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Angiogenesis inhibition and tumor-immune interactions with chemotherapy by a control set-valued method

K. Kassara *, A. Moustafid

Systems and Control Group, University Hassan II, P.O. Box 5366, Casablanca, Morocco

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ABSTRACT

In this paper, two cancer therapies are investigated through their mathematical models. Namely, angiogenesis inhibition (P. Hahndfeldt, D. Panigrahy, J. Folkman, L. Hlatky, Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy, Cancer Res. 59, 1999, 4770–4775) and tumor-immune interactions with chemotherapy (L. De Pillis, W. Gu, K.R. Fister, T. Head, K. Maples, A. Murugan, T. Neal, K. Yoshida, Chemotherapy for tumors: an analysis of the dynamics and a study of quadratic and linear optimal controls. Math. Biosci. 209 (1), 2007, 292–315). The feedback protocols are determined by using a control set-valued method whose mathematical foundations are stated in (K. Kassara, A unified set-valued approach to control immunotherapy, SIAM J. Contr. Optim. 48 (2), 2009, 909–924), and which is demonstrated to be well suited for cancer control.

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1. Introduction

There is growing evidence that mathematical modeling [4,12,25,26] may have a tremendous impact on cancer research, equipping the biologists with new tools for better understanding why cancer develops and expands and for improving its treatment.

The term *angiogenesis* is constituted of two Greek words: angio, to mean blood vessel, and genesis, for beginning. It is used to describe the process of making new blood vessels the human body needs in order to develop and grow. Angiogenesis also means an important process in malignant tumor growth, where very small blood vessels are created, enabling it to expand. Anti-angiogenesis is a targeted therapy that consists of administering drugs called Angiogenesis Inhibitors (AIs), which enable blocking the development of normal new blood vessels, with a view to cut off the supply of oxygen and nutrients to the tumor.

Biologically validated ODE models for such a therapy were developed by Hahnfeldt et al. [13], Sachs et al. [27] and more lately, by d'Onofrio and Gandolfi [8], which stated delayed extensions of the previous models.

We also refer to the work of Anderson and Chaplain [1] which established a class of PDE models for tumor angiogenesis.

As a second cancer therapy we shall treat in this paper, we are concerned with studying the effects of chemotherapy on both the tumor cells and the immune system through the ODE model elaborated by de Pillis et al. [6]. They have included explicit representation of the immune system, as well as chemotherapy treatment and have used both linear and quadratic optimal control methods for deriving adequate values of the chemotherapy drug concentration.

To deal with the above mentioned therapies, we will use a control approach which is based on set-valued analysis and viability theory, see Kassara [14,16] and Kassara and Moustafid [15]. This is an alternative approach to optimal control techniques which are used for fighting cancer through ODE models. It enables the user to establish universal formulas for the feedback protocols with which the tumor can be asymptotically eradicated, taking into account constraints on the administered drugs. These protocols simply can be derived by doing selections from a parameterized set-valued map, and have the advantage to be explicitly dependent upon the cancer stage at each time. Further details are the focus of Section 3.

The paper is structured as follows. Section 2 focuses on the role of control theory as a tool to deal with cancer. In Section 3, the control set-valued approach to cancer will be outlined. Section 4 is devoted to angiogenesis inhibition and Section 5 investigates tumor-immune interactions with chemotherapy. In Section 6, we present concluding remarks and suggestions.

2. Control theory and cancer

The last two decades have seen a new wave of methods for the treatment of several cancer therapies, which are mainly based on mathematical modeling and control theory. Providing biologists and clinicians with challenging tools that might help them to

* Corresponding author.
E-mail addresses: kassarak@ams.org (K. Kassara), a.moustafid@gmail.com (A. Moustafid).

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predict the behavior of the cancer and elaborate adequate protocol strategies in order to fight it, taking into account both the patient quality of life and the model considered for cancer evolution.

For ODE and PDE models, the majority of these protocols demonstrate and spotlight the importance of looking at cancer treatment as a formal optimal control problem. An appropriate objective functional should first be designed, in such a way that when it is optimized, then a minimum of cancer cells are produced. Thereafter, the optimal protocols can be carried out, for instance, as solutions of the Hamilton–Jacobi equation, see Fister and Donnelly [11], Lenhart and Workman [23], Nandaa et al. [25], or else by using alternative methods as in Chereyron and Alamir [5].

Meanwhile, there are quite a few interesting direct methods that focus only on cancer cells, and aim at achieving their null density at a final time, either exactly, approximately or asymptotically. Especially for semi-linear parabolic PDE models, we refer to Kassara and El Jai [9] and Kassara [18]. They sought to expand the zones without tumor cells to the entire tissue by a suitable use of the concept of feedback spreading control by Kassara [17], in investigating the PDE model of Matzavinos et al. [24].

In the same spirit, Kassara [16] has investigated the ODE immunotherapy model of Kirschner and Pannetta [19] by following a direct approach based on viability theory and set-valued analysis, see Aubin [2] and Aubin and Frankowska [3] for viability theory.

For the sake of generality, the method was deeply investigated for an abstract class of ODE models in Kassara [14] and Kassara and Moustafid [15], leading to universal expressions of the protocols that can be provided as selections from parameterized set-valued maps. The latter take into account constraints on the administered substances, which allow for keeping the toxicity to the normal tissue acceptable.

Furthermore, in contrast to the optimal control approach, the set-valued framework allows of highlighting the well known connection between the initial cancer stage and its curability, as well as the minimality and smoothness of a protocol and their impact on the patient quality of life.

3. The set-valued approach

Here we are going to provide a brief outline of the set-valued control approach mentioned above, see Kassara [14] for more mathematical details. It involves the following class of non-linear control systems,

$$\dot{x} = f(x,\tau) + B(x,\tau)u, \tag{1a}$$

$$\dot{\tau} = \tau\psi(x,\tau) \tag{1b}$$

with initial conditions

$$x(0) = x_0, \quad \tau(0) = \tau_0, \tag{1c}$$

where the x_i's denote densities of cells in competition with cancer cells. While, we use $\tau$to denote density of the latter. Therefore the state (x,τ) evolves in $\mathbb{R}^n_+ \times \mathbb{R}_+$. The protocol (control) u stands for rates of the administered substances and takes values within the constraints subset,

$$K \doteq \left[0, u_1^{\max}\right] \times \cdots \times \left[0, u_p^{\max}\right]. \tag{2}$$

The field f and the function ψmap $\mathbb{R}^n \times \mathbb{R}$ into $\mathbb{R}^n$ and $\mathbb{R}$ respectively, and they are sufficiently smooth, while the operator B maps $\mathbb{R}^n \times \mathbb{R}$ into the space $\mathcal{L}(\mathbb{R}^p, \mathbb{R}^n)$.

Definition 1. We call a protocol any control $\bar{u} : [0,\infty) \to K$ such that system (1) has a global solution $(\bar{x},\bar{\tau})$ with values ranging in $\mathbb{R}^n_+ \times \mathbb{R}_+$, and satisfying $\lim_{t\to\infty}\bar{\tau}(t) = 0$.

Note that an important class of cancer models can be described by the family of ODE models (1).

3.1. The main results

Thanks to (1b) we merely get,

$$\bar{\tau}(t) = \tau_0 \exp\left(\int_0^t \psi(\bar{x}(s),\bar{\tau}(s))ds\right),$$

for each t in $[0,\infty)$. As a result, whenever a control $\bar{u}$ produces a trajectory $(\bar{x},\bar{\tau})$ with values in the subset,

$$D_\beta \doteq \{(x,\tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+ | \psi(x,\tau) \leqslant -\beta\}$$

for some $\beta > 0$, it will follow that $\bar{\tau}$ satisfies the exponential estimate,

$$0 < \bar{\tau}(t) \leqslant \tau_0 \exp(-\beta t) \quad \text{for all } t \geqslant 0.$$

Thereby $\bar{u}$ is a protocol in the sense of Definition 1. This leads us to use the regulation map of viability theory as introduced by Aubin [2], which is given in the present setting as follows,

$$\mathcal{F}_\beta(x,\tau) \doteq \{u \in K | (f(x,\tau) + B(x,\tau)u, \tau\psi(x,\tau))' \in T_{D_\beta}(x,\tau)\}, \tag{3a}$$

where

$$T_{D_\beta}(z) \doteq \left\{y \in \mathbb{R}^{n+1} | \liminf_{h\downarrow 0} \frac{d(z+hy, D_\beta)}{h} = 0\right\}, \tag{3b}$$

stands for the *contingent cone* to subset D_β at point $z \in D_\beta$. Consequently, feedback protocols can be provided as continuous selections $u = \sigma(x,\tau)$ of the regulation map given by (3a), that is to say, $\sigma(x,\tau) \in \mathcal{F}_\beta(x,\tau)$ for all $(x,\tau) \in D_\beta$, for appropriate β's.

It is of interest to stress the following fact about the above feedback protocols: because they are supposed to produce viable solutions $(\bar{x},\bar{\tau})$ in subset $D_\beta$the corresponding cancer cells will have decreasing densities, as $\psi(\bar{x}(t),\bar{\tau}(t)) \leqslant 0$ for all t, entails $\dot{\bar{\tau}}(t) \leqslant 0$ for all t.

According to Kassara [14], the regulation map given in (3a) can be expressed for each $(x,\tau) \in D_\beta$, as follows,

$$\mathcal{F}_\beta(x,\tau) = \left| \begin{array}{ll} K & \text{if } \psi(x,\tau) < -\beta, \\ C(x,\tau) & \text{if } \psi(x,\tau) = -\beta, \end{array} \right. \tag{4a}$$

where,

$$C(x,\tau) \doteq \{u \in K | \langle h(x,\tau), u\rangle \geqslant \ell(x,\tau)\}. \tag{4b}$$

Here, the functions $h$and ℓ are given by,

$$h(x,\tau) \doteq -B'(x,\tau)\nabla_x\psi(x,\tau), \tag{4c}$$

$$\ell(x,\tau) \doteq \langle \nabla_x\psi(x,\tau), f(x,\tau)\rangle + \tau\psi(x,\tau)\frac{\partial\psi}{\partial\tau}(x,\tau), \tag{4d}$$

where

$$\nabla_x\psi(x,\tau) \doteq \left(\frac{\partial\psi}{\partial x_1}(x,\tau), \ldots, \frac{\partial\psi}{\partial x_n}(x,\tau)\right)',$$

with $(\cdot)'$ denoting the transpose operator. Now we need to consider the following assumptions.

Assumption 1. There exist functions m_1 and m_2 which map bounded subsets into bounded images, and satisfy for all (x,τ) in D_β,

$$\|f(x,\tau)\| \leqslant m_1(\tau)(\|x\| + 1) \quad \text{and} \quad \|B(x,\tau)\| \leqslant m_2(\tau)\|x\|.$$

Assumption 2. The functions h and ℓ. respectively given by Eqs. (4c) and (4d) satisfy the statement below:

For all $(x,\tau) \in D_\beta$, there exists $u \in K$ such that $\langle h(x,\tau), u\rangle > \ell(x,\tau)$.

In a brief manner, the linear growth Assumption 1 will guarantee the existence of a global solution, i.e. on the horizon $[0,\infty)$. As regards Assumption 2, it first implies that $C(x,\tau)$ is non-empty for all (x,τ), and plays a crucial role in the proof that the minimal selection of the regulation map $\mathcal{F}_\beta$ provides a feedback protocol law, despite its discontinuity.

In the sequel we will use the following notations,

$$\Omega_- \doteq \{(x,\tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+ | \psi(x,\tau) < 0\}, \tag{5a}$$

$$\Omega_+ \doteq \{(x,\tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+ | \psi(x,\tau) \geqslant 0\}. \tag{5b}$$

Then we are in a position to state the first main result, see the proof in [14].

Theorem 1. *Let (x_0,τ_0) belong to Ω_- and assume that there exists β in the interval $[0, -\psi(x_0,\tau_0)]$ for which both Assumptions 1 and 2 are satisfied. Then both the minimal selection and any continuous selection of the regulation map $\mathcal{F}_\beta$ provide feedback protocols for which the cancer cells:*

(a) *have a decreasing density $\bar{\tau}$,*
(b) *satisfy the estimate $\bar{\tau}(t) \leqslant \tau_0 e^{-\beta t}$ for all t.*

Now, we turn to address the issue in which $(x_0,\tau_0) \in \Omega_+$, where Ω_+ is expressed by Eq. (5b). The key idea in order to deal with this instance, consists of trying to bring the cancer to a better stage $(x_1,\tau_1) \in \Omega_-$ at a time t_1, beyond which one then can apply either the minimal protocol law (7) or a continuous protocol law from the family of laws (9). The result below will detail our point of view.

To that end, we need first to introduce the following map,

$$C_\kappa(x,\tau) \doteq \{u \in K | \langle h(x,\tau), u\rangle \geqslant \ell(x,\tau) + \kappa\}, \tag{6}$$

for each $(x,\tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+$, where κ stands for a non-negative number, and h, ℓ are given, respectively in (4c) and (4d).

Theorem 2. *Let (x_0,τ_0) belong to Ω_+. Assume that, for some positive number κ, the map C_κ above has a continuous selection σ_κ for which system (1) admits a solution $(\bar{x},\bar{\tau})$ on the interval $[0,t_1]$ in such a manner that $\kappa t_1 > \psi(x_0,\tau_0)$. Then σ_κ steers system (1) from (x_0,τ_0) to Ω_- at time t_1, i.e., $(\bar{x}(t_1),\bar{\tau}(t_1)) \in \Omega_-$.*

Proof. We get for each $t \geqslant 0$,

$$\psi(\bar{x}(t_1),\bar{\tau}(t_1)) = \psi(x_0,\tau_0) + \int_0^{t_1}\left[\langle \nabla_x\psi(\bar{x}(s),\bar{\tau}(s)), \dot{\bar{x}}(s)\rangle + \dot{\bar{\tau}}(s)\frac{\partial\psi}{\partial\tau}(\bar{x}(s),\bar{\tau}(s))\right]ds.$$

Next, by putting $\bar{u} \doteq \sigma_\kappa(\bar{x},\bar{\tau})$, we use formulas (4c) and (4d) to get

$$\psi(\bar{x}(t_1),\bar{\tau}(t_1)) = \psi(x_0,\tau_0) - \int_0^{t_1}[\langle h(\bar{x}(s),\bar{\tau}(s)), \bar{u}(s)\rangle - \ell(\bar{x}(s),\bar{\tau}(s))]ds.$$

Since $\sigma_\kappa$is a selection of the map $C_\kappa(\cdot)$ then we have

$\psi(\bar{x}(t_1),\bar{\tau}(t_1)) \leqslant \psi(x_0,\tau_0) - \kappa t_1$.

As $\kappa t_1 > \psi(x_0,\tau_0)$ it follows that $\psi(\bar{x}(t_1),\bar{\tau}(t_1)) < 0$. □

3.2. Discussion and important facts

According to Eq. (3a), the minimal selection that is mentioned in Theorem 1 is given by the following expression,

$$\mu_\beta(x,\tau) \doteq \begin{vmatrix} 0 & \text{if } \psi(x,\tau) < -\beta, \\ \pi_{C(x,\tau)}(0) & \text{if } \psi(x,\tau) = -\beta, \end{vmatrix} \tag{7}$$

for all $(x,\tau) \in D_\beta$, where $\pi_{C(x,\tau)}(\cdot)$ denotes the operator of best approximation on the closed convex subset $C(x,\tau)$. Thus, for $\psi(x,\tau) = -\beta$, the value of $\mu_\beta(x,\tau)$ can be derived by solving the quadratic program under linear inequality constraints,

$$\min\{\|u\|^2 \text{ subject to} : u \in K \quad \text{and} \quad \langle h(x,\tau), u\rangle \geqslant \ell(x,\tau)\}. \tag{8}$$

In the remainder of the paper, we therefore will call this law the minimal protocol law.

However, because the total amount of drugs to be minimized corresponds to $\Sigma_{i=1}^p u_i$ (rather than $\Sigma_{i=1}^p u_i^2$), it would be of interest to seek selections $u = \sigma_\star(x,\tau)$ which solve the linear program,

$$\min\{\Sigma_{i=1}^p u_i \text{ subject to} :\ u \in K \text{ and } \langle h(x,\tau), u\rangle \geqslant \ell(x,\tau)\}.$$

Unfortunately, and contrary to the minimal selection, the above selections $\sigma_\star$ need not produce global solutions to the system, furthermore the problem of determining a continuous selection among the minimizers is found to be quite hard.

While, a family of continuous feedback protocols can be provided through the expression below,

$$\zeta_\beta(x,\tau) \doteq \exp(\psi(x,\tau) + \beta)\pi_{C(x,\tau)}(0), \tag{9}$$

for each $(x,\tau) \in D_\beta$. It actually stands for a continuous mapping, because both mappings ψ and $\pi_{C(\cdot,\cdot)}(0)$ are continuous. The latter does, thanks to Assumption 2.

It should be convenient to notice that our approach highlights two notions of great importance in medicine, because they have extreme relevance to the patient quality of life during the treatment. The first notion involves the amounts of the administered drugs that are to be kept at minimum, as expressed in Eq. (7). The second one, turns out to be no less important, and concerns smoothness of the protocols formulated. It actually has received equal attention in our analysis, as demonstrated by Eq. (9).

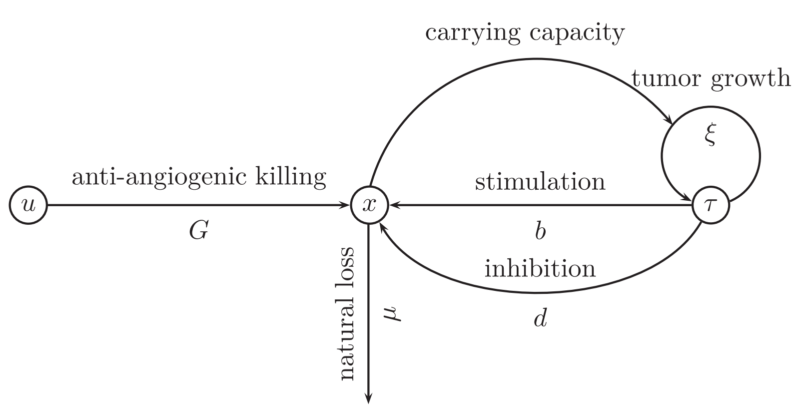

Fig. 1. Interactions between model variables viewed as compartments.

We remark that minimality and smoothness are somewhat opposite concepts here: the so-called minimal protocol law is discontinuous!

It will be appropriate to make the following warning about the feedback control σ_κ in Theorem 2: the corresponding cancer cells need not decrease over the horizon $[0, t_1]$, the aim of that control is only to bring the cancer to the stage described by the domain Ω_-.

The feedback protocol that can be used in the therapy is then given by the expression,

$$\sigma \doteq \begin{vmatrix} \sigma_\kappa & \text{on } [0, t_1], \\ \zeta & \text{on } [t_1, \infty), \end{vmatrix} \tag{10}$$

where ζ stands for a protocol law as derived by Theorem 1, but relatively to the initial cancer stage (x_1, τ_1) which belongs to Ω_-, as required by this theorem. Thereby the cancer cells will decrease beyond time t_1 in contrary to the beginning of the therapy, where the sense of their variation may be uncertain.

Both Theorems 1 and 2 unveil the well known fact in oncology that the curability of a cancer (existence of a protocol) is closely dependent upon its initial stage. This obviously suggests us to make the following associations, which entail the primary cancer staging below:

(a) For $(x_0, \tau_0) \in \Omega_-$ as in Theorem 1, because a protocol does exist and further has the property that cancer cells will exponentially decrease to zero, we thereby devote the condition $(x_0, \tau_0) \in \Omega_-$ to describe a *less developed cancer* corresponding to stage I. This is the less serious instance: the tumor may be eradicated in quite comfortable circumstances.

(b) The instance $(x_0, \tau_0) \in \Omega_+$ that is the purpose of Theorem 2 is more complicated, since existence of a protocol requires more conditions and the cancer cells need not be decreasing in the beginning of the therapy. We then say that the tumor is *more advanced*, or it is in stage II.

(c) Eventually when there is no protocol in the sense of Definition 1, this unfortunately means that cancer is so advanced that it is not curable. We say that it is in stage III.

Table 1
Models for stimulation terms.

Parameter γ	$S(x,\tau)$	Model
1	$b\tau$	Hahnfeldt et al. [13]
0	bx	d'Onofrio and Gandolfi [7]

Table 2
Parameters of model (11).

Coefficient	Interpretation	Value	Dimension
ξ	Tumor growth parameter	0.084	day^{-1}
μ	Natural loss of endothelial support	0.02	day^{-1}
b	Stimulation parameter,'birth'	5.85	day^{-1}
d	Inhibition parameter,'death'	0.00873	mm^{-2} day^{-1}
G	Anti-angiogenic killing parameter	0.15	conc^{-1} day^{-1}
u^{max}	Upper limit on concentration	75	conc

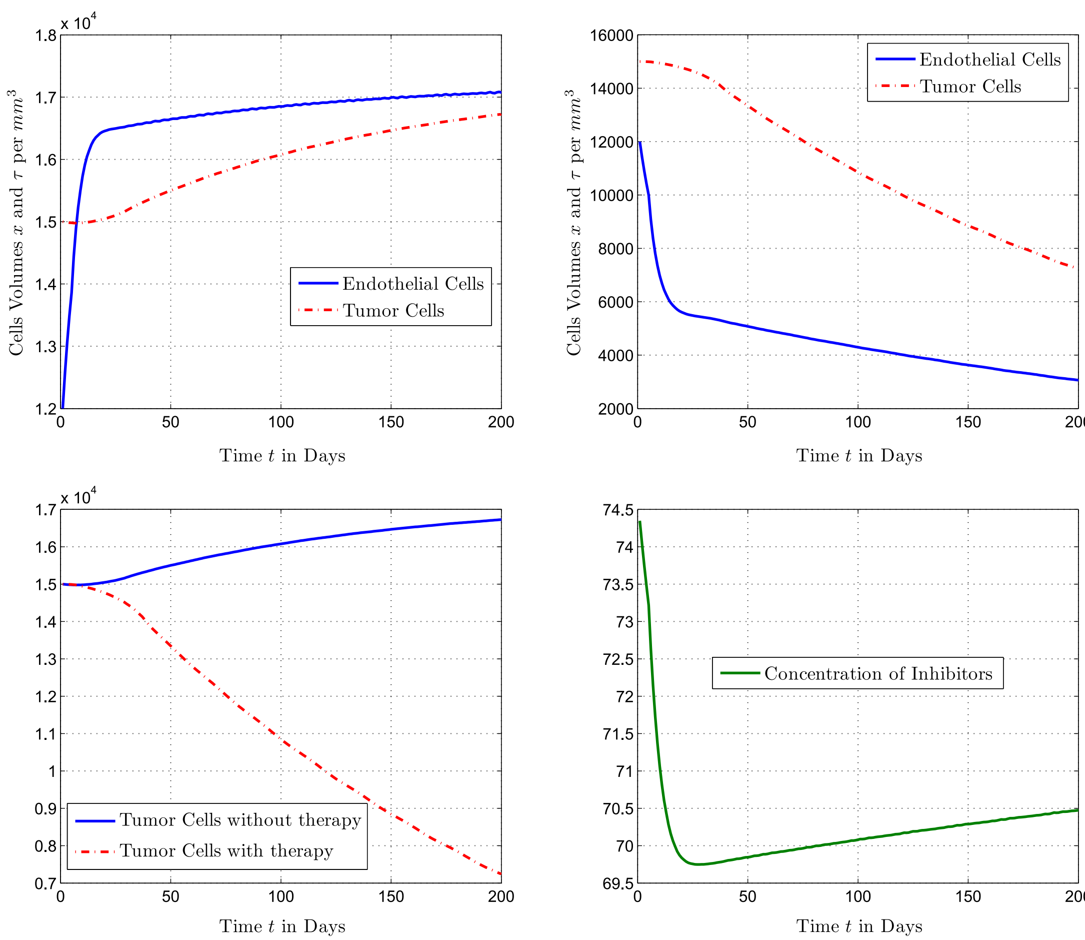

Fig. 2. Treatment for cancer with initial stage $(x_0, \tau_0) \doteq (12000, 15000)$. Top left: evolution under no therapy ($u \equiv 0$). Top right, using anti-angiogenic protocol $u \equiv \zeta_{0.01}$ as expressed by (13). Bottom left, impact of anti-angiogenic therapy on the behavior of tumor cells. Bottom right, plot of the administered inhibitors starting with the maximum value 74.35.

Ultimately, the study reveals the key role that may play function ψ, of Eq. (1b), in cancer staging. As a further remark of interest, one therefore can note the close dependence of both protocols (7) and (9) upon the cancer stage.

4. Application to anti-angiogenic therapy

A naturally arising issue to address, because of extreme medical interest, concerns scheduling AIs in order to eradicate the tumor. One usual approach to deal with, consists of using techniques from optimal control theory like for other cancer therapies, taking the path of Ergun et al. [10], Ledziwicz and Schättler [21] and more recently Ledziwicz et al. [20] and d'Onofrio and Gandolfi [7]. Seeking to determine how to administer AIs in order to minimize the tumor cells volume.

Alternatively to the approaches above, Ledziwicz and Schättler [20–22] have applied geometric methods of non-linear control to deal with a mathematical model for antiangiogenic treatments.

4.1. The model

We consider the family of anti-angiogenesis models built in Hahnfeldt et al. [13]. For each time t the carrying capacity of the vasculature is denoted by $x(t)$, and the volume of primary tumor cells by $\tau(t)$. The models consist of the following non-linear coupled ODEs,

$$\dot{x} = -\mu x + S(x,\tau) - I(x,\tau) - Gxu, \tag{11a}$$

$$\dot{\tau} = \tau\psi_\alpha(x,\tau), \tag{11b}$$

where the terms S and I are provided by the dynamics for the carrying capacity and denote, respectively the stimulation term and the inhibition term. They can be expressed as follows,

$$S(x,\tau) \doteq b\tau^\gamma x^{1-\gamma}, \text{ and } I(x,\tau) \doteq d\tau^{\frac{2}{3}}x, \tag{11c}$$

for all (x,τ), where the parameter γ takes values in the interval $[0,1]$ and the coefficients b and d stand respectively for the birth rate and the death rate. The term μx describes the loss of the endothelial cells through natural causes (death, etc.). The term Gxu represents a loss of endothelial cells due to the additional outside inhibition which the concentration is giving by the indeterminate control term u, with the upper limit $u^{\max}$ previously fixing maximum dose at which inhibitors can be given, the constant G represents the anti-angiogenic killing coefficient.

Dynamics for the volume of primary tumor cells obeys the general logistic growth law of cell growth, in which the function ψ_α has the form,

$$\psi_\alpha(x,\tau) \doteq \xi\left(1 - \left(\frac{\tau}{x}\right)^\alpha\right), \tag{11d}$$

where ξ denotes a tumor growth coefficient and α is a non-negative parameter. Table 1 lists famous instances of the literature corresponding to extreme values of the parameter γ.

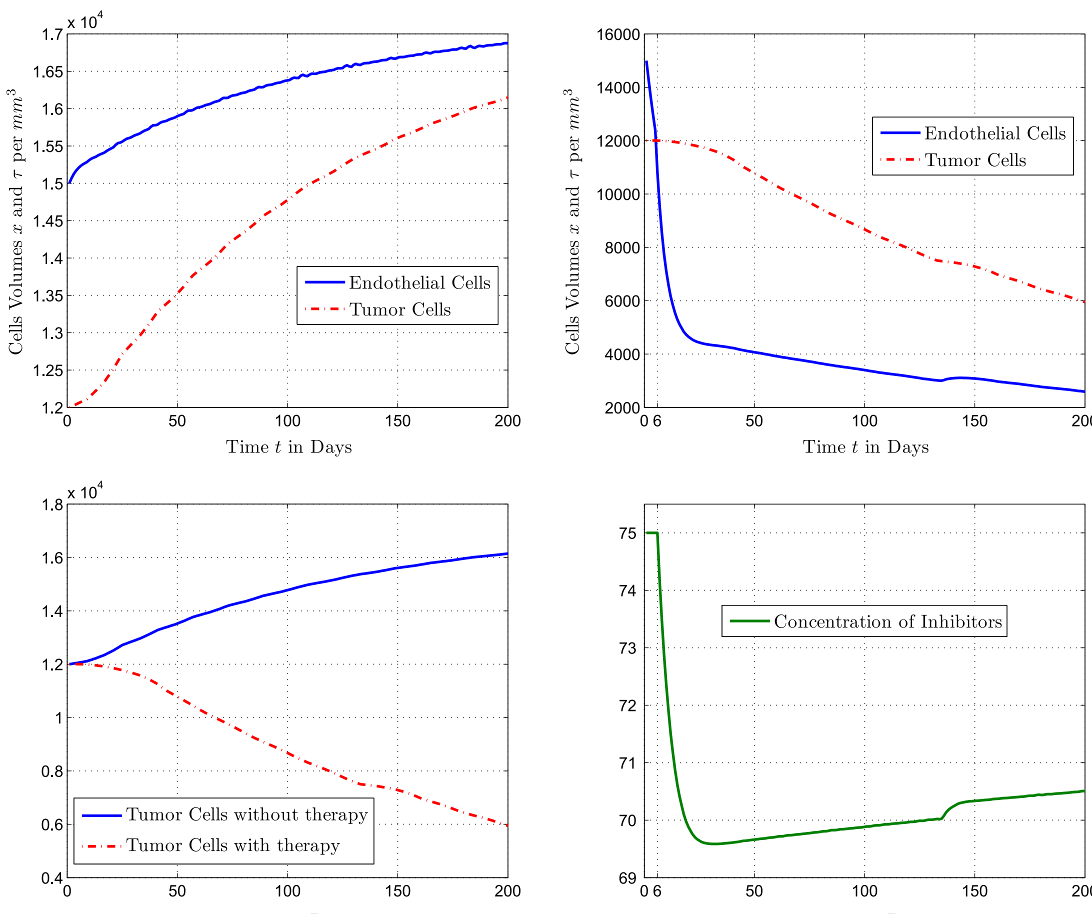

Fig. 3. Anti-angiogenic therapy for cancer with initial stage $(x_0,\tau_0) \doteq (15\,000, 12\,000)$. Top left, evolution under no treatment ($u \doteq 0$). Top right, using the protocol anti-angiogenic therapy with protocol $u \doteq \sigma$ expressed by (13) and (14) with $\kappa = 0.0025$, $t_1 \doteq 6$ days, $(x_1,\tau_1) \doteq (10812, 12002)$ and $\beta = 0.01$. Bottom left, impact of the therapy on the behavior of tumor cells. Bottom right, plot of administered inhibitors.

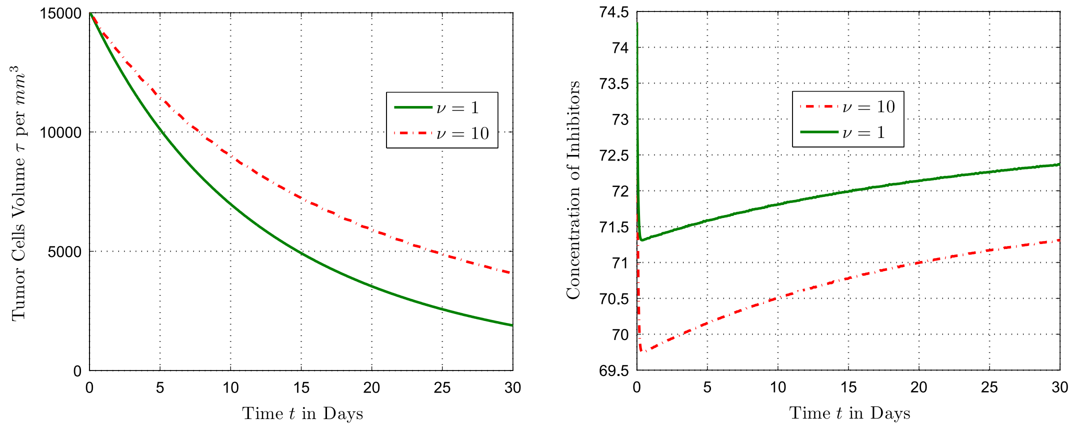

Fig. 4. Model (15) starting at $(x_0, \tau_0) = (12000, 15000)$ with treatments: $u \equiv \zeta^1_{0.01}$ and $u \equiv \zeta^{10}_{0.01}$ expressed by (16).

The presence of the control variable $u$in the x-dynamics (11a) allows one to control indirectly tumor cells volume τ by means of endothelial cells x. In Fig. 1 we give a schematic view showing the key players in tumor anti-angiogenesis interactions.

In the following, we will set the problem of scheduling AI's in the context of the unified set-valued method of Section 3.

4.2. Expression of the protocols

First of all, we note that the Angiogenesis model (11a) obviously satisfies the general setting of the class of systems (1), with the dynamics given as follows,

$$f(x,\tau) \doteq -\mu x + b\tau^{\gamma}x^{1-\gamma} - d\tau^{\frac{2}{3}}x,$$

and,

$$B(x,\tau) \doteq -Gx\tau \quad \text{and} \quad \psi(x,\tau) \doteq \psi_{\alpha}(x,\tau),$$

for all $(x,\tau) \in \mathbb{R}^2_+$. The protocol u has values ranging in the interval $[0, u^{\max}]$.

The expressions of functions h and ℓ, respectively defined by (4c) and (4d), are given by,

$$h(x,\tau) = \alpha\frac{\xi}{G}\frac{\tau^{\alpha}}{x^{\alpha+2}},$$

for all $(x,\tau) \in \mathbb{R}^2_+$, and

$$l(x,\tau) = \alpha\xi\frac{\tau^{\alpha-1}}{x^{\alpha}}\left(\frac{\tau}{x}f(x,\tau) - \psi_{\alpha}(x,\tau)\right),$$

for all $(x,\tau) \in \mathbb{R}^2_+$. Then the minimal selection (7) and the family of continuous selections (9) can be respectively provided as follows,

$$\mu_{\beta}(x,\tau) = \begin{vmatrix} 0 & \text{if } \psi_{\alpha}(x,\tau) < -\beta, \\ \min(u^{\max}, \varrho(x,\tau)) & \text{if } \psi_{\alpha}(x,\tau) = -\beta \end{vmatrix} \tag{12}$$

and,

$$\zeta_{\beta}(x,\tau) = \exp(\psi_{\alpha}(x,\tau) + \beta)\min(u^{\max}, \varrho(x,\tau)), \tag{13}$$

for all $(x,\tau) \in \mathbb{R}^2_+$, where the function ϱ is defined as follows

$$\varrho(x,\tau) \doteq \max\left(0, Gx\left(f(x,\tau) - \frac{x}{\tau}\psi_{\alpha}(x,\tau)\right)\right),$$

for all $(x,\tau) \in \mathbb{R}^2_+$. We also give the expression of the continuous selection σ_{κ} of Eq. (10),

$$\sigma_{\kappa}(x,\tau) = \min(u^{\max}, \vartheta_{\kappa}(x,\tau)), \tag{14}$$

Table 3
Model variables description.

Eq.	Term	Description
(17a)	$g\frac{\tau}{h+\tau}x_1$	Stimulatory effect of tumor cells on effector cells
	$-rx_1$	Death of effector cells
	$-px_1\tau$	Inactivation of effector cells by tumor cells
	$-k_1x_1x_3$	Death of effector cells induced by chemotherapy
	$s_1u_1(t)$	Intervention of immunotherapy over time t
(17b)	$-\delta x_2$	Death of circulating lymphocytes
	$-k_2x_3x_2$	Death of circulating lymphocytes induced by chemotherapy
(17c)	$-\gamma x_3$	Exponential decay of chemotherapy
	$u_2(t)$	Intervention of chemotherapy over time t
	$a\tau(1-b\tau)$	Logistic tumor growth
(17d)	$-c_1x_1\tau$	Death of tumor cells induced by effector cells
	$-k_3x_3\tau$	Death of tumor cells induced by chemotherapy

Table 4
Parameters of model (17).

Parameter	Interpretation	Value	Dimension
a	Tumor growth rate	4.31×10^{-3}	day^{-1}
b	Inverse of carrying capacity	1.02×10^{-14}	cell^{-1}
c_1	Fractional tumor cell kill by effector cells	3.41×10^{-10}	cell^{-1}day^{-1}
f	Death rate of effector cells	4.12×10^{-2}	day^{-1}
g	Maximum effector cell recruitment rate by tumor cells	1.5×10^{-2}	day^{-1}
h	Steepness coefficient of the effector cell recruitment curve	2.02×10^{1}	cell^2
k_2, k_3	Fractional effector cell and circulating lymphocyte kill by chemotherapy	6.00×10^{-1}	day^{-1}
k_1	Fractional tumor cell kill by chemotherapy	8.00×10^{-1}	day^{-1}
p	Effector cell inactivation rate by tumor cells	2.00×10^{-11}	cell^{-1}day^{-1}
s_1	Constant source of effector cells	1.2×10^{4}	cellsday^{-1}
s_2	Constant source of circulating lymphocytes	7.50×10^{8}	cellsday^{-1}
δ	Death rate of circulating lymphocytes	1.2×10^{-2}	day^{-1}
γ	Rate of chemotherapy drug decay	9.00×10^{-1}	day^{-1}

for all $(x,\tau)\in\mathbb{R}^2_+$, where the function ϑ_κ is given as follows

$$\vartheta_\kappa(x,\tau)\doteq\max\left(0, Gx\left(f(x,\tau)-\frac{x}{\tau}\psi_\alpha(x,\tau)\right)+\frac{\kappa}{\alpha}\frac{G}{\xi}\frac{x^{\alpha+2}}{\tau^\alpha}\right).$$

for all $(x,\tau)\in\mathbb{R}^2_+$.

4.3. Numerical simulations

We take $\alpha = 1$, so that the model to investigate is as follows,

$$\dot{x}=-\mu x+b\tau-d\tau^{\frac{2}{3}}x-Gxu, \tag{15a}$$

$$\dot{\tau}=\xi\tau\left(1-\frac{\tau}{x}\right). \tag{15b}$$

Let (x_0,τ_0) be given as an initial vascular endothelial/tumor data. To ensure a successful therapy, we first proceed to check the stage condition in Theorem 1,

$$\psi_1(x_0,\tau_0)<0,$$

which reduces here to $x_0 < \tau_0$. Once checked, we can get the appropriate inhibitor doses by choosing to formulate the protocol law $u\doteq\zeta_\beta(\cdot,\cdot)$, as given by (13) for

$$0<\beta\leqslant-\psi_1(x_0,\tau_0).$$

Contrariwise, if we have $x_0\geqslant\tau_0$, we first try to steer system (15) from the state (x_0,τ_0) to a state (x_1,τ_1) such that $x_1 < \tau_1$, by considering the protocol $u\doteq\sigma_\kappa$ for $\kappa t_1 > \psi_1(x_0,\tau_0)$, and then we can administer inhibitor doses by the continuous selection employed in the first case. We can minimize continuous doses as much as wanted by introducing a non-negative real parameter v in (13) as follows:

$$\zeta^v_\beta(x,\tau)\doteq\exp(v(\psi_1(x,\tau)+\beta))\min(u^{\max},\varrho(x,\tau)). \tag{16}$$

The values of the parameters in model (11), along with their interpretations and dimensions, are listed in Table 2.

Next we provide numerical results concerning two instances with regard to the initial cancer stage. The first one, illustrated in Fig. 2, consists of taking

$$(x_0,\tau_0)\doteq(12\,000, 15\,000),$$

which belongs to Ω_-. In Fig. 4, we propose to vary the parameter v of Eq. (16), considering both values $v = 1$ and $v = 10$.

The second instance leads to Fig. 3 and concerns an initial cancer stage belonging to subset Ω_+. It is given by,

$$(x_0,\tau_0)\doteq(15\,000, 12\,000).$$

5. Application to tumor-immune interactions with chemotherapy

In this section, as a second illustration of our set-valued method, we consider the same model and we assume that an external source of effector-immune cells can also be administered to the patient, in addition to the chemotherapy drugs.

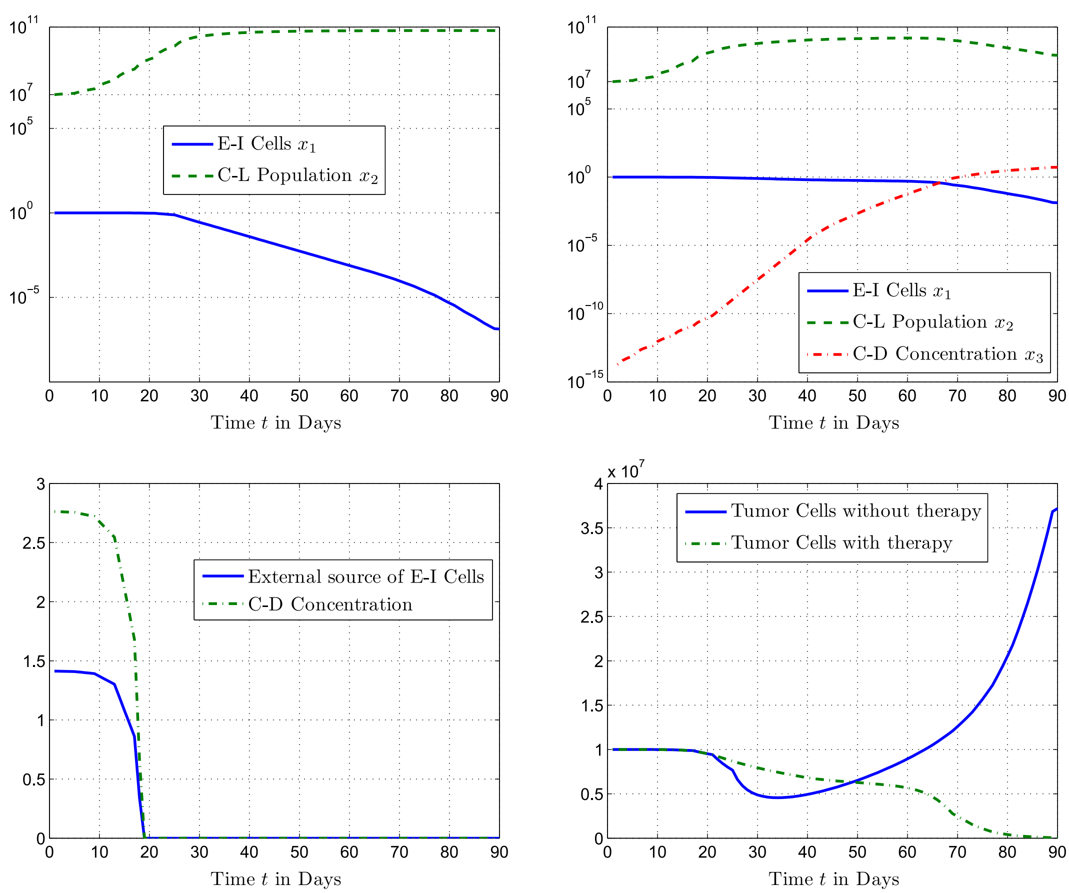

Fig. 5. Treatment of cancer with initial stage (18): Top left, evolution under no therapy ($u\equiv 0$). Top right, under protocol $u\doteq\mu_{0.0298}$ expressed by (7). Bottom left, plot of the protocol. Bottom right, showing the impact of the therapy on tumor cells.

5.1. The model

The densities of cell populations, chemotherapy drug concentration and external effector cells are denoted by the following:

x_1 effector-immune cell population,
x_2 circulating lymphocytes population,
x_3 chemotherapy drug concentration,
τ tumor cell population,
u_1 rate of introduction of external effector-immune cells,
u_2 rate of introduction of chemotherapy drugs.

They are governed by the system of ordinary differential equations:

$$\dot{x}_1 = g\frac{\tau}{h+\tau}x_1 - rx_1 - px_1\tau - k_1x_1x_3 + s_1u_1, \tag{17a}$$

$$\dot{x}_2 = -\delta x_2 - k_2x_3x_2 + s_2, \tag{17b}$$

$$\dot{x}_3 = -\gamma x_3 + u_2, \tag{17c}$$

$$\dot{\tau} = a\tau(1-b\tau) - c_1x_1\tau - k_3x_3\tau. \tag{17d}$$

In Table 3, we provide a summary of equation term descriptions, and in Table 4 a list of parameters along with their biological interpretations, values and dimensions are displayed.

Now, to perform analysis on system (17), we move to the following.

5.2. Expression of the protocols

It is clear that system (17) fits into our set-valued framework, where the corresponding functions are given for each $(x,\tau) \in \mathbb{R}_+ \times \mathbb{R}^3_+$ as follows,

$$f(x,\tau) = \left(-rx_1 + g\frac{\tau}{h+\tau}x_1 - px_1\tau - k_1x_1x_3, -\delta x_2 - k_2x_3x_2 + s_2, -\gamma x_3\right)'$$

and,

$$B(x,\tau) = \begin{pmatrix} s_1 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix}'.$$

While the tumor dynamics is given by,

$\psi(x,\tau) = a(1-b\tau) - c_1x_1 - k_3x_3,$

and its x-gradient is as follows,

$\nabla_x\psi(x,\tau) = (-c_1, 0, -k_3)',$

for each $(x,\tau) \in \mathbb{R}_+ \times \mathbb{R}^3_+$. Now, in order to compute the regulation map as expressed in Eq. (4a), we first need to get the functions h and ℓ given, respectively by Eqs. (4c) and (4d),

$h(x,\tau) = (s_1c_1, k_3)'$

and,

$\ell(x,\tau) = -c_1f_1(x,\tau) - k_3f_3(x,\tau) - ab\tau\psi(x,\tau)$

for each $(x,\tau) \in \mathbb{R}_+ \times \mathbb{R}^3_+$.

This yields the map $C$of Eq. (4b) as follows,

$$C(x,\tau) = \left\{u \in \left[0u_1^{\max}\right] \times \left[0u_2^{\max}\right] | s_1c_1u_1 + k_3u_2 \geqslant \ell(x,\tau)\right\}$$

for each $(x,\tau) \in \mathbb{R}_+ \times \mathbb{R}^3_+$.

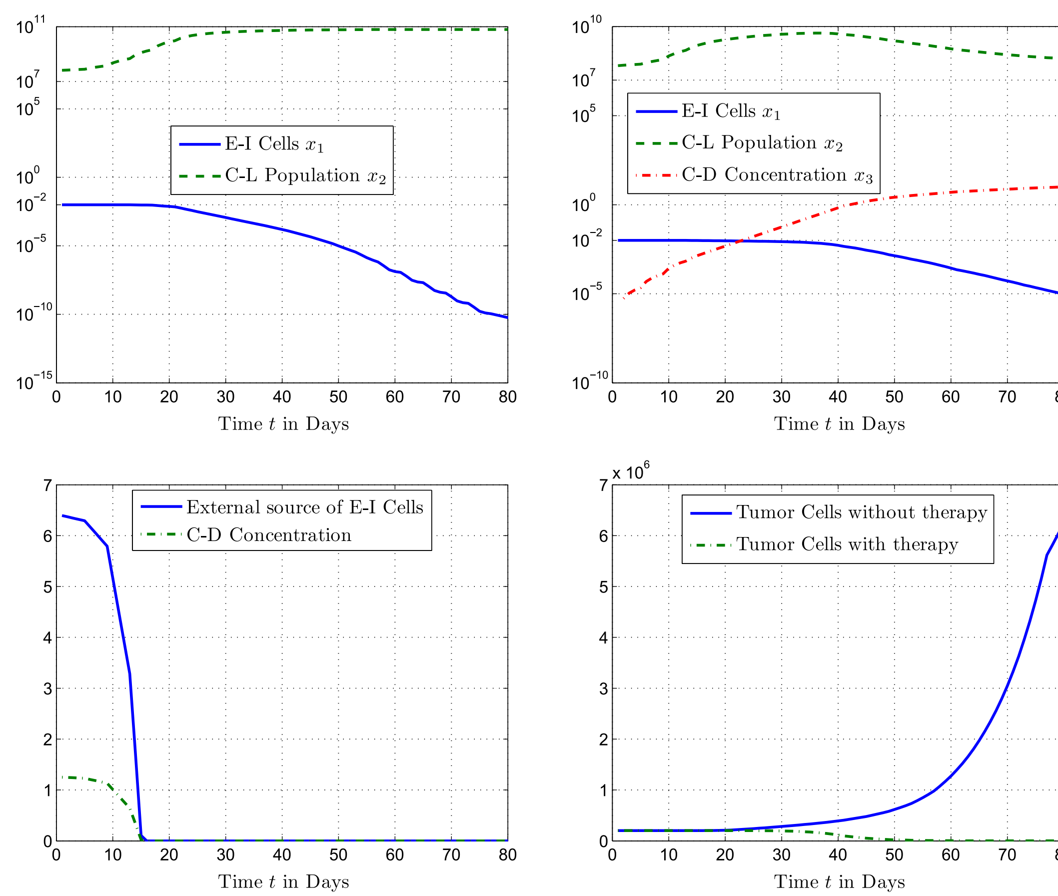

Fig. 6. Treatment of cancer with initial stage (19): Top left, evolution under no therapy ($u \equiv 0$). Top right, under protocol $u \doteq \sigma$ expressed by (10), where we take $\kappa = 0.001$ and $t_1 = 14$ days. Bottom left, plot of the protocol. Bottom right, emphasizing the impact of the treatment on cancers cells.

5.3. Computational simulations

We adopt the treatment method which utilizes the minimal concentration of drugs provided by the protocol law of Eq. (10).

The latter involves the projection operator $\pi_C(\cdot,\cdot)$, which we compute by using the program *quadprog* of the Matlab optimization toolbox, in accord with Eq. (8). Even, we use the ODE solver *ode45* for integrating our differential equations, with the numerical data given in Table 4 below.

The numerical results concern two instances of the initial cancer stage. The first one consists of taking

$$\left| \begin{array}{l} x_0 \doteq (1, 10^7, 0)', \\ \tau_0 \doteq 10^7 \end{array} \right. \tag{18}$$

for which Theorem 1 can be used, as $(x_0, \tau_0) \in \Omega_-$, see the results in Fig. 5. The second example concerns a more complicated stage, for belonging to subset Ω_+. But despite of that, we will experience that it fits into the context of Theorem 2 and thereby the corresponding cancer is curable. Namely, we take it as follows,

$$\left| \begin{array}{l} x_0 \doteq (0.1, 6.5 \times 10^7, 0)', \\ \tau_0 \doteq 2 \times 10^7. \end{array} \right. \tag{19}$$

The obtained simulation results are set in Fig. 6.

6. Conclusion

We conclude with some comments which can be listed as follows:

(i) It is of interest to stress the universal character of our approach. It actually indicates how feedback protocols can be expressed relatively to an important class of cancer ODE models.

(ii) These protocols are simply derived by doing adequate selections from the regulation map, leading to explicit formulas which may be easily carried out, notably the minimal protocol law. On the contrary to the optimal control theory approach which needs:
  (a) be sure of existence of both optimal control and its corresponding trajectory.
  (b) solving the hard associated HJB equations in order to obtain the required optimal protocols, when they exist.

(iii) A further argument why the set-valued framework is well suited for cancer control consists of the fact that it allows us to cope with initial cancer stage and its impact on existence of feedback protocols, seeking to elucidate challenging real situations in biomedicine in which the initial stage of the cancer and its curability are correlated. In fact, both Theorems 1 and 2 clearly highlight the role of initial data, showing for a given patient, how a decision can be made in order appropriate protocols can be formulated.

(iv) Finally, there exist cancer models [23,25] which do not fit in the framework of our approach, because the tumor dynamics (1b) is also involved by the protocols. This instance is currently under evaluation.

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