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Original Article

Improvised Schinder Model for Anaesthesia Drug Delivery in Obese Patients with Optimized Infusion Rate and Patient Safety

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Abstract *- Advancements in the medical domain are emerging day by day, and one such trendy improvement in the anaesthesia drug delivery is Closed-loop systems. It overcomes the major drawbacks in open-loop anaesthesia drug delivery along with the vital benefit related to continuous monitoring of patient-related parameters to verify the level of drug infused. The Closed Loop Anaesthesia Drug Delivery (CLAD) system is a technique to monitor patients' haemodynamic and anaesthetic depth variables to control the infusion rate of Propofol drugs using the Marsh model or Schinder model. During this drug delivery model, many challenges are faced by anaesthesiologists and surgeons. Understanding the pathophysiologic effects and its anaesthetic consequences is very important. The benefits of the Schnider model over the other general patients' model will adjust the dose and infusion rate according to the patient's demographic data. Schinder model suffers from drawbacks related to excessive increase of drug delivery rates during maintenance in obese patients and difficulty setting BMI limits for drug infusion in obese patients. Hence, to address the drawbacks and increase patient safety measures, the proposed model addresses the limitations by focusing on the plasma propofol concentrations instead of whole concentrations. The speed of infusion parameters to monitor cardiac output and lean body mass closely is adjusted to address issues related to obese patients effectively.*

Keywords *- Closed Anaesthesia Drug Delivery (CLAD), Pharmacokinetic and Pharmacodynamics (PK-PD), Drug infusion algorithm, Patient safety, Compartmental model, Propofol.*

1. Introduction

Anaesthesia drug delivery is the common term adopted across various domains in healthcare, as automating such procedures simplifies the tasks of anaesthesia experts. The closed-loop anaesthesia system is introduced to address the drawbacks of the open-loop anaesthesia system in terms of patient safety and feedback. CLAD aims to automate the complete control over brain states such as sedation, unconsciousness and antinociception among the patient community when they receive anaesthesia care. The accuracy and performance of such measures could be validated using numerous measures such as control signals, electroencephalogram (EEG) markers, and Bispectrial index scale (BIS) values. An anaesthetic drug is delivered to patients using a computer-controlled infusion pump based on a model of how the drug effect is reflected in the anaesthetic states of the brain. Such variations or changes are captured by careful observation of EEG markers and BIS values. The focus of research is to closely monitor the depth of anaesthesia levels merely based on BIS values along with additional dynamic patient parameters as BIS is the most widely used control signal in CLAD studies, and maintenance of BIS within the specified range makes the model successful and ensures patient safety. Safety features of CLAD are depicted in figure 1. The proposed model works successively for ASA-II category and obese patients, simulated using MATLAB. The overdosing and under-dosing issues are taken care of at a significant level of 0.05 to address the drawbacks of cardiorespiratory depression. The propofol dose calculated based on input parameters could be verified and validated using Machine Learning algorithms before injecting into the patients, which will increase the safety constraints.

2. Technical Background

Automated control systems widely develop many industrial critical care applications, but their use is limited in medical critical care applications.

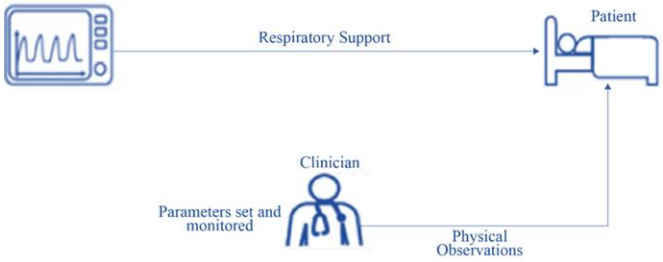

Fig. 1 Safety features of CLAD

As most ICU applications are simulated on virtual patients and after performing suitable testing on these, the evaluation of the closed-loop system has improved the importance of automation in the industry. For example, Rui Correia and Pedro Amorim have developed an application for Alaris GH syringe pumps (ALARIS Medical systems) [1][2]to control the syringe pump remotely. They discussed that to develop the complete model for this, many functionalities like alarm conditions, changing the adjustments to drug rates and data logging, etc, should be included. They have developed the model in LAB-View and use serial communication protocol to enable the improvement of control during the drug infusion process. Thus, the closed-loop procedures replaced the manual operations by operating them automatically. The current work is developed in MATLAB Simulink, and the safety of the proposed model is performed by considering a statistical hypothesis test. The increased risks related to obese patients should be managed and optimized using a multi-organ system, leading to positive outcomes during surgery. Minimally invasive surgery patients improve [31] the pulmonary functions and recovery times. These consequences will reduce the effects on the cardiac, respiratory [32] and metabolic systems of obese patients.

The paper in [3, 4] studies the importance of interoperative propofol dosage during anaesthesia procedures. It produces a study about human errors of anaesthesia during surgical procedures. It does not give feedback about patients in the system. The study concludes that the closed-loop systems with BIS will reduce the propofol dosage side effects. It even reduces the effects of adverse reactions like hypertensive or hypertension and cognitive dysfunction after operation procedures. The paper studies the technical and clinical performance of the CLAD [5] system for anaesthesia and remifentanil using a SEDLine monitor. This SEDLine monitor uses the patient safety index to monitor the EEG pattern during anaesthesia. However, it could not include the drug side effects to oppose the side effects during anaesthesia procedures.

The depth of hypnosis [6, 7] is applied in closed-loop anaesthesia using constrained control concepts to prevent overdosing and decrease blood pressure. Three methods, namely safety preserving control, explicit reference governor and model predictive control, are used to check the pros and cons of closed-loop anaesthesia patient safety measures. The authors designed a closed-loop system that implemented a control algorithm based on anaesthetic depth monitoring and the Patient State Index (PSITM) [8] of the SEDLine monitor for propofol and hemodynamic variables for remifentanil. The importance of using an automated drug delivery system compared to manual control of anaesthesia is understood. The drawbacks of manual control are achieved in CLAD and showed the results. However, their system will not check the drug's side effects during delivery.

Evaluation of American Society of Anaesthesiologists classification The American Society of Anaesthesiologists(ASA) Physical Status (PS) has implemented different categories in a patient's physiological status. This category helps the anaesthetist to predict the possibility of operative risk. The ASAPS category provides a universal, convenient explanation of the overall condition of a surgical patient. This status indicated the scale of the preoperative health situation of the patient. It helps to decide whether the patient can have the surgery or not. The other factors that include predicting the operative risks are [9] age, comorbidities, Extent and duration of the operative procedure, planned anaesthetic techniques, the Professional skills of the surgical team, duration of surgery, available equipment, blood products needed, medications, implants needed, expected postoperative care.

This ASA PS status of a particular patient is decided based on the patient's systematic disease background or medical history, his/her function limitations, physical problems such as the difficulty of the airway, etc. The ASAPS status, i.e. operative risk obtained for one patient, is not the same for all his surgeries. For example, the same highly operative risk patient undergoing cataract surgery under topical anaesthesia is quite different from the operative risk for the same patient undergoing an esophagectomy or cardiac surgery. Some anaesthetists consider this classification based on age, anemia and obesity. Like the FDA, the American Society of Anaesthesiologists Physical Status classification has been approved by ASA delegates.

The proposed system uses the Pharmacokinetic (PK) and Pharmacodynamics (PD) mathematical model that describes the drug response of the human body developed in previous works [10, 11, 12]. From the results of [8], the PK-PD model under Schinder-based patient covariant is used to improve the robustness of the model. This mathematical model predicts the drug concentration and its effect on the target part of the body based on patient age, height, weight, gender and Lean Body Mass (LBM). A Computerized closed-loop anaesthesia drug delivery system for propofol is developed in MAT LAB Simulink. The model includes the patient drug prediction model, patient feedback model, drug infusion algorithm as in [13, 14] and patient safety system.

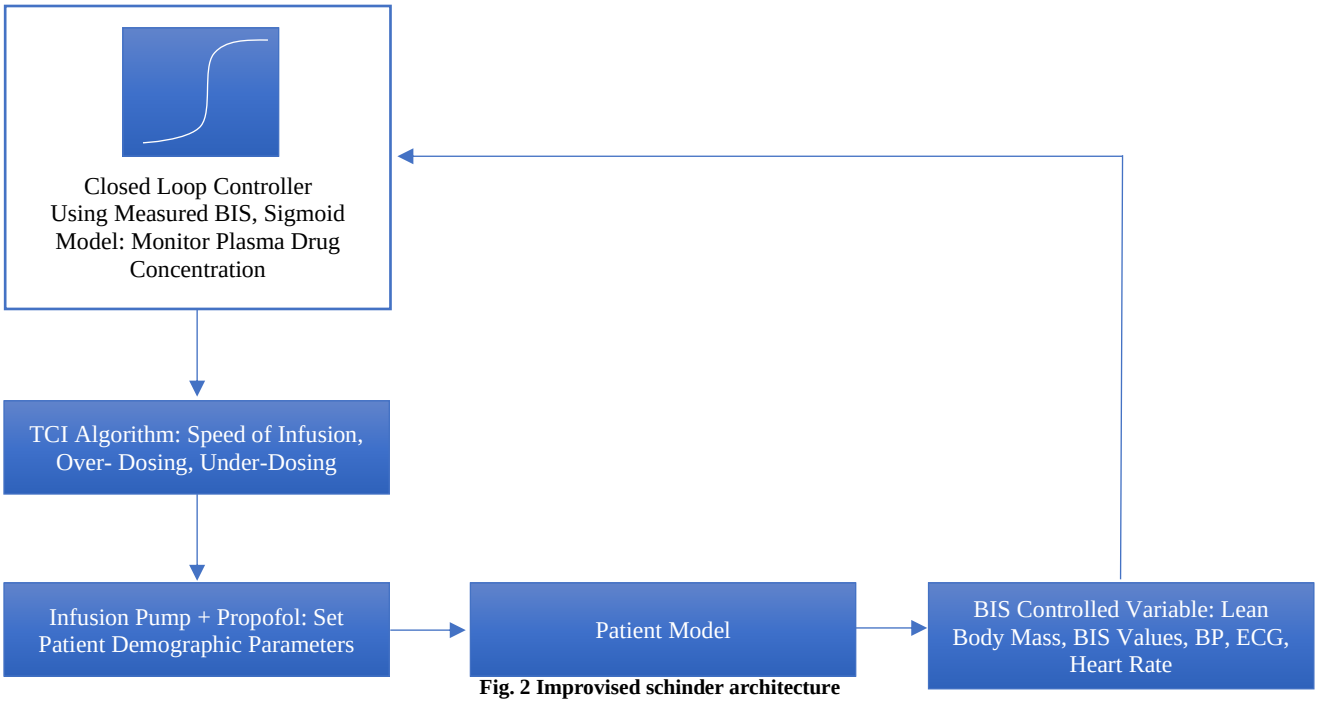

Fig. 2 Improvised schinder architecture

The model implemented from the work of [15, 16] is extended with patient safety metrics of under-dosing and over-dosing. The proposed model is compared with the existing system with a population-based patient model without patient safety constraints. A total of eight different elder patients' published data is considered to evaluate the proposed model.

Hence, based on the literature review carried out on the existing works, it is inferred that the current models adopted widely in hospitals for infusing propofol drug during anaesthesia procedures suffer from the below limitations or research gaps:

- Unable to change BMI index for obese patients in TCI pumps
- The speed of infusion parameter is not focussed, which widely affects the cardiac output of patients
- Infusion pumps are fed with constant patient demographic data
- Variation of propofol drug after infusion is analysed based on whole concentrations
- Over-dosing and under-dosing are not focussed

3. Evaluation of components in the Improvised Schinder Model

The proposed algorithm of the General Anaesthesia procedure developed for the CLAD system with patient safety [17] is simulated, shown in Figure 2, with two general case study scenarios. The model is comprised of three parts. From the diagram, the pump control algorithm with patient safety details about infusion pump drug rate algorithms based on the phases of anaesthesia procedures.

The algorithm includes patient safety metrics of underdosing and over-dosing constraints. The related algorithms will be discussed in the next section. The next block is about the Schinder-based PK-PD model. This module will calculate the drug level concentrations of the patients. The last one is the BIS module; this will convert the drug level concentrations into digitalised values ranging from 0 to 100 using BIS equation normalisation using the sigmoid function [10].

The level of drug to be given to patients using an infusion pump and infusion algorithm is to be calculated based on the reference values achieved based on equation (1). It calculated the BIS rate error, the mean of all BIS values and previous drug infusion rates.

$$Drug\_New \leftarrow f(Drug\_Prev, Km, Kh) \quad (1)$$

Where,
Km = BIserror = |BISmea-BIStar|, Kh = |BISmean-BIStar|
BIserror = error in BIS with respect to target BIS value from measured BIS

- BISmea = measured BIS value.
- BIStar = target BIS value.
- BISmean = mean of all BIS
- Propfol_New ∝ Propofol Previous

Propfol_New =Propofol_Previous * Kerr* Kmean (2)

For a given Infusion rate, the Propofol dose for the new dose is calculated by using the following equation: (2)

- Where Kerr is a proportional constant that is the difference between the actual BIS and the target BIS, and

- Kmean is a proportional constant that is the difference between the mean BIS and the target BIS during the last time interval.
- The target BIS is taken as 50 [18].

The doctor prescribes [18] the drug infusion in µg/kg/min or mg/kg/min. The infusion can be given to the patients in ml/hr. So, unit conversion is required for the prescribed (IR_Actual) to the infusion rate to be delivered by the infusion pump (IR_Pump). The unit conversion block shown in Figure 3 is used for converting physician-prescribed drug infusion units to a number of milliliters per hour to be given to the patient based on the available container and dosage level of the drug.

$$IR_{act} \rightarrow IR_{Pre} * Wt * 60 \quad (3)$$

- IRact = Actual Infusion rate as mg/hr
- IRpre = Infusion rate prescribed by physician mg/kg/min.
- Wt = Weight of the patient (kg)

Algorithm of Unit Conversion for Drug Infusion Rate

Input: Patient Weight (Wt), V← Volume of available drug container (ml), A ← Dose available in the taken volume (mg), mg/kg/min, (X) ← Units actual infusion rate prescribed by physician.
Output: ml/hr(Y) ← Units to be converted to Infusion pump rate.
Step 1: Start
Step 2: Read Wt, V, X, A
Step 3: O ← X * Wt * 60. //Conversion from mg/kg/min to mg/hr
Step 4 : Y ← (O*V)A. //Conversion from mg/hr to ml/hr:
Step 5: Stop

The variations of interpatient variability are reduced in the CLAD system by incorporating the Schinder-based PK PD model; ultimately, this will improve the system's safety. To obtain regulatory approval, the safety system of CLAD needs to be investigated and should be demonstrated [20]. Such a safety mode in the CLAD system will reduce the risk of overdosing and underdosing. This report includes the safety constraint on the drug under/overdosing using patient therapeutic window constraints. The same is demonstrated using MATLAB Simulink. A safety system for CLAD with a constraint on drug dosage prevents drug overdose that leads to respiratory depression and underdosing that leads to patient awareness during anaesthesia. The formalized safety system of CLAD to improve the safety of the system is proposed with the drug therapeutic window by [20]. The therapeutic window proposed by [21] can be used to propose the safety limits for the predicted effective site concentration of Propofol (Ce). According to [21], the safety constraints defined for CLAD anaesthesia delivery of propofol are given by the levels in the equation (4).

$$(1.5)\ \text{mg/l} < Ce(t) < (8)\text{mg/l} \quad (4)$$

Where the value of Ce (t) is calculated or predicted by using the Schinder model [22].

Algorithm for Patient Safety

Input :Ce_Mea (Effective site compartment measured from PK-PD), Ce _Min (Propofol Minimum concentration), Ce _Max (Propofol Maximum concentration)
Output: Infusion rate adjustment for avoiding overdosing and underdosing.
Step 1: Start
Step 2: Read values Ce _Mea, Ce _Min and Ce _Max.
Step 3: If Ce _Mea < Ce _Min then
IR_Infuse ← IR_Infuse+ K*(Ce _Min- Ce _Mea).//Under Dosing
Else if Ce _Max < Ce _Mea
IR_Infuse ←IR_Infuse + K*(Ce _Max- Ce _Mea). //Over Dosing
Else
IR_Infuse_Nochange
End Else
End Else_if
End if
Step 4: Stop
Statistical patient safety of the CLAD

Algorithm for Statistical Patient Safety Test

Input: Two sample BIS sets taken as (BIS_act) Excel file, BIS_Adj Excel file
Output: testing the hypothesis.
State the hypothesis H0 (true statement) and H1 (false statement)
Define the significance levels (α).
Assign the ranks to each sample (r1, r2 . . . .rs1+s2) of two categories from small-est to largest.
Sum the ranks in each group.(here R1 and R2).
Find U Test; – U1 = S1*S2 + (S1*(S1+1)/2) –R1 – U2 = S1*S2 + (S2*(S2+1)/2) –R2 – Find Min (U1,U2) = Umea.
Determine the critical value U from the Critical Value (Ucrit) table.
Compare Ucrit with Umea
Reject H0 if Umea ≤ Ucrit. Otherwise, accept the H0.

3.1. Evaluation of Drug Units conversion

The infusion pump needs the bolus concentration to be in ml/hr, which is needed to deliver the drug concentration to the patient. Conversion between the prescribed units to infusion pump units based on the unit conversion algorithm is shown in Figure 4. The converted unit alone is given as input drug infusion to the PK-PD model. The effective site concentration from the PK-PD is input to the BIS model's patient feedback system. The output of this BIS block is given as the input to the selection phase block.

Figure 3 and 4 shows the infusion rate generation for the actual input of the unit's mg/kg/min and infusion rate generation for pump units of ml/hr. The infusion is evaluated

with 2mg/kg/min during the induction phase, and 1mg/kg/min is considered for the maintenance phase. The related shows that the diagram has two parts: one is with 2mg/kg/min, which happened during the induction phase, and the other is with 1mg/kg/min for the maintenance phase in Figure 3. Figure 4 converted prescribed units to pump infusion rate values using algorithm 1.

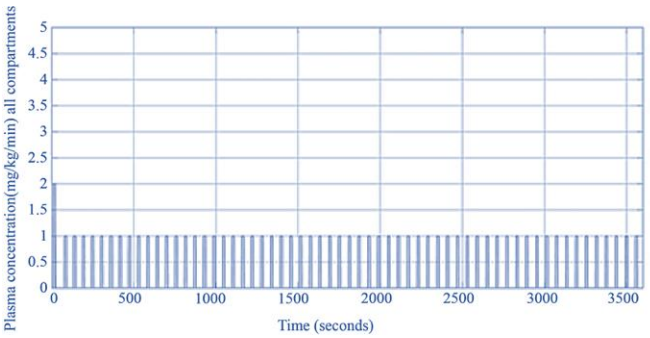

Fig. 3 Infusion rate generation in mg/kg/min

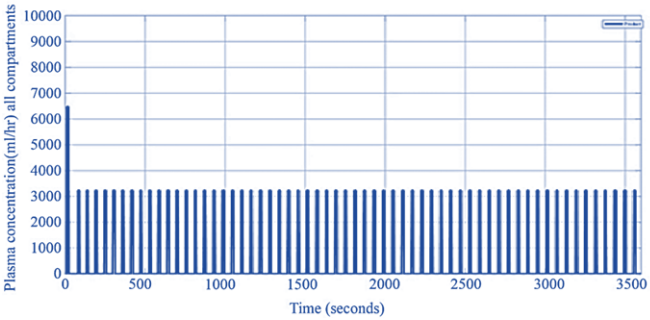

Fig. 4 Infusion rate generation in ml/hr

Table 1. Virtual data taken for simulation in MATLAB (abstracted from [18])

Patient ID	C_{50}	E_0	E_{max}	Υ
1	6.33	98.80	94.10	2.24
2	6.76	98.60	86.00	4.29
3	4.95	96.20	90.80	1.84
4	4.96	94.70	85.30	2.46
5	8.02	92.00	104.0	2.10
6	4.82	91.80	77.90	1.85
7	6.56	95.50	76.40	4.12
8	12.10	90.20	147.00	2.42

3.2. Evaluation of Monitoring Anaesthesia Levels using BIS

This part of the study is a typical case scenario of healthy patients, and another one is for elderly or unhealthy patients. Both results use the induction, maintenance phase, unit conversion and drug constraint algorithm of the drug infusion as discussed in the previous sections. The results are simulated for 120 seconds for the induction phase with a bolus infusion of 2 mg/kg/min and 1 mg/kg/min for the maintenance phase. Later, at 120 seconds, the results follow the maintenance phase of anaesthesia levels.

Table 1 is an example of virtual patient data considered for evaluating the CLAD algorithm of Propofol Infusion in this report. In a closed-loop system for anaesthesia delivery, the Bispectral index scale is used to measure the depth of anaesthesia levels of the patient. As discussed above, the sigmoid-based nonlinear hill function BIS is considered the equation to get the output response of the CLAD system.

This part of the evaluation suggests monitoring interval measures of BIS in a closed-loop drug delivery system. This means how many levels of intervals we can consider for BIS value monitoring of anaesthesia in simulation. Figures 5 and 6 represent the BIS graph for different frequent time intervals.

In Figure 6, the monitoring sample time of simulation is taken for every 10-second interval of time. If there are 1000 seconds of simulation time, the BIS is sampled for every 10 seconds, then nearly 100 samples of BIS are considered, which produces a very optimized level infusion rate. Because of this, the induction phase is reached in this case by 124 seconds.

Similarly, in Figure 6, the monitoring sample time of BIS simulation is performed for every 20-second interval of time. If there are 1000 seconds of simulation time, the BIS is sampled for every 20 seconds, then nearly 50 times the BIS value would be sampled. This produces an optimized level infusion rate but less than the previous case. In this case, the induction phase is reached by 136 seconds. Similarly, monitoring of BIS intervals for other timings of 40 seconds and 60 seconds is measured. The results for other intervals, including 10 seconds and 20 seconds, are represented in Table 2. From the results, it is shown that as the interval time for BIS monitoring increases, the time to reach the induction phase increases.

Table 2. Monitoring time effect during the induction phase for different

SI.No	Interval of monitor(sec)	Time to reach induction phase(sec)
1	10	124
2	20	136
3	40	181
4	60	189

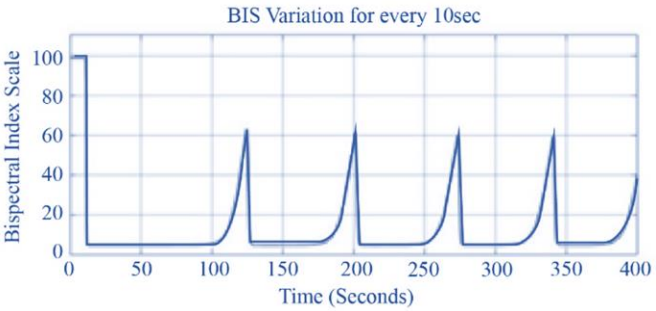

Fig. 5 Monitoring BIS for every 10 seconds

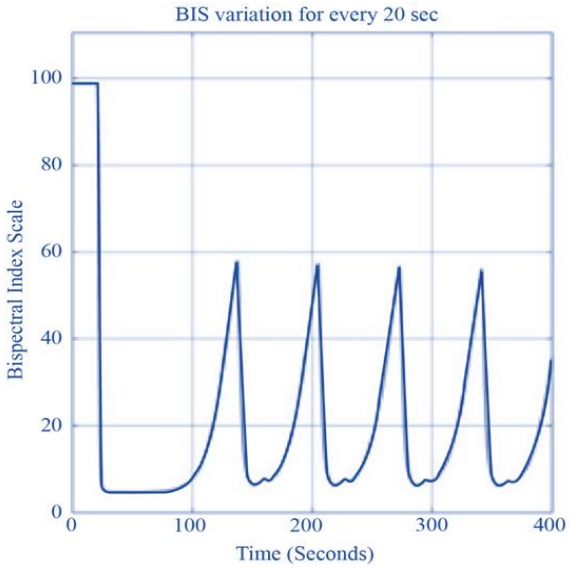

Fig. 6 Monitoring BIS every 20 seconds

Evaluation of patient safety constraints of drug side effects The variations of interpatient variability are reduced in the CLAD system by incorporating the Schinder-based PK PD model. Ultimately, this will improve the system's safety. To obtain regulatory approval, CLAD's safety system must be investigated and demonstrated [11]. Such a safety mode in the CLAD system will reduce the risk of overdosing and underdosing. This report includes the safety constraint on the drug under/overdosing using patient therapeutic window constraints. The same is demonstrated using MATLAB Simulink. A safety system for CLAD with a constraint on drug dosage prevents drug overdose that leads to respiratory depression and under-dosing that leads to patient awareness during anaesthesia.

The formalized safety system of CLAD to improve the safety of the system is proposed with the drug therapeutic window by [23]. The therapeutic window proposed by [24] can be used to propose the safety limits for the predicted effective site concentration of Propofol (Ce). According to [24], the safety constraints defined for CLAD anaesthesia delivery of propofol are given by the levels in the equation (4). By meeting these constraint boundaries, the drug side effects will not be compromised. The effective site concentration limits of the PKPD model with constraints and without constraints are shown in Figures 7 and 8. Figure 7 shows the limits of an effective site compartment based on Schinder based PK PD model. As we noticed here, the level of concentration is suffered by the underdosing drug effect. The graph is represented with three levels of measure; one of the thick lines is the maximum or overdosing limit as 80 mg (Ce_Max), the minimum or under-dosing limit as 15 mg (Ce_Min) and finally, the measured effective site value (Ce). The measured value is often affected by underdosing limits crossing after the initial peak level effect of the concentration.

Similarly, Figure 8 shows the limits of an effective site compartment based on Schinder based PK PD model with added therapeutic constraints. As we noticed, the previous level of concentration suffered by the underdosing drug effect is reduced from these results. The graph is represented with three levels of measure: one of the thick lines is the maximum (Ce_ Adj_Max) or overdosing limit, minimum or under-dosing limit (Ce_Adj_Min) and finally, the measured effective site value (Ce). Whenever the underdosing measure is noticed by using the drug adjustment algorithm, the value is adjusted until it reaches the limits within underdosing.

The comparative results between both cases are tabulated in Table 3. This table compares the response time, peak value effective site concentration, and time. For the case without constraints, the effective site compartment response is 21 sec. The case with constraint has a response time of 7 seconds, so the CLAD with safety constraints is more responsive than the system without constraints.

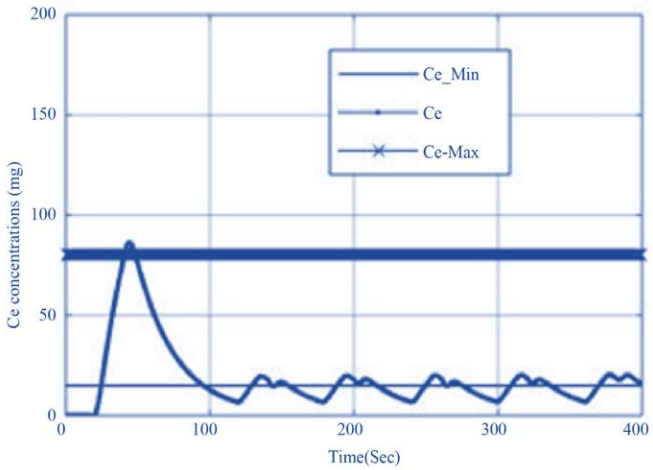

Fig. 7 Effective site concentrations without window constraints

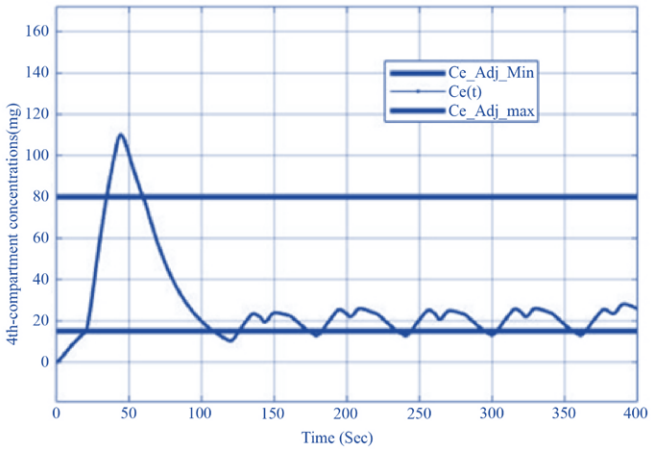

Fig. 8 Effective site compartment concentrations with window-based constraints

Table 3. Propofol Drug Side effects without & with window constraints

Response time(Sec)	Effective site peak value	Peak value(sec)(ϒ=2.25,delay=40)	Induction phase value	BIS
21	86	45	136	57
7	108	46	135	40

Similarly, the peak value without constraint is 86mg, whereas the same value with constraint is 108 mg, and both have the same peak level of time. Similarly, the BIS performance is compared and is shown in Table 3. The table shows that the attainment of the induction phase in both cases is the same, but the value of reaching among 60 to 40 is 40 for case 2, whereas in case 1, it is 57. So, the attainment of the surgery phase is much faster in case 2 compared to case 1.

3.3. Statistical Measure Checking of Patient Safety in CLAD

Mann-Whitney Safety U Test is a popular nonparametric test to compare outcomes between two independent groups. It is used to compare the medians between the two populations. Here, the Man Whitney test compares the safety parametric test on CLAD.

Finally, in the test for anaesthesia, sensitive patients or elderly people need less bolus infusion during induction than healthy patients, according to the results [4]. The induction phase occurs more in elderly patients than in healthy patients.

The elderly or anaesthesia-sensitive patients spend more time in anaesthesia than others, requiring more recovery time than healthy patients. The Mann-Whitney nonparametric safety test is performed by taking data samples of BIS shown in Figure 9 to two cases:

Sample 1: BIS variation without safety constraints.
Sample 2: BIS variation with safety constraints.

Each sample value of the obtained BIS value is compared with the target values of 50. Then, tolerance error with respect to the target value is performed. Four error measures are performed based on their output and are shown in Table 4.

Table 4 shows that the performance error with target BIS having a 10% error is more in BIS output for added drug constraints. Similarly, the added drug constraint scenario improves the performance for another case. The safety test is performed based on the above following procedure for Table 4. Both the samples are taken with the size of 4, and the above procedure is applied. The hypothesis for the CLAD model is taken as follows:

Table 4. BIS Performance error measurement with respect to target BIS value is 50

SL.No	Performance error (PE)	BIS for Sample 1	BIS for Sample 2
1	PE <10	6.40	11.86
2	10≤PE<21	7.34	5.38
3	21≤PE<30	6.90	2.99
4	PE>30	79.36	79.77

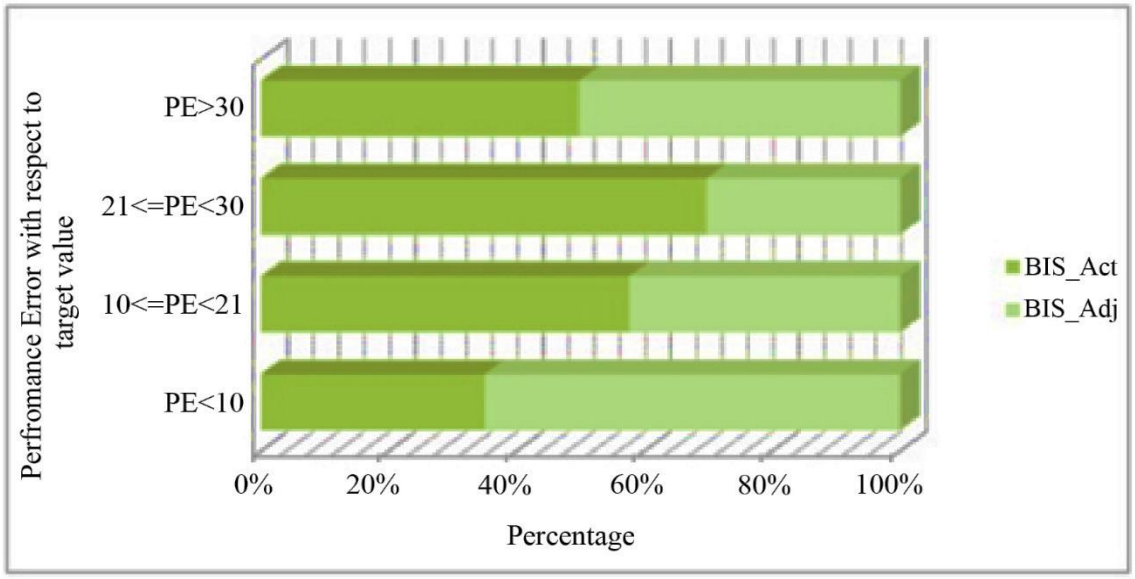

Fig. 9 Comparison of proposed safety drug infusion algorithm with drug infusion algorithm with patient safety and without patient safety measures

- H0: Sample 2 is safer than the sample 1 H1: Sample 1 is safer than the sample 2
- After applying the above procedure R1 = 19, R2 = 17, U1 = 7 and U2 =9.
- From this, the measured critical value (U) = Min(U1, U2) = 7.
- Critical value from the critical value table of Mann Whitney for one-sided is [25] obtained as Ucri = 1 at the significance level (α) 0.05.

From the procedure Umea > Ucri, the considered hypothesis is accepted. Finally, the hypothesis test using Mann Whitney confirms that the implemented computerized integrated closed-loop anaesthesia delivery system is safer when added with the drug window constraints at a significance level of 0.05. From this test, results of including the drug constraints into the CLAD system become safer with 95% [26] assurance with the obtained significance levels of 0.05. This improves the robustness of the system. Likewise, the system will become safer as many safety features are added. When all these safety features are demonstrated clinically, the chance of obtaining commercial approval by the regular bodies is very easy.

From the evaluation of the above results and discussions of statistical tests, the following observations are noted:

1. Anaesthesia-sensitive patients or elderly people need less bolus infusion during induction than healthy patients, as from the results.

2. The induction phase occurs earlier in the elderly than healthy patients.

3. The elderly or anaesthesia-sensitive patients stay longer in anaesthesia than others and require more recovery time than the healthy patients.

4. Conclusion

The closed-loop anaesthesia drug delivery system effectively delivers the exact levels of propofol drug to patients based on the added features in the improvised Schinder model. The parameters added in the improvised Schinder model effectively prevent cardiac-related complications in patients, adjust the drug doses according to varied BMI indexes, and effectively monitor the over-dosing and under-dosing constraints based on the patient's response. Drug side effects are verified by checking the predicted effective site concentrations within the therapeutic Propofol window constraints. The controlled algorithm based on BIS evaluates the induction and maintenance phases. The safety of the proposed system is also checked using the Man Whitney safety test. From the simulation results, it is concluded that the infusion procedure is safe at a significant level of 0.05. The work could be extended by carrying out predictions in the anaesthesia drug delivery doses by adopting deep learning algorithms for an enhanced level of safety and verification, which could be accessed using an IoT interoperable interface with remote access capabilities.

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