International Journal of
Mathematical Modelling & Computations
Vol. 11, No. 03, Summer 2021, 1- 14

General Anti-Angiogenic Therapy Protocols with Chemotherapy

A. Moustafid*

Department of Mathematics, Hassan II University, Casablanca, PO. Code 5366, Morocco.

Abstract. This given paper can be considered as a continuation of previous work, doing on cancer models and their control by a set-valued method, in the context of viability theory. We analyze a class models of ordinary differential equations, taking into account the possibility to directly acting on tumor. However we can augment the class by a simple ordinary differential equation of the tumor control term, and join it to the other variables state. This will allow to exploit results to generalize the approach.

Received: 08 December 2020, Revised: 12 May 2021, Accepted: 13 June 2021.

Keywords: Anti-angiogenic therapy; Chemotherapy; Viability theory; Set-valued analysis.

AMS Subject Classification: 92C50, 93C15, 34H05, 49K15.

Index to information contained in this paper

1. Introduction

The most of tumor growth models are developed in ordinary differential equations tool, and take into consideration the advantage of applying various therapies simultaneously for better cancer control, by assuming their synergistic effect on tumor, and limited side effects due to the over dosage of a particular therapy.

For example, by a partial analysis of the tumor free subspace, [17] shows how coupled anti-angiogenic therapy and chemotherapy, promote a larger reduction of the tumor, than use chemotherapy alone.

While [18] quantifies the anti-angiogenic effect of metronomic chemotherapy, by means of a computational approach.

*Corresponding author. Email: a.moustafid@gmail.com

http://ijm2c.iauctb.ac.ir

Also there are some research works on the tumor growth models, with optimal control strategies:

- [3] optimally controls model of tumor-immune interactions with chemotherapy.
- [12] proposes to model in [16], an optimal control method to reduce the tumor, by minimal total amount of chemotherapy, with low immune levels.
- [19] uses a quadratic control, to minimize the number of tumor cells, with minimal immunotherapeutic and chemotherapeutic drugs administration.
- [2] characterizes optimal control, that minimizes the tumor and usage of immunotherapy and anti-angiogenic drugs.
- [10] investigates as optimal control problems, four models from the literature: the model by d'Onofrio *et al.* [9], the model by the Pillis *et al.* [4], the model in Ergun *et al.* [11], the model of de Pillis *et al.* [5], which contain either immunotherapy, anti-agiogenic therapy, chemotherapy, or combinations of these.

This paper set-valued analysis the problem of cancer control in viability expressions. Section 2 generalizes results in [13], to model of ordinary differential equations with control term on tumor dynamics. Section 3 defines advancement stage tumor upon initial state of model. Section 4 applies method to the model of [9]. Section 5 stimulates numerically application issues.

2. Problem formulation

We consider the following dynamical system of ordinary differential equations:

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

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

where $x \in \mathbb{R}^n_+$, denote densities of cells in competition with tumor cells of density $\tau \in \mathbb{R}_+$.
Both parameters u and v represent the control terms, but they are of different kind: The control u acts indirectly on τ through x according to the x-dynamics (1a), stands for rates of immunotherapeutic or anti-angiogenic agents (e.g., cytokines, antibodies, angiogenesis inhibitors, etc.), and takes values within the constraint subset

$$K = \left[0, u_1^{\max}\right] \times \cdots \times \left[0, u_p^{\max}\right]. \tag{1c}$$

While the control v acts directly on τ according to the tumor dynamics (1b), stands for rates of chemotherapeutic agents (e.g., cyclophosphamide), and takes values within the constraint subset

$$L = \left[0, v_1^{\max}\right] \times \cdots \times \left[0, v_q^{\max}\right]. \tag{1d}$$

The functions f and ψ map $\mathbb{R}^n \times \mathbb{R}$ into $\mathbb{R}^n$ and $\mathbb{R}$ respectively, the operator G maps $\mathbb{R}^n \times \mathbb{R}$ into the spaces $\mathcal{L}(\mathbb{R}^p, \mathbb{R}^n)$, while the operators F and H map $\mathbb{R}^n \times \mathbb{R}$ into the spaces $\mathcal{L}(\mathbb{R}^p, \mathbb{R}^n)$ and $\mathcal{L}(\mathbb{R}^q, \mathbb{R})$ respectively.
The naturally arising problem is of how to administer the protocols u and v, with respect to the constraints (1c) and (1d), in such way as to strictly decrease the tumor cells density τ on the therapy horizon $[0, \infty)$, and asymptotically control τ towards null values.

Hence we have to consider the following control problem:
Find a protocol (u, v) such that

$$\forall t \in [0, \infty), (u(t), v(t)) \in K \times L, \tag{2a}$$

for which

$$\forall t \in [0, \infty), \dot{\tau}(t) < 0, \tag{2b}$$

and

$$\lim_{t \to \infty} \tau(t) = 0. \tag{2c}$$

3. Viability context

3.1 *Augmented model*

It is more convenient to consider the second control v as a third variable, and augment system (1) by the linear differential equations

$$\dot{v}_i = -w_i v_i, \tag{3a}$$

with the auxiliary controls

$$w_i \in [0, w_i^{\max}], \tag{3b}$$

and the initial conditions

$$v_i^0 \in [0, v_i^{\max}], \tag{3c}$$

so the augmented system is as follows

$$\dot{z} = \bar{f}(z, \tau) + \bar{G}(z, \tau)c, \tag{4a}$$
$$\dot{\tau} = \bar{\psi}(z, \tau), \tag{4b}$$

where the state $z = (x, v) \in \mathbb{R}^n_+ \times L$, and the control c is such that

$$c = (u, w) \in K \times P \tag{4c}$$

with

$$P = \left[0, w_1^{\max}\right] \times \cdots \times \left[0, w_q^{\max}\right], \tag{4d}$$

while the dynamics $\bar{f}$ and $\bar{\psi}$ map $\mathbb{R}^{n+q+1}$ into $\mathbb{R}^{n+q}$ and $\mathbb{R}$ respectively, and are defined by the expressions

$$\bar{f}(z, \tau) = (f(x, \tau) + F(x, \tau)v, 0)' \text{ and} \tag{4e}$$
$$\bar{\psi}(z, \tau) = \psi(x, \tau) + H(x, \tau)v, \tag{4f}$$

and the control operator $\bar{G}$ map $\mathbb{R}^{n+q+1}$ into the space $\mathcal{L}(\mathbb{R}^{p+q}, \mathbb{R}^{n+q})$, such that

$$\bar{G}(z,\tau)c = (G(x,\tau)u, B(v)w)' \text{ with} \tag{4g}$$

$$(B(v)w)_i = -w_i v_i. \tag{4h}$$

We have to find a control $c \in K \times L$, for which the solution τ satisfies (2b) and (2c), subject to the dynamics (4a) and (4b). However, according to (3a), the v_i's may be expressed for all $t \geq 0$ as function of w_i's as

$$v_i(t) = v_i^0 \exp\left(-\int_0^t w_i(s)\, ds\right), \tag{5}$$

then by virtue of (3b) and (3c) we have $v(t) \in L$, for all $t \geq 0$, and the constraint (2a) still satisfied.

3.2 *Viability problem*

In this subsection we will formulate the problem in the frame-work of the viability theory. We associate with a non-negative real number α the subset

$$D_\alpha = \{(z,\tau) \in \mathbb{R}^n_+ \times L \times \mathbb{R}_+ \mid \psi_\alpha(z,\tau) \leq 0\}, \tag{6a}$$

where the function ψ_α maps $\mathbb{R}^{n+q+1}$ into $\mathbb{R}$, and depends on the function $\bar{\psi}$ of (4f) as follows

$$\psi_\alpha(z,\tau) = \bar{\psi}(z,\tau) + \alpha\tau. \tag{6b}$$

Proposition 3.1 *Assume that there exists α such that $(z_0,\tau_0) \in D_\alpha$, and a control $c : [0,\infty) \to K \times P$ keeping system (4) globally viable in D_α, then the protocol (u,v) solves problem (2).*

Proof Let $t \geq 0$, and let (z,τ) be the globally viable trajectory in D_α, leading by the control c. According to (4b) and (6) we have the differential inequality

$$\dot{\tau}(t) = \bar{\psi}(z(t),\tau(t)) \leq -\alpha\tau(t),$$

by applying Gronwall's lemma we get the exponential estimate

$$0 \leq \tau(t) \leq \tau_0 \exp(-\alpha t),$$

then in the limit ∞, the tumor is eradicated: $\lim_{t\to\infty} \tau(t) = 0$, with the average speed of therapy α. ■

3.3 *Set-valued approach*

We associate with the system (4), the set-valued map $\mathcal{F}_\alpha$ of regulation defined on the constraint viability D_α in the following way

$$\mathcal{F}_\alpha(z,\tau) = \left\{c \in K \times P \mid (\bar{f}(z,\tau) + \bar{G}(z,\tau)c, \bar{\psi}(z,\tau))' \in T_{D_\alpha}(z,\tau)\right\}, \tag{7a}$$

where

$$T_{D_\alpha}(z,\tau) = \left\{ (y,\zeta) \in \mathbb{R}^{n+q+1} \;\middle|\; \liminf_{h\downarrow 0} \frac{d((z+hy,\tau+h\zeta),D_\alpha)}{h} = 0 \right\}, \qquad (7b)$$

stands for the contingent cone to the constraint viability D_α at point (z,τ).

Lemma 3.2 *Let be α such that $(z_0,\tau_0) \in D_\alpha$. The system (4) is locally viable in the constraint viability D_α if and only if*

$$\text{for all } (z,\tau) \in D_\alpha, \text{ there exists } c_\alpha \in K \times P \text{ such that}$$

$$(\bar{f}(z,\tau) + \bar{G}(z,\tau)c_\alpha, \bar{\psi}(z,\tau))' \in T_{D_\alpha}(z,\tau).$$

Furthermore any single-valued selection of $\mathcal{F}_\alpha$ leads to a local viable solution.

Lemma 3.3 *Let be α such that $(z_0,\tau_0) \in D_\alpha$. If there exists functions m_1 and m_2 mapping bounded subsets of $\mathbb{R}$ into bounded images of $\mathbb{R}$ and such that*

$$\|\bar{f}(z,\tau)\| \le m_1(\tau)(\|z\|+1) \text{ and } \|\bar{G}(z,\tau)\| \le m_2(\tau),$$

then the system (4) is globally viable in the constraint viability D_α.

Proof Let $c_\alpha : D_\alpha \to K \times P$ be a selection of the map $\mathcal{F}_\alpha$ such that the control $(u,v) = c_\alpha(z,\tau)$ leads to a local viable solution (z,τ) to system (4) in D_α. Let (z,τ) be defined over a maximal interval $[0,T)$. We have to prove that $T = \infty$. Indeed, assume that $T < \infty$. The non-negative function $\tau(\cdot)$ is on the decreasing then for all t in $[0,T)$ we have $0 \le \tau(t) \le \tau_0$, then there exists a non-negative constant M such that

$$m_1(\tau(t)) \le M \text{ and } m_2(\tau(t)) \le M,$$

which yields a linear growth for (4a)

$$\begin{aligned} \|\dot{z}(t)\| &\le M\,(\|z(t)\|+1) + M\|c^{\max}\| \\ &\le M\,(\|z(t)\| + \|c^{\max}\| + 1) \end{aligned}$$

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

$$\|z(t)\| \le (\|z_0\| + \|c^{\max}\| + 1)\exp(Mt),$$

then $z(t)$ has a limit denoted by $z(T)$ when $t \to T^-$.
As τ is a non-negative decreasing function, we have

$$\tau(t) \to \tau(T) \text{ when } t \to T^-.$$

Therefore

$$(z(t),\tau(t)) \to (z(T),\tau(T)) \text{ when } t \to T^-,$$

and $(z(T),\tau(T))$ belongs to D_α because it is closed. Now, by considering $(z(T),\tau(T))$ as an initial state it follows that (z,τ) may be prolonged to a viable solution $(\bar{z},\bar{\tau})$ in D_α, starting at $(z(T),\tau(T))$ on some interval $[T,S)$ where

$S > T$, which is in contradiction with the maximality of T, then the solution (z, τ) becomes globally viable in D_α. ■

Lemma 3.4 *If the function ψ_α in* (6b) *is continuously differentiable on D_α, and admits a partial derivative $\partial_i \psi_\alpha$ strictly negative on D_α. Then for each $(z, \tau) \in D_\alpha$ the tangent directions (y, ζ) of $T_{D_\alpha}(z, \tau)$ are characterized by*

$$\begin{cases} y_i \geq 0 & \text{if} \quad z_i = 0, \quad i = 1, \ldots, n+q, \\ \zeta \geq 0 & \text{if} \quad \tau = 0, \\ \dot{\psi}_\alpha(z,\tau)(y,\zeta) \leq 0 & \text{if} \quad \psi_\alpha(z,\tau) = 0. \end{cases}$$

Proposition 3.5 *If for all $(x, \tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+$, and $(u, v) \in K \times L$ we have*

$$\begin{cases} \pi_i\big(f(x,\tau) + G(x,\tau)u\big) \geq 0 & \text{if} \quad x_i = 0, \quad i = 1, \ldots, n, \\ \psi(x,\tau) + H(x,\tau)v \geq 0 & \text{if} \quad \tau = 0, \end{cases}$$

then the map $\mathcal{F}_\alpha$ may be expressed explicitly on the constraint viability D_α as

$$\mathcal{F}_\alpha(z,\tau) = \begin{cases} K \times P & \text{if} \quad \bar{\psi}_\alpha(z,\tau) < 0, \\ C_\alpha(z,\tau) & \text{if} \quad \bar{\psi}_\alpha(z,\tau) = 0, \end{cases} \tag{8a}$$

where

$$C_\alpha(z,\tau) = \{c \in K \times P \mid \langle h(z,\tau), c\rangle \geq \ell_\alpha(z,\tau)\}, \tag{8b}$$

with

$$h(z,\tau) = -\bar{G}'(z,\tau)\nabla_z \bar{\psi}(z,\tau), \tag{9a}$$

$$\ell_\alpha(z,\tau) = \langle \nabla_z \bar{\psi}(z,\tau), \bar{f}(z,\tau)\rangle + \bar{\psi}(z,\tau)\frac{\partial \bar{\psi}}{\partial \tau}(z,\tau) + \alpha\bar{\psi}(z,\tau), \tag{9b}$$

$$\nabla_z \bar{\psi}(z,\tau) = \left(\frac{\partial \bar{\psi}}{\partial x_1}(z,\tau), \ldots, \frac{\partial \bar{\psi}}{\partial x_n}(z,\tau), \frac{\partial \bar{\psi}}{\partial v_1}(z,\tau), \ldots, \frac{\partial \bar{\psi}}{\partial v_q}(z,\tau)\right)'.$$

Proof For all $(z, \tau) \in D_\alpha$ we have

$$\begin{aligned} &\dot{\psi}_\alpha(z,\tau)(\bar{f}(z,\tau) + \bar{G}(z,\tau)c, \bar{\psi}(z,\tau)) \\ &= \langle \nabla\psi_\alpha(z,\tau), (\bar{f}(z,\tau) + \bar{G}(z,\tau)c, \bar{\psi}(z,\tau))'\rangle \\ &= \langle \nabla_z\psi_\alpha(z,\tau), \bar{f}(z,\tau) + \bar{G}(z,\tau)c\rangle + \bar{\psi}(z,\tau)\frac{\partial \psi_\alpha}{\partial \tau}(z,\tau), \end{aligned}$$

then by (6b)

$$\begin{aligned} &\dot{\psi}_\alpha(z,\tau)(\bar{f}(z,\tau) + \bar{G}(z,\tau)c, \bar{\psi}(z,\tau)) \\ &= \langle \nabla_z \bar{\psi}(z,\tau), \bar{f}(z,\tau) + \bar{G}(z,\tau)c\rangle + \bar{\psi}(z,\tau)\frac{\partial \bar{\psi}}{\partial \tau}(z,\tau) + \alpha\bar{\psi}(z,\tau) \\ &= \langle \nabla_z \bar{\psi}(z,\tau), \bar{G}(z,\tau)c\rangle + \langle \nabla_z \bar{\psi}(z,\tau), \bar{f}(z,\tau)\rangle + \bar{\psi}(z,\tau)\frac{\partial \bar{\psi}}{\partial \tau}(z,\tau) + \alpha\bar{\psi}(z,\tau), \end{aligned}$$

then by (4e) and (4g)

$$\begin{aligned}
&\dot{\psi}_\alpha(z,\tau)(\bar{f}(z,\tau)+\bar{G}(z,\tau)c,\bar{\psi}(z,\tau))\\
&=\langle\nabla_x\bar{\psi}(z,\tau),G(x,\tau)u\rangle+\langle\nabla_v\bar{\psi}(z,\tau),B(v)w\rangle+\\
&\quad\langle\nabla_x\bar{\psi}(z,\tau),f(z,\tau)\rangle+\bar{\psi}(z,\tau)\frac{\partial\bar{\psi}}{\partial\tau}(z,\tau)+\alpha\bar{\psi}(z,\tau)\\
&=\langle G'(x,\tau)\nabla_x\bar{\psi}(z,\tau),u\rangle+\langle B'(v)\nabla_v\bar{\psi}(z,\tau),w\rangle+\\
&\quad\langle\nabla_x\bar{\psi}(z,\tau),f(z,\tau)\rangle+\bar{\psi}(z,\tau)\frac{\partial\bar{\psi}}{\partial\tau}(z,\tau)+\alpha\bar{\psi}(z,\tau),
\end{aligned}$$

then by (9)

$$\dot{\psi}_\alpha(z,\tau)(\bar{f}(z,\tau)+\bar{G}(z,\tau)c,\bar{\psi}(z,\tau))=-\langle h(z,\tau),c\rangle+\ell_\alpha(z,\tau),$$

and by (7a) and Lemma 3.4 we get the characterization

$$c\in\mathcal{F}_\alpha(z,\tau)\iff\begin{cases}\pi_i\big(\bar{f}(z,\tau)+\bar{G}(z,\tau)c\big)\geq 0 & \text{if}\quad z_i=0,\quad i=1,\dots,n+q,\\ \bar{\psi}(z,\tau)\geq 0 & \text{if}\quad \tau=0,\\ -\langle h(z,\tau),c\rangle+\ell_\alpha(z,\tau)\leq 0 & \text{if}\quad \bar{\psi}_\alpha(z,\tau)=0.\end{cases}$$

$$c\in\mathcal{F}_\alpha(z,\tau)\iff\begin{cases}\pi_i\big(f(x,\tau)+G(x,\tau)u\big)\geq 0 & \text{if}\quad x_i=0,\quad i=1,\dots,n,\\ \pi_{_i}\big(B(v)w\big)\geq 0 & \text{if}\quad v_i=0,\quad i=1,\dots,q,\\ \pi_{_i}\big(B(v)w\big)\leq 0 & \text{if}\quad v_i=v_i^{\max},\quad i=1,\dots,q,\\ \psi(x,\tau)+H(x,\tau)v\geq 0 & \text{if}\quad \tau=0,\\ -\langle h(z,\tau),c\rangle+\ell_\alpha(z,\tau)\leq 0 & \text{if}\quad \bar{\psi}_\alpha(z,\tau)=0.\end{cases}$$

or for all $i=1,\dots,q$, the inequalities

$$\pi_{_i}\big(B(v)w\big)=-v_iw_i\begin{cases}\geq 0 \text{ if } v_i=0,\\ \leq 0 \text{ if } v_i=v_i^{\max},\end{cases}$$

are verified, then it follows that the regulation law c is characterized by

$$\langle h(z,\tau),c\rangle\geq\ell_\alpha(z,\tau)\text{ if }\bar{\psi}_\alpha(z,\tau)=0.$$

■

Lemma 3.6 *Selection of the set-valued map $\mathcal{F}_\alpha$ may be given on the constraint viability D_α by the expression*

$$c_\alpha(z,\tau)=\pi_{C_\alpha(z,\tau)}(0),\tag{10}$$

where $\pi_{C_\alpha(z,\tau)}(0)$ denotes the projection of 0 onto the closed convex set $C_\alpha(z,\tau)$.

Proof See [13]. ■

4. Cancer control

Let be the sub-set

$$\Omega=\left\{(z,\tau)\in\mathbb{R}^n_+\times L\times\mathbb{R}_+\mid\bar{\psi}(z,\tau)<0\right\},\tag{11}$$

where $\bar{\psi}$ is the function expressed in (4f).

Theorem 4.1 *Assume that there exists $v^0 \in L$ such that $(z_0, \tau_0) \in \Omega$, and there exists $\alpha \in [0, \alpha_0]$, with $\alpha_0 = -\bar{\psi}(z_0, \tau_0)/\tau_0$. If moreover the linear growth condition of Lemma 3.3 is also satisfied, then the selection c_α (10) and its associate global viable solution (z, τ) to the system (4), both provide a solution (u^α, v^α) to problem 2, defined for all $t \in [0, \infty)$ by the components*

$$\begin{cases} u_i^\alpha(t) = \pi_{K_i}\big(c_\alpha(z(t), \tau(t))\big), \text{ for } i = 1, \dots, p, \\ v_i^\alpha(t) = v_i^0 \exp\left(-\displaystyle\int_0^t \pi_{P_i}\big(c_\alpha(z(s), \tau(s))\big)\, ds\right), \text{ for } i = 1, \dots, q. \end{cases} \tag{12}$$

Proof By Lemma 3.6, the regulation map $\mathcal{F}_\alpha$ admits a selection c_α, or (z_0, τ_0) belongs to D_α, then by Lemma 3.3, the selection c_α leads to a solution (z, τ), which is globally viable on D_α, then by Proposition 3.1, the protocol (u^α, v^α) given by (4c) and (5), solves problem 2. ■

On the other hand, if $(z_0, \tau_0) \in \Omega^c$, then there is no protocol that solves the problem (2). Indeed, otherwise we will have for all $t \in [0, \infty)$

$$\bar{\psi}(z(t), \tau(t)) = \dot{\tau}(t) < 0,$$

In particular for $t = 0$ we have

$$\bar{\psi}(z_0, \tau_0) < 0,$$

which is absurd.
To investigate this situation, we associate with a non-negative real number β, the set-valued map $\bar{C}_\beta$ defined by

$$\bar{C}_\beta(z, \tau) = \left\{\bar{c} \in K \times P \mid \langle h(z, \tau), \bar{c}\rangle \geq \bar{\ell}(z, \tau) + \beta\right\}, \tag{13a}$$

where h is given by (9a), and $\bar{\ell}$ is given by

$$\bar{\ell}(z, \tau) = \langle \nabla_z \bar{\psi}(z, \tau), \bar{f}(z, \tau)\rangle + \bar{\psi}(z, \tau)\frac{\partial \bar{\psi}}{\partial \tau}(z, \tau). \tag{13b}$$

Theorem 4.2 *Let (z_0, τ_0) belongs to Ω^c. The selection $\bar{c}_\beta(\cdot) = \pi_{\bar{C}_\beta(\cdot)}(0)$ steers the system (4) from (z_0, τ_0) to Ω, at any time $\bar{t} > \bar{\psi}(z_0, \tau_0)/\beta$, i.e., $(\bar{z}(\bar{t}), \bar{\tau}(\bar{t})) \in \Omega$, where $(\bar{z}, \bar{\tau})$ denotes the solution of system (4) leading on the interval $[0, \bar{t}]$ by the selection $\bar{c}_\beta$, and the corresponding protocol $(\bar{u}^\beta, \bar{v}^\beta)$ to system (1) is given for all $t \in [0, \bar{t}]$ by the components*

$$\begin{cases} \bar{u}_i^\beta(t) = \pi_{K_i}\big(\bar{c}_\beta(\bar{z}(t), \bar{\tau}(t))\big), \text{ for } i = 1, \dots, p, \\ \bar{v}_i^\beta(t) = v_i^0 \exp\left(-\displaystyle\int_0^t \pi_{P_i}\big(\bar{c}_\beta(\bar{z}(s), \bar{\tau}(s))\big)\, ds\right), \text{ for } i = 1, \dots, q. \end{cases} \tag{14}$$

Proof By (4b) we have

$$\bar{\psi}(\bar{z}(\bar{t}), \bar{\tau}(\bar{t})) = \bar{\psi}(z_0, \tau_0) + \int_0^{\bar{t}} \left[\langle \nabla_z \bar{\psi}(\bar{z}(s), \bar{\tau}(s)), \dot{\bar{z}}(s)\rangle + \dot{\bar{\tau}}(s)\frac{\partial \bar{\psi}}{\partial \tau}(\bar{z}(s), \bar{\tau}(s))\right] ds,$$

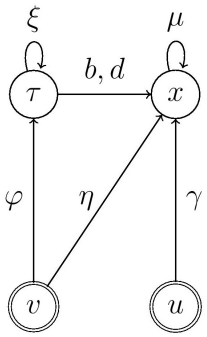


Figure 1. Schematic representation of interactions, and agents effects in the model (15).

then by (4a), (9a) and (13b) we get

$$\bar{\psi}(\bar{z}(\bar{t}), \bar{\tau}(\bar{t})) = \bar{\psi}(z_0, \tau_0) - \int_0^{\bar{t}} \left[\langle h(\bar{z}(s), \bar{\tau}(s)), \bar{c}_\beta(\bar{z}(s), \bar{\tau}(s))\rangle - \bar{\ell}(\bar{z}(s), \bar{\tau}(s))\right] ds,$$

since $\bar{c}_\beta$ is a selection of the map $\bar{C}_\beta$ then we have

$$\bar{\psi}(\bar{z}(\bar{t}), \bar{\tau}(\bar{t})) \leq \bar{\psi}(x_0, \tau_0) - \beta\bar{t},$$

as $\beta\bar{t} > \bar{\psi}(x_0, \tau_0)$ it follows that $\bar{\psi}(\bar{z}(\bar{t}), \tau(\bar{t})) < 0$.
The protocol $(\bar{u}^\beta, \bar{v}^\beta)$ is given by (4c) and (5). ■

For a given initial stage cancer (x_0, τ_0), one of both opposites instances below may arise:

- *Non-advanced stage*: There exists $v_0 \in L$, such that $(x_0, v_0, \tau_0) \in \Omega$, as Theorem 4.1, the tumor will exponentially decreases near to the null values, by the protocol (12), derived from the selection (10).
- *Advanced stage*: There is no protocol in terms of problem (2), but as Theorem 4.2, for an appropriate β, the system (4) may be steered to *non-advanced stage* at time $\bar{t}$, by the selection $\bar{c}_\beta$ of the set-valued map (13).

5. Application example

5.1 *The model*

We consider the model [9] for angiogenic signaling with an anti-angiogenic agent u and a chemotherapeutic agent v. Treating the concentrations of these agents as the controls gives the following controlled dynamics on carrying capacity of the vasculature x and primary tumor volume τ.

$$\dot{x} = b\tau - d\tau^{\frac{2}{3}}x - \mu x - \gamma xu - \eta xv, \tag{15a}$$

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

Descriptions of model entities are given in Tables 1 and 2 below.

Table 1. Description of variables and controls.

Symbol	Description	Unit
x	Carrying capacity of the vasculature	mm^3
τ	Primary tumor volume	mm^3
u	Anti-angiogenic agent	$\left[\frac{\text{mg of dose}}{\text{kg}}\right]$
v	Chemotherapeutic agent	$\left[\frac{\text{mg of dose}}{\text{kg}}\right]$

Table 2. Descriptions of differential equations (15a) and (15b).

Equation	Term	Description
(15a)	$b\tau$	Pro-angiogenic effect exerted by the tumor
	$-d\tau^{\frac{2}{3}}x$	Effect of the endogenous anti-angiogenic factors
	$-\mu x$	Rate of spontaneous vasculature loss
	$-\gamma x u, -\eta x v$	Rates of therapy-induced vasculature loss
(15b)	$-\xi\tau\ln\left(\frac{\tau}{x}\right)$	Gompertzian tumor growth
	$-\varphi\tau v$	Log-kill term

5.2 *Protocol*

Functions m_1 et m_2 in Lemma 3.3 are given here by

$$m_1(\tau) = \max(b\tau; d\tau^{\frac{2}{3}} + \eta v^{\max} + \mu),$$

and

$$m_2(\tau) = \max(\gamma u^{\max}; w^{\max}).$$

The function $\bar{\psi}$ in (4f) is explicitly expressed here by the formulas

$$\bar{\psi}(x, v, \tau) = -\xi\tau\ln\left(\frac{\tau}{x}\right) - \varphi\tau v,$$

and its partial derivatives are as follows

$$\begin{aligned}
\frac{\partial\bar{\psi}}{\partial x}(x, v, \tau) &= \xi\frac{\tau}{x},\\
\frac{\partial\bar{\psi}}{\partial v}(x, v, \tau) &= -\varphi\tau,\\
\frac{\partial\bar{\psi}}{\partial \tau}(x, v, \tau) &= -\xi\ln\left(\frac{\tau}{x}\right) - \xi - \varphi v,
\end{aligned}$$

Now we check that Lemma 3.4 is well filled

$$\begin{aligned}
\frac{\partial\psi_\alpha}{\partial\tau}(x, v, \tau) &= -\xi\ln\left(\frac{\tau}{x}\right) - \xi - \varphi v + \alpha\\
&= \frac{\psi_\alpha(x, v, \tau)}{\tau} - \xi\\
&\leq -\xi\\
&< 0.
\end{aligned}$$

To have a useful expressions of the set-valued maps C_α and $\bar{C}_\beta$, we first express the functions h, ℓ_α, and $\bar{\ell}$, given respectively by (9a), (9b), and (13b).

$$h(x,v,\tau) = \left(\frac{\xi}{\gamma}\frac{\tau}{x^2}, -\varphi\frac{\tau}{v}\right)',$$

$$\begin{aligned}\ell_\alpha(x,v,\tau) = \xi\frac{\tau}{x}(b\tau - d\tau^{\frac{2}{3}}x - \mu x - \gamma x u - \eta x v)\\ + \left(\xi\tau\ln\left(\frac{\tau}{x}\right) + \varphi\tau v\right)\left(\xi\ln\left(\frac{\tau}{x}\right) + \xi + \varphi v - \alpha\right),\end{aligned}$$

$$\begin{aligned}\bar{\ell}(x,v,\tau) = \xi\frac{\tau}{x}(b\tau - d\tau^{\frac{2}{3}}x - \mu x - \gamma x u - \eta x v)\\ + \left(\xi\tau\ln\left(\frac{\tau}{x}\right) + \varphi\tau v\right)\left(\xi\ln\left(\frac{\tau}{x}\right) + \xi + \varphi v\right),\end{aligned}$$

from where

$$C_\alpha(x,v,\tau) = \left\{(u,w)\in[0,u^{\max}]\times[0,w^{\max}]\ \middle|\ \frac{\xi}{\gamma}\frac{\tau}{x^2}u - \varphi\frac{\tau}{v}w \geq \ell_\alpha(x,v,\tau)\right\}, \quad (16)$$

and

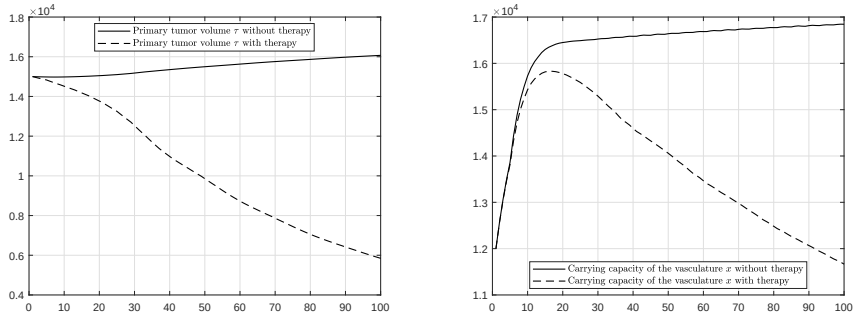
$$\begin{aligned}\bar{C}_\beta(x,v,\tau) = \Bigg\{(\bar{u},\bar{w})\in[0,u^{\max}]\times[0,w^{\max}]\ \Bigg|\ \frac{\xi}{\gamma}\frac{\tau}{x^2}\bar{u}\\ - \varphi\frac{\tau}{v}\bar{w} \geq \bar{\ell}(x,v,\tau) + \beta\Bigg\}.\end{aligned} \quad (17)$$

5.3 *Numerical simulations*

This section illustrates characterized protocol of set-valued map (16), in *non-advanced stage* of tumor for Theorem 4.1, and selection of set-valued map (17), in *advanced stage* for Theorem 4.1. We first consider the *non-advanced stage* in Figure 2, where Figures 2(a) and 2(b) show how we can reduce primary tumor volume and carrying capacity of the vasculature, under combined therapies in Figures 2(c) and 2(d). Next, we consider the *advanced stage* in Figure 3, where Figures 3(a) and 3(b) show how model reaches *non-advanced stage*, within mixed therapies in Figures 3(c) and 3(d). Proposed numerical simulations use parameter values given in Table 3, and agreed with theoretical results of Section 4.

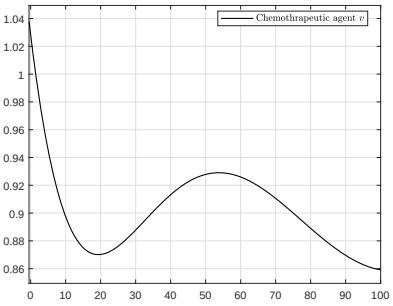
6. Conclusion

Set-valued method in the viability theory is adapted to control general system of cancer models [2–5, 9–12, 16–19], in ordinary differential equations form. Protocols are formalized as selections of regulation maps, adjusting by contingent cones the system to be globally viable, with null convergence of tumor. As an application example of this method we consider the model in [9], which is already studied in [13], with logistic tumor growth, under monotherapy in angiogenesis treatment [8]. By comparing Figures 4(a) and 2(a), we see that by chemotherapy, only half

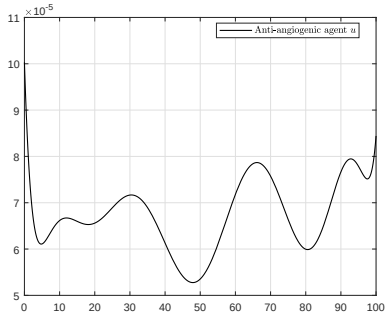


(a)

(b)

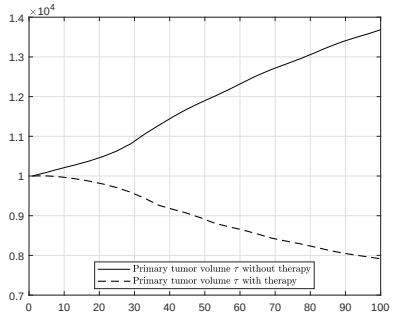


(c)

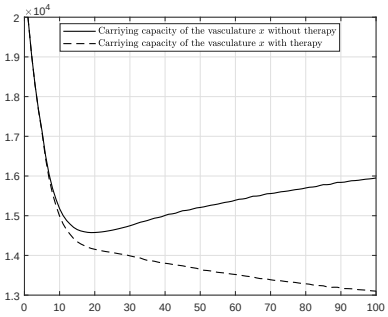


(d)

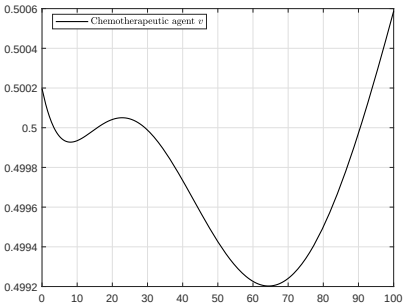
Figure 2. Model (15) started on *non-advanced stage* $(12000, 1, 15000)$.



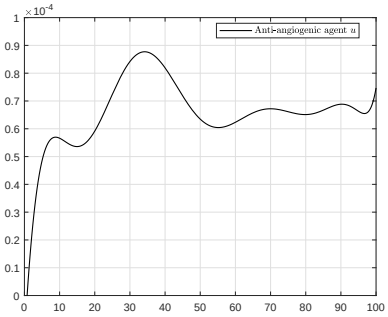
(a)



(b)



(c)



(d)

Figure 3. Model (15) started on *advanced stage* $(20000, 0.5, 10000)$.

Table 3. Description of parameters.

Parameter	Description	Unit	Value
ξ	Tumor growth parameter	$[\text{day}^{-1}]$	$\frac{0.192}{ln10} = 0.084$
b	Tumor-induced stimulation parameter	$[\text{day}^{-1}]$	5.85
d	Tumor-induced inhibition parameter	$[\text{day}^{-1}\text{mm}^{-2}]$	0.00873
μ	Baseline loss of vascular support through natural causes	$[\text{day}^{-1}]$	0.02
γ	Anti-angiogenic elimination parameter	$\left[\frac{\text{kg}}{\text{mg of dose}}\right] \text{day}^{-1}$	0.15
φ	Cytotoxic killing parameter for the tumor	$\left[\frac{\text{kg}}{\text{mg of dose}}\right] \text{day}^{-1}$	0.1
η	Cytotoxic killing parameter for the vasculature	$\left[\frac{\text{kg}}{\text{mg of dose}}\right] \text{day}^{-1}$	$0 - 0.1$
$u^{\max}$	Maximum allowable dose for the anti-angiogenic agent	$\left[\frac{\text{mg of dose}}{\text{kg}}\right] \text{day}^{-1}$	75
$v^{\max}$	Maximum allowable dose for the chemotherapeutic agent	$\left[\frac{\text{mg of dose}}{\text{kg}}\right] \text{day}^{-1}$	$1 - 2$

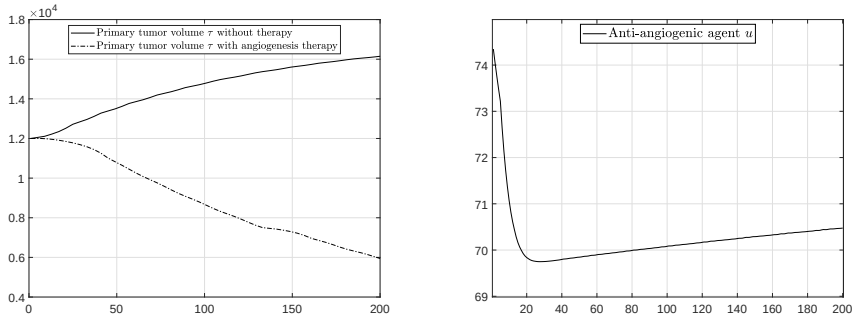
duration of therapy is required to reach tumor at same level $\approx 0.6 \times 10^4$. Involving both anti-angiogenic therapy and chemotherapy yield an effectively better result.

There exists in the literature another works approaching the model (15), we cite for examples:

- [14] answers to the following question: given a priori determined total amounts of agents $\int_0^T u(s)\,ds \leq u^{\max}$ and $\int_0^T v(s)\,ds \leq v^{\max}$, for free terminal time $T > 0$, how can agents $u(t)$ and $v(t)$ best be administered in time, to maximize the reduction of primary tumor volume $\tau(T)$ subject to the model (15); and illustrates the qualitative shape of optimal control solution (u_*, v_*) for combination treatments with anti-angiogenic inhibitors and chemotherapy.
- [20] compares controllability conditions of the model (15), in a class of two-compartmental models of treatment response to anti-angiogenic therapy and its combination with chemotherapy.
- [21] presents sufficient conditions of local controllability of the model (15), in a class of models of treatment response to combined anti-cancer therapies, which include delays in control strategies, and compares results for the models without delays and conditions for relative local controllability of models with delays.
- [7] analysis stability equilibrium and tumor eradication of the model (15), in a class of models of angiogenesis and anti-angiogenesis anti-cancer therapy.
- [6] proposes many mathematical models of tumor angiogenesis, but for analysis and optimization of therapy protocols the most useful seems to be a class of the model (15).
- [15] uses Hamilton-Jacobi-Isaacs formalism, to derive a robust state feedback control of the model (15), guaranteeing tumor contraction maps as a function of the initial state of tumor and the vasculature capacity.

We conclude by mentioning the main characteristics of the method developed in this paper:

- Gives continuous protocols, unlike optimal control solution (u_*, v_*) given in [14].
- Applicable in monotherapy modality [13] or combined therapy, unlike in [20, 21].
- Does not require an analysis on parameter values, unlike the stabilization in [7].
- Functional to several types of ode models used in angiogenic therapy, like in [6].
- Contracts primary tumor volume for any initial positive conditions, like in [15].



(a) (b)

Figure 4. Logistic model in [8], started on $(12000, 15000)$ in [13].

References

[1] J. P. Aubin, Dynamic Economic Theory: A Viability Approach, Springer, Berlin (1997).
[2] A. Bukkuri, Optimal control analysis of combined anti-angiogenic and tumor immunotherapy, Open J. Math. Sci., **3** (2019) 349–357.
[3] L. G. de Pillis, W. Gu, K. R. Fister, T. Head, K. Maples, A. Murugan, T. Neal and K. Yoshida, Chemotherapy for tumors: An analysis of the dynamics and a study of quadratic and linear optimal controls, Math. Biosci., **209** (2007) 292–315.
[4] L. de Pillis and W. Gu and A. Radunskaya, Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations, J. Theor. Biol., **238** (2006) 841–862.
[5] L. de Pillis and A. Radunskaya, A mathematical tumor model with immune resistance and drug therapy: an optimal control approach, J. Theor. Med., **3** (2001) 79–100.
[6] M. Dolbniak and A. Swierniak, Comparison of simple models of periodic protocols for combined anticancer therapy, Comput. Math. Methods Med., **2013** (2013), Article ID 567213, doi:10.1155/2013/567213.
[7] A. d'Onofrio and A. Gandolfi, Chemotherapy of vascularised tumours: Role of vessel density and the effect of vascular pruning, J. Theoret. Biol., **264** (2010) 253–265.
[8] A. d'Onofrio and A. Gandolfi, Tumour eradication by antiangiogenic therapy: analysis and extensions of the model by Hahnfeldt et al. (1999), Math. Biosci., **191** (2004) 159–184.
[9] A. d'Onofrio, U. Ledzewicz, H. Maurer and H. Schättler, On optimal delivery of combination therapy for tumors, Math. Biosci., **222** (2009) 13–26.
[10] M. Engelhart, D. Lebiedz and S. Sager, Optimal control for selected cancer chemotherapy ODE models: A view on the potential of optimal schedules and choice of objective function, Math. Biosci., **229** (2011) 123–134.
[11] A. Ergun, K. Camphausen and L. M. Wein, Optimal scheduling of radiotherapy and angiogenic inhibitors, Bull. Math. Biol., **65** (2003) 407–424.
[12] M. Itik, M. U. Salamci and S. P. Banksa, Optimal control of drug therapy in cancer treatment, Nonlinear Anal., **71** (2009) 1473–1486.
[13] K. Kassara and A. Moustafid, Angiogenesis inhibition and tumor-immune interactions with chemotherapy by a control set-valued method, Math. Biosci., **231** (2011) 135–143.
[14] U. Ledzewicz and H. Schttler, On the role of the objective in the optimization of compartmental models for biomedical therapies, J. Optim. Theory Appl., **187** (2020) 305–335.
[15] A. Mazen, Robust feedback design for combined therapy of cancer, Optim. Control Appl. Meth., **35** (2014) 77–88.
[16] J. M. Murray, Optimal control for a cancer chemotherapy problem with general growth and loss functions, Math. Biosci., **98** (1990) 273–287.
[17] S. T. R. Pinho, F. S. Bacelar, R. F. S. Andrade and H. I. Freedman, A mathematical model for the effect of anti-angiogenic therapy in the treatment of cancer tumours by chemotherapy, Nonlinear Anal. Real World Appl., **14** (2013) 815–828.
[18] D. S. Rodrigues, P. F. A. Manceraa and S. T. R. Pinho, Understanding the antiangiogenic effect of metronomic chemotherapy through a simple mathematical model, Physica A., **464** (2016) 251–266.
[19] S. Sharma and G. P. Samanta, Analysis of the dynamics of a tumor-immune system with chemotherapy and immunotherapy and quadratic optimal control, Differ Equ Dyn Syst., **24 (2)** (2016) 149–171.
[20] A. Świerniak and J. Klamka, Comparison of controllability conditions for models of antiangiogenic and combined anticancer therapy, IFAC Proceedings Volumes, **47** (2014) 11530–11535.
[21] A. Świerniak and J. Klamka, Local controllability of models of combined anticancer therapy with delays in control, Math. Model. Nat. Phenom., **9** (2014) 216–226.