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Evolutionary Dynamics of Cancer Cell Populations under Immune Selection Pressure and Optimal Control of Chemotherapy

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Abstract. Increasing experimental evidence suggests that epigenetic and microenvironmental factors play a key role in cancer progression. In this respect, it is now generally recognized that the immune system can act as an additional selective pressure, which modulates tumor development and leads, through cancer immunoediting, to the selection for resistance to immune effector mechanisms. This may have serious implications for the design of effective anti-cancer protocols. Motivated by these considerations, we present a mathematical model for the dynamics of cancer and immune cells under the effects of chemotherapy and immunity-boosters. Tumor cells are modeled as a population structured by a continuous phenotypic trait, that is related to the level of resistance to receptor-induced cell death triggered by effector lymphocytes. The level of resistance can vary over time due to the effects of epigenetic modifications. In the asymptotic regime of small epimutations, we highlight the ability of the model to reproduce cancer immunoediting. In an optimal control framework, we tackle the problem of designing effective anti-cancer protocols. The results obtained suggest that chemotherapeutic drugs characterized by high cytotoxic effects can be useful for treating tumors of large size. On the other hand, less cytotoxic chemotherapy in combination with immunity-boosters can be effective against tumors of smaller size. Taken together, these results support the development of therapeutic protocols relying on combinations of less cytotoxic agents and immune-boosters to fight cancer in the early stages.

Keywords and phrases: chemotherapy, immunity-boosters, cancer immunoediting, cancer modeling, optimal control

Mathematics Subject Classification: 35Q92, 49J15, 49K15, 65L12, 65M06, 93C15, 97M60

1. Introduction

Increasing evidence suggests that epigenetic and microenvironmental factors play a key role in cancer progression [36]. In particular, it is now generally recognized that the immune system can act as an additional selective pressure, which modulates tumor development and drives the outgrowth of tumor cells with decreased sensitivity to immune attack [14]. The process by which the selective pressure exerted by immune cells sculpts the phenotypic distribution of cancer cells is known as cancer immunoediting [13, 42]. This process may lead to the emergence of resistance to immune effector mechanisms, such as receptor-induced cell death triggered by effector lymphocytes [23, 45]. Furthermore, it has serious implications for immunotherapeutic protocols aimed at boosting the ability of the immune system to fight cancer [30].

On the other hand, a serious limitation to the design of effective anti-cancer treatments is introduced by the non-specificity of cytotoxic drugs, which can cause damage to the immune system. This is one of the main medical concerns with chemotherapy and calls for therapy optimization, i.e., the identification of drug doses and multi-drug combinations that allow an effective control on cancer growth, along with a minimization of the chance for collateral damages [21, 22, 26].

In this respect, experimental evidence supports the idea that the efficacy of anti-cancer protocols can be enhanced by combining immune-boosters, that favor the recruiting of effector immune cells, together with chemotherapy relying on lower concentrations of cytotoxic agents [4, 6, 18, 25, 35, 38, 43, 44].

Motivated by these considerations, we present a mathematical model for the dynamics of a well-mixed sample composed of three cell populations: cancer cells, circulating lymphocytes and effector lymphocytes. Circulating lymphocytes keep in control the system, while effector lymphocytes actively target and kill tumor cells. Cancer and immune cells interact under the effects of chemotherapy, based on the infusion of cytotoxic agents, and immune-boosting, aimed at increasing the concentration of circulating lymphocytes.

A set of Ordinary Differential Equations (ODEs) is used to model the dynamics of immune cells and cytotoxic agents. Effector lymphocytes undergo both clonal expansion, through a Michaelis-Menten type kinetic, and contact inhibition, due to the presence of tumor cells. On the other hand, cancer cells are seen as a structured population and their evolution is ruled by a phenotype-structured equation of integro-differential type [3, 8, 31, 32]. The structuring variable $x \in [0, 1]$ stands for a normalized level of resistance to receptor-induced cell death triggered by effector lymphocytes. Chemotherapy affects cancer and immune cells through exponential mass-action dynamics. Tumor cells undergo Gompertzian growth and, since the cell level of resistance is allowed to change over time through epigenetic modifications, a positive parameter σ is introduced to model the average size of changes in the trait x.

The outline of the paper is as follows:

Section 2. We present the model and discuss the related underlying assumptions.
Section 3. In the asymptotic regime of small epimutations (i.e., in the limit $\sigma \to 0$), we make use of the time rescaling proposed in [10] and the analytical approach used in [9,31] to highlight the ability of the model to reproduce cancer immunoediting (i.e., the selection for cancer cells characterized by high level of resistance to effector lymphocytes). The results obtained are illustrated by means of numerical simulations.
Section 4. We focus on the case where the cancer cell population is homogeneously composed of highly resistant cells and epimutations do not take place. In this framework, we follow the lines of [2,5,7,12,15–17,20,27,28,37–40] and introduce an objective cost functional, that accounts for the systemic cost due to the proliferation of cancer cells and the infusion of cytotoxic agents. In an optimal control setting, we prove the existence of optimal infusion rates that allow the minimization of this cost, under suitable constraints on the delivered dose of cytotoxic agents.
Section 5. We perform numerical simulations aimed at studying the response of cancer and immune cells to chemotherapeutic protocols, that are optimal in the sense clarified in Section 4. Biological

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interpretations of the results obtained are provided, and considerations about possible strategies to enhance the efficacy of anti-cancer treatments are drawn.

2. Mathematical model

The selected reference system is defined by three interacting cell populations: cancer cells, effector lymphocytes and circulating lymphocytes. In the line of [31, 32], we assume the cancer cell population to be structured by a phenotypic variable $x \in [0, 1]$. The variable x stands for a normalized expression level of resistance to receptor-induced cell death triggered by effector lymphocytes [23, 45].

The function $n_T(t, x) \geq 0$ denotes the population density of tumor cells with resistance level x at time t (measured in days). The concentration of circulating lymphocytes, effector lymphocytes and cytotoxic agents at time t are modeled, respectively, by the functions $\varrho_C(t) \geq 0$, $\varrho_E(t) \geq 0$ and $c(t) \geq 0$. The system evolves according to the following set of equations:

$$\frac{\partial n_T(t,x)}{\partial t} = \overbrace{\int M(x,y;\sigma) n_T(t,y)dy - n_T(t,x)}^{\text{epimutations and renewal}} + \overbrace{\alpha_T \ln\left(\frac{\theta_T}{\varrho_T(t)}\right) n_T(t,x)}^{\text{proliferation}} - \overbrace{\left\{\eta_T(x)\varrho_E(t) + K_T\left[c(t)\right]\right\} n_T(t,x)}^{\text{death due to effector lymphocytes and chemotherapy}} \tag{2.1}$$

$$\frac{\mathrm{d}\varrho_E(t)}{\mathrm{d}t} = \overbrace{\alpha_E \varrho_C(t) - \beta_E \varrho_E(t)}^{\text{production by circulating lymphocytes and death}} - \overbrace{K_E\left[c(t)\right]\varrho_E(t)}^{\text{death due to chemotherapy}} + \overbrace{\left[\gamma \frac{\varrho_T(t)}{\xi + \varrho_T(t)} - \eta_E \varrho_T(t)\right] \varrho_E(t)}^{\text{clonal expansion and contact inhibition due to tumor cells}} \tag{2.2}$$

$$\frac{\mathrm{d}\varrho_C(t)}{\mathrm{d}t} = \overbrace{\alpha_C - \beta_C \varrho_C(t)}^{\text{immune-boosting and death}} - \overbrace{K_C\left[c(t)\right]\varrho_C(t)}^{\text{death due to chemotherapy}} \tag{2.3}$$

$$\frac{\mathrm{d}c(t)}{\mathrm{d}t} = \overbrace{\omega V(t) - \nu c(t)}^{\text{delivery of cytotoxic agents and efficacy decay}}, \tag{2.4}$$

with $t \in (0, t_f]$, where t_f is the end-time of observations,

$$\varrho_T(t) := \int n_T(t,x)dx \qquad \text{and} \qquad K_{T,E,C}\left[c(t)\right] := \kappa_{T,E,C}\left(1 - e^{-\mu_{T,E,C}c(t)}\right).$$

The above system of equations relies on the notations and assumptions given hereafter:

- Epimutations lead tumor cells with resistance level y to acquire the resistance level x with a probability described by kernel $M(x, y; \sigma)$, which is such that

$$\int M(x,y;\sigma)dx = 1, \quad \forall y \in [0,1], \quad \forall \sigma > 0. \tag{2.5}$$

We make the assumption that epimutations are rare, so that they preserve, net of renewal, the total number of tumor cells inside the system. Furthermore, since we allow only small epigenetic modifications to occur, we introduce a small parameter $\sigma > 0$ such that M is negligibly small for x outside a σ-neighborhood of y. In particular, we define kernel M as follows:

$$M(x,y;\sigma) := \begin{cases} \frac{1}{2}\delta(x-(y-\sigma)) + \frac{1}{2}\delta(x-(y+\sigma)), & \text{if } \sigma < x < 1-\sigma \\ \frac{1}{2}\delta(x-(y-\sigma)) + \frac{1}{2}\delta(x-y), & \text{if } 0 \le x \le \sigma \\ \frac{1}{2}\delta(x-(y+\sigma)) + \frac{1}{2}\delta(x-y), & \text{if } 1-\sigma \le x \le 1, \end{cases}$$

where δ is the Dirac's delta distribution.

- Tumor cells are assumed to obey a Gompertzian dynamics [34] with proliferation rate $\alpha_T > 0$ and carrying capacity $\theta_T > 0$. They are killed by effector lymphocytes through mass-action dynamics at a rate described by the function $\eta_T(x)$, which satisfies the following assumptions:

$$\eta_T : [0,1] \to \mathbb{R}_+, \quad \eta_T \in W^{2,\infty}([0,1]), \quad \min_{x\in[0,1]} \eta_T(x) = \eta_T(x=1) = \hat{\eta}_T. \tag{2.6}$$

- Effector lymphocytes are produced by circulating lymphocytes at rate $\alpha_E > 0$ and die at rate $\beta_E > 0$. Furthermore, they are assumed to undergo clonal expansion due to the presence of tumor cells at rate $\gamma > 0$, through a Michaelis-Menten type kinetic modeled by the factor $\frac{\varrho_T(t)}{\xi+\varrho_T(t)}$, while their growth is inhibited by contact with tumor cells at rate $\eta_E > 0$.
- The concentration of circulating lymphocytes is assumed to be enhanced by immune-boosters at a constant rate $\alpha_C > 0$, while the death rate of these cells is modeled by the parameter $\beta_C > 0$.
- The infusion rate of chemotherapeutic agents at time t is modeled by the smooth function $V(t) \ge 0$, the related uptake rate is described by the parameter $\omega > 0$ and their efficacy is assumed to decay over time at constant rate $\nu > 0$.
- Tumor cells, circulating and effector lymphocytes are killed by cytotoxic agents at rates $\kappa_{T,C,E} > 0$ through a mass-action dynamics of the exponential form. Following [38], we assume cytotoxic agents to be designed to kill more effectively cancer cells than immune cells, i.e.,

$$\kappa_C \le \kappa_E < \kappa_T. \tag{2.7}$$

Cell sensitivities to chemotherapeutic agents are modeled by the parameters $\mu_{T,C,E}$.

3. Evolutionary dynamics of cancer cells in the limit of small epimutations and immunoediting

Under the time rescaling used in [8–10] to study evolutionary dynamics of phenoty-structured populations in the limit of small mutations and many generations, Eqs. (2.1)-(2.4) read as follows:

$$\sigma\frac{\partial n_{T\sigma}(t,x)}{\partial t} = \int M(x,y;\sigma)n_{T\sigma}(t,y)dy - n_{T\sigma}(t,x) + P_{T\sigma}(t,x)n_{T\sigma}(t,x) \tag{3.1}$$

$$\sigma\frac{\mathrm{d}\varrho_{E\sigma}(t)}{\mathrm{d}t} = \alpha_E\varrho_{C\sigma}(t) + \left\{\gamma\frac{\varrho_{T\sigma}(t)}{\xi+\varrho_{T\sigma}(t)} - \beta_E - \eta_E\varrho_{T\sigma}(t) - K_E\left[c_\sigma(t)\right]\right\}\varrho_{E\sigma}(t) \tag{3.2}$$

$$\sigma\frac{\mathrm{d}\varrho_{C\sigma}(t)}{\mathrm{d}t} = \alpha_C - \left\{\beta_C + K_C\left[c_\sigma(t)\right]\right\}\varrho_{C\sigma}(t) \tag{3.3}$$

$$\sigma\frac{\mathrm{d}c_\sigma(t)}{\mathrm{d}t} = \omega V_\sigma(t) - \nu c_\sigma(t), \tag{3.4}$$

where $P_{T\sigma}(t,x) = P_{T\sigma}(\varrho_{T\sigma}(t), \varrho_{E\sigma}(t), c_\sigma(t), x)$ with

$$P_{T\sigma}(\varrho_{T\sigma}(t), \varrho_{E\sigma}(t), c_\sigma(t), x) := \alpha_T \ln\left(\frac{\theta_T}{\varrho_{T\sigma}(t)}\right) - \eta_T(x)\varrho_{E\sigma}(t) - K_T\left[c_\sigma(t)\right]. \tag{3.5}$$

We introduce the following biologically consistent initial conditions:

$$n_{T\sigma}(t=0,x) = n_T^0(x) \in L^1([0,1]), \quad n_T^0(\cdot) > 0 \ \text{ a.e. on } [0,1], \tag{3.6}$$

$$\varrho_{E\sigma}(t=0) = \varrho_E^0 > 0, \quad \varrho_{C\sigma}(t=0) = \varrho_C^0 > 0, \quad c_\sigma(t) = c^0 > 0, \tag{3.7}$$

and characterize the asymptotic dynamics of $n_{T\sigma}(t,x)$ in the regime of small epimutations.

In particular, since for any $\sigma > 0$, functions $n_{T\sigma}$, $\varrho_{E\sigma}$, $\varrho_{C\sigma}$ and c_σ are uniformly bounded from above and persistence (i..e, the fact that $n_{T\sigma}$, $\varrho_{E\sigma}$, $\varrho_{C\sigma}$ and c_σ stay uniformly positive) can be easily verified in view of assumptions (3.9)-(3.10), a characterization of $n_{T\sigma}(t,x)$ in the limit $\sigma \to 0$ is provided by the following theorem, which can be proved in the same way as that presented in [9, 31] and so it is left without proof:

Theorem 3.1 (Evolution of cancer cells in the regime of small epimutations and immunoediting)**.** *Let us define*

$$R_{T\sigma}(t,x) := \int_0^t P_{T\sigma}(\varrho_{T\sigma}(s), \varrho_{E\sigma}(s), c_\sigma(s), x)ds \ \in \ W^{2,\infty}((0,t_f)\times[0,1]) \tag{3.8}$$

and assume V_σ to be uniformly bounded. Furthermore, let us assume

$$\beta_E > \gamma, \quad \beta_C > \kappa_C, \quad \alpha_T > \kappa_T, \quad \frac{\gamma}{\eta_E} \geq \theta_T + \xi \tag{3.9}$$

and

$$\frac{(\alpha_T - \kappa_T)(\beta_E - \gamma)}{\alpha_E \hat{\eta}_T} \geq \frac{\alpha_C}{\beta_C - \kappa_C}. \tag{3.10}$$

Then,

$$\lim_{\sigma\to 0}\int_0^1 \varphi(x) n_{T\sigma}(t,x)dx = \lim_{\sigma\to 0}\int_0^1 \varphi(x) n_T^0(x) e^{\frac{R_{T\sigma}(t,x)}{\sigma}}dx,$$

for all smooth test functions φ in the completion of $C_c^\infty((0,1))$ in $W^{2,\infty}([0,1])$ and for $t \in [0,t_f]$. Furthermore, there exist a subsequence of $n_{T\sigma}$, denoted again as $n_{T\sigma}$, and a subsequence of $R_{T\sigma}$, denoted again as $R_{T\sigma}$, such that, in the limit $\sigma \to 0$,

$$n_{T\sigma} \rightharpoonup n_T \ \text{ on } \ w^* - L^\infty((0,t_f), \mathcal{M}^1([0,1]))$$

and

$$R_{T\sigma} \to R_T \ \text{ uniformly in } \ [0,t_f]\times[0,1],$$

where

$$n_T \in L^\infty((0,t_f), \mathcal{M}^1([0,1])), \quad R_T(t,x) := \int_0^t P_T(s,x)ds \in W^{2,\infty}((0,t_f)\times[0,1]).$$

Function R satisfies

$$\max_{x\in[0,1]} R_T(t,x) = R_T(t,x=1) = 0 \quad \forall t \in [0,t_f] \tag{3.11}$$

and, under the additional assumption

$$n_T^0(\cdot) > 0 \ \text{ a.e. on } \ R_T(t,\cdot)^{-1}(0), \tag{3.12}$$

the limit measure results

$$n_T(t,x) = \varrho_T(t)\delta(x-1), \qquad \text{for a.e. } \ t \in [0,t_f]. \tag{3.13}$$

In order to illustrate the asymptotic results established by Theorem 3.1, we numerically solve the Cauchy Problem defined by coupling Eqs.(3.1)-(3.4) with initial conditions (3.6) and (3.7), in the limit $\sigma \to 0$.

Numerical simulations are performed in MATLAB by means of an implicit-explicit finite difference scheme for Eq. (3.1) combined with standard finite difference schemes for Eqs. (3.2)-(3.4). The interval $[-0.5, 1.5]$ is chosen as x-domain instead of the interval $[0, 1]$ to show how the obtained results are not affected by boundary effects. A uniform discretization with 400 points of interval $[-0.5, 1.5]$ is used. Interval $[0, t_f]$ with $t_f = 120$ days is selected as t-domain (time step $dt = 0.005$).

We choose the initial conditions given hereafter

$$n_{T\sigma}(t=0,x) := C_0 e^{-x^2/\sigma}, \quad C_0 \in \mathbb{R}_+ \; s.t. \int n_T^0(x)dx = 9.8 \times 10^2, \quad \sigma := 5 \times 10^{-2},$$

$$\varrho_E^0 = 2 \times 10^2, \quad \varrho_C^0 = 3 \times 10^3, \quad c^0 = 1.$$

The above definition for $n_{T\sigma}(t=0,x)$ mimics an evolutionary scenario where most of the cancer cells are characterized by a low level of resistance to effector lymphocytes at time $t = 0$, i.e., $n_{T\sigma}(t=0,x)$ is mainly concentrated in $x = 0$. Furthermore, the following definitions are used in order to satisfy the hypothesis of Theorem 3.1:

$$\alpha_T := 5 \times 10^{-1}, \quad \alpha_C := 1.5 \times 10^3, \quad \kappa_{C,E} := 6 \times 10^{-4}, \quad \kappa_T := 8 \times 10^{-4},$$

$$\eta_T(x) := \hat{\eta}_T[1 + (1-x)^2], \qquad V_\sigma(t) = V(t) := \hat{V} \sin(0.5\pi t)_+ ,$$

where $\hat{\eta}_T := 5 \times 10^{-5}$ and $\hat{V} := 1 \times 10^{-1}$. The definitions of $\eta_T(x)$ and $V_\sigma(t)$ are chosen for illustration purposes. The other parameters of the model are set equal to the values provided by Table 1. Further considerations about the choice of the parameters can be found in Section 5.

The numerical results summarized by Figs. 1-2 illustrate the analytical results established by Theorem 3.1. In fact, $n_{T\sigma}(t,x)$ tends to concentrate as a Dirac mass in $x = 1$. From the biological perspective, these results highlight the ability of the model to reproduce cancer immunoediting. In fact, they show how the selective pressure exerted by effector lymphocytes sculpts the phenotypic distribution of the cancer cell population and paves the way for the emergence of resistance to immune effector mechanisms.

4. Optimal control problem: existence and necessary optimality conditions

We focus here on a cancer cell population homogeneously composed of highly resistant cells (i.e., cells characterized by the resistance level $x = 1$), where epimutations do not take place. Under this scenario, the dynamics of the system at hand can be described by the Cauchy problem defined by the following set of ODEs:

$$\frac{\mathrm{d}\varrho_T(t)}{\mathrm{d}t} = \left\{ \alpha_T \ln\left(\frac{\theta_T}{\varrho_T(t)}\right) - \hat{\eta}_T \varrho_E(t) - K_T[c(t)] \right\} \varrho_T(t) \tag{4.1}$$

$$\frac{\mathrm{d}\varrho_E(t)}{\mathrm{d}t} = \alpha_E \varrho_C(t) + \left\{ \gamma \frac{\varrho_T(t)}{\xi + \varrho_T(t)} - \beta_E - \eta_E \varrho_T(t) - K_E[c(t)] \right\} \varrho_E(t) \tag{4.2}$$

$$\frac{\mathrm{d}\varrho_C(t)}{\mathrm{d}t} = \alpha_C - \{\beta_C + K_C[c(t)]\} \varrho_C(t) \tag{4.3}$$

$$\frac{\mathrm{d}c(t)}{\mathrm{d}t} = \omega V(t) - \nu c(t) \tag{4.4}$$

endowed with initial conditions

$$\varrho_{T,C,E}(t=0) = \varrho_{T,C,E}^0 > 0 \quad \text{and} \quad c(t=0) = c^0 > 0. \tag{4.5}$$

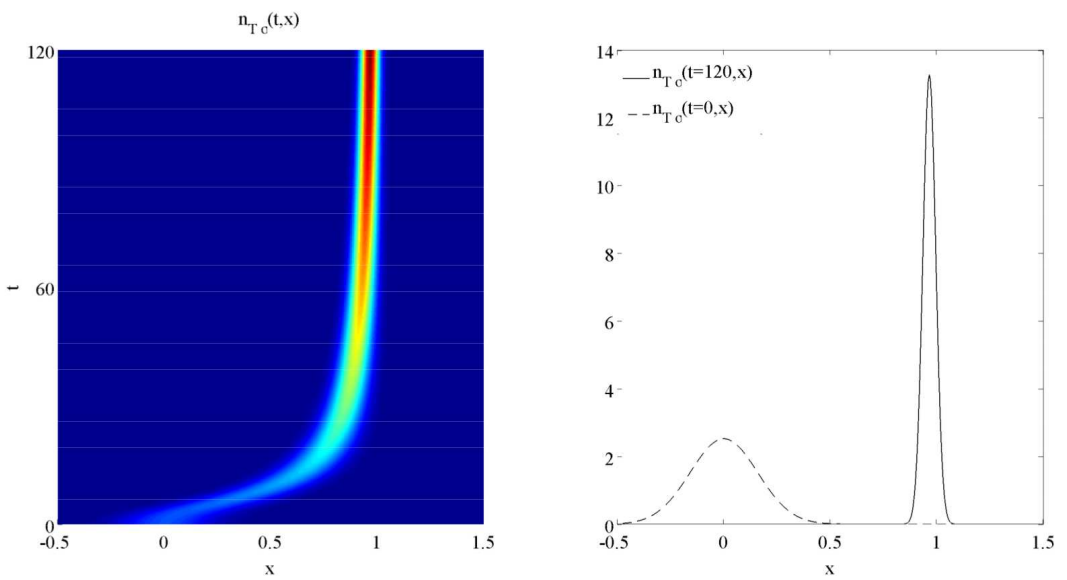

FIGURE 1. **Evolutionary dynamics of cancer cells and immunoediting in the limit of small epimutations.** (Left panel) Plot of $n_{T\sigma}(t,x)$. (Right panel) Plots of $n_{T\sigma}(t=0,x)$ (dashed line) and $n_{T\sigma}(t=120,x)$ (solid line).

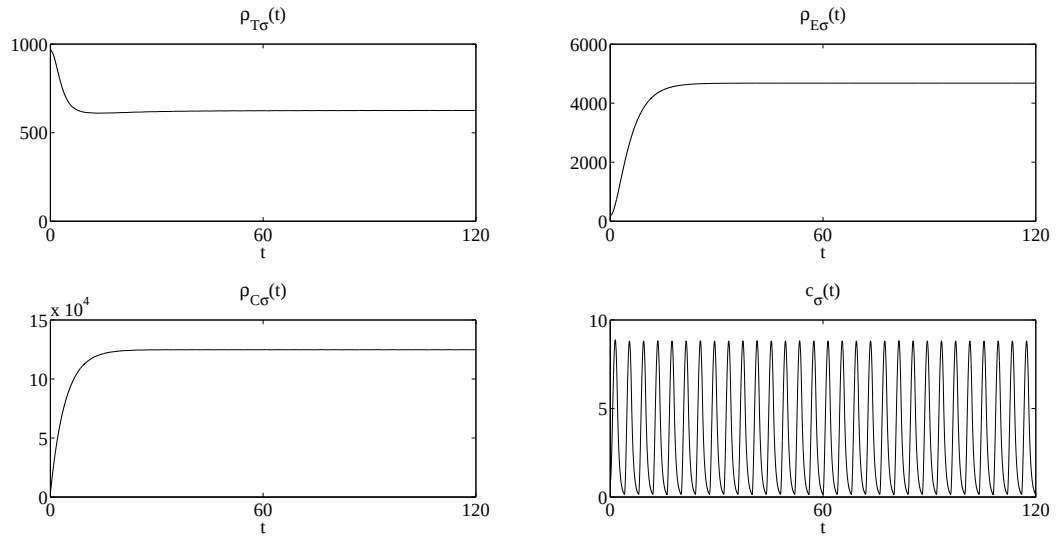

FIGURE 2. **Dynamics of the cell densities and the concentration of chemotherapeutic agents in the limit of small epimutations**. (Top-left panel) Plot of $\varrho_{T\sigma}(t)$. (Top-right panel) Plot of $\varrho_{E\sigma}(t)$. (Bottom-left panel) Plot of $\varrho_{C\sigma}(t)$. (Bottom-right panel) Plot of $c_\sigma(t)$.

Eqs. (4.1)-(4.4) can be seen as a reduced version of Eqs.(3.1)-(3.4) and are analogous to the ones presented in [38], apart from the fact that chemotherapies affect here cancer and immune cells through mass-action dynamics of the exponential form.

Cancer growth and chemotherapy imply a systemic cost for the human body, in general, and the immune cell populations at hand, in particular. Therefore, with the aim of checking the possibility for optimized anti-cancer protocols (i.e., therapies relying on a suitable minimization of the systemic cost at stake), we introduce a functional $J[V(t), \varrho_T(t)]$ that embodies this cost. We look for the existence of infusion rates allowing the minimization of this functional over $[0, t_f]$, under the conditions imposed by Eqs.(4.1)-(4.4). Since the collateral damages of cytotoxic agents imply a constrain on the infused dose, not all possible doses are admitted. This can be translated into mathematical terms by introducing a control set U and looking for $V(t) \in U$.

We define the objective cost functional as follows:

$$J[V(t), \varrho_T(t); t_f] := J_1[V(t); t_f] + J_2[\varrho_T(t); t_f], \quad \text{for } \ t \in [0, t_f], \tag{4.6}$$

where the functionals J_1 and J_2 measure, respectively, the systemic costs due to the proliferation of tumor cells and the infusion of chemotherapeutic agents. Among the possible definitions for $J_1[V(t)]$ and $J_2[\varrho_T(t)]$, we select the ones given hereafter:

$$J_1[V(t); t_f] := \varepsilon \int_0^{t_f} V^2(t)\, dt, \qquad J_2[\varrho_T(t); t_f] := \int_0^{t_f} \frac{\varrho_T(t)}{\varrho_T^0}\, dt\,, \tag{4.7}$$

which measure, respectively, the concentrations of tumor cells and cytotoxic agents inside the system over the time interval $[0, t_f]$. It is worth noting that the concentration of cancer cells at a given time instant t is normalized with respect to that at $t = 0$. Furthermore, a quadratic dependance on function V has been introduced to account for the nonlinear dependance of side effects on the infusion rate of cytotoxic agents [1, 34]. Finally, the coefficient ε is a positive weight constant on the control, and it stands for a measure of the level of collateral damage of chemotherapy. The higher the weight the greater the level of collateral damage.

At first, using the fact that the supersolutions $\overline{\varrho_T}$, $\overline{\varrho_E}$, $\overline{\varrho_C}$ and $\overline{c}$ of

$$\frac{\mathrm{d}\overline{\varrho_T}(t)}{\mathrm{d}t} = \tilde{\alpha}_T \overline{\varrho_T}(t), \quad \frac{\mathrm{d}\overline{\varrho_E}(t)}{\mathrm{d}t} = \gamma \overline{\varrho_E}(t) + \alpha_E \overline{\varrho_C}(t), \quad \frac{\mathrm{d}\overline{\varrho_C}(t)}{\mathrm{d}t} = \alpha_C, \quad \frac{\mathrm{d}\overline{c}(t)}{\mathrm{d}t} = \omega V(t),$$

are bounded on a finite time interval, we prove that there exists an optimal control that minimizes the objective functional (4.7). On account of brevity, in the above equations we have made use of the notation $\tilde{\alpha}_T = \alpha_T \ln\theta_T$.

Null solutions are subsolutions. Therefore, we can use a comparison result to see that the original system defined by (4.1)-(4.4) is bounded. Since we are dealing with a bounded system, the next step is to prove the existence of the optimal control. This can be accomplished by using a result from Fleming and Rishel (see [19], Corollary 4.1).

Theorem 4.1 (Existence)**.** *Given the objective functional $J[V(t), \varrho_T(t)]$ defined by* (4.6),(4.7)*, with $U = \{V(t)$ piecewise continuous $\mid 0 \le V(t) \le 1\,,\ \forall t \in [0, t_f]\}$, subject to system* (4.1)-(4.4)*, with initial conditions* (4.5)*, there exists an optimal control $V_{opt}(t) \in U$ such that*

$$\min_{V(t)\in U} J[V(t), \varrho_T(t)] = J[V_{opt}(t), \varrho_T(t)],$$

if the following conditions are satisfied:

i) The class of all initial conditions with a control $V(t) \in U$, such that each state equation is satisfied, is not empty.

ii) The admissible control set U is closed and convex.

iii) Each right-hand side of the state system is continuous, bounded above by a sum of the bounded control and the states, and can be written as a linear function of $V(t)$ with coefficients depending on the time and the state.

iv) The integrand of $J(V(t))$ is convex on U and it is bounded from below by $C_1V^2(t)$, with $C_1 > 0$.

Proof. Since the system (4.1)-(4.4) has bounded coefficients and the solutions are bounded on a finite time interval, we can use a result from Lukes (see [33], Theorem 9.2.1) to establish the existence of solutions to the state system. Dealing with the second condition, let us stress that the set U is closed and convex by definition. The third condition requires the right-hand side of system (4.1)-(4.4) to be continuous. Since ϱ_T is non-negative, this avoid the chance for $\gamma\frac{\varrho_T}{\xi+\varrho_T}\varrho_E$ to be undefined. Therefore, the entire system is continuous.

We denote by $\boldsymbol{m}(\boldsymbol{F}(t))$ the right-hand side of system (4.1)-(4.4) without the control variable $V(t)$ and let

$$\boldsymbol{f}(\boldsymbol{F}(t),V(t)) = \boldsymbol{m}(\boldsymbol{F}(t)) + \begin{pmatrix} 0 \\ 0 \\ \alpha_C \\ \omega V(t) \end{pmatrix}, \qquad \text{with} \quad \boldsymbol{F}(t) = \begin{pmatrix} \varrho_T(t) \\ \varrho_E(t) \\ \varrho_C(t) \\ c(t) \end{pmatrix}.$$

Using the boundedness of the solutions, we obtain

$$|\boldsymbol{f}(\boldsymbol{F},V)| \le \left| \begin{pmatrix} \tilde{\alpha}_T & 0 & 0 & 0 \\ 0 & \gamma & \alpha_C & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} \varrho_T \\ \varrho_E \\ \varrho_C \\ c \end{pmatrix} \right| + \left| \begin{pmatrix} 0 \\ 0 \\ \alpha_C \\ \omega V \end{pmatrix} \right| \le C_0(|\boldsymbol{F}| + |V|),$$

where C_0 depends on the coefficients of the state system (4.1)-(4.4).

In order to prove the convexity of the integrands of J, we need to verify that

$$J((1-s)u + sv, \varrho_T) \le (1-s)J(u,\varrho_T) + sJ(v,\varrho_T), \tag{4.8}$$

for all $s \in (0,1)$. Evaluating the difference between $J((1-s)u+sv,\varrho_T)$ and $(1-s)J(u,\varrho_T)+sJ(v,\varrho_T)$, we obtain:

$$\begin{aligned} & J((1-s)u+sv,\varrho_T) - [(1-s)J(u,\varrho_T) + sJ(v,\varrho_T)] \\ &= \frac{\varrho_T}{\varrho_T^0} + \varepsilon(u^2 - 2su^2 + s^2u^2 + s^2v^2 - 2s^2uv + 2svu) \\ &\quad - \left(\frac{\varrho_T}{\varrho_T^0} + \varepsilon u^2 - \varepsilon u^2 s + \varepsilon s v^2\right) \\ &= \varepsilon(s^2 - s)(u-v)^2 < 0. \end{aligned}$$

Since $s \in (0,1)$, we have $(s^2-s) < 0$ and the above equality leads us to conclude that (4.8) is verified.

Finally,

$$\frac{\varrho_T(t)}{\varrho_T^0} + \varepsilon V^2(t) \ge \varepsilon V^2(t),$$

which gives $C_1V^2(t)$ as lower bound, with $C_1 = \varepsilon$. □

Provided the existence result established by Theorem 4.1, the optimal control $V_{opt}(t)$ can be characterized by using the Pontryagin's Maximum/ Minimum Principle [41] to obtain:

Theorem 4.2 (Necessary optimality conditions)**.** *Given an optimal control $V_{opt}(t)$, and the solutions to the corresponding state system that minimize the functional $J[V(t), \varrho_T(t)]$ defined by* (4.6),(4.7)*, there exist adjoint variables $\lambda_i(t)$ for $i = 1, 2, 3, 4$ satisfying the following*:

$$\begin{aligned}
\frac{d\lambda_1(t)}{dt} &= \lambda_1(t)\left[\alpha_T\left(1-\ln\frac{\theta_T}{\varrho_T(t)}\right)+\beta_T\varrho_E(t)+\kappa_T(1-e^{-\mu_T c(t)})\right]\\
&\quad+\lambda_2(t)\left[\eta\varrho_E(t)-\gamma\frac{1}{(\xi+\varrho_T(t))^2}\varrho_E(t)\right]-\frac{1}{\varrho_T^0}\,,\\
\frac{d\lambda_2(t)}{dt} &= \lambda_1(t)\beta_T\varrho_T(t)+\lambda_2(t)\left[\beta_E-\gamma\frac{\varrho_T(t)}{\xi+\varrho_T(t)}+\eta\varrho_T(t)+\kappa_E(1-e^{-\mu_E c(t)})\right]\,,\\
\frac{d\lambda_3(t)}{dt} &= -\lambda_2(t)\alpha_E+\lambda_3(t)[\beta_C+\kappa_C(1-e^{-\mu_C c(t)})]\,,\\
\frac{d\lambda_4(t)}{dt} &= \lambda_1(t)\kappa_T\mu_T e^{-\mu_T c(t)}\varrho_T(t)+\lambda_2(t)\kappa_E\mu_E e^{-\mu_E c(t)}\varrho_E(t)\\
&\quad+\lambda_3(t)\kappa_C\mu_C e^{-\mu_C c(t)}\varrho_C(t)+\lambda_4(t)\nu\,,
\end{aligned}$$

where $\lambda_i(t_f) = 0$ for $i = 1, 2, 3, 4$. The optimal control $V_{opt}(t)$ can be represented as

$$V_{opt}(t)=\min\left\{1,\left(-\frac{\lambda_4(t)\omega}{2\varepsilon}\right)^+\right\}. \tag{4.9}$$

Proof. For the objective functional (4.7), the Hamiltonian is defined as

$$\begin{aligned}
H(t) &= \frac{\varrho_T(t)}{\varrho_T^0}+\varepsilon V^2(t)+\lambda_1(t)[\alpha_T\varrho_T(t)\ln\frac{\theta_T}{\varrho_T(t)}-c(t)\varrho_E(t)\varrho_T(t)\\
&\quad-\kappa_T(1-e^{-\mu_T c(t)})\varrho_T(t)]\\
&\quad+\lambda_2(t)\left[\alpha_E\varrho_C(t)-\beta_E\varrho_E(t)+\gamma\frac{\varrho_T(t)}{\xi+\varrho_T(t)}\varrho_E(t)\right]\\
&\quad-\lambda_2(t)\left[\eta\varrho_E(t)\varrho_T(t)-\kappa_E(1-e^{-\mu_E c(t)})\varrho_E(t)\right]\\
&\quad+\lambda_3(t)[\alpha_C-\beta_C\varrho_C(t)-\kappa_C(1-e^{-\mu_C c(t)})\varrho_C(t)]\\
&\quad+\lambda_4[-\nu c(t)+\omega V(t)]\,.
\end{aligned} \tag{4.10}$$

Since the control V is bounded, we introduce the Lagrangian as follows:

$$\mathcal{L}(t) = H(t) - w_1(t)V(t) - w_2(t)(1-V(t))\,.$$

Here, $H(t)$ is the Hamiltonian as defined in (4.10) and $w_i(t) \geq 0$, $i = 1, 2$, are penalty multipliers, such that $w_1(t)V(t) = 0$ and $w_2(t)(1 - V(t)) = 0$ at the optimal $V_{opt}(t)$. To characterize V_{opt}, we analyze the necessary optimality condition $\frac{\partial\mathcal{L}}{\partial V} = 0$. Here, $\frac{\partial\mathcal{L}}{\partial V} = \frac{\partial H}{\partial V} - w_1 + w_2 = 0$, or $2\varepsilon V + \lambda_4\omega - w_1 + w_2 = 0$.

Solving for the optimal control yields

$$V_{opt}(t) = \frac{-\lambda_4(t)\omega + w_1(t) - w_2(t)}{2\varepsilon}\,.$$

To achieve an explicit expression for the optimal control, i.e., without w_1 and w_2, a standard optimality technique can be applied. In particular, the following three cases can be considered:

i) On the set $\{t \,|\, 0 < V_{opt}(t) < 1\}$, $w_1(t) = 0 = w_2(t)$. Hence the optimal control is

$$V_{opt}(t) = \frac{-\lambda_4(t)\omega}{2\varepsilon}\,.$$

ii) On the set $\{t \,|\, V_{opt}(t) = 1\}$, $w_1(t) = 0$. Therefore,

$$1 = V_{opt}(t) = \frac{-\lambda_4 \omega - w_2(t)}{2\varepsilon}\,.$$

This implies that $0 \leq w_2(t) = -\lambda_4(t)\omega - 2\varepsilon$ and $1 = V_{opt}(t) \leq \dfrac{-\lambda_4(t)\omega}{2\varepsilon}$.

iii) On the set $\{t \,|\, V_{opt}(t) = 0\}$, $w_2(t) = 0$. Hence,

$$0 = V_{opt}(t) = \frac{-\lambda_4(t)\omega + w_1(t)}{2\varepsilon}\,.$$

Since $w_1(t) \geq 0$, then $\dfrac{-\lambda_4(t)}{2\varepsilon} \leq 0$. We notice that, in this case,

$$\left(\frac{-\lambda_4(t)}{2\varepsilon}\right)^+ = 0 = V_{opt}(t).$$

Combining these three cases together, it is possible to conclude that the optimal control is characterized by (4.9). The optimality system consists in the state system linked to the adjoint system, with initial and transversality conditions, as well as with identity (4.9). □

Remark 4.3. Let us note that the second derivative of the Lagrangian $\mathcal{L}$ with respect to V is positive; thus, a minimum occurs at V_{opt}. Furthermore, solving Eq. (4.4) yields

$$c(t) = c^0 e^{-\nu t} + \omega \int_0^t e^{-\nu(t-s)} V(s)\, ds\,.$$

As a result, if $V^{(1)}(t) \geq V^{(2)}(t)$, then $c^{(1)}(t) \geq c^{(2)}(t)$, where $c^{(i)}(t)$ denotes the fourth state component of the model defined by (4.1)-(4.4) and corresponding to the control $V^{(i)}(t)$.

5. Optimal control problem: numerics and biological considerations

In light of the results established in the previous section, we numerically investigate the controlled dynamics of Eqs. (4.1)-(4.4). In particular, we aim at illustrating how the solutions to the Cauchy Problem defined by endowing these equations with initial conditions (4.5) can be influenced by certain parameters, or initial conditions, which are make to vary, while the other ones are kept fixed. From a biological perspective, this means to use the present model as an *in silico* laboratory, where we study the response of cancer and immune cells to chemotherapeutic protocols that are optimal in the sense clarified in Section 4.

Simulations are performed in MATLAB. We use a version of the commercial software package MISER3 [24] to solve the optimal control problem [11] and evaluate the optimal infusion rate V_{opt} at each time $t \in [0, t_f]$, with $t_f = 100$ days. Along simulations, we tune the values of parameters ε (i.e., the level of collateral damage of chemotherapeutic agents) and $\kappa_{T,C,E}$ (i.e., the death rates of cells due to chemotherapeutic agents), as well as the value of the initial condition ϱ_T^0 (i.e., the initial concentration of cancer cells), according to the aim of the numerical analysis to be developed. In particular, the following cases are considered:

Case 1. $\varrho_0^T := 1.00 \times 10^2$, $\varepsilon = 10^{-6}$, $\kappa_{C,E} := 6 \times 10^{-1}$, $\kappa_T := 8 \times 10^{-1}$
Case 2. $\varrho_0^T := 1.00 \times 10^2$, $\varepsilon = 10^{-4}$, $\kappa_{C,E} := 6 \times 10^{-1}$, $\kappa_T := 8 \times 10^{-1}$
Case 3. $\varrho_0^T := 1.00 \times 10^2$, $\varepsilon = 1$, $\kappa_{C,E} := 6 \times 10^{-1}$, $\kappa_T := 8 \times 10^{-1}$

Case 4. $\varrho_0^T := 1.00 \times 10^7$, $\varepsilon = 1$, $\kappa_{C,E} := 6 \times 10^{-1}$, $\kappa_T := 8 \times 10^{-1}$
Case 5. $\varrho_0^T := 1.00 \times 10^2$, $\varepsilon = 1$, $\kappa_{C,E} := 6 \times 10^{-3}$, $\kappa_T := 8 \times 10^{-3}$.

From a biological perspective, the parameter settings related to Cases 1-3 mimic three distinct scenarios where three different kinds of chemotherapeutic agents, characterized by increasing levels of collateral damage, are delivered. On the other hand, Case 4 refers to the situation where, among the three classes of cytotoxic agents at hand, the ones characterized by the highest level of collateral damage are infused within a cancer cell population which is initially larger than that of the previous cases. Finally, focusing on a cancer cell population of the same size as the ones considered in Cases 1-3, a fourth kind of chemotherapeutic agents with lower cytotoxic effects is used in Case 5.

The other parameters of the model are kept fixed and equal to the values summarized by Table 1, which are selected in view of the considerations drawn in [38], in order to make the cell dynamics to be biologically consistent, as well as to ensure the convergence of the optimal control algorithm. We recall that the value of the time variable t is expressed in units of days; this choice is consistent with the values of the parameters in Table 1.

Parameter	Description	Value
θ_T	Carrying capacity of the cancer cell population	1×10^3
α_T	Proliferation rate of cancer cells	4.31×10^{-3}
$\tilde{\eta}_T$	Killing rate of cancer cells	3.41×10^{-10}
β_E	Death rate of effector lymphocytes	4.12×10^{-2}
γ	Recruitment rate of effector lymphocytes	1.50×10^{-2}
ξ	Steepness of the effector lymphocytes' recruitment	2.02×10^1
η_E	Inhibition rate of the effector lymphocytes'	2.00×10^{-11}
α_E	Production rate of effector lymphocytes	1.00×10^{-3}
β_C	Death rate of circulating lymphocytes	1.20×10^{-2}
ν	Decay rate of chemotherapeutic agents	9.00×10^{-1}
μ_T	Sensitivity of cancer cells to chemotherapies	7.00×10^{-2}
μ_C	Sensitivity of circulating lymphocytes to chemotherapies	1.00×10^{-2}
μ_N	Sensitivity of effector lymphocytes to chemotherapies	1.00×10^{-3}
α_C	Enhancement rate of circulating lymphocytes	7.5×10^3
ω	Chemotherapy effectiveness rate	10
ρ_C^0	Initial concentration of circulating lymphocytes	6.25×10^2
ρ_E^0	Initial concentration of effector lymphocytes	3×10^2
c^0	Initial concentration of cytotoxic agents	1

TABLE 1. Values of the parameters used during simulations.

It is worth noting that Figs. 3-7 show the trends of the following normalized functions

$$\frac{\varrho_{T,E,C}(t)}{\max\limits_{t\in[0,t_f]} \varrho_{T,E,C}(t)}, \qquad \frac{c(t)}{\max\limits_{t\in[0,t_f]} c(t)}, \tag{5.1}$$

instead of that of $\varrho_{T,E,C}(t)$ and $c(t)$, in order to allow a more effective comparison between the results obtained in Cases 1-5. The values of $V_{opt}(t)$ resulting from numerical simulations are fitted using a step-like interpolator to obtain the trends in Figs. 3-7.

5.1. Computational analysis

Under the parameter settings related to Cases 1-3, the dynamics of $\varrho_{E,C}(t)$ remain qualitatively unaltered, and the two functions undergo a monotonic increase over the whole simulation time window. In Cases 1-2, the function c increases and then decreases after a certain time, while a monotonic decrease of $c(t)$

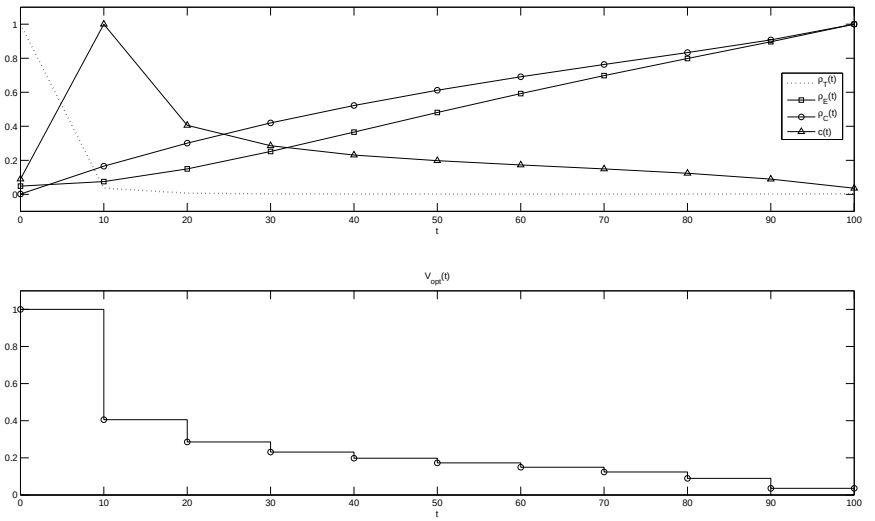

FIGURE 3. **Case 1.** (Top panel) Trends of $\varrho_T(t)$ (dotted line), $\varrho_E(t)$ ($\square$), $\varrho_C(t)$ ($\circ$) and $c(t)$ ($\triangle$). Each function is normalized with respect to the maximum value attained over $[0, t_f = 100]$, see (5.1). (Bottom panel) Trend of $V_{opt}(t)$.

occurs over $[0, t_f]$ in Case 3. With reference to $\varrho_T(t)$, a monotonic decreasing trend toward zero, an initial decreasing trend followed by a growth after a certain time instant close to t_f and a monotonic increasing trend can be, respectively, observed in Cases 1-3. Finally, $V_{opt}(t)$ is monotonically decreasing in the three cases at hand and it ranges between values that become progressively lower from Case 1 to Case 3.

On the other hand, making reference to Cases 4-5, a monotonic increase and decrease of $\varrho_E(t)$ and $\varrho_T(t)$ can be, respectively, observed. Function ϱ_C is monotonically increasing in Case 4, while it remains close to its initial value in Case 5. Finally, $V_{opt}(t)$ is monotonically decreasing in Case 4, while it decreases and then undergoes a slight increase at a certain time instant close to t_f in Case 5. It is worth noting that the values of $V_{opt}(t)$ in Case 5 are much smaller than that attained in Case 4.

5.2. Biological considerations

If the level of collateral damage of chemotherapeutic agents is sufficiently low (i.e., Case 1), the value of the optimal infusion rate can be sufficiently high, so that the cancer population is pushed toward extinction (see Fig. 3). If the level of collateral damage is higher (i.e., Case 2), then the optimal infusion rate becomes lower and cancer resurgence can occur (see Fig. 4). Even worst, if the level of collateral damage is too high (i.e., Case 3), and so the optimal infusion rate is too low, then the chemotherapeutic treatment becomes ineffective and malignant cells proliferate (see Fig. 5).

On the other hand, if the same kind of highly toxic chemotherapeutic agents are used against a sufficiently larger cancer cell population (i.e., Case 4), then tumor eradication can be achieved, since the optimal infusion rate can become higher (see Fig. 6). As a result, we are led to conclude that, in those cases where the level of collateral damage is high, optimal (in the sense considered here) chemotherapeutic protocols work better for tumors of larger size.

With reference to cancer cell populations of smaller size, and in the presence of high levels of collateral damage, making use of cytotoxic agents characterized by lower cytotoxicity in combination with immunity-boosters is a possible way to enhance the effectiveness of anti-cancer treatments (i.e., Case 5). In fact, in this way, an effective circulating lymphocyte response can be preserved (i.e., the concentration

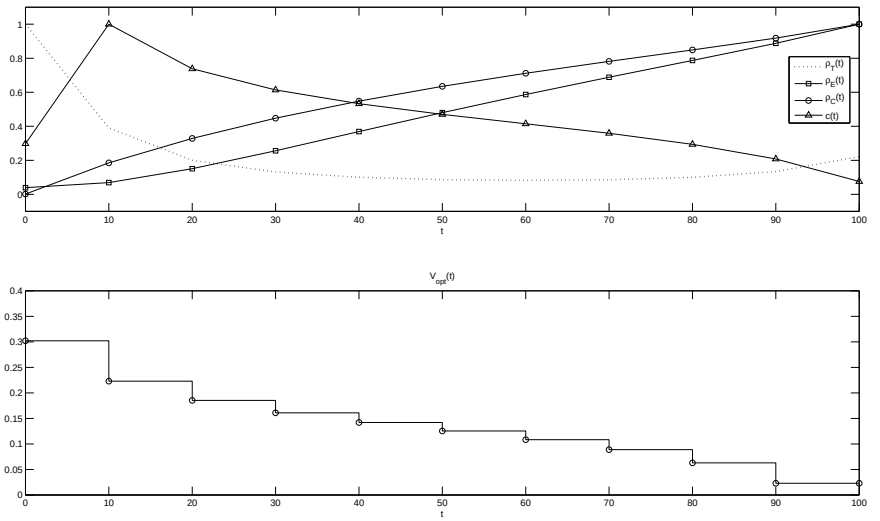

FIGURE 4. **Case 2**. (Top panel) Trends of $\varrho_T(t)$ (dotted line), $\varrho_E(t)$ ($\square$), $\varrho_C(t)$ ($\circ$) and $c(t)$ ($\triangle$). Each function is normalized with respect to the maximum value attained over $[0, t_f = 100]$, see (5.1). (Bottom panel) Trend of $V_{opt}(t)$.

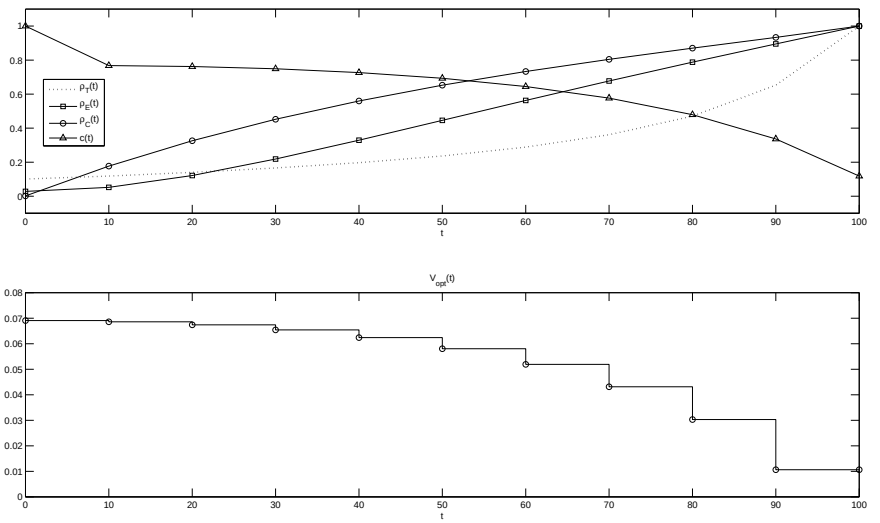

FIGURE 5. **Case 3**. (Top panel) Trends of $\varrho_T(t)$ (dotted line), $\varrho_E(t)$ ($\square$), $\varrho_C(t)$ ($\circ$) and $c(t)$ ($\triangle$). Each function is normalized with respect to the maximum value attained over $[0, t_f = 100]$, see (5.1). (Bottom panel) Trend of $V_{opt}(t)$.

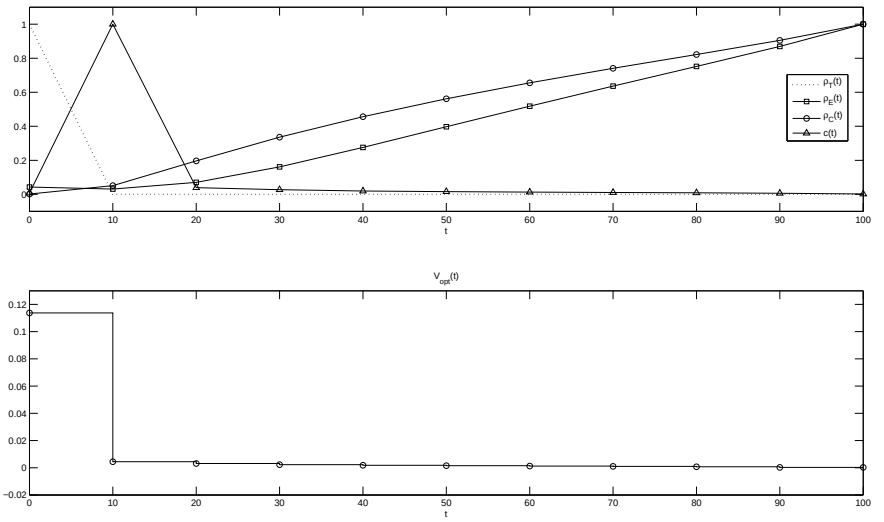

FIGURE 6. **Case 4**. (Top panel) Trends of $\varrho_T(t)$ (dotted line), $\varrho_E(t)$ ($\square$), $\varrho_C(t)$ ($\circ$) and $c(t)$ ($\triangle$). Each function is normalized with respect to the maximum value attained over $[0, t_f = 100]$, see (5.1). (Bottom panel) Trend of $V_{opt}(t)$.

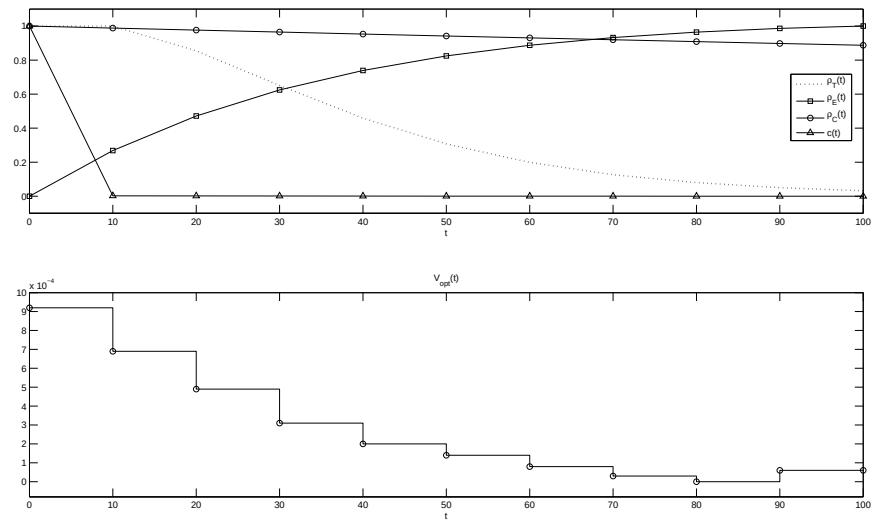

FIGURE 7. **Case 5**. (Top panel) Trends of $\varrho_T(t)$ (dotted line), $\varrho_E(t)$ ($\square$), $\varrho_C(t)$ ($\circ$) and $c(t)$ ($\triangle$). Each function is normalized with respect to the maximum value attained over $[0, t_f = 100]$, see (5.1). (Bottom panel) Trend of $V_{opt}(t)$.

of circulating lymphocytes can remain at a relatively constant level) and, thus, a sufficiently strong proliferation of effector lymphocytes can be maintained. As a consequence, tumor eradication can be achieved through immune action (see Fig. 7), even if the optimal infusion rate is low due to the constraints imposed by high levels of collateral damage.

These results highlight limitation in the usage of therapeutic protocols relying on chemotherapy only. In fact, they suggest that, while chemotherapeutic drugs characterized by high cytotoxic effects can be useful for treating tumors of large size, combination therapies relying on less cytotoxic chemotherapy in combination with immunity-boosters can be more effective against tumors of smaller size. Taken together, these results support the development of therapeutic protocols relying on combinations of less cytotoxic agents and immune-boosters to fight cancer in the early stages.

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