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Modeling and optimized controller for cardiac drug infusion system

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Abstract

Background: Manual drug infusion during surgeries is inaccurate and time-consuming which has been adopted technique in most of the hospitals. **Methods:** Based on clinical data, it is evident that the manual control is inaccurate and takes prolonged time to bring into effect, if any change in infusion rate is required during clinical practice. Considering this drawback, the modeling of cardiovascular system (CVS) and baroreceptor (BR) is developed using miscellaneous differential equations based on compartmental approach. The control variables are mean arterial pressure (MAP) and cardiac output (CO) obtained from CVS-BR model. **Findings:** The manipulated variables are noradrenaline (NAR) and nitroglycerine (NG) infusion rate which is modeled using the relationship between volume and drug mass effect equations on CVS-BR model. For the open loop transfer function derived from the model, relative gain array (RGA) analysis is performed to identify the influence of maximum effect of manipulated variables on the physiological parameters. The simulation results obtained from MATLAB are correlated using time domain specifications and error criteria. The performance index reveals the least error and facilitates in accurate infusion of drugs to the patient during cardiovascular surgeries. **Novelty:** The automatic controller during surgery provides safe operating condition and speedy recovery of the patients and also helps the anaesthetist to monitor and regulate the physiological variables.

Keywords: Control strategy; Error criteria; Drug infusion; Modeling; Relative gain array; Simulation

1 Introduction

Human cardiovascular system helps in supplying sufficient amount of oxygen to all vital organs and tissues through the flow of blood. Due to current lifestyle and other circumstances, people are suffering from various diseases related to cardiovascular system of which surgery remains to be the only treatment. The most common heart surgeries performed in humans irrespective of age are coronary artery bypass grafting and

valve replacement surgery. During the surgical procedure, cardiac drugs used in clinical practice are noradrenaline (NAR) with a dose of 0.1-3 ($\mu\text{g/kg/min}$) and nitroglycerine (NG) with specific dosage of 0.1-1.5 ($\mu\text{g/kg/min}$). These drugs were used to maintain the hemodynamic variables such as mean arterial pressure (MAP) and cardiac output (CO). The cardiac drugs are infused through a syringe pump by the anaesthetist manually. Since, under dose and over dose of the drugs result in several life threatening consequences during surgery, leading to delay in patient's recovery, an automatic control and regulation of cardiac drugs is necessary and it also helps the anesthetists to concentrate on other tasks during surgery. The work presented in this article, concentrates on the optimization algorithm that has been developed to tune the parameters of Proportional-Integral controller. This controller in turn regulates the drug infusion rate infused into patients during cardiovascular surgery. It also focuses on the performance of the algorithm that have been developed when compared with the conventional method used for tuning the control parameters, such as relay tuning technique.

2.2. Materials and Methods

2.1 Modeling

The initial work is carried out by observing the clinical data such as MAP, CO and dosage of NAR and NG during surgery. The modeling of cardiovascular system (CVS) is performed by considering four compartments such as left heart, systemic circulation, right heart and pulmonary circulation as shown in Figure 1⁽¹⁻⁴⁾.

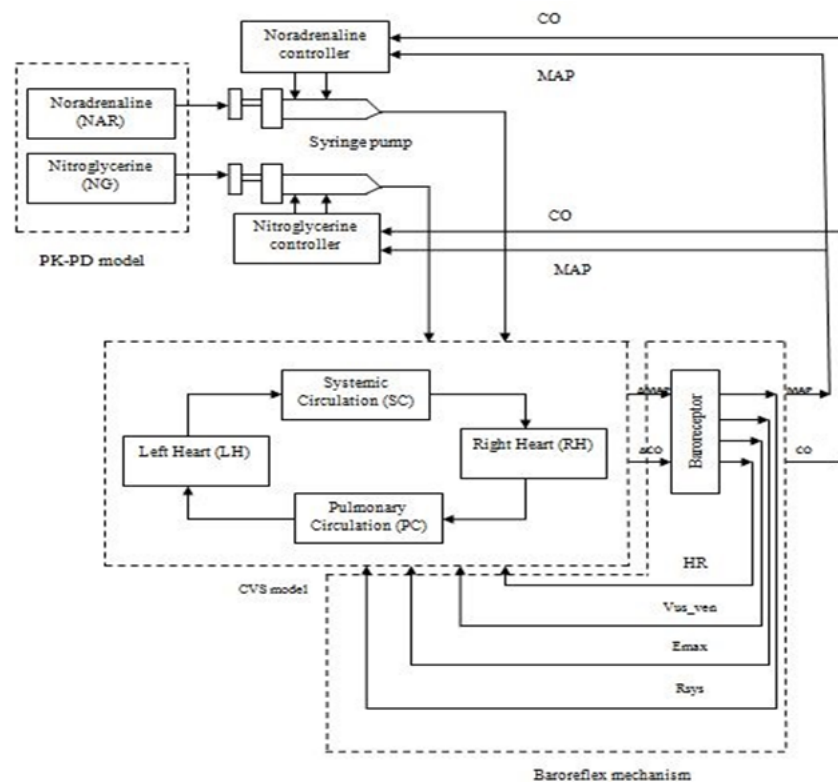


Fig 1. Block diagram of cardiac drug control system

The differential equations were derived based on the following three equations-

$$P_{sys1} - P_{sys2} = R_{sys1} Q_{sys1} + L_{sys1} \frac{dQ_{sys1}}{dt} \quad (1)$$

$$\frac{dV_{sys1}}{dt} = Q_{lv} - Q_{sys1} \quad (2)$$

$$P_{sys1} = \frac{1}{C_{sys1}} (V_{sys1} - V_{us,sys1}) \quad (3)$$

Where P_{sys1} and P_{sys2} are the aortic systemic pressure in partition 1 and partition 2. R_{sys1} represent viscosity, L_{sys1} represents inertia and C_{sys1} represents elastance properties, Q_{sys1} and V_{sys1} represents flow and volume and V_{us} represents unstressed volume. The flow (input) and pressure (output) relationship equations obtained for CVS model have been based on eq. (1)-(3) are-

$$\frac{dQ_{lv}}{dt} = \frac{1}{L_{lv}} (P_{lv} - P_{as}), \text{ when aortic valve is open} \quad (4)$$

$Q_{lv} = 0$, when aortic valve is closed

$$\frac{dV_{lv}}{dt} = Q_{la} - Q_{lv} \quad (5)$$

$$P_{lv} = E_{lv} (V_{lv} - V_{dlv})$$

$$\frac{dV_{lv}}{dt} = Q_{la} - Q_{lv} \quad (6)$$

where Q_{lv} is left ventricular flowrate

L_{lv} is inertial vessel properties of left ventricles

P_{lv} is left ventricular pressure

P_{as} is systemic aortic pressure

V_{lv} is left ventricular volume

E_{lv} is elastance of left ventricle

V_{dlv} is left ventricular volume at zero pressure

R_{sys} is systemic resistance

P_{a1} is pressure at systemic arterial section 1

cardiovascular system which helps in short term regulation of MAP by altering the circulatory parameters such as Systemic Resistance (R_{sys}), Maximum Elastance (E_{lmax}) and Unstressed Ventricular Volume (V_{us_ven})^(5,6). The change in circulatory parameters is provided based on the feedback action called as baroreflex action⁽⁷⁾. This feedback system based on circulatory parameters is modeled as-

$$BFC_{in} = \frac{\exp^{\alpha(MAP - MAP_{nom})}}{1 + \exp^{\alpha(MAP - MAP_{nom})}} \quad (7)$$

Where MAP_{nom} is the nominal value of MAP and α is the constant.

$$R_{sys} = R_{sys_{base}} - (B_{R_{sys}}) R_{sys_{base}} \quad (8)$$

$$E_{lmax} = E_{lmax_{base}} - (B_{E_{lmax}}) E_{lmax_{base}} \quad (9)$$

$$V_{us_ven} = V_{us_ven_{base}} - (B_{V_{us_ven}}) V_{us_ven_{base}} \quad (10)$$

Where $B_{R_{sys}}$, $B_{E_{lmax}}$ and $B_{V_{us_ven}}$ represents the output from baroreceptor model for that instant, while $R_{sys_{base}}$, $E_{lmax_{base}}$ and $V_{us_ven_{base}}$ are the nominal values of the circulatory parameters. The CVS-BR model output such as Aortic Pressure (P_{as}) and CO. Sensitivity analysis is performed to verify the tolerance of the baroreceptor to continuous regulation of MAP by modifying

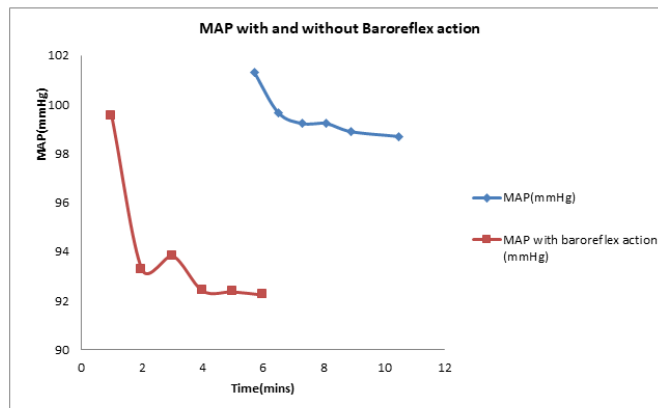


Fig 2. Analysis of baroreceptor mechanism

the circulatory parameters based on the MAP obtained from cardiovascular model. The circulatory parameters are modified continuously using the Equations (8) – (10). This analysis is carried out only with MAP because CO values increased with respective MAP value and MAP is the major parameter that has to be regulated during high and low pressure conditions. From this analysis, it is verified that baroreceptor is responsible for short term regulation of MAP and the dynamic action provided by baroreceptor. This has been presented in Figure 2 by comparing it to the MAP values obtained without baroreceptor model and with baroreflex mechanism.

Drug modeling equations for NAR and NG are derived based on the pharmacokinetics and pharmacodynamics of the drugs⁽⁸⁾. The infusion of drug along with the blood flow in the left heart Q_{lv} is represented as-

$$\frac{dV}{dt} = Q_{x-} - Q_{x+} \quad (11)$$

where x represents the compartment being considered, Q_{x-} is the input flow from previous compartment and Q_{x+} is the output flow from next compartment. The amount of drug entering into the compartments of CVS model is derived as-

$$\frac{dM}{dt}_{j,x} = (Conc_{dg}Q)_{j,x-} - (Conc_{dg}Q)_{j,x+} - \left(\frac{M}{\tau_{1/2}} \right)_{j,x} \quad (12)$$

Where $Conc_{dg} = M/V$, M is the mass of drug in compartment and V is the volume of the compartment and $\tau_{1/2}$ is the half-life of the drug in the compartment. This drug model is then combined with CVS-BR model⁽⁹⁻¹¹⁾. The open-loop response is obtained by varying the infusion rate based on the clinical analysis. The response depicted the effect of drugs on CVS-BR model. From the response, MAP and CO is observed and the transfer function model is developed as-

$$\begin{bmatrix} CO \\ MAP \end{bmatrix} = \begin{bmatrix} \frac{5.133}{15.22s+1}e^{-2s} & \frac{5.0112}{15.09s+1}e^{-0.95s} \\ \frac{3.009}{11.2s+1}e^{-0.2s} & \frac{-3.225}{10.33s+1}e^{-0.95s} \end{bmatrix} \begin{bmatrix} NAR \\ NG \end{bmatrix} \quad (13)$$

Since there are two manipulated variables and two control variables, it becomes a multi-input-multi-output (MIMO) system. To determine the maximum effect of drug on hemodynamic variables and to eliminate loop interactions, relative gain array (RGA) analysis was utilised and stability analysis performed using Neider-Linski index (NI) as shown in Table 1. From RGA analysis, it is evident that noradrenaline is having maximum effect on CO and nitroglycerine is having maximum effect on MAP.

2.2 Bacterial foraging optimization algorithm (BFOA)

In this work, the conventional PI controller is developed based on optimization algorithm⁽¹²⁾. BFOA is used to determine the optimal values of PI controller in regulating MAP and CO by controlling the infusion rate of NAR and NG^(13,14). This

Table 1. RGA analysis and NI index

RGA (Λ)	Loop Interaction	NI
0.5233	Cardiac Output (CO)/ Noradrenaline Mean Arterial Pressure (MAP)/ Nitroglycerine	1.911

algorithm is developed based on the foraging behaviour of *E.coli* bacterium. BFOA is an evolutionary algorithm which involves the following four life cycles of *E.coli* bacterium.

2.2.1 Chemotaxis

This process involves the movement of *E.coli* bacterium using flagella. The movement of bacterium is classified as swimming where the bacteria move in search of food and nutrients in one direction for a period of time and tumbling where the bacterium moves in random directions⁽¹⁵⁾. The bacterium alters between these two modes in its entire lifetime. Assuming that h^{th} bacterium is taking l^{th} chemotactic, m^{th} reproductive, v^{th} elimination and dispersal step which is represented as $\phi^h(l, m, v)$. If $x(h)$ is the size of the tumbling movement, then the chemotaxis is computed as

$$\phi^h(l, m, v) = \phi^h(l, m, v) + x(h) \frac{\delta(h)}{\sqrt{\delta^T(h) \delta(h)}} \quad (14)$$

where δ represents the vector of elements in random direction which lies between (-1 1).

2.2.2 Swarming

Here a group of bacteria convene together to form a swarm, and they travel in stable spatio-temporal patterns. They move in nutrient gradient with concentric patterns of swarms. They appear like a semisolid matrix when placed with single nutrient chemo-effector. The bacteria move in groups with high bacterial density in search of the richest food location.

2.2.3 Reproduction

This reproduction stage is reached at every chemotactic step. At this stage, the healthier bacterium gets divided into two bacteria whereas the low prioritized healthy bacterium ultimately dies i.e., the bacterium yielding lowest value of objective function and this stage maintains the population size of the bacteria at constant value.

2.2.4 Elimination and Dispersal

When some sudden changes occur in the environment where a group of bacteria live, it may kill them or disperse them into a new environment. Suppose if there is a rise in temperature in the location where bacteria live with high nutrient concentration, it may lead to death of bacteria. Sometimes they get relocated as it happens in human intestines. This process is simulated in the algorithm by randomly initializing the new replacements over the search space. The parameters involved in BFOA to determine the optimized value of PI controller is shown in Table 2.

Table 2. Parameters of Bacterial foraging optimization algorithm

Parameters	Values
Dimension of search space, d	2
Total number of bacteria in the population, T_b	10
number of chemotactic steps, N_{ch}	5
Swimming length, N_{sl}	4
Number of reproduction steps, N_{rep}	4
Number of elimination and dispersal events, N_{ed}	2
Probability of elimination and dispersal, P_{ed}	0.25
Number of steps involved in tumble movement, $x(h)$	0.05

PI controller is the most commonly used control algorithm among the conventional controllers. It works with the combination of proportional and integral mode^(16–18). The ideal form of PI controller is represented as

$$C_{out} = C_{out_{bias}} + K_c e(t) + \frac{K_c}{\tau_i} \int e(t) dt \quad (15)$$

Where, C_{out} is the controller output

$C_{out\ bias}$ is the controller bias

$e(t)$ is the process error where $e(t)=SV-PV$

SV is the reference set point and PV the measured process output

K_c is the controller gain (tuning parameter) and τ_i is the integral time (tuning parameter), where $K_C=K_P$ and $K_I=1/\tau_i$.

BFOA is employed to search for optimal controller parameters to minimize the time domain objective function. A performance index can be defined by the Integral of Time Absolute Error (ITAE) of the drug infusion and hemodynamic variables (MAP and CO). Accordingly, the objective function J is set to be-

$$J = \int_0^{\infty} t (|\Delta NAR| + |\Delta NG| + |\Delta MAP| + |\Delta CO|) dt \quad (16)$$

Based on this performance index J, optimization problem can be stated as: Minimize J subjected to-

$$J = \int_0^{\infty} t (|\Delta NAR| + |\Delta NG| + |\Delta MAP| + |\Delta CO|) dt \quad (17)$$

$$K_I^{min} \leq K_I \leq K_I^{max} \quad (18)$$

3 Results and Discussion

Based on BFOA, the PI values are optimized and best solution is obtained. The closed loop response obtained using BFOA is then compared with conventional PI controller tuned using relay tuning method as shown in Figure 3 A - B and the output responses of MAP and CO are shown in Figure 3 C - D.

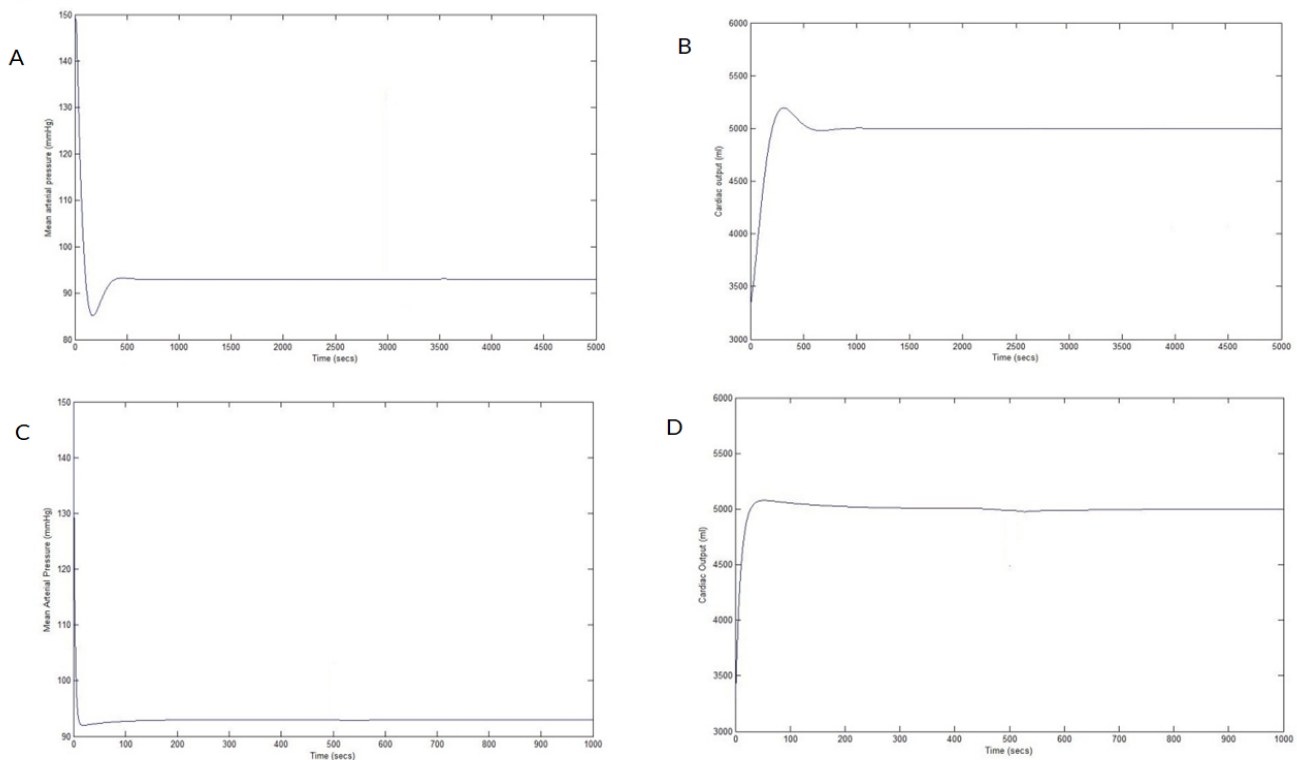


Fig 3. A) Mean arterial pressure response using relay tuning technique, B) Cardiac output response using relay tuning technique, C) Mean arterial pressure response using BFOA, D) Cardiac output response using BFOA

The corresponding controlled infusion rate of NAR and NG are depicted in Figure 4 A - B. When a disturbance is introduced at the time of 500 seconds, the PI controller performed rapidly and regulated MAP and CO at 510 seconds. The controlled infusion rate of NAR and NG are shown in Figure 4 C - D. The regression analysis is also presented in Figure 5 A - B.

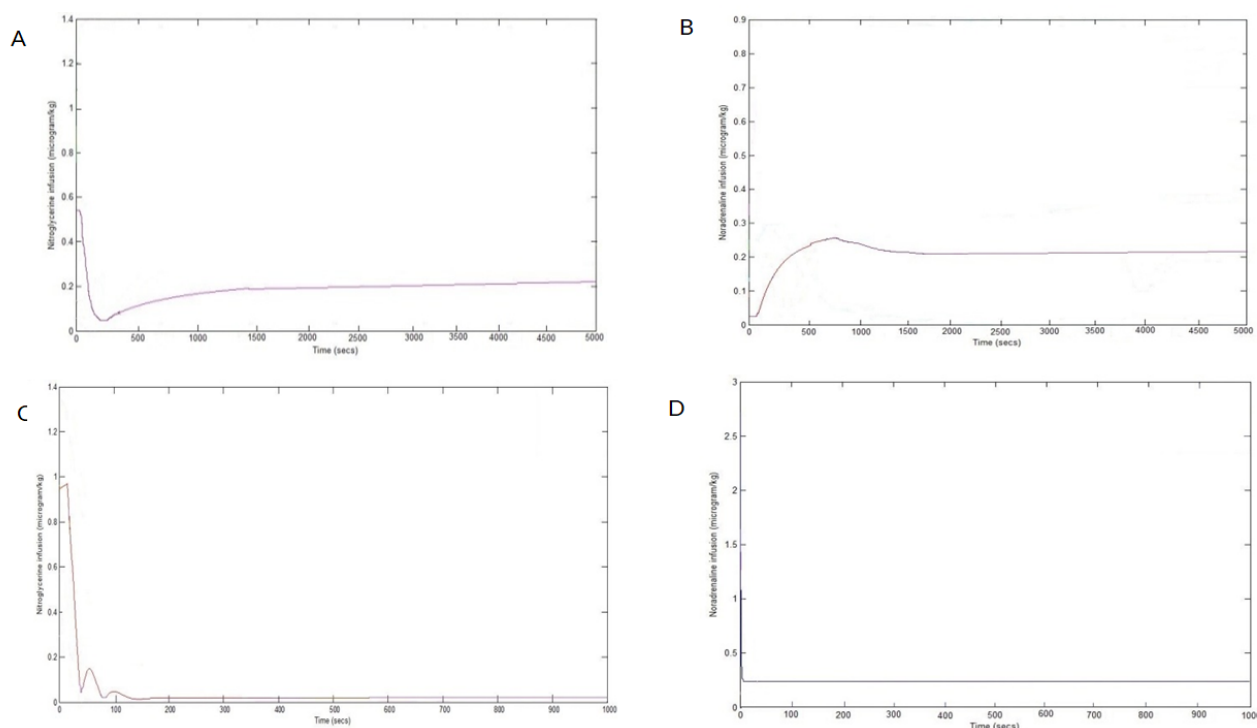


Fig 4. A) Controlled infusion rate of nitroglycerine using relay tuning technique, B) Controlled infusion rate of noradrenaline using relay tuning technique, C) Controlled infusion rate of nitroglycerine using BFOA, D) Controlled infusion rate of noradrenaline using BFOA

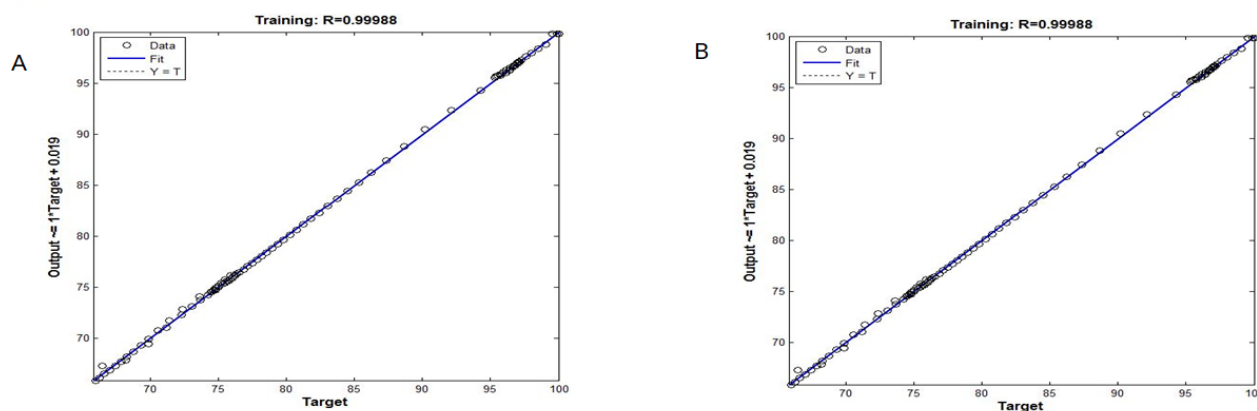


Fig 5. A) Regression analysis of Mean Arterial Pressure, B) Regression analysis of Cardiac Output

The performance of the controller is evaluated using time domain specifications and their respective values, discussed in Table 3.

Table 3. Time domain specifications

Con-trollers	Hemodynamic Parameters	Rise Time (secs)	Peak Time (secs)	Settling Time (secs)	Steady state error (E_{ss})
PI-ZN	Mean Arterial Pressure (MAP) (mmHg)	66.9761	231.4122	330.8738	0.0754
	Cardiac Output (CO) (ml)	152.1225	314.4125	505.5532	3.5953
PI-BFOA	Mean Arterial Pressure (MAP) (mmHg)	4.3561	7.2387	17.4577	1.5342e ⁻⁶
	Cardiac Output (CO) (ml)	4.8997	8.4	18.5881	0.0148

4 Conclusion

A combined four compartmental model of cardiovascular system with baroreceptor model and drug model is presented. In this work, the optimization technique is used to determine the optimal values of PI controllers in regulating Mean Arterial Pressure (MAP) and Cardiac Output (CO) by controlling the infusion rate of Noradrenaline (NAR) and Nitroglycerine (NG). This simulation study helped in analyzing automatic regulation of hemodynamic parameters which can provide better control allowing anaesthetists to focus on more critical issues which will result in reduction in amount of drugs infused and their side effects. This will lead to less time spent by patients during post surgical treatment and above all provides a safer platform during surgical procedure. This work also helps in analyzing the effects of drugs on physiological variables instead of conducting clinical trials on animals as the initial step. This work can be further extended by developing a switching based controller for the infusion of two drugs simultaneously. In order to carry out this work, interaction between the two drugs must be analyzed and clinical trials can be carried out which helps in fine-tuning of the controller.

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