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The Optimal Impulsive Drug Schedule for Cancer Immunotherapy

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Abstract: ***The aim of this work is to resolve the problem of finding the optimal therapeutic protocols in cancer immunotherapy including the best dosage and timing of immunotherapy drug. We formulate this problem as an optimization problem by applying the theory of optimal impulsive control using a mathematical model of five ordinary differential equations that describe the kinetics of several populations (tumor cells and three types of immune cells) as well as the intervention of immunotherapy with interleukin2.***

Keywords: immunotherapy. Interleukin-2, impulsive optimal control. drug schedule.

1. Introduction

Mathematical modeling in the field of health, especially oncology, represents now a very rich area of research, it helps to understand the development of cancer and predict its evolution. There are several mathematical models which are, in some cases, validated with experimental results. One distinguishes those that describe the development of the tumor [1]-[9], those representing the interaction with immune cells [10]-[12] and those that consider the intervention of one or more therapies [13]-[17].

One of the most recent approaches to cancer therapy is the immunotherapy, it is based on stimulating the body's defenses against cancer cells with activators such as the interleukin2 (IL2) which is the main cytokine responsible for the activation of lymphocytes. The types of cancers treated in general with immunotherapy by continuous infusion or injections of IL-2, are the renal carcinomas and some types of melanomas. The treatment with IL-2 alone or in conjunction with other therapies has produced beneficial effects in the treatment of metastatic melanoma [18] and metastatic renal cancer [19]. Several lines of evidence suggest that the use of immunotherapy with the cytokine IL-2 can boost the immune system to fight cancer. The use of the interleukin-2 on human and animal immune system was studied by Rosenberg et al.[20], the experiments have demonstrated that IL-2 partially restores the immune deficiencies and immune response, it allows the generation of lymphokine activated killer cell (LAK) and stimulates the activated T cell migration. IL-2 improves also the activity of CTL in different stages of the disease [17],[21]-[23] and promotes CTL proliferation [24], also increases the NK cells cytotoxicity [25]-[27].

Experimental studies on animals [28]-[30] and humans[31] have shown that treatment with maximal dose of IL-2 could produce regression of the tumor, specially the metastatic renal cell carcinoma [32], but it has a variety of toxic effects that limit its use. In contrast, several preclinical studies have suggested that the prolonged administration strategies with low dose of IL-2 might be more effective [33]. The usage of IL-2 with low dose for long time has double benefits; it enhances the antitumor action of IL-2 and at the same time minimizes its toxicity. In Rosenberg et al.[20] trials, the administration of IL-2 at low doses had no side effects and could also lead to the regression of tumor for patients with melanoma and renal carcinoma for different ways of IL-2 administration, only or in combination with the lymphokine activated killer cell (LAK).

The administration of IL-2 depends on the type of cancer and how advanced it is, the type of immunotherapy and how the body reacts to treatment. The optimal administration of IL-2 is unknown, it is generally administrated for metastatic renal cell carcinoma and metastatic melanoma with such that: 600,000 IU/kg (0.037 mg/kg) IV over 15 min every 8h for a maximum of 14 doses, then 9 days of rest, then a maximum of 14 more doses [34].

However, we can define the optimal dosing regimen for IL-2 based on some techniques of optimization such as the optimal control theory which has contributed to the development of treatment strategies against cancer and to achieve different objectives: improving the effectiveness of treatment [35]-[44], to predict the optimal duration of therapy [45], [46] and also to determine the optimal dose that minimizes both the tumor mass and side effects of therapy [15], [47], [48].

The optimal control problem studied in this paper is different from the conventional ones, in one hand we consider a mathematical model of De Pillis et al.[14] consisting of six differential equations describing a continuous evolution in time of tumor and immune cells. In the other hand we define

the control variable, which represents the dosage amount of IL-2, as not continuous in time due to the discrete manner of tacking the IL-2 doses. This has been referred to as hybrid system where the discrete and continuous behaviors are present. In order to solve this problem we formulate it as an impulsive optimal control problem, for which the main goal is to minimize the tumor cells number, then we apply theoretical and numerical methods used in such cases [49]-[51].

2. Model of tumor-immune cells dynamics with therapy intervention

One of the tumor-immune system and therapy intervention model is that developed by de Pillis et al. [14]. The authors in this work update the model of de Pillis et al.[52], to which they added additional cell interaction terms as well as chemotherapy and immunotherapy effects. Using a system of ordinary differential equations, the model describes the kinetics of four populations: tumor cells and three types of immune cells, as well as the chemotherapy and immunotherapy drugs concentrations in the bloodstream.

In this paper we are interested by studying only the interaction of immunotherapy (with IL-2) and tumor-immune cells. For this reason we turn off the chemotherapy by setting $M = 0$, with M is the concentration of chemotherapy drug in the bloodstream. In what follows, the tumor cells are denoted by T, the natural killer cells are denoted by N, the tumor specific T cells (CD8+T) are denoted by L, the Circulating lymphocyte cells are denoted by C and the immunotherapy with IL-2 concentration in the bloodstream is denoted by I.

Tumor cells equation: it is assumed that the tumor cell population grows logistically, $aT(1-bT)$, in the absence of an immune response. The death of tumor cells due to NK cells takes the form $-cNT$, whereas the death due to CD8+T is given by $-DT$. The presence of tumor cells stimulates the NK cells, $g\frac{T^2}{h+T^2}N$, and CD8+T cells, $j\frac{D^2T^2}{K+D^2T^2}L$.

NK cells equation: the source of the NK cell population, eC, is represented as a fraction of the circulating lymphocyte population, a simplification meant to represent the complex cascade of biological events that leads to NK cell stimulation. It's also assumed that a fraction of NK cells die when they have interaction with a tumor cell, this gives the term $-pNT$.

CD8+T cells equation: it's assumed that CD8+T cells have a linear natural death rate, $-mL$, as well as a quadratic death rate, $-uNL^2$. The CD8+T cells may also die through interaction with the tumor and this is represented by a mass action term $-qLT$. Interactions of the tumor with the larger lymphocyte populations, N and C, stimulate CD8+T production, these stimulatory terms are represented by the two positive mass action terms, $-r_1NT$, $-r_2CT$.

The Circulating lymphocytes equation: it's assumed that the Circulating lymphocytes have a constant source term and a linear death rate.

The immunotherapy equation: although naturally produced, the cytokine IL-2 is often used to treat cancer. This model assumes a linear decay rate, additionally, when a CD8+T cells is stimulated by IL-2 it will secrete more IL-2 as represented by $\frac{p_I LI}{g_I + I}$.

All of the model assumptions and parameter values are mentioned in [14].

In the literature [38],[53]-[55], the cancer drugs administration may be considered in different ways, we note in this regard the continuous drug treatment regimens of immunotherapy presented by the control function u(t) which is continuous in time. However, this way is sometimes judged as far from the real way of cancer drugs administration for which only the pulse-dose make sense. In this work, we aim to study an optimal control problem in which the dynamical system involves a finite number of switching times t_i and state jump at each of these switching times. At injection times t_i, $i = 1,2,,...,n$, the IL-2 concentration in bloodstream increases by an amount u_i, $i = 1,2,,...,n$, with n is the total number of IL-2 injections during the treatment period.

For $t \neq t_i$ the tumor-immune dynamics with drugs intervention is given by:

$$\begin{cases} \frac{dT}{dt} = aT(1-bT) - cNT - DT, \\ \frac{dN}{dt} = eC - fN + g\frac{T^2}{h+T^2}N - pNT, \\ \frac{dL}{dt} = -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + (r_1N + r_2C)T \\ -uNL^2 + \frac{p_I LI}{g_I + I}, \\ \frac{dC}{dt} = \alpha - \beta C \\ \frac{dI}{dt} = -\mu_I I \end{cases} \quad (1)$$

With

$$D = d\frac{(L/T)^l}{s+(L/T)^l}$$

At $t = t_i$ the IL-2 concentration in the bloodstream is given by:

$$I(t_i^+) = I(t_i) + u_i \tag{2}$$

Where $I(t_i)$ is the concentration of IL-2 immediately before the injection, $I(t_i^+)$ is the concentration of IL-2 immediately after the injection and u_i is the IL-2 amount at the i^{th} IL-2 injection time t_i, with $i = 1,2,...,n$.

3. Optimal impulsive control problem

We aim to find the optimal strategy of treatment which gives the optimal dosage and timing of injections. To describe this optimal control problem, we reformulate the IL-2 dosing using a control function as the sum of Dirac-delta function at time t_i as follow:

$$U(t) = \sum_{i=1}^{n} u_i \delta_i \tag{3}$$

So, we can rewrite the hybrid system (1)-(2) as

$$\begin{cases} \frac{dT}{dt} = aT(1-bT) - cNT - DT, \\ \frac{dN}{dt} = eC - fN + g\frac{T^2}{h+T^2}N - pNT, \\ \frac{dL}{dt} = -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + (r_1N + r_2C)T \\ -uNL^2 - K_L + \frac{p_I LI}{g_I + I}, \\ \frac{dC}{dt} = \alpha - \beta C \\ \frac{dI}{dt} = -\mu_I I + u(t) \end{cases} \tag{4}$$

The optimal control for cancer immunotherapy has been extensively studied in the literature (see for example [38], [53]-[55]). In these works a continuous control function is used to indicate the continuous dosing of immunotherapy. The study of this optimal control problem is based on some standard theories such as the Pontryangin's maximum principle generally used to find the optimal control u^* in terms of the state and the adjoint variables.

In this paper we are interesting in special class of optimal control problems, called optimal impulsive control problems, in which the dynamical system (4) involves a finite number of switching times t_i, together with a state jump u_i, $i = 1,2,...,n$. The state jumps from being continuous to being discrete when the continuous state trajectory crosses one of the switching times t_i, $i = 1,2,...,n$ [50], [51]. In this case, the optimal control problem may be presented as follow:

Find vector $(\xi^*, u^*) \in R^{2n}$ such as

$$J(\xi^*, u^*) = min_{(\xi,u)\in\Gamma}(\xi, u)$$

Where Γ, the impulsive control variable space and $(\xi, u) = (t_1, t_2, ..., t_n; u_1, u_2, ..., u_n)$ with $t_i = 1,...,n$ indicates the jump times, and $u_i = 1,...,n \geq 0$ the optimal control with state jump.

Each jumping procedure is carried out according to the following schedule:

$S = (\xi, u) = \{(t_i, u_i) : i = 1,...,n, 0 \leq t_1 \leq t_2 \leq ... \leq t_n \leq t_{final},$
$u_i \geq 0\ i = 1,2,...,n\}$

As result, our optimal impulsive control problem may be defined as follows:

Problem (P): Subject to the system (4) with the initial condition $(T_0, N_0, L_0, C_0, I_0)$, find a schedule $S = (\xi, u) \in \Gamma$ such that the total number of tumor cells during the treatment period can be minimized.

$$J(\xi, u) = J(t_1, t_2, ..., t_n, u_1, u_2, ..., u_n) = \int_0^{t\ final} T(t)dt \tag{5}$$

We are looking for an optimal vector
$(\xi^*, u^*) = (t_1^*, t_2^*, ..., t_n^*, u_1^*, u_2^*, ..., u_n^*)$ such that:
$J(\xi^*, u^*) = \min\{J(\xi, u) \mid (\xi, u) \in \Gamma\}$

We can notice that the objective function depends on the injection times $t^*_{i=1,...,n}$ and the dosage amounts $u^*_{i=1,...,n}$, which means that the problem (P) cannot be resolved directly using classical optimization technique. Due to the difficulty to resolve this class of impulsive control problems, Liu et al. [50] have developed a computational method by transforming them into optimal parameter selection problems. We will use this method to resolve our impulsive control problem in the next section.

4. Existence of an optimal solution for problem (P)

In order to use the result of the existence of an optimal solution, theorem III 4.1, from Fleming and Rishel [56], we must cheek that:

- The control variable space Γ is compact.

- The function $S \to J(S)$ is continuous.

As we can see, from the definition of the space Γ, we can deduce that it is compact. To cheek the continuity of the objective function $J(S)$ with respect to the control space S we transform the system (4) to an equivalent system with the control variables $(t_i, u_i), i = 1,...,n$ as parameters, as it is proposed by Liu et al.[50].

Let $X = (T, N, L, C, I)^T$ and rewrite system (4) as:

$$\begin{cases} X'(t) = F(X) + \sum_{i=1}^{n} u_i \delta_i e_5 ; t_0 \le t \le t_{final} \\ X(0) = X_0 = (T_0, N_0, L_0, C_0, I_0) \end{cases} \quad (6)$$

Where $F : \mathbb{R}^5 \to \mathbb{R}^5$ and $e_5 = (0,0,0,0,1)^T$.
We associate for X, the corresponding variable Y such as:

$$Y_{ij} = X_j(t_{i-1} + (t_i - t_{i-1})s); s \in [0,1] \quad (7)$$

Where the index i, $i = 1,...,n+1$ represents the time interval (t_{i-1}, t_i) and j, $j = 1,...,5$ denotes the j^{th} state in system (6), with $t_0 = 0$ and $t_{n+1} = t_{final}$.

We rewrite the system (1) in terms of the equivalent system using a discrete scheme on the index i as follows:

$$\begin{cases} \frac{dY_{i1}}{ds} = (t_i - t_{i-1})[aY_{i1}(1 - bY_{i1}) - cY_{i2}Y_{i1} - DY_{i1}], \\ \frac{dY_{i2}}{ds} = (t_i - t_{i-1})[eY_{i4} - fY_{i2} + g\frac{Y_{i1}^2}{h + Y_{i1}^2}Y_{i2} \\ - pY_{i2}Y_{i1}], \\ \frac{dY_{i3}}{ds} = (t_i - t_{i-1})[-mY_{i3} + j\frac{D^2 Y_{i1}^2}{k + D^2 Y_{i1}^2}Y_{i3} \\ - qY_{i3}Y_{i1} + (r_1 Y_{i2} + r_2 Y_{i4})Y_{i1} \\ - uY_{i2}Y_{i3}^2 + \frac{p_I Y_{i3} Y_{i5}}{g_I + Y_{i5}}], \\ \frac{dY_{i4}}{ds} = (t_i - t_{i-1})[\alpha - \beta Y_{i4}] \\ \frac{dY_{i5}}{ds} = (t_i - t_{i-1})[-\mu_I Y_{i5}] \end{cases} \quad (8)$$

The initial conditions are:
For $i = 1$, $Y_{11}(0) = T_0$, $Y_{12}(0) = N_0$, $Y_{13}(0) = L_0$, $Y_{14}(0) = C_0$, $Y_{15}(0) = I_0$.
For $i \neq 1$ and $j = 2,...,4$, $Y_{ij}(0) = Y_{(i-1)j}(1)$.
$Y_{i5}(0) = Y_{(i-1)5}(1) + u_{i-1}$.

Applying the transformation mentioned in (7) for which $t = t_{i-1} + (t_i - t_{i-1})s), s \in [0,1]$, then the objective function (5) become:

$$\int_0^{t_{final}} T(t)dt = \sum_{i=1}^{n} \int_{t_{i-1}}^{t_i} T(t)dt = \sum_{i=1}^{n} (t_i - t_{i-1}) \int_0^1 Y_{i1}(s)ds \quad (9)$$

We can notice that the continuity of the objective function (5) with respect to the dose time t_i and dose amount u_i is equivalent to the continuity of the transformed function (9) with respect to t_i and u_i. The continuity of Y_{i1} with respect to t_i and u_i is obtained due to the continuity of solutions of (8), which gives the continuity of the objective function (5) with respect to t_i and u_i and implies the existence of an optimal solution for Problem (P).

5. Computational Method

Now, we utilize a generalized variational equation to calculate the derivatives of the objective function with respect to t_i and u_i and then apply the gradient based methods to search for the minimum of the objective function. The gradient of the objective function (5) with respect to the dose times t_i and dose amount u_i are resolved using the following propositions.

Proposition 1 Consider IL-2 injection at time t_i with dose amount u_i. For $t \ge t_i$, $(u_1(t),...,u_5(t), z(t))$ with $u = (u_1,...,u_5)$ solves the following equations:

$$\begin{aligned} &\frac{du}{dt} = \nabla_X F(X(t)).u(t), \\ &\frac{dz}{dt} = \nabla_X L(X(t)).u(t), \\ &u(t_i) = F(X(t_i)) - F(X(t_i) + u_i e_5), \\ &z(t_i) = L(X(t_i)) - L(X(t_i) + u_i e_5), \end{aligned} \quad (10)$$

and

$$z(t_{final}) = \frac{\partial X_6(t_{final})}{\partial t_i} = \frac{\partial J}{\partial t_i}.$$

With

$$L(X(t)) = T(t),$$
$$\frac{dX_6(t)}{dt} = L(X(t)), \forall t \in [0, t_{final}]$$
$$X_6(t_{final}) = J = \int_0^{t_{final}} T(t)dt, \quad X_6(0) = 0.$$

The formulation of the lagrange problem is presented in Lemma 4.1 in [49].

Proposition 2 Consider IL-2 injection at time t_i with dose amount u_i. For $t \geq t_i$, $(U_1(t),...,U_5(t),Z(t))$ with $U=(U_1,...,U_5)$ solves the following equations:

$$\begin{aligned}
&\frac{dU}{dt} = \nabla_X F(X(t)).U(t),\\
&\frac{dZ}{dt} = \nabla_X L(X(t)).U(t),\\
&U(t_i) = e_5,\\
&Z(t_i) = 0,
\end{aligned} \tag{11}$$

and

$$Z(t_{final}) = \frac{\partial X_6(t_{final})}{\partial u_i} = \frac{\partial J}{\partial u_i}.$$

These two propositions give us the calculation of the partial derivatives $\frac{\partial J}{\partial t_i}$ and $\frac{\partial J}{\partial u_i}$ which represent the basic elements for the numerical solution of the optimal control problem (P).

6. Numerical simulation

We will resolve our problem using the following optimization algorithm:

Step 0:

- Fix the final time t_{final}, and the number of injections n
- Initialize the variables T, N, L, C, I, and the schedule $(t_1^0,t_2^0,...,t_n^0,u_1^0,u_2^0,...,u_n^0)$.

For $i=1,...,n$

Step 1: Solve the system (1) via the fourth-order Runge-Kutta method. At the same time, solve the equations (10) and (11).

Step 2: Compute the gradient of the objective function with respect to t_i and u_i.

Step 3: Update the schedule using the steepest decent method as follow:

$$t_i^{k+1} = t_i^k + h_t \frac{\partial J}{\partial t_i},\ u_i^{k+1} = u_i^k + h_u \frac{\partial J}{\partial u_i}.$$

Where k is the iterations, and h_t and h_u are small positive parameters. Go to step 0.

Each iteration corresponds to one day. The initial condition of the first time t_0^1, expressed in days, is considered to be equal to 5 day as the initial day of starting treatment. Knowing that IL-2 is usually administered in 5-day cycles [57] all the next initial conditions of converged injections times t_i^0, $i=2,...,n$ follow the rule of the following iterative scheme:

$$t_{i+1}^0 = t_{i=1...,n-1}^0 + t_1^0$$

For the number of doses $n=5$ the computational method converges to five dose times. The first dose time converges from 5 days to 7 days, the second increases from 10 days to 12 days, the third converges from 15 days to 18 days, the fourth one converges from 20 days to 23 days and finally the last one increase from 25 days to 27 days. This is illustrated in Figure 1(a).

The numerical simulations indicate that if the IL-2 is administered one, two or three times ($n=1,2,3$), the treatment cannot be efficient in tumor eradication. While, for $n=4$ we have noticed that the number of tumor cell population become to decrease and this number decreases remarkably for $n=5$. Further noticed is that for $n>5$ we have obtained the same result as $n=5$. For this reason we will consider in the rest of our simulations five injections of IL-2.

As it is noticed in Figure 1(b), the doses of the five injections increase from the same value $u_i = 72{,}000 IU/kg$, $i=1,...,5$ and finish up converging to different dosages. The dose of the first and the second injection converge to alike low amount $\approx 7.2\times10^4\, IU/kg$ it is noticed that the second injection dose is a little higher than the first one. The third injection dose increases to $2.3\times10^5\, IU/kg$, the fourth injection dose converges to $5\times10^5\, IU/kg$ and finally the last one increases to a high level $6.8\times10^5\, IU/kg$ which is cannot be considered as high amount (the high amount used in Rosenberg et al.[19] is 7.2×10^5 IU/kg). The third and the fourth injection are administered for longer time than the first, the second and the five.

We present in Figure 2 and Figure 3 the tumor cell population's evolution as well as the evolution of NK cells, CD8+T cells and the Circulating lymphocytes before starting the therapy and after administering the IL-2. The Figure 2 shows the evolution over time of the tumor and immune cell populations calculated via the numerical solution of the system (1) when no treatment is administered. We examine an initial tumor burden of 10^7 cells, we notice that the immune system is unable to respond very well, which explains the increasing number of tumor cells that grow to a dangerous level. We can see the immunologic effects of growing tumor on immune cells.

The Figure 3 presents plots of the tumor cell population and immune cell population in the presence of immunotherapy intervention. A situation for which the cancer is large enough and considered potentially detectable. By using the optimal schedule obtained in Figure 1, the tumor mass of 10^7 cells decreases remarkably under the quarter of the initial size.

The optimal strategy suggests that the best way to control tumor cell population is to start with low doses of IL-2 and to increase the dose gradually in order to prepare the body for

receiving high dose of IL-2. The use of repeated low doses of IL-2 (the fist and the second dose) from 5 days to 7 days and from 10 days to 12 days reduce the tumor cells number as it is presented in Figure 4(a) and increase the number of CTL cells as it is shown in Figure 4(b) we can notice that this number has risen from the initial value 10 to 2×10^{11} after the second injection in day 10. This may be explained by the stimulating effect of IL-2 on CTL cells which active their proliferation and augment their number [17], [21]-[24].

We can also notice that the number of NK cells decreases too fast before starting therapy and diminished gradually after the first and the second injection, this is may be explained by the strategy of NK cells to kill the cancerous cells. Before the IL-2 injection, the NK cells intervene to destroy tumor cells and they are destroyed along with them which explain the significant decrease. After the first and second dose, the IL-2 increases the cytotoxicity of NK cells [25]-[27], they don't die along with tumor cell in their first contact but they adopt such a competence to destroy more than one cancerous cell.
The patient's immunological health is measured by the number of circulating lymphocytes which should not drop below a threshold. This threshold is considered to be in the order of 10^8 cells (see [58]).

The stimulated effect of IL-2 on immune cells leads to decrease the number of tumor cells after the second injection in day 10, the third injection in day 15, the fourth injection in day 20 and the last high injection dose in day 25. After the last injection, we can remark as it is shown in Figure 4(d) that the tumor cells number decrease by coming close to the day 100, which explains the decreasing number of CTL cells. In addition, the circulating lymphocytes number doesn't drop below the defined threshold, as it is presented in Figure 3, which means that the patient's body is responding positively to the therapy without noticing any significant toxicity.

7. Conclusion

The problem of finding an optimal schedule for immunotherapy with IL-2 is studied in this work by formulating it as an impulsive optimal control problem for which the results provide us with some elements of answer to the questions: when it is advantageous to take the IL-2 dose? and how much of IL-2 should be taken?

The model used in this paper is that developed by De Pillis et al. [14] using a system of ordinary differential equations. This model describes the kinetics of four populations: tumor cells and three types of immune cells, as well as the IL-2 drug concentrations in the bloodstream.

The case of continuous administration of IL-2 using this same model has been studied in Zouhri et al. [48], their numerical simulations show that the immunotherapy with IL-2 administered alone for tumor burden of 10^6 cells was capable to reduce remarkably the tumor cell number, the optimal treatment consists of giving the entire high dose of IL-2 $\approx 5\times10^6$ at the beginning of the treatment then the IL-2 is turned off. In contrast, this same administration of IL-2 was not effective neither in killing tumor of size 10^7 cells nor in reducing the cancerous cell number.

The impulsive optimal control approach applied in this work has allowed administering the IL-2 in discrete manner. The numerical simulations are generated using a computational method which combines a fourth order Runge-Kutta scheme with an optimization method. The results show that for five injections (n=5) and five injection times a tumor size of 10^7 is reduced under the quarter of its initial size. The dosage program recommends to start with low doses of IL-2, in order to stimulate the activity of CTL and NK cells, then to increase progressively the dose until reaching a high dose.

Through the decreasing number of Tumor cells and CTL cells and the number of the circulating lymphocytes which has not dropped below the threshold (Figure 3), it's is deduced that this high dose has no toxicity effects and the dosage program was efficient in tumor size minimization.

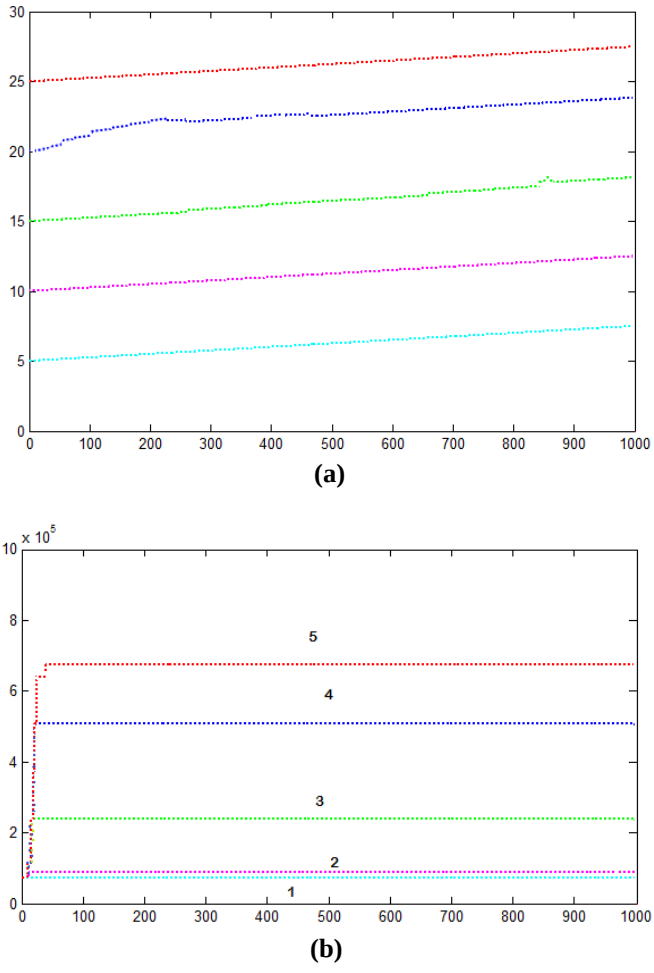


Figure 1: The evolution of the optimal schedule over time. a) Evolution of the five injection times. b) Evolution of the five injections amounts.

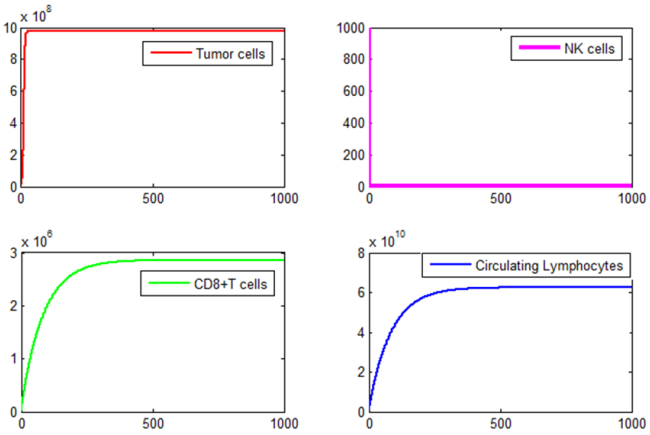


Figure 2: Tumor and immune cell populations over time when no treatment is administered. Initial conditions: 10^7 Tumor cells, 10^3 NK cells, 10 $CD8^+T$ cells, 6×10^8 circulating lymphocytes.

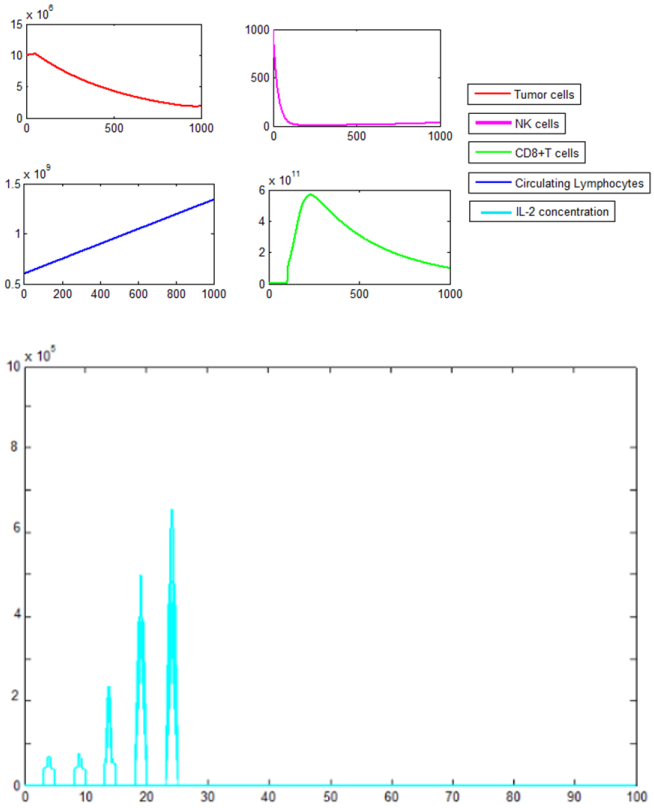
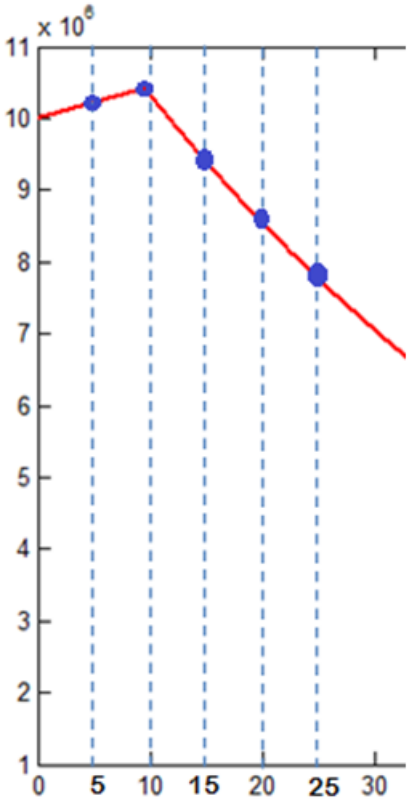
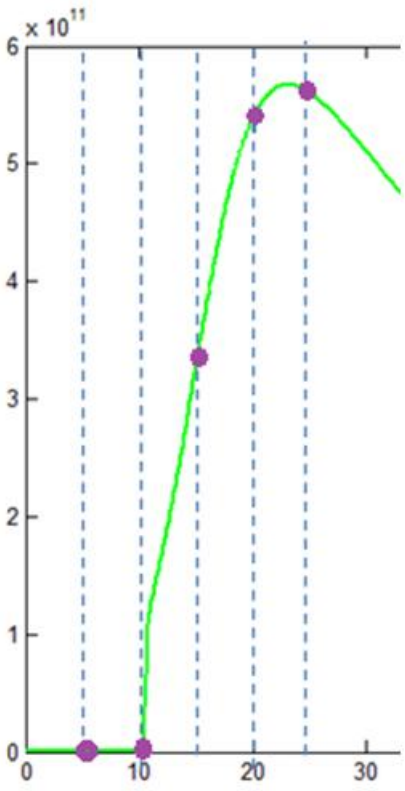


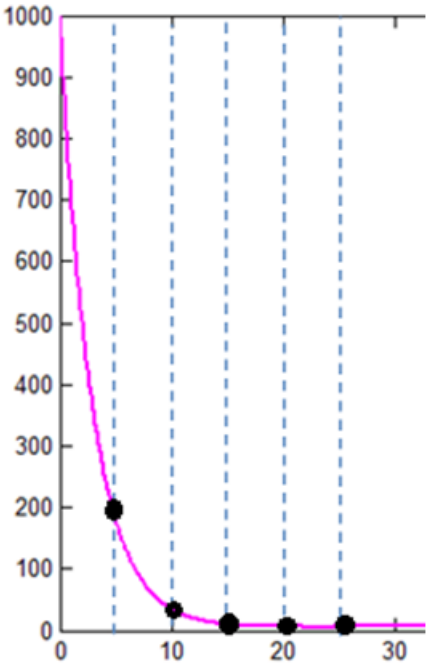
Figure 3: Tumor and immune cell populations over time when IL-2 is administered. Initial conditions: 10^7 Tumor cells, 10^3 NK cells, 10 $CD8^+T$ cells, 6×10^8 circulating lymphocytes, IL-2 dosage equals to 7.2×10^4 IU/kg injected in day 5, $7.6\times10^4\,IU/kg$ injected in day 10, $2.3\times10^5\,IU/kg$ injected in day 15, $5\times10^5\,IU/kg$ injected in day 20 and $6.8\times10^5\,IU/kg$ injected in day 25



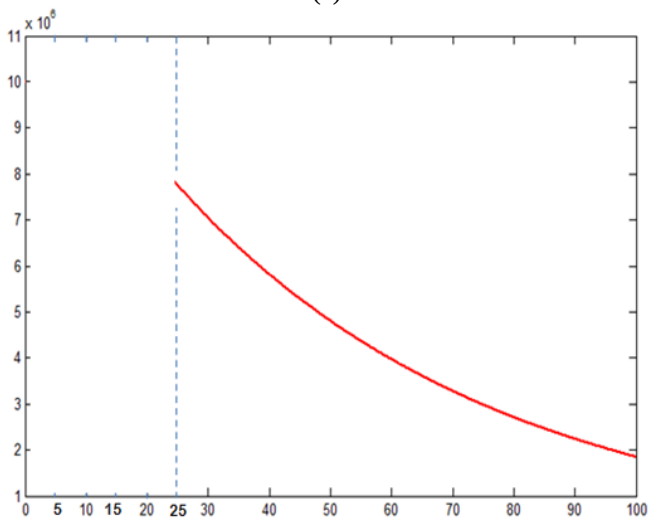
(a)



(b)



(c)



(d)

Figure 4: Shapes of curves: a) and d) the tumor cell population before and after the last injection respectively. b) the CD8+T cells evolution and c) the NK cells evolution during the therapy for a dosage equals to 7.2×10^4 IU/kg injected in day 5, $7.6\times10^4\,IU/kg$ injected in day 10, $2.3\times10^5\,IU/kg$ injected in day 15, $5\times10^5\,IU/kg$ injected in day 20 and $6.8\times10^5\,IU/kg$ injected in day 25.

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