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Model Predictive Control of Melanoma Treatment Enhanced by Particle Swarm Optimization

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Abstract. This study analyzes the growth dynamics of melanoma tumor cells and develops a model predictive controller (MPC) using four well-known optimizers to suppress tumor growth, proposing an MPC framework that integrates multiple metaheuristic algorithms for regulating tumor size. All modelling, control design, and simulations are performed in MATLAB, and results indicate that a PSO-based MPC offers satisfactory response and rapid convergence, achieving effective tracking and disturbance rejection, with the study assuming precise drug dosing is feasible and demonstrates substantial tumor-size reduction through the integration of MPC with metaheuristic optimization. Simulation findings reveal that the PSO-based MPC achieved notable improvement in tumor reduction and overall control performance, outperforming other metaheuristic approaches, as evidenced by comparative error metrics: ITAE $\approx 1.9377 \times 10^3$, IAE ≈ 244.45, MSE $\approx 4.6863 \times 10^3$.

Keywords. Model predictive control, Melanoma cancer, Tumor growth control, Biomedical control systems, Metaheuristic optimization.

MSC. 90C34; 90C40.

1 Introduction

Cancer typically arises when the regulatory mechanisms that control growth and cell division fail. This functional defect results from genetic damage, often caused by chemicals, hormones, and sometimes viruses [6]. Melanoma is the most common form of skin cancer, and malignant melanoma accounts for about 2% of all cancers [27]. However, studies indicate it is responsible for about 1% of cancer deaths. Risk factors for melanoma include white race, extensive sun exposure, family history, genetic predisposition, a prior history of melanoma, immunosuppression, and abnormal moles. Early detection offers the best chance for effective treatment.

People with early-stage melanoma make up about 70-80% of people with melanoma and can be cured by surgically removing the main tumor [34]. However, when melanoma is diagnosed at a later stage, there is a risk of it spreading to the nearest lymph nodes and other parts of the body, including the lungs, liver, bones, and brain, which is called metastasis. This spread occurs through the blood or lymph nodes.

Malignant tumors such as melanoma have many vessels and grow rapidly. In melanoma stem cells, the activity of Notch and Wnt pathways is higher than in normal stem cells, and considering their important role in various cellular processes, any changes in these pathways will lead to changes in cell behavior and lack of cell control and tumor development [39]. Therefore, it seems that targeting these pathways can play an important role in tumor control [21]. Based on research, dual antiplatelet therapy (DAPT) can be a suitable inhibitor for the Notch signaling pathway [25]. Several studies have been conducted on the effective inhibition of the Notch signaling pathway on cancer treatment. These studies show that the use of inhibitors like DAPT can have positive and negative effects on skin cancer treatment, in other words, in some cases DAPT can reduce tumor growth and in some cases, it may lead to disease progression and drug resistance [9, 20, 35, 36]. Therefore, the use of DAPT as an effective inhibitor in cancer treatment is highly dependent on the dose and application treatment plan.

Determining the exact drug dose for each patient is a problem of cancer treatment, which reduces drug side effects and drug resistance. So far, various researchers have used conventional methods of control theory to increase the effectiveness of treatment and reduce side effects. For example, Scagliotti et al., have investigated advanced approaches to the treatment of pharmacological cancer using optimal control [29]. They employ a Lotka-Volterra model to describe the two competing subpopulations. Finally, inspired by numerical evidence, they suggested a type of known adaptive therapy (AT) that is called AT “off - on.” In another paper, a competitive model was developed between drug - sensitive cells and drug - resistant cells in which the pulse intervention was introduced. In addition, based on the optimal pulse control theory, three optimal pulse control strategies were proposed in the cancer treatment process by controlling the interval and pulse dose and minimizing the number of tumor cells at the end of the day at the lowest cost. The results show that the combined control strategy had the best effect [19]. Kova’cs and colleagues investigated the combined treatment of antiviral drugs and minimum dose administration in a short period of time using optimal control for a delay differential equation for hepatitis B [17]. Housman et al. considered drug effectiveness in an optimal control problem for an abstract mathematical model for chemotherapy. The purpose of this research is to investigate the qualitative changes in optimal control structures that occur by changing pharmacometrics models [14]. Nazari Monfared et al considered the minimization of the mean population of cancer cells with mini-

mal drug injection to avoid the destructive side effects of these chemotherapeutic agents [23]. Chhetri and colleagues have investigated the optimal drug methods and the effectiveness of combined therapy in the treatment of COVID-19, and the results show that the drugs reduce the number of infected cells and the viral load in case of single or combined injection [7]. Bachman et al presented and validated an optimal dosing algorithm (optidose) that manages the optimal drug regimen for pharmacokinetic models in different scenarios by solving the optimal control problem [1]. Yazdan Batmani and Khaloozade developed a compartmental model for the proper description of drug resistance and applied two dynamic fitting constraints of anticancer drugs to prevent drug toxicity. The goal is to simultaneously minimize the size of the tumor and the side effects of the anticancer drug, which is defined and solved using two objective functions [3]. Moradi et al presented an adaptive robust control strategy to determine drug consumption and thus tumor volume in chemotherapy and compared and investigated the performance of the uncertainty process in three nonlinear models [22]. Using distributed evolutionary computing software, Tan et al presented the optimal control of drug timing in cancer chemotherapy [31].

Using MPC, Chen et al showed the timing of tamoxifen dose for tumor patients and also investigated the effect of the estimation horizon and the magnitude of the parameter difference. Jeffry et al presented a predictive control algorithm of the nonlinear MPC model for tamoxifen drug injection using the Saturating-rate cell-cycle (SCM) model, which reduces tumor volume in 4 months using animal simulations.

Cancer modeling has been studied from a mathematical perspective for more than four decades. However many cellular processes and special parameters have not yet been presented in modeling, and in fact, mathematical modeling is related to limitations such as the complexity of biological systems. These complications are discussed in different dimensions and sizes such as genes, molecules, cells, tissues, organs, etc. [30]. So far, various methods have been used for the mathematical modeling of cancer, and most of these models have been introduced using ordinary differential equations and in some cases partial differential equations. These models have been presented for tumor treatment, antiangiogenic treatment, chemotherapy, radiotherapy, radiology or a combination of these treatments [2, 8, 11, 13, 18, 28, 33, 38].

Many factors, including drug delivery, patient conditions, and type of treatment may affect the effectiveness of treatment. However, drug resistance is more important than all the mentioned cases [4]. Drug resistance is one of the issues that play an important role in cancer treatment and sometimes prevents the drug from entering the cell. The resistance of cancer cells to different drugs, without structural and functional connection with each other, is still one of the biggest obstacles in the way of chemotherapy. According to the reported studies, drug resistance occurs against any effective and new drug. Therefore, the ability to predict and overcome drug resistance will be very effective in improving treatment. Recent studies emphasize the importance of incorporating advanced control strategies and metaheuristic optimization to personalize chemotherapy dosing, overcoming traditional limitations in fixed-dose administration and drug resistance dynamics ([10, 12, 32])

In the relevant literature, probabilistic and deterministic models have been presented to describe the process of drug resistance in tumors ([3, 16, 22, 24, 37]). In some models, drug resistance has been investigated by dividing tumor cells into drug-resistant and drug-sensitive parts. In some studies, drug resistance has been studied with the concept of the cell cycle [31]. In this paper, a mathematical model of ordinary differential equations is introduced to describe the dynamics of tumor growth in skin cancer in the presence of induced drugs, drug sensitivity and drug resistance are considered in the model, and a new dynamic model of drug resistance is introduced. The parameters of the model are identified based

on data obtained from experiments on mice with tumors treated with DAPT inhibitor. The estimated model is evaluated by comparing experimental data and model outputs. In previous work in this field, the drug dosage amount is an integer multiple of the base amount. Therefore, the allowable amount for dosage in a set is finite. In this paper, our initiative is that instead of the dose value always being considered as an integer multiple of the base value and the allowable value for the dose in a set being limited, we considered the problem as unbounded and non-convex, and we can also in addition to whole numbers, let us also consider fractional numbers of dose injection. The introduction of fractional dosing extends the feasible solution space beyond discrete levels, allowing more precise tailoring of drug amounts to individual tumor response. This fractional flexibility reflects more realistic dosing adjustments in clinical oncology, as evidenced by studies recommending adaptive dose modifications based on toxicity thresholds and pharmacodynamic response ([12, 32]).

The fractional amount of the drug makes the problem non-convex because there may be an infinite number, so we use meta-heuristic algorithms to determine the optimal amount of the drug.

In this paper, a finite set model predictive control (FSMPC) method is proposed for dose adjustment using a guaranteed tumor growth model for any animal model. Using this model, we show whether the DAPT inhibitor was effective in treating mice or exacerbated tumor growth. This study was carried out to improve the efficiency of DAPT drug using a mathematical model. The control design aims to reduce the tumor size in a limited number of days with less injection of DAPT inhibitor.

2 Mathematical Model

In this section, we develop a mathematical model for the growth of melanoma tumor cells that are treated with Notch signaling pathway inhibitors in cancer stem cells. The model is formulated as a system of ordinary differential equations (ODEs). We then incorporate the anticancer drug DAPT through a pharmacokinetic/pharmacodynamic (PK/PD) framework, accounting for both drug sensitivity and drug resistance as factors that can enhance tumor growth under treatment. The tumor dynamics under therapy are organized into three components: (1) the baseline (unrestricted) growth of tumor cells, (2) the drug's effect in reducing growth and the overall therapeutic benefit, and (3) the potential for tumor regrowth and disease recurrence due to drug resistance. These three parts are explained in detail below.

2.1 Dynamics of Normal Tumor Growth

We employ the Gompertz model [15] to describe normal tumor growth dynamics. This model states that, given adequate environmental and nutritional conditions, tumor growth proceeds until access to vital resources becomes limiting, causing the growth rate to decline and the tumor volume to approach a maximum carrying capacity. The Gompertz model is chosen because it accurately captures sigmoidal tumor growth, wherein proliferation slows as the tumor approaches resource limitations, making it particularly well-suited for modeling melanoma progression dynamics [13, 15]. The Gompertz differential equation is stated as follows:

$$y(t) = y \cdot e^{\frac{p}{\beta}\left(1-e^{-\beta t}\right)}, \tag{1}$$

where $y(t)$ is the size of the tumor at time t, $\dot{y}$ is the initial size of the tumor, p, which has a positive value, is the value of the tumor growth rate, and positive β indicates the rate of tumor growth reduction due to the natural death of tumor cells. The Gompertz equation can also be written in the form of the following differential equation:

$$\dot{y}(t) = \alpha y(t) \log\left(\frac{\theta}{y(t)}\right), \tag{2}$$

where $\alpha > 0$ is the value of the tumor growth rate and $\theta > 0$ indicates the maximum accessible size of the tumor [26].

The drug exerts its therapeutic effect by decreasing the tumor growth rate through multiple cellular mechanisms

Pharmacological actions are divided into two groups: pharmacokinetics (PK) and pharmacodynamics (PD). Simply put, pharmacokinetics describes what the body does to the drug, and pharmacodynamics describes what the drug does to the body. Pharmacokinetic data is about the absorption, distribution, metabolism and elimination of drugs in the body. To describe how the drug affects the body when it enters the body, we use a first-order system with the time constant τ_c as follows:

$$\dot{C}(t) = -\frac{1}{\tau_c} c(t) + \frac{k_c}{\tau_c} u(t), \tag{3}$$

where C is the rate of cell death caused by the effect of the drug per unit volume, τ_c and k_c are positive constant parameters. u indicates the prescribed drug rate, which is described as follows:

$$u(t) = \sum_{n=1}^{n_{shot}} A.(t)\, \delta(t - t_n), \tag{4}$$

where $\delta(t - t_n)$ is the impulse function, t_n is the time of drug injection and $A.(t)$ is the amount of drug injected at each time. n_{shot} specifies the number of injections in each treatment, which is different in different models.

3 Drug Resistance

When the drug is administered, in addition to the first-order process described in relation to equation (3) that reduces tumor volume, another process arises that counteracts this reduction under treatment. This opposing process represents the development of drug resistance following injection. Drug resistance is influenced by multiple biological factors and is modeled here using a combination of first- and second-order dynamics to capture its development and evolution. The resistance dynamics are described as follows:

$$\begin{aligned} R(t) &= R_1(t) + R_2(t), \\ \dot{R}_1(t) &= -\frac{1}{\tau_1} R_1(t) + \frac{k_1}{\tau_1} u(t), \\ \dot{R}_2(t) &= -\frac{1}{\tau_2} R_2(t) + \frac{k_2}{\tau_2} R_1(t), \end{aligned} \tag{5}$$

where R is the resistance rate of tumor cells per drug dose unit and τ_1, τ_2, k_1 and k_2 are the time constants and gains related to the drug resistance process, respectively.

In this study, the injection of the anticancer drug DAPT is considered in two ways: intravenous (IV) injection, where the drug is injected directly into the patient's vein, or intratumoral (IT) injection, where the drug is injected locally at the tumor site. Therefore, the described pharmacokinetic model is written for both injections. The two inputs (IT and IV) considered for the model have no effect on the performance and they affect the tumor separately so that if one input is removed, it will not affect the performance of the second input.

According to the pharmacokinetic model described in relations (3) and (5), the complete model of melanoma tumor growth under Notch signaling pathway inhibitor considering the pharmacodynamic model is as follows:

$$\begin{aligned} \dot{y}(t) &= \alpha y(t) \log\left(\frac{\theta}{y(t)}\right) - C_{total}(t)\, y(t) + A(t)\, R_{total}(t), \\ C_{total}(t) &= C_{IT}(t) + C_{IV}(t), \\ R_{total}(t) &= R_{IT}(t) + R_{IV}(t). \end{aligned} \tag{6}$$

Here, $A(t)$ is defined as follows:

$$A(t) = \begin{cases} A.(t_1) & (t_1, t_2) \\ \vdots & \vdots \\ A.(t_{n-1}) & (t_{n-1}, t_n) \\ A.(t_{n-shot}) & (t_{n-shot}, t_{end}) \end{cases} \tag{7}$$

In Equations (6), the terms $A(t)\, R_{total}(t)$ and $C_{total}(t)\, y(t)$ represent, respectively, the drivers of cell death and the drivers of drug resistance. The cell death factor reduces tumor volume, while the drug-resistance factor increases it within the context of the normal tumor growth model. The interaction between these two factors determines the net effect of the treatment on the disease. If the cell-death factor dominates over the drug-resistance factor, the treatment is deemed to have a positive effect. The net impact of the drug on the disease is defined as the difference between these two factors.

4 Model Data

The mathematical model described in the previous section was identified using experimental data from 13 mice. To establish a melanoma tumor model, 2×10^6 A375 cells were injected into the flank of each of the 13 mice. Tumors formed after 5 days, and the animals were randomly assigned to a control group $n = 3$ and a treatment group $n = 10$. Once tumors reached an appropriate size for drug administration (length and width 4–6 mm), treatment commenced. The control group did not receive any drug and tumors were measured daily to establish baseline growth rates and provide a comparative reference for the treated group.

In the treatment group, melanoma-bearing mice received DAPT via intratumoral (IT) and intravenous (IV) injections. For IT administration, the dose was 6.5 mg/kg; for IV administration, the dose was 259.6 mg/kg. The dosing schedule was designed to maintain a correct ratio between routes, and tumor volumes were measured under the supervision of an expert during real-time injections.

Due to progressive deterioration in the animals' condition in both groups, ethical considerations necessitated humane endpoints. All animals were euthanized when predefined criteria were met, limiting the trial to a maximum duration of 16 days cited in the referenced work [15].

5 Designing an Optimal Drug Program

Predictive control was introduced in industrial processes for the first time. This approach is a powerful tool for controlling systems, particularly multi-variable nonlinear systems, and it enables optimal control under varying conditions of the system variables. All model-based predictive control (MPC) methods rely on a system model and form the core of this control strategy, since they are used both to predict the effects of future inputs and to estimate the current state of the process from past states and inputs [5]. Model-based predictive control methods are typically categorized into two groups: continuous-set (or unconstrained) control and discrete-set (or constrained) control. In this framework, the control signal is obtained by optimizing a cost function over a time interval defined by a forecast horizon, which spans from the present time to a future time step.

All predictive control methods can be described according to the approach outlined below and illustrated in Figures 1-2.

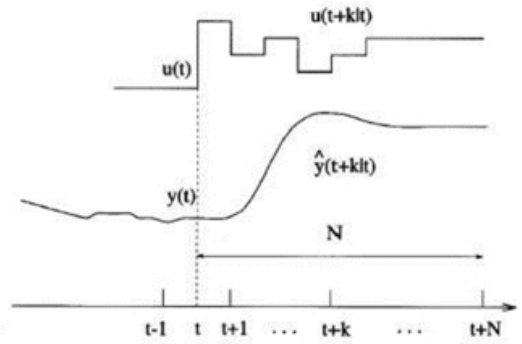

Figure 1: Visualization of future control and output signals in the MPC framework

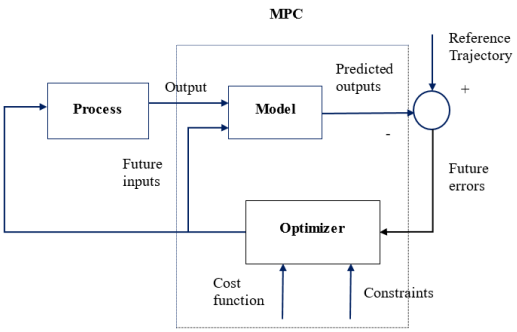

Figure 2: Basic structure in MPC method.

Future outputs for N forecast horizons at each time t are predicted using the process model. These predicted outputs $\hat{y}\,(t+k\,|t\,)$ (variable output value at time $t+k$ calculated at time t) for $k=1,\ldots,N$ depend on the known values of output and input in the past and the control signals in the future time have $u\,(t+k\,|t\,)$ for $k=0,\ldots,N-1$ The control signal in the future time is obtained with the help of optimizing a specific objective function to keep the process as close as possible to the reference path $w\,(t+k)$, which objective function can be a quadratic function of the error between the previous output signal. It is foreseen and the reference path is predicted as well as the control effort.

In general, the structure of predictive control rests on three core concepts: a process model, an objective function, and the cost-minimization process used to derive the control action. The model, which lies at the heart of predictive control, must accurately represent the system dynamics to predict future outputs and facilitate implementation. Because predictive control methods vary, several model types are employed, including impulse-response, step-response, transfer-function, and state-space representations. Among these, the state-space form is particularly common in academic research due to its straightforward expression for stability analysis and other control criteria.

The optimization process is another essential component of predictive control, generating the control signal. When the cost function is quadratic and the model is linear and unconstrained, the optimal solution is obtained in closed form; otherwise, iterative optimization with higher computational demands is required. The size of the optimization problem depends on the number of variables and the length of the forecast horizon.

To implement this method, the basic structure is illustrated in Figure 2. The model forecasts the system output using past inputs and outputs, as well as planned future inputs. The predicted output is compared to a reference, and the resulting tracking error serves as input to the optimizer. The optimizer computes future inputs over the horizon, guided by the cost function and problem constraints.

Predictive control methods differ in their choice of cost functions. The overarching objective is to produce a future output that follows the reference signal within the forecast horizon while minimizing the required control effort. A general expression for such an objective function is given below:

$$J\,(N_1,N_2,N_u)=\sum_{j=N_1}^{N_2}\delta\,(j)\,[\hat{y}\,(t+j\,|t\,)-w\,(t+j)]^2+\sum_{j=1}^{N_u}\lambda\,(j)\,[\Delta u\,(t+j-1)]^2, \tag{8}$$

where N_1, N_2 are the minimum and maximum values of the prediction horizon and N_u is the control horizon. The coefficients δ_j and λ_j, which are usually constant or exponential sequences, are weights to determine the relative importance of reducing the tracking error and minimizing the control effort [5].

In cancer-treatment discussions, predicting how tumor size will change in response to a specific drug dose until the next administration session can be a valuable and distinctive advantage for designing an optimal treatment regimen and assisting clinicians in prescribing a protocol.

In this study, our approach to targeted melanoma treatment prescribes a drug program based on fractional dosing: IT (intratumoral) injections with coefficients in the range $[0,4]$, and IV (intravenous) injections with coefficients in $[0,1]$. The use of fractional doses introduces non-convexity, since there are infinitely many possible values. To obtain an optimal solution, we employ a meta-heuristic optimization algorithm.

- Let input u denote IT administration, varying between 0 and 5 to reflect fractional IT doses.

- Let input ν denote IV administration, ranging from 0 to 1.

The slightly different upper bounds reflect distinct clinical dose scaling for localized versus systemic administration.

Our goal is a general, inclusive optimal solution for melanoma treatment. To this end, we integrate an improved model-predictive control (MPC) framework with a meta-heuristic search to determine effective dosing.

To prevent drug saturation and adverse effects, we impose a rest period of several days between administrations. Specifically:

- After the first measurement of tumor volume (model output), the drug is delivered within the allowed dose set.
- After a few days of rest, tumor volume is measured again and treatment resumes within the allowable dosages.
- This cycle continues through the treatment period, with a daily rest interval.

The rest interval is set to one day, and the optimization problem seeks the daily dose that optimizes tumor reduction on the following day.

Time-limited predictive control has been proposed in the literature [15]. In that framework, multiple modes for inputs U and V are considered, but practical implementations often constrain the number of control modes due to measurement accuracy and injection-device calibration. In our formulation, input u can assume any value in $[0, 5]$, and input ν can take any value in $[0, 1]$, including fractional values. While this makes the problem non-convex with potentially many states, we address it with a predictive-control backbone guided by a meta-heuristic optimization algorithm to determine the optimal daily dose.

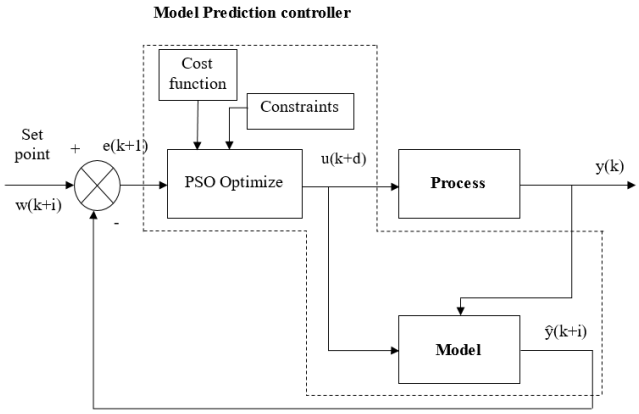

Figure 3: Schematic of predictive control optimized with meta-hurestic algorithms.

To enhance clarity, Figure 4 presents the detailed structure of the PSO-MPC algorithm used in this study, illustrating the iterative optimization and feedback loop used to determine the optimal daily drug dosages. In this work, predictive control is optimized with the aid of GA, DE, PSO, and ABC algorithms [**?**]. The abbreviations used throughout are: PSO, GA, ABC, DE.

The proposed MPC optimization proceeds as follows: the PSO-based controller uses the process model to search for control actions that satisfy process constraints and minimize a cost function. The PSO-driven MPC architecture is depicted in Figure 4.

The MPC-PSO approach can reduce fluctuations and improve the system response. The operation of the PSO-MPC algorithm is described in the steps below:

1. While utilizing the process model, evaluate the process outputs.
2. Perform a PSO search to identify optimal control actions that maximize (or minimize, depending on your cost formulation) the cost function while satisfying the process constraints.
3. Implement the optimal control actions obtained in Step 2 in the process.
4. Repeat Steps 1–3 over time.

6 Results

As the prediction horizon decreases, the system responds more quickly, but the magnitude of the control action (jumps) increases. Here, the horizon refers specifically to the prediction horizon N, which defines the length of the future time window used in the MPC optimization at each decision step. Additionally, we present the standard error metrics: Integral Absolute Error (IAE), Integral Time Absolute Error (ITAE), and Mean Squared Error (MSE).

The output, i.e., tumor volume, is shown in Figure 5, while the drug injection doses determined by the PSO algorithm are shown in Figure 6. The observed tumor regrowth despite ongoing drug administration in Figure 5 reflects the cumulative effect of induced drug resistance dynamics, modeled by a resistance term that gradually reduces drug efficacy over repeated cycles.

In Figure 5, the label "mpc[10]" denotes the reference predictive-control result at day 12. Decimal time points on the axis arise from continuous-time simulations rather than discrete measurement days, yielding non-integer timestamps. This timeline is synchronized with the injection-time axis in Figure 6 via internal model sampling.

Table 1: Control accuracy results for different methods

Method	**ITAE**	**IAE**	**MSE**
DE	1.9448×10^3	244.6927	4.6909×10^3
GA	3.9448×10^3	544.6927	6.6909×10^3
ABC	1.9785×10^3	246.7000	4.7031×10^3
PSO	1.9377×10^3	**244.4500**	4.6863×10^3
Ref. [15]	6.8211×10^3	635.0200	1.8980×10^4

The reference trajectory used for calculating tracking errors is defined as the desired reduction in tumor size towards zero residual tumor volume, serving as the treatment objective during the prediction horizon.

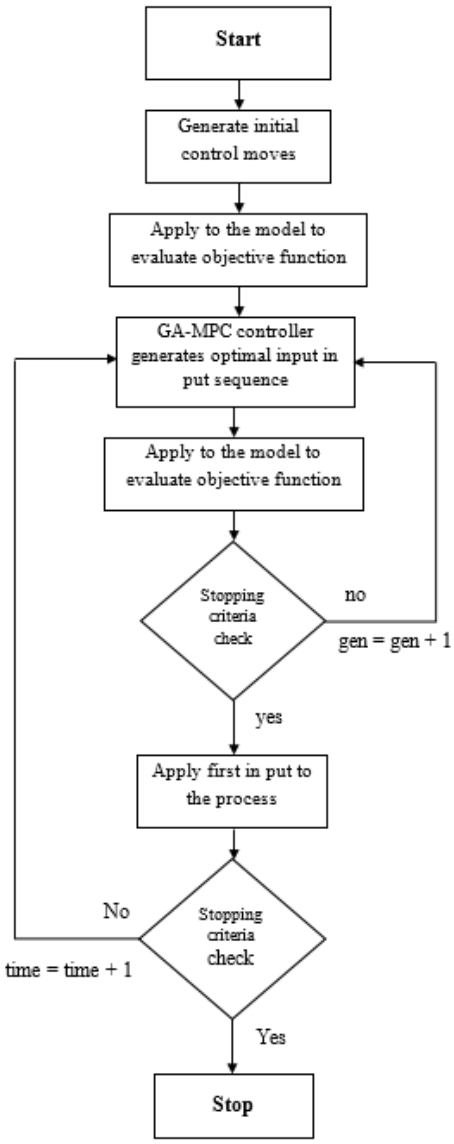

Figure 4: Schematic of predictive control optimized with meta-hurestic algorithms.

The results indicate that the PSO-based MPC performs better than the others optimization methods with the control signal's delay and limit (Table 1). The simulation results achieve the main objectives, and the algorithms perform well. The PSO algorithm not only demonstrated superior accuracy but also achieved faster convergence compared to GA, ABC, and DE, reducing computational burden while maintaining robustness in the presence of nonlinear tumor dynamics.

In a direct comparison among metaheuristic algorithms, all algorithms were executed with the same initial population size. The results showed that the PSO algorithm was able to converge within approximately 150 iterations and reach the final optimal solution, whereas other algorithms required more

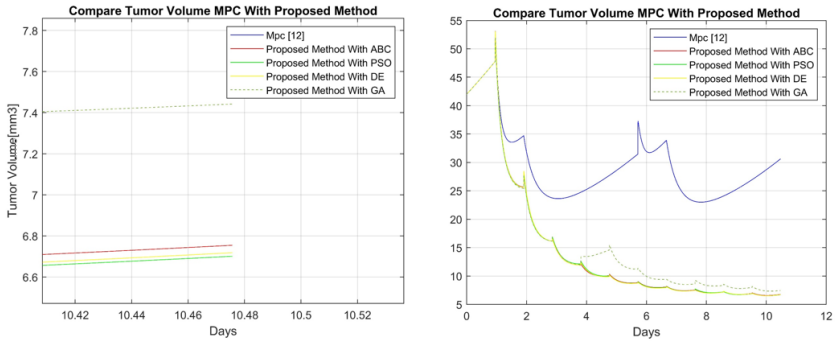

Figure 5: Comparison of tumor size using predictive control algorithms and meta-heuristic algorithms.

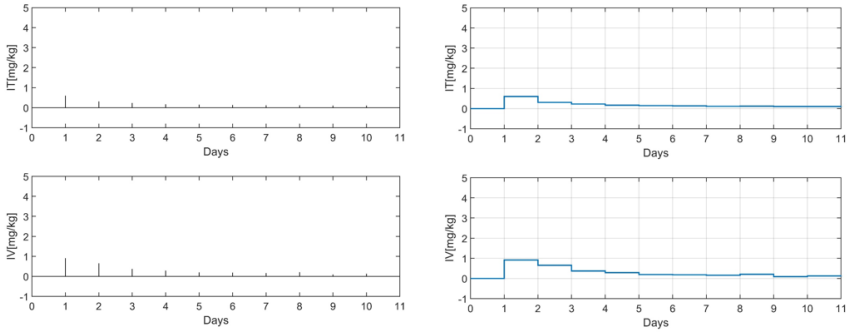

Figure 6: Drug injection dose according to PSO algorithm.

iterations to achieve comparable results and, in some cases, became trapped in local optima. This finding indicates that PSO, in addition to its faster convergence speed, has a greater ability to find solutions close to the global optimum and therefore demonstrates superior performance compared to other algorithms.

Stability and Robustness Analysis

The stability and robustness analysis of the proposed PSO-based Model Predictive Control (MPC) system is of paramount importance to ensure its practical applicability in melanoma cancer treatment. In this study, the MPC approach was designed based on an accurate nonlinear mathematical model of tumor growth, incorporating the dynamics of drug pharmacokinetics, pharmacodynamics, and resistance mechanisms. One of the core advantages of MPC lies in its predictive capability to forecast future tumor states based on current and past observations while optimizing drug dosage within the system's operational and safety constraints. The closed-loop stability of MPC stems from its ability to continuously update control actions at each time step while respecting dose limitations and tumor growth dynamics, preventing system divergence or uncontrolled tumor growth. Furthermore, by incorporating metaheuristic optimization algorithms such as Particle Swarm Optimization (PSO), the system can explore a broader

solution space efficiently, even when the problem is non-convex due to fractional dosage levels, multiple drug administration routes, and complex tumor behavior.

The PSO algorithm enhances robustness by dynamically adjusting drug doses in response to variations in tumor response, patient-specific pharmacokinetic parameters, and unforeseen disturbances, such as sudden changes in drug absorption or metabolism. Since tumor growth models are often subject to modeling inaccuracies and biological variability across patients, the robustness of the proposed controller ensures that satisfactory performance is maintained even in the presence of these uncertainties. Specifically, the PSO optimizer adapts the control input by searching for optimal solutions that minimize the cost function while respecting state constraints on tumor volume and dosage safety limits. This flexibility allows the system to avoid both under-dosing, which may lead to ineffective treatment, and over-dosing, which can result in toxicity or increased resistance development.

The predictive model also accounts for the cumulative effects of drug resistance, where the sensitivity of tumor cells to DAPT diminishes over repeated administrations. The ability of the PSO-MPC framework to adaptively adjust dosage while considering this resistance dynamic contributes to improved robustness against temporal changes in treatment efficacy. The stability of the controller under such conditions is supported by the fact that MPC recalculates optimal inputs at each time horizon based on updated tumor size measurements, thus inherently maintaining the system within safe operational boundaries. Moreover, by incorporating drug holidays (rest periods), the control scheme further mitigates the risk of drug accumulation and supports biological recovery, thereby enhancing long-term stability.

The robustness analysis extends to parameter uncertainties, such as variations in growth rate (α), maximum tumor capacity (θ), drug efficacy (kc), drug resistance dynamics (kr), and time constants ($\tau c, \tau r$). In real-world clinical scenarios, these parameters may vary significantly between patients due to genetic differences, prior treatments, immune system conditions, and tumor heterogeneity. The PSO-based MPC system was tested under parameter perturbations to evaluate its ability to maintain stable control performance despite such variations. Simulation results demonstrated that even with $\pm 20\%$ variation in key model parameters, the PSO-MPC algorithm effectively maintained tumor suppression within the desired limits while avoiding unsafe dosage excursions.

The closed-loop stability analysis in Model Predictive Control (MPC) methods is one of the most fundamental issues with critical importance in both theoretical foundations and practical applications. In the absence of guaranteed stability, any optimization in determining the drug dosage or control policy may lead to divergence, accelerated tumor growth, or even unsafe conditions for the patient. In the present study, our control strategy is based on the Finite-Set Model Predictive Control (FSMPC) framework introduced in the reference article introduced by [15]. In that work, the MPC structure was formulated such that, by considering an appropriate cost function, imposing hard constraints on the state and input variables, and selecting a specific prediction horizon, closed-loop stability is theoretically ensured. The key point here is that in FSMPC, due to the finite and limited decision space (where drug dosage values are defined as a discrete set of possible options), the entire set of choices is evaluated at each time step and the best option is selected. Therefore, the optimization problem has a unique solution, which itself is one of the foundations of stability assurance. In our method, the main MPC structure and its constraints remain unchanged; the only difference lies in the optimization procedure, where instead of exhaustive search, we employed the metaheuristic Particle Swarm Optimization (PSO) algorithm. Thus, the stability guarantees established in the reference work remain valid, since stability in MPC depends

on the model structure, cost function, and constraints, and the choice of optimization algorithm only affects computational efficiency, not the fundamental stability properties.

7 Conclusion

- *Rest Period Determination:* Acknowledging inter-sample heterogeneity in tumor dynamics and drug response, we determine the most appropriate rest interval for each animal specimen. The rest period is selected via a predictive control and optimization framework targeting the final tumor volume at the end of treatment and is held constant throughout the course of therapy. For consistency, the resting interval for drug administration is one day per cycle.
- *Personalized MPC-Based Cancer Therapy:* This paper advances a personalized cancer-treatment paradigm based on model predictive control (MPC) enhanced by metaheuristic optimization. We develop a mathematical model that captures the dynamic behavior of tumor growth, incorporating the impact of drug resistance. The model enables assessment of how the drug regimen influences tumor suppression under control. Model parameters are estimated using recursive least squares (RLS). The MPC framework yields a predicted treatment plan, including dosage schedules.

Despite intrinsic drug resistance in targeted melanoma therapy, simulation results demonstrate that the tumor can be maintained in a controlled state through an optimized pharmacological regimen. The proposed approach achieves substantial tumor reduction while minimizing deleterious effects on healthy tissue.

Declarations

Availability of Supporting Data

All data generated or analyzed during this study are included in this published paper.

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Conflict of Interest

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

Author Contributions

Masrour Dowlatabadi: Conceptualization; Methodology; Formal analysis; Investigation; Software; Writing – original draft; Visualization. Maryam Nikbakht: Methodology; Validation; Resources; Writing – review & editing; Supervision; Theoretical developments; Project administration.

Artificial Intelligence Statement

Artificial intelligence (AI) tools, including large language models, were used solely for language editing and improving readability. AI tools were not used for generating ideas, performing analyses, interpreting results, or writing the scientific content. All scientific conclusions and intellectual contributions were made exclusively by the authors.

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