General Chemotherapy Protocols

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Abstract –In this paper we treat the problem of cancer control by chemotherapy, through general model in ordinary differential equation form of tumor dynamics. The model is augmented by an ordinary linear differential equation of chemotherapy drugs, and the control problem is reset in the framework of the viability theory. Set-valued analysis method is applied to design procedures leading to the formulation of treatment protocols, which are single-valued selections of set-valued maps, and divide in two categories according to the advancement of initial state cancer, which is characterized by specific set-valued map, upon the strict negativity of the dynamic tumor function at the initial state. Protocols corresponding to non-advanced stage cancer, ensures the decreasing of tumor cells, unlike the ones of advanced stage. Logistic model is considered from the literature to illustrate effects of feedback protocols, by which tumor cells is controlled to be on exponentially decreasing all over chemotherapy horizon, under normalized carrying capacity to reach infinitesimal values.

Keywords: Chemotherapy, viability theory, set-valued analysis

1. Introduction

In the literature, there are various works on cancer model forms, and their chemotherapy control by different approaches. Optimal control theory is used to minimize the size of the tumor in Gompertz law, at finite time with a limited amount of chemotherapeutic drugs [1, 2], and for all the standard models for tumor development : Linear, Logistic, and Gompertzian types [3], and for basic general equations of tumor growth [4], and for Gompertz model of growth, under : Skipper and Holford-Sheiner hypothesis [5]. State dependent Riccati equation based optimal control technique is developed for a Gompertz model, to reduce the tumor growth up [6].

Input-state feedback linearization method is concepted for manipulation of chemotherapeutic drug usage, under : Skipper, Holford-Sheiner, and Norton-Simon hypothesis, to minimize tumor volume in Gompertz growth [7]. Maximum principle differential-geometric techniques, are used to minimize tumor volume at fixed time horizon [8]. Optimal control technique is deployed to determine the minimum amount of needed chemotherapy drug, able to reduce or eliminate the tumor mass, depicted by Gompertz growth, under : Skipper, Holford-Sheiner, and Norton-Simon hypothesis [9]. Qualitative and quantitative differences is compared between fixed and free treatment duration, of optimal chemotherapeutic protocols [10]. Optimal cancer chemotherapy is compared between tumor growth models based on ordinary differential and stochastic equations [11]. Optimal control theory is used to produce expressions for the continuous-time optimal control, able to reduce the tumor population [12], under Gompertz growth equation model. Optimal treatment protocol predictions are given for general function fitness tradeoffs [13]. Optimal chemotherapy schedules minimizes the number of Gompertzian tumor cell populations [14]. The measure theoretical approach approximates optimal control and optimal states, solutions of : linear, quadratic, and non-linear objectives functions, for general compartmental models in cancer chemotherapy [15]. Optimal chemotherapeutic agent controls general pharmacodynamic model by Michaelis-Menten type equation [16]. Optimal combination chemotherapy controls tumor size, satisfying a differential equation whose structure is based on cell kinetic considerations [17]. Optimal bang-bang protocols control a class of mathematical models based on cell-cycle kinetics, subject to a linear objective [18]. Singular control solutions solve some optimal protocol problems for simplest models of cancer chemotheray [19]. Hilbert uniqueness method

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approaches linear quadratic optimal control problem, for compartment system model of chemotherapy cancer [20]. Pontryagin's maximum principle minimizes cost function for cancer chemotherapeutic model in compartments form [21]. Moving horizon estimation and extended Kalman filter are compared for chemotherapy optimization [22]. Optimal cancer chemotherapy treatments control Malthusian tumor cell growth [23]. Stability theory is designed to characterize equilibrium tumor in Logistic growth, with a periodic function representing the chemotherapeutic effects on tumor [24], and with continuous constant infusion treatment [25], and to exponential-kill model under Norton-Simon hypothesis [26, 27]. Qualitative analysis characterizes the global stability of zero and existence and uniqueness of attractive periodic solution, to Logistic tumor model in periodic chemotherapy [28]. Periodic chemotherapy drug describes acceptable number of doses, before Logistic tumor regrowth due to drug resistance [29]. Global stability of the tumor-free equilibrium is derived by simple condition and the existence, of a periodic solution is proved in the case when the tumor-free equilibrium was unstable, for Logistic integro-differential equation of tumor growing in vivo to periodic exposure to chemotherapy [30, 31]. Norton-Simon-like model of chemotherapy my imply multi-stability of tumor [32]. Lyapunov stability analysis is used to address the design of chemotherapeutic procedures for Gompertzian cancer model [33]. Composite adaptive control strategy reduces cancer tumor volume and identifies tumor parameters for three models, including : Skipper, Holford-Sheiner, and Norton-Simon hypothesis, during the drug delivery process in chemotherapy [34]. Fuzzy system approach is employed to program the amount of administrated drug, to reduce and maintain the size of tumor in Gompertz growth, under : Skipper, Holford-Sheiner, and Norton-Simon hypothesis [35]. H-infinity optimization theory is used to concept robust control for three cell-kill cancer models, including : Skipper, Holford-Sheiner, and Norton-Simon hypothesis [36]. Computational methods is utilized by an estimation of distribution algorithm and genetic algorithms, to address the optimization problem of cancer chemotherapy, on Gompertzian growth model with linear cell-loss effect [37]. Evolutionary algorithms are applied to multi-objective optimization problem of cancer chemotherapy [38], for the same model as in [37]. Adaptive elitist-population based genetic algorithm solves the problem of drug scheduling in cancer chemotherapy [39]. Direct optimization procedure, based on the Luus-Jaakola algorithm is purposed to minimize the size of tumor, at the end of a fixed period treatment by chemotherapeutic effects, outlined by Martin model [40, 41]. Taganchi immune algorithm is proposed for optimizing multi-dose drug schedules, that minimize the number of tumor cells [42]. Levenberg-Marquardt algorithm theoretically examines the efficacy of several clinical chemotherapeutic protocols, for exponential and Gompertz tumor growth [43]. Feedback controller yields in a strongly monotone closed-loop system and reduces the tumor burden to the zero value [44], and increases the normal and immune cell populations to reach their maximum possible values, of chemotherapeutic model in [45]. In the present work, we use from [46, 50] a set-valued method based on viability theory to approach a one-dimensional model including the effects of chemotherapy on the tumor [24], admissible protocols reverse the tumor growth, to be exponentially decaying on infinite horizon. This paper is structured as follows : Section 2 defines the general model of chemotherapy, we launch there the associated control problem, subsequently we formulate the corresponding viability problem, then we use the set-valued analysis as approach. Section 3 stages the cancer in two cases following conditions on the initial state. Section 4 investigates the model of [24], with chemotherapy treatment applied continuously, we present there some numerical simulations, which are in accordance with theoretical results.

2. Problem and Viability Approach

2.1. Control Problem

We consider a dynamical of ordinary differential equation, in the form

$$\dot{\tau} = \psi(\tau, v). \tag{1}$$

Where the state τ stills for tumor cells density (number or volume), and takes values in the non-negative interval $[0, \infty)$, with the initial condition

$$\tau(0) = \tau_0 > 0. \tag{2}$$

While the control term v stands for rate of chemotherapeutic agent, and takes values within the constraint subset

$$V = [0, v^{max}]. \tag{3}$$

The non-linear function ψ maps $\mathbb{R} \times \mathbb{R}$ into $\mathbb{R}$.

The naturally arising control problem is of how to administer v with respect to the constraint (3), in order to reduce τ.

We have to consider the following control problem

Find a protocol v such that

$$\forall t \in [0, \infty), v(t) \in V, \tag{4}$$

for which

$$\lim_{t\to\infty}\tau(t) = 0. \tag{5}$$

2.2. Viability Problem

It is more convenient to consider the control term v as a second variable and augment system (2.1) by the linear differential equation

$$\dot{v} = -\gamma v + w, \tag{6}$$

with the initial condition

$$v(0) = v_0 \in V, \tag{7}$$

and the auxiliary control

$$w \in W, \tag{8}$$

where

$$W = [0, \gamma v^{\max}]. \tag{9}$$

We will formulate the control problem (2.1) in the framework of the viability theory [48]. We associate with a non-negative real number α the subset

$$D_\alpha = \{(\tau, v) \in \mathbb{R}_+ \times V \mid \psi_\alpha(\tau, v) \le 0\}, \tag{10}$$

where the function ψ_α depends on the function ψ of (1) as follows

$$\psi_\alpha(\tau, v) = \psi(\tau, v) + \alpha\tau. \tag{11}$$

Proposition 1 Assume that there exists a control $w: [0,\infty) \to W$ leading to a globally viable solution $(\bar{\tau}, \bar{v})$ to the augmented system (2.1)-(2.2) in some subset D_α, then $\bar{v}$ is a protocol in the sense of the problem (2.1).

Proof. Let $t \ge 0$. According to (6)-(7), the solution $\bar{v}$ may be expressed in function of the supplement control w as

$$\bar{v}(t) = \exp^{-\gamma t}\left(v_0 + \int_0^t \exp^{\gamma s} w(s)\, ds\right), \tag{12}$$

and the constraint (4) still satisfied by virtue of (8)-(9)

$$\forall t \in [0,\infty), \bar{v}(t) \in V, \tag{13}$$

By (1) and (2.2) we have the differential inequality

$$\dot{\bar{\tau}}(t) = \psi(\bar{\tau}(t), \bar{v}(t)) \le -\alpha\bar{\tau}(t), \tag{14}$$

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

$$0 \le \bar{\tau}(t) \le \tau_0 \exp(-\alpha t),$$

then

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

Remark 1 The viability of the solution $(\bar{\tau}, \bar{v})$ in the subset D_α, requires that the initial state data (τ_0, v_0) belongs to D_α too. But we will deal with this necessary condition in Section 3.

Remark 2 The tumor cells density $\bar{\tau}$ will be on the decreasing because of (14), which is beneficial to the patient quality of life during the treatment.

Remark 3 System (2.2) is introduced for mathematical reasons : (13), (17), (18), and (19), but this augmentation can be biologically considered as the rate of change in the amount of the concentration v of chemotherapy drug over time, with proportional decays out of the system (2.1) trough the term $-\gamma v$, and outside source term of treatment w.

2.3. Set-valued Analysis

We associate with the augmented system (2.1)-(2.2), the set-valued map F_α of regulation defined on the constraint viability domain D_α (10) in the following way

$$\begin{aligned} F_\alpha(\tau, v) \quad &= \{w \in W \\ &\mid (\psi(\tau, v), -\gamma v + w)' \\ &\in T_{D_\alpha}(\tau, v)\}. \end{aligned} \tag{15}$$

where

$$\begin{aligned} T_{D_\alpha}(\tau, v) \quad &= \{(\bar{\tau}, \bar{v}) \in \mathbb{R} \times \mathbb{R} \\ &\mid \liminf_{h\downarrow 0} \frac{d_{D_\alpha}(\tau + h\bar{\tau}, v + h\bar{v})}{h} \\ &= 0\}. \end{aligned} \tag{16}$$

stands for the tangent cone to the subset D_α at point (τ, v).

Lemma 1 Let be α such that $(\tau_0, v_0) \in D_\alpha$. The augmented system (2.1)-(2.2) is locally viable in the constraint viability domaine D_α if and only if for all $(\tau, v) \in D_\alpha$, there exists $w_\alpha \in W$, such that

$$(\psi(\tau, v), -\gamma v + w_\alpha)' \in T_{D_\alpha}(\tau, v).$$

i.e., if and only if the set-valued map F_α is strict, and the single-valued selection w_α of F_α leads to a global viable solution.

Proof. Let $w_\alpha: D_\alpha \to W$ be a single-valued selection of the set-valued map F_α, such that the control $w = w_\alpha(\tau, v)$, leads to a local viable solution $(\bar{\tau}, \bar{v})$ to the augmented system (2.1)-(2.2) in D_α, over a maximal interval $[0, \bar{t})$. We have to prove that $\bar{t} = \infty$. Indeed, assume that $\bar{t} < \infty$. As $\bar{\tau}$ is a non-negative decreasing function, we have

$$\bar{\tau}(t) \to \bar{\tau}(\bar{t}) \quad when \quad t \to \bar{t}^-.$$

By (6), (8), and (9) we have

$$\begin{aligned}|\dot{\bar{v}}(t)| &\leq \gamma\bar{v}(t) + w(t)\\ &\leq \gamma\bar{v}(t) + \gamma v^{\max},\end{aligned}$$

then by applying Gronwall's Lemma we get the exponential estimate

$$|\bar{v}(t)| \leq (v_0 + v^{\max})\exp(\gamma t), \tag{17}$$

Then $\bar{v}(t)$ has a limit denoted by $\bar{v}(\bar{t})$ when $t \to \bar{t}^{-}$. Therefore

$$(\bar{\tau}(t), \bar{v}(t)) \to (\bar{\tau}(\bar{t}), \bar{v}(\bar{t}))$$

when $t \to \bar{t}^{-}$,

and $(\bar{\tau}(\bar{t}), \bar{v}(\bar{t}))$ belongs to D_α because it is closed. Now, by considering $(\bar{\tau}(\bar{t}), \bar{v}(\bar{t}))$ as an initial state it follows that $(\bar{\tau}, \bar{v})$ may be prolonged to a viable solution $(\bar{\tau}, \bar{v})$ in D_α, starting at $(\bar{\tau}(\bar{t}), \bar{v}(\bar{t}))$ on some interval $[\bar{t}, t^{\max})$ where $t^{\max} > \bar{t}$, which is in contradiction with the maximality of $\bar{t}$, then the solution $(\bar{\tau}, \bar{v})$ becomes globally viable in D_α.

Now to give an explicit expression to the tangent cone T_{D_α} (16), we appeal the following Lemma [46].

Lemma 2 If the function ψ_α in (11) is continuously differentiable on D_α, and admits a partial derivative $\partial\psi_\alpha$ strictly negative on D_α. Then for each $(\tau, \mathrm{v}) \in \mathrm{D}_\alpha$ the tangent directions $(\bar{\tau}, \bar{\mathrm{v}})$ of $\mathrm{T}_{\mathrm{D}_\alpha}(\tau, \mathrm{v})$ are characterized by

$$\begin{cases} \bar{\tau} \geq 0 & \text{if} \quad \tau = 0, \\ \bar{\mathrm{v}} \geq 0 & \text{if} \quad \mathrm{v} = 0, \\ \bar{\mathrm{v}} \leq 0 & \text{if} \quad \mathrm{v} = \mathrm{v}^{\max}, \\ \dot{\psi}_\alpha(\tau, \mathrm{v})(\bar{\tau}, \bar{\mathrm{v}}) \leq 0 & \text{if} \quad \psi_\alpha(\tau, \mathrm{v}) = 0. \end{cases}$$

Corollary 1 For each $(\tau, \mathrm{v}) \in \mathrm{D}_\alpha$ the tangent directions $(\bar{\tau}, \bar{\mathrm{v}})$ of $\mathrm{T}_{\mathrm{D}_\alpha}(\tau, \mathrm{v})$ are characterized by reduced inequalities

$$\begin{cases} \bar{\tau} \geq 0 & \text{if} \quad \tau = 0, \\ \dot{\psi}_\alpha(\tau, \mathrm{v})(\bar{\tau}, \bar{\mathrm{v}}) \leq 0 & \text{if} \quad \psi_\alpha(\tau, \mathrm{v}) = 0. \end{cases}$$

Proof. Thanks to equation (6)

• If $v = 0$,

then

$$-\gamma v + w = w \geq 0. \tag{18}$$

• If $v = v^{\max}$,

then

$$\begin{aligned}-\gamma v + w &= -\gamma v^{\max} + w\\ &\leq -\gamma v^{\max} + w^{\max}\\ &\leq -\gamma v^{\max} + \gamma v^{\max}\\ &\leq 0.\end{aligned} \tag{19}$$

To give a useful expression to the set-valued map F_α (15), we need to consider the following assumption.

Assumption 1

$$\forall(\tau, v) \in \mathbb{R}_+ \times [0, v^{\max}], \psi(\tau, v) \geq 0 \quad if \quad \tau = 0.$$

And we set functions h and ℓ by expressions

$$h(\tau, v) = \partial_v\psi(\tau, v), \tag{20}$$

and

$$\ell(\tau, v) = \psi(\tau, v)\partial_\tau\psi(\tau, v) - \gamma v\partial_v\psi(\tau, v). \tag{21}$$

Proposition 2 If Assumption 1 is satisfied then the set-valued map F_α may be expressed explicitly on the subset D_α as

$$\mathrm{F}_\alpha(\tau, \mathrm{v}) = \begin{cases} \mathrm{W} & \text{if} \quad \psi(\tau, \mathrm{v}) + \alpha\tau < 0, \\ \mathrm{W}_\alpha(\tau, \mathrm{v}) & \text{if} \quad \psi(\tau, \mathrm{v}) + \alpha\tau = 0, \end{cases} \tag{22}$$

with

$$\begin{aligned}W_\alpha(\tau, v) &= \{w \in W\\ &\quad | \, h(\tau, v)w + \ell(\tau, v)\\ &\quad + \alpha\partial_\tau\psi(\tau, v) \leq 0\}.\end{aligned} \tag{23}$$

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

$$\begin{aligned}\dot{\psi}_\alpha(\tau, v)(\psi(\tau, v), -\gamma v + w) &= \langle \nabla\psi_\alpha(\tau, v)\\ &\quad , (\psi(\tau, v), -\gamma v + w)' \rangle\\ &= \psi(\tau, v)\partial_\tau\psi_\alpha(\tau, v)\\ &\quad -\gamma v\partial_v\psi_\alpha(\tau, v)\\ &\quad +w\partial_v\psi_\alpha(\tau, v),\end{aligned}$$

by (11)

$$\begin{aligned}\dot{\psi}_\alpha(\tau, v)(\psi(\tau, v), -\gamma v + w) &= \psi(\tau, v)\partial_\tau\psi(\tau, v)\\ &\quad +\alpha\partial_\tau\psi(\tau, v)\\ &\quad -\gamma v\partial_v\psi(\tau, v)\\ &\quad +w\partial_v\psi(\tau, v),\end{aligned}$$

then by (2.3)

$$\begin{aligned}\dot{\psi}_\alpha(\tau, v)(\psi(\tau, v), -\gamma v + w) &= h(\tau, v)w\\ &\quad +\ell(\tau, v)\\ &\quad +\alpha\partial_\tau\psi(\tau, v).\end{aligned}$$

Lemma 3 A continuous single-valued selection of the set-valued map F_α may be given on the subset D_α by the expression

$$w_\alpha(\tau, v) = \pi_{W_\alpha(\tau, v)}(0), \tag{24}$$

where π denotes the operator of best approximation.

3. Cancer Stage

We introduce the set-valued map Ω defined for each $\tau \in \mathbb{R}_+$ by

$$\Omega(\tau) = \{v \in V \mid \psi(\tau, v) < 0\}, \tag{25}$$

where ψ is the function (1), and V is the set constraint (3), and we denote by v_0 its minimal single-valued selection given for all $\tau \in \mathbb{R}_+$ by

$$v_0(\tau) = \pi_{\Omega(\tau)}(0). \tag{26}$$

Theorem 1 Assume that the subset $\Omega(\tau)$ (25) is non-empty at the initial tumor state $\tau_0 : \Omega(\tau_0) \neq \emptyset$. Let be the minimal initial control $v_0 = v_0(\tau_0)$ given by (26), and a parameter $\alpha \in (0, \alpha_0]$, where $\alpha_0 = \frac{-\psi(\tau_0, v_0)}{\tau_0} > 0$.

The continuous single-valued selection w_α (24) provides global viable solution $(\bar{\tau}, \bar{v})$ on the subset D_α, with protocol solution $\bar{v}$ (12) of the control problem (2.1).

Proof. $\alpha \in (0, \alpha_0]$ implies that the initial state (τ_0, v_0) belongs to the subset D_α, the continuous single-valued selection w_α (24) given in Lemma 3, leads to a solution $(\bar{\tau}, \bar{v})$, which is globally viable on D_α, then by Proposition 1, the component $\bar{v}$ is a protocol.

We associate with a non-negative real number β, the set-valued map $\bar{W}_\beta$ defined by

$$\begin{aligned} \bar{W}_\beta(\tau, v) \quad &= \{\bar{w} \in W \\ &\mid h(\tau, v)\bar{w} + \ell(\tau, v) \\ &+ \beta \leq 0\}. \end{aligned} \tag{27}$$

where h and ℓ are functions given by (20) and (21) respectively.

Theorem 2 Assume that the subset $\Omega(\tau)$ (25) is empty at the initial tumor state $\tau_0 : \Omega(\tau_0) = \emptyset$. Let be a time $\bar{t} > \frac{\psi(\tau_0, v_0)}{\beta}$ where : the initial control $v_0 \in V$ (3), and β a parameter for which the set-valued map $\bar{W}_\beta$ (27) is strict, and let $(\bar{\tau}, \bar{v})$ the solution to the augmented system (2.1)-(2.2) on the interval $[0, \bar{t}]$, by the minimal single-valued selection $\bar{w}_\beta$ of the set-valued map $\bar{W}_\beta$ defined by

$$\bar{w}_\beta(\tau, v) = \pi_{\bar{W}_\beta(\tau, v)}(0). \tag{28}$$

We have $\Omega(\bar{\tau}(\bar{t})) \neq \emptyset$, with the corresponding control $\bar{v}$ (12) on the model (2.1) over the interval $[0, \bar{t}]$.

Proof. By (1) we have

$$\begin{aligned} \psi(\bar{\tau}(\bar{t}), \bar{v}(\bar{t})) \quad &= \psi(\tau_0, v_0) \\ &+ \int_0^{\bar{t}} [\dot{\bar{\tau}}(s)\partial_\tau \psi(\bar{\tau}(s), \bar{v}(s)) \\ &+ \dot{\bar{v}}(s)\partial_v \psi(\bar{\tau}(s), \bar{v}(s))]\, \mathrm{d}s, \end{aligned}$$

then by (20) and (21) we get

$$\begin{aligned} \psi\big(\bar{\tau}(\bar{t}), \bar{v}(\bar{t})\big) \quad &= \psi(\tau_0, v_0) \\ &+ \int_0^{\bar{t}} [h(\bar{\tau}(s), \bar{v}(s))\bar{w}_\beta(\bar{\tau}(s), \bar{v}(s)) \\ &+ \ell(\bar{\tau}(s), \bar{v}(s))]\, \mathrm{d}s, \end{aligned}$$

since $\bar{w}_\beta$ is a single-valued selection of the set-valued map $\bar{W}_\beta$ then we have

$$\psi(\bar{\tau}(\bar{t}), \bar{v}(\bar{t})) \leq \psi(\tau_0, v_0) - \beta\bar{t},$$

as $\beta\bar{t} > \psi(\tau_0, v_0)$ it follows that $\psi(\bar{\tau}(\bar{t}), \bar{v}(\bar{t})) < 0$.

Remark 4 Note that the decreasing of the tumor cell density $\bar{\tau}$ is uncertain on $[0, \bar{t}]$, and may be disadvantageous to the patient quality of life in the beginning of treatment.

Indeed, otherwise for all $[0, \bar{t}]$ we will have $\psi(\bar{\tau}(t), \bar{v}(t)) = \dot{\bar{\tau}}(t) \leq 0$, particularly for $t = 0$ we will have $\psi(\tau_0, v_0) \leq 0$, which is absurd.

The existence's protocol depends on initial state (τ_0, v_0) of the augmented system (2.1)-(2.2), closely to the non-emptiness of the subset $\Omega(\tau_0)$ of V. This leads to stage the cancer as follow :

- $\Omega(\tau_0) \neq \emptyset$: As Theorem 1, there exists an element $v_0 \in \Omega(\tau_0)$, minimal in norm, such that $(\tau_0, v_0) \in D_\alpha$, and by Remarks 1 and 2 the protocol $\bar{v}$ will decreases the tumor cells density $\bar{\tau}$ on $[0, \infty)$. We then say that the tumor is on *non-advanced stage*.
- $\Omega(\tau_0) = \emptyset$: As Remark 3, the augmented system (2.1)-(2.2) must be firstly steered to the *non-advanced stage* at time $\bar{t}$, but the used control $\bar{v}$ cannot ensures the decreasing of tumor cells density $\bar{\tau}$ on $[0, \bar{t}]$. We then say that the tumor is on *advanced stage*.

4. Application Example

We consider the ode model in [24], to control tumor cells density $\tau(t)$, continuously by chemotherapy drug $v(t)$, over time t.

$$\dot{t} = \tau([1 - v] - \tau). \tag{29}$$

The dynamic function ψ in (1) is expressed as

$$\psi(\tau, v) = \tau([1 - v] - \tau),$$

which will verify the non-negative condition in Assumption 1

$$\psi(0, v) = 0,$$

and the negative condition in Lemma 2

$$\partial_v \psi_\alpha(\tau, v) = -\tau < 0.$$

The numerical simulation in this research is illustrated in three graphs. We solve equation (29) with null control $v = 0$, Figure 1 pictures the Logistic tumor cells density τ from the initial state $\tau_0 = 2$ to the non-null limit state $\lim_{t \to \infty} \tau(t) = 1 > 0$, in absence of chemotherapy treatment. We solve equation (29) coupled with equation

$\dot{v} = -v + w$ (we take $\gamma = 1$), by the feedback control $w = w_{1.5}(\tau, v)$ (24) with $\alpha = 1.5$, Figure 2 pictures decrease of tumor cells density $\bar{\tau}$ from the initial state $\tau_0 = 2$ to the null limit state $\lim_{t\to\infty}\bar{\tau}(t) = 0$, in presence of chemotherapy treatment protocol $\bar{v}$ (12) with the initial drug $v_0 = 0.5$, pictured by Figure 3.

5. Conclusion

A set-valued method is developed to control tumor growth model with chemotherapy (2.1). Selection w_α (24) of set-valued map F_α (2) provide global viable solution $(\bar{\tau}, \bar{v})$ to the augmented system (2.1)-(2.2), subject to the control problem (2.1). The initial tumor state τ_0 (2), is deterministic to design treatment strategies, tumor in *advanced stage* : $\Omega(\tau_0) = \emptyset$, must be controlled on the time interval $[0, \bar{t}]$ to *non-advanced stage* : $\Omega(\bar{\tau}(\bar{t})) \neq \emptyset$, before applying protocol $\bar{v}$ on the infinite therapy horizon $[\bar{t}, \infty)$. The proposed method is successfully applied to the Logistic model (29) appearing in [24], and can be applied to others cancer models (see [49]).

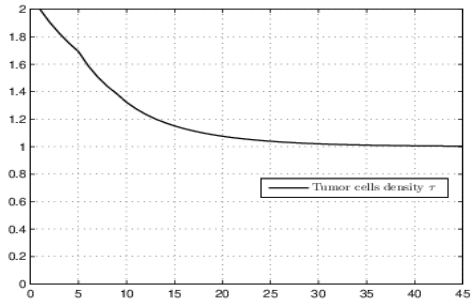

Figure 1 : Tumor function without treatment.

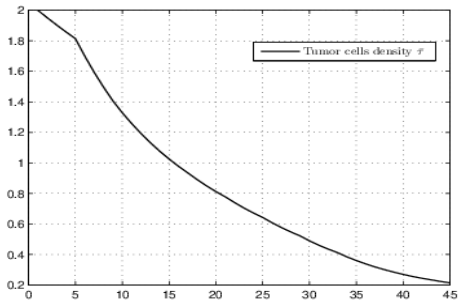

Figure 2 : Tumor response to protocol in Figure 3.

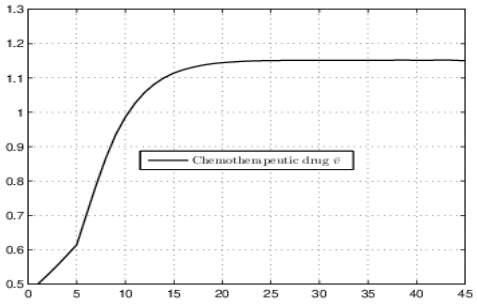

Figure 3 : Drug function.

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References

[1] W. Krabs, S. Pickl, "An optimal control problem in cancer chemotherapy", Applied Mathematics and Computation, Vol. 217: 1117-1124, 2010.

[2] N. N. Subbotina, N. G. Novoselova, "chemotherapy of a malignant tumor growing according to the Gompertz law", International Federation of Automatic Control, Vol. 51, No. 32: 855-860, 2018.

[3] M. Leszczyński, U. Ledzewicz, H. Schättler, "Optimal control for a mathematical model for chemotherapy with pharmacometrics", Mathematical Modelling of Natural Phenomena, Vol. 15, 2020.

[4] G. W. Swan, "General applications of optimal control theory in cancer chemotherapy", Institute of Mathematics and its Applications Mathematics Applied in Medicine & Biology, Vol. 5: 303-316, 1988.

[5] L. A. Fernández, C. Pola, "Catalog of the optimal controls in cancer chemotherapy for the Gompertz model depending on PK/PD and integral constraint", Discrete and continuous dynamical systems series B, Vol. 19, No. 6: 1563-1588, 2014.

[6] S. P. Zanjani, M. J. Mahjoob, S. Amanpour, R. Kheirbakhsh, M. H. Akhoundzadeh, "A supplemental treatment for chemotherapy : Control simulation using a mathematical model with estimated parameters based on in vivo experiment", International Federation of Automatic Control, Vol. 49, No. 26: 277-282, 2016.

[7] E. Sharifnia, Y. B. Lari, M. Eghtesad, "Nonlinear tracking control for reducing cancerous tumor volume using three different cell kill models", International Conference on Mechanical Engineering, 2017.

[8] J. M. Greene, C. S.Tapia, E. D. Sontag, "Control

structures of drug resistance in cancer chemotherapy", Institute of Electrical and Electronics Engineers Conference on Decision and Control, 5195-5200, 2018.

[9] K. R. Fister, J. C. Panetta, "Optimal control applied to competing chemotherapeutic cell-kill strategies", Society for Industrial and Applied Mathematics Journal on Applied Mathematics, Vol. 63, No. 3: 1954-1971, 2003.

[10] J. L. Boldrini, M. I. S. Costa, "The influence of fixed and free final time of treatment on optimal hemotherapeutic protocols", Mathematical and Computer Modelling, Vol. 27, No. 6: 59-72, 1998.

[11] R. Eidukeričius, "Deterministic and stochastic modelling of tumor growth and optimal chemotherapy", Applied Mathematics and Computer Science, Vol. 4, No. 2: 233-237, 1994.

[12] G. W. Swan, "Optimal Control Applications in the Chemotherapy of Multiple Myeloma", Institute of Mathematics and its Applications Journal of Mathematics Applied in Medicine & Biology, Vol. 2: 139-160, 1985.

[13] P. A. Orlando, R. A. Gatenby, J. S. Brown, "Cancer treatment as a game : integrating evolutionary game theory into the optimal control of chemotherapy", Physical Biology Vol. 9, No. 6, 2012.

[14] A. Remesh, "Tachling the problems of tumor chemotherapy by optimal drug scheduling", Journal of Clinical and Diagnostic Research, Vol. 7, No. 7: 1404-1407, 2013.

[15] M. H. N. Skandari, M. H. Farahi, "Optimal control for general n-compartmental models in cancer chemotherapy using measure theoretical approach", International journal of sensing, computing & control, Vol. 2, No. 1: 27-37, 2012 .

[16] M. Leszczyński, E. Ratajczyk, U. I. Ledzewicz, H. Schättler, "Sufficient conditions for optimality for a mathematical model of drug treatment with pharmacodynamics", Opuscula Mathematica, Vol. 37, No. 3: 403-419, 2017.

[17] F. M. F. Loho Pereira, M. R. M. Pinho, C. E. Pedreira, M. H. R. Fernandes, "Design of multidrug cancer chemotherapy via optimal control", International Federation of Automatic Control Proceedings Volumes, Vol. 23: 231-236, 1990.

[18] A. Świerniak, U. Ledzewicz, H. Schättler, "Optimal control for a class of compartmental models in cancer chemotherapy", International Journal of Applied Mathematics and Computer Science, Vol. 13, No. 3: 357-368, 2003.

[19] A. Świerniak, Z. Duda, "Singularity of optimal control in some problems related to optimal chemotherapy", Mathematical and Computer Modelling, Vol. 19, No. 6-8: 255-262, 1994.

[20] O. El Kahlaoui, M. Rachik, N. Yousfi, M. Laklalech, O. I. Kacemi, "On the analysis of a biological system : Compartment model approach", Applied Mathematical Sciences, Vol. 1, No. 41: 2001-2022, 2007.

[21] O. Balatif, M. Rachik, I. Abdelbaki, Z. Rachik, "Optimal control for multi-input bilinear systems with an application in cancer chemotherapy", International Journal of Scientific and Innovative Mathematical Research, Vol. 3, No. 2: 22-31, 2015 .

[22] M. Siket, G. Eigner, D. A. Drexler, I. Rudas, L. Kovács, "State and parameter estimation of a mathematical carcinoma model under chemotherapeutic treatment", Applied Sciences, Vol. 10, No. 24, 2020.

[23] M. I. S. Costa, J. L. Boldrini, R. C. Bassanezi, "Optimal chemotherapy : A case study with drug resistance, saturation effect, and toxicity", Institute of Mathematics and its Applications Journal of Mathematics Applied in Medicine & Biology, Vol. 11, No. 1: 45-59, 1994.

[24] J. C. Panetta, "A logistic model of periodic chemotherapy", Applied Mathematics Letters, Vol. 8: 83-86, 1995.

[25] A. D'Onofrio, A. Gandolfi, S. Gattoni, "Chemotherapy of vascularised tumours : Role of vessel density and the effect of vascular "pruning" ", Journal of Theoretical Biology, Vol. 2: 253-264, 2010.

[26] Á. G. Lópeza, K. C. Iaroszb, A. M. Batistad, J. M. Seoanea, R. L. Vianae, M. A. F. Sanjuána, "Nonlinear cancer chemotherapy : Modelling the Norton-Simon hypothesis", Communications in Nonlinear Science and Numerical Simulation, Vol. 70: 307-317, 2019.

[27] P. Castorina, D. Carcò, C. Guiot, T. S. Deisboeck, "Tumor growth instability and its implications for chemotherapy", American Association for Cancer Research, Vol. 69, No. 21: 8507-8515, 2009.

[28] S. Xu, "Qualitative analysis of a general periodic system", Communications of the Korean Mathematical Society, Vol. 33 No. 3: 1039-1048, 2018.

[29] J. C. Panetta, "A logistic model of periodic chemotherapy with drug resistance", Applied Mathematics Letters, Vol. 10, No. 1: 123-127, 1997.

[30] H. V. Jain, H. M. Byrne, "Qualitative analysis of an integro-differential equation model of periodic chemotherapy", Applied Mathematics Letters, Vol. 25: 2132-2136, 2012.

[31] T. Henson, J. Surendrakumari, "Application of integro-differential equation in periodic chemotherapy", International Journal of Computing Algorithm, Vol. 3: 812-814, 2014.

[32] A. D'Onofrio, A. Gandolfi, S. Gattoni, "The

Norton–Simon hypothesis and the onset of non-genetic resistance to chemotherapy induced by stochastic fluctuations", Physica A, Vol. 391: 6484-6496, 2012.

[33] B. A. Costa, J. M. Lemos, "Drug administration design for cancer Gompertz model based on the Lyapunov method", Controlo, 131-141, 2016.

[34] M. Sharifi, H. Moradi, "Nonlinear composite adaptive control of cancer chemotherapy with online identification of uncertain parameters", Biomedical Signal Processing and Control, Vol. 49: 360-374, 2019.

[35] A. Al Khoei, M. R. Zakerzadeh, M. Ayati, "Chemotherapy treatment scheduling via fuzzy system approach", 4th International Conference on Electrical, Computer, Mechanical and Mechatronics Engineering, 2016.

[36] H. Moradi, G. Vossoughi, H. Salarieh, "Optimal robust control of drug delivery in cancer chemotherapy : A comparison between three control approaches", computer method and program in biomedicine, Vol. 112: 69-83, 2013.

[37] A. Petrovski, S. Shakya, J. McCall, "Optimising cancer chemotherapy using an estimation of distribution algorithm and genetic algorithms", GECCO '06 : Proceedings of the 8th annual conference on Genetic and evolutionary computation, 413-418, 2006.

[38] A. Petrovski, J. McCall, "Multi-objective optimisation of cancer chemotherapy Using Evolutionary Algorithms", The Open Access Institutional Repository at The Robert Gordon University, 531-545, 2001.

[39] Y. Liang, K. S. Leung, T. S. K. Mok, "A novel evolutionary drug scheduling model in cancer chemotherapy", Institute of Electrical and Electronics Engineers Transactions on Information Technology in Biomedicine, Vol. 10, No. 2: 237-245, 2006.

[40] R. Luus, F. Hartig, F. J. Keil, "Optimal drug scheduling of cancer chemotherapy". Periodica Polytechnica Chemical Engineering, Vol. 38, No. 1-2: 105-109, 1994.

[41] R. Luus, F. Hartig, F. J. Keil, "Optimal drug scheduling of cancer chemotherapy by direct search optimization", Hungarian Journal of Industrial Chemistry Veszprém, Vol. 23: 55-58, 1995.

[42] J. T. Tsai, W. H. Ho, "Optimized drug schedulling for cancer chemotherapy using improved immune algorithm", International Journal of Innovative, Computing, Information and Control, Vol. 9, No. 7: 2821-2838, 2013.

[43] E. Shochat, D. Hart, Z. Agur, "Using computer simulations for evaluating the efficacy of breast cancer chemotherapy protocols", Mathematical Models and Methods in Applied Sciences, Vol. 9, No. 4: 599-615, 1999.

[44] H. Agahi, M. J. Yazdanpanah, "Constrained control approach for monotone systems : Application to tumour chemotherapy", IET Control Theory & Applications, Vol. 13: 996-1005, 2019.

[45] L.G. De Pillis, A. Radunskaya, "A mathematical tumor model with immune resistance and drug therapy : an optimal control approach", Computational and Mathematical Methods in Medicine, Vol. 3, No. 2: 79-100, 2001.

[46] K. Kassara, A. Moustafid, "Angiogenesis inhibition and tumor-immune interactions with chemotherapy by a control set-valued method", Mathematical Biosciences, Vol. 231: 135-143, 2011.

[47] L. G. 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", Mathematical Biosciences, Vol. 209, No. 1: 292-315, 2007.

[48] J. P. Aubin, "Dynamic economic theory : A viability approach", Springer, Berlin, 1997.

[49] S. Saravi, M. Saravi, "A short survey in application of ordinary differential equations on cancer research", American Journal of Computational and Applied Mathematics, Vol. 10, No. 1: 1-5, 2020.

[50] A. Moustafid, "General anti-angiogenic therapy protocols with chemotherapy", International Journal of Mathematical Modelling & Computations, 2021.