Feedback protocols for anti-angiogenic therapy in the treatment of cancer tumors by chemotherapy

1st Amine Moustafid
Department of Mathematics and Computer Science, University Hassan II, Faculty of Sciences Aïn Chock, Casablanca, Morocco.
a.moustafid@gmail.com 0000-0002-9121-0745

***Abstract*—In this paper we deal with cancer control via a treatment model. A set-valued control method is used, to design the procedures leading to the formulation of model protocols, by which cancer cells are eradicated. These protocols are provided as selections of specific set-valued maps, depend upon the initial stage of cancer, and divide into two inconsistent types responding to two concerns: smoothness of treatment or minimal-dose therapy.**

***Index Terms*—Anti-angiogenic therapy, Chemotherapy, Set-valued analysis, Viability theory**

I. Introduction

Mathematical modelling of cancer, whether by ordinary differential equations (ODEs), delay differential equations [24], [31], partial derivatives equations (PDEs) [15], or even stochastic differential equations [18], [19], [23], is useful not only to gain a broad understanding of the tumor dynamics, but also to investigate the problems associated to control cancer.

Several studies address the subject of cancer control, by evoking different approaches, depending upon the model type. All of them aim at seeking protocol laws to destroy cancer cells, taking into account patient quality of life that can be described by constraints on both healthy cells and the administered drug doses.

For ODE models, as considered in this paper, numerous studies use optimal control techniques, which consist of designing a suitable criterion that involves minimizing cancer cells, for examples:

- [4] controls the model in [3], in order to attain the goal of reducing the amount of cancer cells, with acceptable consequence on other states, by two different optimal strategies: closed-loop SDRE (State-Dependent Ricatti Equation), and open-loop method utilizing steepest descent technique, the results of each are compared together, to figure out which one is the better choice.
- [40] presents optimal control method results for four different cancer models based on two sets of ODEs, and contain either chemotherapy, immunotherapy, anti-angiogenic therapy or combinations of these therapies, the optimal control problems in questions are solved numerically with Bock's direct multiple shooting approach.
- [17] uses Pontryagin's Maximum Principle to give an optimal control of bang-bang form.
- [16] illustrates and discusses three different approach for the control function: continuous, impulsive and hybrid.
- [29] uses for a well known model of the tumor-immune system interaction [5], an optimization algorithm to find optimal protocols as impulse-like drug administrations.

Much less frequently, there are studies using various different approaches:

- ◦ [39] uses an asymptotic approach to give sufficient conditions on both model and treatment parameters [5], under which all trajectories in the positive orthant tend to the tumor-free equilibrium point.
- ◦ [35] performs a quantitative analysis to discusses the impact of delay in immunotherapy with interleukin-2, at different antigenicity levels.
- ◦ [7] studies by the qualitative theory of differential equations the immunotherapeutic models of Kuznetsov and Stepanova, in meta-models form (i.e., family of models), and gives a general result on global eradication of cancer under immunotherapy.
- ◦ [34] proposes a generalization of d'Onofrio's background model, where one parameter is assumed to be time dependent, keeping all other parameters constant, and done a qualitative-asymptotic analysis for the second-order Taylor expansion of the model.

The approach using techniques of viability theory and set-valued analysis has been initiated since [2], by providing feedback protocols for immunotherapy model of [5], over a finite horizon. This set-valued approach is performed in [1], with respect to a wide class of ODEs. In the following, we give a concise overview along with main facts that is noteworthy to mention:

- ∗ The provided protocols aim at asymptotically eliminate cancer cells, taking into account constraints that may involve both injected drugs and cells in competition with cancer cells.
- ∗ They are given in feedback form as selections of adequately designed multifunctions, leading to two incompatible sets of protocol laws: one set is constituted of continuous laws, for a smooth therapy, and another set involves the minimal law for minimum drug doses, to minimize their side-effects. The former laws can easily be derived through universal formulas, while the latters need solving a convex quadratic program. Both laws have to be used depending on medical preferences.

- Further the therapy protocol design, the approach allows for a slight representation of *cancer staging* as known in medicine, providing mathematical criteria to categorize initial cancer stages given both their curability and the kind of protocols that can be formulated. Thus by this vision, a real medical strategy can be followed after diagnosis of the disease. In the case of stage 1, the applied medical protocols lead to decreasing cancer cells in respect of patient quality of life. Stage 2 describes cancers that can be amenable to stage 1 in a finite horizon, only after what decreasing cancer cells are guaranteed. While stage 3 characterizes cancers that are incurable, corresponding to late-stage cancers. See technical details in Section II.

In [6] we employ the previous set-valued method to address two cancer therapies: namely anti-angiogenic therapy, through its descriptive model established in [8], and chemo-immuno therapy, as treated in [9].

Newer approaches that combine anti-angiogenic drugs with chemotherapy, other targeted drugs, or radiation may work better than using them alone (mono-therapy). Coupled anti-angiogenic and chemotherapy promote a larger reduction of the tumor than use chemotherapy alone [3]. Along the same lines: [32] optimized and rationalized the association between anti-angiogenic and cytotoxic drugs in the treatment, to improve the anti-tumor efficacy, and [41] founded that metronomic schedules are more effective in eliminating tumour cells mainly due to their chemotherapeutic action on endothelial cells and that more frequent, low drug doses also entail outcomes in which the survival time of patient is increased, and [42] used Hamilton-Jacobi-Isaacs (HJI) partial differential equation, to derive a robust state feedback control of the combined therapy of cancer using chemotherapy and angiogenic inhibition, which guaranteed tumor contraction maps as a function of the initial state of tumor and the vasculature capacity. Other mixed therapies prove their capacity to eliminate the entire tumor than either single modality treatment, so it is in [11] which extracts situations where neither chemotherapy nor immunotherapy alone are efficient to control tumor growth. As well in [37] where such combination treatments have been suggested as a promising alternative to mono-therapy. In the study [36] both treatments concurrently is favorable, due to the lower toxicity and greater immune stability. For this combination therapy, as mentioned earlier, we already approach it by means of chemo-immuno model [9], so in article [6]. While [43] investigates how virotherapy could enhance chemotherapy. A comprehensive review of mathematical models for combination cancer therapy has been carried out in [44]. A Multi-Objective approach identifies the effective combination of therapeutic targets in cancer cells [45].

For instance we choose as subject for the method by [1], the model developed in [3], which combines between anti-angiogenic and chemotherapy. Based on the competition between normal cells and cancer cells as well as endothelial cells associated to angiogenic process, which helps cancer cells to growth. The effects of anti-angiogenic and chemotherapy agents are obviously included in the model.

The current paper is organized as follows: Section II is an overview of the set-valued control method developed by [1], in Subsection III-A, a detailed description of model of [3] is given, Subsection III-B is an application of the method to the model, this is followed in Subsection III-C with numerical examples and interpretations. We conclude in Section IV with a discussions.

II. The set-valued control method

This section is dedicated to summarize the general method developed in [1], and which we are going to apply on Pinho's model. It deals with the specific class of ODEs

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

conditioned initially at $t = 0$ by

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

- The state (x,τ) evolves in $\mathbb{R}^n_+ \times \mathbb{R}_+$:

$$\forall t \in [0,\infty[, (x(t),\tau(t)) \in \mathbb{R}^n_+ \times \mathbb{R}_+. \tag{2}$$

  This positivity condition represents the biological feasibility of interactive cells densities x_i, and tumor cell burden τ. Note that (1b) involves that whenever $\tau_0 = 0$ then there are no cancer cells in the tissue for all time. This is due to formula,

$$\bar{\tau}(t) = \tau_0 \mathrm{e}^{\int_0^t \psi(\bar{x}(s),\bar{\tau}(s))\mathrm{d}s}, \quad \text{for all } t \geq 0,$$

  for any solution $(\bar{x},\bar{\tau})$ of system (1).
- The control $u = u(t)$ evolves in the constraints subset of $\mathbb{R}^p$, defined by

$$K_p = [0, u_1^{\max}] \times \cdots \times [0, u_p^{\max}], \tag{3}$$

  where the components u_i stand for the doses of treatments, that can be administered continuously by some kind of portable pumps or straps to the patient's blood circulation, with the maximal tolerated doses $u_i^{\max}$.
- The functions f and ψ map $\mathbb{R}^n_+ \times \mathbb{R}_+$ into $\mathbb{R}^n$ and $\mathbb{R}$ respectively, ψ is supposed to be of class $\mathcal{C}^1$ on $\mathbb{R}^n_+ \times \mathbb{R}_+$, while $B(x,\tau) \in \mathbb{R}^{n\times p}$, and $B'(x,\tau) \in \mathbb{R}^{p\times n}$ denotes its transpose.

We remark that the right-hand side of (1a) is linear with respect to the control term u, while in the tumor dynamics (1b), the tumor cell burden τ can be extracted, this structure of the prototype (1) is well justified by a vast majority of ODE models in the literature [10]–[14], [22], [27], [28], [30], [33], [38], including the one of [3].

But there exists another varieties of models, like those using a direct control on cancer cells, in [20] for example, cancer cells can be killed by an external injection of ACI (Adoptive Cellular Immunotherapy), depicted by the control function $\epsilon_2 = \epsilon_2(t)$, at a rate proportional to the product of the

tumor cell burden, nevertheless, to approach this type of ODE models, we can augment the general model 1 by a suitable differential equation (for e.g., $\dot{\epsilon}_2(t) = -\epsilon_2(t) + v(t)$, where $v(t)$ is the auxiliary control).

Definition 2.1: We call a protocol any control $\bar{u}\colon [0,\infty[\to K_p$, such that system 1 has a solution $(\bar{x},\bar{\tau})\colon [0,\infty[\to \mathbb{R}^n_+ \times \mathbb{R}_+$, which satisfies

$$\lim_{t\to\infty} \bar{\tau}(t) = 0.$$

Definition 2.2: To each $\beta > 0$, we define the subset

$$D_\beta = \{(x,\tau) \in \mathbb{R}^n \times \mathbb{R} \mid \psi(x,\tau) \leq -\beta\}. \tag{4}$$

A solution $(\bar{x},\bar{\tau})$ of system 1 is said to be viable in the subset D_β on an interval $[0,\bar{t}[$, if

$$\forall t \in [0,\bar{t}[,\ (\bar{x}(t),\bar{\tau}(t)) \in D_\beta.$$

Proposition 2.3: Whenever a control $\bar{u}$ produces a viable solution $(\bar{x},\bar{\tau})$ on $[0,\infty[$ in the subset D_β, for an appropriate β, then it follows that $\bar{u}$ is a protocol in the sense of Definition 2.1.

Proof 2.4: For $t \geq 0$, (1b) is written

$$\dot{\bar{\tau}}(t) = \bar{\tau}(t)\psi(\bar{x}(t),\bar{\tau}(t)),$$

by viability of $(\bar{x},\bar{\tau})$ in D_β we get the differential inequality

$$\dot{\bar{\tau}}(t) \leq -\beta\bar{\tau}(t), \tag{5}$$

and by applying Gronwall's lemma we get the exponential estimate

$$0 < \bar{\tau}(t) \leq \tau_0 \mathrm{e}^{-\beta t},$$

then

$$\lim_{t\to\infty} \bar{\tau}(t) = 0.$$

Remark 2.5: Inequality (5) implies that $\dot{\bar{\tau}}(t) \leq 0$ for all t, i.e., tumor cell burden $\bar{\tau}$ will be on the decreasing, which is beneficial to the patient's quality of life during the treatment. The idea was first to give protocols to control tumor cell burden τ to 0, but it turns out that such protocols keep τ on decreasing sens overall $[0,\infty[$, with the exponential estimate $\tau_0\mathrm{e}^{-\beta t}$, where τ_0 is the initial tumor cell burden and $(-\beta)$ is the decay rate.

Remark 2.6: The viability of the solution $(\bar{x},\bar{\tau})$ in the subset D_β, requires the initial condition $\psi(x_0,\tau_0) < 0$, which is not always satisfied, but we will deal with this necessary condition in the next.

According to [1], such protocol may be characterized as a selection of the set-valued map $C_\beta(\cdot)$ defined on the subset D_β by

$$C_\beta(x,\tau) = \{u \in K_p \mid \langle \hbar(x,\tau), u\rangle_p \geq \ell(x,\tau)\}, \tag{6}$$

where functions $\hbar$ and ℓ are given by

$$\hbar(x,\tau) = -B'(x,\tau)\nabla_x\psi(x,\tau), \tag{7a}$$

$$\ell(x,\tau) = \langle \nabla_x\psi(x,\tau), f(x,\tau)\rangle_n + \tau\psi(x,\tau)\frac{\partial\psi}{\partial\tau}(x,\tau), \tag{7b}$$

with

- $\langle\cdot,\cdot\rangle_i$ is the euclidean inner product in $\mathbb{R}^i$, for $i = p, n$.
- $\nabla_x\psi(x,\tau)$ is the gradient vector at point x:

$$\nabla_x\psi(x,\tau) = \left(\frac{\partial\psi}{\partial x_1}(x,\tau),\cdots,\frac{\partial\psi}{\partial x_n}(x,\tau)\right)'.$$

To neatly give the set-valued characterization of protocol, we consider prior the following notation and hypothesis, and launch the ensuing theorem.

$$\Omega_- = \left\{(x,\tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+ \mid \psi(x,\tau) < 0\right\}. \tag{8}$$

Hypothesis 2.7: The functions $\hbar$ and ℓ respectively given by formulas (7a) and (7b) satisfy the statement below

$$\forall (x,\tau) \in D_\beta, \exists u \in K_p\colon \langle \hbar(x,\tau), u\rangle_p > \ell(x,\tau).$$

Theorem 2.8: Let $(x_0,\tau_0) \in \Omega_-$ and $\beta_0 = -\psi(x_0,\tau_0) > 0$. Assume that there exists $\beta \in]0,\beta_0]$ for which Hypothesis 2.7 is checked. The selection s_β of the set-valued map $C_\beta(\cdot)$, having expression

$$s_\beta(x,\tau) = u \in C_\beta(x,\tau),\ \text{such as } \|u\| \longrightarrow \min, \tag{9}$$

provides a viable solution $(\bar{x},\bar{\tau})$ in the subset D_β on a maximal interval $[0,t^{\max}[$.

If in addition

Hypothesis 2.9: $\limsup\limits_{\substack{t\to t^{\max}\\ t<t^{\max}}} \|(\bar{x}(t),\bar{\tau}(t))\| < \infty$,

then $t^{\max} = \infty$, and s_β becomes a protocol.

Remark 2.10: The Hypothesis 2.9 will prolongs the local viability of the solution $(\bar{x},\bar{\tau})$ over $t^{\max}$, to be global on the infinite interval $[0,\infty[$, while Hypothesis 2.7 is introduced so that the selection s_β will be well defined on D_β, but it turned out that Hypothesis 2.7 ensures in addition the continuity of s_β on D_β.

Now to do without the initial condition $\psi(x_0,\tau_0) < 0$ of Remark 2.6, we consider the following subset

$$\Omega_+ = \left\{(x,\tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+ \mid \psi(x,\tau) \geq 0\right\}, \tag{10}$$

and we associate to each $\kappa > 0$ the set-valued map $C_\kappa(\cdot)$, having expression

$$C_\kappa(x,\tau) = \{u \in K_p \mid \langle \hbar(x,\tau), u\rangle_p \geq \ell(x,\tau) + \kappa\}, \tag{11}$$

where the functions $\hbar$ and ℓ still given by formula (7a) and (7b), then we set the ensuing theorem under the following hypothesis

Hypothesis 2.11:

$$\forall (x,\tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+, \exists u \in K_p\colon \langle \hbar(x,\tau), u\rangle_p > \ell(x,\tau) + \kappa.$$

Theorem 2.12: Assume that $(x_0,\tau_0) \in \Omega_+$. The minimal selection s_κ of the set-valued map $C_\kappa(\cdot)$, having expression

$$s_\kappa(x,\tau) = u \in C_\kappa(x,\tau),\ \text{such as } \|u\| \longrightarrow \min, \tag{12}$$

steers the system 1 from Ω_+ to Ω_- on the interval $[0,t_1]$, provided that $\kappa t_1 > \psi(x_0,\tau_0)$. i.e., system 1 admits a solution $(\bar{x},\bar{\tau})$ on $[0,t_1]$, such that $(\bar{x}(t_1),\bar{\tau}(t_1)) \in \Omega_-$.

Proof 2.13: For $t \geq 0$,

$$\frac{\mathrm{d}}{\mathrm{d}t}\psi(\bar{x}(t),\bar{\tau}(t)) = \langle \nabla_x \psi(\bar{x}(t),\bar{\tau}(t)), \dot{\bar{x}}(t)\rangle_n + \dot{\bar{\tau}}(t)\frac{\partial \psi}{\partial \tau}(\bar{x}(t),\bar{\tau}(t)),$$

next, we use the dynamics (1a) and (1b), and the formulas (7a) and (7b) to write this differentiating in terms of the functions $\hbar$ and ℓ, and the selection s_κ:

$$\frac{\mathrm{d}}{\mathrm{d}t}\psi(\bar{x}(t),\bar{\tau}(t)) = \ell(\bar{x}(t),\bar{\tau}(t)) - \langle \hbar(\bar{x}(t),\bar{\tau}(t)), s_\kappa(\bar{x}(t),\bar{\tau}(t))\rangle_p,$$

or the selection s_κ is continuous (due to Hypothesis 2.11), then by integrating from $t = 0$ to t_1 we get

$$\psi(\bar{x}(t_1),\bar{\tau}(t_1)) = \psi(x_0,\tau_0) - \int_0^{t_1} \left[\langle \hbar(\bar{x}(t),\bar{\tau}(t)), s_\kappa(\bar{x}(t),\bar{\tau}(t))\rangle_p - \ell(\bar{x}(t),\bar{\tau}(t))\right] \mathrm{d}t,$$

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

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

as

$$\kappa t_1 > \psi(x_0,\tau_0),$$

it follows that

$$\psi(\bar{x}(t_1),\bar{\tau}(t_1)) < 0.$$

Remark 2.14: The existence and the continuity of the selection s_κ require the Hypothesis 2.11.

Corollary 2.15: If the final state $(\bar{x}(t_1),\bar{\tau}(t_1))$ satisfies hypotheses of Theorem 2.8 as an initial one of system (1) at time $t_0 = t_1$, then

$$\left| \begin{array}{l} s_\kappa(\bar{x}(t),\bar{\tau}(t)) \text{ if } t \in [0,t_1], \\ s_\beta(\bar{x}(t),\bar{\tau}(t)) \text{ if } t \in [t_1,\infty[, \end{array} \right. \tag{13}$$

is a protocol.

Remark 2.16: The protocol (13) will increase the corresponding tumor cell burden $\bar{\tau}$ on an neighborhood of $t_0 = 0$, relatively to the interval $[0,t_1]$, which may be disadvantageous to the patient's quality of life in the beginning of treatment.
The condition $\kappa t_1 > \psi(x_0,\tau_0)$ can be regarded as a conflict between the continuity of protocol (13) at $(\bar{x}(t_1),\bar{\tau}(t_1))$, and the minimality of period t_1.
The protocol's existence is independent of any condition on initial state (x_0,τ_0), contrary to the decreasing of the corresponding tumor cell burden $\bar{\tau}$ which closely depends on sign of $\psi(x_0,\tau_0)$. This leads to stage the cancer as follow:

- $\psi(x_0,\tau_0) < 0$: As pointed out in Remark 2.5, the protocol (9) will decrease the cancer cells $\bar{\tau}$ on $[0,\infty[$. We then say that the cancer is non-advanced, or it is in stage I.
- $\psi(x_0,\tau_0) \geq 0$: As Remark 2.16, the protocol (13) cannot ensures the decreasing of cancer cells $\bar{\tau}$ on $[0,t_1]$. In this case we say that the cancer is advanced, or it is in stage II.

The initial state (x_0,τ_0) is deterministic to distinguish treatment strategies I and II. To cope with the advanced stage: $\psi(x_0,\tau_0) \geq 0$, we must transfer (x_0,τ_0) to a state (x_1,τ_1) of better stage, ie. $\psi(x_1,\tau_1) < 0$ at a time $t_1 > 0$, before joining the interval of decreasing $[t_1,\infty[$. Ultimately, the study reveals the key role that play the function ψ in cancer staging and designing protocols (9) and (13).

III. Application to the Model

A. The model

The model [3] under study is a normalized system of five ODEs, modeling continual interplay between normal cells: NCs, endothelial cells: ECs, chemotherapy agent: CA, anti-angiogenic agent: AA of concentration x_i, respectively, for $i = 1,2,3,4$ (here the integer $n = 4$); and cancer cells: CCs of concentration τ.

$$\dot{x}_1 = f_1(x,\tau), \tag{14a}$$
$$\dot{x}_2 = f_2(x,\tau), \tag{14b}$$
$$\dot{x}_3 = \delta + f_3(x,\tau), \tag{14c}$$
$$\dot{x}_4 = \phi + f_4(x,\tau), \tag{14d}$$
$$\dot{\tau} = \tau\psi(x,\tau), \tag{14e}$$

initial conditions are given by

$$x_i(t=0) = x_0^i \geq 0, \text{ for } i = 1,2,3,4; \tag{14f}$$
$$\tau(t=0) = \tau_0 \geq 0. \tag{14g}$$

Parameters $\delta = \delta(t)$ and $\phi = \phi(t)$ are the respective instantaneous infusion doses of CA and AA. (δ,ϕ) is almost continuous within numerical values of the reduced constraint subset (here the number of therapeutic agents $p = 2$)

$$K_2 = \left[0,\delta^{\max}\right] \times \left[0,\phi^{\max}\right], \tag{15}$$

defined by

$$\{(\delta,\phi) \in \mathbb{R}^2 \mid 0 \leq \delta \leq \delta^{\max} \text{ and } 0 \leq \phi \leq \phi^{\max}\}.$$

Infusion doses CA(δ) and AA(ϕ) are based on cyclophosphamide and TNP-470 respectively.

The model variables x_i and τ are assumed to interact as follows:

1) Normal cells.
   a) NCs grow logistically in the absence of CCs and AA,
   b) CCs destroy NCs at a rate proportional to the product of CCs,
   c) CA kills NCs at a rate governed by Michaelis-Menton kinetics with parameters p_3 and a_3.
2) Endothelial cells.
   a) ECs increase logistically to normalized carrying capacity,
   b) CCs stimulate ECs to grow at a rate directly proportional to CCs,
   c) AA kills ECs at a rate again governed by Michaelis-Menton term.

3) Chemotherapy agent.
   a) CA decays at a constant rate,
   b) CA decreases due to its action on NCs and CCs at a rates modeled by Michaelis-Menton dynamics.
4) Anti-angiogenic agent.
   a) AA degrades at a constant rate,
   b) AA decreases because of its action on ECs at a rate again modeled by Michaelis-Menton factor.
5) Cancer cells.
   a) CCs exhibit logistic proliferation rate with varying carrying capacity depending on ECs: The ECs increase the carrying capacity of the CCs,
   b) NCs eliminate CCs at a rate proportional to the product of NCs,
   c) CA kills CCs at a rate in Michaelis-Menton form.

Under the above considerations, functions f_i and ψ are expressed as

$$f_1(x,\tau) = \alpha_1 x_1(1-x_1) - q_1 x_1 \tau - p_1(x_2,x_4)\frac{x_1 x_3}{a_1+x_1}, \tag{16a}$$

$$f_2(x,\tau) = \beta\tau + \alpha_3 x_2(1-x_2) - \frac{p_3 x_2 x_4}{a_3+x_2}, \tag{16b}$$

$$f_3(x,\tau) = -\left[\xi + d_1\frac{x_1}{a_1+x_1} + d_2\frac{\tau}{a_2+\tau}\right] x_3, \tag{16c}$$

$$f_4(x,\tau) = -\left[\eta + d_3\frac{x_2}{a_3+x_2}\right] x_4, \tag{16d}$$

$$\psi(x,\tau) = \alpha_2\left[1-\frac{\tau}{1+\gamma x_2}\right] - q_2 x_1 - p_2(x_2,x_4)\frac{x_3}{a_2+\tau}, \tag{16e}$$

with

$$p_i(x_2,x_4) = p_{i0} + p_{i1}x_2 + p_{i2}x_4, \text{ for } i=1,2. \tag{16f}$$

Table I describes the model terms, and Table II lists the values of the positive constants parameters $\alpha_i, q_i, a_i, d_i, p_{ij}, \gamma, \beta, p_3, \xi$, and η (units are in days^{-1} except for the a_i's, and γ whose units are volume).

1 shows model interactions between the different interveners x_1, x_2, τ, and with therapy agents x_3, x_4.

B. Explicit expressions of protocols

According to [3], for all non-negative initial state (14f) and (14g), all solutions $(\bar{x},\bar{\tau})$ of model (14) remain in the non-negative orthant

$$\mathbb{R}^5_+ = \{(x_1,x_2,x_3,x_4,\tau)' \in \mathbb{R}^5 \mid x_i \geq 0, \text{ for } i=1,2,3,4; \text{ and } \tau \geq 0\},$$

so the model fulfills the positivity condition (2).

To give useful expressions of protocols (9) and (13) for the model (14), we have to explicit functions $\hbar$ and ℓ, given by (7a) and (7b), so we have to calculate partial derivatives of function ψ as expressed by (16e).

Entity	Term	Description
x_1	$\alpha_1 x_1(1-x_1)$	Logistic NCs growth
	$-q_1 x_1 \tau$	NCs death by CCs
	$-p_1(x_2,x_4)\frac{x_1 x_3}{a_1+x_1}$	NCs death by CA per concentration of ECs and AA
x_2	$\beta\tau$	CCs creation due to ECs
	$\alpha_3 x_2(1-x_2)$	Logistic ECs growth
	$-\frac{p_3 x_2 x_4}{a_3+x_2}$	ECs death by AA
x_3	$-\xi x_3$	CA washout
	$-d_1\frac{x_1 x_3}{a_1+x_1}$	CA combination with NCs
	$-d_2\frac{\tau x_3}{a_2+\tau}$	CA combination with CCs
x_4	$-\eta x_4$	AA washout
	$-d_3\frac{x_2 x_4}{a_3+x_2}$	AA combination with ECs
τ	$\alpha_2\tau\left[1-\frac{\tau}{1+\gamma x_2}\right]$	Logistic CCs growth
	$-q_2 x_1 \tau$	CCs death by NCs
	$-p_2(x_2,x_4)\frac{\tau x_3}{a_2+\tau}$	CCs death by CA per concentration of ECs and AA

TABLE I
TERMS OF MODEL (14).

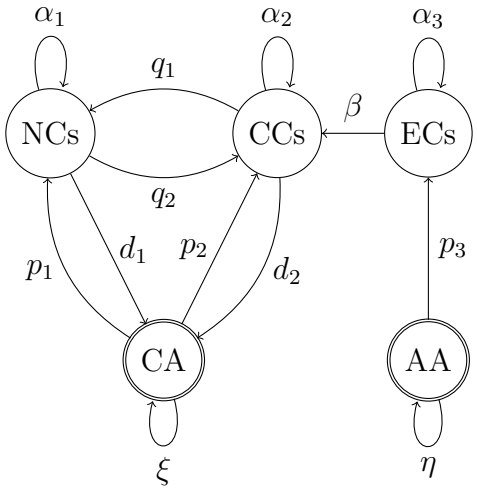

Fig. 1. Interactions in model (14) between compartments of cells, NCs, CCs and ECs, and compartments of agents, CA and AA.

$$\left|\begin{aligned}
&\frac{\partial\psi}{\partial x_1}(x,\tau) = -q_2,\\
&\frac{\partial\psi}{\partial x_2}(x,\tau) = \frac{\alpha_2\gamma\tau}{(1+\gamma x_2)^2} - \frac{p_{21}x_3}{a_2+\tau},\\
&\frac{\partial\psi}{\partial x_3}(x,\tau) = -\frac{p_2(x_2,x_4)}{a_2+\tau},\\
&\frac{\partial\psi}{\partial x_4}(x,\tau) = -\frac{p_{22}}{a_2+\tau},\\
&\frac{\partial\psi}{\partial\tau}(x,\tau) = \frac{x_3 p_2(x_2,x_4)}{(a_2+\tau)^2} - \frac{\alpha_2}{1+\gamma x_2},
\end{aligned}\right.$$

whence

$$\begin{aligned}\ell(x,\tau) &= -q_2 f_1(x,\tau)\\ &+f_2(x,\tau)\left[\frac{\alpha_2\gamma\tau}{(1+\gamma x_2)^2}-\frac{p_{21}x_3}{a_2+\tau}\right]\\ &-\frac{p_2(x_2,x_4)}{a_2+\tau}f_3(x,\tau)-\frac{p_{22}}{a_2+\tau}f_4(x,\tau)\\ &+\tau\psi(\tau,x)\left[\frac{x_3p_2(x_2,x_4)}{(a_2+\tau)^2}-\frac{\alpha_2}{1+\gamma x_2}\right],\end{aligned}$$

the operator $B(x,\tau)$ is represented by the matrix

$$B=\begin{pmatrix}0&0&1&0\\0&0&0&1\end{pmatrix}',$$

then

$$\hbar(x,\tau)=\left(\frac{p_2(x_2,x_4)}{a_2+\tau},\frac{p_{22}}{a_2+\tau}\right)',$$

and so, set-valued maps $C_\beta(\cdot)$ and $C_\kappa(\cdot)$ given by (6) and (11) are expressed as follows

$$C_\beta(x,\tau)=\left\{u\in K_2 \mid \frac{p_2(x_2,x_4)}{a_2+\tau}\delta+\frac{p_{22}}{a_2+\tau}\phi\geq\ell(x,\tau)\right\},$$

and

$$C_\kappa(x,\tau)=\left\{u\in K_2 \mid \frac{p_2(x_2,x_4)}{a_2+\tau}\delta+\frac{p_{22}}{a_2+\tau}\phi\geq\ell(x,\tau)+\kappa\right\},$$

then, selections s_β (9) and s_κ (12) are defined on $\mathbb{R}^4_+\times\mathbb{R}_+$ by

$$s_\beta(x,\tau)=(\delta,\phi)\in C_\beta(x,\tau),\ \text{such as}\ \delta^2+\phi^2\longrightarrow\min, \tag{17}$$

and

$$s_\kappa(x,\tau)=(\delta,\phi)\in C_\kappa(x,\tau),\ \text{such as}\ \delta^2+\phi^2\longrightarrow\min. \tag{18}$$

To complete our analysis we have to check the Hypothesis 2.9 of Theorem 2.8, for that we will use the following estimations of $\bar{x}_i$ and $\bar{\tau}$, taken from the proof of [3]

$$\begin{cases}\bar{x}_1(t)\leq 1,\\ \bar{x}_3(t)\leq\dfrac{\delta^{\max}}{\xi},\\ \bar{x}_4(t)\leq\dfrac{\phi^{\max}}{\eta},\\ \bar{x}_2(t)\leq M,\\ \bar{\tau}(t)\leq 1+\gamma M,\end{cases}$$

where the constant M is given by

$$M=\frac{1}{2}\left(1+\frac{\gamma\beta}{\alpha_3}\right)+\frac{1}{2}\sqrt{\left(1+\frac{\gamma\beta}{\alpha_3}\right)^2+\frac{4\beta}{\alpha_3}},$$

then

$$\|(\bar{x}(t),\bar{\tau}(t))\|\leq\max\left(\frac{\delta^{\max}}{\xi},\frac{\phi^{\max}}{\eta},1+\gamma M\right),$$

it follows that Hypothesis 2.9 is well checked.

Remark 3.1: For $\bar{\tau}$ we can also use the estimation

$$\forall t\in[0,t^{\max}[,\ \bar{\tau}(t)\leq\tau_0,$$

then Hypothesis 2.9 can be reduced to

$$\limsup_{\substack{t\to t^{\max}\\ t<t^{\max}}}\|\bar{x}(t)\|<\infty.$$

Hypotheses 2.7 and 2.11 are kept to the next section to be checked numerically.

C. Numerical simulations

In order to illustrate analytical results of previous section, we propose to state model (14) at stages I and II. We use the ordinary differential equations solver *ode45* of *matlab* to integrate model (14), concurrently with the quadratic programming solver *Quadprog* to return numerical approximations of selections (17) and (18).

The parameter values in Table II are taken into account of the simulations.

Parameter	Value
α_1	$0.0068\ \text{day}^{-1}$
α_2	$0.01\ \text{day}^{-1}$
α_3	$0.002\ \text{day}^{-1}$
q_1	$0.00702\ \text{day}^{-1}$
q_2	$0.00072\ \text{day}^{-1}$
γ	0.1615
β	$0.00371\ \text{day}^{-1}$
a_1	1.1
a_2	4.6205
a_3	4.6666
d_1	$0.0002\ \text{day}^{-1}$
d_2	$0.032\ \text{day}^{-1}$
d_3	$0.032\ \text{day}^{-1}$
p_{10}	$1.2\times10^{-7}\ \text{day}^{-1}$
p_{20}	$0.20581\ \text{day}^{-1}$
p_3	$1.7143\ \text{day}^{-1}$
p_{11}	$4.2\times10^{-8}\ \text{day}^{-1}$
p_{12}	$1.0\times10^{-7}\ \text{day}^{-1}$
p_{21}	$0.00431\ \text{day}^{-1}$
p_{22}	$19.4872\ \text{day}^{-1}$
ξ	$0.01813\ \text{day}^{-1}$
η	$0.136\ \text{day}^{-1}$

TABLE II
PARAMETERS OF MODEL (14).

The used numerical values of infusion rates of parameters δ and ϕ are based on their actual doses per tumor mass: $mg/(kg)(day)$.

Respectively, the numerical results seen in Figures 2 and 3 correspond to the following particular initial stages I and II, which belong subsets Ω_- and Ω_+, defined by (8) and (10).

$$\text{I:}\begin{cases}x_0^1=0.999998, & x_0^2=0.728255,\\ x_0^3=0.181034, & x_0^4=0.00171038,\\ \tau_0=0.6,\end{cases} \tag{19a}$$

and

$$\text{II:}\begin{cases}x_0^1=1, & x_0^2=1,\\ x_0^3=0.001, & x_0^4=0.1,\\ \tau_0=1.\end{cases} \tag{19b}$$

1) The numerical approach in Figure 2 illustrates the effects of the protocol on CCs, NCs, and ECs, which:
   a) Reverses the growth of CCs and make it on strict decreasing.
   b) Keeps NCs which is viewed as indicator of the patient's health on acceptable levels.
   c) Deprives CCs of useful ECs densities.
2) As Figure 3, it confirm Remark 2.16, CCs have a slight growth at the start of therapy, precisely on the time interval $[0, 10]$.

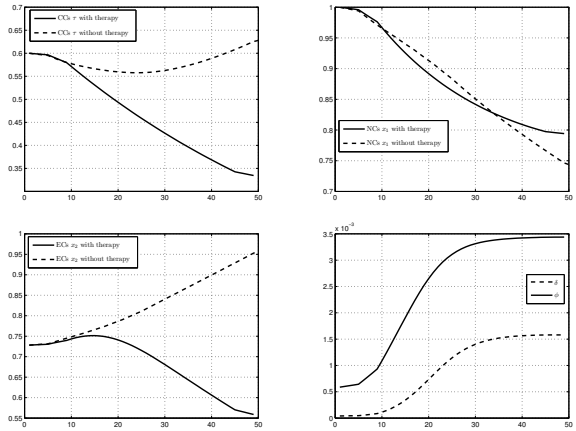

Fig. 2. Time evolution of CCs, NCs, and ECs, in absence of therapy: $(\delta, \phi) \equiv 0$ and presence of therapy: $(\delta, \phi) \equiv s_\beta(\bar{x}(t), \bar{\tau}(t))$, with $\beta = 0.00584$. (β is the parameter introduced in Definition 2.2).

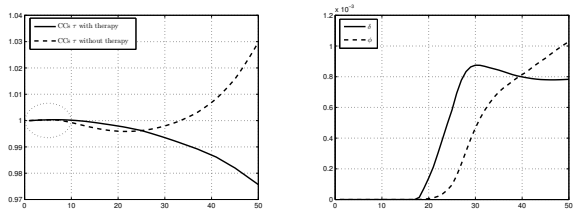

Fig. 3. Behavior of cancer cells τ, in absence of therapy: $(\delta, \phi) \equiv 0$ and presence of therapy: $(\delta, \phi) \equiv (13)$, with $t_1 = 30$ and $\kappa = 10^{-5} \approx 0$. ($\kappa$ is very small that (13) be continuous, as in Remark 2.16).

IV. Conclusion

The set-valued method [1], [6] is adapted to control Pinho's model (14). Numerical simulations in Figures 2 and 3 agreed with the theoretical characterization of the protocols (9) and (13). The main advantages of this method over others is that it:

1) Does not request complicated conditions to models subject of study, just
   a) The smoothness propriety of the function ψ, that it be of class $\mathcal{C}^1$ on $\mathbb{R}^n_+ \times \mathbb{R}_+$.
   b) The upper limit Hypothesis 2.9, which can be given by using comparison method, like the standard Kamke comparison theory used in the proof of [3].
2) Solves the setting control problem in Definition 2.1, for any value taken by the initial state (x_0, τ_0) in $\mathbb{R}^n_+ \times \mathbb{R}_+$, even the system 1 is in advanced stage I: $\psi(x_0, \tau_0) \geq 0$, we manage to build a protocol.
3) Gives continuous protocols on state feedback, with minimal norms (in the frame-work of set-valued analysis), which constitute lively advantages to the patient over the therapy session.
4) Provides protocols by doing simple selections, contrary to those given by the optimal control theory, which uses the result developed by Fleming and Rishel to establish the existence of an optimal control, and the classical Pontryagin's Maximum Principle to characterize optimal control, and some propositions to prove the uniqueness of the optimality system, in which state system is coupled with co-state system [9], [20], [21].
5) Does not require an analysis that puts into account the parameter values, unlike the case if we seek to stabilize the model (14) around its equilibrium points.
   In [3] for example, the equilibrium points of sub-models (in the absence of CA or AA) and the full-model (in the presence of both CA and AA), depend on constant parameters of Table II, and on variable parameters δ and ϕ, and these parameters also determine the nature of the equilibria.
6) Is applicable not perforce around the equilibrium points, but to the entire dynamics of the system (free state x).
7) Is a qualitative analysis with non-specific system parameters, that can vary greatly from patient to another [11], or can depend on time during the therapy for a given patient [23].
8) Is useful to approach another problem situations, apart from controlling cancer, inspired by the work carried out in [1], and [6], [25] adapts a unified set-valued method, to approach the asymptotic null-controllability with mixed constraints on state and control.

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