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Set-Valued Control of Cancer by Combination Chemotherapy

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Abstract

A mathematical model of ordinary differential equations is considered to analyze the pharmacokinetics of multi-chemotherapeutic drugs and their pharmacodynamic effects on homogeneous tumors. Set-valued analysis is used to design protocols of drug administration and applied to decrease tumor density under their carrying capacity of Gompertz growth and converge to zero.

1. Introduction

Several works were carried out on cancer control by the combination of multi-chemotherapeutic agents to have more effects on tumor cells, and their density [1]. Uses multi-objective optimization method to minimize the area under the curve of tumors as well as the side effects on the patient during chemotherapy [2]. Introduces an adaptive neural networks control approach, based on feedback linearization, in order to optimize chemotherapy regimens [3]. Develops optimal therapeutic strategies, subject to reducing tumor size and toxicity throughout treatment [4]. Employs swarm intelligence for optimization of cancer chemotherapy [5]. Uses evolutionary algorithms to minimize tumor and maximize patient survival time [6]. Applies genetic algorithms to eradicate tumor [7]. Computes the optimal doses of CAF (Cyclophosphamide, Adriamycin, and Fluorouracil) regimen for each patient suffering with breast cancer stage IIB in adjuvant chemotherapy [8]. Develops a mixed-integer program for combination chemotherapy optimization to reduce the number of cancer cells in the body [9]. Deals with the optimisation of multi-drug chemotherapy in order to better cope with the occurrence of drug-resistant cancer cells [10]. Subjects a multi-drug chemotherapy schedule optimisation problem to local optima network.
In this work, we adapt the set-valued analysis methods developed in the previous works [11–18], to approach a model of combined chemotherapy control in cancer, and make the solution viable on decreasing subset, with converging tumor density towards zero [11]. Investigates a general class of immunotherapy ODE models and gives some numerical examples [12]. Evokes viability and set-valued theories to provide chemotherapy protocol laws [13]. Illustrates the approach by two applications on anti-angiogrnic therapy and tumor-immune with chemotherapy [14]. Generalizes the method to anti-angiogenic therapy with chemotherapy [15]. Treats the problem of cancer control by chemotherapy through a general model in ordinary differential equation form of tumor dynamics [16]. Analysis a tuberculosis (TB) infection model with the treatment of four ordinary differential equations, namely, susceptible, latent, infected, and treated individuals [17]. Proposes an extension of the classical SEIR-type models to describe and control the spread of COVID-19 in Morocco [18]. Controls general class of ordinary differential equations that model the temporal evolution of diseases spread and applies the approach to a SIRS model for several diseases such that influenza and malaria.
The rest of this paper is organized as follows: Section 2 lunches the general model and states the associated viability problem. Section 3 approaches the problem with some tools of the set-valued analysis. Section 4 figures some numerical calculus of analytical results on a model example. Section 5 concludes the paper.

2. General Model and Problem Formulation

Pharmacokinetiks of chemotherapeutic drugs

$$u \in U = \prod_{i=1}^{n} \left[u_i^{\min}, u_i^{\max} \right],$$

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and their pharmacodynamics on tumor density

$$\tau \in \mathbb{R}_+ = [0,\infty),$$

are modeled by the coupled ordinary differential equations

$$\dot{\tau} = \psi(\tau) - G(u)\tau, \text{ with } \tau(0) = \tau_0 \in \mathbb{R}_+^*, \tag{2.1a}$$
$$\dot{u} = f(u,v), \text{ with } u(0) = u_0 \in U, \tag{2.1b}$$

with the explicit expressions of the functions ψ and G in (2.1a)

$$\psi(\tau) = -\xi\tau\ln\left(\frac{\tau}{\theta}\right), \tag{2.1c}$$
$$G(u) = \sum_{1\leq i\leq n}\kappa_i u_i + \sum_{1\leq i<j\leq n}\kappa_{ij}u_i u_j, \tag{2.1d}$$

where in (2.1c) ξ and θ are the parameters of the Gompertz growth function, and in (2.1d) κ_i is the effectiveness coefficient of the i-th drug, while κ_{ij} is the coefficient of the potentialization in drug cytotoxicity induced by the presence of i-th and j-th drugs.
And with the explicit expression of the vector function f in (2.1b)

$$f(u,v) = \left(-f_1u_1 + \frac{v_1}{V_1}, \cdots, -f_nu_n + \frac{v_n}{V_n}\right)', \tag{2.1e}$$

where the parameters V_i are the volumes of distribution, and the parameters f_i are the elimination rates, and the input functions $v_i(t)$ are the protocol administration, associated to the compartments u_i.
We have to find input control function v, expressing the protocol administration, and satisfying the constraint

$$\forall t \in [0,\infty),\ v(t) \in V = \prod_{i=1}^{n}\left[f_iV_iu_i^{\min}, f_iV_iu_i^{\max}\right], \tag{2.2a}$$

by which the tumor density τ is as follows

$$\lim_{t\to\infty}\tau(t) = 0. \tag{2.2b}$$

We will formulate the control problem (2.2) in the framework of the viability theory [19].
To each real number $\alpha > 0$, we define the function

$$\psi_\alpha(\tau,u) = \psi(\tau) - G(u)\tau + \alpha\tau, \tag{2.3a}$$

where the functions ψ and G still given by (2.1c) and (2.1d) respectively, and we associate the subset

$$D_\alpha = \{(\tau,u) \in \mathbb{R}_+ \times U \mid \psi_\alpha(\tau,u) \leq 0\}. \tag{2.3b}$$

Proposition 2.1. *Let be α such that $(\tau_0,u_0) \in D_\alpha$.*
If the system (2.1) is globally viable in the subset D_α by a control $v : [0,\infty) \to V$, then v is a protocol in the sense of the problem (2.2).

Proof. Let $t \geq 0$.
By (2.1a) and (2.3) we have the differential inequality

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

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

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

then

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

□

3. Set-Valued Approach

We associate with the system (2.1), the regulation map F_α defined on the subset D_α (2.3b) in the following way

$$F_\alpha(\tau,u) = \{v \in V \mid (\psi(\tau) - G(u)\tau, f(u,v))' \in T_{D_\alpha}(\tau,u)\}, \tag{3.1a}$$

where

$$T_{D_\alpha}(\tau,u) = \left\{(\hat{\tau},\hat{u}) \in \mathbb{R}\times\mathbb{R}^n \mid \liminf_{h\downarrow 0} \frac{d_{D_\alpha}(\tau+h\hat{\tau}, u+h\hat{u})}{h}\right\}, \tag{3.1b}$$

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

Lemma 3.1. *Let be α such that $(\tau_0,u_0) \in D_\alpha$.*
The system (2.1) is locally viable in the subset D_α, if and only if for all $(\tau,u) \in D_\alpha$ there exists $v_\alpha \in V$ such that

$$(\psi(\tau) - G(u)\tau, f(u,v_\alpha))' \in T_{D_\alpha}(\tau,u). \tag{3.2}$$

i.e., if and only if the regulation map F_α is strict.

Corollary 3.2. *Let be α such that $(\tau_0,u_0) \in D_\alpha$.*
If the regulation map F_α admits a single-valued selection v_α, then the system (2.1) is globally viable in the subset D_α by the protocol v_α.

Proof. Let be α such that $(\tau_0,u_0) \in D_\alpha$, and $v_\alpha : D_\alpha \to V$ a single-valued selection of the regulation map F_α.
According to the Lemma 3.1, the system (2.1) under the depending state control $v = v_\alpha(\tau,u)$, admits to a local viable solution $(\bar{\tau},\bar{u})$ in the subset D_α, over a maximal time interval $[0,\bar{t})$.
We have to prove that $\bar{t} \to \infty$:
As $\bar{\tau}$ is a non-negative decreasing function, then $\bar{\tau}(t)$ has a limit denoted by $\bar{\tau}(\bar{t})$ when $t \to \bar{t}^-$.
By (2.1b), (2.1e), and (2.2a) we have

$$\|\dot{\bar{u}}(t)\| \le \|f\|\|\bar{u}(t)\| + \|f\|\|u^{\max}\|,$$

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

$$\|\bar{u}(t)\| \le (\|u_0\| + \|u^{\max}\|)\exp(\|f\|t),$$

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

$$(\bar{\tau}(t),\bar{u}(t)) \to (\bar{\tau}(\bar{t}),\bar{u}(\bar{t})) \text{ when } t \to \bar{t}^-,$$

and $(\bar{\tau}(\bar{t}),\bar{u}(\bar{t}))$ belongs to D_α because it is a closed subset.
Now, by considering $(\bar{\tau}(\bar{t}),\bar{u}(\bar{t}))$ as an initial state to the system (2.1), it follows that $(\bar{\tau},\bar{u})$ may be prolonged to a viable solution $(\bar{\tau},\bar{u})$ in D_α, starting at $(\bar{\tau}(\bar{t}),\bar{u}(\bar{t}))$ 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 $(\bar{\tau},\bar{u})$ becomes globally viable in D_α.
Finally the Proposition 2.1 confirms that v_α is a protocol. □

Now to give an explicit expression to the tangent cone T_{D_α} (3.1b), we appeal the following Lemma

Lemma 3.3. *If the function ψ_α (2.3a) is continuously differentiable on D_α, and admits a partial derivative $\partial\psi_\alpha$ strictly negative on D_α. Then for each $(\tau,u) \in D_\alpha$ the tangent directions $(\hat{\tau},\hat{u})$ of $T_{D_\alpha}(\tau,u)$ are characterized by*

$$\hat{u}_i \ge 0 \text{ if } u = u_i^{\min}, \text{ for } i = 1,\cdots,n, \tag{3.3a}$$
$$\hat{u}_i \le 0 \text{ if } u = u_i^{\max}, \text{ for } i = 1,\cdots,n, \tag{3.3b}$$
$$\dot{\psi}_\alpha(\tau,u)(\hat{\tau},\hat{u}) \le 0, \text{ if } \psi_\alpha(\tau,u) = 0. \tag{3.3c}$$

Corollary 3.4. *For each $(\tau,u) \in D_\alpha$ the tangent directions $(\hat{\tau},\hat{u})$ of $T_{D_\alpha}(\tau,u)$ are characterized by the inequality*

$$\dot{\psi}_\alpha(\tau,u)(\hat{\tau},\hat{u}) \le 0, \text{ if } \psi_\alpha(\tau,u) = 0. \tag{3.4}$$

Proof. Thanks to the expression (2.1e)

- If $u_i = u_i^{\min}$, then

$$\begin{aligned} -f_i u + \frac{v_i}{V_i} &= -f_i u_i^{\min} + \frac{v_i}{V_i} \\ &\ge -f_i u_i^{\min} + f_i u_i^{\min} \\ &\ge 0. \end{aligned}$$

- If $u_i = u_i^{\max}$, then

$$\begin{aligned} -f_i u + \frac{v_i}{V_i} &= -f_i u_i^{\max} + \frac{v_i}{V_i} \\ &\le -f_i u_i^{\max} + f_i u_i^{\max} \\ &\le 0. \end{aligned}$$

□

To give a useful expression of the regulation map F_α (3.1a), we set the functions h_α and ℓ_α by the expressions

$$h_\alpha(\tau,u)=\left(\frac{\partial_{u_1}\psi_\alpha(\tau,u)}{V_1},\cdots,\frac{\partial_{u_n}\psi_\alpha(\tau,u)}{V_n}\right)', \tag{3.5a}$$

$$\ell_\alpha(\tau,u)=(\psi(\tau)-G(u)\tau)\partial_\tau\psi_\alpha(\tau,u)-\sum_{1\le i\le n} f_i u_i\partial_{u_i}\psi_\alpha(\tau,u). \tag{3.5b}$$

Corollary 3.5. *The regulation map F_α is expressed explicitly on the subset D_α as*

$$F_\alpha(\tau,u)=\begin{cases} V & \text{if} \quad \psi_\alpha(\tau,u)<0,\\ V_\alpha(\tau,u) & \text{if} \quad \psi_\alpha(\tau,u)=0,\end{cases} \tag{3.6a}$$

with

$$V_\alpha(\tau,u)=\{v\in V \mid \langle h_\alpha(\tau,u),v\rangle+\ell_\alpha(\tau,u)\le 0\}. \tag{3.6b}$$

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

$$\begin{aligned}\dot\psi_\alpha(\tau,u)(\psi(\tau)-G(u)\tau,f(u,v)) &= \langle\nabla\psi_\alpha(\tau,u),(\psi(\tau)-G(u)\tau,f(u,v))'\rangle\\ &= (\psi(\tau)-G(u)\tau)\partial_\tau\psi_\alpha(\tau,u)-\sum_{1\le i\le n} f_i u_i\partial_{u_i}\psi_\alpha(\tau,u)+\sum_{1\le i\le n} v_i\frac{\partial_{u_i}\psi_\alpha(\tau,u)}{V_i},\end{aligned}$$

then by (3.5)

$$\dot\psi_\alpha(\tau,u)(\psi(\tau)-G(u)\tau,f(u,v))=\langle h_\alpha(\tau,u),v\rangle+\ell_\alpha(\tau,u). \tag{3.7}$$

□

Proposition 3.6. *A single-valued selection of the regulation map F_α may be given on the subset D_α by the expression*

$$v_\alpha(\tau,u)=\pi_{V_\alpha(\tau,u)}(0), \tag{3.8}$$

where π denotes the operator of best approximation.

Remark 3.7. *As Lemma 3.1, the viability of the solution $(\bar\tau,\bar u)$ demands the necessary following condition, between initial tumor density $\bar\tau(0)$ and initial control $\bar u(0)$*

$$\frac{\psi(\bar\tau(0))}{\bar\tau(0)}<G(\bar u(0)). \tag{3.9}$$

To deal with this situation, we introduce the set-valued map

$$W_\beta(\tau,u)=\{v\in V \mid \langle h(\tau,u),v\rangle+\ell(\tau,u)\le-\beta\}, \tag{3.10a}$$

where β is a non-negative real number, and the functions h and ℓ are given by the expressions

$$h(\tau,u)=\left(\frac{\partial_{u_1}\Phi(\tau,u)}{V_1},\cdots,\frac{\partial_{u_n}\Phi(\tau,u)}{V_n}\right)', \tag{3.10b}$$

$$\ell(\tau,u)=(\psi(\tau)-G(u)\tau)\partial_\tau\Phi(\tau,u)-\sum_{1\le i\le n} f_i u_i\partial_{u_i}\Phi(\tau,u), \tag{3.10c}$$

and the function Φ is given by the expression

$$\Phi(\tau,u)=\psi(\tau)-G(u)\tau, \tag{3.10d}$$

where the functions ψ and G still given by (2.1c) and (2.1d) respectively.

Theorem 3.8. *Let be (τ_0,u_0) an initial state such that $\dfrac{\psi(\tau_0)}{\tau_0}\ge G(u_0)$.*
The minimal selection w_β of the set-valued map W_β

$$w_\beta(\tau,u)=\pi_{W_\beta(\tau,u)}(0), \tag{3.11}$$

controls the system (2.1) to a final state $(\bar\tau(\bar t),\bar u(\bar t))$ such that $\dfrac{\psi(\bar\tau(\bar t))}{\bar\tau(\bar t)}<G(\bar u(\bar t))$ (3.9), on the interval $[0,\bar t]$ where $\bar t>\dfrac{\Phi(\tau_0,u_0)}{\beta}$.

Proof. By dynamic equations (2.1a) and (2.1b) we have

$$\Phi(\bar\tau(\bar t),\bar u(\bar t))=\Phi(\bar\tau(0),\bar u(0))+\int_0^{\bar t}\dot\Phi(\bar\tau(s),\bar u(s))(\psi(\bar\tau(s))-G(\bar u(s))\bar\tau(s),f(\bar u(s),w_\beta(s)))\,\mathrm{d}s,$$

then by the formula (3.7) we get

$$\Phi(\bar\tau(\bar t),\bar u(\bar t))=\Phi(\tau_0,u_0)+\int_0^{\bar t}[\langle h(\bar\tau(s),\bar u(s)),w_\beta(\bar\tau(s),\bar u(s))\rangle+\ell(\bar\tau(s),\bar u(s))]\,\mathrm{d}s,$$

since w_β is a single-valued selection of the set-valued map W_β then we have

$$\Phi(\bar\tau(\bar t),\bar u(\bar t))\le\Phi(\tau_0,u_0)-\beta\bar t,$$

as $\beta\bar t>\Phi(\tau_0,u_0)$ it follows that $\Phi(\bar\tau(\bar t),\bar u(\bar t))<0$. □

4. Particular Model and Numerical Simulation

To give numerical simulations for the analytical results of the previous section, we consider the following model from the paper [20], which describes the phamacokinetiks of Etoposide drug $u_1 \in U_1 = [u_1^{\min}, u_1^{\max}]$ and Cisplatin drug $u_2 \in U_2 = [u_2^{\min}, u_2^{\max}]$, and their pharmacodynamics on tumor the density $\tau \in \mathbb{R}_+ = [0, \infty)$

$$\begin{aligned} \dot{\tau} &= \psi(\tau) - G(\tilde{u}_1, \tilde{u}_2)\tau, && (4.1a)\\ \dot{u}_1 &= f_1(u_1, v_1), && (4.1b)\\ \dot{u}_2 &= f_2(u_2, v_2), && (4.1c) \end{aligned}$$

where the explicit expressions of the functions ψ are G are given as follows

$$\begin{aligned} \psi(\tau) &= -\xi\tau \ln\left(\frac{\tau}{\theta}\right), && (4.1d)\\ G(\tilde{u}_1, \tilde{u}_2) &= \kappa_1\tilde{u}_1 + \kappa_2\tilde{u}_2 + \kappa_{12}\tilde{u}_1\tilde{u}_2, && (4.1e) \end{aligned}$$

with

$$\tilde{u}_i = [u_i - u_i^{\min}]H[u_i - u_i^{\min}], \text{ for } i = 1, 2, \tag{4.1f}$$

where $H(\cdot)$ is the Heaviside's step function

$$H[u_i - u_i^{\min}] = \begin{cases} 1, & u_i \geq u_i^{\min}, \\ 0, & u_i < u_i^{\min}, \end{cases} \tag{4.1g}$$

and f_1, and f_2 are given as follows

$$\begin{aligned} f_1(u_1, v_1) &= -f_1 u_1 + \frac{v_1}{V_1}, && (4.1h)\\ f_2(u_2, v_2) &= -f_2 u_2 + \frac{v_2}{V_2}. && (4.1i) \end{aligned}$$

The numerical values of the model parameters are grouped in the Table 1.
For the non-advanced stage of tumor $\Phi(\tau_0, u_0) < 0$, we initiate the model (4.1) at the four states $(2,0,0)$, $(2,0.1,0)$, $(2,0,0.01)$, $(2,0.1,0.01)$, to compare between single and coupled effects of chemo-therapies on the tumor density in Figure 4.1, so by the protocols of Figure 4.3, while Figure 4.2 illustrates their corresponding pharmacokinetics, concerning the viability parameter α of (2.3b) we take 20 (without unit) as numerical value. In the following scheme we combine the numerical methods of Euler by step $\bar{h} > 0$ and Uzawa of parameter $\lambda \in \mathbb{R}_+^5$ to discretize and solve the model

$$\begin{cases} \dot{\tau} = \psi(\tau) - G(\tilde{u})\tau, \\ \dot{u} = f(u, v), \\ v = v_\alpha(\tau, v) \in F_\alpha(\tau, u), \\ t_0 \in \mathbb{R}_+, (\tau_0, u_0) \in D_\alpha. \end{cases} \tag{4.2}$$

1. Initialization
   (a) $t_0 \in \mathbb{R}_+$,
   (b) $(\tau_0, u_0) \in D_\alpha$,
   (c) $\lambda^0 \in \mathbb{R}_+^5$,
2. Iteration
   (a) $t_{n+1} = t_n + \bar{h}$,
   (b)
   $$\begin{cases} \tau_{n+1} = \tau_n + \bar{h}\left(-\xi\tau_n \ln\left(\frac{\tau_n}{\theta}\right)\right), \\ u_1^{n+1} = u_1^n + \bar{h}\left(-f_1 u_1^n + \frac{v_1^n}{V_1}\right), \\ u_2^{n+1} = u_2^n + \bar{h}\left(-f_2 u_2^n + \frac{v_2^n}{V_2}\right), \end{cases}$$
   (c)
   $$\begin{cases} v_1^n = -\lambda_5^n h_\alpha^1(\tau_n, u_n) + \lambda_3^n - \lambda_1^n, \\ v_2^n = -\lambda_5^n h_\alpha^2(\tau_n, u_n) + \lambda_4^n - \lambda_2^n, \end{cases}$$
   (d)
   $$\begin{cases} \lambda_1^{n+1} = \max(\lambda_1^n + \sigma(v_1^n - v_1^{\max}), 0), \\ \lambda_2^{n+1} = \max(\lambda_2^n + \sigma(v_2^n - v_2^{\max}), 0), \\ \lambda_3^{n+1} = \max(\lambda_3^n - \sigma v_1^n, 0), \\ \lambda_4^{n+1} = \max(\lambda_4^n - \sigma v_2^n, 0), \\ \lambda_5^{n+1} = \max(\lambda_5^n + \sigma(h_\alpha^1(\tau_n, u_n)v_1^n + h_\alpha^2(\tau_n, u_n)v_2^n + \ell_\alpha(\tau_n, u_n), 0), \text{ with } 0 < \sigma < \frac{2}{\|h_\alpha(\tau, u)\|}. \end{cases}$$

For the advanced stage of tumor $\Phi(\tau_0,u_0)\geq 0$, we choose $(0.5,0,0)$ as initial state to the model (4.1), and parameter $\beta=0.1$ (3.10a) (without unit). Tumor density in Figure 4.5 needs the minimal time $\bar{t}=6$ (by days) of Figure 4.8, before reaching the non-advanced stage $\Phi(\tau(\bar{t}),u(\bar{t}))<0$, so by the controls of Figure 4.7. We follow the preceding algorithm to approach the minimal selection (3.11) and analyze the model

$$\begin{cases} \dot{\tau}=\psi(\tau)-G(\tilde{u})\tau, \\ \dot{u}=f(u,v), \\ v=w_\beta(\tau,v)\in W_\beta(\tau,u), \\ t\in[t_0,\bar{t}], \\ t_0\in\mathbb{R}_+,\Phi(\tau_0,u_0)\geq 0, \end{cases} \tag{4.3}$$

with the both modifications on the initialization 1. (b) and the iteration 2. (d) to

1. (b) $\Phi(\tau_0,u_0)\geq 0$, and
2. (d) $\lambda_5^{n+1}=\max(\lambda_5^n+\sigma(h_1(\tau_n,u_n)v_1^n+h_2(\tau_n,u_n)v_2^n+\ell(\tau_n,u_n)+\beta,0)$, where $0<\sigma<\dfrac{2}{\|h(\tau,u)\|}$.

Parameter	Value	Unit	Description	Reference
ξ	0.006	d^{-1}	Gompertz growth parameter	[20]
θ	1	kg	Carrying capacity	[20]
k_1	10	$d^{-1}g^{-1}.\ell$	Coffecient of u_1 effectiveness	[20]
k_2	5	$d^{-1}g^{-1}.\ell$	Coffecient of u_2 effectiveness	[20]
k_{12}	2×10^4	$d^{-1}.g^{-2}.\ell^{-2}$	Coefficient of the cytotoxicity by u_1 and u_2	[20]
f_1	2	d^{-1}	Elimination rate of u_1	[20]
f_2	0.1	d^{-1}	Elimination rate of u_2	[20]
V_1	25	ℓ	Volume of distribution for u_1	[20]
V_2	40	ℓ	Volume of distribution for u_2	[20]
$u_1^{\max}$	5	$mg.\ell^{-1}$	Upper bound of u_1	[20]
$u_2^{\max}$	10	$mg.\ell^{-1}$	Upper bound of u_2	[20]
$u_1^{\min}$	10^{-4}	$g.\ell^{-1}$	Lower bound of u_1	[20]
$u_2^{\min}$	10^{-4}	$g.\ell^{-1}$	Lower bound of u_2	[20]

Table 1: Parameter Values with Units and Descriptions

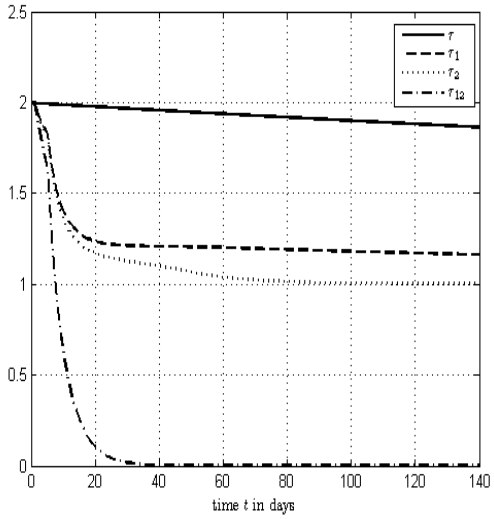

Figure 4.1: Tumors densities τ, τ_1, τ_2, and τ_{12}, under null-control $v=0$, single protocols v_α^1, v_α^2, and coupled protocol (v_α^1,v_α^2) respectively.

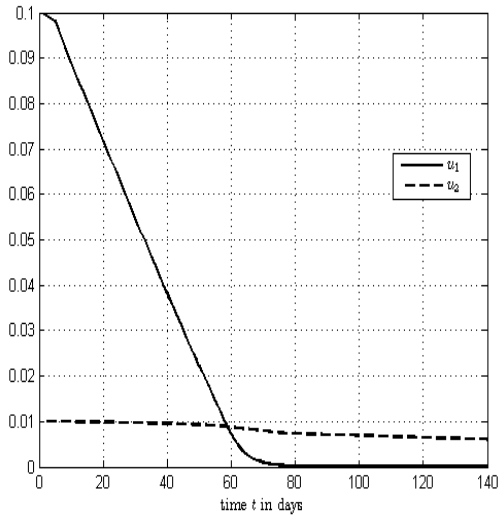

Figure 4.2: Pharmacokinetics u_1 of Etoposide and u_2 of Cisplatin

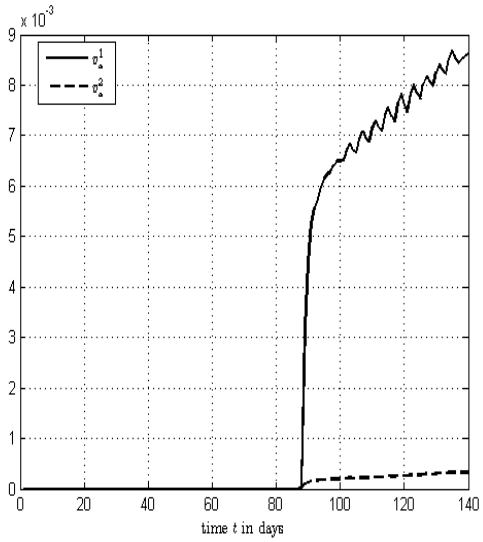

Figure 4.3: Etoposide v_α^1 and Cisplatin v_α^2 Protocols

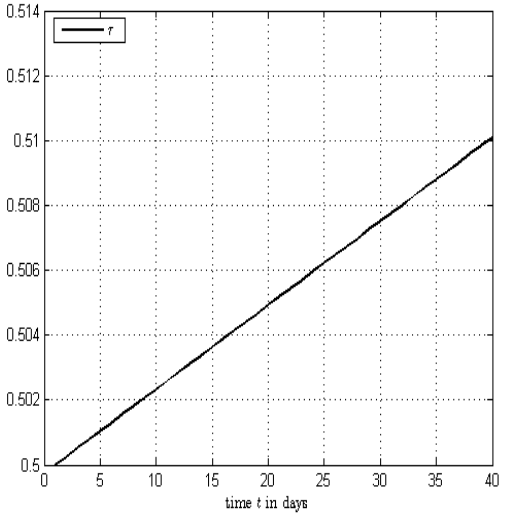

Figure 4.4: Tumor τ in Advanced Stage

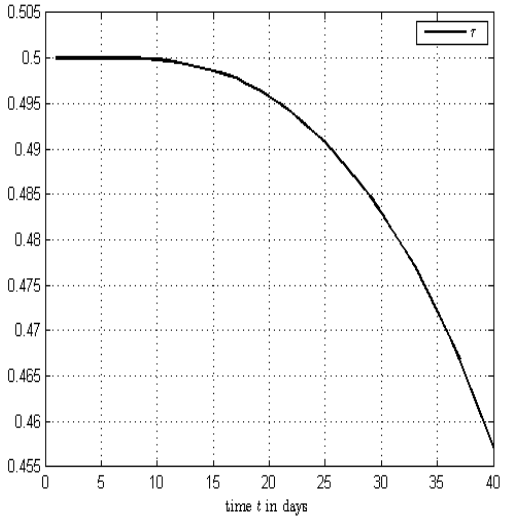

Figure 4.5: Tumor τ in Transition from Advanced Stage to Non-Advanced One

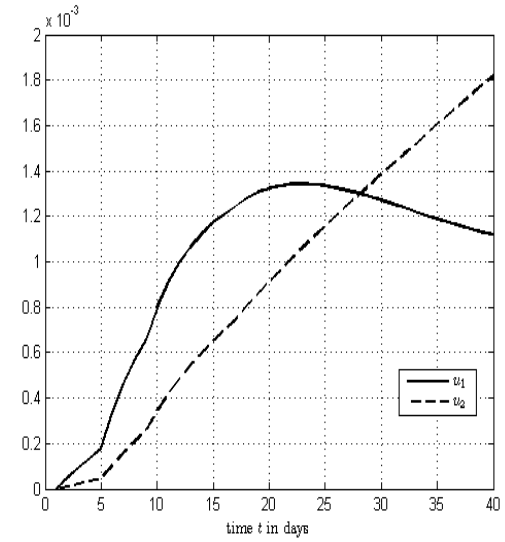

Figure 4.6: Pharmacokinetics u_1 of Etoposide and u_2 of Cisplatin for the Stages Transition

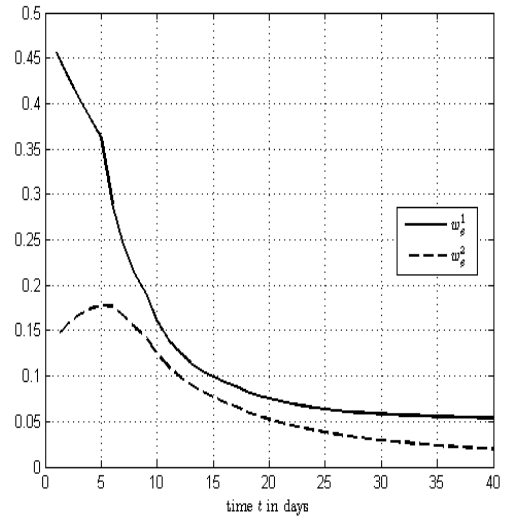

Figure 4.7: Etoposide w_β^1 and Cisplatin w_β^2 Controls of Stages Transition.

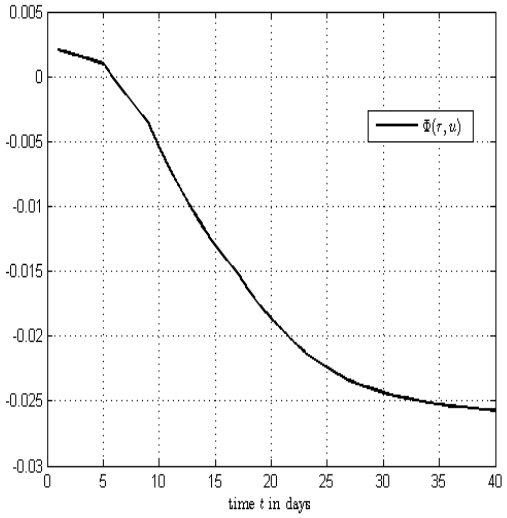

Figure 4.8: Sign of the Indicator Function Φ of the Tumor Stages and the Minimal Time $\bar{t}$

5. Conclusion

The control problem of the tumor density (2.2) is successfully approached by the set-valued analysis, the single-valued selection v_α (3.8) of the regulation map F_α (3.1a) controls the general model (2.1) to be globally viable in the subset D_α (2.3b), and strictly decreases the tumor density $\bar{\tau}$ under the carrying capacity $\theta = 1\,kg$ (2.1c) towards zero $\bar{\tau}(\infty) = 0\,kg$ (2.2b), under the exponential estimate $\bar{\tau}(t) \leq \tau_0 \exp(-\alpha t)$, for all $t \in [0,\infty)$. The protocols of the numerical model (4.2) given in Figure 4.3 are in feedback forms $v_\alpha^i = v_\alpha^i(\tau,u)$ for $i = 1,2$, and their combination provides a considerable reduction of the tumor density in Figure 4.1, where $\bar{\tau}_{12}(t) \ll \bar{\tau}_2(t) < \bar{\tau}_1(t) \ll \tau(t)$ for all $t \in [0,\infty)$, yet $\tau(\infty) = \theta \neq 0$ when there is no therapy, while $\bar{\tau}_{12}(\infty) = \bar{\tau}_2(\infty) = \bar{\tau}_1(\infty) = 0$, under mono-chemo-therapies v_α^1, and v_α^2, and multi-chemo-therapies (v_α^1, v_α^2) respectively. Nonetheless if the tumor density τ is in advanced stage $\Phi(\tau_0,u_0) \geq 0$, the minimal selection w_β (3.11) of the set-valued map W_β (3.10a) controls the general model (2.1) to the non-advanced stage $\Phi(\bar{\tau}(\bar{t}),\bar{u}(\bar{t})) < 0$ on $[0,\bar{t}]$, where the staging function Φ of cancer is given by (3.10d), which is in complete conformity with the numerical simulations of the specific model (4.3) figured by 4.4, 4.5, 4.6, 4.7, and 4.8.

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References

[1] Y. Batmani, H. Khaloozadeh, *Multi objective optimization of drug regimens in cancer chemotherapy using a PK-PD model*, 19*th* Iranian Conference on Electrical Engineering, (2011), 1-1.
[2] A. Floares, C. Floares, M. Cucu, L. Lazar, *Adaptive neural networks control of drug dosage regimens in cancer chemotherapy*, Proceedings of the International Joint Conference on Neural Networks, **1** (2003), 154-159.
[3] M. M. Hadjiandreou, G. D. Mitsis, *Mathematical modeling of tumor growth, drug-resistance, toxicity, and optimal therapy design*, IEEE Trans. Biomed. Eng., **61**(2) (2014), 415-425.
[4] A. Petrovski, J. McCall, B. Sudha, *Multi-objective optimization of cancer chemotherapy using swarm intelligence*, AISB Symposium on Adaptive and Emergent Behaviour and Complex Systems, UK Society for AI, (2009).
[5] A. Petrovski, J. McCall, *Multi-objective optimisation of cancer chemotherapy using evolutionary algorithms*, International Conference on Evolutionary Multi-Criterion Optimization, Springer, Berlin, Heidelberg, (2001).
[6] J. McCall, *Genetic algorithms for modelling and optimisation*, J. Comput. Appl., **184**(1) (2005), 205-222.
[7] H. Khaloozadeh, Y. Pedram, H. S. Fatemeh, *The optimal dose of CAF regimen in adjuvant chemotherapy for breast cancer patients at stage IIB*, Math. Biosci., **213**(2) (2008), 151-158.
[8] T. Ajayi, S. Hosseinian, A. J. Schaefer, C. D. Fuller, *Combination Chemotherapy Optimization with Discrete Dosing*, arXiv preprint, (2021).

[9] A. Petrovski, *An application of genetic algorithms to chemotherapy treatment*, Ph.D. Thesis, Robert Gordon University, 1998.
[10] S. L. Thomson, G. Ochoa, *The Local Optima Level in Chemotherapy Schedule Optimisation*, European Conference on Evolutionary Computation in Combinatorial Optimization (Part of EvoStar), Springer, Cham, (2020).
[11] K. Kassara, *A* unified set-valued approach to control immunotherapy, SIAM J. Control Optim., **48** (2009), 909-924.
[12] M. Serhani, H. Essaadi, K. Kassara, A. Boutoulout, *C*ontrol by viability in a chemotherapy cancer model, Acta Biotheor., **67** (2019), 177-200.
[13] K. Kassara, A. Moustafid, *Angiogenesis inhibition and tumor-immune interactions with chemotherapy by a control set-valued method*, Math. Biosci., **231** (2011), 135-143.
[14] A. Moustafid, *General Anti-Angiogenic Therapy Protocols with Chemotherapy*, Int. J. Math. Model. Computations, **11**(3) (2021).
[15] A. Moustafid, *General chemotherapy protocols*, J. Appl. Dynamic Syst. Control, **4** (2021), 18-25.
[16] L. Boujallal, O. Balatif, M. Elhia, *A set-valued approach applied to a control problem of tuberculosis with treatment*, IMA J. Math. Control Inf., **38** (2021), 1010-1027.
[17] M. Elhia, L. Boujallal, M. Alkama, O. Balatif, M. Rachik, *Set-valued control approach applied to a COVID-19 model with screening and saturated treatment function*, Complexity, (2020).
[18] L. Boujallal, M. Elhia, O. Balatif, *A novel control set-valued approach with application to epidemic models*, J. Appl. Math. Comput., **65** (2021), 295-319.
[19] J. P. Aubin, *Dynamic Economic Theory: A Viability Approach*, Springer, Berlin, 1997.
[20] A. Iliadis, *Optimizing drug regimens in cancer chemotherapy*, Basic Clin. Pharmacol. Toxicol., **96**(3) (2005), 269-270.