary compartment. The same effect is reflected in slow peripheral compartment and the effect site compartment.

In contrast to age, the weight of a patient does not significantly affect the plasma drug concentration profile. To investigate this effect, the concentration in patients' 2 and 7 ($\Delta$weight = 30 kg) has been compared (Fig. 6C and D). It can be seen that the concentration of Propofol in the primary compartment of patient 2 decays at a relatively same rate as that of patient 7. The minor difference in the responses is due to difference in ages of the patients. Same fashion is observed regarding flow of drug to other compartments.

The designed controller with the derived patient's model is then simulated as per the dataset (Table 2). Simulation results shown in Fig. 7 present the hypnosis level of 8 patients after the infusion of drug for surgery. These

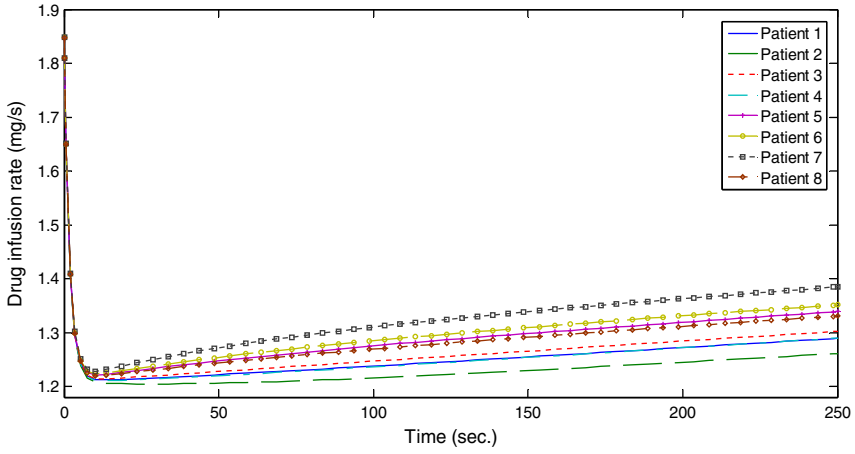


**Figure 9** Propofol infusion rate for various patients.

responses indicate both the induction and maintenance phases of anesthesia. Initially, during induction phase, patient is in awake state (DOH level near 100) and then it enters into moderate hypnotic state (DOH level of 40–60). This level is maintained for safe execution of surgical procedures. In this study, all the patients achieved the ideal hypnosis level. However, for the sake of quantification, Fig. 8 shows steady state error considering DOH level of 50 as reference. The error bounded in between $\pm 5$ is still within acceptable range for surgical operations.

The designed SMC provides different rates of Propofol infusion corresponding to different patients (Fig. 9) due to difference in patients' parameters like age, weight, height, gender and LBM to maintain the desired level of DOH. The controller initially permits injection of large amount of drug to bring the patient in unconsciousness state in induction phase of anesthesia. Once the desired hypnosis level is achieved, then the controller strictly maintains the specific infusion rate throughout the maintenance phase of anesthesia for each patient.

## Conclusions

This paper proposes SMC-based law for adequate and safe delivery of Propofol anesthesia for achieving desired hypnosis levels. Simulation results based on the dataset comprising of 8 real patients with different clinical parameters clearly witness efficacy of the presented approach. With the help of medical professionals at National Institute of Health (NIH) Pakistan, we are going to test the proposed CLAN in real surgical scenario after meeting medical safety standards. It is imperative to demonstrate practical benefits of CLAN to convince clinicians. The CLAN technique, though potentially the eventual goal of anesthetic drug infusion is still in early stages of research. It is anticipated that such a CLAN system based on a non-linear and robust control will replace manual administration as well as TCI system in very near future.

## Conflicts of interest

The authors declare no conflicts of interest.

## References


1. Bibian S [PhD Thesis] Automation in Clinical Anesthesia. Canada: University of British Columbia; 2006.
2. Dong C [PhD Thesis] Closed Loop Controlled Total Intravenous Anaesthesia. UK: University of Plymouth; 2003.
3. Warpechowski P, Santos ATL, Pereira PJI, et al. Effects of propofol on the cardiac conduction system. Rev Bras Anestesiol. 2010;60:441–4.
4. Absalom AR, Sutcliffe N, Kenny GNC. Closed-loop control of anesthesia using bispectral index: performance assessment in patients undergoing major orthopedic surgery under combined general and regional anesthesia. Anesthesiology. 2002;96:67–73.
5. Liu N, Chazot T, Genty A, et al. Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop versus manual control: a prospective, randomized, multicenter study. Anesthesiology. 2006;104:686–95.
6. Simoni RF, Miziara LEDPG, Esteves LO, et al. Pharmacodynamic evaluation and physical/chemical analysis of two formulations of propofol used in target-controlled infusion. Rev Bras Anestesiol. 2013;63:66–72.
7. Nunes RR, Chave IMM, Alencar JCGD, et al. Bispectral index and other processed parameters of electroencephalogram: an update. Rev Bras Anestesiol. 2012;62:111–7.
8. Ionescu CM, De Keyser R, Torrico BC, et al. Robust predictive control strategy applied for propofol dosing using BIS as a controlled variable during anesthesia. IEEE Trans Biomed Eng. 2008;55:2161–70.
9. Struys M, De smet T, Greenwald S, et al. Performance evaluation of two published closed-loop control systems using bispectral index monitoring: a simulation study. Anesthesiology. 2004;100:640–7.
10. Lan JY, Abbod MF, Yeh RG, et al. Review: intelligent modeling and control in anesthesia. J Med Biol Eng. 2012;32:293–307.
11. Absalom AR, Struys MMRF. An overview of target controlled infusions and total intravenous anaesthesia. San Diego, CA, USA: Academia Press; 2007.
12. Soltesz K, Heusden K, Dumont GA, et al. Closed-loop anesthesia in children using a PID controller: a pilot study. In: IFAC conference on advances in PID control. 2012.
13. Sakai T, Matsuki A, White PF, et al. Use of an EEG-bispectral closed-loop delivery system for administering propofol. Acta Anaesthesiol Scand. 2000;44:1007–10.
14. Ingole DD, Sonawane DN, Naik VV, et al. Linear model predictive controller for closed-loop control of intravenous anesthesia with time delay. ACEEE Int J Control Syst Instrum. 2013;4:8–15.
15. Zhusubaliyev TZ, Medvedev A, Silva MM. Bifurcation analysis of PID-controlled neuromuscular blockade in closed-loop anesthesia. J Process Control. 2015;25:152–63.
16. Heusden KV, Dumont GA, Soltesz K, et al. Design and clinical evaluation of robust PID control of propofol anesthesia in children. IEEE Trans Control Syst Technol. 2014;22:491–501.
17. Soltesz K, Dumont GA, Ansermino JM. Assessing control performance in closed-loop anesthesia. In: 21st Mediterranean conference on control and automation. 2013. p. 191–6.
18. West N, Dumont GA, Heusden KV, et al. Robust closed-loop control of induction and maintenance of propofol anesthesia in children. Pediatr Anesth. 2013;23:712–9.
19. Ajwad SA, Iqbal J, Ullah MI, et al. A systematic review of current and emergent manipulator control approaches. Front Mech Eng. 2015;10:198–210.
20. Shargel L, Wu-Pong S, Yu AB. Applied biopharmaceutics and pharmacokinetics. NY, USA: McGraw-Hill; 2007.
21. Heusden KV, Soltesz K, Khosravi S, et al. Quantification of the variability in response to propofol administration in children. IEEE Trans Biomed Eng. 2013;60:2521–9.
22. Coppens MJ, Eleveld DJ, Proost JH, et al. An evaluation of using population pharmacokinetic models to estimate pharmacodynamic parameters for propofol and bispectral index in children. Anesthesiology. 2011;115:83–93.
23. Bibian S, Ries CR, Huzmezan M, et al. Introduction to automated drug delivery in clinical anesthesia. Eur J Control. 2005;11:535–57.
24. Schnider TW, Minto CF, Cambus P, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology. 1998;88:1170–82.
25. Hendrickx JF [PhD Thesis] The Pharmacokinetics of Inhaled Anesthetics and Carrier Gases. Belgium: Ghent University; 2004.
26. Islam RU, Iqbal J, Khan Q. Design and comparison of two control strategies for multi-DOF articulated robotic arm manipulator. Control Eng Appl Inform. 2014;16:28–39.
27. Ajwad SA, Ullah MI, Khelifa B, et al. A comprehensive state-of-the-art on control of industrial articulated robots. J Balk Tribol Assoc. 2014;20:499–521.