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Metaheuristics and Pontryagin's minimum principle for optimal therapeutic protocols in cancer immunotherapy: a case study and methods comparison

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Abstract In this paper, the performance appropriateness of population-based metaheuristics for immunotherapy protocols is investigated on a comparative basis while the goal is to stimulate the immune system to defend against cancer. For this purpose, genetic algorithm (GA) and particle swarm optimization (PSO) are employed and compared with modern method of Pontryagin's minimum principle (PMP). To this end, a well-known mathematical model of cell-based cancer immunotherapy is described and examined to formulate the optimal control problem in which the objective is the annihilation of tumour cells by using the minimum amount of cultured immune cells. In this regard, the main aims are: (i) to introduce a single-objective optimization problem and to design the considered metaheuristics in order to appropriately deal with it; (ii) to use the PMP in order to obtain the necessary conditions for optimality, i.e. the governing boundary value problem; (iii) to measure the results obtained by using the proposed metaheuristics against those results obtained by using an indirect approach called forward-backward sweep method (FBSM); and finally (iv) to produce a set of optimal treatment strategies by formulating the problem in a bi-objective form and demonstrating its advantages over single-objective optimization problem. A set of obtained results conforms the performance capabilities of the considered metaheuristics.

Keywords Cancer immunotherapy · optimal control · metaheuristics · particle swarm optimization · genetic algorithm · Pontryagin's minimum principle · forward-backward sweep method.

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1 Introduction

Cancer is still one of the major causes of death in the world and as yet there is not a fully comprehensive knowledge of its appearance and elimination. The necessity of addressing preventive measures, medical research, and more effective treatment strategies has been persistently obvious. It is anticipated that cancer will be the most important obstacle to improving life expectancy in the current century. There has been an estimated 18.1 million cancer cases and 9.6 million cancer deaths in 2018. A detailed status report has been given by Bray et al. (2018).

Patients usually undergo cancer treatments, which are most likely to have the highest degree of effectiveness and the fewest side effects depending on the cancer type and how advanced it is. Surgery, radiation therapy, chemotherapy, targeted therapy, hormone therapy, and immunotherapy are considered as the most important types of treatment. Radiotherapy, chemotherapy, and targeted therapy have made limited progress in recent years (Vrána et al. 2018). However, efforts to investigate more successful treatment strategies have been made through immunotherapy (Kirschner and Panetta 1998; Rosenberg 2014; Tran et al. 2017; Gopalakrishnan et al. 2018; Wilson et al. 2018; Arabameri et al. 2018) and the use of immune system to treat cancer patients has achieved prominence as a successful treatment plan.

Cancer immunotherapy is aimed at engaging the immune system ability to recognize and destroy cancerous cells (Evans et al. 2018). It exploits the fact that cancer cells often have molecules on their surface—the tumour antigens—that may be detected by the immune system. Tumours are antigenic tissues due to their many genetic mutations. This antigenicity is not generally changed into effective immunogenicity. Tumour immunology recognizes antigens and develops strategies to improve antitumour immunity. Recent clinical successes, in the form of several approaches to cancer immunotherapy, support the concept that therapeutic utilization of immune system can actually succeed in important effects on cancer patients (Khalil et al. 2015).

Adoptive cell therapy (ACT) is a type of cancer immunotherapy that refers to the transfer of *activated immune cells* to a patient. T cells (a type of lymphocyte, one of the sub-types of white blood cells) are taken from the patient and cultured in the laboratory with the goal of improving immune functionality, then returned to the patient. For instance, cytotoxic T cells—an example of *effector cells*—become activated and capable of responding to cancer cells. Effector cells are any of different types of relatively short-lived activated cells that defend the body in an immune response. ACT may be accompanied by the administration of Interleukin-2 (IL-2). IL-2 is a type of cytokine (cytokines are molecules, important for basic activities of cells such as development, repair, and immunity) that controls the activities of lymphocytes. It specifically plays essential roles in immune system by direct effects on T cells (Kirschner and Panetta 1998; Rosenberg 2014; Rosenberg and Restifo 2015; Spranger et al. 2017).

In parallel with scientific research on cancer immunotherapy, which leads to important medical advances, the theoretical study of tumour–immune dynamics has provided valuable insights into the cancer–immune interaction. The role of the key components of immunity in cancer dynamics, cancer characteristics, and various factors as immune profiles are theoretically assessed and tumour dynamics (i.e., long term tumour recurrence and short term oscillations) are comprehensively described in mathematical modelling (Kirschner and Panetta 1998; Castiglione and Piccoli 2006; Banerjee and Sarkar 2008; Altrock et al. 2015; Cappuccio et al. 2006; d'Onofrio 2008; Eftimie et al. 2011; Soto-Ortiz and Finley 2016; Kosinsky et al. 2018; Valentinuzzi et al. 2018).

Improvements in efficiency of treatment strategies, however, can be obtained by considering an appropriate optimality criterion to be achieved, where the immuneostimulants and cancer-killing agents consumption is a major concern. The optimality conditions may be derived by employing: (i) the calculus of variations and Pontryagin's minimum principle (PMP) that leads to a nonlinear two-point boundary-value problem (TPBVP) (see Pontryagin et al. 1962); (ii) the method of dynamic programming and solving the Hamilton–Jacobi–Bellman equation (Bellman and Kalaba 1966).

Optimal control theory covers a wide range of methods of obtaining the optimum value of a performance measure. Specifically, these methods may be categorized under three macro-headings:

i. indirect methods in which the calculus of variations is used to determine the optimality conditions. The indirect multiple-shooting and the indirect collocation methods fall into this category;
ii. direct methods in which the optimal control problem is translated into a nonlinear optimization problem by making an appropriate approximation of the state and/or control of the optimal control problem. Direct collocation methods are the most notable approaches to optimal control problems; and,
iii. pseudospectral methods for optimal control (Ross and Karpenko 2012).

Ghaffari and Naserifar (2010) utilize a the well-known cancer-immunotherapy model, introduced by Kirschner and Panetta (1998). They adopt the forward-backward sweep method (FBSM) for solving the optimal control problem. In this paper, the genetic algorithm (GA) and the particle swarm optimization (PSO) are used to provide optimal treatment strategies with the aim of comparing the results with those obtained by Ghaffari and Naserifar (2010), and demonstrating the capability of these metaheuristics.

In the literature, several different optimal control problems are observed which can be categorized according to the objective function, the model used for describing the immune-cancer dynamics, and the method of solving the problem. A detailed literature on optimization problems in cancer immunotherapy is given in Section 2. The Kirschner–Panetta model, used in this paper, is briefly described in Section 3. Section 4 is devoted to the formulation of the single-objective optimal control problem. The GA and the PSO are described in Section 5. Section 6 makes a comparison between the methods used here and the method adopted by Ghaffari and Naserifar (2010). Section 7 is devoted to formulating the problem in the form of a bi-objective optimization problem. Finally, a brief summary of the results are given in Section 8 and the pros and cons of the methods are highlighted.

2 Related literature and contribution of the paper

The literature on optimal control problems in cancer immunotherapy is vast, however, the main body of the works focuses on the indirect methods (Castiglione and Piccoli 2006; Burden et al. 2004; Piccoli and Castiglione 2006; Castiglione and Piccoli 2007; Cappuccio et al. 2007; Pillis et al. 2008; Ghaffari and Naserifar 2010; Ledzewicz et al. 2013; Elmouki and Saadi 2016; Ravindran et al. 2017). Very few works devote their attention to metaheuristics and, in addition, usually introduce a single approach without making comparisons between different methods.

The PMP is the topic of the works by Burden et al. (2004), and Ghaffari and Naserifar (2010). Both papers utilize the Kirschner–Panetta model (see the original paper by Kirschner and Panetta 1998) to produce optimal treatment protocols, where their objective is to simultaneously cope with the volume of cancer cells *during* the therapy and to minimize the total amount of the effector cells used during the treatment. Specifically, Ghaffari and Naserifar (2010) add a payoff term to the objective functional, originally proposed by Burden et al. (2004), in order to minimize the cancer cells at *end* of the treatment. Their optimal solutions turn out to be virtually bang-bang controls, i.e. the optimal controls (the amount of drug as a function of time) switch from upper (lower) bound to the other and are strictly never in between.

The distinguishing feature of the contributions made by Castiglione and Piccoli (2006), Piccoli and Castiglione (2006), Castiglione and Piccoli (2007), and Cappuccio et al. (2007) is that the drug administration is considered as a set of instant injections during a particular period of treatment. In fact, the impulsive control function is defined as the sum of finite number of Dirac delta functions representing N injections (of u_i amount of drug at time t_i). They employ the so-called needle variations (originally used by Pontryagin and his colleagues to prove the PMP) and establish their propositions in order to compute the derivatives of the objective function with respect to its variables t_i and u_i. Thus the optimal control problem is translated into a minimization problem that can be solved by using any numerical scheme such as steepest descent method. Castiglione and Piccoli (2006) minimize the final value of tumour mass, and then, Piccoli and Castiglione (2006) add another term in order to minimize the time period during which the cancer cells are above a fixed threshold, and finally, Cappuccio et al. (2007) take this approach and (at the same time) minimize the final tumour mass, the integral cost of tumour exceeding a fixed maximum, the total amount of drug.

A direct collocation method is employed by Pillis and Radunskaya (2003). The authors' aim is to minimize the tumour mass during and at the end of treatment. Minelli et al. (2011) formulate two (continuous and discrete) optimal problems, where the goal is to minimize both the cancer cells at the final time and the total amount of the medicine. The idea of the authors is the use of direct transcription and collocation method for the solution of continuous problem, and the use of direct transcription and multiple-shooting method for the discrete control problem.

Houy and Grand (2019) take the cancer-immune model introduced by Soto-Ortiz and Finley (2016). Their objective is to design an optimal course of immune cell injections in order to eradicate the tumour over a 4000-day period. The authors shift the focus onto a heuristic approach, i.e. the Monte Carlo tree search algorithm—a method for finding optimal decisions in a given domain by taking random samples in the decision space (see the article by Browne et al. 2012)

Finally, the GA is the approach, adopted by Lollini et al. (2006), Pennisi et al. (2009), Kiran and Lakshminarayanan (2013), and Qomlaqi et al. (2017), in dealing with cancer therapy. Lollini et al. (2006) use the immune-cancer model proposed by Celada and Seiden (1992) while their goal is to attain the minimum number of drug injections in a 400-day period of treatment to completely eliminate the tumour. Kiran and Lakshminarayanan (2013) formulate a multi-objective optimization problem. They integrate chemotherapy with immunotherapy to determine what schedule (time and dosage of injections) and which type of therapy could be more successful in taking control of tumour evolution. The authors use a version of GA, called non-dominated sorting genetic algorithm II (NSGA-II), a method devised by Deb et al. (2002) for dealing with multi-objective optimization problems. NSGA-II is also used by Batmani and Khaloozadeh (2013) for presenting an optimal treatment strategy, and coping with drug resistance and side effects.

In contrast to the works presented in the literature, which are mainly based on employing only a single method, the results obtained in this paper are based on exploiting the characteristics of two metaheuristics in order to provide a comparison with the results obtained by using the FBSM and to challenge the validity of proposed solutions.

Regarding the obtained solutions, the main aspects of contributions, made in this paper, are as follows:

i. in order to sufficiently employ the GA, the optimal control problem is translated to a discrete binary-valued problem;
ii. single-point, two-point, and uniform crossover are simultaneously used to ensure exploration-exploitation utility in parallel with each other;
iii. different to the simple GA that suffers the so-called premature convergence, in this paper, the GA is specially designed to preserve the population diversity (Pandey et al. 2014);
iv. unlike the original PSO, introduced by Kennedy and Eberhart (1995), the constriction coefficients (Clerc and Kennedy 2002) are employed and properly defined in order to induce the swarm to display exploration (versus exploitation) tendency and converge on optimum solutions;
v. the optimal therapeutic protocols are enhanced by formulating the problem in a bi-objective form.

3 The Kirschner–Panetta model

In this section, the fundamental elements of Kirschner–Panetta model, introduced originally by Kirschner and Panetta (1998), are detailed:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = cy - \mu_2 x + \frac{p_1 x z}{g_1 + z} + s_1, \tag{1a}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = r_2 y \left(1 - by\right) - \frac{axy}{g_2 + y}, \tag{1b}$$

$$\frac{\mathrm{d}z}{\mathrm{d}t} = \frac{p_2 x y}{g_3 + y} - \mu_3 z + s_2, \tag{1c}$$

with initial conditions:

$$x\left(0\right) = x_0,\; y\left(0\right) = y_0,\; z\left(0\right) = z_0. \tag{1d}$$

Table 1: Parameters in (1) and their units/descriptions; IU: International Unit (standard measure of IL-2), L: Litre.

Parameter	Value	Unit	Description
c	$0 \le c \le 0.05$	day^{-1}	The antigenicity of tumour; larger values of c represent well recognized antigens
μ_2	3.00×10^{-2}	day^{-1}	Multiplicative inverse of the natural lifespan for effector cells
p_1	1.245×10^{-1}	day^{-1}	Proliferation rate of effector cells estimated by using experimental data (see Kuznetsov et al. 1994)
g_1	2.00×10^{7}	IU.L^{-1}	Threshold for proliferation of effector cells stimulated by IL-2
s_1		cell.day^{-1}	External source of effector cells
r_2	1.80×10^{-1}	day^{-1}	The logistic growth rate of tumour cells in the absence of an immune response
b	1.00×10^{-9}	cell^{-1}	Multiplicative inverse of the tumour's carrying capacity
a	1.00	day^{-1}	Immune system's strength to eliminate cancer cells
g_2	1.00×10^{5}	cell	Threshold for cancer removal
p_2	5.00	$\text{IU.L}^{-1}\text{.cell}^{-1}\text{.day}^{-1}$	production rate of IL-2
g_3	1.00×10^{3}	cell	Threshold for production of IL-2 due to the interaction between cancer cells and effector cells
μ_3	1.00×10^{1}	day^{-1}	Multiplicative inverse of the lifespan for IL-2
s_2		$\text{IU.L}^{-1}\text{.day}^{-1}$	External source of IL-2

Table 1 provides a brief description of the parameters in (1). The proposed model presents the immune-tumour dynamics by defining three populations: (i) x indicates

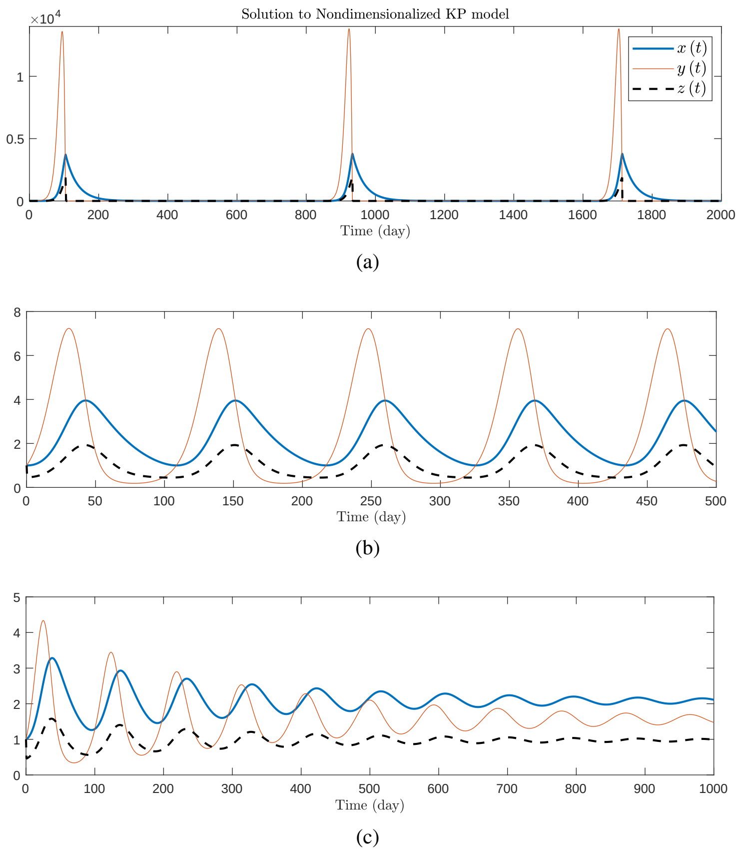


Fig. 1: Solutions to nondimensionalized Kirschner–Panetta model for different values of c. The tumour carrying capacity is scaled to $10^5\,(\text{cell})$. (a) $c = 1.00 \times 10^{-2}\,(\text{day}^{-1})$; (b) $c = 2.97 \times 10^{-2}\,(\text{day}^{-1})$; (c) $c = 4.00 \times 10^{-2}\,(\text{day}^{-1})$.

the effector cells (effectors); (ii) y shows the cancer cells; and (iii) z represents the IL-2. The model incorporates the most important concepts of tumour-immune dynamics including the feature of IL-2, and is able to show both tumour regression for a highly antigenic tumour (i.e. larger values of c; see Table 1) and uncontrolled tumour growth for a low antigenic tumour.

Furthermore, according to (1):

1. equation (1a) depicts the rate of change of effector cells over time. Specifically,
   i. effectors grow in the presence of tumour cells (the first term on the right-hand side of (1a)), where parameter c shows the antigenicity of the tumour. Larger values of c denote well-recognized antigens;
   ii. the third term on the right-hand side of (1a), which is of Michaelis-Menten form, indicates effector cell proliferation, stimulated by IL-2;
   iii. s_1 denotes the administration of effector cells as an external source of medicine;

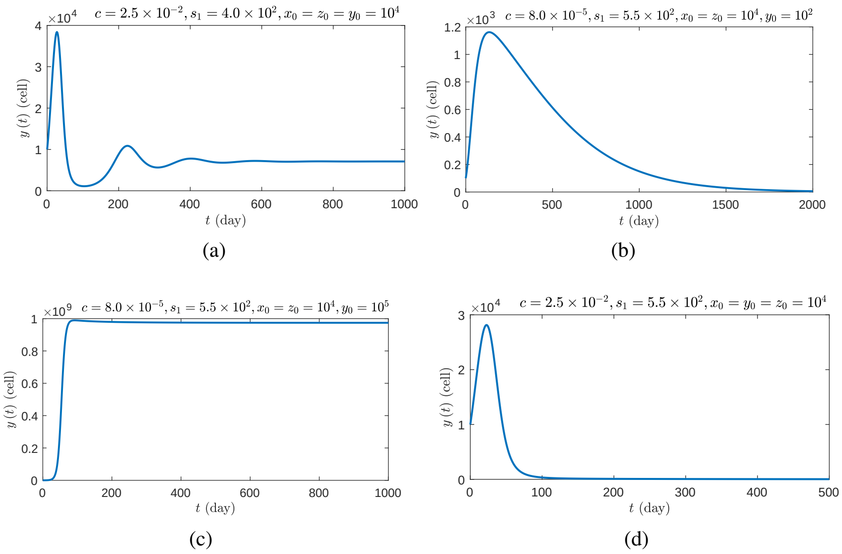


Fig. 2: Graph of $y(t)$ for ACT therapy (i.e. $s_1 \neq 0$, $s_2 = 0$). (a) $c = 2.5 \times 10^{-2}\,(\text{day}^{-1})$, $s_1 = 4.0 \times 10^2\,(\text{cell/day})$, $x_0 = 1.0 \times 10^4\,(\text{cell}), y_0 = 1.0 \times 10^4\,(\text{cell}), z_0 = 1.0 \times 10^4\,(\text{IU.L}^{-1})$; (b) $c = 8.0 \times 10^{-5}\,(\text{day}^{-1})$, $s_1 = 5.5 \times 10^2\,(\text{cell/day})$, $x_0 = 1.0 \times 10^4\,(\text{cell}), y_0 = 1.0 \times 10^2\,(\text{cell}), z_0 = 1.0 \times 10^4\,(\text{IU.L}^{-1})$; (c) $c = 8.0 \times 10^{-5}\,(\text{day}^{-1})$, $s_1 = 5.5 \times 10^2\,(\text{cell/day})$, $x_0 = 1.0 \times 10^4\,(\text{cell}), y_0 = 1.0 \times 10^5\,(\text{cell}), z_0 = 1.0 \times 10^4\,(\text{IU.L}^{-1})$; (d) $c = 2.5 \times 10^{-2}\,(\text{day}^{-1})$, $s_1 = 5.5 \times 10^2\,(\text{cell/day})$, $x_0 = 1.0 \times 10^4\,(\text{cell}), y_0 = 1.0 \times 10^4\,(\text{cell}), z_0 = 1.0 \times 10^4\,(\text{IU.L}^{-1})$.

   iv. effectors naturally decay with an average lifespan of $1/\mu_2\,(\text{day})$;
2. the rate of change of tumour cells is governed by (1b):
   i. the first term on the right-hand side of (1b) illustrates that in the absence of any immune response, the growth of cancer cells follows the sigmoid function, i.e. the solution to the logistic differential equation: $\dot{y} = r_2 y(1 - by)$, where the tumour's carrying capacity is equal to $1/b = 10^9\,(\text{cell})$; and,
   ii. the second term indicates the interaction of cancer cells with the effectors where the tumour growth is brought under control;
3. equation (1c) governs the IL-2:
   i. the first term on the right-hand side of (1c) shows the natural production of the IL-2 due to the interaction between effectors and tumour;
   ii. the second term indicates the decay of IL-2 with an average rate equal to $1/\mu_3\,(\text{day})$; and finally,
   iii. s_2 denotes the dose of IL-2 per day as an external administration.

The Kirschner–Panetta model is capable of exploring three different treatment possibilities: (i) ACT therapy, i.e. $s_1 > 0$, and $s_2 = 0$; (ii) IL-2 therapy ($s_1 = 0$, and $s_2 > 0$); and (iii) combined treatment, i.e. $s_1 > 0$, and $s_2 > 0$.

If untreated ($s_1 = s_2 = 0$), it is impossible for immune system to eliminate the cancer cells. This case is illustrated in Fig. 1, where (depending on the different values of parameter c) the long term tumour recurrence and short term oscillations can be observed. Specifically: (i) for $8.6 \times 10^{-5} \le c \le 3.25 \times 10^{-2}$ the solutions to (1) are stable limit cycles with different period and amplitude dependent on the value of c (see Fig. 1a and Fig. 1b); and (ii) for $c \ge 3.25 \times 10^{-2}$ the oscillations become smaller and settle quickly on a stable steady state.

ACT therapy may leads to totally different conditions. Roughly speaking,

i. an injection of effector cells less than the critical value $s_{1,cr} = (r_2 g_2 \mu_2)/a = 540 \left(\text{cell.day}^{-1}\right)$ fails to completely eradicate cancer cells. This case is shown in Fig. 2a;
ii. for lower values of c, injections more than the critical value (i.e. $s_1 \ge s_{1,cr}$) lead to a region of bistability, i.e. (dependent on the initial conditions) the system tends to either a stable tumour-free steady state or a tumour survival (see Fig. 2b and Fig. 2c);
iii. for larger values of c and $s_1 \ge s_{1,cr}$, the system will definitely tends to a stable (free of tumour) steady state. Fig. 2d illustrates this last case.

Treatment by only using IL-2 does not significantly vary the dynamics of the system. Thus, it would be impossible for IL-2 therapy to result in the removal of cancer cells. Although too much use of IL-2—more than the critical value $s_{2,cr} = (\mu_2 \mu_3 g_1)/(p_1 - \mu_2) \approx 63.5 \times 10^6 \left(\text{IU.L}^{-1}.\text{day}^{-1}\right)$—may theoretically lead to the elimination of cancer cells, it will, in turn, cause an uncontrollable increase in effectors and damaging side effects.

Finally, a treatment strategy, based on the administration of effectors and IL-2 in combination, boosts immune system's chances of eliminating the tumour. And again, the dosage of IL-2 must be restricted to $s_{2,cr}$ in order to prevent harmful side effects. In comparison with ACT therapy, cancer cells with a smaller value of c even, can be eradicated by using lower amount of injected effectors. The adequate explanation is that the administration of IL-2 (with any value less than $s_{2,cr}$) makes a reduction in the amount of injected effectors required to eliminate cancer cells, i.e. the tumour-free steady state will be stable while $s_2 < s_{2,cr}$ and $s_1 > \frac{(\mu_3 g_1 + s_2) - \frac{p_1 s_2}{\mu_2}}{(\mu_3 g_1 + s_2)} \times s_{1,cr}$. Fig. 3 demonstrates how an administration of IL-2 in combination with effectors provokes a better response.

4 Description of the optimal control problem

First, a few basic concepts of the optimal control theory, restricted to systems described by ordinary differential equations, are recalled. Then, the optimal control problem of cancer immunotherapy is formulated by referring back to Kirschner–Panetta model.

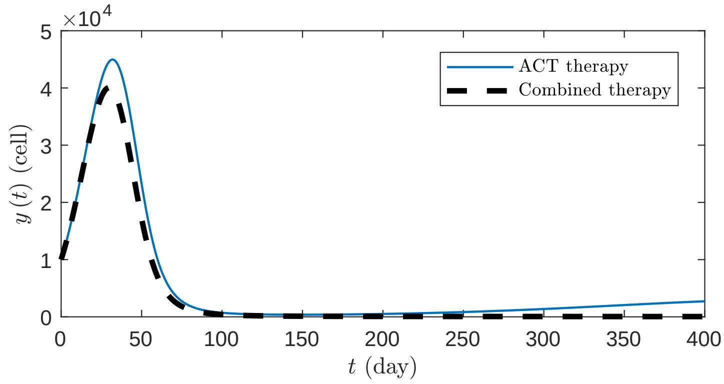


Fig. 3: A comparison of $y(t)$ in: (i) ACT therapy ($s_1 = 500\,(\text{cell/day})$ and $s_2 = 0$) and (ii) combined therapy ($s_1 = 500\,(\text{cell/day})$ and $s_2 = 4.0 \times 10^6 \left(\text{IU.L}^{-1}\right)/\text{day}$); in both cases: $c = 1.8 \times 10^{-2} \left(\text{day}^{-1}\right)$, $x_0 = y_0 = 1.0 \times 10^4(\text{cell})$, and $z_0 = 1.0 \times 10^4 \left(\text{IU.L}^{-1}\right)$.

4.1 A review of the fundamental concepts

Given the system:

$$\begin{cases} \dot{\mathbf{x}} = \mathbf{f}\left(\mathbf{x}(t), \mathbf{u}(t), t\right), \\ \mathbf{x}(0) = \mathbf{x}_0, \end{cases} \tag{2}$$

a measure (in Bolza form) of quantitatively evaluating the system's performance may be defined as:

$$J(\mathbf{u}) = h\left(\mathbf{x}(t_f)\right) + \int_0^{t_f} g\left(\mathbf{x}, \mathbf{u}, t\right) \mathrm{d}t, \tag{3}$$

where $\mathbf{x}^T = (x_1, x_2, \ldots, x_n) \in X \subset \mathbb{R}^n$ is the state vector, $\mathbf{u}^T = (u_1, u_2, \ldots, u_m) \in U \subset \mathbb{R}^m$ is the control input vector (X and U denote the set of admissible state trajectories and the set of admissible controls respectively), $\mathbf{f}^T = (f_1, f_2, \ldots, f_n)$ is a continuously differentiable vector-valued function (in all its arguments), h is a differentiable scalar function, and finally g is a continuously differentiable function in its arguments.

The first term on the right-hand side of (3) indicates a function value on the boundary called the *payoff* term, while the second term, the integral functional, represents the performance of the system over the entire time interval: $[0, t_f]$. The system follows some state trajectory when a control input is applied, and performance measure $J(\mathbf{u})$ assigns a unique real number to the state trajectory. Thus an optimal control problem may be described as: find an admissible control $\mathbf{u}^* \in U$ (and the corresponding admissible trajectory $\mathbf{x}^* \in X$) that minimizes the performance measure $J(\mathbf{u})$:

$$\min_{\mathbf{u}} J(\mathbf{u}), \tag{4a}$$

subject to:

$$\dot{\mathbf{x}} = \mathbf{f}\left(\mathbf{x}\left(t\right), \mathbf{u}\left(t\right), t\right), \tag{4b}$$
$$\mathbf{x}\left(0\right) = \mathbf{x}_0, \tag{4c}$$
$$\mathbf{u}\left(t\right) \in U, \text{for all } t \in \left[0, t_f\right]. \tag{4d}$$

The constraint in (4b) can be transferred to the objective functional, $J\left(\mathbf{u}\right)$, by introducing Lagrange multiplier $\boldsymbol{\lambda}^T\left(t\right) = \left(\lambda_1\left(t\right), \lambda_2\left(t\right), \ldots, \lambda_n\left(t\right)\right)$ (also called the co-state vector) :

$$J\left(\mathbf{u}\right) = h\left(\mathbf{x}\left(t_f\right)\right) + \int_0^{t_f} \Big(g\left(\mathbf{x}, \mathbf{u}, t\right) + \boldsymbol{\lambda}^T\left(t\right)\left(\mathbf{f}\left(\mathbf{x}, \mathbf{u}, t\right) - \dot{\mathbf{x}}\right)\Big)\, \mathrm{d}t.$$

After defining the Hamiltonian function

$$H\left(\mathbf{x}, \mathbf{u}, \boldsymbol{\lambda}, t\right) = g\left(\mathbf{x}, \mathbf{u}, t\right) + \boldsymbol{\lambda}^T\left(t\right)\mathbf{f}\left(\mathbf{x}, \mathbf{u}, t\right), \tag{5}$$

a simple version of the PMP gives the necessary conditions for $\mathbf{u}\left(t\right)$ to be *potentially* an optimal control, where the terminal time t_f and the terminal state $\mathbf{x}\left(t_f\right)$ are considered to be fixed and free (not restricted) respectively: let $\mathbf{u}^* : \left[0, t_f\right] \rightarrow U \subset \mathbb{R}^m$ be an optimal control, and let $\mathbf{x}^* : \left[0, t_f\right] \rightarrow X \subset \mathbb{R}^n$ (and $\boldsymbol{\lambda}^*$) be the corresponding optimal state (and co-state) trajectory. Then the optimality set (i.e., $\mathbf{u}^*$, $\mathbf{x}^*$, and $\boldsymbol{\lambda}^*$) satisfies simultaneously the set of the following conditions:

i. the state equation:

$$\frac{\mathrm{d}\mathbf{x}^*}{\mathrm{d}t} = \frac{\partial H}{\partial \boldsymbol{\lambda}}\left(\mathbf{x}^*, \mathbf{u}^*, \boldsymbol{\lambda}^*, t\right), \quad \forall t \in \left[0, t_f\right], \tag{6}$$

with initial conditions on the state vector:

$$\mathbf{x}^*\left(0\right) = \mathbf{x}_0; \tag{7}$$

ii. the co-state equation:

$$\frac{\mathrm{d}\boldsymbol{\lambda}^*}{\mathrm{d}t} = -\frac{\partial H}{\partial \mathbf{x}}\left(\mathbf{x}^*, \mathbf{u}^*, \boldsymbol{\lambda}^*, t\right), \quad \forall t \in \left[0, t_f\right], \tag{8}$$

with terminal conditions on the co-state vector (transversality conditions):

$$\boldsymbol{\lambda}^*\left(t_f\right) = \frac{\mathrm{d}h}{\mathrm{d}\mathbf{x}}\left(\mathbf{x}^*\left(t_f\right)\right); \tag{9}$$

iii. optimality condition (i.e. the optimal control $\mathbf{u}^*$ minimizes the Hamiltonian function):

$$H\left(\mathbf{x}^*, \mathbf{u}^*, \boldsymbol{\lambda}^*, t\right) \leq H\left(\mathbf{x}^*, \mathbf{u}, \boldsymbol{\lambda}^*, t\right), \quad \forall t \in \left[0, t_f\right], \forall \mathbf{u} \in U. \tag{10}$$

Concerning the minimization of the Hamiltonian function, the inequality in (10) is transformed straightforwardly to $\frac{\partial H}{\partial \mathbf{u}} = 0$, provided that the optimal control $\mathbf{u}^*$ is strictly within the set of admissible controls for all time in the interval $[0, t_f]$ (i.e. not on the boundary). In this case, the boundary does not affect the solution. However, $\frac{\partial H}{\partial \mathbf{u}}$ may not be equal to zero when the optimal control lies on the boundary during a subinterval $[t_1, t_2]$ of the interval $[0, t_f]$. A specific point is raised when U, the set of admissible controls, is composed of scalar piecewise continuous functions $u\,(t)$ such that $a \leq u\,(t) \leq b$ (and $a, b \in \mathbb{R}$). In this case, it can be shown that $\frac{\partial H}{\partial u}$ is non-negative (non-positive respectively) if the optimal control $u^*\,(t)$ lies on the lower boundary a (upper boundary b respectively). A heuristic proof has been given by Lenhart and Workman (2007, section 8). In summary:

$$\begin{cases} u^*\,(t) = a & \text{implies} \quad \frac{\partial H}{\partial u} \geq 0 \ \text{ at time } t, \\ a < u^*\,(t) < b & \text{implies} \quad \frac{\partial H}{\partial u} = 0 \ \text{ at time } t, \\ u^*\,(t) = b & \text{implies} \quad \frac{\partial H}{\partial u} \leq 0 \ \text{ at time } t. \end{cases} \tag{11}$$

4.2 Optimal control applied to Kirschner–Panetta model

In this section, the optimal control problem of cancer treatment is formulated by adopting the PMP approach. Ghaffari and Naserifar (2010) consider a problem for ACT therapy, i.e. effectors are the only external source for treatment ($s_1 > 0$ and $s_2 = 0$). The performance of Kirschner–Panetta model is controlled by the specified objective functional:

$$J\,(\mathbf{u}) = Ay\,(t_f) + \int_0^{t_f} \left(y\,(t) - x\,(t) - z\,(t) + \frac{1}{2} B(u\,(t))^2 \right) \mathrm{d}t. \tag{12}$$

The control input, $u\,(t)$, is the percentage of a fixed amount of s_1 and therefore bounded by $0 \leq u\,(t) \leq 1$. The positive real parameters, A and B, are the weight factors. The payoff term, $Ay\,(t_f)$, refers to the minimization of cancer cells at the final time. The integrand in the second term on the right-hand side of (12) consists of: (i) $y\,(t)$ to minimize the cancer cells during the treatment; (ii) $-x\,(t) - z\,(t)$ to keep the effector cells and IL-2 at a high level; and (iii) the quadratic form, $\frac{1}{2} B(u\,(t))^2$, to minimize the total amount of injected effector cells during the therapy, where the minimization of total used effector cells is B times as important as cancer cells.

For a *fixed* final time and a *free* final state, the problem is considered as follows:

$$\min_{0 \leq u \leq 1} Ay\,(t_f) + \int_0^{t_f} \left(y\,(t) - x\,(t) - z\,(t) + \frac{1}{2} B(u\,(t))^2 \right) \mathrm{d}t, \tag{13a}$$

subject to:

$$\begin{cases} \dfrac{\mathrm{d}x}{\mathrm{d}t} = cy - \mu_2 x + \dfrac{p_1 x z}{g_1 + z} + u\left(t\right) s_1, \\ \dfrac{\mathrm{d}y}{\mathrm{d}t} = r_2 y \left(1 - by\right) - \dfrac{axy}{g_2 + y}, \\ \dfrac{\mathrm{d}z}{\mathrm{d}t} = \dfrac{p_2 xy}{g_3 + y} - \mu_3 z, \end{cases} \tag{13b}$$

$$x\left(0\right) = 1, y\left(0\right) = 1, z\left(0\right) = 1 \tag{13c}$$

The Hamiltonian function is obtained by referring to (5), (13a), and (13b):

$$\begin{aligned} H\left(x, y, z, \lambda_1, \lambda_2, \lambda_3, u\right) = y\left(t\right) - x\left(t\right) - z\left(t\right) + \frac{1}{2} B \left(u\left(t\right)\right)^2 \\ + \lambda_1 \left(cy - \mu_2 x + \frac{p_1 x z}{g_1 + z} + u\left(t\right) s_1\right) \\ + \lambda_2 \left(r_2 y \left(1 - by\right) - \frac{axy}{g_2 + y}\right) \\ + \lambda_3 \left(\frac{p_2 xy}{g_3 + y} - \mu_3 z\right). \end{aligned} \tag{14}$$

This leads to the final formulation of the problem by using (6)-(9), (11), and (14):

$$\frac{\mathrm{d}x}{\mathrm{d}t} = cy - \mu_2 x + \frac{p_1 x z}{g_1 + z} + u\left(t\right) s_1, \tag{15a}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = r_2 y \left(1 - by\right) - \frac{axy}{g_2 + y}, \tag{15b}$$

$$\frac{\mathrm{d}z}{\mathrm{d}t} = \frac{p_2 xy}{g_3 + y} - \mu_3 z, \tag{15c}$$

$$\frac{\mathrm{d}\lambda_1}{\mathrm{d}t} = 1 + \left(\mu_2 - \frac{p_1 z}{g_1 + z}\right)\lambda_1 + \frac{ay\lambda_2}{g_2 + y} - \frac{p_2 y \lambda_3}{g_3 + y}, \tag{15d}$$

$$\frac{\mathrm{d}\lambda_2}{\mathrm{d}t} = -1 - c\lambda_1 - \left(r_2 - 2r_2 by - \frac{a g_2 x}{\left(g_2 + y\right)^2}\right)\lambda_2 - \frac{p_2 g_3 x}{\left(g_3 + y\right)^2}\lambda_3, \tag{15e}$$

$$\frac{\mathrm{d}\lambda_3}{\mathrm{d}t} = 1 - \frac{p_1 g_1 x}{\left(g_1 + z\right)^2}\lambda_1 + \mu_3 \lambda_3, \tag{15f}$$

with boundary conditions:

$$x\left(0\right) = 1,\ y\left(0\right) = 1,\ z\left(0\right) = 1,\ \lambda_1\left(t_f\right) = 0,\ \lambda_2\left(t_f\right) = A,\ \lambda_3\left(t_f\right) = 0, \tag{15g}$$

and the control is characterized by

$$u\left(t\right) = \begin{cases} 0 & \text{if } \lambda_1 \geq 0, \\ -\frac{s_1}{B}\lambda_1 & \text{if } -\frac{B}{s_1} < \lambda_1 < 0, \\ 1 & \text{if } \lambda_1 \leq -\frac{B}{s_1}. \end{cases} \tag{15h}$$

The two-point boundary value problem (TPBVP), obtained above, may be solved by using any of indirect methods such as indirect shooting or collocation methods. However, Ghaffari and Naserifar (2010) adopt the FBSM. Although the method is fully introduced in the book by Lenhart and Workman (2007), for the sake of convenience, a brief description of FBSM will be provided in Section 6.

In the following sections, the GA and the PSO are briefly described and then adopted to solve the problem. Solving this type of problems will generally result in bang-bang solutions, i.e. the optimal control switches periodically from upper bound $u = 1$ to lower bound $u = 0$ (Ghaffari and Naserifar 2010). Thus the inputs in the proposed metaheuristics, can be limited to binary-valued controls (i.e. $u(t) \in \{0, 1\}, \forall t \in [0, t_f]$) and, in turn, represent the total number (and order) of the days with treatment.

Although Ghaffari and Naserifar (2010) state that initial conditions, $x(0)$, $y(0)$, and $z(0)$, are normalized to 1.0, the model is not scaled at all and the primary values (given in Table (1)) are used for the optimal problem. Therefore, those values are also used here in order to make a real and meaningful comparison between the results. This simply means that the problem is solved for non-scaled model with initial conditions equal to 1.0. Nonetheless, the scaled system is used in formulation of the bi-objective optimization problem (see Section 7.4).

5 Metaheuristic approaches

Metaheuristics offer viable alternatives to more traditional algorithms in order to find optimal (or as optimal as possible) solutions for complicated optimization problems when the classic and exact methods fail to carry out the task in a reasonable trial period. A metaheuristic is an algorithmic framework composed of a set of strategies to guide the search process where the goal is to efficiently explore the search space for quasi-optimal (even optimal) solutions. The practical significance of metaheuristics has been grasped in diverse branches of science and engineering such as computational biology, machine learning and data mining, electronics and telecommunications, system modelling, and control. the GA and the PSO are most well-known for their capability of efficiently fitting with a vast range of applications even multimodal and multi-objective optimization problems. In the following sections, the GA and the PSO will be brought in, to observe how the method, used by Ghaffari and Naserifar (2010), deals with the highly nonlinear problem described in (13).

5.1 Genetic algorithm

A GA employs a set of mechanisms inspired by biological evolution together with the genetics-based operators (i.e. crossover and mutation) and is generally used to generate high-quality solutions to optimization problems. The algorithm was initially introduced by Holland (1975) and further developed by Goldberg (1989). Over the past years, different versions of the algorithm have been presented, however, they are all based on the main concepts of the original algorithm. A simple GA begins by creating a random initial population of n solutions (these solutions are often expressed as binary-valued strings) and then creates the next generations (new populations) by performing the following stages:

1. computes the cost function (i.e. the objective function, if the problem is minimization) for each member (individual) of current population and assigns a cost value to each one;
2. some of the best individuals of current generation (i.e. individuals with lower cost values) are passed to the next generation (called *elitist* selection strategy). These individuals are called elites and are n_{elite} in number. The elitist strategy guarantees that the quality of solutions will not decrease during the sequence of new generations;
3. selects individuals called parents to produce new individuals called offspring. Probably, the individuals with better cost values are more likely to be selected in each selection process. The individuals are selected based on sampling with replacement, so that an individual may be selected several times;
4. combines the entries of a pair of selected parents by using *crossover* rules to produce two new offspring, then these offspring are passed to the next generation. Crossover fraction, f_c, specifies the number of crossover offspring, n_c, which are moved to the next generation: $n_c = \texttt{round}\,(f_c \times (n - n_{elite}))$;
5. makes changes to some entries of a single selected parent by using *mutation* rules in order to create new offspring called mutants. The remaining part of the next generation, n_m, is composed of mutants, i.e. $n_m = n - (n_{elite} + n_c)$;
6. the algorithm stops when a stopping criterion is met.

In a simple GA, the search process converges when the genetic nature of the GA operators leads to a uniform generation with (almost) identical individuals. Thus, the operators are no longer capable of producing new offspring superior to their parents. Unfortunately, the population uniformity may occur before finding the true optimum—a common problem with GAs called *premature convergence*. Roughly speaking, the population reaches a sub-optimal position while more successful offspring cannot be produced. It is widely recognized that the intuitive cause of premature convergence is the loss of the diversity of the population, and therefore the use of methods for maintaining population diversity could be a potential strategy to reduce the chance of premature convergence. Crowding methods (replacing similar parents with new offspring) and fitness sharing (penalizing the individuals in densely populated areas), which are well-known approaches to multimodal optimization problems, give promising results in the maintenance of population diversity (see the survey article provided by Pandey et al. (2014)).

In this paper, with regard to a good spread of individuals, a direct approach to diversity preservation is adopted in order to base an estimate on the density of individuals in the population. To this end, the assessment of the distance between an individual and its surrounding individuals is carried out based on the concept of *crowding distance* (inspired by the NSGA-II; see the original work done by Deb et al. 2002).

The proposed GA The algorithm is first initialized by creating a random population of n individuals, then n_c crossover offspring and n_m mutants are produced by choosing any of the crossover patterns and mutation rules respectively. Let N indicate the total of all these parents, crossover offspring, and mutants, i.e. $N = n + n_c + n_m$ and let J_i denote the cost value of the i-th individual where $i = 1, 2, \ldots, N$. The members of the population are first sorted according to their cost values, so that the first and last individuals at the top and bottom of the list correspond to the best (lowest) cost, J_{min}, and the worst cost, J_{max}, respectively. The first $n/2$ of the best individuals are directly moved to the next generation while the remaining individuals are selected based on crowding distance. The crowding distance of each individual is considered an index of the interval covered by that individual in the objective space (range of the cost function). Thus, the i-th individual's crowding distance, d_i, is defined as the normalized *cost* difference between its two nearest individuals on either side. The crowding distances of a population with N individuals are calculated as follows:

$$d_i = \begin{cases} \dfrac{J_{i+1} - J_{i-1}}{J_{max} - J_{min}} & \text{if } i \in \{2, \ldots, N-1\}, \\ \infty & \text{if } i \in \{1, N\}. \end{cases} \tag{16}$$

Individuals with higher amount of crowding distance are far superior to those with lower crowding distance values, and contribute greatly to a more diverse population. Thus the individuals are arranged in descending order of crowding distance and the first $n/2$ of individuals are selected to form the remaining part of the next generation. The crowding distances of the first and last individuals are considered equal to *infinity* in order to be transferred to next generation. A pseudo-code of the proposed GA is given in Algorithm 1 where an I-iteration run is considered the stopping criterion.

Algorithm 1 — Pseudo-code of the proposed GA

Create a random population of n parents, where n is a positive even integer; ▷ **Initialization**
for $i = 1 : n$ **do**
    Compute J_i;
end for
for $i = 1 : I$ **do** ▷ **Iterative phase**
    Produce n_c crossover offspring;
    Produce n_m mutants;
    Merge parents, offspring, and mutants to have a population of $N = n + n_c + n_m$ individuals;
    for $j = 1 : N$ **do**
        Calculate J_j;
    end for
    Sort the merged population according to cost value in ascending order;
    Store the first individual (at the top of the list) as the best solution in current generation;
    Transfer the first $n/2$ individuals to the next generation and remove them from the list;
    for $j = 1 : N - \frac{n}{2}$ **do**
        Calculate the crowding distance of j-th individual, d_j, by using (16);
    end for
    Re-order the remaining $N - n/2$ individuals in descending order of crowding distance;
    Transfer the first $n/2$ individuals to the next generation;
end for
Return the best individual and its corresponding cost value.

Concerning the proposed algorithm, some remarkable points are in order:

1. the algorithm does not require any user-defined parameter for diversity preservation;
2. instead of defining a genotypic difference (bit-wise diversity) measure in the individual space, the distance is evaluated in the objective space;
3. the worst solution, for which the value of crowding distance equates to infinity, is transferred to the next generation to help the population diversity of subsequent generations.

Implementation of the proposed GA for optimal medication regimen The proposed GA, described in Algorithm 1, is implemented by using MATLAB computing environment to assess the cost in (13a) and formulate the optimal ACT strategies. All the parameters of the Kirschner–Panetta model are reported in Table 1. Specifically the following two cases are considered in order to provide a valid (and fair) comparison with the results obtained by Ghaffari and Naserifar (2010):

1. $s_1 = 550\ \left(\text{cell.day}^{-1}\right)$, $c = 0.025\ \left(\text{day}^{-1}\right)$, $A = 10^3$, $B = 1$;
2. $s_1 = 550\ \left(\text{cell.day}^{-1}\right)$, $c = 0.040\ \left(\text{day}^{-1}\right)$, $A = 10^3$, $B = 10^4$.

In both cases the treatment strategies are developed over a 350-day period of time, i.e. $t_f = 350\ (\text{day})$. Each individual represents an input control (a position in the search space), $u = (u_1, u_2, \ldots, u_{350})$, a 350-tuple row vector with binary-valued entries, i.e. $u_i \in \{0, 1\}$ for $i = 1, 2, \ldots, 350$, so that there exist 350 binary decision variables. The cost function takes each individual as an input, then converts it into a piecewise continuous function and calculates the corresponding cost value, J. The crowding distance is calculated for the full population. At the initialization stage the full treatment input ($u_i = 1$ for $i = 1, 2, \ldots, 350$) and null treatment input ($u_i = 0$ for $i = 1, 2, \ldots, 350$) are included in the list of initial population in order to improve the initial diversity and performance of the algorithm. The population size is $n = 200$, the number of crossover offspring and mutants are equal to $n_c = 0.7 \times n$ and $n_m = 0.3 \times n$ respectively, and the algorithm runs over 100 iterations.

5.2 Particle swarm optimization

The PSO is a nature-inspired metaheuristic that arises from interactions and information flow between individuals (or particles) of a population. The population possesses the ability to arrange its particles in a purposeful manner (self-organization). The PSO begins with creating a random population of n particles where each particle finds its position in the search space and carries out a corresponding evaluation of cost function. The search space is *often* (at least in this paper) the d-dimensional real space, $\mathbb{R}^d$, so that a particle's *position* denotes a d-tuple vector $\vec{\mathbf{x}}$ in (a subset of) $\mathbb{R}^d$. During the coming iterations, the i-th particle changes its previous position, $\vec{\mathbf{x}}_i\,(k)$ at k-th iteration, to the new position, $\vec{\mathbf{x}}_i\,(k+1)$, by moving in its new direction (called velocity), $\vec{\mathbf{v}}_i\,(k+1)$, i.e.

$$\vec{\mathbf{x}}_i\,(k+1) = \vec{\mathbf{x}}_i\,(k) + \vec{\mathbf{v}}_i\,(k+1)\,. \tag{17}$$

How the particle moves to the new position is dependent on three factors, i.e. in each step (iteration), the particle tends to move:

1. in its previous direction, $\vec{\mathbf{v}}_i\,(k)$;
2. towards its best previously experienced position, $\vec{\mathbf{b}}_i\,(k)$, up to the k-th iteration;
3. towards the best global position among all particles, $\vec{\mathbf{g}}\,(k)$, up to the k-th iteration.

Thus, the j-th projection (component) of the i-th particle's new velocity is defined as:

$$v_{ij}\,(k+1) = v_{ij}\,(k) + c_1\,r_1\,\left(b_{ij}\,(k) - x_{ij}\,(k)\right) + c_2\,r_2\,\left(g_j\,(k) - x_{ij}\,(k)\right), \quad (18)$$

where $j = 1, 2, \ldots, d$, and b_{ij}, x_{ij}, and g_j denote the j-th component of the vectors $\vec{\mathbf{b}}_i$, $\vec{\mathbf{x}}_i$, and $\vec{\mathbf{g}}$ respectively. Obviously, in the initialization stage the velocity of each particle is equal to zero, i.e. $v_{ij}\,(0) := 0$ for all $i \in \{1, 2, \ldots, n\}$ and $j \in \{1, 2, \ldots, d\}$. The parameters c_1 and c_2, called acceleration coefficients (both of them equal to 2.0 in original version), denote the rates at which the particle deviates from its neighbourhood and moves to the best global position ever found. The coefficients r_1 and r_2 are both random scalars uniformly distributed in the interval $[0, 1]$, in order to include randomness in the movement of the particles.

After the appearance of its original version, the algorithm has undergone marked changes and, in consequence, its overall performance has greatly improved. Bonyadi and Michalewicz (2017), the authors conduct a thorough review of research on PSO and compile a list of articles incorporating considerable modifications into the original algorithm with a primary focus on single objective optimization problems.

The so-called *swarm explosion* is a major problem with the basic PSO. The explosion refers to the particles' velocities and positions speeding towards infinity without control as a result of random weighting parameters in (18). An early solution to moderately tackle the issue of explosion is to restrict v_{ij} to the closed interval $[-V_{max}, V_{max}]$ where the positive real number V_{max} is bounded by $0.1 \times x_{max} \leq V_{max} \leq 1.0 \times x_{max}$, and x_{max} denotes the maximum absolute value of bounds defined for elements of position vector. Another improvement is made by Shi and Eberhart (1998) to assist in the balance between exploration and exploitation aspects of search process. The first part on the right-hand side of (18) provides the exploration of search space; conversely, the other parts cause the swarm to be attracted to the initial best position (greater exploitation of local search data). As a consequence, an *inertia weight*, w, is introduced to balance exploration against exploitation:

$$v_{ij}\,(k+1) = w\,v_{ij}\,(k) + c_1\,r_1\,\left(b_{ij}\,(k) - x_{ij}\,(k)\right) + c_2\,r_2\,\left(g_j\,(k) - x_{ij}\,(k)\right), \quad (19)$$

with a typical inertia range of 0.9–1.2. However, further experiments, conducted on inertia weight, show that a linear reduction in w from 0.9 to 0.4 during a run improves the performance (Eberhart and Shi 2000).

Clerc and Kennedy (2002) provide a mathematical methodology (based on an eigenvalue analysis of the search procedure) to assess stability and convergence of the PSO. The research indicates that the inclusion of appropriately defined *constriction* coefficient, χ, results in the prevention of explosion and an increase in the convergence rate:

$$v_{ij}(k+1) = \chi \left[v_{ij}(k) + c_1 r_1 \left(b_{ij}(k) - x_{ij}(k) \right) + c_2 r_2 \left(g_j(k) - x_{ij}(k) \right) \right],$$
$$\chi = \frac{2}{\left| 2 - \phi - \sqrt{\phi^2 - 4\phi} \right|}, \qquad \phi = c_1 + c_2. \tag{20}$$

The parameter ϕ must be *greater* than 4.0 to prevent the explosion of particles, however, as ϕ increases the diversity of the swarm reduces. Typically, ϕ is set to 4.1 (with $c_1 = c_2 = \phi/2$) in order to guarantee the convergence and to avoid premature convergence. This method is used here to set the PSO parameters and the random perturbation of position is evaluated by using (20).

Implementation of PSO for optimal medication regimen The algorithm is implemented by using MATLAB computing environment for the two previously mentioned cases in Section 5.1 where $\phi = 4.10$, $c_1 = 2.05$, $c_2 = 2.05$, and the constriction factor is therefore equal to 0.729. Each particle represents a piecewise continuous function alternating between 0 and 1. The PSO initializes with creating a random population of 200 particles and ends with completing 100 iterations. Again, the full treatment input ($u(t) = 1$ for all $t \in [0, 350]$) and null treatment input ($u(t) = 0$ for all $t \in [0, 350]$) are included in the list of initial population.

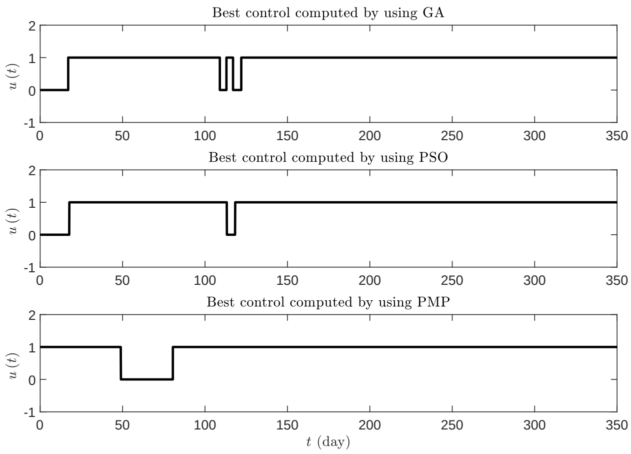
6 Comparison between the GA, the PSO, and the FBSM

Ghaffari and Naserifar (2010), in their approach to the minimization of objective functional (12), focus on the PMP approach that, in turn, leads to generating the boundary value problem (15)—the necessary conditions that the control, the state, and the co-state variables need to satisfy. This boundary value problem can be solved by multiple shooting, indirect shooting, and indirect collocation methods. Ghaffari and Naserifar (2010) solve the problem by using the FBSM (Lenhart and Workman 2007). This method takes advantage of the fact that the values of co-state variables are *not* required to solve the state equations. For convenience, the outline of the method is provided with regard to problem (15):

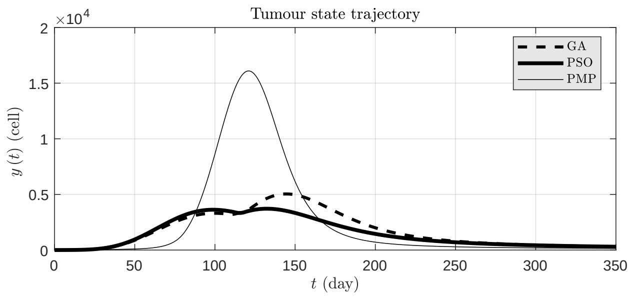
1. make an initial guess for the control input, u, over the interval $[0, t_f]$;
2. use the initial conditions ($x(0) = 1$, $y(0) = 1$, and $z(0) = 1$), and the control, u, to solve the state equations (15a)–(15c), by using any of numerical methods such as the fourth-order Runge–Kutta method. Store the values of state variables, x, y, and z;
3. use the transversality conditions ($\lambda_1(t_f) = 0$, $\lambda_2(t_f) = A$, and $\lambda_3(t_f) = 0$), and the values of state variables, x, y, and z, to solve the co-state equations (15d)–(15f) backward in time, i.e. by integration from final time, $t = t_f$, to initial time, $t = 0$. store the values of co-state variables, λ_1, λ_2, and λ_3;
4. use the co-state variable, λ_1, to update the control, u, by referring to (15h). Store the updated values of control, u;
5. return to (step) number 2, unless a stopping criterion is met. In this case, give the current values of control, states, and co-states as solutions.

Although the method can be easily programmed, it suffers a major problem that is inherent in indirect methods. These methods are very sensitive to the initial guess of unknown conditions or variables (Betts 1998). As stated by Lenhart and Workman (2007, page 50), the FBSM may run into difficulties with *convergence* and therefore the initial guess requires adjusting. While the FBSM requires too many runs in order to find an appropriate initial guess, on the other hand, the GA and the PSO are capable of finding acceptable solutions even by a single run.

Fig. 4 shows (for the first case with $c = 0.025\ (\mathrm{day}^{-1})$) the best controls and corresponding tumour state trajectories obtained by using the GA, the PSO, and the FBSM used by Ghaffari and Naserifar (2010).



(a)



(b)

Fig. 4: The optimal control, $u\,(t)$, and corresponding tumour state trajectory, $y\,(t)$, obtained by using the proposed GA, the PSO, and the FBSM for $c = 0.025\ (\mathrm{day}^{-1})$ and $B = 1.0$; (a) the optimal controls; (b) the tumour state trajectories.

Fig. 5 shows the optimal solutions and corresponding tumour state trajectories for the second case with $c = 0.040\ (\text{day}^{-1})$. For convenience, a brief summary of the obtained results is given in Table 2.

Minimum value of objective functional (12): in case 1, the minimum value of objective function, obtained by using the GA and the PSO, equates to -6.546×10^6 and -6.553×10^6 respectively. On the other hand, the minimum cost value obtained by using the FBSM is equal to -6.203×10^6. Similarly, in case 2, the minimum value of objective function, obtained by using the GA and the PSO is equal to -5.314×10^6 and -5.313×10^6 respectively. This value equates to -4.982×10^6 for the FBSM. In both cases, the minimum values of cost function (12), obtained by the GA and the PSO, are less than those obtained by Ghaffari and Naserifar (2010). These results demonstrate the effectiveness of the proposed metaheuristics (compared to the FBSM) in dealing with the highly nonlinear single-objective problem (13).

In terms of minimum cost, these results show the proposed metaheuristics' capabilities of finding acceptable solutions, compared to the FBSM. This can be considered as a good marker of the effectiveness of these metaheuristics.

Table 2: Minimum values of the cost function (12) and percentage of total days with treatment for case 1: $c = 0.025\ \left(\text{day}^{-1}\right)$, $B = 1.0$, and case 2: $c = 0.040\ \left(\text{day}^{-1}\right)$, $B = 1.0 \times 10^4$, obtained by using the GA, the PSO, and the FBSM used by Ghaffari and Naserifar (2010). y_{end}: cancer cells at the final time; y_{max}: the maximum value of $y\,(t)$; y_{int}: the time integral of $y\,(t)$.

Method	Case 1	Case 2
FBSM	Minimum cost: -6.203×10^6 Days with treatment: 318 $y_{end} = 146(\text{cell})$ $y_{max} = 1.6 \times 10^4(\text{cell})$ $y_{int} = 8.8 \times 10^5(\text{cell.day})$	Minimum cost: -4.982×10^6 Days with treatment: 258 $y_{end} = 113(\text{cell})$ $y_{max} = 1.7 \times 10^4(\text{cell})$ $y_{int} = 1.3 \times 10^6(\text{cell.day})$
GA	Minimum cost: -6.546×10^6 Days with treatment: 320 $y_{end} = 282(\text{cell})$ $y_{max} = 5.0 \times 10^3(\text{cell})$ $y_{int} = 7.2 \times 10^5(\text{cell.day})$	Minimum cost: -5.314×10^6 Days with treatment: 254 $y_{end} = 101(\text{cell})$ $y_{max} = 3.1 \times 10^4(\text{cell})$ $y_{int} = 1.5 \times 10^6(\text{cell.day})$
PSO	Minimum cost: -6.553×10^6 Days with treatment: 324 $y_{end} = 297(\text{cell})$ $y_{max} = 4.7 \times 10^3(\text{cell})$ $y_{int} = 6.1 \times 10^5(\text{cell.day})$	Minimum cost: -5.313×10^6 Days with treatment: 256 $y_{end} = 117(\text{cell})$ $y_{max} = 2.6 \times 10^4(\text{cell})$ $y_{int} = 1.4 \times 10^6(\text{cell.day})$

Final value and the time integral of cancer cells: one major item, which has been considered in the objective functional (12), is the minimization of the final state of tumour cells that is denoted by y_{end} in Table 2. In case 2, the obtained values of y_{end} are rather similar, however, the performance of the FBSM is quite better than metaheuristics. While, in case 1, the FBSM shows a better performance, the metaheuristics

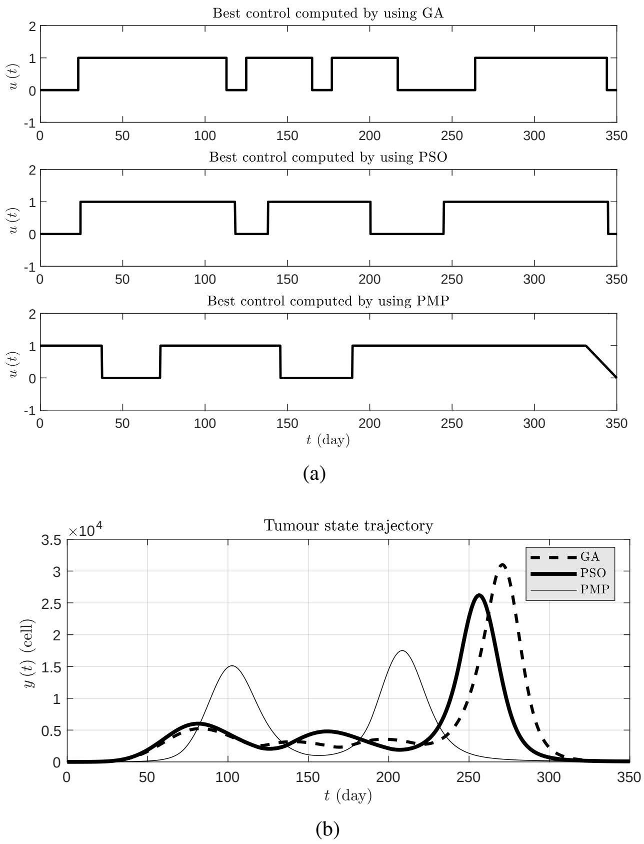


Fig. 5: The optimal control, $u(t)$, and corresponding tumour state trajectory, $y(t)$, obtained by using the proposed GA, the PSO, and the FBSM for $c = 0.040$ (day^{-1}) and $B = 1.0 \times 10^4$; (a) the optimal controls; (b) the tumour state trajectories.

show higher effectiveness compared to the indirect method, however, in case 2, the GA and PSO do not have any particular advantage over the FBSM.

In case 1, the percentage of the total days with treatment is 92% for the GA, 93% for the PSO, and 91% for the FBSM. This means that the total drug usage in the indirect method is less than those of metaheuristics. However, for this method, Fig. 4b shows that the total amount of tumour cells during the treatment is much more than those obtained by using metaheuristics. For the second case in contrast, the percentage of the total days with treatment is 71% for the GA, 72% for the PSO, and 75% for the FBSM, which means that the total amount of the effector cells, obtained by using the metaheuristics, are less than that of the FBSM.

7 Bi-objective optimization problem

The goal of this section is to formulate the problem in a bi-objective form (Deb 2014). In this case, instead of a single solution, a set of optimal solutions is obtained which provides better insight into the problem. Before anything else, a short description of multi-objective problems is provided, then the problem is described and solved by using the NSGA-II, devised by Deb et al. (2002).

7.1 A brief overview of multi-objective optimization problems

A multi-objective optimization problem (MOP) refers to that involving more than one objective function. If $x = (x_1, x_2, \ldots, x_d) \in X$ denotes the decision vector, where X is the set of feasible decision vectors, then the goal is to simultaneously minimize a set of functions $f_1(x)$, $f_2(x)$, ..., $f_k(x)$, which can be considered components of an objective vector $f: X \to \mathbb{R}^k$:

$$\min_{x \in X} f(x) = (f_1(x), f_2(x), \ldots, f_k(x)). \tag{21}$$

There are two euclidean spaces to be considered in MOPs:

1. the d-dimensional space of the decision vector x (called decision space);
2. the k-dimensional space of the objective functions (objective space) in which each coordinate axis corresponds to a component of the objective vector f.

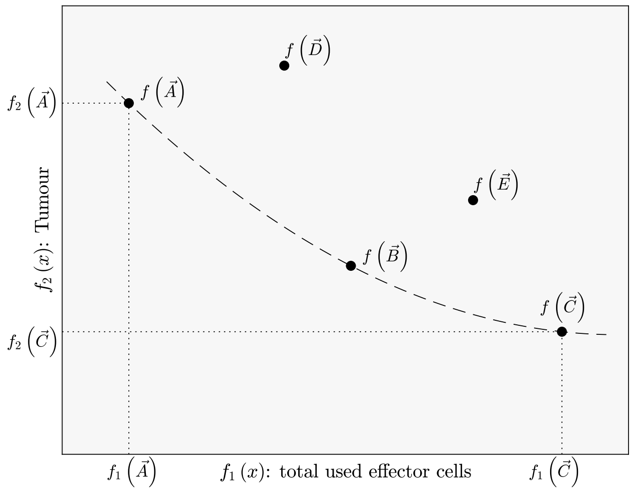


Fig. 6: A schematic diagram of objective space.

The most important thing about MOPs is that decreasing an objective almost (not necessarily) leads to increasing some of other objectives. For example, minimizing the total amount of injected effector cells (as an objective) cannot be achieved without causing a simultaneous increase in the final amount of cancer cells (as another objective). In other words, minimization of total injected drug conflicts with minimization of cancer cells. This example is illustrated by a schematic diagram in Fig. 6. The horizontal axis shows the first objective function (the total drug) and the vertical axis corresponds to the second objective—the tumour cells. Some typical decision vectors (i.e. $\vec{A}, \ldots, \vec{E}$) are mapped onto the objective space. Obviously, *none* of decision vectors $\vec{A}$, $\vec{B}$, and $\vec{C}$ are superior to each other. For instance, vector $\vec{A}$ gives a better cost value of the first objective than vector $\vec{C}$, i.e. $f_1(\vec{A}\,) < f_1(\vec{C}\,)$, but vector $\vec{C}$ gives a lower amount of tumour in comparison to $\vec{A}$, i.e. $f_2(\vec{C}\,) < f_2(\vec{A}\,)$. This is the reason why there is not a unique optimal solution to an MOP and therefore the notion of "optimum" changes. However, the decision vector $\vec{D}$ is not a good candidate, because $f_1(\vec{A}\,) < f_1(\vec{D}\,)$ and $f_2(\vec{A}\,) < f_2(\vec{D}\,)$ (and the so-called term is: "$\vec{A}$ dominates $\vec{D}$"). Similarly, the decision vector $\vec{E}$ cannot be a good choice since dominated by $\vec{B}$.

A decision vector $x \in X$ is said to dominate another vector $y \in X$ (denoted by $x \preceq y$, or $x \operatorname{dom} y$) if and only if $\forall i \in \{1, \ldots, k\}$: $f_i\,(x) \leq f_i\,(y)$ and $\exists j \in \{1, \ldots, k\}$: $f_j\,(x) < f_j\,(y)$, where k is the number of objective functions (see (21)). If there is no $y \in X$ that dominates x, then x is called a *non-dominated* solution. Moreover, a non-dominated solution is an optimal solution—called *Pareto optimal solution*—and (vise versa) if a decision vector is a Pareto Optimal solution, then it is a non-dominated solution. In Fig. 6, vectors $\vec{A}$, $\vec{B}$, and $\vec{C}$ are obviously Pareto optimal solutions. *Pareto optimal set*, denoted by X_p, is defined as the set of all non-dominated solutions. Its corresponding map onto the objective space, $f\,(X_p)$, is called *Pareto front* ($f(\vec{A}\,)$, $f(\vec{B}\,)$, $f(\vec{C}\,)$, and possibly the dashed curve in Fig. 6). Obviously, if a decision vector is found that dominates (for example) the Pareto optimal solution $\vec{A}$, then the decision vector $\vec{A}$ is no longer a Pareto optimal solution and the Pareto front (dashed curve shown in Fig. 6) changes.

7.2 Main approaches to MOPs

The (ideal) goal in MOPs is to (hopefully) identify the true Pareto optimal set (which possibly consists of infinitely many Pareto optimal solutions) but, in practice, this may be impossible. In general, a large and complex search space (and a highly nonlinear system) gives rise to difficulties for traditional methods (for instance, a multiple objective linear program) to be capable of finding the true Pareto optimal set. For many problems, in addition, there generally exists an enormous amount of Pareto solutions (perhaps infinite). In this regard, production of a *finite* set of Pareto optimal solutions as a representative of Pareto optimal set is in order.

A broad category of approaches to MOPs (called "*a priori*" methods) refers to strategies in which the original MOP is converted into a *single-objective* problem. Here, a decision maker (an expert in the problem field) is necessary to be asked for preference information based on which the (single) best solution is found. Weighted sum method, ϵ-constraint method, and goal programming fall into this category.

By contrast, "*a posteriori*" methods tackle the problem as it is (*not* to convert it into a single-objective problem) and produce a representative set of finite Pareto solutions, among which an expert (in the field) chooses the appropriate solution. Normal boundary intersection, and normal constraint belong to "a posteriori" category. A detailed list of MOP methods can be found in the article by Marler and Arora (2004), although other classification methodologies can be observed in the book by Coello et al. (2007).

A redeeming feature of "a priori" methods is that common approaches to single-objective problems can be taken. However, an objective assessment of *weights*, *goals*, and *constraints*, is usually difficult. Even worse, difficulties may arise due to a relative lack of background knowledge. In general, the optimizer attempts to use various sets of weights or constraints to produce a set of Pareto solutions, however, this strategy cannot always lead to a diverse set of solutions. The weighted sum method is, in addition, very sensitive to the configuration of objective domain (non-convex regions may not be discovered in general). Although production of solutions associated with non-convex regions is *not* beyond the capabilities of ϵ-constraint method, a prior knowledge of problem is required to appropriately choose a suitable range of constraints. In "a posteriori" methods, an algorithm has to be repeatedly run in order to find a Pareto optimal solution over each run.

On the other hand, evolutionary algorithms are always being improved. These methods have attracted a lot of attention due to their efficiency and ease of implementation. Coello et al. (2007) provide a thorough and comprehensive review and study of MOPs and multi-objective evolutionary algorithms (such as niched pareto GA, non-dominated sorting GA, and strength pareto evolutionary algorithm). In this work, the proposed problem is solved by using the NSGA-II (Deb et al. 2002). Thus a brief description of the algorithm is provided here for convenience.

7.3 A short overview of NSGA-II

Similar to a simple GA, first of all, a population of n individuals is produced. At each iteration n_c and n_m crossover offspring and mutants are produced where N indicates the total of all parents, crossover offspring, and mutants, i.e. $N = n + n_c + n_m$. The vector of cost functions, $(J_1, \dots, J_d) \in \mathbb{R}^d$, is evaluated for each individual.

All the individuals must be compared to one another in order to realize how many times each individual is dominated by others. A so-called *non-domination rank* is assigned to each individual. The rank of any individual that is not dominated at all is equal to 1. All these individuals, for which the non-domination rank is equal to 1, belong to the first set of Pareto solutions denoted by $\mathcal{F}_1$. If an individual is dominated one time, its non-domination rank is equal to 2 and therefore it belongs to the second set of Pareto solutions, $\mathcal{F}_2$, and so on. In order to easily illustrate how the individuals transfer to the next generations, a population of $n = 50$ individuals is considered. At each generation, the total number of crossover offspring, mutants, and parents is, for instance, equal to $N = 100$.

Fig. 7 shows a representative sample of iterations in which 50 individuals must be selected from 100 members for the next generation. The first two sets of Pareto

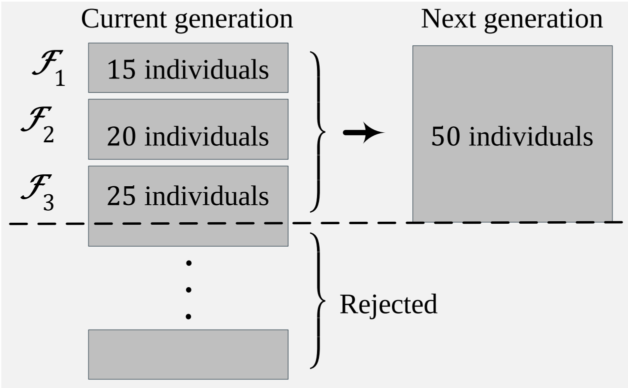


Fig. 7: Selection procedure in NSGA-II.

solutions, namely $\mathcal{F}_1$ and $\mathcal{F}_2$ with a total number of 35 individuals, are definitely selected for the next generation. The remaining 15 individuals must be selected from 25 individuals in $\mathcal{F}_3$. However, the members of $\mathcal{F}_3$ have no particular superiority over one another in terms of non-domination rank. Thus, the members in $\mathcal{F}_3$ are sorted in descending order of crowding distance (see Section 5) and then the best 15 individuals at the top of the list are selected for the next generation.

For each individual, the distance value corresponding to *each* objective must be calculated by using (16). Then, the overall crowding distance of that individual is equal to the *sum* of the distance values corresponding to each objective. In summary, the first priority is selection based on non-domination, and the remaining individuals are chosen based on crowding distance to preserve the diversity of Pareto solutions. Over each iteration, the algorithm improves the quality of solutions and finally the first set of Pareto solutions, $\mathcal{F}_1$, converges on the Pareto optimal solutions.

7.4 Problem statement and results

In Section 4, a single objective problem was considered in the form of the weighted sum of: (i) the total use of effector cells; (ii) the state variables; and (iii) the final value of cancer cells. As stated before, this method (formulation of the problem in a single objective form) has a major disadvantage: it requires various sets of weight values, to produce different optimal treatment plans. This restricts the decision maker to a very limited set of strategies. To cope with this restriction, the performance of the cancer-immune system can be optimized by formulation of a multi-objective problem.

In this regard, the aforementioned problem is now formulated in a bi-objective form. In addition, since the administration of IL-2 plays a major role in improving the immune system performance, the external source of IL-2 will be considered here as the second control input.

The first objective, J_1, is defined as:

$$J_1 = \frac{1}{2\,t_f}\int_0^{t_f}[u_1(t) + u_2(t)]\mathrm{d}t, \tag{22}$$

to minimize the total drugs used during the treatment, where the piecewise continuous control inputs, u_1 and u_2, denote effectors and IL-2, respectively. The second objective is defined as follows:

$$J_2 = \phi\, y(t_f) + (1-\phi)\frac{1}{t_f}\int_0^{t_f} y(t)\mathrm{d}t, \quad \phi \in [0,1], \tag{23}$$

to minimize the cancer cells during the treatment period and, in addition, to minimize the final state of cancer cells. the coefficient ϕ, which is set to 0.3, indicates the importance of minimizing the final state in comparison to minimizing the running cost of state trajectory during the treatment period. This parameter is arbitrary set to 0.3 and is of no clinical significance. In conclusion, the bi-objective problem is described as follows:

$$\min(J_1, J_2),$$

subject to:

$$\begin{aligned}
&\frac{\mathrm{d}x}{\mathrm{d}t} = cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + u_1(t)\, s_1,\\
&\frac{\mathrm{d}y}{\mathrm{d}t} = r_2 y(1 - by) - \frac{axy}{g_2 + y},\\
&\frac{\mathrm{d}z}{\mathrm{d}t} = \frac{p_2 xy}{g_3 + y} - \mu_3 z + u_2(t)\, s_2,\\
&x(0) = 10^4(\text{cell}),\ y(0) = 10^4(\text{cell}),\ z(0) = 10^4\left(\text{IU.L}^{-1}\right),\\
&\forall t \in [0, t_f]:\ u_1(t), u_2(t) \in \{0,1\}.
\end{aligned} \tag{24}$$

A 350-day period is taken into account for treatment, i.e. $t_f = 350\ (\text{day})$. The daily dosage of IL-2 is set to $s_2 = 3.0 \times 10^6\ \left(\text{IU.L}^{-1}.\text{day}^{-1}\right)$—less than the critical amount of IL-2. The daily dosage of effector cells is considered to be equal to the minimum amount that is allowed: $s_1 = 506.9\ \left(\text{cell.day}^{-1}\right)$ (see Section 3 for critical values of s_1 and s_2 in combined therapy).

The model will be normalized such that all the initial conditions, $x(0)$, $y(0)$, and $z(0)$ are equal to 1.0. Thus the consequent changes in the values of the parameters are shown in Table 3. Kirschner and Panetta (1998) give a detailed information on how to normalize the model.

The problem are coded in MATLAB computing environment. Each individual contains two decision vectors corresponding to the control inputs, $u_1(t)$ and $u_2(t)$. Each decision vector, produced by NSGA-II, is defined as a 350-tuple binary-valued vector and then is decoded as a meaningful control input for evaluation of objective functions. The NSGA-II is run over 100 iterations with a population of 200 individuals.

Table 3: Values of the parameters in the normalized Kirschner–Panetta model, used in problem (24).

Parameter	**Value**
c	2.50×10^{-2}
μ_2	3.00×10^{-2}
p_1	1.245×10^{-1}
g_1	2.00×10^{3}
s_1	5.07×10^{-2}
r_2	1.80×10^{-1}
b	1.00×10^{-5}
a	1.00
g_2	1.00×10^{1}
p_2	5.00
g_3	1.00×10^{-1}
μ_3	1.00×10^{1}
s_2	3.00×10^{2}

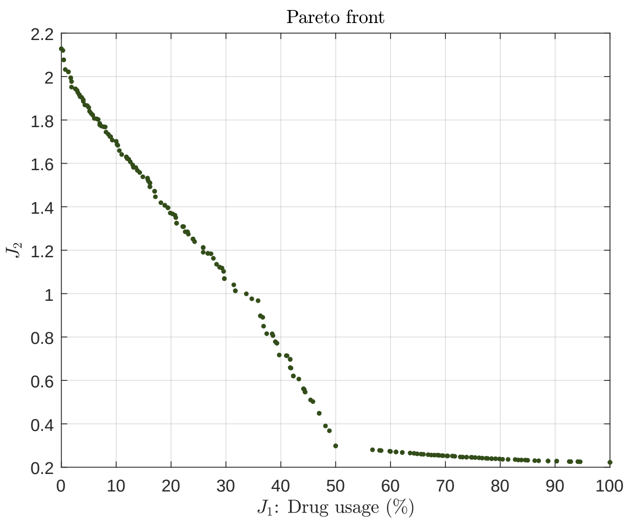


Fig. 8: Pareto front obtained by NSGA-II for the parameter values given in Table 3.

The Pareto front is illustrated in Fig. 8. The horizontal axis is related to the first objective, J_1, and shows the percentage of the total days with treatment. The vertical axis shows the second objective in (23). Each point of Pareto front corresponds to a non-dominated solution. The Pareto front enables the decision maker to observe all possible situations and choose a specific treatment strategy.

As an example, Fig. 9 shows the tumour trajectories, corresponding to 50% and 100% drugs usage, and demonstrates how the combined therapy enhances the immune

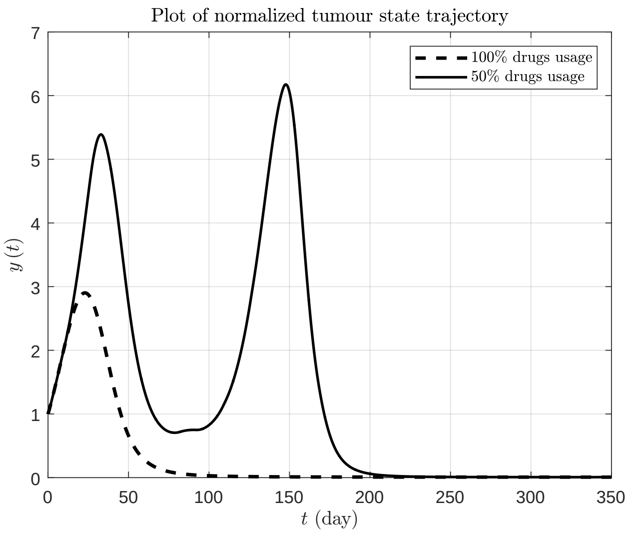


Fig. 9: Tumour state trajectories corresponding to the 50% and 100% drugs usage.

system in comparison with the ACT therapy. Obviously, in the case of 50% drugs usage, the tumour is completely eliminated after 200 days, and the treatment period is reduced to 100 days for 100% drugs usage.

8 Conclusion

The main goal of this work is to examine the performance of an *indirect* method of solving optimal control problems, called forward-backward sweep method (FBSM), in the context of biological systems. For this purpose, the work by Ghaffari and Naserifar (2010) is brought back. They use exactly this method for developing cancer treatment protocols, based on the Kirschner–Panetta model of cancer immunotherapy. The genetic algorithm (GA) and the particle swarm optimization (PSO) are also used along with the aforementioned method, in order to provide an objective assessment of their performance.

The FBSM suffers the difficulties that are inherent in using indirect methods, i.e. the need to make an initial guess at control (or co-state variables, or unknown conditions) and, more importantly, the sensitivity of the method to the initial guess. In other words, a serious problem will arise if the method does not converge to a solution, and consequently, the initial guess requires adjusting over and over again. In actual fact, this is an utterly time-consuming process. This situation becomes even more difficult when the method is used in the context of biological problems. Biological systems are normally difficult to be described in terms of parameters. For example, in the Kirschner–Panetta model, the parameter c is considered as a measure of the tumour antigenicity and therefore cannot have a fixed value for different types of tumours and patients (see Table 1). These different parameter values not only intensify the running costs also could lead to different optimal results.

At the first step, the problem is formulated in a single-objective form. Compared to the FBSM, the metaheuristics appear to be rather more successful in minimizing the cost function (12) and therefore their performance remains competitive with classic methods such as the FBSM. As an important point, it must be mentioned that solutions to the problem of this type are typically bang-bang controls. This means the individuals, in the proposed metaheuristics, can be easily defined as binary-valued vectors, and then, converted into piecewise continuous functions as control inputs. Otherwise, It will be very hard (even impossible) to utilize these metaheuristics for dealing with those problems that their inputs are *not* bang-bang controls. This can be considered as a major disadvantage of the proposed metaheuristics.

At the second step, the optimal problem is formulated in a bi-objective form, where, the IL-2 is also used to enhance the immune system. Formulating the problem in a multi-objective form provides the decision maker with a wide variety of optimal solutions. The bi-objective problem appears to be superior to the single-objective problem, since the decision maker is given the opportunity of observing a set of non-dominated optimal solutions in order to select the most appropriate treatment strategy.

CRediT statement on transparency in authors' contributions

Conceptualization: [Sima Sarv Ahrabi]; methodology: [Sima Sarv Ahrabi]; formal analysis: [Sima Sarv Ahrabi]; Writing–original draft: [Sima Sarv Ahrabi]; supervision: [Sima Sarv Ahrabi]; Writing–review and editing: [Sima Sarv Ahrabi] and [Alireza Momenzadeh]; Software [Sima Sarv Ahrabi] and [Alireza Momenzadeh]; validation: [Sima Sarv Ahrabi]; resources: [Alireza Momenzadeh]; and visualization: [Alireza Momenzadeh].

Compliance with ethical standards

- Funding: This study has not been funded;
- Conflicts of interest: The authors declare that they have no conflict of interest;
- Ethical Approval: This work does not contain any studies with human participants or animals, performed by any of the authors, and any work involving chemicals, procedures or equipment that have any unusual hazards inherent in their use.

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References

Altrock PM, Liu LL, Michor F (2015) The mathematics of cancer: integrating quantitative models. Nat Rev Cancer 15(12):730, doi:10.1038/nrc4029

Arabameri A, Asemani D, Hadjati J (2018) A structural methodology for modeling immune-tumor interactions including pro- and anti-tumor factors for clinical applications. Math Biosci 304:48–61, doi:10.1016/j.mbs.2018.07.006

Banerjee S, Sarkar RR (2008) Delay-induced model for tumor–immune interaction and control of malignant tumor growth. Biosyst 91(1):268–288, doi:10.1016/j.biosystems.2007.10.002

Batmani Y, Khaloozadeh H (2013) Optimal drug regimens in cancer chemotherapy: A multi-objective approach. Comput Biol Med 43(12):2089–2095, doi:10.1016/j.compbiomed.2013.09.026

Bellman RE, Kalaba R (1966) Dynamic programming and modern control theory. Academic Press

Betts JT (1998) Survey of numerical methods for trajectory optimization. Journal of guidance, control, and dynamics 21(2):193–207

Bonyadi MR, Michalewicz Z (2017) Particle swarm optimization for single objective continuous space problems: a review. Evol Comput 25(1):1–54, doi:10.1162/EVCO_r_00180

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(6):394–424, doi:10.3322/caac.21492

Browne CB, Powley E, Whitehouse D, Lucas SM, Cowling PI, Rohlfshagen P, Tavener S, Perez D, Samothrakis S, Colton S (2012) A survey of Monte Carlo tree search methods. IEEE Trans Comput Intell AI in Games 4(1):1–43, doi:10.1109/TCIAIG.2012.2186810

Burden T, Ernstberger J, Fister KR (2004) Optimal control applied to immunotherapy. Discrete Control Dyn-B 4(1):135–146, doi:10.3934/dcdsb.2004.4.135

Cappuccio A, Elishmereni M, Agur Z (2006) Cancer immunotherapy by interleukin-21: potential treatment strategies evaluated in a mathematical model. Cancer Res 66(14):7293–7300, doi:10.1158/0008-5472.CAN-06-0241

Cappuccio A, Castiglione F, Piccoli B (2007) Determination of the optimal therapeutic protocols in cancer immunotherapy. Math Biosci 209(1):1–13, doi:10.1016/j.mbs.2007.02.009

Castiglione F, Piccoli B (2006) Optimal control in a model of dendritic cell transfection cancer immunotherapy. Bull Math Biol 68(2):255–274, doi:10.1007/s11538-005-9014-3

Castiglione F, Piccoli B (2007) Cancer immunotherapy, mathematical modeling and optimal control. J Theor Biol 247(4):72–732, doi:10.1016/j.jtbi.2007.04.003

Celada F, Seiden PE (1992) A computer model of cellular interactions in the immune system. Immunol Today 13(2):56–62, doi:10.1016/0167-5699(92)90135-T

Clerc M, Kennedy J (2002) The particle swarm - explosion, stability, and convergence in a multidimensional complex space. IEEE Trans Evol Comput 6(1):58–73, doi:10.1109/4235.985692

Coello CAC, Lamont GB, van Veldhuizen DA (2007) Evolutionary algorithms for solving multi-objective problems, 2nd edn. Springer US, Springer Nature Switzerland, doi:10.1007/978-0-387-36797-2

Deb K (2014) Multi-objective optimization. In: Search methodologies: introductory tutorials in optimization and decision support techniques, 2nd edn, Springer, Boston, MA, pp 403–449, doi:10.1007/978-1-4614-6940-7_15

Deb K, Pratap A, Agarwal S, Meyarivan T (2002) A fast and elitist multiobjective genetic algorithm: NSGA-II. IEEE Trans Evol Comput 6(2):182–197, doi:10.1109/4235.996017

d'Onofrio A (2008) Metamodeling tumor–immune system interaction, tumor evasion and immunotherapy. Math Computer Modell 47(5-6):614–637, doi:10.1016/j.mcm.2007.02.032

Eberhart RC, Shi Y (2000) Comparing inertia weights and constriction factors in particle swarm optimization. In: proceedings of the 2000 congress on evolutionary computation, IEEE, vol 1, pp 84–88, doi:10.1109/CEC.2000.870279

Eftimie R, Bramson JL, Earn DJD (2011) Interactions between the immune system and cancer: a brief review of non-spatial mathematical models. Bull Math Biol 73(1):2–32, doi:10.1007/s11538-010-9526-3

Elmouki I, Saadi S (2016) BCG immunotherapy optimization on an isoperimetric optimal control problem for the treatment of superficial bladder cancer. Int J Dynam Control 4(3):339–345, doi:10.1007/s40435-014-0106-5

Evans ER, Bugga P, Asthana V, Drezek R (2018) Metallic nanoparticles for cancer immunotherapy. Mater Today 21(6):673–685, doi:10.1016/j.mattod.2017.11.022

Ghaffari A, Naserifar N (2010) Optimal therapeutic protocols in cancer immunotherapy. Comput Biol Med 40(3):261–270, doi:10.1016/j.compbiomed.2009.12.001

Goldberg DE (1989) Genetic algorithms in search, optimization and machine learning, 1st edn. Addison-Wesley Publishing Company, Inc., Boston, MA, USA

Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA (2018) The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. Cancer Cell 33(4):570–580, doi:10.1016/j.ccell.2018.03.015.

Holland JH (1975) Adaptation in natural and artificial systems: an introductory analysis with applications to biology, control, and artificial intelligence. University of Michigan Press

Houy N, Grand GL (2019) Optimizing immune cell therapies with artificial intelligence. J Theor Boil 461:34–40, doi:10.1016/j.jtbi.2018.09.007

Kennedy J, Eberhart RC (1995) Particle swarm optimization. In: proceedings of ICNN'95-International Conference on Neural Networks, IEEE, vol 4, pp 1942–1948, doi:10.1109/ICNN.1995.488968

Khalil DN, Budhu S, Gasmi B, Zappasodi R, Hirschhorn-Cymerman D, Plitt T, Henau OD, Zamarin D, Holmgaard RB, Murphy JT, Wolchok JD, Merghoub T (2015) Chapter one - the new era of cancer immunotherapy: Manipulating t-cell activity to overcome malignancy. In: Immunotherapy of Cancer, Advances in Cancer Research, vol 128, Elsevier Inc. Academic Press, pp 1–68, doi:10.1016/bs.acr.2015.04.010

Kiran KL, Lakshminarayanan S (2013) Optimization of chemotherapy and immunotherapy: *In silico* analysis using pharmacokinetic-

pharmacodynamic and tumor growth models. J Process Control 23(3):396–403, doi:10.1016/j.jprocont.2012.12.006
Kirschner D, Panetta JC (1998) Modeling immunotherapy of the tumor–immune interaction. J Math Biol 37(3):235–252, doi:10.1007/s002850050127
Kosinsky Y, Dovedi SJ, Peskov K, Voronova V, Chu L, Tomkinson H, Al-Huniti N, Stanski DR, Helmlinger G (2018) Radiation and PD-(L)1 treatment combinations: immune response and dose optimization via a predictive systems model. J Immunother Cancer 16(1):17, doi:10.1186/s40425-018-0327-9
Kuznetsov VA, Makalkin IA, Taylor MA, Perelson AS (1994) Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis. Bull Math Biol 56(2):295–321, doi:10.1007/BF02460644
Ledzewicz U, Mosalman MSF, Schättler H (2013) Optimal controls for a mathematical model of tumor-immune interactions under targeted chemotherapy with immune boost. Discrete Control Dyn-B 18(4):1031–1051, doi:10.3934/dcdsb.2013.18.1031
Lenhart S, Workman JT (2007) Optimal control applied to biological models. Chapman and Hall/CRC, doi:10.1201/9781420011418
Lollini PL, Motta S, Pappalardo F (2006) Discovery of cancer vaccination protocols with a genetic algorithm driving an agent based simulator. BMC Bioinform 7(1):352, doi:10.1186/1471-2105-7-352
Marler RT, Arora JS (2004) Survey of multi-objective optimization methods for engineering. Struct Multidisc Optim 26(6):369–395, doi:10.1007/s00158-003-0368-6
Minelli A, Topputo F, Bernelli-Zazzera F (2011) Controlled drug delivery in cancer immunotherapy: Stability, optimization, and monte carlo analysis. SIAM J Appl Math 71(6):2229–2245, doi:10.1137/100815190
Pandey HM, Chaudhary A, Mehrotra D (2014) A comparative review of approaches to prevent premature convergence in GA. Appl Soft Comput 24:1047–1077, doi:10.1016/j.asoc.2014.08.025
Pennisi MA, Pappalardo F, Zhang P, Motta S (2009) Searching of optimal vaccination schedules. IEEE Eng Med Biol Mag 28(4):67–72, doi:10.1109/MEMB.2009.932919
Piccoli B, Castiglione F (2006) Optimal vaccine scheduling in cancer immunotherapy. Physica A 370(2):672–680, doi:10.1016/j.physa.2006.03.011
Pillis LGD, Radunskaya AE (2003) The dynamics of an optimally controlled tumor model: a case study. MathComput Model 37(11):1221–1244, doi:10.1016/S0895-7177(03)00133-X
Pillis LGD, Fister KR, Gu W, Head T, Maples K, Neal T, Murugan A, Kozai K (2008) Optimal control of mixed immunotherapy and chemotherapy of tumors. J Biol Syst 16(1):51–80, doi:10.1142/S0218339008002435
Pontryagin LS, Boltyansky VG, Gamkrelidze RV, Mishchenko EF (1962) The mathematical theory of optimal processes. Interscience Publishers, New York
Qomlaqi M, Bahrami F, Ajami M, Hajati J (2017) An extended mathematical model of tumor growth and its interaction with the immune system, to be used for developing an optimized immunotherapy treatment protocol. Math Biosci 292:1–9, doi:10.1016/j.mbs.2017.07.006

Ravindran NS, Sheriff MM, Krishnapriya P (2017) Analysis of tumour-immune evasion with chemo-immuno therapeutic treatment with quadratic optimal control. J Biol Dyn 11(1):480–503, doi:10.1080/17513758.2017.1381280

Rosenberg SA (2014) IL-2: the first effective immunotherapy for human cancer. J Immunol 192(12):5451–5458, doi:10.4049/jimmunol.1490019

Rosenberg SA, Restifo NP (2015) Adoptive cell transfer as personalized immunotherapy for human cancer. Science 348(6230):62–68, doi:10.1126/science.aaa4967

Ross IM, Karpenko M (2012) A review of pseudospectral optimal control: from theory to flight. Annu Rev Control 36(2):182–197, doi:10.1016/j.arcontrol.2012.09.002

Shi Y, Eberhart RC (1998) A modified particle swarm optimizer. In: proceedings of 1998 IEEE international conference on evolutionary computation. IEEE world congress on computational intelligence, IEEE, pp 69–73, doi:10.1109/ICEC.1998.699146

Soto-Ortiz L, Finley SD (2016) A cancer treatment based on synergy between anti-angiogenic and immune cell therapies. J Theor Biol 397:197–211, doi:10.1016/j.jtbi.2016.01.026

Spranger S, Dai D, Horton B, Gajewski TF (2017) Tumor-residing batf3 dendritic cells are required for effector T cell trafficking and adoptive T cell therapy. Cancer Cell 31(5):711–723, doi:10.1016/j.ccell.2017.04.003

Tran E, Robbins PF, Rosenberg SA (2017) 'final common pathway' of human cancer immunotherapy: targeting random somatic mutations. Nat Immunol 18(3):255–262, doi:10.1038/ni.3682

Valentinuzzi D, Simoncic U, Ursic K, Vrankar M, Turk M, Jeraj R (2018) Predicting tumour response to anti-PD-1 immunotherapy with computational modelling. Phys Med Biol doi:10.1088/1361-6560/aaf96c

Vrána D, Matzenauer M, Neoral Č, Aujeskỳ R, Vrba R, Melichar B, Rušarová N, Rušarová N, Bartoušková M, Jankowski J (2018) From tumor immunology to immunotherapy in gastric and esophageal cancer. Int J Mol Sci 20(1):13, doi:10.3390/ijms20010013

Wilson DR, Sen R, Sunshine JC, Pardoll DM, Green JJ, Kim YJ (2018) Biodegradable STING agonist nanoparticles for enhanced cancer immunotherapy. Nanomed Nanotechnol Biol Med 14(2):237–246, doi:10.1016/j.nano.2017.10.013