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Automatic Control of Hypnosis in Propofol Anesthesia Administration based on ISTSMC

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Abstract

Propofol infusion in anesthesia administration requires continual adjustment in manual drug delivery system to regulate the hypnosis level. Such regulation of hypnosis in multi-tasking surgical scenario become more challenging and risky, directs to automation in anesthesia. This paper proposes a nonlinear control based on Integral Super-twisting Sliding Mode Control (ISTMSC) of Propofol administration. The patient model is derived using pharmacokinetic and pharmacodynamics modelling based on clinical parameters, like age, height, and weight. The controller response is investigated to regulate the hypnosis level between 40 and 60 on Bispectral Index Scale (BIS). The plasma drug concentration in different compartments of the boy shows the metabolism of drugs within body. The hypnosis level is plotted for different patients shows the cortically activity of the brain required for general surgery.

Keyword: Pharmacokinetic and Pharmacodynamics model, Sliding mode control, linear observer, sigmoid model, hypnosis.

I. Introduction

Advancement in control engineering totally diverts the concepts of manual drug delivery system in clinical surgery. In current era, the surgical procedure can be carried out with little efforts. This advancement is possible with research outcomes in health care engineering. Initially the surgical procedure needs fast execution due to lack of anesthetics. Different schemes like application of cold, nerve's compression were applied to keep the patient unconscious [I]. In 1840, Hickman invented the inhalation gases, which enable the invasive surgeries. C.W. Long in 1842, used diethyl-ether for first surgical procedure. This idea leads to term anesthesia meaning lack of sense. [II]. Three main ingredients of anesthesia are hypnotic i.e. lack of

conscious, analgesic i.e. lack of pain, and areflexia i.e. lack of movements. Moreover anesthesia administration consists of three main phases including induction, maintenance and emergence phase [III]. In first phase anesthetic being administered to bring the patient to desired unconscious level. In second stage the surgical procedure is performed with optimum delivery of drug infusion. When surgical procedure is completed, directs to emergence phase to stop the drug infusion and skin closure procedure is performed to bring the patient to awake state. The general surgery is performed during maintenance phase of anesthesia with hypnosis level between 40 and 60 on BIS. The best threshold level is 50 for smooth induction of surgical procedure [IV-VIII].

During general anesthesia Propofol used as hypnotic agent and fast acting opioids e.g. Remifentanil used as pain killer. Both of these drugs have synergistic effect. Propofol having fast metabolism level and lesser side effects to the patient [IX]. There are two main issues in manual delivery of anesthesia, under-dosing and over-dosing of anesthetics. Under-dosing of anesthetics cause awareness which directs to vomiting as well as anxiety and over-dosing of anesthesia leads to cardiovascular collapse. Both of these states are unaffordable during surgery [X]. This careful management is the key factor in successful induction of surgical procedure. Such limitation of manual drug delivery of anesthetics leads to motivation of automation in anesthesia. Targeted Controlled Infusion (TCI) is a computer assisted open loop system, which administers the adjusted level of drug without considering the feedback signal. Such system is based on population based pharmacokinetic and pharmacodynamic modelling. Pharmacokinetic shows, that how the drug is metabolized by the body and pharmacodynamic identify the drug effect on the depth of hypnosis. The effect site concentration is mapped through nonlinear sigmoid model. It maps the hypnosis level between 0 and 100. Moreover 100 indicate the fully awake state and 0 presents the dead state. The general surgery is performed between 40 and 60 on BIS [XI]. A closed loop control system offers several advantages as compared to TCI system including automatic regulation of hypnosis level as well as drug infusion rate, reducing the inter-patient and intra-patient variability and eliminating the anesthesiologist intervention [XII]. Closed loop control of anesthesia was introduced and executed by Chao Dong in doctoral work in 2003. He derived three compartmental model of patient and linearized it by using linear regression in his thesis work. He applied Proportional Integral Derivative (PID) control technique on hypothetical patient and obtained the desired result in form of hypnosis level, but linearizing the nonlinear sigmoid model, part of data can be lost and actual result cannot be obtained [XIII].

Slotesz works on the same procedure and control the hypnotic and analgesic component of anesthesia. He developed a closed loop system, which consists of hypnotic agent i.e. Propofol and analgesic component i.e. Remifentanil. Slotesz

applied PID control technique having adaptive behavior to achieve the desired hypnotic level. In his work, he derived the patient model from the clinical data of silico patient after many trials. The drug administration maintained in optimum level during induction and maintenance phase of anesthesia in general surgical procedure. The importance of Slotesz work reveals due to his practical experiments, which were carried out on 47 validated models, which attained the inter-patient variability [XIV-XVI]. The controller designed for Propofol and Remifentanil are multi input, but Remifentanil metabolizes faster than Propofol [XVII]. Slotesz did not focus to handle the intra-patient variability like blood pressure variation, bleeding, which can affect the smooth conduction of surgery. The corresponding control law is based on the state of the patient in three compartmental model referred as PK-PD model. This model relies on measurement of BIS level and drug administered to the patient. ISTSMC algorithms are applied to develop automated control of hypnosis regulation. Sliding Mode Control (SMC) is a nonlinear control algorithm shows robust behavior towards higher order nonlinear systems. SMC offers low sensitivity to plant structure variations and disturbances by moving the state trajectory toward the user defined surface [XVIII].

This paper is categorized as follows; Section 2 explains the compartmental model of the patient. Section 3consists of controller design and section 4 explains the results and discussions. Moreover, section 5 comments on conclusion.

II. Compartmental Model of Patient

The dynamics of infusion drugs in patient body is classified into pharmacokinetics (PK) pharmacodynamics (PD) [19]. The PK model shows that how the drug is metabolized within plasma of the human blood [20]. The PD model exhibits the drug concentration at the effect site like brain [21]. The blood within human body acts as a carrier of the drug to different organs of the body. The human body is divided into different compartments on the basis of the drug flow rate, including primary, rapid peripheral and slow peripheral compartment [I].Primary compartment (intravascular blood) with volume V_1 is shown in centre of Figure 1. Moreover the muscles are represented by rapid peripheral compartment V_2 and fates are represented by slow peripheral compartment V_3. Both of these compartments are connected to the primary compartment through k_{12}, k_{21}, k_{13}, and k_{31} are weighted rate constants. The flow of drug amongst different compartments occurred in exponential fashion [IV]. The overall effect of the drug is measured on brain in terms of cortical activity measured on BIS.

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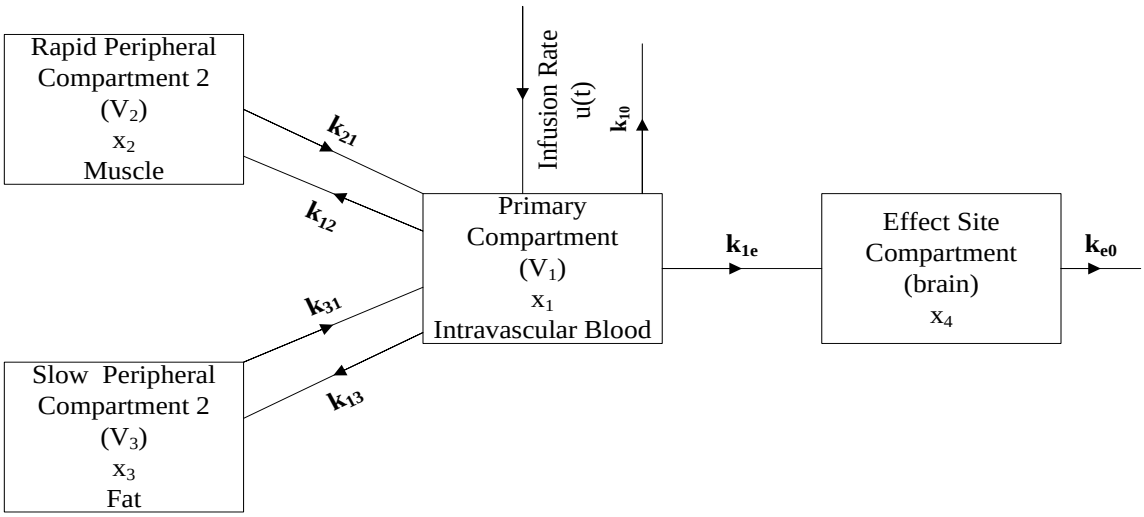


Figure1. Block diagram of PK and PD models

To derive the PK model, state equations corresponding to the three compartments can be written as:

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

$$\dot{d_2}(t) = k_{12}x_1(t) - k_{21}x_2(t) \quad (2)$$

$$\dot{d_3}(t) = k_{13}x_1(t) - k_{31}x_3(t) \quad (3)$$

The PD model predicts the effect site concentration as given by “equation (1)”

$$\dot{d_4}(t) = k_{1e}x_1(t) - k_{e0}x_4(t) \quad (4)$$

where k_{e0} shows the elimination rate constant at effect site and k_{e1} shows the weighted rate constant at effect site compartment.
The description of the state variable in equation (1-4) is given in “Table 1”.

Table 1. State variables with description.

State Variables	Description	Unit
x_1	Amount of drug in primary compartment	mg
x_2	Amount of drug in rapid peripheral compartment	mg
x_3	Amount of drug in slow peripheral compartment	mg
u(t)	drug infusion	mg/sec

The output of infusion drug based on their effect at brain site mapped through non linear sigmoid model is shown in equation 5

$$BIS(t) = E_0 - E_{max} \times \frac{x_4^{\gamma}}{(x_4 + C_{50}^{\gamma})} \quad (5)$$

The description of the sigmoid model parameters is shown in table 2.

Table 2. Sigmoid model parameters

Parameter	*Description*
E_0	Indicates the fully awake stage
E_{max}	Maximum effect achieved using hypnotic agent
C_{50}	50% of the maximum effect
γ	Slope of sigmoid curve.

Based on the patient's attributes, clinical parameters based on Schneider three compartmental models for Propofol are given in "Table 3". [XXII, XXIII]

Table 3. Clinical parameters of PK-PD model

Clinical parameter	Formula
Lean Body Mass(LBM)	LBM (male) = $1.1 \times W - 128 \times$
	LBM (female) = $1.07 \times W - 148 \times$
Weighted rate constants	$k_{10} =$; $k_{13} =$; $k_{21} =$; $k_{31} =$;
Volume of Compartment	$V_1 = 4.27[l]$
	$V_2 = 18.9 - 0.391(Age - 53)[l]$
	$V_3 = 238[l]$
Clearance	$C_{l1} = 1.89 + 0.0456(W - 77) - 0.0681(LBM - 59) + 0.0264(H - 177$
	$C_{l2} = 1.29 - 0.024(Age - 53)$
	$C_{l3} = 0.836$

III. Integral Super-twisting Sliding Mode Control Design

The nonlinear ISTSMC consists of nonlinear sliding surface with desired properties, such robustness to external disturbances. The ISTSMC delivered better transient response and minimum steady state error in the presence of disturbances, which is proved by lyapnove stability theorem and LaSalle Invariance theorem [XX-XXV].
In order to achieve the desired performance, the sliding surface is selected as, [XXVI, XXVII].

$$\sigma = \dot{e} + d_1 e + d_2 \int e\, dt \quad (6)$$

$$e = BIS_{des} - BIS_{act}, \quad (7)$$

where $\mathrm{BIS_{des}} = 50$ is the require output for general surgery and $d_1 \in \Re^+$ is a design parameter.

The dynamics of the patient model under the ideal sliding mode($\sigma = 0$) is governed by

$$\sigma = \dot{e} + d_1 e + d_2 \int e\, dt = 0 \tag{8}$$

The above result implies that $e(t)$ asymptotically converges to zero as,

$$e(t) = e(0) t e^{-d_1 t} \tag{9}$$

The control law is designed by taking the derivative of Equation (8) ,

$$\dot{\sigma} = \ddot{e} + d_1 \dot{e} + d_2\, e \tag{10}$$

$$\dot{e} = 0 - E_{max} \times \frac{d}{dt}\left(\frac{x_4(t)^{\gamma}}{(x_4(t)+C_{50}^{\gamma})}\right) \tag{11}$$

$$\ddot{e} = E_{max} x_4^{\gamma} \ddot{x_4}(u)/(K+x_4)^2 - 2 \times E_{max} x_4^{\gamma} \dot{x_4}^2/(K+x_4)^3 + \left(2 \times E_{max} \gamma x_4^{\gamma-1} \dot{x_4}^2\right)/(K+x_4)^2 - \left(\frac{E_{max} \gamma x_4^{\gamma-1} \ddot{x_4}(u)}{K+x_4}\right) - (\gamma-1) \times \left(\frac{E_{max} \gamma x_4^{\gamma-2} \dot{x_4}^2}{K+x_4}\right) \tag{12}$$

where $K = C_{50}^{\gamma}$,

Finite time convergence can be obtained by considering reachability law as,

$$\dot{\sigma} = -k_1 |\sigma|^{\frac{1}{2}} sign(\sigma) - k_2 \int sign(\sigma) d\tau \tag{13}$$

Where $k_1, k_2 \in \Re^+$ are the controller gains,

Comparing the value of $\dot{\sigma}$ from equation (10) and equation (13) to find the u.

$$-k_1 |\sigma|^{\frac{1}{2}} sign(\sigma) - k_2 \int sign(\sigma) d\tau = [E_{max} x_4^{\gamma} \ddot{x_4}(u)/(K+x_4)^2 - 2 \times E_{max} x_4^{\gamma} \dot{x_4}^2/(K+x_4)^3 + (2 \times E_{max} \gamma x_4^{\gamma-1} \dot{x_4}^2)/(K+x_4)^2 - \left(\frac{E_{max} \gamma x_4^{\gamma-1} \ddot{x_4}(u)}{K+x_4}\right) - (\gamma-1) \times \left(\frac{E_{max} \gamma x_4^{\gamma-2} \dot{x_4}^2}{K+x_4}\right)] + x_1 \dot{e} + x_2 e + [-k_1 |\sigma|^{\frac{1}{2}} sign(\sigma) - k_2 \int sign(\sigma) d\tau] \tag{14}$$

$$u = [2 \times E_{max}\, x_4^{\gamma} \dot{x_4}^2/(K+x_4)^3 - (2 \times E_{max} \gamma x_4^{\gamma-1} \dot{x_4}^2)/(K+x_4)^2 + (\gamma-1) \times \left(\frac{E_{max} \gamma x_4^{\gamma-2} \dot{x_4}^2}{K+d_4}\right) - d_1 \dot{e} - d_2 e] \times \left(\frac{x_4(K+x_4)^2}{E_{max} x_4^{\gamma} \times (x_4(1-\gamma) - K\gamma) \times (-0.456 x_4 + 0.1068)}\right) + ((k_{10} + k_{12} + k_{13}) x_1 - k_{21} x_2 - k_{31} x_3) + [-k_1 |\sigma|^{\frac{1}{2}} sign(\sigma) - k_2 \int sign(\sigma) d\tau] \tag{15}$$

IV. Results and Simulations

The figure 2 shows the closed loop system for automation in anesthesia. The mathematical model of the patient consists of three compartment represented by PK-PD model. The outputs from the PK-PD model are mapped on sigmoid model represent the hypnosis level of the patient at the brain as a sensor. The The controller block administered the drug infusion to patient model.

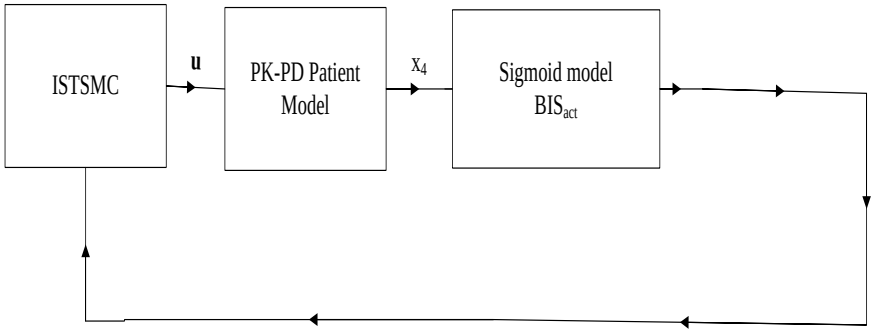


Figure 2: Block diagram of observe design for automatic control of drug infusion

The figure 3 shows the plasma drug concentration of different compartment of the body including primary compartment, rapid peripheral compartment, slow peripheral compartment and effect site compartment.. Initially the drug concentration is maximum in primary compartment (intravascular blood) and exponentially decay to other compartments of the body based on the weighted rate constants. As the plasma drug concentration is decay in primary compartment leads to gradual increase in the rapid (muscles) and slow peripheral compartments of the body.

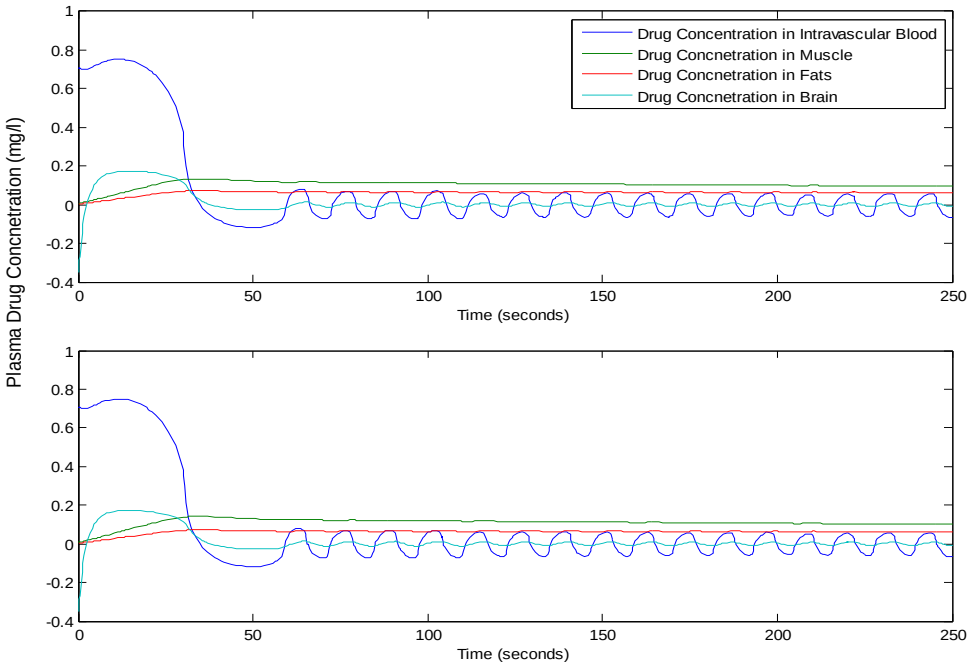
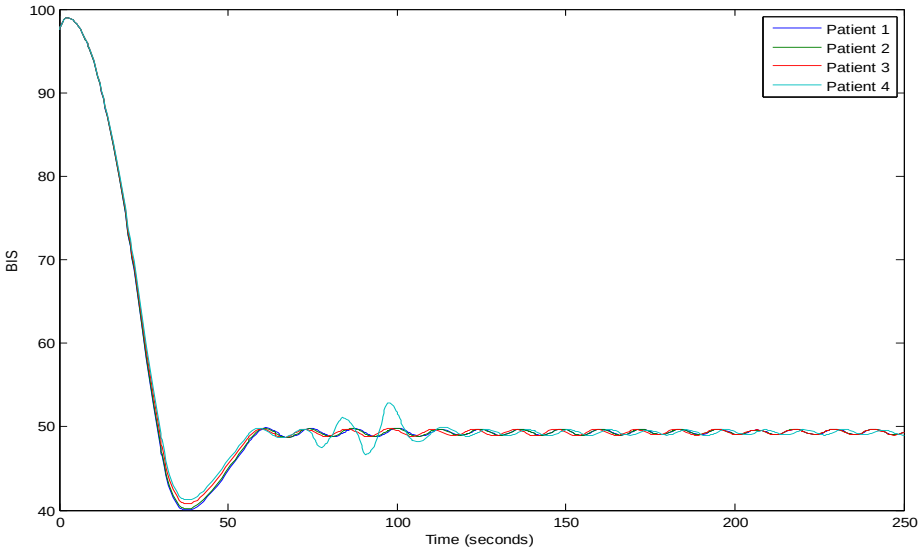


Figure3. Plasma drug concentration

Figure 4 shows the hypnosis level on BIS monitor for 4 patients. The induction phase is completed in 50 seconds which leads to maintenance phase. The surgical procedure is performed in maintenance phase of anesthesia. The figure 4 shows achieved the desired level of hypnosis for all 4 patients in maintenance phase.



A.

Figure 4. BIS level for 4 Patients

The figure 5 shows the drug infusion level for all patients based on ISTSMC mechanism. Initially the drug infusion is maximum during induction phase of anesthesia to bring the patient to desired hypnotic level and then decreases gradually in maintenance phase of anesthesia. The oscillating behavior shows that controller provides drug infusion in varying level to the patient.

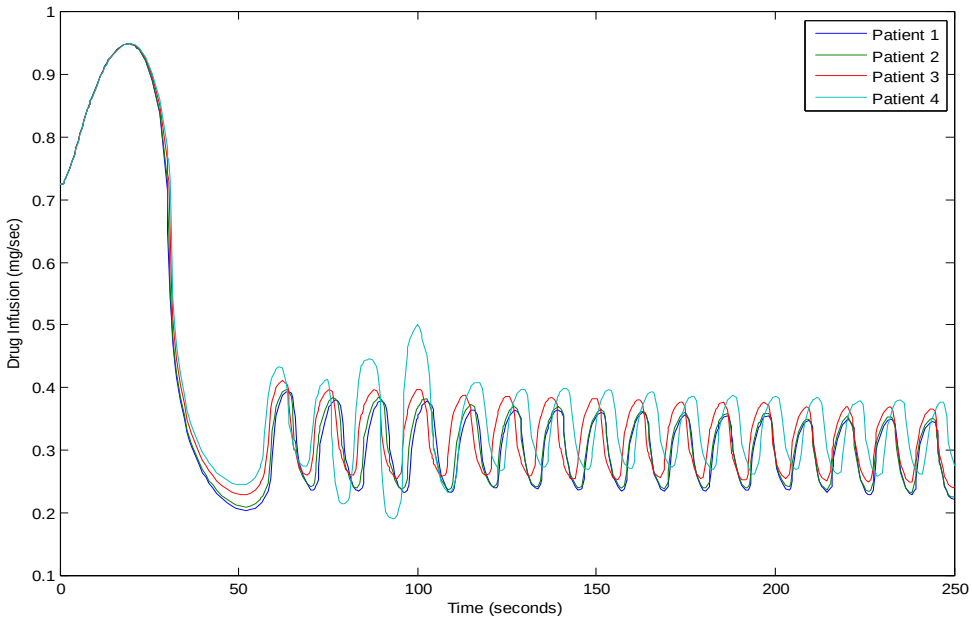


Figure 5: Infusion drug of controller

V. Conclusion

This paper proposes automatic control of drug infusion to regulate the hypnosis level using ISTSMC strategy. The rate of metabolism of drugs within different compartments of the body represented by plasma drug concentration. The desired hypnosis level required for general surgical procedure achieved on BIS between 40 to 60.The controller administered optimum level of drug infusion to maintain the hypnosis in maintenance phase of anesthesia. ISTSMC achieved the optimum performance in close loop control of anesthesia.

VI. Competing Interest

The authors declare that they have no competing interests.

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