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PI-D CONTROLLER BASED ON AN IMPROVED CROW SEARCH ALGORITHM FOR CANCER GROWTH TREATMENT

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Abstract: The number of cancer diagnoses and deaths worldwide is rising every year despite technological advancements in diagnosing and treating multiple forms of cancer. An oncolytic virus is a type of tumour-killing virus that can infect and analyze cancer cells while mostly preserving normal cells. The oncolytic Vesicular-Stomatitis Virus therapeutic's cell cycle-specific action mathematically investigated. An optimal Proportion Integral-Derivative (PI-D) controller is introduced in this paper based on a suggested Improved Crow Search Algorithm (ICSA) to enhance the outcome of oncolytic virotherapy. The control technique was tested in a computer using MATLAB simulation. The suggested ICSA is used to tune the parameters of the PI-D controller. The ICSA used the inertia factor and boundary handle mechanism in the position update equation to balance exploration and exploitation. The simulation results show that decrease in total dose, tumour cells to 30%, the tumour remain in the treatment area from day 30 onwards. Furthermore, the ICSA algorithm outperforms the CSA and PSO algorithms by 34.5497×10^{-6} and 15.2573×10^{-6}, respectively, indicating the robustness of treatment methods that can accomplish tumour reduction through biological parameters ambiguity.

Keywords: *Oncolytic virotherapy, feedback mechanism, biotherapy, PI-D control, robust control, ICSA, PSO algorithm.*

1. Introduction

The number of cancer cases and deaths is increasing worldwide every year despite medical advances in diagnosing and treating many types of cancer [1]. Chemotherapy and radiation therapy kills cancer cells and damages the body's cells simultaneously [2]. An oncolytic virus is a type of tumour-killing virus that can infect and analyze cancer cells while leaving normal cells largely intact [2]. When oncolytic viruses are given to patients or directly injected into a tumour, these viruses spread through the tumour and infect cancer cells. These viruses can replicate in infectious cancer cells. When infectious cancer cells degenerate, their explosion can lead to new viruses that can infect more neighbouring cancer cells [3]. Mathematical models trained on clinical trial data can generate hypotheses and answer the question of "what if" testing performance is verified in silico to guide and validate future trials and analyze and simulate complex biological systems dynamics at low cost [4]. Therefore, it is vital to use a reliable mathematical model with sufficient descriptive power and predictability to perform such theoretical analyses. Selection of medication, dosage, and treatment schedule has become a

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bewildering issue due to the complexity and heterogeneity of the disease.

All over the world, cancer scientists and clinicians are looking to use the available treatment options in a more effective way to improve treatment outcomes and the quality of a patient's life [5]. Different treatment protocols are followed in cancer treatment, for example, controlling a low dose for a long time or a high dose followed by a low dose [5]. Depending on the system model and the objective function, the optimal controller is used to derive the optimal solution [5].

Many control goals can define according to the required conditions. For example, the common goal-directed is to reduce the number of cancer cells at the end of the treatment. With this primary goal, there are many conditions, such as maintaining the drug level within a specific concentration or less than the permissible limit and the number of normal cells and immune cells [5].

Optimization is a method of determining the right set of variables to accomplish the intended goal (s) precisely or approximately, probably by trial and error. Nature-inspired optimization algorithms are metaheuristic algorithms focused on biological principles, swarm behaviour, and chemical or physics processes [6]. For example, the Crow Search Algorithm, inspired by crow nature, was first published in [7], with its primary use in engineering problems with constraints.

Interactions between virotherapy and control theory have illustrated in many previous studies. For instance, Yongmei et al. in [8] used Optimal control, virotherapy with targeted control to reduce the tumour size. Still, the model they used didn't have an equilibrium point, so the tumour could strongly return. On the other hand, Joseph et al. in [9] use an ideal control for chemotherapy in combination with virotherapy to improve the results of chemotherapy and virotherapy. So that reduced the total tumour size was appropriate, the results showed the treatment program's success, and the amount of optimal medication for chemotherapeutic and virus combination is half of the respective maximum tolerated doses.

Anita et al. in [10] use state-dependent algebraic Riccati equation (SDARE) (similar to linear LQR while SDARE is a nonlinear approach used with nonlinear control) to extract the optimal infusion rate for virotherapy using robust and optimal control virotherapy, the number of cancer cells is reduced almost to 60%.

In this paper, the same mathematical model in [10] investigated and an optimal Proportion Integral-Derivative (PI-D) controller based on an improved crow search algorithm for its parameters used to manage the amount of medication given to patients.

The remaining sections of this paper organized as follows; the mathematical model reviewed in the second section and the improve crow search algorithm shown in the third section. The fourth section discusses the PI-D controller's architecture. The fifth part addresses the simulation results and analysis of the proposed controllers, and six provides the conclusion.

2. Cell Cycle-Specific Model

Various models for cancer therapy using oncolytic virotherapy suggested, and all models are novel due to variations in the underlying virus. A mathematical model for cell cycle-specific activity of the oncolytic Vesicular-Stomatitis Virus (VSV) therapeutic will depend in this paper. VSV is an RNA virus that shows anti-tumour efficacy in many human cancer cell lines, including the breast, prostate, cervical,

and hematologic cancers [11]. It has distinct characteristics as it can only be transmissible when the tumour cells are in the active stages of the cell cycle [12].

During the decomposition process of breaking the membrane of cancer cells next to destroy the cancer cells, the virus can activate the immune system of the human body, where this device will be responsible for removing the virus later after the process of decomposition [13]. Joseph et al. in [11] developed an age structure ordinary differential equations (ODEs) mathematical model for VSV virus.

VSV cannot attack cancer cells in the resting stage G_0, but it can attack them in the rest of the stages, so the tumour is divided into two groups [11]. Q is the volume of cancer cells in the resting phase of the cell cycle, S size of cancer cells in the rest of the stages of the cell cycle, including the growth cycle, DNA analysis, and mitosis [11]. Another group is I cancer cells are infectious by the virus and V virus. According to Anita et al. in [10], the model developed by Joseph et al. in [11] can regard as a control system with the virus as input. As seen below, the model can express as a set of differential equation systems [10]:

$$\begin{aligned} \dot{Q} &= b_1 + 2a_1S - a_1Q - d_1 \\ \dot{S} &= b_2 + a_1Q - a_2S - \frac{kSV}{N} - d_2S \\ \dot{I} &= \frac{kSV}{N} - \delta I \\ \dot{V} &= \alpha I - \frac{kSV}{N} - d_3V \end{aligned} \quad (1)$$

where N is the number of cells and viruses in mm^3, assume to be $N(t) = Q(t) + S(t) + I(t) + V(t)$, a_1The rate of change of silent cells into active cells (day^{-1}), a_2The rate active cell division (day^{-1}), b_1The number of Q cells increased,b_2 The number of S cells increased, d_1 The natural death rate of cell Q (day^{-1}), d_2 The natural death rate of cell S (day^{-1}), d_3 Free Virion decay (day^{-1}), α Virion production (day^{-1}), δ Infected cell elimination (day^{-1}), k Kinetic coefficient (day^{-1}) [11].

Because of the ability of leukocytes, which function as antibodies, to recognize the virus as a foreign target and destroy it, immunological responses in the human body regarded as system disruptions [10]. As a result, the virotherapy model can be thought of as a three-dimensional structure, as seen below[10]:

$$\begin{aligned} \dot{Q} &= b_1 + 2a_1S - a_1Q - d_1 + e_1W \\ \dot{S} &= b_2 + a_1Q - a_2S - \frac{kSV}{N} - d_2S + e_2W \\ \dot{I} &= \frac{kSV}{N} - \delta I + e_3W \end{aligned} \quad (2)$$

where e_i for $i = 1,2,3$ are weighting for disturbance, result from the body's immune reaction to the infection, there is a disruption in the system's I compartment.

The virus V in the growth model (1) controls the growth of cancer cells. So system (2) can be handled as a control system with a control input V and three states Q, S and I. Parameters and their values included in Table 1.

Table 1. Parameter's value [11]

Parameter	Value	Unit
a_1	0.6	day^{-1}
a_2	0.5	day^{-1}
b_1	0.07	day^{-1}
b_2	0.005	day^{-1}
d_1	1×10^{-5}	day^{-1}
d_2	0.2	day^{-1}
d_3	0.3	day^{-1}
α	4	day^{-1}
δ	0.8	day^{-1}
k	4	day^{-1}
$[e_1\ e_2\ e_3]$	[0 0 0.5]	day^{-1}

3. Control Structure

The PID algorithm is one of the most common feedback controller algorithms used in industrial processes and has been used successfully for more than 50 years [14]. When PID applied to a specific function, the efficiency of the controller depends on the tuning parameters. Tuning refers to the best adjustment of controller parameters, i.e., Kp, Ki and Kd for a PID controller. There are various performance parameters to adjust the performance of a controller, such as settling time, overshoot rise time and error steady-state and integral indices [15]. PIDs require less information about the process than full mathematical models, and it tries to reduce the error by adjusting the controller's input [16]. P, I, and D, three different constant parameters, have been used in the calculation formulas (3). These parameters can interpret in terms of time, with P referring to the current error, I to the accumulation of previous errors, and D to impending errors [14]. The specific process can only need one function to achieve proper control action by setting all other variables to zero. "Since the absence of an integral term can prevent the device from reaching its target range" [14], "the derivative function is sensitive to measurement noise" [14], and avoid derivative pick the PI controller with the derivative D in feedback used. The controller law became:

$$u(t) = Kp\, e(t) + Ki \int_0^t e(\alpha)d\alpha - Kd \frac{d}{dt} Q(t) \quad (3)$$

where Kp stands for proportional gain, Ki for value integral gain, Kd for derivative gain, e for error, t for sudden time (the current), and α are the integration parameters (takes value from (0 - t)). The block diagram of the proposed controller describes in Figure 1. The control signal's upper and lower limits set by the saturation block, which outputs the signal but only up to a certain magnitude until capping the output at the threshold. The controller appointed to administer three high doses at varying intervals of two days between one quantity and another using switch.

Since cell cycle-specific activity of the oncolytic (VSV) is a nonlinear system, the traditional methods like Zeigler-Nichols (Z-N) and Cohen Coon (C-C) can't use to tune the parameters of the PI-D. The current popular approach is to use algorithms inspired by nature to overcome difficulties and find an optimal solution that is surprisingly effective[17], Improved Crow Search Algorithm (ICSA) is proposed in this paper to obtain optimal values for PI-D parameters (Kp, Ki, and Kd).

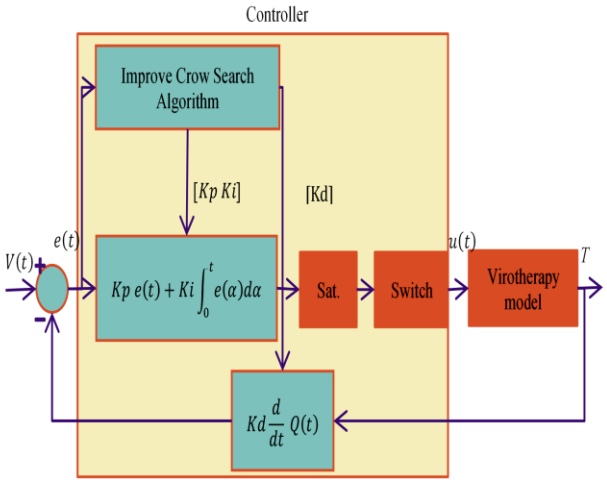

Figure 1. Block diagram of the suggested PI-D controller based on optimization algorithm

4. Improve Crow Search Algorithm (ICSA)

The Crow search algorithm (CSA) algorithm inspired by the intelligent behaviour of crows in hiding food. It has been widely used to solve many optimization problems and has proven itself compared to many modern optimization algorithms available in the litterateurs [17]. Generally, the adjustable parameters of CSA are

population (flock) size (N), Flight length (FL) (Large values lead to global search while small values lead to local search), awareness probability (AP) (control the balance between exploration and exploitation) and the maximum number of iterations (Maxiter). Therefore, the following steps can implement CSA:

1. Define the optimization problem and initialize the decision variables and any constraints needed.
2. Each crow initialized the position and memory (each crow represents a viable solution to the optimization problem).
3. Evaluate the position of each crow using a fitness function.
4. Generate a new position in the search space based on Eq. (4).
5. Determine the viability of new positions.
6. Evaluate the new position's fitness feature.
7. Update the crow memory by the new position.
8. Verify the termination criterion.

$$P_{\mathrm{i}}^{t+1} = \begin{cases} P_{\mathrm{i}}^{t} + r_i \times FL_i^t \times \left(M_j^t - P_{\mathrm{i}}^{t}\right), \\ if\ r_j \geq AP_{\mathrm{i}}^{t} \\ a\ random\ position, \\ otherwise \end{cases} \quad (4)$$

where P_{i}^{t} Position matrix representing the position of each crow i at iteration t, M_j^t Memory matrix where hiding places positions are stored, r_i and r_j are random numbers with a uniform distribution between 0 and 1.

In the original CSA, "the constraints are directly handled. It means that each solution that cannot satisfy the conditions altogether will be considered as infeasible and abandoned "[7]. The rejection of impossible solutions may be severe flaws to the design space problems and dominated by constraints. Hence, creating a possible design for such problems may take an enormous number of successive trials [7]. To maintain a good balance between exploration and exploitation, the following additions propose: First, multiply the current position equation by the inertia factor β [18].β's value would decline over time. The linear regression of factor β is determined as follows in general [19]:

$$\beta(t) = \beta max - (\beta max - \beta min) * \frac{iter}{\mathrm{Maxiter}} \quad (5)$$

where iter represents the number of repetitions, βmax and βmin are upper and lower limits of β factor. Equations of position update become:

$$P_{\mathrm{i}}^{t+1} = \begin{cases} \beta \times P_{\mathrm{i}}^{t} + r_i \times FL_i^t \times \left(M_j^t - P_{\mathrm{i}}^{t}\right), \\ if\ r_j \geq AP_{\mathrm{i}}^{t} \\ a\ random\ position, \\ otherwise \end{cases} \quad (6)$$

Secondly, adding a treatment to the new position produced before determining the viability of new positions. The pseudo-Code of the proposed algorithm:

Input:

- Number of iterations (Maxiter)
- Flock size (N)
- Dimension (Pd)
- Awareness probability (AP)
- Flight length (FL)
- Inertia weight ($\beta max - \beta min$)
- Tolerances

Initialization:

- Randomly scatter the position (x) of N crows in the search space.
- Put these Initialize positions in the memory (M) of crows.
- Evaluate the fitness value for N different crows and save it in $\mathbf{f_0}$.

- Save the minimum value of fitness in **fmin$_0$**.
- Save the values of a crow which give the best fitness in the **fitmin**.
- While iter ≤ Maxiter and tolerance >10^{-12}.
- Calculate inertia factor using Eq. (5).
- Generate random conduct crow for chasing.
- For i =1: N
- If rand ≥ AP
  generation of a new position for crow Eq. (6).
  else
  generation of a new position for crow Eq. (6)
  end

Calculate:

- Handling boundary violations.
- Evaluating fitness and save it in **f**.
- Updating memory and fitness if the **f** < **f$_0$**.
- Save the minimum value of fitness in **fmin**.
- Updating gbest and best fitness if **fmin** < **fmin$_0$**.
- Calculating tolerance.
- displaying iterative results.
- iter=iter+1.

end

5. Simulation Results and Analysis

The MATLAB v.2018 program used to simulate the suggested PI-D based on ICSA. Error at steady-state measured to choose the dominant parameters by the ICSA and the CSA PSO algorithms for comparison. The parameters used in optimization algorithms listed in Table 2 (the initial value of Q, S, I, W selected as: 0.7, 0.3, 0, 0.01).

Table 2. Optimization algorithms parameters

Parameters	Value	Algorithm
population size (N)	25	CSA, PSO
Max iteration ($Maxiter$)	50	
Problem dimension (Pd)	5	
Awareness probability (AP)	1.2	
Flight length (FL)	0.3	
Inertia weight (β_{max}-β_{min})	(0.9 – 0.4)	
Learning rates ($c1, c2$)	2	PSO

If the system (1) simulation over time, the cell counts I and V are zero because the virus treatment has not yet given; And that both cells Q and S grow exponentially, and the rate of growth of S cell is more than Q cells. It is undesirable because the number of cancer cells becomes uncontrollable and poses a risk to the patient's body. The proportion of cells in each group without being control shown in Figure 2.

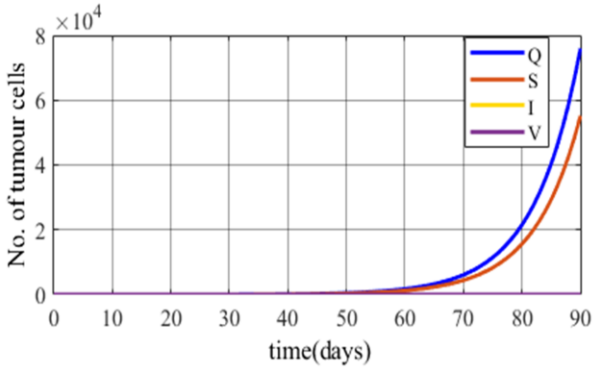

Figure 2. System (1) as growth model proportion of cells in each group without control

The same procedure as in [20] used to enhances treatment outcomes and decreases dosage concentration (where a high dose may be hazardous). In addition, it observed that giving high doses at the beginning of treatment provides better results than several low doses[20].

5.1 Simulation Of System (2) Based ICSA With Feedback From Different State

The effect of state feedback on the controller's performance also tested; Figure 3 shows the impact of feedback from the various state on total output.

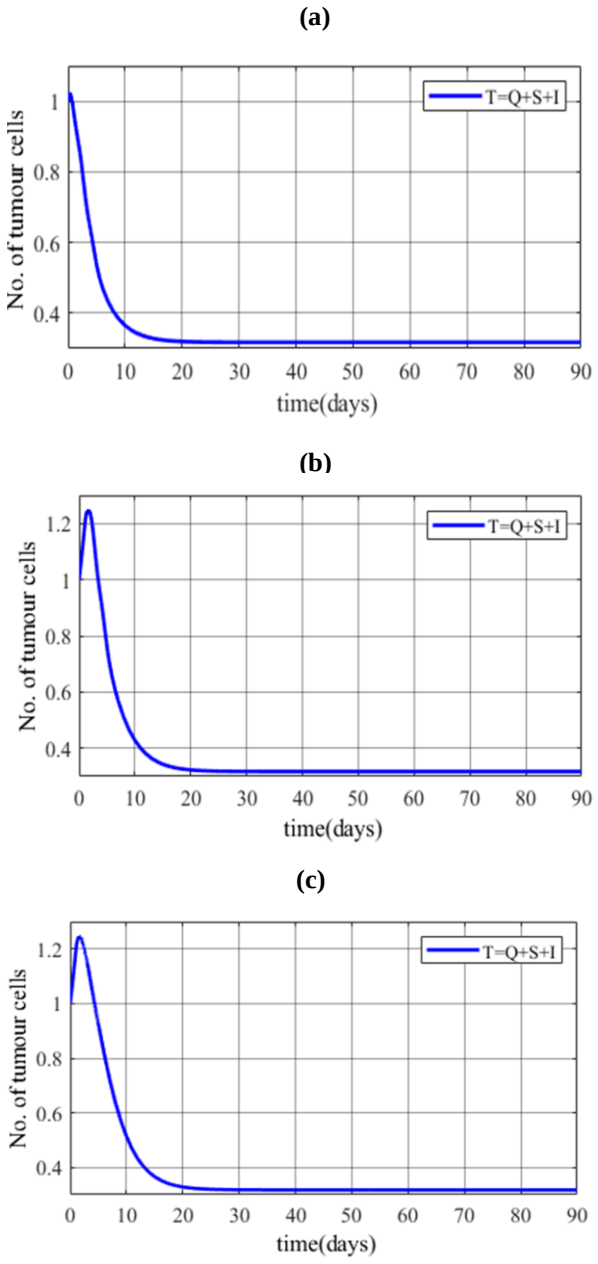

Figure 3. Effect of feedback from various state on total output where a, b and c refer to feedback from Q,S, and I respectively

The results show that feedback from state Q is most effective in reducing peak tumour size (pts) at the beginning of treatment as it represents the cells that make up the tumour core; Table 3 shown the peak tumour size (pts) when feedback comes from various states. Furthermore, the result shows the possibility of eliminating quiescent cells to reduce the size of the tumour in general, as these cells can turn into proliferating cancer cells (proliferate aggressively) or necrotic cells (removed by phagocytosis) depending on the availability of nutrient and oxygen [16].

Table 3. Effect of the feedback on pts

Feedback	P	I	D	pts
***Q* (a)**	8.7341	2.2862	3.0854	**1.022**
***S* (b)**	6.5468	11.3831	4.3585	1.245
***I* (c)**	4.9729	1.0515	5.0539	1.247

5.2 Comparison Simulation Of System (2) With Different Optimization Algorithms

The system's response (2) when PI-D controller applied based on ICSA for parameter optimization, and feedback takes from state Q Shown in Figure 4.

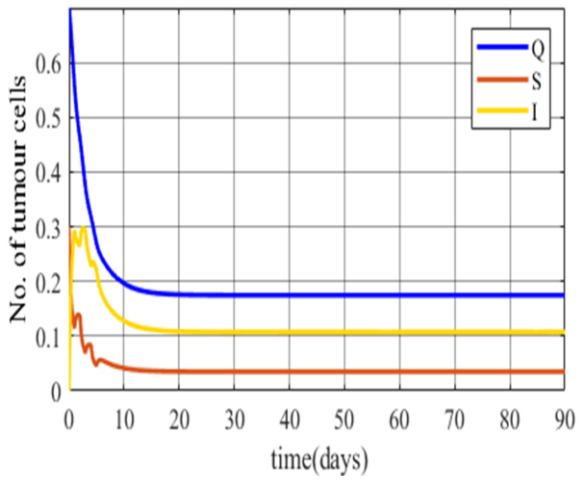

Figure 4. States Q, S and I when PI-D applied and ICSA used for parameter optimization

Because "Studies of a broad array of human solid tumour types revealed that cell cycle progression lasts two days, on average" [11]. The performance of the proposed control based on different optimization algorithms follows the

protocol of injection a high dose at days 0, 2, 4 and calculate the error at a steady-state used for the comparison between them shown in Figures 5 and 6.

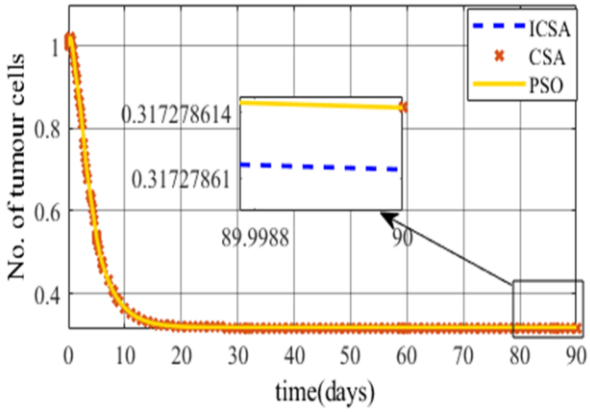

Figure 5. The total ouput (T =Q+S+I) when PI-D applied and used different algorthims for parameter optimization

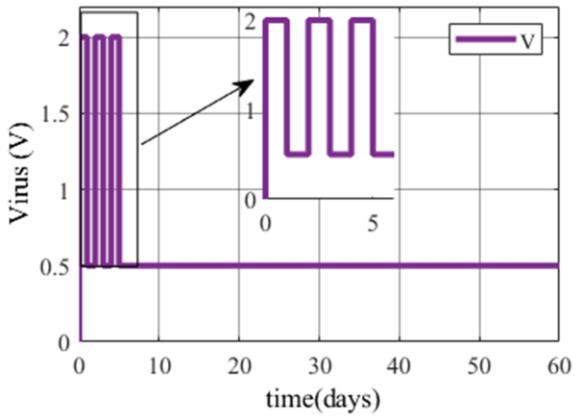

Figure 6. Maximum virus injection at days 0, 2, 4

The ICSA outperforms the CSA and PSO algorithms by 34.5497×10^{-6} and 15.2573×10^{-6} respectively. Simulating the injection at separated days contributed to reducing the total dose, and enhancing total output and maintaining tumour size to approximately less than 30%.

6. Conclusion

This paper recommends that ICSA be used in conjunction with a PI-D controller to limit the number of viral particles injected to minimize tumour cell numbers. The mathematical model of age structure has considered, which is crucial in cancer modelling since taking into account the time cells spend in the cell cycle. The efficiency of the proposed controllers improves by using optimization algorithms. According to simulation results, the ICSA algorithm outperforms the CSA and PSO as it let the tumour stable at minimum error steady-state. The PI-D controller reduces the tumour's size to a low-risk level, so it would be easier to suppress it later by surgery and allow affected patients to survive as long as possible. The simple PI-D controller shrinks the tumour more than the control used on the same mathematical model in the literature.

Furthermore, there are no recurrences of the tumour after therapy completed. Further statistical and experimental research is needed to understand better the relationship between cell cycle phases and the number of viral injection doses. However, these findings may help develop virus therapies and control strategies that ensure tumour regression with minimal side effects.

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Conflict of interest

The authors confirm that the publication of this article causes no conflict of interest.

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