

The Impact of Fractional-Order Control on Blood Pressure Regulation

Shaival H. Nagarsheth, Sardar Vallabhbhai National Institute of Technology, India

 <https://orcid.org/0000-0001-9867-8167>

Shambhu N. Sharma, Sardar Vallabhbhai National Institute of Technology, India

ABSTRACT

This paper presents a fractional-order framework for control of blood pressure regulation system. A new perspective is explored to control the blood pressure in lieu of the conventional control framework. A multi-variable scenario is adopted to control two outputs: mean arterial blood pressure (MABP) and cardiac output (CO) simultaneously. Three fractional-order controllers are designed and tuned optimally for the multi-input multi-output (MIMO) blood pressure regulation system. To test the effectiveness of the designed fractional controllers, control investigations are carried out based on controller performance indices and sensitivity performance indices. Stability analysis and sensitivity analysis are carried out in order to assure stable as well as robust feedback design. Sensitivity analysis of the paper reveals the controller's ability to handle model uncertainties of the blood pressure regulation system. Numerical simulation results of the paper unfold the best suitable fractional-order controller for the enhanced closed-loop performance of the blood pressure regulation system.

KEYWORDS

Blood Pressure Regulation, Fractional-Order Controller, Multi-Variable System, Particle Swarm Optimization (PSO)

1. INTRODUCTION

A major issue in post-operative control is the patient's hypertension. It is important to maintain the patient's physiological parameters prior to and post-medical treatments (Araki & Furutani, 2005). The most significant physiological parameter is blood pressure, which can be controlled via drug infusion. This is not a trivial task as one has to titrate the drug accurately with proper knowledge of the dynamics of the process. The lack of accuracy and timely infusion of the drug may lead to fluctuations in the blood pressure level. This causes pernicious oscillations in the blood pressure level leading to either hypertension or shock (Bailey & Haddad, 2005). The most widely used drug for the control of Mean Arterial Blood Pressure (MABP) is anti-hypertensive Sodium Nitroprusside (SNP) and for Cardiac Output (CO) is Dopamine (DPM) (Behbehani & Cross, 1991). Dopamine (DPM) is the potent vasopressor agent used for critically ill patients in Intensive Care Unit (ICU), Intensive Cardiac Care Unit (ICCU), Surgical Intensive Care Unit (SICU), Medical Intensive Care Unit (MICU) etc. The onset of action starts within five minutes of Intravenous (IV) administration of DPM. In present scenario dosage of DPM is as per lean body weight (Holmes et al., 2005; Geremia et al., 2012). Immediate infusion rates, i.e. 2 to $5 \mu\text{g kg}^{-1}\text{min}^{-1}$ and 5 to $15 \mu\text{g kg}^{-1}\text{min}^{-1}$ cause

DOI: 10.4018/IJEHMC.20210501.oa3

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direct stimulation and increase in Mean Arterial Blood Pressure (MABP) and Cardiac Output (CO). Certain researchers (Cheng et al., 2019; Tufano et al., 2010) have studied the comparative efficacy of vasoactive medication suggesting the use of other inotropic agents such as Nor-epinephrine and Dobutamine. Though there are other inotropic agents available for CO control in acute heart failure syndrome, DPM still remains an essential drug in the patients of septic shock and it is used as the first-line vasopressor in hypertensive emergencies. Epidemiological studies focusing on temporal trends in ICU (Thongprayoon et al., 2016) also revealed that DPM was used in 14% cases in SICU and 50% cases in ICCU over a span of seven years.

Sodium Nitroprusside, a potent vasodilator, is used extensively in the treatment of hypertensive emergencies due to its favourable pharmacokinetic parameters and immediate onset of action (duration 1 to 2 minutes). Recent literature (Benken, 2018) has stated that the dosage of IV infusion, i.e. 0.25 to 10 $\mu\text{g kg}^{-1}\text{min}^{-1}$ titration by 0.1 to 0.2 $\mu\text{g kg}^{-1}\text{min}^{-1}$ results in a significant decrease in MABP. A study (Mullens et al., 2008) has also concluded that SNP vasodilatation has favourable long term clinical outcomes and it remains an excellent therapeutic choice.

In current Indian scenario of government and private setups, Med captain's infusion syringe pumps are most commonly used in ICU and ICCU for injectable vasopressors and vasodilators and the fluctuations in physiological parameters are mostly monitored on Philips IntelliVue MP5. Looking at the importance of DPM and SNP in control of MABP and CO in cardiac patients, the lack of automatic control for the simultaneous regulation of MABP and CO may lead to increase in the time spent by ICU nurses in attending the cardiac patient for monitoring blood pressure. According to a survey (Bequette, 2013), 73% of the myocardial revascularization patients suffer from post-operative hypertension and require control of blood pressure. The same survey revealed that the Intensive Care Unit (ICU) nurses spend 26% of their time in attending the hypertensive patient post-operation for monitoring blood pressure. Thus, open-loop manual control may lead to a tedious job for the ICU personnel. On the other hand, the development of an automatic closed-loop control unit can provide timely and desirable performance with accuracy. Moreover, the automated closed-loop system controls primary variables and also monitors secondary variables for diagnostics. That allows the physician to spend more time monitoring the patient for conditions that are not easily measured and keeps the physician always 'in the loop' (Rao et al., 1999). Thus, closed-loop automatic control may lead to a reduced attendance time for the nursing staff as well as the physicians and surgeons.

The development and investigation of novel control strategies have become a paramount issue amongst the researchers. Different control strategies are available for the control of blood pressure under a variety of conditions (Isaka & Sebal, 1993), i.e. post-operative blood pressure control (Gao & Er, 2005), during anaesthesia (Frei et al., 2000; Meier et al., 1992), during surgical operation (Furutani et al., 1995) etc. Coleman et al. (1974) presented control of Cardiac Output (CO) via a mathematical model comprising of two dissimilar blood flow channels. In Hahn et al. (2002) an adaptive control strategy is proposed for the drug infusion. Computer simulations for the closed-loop control of blood pressure utilizing multiple drug inputs are presented by McInnis & Deng (1985). Shahin & Maka (2007, 2011a, 2011b) gives a very good insight on the linear state-space model, physiological model and control technique for blood pressure regulation system. A non-square model-based drug infusion strategy for the MIMO control problem of MABP and CO is attempted by Rao et al. (1999). The multi-input multi-output model representing the input-output relationship between the drug to be injected and the blood pressure comprises of time delays, parameter uncertainties and unknown disturbances (Slate et al., 1979). Thus, the regulation of blood pressure with CO simultaneously becomes a challenging problem from the control engineering perspective (Malagutti et al., 2013). A Single-Input Single-Output (SISO) model predictive controller based on a discrete model obtained via experimentation may not be reliable since they cause pernicious oscillations in the MABP (Bequette, 2007). For example, the IVAC titrator to regulate the MABP was discontinued due to several reasons (Doyle et al., 2011). Hence, desirable performance cannot be achieved with a single controller. Saxena & Hote (2012) also presented a conventional Single-Input Single-Output

framework for the control of MABP utilizing IMC tuned integer-order PI/PID controller. In recent years, fractional-order controllers have gained popularity due to the fact that they add the degree of freedom, which leads to a superior control performance keeping the implementation feasible (Monje et al., 2010). Despite the universality of the fractional controller and the vital role of the blood pressure regulation, the fractional-order control of the mean arterial pressure and cardiac output is sparingly researched (Urooj & Singh, 2019). Hence, it is worthwhile to explore and investigate the impact of fractional control on the MIMO control problem of blood pressure regulation.

The chief intent of this paper is to design three fractional-order controllers for the blood pressure regulation system. The blood pressure problem under consideration is a MIMO control problem. Hence, the three separate fractional-order controllers for two outputs (MABP and CO) each are designed. The two manipulated variables, i.e. drugs to be infused to control, are Sodium Nitroprusside and Dopamine. The controllers' parameters are tuned optimally with the help of Particle Swarm Optimization (PSO) algorithm. The designed controllers are then investigated from the control perspective to study the relationship and behaviour of the closed-loop system associated with the blood pressure system model under the disturbance and set-point tracking (Monje et al., 2010). The fractionality in the controller introduces mathematical subtleties and hence a graphical representation is adopted to test the stability of the designed closed-loop. Moreover, patients are sensitive to intravenous infusion of drugs, so significant sensitivity analysis is demonstrated as well for the designed closed-loop. Sensitivity analysis reveals the ability of the controller to handle the parameter uncertainty and input disturbances as well. The numerical simulation results of the paper illustrate the superiority of the fractional-order control, in contrast to the conventional controller, based on the controller and the sensitivity performance indices.

2. METHODS

This section covers fractional-order PID controller, fractional-filter-PI controller and Particle Swarm Optimization (PSO) methods. The fractional-filter-PI controller is bifurcated in two cases: (i) Internal model tuned Fractional-Filter-PI (FF-PI-IMC) (ii) PSO tuned Fractional-Filter-PI (FF-PI-PSO). Based on these methods, three optimally tuned fractional-order controllers are designed for the blood pressure regulation system.

2.1 Fractional-Order PID Controller

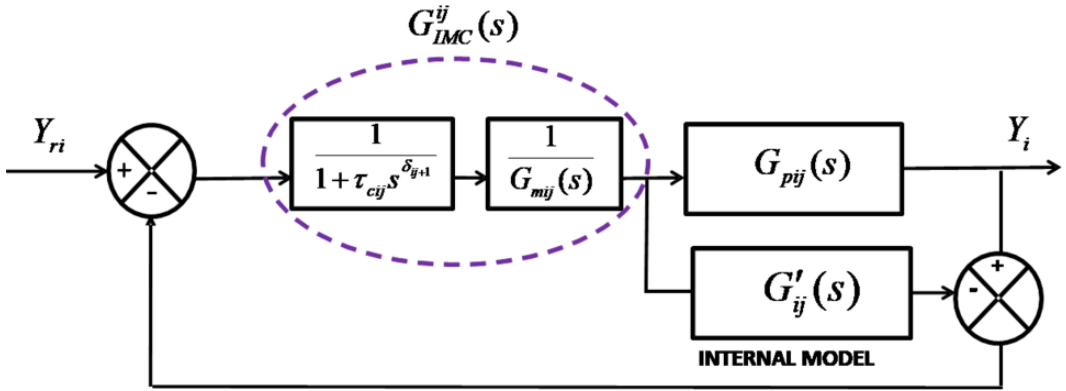
The ubiquitous fractional-order PID controller can be structured by an integro-differential equation (Monje et al., 2010), i.e.:

$$C_{ij}(t) = k_p^{ij} e_{ij}(t) + k_I^{ij} \mathfrak{D}^{-\lambda_{ij}} e_{ij}(t) + k_D^{ij} \mathfrak{D}^{\mu_{ij}} e_{ij}(t) \quad (1)$$

where the term $\mathfrak{D}^{-\lambda_{ij}}$ denotes the fractional-order anti-derivative or fractional-order integral of order $\lambda_{ij} \in \mathbb{R}^+$. The term $\mathfrak{D}^{\mu_{ij}}$ denotes the fractional-order derivative. The terms k_p^{ij} , k_I^{ij} and k_D^{ij} have the interpretations as proportional, integral and derivative gain respectively associated with the fractional-order PID controller of the i th output with respect to j th input. The error signal is represented by $e_{ij}(t)$. Applying the Laplace transform to equation (1) with zero initial conditions, we get:

$$C_{ij}(s) = k_p^{ij} + k_I^{ij} \frac{1}{s^{\lambda_{ij}}} + k_D^{ij} s^{\mu_{ij}} \quad (2)$$

Figure 1. Schematic of a generalized internal model control



Equation (2) is the fractional-order PID controller transfer function. On the other hand, the conventional integer-order PID controller is given by:

$$C_{ij}(s) = k_p^{ij} + k_I^{ij} \frac{1}{s} + k_D^{ij} s \quad (3)$$

The difference between the integer-order PID and the fractional-order PID is that the derivative and the integral action add fractionality in the controller transfer function resulting in the added degree of freedom. Conventional PID has three parameters to tune and the fractional-order PID has five parameters to tune. Hence, providing more flexibility, which results in superior closed-loop performance (Podlubny, 1999).

2.2 Fractional-Filter-IMC-PI

Internal Model Control (IMC) was proposed to provide a formal model-based method for tribulation free controller tuning (Skogestad, 2003). In this section, a fractional-filter IMC tuned PI Controller is presented. Consider a closed-loop system, whose plant transfer function is denoted by $G_{pij}(s)$. The plant transfer function represents an input-output relationship, for example, the relation of SNP to MABP. Considering that the plant is controlled via an IMC-based controller $G_{IMC}^{ij}(s)$, then the closed-loop associated with such a system can be depicted as in Figure 1.

The internal model of the plant $G_{pij}(s)$ is represented by $G'_{ij}(s)$. The internal model is the approximated version of the actual real-life relationship of the input-output. The generalized IMC transfer function consists of two parts: (i) a fractional-filter $f_{cij}(s) = 1/(1 + \tau_{cij}s^{\delta_{ij}+1})$ (ii) an inverse of the minimum-phase part $G_{mij}^{-1}(s)$ of the internal model $G'_{ij}(s)$. The term τ_{cij} and δ_{ij} has the interpretation as the fractional filter parameter and the filter fractionality. From the block diagram, the structure of the IMC-based fractional controller can be stated as:

$$C_{ij}(s) = \frac{G_{IMC}^{ij}(s)}{(1 - G_{IMC}^{ij}(s)G'_{ij}(s))} \quad (4)$$

Furthermore, the above controller (4) in terms of the fractional filter can be written as:

$$C_{ij}(s) = \frac{f_{cij}(s)(G_{mij}(s))^{-1}}{(1 - f_{cij}(s)(G_{mij}(s))^{-1}G'_{ij}(s))} \quad (5)$$

The controller in (5) is a generalized fractional-order IMC tuned controller. The blood pressure regulation system's transfer function associated with the i th output and j th input is denoted by (Bequette, 2007):

$$G_{pij}(s) = \frac{k_{ij} e^{-\theta_{ij}s}}{(1 + \tau_{ij}s)} \quad (6)$$

Combining (5) and (6), the IMC-based fractional controller is obtained as:

$$C_{ij}(s) = \frac{(\tau_{ij}s + 1)/k_{ij}(\tau_{cij}s^{\delta_{ij}+1} + 1)}{1 - (1/(\tau_{cij}s^{\delta_{ij}+1} + 1))} = \frac{\tau_{ij}s + 1}{k_{ij}(\tau_{cij}s^{\delta_{ij}+1})} \quad (7)$$

Furthermore, (7) can be rephrased as a combination of fractional-filter cascaded with the integer-order PI controller, i.e.:

$$C_{ij}(s) = \frac{1}{\tau_{cij}s^{\delta_{ij}}} \left(\frac{\tau_{ij}}{k_{ij}} + \frac{1}{k_{ij}s} \right) \quad (8)$$

The above (8) describes a general structure of the proposed fractional-filter PI controller associated with the i th output and j th input. A note on how to achieve the tuning of the above-mentioned controllers in (3) and (8) is given in *Remark 1*.

2.3 Particle Swarm Optimization (PSO)

Several optimization algorithms are available to tune the parameters of a controller optimally. Kennedy & Eberhart (1995) proposed a population-based optimization algorithm called the Particle Swarm Optimization (PSO). The algorithm was inspired by the behaviour of bird flocking. In recent years, PSO has become a better-developed optimization algorithm (Ding et al., 2019). The optimization algorithm is employed to minimise the value of a certain cost function. The algorithm starts with N number of particles (solutions) moving for optima in the search space of dimension D . The p th particle moves with definite velocity ν_p and position x_p . The particles moves in the space randomly searching for the best possible position to converge and minimise the cost function. This procedure is carried out until the best position is achieved until the maximum number of iteration is reached. The velocity and position of the p th particle at k th iteration is given by:

$$\nu_p(k+1) = w\nu_p(k) + c_1r_1(\rho_p - x_p(k)) + c_2r_2(\rho_{gp} - x_p(k)) \quad (9)$$

$$x_p(k+1) = x_p(k) + \nu_p(k+1) \quad (10)$$

where the terms c_1 and c_2 denotes the personal learning coefficient and global learning coefficient respectively. w is the inertia weight, ρ_p is the best individual particle position, and ρ_{gp} is the global best position for all particles. Terms r_1 and r_2 are two random values in the range of $(0, 1)$ respectively.

Remark 1: It is desired to achieve the optimal tuning for parameters of the fractional-order controller in (3) and (8). For the fractional-PID controller of (3), the values of five parameters $(k_p^{ij}, k_I^{ij}, k_D^{ij}, \lambda_{ij}, \mu_{ij})$ are obtained from the PSO algorithm. For the fractional-filter PI controller (8), there arise two cases: (i) IMC tuned Fractional-filter PI controller (FF-PI-IMC). Here, the PI controller parameters are represented directly in terms of the system parameters. The rest of the two parameters, i.e., filter parameter τ_{cij} and the filter fractionality δ_{ij} are tuned via PSO algorithm. (ii) Fractional-filter PI controller (FF-PI-PSO), whose all the four parameters are tuned via PSO algorithm. The cost function to be minimized is the Integral Squared Error (ISE), i.e. $ISE = \int_0^t e_{ij}(\tau) d\tau$. Thus, there are three different fractional-order controllers to be effectuated on the MIMO blood pressure regulation system in order to investigate the behaviour of the system.

3. DESIGN OF FRACTIONAL-ORDER CONTROLLERS FOR BLOOD PRESSURE REGULATION SYSTEM

A two-input two-output system is represented by:

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \frac{k_{11} \exp(\theta_{11}s)}{\tau_{11}s + 1} & \frac{k_{12} \exp(\theta_{12}s)}{\tau_{12}s + 1} \\ \frac{k_{21} \exp(\theta_{21}s)}{\tau_{21}s + 1} & \frac{k_{22} \exp(\theta_{22}s)}{\tau_{22}s + 1} \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \end{pmatrix} \quad (11)$$

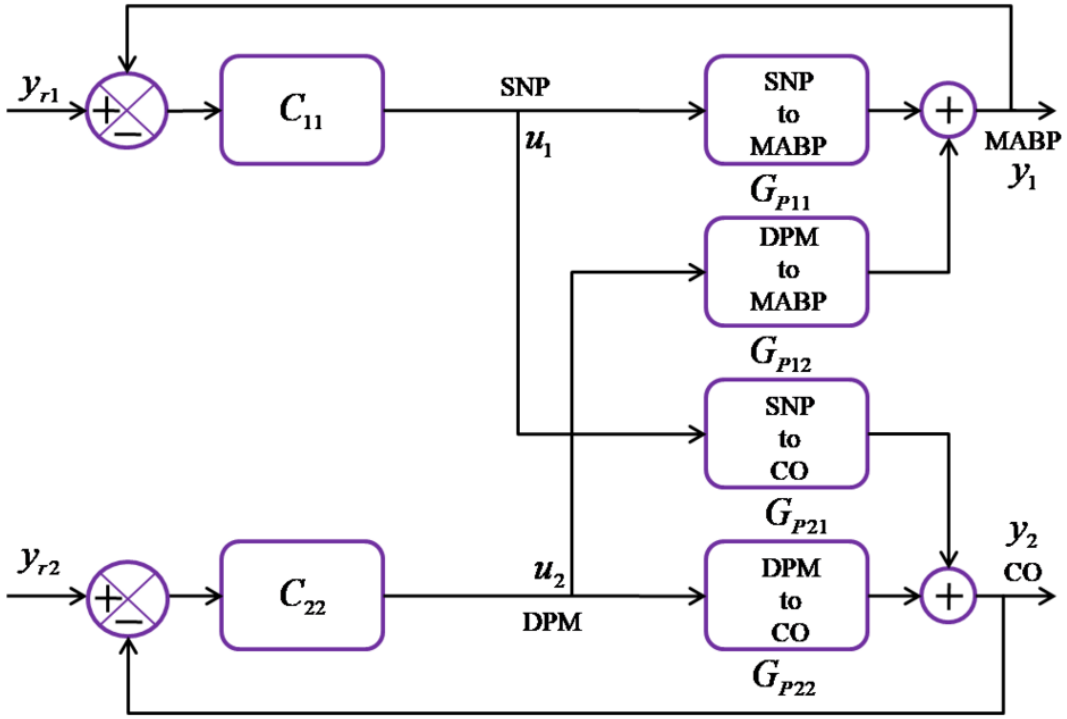
where y_1, y_2, u_1 and u_2 are outputs and inputs respectively. The terms $k_{ij}, \theta_{ij}, \tau_{ij}$ denote the process gain, dead time and time constant associated with the i th input and j th output respectively. The relationship matrix is called the transfer function matrix and its components are called a system transfer function, i.e.:

$$G_{pij} = \frac{k_{ij} \exp(\theta_{ij}s)}{\tau_{ij}s + 1}, i = 1, 2 \text{ and } j = 1, 2$$

For the specific case of blood pressure regulation, the general structure of the MIMO representation (11) can be recast as (Bequette, 2007):

$$\begin{pmatrix} MABP \\ CO \end{pmatrix} = \begin{pmatrix} \frac{-6 \exp(-0.75s)}{0.67s + 1} & \frac{3 \exp(-s)}{2s + 1} \\ \frac{12 \exp(-0.75s)}{0.67s + 1} & \frac{5 \exp(-1s)}{5s + 1} \end{pmatrix} \begin{pmatrix} SNP \\ DPM \end{pmatrix} \quad (12)$$

Figure 2. Schematic of MIMO blood pressure regulation problem



The above (12) represents the relationship between the two drugs, i.e. Sodium Nitroprusside (SNP), Dopamine (DPM), with the two outputs to be controlled, i.e. Mean Arterial Pressure (MABP), Cardiac Output. Note that the first component of the transfer function matrix G_{p11} denotes the relation of SNP to MABP. Similarly, the second component G_{p12} represents the relation of DPM to MABP, the third component G_{p21} represents the relation of SNP to CO and the fourth component G_{p22} represents the relation of DPM to CO. Consider the pairing, SNP-MABP and DPM-CO as it is used in practice (Seborg et al., 2004). Here, the controllers for controlling the MABP through SNP and controlling the CO through DPM are designed. The interactions are introduced via the relation of SNP to CO and DPM to MABP. The control structure for the two-input two-output multivariable blood pressure regulation system is depicted in Figure 2.

It is clear from Figure 2 that the controllers C_{11} and C_{22} controls MABP and CO respectively. However, they are also responsible for the control of interactions from the other loop.

Once the input-output pairing is decided, the designed controllers are now tuned by utilizing the PSO algorithm as mentioned in Section 2.3. Thus, utilizing (9)-(10) with the following conditions in the algorithm, the PSO tuned fractional-order controllers are obtained:

- For FOPID - $(k_p^{ij}, k_I^{ij}, k_D^{ij}, \lambda_{ij}, \mu_{ij})$, FF-PI-PSO- $(k_p^{ij}, k_I^{ij}, \lambda_{ij}, \mu_{ij})$ and FF-PI-IMC- (λ_{ij}, μ_{ij}) are tuned.
- Thirty particle swarms are taken for the evolutions.
- Total numbers of iterations are set to 50.
- The value of personal learning and global learning coefficients are taken as 2 and 1.5 respectively.
- The inertia weight is kept 1.

The PSO algorithm is implemented using MATLAB© on Intel(R) Core(TM) i7-7700 3.60 GHz machine with 8.00 GB RAM. The algorithm runs until the objective function is met, i.e. minimization of the Integral Squared Error or up to 50 iterations. The resultant controllers are given in Table 1.

4. RESULTS

Control investigations are carried out utilizing the designed fractional-order controllers of the paper (Table 1). First, stability assessment of three closed-loops resulting from the three designed controllers is demonstrated. Then, the results generated from the reference tracking response are presented to compare the fractional-order controllers of the paper with the conventional integer-PI controller (Seborg et al., 2004). Finally, to test the effectiveness of the controller under disturbances and uncertainties, sensitivity assessment results are portrayed.

4.1 Stability Assessment

The fractionality of the controller contributes to the fractional quasi-characteristic polynomial in lieu of the traditional characteristic polynomial. Thus, stability assessment is not straight forward. The roots of the associated fractional quasi-characteristic polynomial are intractable. The notion of mapping the roots to the Riemann surface is adopted (Monje et al., 2010). The fractional quasi-characteristic polynomial associated with the closed-loop resulting from the FF-PI-IMC is expressed as:

$$\zeta_{ij}(s, \theta) = \tau_{cij} s^{\delta_{ij}} + \exp(\theta_{ij} s) \quad (13)$$

Consider $s^{\delta_{ij}} = w$, $\delta_{ij} = r_{ij}/v_{ij}$, $1/\delta_{ij} = v_{ij}$, $\delta_{ij} > 0$, r_{ij} and v_{ij} are integers. Then the natural quasi-characteristics degree polynomial associated with (13) can be described as:

$$\zeta_{ij}(w) = \tau_{cij} w^{r_{ij}} + \exp(\theta_{ij} w^{v_{ij}}) \quad (14)$$

The roots of (14) must obey the condition $|\angle w| > (\beta\pi/2)$ for the designed closed-loop system to be constant. Here, $|w| > (\beta\pi/2)$, where w indicates roots of natural quasi-characteristics degree polynomial, β indicates the greatest common divisor. The above condition tells that the angle of all roots must lie outside the principal sheet generated by $\beta\pi/2$ on the Riemann surface. To test the above condition, the characteristic polynomials of all controllers mentioned in Table 1 are examined via FOMCON toolbox of MATLAB©. The graphical illustration of the location of the roots, on the Riemann surface, associated with fractional-order controllers of the paper is shown in Figure 3.

Table 1. Fractional controllers for both the loops of blood pressure regulation system

Fractional Controllers	Loop 1	Loop 2
FOPID-PSO	$-0.25 - 0.09s^{-0.98} - 0.0274s^{0.91}$	$0.19 + 0.88s^{-0.88} - 0.08s^{0.82}$
FF-PI-PSO	$1.9s^{-0.19}(-0.18084 - 0.0531s^{-1})$	$3.427s^{-0.00274}(0.6320 - 0.07s^{-1})$
FF-PI-IMC	$10.8s^{-0.01}(-0.11166 - 0.16667s^{-1})$	$4.2s^{-0.06653}(1 + 0.2s^{-1})$

Figure 3. Stability assessment of all the three fractional controllers

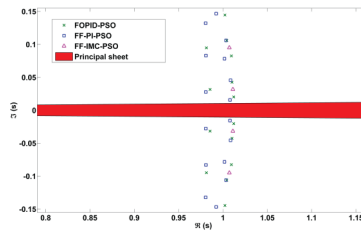


Figure 3 depicts the stability assessment for all three controllers, i.e., FOPID-PSO, FF-PI-PSO and FF-PI-IMC. It can be inferred from Figure 3 that all the roots are lying outside the principle sheet indicated by the red area. Thus, the designed fractional controllers of the paper preserve the stability of the blood pressure system.

4.2 Reference Tracking

To observe the impact of fractional-order controllers of the paper on the blood pressure regulation problem, closed-loop investigations are carried out. Numerical simulations are demonstrated for the step-change in desired (reference) values of the two outputs: MABP and CO. Responses generated from the effectuation of the three fractional-order controllers of the paper are compared for quantitative analysis. Simulation results are compared with the conventional IMC tuned integer-PI controller (Seborg et al., 2004).

Figure 4 shows the closed-loop reference tracking response. Figure 4(a) and Figure 4(b) are associated with the closed-loop response when the desired value of the MABP is changed by 1 mmHg. Similarly, Figure 4(c) and Figure 4(d) are associated with the closed-loop response when the desired value of the CO is changed by 1 L/(kg·min). It is observed from Figure 4(a) that all the proposed fractional controllers give a better response in contrast to the conventional integer-PI controller. The fractional-PID controller has greater overshoot in comparison to the other two fractional controllers (Table 2). The controller performance indices are depicted in Table 2 for the step-change in the desired value of MABP. While tracking the desired value of MABP due to the infusion of the drug SNP the Cardiac Output changes as well.

The duty of the controller of loop 2 is to reject that interaction and maintain the Cardiac Output at its desired value. This is displayed in Figure 4(b). The integer-PI controller takes the maximum time to re-state the Cardiac Output. The FOPID-PSO takes the least time to settle. On the other hand, FOPID-PSO has the highest undershoot in the Cardiac Output in contrast to the other controllers. The most important performance index in the drug delivery system could be the controller's efforts to achieve the desired output. The more the efforts a controller needs, the more the input (drug infusion) is required to achieve the desired output. To measure this, Integral Squared Control Input (ISCI) is employed. Based on the ISCI values depicted in Table 2, the FF-PI-IMC gives most promising results of the step change in the desired value of MABP accompanied with a smoother response for the interaction in the Cardiac Output as well.

Figure 4(d) displays the Cardiac Output reference tracking response resulting from all the four controllers. Figure 4(c) shows how the controllers try to maintain the Mean Arterial Blood Pressure by rejecting the interactions while the Cardiac Output is being tracked to its desired value. Note that, Dopamine is the drug being manipulated in order to control the Cardiac Output. Observing Figure 4(c), it is noticed that the FF-PI-IMC controller has the highest overshoot in MABP, which requires more time to settle. In contrast, FF-PI-PSO provides very less ISE, ISCI values for both the loops, see Table 3 for numerical values obtained graphically from Figs. 4(c) and 4(d).

Figure 4. A closed-loop response comparison of four controllers for a unit step change

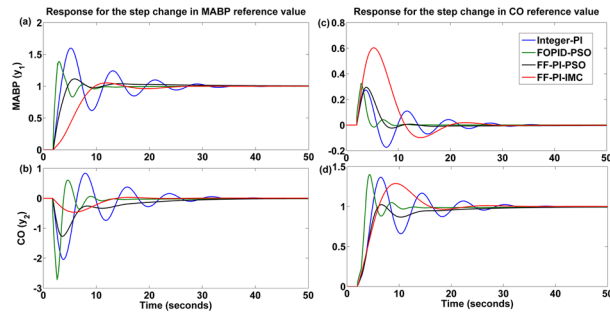


Table 2. Controller performance indices for the step-change in the desired value of MABP

Controller	Loop 1				Loop 2			
	ISE	ISCI	OS	ST	ISE	ISCI	OS	ST
Integer-PI	2.521	0.3607	1.59	26.98	11.97	1.942	0.836	20.89
FOPID-PSO	1.121	0.4291	1.38	10.98	7.186	2.056	0.607	7.61
FF-PI-PSO	1.585	0.3326	1.115	10.18	5.084	1.599	-	15.62
FF-PI-IMC	3.5	0.2521	1.05	23.43	1.099	1.58	0.02	10.18

ISE: Integral Squared Error, ISCI: Integral Squared Control Input, OS: Overshoot, ST: Settling time.

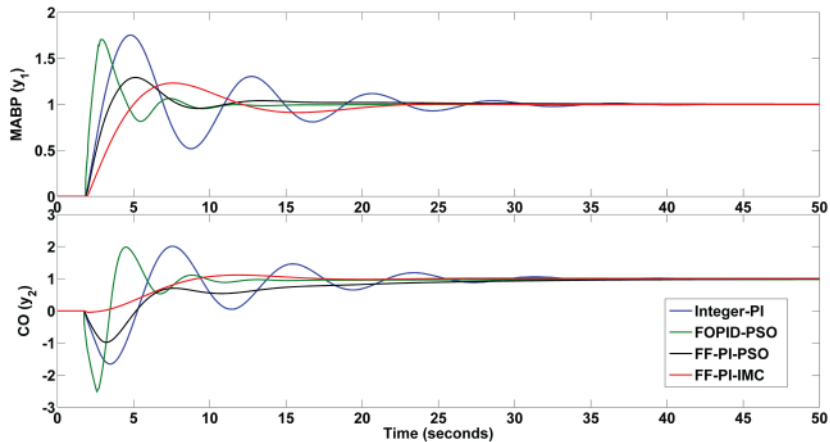
Now, a simultaneous change in the desired values of both the outputs: MABP and CO is given. The closed-loop response of both the controllers to achieve the desired value simultaneously is investigated. Figure 5 demonstrates the same. It is clearly visible that FF-PI-PSO and FF-PI-IMC give a better response in contrast to FOPID-PSO and integer-PI controllers. The scenario of simultaneous change in the desired value and tracking the desired output simultaneously is the most common practical scenario and need. Though FOPID-PSO controller offers the least settling time, it also suffers from exhibiting larger overshoot and undershoot (green lines in Figure 5). For the CO reference tracking, all the controllers experience an undershoot in the response except the FF-PI-IMC controller. Moreover, FF-PI-IMC controller also offers the least overshoot in contrast to all the other controllers but suffers from a larger settling time, see Figure 5. On the other hand, the FF-PI-PSO controller exhibits lesser overshoot and undershoot in comparison to integer-PI and FOPID-PSO and lesser settling time in comparison to the FF-PI-IMC.

Figures 6(a) and 6(b) show the comparison of the closed-loop responses for change in the set-point of MABP by +15 mmHg and -20 mmHg, respectively. Precisely, Figure 6(a) depicts the

Table 3. Controller performance indices for the step-change in the desired value of CO

Controller	Loop 1				Loop 2			
	ISE	ISCI	OS	ST	ISE	ISCI	OS	ST
Integer-PI	0.2375	0.1064	0.328	24.64	2.912	0.4933	1.367	20.4
FOPID-PSO	0.11	0.1057	0.271	8.101	2.897	0.7613	1.402	7.59
FF-PI-PSO	0.2058	0.0938	0.294	9.34	2.488	0.4597	1.023	18.12
FF-PI-IMC	1.543	0.0941	0.603	18.81	2.724	0.7052	1.289	21

Figure 5. Closed-loop response to a simultaneous pair of step changes in MABP and CO



comparison of the proposed fractional-order controller (FF-PI-PSO) with the existing experimental results from Luspay & Grigoriadis (2015). Similarly, Figure 6(b) compares the same with the existing experimental results of Mallagutti et al. (2013). The evaluation of the controllers' performance is adjudged via controller performance indices (Table 4). From Figures 6(a) and 6(b) it is clear that the proposed fractional controller does not possess an overshoot with less settling time and less ISE measure. The values of ISE, OS and ST in Table 4 reveal the better performance of the proposed controller in contrast to other controllers.

4.3 Sensitivity Assessment

Uncertainty is the bitter fact of the blood pressure regulation system. A single model cannot define the dynamics of all patients. Thus, there is a variation in the dynamics of the blood pressure system from

Figure 6. Comparison of closed-loop results for the regulation of MABP

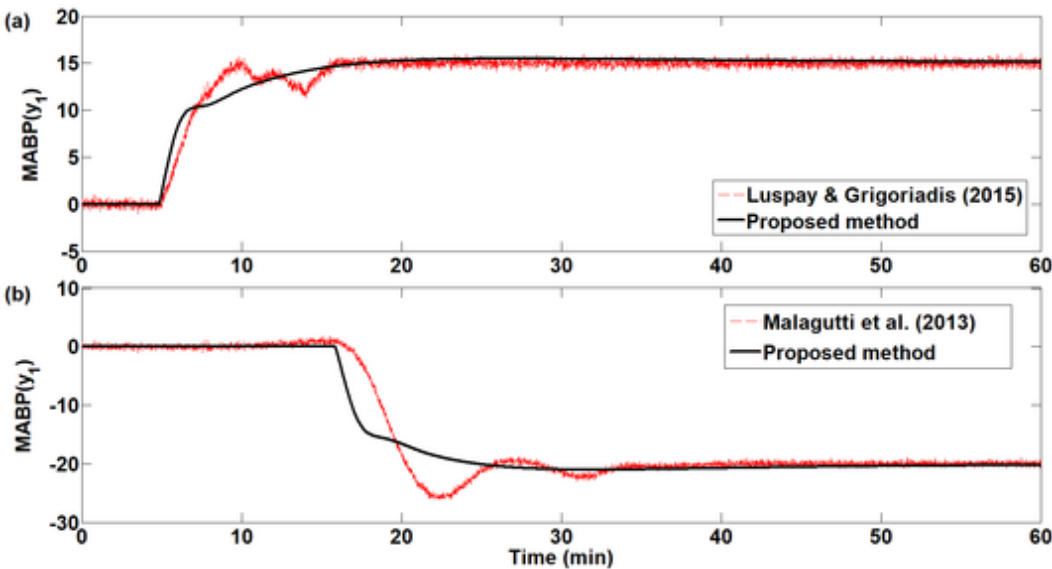


Table 4. Controller performance indices

Method	For step-input of +15			Method	For step-input of -20		
	ISE	OS	ST		ISE	OS	ST
Proposed method	63.22	-	16.1	Proposed method	77.04	-	23.83
Luspay & Grigoriadis (2015)	104.08	0.86	16.2	Malagutti et al. (2013)	209.01	6.07	34.11

patient to patient and a single controller tuned for a particular dynamics may not give satisfactory results for every single patient. It is reported in Bequette (2007) that the uncertainty in the blood pressure regulation MIMO model is averaged to be ranging from 33% to 150%. Note that the uncertainty can be regarded as the variation in the process parameters. These variations arise due to the difference in the behaviour of the patients' body to the infusion of the drug inside the body. The drug infusion may lead to different behaviour in the Mean Arterial Blood Pressure and Cardiac Output. This results in a different model to represent the input-output relationship. Thus, a controller designed should be insensitive to the changes in the dynamics. Hence, it is evident to carry out the sensitivity analysis in order to investigate the efficacy of the designed fractional-order controllers of the paper (Åström & Murray, 2008). The absolute sensitivity can be calculated numerically by the following function:

$$|S_i(s)| = \left| \frac{1}{1 + G_i(s)} \right|$$

where $G_i(s)$ is the forward-path transfer function associated with the i th closed-loop. The sensitivity assessment can be bifurcated into two parts: (i) the absolute sensitivity associated with frequencies $\omega \leq \omega_c$ tells about the attenuation property of the closed-loop system (ii) the portion of the absolute sensitivity plot for frequencies $\omega > \omega_c$ displays the amplification of input disturbances and process parameter variations (Åström & Häggglund, 2006). Note that the frequency ω_c is the frequency where the absolute sensitivity $|S_i(s)| = 1$ (Goodwin et al., 2001).

Figure 7 shows the plot of absolute sensitivity for both the closed-loops, i.e. (i) loop for control of Mean Arterial Blood Pressure (ii) loop for control of Cardiac Output. Figure 7 shows the assessment of sensitivity associated with all the four controllers under investigations. It is observed from Figure 7(a) that for closed-loop 1 the FOPID-PSO displays maximum absolute sensitivity. On the other hand, FF-PI-PSO attends the least value of the maximum absolute sensitivity. This indicates that the

Figure 7. The sensitivity assessment for both the closed-loops

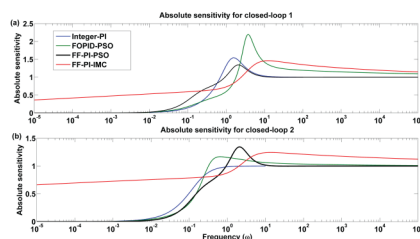


Table 5. Sensitivity performance indices

Controllers	Loop 1		Loop 2	
	S_m	ω_m	S_m	ω_m
Integer-PI	1.545	1.518	1.00	1.831
FOPID-PSO	2.2	3.763	1.167	0.6234
FF-PI-PSO	1.415	2.02	1.4	2.067
FF-PI-IMC	1.465	11.38	1.242	11.38

FF-PI-PSO controller will result in the minimum amplification of input disturbances and parameter uncertainties. Thus, for closed-loop, the FF-PI-PSO displays the least sensitivity to parameter variations, which confirms that the concerned controller can handle various model changes due to difference of behaviour from patient to patient.

Interestingly, the maximum absolute sensitivity S_m tells about the maximum amplification that can occur. So the controller experiencing a higher value of S_m will lead to greater amplification. Moreover, the inverse of S_m denotes the stability margin of the loop. Hence, the lower the S_m higher is the value of the stability margin. That will ensure greater stability of the system (Åström & Hägglund, 2006). Figure 7(b) shows the sensitivity assessment for closed-loop 2. In both cases, the FF-PI-IMC controller has the least attenuation property for the input disturbances as well as for uncertainties. FF-PI-PSO controller shows a higher value of S_m , in contrast to the other controllers, indicating higher amplification for closed-loop 2, i.e. controlling of Cardiac Output. The graphically interpreted sensitivity performance indices are depicted in Table 5.

The frequency ω_m denotes the frequency at which maximum absolute sensitivity is achieved. The less the S_m the better is the controller. Moreover, the recommended range of the maximum absolute sensitivity is $1.4 \leq S_m \leq 2$ (Åström & Hägglund, 2006). Based on this range, the FF-PI-PSO gives the most consistent performance for both MABP and CO simultaneously, as seen from the values of Table 5. All the other controllers either perform well for only one loop or do not perform well at all for either of the loops. For example, FOPID-PSO does not perform well for loop 1, but its performance improves for loop 2.

5. DISCUSSION

This paper demonstrates a fractional framework to control the Mean Arterial Blood Pressure and Cardiac Output simultaneously. The proposed control is based on the Multi-Input Multi-Output approach in lieu of the conventional Single-Input Single-Output approach. This paper achieves the design of three fractional-order controllers, i.e. PSO tuned Fractional-order PID, PSO tuned Fractional-filter PI and IMC based Fractional-filter PI controllers. Several investigations are carried out in the sense of stability, reference tracking and sensitivity. All the three fractional-controller of the paper are compared with each other and also with a conventionally used integer-PI controller. For comparison to being worth, all the controllers are tuned to have the optimized parameters in order to minimise the Integral Squared Error (ISE) performance index. The numerical simulation results of the paper reveal that the fractional-order controllers of the paper offer better overall performance in contrast to the conventionally used integer-PI controller.

Few implementation issues in a real-time control system are: (i) need of consistent communication standards, i.e. blood pressure sensor with the existing monitoring devices should be easy to set up (Doyle et al. 2011); (ii) computational time and competitive pricing; (iii) Real-time realization of the fractional-order controller (Monje et al., 2010).

The first issue can be solved by advances in processor-based technology with new communication standards in order to meet the requirement of the present state of the art (blood pressure monitors and drug infusion pumps). In the second issue, the proposed procedure includes an online optimization algorithm. That raises the concern of synergy between the time taken to calculate the control action and the sampling time of the sensor. In the actual practical field, the algorithm can be implemented on computational viable commercial microcontrollers with the proper guidance of expert doctors under the management of the hospital. That may further decide the total computational cost of the project, which is the subject matter for future scope. In the third issue, the real-time realization of the fractional-order controllers can be performed by the use of finite-dimensional integer-order approximation (Monje et al., 2010). Continuous-time Oustaloup approximation with a behaviour close to the desired and easier to handle implementation is the standard solution for the fractional-order controllers, which is available in (Oustaloup et al., 2000; Nagarsheth & Sharma, 2020).

Out of the three proposed fractional-order controllers, the paper stresses on the most feasible fractional controller for further studies. The FF-PI-PSO controller offers a comparatively considerable overshoot and undershoot with better ISCI values (Tables 2 and 3). The less ISCI values confirm the less use of drugs, i.e. Sodium Nitroprusside and Dopamine, for the control of Mean Arterial Blood Pressure and Cardiac Output. The FOPID-PSO controller implementation becomes cryptic. On the other hand, the Fractional-filter PI controller is easy to implement since the fractional-filter is the only fractional part to be approximated and implemented. Embedding a cascaded fractional-filter with the practically viable integer-PI will serve the purpose of the implementation of FF-PI. The beauty of the fractional-filter controllers is that with little modification they can be embedded into the existing system without changing the whole framework and structure of the controller. The FF-PI-IMC may not be recommended since IMC is a model-based technique and model uncertainties are evident. In IMC the PI parameters remain fixed. On the other hand, there are two extra parameters for precise tuning of the FF-PI-PSO. The four parameters of FF-PI-PSO give more flexibility in contrast to FF-PI-IMC and FF-PI-PSO is easier to implement practically in contrast to FOPID-PSO as well. Robust performance (less sensitive to the process uncertainties) and more operating range of the proposed method (Table 5) will be helpful in inter-patient fluctuations as well as inpatient fluctuations in physiological parameters which will further decrease the patient attendance time by the staff.

Thus, investigations of this paper recommend FF-PI-PSO in lieu of the other controllers for the improved performance in controlling the Mean Arterial Blood Pressure and Cardiac Output simultaneously. However, the major challenge is the variation of the process gain with respect to time as well as from patient to patient. This encourages for detailed experimental investigations as future work of the proposed research conclusion for the introduction of the recommended fractional-order controller to regulate the blood pressure. That can be performed under the guidance of expert doctors and hospital management with further modifications based on the results and outcomes. The use of standard commercial communication standards is highly encouraged. An adaptive technique can also be employed in combination with the proposed fractional controller of the paper to tune the parameters optimally, based on changes in the behaviour of the input-output relationship.

Conflict of Interest: Authors declare that they have no conflict of interest.

Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

REFERENCES

- Araki, M., & Furutani, E. (2005). Computer control of physiological states of patients under and after surgical operation. *Annual Reviews in Control*, 29(2), 229–236. doi:10.1016/j.arcontrol.2005.05.001
- Åström, K. J., & Hägglund, T. (2006). *PID controllers: Theory, Design, and Tuning*. Instrument Society of America.
- Åström, K. J., & Murray, R. M. (2008). *Feedback Systems: An Introduction for Scientists and Engineers*. Princeton University Press. doi:10.1515/9781400828739
- Bailey, J. M., & Haddad, W. M. (2005). Drug dosing control in clinical Pharmacology. *IEEE Control Systems Magazine*, 25(2), 35–51. doi:10.1109/MCS.2005.1411383
- Behbehani, K., & Cross, R. R. (1991). A controller for regulation of mean arterial blood pressure using optimum Nitroprusside infusion rate. *IEEE Transactions on Biomedical Engineering*, 38(6), 513–521. doi:10.1109/10.81575 PMID:1879839
- Benken, S. T. (2018). Hypertensive Emergencies. In B. A. Boucher & C. E. Haas (Eds.), *CCSAP 2018 Book 1: Medical Issues in the ICU* (pp. 7–30). American College of Clinical Pharmacy.
- Bequette, B. W. (2013). Control in physiology and medicine. In E. Carson & C. Cobelli (Eds.), *EDs.*, *Modelling Methodology for Physiology and Medicine* (pp. 13–44). Elsevier Inc.
- Bequette, B. W. (2007). III. Modeling and control of drug infusion in critical care. *Journal of Process Control*, 17(7), 582–586. doi:10.1016/j.jprocont.2007.01.015
- Cheng, L., Yan, J., Han, S., Chen, Q., Chen, M., Jiang, H., & Lu, J. (2019). Comparative efficacy of vasoactive medications in patients with septic shock: A network meta-analysis of randomized controlled trials. *Critical Care (London, England)*, 23(1), 1–14. doi:10.1186/s13054-019-2427-4 PMID:31088524
- Coleman, T. G., Manning, R. D., Norman, R. A., & Guyton, A. C. (1974). Control of cardiac output by regional blood flow distribution. *Annals of Biomedical Engineering*, 2(2), 149–163. doi:10.1007/BF02368487
- Ding, T., Zhang, W., Yu, L., & Lu, K. (2019). The accuracy and efficiency of GA and PSO optimization schemes on estimating reaction kinetic parameters of biomass pyrolysis. *Energy*, 176, 582–588. doi:10.1016/j.energy.2019.04.030
- Doyle, F. J., Bequette, B. W., Middleton, R., Ogunnaike, B., Paden, B., Parker, R. S., & Visdwasagar, M. (2011). Control in biological systems. In T. Samad & A. Annaswamy (Eds.), *The impact of control technology* (pp. 57–68). IEEE Control System Society.
- Frei, C. W., Derighetti, M., Morari, M., Glatfelder, A. H., & Zbinden, A. M. (2000). Improving regulation of mean arterial blood pressure during anaesthesia through estimates of surgery effects. *IEEE Transactions on Biomedical Engineering*, 47(11), 1456–1464. doi:10.1109/10.880097 PMID:11077739
- Furutani, E., Araki, M., Sakamoto, T., & Maetani, S. (1995). Blood pressure control during surgical operations. *IEEE Transactions on Biomedical Engineering*, 42(10), 999–1006. doi:10.1109/10.464374 PMID:8582730
- Gao, Y., & Er, M. J. (2005). An intelligent adaptive control scheme for postsurgical blood pressure regulation. *IEEE Transactions on Neural Networks*, 16(2), 475–483. doi:10.1109/TNN.2004.841798 PMID:15787153
- Goodwin, G. C., Graebe, S. F., & Salgado, M. E. (2001). *Control Systems Design*. Prentice-Hall.
- Hahn, J., Edison, T., & Edgar, T. F. (2002). Adaptive imc control for drug infusion for biological systems. *Control Engineering Practice*, 10(1), 45–56. doi:10.1016/S0967-0661(01)00108-3
- Holmes, C. L. (2005). Vasoactive drugs in the intensive care unit. *Current Opinion in Critical Care*, 11(5), 413–417. doi:10.1097/01.ccx.0000176696.70013.da PMID:16175026
- Isaka, S., & Sebald, A. V. (1993). Control strategies for arterial blood pressure regulation. *IEEE Transactions on Biomedical Engineering*, 40(4), 353–363. doi:10.1109/10.222328 PMID:8375872
- Kennedy, J., & Eberhart, R. (1995). Particle Swarm Optimization. *Proceedings of International Conference on Neural Networks (ICNN)*, 4, 1942–1948. doi:10.1109/ICNN.1995.488968

- Luspay, T., & Grigoriadis, K. (2015). Robust linear parameter-varying control of blood pressure using vasoactive drugs. *International Journal of Control*, 88(10), 2013–2029. doi:10.1080/00207179.2015.1027953
- Malagutti, N., Dehghani, A., & Kennedy, R. A. (2013). Robust control design for automatic regulation of blood pressure'. *IET Control Theory & Applications*, 7(3), 387–396. doi:10.1049/iet-cta.2012.0254
- Marinosci, G. Z., De Robertis, E., De Benedictis, G., & Piazza, O. (2012). Dopamine use in intensive care: are we ready to turn it down? *Translational Medicine @ Unisa*, 4(11), 90–94.
- McInnis, B. C., & Deng, L. Z. (1985). Automatic control of blood pressures with multiple drug inputs. *Annals of Biomedical Engineering*, 13(3–4), 217–225. doi:10.1007/BF02584240 PMID:4037454
- Meier, R., Nieuwland, J., Zbinden, A. M., & Hacisalihzade, S. S. (1992). Fuzzy logic control of blood pressure during anaesthesia. *IEEE Control Systems Magazine*, 12(6), 12–17. doi:10.1109/37.168811
- Monje, C. A., Chen, Y. Q., Vinagre, B. M., Xue, D., & Feliu, V. (2010). *Fractional-order Systems and Controls: Fundamentals and Applications*. Springer-Verlag. doi:10.1007/978-1-84996-335-0
- Mullens, W., Abrahams, Z., Francis, G. S., Skouri, H. N., Starling, R. C., Young, J. B., Taylor, D. O., & Tang, W. H. W. (2008). Sodium Nitroprusside for Advanced Low-Output Heart Failure. *Journal of the American College of Cardiology*, 52(3), 200–207. doi:10.1016/j.jacc.2008.02.083 PMID:18617068
- Nagarsheth, S. H., & Sharma, S. N. (2020). The combined effect of fractional filter and Smith Predictor for enhanced closed-loop performance of integer order time-delay systems: Some investigations. *Archives of Control Sciences*, 30(1), 47–76.
- Oustaloup, A., Levron, F., Mathieu, B., & Nanot, F. M. (2000). Frequency-band complex noninteger differentiator: Characterization and synthesis. *IEEE Transactions on Circuits and Systems. I, Fundamental Theory and Applications*, 47(1), 25–39. doi:10.1109/81.817385
- Podlubny, I. (1999). Fractional-order systems and $PI^\lambda D^\mu$. *IEEE Transactions on Automatic Control*, 44(1), 208–214. doi:10.1109/9.739144
- Rao, R. R., Huang, J. W., Bequette, B. W., Kaufman, H., & Roy, R. J. (1999). Control of a nonsquare drug infusion system: A simulation study. *Biotechnology Progress*, 15(3), 556–564. doi:10.1021/bp9900514 PMID:10356276
- Rao, R. R., Aufderheide, B., & Bequette, B. W. (1999). Multiple model predictive control of hemodynamic variables: An experimental study. *Proceedings of the American Control Conference*, 2(May), 1253–1257.
- Saxena, S., & Hote, Y. V. (2012). A simulation study on optimal IMC based PI/PID controller for mean arterial blood pressure. *Biomedical Engineering Letters*, 2(4), 240–248. doi:10.1007/s13534-012-0077-4
- Seborg, D. E., Edgar, T. F., & Mellichamp, D. A. (2004). *Process Dynamics and Control*. New York: John Wiley and Sons.
- Shahin, M., & Maka, S. (2007). Linear state space model for long-term blood pressure regulation. *International Journal of Biomedical Engineering and Technology*, 1(2), 190–203. doi:10.1504/IJBET.2007.015860
- Shahin, M., & Maka, S. (2011). Control oriented technique for the nonlinear element extraction of long term blood pressure regulation. *International Journal of Biomedical Engineering and Technology*, 7(1), 73–86. doi:10.1504/IJBET.2011.042499
- Shahin, M., & Maka, S. (2011). Control relevant physiological model of the long-term blood pressure regulatory system. *International Journal of Biomedical Engineering and Technology*, 5(4), 371–389. doi:10.1504/IJBET.2011.039927
- Skogestad, S. (2003). Simple analytic rules for model reduction and PID controller tuning. *Journal of Process Control*, 13(4), 291–309. doi:10.1016/S0959-1524(02)00062-8
- Slate, J. B., Sheppard, L. C., Rideout, V. C., & Blackstone, E. H. (1979). A model for design of a blood pressure controller for hypertensive patients. *IFAC Proceedings Volumes*, 12(8), 867–874. doi:10.1016/S1474-6670(17)65503-4

Thongprayoon, C., Cheungpasitporn, W., Harrison, A. M., Carrera, P., Srivali, N., Kittamongkolchai, W., Erdogan, A., & Kashani, K. B. (2016). Temporal trends in the utilization of vasopressors in intensive care units: An epidemiologic study. *BMC Pharmacology & Toxicology*, 17(1), 1–9. doi:10.1186/s40360-016-0063-z PMID:27154548

Tufano, R., Piazza, O., & De Robertis, E. (2010). Guidelines and the medical “art.”. *Intensive Care Medicine*, 36(9), 1612–1613. doi:10.1007/s00134-010-1885-6 PMID:20397004

Urooj, S., & Singh, B. (2019). Fractional-order PID control for postoperative mean arterial blood pressure control scheme. *Procedia Computer Science*, 152, 380–389. doi:10.1016/j.procs.2019.05.002

Shaival H. Nagarsheth received the B.E. degree in Instrumentation & Control from Sarvajani College of Engineering & Technology, Surat, Gujarat, India in 2014, with a gold medal. In 2016 he received his M. Tech degree in Instrumentation & Control with specialization in Control & Automation from Nirma University, Ahmedabad, Gujarat, India, with a gold medal. He is currently pursuing his doctoral degree in control theory from the Electrical Engineering Department at Sardar Vallabhbhai National Institute of Technology, Surat, Gujarat, India. His research includes matrix calculus, controller design for multivariable systems, sensitivity integrals, fractional control design. He is a member of the IEEE Young Professionals, IEEE student member, IEEE Control System Society, IEAE student member, ISA student member, IFAC Affiliate, IFAC-ACDOS (NMO) member.

Shambhu N. Sharma received the BE degree from Government College of Engineering, Rewa (M.P.), India in 1994, the M Tech degree from Banaras Hindu University (Now IIT BHU), UP, India in 2000, and the Ph.D. degree from Delhi University in 2007. Currently, he is working as a Professor in the Electrical Engineering Department of the National Institute of Technology, Surat, India. He specializes in the areas of stochastic systems, control theory, stochastic filtering, and stochastic differential equations with applications to electrical and electronic networks. One of his works is known as a pioneering work in stochastic systems. In addition to these, he is also interested in multivariable system theory as well as non-linear system theory. He had a visiting academic appointment at the Department of Systems and Control of Jozef Stefan Institute, Ljubljana, the Republic of Slovenia under the joint program of the Indian National Science Academy (INSA, New Delhi) and the Slovenian Academy of Sciences and Arts (SASA, Ljubljana).