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Optimal drug administration of mixed cytotoxic and immunostimulating agents for cancer treatment via multi-objective optimization

Administração ótima de medicamentos da combinação de agentes citotóxicos e imunoestimulantes para tratamento de câncer via otimização multiobjetivo

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ABSTRACT

Cancer represents a significant concern in terms of global public health, standing out as one of the main causes of death and a barrier to the advancement of life expectancy. The costs associated with cancer treatment have grown above the rate of inflation, driven by the increase in the number of new patients diagnosed, costs of materials and drugs involved, and inefficiency of care, which is becoming increasingly complex and uncoordinated. The mixed administration of immunotherapy and chemotherapy drugs plays a key role in cancer treatment. However, such treatments combination can present challenges arising from the complex interactions between these two therapeutic modalities. This work aims to identify the optimal combination of treatments that allows for minimizing both the tumor volume and the adverse effects resulting from the joint administration of drugs through a multi-objective optimization approach, establishing guidelines for optimal drug administration in the context of combined immunotherapy and chemotherapy.

Keywords: Cancer Treatment; Chemotherapy; Immunotherapy; Optimal Control; Multi-objective Optimization

RESUMO

O câncer representa uma preocupação significativa em termos de saúde pública mundial, destacando-se como uma das principais causas de morte e uma barreira ao avanço da expectativa de vida. Os custos associados ao tratamento do câncer têm crescido acima da taxa de inflação, impulsionados pelo aumento do número de novos pacientes diagnosticados, pelos custos dos materiais e medicamentos envolvidos e pela ineficiência dos cuidados, que estão se tornando cada vez mais

complexos e descoordenados. A administração conjunta de imunoterapia e quimioterapia desempenha um papel fundamental no tratamento do câncer. No entanto, tais tratamentos combinados podem apresentar desafios decorrentes das complexas interações entre estas duas modalidades terapêuticas. Este trabalho visa identificar a combinação ideal de tratamentos que permita minimizar tanto o volume tumoral como os efeitos adversos resultantes da administração conjunta de medicamentos através de uma abordagem de otimização multiobjetivo estabelecendo diretrizes para a administração ideal de medicamentos no contexto da imunoterapia combinada e quimioterapia.

Palavras-chave: Tratamento do Câncer; Quimioterapia; Imunoterapia; Controle Ótimo; Otimização Multi-objetivo

1 INTRODUCTION

According to Tan et al. (2020), the mixed administration of immunotherapy and chemotherapy drugs plays a key role in cancer treatment. Immunotherapy operates by stimulating the immune system, inciting it to recognize and eliminate cancer cells, while chemotherapy employs cytotoxic agents to directly attack tumor cells. However, as mentioned by Lake and Robinson (2005), the combination of immunotherapy and chemotherapy can present challenges arising from the complex interactions between these two therapeutic modalities.

When used concomitantly, the immunostimulatory properties of immunotherapy may interfere with the efficacy of chemotherapy, whereas the immunosuppressive effects induced by chemotherapy may compromise the efficacy of immunotherapy. For instance, Pillis et al. (2008) highlight that immunotherapy can trigger a wide range of adverse effects, including cytokine storms, the severity of which can be accentuated when combined with chemotherapy. Therefore, careful assessment and ongoing monitoring of patient's status and response to treatment are imperative to ensure a successful combination of immunotherapy and chemotherapy (Borcoman et al., 2019).

Computational models with the purpose of simulating the response to treatments involving the combination of immunotherapy and chemotherapy enable the systematic planning of individualized therapeutic strategies, in addition to providing comprehensive information on the complex multifactorial interactions between tumor cells, the immune system, and the chemotherapeutic agents (Laleh et al., 2022).

In this work the concepts of conflict between objectives in multi-objective

optimization applied to the administration of therapeutic drugs in combined immunotherapy and chemotherapy for cancer treatment are presented. In this case, the main aim is to balance the interactions between tumor cells, the immune system and chemotherapeutic agents. This approach involves the introduction of a trade-off between objectives, such as the minimization of tumor cells and the toxicity of drug administration, together with the maximization of immunocompetent cells, thus allowing the optimization of the respective levels involved.

2 BIOLOGICAL MODELING OF CANCER DYNAMICS

Biological systems exhibit inherent dynamism, non-linearity, and intricate complexity, comprising numerous action variables. As a result, the utilization of mathematical modeling assumes a significant role in elucidating various aspects of their dynamic behavior. Moreover, such models facilitate the control and prediction of the evolution of these systems. Consequently, the process of constructing models is increasingly recognized and valued not only by experimentalists but also by clinicians (Chaplain and Matzavinos, 2006).

2.1 Stepanova's classic model

Steponova's classic mathematical model offers a comprehensive depiction of the dynamic interplay between the growth of cancer cell volume and the activity of the immune system response. Comprising a set of two interconnected ordinary differential equations, this model enables the derivation of clinically observed characteristics by means of its parameterization (Ledzewicz et al., 2011b). Over the course of time, this model has served as a foundational framework for various extensions and generalizations, thereby giving rise to multiple alternative models (Ledzewicz and Schättler, 2020).

In light of determining the general formulation of the Stepanova model, one need to consider a tumor growth model $F(x)$, where x represents the tumor volume. The function F is a positive, double differentiable function defined within the finite range $(0, x_\infty)$, with x_∞ indicating the fixed carrying capacity for cancer. Additionally, the model incorporates the density of immunocompetent cells, represented by the dimensionless quantity y, which relates to various types of activated T cells during the

immune response, to obtain (Stepanova, 1979):

$$\begin{cases} \dot{x} = \mu_C x F(x) - \gamma x y \\ \dot{y} = \mu_I (x - \beta x^2) y - \delta y + \alpha \ . \end{cases} \tag{1}$$

In the above equation, the parameter μ_C serves as a coefficient associated with tumor growth, derived from the function $F(x)$. The symbol γ indicates the rate at which cancer cells are eliminated through the activity of T cells. Consequently, the term $\gamma x y$ captures the favorable impact of the immune response on the volume of cancer. Thus, the first equation within the aforementioned model represents the dynamics of tumor growth. In the second equation, the first term represents lymphocyte proliferation, which exhibits proportionality to the tumor volume x and is stimulated by tumor antigen.

Stepanova (1979) posits that extensive tumors hinder the activity of the immune system, primarily due to insufficient stimulation of immune forces and the overall suppression of immune lymphocytes caused by the tumor. This suppression is captured in the model through the inclusion of the term βx^2. The coefficients μ_I and β play a crucial role in calibrating these interactions. When combined with the variable y, they collectively depict the state-dependent impact of cancer cells on the stimulation of the immune system. Additionally, the coefficient α quantifies the constant influx of T cells originating from primary organs, while δ represents the natural death rate of T cells (Ledzewicz et al., 2012).

2.2 Optimal control based on modified Stepanova model

Extensive research has been conducted in the field of optimal control to identify the optimal combination of chemotherapy and immunotherapy, as well as the most efficacious administration methods. A commonly employed model for this purpose, introduced by Onofrio et al. (2012), represents a modified version of Stepanova's model given by:

$$\begin{cases} \dot{x} = -\mu_C x \ln\left(\dfrac{x}{x_\infty}\right) - \gamma x y - k_x x u \\ \dot{y} = \mu_I (x - \beta x^2) y - \delta y + \alpha + k_y y v \ . \end{cases} \tag{2}$$

Here, the parameter k_x represents the rate of tumor cell death induced by chemotherapy, while k_y indicates the rate of immune cell proliferation facilitated by immunotherapy. In this specific case, the function $F(x)$ is expressed as $F(x) = -\ln(x/x_\infty)$ to capture the characteristics of Gompertzian growth. Based on medical evidence, numerous tumors exhibit a Gompertzian growth pattern (Norton, 1988; Norton and Simon, 1977). The variables u and v represent the blood profiles of a cytotoxic agent and a generic immunostimulating agent, respectively.

In an uncontrolled system, where both $u = 0$ and $v = 0$ simultaneously, there exist two locally asymptotically stable equilibrium points: one at the microscopic level and another at the macroscopic level. These equilibrium points are characterized by distinct regions of attraction, separated by the stable manifold of an intermediate saddle point. Hence, the initial condition (x_0, y_0) within the domain of malignant cancer growth needs to be efficiently transitioned towards the region of attraction associated with the stable and benign equilibrium point. To achieve this, the primary objective is typically to minimize the population of cancer cells (x) while preserving the density of T cells (y) from depletion. Introducing the cytotoxic agent ($u = 1$) theoretically enables the reduction of cancer volume to a sufficiently small chronic state, disregarding the side effects. However, the presence of drug-related side effects renders this approach impractical (Ledzewicz et al., 2011a).

3 MULTI-OBJECTIVE OPTIMIZATION

Multi-objective optimization entails the pursuit of two fundamental objectives. One crucial objective involves making progress towards the Pareto optimal front. Simultaneously, it is imperative to uphold a diverse array of solutions on the non-dominated front. Given the equal importance assigned to all objectives within the realm of multi-objective optimization, the attainment of a diverse set of solutions in close proximity to the Pareto optimal front offers a plethora of optimal solutions (Deb, 2001).

3.1 Defining the objective function

In order to identify the optimal solution for a given problem, the selection of an objective function becomes crucial. This function serves as a metric to determine the

superiority of one candidate solution over another. Let $\mathbf{F}$ and $\mathbf{G}$ be non-empty sets contained within $\mathbb{R}^n$, where $\mathbf{F} \subseteq \mathbf{G}$, and let $f : \mathbf{G} \to \mathbb{R}$ represent a specified function. Additionally, $\mathbf{G}$ can take the form of either $\mathbb{R}^n$ or $\mathbf{F}$. Building upon these definitions, an optimization problem can be defined as a generic problem aimed at finding a solution $\bar{\mathbf{x}} \in \mathbf{F}$ such that $f(\bar{\mathbf{x}}) = \min_{\mathbf{x} \in \mathbf{F}} f(\mathbf{x})$.

The objective function $f(\cdot)$ and the feasible set $\mathbf{F}$ hold significant roles in the formulation of the problem. Within this context, any $\mathbf{x} \in \mathbf{F}$ is referred to as a feasible point or feasible solution within the set $\mathbf{G}$. Moreover, the optimal solution of the set $\mathbf{G}$ is denoted as $\bar{\mathbf{x}} \in \mathbf{F}$, satisfying the aforementioned equation. The formulation of the general multi-criteria decision-making problem can be expressed as follows:

$$\begin{cases} \text{min} & \mathbf{F}(\mathbf{x}) \\ \text{subjected to} & \mathbf{G}(\mathbf{x}) = 0,\ \mathbf{H}(\mathbf{x}) \leq 0. \end{cases} \tag{3}$$

where $\mathbf{x}$ represents the decision variables vector, while $\mathbf{F}(\mathbf{x})$ denotes the vector of objectives to be minimized. The constraints $\mathbf{G}(\mathbf{x}) = \mathbf{0}$ and $\mathbf{H}(\mathbf{x}) \leq \mathbf{0}$ establish the boundaries of the feasible solution space.

The mathematical objective consists of a weighted average of the penalty term $Ax(t_f) - By(t_f)$, which drives the system to traverse from the malignancy region to the benign region of the state space through the separatrix. Additionally, this mathematical objective takes into account the cumulative side effects of chemotherapy $\int_0^{t_f} u(t)dt \leq u_{max}$ and immune system enhancement $\int_0^{t_f} v(t)dt \leq v_{max}$, considered as an indirect measure of treatment side effects. Lastly, a small penalty term at the terminal time t_f is considered to make the mathematical problem well-posed. Thus, the general expression for the mathematical objective takes the form:

$$J(u, v) = Ax(t_f) + By(t_f) + C \int_0^{t_f} u(t)dt + D \int_0^{t_f} v(t)dt + St_f. \tag{4}$$

The rate dose integrals model the side effects of therapies on healthy tissue, and if there is data regarding drug severity, this will be reflected in the choices for C and D. Naturally, the specific type of tumor and even the cancer stage the patient is in will also factor into the calibration of these coefficients. For cases with a more advanced stage, higher side effects may need to be tolerated, thus leading to smaller values for C and D. In general,

the coefficients C, D, and S are variable choices that can be adjusted to calibrate the optimal response of the system (Onofrio et al., 2012).

3.2 Genetic Algorithm NSGA-II

The Non-dominated Sorting Genetic Algorithm (NSGA), proposed by Srinivas and Deb (1994), stands as one of the first evolutionary algorithms in the field. However, the NSGA algorithm has faced criticism regarding its (*i*) high computational complexity for non-dominated ordering, (*ii*) absence of elitism, and (*iii*) need for specifying a sharing parameter σ_{share}. In response, Deb et al. (2002) introduced an enhanced version, NSGA-II, which aimed to address these concerns and improve the algorithm performance.

NSGA-II algorithm can be outlined in a step-by-step manner as follows. Initially, a random population denoted as P_0 is generated. Subsequently, the population is partitioned into distinct levels of non-domination, with each solution assigned a fitness value corresponding to its non-domination level (where level 1 represents the best). Then, the algorithm assumes a minimization objective for fitness. The creation of a descendant population, denoted as Q_0 and of size *N*, is achieved through the utilization of binary selection tournament operators, population tournament operators (which can be seen in details in the work of Deb et al. (2002)), recombination, and mutation operators.

4 RESULTS

All variables considered in simulations are given in Table 1. The numerical values used for the parameters α, β, γ, and δ are directly sourced from the work of Kuznetsov et al. (1994), where these parameters were estimated based on *in vivo* experimental data for BCL1 B-cell lymphoma in the spleens of mice. In the same article, a classical logistic term is employed to model cancer growth. Consequently, adjustments to the remaining parameters were necessary to account for Gompertzian growth through linear data fitting (Ledzewicz et al., 2012). Furthermore, the functional form $(x - \beta x^2)y$ used in the Stepanova model represents a quadratic expansion of the term employed in Kuznetsov et al. (1994).

Table 1 – Numerical values for the variables and parameters used in computations (d'Onofrio, 2012)

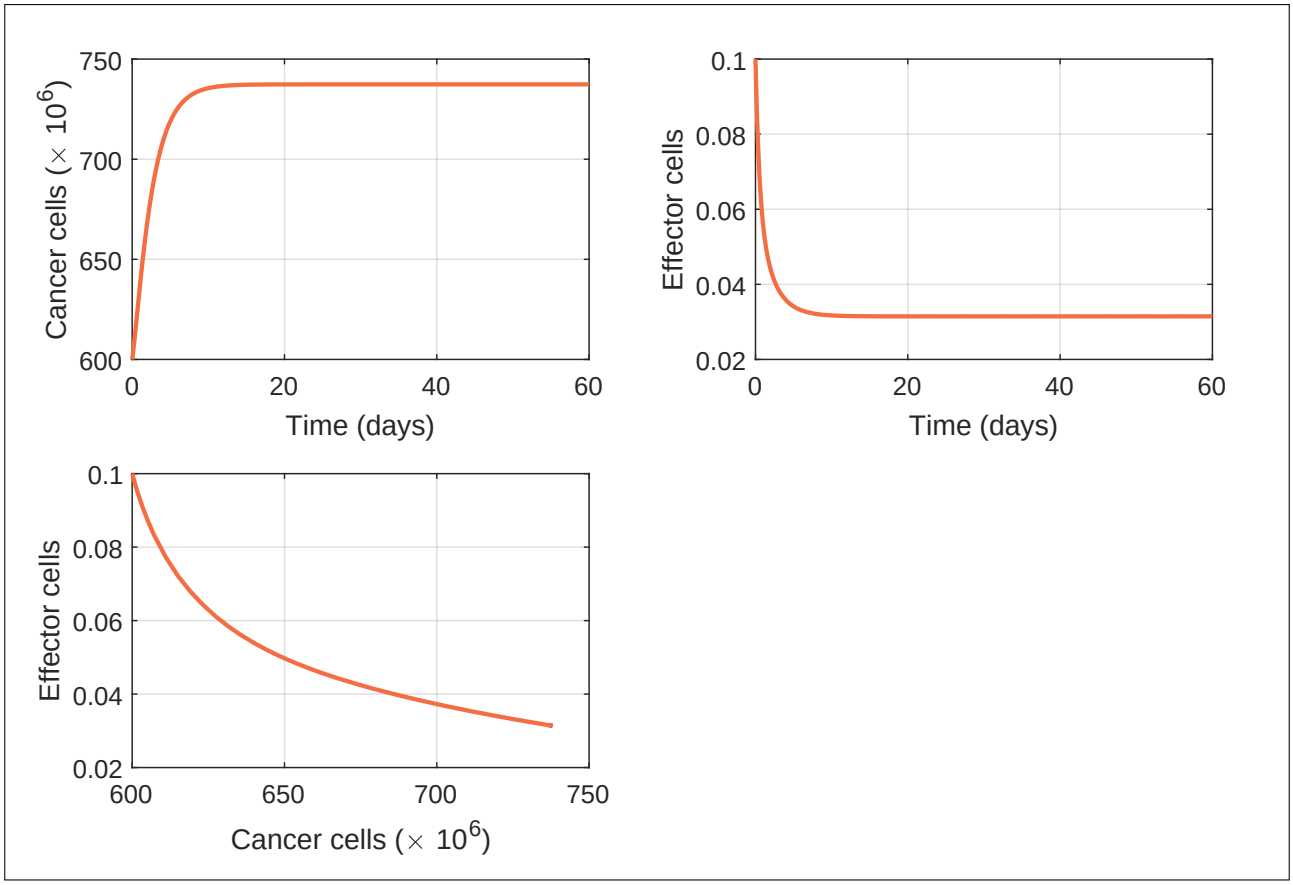
Parameter	Interpretation	Numerical value	Dimension
x	Tumor volume	-	10^6 cells
x_0	Initial volume for x	600	10^6 cells
y	Immune-competent cell density	-	Non-dimensional
y_0	Initial volume for y	0.10	Non-dimensional
α	Rate of influx	0.1181	1/day
β	Inverse threshold for tumor suppression	0.00264	Non-dimensional
γ	Interaction rate	1	10^7 cells/day
δ	Death rate	0.37451	1/day
μ_C	Tumor growth parameter	0.5599	10^7 cells/day
μ_I	Tumor stimulated proliferation rate	0.00484	10^7 cells/day
x_∞	Fixed carrying capacity	780	10^6 cells
k_x	Killing parameter of chemotherapy	1	10^7 cells/day
k_y	Rate of immune cells proliferation	0.10	10^7 cells/day

Source: the authors, 2024

Figure 1 depicts the dynamic profile of the tumor and immunocompetent cells, considering the model by Stepanova (1979) and the parameter sets from Table 1. Through upper left and right figures, it is evident that the tumor grows significantly, reaching a malignant equilibrium state in the absence of any treatment, accompanied by a substantial reduction in the density of immune-competent cells. The bottom figure reveals a temporal correlation between the tumor volume x and the density of effector cells y. Analysis of these figures leads to the conclusion that the model under consideration entails conflicting objectives in the joint administration problem of immunotherapy and chemotherapy treatments. This is due to the need to simultaneously reduce tumor volume and avoid depletion of immune-competent cell

density, while also considering the minimization of medication dosage to mitigate side effects.

Figure 1 – Dynamic profile of the tumor and immunocompetent cells for the uncontrolled system



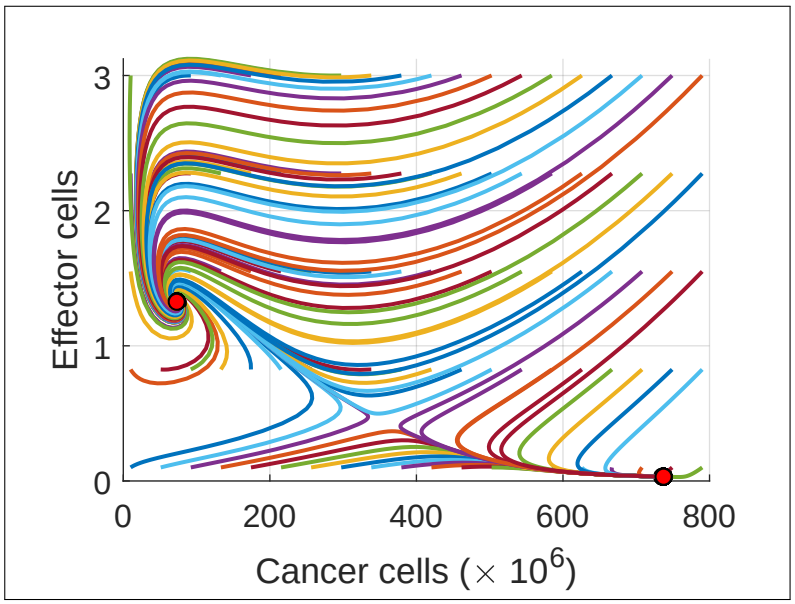
Source: The authors, 2024

The phase portrait of the mathematical model is presented in Figure 2. To generate these results, we consider the set of parameters outlined in Table 1 and different values for initial conditions $(x_0; y_0)$ in the following ranges: [10 790]×[0.1 3]. The uncontrolled model exhibits two locally asymptotically stable equilibrium points. The macroscopic malignant equilibrium occurs at $(x_m; y_m) = (737.4; 0.031)$, while the benign equilibrium takes place at $(x_b; y_b) = (73.07; 1.320)$. Additionally, these regions of attraction are separated by the stable manifold of an intermediate saddle point at $(x_s; y_s) = (356.2; 0.439)$.

It is relevant to emphasize the fact that the treatment's performance is highly dependent on the initial conditions, as there is a coexistence of macroscopic and

microscopic equilibria point. The initial states of the system can be estimated with some uncertainties before designing drug injection schemes. The objective of cancer treatment can then be formulated to steer the initial conditions from the attraction region of the malignant equilibrium to the attraction region of the benign equilibrium.

Figure 2 – Phase portrait for the uncontrolled system



Source: The authors, 2024

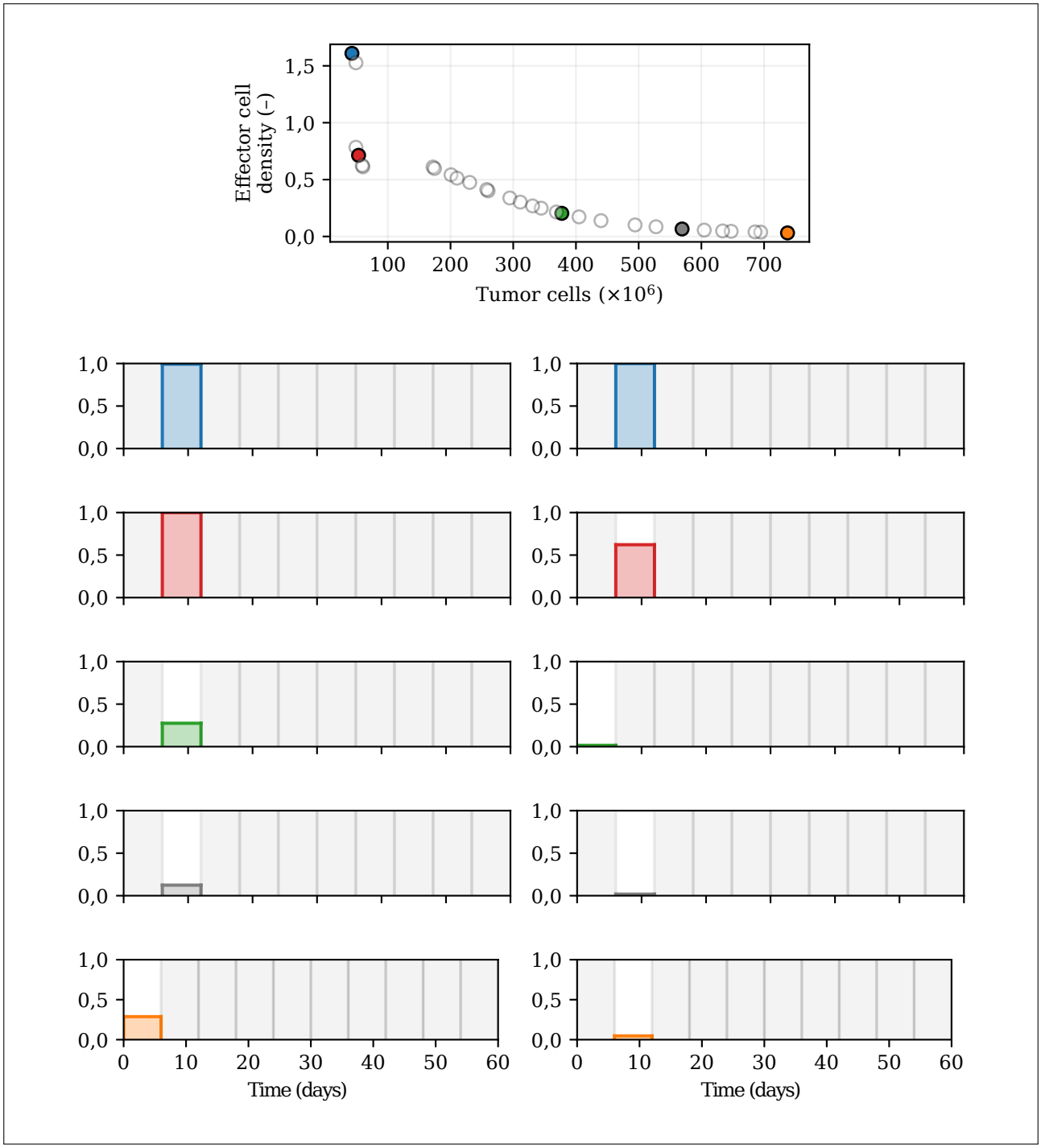
In the context of the problem under investigation, it is imperative to discretize the control variables u and v. In light of this, the proposed approach involves the transformation of the original optimal control problem into a nonlinear optimization problem. To achieve this, the time interval $[0, t_f]$ is subjected to discretization, employing N_{elem} time nodes, with each node designated as t_i, where $i = 0, \ldots, N_{elem} - 1$, and it follows that $t_0 \leq t_i \leq t_f$. Within each of the $N_{elem} - 1$ time subintervals, denoted as $[t_i, t_{i+1}]$, the control variables are treated as piecewise constants, specifically, $u(t) = u_i$ and $v(t) = v_i$ for $t_i \leq t < t_{i+1}$, subject to the constraints $u_{min} \leq u_i \leq u_{max}$ and $v_{min} \leq v_i \leq v_{max}$.

We are engaged in the resolution of a multi-objective optimization problem wherein our objective is the simultaneous minimization of $x(t)$ and maximization of $y(t)$ at $t = t_f$, with $t_f = 60$ days. This optimization task is characterized by four decision variables: $0 \leq u \leq 1$, $0 \leq v \leq 1$, $1 \leq t_u \leq 10$, and $1 \leq t_v \leq 10$. Here, t_u and t_v correspond to the discrete subintervals deemed most appropriate for the administration of

medication in each respective treatment regimen. Consequently, t_u and t_v are confined to natural numbers spanning the interval from one to the upper limit of subintervals considered, which, in our specific case, is ten. Notably, u and v are likewise constrained to natural numbers.

To solve the proposed problem, the NSGA-II method was executed for 100 generations with 30 individuals in the population, simulated binary crossover with a probability of 0.9, polynomial mutation with a distribution index of 20, and tournament selection. Figure 3 displays the results of the Pareto Optimal Front along with the discretized drug administration profiles u (on the left) and v (on the right) generated during the simulations. Among all the non-dominated solutions, five points are specifically highlighted for further discussion, each representing the administration of cytotoxic agents (u) and immune-boosting interventions (v) for different scenarios. Observing the profiles, it is evident that the first two drug administration profiles were successful in altering the initial condition (x_0, y_0) within the domain characterized by malignant cancer growth, steering it towards the attraction region associated with the stable and benign equilibrium point at the final time t_f. However, this achievement came at the cost of high levels of cytotoxic $(u = 1)$ and immunotherapeutic $(v = 1)$ agents administration during the second treatment time interval, rendering this approach impractical due to drug-related side effects. The third point under analysis exhibits considerably lower drug administration levels compared to the previous cases. Here, the cytotoxic agent was applied during the second treatment interval, while immune reinforcement was administered during the initial time interval. Although the benign equilibrium was not reached by the final time t_f, there is a notable reduction in tumor cell volume (x) at the final time, with the system approaching the stable manifold of the intermediate saddle point. Regrettably, points related to cases four and five failed to lead the system out of the malignant equilibrium region due to extremely low medication dosages and incorrect intervals for drug administration. These figures underscore the impact of countless combinations of drug administration dosages and application time intervals for mixed chemotherapy and immunotherapy.

Figure 3 – Pareto Optimal Front (on the top) and chemotherapy (on the left) and immunotherapy (on the right) drugs administration profiles

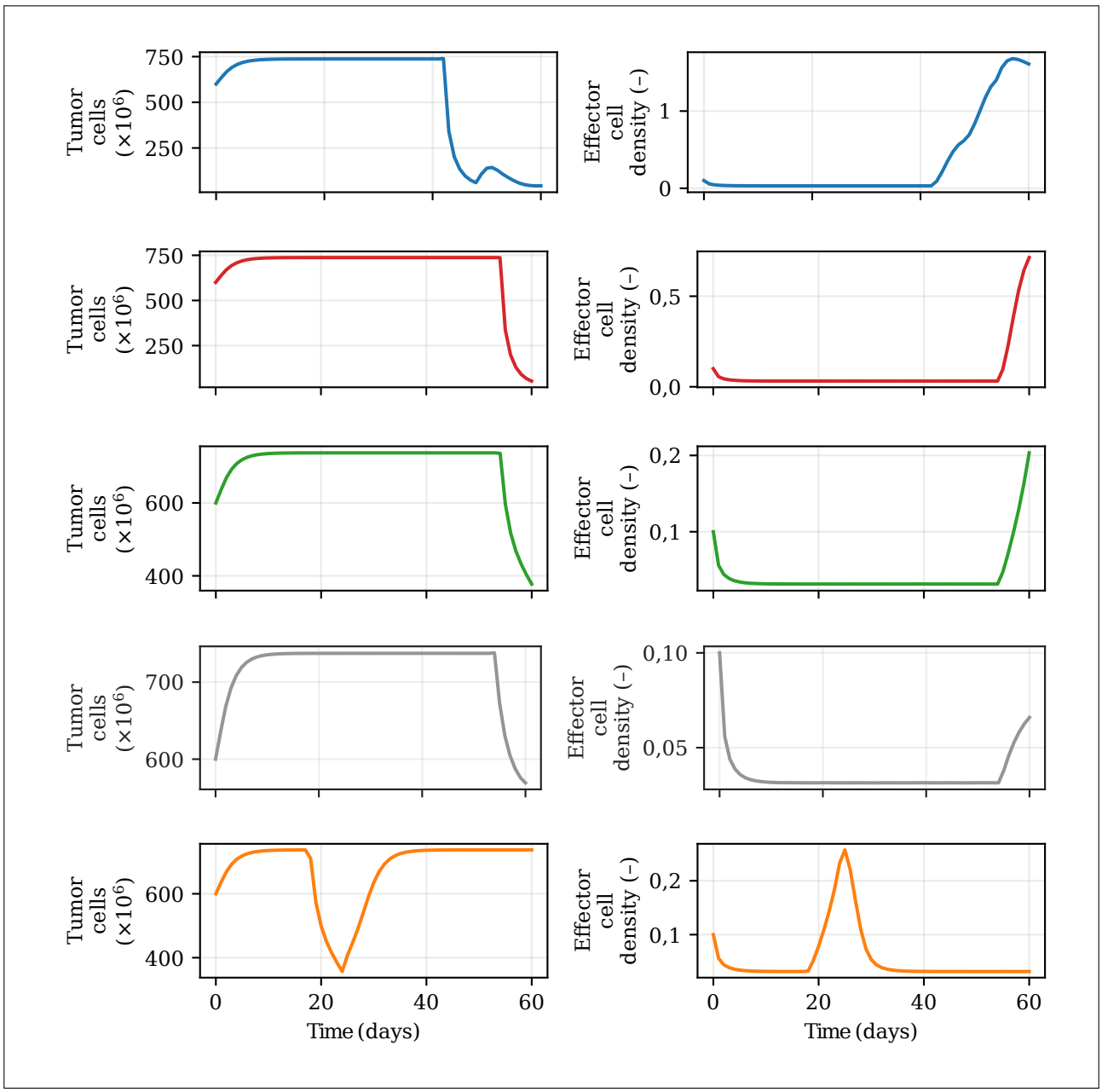


Source: The authors, 2024

In Figure 4 are presented the system outcomes related to the numeric values for the parameters defined in Table 1 and the control choices given in the previous figure. As the values for x and y are computed for the objective functions just in the final time t_f,

their time profiles must be taken into account in a qualitative point of view. However, it is clear the relation between their final values and the Pareto Front. The first two cases show a significant reduction in the cancer cells volume while keeping the effector cells in an elevated value next to the final time of the treatment. In the third case one can see an improvement for the patient conditions, but without a satisfactory conclusion for its risk situation. In the last two cases the treatment failed.

Figure 4 – Cancer cells (on the left) and effector cells (on the right) evolution over time for the treatment scenarios highlighted in the Pareto Optimal Front



Source: The authors, 2024

5 CONCLUSIONS

The main aim of this work was to develop a methodology based on multi-objective optimization for cancer therapy drug administration by decreasing the number of tumor cells while checking the number of immune-competent cell density. Another interest was to reduce the side effects of both cytotoxic chemotherapy and immunotherapy. Through the Pareto Optimal Front analysis, it was possible to take into account a set of considerable drug administration profiles for the mixed immunotherapy and chemotherapy treatment. On the extreme left part of the Pareto Front $(x < 100 \times 10^6)$ were situated the best outcome for the *in silico* experiments, where the combination of the citotoxic and immunostimulating agents were capable to bring the system from the initial malignant equilibrium into the benign equilibrium. These results were achieved with just a six days interval treatment, what is a desirable treatment for the patient to suffer less with the treatment inherent side effects, besides leading it to a faster recovering.

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REFERENCES

Borcoman, E., Kanjanapan, Y., Champiat, S., Kato, S., Servois, V., Kurzrock, R., Goel, S., Bedard, P., and Le Tourneau, C. (2019). Novel patterns of response under immunotherapy. *Annals of Oncology*, *30*(3), 385-369.

Chaplain, M. and Matzavinos, A. (2006). Mathematical modelling of spatio-temporal phenomana in tumour immunology. *Lecture Notes in Mathematics*, *1872*.

Deb, K. (2001). *Multi-objective optimization using evolutionary algorithms*. England: John Wiley & Sons.

Deb, K., Pratap, A., Agarwal, S., and Meyarivan, T. (2002). A fast and elitist multiobjective genetic algorithm: NSGA-II. *IEEE Transactions on Evolutionary Computation*, *6*(2). doi: 10.1109/4235.996017.

Kuznetsov, V. A., Makalkin, I. A., Taylor, M. A., and Perelson, A. S. (1994). Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bulletin of Mathematical Biology*, *56*(2). doi: 10.1007/BF02460644.

Lake, R. A. and Robinson, B. W. (2005). Immunotherapy and chemotherapy - a practical partnership. *Nature Reviews Cancer*, *5*(5). doi: 10.1038/nrc1613.

Laleh, N. G., Loeffler, C. M. L., Grajek, J., Staňková, K., Pearson, A. T., Muti, H. S., Trautwein, C., ..., and Kather, J. N. (2022). Classical mathematical models for prediction of response to chemotherapy and immunotherapy. *PLoS Computational Biology*, *18*(2). doi: 10.1371/journal.pcbi.1009822.

Ledzewicz, U., Naghnaeian, M., and Schättler, H. (2011a). Dynamics of tumor-immune interaction under treatment as an optimal control problem. *Discrete and Continuous Dynamical Systems- Series A*.

Ledzewicz, U., Naghnaeian, M., and Schättler, H. (2011b). An optimal control approach to cancer treatment under immunological activity. *Applicationes Mathematicae*, *38*(1). doi: 10.4064/am38-1-2.

Ledzewicz, U., Naghnaeian, M., and Schättler, H. (2012). Optimal response to chemotherapy for a mathematical model of tumor-immune dynamics. *Journal of Mathematical Biology*, *64*(3). doi: 10.1007/s00285-011-0424-6.

Ledzewicz, U. and Schättler (2020). On the role of the objective in the optimization of compartmental models for biomedical therapies. *Journal of Optimization Theory and Applications*, *187*(2). doi: 10.1007/s10957-020-01754-2.

Norton, L. (1988). A gompertzian model of human breast cancer growth. *Cancer Research*, *48*.

Norton, L. and Simon, R. (1977). Growth curve of an experimental solid tumor following radiotherapy. *Journal of the National Cancer Institute*, *58*(6). doi: 10.1093/jnci/58.6.1735.

Onofrio, A., Ledzewicz, U., and Schättler, H. (2012). On the Dynamics of Tumor-Immune System Interactions and Combined Chemo- and Immunotherapy. In Onofrio, A., Cerrai, P., and Gandolfi, A., editors, *SEMA SIMAI Springer Series*. (pp. 249-266). Milano: Springer Milan. doi: 10.1007/978-88-470-2571-4_13.

Pillis, L. G. D., Fister, K. R., Gu, W., Head, T., Maples, K., Neal, T., Murugan, A., and Kozai, K. (2008). Optimal control of mixed immunotherapy and chemotherapy of tumors. *Journal of Biological Systems*, *16*(1). doi: 10.1142/S0218339008002435.

Stepanova, N. V. (1979). Course of the immune reaction during the development of a malignant tumour. *Biophysics*, *24*(5).

Tan, S., Li, D., and Zhu, X. (2020). Cancer immunotherapy: Pros, cons and beyond. *Biomedicine and Pharmacotherapy*, *124*. doi: 10.1016/j.biopha.2020.109821.

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