BIS Performance for CLAD PK-PD Model

Usharani Shola, Neelanarayanan V

Abstract: (Please read carefully abstract of the template). Giving anesthesia in operating rooms is generally a practice of making patients unconsciousness and ensuring safe surgery to the patients. Some of the procedures are fixed, few are predefined and some need patient response to alter the anesthetic drugs infusions to reach the required hemodynamic values. The automation in drug delivery will minimize the distractions of anesthetist and he can spend more time for direct care of patient. In the view of automatic drug delivery system, developing the relationship between depth of anesthesia and the delivery of intravenous anesthetic drugs is important. This article discuss about these relationship and defined Simulink model for the same. The results are taken based on the BIS score. This score is compared with target value, the tolerance percentage levels of reaching the target value is discussed for both male and female patients.

Index Terms*: Closed Loop Automatic Drug Delivery System (CLADS), Depth of Anesthesia (DOA), PK-PD (Pharamacokinetic-Pharmacodynamic) Model, Sigmoid Function, Bispectral Index Scale (BIS), Simulink.

I. INTRODUCTION

The advancements in technology change the procedure of treating medicine during surgery. Because of these the surgical processes are performed very easily. An enormous research outcomes in modern anesthesia made this was happen. Before the advancement of anesthesia the surgery is performed through trail techniques like application of cold, compression of nerve or reduction in cerebral perfusion to make the patient not to sense. After inhalation gases introduced in 1840, then it moved towards for anesthesia discovery. All these make advancement of conduction of invasive operations. The concept of anesthesia is making lack of aesthesia i.e. sense.Anesthesia is a reversible [7] consciousness level of a patient, it guarantees patient's hypnosis, and muscle relaxation sensation levels. Anesthesia is used in many medical applications like surgery operation with incision, dental surgery etc., It is often plays role in surgery and in the intensive care unit (ICU). It blocks the pain of surgery; hypnotics produce unconsciousness, while muscle relaxants prevent unwanted movement of muscle tone. Maintaining safe and protective surgery for patients while monitoring the vital signs of a patient is very complex task for anesthetist. The process of drug delivery administration is done either through simple manual delivery and computer-assisted automated target controlled Infusion (TCI). In manual process the physician administrates the drug based on the patient demographics. As part of anesthetist he\she could estimate the drug outcome in the patient's body and measure the corresponding drug infusion rates, based on vital parameters during surgery period. TCI is based on patient's Pharmacokinetic (PK) and Pharmacodynamics (PD) models for measuring the adequate infusion levels. Basically it is an open loop control method, where it takes past and present infusion rates through these models and it predicts the rate of drug to be infused through the patients. This predicted value will be used to track the referenced concentration. TCI approaches may not always be safe [15] for the patient since it did not include any measured variable feedback control variable from the patients and even the desired level of sedation is reached. The consequences will result the adverse events to patients. Even for more stress situations, the surgeon has to deal with routine assessments and simultaneously solve complex problems immediately. The automation of some routine actions of the anesthetist can reduce the workload and consequently increase the safety of the patient. The current automatic drug delivery simulation study was designed to evaluate the Propofol–BIS closed-loop system during induction, maintenance, and emergence of anesthesia. In particular, it is expected that the closed-loop system would reduce time spent with BIS values to reach outside predetermined limits and would enable faster recovery times without increasing the incidence of adverse events[14].

II. BACKGROUND

The advances in monitoring the nervous system made the process of automatic closed loop drug delivery system very easy. It optimizes the operative condition of the surgeon. It protects the patients during surgeon procedures. CLAD will stabilize the effects of hemodynamic parameters during surgical procedures if the closed loop controlled is designed robustly. This process prevents the awareness to the patient during surgery. Two different kinds of anesthetic agents are used: inhaled agents and Intravenous agents. Mostly total IV usually involved for Propofol hypnotic agent during anesthesia of surgery. The anesthesia to the patients involved three phases namely Induction, Maintenance and Emergence. Like the three phases the anesthesia involves the monitoring of hypnosis, nociception and muscular relaxation for anesthesia during surgery for automatic adjustment of drug delivery. The Heart Rate(HR) [4] ,Respiration Rate (RR), Minute ventilation, Airway pressure, End-tidal Co2, BP & Oxygen saturation through pulse oximetry are the hemodynamic parameters to be maintained stable during smooth anesthesia procedures. This article mainly focus the component of monitoring hypnosis sensing that involves observing EEG of anesthetized patient. The anesthetized patient drug effects are measured based on EEG is measured via BIS monitors, DOH

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monitor or Neuro Sense monitors. These monitors sense the characteristics of EEG in the form of BIS, DOH and bilateral index levels. The most frequently measured anesthetic variable is BIS. It ranges from 0 (No EEG Signal) to 100(awake EEG Signal). This value varies from one phase to phase. For the induction phase the BIS value changes from Awake Signal to unconscious level with BIS value 60. After that the patient enters to maintenance phase for doing the surgery. Then the BIS value varies from 60 to 40. All these values are monitored and surgery is performed smoothly without bringing the awareness to the patient. In this paper the basic components of closed loop anesthesia system is discussed and the simulation results are produced based on BIS values. Four performance measures of BIS values are discussed as excellent, good, poor & inadequate. In overall surgery time how much percentage of each performance was discussed from the results.

III. CLOSED LOOP CONTROLLED ANESTHESIA

Closed loop system is not a new technology in medicine. There are many real world examples included in it. For example, automatic control of arterial blood pressure is infused through sodium nitroprusside drug [8] to treat the increased blood pressure after open-heart surgery at ICU for cardiac surgical procedures. The system consists of sensors, control algorithms and insulin pump based on the requirement of medical scenario is going to be used. These systems will be affected by unsteady disturbances due to variations in hemodynamics of the patients, delays of measurements from insulin data and noisy data from sensors. The automated drug delivery [11] system has more than one controller that monitors [12] one or more parameters, and adjusts the administration response of drug assistance to maintain the desired ranges through a dedicated algorithm The goal of this closed loop anesthesia is to describe the development of administration of anesthesia agents depending upon the patient's response during surgical procedures. As shown in Figure 1: for closed loop drug delivery system the output values of hemodynamic values (BIS, HR, BP & others) of patient are sensed, feed backed to controller . At the controller the feedback values is compared with the set point. The measured error of the controller actuates the input to the infusion pump. Then the pump based on the controller algorithm will initiate new infusion rate or same infusion rate as new drug dosage to the patient.

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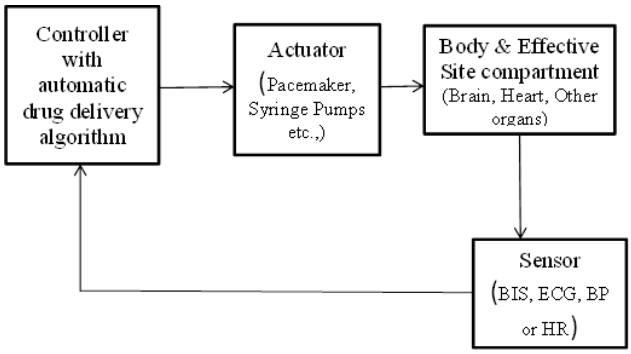

Figure 1: Architecture of closed loop system in automatic drug delivery system

Automatic control of drug delivery for anesthesia needs to be established to provide significant control of drug delivery of anesthesiology in biomedical field. This model uses different closed loop controller design with variance of patient characteristics like in patient variability and intra patient variability. The model consists of PK-PD model that shows the drug distribution in the body based on metabolism of patient. The main part of anesthesia is maintaining depth of hypnosis (DOH) at brain. It is an activity of consciousness and monitored through Bispectral Index scale (BIS). The normal consciousness state of BIS is 100 or near to it. Standard range for BIS is 40 to 60 for general surgery. The PK-PD provides the concentration level at target organ for example, Brain, Heart. This concentration can be used to get the BIS value by using nonlinear sigmoid model (6]. This system with a BIS guided can be administrated successfully for administration of Propofol as IV anesthetic in various situations like, non-cardiac surgery, cardiac surgery, post-operative sedations etc.,

IV. CLAD WITH PK-PD 3-COMPARTMENTAL MODEL

From the Figure 2 the Simulink model for drug delivery system consists of a control variable with target based drug delivery system algorithm. This is representative for target specific therapeutic effects. Clinically relative set point of target concertation is enabled. Based on the control variable, the BIS error will actuates the rate of concentration into the patient system. The variations of concentrations for different compartments are listed in Table 1 are used and the PK-PD equations (from Table [1] to [9]) are developed in MATLAB [1] Simulink model. As shown in Figure 3 for PK-PD with 4 compartments. Each compartment is modelled [9] based on the equations given from equations (1), (2) and (3) respectively. Finally from compartment1 the drug moves to the effective site compartment and is represented by the equation (7), (8) & (9). The effective site (18) compartment value obtained (Ce(t)) is used for measuring the depth of hypnosis value. The equations for BIS calculated from Ce(t), E0, Emax is given at equation (9) and is modelled through non-linear sigmoid function , represented through Figure 4 which is going to be discussed shortly at results and discussion.

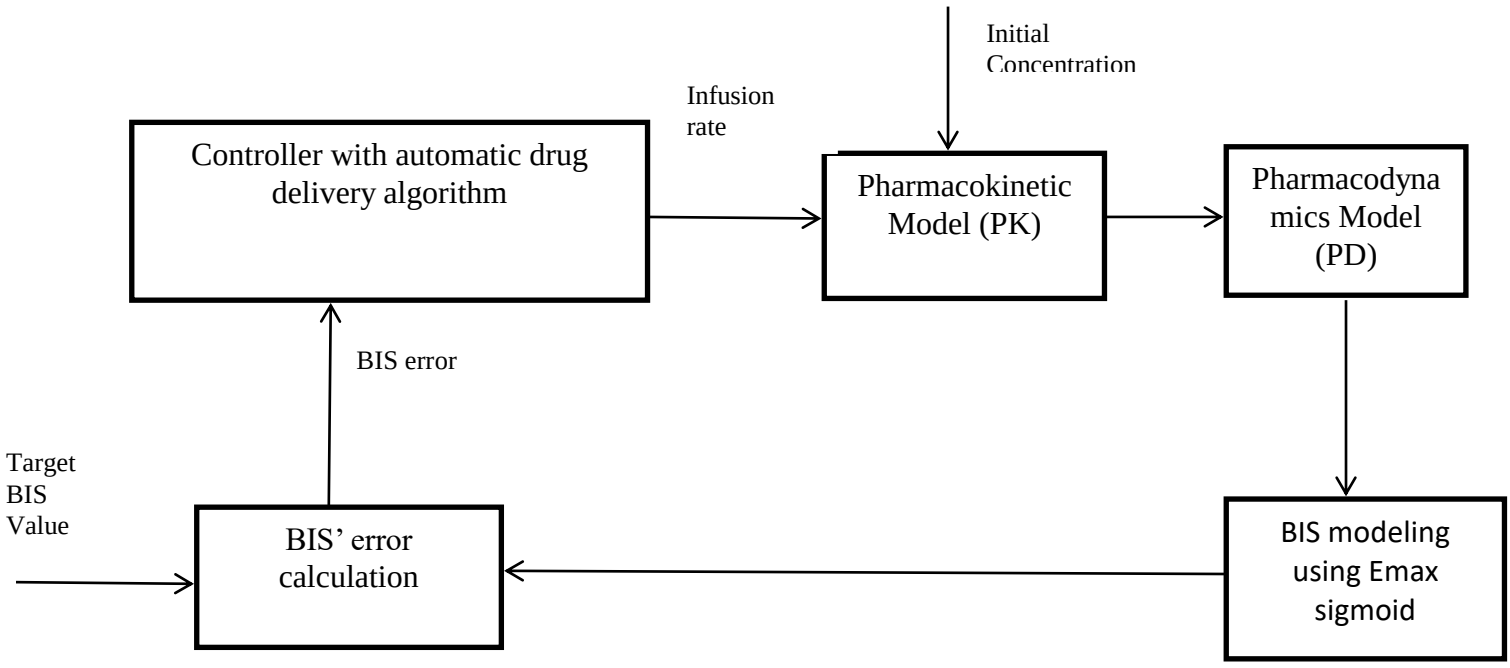

Figure 2. Simulink model for closed loop automatic drug delivery system for Anesthesia

Table 1. List of PK-PD Equations used for Simulations

Source: Usharani Shola, Neelanarayanna V., 2019[19])

SL.No	Equation
1.	$\frac{dX_1}{dt} = I_s - (K_{12} + K_{13} + K_{10})X_1 + K_{21} * X_2 + K_{31} * X_3$
2.	$\frac{dX_2}{dt} = (K_{12} * X_1) - (K_{21} * X_2)$
3.	$\frac{dX_3}{dt} = (K_{13} * X_1) - (K_{31} * X_3)$
4.	$LBM = 1.1\,Wt - 128 * \left(Wt/Ht\right)2$ for Male
5.	$LBM = 1.07\,Wt - 148 * \left(Wt/Ht\right)2$ for Female
6.	$C_1(t) = X_1(t)/V1$
7.	$\frac{dCe}{dt} = K1eCp(t) - Ke0Ce(t)$
8.	$Ce(t) = 0.1068X_1\,(t) - 0.456Ce(t)$
9.	$BIS(t) = E0 - Emax\left(\frac{Ce(t)^{\gamma}}{Ce(t)^{\gamma} + Ce50^{\gamma}}\right)$
10	$U(t) = Kpe(t) + Ki\int e(t)dt + Kd\frac{de(t)}{dt}$
11	$e(t) = BIS_{ref} - BIS_{act}.$

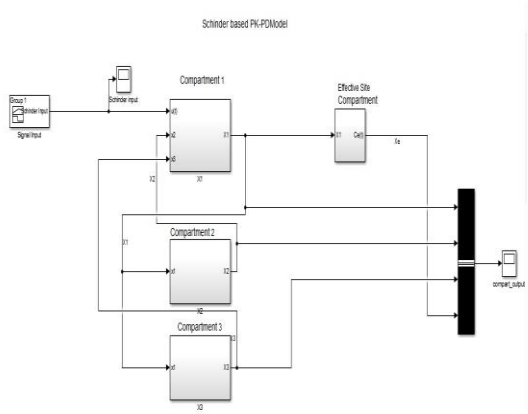

Figure 3. Simulink model for PK-PD

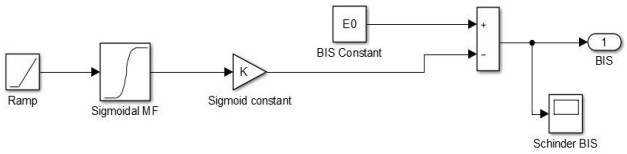

Figure 4. Simulink model for BIS sigmoid, E0 is the BIS value at awake state, Xe(t) Effective site concentration

The outcome of BIS of the closed loop simulation was analyzed by the efficacy of BIS[17]. It is the score that the measured value of BIS is maintained as close as possible to target value of 50. It was considered in four measures: BIS_SC_EXC (BIS Score under Excellent performance), BIS_SC_Go(BIS Score under Good performance), BIS_SC_Po(BIS Score under Poor performance) and finally

BIS_SC_Ina (BIS Score Inadequate performance). These are measured as the BIS values that are within 10%, from 11% to 20%, from 21% to 30% and >30% of the target BIS value of 50 respectively. This clinical performance score is evaluated using methods of Varvel and Colleagues. (2013). Performance measure is derived from the difference of measured BIS with target BIS value with the formula is given below;

$$PE = \frac{BIS_{Measured} - BIS_{target}}{BIS_{target}} * 100 \rightarrow (11)$$

From the above equation (11), the tolerance level of measured value with respect to target value compared. All the score percentage is calculated and results are discussion in the next section.

V. RESULTS & DISCUSSION

The scheme of anesthetic administration given in this paper consists of a controller –less paradigm. With this scheme two different patients are considered for result purpose and details of patients can be referred from [6]. From the model the concentration at each compartment is calculated using Schinder model [2][16] is discussed above (Table [1]). The patient data, their PK values and PD parameters are calculated by substituting the patient details into the above discussed equations. The 3-compartmental PK model for plasma characteristics and effective site compartment for BIS is given in the below figures. For both the patients the controlled input is considered as shown in Figure 5. The pharmacokinetic characteristics of drug are defined as absorption, elimination clearance and data transfer rates [19] , the drug enters from central compartment is distributed through other compartments till equilibrium state is reached. Based on the initially the primary compartment the drug concentration rate is high as it distributing to other compartments, its values decay as time goes. Where in other compartments these values slowly increase and finally reach to equilibrium state in all compartments. The Pharmacokinetic characteristics of the discussed can be seen from the below graphs shown at Figure 6 & Figure 7. These two graphs represents the rate of change of drug concentration with respect to time in all the four compartments after the infusion of drug in the body as the drug moves between primary and other peripheral compartments decay in exponential fashion in primary and rises in other for two different patients. The effective site compartments follows the similar characteristics of primary compartment as its concentration directly related through first compartment. The similar characteristics are verified through 8 different patients and find the similar variations and are shown in Figure 8 & Figure 9.The flow of drug in all the compartments represented through the rate of constants, similarly the output of BIS is indicated through the BIS plot inn Figure 10. The entire BIS level [10]is divided into two parts; the range of induction phase where the patient loses its consciou levels and ready for the surgery. Then the maintain phase [21] where the patient is performed by surgery during this period. The DOH levels need to be maintained between 40 to 60 during this phase. Within some fraction of seconds the BIS level need to be converges to BIS level of surgery. In order to retain these characteristics the sigmoid funciton is used. A sigmoid function has a characteristic of "S"-shaped function . it is a special case of the logistc fucntion which is represented (12) by the following function as;

$$f(x) = K/1 + e^{-a(x-c)} \rightarrow (12).$$

Where e is the natural logarithm base
c is the x-value midpoint function
K is the curve's maximum value.
a is the logistic grow rate or steepness of the curve.
When the value of K =1, a = 1 and c =0, the logistic function is standard sigmoid function and is graph represented as shown in Figure 11. From the figure the threshold values of sigmoid function are ranging from 0 to 1. But in the article BIS level requires two types of thresholds one for E0 = Maximum BIS level in awake state for certain period and minimum value of in between 40 to 60 with reversed S-shape of sigmoid function. To perform the required charachteristics the sigmoid funciton to be modeleld for BIS as BIS (t) = E0-L*Sigmoid function →(13)

This equation can be compared with equation (9) listed above. From the equation the left side is converted to sigmoid function with E0 is as such, but Emax of effective site compartment is modeled through sigmoid funciton and target BIS value . The midpoint point of sigmoid curve shown from the figure can be set based on the time of BIS level required to maintain to the validated range of 40 to 60.This process of modeling Emax is called Emax sigmoid model function. The Emax or L for the above equation are taken randomly and checked the charaacteritics for BIS. If required surgical levels are required to meet by 40sec then this mid point should be kept at 20sec. From the discussion all the above parameters different levels of BIS for 8 different patinets are considered and are plotted are shown in Figure 12. BIS levels for all patients shows responses of both induction and maintenance phases of anesthesia. Durign start of induction phase the patient is without drug and DOH is almost near to 100, then after infusing the drug the DOH level reduces and reaches in between 40-60. This level is maintained for patient safety time end of that phase. The error bound also within the limited range of accepatance by surgical procedures.

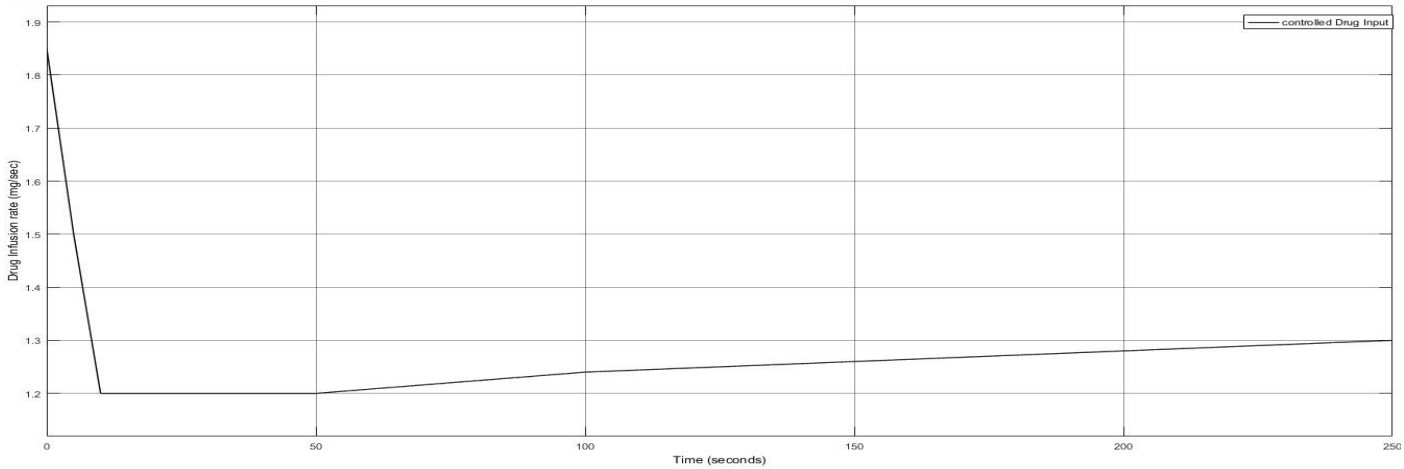

Figure 5. Controller Input

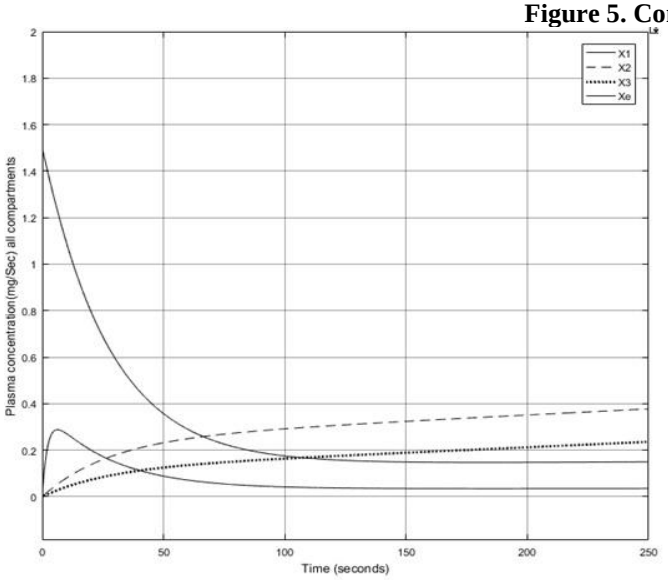

Figure 6. Each Compartment Characteristics for Patient-I

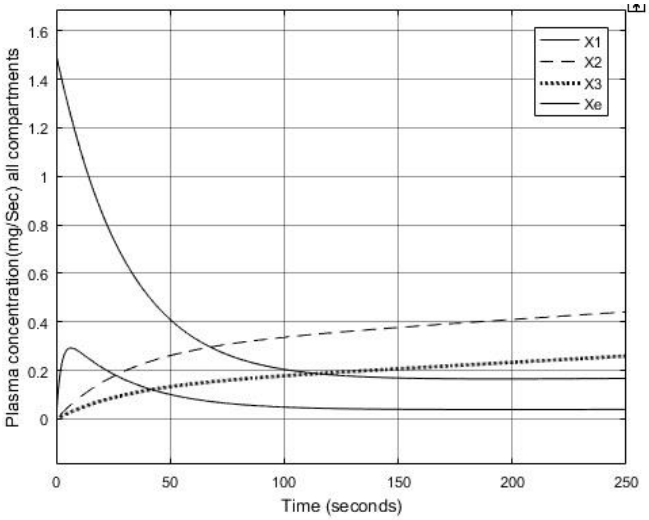

Figure 7. Compartment characteristics for patient-II

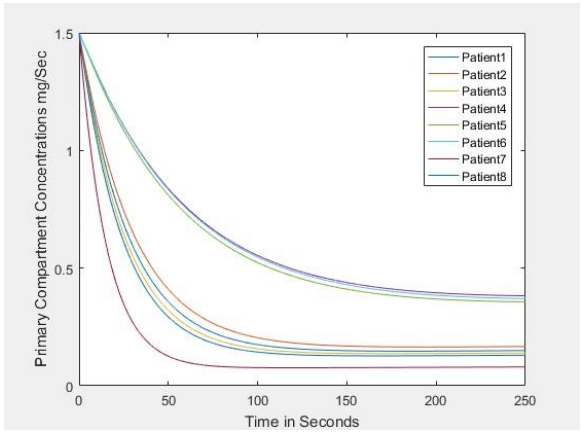

Figure 8. Primary compartment plasma characteristics for 8 different patients

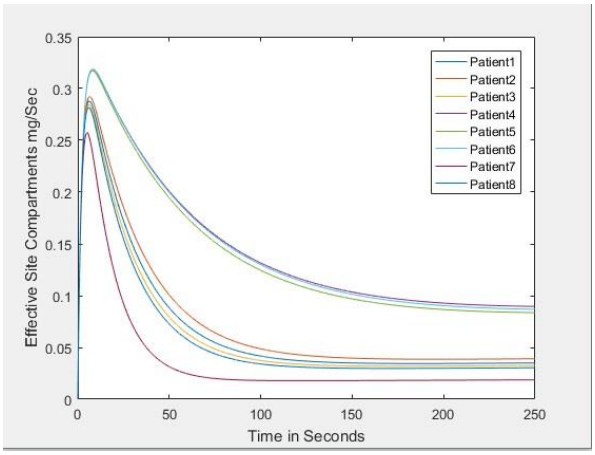

Figure 9. Effective site compartment characteristics for8 different patients

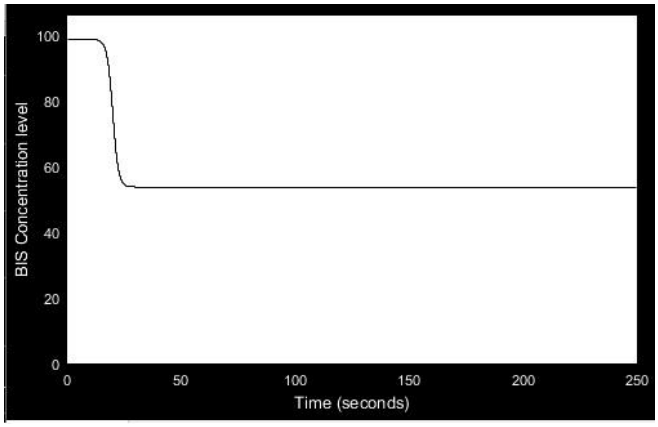

Figure 10 .BIS levels based on drug input

The different rates of concetrations & BIS level corresponding to different patinets are due to the difference in patients parameters like age,weight, height, gender and LBM. The controller input give to the model shows that initially it permits large amounts of infusion and brings the patient to unconsciousness and once the desired levels of DOH are reached the input is maintained constant.Out of 8 patients with approximately 250 samples of data 40% time involved induction phase for all the patients and remaining 60% involved maintenance phase. As discussed above the BIS score performance is evaluated for maintenance phase and is represented in Figure 13. As shown for both female of patient 8 & male of patient 7 (data taken from; [13]) the BIS evaluation score of Excellence is almost 95% reached to the target level , 3% to 2 % in Good, Poor level finally 1% to Inadequate levels. Thus it shows that the simulation Maintains the target levels of up to 95% through PK-PD simulation of automatic drug delivery model.

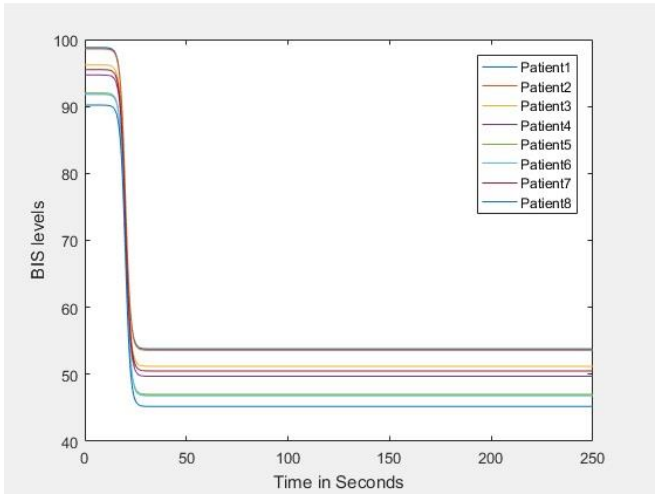

Figure 12. BIS level characteristics for 8 different patients

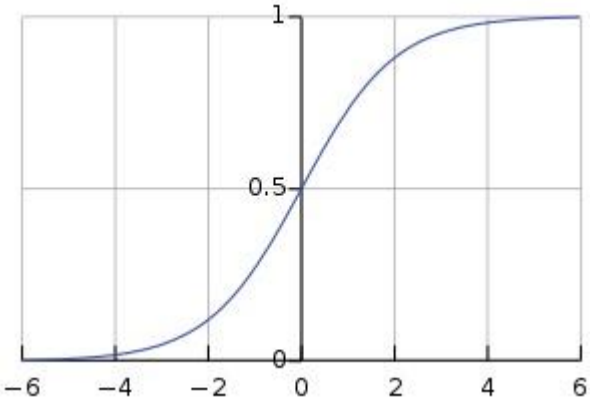

Figure 11. Sigmoid function for k=1,a=1 & c=0.

VI. CONCLUSION

In previous work the patient model is checked with different parameter set and chosen one set that suits well based on patient parameters that meets the inter patient variability model. From the set Schinder data parameter set produces the drug flow constants through calculations based on patient parameters. This paper presents the safe delivery of Propofol anesthesia based on the defined controller input through closed loop PK-PD Simulink model. Simulation results are based on 8 different patients with different clinical parameters. All results clearly replicate the existing model characteristics. We are going to extend this model by including automatic drug delivery system through the optimized drug delivery control system algorithm. The generated algorithm and mathematical models are validated by checking their accuracy parameters used for computer based drug delivery system. This concludes that by using very robust control can replace the manual administration and TCI based drug delivery systems in future. This will reduces the work of anesthetist, and he/she can concentrate more towards patient safety.

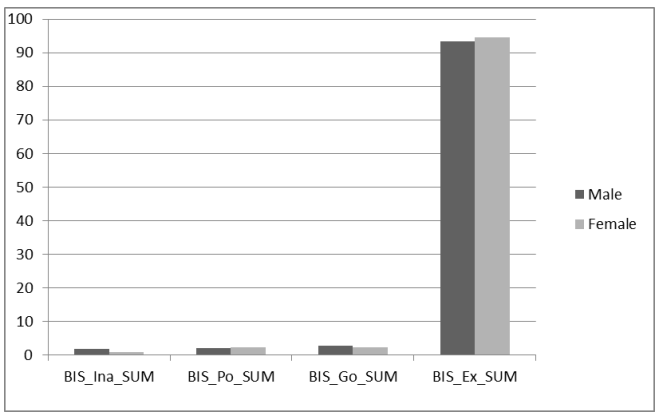

Figure 13. BIS Score performance evaluation for Male & Female

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