

# **Autonomous Drugs Optimal Management, Part V: Anesthesia Control for Atracurium Drug using PD-PI and PD-I Controllers Compared with a PID Controller**

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## **Abstract:**

This paper is the fifth in a series of research papers studying the autonomous drug optimal management. It handles the control of the anesthesia-atracurium drug infusion rate using a PD-PI and PD-I controllers from the second generation of PID controllers. The relationship between the bispectral index and the site-effect concentration of the drug is investigated and presented graphically for two anesthesia drugs. Some tuning techniques for the proposed controllers are proposed based on zero/pole cancellation, trial-and-error techniques and using the MATLAB optimization toolbox. The step time response of the control system using the proposed controllers is presented and compared with that of a conventional PID controller from the first generation of PID controllers tuned in in the present research work. The comparison reveals the best controller among the three ones presented depending on a graphical and quantitative comparison study for reference input tracking.

**Keywords** — Anesthesia control, Atracurium Drug, BIS index, PD-PI controller, PD-I controller, PID controller, controller tuning.

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## **I. INTRODUCTION**

Anesthetic drugs are essential for surgical operations or other medical procedures for: unconsciousness, pain free, no motion and muscles relaxation [1]. However, the administration of an incorrect dosage of an anesthetic drug can lead to respiratory arrest, cardiac failure or patient waking up during surgery [2]. Because of this the importance of the present research arises leading to optimal regulation of the anesthesia drug and maintaining the desired '*bispectral index*' (BIS). We start by presenting some of the efforts by research scientists to achieve this objective since 2000:

Schutler and Ihmsen (2000) outlined that target-controlled infusion was a common type of propofol administration requiring accurate knowledge of its

pharmacokinetics (PK). They described the propofol PK using a three compartments model improved by the inclusion of age and weight [3]. Bibian et al. (2005) addressed the pharmacological principles of clinical anesthesia for control engineers covering drug dose versus response relationships. They presented a chart for the BIS monitor as a monitor for consciousness with scale from 0 to 100 defining the deep hypnotic, moderate hypnotic and high hypnotic states. They outlined the opinion of some studies that 20-30 % reduction in the total amount of anesthetic drugs could be achieved during the maintenance phase by keeping the BIS in the 40-60 range [4]. Abdulla (2012) developed patient dose-response models and provided an adequate drug administration regimen for anesthesia to avoid under or over dosing of patients. He designed the controllers to compensate

for patient's inherent drug response variability to achieve the best disturbance rejection and maintain optimal set-point response. He investigated the use of a robust internal model controller based on the BIS index compared with a conventional PID controller and an internal model control [5]. Heusden et al. (2014) described the design of a robust PID control for propofol infusion in children. They tuned the controller for robustness margins for the identified uncertainty. They concluded that a robust-tuned-PID could accommodate the inner-patient variability in children and maintain breathing in most objects [6].

Araujo et al. (2014) presented the automatic drug administration for the regulation of BIS index in the anesthesia process during clinical surgery through controlling the concentration target for propofol and remifentanil drugs. They derived PK and PD models for 42 patients reduced to nominal model by taking the average of the models. They employed three PID controllers: linear PID, type-1 fuzzy PID and interval type-2 fuzzy PID to regulate the BIS index. They tuned the controllers using q genetic algorithm. They concluded that type-2 fuzzy PID was the best controller [7]. Talebian (2016) outlined that anesthesia control involves adjusting drug dosage by monitoring patient's vital and clinical signs which a control system can replace. He investigated the  $L_1$  adaptive control applied to 44 simulated cases. He concluded that the  $L_1$  adaptive control in its current form was not applicable to closed-loop control of anesthesia. He developed a PID auto-tuning algorithm tested on his 44 cases [8].

Eleveld et al. (2018) outlined that PK and PD models are used in target-controlled-infusion systems for the optimal drug administration to achieve a desired target concentration. They analyzed propofol concentration, BIS observation, age up to 88 years, weight up to 160 kg. They developed a PK-PD model to predict the propofol concentration and BIS for broad population which was useful in target-controlled-infusion in anesthesia and sedation [9]. Veerakumar et al. (2020) outlined that anesthesia is a way to control pain during a surgery and helps to maintain the patient blood pressure, blood flow and heart rate. They studied the propofol drug delivery using closed-loop technology and BIS to measure the

depth of anesthesia. Their control strategy was based on using a PID controller and a BIS and used an auto-tuned PID controller [10]. Pawlowski et al. (2022) proposed and analyzed a model predictive control system for the depth of hypnosis considering simultaneous co-administration of the hypnotic and analgesic drugs and their effect on the BIS scale. Tey used the nonlinear MISO model to predict the remifentanil influence over the propofol hypnotic effect to provide the optimal dosage for the desired BIS level. They tested their approach using simulated nonlinear PK/PD model and evaluated the robustness of the proposed control system [11].

Paolino et al. (2024) investigated the use of a PK/PD model for the design of a PID controller for total intravenous anesthesia. They used the administration of propofol as a manipulated variable and the BIS signal as the process variable and tuned the PID controller using the Eleveld model. They concluded that the development of a PK/PD model for control design would be beneficial to increase the overall performance of the control system [12]. Schiavo et al. (2025) presented a BIS controlled closed-loop system based on the use of a PID control algorithm receiving the BIS index value, calculating the infusion rates of propofol and remifentanil sent to the pumps [13].

## **II. THE CONTROLLED ANESTHESIA AS A PROCESS**

- There is no automatic control without process modeling. This is the 'abc' of automatic control. Therefore, the first step now is to investigate a model for anesthesia regulation in an open-loop fashion specially a linear model. This depends on the type of drug used in performing the anesthesia operation prior to surgery of any other medical operation to avoid pain and consciousness. A pharmacokinetic (PK) and pharmacodynamic (PD) models define the dynamics of the anesthetic drug concentration in three-compartment dynamic model (PK-PD model) as an anesthesia process transfer function. We denote the PK-model transfer function as  $G_{PK}(s)$ , the PD-model transfer function as

$G_{PD}(s)$  and the PK-PD model transfer function as  $G_{PKPD}(s)$ . For an atracurium anesthesia drug, the PK-model was defined by Favero as [14]:

$$G_{PK}(s) = K_1 K_2 K_3 \alpha^3 / [(s+K_1\alpha)(s+K_2\alpha)(s+K_3\alpha)] \quad (1)$$

Where:

$G_{PK}(s) = C_p(s)/U(s)$  = ratio between the Laplace transform of the drug concentration in the blood compartment and the Laplace transform of the drug infusion rate.

The parameters of the PK-model in Eq.1 for the atracurium drug are given as [14]:

$$K_1 = 1, K_2 = 4, K_3 = 10, \alpha = 0.0374 \quad (2)$$

- The PD-model for an anesthetic drug has a transfer function  $G_{PD}(s)$  given by Bibian as [4]:

$$G_{PD}(s) = \frac{C_e(s)}{C_p(s)} = k_{eo}/(s + k_{eo}) \quad (3)$$

where:  $C_e(s)$  = Laplace transform of the effect-site concentration,  $k_{eo}$  is a rate constant.

- Shanks et al outlined that the rate constant  $k_{eo}$  for an atracurium drug has a value between 0.1 and 0.12 1/min [15] (for purpose of simulation, we have taken it as 0.1).
- With the consideration of Eqs.1, 2 and 3, the PK-PD transfer function model  $G_{PKPD}(s)$  becomes:

$$G_{PKPD}(s) = K / [(s + a_1)(s + a_2)(s + a_3)(s + k_{eo})] \quad (4)$$

Where:

$$\begin{aligned} K &= K_1 K_2 K_3 k_{eo} \alpha^3 = 2.0925 \times 10^{-7} \\ a_1 &= K_1 \alpha = 0.00374 \\ a_2 &= K_2 \alpha = 0.01496 \\ a_3 &= K_3 \alpha = 0.03340 \end{aligned} \quad (5)$$

- The effectiveness of any proposed control system for the anesthesia process can be measured by a number of parameters, the most important one of them is the 'bispectral (BIS) index' [7], [9], [10], [11], [12], [13] and [16].
- The BIS index did not merge with the PK and PD models because it has a nonlinear relationship with the effect-site concentration  $C_e$  appeared in the PD-model (Eq.3). This nonlinear relationship is known as Hill's model and gives the BIS index as [16]:

$$BIS = E_o - E_{mx} C_e^\gamma / (C_e^\gamma - C_{50}^\gamma) \quad (6)$$

Where:  $E_o$  = initial BIS,  $E_{mx}$  = maximum BIS on the BIS scale,  $C_{50}$  = effect-site concentration at  $E_{mx}/2$  and  $\gamma$  = Hill's coefficient.

- The recommended range of the BIX index is [17]:

$$40 \leq BIS \leq 60 \quad (7)$$

- The parameters of Hill's model of Eq.6 for the atracurium and propofol drugs are respectively [14], [8]:

$$E_o = 100, E_{mx} = 94, C_{50} = 3.2425, \gamma = 2.6677 \quad (8)$$

$$E_o = 100, E_{mx} = 100, C_{50} = 3.80, \gamma = 1.20 \quad (9)$$

- The parameters in Eqs.8 and 9 are used to plot the BIS against  $C_e$  in the range  $0 \leq C_e \leq 10$  using Eq.6 for atracurium and propofol anesthetic drugs as shown in Fig.1 using the MATLAB 'plot' command [18]. A line at the optimal BIS value of 50 is also drawn.

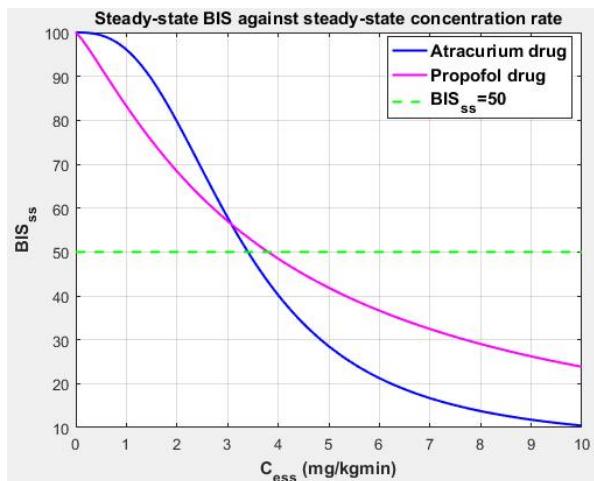


Fig.1 Plotting of BIS against  $C_e$  for atracurium and propofol drugs.

- The unit step time response of the anesthesia process with atracurium drug as a process is defined by Eq.4 with model parameters given by Eqs.5 and 3 is shown in Fig.1 as generated by the step command of MATLAB [19] for a 3.40166 mg/(kgmin) drug administration rate as an input. The step response in Fig.1 shows also the  $C_e$  values corresponding to a BIS value of 50 (is the desired optimal value) and 60 (upper limit of BIS).

## COMMENTS:

- Maximum overshoot: zero
- Settling time to  $\pm 2\%$  tolerance: 1161.3 s
- Rise time: 623.0 s
- Time to BIS = 60: 10 min

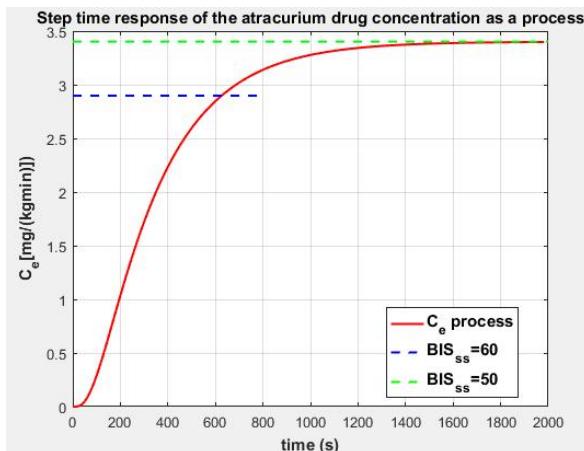


Fig.2 Step time response of the atracurium drug infusion process.

### III. CONTROLLING THE ATRACURIUM ADMINISTRATION USING A PID CONTROLLER

- The conventional PID controller is the father of the PID controllers of the first generation introduced in the 20<sup>th</sup> century. It was proposed to regulate anesthetic drugs infusion by a number of researchers [6], [7], [8], [10], [12] and [13]. A PID controller has a transfer function,  $G_{PID}(s)$  given by:  

$$G_{PID}(s) = K_{pc1} + (K_{i1}/s) + K_{d1}s \quad (10)$$
- The PID controller has three gain parameters: proportional gain  $K_{pc1}$ , integral gain  $K_{i1}$  and a derivative gain  $K_{d1}$  tuned for good performance for the control system and achieving the desired objective of attaining a BIS having a 50 value.
- Using the atracurium-anesthesia process in Eq.4 and its parameters in Eq.5 and the PID controller in Eq.10, we have tuned the PID controller parameters using an ITAE performance index [20] and the MATLAB optimization toolbox [21] providing the following tuned controller parameters:

$$K_{pc1} = 0.76783; \quad K_{i1} = 0.002775; \quad K_{d1} = 0.0000981 \quad (11)$$

- With the PID controller tuned, Eqs.4, 5, 10 and 11 are used to plot the step time response of the atracurium administration regulation control system using the MATLAB 'step' and 'plot' commands [18], [19] providing the step time response shown in Fig.3 for a desired BIS of 50 (corresponding to a desired effect-site concentration of 3.40166 mg/(kgmin)).

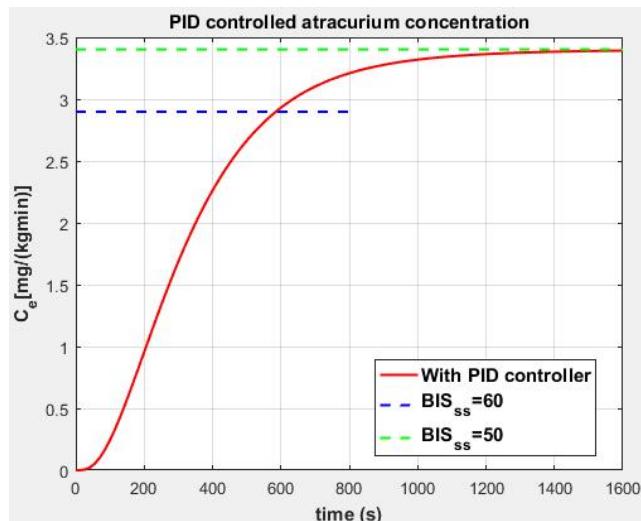


Fig.3 Step time response of a PID controlled atracurium drug.

## COMMENTS:

- Maximum overshoot: zero
- Settling time to  $\pm 2\%$  tolerance: 1047.6 s
- Rise time: 556.0 s
- Time to BIS = 60: 9.67 min
- Steady-state error: zero

### IV. CONTROLLING THE ATRACURIUM ADMINISTRATION USING A PD-PI CONTROLLER

- The PD-PI controller is one of the second generation of PID controllers introduced by Prof. Galal Hassaan since 2014 to control processes having bad dynamics such as: a first-order-delayed process [22], highly oscillating second-order process [23], Integrating plus time-delay process [24], BLDC motor [25], blending process [26],

greenhouse humidity process [27], liquefied natural gas tank level process [28] and human blood urine nitrogen [29]. It has the transfer function  $G_{c2}(s)$  given by [25]:

$$G_{c2}(s) = (K_{pc2} + K_{d2}s)(K_{pc3} + K_{i3}/s) \quad (12)$$

Where:

$K_{pc2}$  = proportional gain of the PD control.

$K_{d2}$  = derivative gain of the PD control.

$K_{pc3}$  = proportional gain of the PI control.

$K_{i3}$  = integral gain of the PI control.

- The PD and PI control modes of the PD-PI controller are set in cascade after the error detector of the single closed-loop block diagram of the proposed control system for the anesthesia drug.
- The four parameters of the PD-PI controller are tuned as follows:
  - ⊕ The transfer function of the PD-PI controller in Eq.12 is rewritten in the form of simple poles of the controlled process (Eq.4) as follows:

$$G_{c2}(s) = \left( \frac{K_{d2}K_{pc3}}{s} \right) \left[ s + \left( \frac{K_{pc2}}{K_{d2}} \right) \right] \left[ s + \left( \frac{K_{i3}}{K_{pc3}} \right) \right] \quad (13)$$

- ⊕ The PD-PI controller has two simple zeros as depicted in Eq.13 and the anesthesia-drug has 4 simple poles as depicted by Eq.4.
- ⊕ The zero/pole cancellation technique [30] is applied to the open-loop transfer function of the block diagram loop for the anesthesia-drug control. The first controller zero (in Eq.13) is chosen to cancel the simple pole ( $s+0.00374$ ) of the anesthesia-drug process in Eq.4 providing the following relationship between the PD control parameters as:

$$K_{d2} = K_{pc2}/0.00374 \quad (14)$$

- ⊕ The second zero of the PD-PI controller in Eq.13 is cancelled with the second pole of the process in Eq.4 providing the following relationship between the PI control parameters as:

$$K_{i3} = 0.01496K_{pc3} \quad (15)$$

- ⊕ The transfer function of the closed-loop control system,  $M_2(s)$  is deduced using

Eqs.4 and 12 in a unit feedback single loop control system and after the application of the zero/pole cancellation technique producing Eqs.14 and 15. The result is as follows:

$$M_2(s) = K_{22}/(s^3 + 0.1374s^2 + 0.00374s + K_{22}) \quad (16)$$

Where:

$$K_{22} = KK_{d2}K_{pc3} \quad (17)$$

⊕ Now, applying the Routh-Hurwitz criterion [31] on the characteristic equation of the control system incorporating the PD-PI controller and the anesthesia-drug process provides the maximum value of  $K_{22}$  as:

$$K_{22max} = 0.000514 \quad (18)$$

⊕ Using Eq.16 simplifies the tuning process to adjusting only one parameter  $K_{22}$ . For control system stability, it has to be less than 0.000514 as depicted from Eq.18. Using the trial-and-error technique for the PD-PI controller tuning [32], good control system performance is obtained using:

$$K_{22} = 0.000038 \quad (19)$$

⊕ Now, let  $K_{pc2} = 1$  where Eq.14 gives  $K_{d2}$  as:

$$K_{d2} = 267.3797 \quad (20)$$

⊕ Combining Eqs.17 and 20 gives  $K_{pc3}$  as:

$$K_{pc3} = 0.57193 \quad (21)$$

⊕ Combining Eqs.15 and 21 gives  $K_{i3}$  as:

$$K_{i3} = 0.008556 \quad (22)$$

- The step time response for reference input tracking of a desired BIS of 50 (corresponding to a desired effect-site concentration of 3.40166 mg/(kgmin) using the PD-PI controller transfer function in Eq.16 and process transfer function in Eq.4 is obtained using the command 'step' of MATLAB [19] as shown in Fig.4.

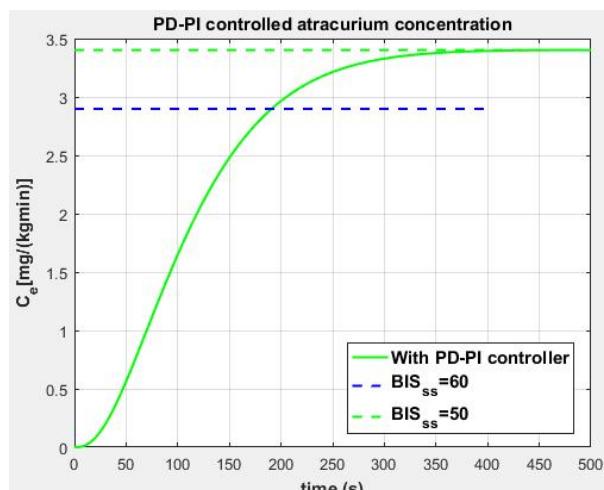


Fig.4 Step time response of a PD-PI controlled atracurium drug.

## COMMENTS:

- Maximum overshoot: zero
- Settling time to  $\pm 2\%$  tolerance: 303.8 s
- Rise time: 176.7 s
- Time to BIS = 60: 3.14 min
- Steady-state error: zero

## V. CONTROLLING THE ATRACURIUM ADMINISTRATION USING A PD-I CONTROLLER

- The PD-I controller is one of the second generation of PID controllers introduced by prof. Galal Hassaan (one of the authors) since 2014 where he first applied it in 2022 to control underdamped second-order-like processes [33]. A PD-I controller consists of two cascaded control elements: A PD-control mode in the forward path just after the error detector and an I-control mode in cascade with the PD-element followed by the controlled process. It has the transfer function equation [33]:

$$G_{c3}(s) = (K_{pc4} + K_{d4}s)(K_{i4}/s) \quad (23)$$

Where:

$K_{i4}$  = integral gain of the I-control mode.

$K_{pc4}$  = proportional gain of the PD-control mode.

$K_{d4}$  = derivative gain of the PD-control mode.

- The three gain parameters of the PD-I controller are tuned as follows:
  - The transfer function of the closed-loop control system for the control of the atracurium drug infusion rate is derived and used to find the ITAE performance index [20] which is then minimized using the MATLAB optimization toolbox [21].
  - The result of the tuning operation reveals the following three gain parameters of the PD-I controller:
 
$$K_{pc4} = 0.38512, K_{d4} = 99.9998, K_{i4} = 0.008948 \quad (24)$$
  - The step time response for reference input tracking of a desired BIS of 50

(corresponding to a desired effect-site concentration of 3.40166 mg/(kgmin) using the PD-I controller transfer function in Eq.23 and process transfer function in Eq.4 is obtained using the command 'step' of MATLAB [19] as shown in Fig.5.

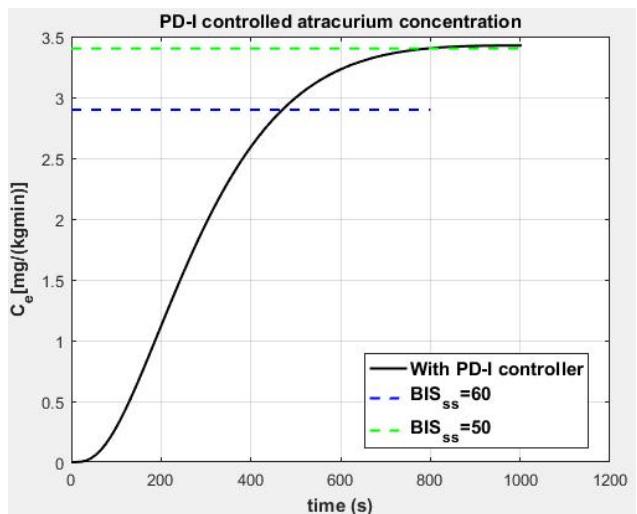


Fig.5 Step time response of a PD-I controlled atracurium drug.

## COMMENTS:

- Maximum overshoot: 0.713 %
- Settling time to  $\pm 2\%$  tolerance: 681.4 s
- Rise time: 414.1 s
- Time to BIS = 60: 7.68 min
- Steady-state error: zero

## VI. COMPARISON ANALYSIS

- To evaluate the effectiveness of using the proposed controllers, the step time response for a desired 50 BIS index is compared with that using a PID controller tuned by us.
- A graphical comparison is presented in Fig.6 showing three step time responses for a PID controller, PD-PI controller and PD-I controller.
- A quantitative comparison for the time-based characteristics of the control systems proposed to control the atracurium drug is given in Table 1 for reference step input tracking (desired BIS index).

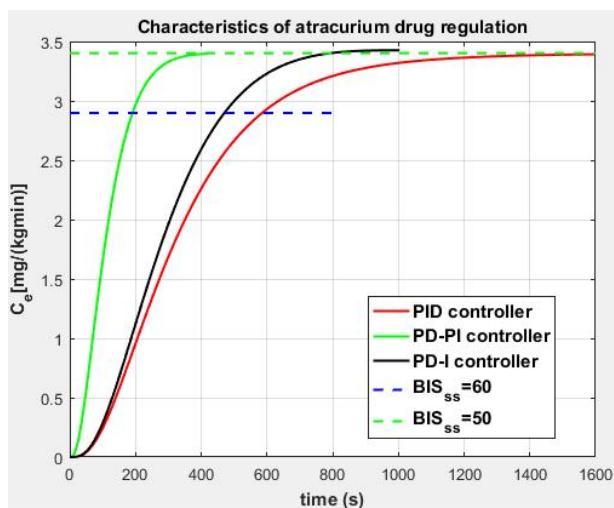


Fig.6 Atracurium drug control using three controllers.

TABLE 1  
CHARACTERISTICS COMPARISON FOR  
ATRACURIUM DRUG INFUSION RATE CONTROL

Controller	Without control	PID controller	PD-PI controller	PD-I controller
OS <sub>max</sub> (%)	0	0	0	0.713
T <sub>s</sub> (s)	1161.3	1047.6	303.8	681.4
T <sub>r</sub> (s)	623.0	556	176.7	414.1
T <sub>s60BIS</sub> (min)	10	9.67	3.14	7.68

OS<sub>max</sub>: Maximum percentage overshoot.T<sub>s</sub>: Settling time for 2% tolerance.T<sub>r</sub>: Rise time.T<sub>s60BIS</sub>: Settling time at BIS = 60.

## VII. CONCLUSIONS

- This research paper investigated the use of PD-PI and PD-I controllers from the second generation of PID controllers compared with a PID controller from the first generation of PID controllers to control the infusion rate of atracurium drug for anesthesia during surgery.
- The process under control was identified for a three-compartment model as a 0/4-order transfer function model providing zero overshoot, zero steady-state error and 1161.3 s settling time (19.35 min). The challenge for control engineer in this automatic control application is to propose a controller capable of providing fast time-response because of the critical situation of the anesthesia process.
- The performance of the proposed controllers was assigned through the investigation of

the step time response of the control system comprising the controllers and the atracurium drug infusion rate process.

- The tuning technique used to optimize the controllers' parameters was based on the zero/pole cancellation technique, the trial-and-error technique and using the optimization toolbox of MATLAB and an ITAE performance index.
- The relationship between the '*bispectral (BIS) index*' and the '*effect-site concentration*' which was a nonlinear one was presented graphically for propofol and atracurium anesthesia-drugs.
- The two proposed controllers (PD-PI and PD-I) and the PID controller succeeded to eliminate completely the maximum percentage overshoot of the closed-loop control system for reference input tracking.
- The settling time of the step input tracking time response (for 2 % tolerance) was assigned to be 303.8 and 681.4 s for the PD-PI and PD-I controllers compared with 1161.3 s for uncontrolled process and 1047.6 s for PID-controlled process respectively.
- The proposed controllers succeeded to provide a step time response having a rise time of 176.7 s and 414.1 s for the PD-PI and PD-I controllers compared with 623 s for uncontrolled process and 556 s for the PID-controlled process.
- The proposed controllers succeeded to provide a step time response capable of reaching the 60 BIS level after 3.14 and 7.68 min for the PD-PI and PD-I controllers compared with 10 min without process control and 9.67 min for the PID-controlled anesthesia process.
- The proposed controllers and the PID controller succeeded to provide step time response for reference input tracking without any steady-state error because of the presence of 's' in their transfer function denominator.
- The PD-PI controller has proved in this application to be the best controller because of its outstanding step time response without

any overshoot, undershoot or steady-state error with settling time of only 5 min and reaching the BIS level of 60 in about 3.1 min.

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- He learned chemistry, astronomy, medicine, pharmacy and philosophy.
- He worked as the court alchemist and physician for ministers of Caliph Haron Asl-Rashid.
- He died in 815 AC with age of 94.
- He wrote about 1300 books on mechanical devices.
- He wrote hundreds of books on chemistry and 300 books on philosophy.
- Among his books: '*Book of balance*' and '*book of stones*'.
- Some of his books were translated to Latin and other European languages and used in Europe for several centuries.
- He introduced the '*experimental methodology*' into chemistry.
- He invented several chemical processes used in '*modern chemistry*'.
- This is why we dedicate our research work in this research paper to the great '*scientist Jabir ibn Hayyan*'.

## **DEDICATION**



### **JABIR IBN HAYYAN [34]**

- Father of '*Arab chemistry*'.
- One of the founders of '*modern pharmacy*'.
- He was born in Khorasan of Iran in 721 AC.
- His father was a pharmacist from Yemen and lived in Kofa of Iraq during Umayyads.
- Jaber moved to Kofa after Abbasid's dynasty took over after Umayyads.