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Viability Control of Chemo-Immunotherapy and Radiotherapy by Set-Valued Analysis

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Abstract. In this paper we set-valued analyze the problem of asymptotic stabilizing the tumor size. A mathematical model of exponential tumor growing caused by carcinogenic substance is considered, with chemotherapy, immunotherapy, and radiotherapy effects. We control the model to be viable in therapeutic domains, and reverse the exponential growing of the tumor size. The obtained controls derive from the derivative cone of therapeutic domains as solution of minimizing problem.

Keywords: Chemotherapy· Immunotherapy· Radiotherapy· Anti-angiogenic Therapy· Virotherapy· Differential Equations· Viability Theory· Set-valued Analysis· Tube· Exponential Stability

1 Introduction

Many studies have been conducted on combined therapies to cope with cancer, by different approaches for various mathematical models based on ordinary differential equations ODEs, partial differential equations PDEs, fractional differential equations FDEs, and delayed differential equations DDEs.

ODEs: [1] Develops a model to describe the interactions between immune and tumor cells, as well as to simulate the interventions of chemotherapy and immunotherapy on the dynamics of tumor cells growth, by using the Runge-Kutta method compared with the explicit Euler and Heun's methods. [2] Constructs a nonlinear model of dynamics between tumor cells, immune cells, and three forms of therapy: chemotherapy, immunotherapy, and radiotherapy, as well as to generate optimized combination therapy plans using optimal control theory. [3] Applies the singular perturbed vector field SPVF method, to identify the equilibrium points of a chemo-immunotherapy model and investigate their stability. [4] Performs a stability analysis of a chemo-immunotherapy model, to determine conditions for tumor-free equilibrium to be stable. [5] Sets up an optimal control problem relative to a chemo-immunotherapy model, so as to minimize the number of tumor cells, and the chemotherapeutic and immunotherapeutic drugs administration. [6] Investigates the action of the immun system, as well as the role of chemo-immunotherapy in promoting cancer cure, by means of numerical simulations and the classical linear stability analysis. [7] Extends a model of tumor growth, to include the effects of radiotherapy, chemotherapy, and combined radiotherapy and chemotherapy, as well as to make effective therapy. [8] Models the tumor immune microenvironment TIME, and the effects of radiation and immunotherapy thereon. [9] Adds the radiotherapy to a Kuznetsov model, for the interaction between effector cells and cells in a growing tumor, and uses the computing environment Matlab to obtain the therapeutic diagrams, in which case the tumor is reduced to the subclinical stage. [10] Shows how the anti-angiogenic agent may help the chemotherapy agent in controlling the cancer. [11] Develops a near optimization model, to maximize total weighted damage of cancer cells, minimize total weighted side effect, and minimize total dose related therapy costs. [12] Presents an optimizing algorithm of radiotherapy, in order to increase the efficiency in combination with anti-angiogenic therapy. [13] Investigates combined radiotherapy and anti-angiogenic therapy under varied tumor radiosensitivity. [14] Predicts how to coordinate anti-angiogenic therapy with radiotherapy or chemotherapy, to maximize therapeutic effects. [15] Develops a biomathematical model of combined immun-chemotherapy, in order to predict yet untested therapy regimen. [16] Develops a model involving periodic applications of immunotherapy with chemotherapy (radiotherapy), to investigate how to enhance the efficacy of chemotherapy (radiotherapy) and reduce its side-effects. [17] Checks the controllability and observability for a mathematical model of immunotherapy and chemotherapy for cancer. [18] Uses set-valued analysis to approach the problem of decreasing and asymptotically stabilizing tumor cells, by anti-angiogenic therapy combined with radiotherapy, as well as in in [19] by tumor-immune with chemotherapy, so as in [20, 21] by anti-angiogenic

therapy with chemotherapy, while in [22] chemotherapy is used alone. [23] Studies the optimal effects of immuno-chemotherapy in the presence of gene therapy. [24] Focuses on the effects of chemotherapy and immunotherapy, used singulary or in combination on two cancer populations. [25] Solves ODEs part of system modeling chemo-radiotherapy within the Caratheodory framework, and plugs the solution into PDEs part which is solved by using a fixed-point theorem, the mixing of treatments ensures significant reduction of the population of cancer cells.

PDEs: [26] Models the combination therapy comprising chemotherapy and immunotherapy, controlled with optimized drugs. [27] Develops a mathematical model of the spatiotemporal dynamics of chemovirotherapy treatment to cancer, and uses traveling wave solutions, to determine the minimum wave speed of tumor invasion, and simulates the effective of chemovirotherapy to either chemotherapy or virotherapy. [28] Inspects a spatiotemporal model, in order to minimize the evolution of the tumor, by an optimal combination of virotherapy with Mitogen-activated protein kinase MEK inhibitors. [29] Presents a model of the TIME within cancer-associated fibroblasts CAFs and angiogenic cells in the microenvironment, and quantifies three states: elimination, equilibrium, and escape from cancer immunoediting. [30] Derives from a PDEs cancer model of chemotherapeutic effects on tumor cells, normal cells, and immune cells with an external source rate, a system of FDEs and explores the application of the reduced differential transform method RDTM.

FDEs: [31] Examines existence and uniqueness of the solution of mixed chemotherapy and immunotherapy cancer treatment model, by using the fixed-point theorem. [32] Reviews some cancer models of combined immunotherapy and chemotherapy. [33] Investigates as an optimal control problem the effects of chemotherapy treatment on the growth of tumors, by using a model of tumor-immune surveillance. [34] Models the effects of obesity on cancerous tumors growth with Caputo time fractional derivative, and compares three different treatment strategies: chemotherapy, immunotherapy and their combination. [35] Optimally controls the variables of immunotherapy and anti-angiogenic therapy, to reduce the load of cancer cells with a discrete time-delay. [36] Investigates the optimal control of combined chemo-immunotherapy.

DDEs: [37] Uses the Pontryagin minimum principle with delays in both state and control, to minimize the side effects as well as the cost of the treatment, on fighting cancer tumor growth, by a combination of oncolytic virotherapy and chemotherapy. [38] Applies optimal control theory on a model, to minimize the cost associated with the immuno-chemotherapy, and to reduce load of tumor cells. [39] Analyzes an optimal control problem of a delayed tumor-immune model system, that reveals the effects of combined immunotherapy and chemotherapeutic drug.

Another interesting works in the literature should be cited therein: [40] Uses a randomized methodology, in order to probabilistically certify the existence of a control structure for cancer model including chemotherapy and immunotherapy. [41] Introduces a mathematical model of radio-immunotherapy for tumor, in

linear and exponential spatial dependency forms, and formulates the dose distributions model of radiotherapy with immune response. [42] Reviews the biological modeling of thermoradiotherapy, and uses temperature dependent model parameters, to evaluate the effectiveness of different treatment strategies. [43] Derives a Takagi-Sugeno fuzzy model from an ODEs Stepanova model, and designs strategy for cancer treatment, by resorting to the combination of immunotherapy and chemotherapy, with an effective positive control. [44] Introduces an optimized radial basis function RBF neural network for breast cancer classification. [45] Improves immunovirotherapies by first conducting extensive mathematical investigations using relevant data, before proceeding to pre-clinical and finally clinical trials.

In this paper we propose to extend the set-valued method of papers [18–21] into non autonomous model of three mixed therapies of immunotherapy, chemotherapy, and radiotherapy. Section 2 presents the model and states the associated control problem in the viability form. Section 3 approaches the viability problem in the frame-work of the set-valued analysis. Section 4 discretizes the controlled model by combined methods of Euler and Uzawa, to simulate numerically the tumor state and controls solutions. Section 5 recaps the theoretical and numerical results, and concludes with a remark on the effectiveness of combination therapies in tumor reducing.

2 Mathematical model presentation and control problem statement

2.1 The model

The model under consideration from [46] is a system of four ordinary differential equations, which describes the dynamical interactions in time $t \geq 0$, between tumor size $y(t)$ and drugs of chemotherapy $M(t) \in [0, M^{\max}]$, immunotherapy $I(t) \in [0, I^{\max}]$, and radiotherapy $R_d(t) \in [0, R_d^{\max}]$, which are controllable by $v_M(t)$, $v_I(t)$, and $h_m(t)$ respectively.

$$\dot{y} = \gamma_1 e^{\alpha_1 t} y - \alpha_2 M y - \alpha_3 I y - \alpha_4 R_d y, \tag{1}$$

$$\dot{M} = v_M - d_4 M, \tag{2}$$

$$\dot{I} = v_I - d_5 I, \tag{3}$$

$$\dot{R}_d = h_m - d_6 R_d, \tag{4}$$

with the initial states

$$y(0) = y_0, M(0) = M_0, I(0) = I_0, R_d(0) = R_{0d}. \tag{5}$$

Table 1 describes the parameters model, and Table 2 gives their numerical values.

Equation	Parameter	Description	Source
(1)	γ_1	tumor causing agent or substance in the body	[46]
	α_1	tumor growth rate and proliferation	[46]
	α_2	elimination rate of tumor cells by interacting with chemotherapeutic drugs	[46]
	α_3	elimination rate of tumor cells by interacting with immunotherapeutic drugs	[46]
	α_4	elimination rate of tumor cells by coming in contact with radiation treatment	[46]
(2)	d_4	fading rate of chemotherapy drug from the body	[46]
(3)	d_5	fading rate of immunotherapy drug from the body	[46]
(4)	d_6	fading rate of radiothrerapy drug from the body	[46]

Table 1. Parameters descriptions.

2.2 The problem

The paper [46] solves analytically the problem of controlling tumor size $y(t)$, by the application of mixed combination of therapies $(M(t), I(t), R_d(t))$, for faster reducing of the tumor size $y(t)$, obtained solutions of chemotherapy $v_M(t)$, immunotherapy $v_I(t)$, and radiotherapy $h_m(t)$ are independent and developed by numerical simulations codes using Wolfram Mathematica Software.
This paper proposes to solve the following problem of tumor size $y(t)$ stabilizing

Problem 1. Find a control $u = (v_M, v_I, h_m)^T$ from-in

$$U = [0, d_4 M^{\max}] \times [0, d_5 I^{\max}] \times [0, d_6 R_d^{\max}], \tag{6}$$

to reduce tumor size y, in the asymptotic stability sense

$$\lim_{t \to \infty} y(t) = 0. \tag{7}$$

Let be the tube K_α, i.e., the set-valued map $t \rightsquigarrow K_\alpha(t)$, from $[0, \infty[$ to $\mathbb{R}_+ \times \mathbb{R}_+^3$, such that

$$K_\alpha(t) = \{(y, x) \in \mathbb{R}_+ \times U, \psi(t, y, x) \leq -\alpha\}, \tag{8}$$

with $x = (M, I, R_d)^T$,
where the function

$$\psi(t, y, x) = \gamma_1 e^{\alpha_1 t} - \alpha_2 M - \alpha_3 I - \alpha_4 R_d, \tag{9}$$

with $\alpha \in \mathbb{R}_+^*$.

Proposition 1. *If there exists a control u such that the tube K_α by (8) is viable under the model (1-2-3-4-5), then the control u is a solution to the Problem 1.*

Proof. K_α is viable under the model (1-2-3-4-5) means that it has a differentiable viable solution (y, x) in the sub-set $K_\alpha(t)$, i.e., for all $t \geq 0$ we have the belonging

$$(y(t), x(t)) \in K_\alpha(t),$$

which implies by (1) and (9) that

$$\dot{y}(t) = \psi(t, y, x)y \leq -\alpha y(t), \tag{10}$$

and by integrating

$$y(t) \leq y_0 e^{-\alpha t}, \tag{11}$$

then

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

Remark 1. Thanks to the dynamics (1) the tumor size solution y may be written as

$$y(t) = y_0 e^{\frac{\gamma_1}{\alpha_1}(e^{\alpha_1 t} - 1)} \times e^{-\int_0^t (\alpha_2 M(\tau) + \alpha_3 I(\tau) + \alpha_4 R_d(\tau))\, \mathrm{d}\tau},$$

by which $y(t) \neq 0$ for all $t \geq 0$, when the initial size $y_0 \neq 0$, whence the choice of the control objective (7).

Remark 2. In addition to the asymptotic stability (7), the tumor size y is a decreasing function, since the derivative $\dot{y}$ is strictly negative as (10), and the $Graph(y)$ is convex which rends the decreasing more considerable, however large values of the parameter α may decrease further the tumor size y.

3 Set-valued analysis approach

3.1 Contingent derivative characterization

Theorem 1. *Let be $\alpha > \alpha_1$.*

If there exists a control u such that for all $t \geq 0$ and for all $(y, x) \in K_\alpha(t)$

$$f(t, y, x, u) \in DK_\alpha(t, y, x)(1), \tag{12}$$

where

$$f(t, y, x, u) = (\psi(t, y, x)y, v_M - d_4 M, v_I - d_5 I, h_m - d_6 R_d)^T, \tag{13}$$

and

$$\begin{aligned} DK_\alpha(t, y, x)(1) = \{&(\bar{y}, \bar{x}) \in \mathbb{R}^4, \\ &\liminf_{h \downarrow 0} d\Big((\bar{y}, \bar{x}), \frac{K_\alpha(t + h) - (y, x)}{h}\Big) = 0\}, \end{aligned} \tag{14}$$

is the contingent derivative of the tube K_α at (t, y, x) in the forward direction 1.

Then the tube K_α is viable under the model (1-2-3-4-5), and the control u is a solution to the Problem 1.

Proof. The function f of (13) is continuous from $\mathbb{R}_+ \times \mathbb{R}_+ \times \mathbb{R}^3_+ \times \mathbb{R}^3_+$, and has uniform linear growth in the sense that

$$\exists c > 0, \forall t \geq 0, \forall (y,x) \in K_\alpha(t), \forall u \in U, \|f(t,y,x,u)\| \leq c(\|(y,x)\| + 1),$$

where the constant

$$c = \max(\alpha_2 M^{\max}, \alpha_3 I^{\max}, \alpha_4 R_d^{\max}, \gamma_1 y_0, d_4, d_5, d_6, d_4 M^{\max}, d_5 I^{\max}, d_6 R_d^{\max}),$$

indeed

$$\begin{aligned}
\|f(t,y,x,u)\| &= \|(\psi(t,y,x)y, v_M - d_4 M, v_I - d_5 I, h_m - d_6 R_d)\|, \\
&= |\psi(t,y,x)|y + |v_M - d_4 M| + |v_I - d_5 I| + |h_m - d_6 R_d|, \\
&\leq \gamma_1 e^{\alpha_1 t} y + \alpha_2 M^{\max} y + \alpha_3 I^{\max} y + \alpha_4 R_d^{\max} y \\
&+ d_4 M^{\max} + d_4 M \\
&+ d_5 I^{\max} + d_5 I \\
&+ d_6 R_d^{\max} + d_6 R_d,
\end{aligned}$$

by (11)

$$\begin{aligned}
\|f(t,y,x,u)\| &\leq \gamma_1 e^{\alpha_1 t} y_0 e^{-\alpha t} + \alpha_2 M^{\max} y + \alpha_3 I^{\max} y + \alpha_4 R_d^{\max} y \\
&+ d_4 M^{\max} + d_4 M \\
&+ d_5 I^{\max} + d_5 I \\
&+ d_6 R_d^{\max} + d_6 R_d, \\
&\leq (\alpha_2 M^{\max} + \alpha_3 I^{\max} + \alpha_4 R_d^{\max}) y + d_4 M + d_5 I + d_6 R_d \\
&+ \gamma_1 y_0 e^{(\alpha_1 - \alpha)t} + d_4 M^{\max} + d_5 I^{\max} + d_6 R_d^{\max},
\end{aligned}$$

or $\alpha > \alpha_1$, then $e^{(\alpha_1 - \alpha)t} < 1$, by consequent

$$\begin{aligned}
\|f(t,y,x,u)\| &\leq (\alpha_2 M^{\max} + \alpha_3 I^{\max} + \alpha_4 R_d^{\max}) y + d_4 M + d_5 I + d_6 R_d \\
&+ \gamma_1 y_0 + d_4 M^{\max} + d_5 I^{\max} + d_6 R_d^{\max}, \\
&\leq c(\|(y,x)\| + 1),
\end{aligned}$$

then by [47] the tube K_α is viable under the model (1-2-3-4-5), and by the Proposition 1 the control u is solution to the Problem 1.

Lemma 1 ([47]). *The graph of the contingent derivative of the tube K_α is the contingent cone to its graph*

$$\forall (t,y,x) \in Graph(K_\alpha), Graph(DK_\alpha(t,y,x)) = T_{Graph(K_\alpha)}(t,y,x), \tag{15}$$

$$\begin{aligned}
T_{Graph(K_\alpha)}(t,y,x) &= \{(\bar{t},\bar{y},\bar{x}) \in \mathbb{R}^5, \\
\liminf_{h \downarrow 0} \frac{d((t+h\bar{t}, y+h\bar{y}, x+h\bar{x}), Graph(K_\alpha))}{h} &= 0\}.
\end{aligned} \tag{16}$$

Lemma 2 ([19]). *The contingent cone $T_{Graph(K_\alpha)}(t,y,x)$ in (16) is explicitly described as follows*

- *For $\psi(t,y,x) < -\alpha$*
$$T_{Graph(K_\alpha)}(t,y,x) = \mathbb{R}^5.$$
- *For $\psi(t,y,x) = -\alpha$*
$$(\bar{t},\bar{y},\bar{x}) \in T_{Graph(K_\alpha)}(t,y,x),$$
iff
$$\dot{\psi}(t,y,x)(\bar{t},\bar{y},\bar{x}) \leq 0,$$
and
$$\begin{cases} \bar{t} \geq 0 \text{ if } t = 0, \\ \bar{y} \geq 0 \text{ if } y = 0, \\ \bar{M} \geq 0 \text{ if } M = 0, \\ \bar{I} \geq 0 \text{ if } I = 0, \\ \bar{R}_d \geq 0 \text{ if } R_d = 0, \end{cases}$$
and
$$\begin{cases} \bar{M} \leq 0 \text{ if } M = M^{\max}, \\ \bar{I} \leq 0 \text{ if } I = I^{\max}, \\ \bar{R}_d \leq 0 \text{ if } R_d = R_d^{\max}. \end{cases}$$

3.2 Scalar projection characterization

Corollary 1. $f(t,y,x,u) \in DK_\alpha(t,y,x)(1)$ *iff*

$$\begin{cases} u \in U & \text{if } \psi(t,y,x) < -\alpha, \\ \langle \hbar, u \rangle \geq \ell(t,x) & \text{if } \psi(t,y,x) = -\alpha, \end{cases} \tag{17}$$

where

$$\ell(t,x) = \gamma_1 \alpha_1 e^{\alpha_1 t} + \alpha_2 d_4 M + \alpha_3 d_5 I + \alpha_4 d_6 R_d, \tag{18}$$

and

$$\hbar = (\alpha_2, \alpha_3, \alpha_4)^T. \tag{19}$$

Proof. By Lemma 2, the elements u such that $f(t,y,x,u) \in DK_\alpha(t,y,x)(1)$ are characterized as follows

- For $\psi(t,y,x) < -\alpha$
$$\forall u \in U, f(t,y,x,u) \in DK_\alpha(t,y,x)(1) = \mathbb{R}^4.$$
- For $\psi(t,y,x) = -\alpha$
if
$$\dot{\psi}(t,y,x)(1, f(t,y,x,u)) \leq 0,$$

and

$$\begin{cases} 1 \geq 0 \text{ if } \quad t = 0, \\ \psi(t,y,x)y \geq 0 \text{ if } \quad y = 0, \\ v_M - d_4 M \geq 0 \text{ if } M = 0, \\ v_I - d_5 I \geq 0 \text{ if } \quad I = 0, \\ h_m - d_6 R_d \geq 0 \text{ if } R_d = 0, \end{cases}$$

and

$$\begin{cases} v_M - d_4 M \leq 0 \text{ if } M = M^{\max}, \\ v_I - d_5 I \leq 0 \text{ if } \quad I = I^{\max}, \\ h_m - d_6 R_d \leq 0 \text{ if } R_d = R_d^{\max}. \end{cases}$$

As

$$\begin{cases} 1 \geq 0 \text{ for } \quad t = 0, \\ 0 \geq 0 \text{ for } \quad y = 0, \\ v_M \geq 0 \text{ for } M = 0, \\ v_I \geq 0 \text{ for } \quad I = 0, \\ h_m \geq 0 \text{ for } R_d = 0, \end{cases}$$

and

$$\begin{cases} v_M - d_4 M \leq 0 \text{ if } M = M^{\max}, \text{ for } v_M \leq d_4 M^{\max}, \\ v_I - d_5 I \leq 0 \text{ if } \quad I = I^{\max}, \text{ for } v_I \leq d_5 I^{\max}, \\ h_m - d_6 R_d \leq 0 \text{ if } R_d = R_d^{\max}, \text{ for } h_m \leq d_6 R_d^{\max}. \end{cases}$$

Then

$$f(t,y,x,u) \in DK_\alpha(t,y,x)(1) \iff \dot{\psi}(t,y,x)(1, f(t,y,x,u)) \leq 0,$$

or

$$\dot{\psi}(t,y,x)(1, f(t,y,x,u)) = \frac{\partial \psi}{\partial t}(t,y,x) \times 1 + \frac{\partial \psi}{\partial y}(t,y,x) f_1(t,y,x,u)$$
$$+ \frac{\partial \psi}{\partial M}(t,y,x) f_2(t,y,x,u) + \frac{\partial \psi}{\partial I}(t,y,x) f_3(t,y,x,u) + \frac{\partial \psi}{\partial R}(t,y,x) f_4(t,y,x,u),$$

then

$$\begin{aligned} \dot{\psi}(t,y,x)(1, f(t,y,x,u)) &= \gamma_1 \alpha_1 e^{\alpha_1 t} \\ &+ 0 \times (\gamma_1 e^{\alpha_1 t} - \alpha_2 M - \alpha_3 I - \alpha_4 R) \\ &- \alpha_2 (v_M - d_4 M) - \alpha_3 (v_I - d_5 I) - \alpha_4 (h_m - d_6 R), \end{aligned}$$

thus

$$\begin{aligned} \dot{\psi}(t,y,x)(1, f(t,y,x,u)) &= \gamma_1 \alpha_1 e^{\alpha_1 t} \\ &+ \alpha_2 d_4 M + \alpha_3 d_5 I + \alpha_4 d_6 R \\ &- \alpha_2 v_M - \alpha_3 v_I - \alpha_4 h_m, \end{aligned}$$

by (18) and (19)

$$\dot{\psi}(t,y,x)(1, f(t,y,x,u)) = \ell(t,x) - \langle \hbar, u \rangle.$$

Corollary 2. *The control*

$$u(t,x) = \min_{u \in U}\{\langle \hbar, u\rangle \geq \ell(t,x)\}, \tag{20}$$

is a solution to the Problem 1.

Proof. The control (20) is solution to the characterization (17):

- For $\psi(t,y,x) < -\alpha$
$$u(t,x) \in U.$$
- For $\psi(t,y,x) = -\alpha$
$$\langle \hbar, u(t,x)\rangle \geq \ell(t,x).$$

4 Numerical resolution

4.1 Numerical model

In what follows we give a numerical scheme based on combined methods of Euler and Uzawa, to solve the controlled model by $(v_M(t), v_I(t), h_m(t)) = u(t,x)$ (20)

$$\dot{y} = \gamma_1 e^{\alpha_1 t} y - \alpha_2 M y - \alpha_3 I y - \alpha_4 R_d y, \tag{21}$$
$$\dot{M} = v_M(t, M, I, R_d) - d_4 M, \tag{22}$$
$$\dot{I} = v_I(t, M, I, R_d) - d_5 I, \tag{23}$$
$$\dot{R}_d = h_m(t, M, I, R_d) - d_6 R_d. \tag{24}$$

4.2 Algorithm

1. Initialization
   (a) $t_0 \in \mathbb{R}_+$,
   (b) $(y_0, M_0, I_0, R_{0d}) \in K_\alpha(t_0)$,
   (c) $\lambda^0 \in \mathbb{R}^6_+$,
2. Iteration
   (a) $t_{n+1} = t_n + h$,
   (b)

$$\begin{cases} y_{n+1} = y_n + h(\gamma_1 e^{\alpha_1 t_n} y_n - \alpha_2 M_n y_n - \alpha_3 I_n y_n - \alpha_4 R^d_n y_n), \\ M_{n+1} = M_n + h(v_M(t_n, M_n, I_n, R^d_n) - d_4 M_n), \\ I_{n+1} = I_n + h(v_I(t_n, M_n, I_n, R^d_n) - d_5 I_n), \\ R^d_{n+1} = R_n + h(h_m(t_n, M_n, I_n, R^d_n) - d_6 R^d_n), \end{cases} \tag{25}$$

   (c)

$$\begin{cases} v_M(t_n, M_n, I_n, R^d_n) = -\lambda^n_6 \alpha_2 + \lambda^n_4 - \lambda^n_1, \\ v_I(t_n, M_n, I_n, R^d_n) \ = -\lambda^n_6 \alpha_3 + \lambda^n_5 - \lambda^n_2, \\ h_m(t_n, M_n, I_n, R^d_n) = -\lambda^n_6 \alpha_4 + \lambda^n_6 - \lambda^n_3, \end{cases} \tag{26}$$

Parameter	value	Source
t_0	0	—
y_0	50	[46]
M_0	50	[46]
I_0	50	[46]
R_{0d}	50	[46]
α	77	$-\psi(t_0, y_0, M_0, I_0, R_{0d})$
$M^{\max}$	Not specified	—
$I^{\max}$	Not specified	—
$R_d^{\max}$	Not specified	—
γ_1	20	[46]
α_1	0.35	[46]
α_2	0.54	[46]
α_3	0.65	[46]
α_4	0.75	[46]
d_4	0.3	[46]
d_5	0.6	[46]
d_6	0.8	[46]

Table 2. Parameters values.

(d)

$$\begin{cases} \lambda_1^{n+1} = \max(\lambda_1^n + \sigma(v_M(t_n, M_n, I_n, R_n^d) - v_M^{\max}), 0), \\ \lambda_2^{n+1} = \max(\lambda_2^n + \sigma(v_I(t_n, M_n, I_n, R_n^d) - v_I^{\max}), 0), \\ \lambda_3^{n+1} = \max(\lambda_3^n + \sigma(h_m(t_n, M_n, I_n, R_n^d) - h_m^{\max}), 0), \\ \lambda_4^{n+1} = \max(\lambda_4^n - \sigma v_M(t_n, M_n, I_n, R_n^d), 0), \\ \lambda_5^{n+1} = \max(\lambda_5^n - \sigma v_I(t_n, M_n, I_n, R_n^d), 0), \\ \lambda_6^{n+1} = \max(\lambda_6^n - \sigma h_m(t_n, M_n, I_n, R_n^d), 0), \\ \lambda_7^{n+1} = \max(\lambda_7^n + \sigma(\langle \hbar, u(t_n, M_n, I_n, R_n^d)\rangle \\ \qquad - \ell(t_n, y_n, M_n, I_n, R_n^d)), 0), \end{cases} \tag{27}$$

with $0 < \sigma < \frac{2}{\|\hbar\|}$, where the norm $\|\hbar\| = \sqrt{\alpha_1^2 + \alpha_2^2 + \alpha_3^2}$.

Remark 3. The variant of an infeasible interior-point algorithm presented in [48], may be also used to solve the problem of minimization (20).

Remark 4. As $M^{\max}$, $I^{\max}$, and $R_d^{\max}$, are not specified, the norm of the control $u(t, x)$ may be explicitly obtained by doing projection of $0_{\mathbb{R}^3}$ on the hyper-planes

$$H = \{(u_1, u_2, u_3) \in \mathbb{R}^3_+, \alpha_1 u_1 + \alpha_2 u_2 + \alpha_3 u_3 \geq \ell(t, x)\}, \tag{28}$$

with the expression

$$\|u(t, x)\| = \frac{|\alpha_1 \times 0 + \alpha_2 \times 0 + \alpha_3 \times 0 - \ell(t, x)|}{\sqrt{\alpha_1^2 + \alpha_2^2 + \alpha_3^2}} = \frac{|\ell(t, x)|}{\sqrt{\alpha_1^2 + \alpha_2^2 + \alpha_3^2}}. \tag{29}$$

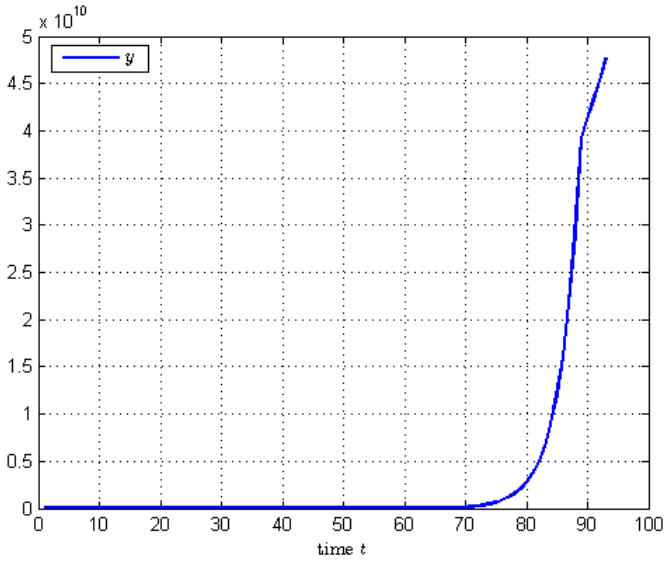

Fig. 1. Exponential tumor size y increase without any therapy, from the initial state $y_0 = 50$.

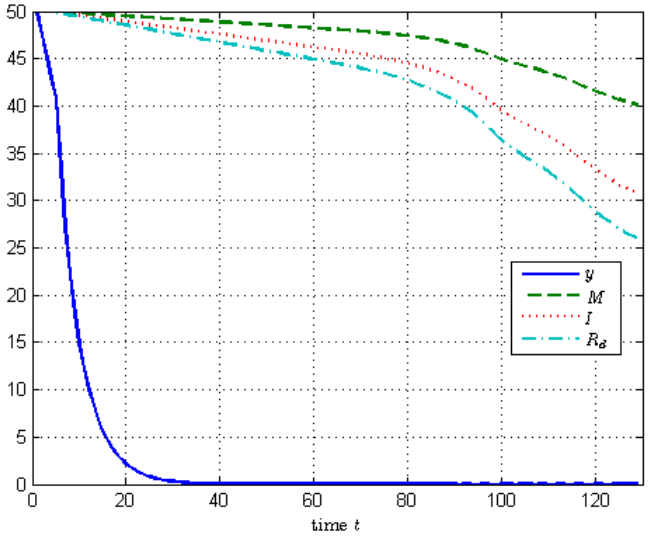

Fig. 2. Exponential tumor size y decrease under combined therapy (M, I, R_d), from the initial state $y_0 = 50$, with the initial therapy $(M_0, I_0, R_{0d}) = (50, 50, 50)$.

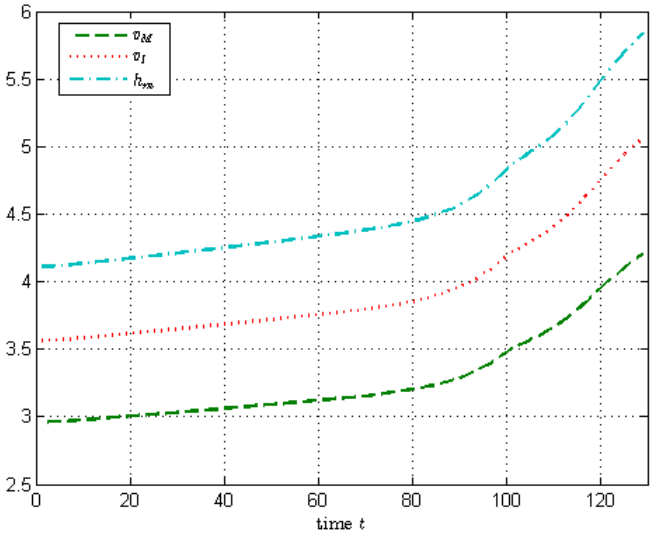

Fig. 3. Applied control $(v_M, v_I, h_m) = u(t, x)$ given by (20).

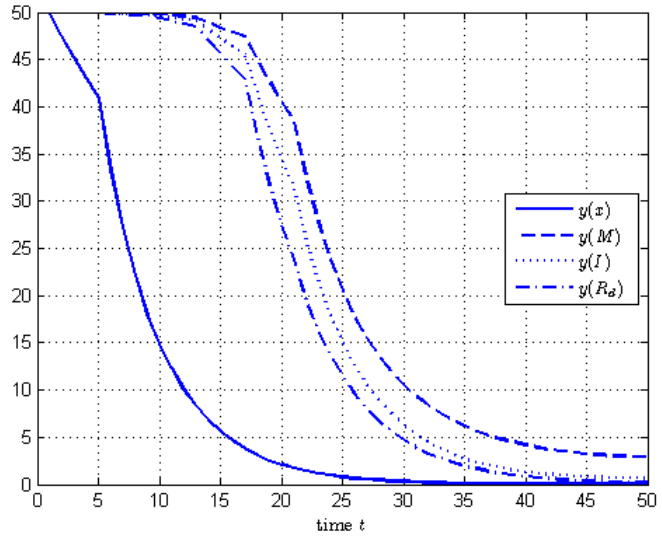

Fig. 4. Comparison of tumor size y reduction under multi-therapies $x = (M, I, R_d)$, and mono-therapies M, I, and R_d, from the initial size $y_0 = 50$, with the initial therapies $M_0 = I_0 = R_{0d} = 50$.

5 conclusion

The exponential growth of tumor size $y(t) = y_0 e^{\frac{\gamma_1}{\alpha_1}(e^{\alpha_1 t}-1)}$ of the dynamics (21) in the absence of therapy $(v_I(t), v_M(t), h_m(t)) = (0, 0, 0)$, see Fig. 1, is reversed to an upper exponential decreasing $y(t) \leq y_0 e^{-\alpha t}$ (11) with $\alpha > \alpha_1$, towards null limit (7), see Fig. 2, by the therapy $(v_I(t), v_M(t), h_m(t)) = u(t, x)$ solution to the minimization problem (20), which is numerically solved in the Section 4 by Uzawa method (26-27) of parameter (λ, σ), to get numerical solution (y, x) of discretized model (25) by Euler method of step h, see Fig. 3. The control $u(t, x)$ is characterized by the contingent derivative DK_α (14), where the tube K_α by (8) is viable under the model (21-22-23-24). The interest of therapies combination is manifested in Fig. 4, where the tumor size $y(x)$ under all therapies with the total amount (29), is much lower than other sizes $y(M)$, $y(I)$, and $y(R_d)$ corresponding to the mono-therapies, i.e., $y(x) < \min(y(M), y(I), y(R_d))$.

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