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Closed loop fractional order drug delivery control scheme for chemotherapy

Nikhil Pachauri [a], Drishti Yadav [b], Tarun Kumar Sharma [c], Om Prakash Verma [d,*], Chang Wook Ahn [a]

[a] AI Graduate School, Gwangju Institute of Science and Technology, 123 Cheomdangwagi-ro, Buk-gu, Gwangju, 61005, South Korea
[b] Faculty of Informatics, Institute of Computer Engineering, Technische Universität Wien, 1040, Vienna, Austria
[c] Department of Computer Science and Engineering, Shobhit University Gangoh, Saharanpur 247341, India
[d] Department of Instrumentation and Control Engineering, Dr. B. R. Ambedkar National Institute of Technology Jalandhar 144011, India

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ABSTRACT

Chemotherapy is one of the most extensively utilized cancer treatment strategies worldwide. It is intended to eliminate fast-developing cancer cells in a patient's body. The amount of chemotherapeutic drug that must be administered precisely into a patient's body determines the efficacy of the treatment and governs the patient survival during chemotherapy. Therefore, controlling the chemotherapeutic drug dose delivered to the patient is essential. This research aims to propose a two-degree-of-freedom fractional order proportional–integral–derivative (2FOPID) controller with a set point filter for implementing an automatic drug delivery control scheme during chemotherapy. The Whale optimization algorithm (WOA) is used to tune the parameters of the 2FOPID controller, resulting in a WOA-tuned 2FOPID controller (W2FOPID). The performance of the proposed W2FOPID is compared with the Integral–Proportional–Derivative (IPD), Internal Model Control (IMC), and Fractional Order IMC (FOIMC) schemes. The experimental results demonstrate that the proposed W2FOPID controller is effective, accurate, and robust for drug concentration control during chemotherapy. W2FOPID outperforms IPD, IMC, and FOIMC schemes in terms of Integral Absolute Error by 79.9%, 25.3%, and 23.36%, respectively. In addition, W2FOPID exhibits excellent set-point tracking, noise suppression and uncertainty handling capabilities.

1. Introduction

According to the Indian Council of Medical Research (ICMR), 1.39 million cancer cases were reported in India in the year 2020. It is estimated that the number of cancer cases are likely to increase up to another 12% by 2025 [1]. However, in global scenario, the new cancer cases are expected to rise by 80% in developing countries and by 40% in developed countries, with 13 million cancer deaths predicted by 2030 [2]. This is an alarming situation which needs to be addressed *via* collaborative multi-disciplinary efforts in order to foster the existing health care system. In general, cancers are a group of diseases categorized by uncontrolled cell growth and division, consequently leading to irregular tissue development [3]. This involves the conversion of normal cells into malignant cells in three stages: initiation, promotion and metastasis. Malignant tumor cells have the capability to breach into nearby tissues and kill the normal (healthy) cells. These cells may extend to other body parts *via* lymphatic framework or blood circulation system, resulting in the formation of new tumors. Acknowledging the increasing rates of cancer, oncologists are

* Corresponding author.
E-mail addresses: nikhilpchr@gmail.com (N. Pachauri), drish131196@gmail.com (D. Yadav), taruniitr1@gmail.com (T.K. Sharma), vermaop@nitj.ac.in (O.P. Verma), c.wan@gist.ac.kr (C.W. Ahn).

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determined to develop competent treatment methods and therapeutic measures to restrict the tumor growth. Common treatment methods for cancer include surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy, hormone therapy, and stem cell transplantation [4]. Among these methods, chemotherapy has grabbed huge attention among the scientific and cancer research communities. Chemotherapy works by targeting the fast growing and reproducing cells. However, the fundamental issue with chemotherapeutic drugs (for *e.g.*, Chlorambucil, Cyclophosphamide, Cisplatin, Carboplatin, etc.) is that they not only kill fast-growing malignant cells, but also extinguish the normal ones. Due to this reason, it becomes essential to maintain and regulate a specific level of the proper chemotherapeutic drug in the patient's body.

1.1. Literature survey

Previous research works indicate that different optimization techniques have been employed for the accurate estimation of optimum chemotherapeutic drug scheduling based on parameterization and analytical gradient [5], adaptive elitist population based genetic algorithm (GA) [6,7], memetic algorithm [8], and paladin-distributed evolutionary control algorithm [9]. When drug concentration and toxicity deviate from their optimal values throughout the treatment process, the strategies discussed using analytical gradient to paladin-distributed evolutionary control algorithm were ineffective. Since the aforementioned schemes are open loop in nature, they are incapable of regulating the drug dose in precise manner. To curb this problem, researchers have utilized the closed-loop control of drug concentration during chemotherapy. A cascaded PID (Proportional–Integral–Derivative) control scheme based on GA has been proposed to control the cancer growth in [10]. Further, its performance is compared with conventional PID and other drug scheduling methods. Moreover, multi-objective GA (MOGA) based PID, and I-PD (Integral–Proportional–Derivative) controllers have been implemented for single as well as multi-drug planning strategies to control cancer growth [11,12]. The reported results demonstrate that the proposed strategies are more robust towards parametric variations. In another pioneer work, three control schemes for optimal robust drug delivery control were designed and compared [13]. Also, H_∞ based new robust control arrangement has been employed to control the angio-genic inhibition of tumor growth [14]. The results exhibit the efficiency of the recommended control scheme for different tumor volumes. Another work used an adaptive PI controller based on Lyapunov method to control the tumor size [15]. The results indicate that the system is globally stable and robust towards variations in model parameters. Further, Modified FOIMC [16], PID [17,18], 2-DOF-PID (2-Degree of Freedom-PID) [19], and optimal control schemes [20] have been put forward for the drug dose control at the tumor site. In addition, NASGA-II optimized control for multi-drug regime during chemotherapy are reported [21,22]. Other strategies include development of various types of fuzzy logic controllers for control of anti-cancer drug delivery systems [23,24]. Also, reinforcement-learning based control [25], robust optimal control [26], and adaptive control [27] schemes have been implemented in this context.

1.2. Problem statement

A large body of literature shows that various control algorithms for closed-loop drug concentration control have been developed. However, every control algorithm has its own merits and demerits. For instance, PID control is simple in implementation, but it is unable to address servo and regulatory problem simultaneously, due to its single closed loop structure. Also, the design and implementation of an IMC requires the accurate transfer function model of a system. In case of intelligent controllers (such as fuzzy control schemes), it is required to develop a well-defined rule base, which is intricate and computationally exhaustive. Reinforcement learning, on the other hand, can result in an overload of states, which can dilute the results. Further, an accurate control law is required to implement the adaptive control scheme.

Under the viewpoint of above discussion, a two degree-of-freedom fractional order PID (2FOPID) with a set point filter is proposed for drug concertation control. The preceding setpoint filter in this control algorithm helps to improves the transient response, thereby improving the setpoint tracking. On the other hand, the traditional closed loop will improve the disturbance rejection capability of the control algorithm. Furthermore, fractional order integral and derivative terms provide additional tuning parameters for the control engineer to improve the system's transient and steady-state performance. Further, in order to estimate the optimum values of controller parameters, Whale Optimization Algorithm (WOA), a nature-inspired optimization technique which replicates the actions of humpback whales, has been utilized [28]. The key features of this work are summarized below:

1. Design of a 2FOPID controller with a set point filter for an automatic drug delivery control scheme.
2. Estimation of the Gain and fractional powers of Integral and Derivative terms of 2FOPID controller using WOA.
3. Comparison of WOA (towards controller design) with other algorithms, including Genetic Algorithms (GA), Simulated Annealing (SA), Grey Wolf Optimization (GWO), and Krill herd (KH).
4. Comparison of the proposed WOA-tuned 2FOPID (W2FOPID) controller with IPD, IMC, and FOIMC control techniques.
5. Investigation of the robustness of the proposed W2FOPID controller pertaining to set-point tracking, noise suppression and parametric uncertainty.

The remainder of this article is organized as follows: In Section 2, the cancer patient mathematical model is discussed. Section 3 then discusses the two degree-of-freedom fractional order PID (2FOPID) with set point filter control strategy. Section 4 provides a brief overview of the WOA. Section 5 presents the simulation results, followed by the discussions in Section 6. Finally, Section 7 presents the concluding remarks.

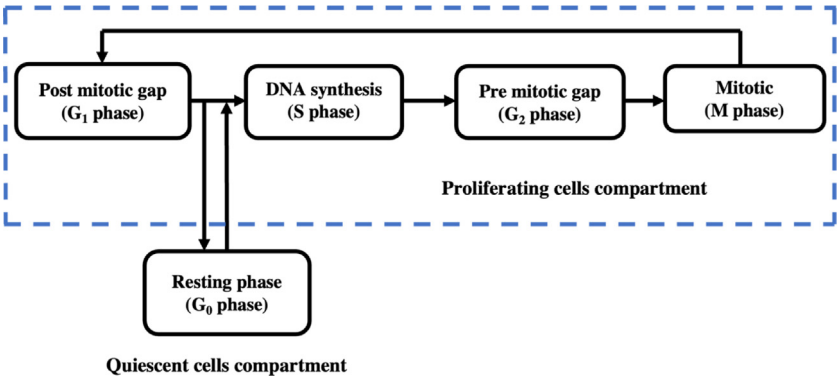


Fig. 1. Different phases of cell cycle for P and Q cells.

2. Mathematical model

Latest therapeutic studies have focused on emerging forms of treatment, such as personalized therapy and patient-specific clinical intervention [29,30]. The presence of multiple tumors, as well as cancer drug tolerance, are the key barriers to the medical interpretation of such methods [31,32]. If the dosage of the cytotoxic drug infused is minimal, there is no need for a planned and coordinated medication intervention to reduce the adverse consequences and the level of toxic effect throughout the patient's body. On the other hand, it is important to break a medication regime for a high initial dosage. With a heavy preliminary drug dose, there may be resurgence in the population of cancer cells, which can endanger the patient's life. The selection of the initial dose of prescribed medication is, therefore, quite challenging. Thus, the estimation of an appropriate initial dose of cytotoxic drug, to avoid undesirable side effects while optimizing the ability to kill cancer cells, is a difficult task. In addition, testing all possible medications and procedures during clinical studies is unethical and exhaustive; therefore very few tests on a participant are permitted. Usually, experimental and clinical investigations can be fostered by using mathematical models to obtain better insights of the effect of drug infusion routine [4]. The use of mathematical models unquestionably accelerates cancer research and improves healthcare. It establishes a link between the medications, the tumor, and the normal body cells. This makes it easier to examine dozens of new medication methods and drug regimes. It is feasible to pick the right one that increases the likelihood of patient survival [33,34]. Previous literature supports a number of chemotherapy-based mathematical models for cancer treatment [35,36], in which the chemotherapeutic intervention activities are based on the cell cycle frameworks. These models are utilized in the design and implementation of appropriate control schemes for automatic drug delivery systems.

This work utilizes a two-compartment cell-cycle specific cancer patient model for studying the impact of chemotherapeutic drug on cancer cell growth. The model under consideration also demonstrates the effect of the toxic drug on normal cells. First-order linear ordinary differential equations are used to represent this model [11]. This limits the mathematical model towards exponential progression and decline without intermediate balance. Nevertheless, it is an appropriate effort, since a successful chemotherapy regimen would prevent the development of the tumor near its carrying capacity. Nonlinearity due to logistic or Gompertz growth can be neglected, which allows to use a simpler model [14,35]. Fig. 1 demonstrates cell cycle phases for proliferating (P) and quiescent (Q) cancer cells [11].

P cells are the rapid-splitting cancer cells which are entirely sensitive initial cell population and Q cells are the non-cyclic cancer cell at the start of the treatment. The rate of change of P and Q cells are given by Eqs. (1)–(2).

$$\frac{dP}{dt} = (a - m - n)\,P(t) + bQ(t) - g(t)\,P(t) \tag{1}$$

$$\frac{dQ}{dt} = mP(t) - bQ(t), Q(0) = Q_0 \tag{2}$$

The administration of chemotherapeutics not only affect the growth rate of P and Q cells but also the growth rate of normal (Y) cells. The rate of change in the population of Y cells and the drug effect are expressed using Eqs. (3)–(4).

$$\frac{dY}{dt} = \theta Y(t)\left(1 - \frac{Y(t)}{J}\right) - g(t)\,Y(t), Y(0) = Y_0 \tag{3}$$

$$g(t) = f_1 D_c(t) \tag{4}$$

Here, θ and J are growth rate and carrying capacity of the normal cell. $g(t)$ is the rate of cancerous cell killing per unit drug and f_1 is a constant that relates the cell kill rate and drug concentration. Also, the relationship between the drug dose (that is to be infused to the patient intravenously, $u(t)$) and the rate of change in drug concentration (D_c) at the tumor site is given by Eq. (5). λ is the drug decay which is associated with the metabolism of the drug inside the patient's body. In addition to this, adverse effect of chemo drug in terms of toxicity (T) is given by Eq. (6).

$$\frac{dD_c}{dt} = u(t) - \lambda D_c(t), D_c(0) = D_0 \tag{5}$$

Table 1
Description of Cancer model parameters.

Parameters	Description	Values
a	Rate of growth of P cells	0.5 day^{-1}
m	Mutation rate of P cells to Q cells	0.218 day^{-1}
n	The natural end of cycling cells	0.477 day^{-1}
b	Mutation rate of Q cells to P cells	0.05 day^{-1}
θ	The rate of normal cell growth	0.1 day^{-1}
ρ	Drug toxicity elimination rate constant	0.38
J	The carrying capacity of normal cell	10^9
P	The proliferating cells population	2×10^{11}
Q	The quiescent cells population	8×10^{11}
Y	The normal cell population	10^9
Y_{min}	The limitation of normal cell	10^8

$$\frac{dT}{dt} = D_c(t) - \rho T(t), T(0) = T_0 \tag{6}$$

During chemotherapy, the chosen drugs reduce the cancer cells and also produce adverse effects on the other body parts, if the concentration levels are not properly chosen. Hence, a set of constraints are imposed in the model to maintain appropriate levels of drugs during treatment as given in Eqs. (7)–(8).

$$10 < D_c(t) \leq 50 \tag{7}$$

$$T(t) \leq 100 \tag{8}$$

Further, the proportion of normal cells should also be kept inside some bounds throughout the treatment in order to increase the life span of the patient under treatment as expressed by Eq. (9).

$$Y_{min} \leq Y(t) \leq J, \forall t \in [0, T] \tag{9}$$

The interpretation of the underlying model variables and their initial values were taken from previous literature [11] and their description is given in Table 1. Further, the model is simulated on MATLAB 2018a, in order to develop closed loop control scheme for the estimation of optimum drug scheduling during chemotherapy. In real time, closed loop control is implemented using a biosensor for continuous monitoring of the drug concentration directly from the blood plasma. Also, a programmable infusion pump can be used to inject the amount of drug dose as per the requirement [37,38].

3. 2FOPID control scheme

During the treatment process, an efficient control algorithm is essential to maintain and regulate the drug concentration at its reference value. Here, a 2FOPID control scheme with a set point filter is proposed to select the quantity of drug to be infused into the patient's blood stream. The 2FOPID controller has 8 parameters: proportional gain K_P, integral gain K_I, derivative gain K_D, fractional power of integrator ψ, fractional power of derivative υ, set point weighting variables (c_1 and c_2) and derivative filter coefficient (N). The drug level is continuously measured at the tumor site (*i.e.*, $y(t)$) and is fed back to the controller. The controller compares the measured value (*i.e.*, $y(t)$) with the prescribed reference value (*i.e.*, $r(t)$) and computes the error. The reference step signal with explicit value is taken into account, which confirms the constant level of medication at the tumor location during the therapy. Based on the difference between the reference and measured drug concentrations, the 2FOPID controller infuses appropriate drug dose into the patient's body. When the error is zero, cancer cell eradication is high. On the other hand, for non-zero error, the eradication is comparatively low. For the 2FOPID controller, the relationship between the error and the controller output (*i.e.*, $u(t)$) is given by Eq. (10). It is the generalized time domain representation of the two degree of freedom controller.

$$u(t) = K_P \left\{ \left(c_1 r(t) - y(t)\right) + \frac{1}{T_i} \int (r(t) - y(t))(dt)^{-\psi} + T_d \frac{d^{\upsilon}}{dt^{\upsilon}} \left(c_2 r(t) - y(t)\right) \right\} \tag{10}$$

In general, derivative term improves the transient behavior of the closed loop system [39] as well as make the system susceptible towards noise. To curb this issue, the derivative term will be written in terms of a first order filter with coefficient N. This will help the controller to further improve its performance under the influence of noise and parametric uncertainty. Eq. (10) may be transformed into the Laplace domain as presented in Eq. (11).

$$U(s) = K_P \left\{ \left(c_1 R(s) - Y(s)\right) + \left\{ \frac{1}{T_I s^{\psi}} \right\} (R(s) - Y(s)) + \left\{ \frac{T_D s^{\nu}}{N s^{\nu} + 1} \right\} (c_2 R(s) - Y(s)) \right\} \tag{11}$$

Usually, one of the most challenging tasks in controller design is to achieve a fair balance between tracking and disturbance rejection capabilities. The use of a two-degree-of-freedom control scheme, with an appropriate set point filter to retrieve the set point independently from the feedback controller, is an effective solution to this problem. This study makes a contribution by designing a fractional set-point filter that can be used in a normal two-degree-of-freedom control scheme. The designed strategy achieves great results in terms of low settling time and reduced overshoot simultaneously. This differs from the traditional set-point

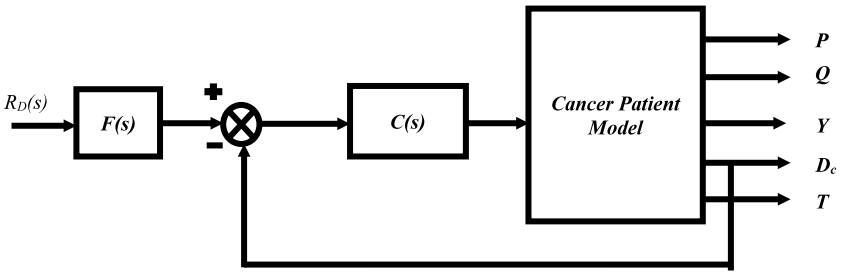


Fig. 2. Block diagram for set point filter type 2FOPID based closed loop drug concentration control.

filter design, which employs a low-pass filtering strategy to reduce overshoot at the cost of rise time [40]. Fig. 2 illustrates the set point filter type 2FOPID control scheme for closed loop drug concentration control.

In Fig. 2, $R_D(s)$ is the reference drug concentration which is to be maintained at the tumor site for the whole period of treatment process. The configuration and magnitude of $R_D(s)$ is critical, as the eradication of malignant cells depends on the amount of drug infused at the tumor site. Also, $F(s)$ is the set point filter which will improve the set point tracking capability and $C(s)$ improves the disturbance rejection capability of the overall closed loop system.

$$F(s) = \frac{1 + (1 - c_1) T_I s^{\Psi} + (1 - c_2) T_I T_D s^{\Psi} \left\{ \frac{s^{\nu}}{N s^{\nu} + 1} \right\}}{1 + T_I s^{\Psi} + T_I T_D s^{\Psi} \left\{ \frac{s^{\nu}}{N s^{\nu} + 1} \right\}} \tag{12}$$

$$C(s) = K_P \left\{ 1 + \frac{1}{T_I s^{\Psi}} + T_D \left\{ \frac{s^{\nu}}{N s^{\nu} + 1} \right\} \right\} \tag{13}$$

Further, fractional order integral and differential operator is implemented using "Oustaloup approximation". This approach employs the $2M$ +1 order filter that suits inside the defined frequency band $[\alpha_L, \alpha_H]$. The fractional order transfer function of power μ is expressed by Eq. (14) [41].

$$s^{\mu} = G \prod_{k=-M}^{M} \frac{\left(s + \alpha_{z_k}\right)}{\left(s + \alpha_{p_k}\right)} \tag{14}$$

Here, G is the gain, α_{z_k} and α_{p_k} represents the zero and pole frequencies. These zero and pole frequencies are mathematically expressed by Eqs. (15) and (16).

$$\alpha_{z_k} = \alpha_L \left(\frac{\alpha_H}{\alpha_L} \right)^{\frac{k + M + \frac{1}{2}(1-\mu)}{2M+1}} \tag{15}$$

$$\alpha_{p_k} = \alpha_L \left(\frac{\alpha_H}{\alpha_L} \right)^{\frac{k + M + \frac{1}{2}(1+\mu)}{2M+1}} \tag{16}$$

It is worth mentioning that researchers endorse the design of chemotherapy drug scheduling for a treatment period of 84 days (*i.e.*, 12 weeks) [11]. Therefore, in order to demonstrate the efficiency of the proposed W2FOPID controller for optimal chemotherapeutic drug scheduling, the treatment period of 84 days is considered in the present work.

4. Whale Optimization Algorithm (WOA)

Recent advancements in optimization techniques provide an adequate scope for solving the problems of controller tuning. Several nature-inspired approaches are becoming increasingly prevalent in optimization [42–44] and controller tuning applications [45,46]. WOA has received widespread attention among the research communities across multiple disciplines due to its simplicity, adaptability, computational efficiency, and intermittent nature [28]. It is relatively easy to apply and effective when compared to other swarm intelligence methods, making it a good choice over other nature-inspired algorithms. The algorithm necessitates fewer control parameters; in practice, only one parameter (time interval) must be fine-tuned.

In general, a single optimization method is incapable of answering all optimization problems, in view of the 'no free-lunch' theorem [19,47]. Taking this into account, various optimization techniques were employed in this work to select the most appropriate technique for optimum 2FOPID controller tuning. Specifically, the WOA was used for fine-tuning of 2FOPID controller parameters, and its performance was compared with GA, SA, GWO, and KH. Whale Optimization Algorithm (WOA) is an optimization approach, enthused by the "bubble-net" hunting strategy of humpback whales [28]. The humpback whales hunt schools of krill or small fishes near the surface. They swim nearby the prey, inside a shrinking circle and along a spiral-shaped track, at once. This in turn creates distinct bubbles along a circle or "9"-shaped path. To mimic this performance in WOA, a probability of 50% is provided

to select among the shrinking encircling phenomena and the spiral-shaped pathway for updating the whale's position. The encircling prey behavior is demonstrated by Eqs. (17) and (18).

$$\vec{D} = \left|\vec{C}.\overrightarrow{X^*(t)} - \overrightarrow{X(t)}\right| \tag{17}$$

$$\overrightarrow{X(t+1)} = \overrightarrow{X^*(t)} - \vec{A}.\vec{D} \tag{18}$$

Here, the notations are

t	: Current iteration
$\vec{A}$, $\vec{C}$	: Coefficient vectors
$\vec{X}$	: Position vector
$\vec{X}*$	: Position vector of the best solution obtained so far

Furthermore, $\vec{A}$ and $\vec{C}$ are given by

$$\vec{A} = 2.\vec{a}.\vec{r} - \vec{a} \tag{19}$$

$$\vec{C} = 2.\vec{r} \tag{20}$$

Here, $\vec{a}$ is linearly decreased from 2 to 0 over the course of iterations (in both exploration and exploitation phases) and $\vec{r}$ is a random vector in [0, 1]. Generally, $\vec{A}$ is a random value in the interval $[-a, a]$ where a is decreased from 2 to 0 over the course of iterations. The Bubble-net attacking mode (or the exploitation phase) is demonstrated by Eqs. (21) and (22).

$$\overrightarrow{X(t+1)} = \vec{D'}.e^{bl}.\cos(2\pi l) + \overrightarrow{X^*(t)} \tag{21}$$

Here, the notations are as follows:
$\vec{D'} = \left|\overrightarrow{X^*(t)} - \overrightarrow{X(t)}\right|$ = Distance of the ith whale to the prey (best solution obtained so far),
b = a constant for defining the shape of the logarithmic spiral,
l = random number in $[-1, 1]$.
It is to be noted that the "." in the above equations represents element-by-element multiplication. Assuming a probability of 0.5 for selecting among either the shrinking encircling mechanism or the spiral model for position update, we take the following mathematical model:

$$\overrightarrow{X(t+1)} = \left\{ \begin{array}{cc} \overrightarrow{X^*(t)} - \vec{A}.\vec{D} & if\ p < 0.5 \\ \vec{D'}.e^{bl}.\cos(2\pi l) + \overrightarrow{X^*(t)} & if\ p \geq 0.5 \end{array} \right\} \tag{22}$$

where p = a random number in $[0, 1]$.
The exploration phase (or the searching phase) is demonstrated by Eqs. (23) and (24).

$$\vec{D} = \left|\vec{C}.\overrightarrow{X_{rand}} - \vec{X}\right| \tag{23}$$

$$\overrightarrow{X(t+1)} = \overrightarrow{X_{rand}} - \vec{A}.\vec{D} \tag{24}$$

Here, $\overrightarrow{X_{rand}}$ is a random position vector (*i.e.*, a random whale) chosen from current population.

The flow chart in Fig. 3 shows the methodology of WOA. Further, there are certain objectives that need to be satisfied while evaluating the optimum values of 2FOPID parameters [17]. These objectives are enlisted below:

1. The population of cancer cells should be as low as possible, at the end of the treatment. Prior to the initiation of the treatment process, the population size for P cells is equal to 2×10^{11}. However, while designing the closed loop scheme, the reference value for reduction in the population of P cells is considered to be greater than or equal to 65%.
2. Like P cells, the population of the Q cells also reduce at the end of the treatment. The initial population size for Q cells is 8×10^{11}. The reference value for reduction in the population of Q cells is considered to be greater than or equal to 55%.
3. The population of normal cells indicates the patient's physiological condition during treatment. The minimum value considered in this work is 1×10^{8}.
4. The value of toxicity should be less than 100, as given in Eq. (8).

5. The value of drug concentration at the tumor site should be maintained between 10 to 50 mg/ml.

In the present work, the population size is set to 30. The maximum number of iterations (set to 100) is chosen as the stopping criteria. The population is initialized randomly using uniform distribution.

5. Simulation results

Here, W2FOPID based scheduling mechanism has been proposed to hold the dosage of the drug to its required level. The W2FOPID controller is built with the help of approximation of Oustaloup fifth-order filter with range of frequencies $\left[10^{-3}, 10^{3}\right]$ rad/s. The block diagram representation of WOA tuned 2FOPID based drug scheduling during chemotherapy is illustrated in Fig. 4.

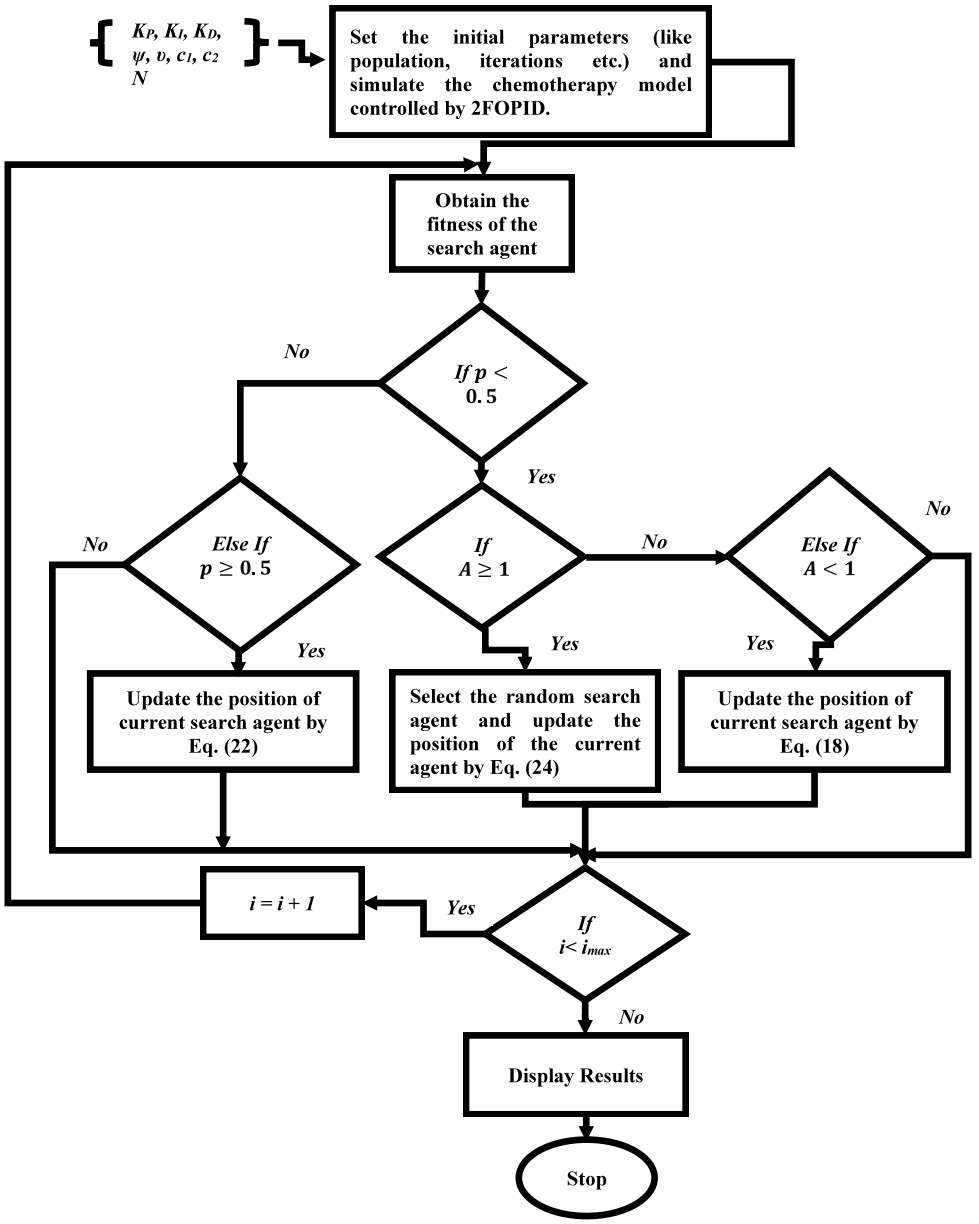


Fig. 3. Flowchart for Whale Optimization Algorithm.

Optimizing the controller parameters involves choosing a suitable cost function to be optimized. In this study, a combination of P cells and average toxicity is taken as the cost function (H) to be minimized, expressed by Eq. (25) where n signifies the number of design constraints.

$$H = \left(w_1 \times P\left(t_f\right)\right) + \left(w_2 \times \left\{\frac{1}{t_f}\int_0^{t_f} T\left(t\right) dt\right\}\right) \tag{25}$$

where the sum of the weights w_1 and w_2 should be equal to 1 [16] and given by Eq. (26).

$$\sum_{j=1}^{n} w_j = 1 \tag{26}$$

WOA has been employed to estimate the 2FOPID design variables, *i.e.*, to tune the 2FOPID controller parameters. In addition, a comparative analysis has been carried out to compare the tuning of the 2FOPID parameters *via* WOA with GA, SA, GWO, and KH. Fig. 5 shows the convergence graphs of various techniques employed for controller tuning. Here, the bounds of the design variables

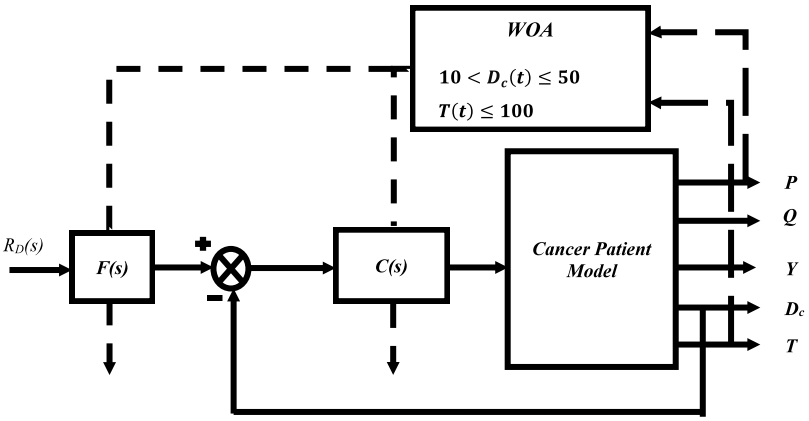


Fig. 4. WOA tuned 2FOPID based drug scheduling during chemotherapy.

Table 2
Quantitative comparison of all the optimization techniques.

Algorithm	Fitness value ($\times 10^{10}$)	NFEs[a]
SA	2.8221651	300
GA	2.8189952	800
KH	2.8190643	2000
GWO	2.8189949	200
WOA	2.8189946	60

[a]NFEs represent Number of Function Evaluations.

(*i.e.*, tuning parameters), population size, stopping condition and cost function are assumed to be the same. As per the literature [13,17–19], there is no thumb rule for determining the lower and upper bounds. In this study, rigorous experimentation is performed using the trial and error method for deciding the bounds. Firstly, the critical values of the gain parameters and fractional power are evaluated for which the system will give a stable response. Thereafter, based on these critical values, the bounds are decided. The bounds considered for the tuning purpose are $K_P \in [1,5]$, $K_I \in [1,5]$, $K_D \in [0,1]$,$\psi \in [0,1]$,$\upsilon \in [0,1]$, $c_1 \in [0,1]$, $c_2 \in [0,1]$, $N \in$ [0, 2].

In Fig. 5, the curves represent the plot of the fitness value of the cost function (H) versus the number of iterations. The plots reveal that WOA is very competitive and exhibits good convergence behavior compared to other state-of-the-art optimizers. Three different convergence behaviors can be observed from Fig. 5. Firstly, it is observed that the convergence speeds up with the increasing number of iterations for all the optimization algorithms. Secondly, we observe rapid convergence from the early stages of iterations for WOA and GWO. The convergence curves of WOA and GWO demonstrate that the favorable areas of the solution space are exploited quickly and easily. Thirdly, we observe convergence towards the global optima only in the final iterations for KH optimizer. This behavior is most likely because KH is unable to find a good solution in the early iterations, and hence it continues searching in the solution space to converge at the global optimum. It is revealed that KH (Fig. 5(c)) is unable to estimate the optimal region even after the fulfillment of the specified stopping criterion. On the other hand, GA (Fig. 5(b)) converges around 70th iteration; the probable reason might be the inconsistent parametric settings of GA. SA (Fig. 5(a)) converges to its minimum value of cost function within 15 iterations, but the fitness value is higher than that of GA. This may be due to the improper selection of an appropriate cooling schedule. However, WOA (Fig. 5(e)) manages to estimate the optimum region and is relatively efficient, as it takes only 3 generations to find the optimum solution. WOA provides a high convergence rate with considerable precision as compared to GWO (Fig. 5(d)).

Further, Table 2 shows the quantitative comparison of all the optimization techniques in terms of fitness values and Number of Function Evaluations (NFEs). From Table 2, it is quite evident that WOA beats other algorithms in terms of fitness value and NFEs. Hence, it may be concluded that for the present application, WOA is the most appropriate optimization technique among others.

Usually, the concentration of the drug must be maintained at the specified level for effective anticancer therapy. This is accomplished by utilizing pre-set nature of step signal, defined as step input. As mentioned earlier, the value of drug concentration should be taken between 10 to 50 mg/ml. For this purpose, three different reference points S1 = 12.08, S2 = 12.17, and S3 = 11.66 are considered for drug concentration [24]. The value of drug concentration is relatively low, as researchers are investigating the effect of 'comparatively lower doses with longer period' (called Metronomic therapy) instead of the traditional 'comparatively higher dose for shorter period' [17]. Initially, the W2FOPID controller is optimized for set-point value of S1 = 12.08. After obtaining the optimum controller parameters, these parameters can be used for different set points, without any re-tuning. Inspecting the controller for various set points verifies its capability to handle process uncertainties. The performance comparison of the proposed W2FOPID controller (for 12.08 reference point) with IPD, IMC and FOIMC [24] is illustrated in Fig. 6. Also, Table 3 shows the parametric values

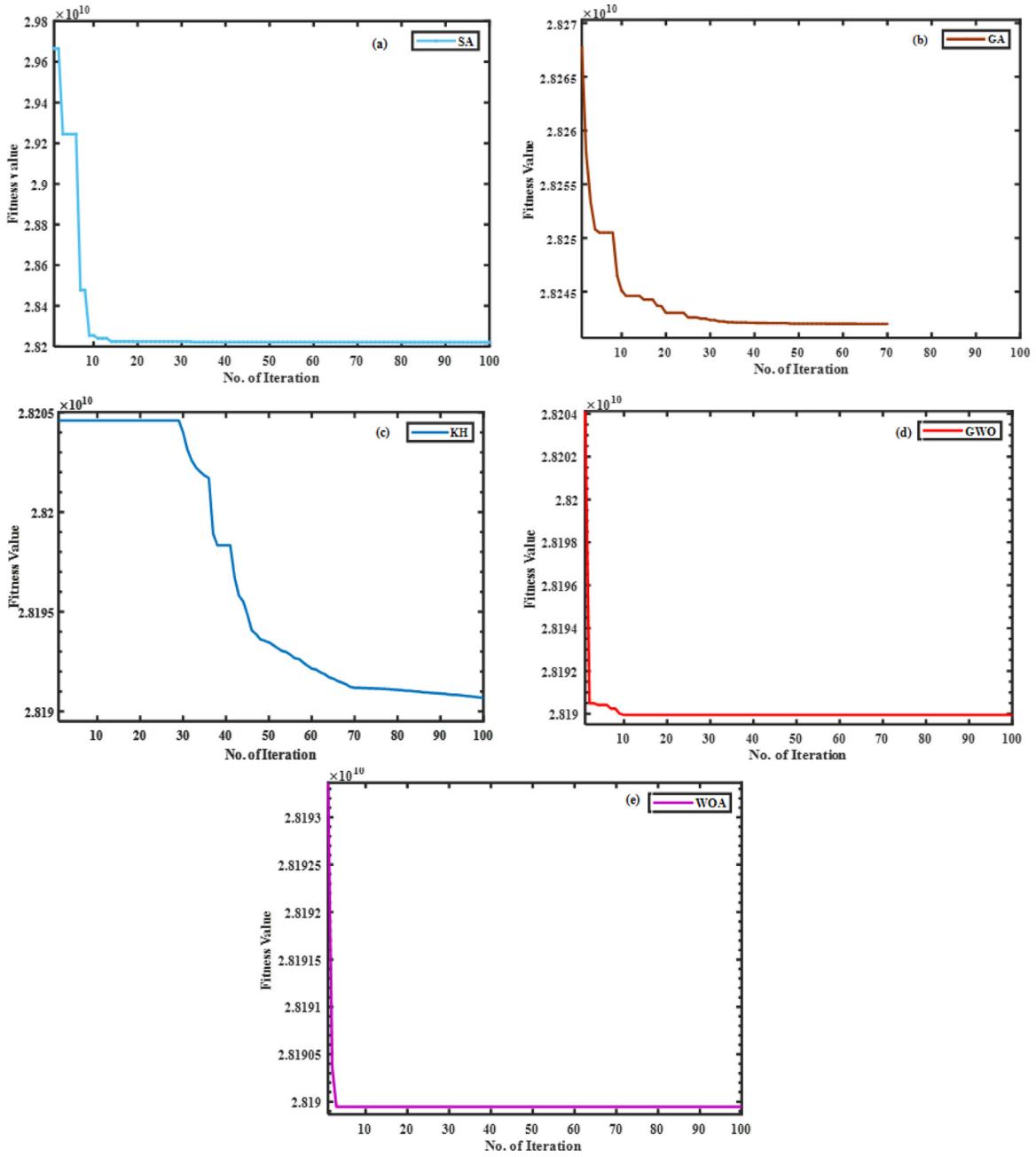
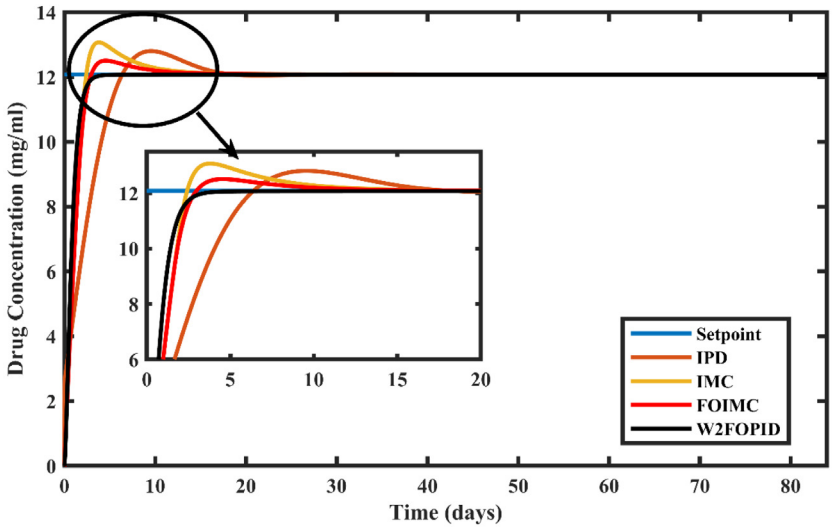


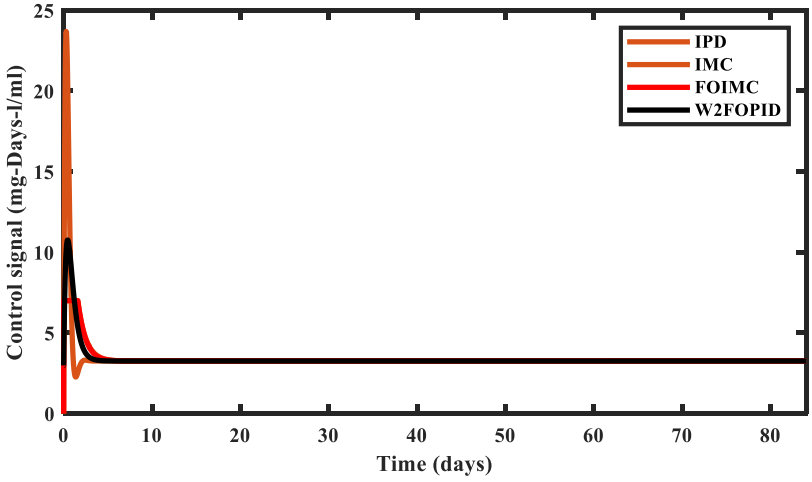
Fig. 5. Convergence graphs of various optimization techniques for tuning of 2FOPID: (a) SA (b) GA (c) KH (d) GWO (e) WOA.

Table 3
Parametric values of designed controllers for drug concentration control.

Controller	K_P	K_I	K_D	ψ	υ	c_1	c_2	N	Filter coefficient	
									η (for IMC)	β (for FOIMC)
IPD [17]	0.34	0.162	0.273	–	–	–	–	–	–	–
IMC [24]	–	–	–	–	–	–	–	–	0.72	–
FOIMC [24]	–	–	–	–	–	–	–	–	–	0.97
W2FOPID (proposed)	4.25	4.95	0.105	0.9978	0.9773	0.058	0.000512	0.13	–	–



(a) Drug Concentration



(b) Control Signal

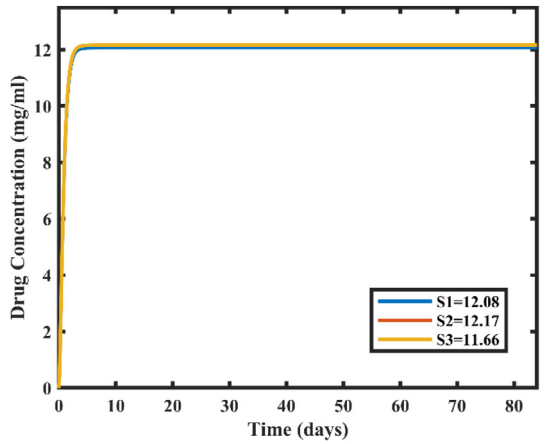
Fig. 6. Performance assessment of W2FOPID controller for drug control.

Table 4
Performance comparison of controllers on the basis of time response specifications.

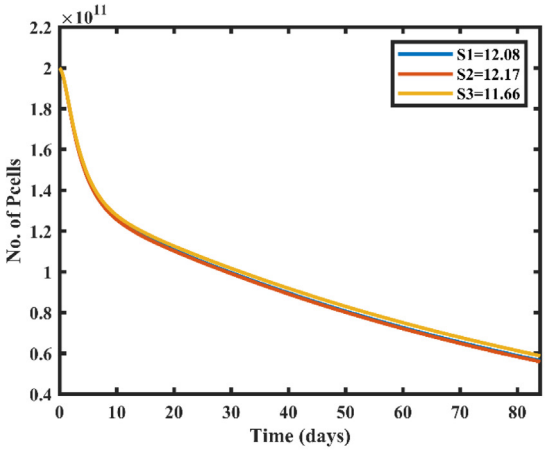
Controllers	% O.S. (Overshoot)	T_s (Settling time in days)	T_r (Rise time in days)
IPD [17]	5.9571	14.5691	4.8116
IMC [24]	8.1525	9.2951	1.8367
FOIMC [24]	3.5046	7.3769	1.9540
W2FOPID (proposed)	0	2.6938	1.5497

for all the controllers designed for drug concentration control. In addition, Table 4 shows the comparison of different controllers with reference to various time response specifications.

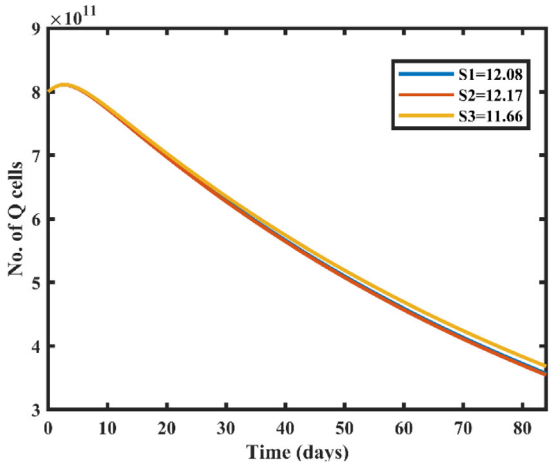
From Table 4, it is quite obvious that the proposed W2FOPID controller improves the settling time and rise time with 0% overshoot among other controllers. This validates that the proposed controller exhibits satisfactory behavior in the steady and transient states. Moreover, an implementation of the proposed W2FOPID for three different step inputs [24] is shown in Fig. 7. Initially the error (difference between the measured and desired drug concentrations) is high, so a high drug dose is infused to the patient at the beginning of the treatment. Such an action will initiate the killing of the P cells and Q cells. When the error is small, the infused drug dose is also reduced and it settles down to a minimum value for the entire treatment period as shown in Fig. 7.



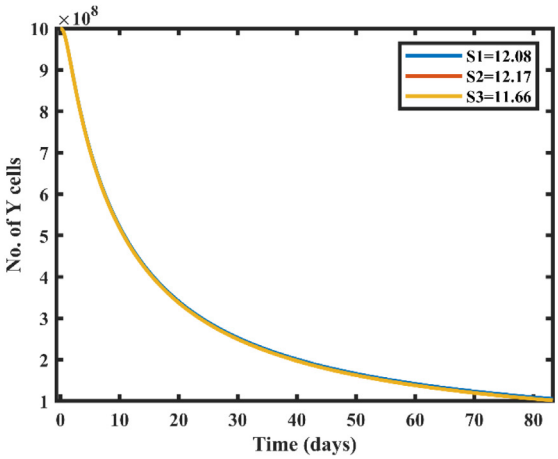
(a) Drug Concentration



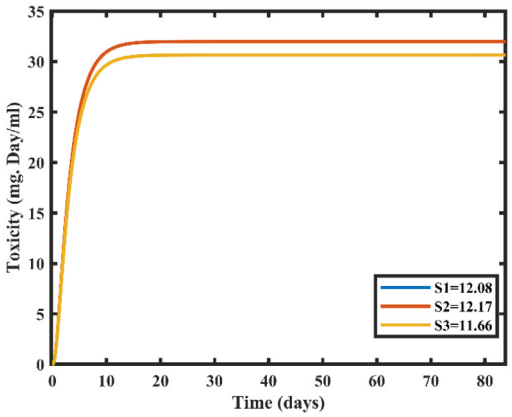
(b). No. of *P* cells



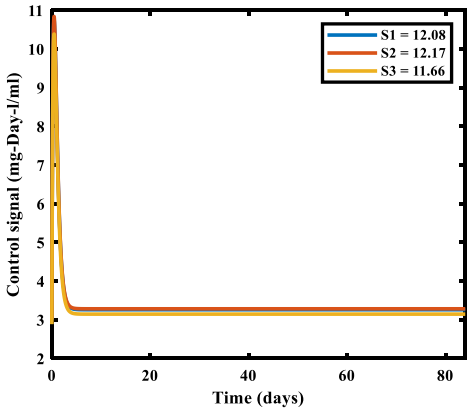
(c) No. of *Q* cells



(d) No. of *Y* cells



(e) Toxicity



(f) Control Signal

Fig. 7. Performance analysis of W2FOPID for set points S1, S2 and S3.

Table 5
Quantitative analysis of proposed controller for uncertainty in model parameters (a, m, n and ρ).

Model parameters	% Reduction in P cells	% Reduction in Q cells	Remaining Y (normal) cells
Optimum values	70.17%	57.13%	1.2263×10^8
Parameters vary by ±5%	70.15%	57.10%	1.2264×10^8
Parameters vary by ±10%	70.10%	57.09%	1.2266×10^8
Parameters vary by ±20%	70.05%	57.00%	1.2267×10^8

Further, the efficiency of the designed W2FOPID controller is inspected by comparing its performance with IPD, IMC and FOIMC [24] for servo problem. As the variations in set-point value will totally change the process dynamics, an exhaustive study of set-point monitoring is conducted by acknowledging three reference values. Fig. 8(a) demonstrates a comparison of all the controllers for set-point monitoring. It is evident that W2FOPID greatly reduces overshoot and settling time and, hence, performs better than other controllers. Fig. 8(b) shows the corresponding control signals. Further, deviations for P, Q and Normal (Y) cells are presented in Fig. 8(c), (d) and (e). The value of Integral Absolute Error (IAE) for W2FOPID is 13.266, which is less as compared to IPD (64.9), IMC (17.71), and FOIMC (17.30).

Fig. 9 demonstrates the comparison of all the controllers based on the left-over cell populace. From Fig. 9, it is evident that in case of W2FOPID, the remaining cancerous cells are less in number and the number of normal cells is comparatively high.

In addition, the robustness of the proposed W2FOPID controller is investigated for parametric uncertainty and noise suppression. The articulated cancer model is utilized to evaluate the optimal medication scheduling procedure. The model parameter values are dependent on the person's metabolic conditions as well as on the tumor's traits. For the duration of therapy, these values are deemed to be same. However, the controller should work efficiently against parametric uncertainties. So, uncertainties of ±5%, ±10%, and ±20% are considered in the model parameters (a, m, n and ρ). The quantitative analysis of proposed controller against parametric uncertainty for S3 = 11.66 is given in Table 5. From Table 5, it can be concluded that the proposed W2FOPID controller is able to handle the parametric uncertainty efficiently. Furthermore, the variations of ±5%, ±10%, and ±20% are also considered in the model parameter λ (*i.e.*, drug decay) for S3 = 11.66. The performance of the proposed controller in order to handle this uncertainty is recorded in Fig. 10. From the figure it can be observed that W2FOPID efficiently manages the variations in model parameter λ. The remaining population of Y cells for ±5%, ±10%, and ±20% uncertainties are 1.2265×10^8, 1.2268×10^8, and 1.2270×10^8 respectively. It is evident from Table 5 and Fig. 10 that the proposed W2FOPID control strategy is favorably stable and robust despite the uncertainties in various model parameters on account of its closed-loop behavior. We observe that despite variations in model parameters, the number of normal (Y) cells is nearly same as computed with optimal model parameters (without any uncertainty). In addition, parametric uncertainties have no significant impact on the reduction in P cells and Q cells, thereby exhibiting a robust behavior of the proposed W2FOPID controller.

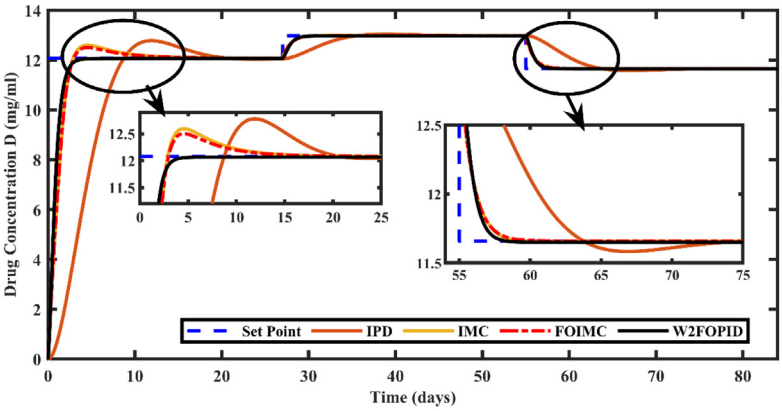
Further, in order to test the robustness of the proposed controller towards noise suppression, a sensor noise of amplitude −0.06 to +0.06 is introduced in the feedback path of the closed-loop chemotherapeutic system. Fig. 11 shows the drug concentration control by various control schemes with reference to noise. It is evident from the simulation results that W2FOPID rejects the sensor noise effectively. Also, from the Integral Square of Errors (ISE) values (Fig. 12), it is validated that W2FOPID has superior ability for noise suppression, in contrast to IMC and FOIMC.

6. Discussion

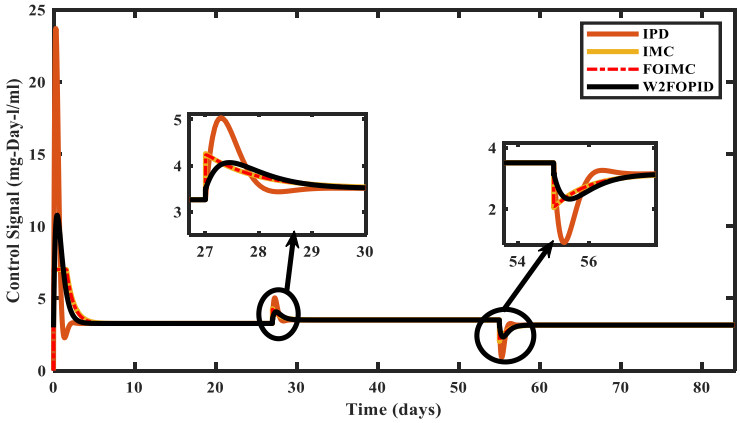
Cancer cell eradication depends on the medicine dosage delivered to the patient at the tumor location. A high medicine dosage eliminates tumor cells more quickly, but it also raises the level of toxicity in the patient's body. If the degree of toxicity exceeds a particular barrier, the number of normal cells rapidly declines, endangering the person's life. In this work, we proposed a combination of fractional calculus and integer order two-degree-of-freedom PID (2FOPID) for precise concentration control of cytotoxic chemotherapeutic drug at the tumor location. The WOA was chosen to determine the optimal values of the controller settings after a thorough quantitative evaluation with GA, SA, KH, and WOA. It has been observed that WOA needs 3 iterations to converge and also has a lower objective function value in comparison to other algorithms.

Moreover, the performance of W2FOPID controller is compared with previously designed controllers [17,24]. The results reveal that the W2FOPID controller precisely controls the drug concentration when compared to IPD, IMC and FOIMC controllers. The concentration reaches to its threshold value in 1.4633 days and settles to its final value in 3.7107 days. It is also noticed that the population of P cells decreases to its minimum value with less value of toxicity. Moreover, the efficiency of the proposed controller has been confirmed by comparing its performance with other controllers (IMC and FOIMC) for set-point tracking and noise suppression. It is shown that W2FOPID accurately tracks the variation in set-point (as verified from the values of IAE) and effectively suppresses noise (as evident from the ISE values). In addition, it is worth mentioning that the proposed control strategy is substantially stable and effective even with huge uncertainties in the model. The simulation results demonstrate that regardless of the model uncertainties (from small range of ±5% to large range of ±20%), the % reduction in cancer cells is nearly same as obtained with optimum model parameters with no uncertainty.

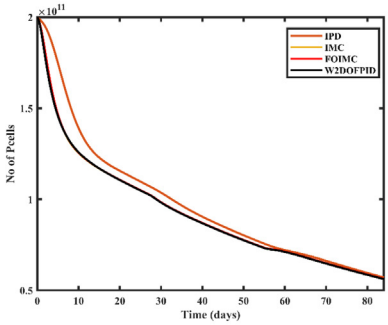
Nonetheless, this research is subject to several limitations. In real-time scenario, the chemotherapeutic treatment also depends on the patient's metabolism. Therefore, there may be significant deviations between simulation results and real-time data. Uncovering of metabolic alterations and analyzing disruptive metabolic interventions are paradigms to advance our knowledge of cancer growth



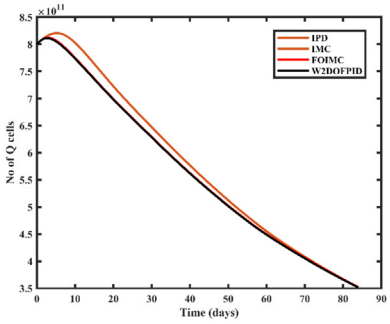
(a) Servo performance of the designed W2FOPID Controller



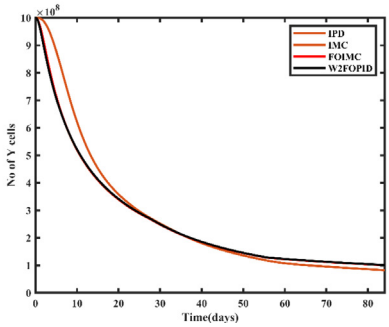
(b) Control Signal



(c) *P* cells



(d) *Q* cells



(e) *Y* cells

Fig. 8. Comparison of various controllers for set-point tracking.

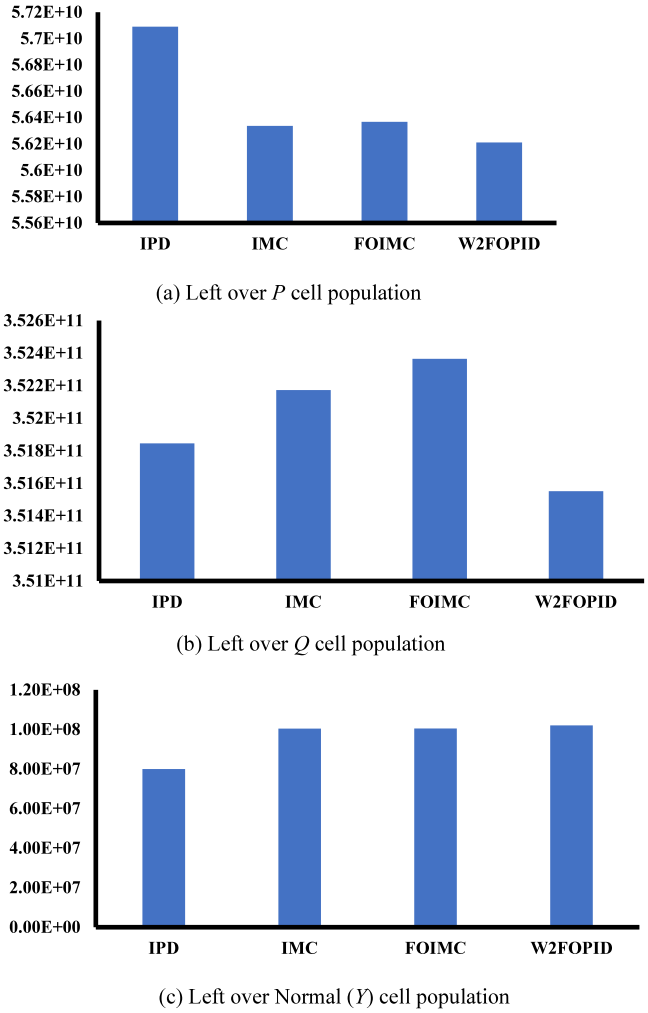


Fig. 9. Comparative analysis of controllers with respect to left over population of cells.

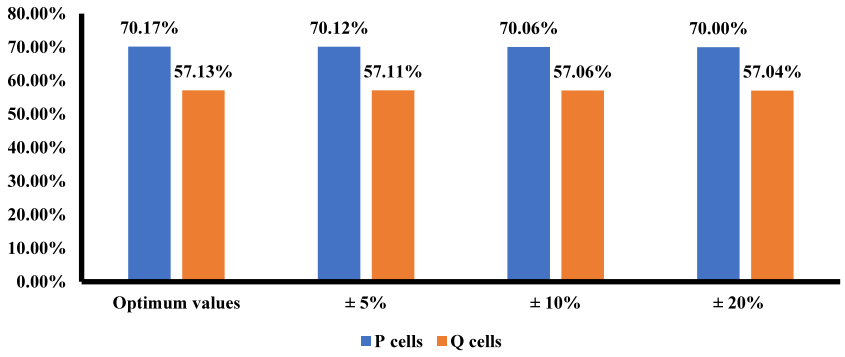


Fig. 10. Variations in P cells and Q cells for uncertainty in model parameter λ.

and develop robust control policies for treatment. In addition, the mathematical model examined in this work is semi-rigorous since it did not incorporate the protein binding limitations for drug delivery. The suggested controller efficacy might also be assessed on a rigorous cancer patient model that incorporates all genetic and morphological variables of the patient. Previous research has indicated that discoveries based on mathematical models may be clinically evaluated with good outcomes. However, mathematical

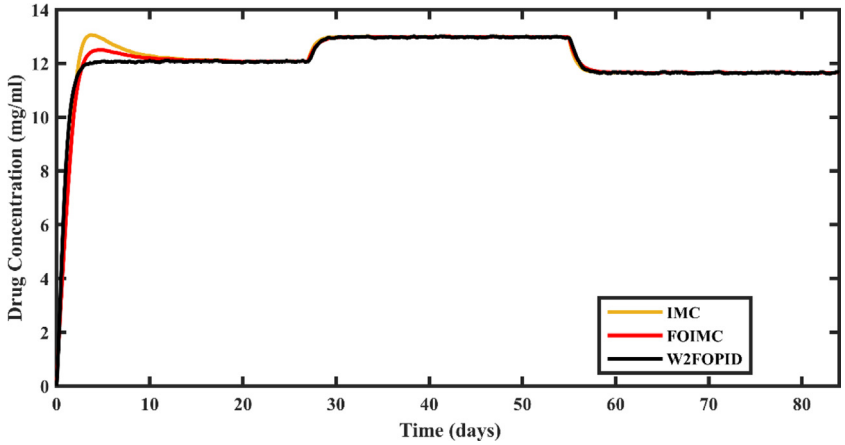


Fig. 11. Drug concentration.

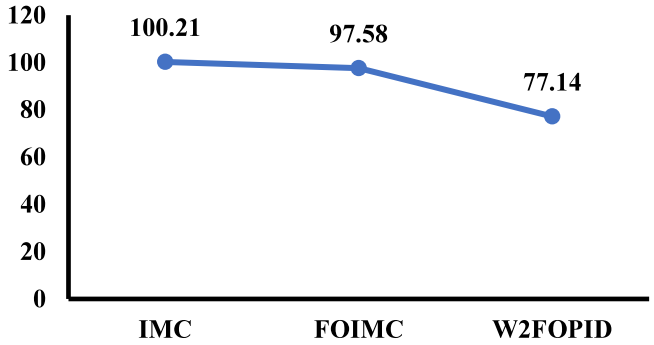


Fig. 12. ISE comparison for noise suppression.

models have the following drawbacks: (1) Inconsistency in the effectiveness of a mathematical model-based research against real-time therapy and, (2) The prediction potential of a mathematical model is determined by its correctness, physiological assumptions, and availability of dataset. Because of technological advancements, increasingly intricate discoveries into tumor biology are being made, such as unicellular genetics, chromosomal diversity, micro-environment, and so on. To fill the space between the precise mathematical model and real patient, all these elements must be included into model equations. Moreover, in chemotherapy, there are high chances for a specific volume of cancer cells to be resistant and/or build resistances during treatment. Therefore, future works may integrate the cancer patient model with these resistances to obtain more realistic results.

7. Conclusion

In this article, a two-degree-of-freedom fractional order PID controller (2FOPID) with a set point filter is proposed for drug concentration control during chemotherapy. The introduction of the set point filter has improved the set point tracking performance of the proposed control scheme. The optimum values of the design parameters of 2FOPID are estimated using WOA, leading to W2FOPID. The convergence behavior of WOA is compared with that of GA, SA, KH, and GWO. Furthermore, the performance of the W2FOPID is compared with that of the IMC, IPD, and FOIMC controllers for set point tracking. The proposed method effectively determines the suitable drug concentrations in every interval without violating the constraints. A robustness analysis by varying model parameters in the range of ±5% to ±20% is performed. Results indicate that the variation in reduction in P cells, Q cells, and Y cells is minimal in the entire deviation range. It shows the stable performance of the proposed W2FOPID controller in single-drug scheduling for cancer treatment. Furthermore, the proposed controller also exhibits better noise suppression capabilities (with a minimum ISE) as compared to IMC and FOIMC controllers. On the whole, it can be established that the W2FOPID controller is effective, accurate, and robust for drug concentration control. These results will assist oncologists and therapists to enhance the drug delivery process *via* optimal control of drug dosage. In future, we will try to apply the proposed control scheme on real-time data with a more rigorous mathematical model of a cancer patient. Further, the performance of the proposed W2FOPID control scheme for multi-drug scheduling is worth researching.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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