Mathematical Modeling and Lyapunov-Based Drug Administration in Cancer Chemotherapy

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Abstract: In this paper a new mathematical model is developed for the dynamics between tumor cells, normal cells, immune cells, chemotherapy drug concentration and drug toxicity. Then, the theorem of Lyapunov stability is applied to design treatment strategies for drug protocols that ensure a desired rate of tumor cell kill and push the system to the area with smaller tumor cells. Using of this theorem a condition for drug administration to patients so that solution of the system of equations always tends to tumor free equilibrium point is proposed.

Keywords: Lyapunov stability, cancer, chemotherapy.

1 Introduction

The Cancer is one of the greatest killers in the world, particularly in western countries, although medical activity has been successful, despite great difficulties, at least for some pathologies. A great effort of human and economical resources is devoted, with successful outputs (but also with failures), to cancer research with particular attention to experimental and theoretical immunology [1]. A specific area of study is that of the immune system dynamics. Mammalian immune system can be considered one of the most complex systems nature has ever created. It is in charge to fight against all kind of potentially dangerous agent which destroys the anatomic barriers of the host organism. The immune system is composed by a variety of organs, cells and molecules acting in concert to achieve the basic functions of the immune system, that is, recognition, response and memory. When the immune system does not work properly the results is a disease. In the case of a tumor, the immune system should be able to detect the anomalous cells and kill them. Failure in this task results in an uncontrolled growth of the tumor mass [2].

Mathematical models can provide insights into the dynamics of immune system *in vivo*. A simple model may play a significant role in the development of a better understanding of the disease and the various drug therapy strategies used against it. Mathematical modeling of immune system has a long history; in 1973 Bell [3] proposed a model consisting of a system of two equations based on the classic predator-prey interaction. Later in 1973, Aroesty et al. [4] developed a model that more accurately characterized the tumor growth rate. In 1986 Boer and Hogeweg [5] proposed a model that describes the immune system response to tumor cells. In 1994 Kuznetsov et al. [6] modeled interaction between tumor cells and immune cells. Recently, there are a lot of researches that develop the various mathematical descriptions of cancer and the immune responses [4, 6-10].

One of the important goals for a mathematical model is to find a desirable treatment protocol for patients. Also, mathematical models have been constructed to aid in describing the mechanisms of cytotoxic drug availability and action on tumor cell populations and in expressing constraints of drug use due to the subsequent toxicities. Using of optimal control theory to design optimal chemotherapy strategies is a routine task. Many authors have used this theory to design treatment protocol, see for example [11-15]. But regarding to parameters of system which are different from one patient to another, solution for optimal control problem should be carried out for each patient separately. Also, solution for an optimal control problem is not an easy task and requires spending lots of time. If we want to have drug delivery by using mathematical models applicably, by acceptation of a model for cancer growth if doctors want to use the model for their patients inevitably they must be familiar with solution for optimal control problems while this is a difficult task.

In this research a new mathematical model is suggested for the dynamics between tumor cells, normal

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cells, immune cells, chemotherapy drug concentration and drug toxicity. In continuing in order to gain protocol treatment, instead of using the optimal control theory, Lyapunov stability theorem has been used. Using this method provides a technique for drug administration based on system's parameters (different patients).

2 Mathematical Model

Mathematical models of tumor-immune interactions provide an analytic framework in which to address specific questions about tumor-immune dynamics and the response of the tumor diseases to treatment. The model we present tracks three cell populations, one drug concentration in the bloodstream and a term of drug toxicity. It is much like the model developed by de Pillis and Radunskaya [16], but differs in two respects. First, the model presented here includes a term of drug toxicity. Second, in order to simplify the process of finding Lyapunov function, the dose–response dynamics is represented by mass-action term instead of exponentially decaying term and also the effects of drug on normal and immune cells have been neglected, in fact measure of toxicity of drugs is calculated in one term separately.

The assumptions that were used to determine the model equations are outlined below, followed by a discussion of the model equations themselves.

- Both tumor and normal cell populations are homogeneous, i.e., their growth dynamics are the same for all parts of the population.
- Both tumor and normal cell populations obey logistic dynamics.
- Tumor cells and Normal cells compete for available resources.
- Tumor cells and immune cells compete in a predator-prey fashion.
- It is assumed that the drug is delivered by infusion, and there is an instantaneous mixing of drug with plasma, as well as an immediate delivery of the drug to the tumor site.
- The cytotoxic drug kills only tumor and effect of that on normal and immune cells has been neglected.
- The rate of metabolism of drug inside the body is assumed to be directly proportional to the cumulative drug toxicity τ with a proportion constant η.

The cell populations, drug toxicity and drug concentration in this model at time t are denoted by:

- $N(t)$, Normal cell population,
- $T(t)$, Tumor cell population,
- $I(t)$, Immune cell population,
- $\tau(t)$, drug toxicity,
- $u(t)$, chemotherapy drug concentration.

The model is given by the following set of ordinary differential equations:

$$\dot{N} = r_2 N(1 - b_2 N) - c_4 TN \quad (1)$$

$$\dot{T} = r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2 uT \quad (2)$$

$$\dot{I} = s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I \quad (3)$$

$$\dot{\tau} = u - \eta\tau \quad (4)$$

$$\dot{u} = V - \gamma u \quad (5)$$

These equations have the general initial conditions $N(0) = N_0$, $T(0) = T_0$, $I(0) = I_0$, $\tau(0) = \tau_0$ and $u(0) = u_0$, where each initial value is positive.

The first equation describes the rate of change for the normal cell population. The normal cell population is assumed to grow logistically (term 1), while normal cells are killed by the tumor cells through a mass-action dynamic, $-c_4TN$. The second equation marks the rate of change of the tumor cells. The tumor cell population grows logistically. The reaction of tumor cells to immune cells and normal cells can result in the death of tumor cells, represented by the two competition terms, $-c_2IT$ and $-c_3TN$. Finally, chemotherapy affects tumor cell population through a mass-action dynamic of the form $-a_2uT$. Equation (3) describes the rate of change for the immune cell population. The immune cells have a constant source rate s, while death is proportional to the population of immune cells through the term $-d_1I$. Immune cells are also recruited by tumor cells through a Michaelis–Menten term, $\rho IT/(\alpha+T)$, which serves to provide a saturation effect. Additionally, immune cells are inactivated through contact with tumor cells according to a mass-action dynamic $-c_1IT$. The relationship between the cumulative drug toxicity and the drug concentration inside the body, Equation (4), is added to the aforementioned mathematical model. The cumulative drug toxicity τ increases with the concentration of drug, u, and decreases with the rate of metabolism of drug inside the body. The rate of metabolism of drug inside the body is assumed to be directly proportional to the cumulative drug toxicity τ with a proportion constant η. The concentration of drug is assumed to decay exponentially. Equation (5) describes the change of drug concentration. The rate to deliver drug is denoted by the variable V where the half-life of drug is represented by γ which depends on the biochemical property of the drug.

The developed mathematical model in this paper has many similarities with the famous model of de Pillis and Radunskaya [16], but there are two main differences between them. First, one new term for drug toxicity has been added to the model. Second, instead of expressing the dynamic response of the drug with an exponential term, it is given with a mass-action term. Also, drug toxicity effects on healthy and cancerous cells are

neglected. In fact, amount of drug toxicity is calculated by another term separately.

3 Nondimensionalization and Analysis

For ease of analysis, we consider the system of Equations (1)-(4) in the absence of treatment. To further clarify the dependence of the system on parameters and to find the Lyapunov function, we non-dimensionalize the system as follows. Let the nondimensionalized state variables be:

$$\overset{*}{N} = b_2 N, \quad \overset{*}{T} = \frac{1}{\alpha} T, \quad \overset{*}{I} = \frac{r_2}{s} I, \quad \overset{*}{t} = r_2 t$$

and the corresponding parameters be:

$$\overset{*}{\rho} = \frac{\rho}{r_2}, \qquad \overset{*}{c_1} = \frac{\alpha c_1}{r_2}, \qquad \overset{*}{c_2} = \frac{c_2 s}{r_2^2}, \qquad \overset{*}{c_3} = \frac{c_3}{b_2 r_2},$$

$$\overset{*}{c_4} = \frac{\alpha c_4}{r_2}, \qquad \overset{*}{d} = \frac{d_1}{r_2}, \qquad \overset{*}{r} = \frac{r_1}{r_2}, \qquad \overset{*}{b} = \alpha b_1$$

Then, dropping the over-bar notation for convenience, we obtain the following scaled model:

$$\dot{N} = N(1-N) - c_4 TN \tag{6}$$

$$\dot{T} = rT(1-b_1 T) - c_2 IT - c_3 TN \tag{7}$$

$$\dot{I} = 1 + \frac{\rho IT}{1+T} - c_1 IT - dI \tag{8}$$

$$\dot{\tau} = -\eta\tau \tag{9}$$

with initial conditions: $N(0) = N_0$, $T(0) = T_0$, $I(0) = I_0$, $\tau(0) = \tau_0$. Studying equilibria of the system and their stability is an important task because the state variables lie on one of these points after treatment.

This system of equations has several equilibrium points. These equilibrium points are classified in summary as Equations (10)–(13).

$$\dot{N} = 0 \;\Rightarrow\; N(1-N) - c_4 TN = 0 \tag{10}$$
$$\Rightarrow\; N = 0 \quad or \quad N = 1 - c_4 T$$

$$\dot{T} = 0 \;\Rightarrow\; rT(1-b_1 T) - c_2 IT - c_3 TN = 0 \tag{11}$$
$$\Rightarrow\; T = 0 \quad or \quad T = \frac{r - c_2 I - c_3 N}{r_1 b_1}$$

$$\dot{I} = 0 \;\Rightarrow\; 1 + \frac{\rho IT}{1+T} - c_1 IT - dI = 0 \tag{12}$$
$$\Rightarrow\; I = \frac{1+T}{(1+T)(d+c_1 T) - \rho T}$$

$$\dot{\tau} = 0 \;\Rightarrow\; -\eta\tau = 0 \;\Rightarrow\; \tau = 0 \tag{13}$$

Equilibrium points:

- $(0,0,\frac{1}{d},0)$, normal and tumor cells are both destroyed (death equilibrium).
- $(0,a,f(a),0)$, normal cells are destroyed and tumor cells remain (death equilibrium).
- $(1,0,\frac{1}{d},0)$, tumor cells are destroyed and normal cells remain (tumor free equilibrium).
- $(g(b),b,f(b),0)$, depending on parameters of system we have 1, 2 or 3 equilibrium points. Now if values of g(b) and b are in acceptable rang for normal and cancerous cells, these equilibrium points could be desirable points for us.

One could see in some of these equilibrium points normal cells are destroyed completely, these points are called death points. In other points both normal and tumor cells exist but there is only one point which all tumor cells are destroyed and normal cells survive completely. This point is called tumor free point.

Disregarding that tumor free point is stable or unstable, efforts of doctors have been always oriented to reach to this point. Because complete therapy of disease and complete destruction of tumor cells happen at this equilibrium point. Meanwhile it seems to be necessary to find a therapeutic protocol which, with neglecting what the initial conditions of system are, be able to incline the solution of equations toward this stable point. For this purpose we need a drug administration method which could grantee (at least at presence of drug) the global stability of this equilibrium point.

4 Global stability of the Tumor Free

In this section, we briefly discuss how to apply Lyapunov's direct method for designing desirable drug protocol. This technique requires hypothesizing a Lyapunov function candidate and then finding a control law to make this candidate a real Lyapunov function.

Lyapunov function definition: if, in a ball B_R, the function $V(x)$ is positive definite and has continuous partial derivatives, and if its time derivative along any state trajectory of system is negative semi-definite, i.e, $\dot{V}(x) \le 0$, then $V(x)$ is said to be a Lyapunov function for the system.

Global stability: Assume that there exists a scalar function V of the state x, with continuous first order derivatives such that

- $V(x)$ is positive definite
- $\dot{V}(x)$ is negative definite
- $V(x) \to \infty \quad as \quad \|x\| \to \infty$

then the equilibrium at the origin is globally asymptotically stable.

Theorem: The tumor free steady state, $E_0 = (1, 0, 1/d, 0, 0)$, is globally asymptotically stable if:

$$u \geq \frac{-c_3 N + r - c_2 I - b_1 rT}{a_2} \tag{14}$$

Proof: Define a Lyapunov function,

$$V(x) = \frac{a}{2}\left(I - \frac{1}{d}\right)^2 + b\,Ln(T+1) + \frac{c}{2}(N-1)^2 + g\tau + f\,u \tag{15}$$

Along the trajectories of system, we have:

$$\dot{V}(x) = a(I - \frac{1}{d})\dot{I} + b\frac{1}{1+T}\dot{T} + c(N-1)\dot{N} + g\,\dot{\tau} + f\,\dot{u} \tag{16}$$

So,

$$\begin{aligned}\dot{V}(x) = \quad & a(I - \frac{1}{d})\left[1 + \frac{\rho IT}{1+T} - c_1 IT - dI\right] \\ & + b\frac{1}{1+T}\left[rT(1-b_1T) - c_2 IT - c_3 TN - a_2 uT\right] \\ & + c(N-1)\left[N(1-N) - c_4 TN\right] \\ & + g\left[u - \eta\tau\right] \\ & + f\left[V - \gamma u\right]\end{aligned} \tag{17}$$

After simplifying equations, one could have:

$$\begin{aligned}\dot{V}(x) = \quad & -ad(I - \frac{1}{d})^2 + a\rho\frac{I^2T}{1+T} - \frac{a\rho}{d}\frac{IT}{1+T} \\ & - ac_1 I^2 T + \frac{ac_1}{d} IT\left(\frac{1+T}{1+T}\right) \\ & + br\frac{T}{1+T} - bb_1 r\frac{T^2}{1+T} - bc_2\frac{IT}{1+T} \\ & - bc_3\frac{TN}{1+T} - ba_2 u\frac{T}{1+T} \\ & - cN(N-1)^2 - cc_4 T\left(N+1-1\right)(N-1) \\ & + g\left[u - \eta\tau\right] \\ & + f\left[V - \gamma u\right]\end{aligned} \tag{18}$$

and then

$$\begin{aligned}\dot{V}(x) = \quad & -ad(I - \frac{1}{d})^2 + a\rho\frac{I^2T}{1+T} - \frac{a\rho}{d}\frac{IT}{1+T} - ac_1 I^2 T \\ & + \frac{ac_1}{d}\frac{IT}{1+T} + \frac{ac_1}{d}\frac{IT^2}{1+T} \\ & + br\frac{T}{1+T} - bb_1 r\frac{T^2}{1+T} - bc_2\frac{IT}{1+T} \\ & - bc_3\frac{TN}{1+T} - ba_2 u\frac{T}{1+T} \\ & - cN(N-1)^2 - cc_4 T\left(N-1\right)^2 \\ & - cc_4 TN + cc_4 T\left(\frac{1+T}{1+T}\right) \\ & + g\,u - g\eta\tau \\ & + fV - f\gamma u\end{aligned} \tag{19}$$

Finally,

$$\begin{aligned}\dot{V}(x) = \quad & -ad(I - \frac{1}{d})^2 - ac_1 I^2 T - bc_3\frac{TN}{1+T} \\ & - cN(N-1)^2 - cc_4 T\left(N-1\right)^2 - cc_4 TN \\ & + (br - ba_2 u + cc_4)\frac{T}{1+T} \\ & + (a\rho I_0 - \frac{a\rho}{d} + \frac{ac_1}{d} - bc_2)\frac{IT}{1+T} \\ & + (\frac{ac_1}{d} I_0 - bb_1 r + cc_4)\frac{T^2}{1+T} \\ & + u(g - f\gamma) \\ & + (fV - g\eta\tau)\end{aligned} \tag{20}$$

In order that $\dot{V}(x)$ be negative definite all negative equations should be negative as well, so we have:

$$br - ba_2 u + cc_4 \leq 0 \quad \Rightarrow \quad b \geq \frac{cc_4}{a_2 u - r} \tag{21}$$

$$a\rho I_0 - \frac{a\rho}{d} + \frac{ac_1}{d} - bc_2 \leq 0 \Rightarrow \quad a \leq \frac{bc2}{\rho I_0 - \frac{\rho}{d} + \frac{c_1}{d}} \tag{22}$$

$$\frac{ac_1}{d} I_0 - bb_1 r + cc_4 \leq 0$$

$$\Rightarrow b \geq \frac{cc_4}{b_1 r - \frac{c_2 c_1 I_0}{(\rho I_0 - \frac{\rho}{d} + \frac{c_1}{d})d}} \tag{23}$$

If values of *f, g, c, b* and *a* are selected as bellow $V(x)$ function will be a Lyapunov function.

$$\begin{aligned} & b = Max\left(\frac{cc_4}{b_1 r - \frac{c_2 c_1 I_0}{(\rho I_0 - \frac{\rho}{d} + \frac{c_1}{d})d}}, \frac{cc_4}{a_2 u - r}\right), \\ & a = \frac{bc2}{\rho I_0 - \frac{\rho}{d} + \frac{c_1}{d}},\ c = \forall,\ g \leq \gamma f \text{ and } f(V - \gamma\eta\tau) \leq 0 \end{aligned} \tag{24}$$

If *b* is assumed very big value and *f, g, c* and *a* are assumed very small values then we have:

$$\begin{aligned}\dot{V}(x) = & -bc_3\frac{TN}{1+T} + (br - ba_2 u)\frac{T}{1+T} \\ & - bc_2\frac{IT}{1+T} - bb_1 r\frac{T^2}{1+T}\end{aligned} \tag{25}$$

$$\dot{V}(x) = \quad b\frac{T}{1+T}(-c_3 N + r - a_2 u - c_2 I - b_1 rT) \tag{26}$$

To have $\dot{V}(x)$ as negative definite we should have:

$$\begin{aligned} & -c_3 N + r - a_2 u - c_2 I - b_1 rT \leq 0 \\ & \Rightarrow \quad -c_3 N + r - c_2 I - b_1 rT \leq a_2 u \end{aligned} \tag{27}$$

By keeping following condition one could guarantee that solution of equations goes to tumor free equilibrium point.

$$u \geq \frac{-c_3 N + r - c_2 I - b_1 r T}{a_2} \quad (28)$$

5 Simulations for Lyapunov-based Drug Administration

In this part the behavior of developed mathematical model for 2 patients based on Lyapunov theorem is considered which onetime is in absence of chemotherapy and another time is with presence of chemotherapy. Parameters of system for these 2 persons are such that for first person tumor free equilibrium point is a stable point and for second one tumor free point in an unstable equilibrium point. These parameters are given for 2 persons in Table 1. Most of the parameters were taken from the ref [16], and these are noted in the Table 1.

Table 1. Parameter values for patient 1 and patient 2

Parameter	P1	P2	Units	Description	Reference
a_2	0.3	0.3	day^{-1}	Fractional tumor cell kill by chemotherapy	[16]
b_1	1	1	$cells^{-1}$	$1/b_1$ is tumor carrying capacity	[16]
b_2	1	1	$cells^{-1}$	$1/b_2$ is normal cells carrying capacity	[16]
c_1	1	1	$cell^{-1}\ day^{-1}$	Fractional immune cell kill by tumor cells	[16]
c_2	0.5	0.2	$cell^{-1}\ day^{-1}$	Fractional tumor cell kill by immune cells	Estimated
c_3	1	1	$cell^{-1}\ day^{-1}$	Fractional tumor cell kill by normal cells	[16]
c_4	1	1	$cell^{-1}\ day^{-1}$	Fractional normal cell kill by tumor cells	[16]
r_1	1.5	1.5	day^{-1}	Tumor growth rate	[16]
r_2	1	1	day^{-1}	Normal cells growth rate	[16]
d_1	0.2	0.2	day^{-1}	Immune cells death rate	[16]
s	0.33	0.33	$cell\ day^{-1}$	Constant source of immune cells	[16]
α	0.3	0.3	$cell$	Steepness coefficient of the immune cell recruitment curve	[16]
ρ	0.01	0.01	day^{-1}	Maximum immune cell recruitment rate by tumor cells	[16]
η	0.5	0.5	day^{-1}	Rate of drug toxicity decay	[16]
γ	0.9	0.9	day^{-1}	Rate of chemotherapy drug decay	[16]

5.1 Patient 1

In this part first the system of equations for patient 1 with initial condition of *I(0)=.1*, *T(0)=.25* and *N(0)=1* in absence of chemotherapy has been solved. As can be observed from Fig. 1, although the tumor free point for patient 1 is a stable point but initial conditions of patient are not in the attraction region of tumor free equilibrium point, so the solution of equations proceed to one of the equilibrium point of system which has many cancerous cells.

In addition the system of equations for the patient 1 with aforementioned initial conditions but this time in the presence of chemotherapy and using of drug administration condition, extracted from Lyapunov stability theorem, is solved. As shown in Fig. 2 solution of the system of equations are guided toward tumor free equilibrium point in which after approximately 40 days all cancerous cells are destroyed and healthy cells are at desirable situation. In Fig. 3 the method of drug administration to patient using of condition resulted from Lyapunov theorem is shown. One could see that for 3 days and approximately within days 2, 4 and 5 drug is given to patient. As system stands in attraction region of tumor free there is no need for drug administration and solution of equations goes spontaneously toward tumor free equilibrium point.

5.2 Patient 2

In this part the system of equations for parameters of patient 2 (Table 1) with initial conditions of *I(0)=.1, T(0)=.25* and *N(0)=1* in absence of chemotherapy is solved. The tumor free equilibrium point for given parameters of patient 2 is an unstable equilibrium point and as shown in Fig. 4 finally system tends toward one of the death equilibrium points.

In addition the system of equations for the patient 2 with selected initial conditions and in the presence of drug and with use of drug administration condition extracted from Lyapunov stability theorem is solved. Although, tumor free equilibrium point as shown in Fig. 5 is unstable equilibrium point in absence of drug but in presence of drug and after 10 days stands at this equilibrium point. Fig. 6 is representative of the method for drug delivery for complete therapy of disease. As shown for keeping the system at this point drug administration must be done continuously. But continuum drug administration regarding harms of drug

and amount of produced poison is an impossible task. Also, doctors continue chemotherapy until the number of cancerous cells is greater than 10^7.

5.3 Modifying the Condition of Drug Administration

In this part in accordance with doctors work and making the method of drug administration much more actual another condition is added to condition of drug administration. This condition says, drug administration is allowed until the number of cancerous cells are greater that 10^7. Recalculation of equations for patient 2 by putting new condition into consideration is shown in Fig. 7. As shown in this figure after the number of cancerous cells becomes less than 10^7, the drug administration (Fig. 8) will be stopped. In addition, good consistency is observed between the behavior of developed model and other known behavior from cancerous tumors (including growth, death and dormancy. All of these behaviors are given in Fig. 7. In this figure, cancerous cells have started growing (growth period) and after drug delivery their amount is reduced (death period) and at the end when the drug delivery is stopped they start growing again (dormancy period).

As equilibrium point is an unstable point after sometime cancerous cells start growing again and their amount reach to a considerable amount. For solving this problem 2 solutions are presented. First, after that number of cancerous cells passed over certain amount chemotherapy can be applied again. The weak point of this method is that drug administration to patient is continuing. Second way for such patients is to apply vaccine therapy after chemotherapy. Vaccine therapy causes parameters of system to change and as result tumor free point will be stable point. In future works vaccine therapy will be considered for this model.

6 Conclusions

In this article a new mathematical model is proposed for studying the behavior of cancerous cells in presence of chemotherapy. Using of Lyapunov stability theorem a condition for therapy of cancerous patients is proposed. One could see with the use of this method of drug administration, system of equations solution always tends to tumor free equilibrium point. It could be observed that with use of extracted drug administration condition, there is no need for calculation of attraction regions at free tumor equilibrium point. Drug administration will be stopped after system enters attraction regions of free tumor point. This task causes decline of amount of drug administration during the therapy. Difficulty to find Lyapunov candidate function is one of the drawbacks of this method. In future works effect of vaccine therapy in combination with chemotherapy on the model will be studied.

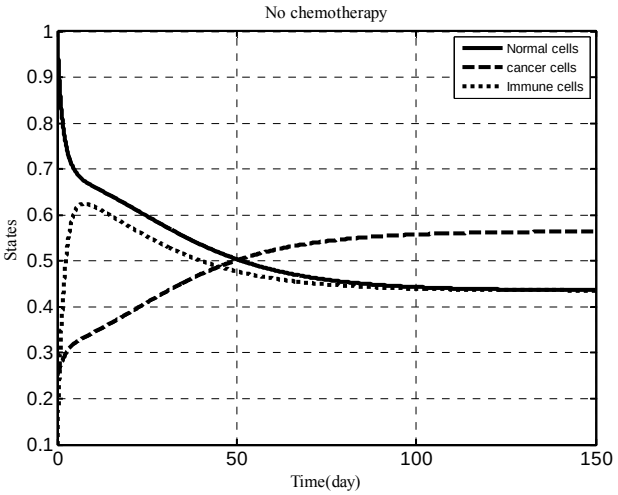


Fig. 1. Patient 1: behavior of the system of equations in absence of chemotherapy

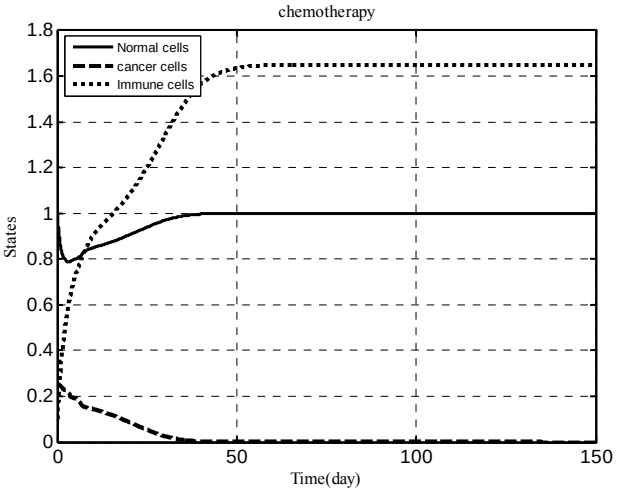


Fig. 2. Patient 1: behavior of the system of equations in presence of chemotherapy

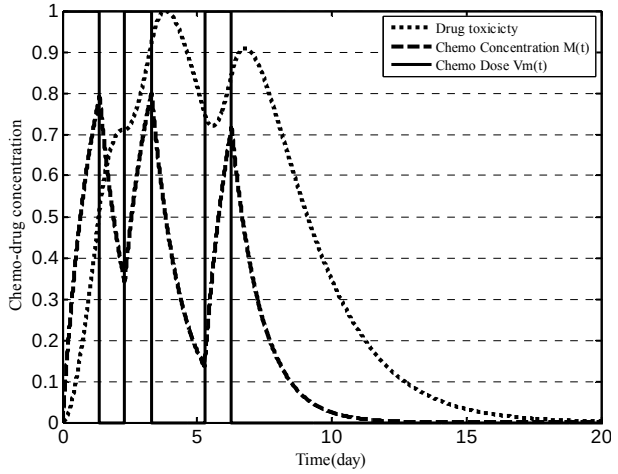


Fig. 3. Patient 1: Drug administration using condition extracted from Lyapunov stability theorem.

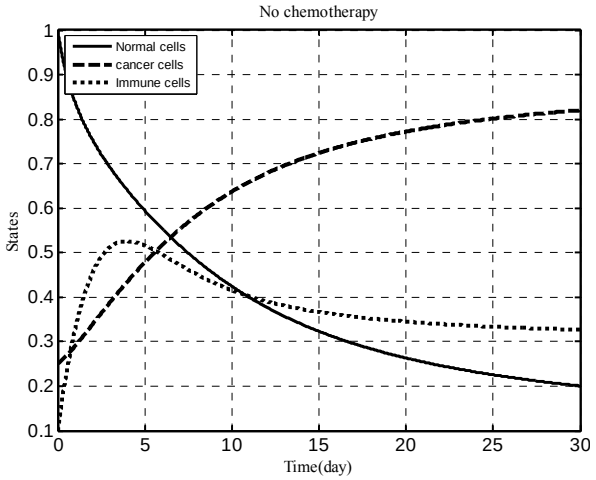


Fig. 4. Patient 2: behavior of the system of equations in absence of chemotherapys

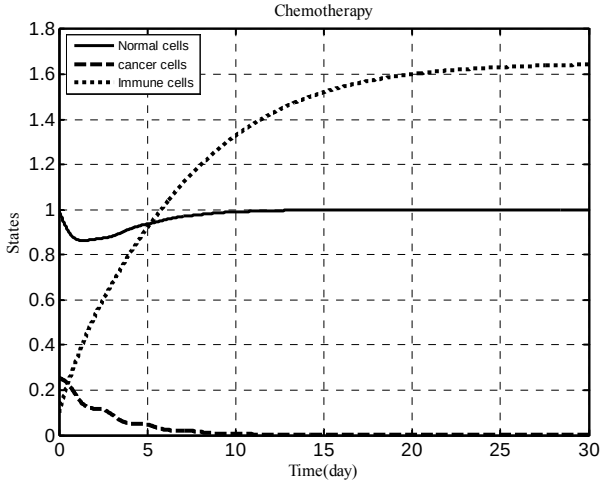


Fig. 5. Patient 2: behavior of the system of equations in presence of chemotherapy

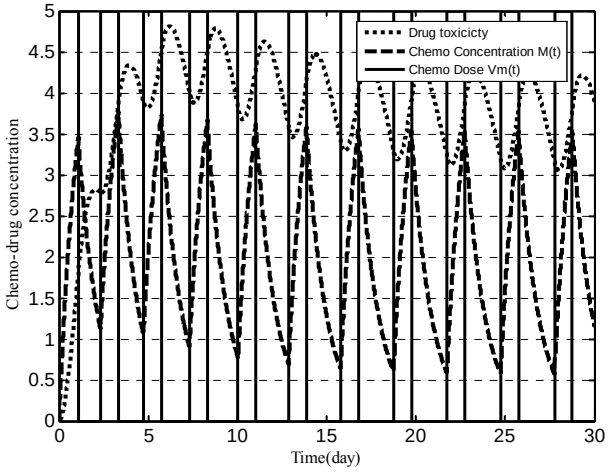


Fig. 6. Patient 2: Drug administration using condition extracted from Lyapunov stability theorem.

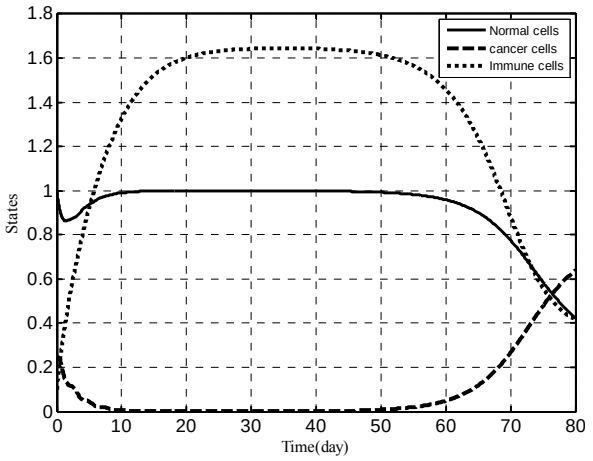


Fig. 7. Patient 2: behavior of the system of equations in presence of new chemotherapy condition

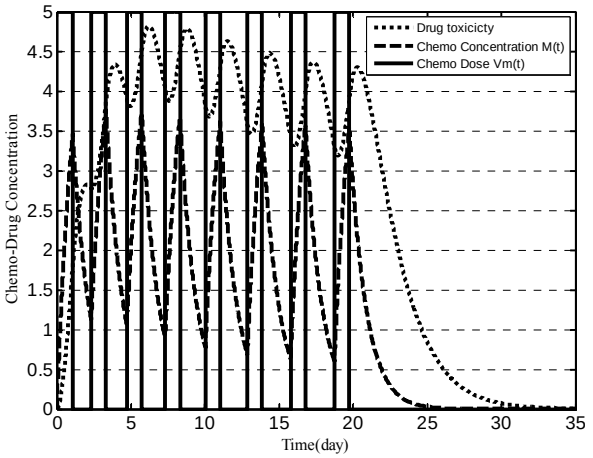


Fig. 8. Patient 2: Drug administration using two conditions extracted from Lyapunov stability theorem and doctor's investigations work

References

[1] Bellomo N. and Prezios Li, "Modeling and mathematical problems related to tumor evolution and its interaction with the immune system," *Mathematical and Computer Modeling*, Vol. 32, pp. 413-452, 2000.

[2] Castiglione F. and Piccoli B., "Optimal Control in a model of dendritic cell transfection cancer immunotherapy," *Bulletin of Mathematical Biology*, Vol. 68, pp. 255–274, 2006.

[3] Bell G. I., "Predator-prey equations simulating an immune response," *Mathematical Biosciences*, Vol. 16, pp. 291-314, 1973.

[4] Aroesty J., Lincoln T., Shapiro N. and Boccia G., "Tumor growth and chemotherapy: Mathematical methods, computer simulations, and experimental foundations," *Mathematical Biosciences*, Vol. 17, pp. 243-300, 1973.

[5] De Boer R. J. and Hogeweg P., "Interactions between macrophages and T-lymphocytes: tumor sneaking through intrinsic to helper T cell dynamics," *Journal of Theoretical Biology,* vol. 120, No. 3, pp. 331–351, 1986.

[6] Kuznetsov V., Makalkin I., Taylor M. and Perelson A., "Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis", *Bulletin of Mathematical Biology,* Vol. 56, No. 2, pp. 295-321, 1994.

[7] Castiglione F. and Piccoli B., "Cancer immunotherapy, mathematical modeling and optimal control," *Journal of Theoretical Biology,* Vol. 247, pp. 723-732, 2007.

[8] De Pillis L. G. and Radunskaya A.E., "A mathematical tumor model with immune resistance and drug therapy: an optimal control approach," *Journal of Theoretical Medicine*, Vol. 3, pp. 79-100, 2001.

[9] De Pillis L. G. and Radunskaya A.E., "Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations," *Journal of Theoretical Biology,* Vol. 238, pp. 841-862, 2005.

[10] Kuznetsov V. and Knott G., "Modeling tumor re growth and immunotherapy," *Mathematical and Computer Modeling*, Vol. 33, pp. 1275-1287, 2001.

[11] Martin R. B., Fisher M.E., Minchin R.F. and Teo K. L., "Optimal control of tumor size used to maximize survival time when cells are resistant to chemotherapy," *Mathematical Biosciences*, Vol. 110, pp. 201-219, 1992.

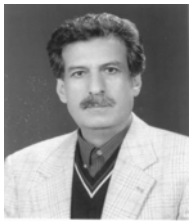
[12] Martin R., and Teo K. L., "Optimal control of drug administration in cancer chemotherapy," *World Scientific*, Singapore, 1993.

[13] Murray J. M., "Optimal control for a cancer chemotherapy problem with general growth and loss functions," *Mathematical Biosciences*, Vol. 98, pp. 273-287, 1990.

[14] Swan G. W., "Role of optimal control theory in cancer chemotherapy," *Mathematical Biosciences*, Vol. 101, pp. 237-284, 1990.

[15] Swierniak A., Ledzewicz U. and Schattler H., "Optimal control for a class of compartmental models in cancer chemotherapy," *International Journal of Applied Mathematics and Computer Science,* Vol. 13, pp. 357-368, 2003.

[16] De Pillis L. G. and Radunskaya A.E., "The dynamics of an optimally controlled tumor model: a case study," *Mathematical and Computer Modeling*., Vol. 37, No. 11, pp. 1221-1244, 2003.



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