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Modeling Multi-Mutation And Drug Resistance: A Case of Immune-Suppression

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Abstract

A model that takes into account multi-mutation and drug resistance in a case of simple immune system and immune-suppression caused by drug resistant tumor cells is proposed. Since methods for revising therapeutic approaches (immunotherapy and chemotherapy) during cancer treatment are still being explored, we analyzed mathematically and simulated numerically with the aid of MATLAB software the corresponding tumor-immunotherapy model to determine the effectiveness of the immunotherapy. Through the mathematical analysis, the existence, the uniqueness and the boundedness of solutions are shown. The non-tumor states are stable, under conditions only in the presence of the immunotherapy drug and in the absence of the drug resistant tumor cells. The numerical results show the behavior of the tumor cells and immune system cells in the absence and in the presence of the immunotherapy drug. This study provides an efficient treatment strategie to cancer in the absence and in the presence of the drug resistant tumor cells.

AMS subject classification:
Keywords: Cancer modeling, Drug resistance, Mutation, Immune system, Immunotherapy, Immune-Suppression, Chemotherapy.

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1. Introduction

Cancer is a disease characterized by the uncontrolled proliferation of cells, linked to an escape from the regulation mechanisms that ensures the harmonious development of our organism. By multiplying anarchically, they cause increasing tumors that develop by invading and destroying the surrounding areas (organs). By destroying its environment, cancer can become a real danger to the survival of the living being. There are several types of cancer treatments: surgery, chemotherapy, targeted therapies, radiotherapy immunotherapy and hormone therapy. Surgery and radiotherapy are local treatments while chemotherapy and hormone therapy act throughout the body. The Immunotherapy is a type of treatment that helps the immune system fight cancer. The most common therapeutic approach to reduce the population of cancer cells and control their progression is some combination of the chemotherapy and immunotherapy [1]. However, on several occasions, the success of this treatment has failed due to the lack of knowledge of the type of tumor cells that can be created during cell division, the effects that these tumors can have on the immune system [2] and how the combination should be made. To improve the therapeutic approach according to the type and proliferation of tumor cells, a lot of research has been done. Feizabadi & Witten [3] introduced a model to study the behavior of tumor and normal cells during a course of chemotherapy. Feizabadi & Witten [1] added the effects of a simple immune system and immunodeficiency. Before that, Kirschner & Panetta [4] modeled immunotherapy of the tumor-immune interaction, explored the effects of adoptive cellular immunotherapy on the model and described under what circumstances the tumor can be eliminated. This model of Kirschner & Panetta [4] has been globally and analytically explored by Kirschner & Tsygvintsev [5] to show under what conditions tumor clearance can be achieved. The proliferation of cancer cells depends on many factors including, but not limited to, cell growth rate, mutual interaction of cancer cells with surrounding normal cells, immune system response to cancer treatment strategies. This also depends on the mutations that may occur during cell division, which results in the inapplicability of chemotherapeutic treatments. Drug-induced resistance is a signifcant challenge faced by scientists nowadays and is one of the main obstacles that can lead to therapeutic failure during cancer treatment. Different genetic alterations occur when the responsive tumor cells divide. Among the new generations of tumor cells, we have the tumor cells that are still responsive to the chemotherapy drug and are know as wild tumor cells, denoted by T. Some can express an intrinsic resistance to a specific chemotherapeutic agent [6]. These are the resistant tumor cells denoted by T_R. In addition, some tumor cells may carry a gene that can develop resistance induced by the chemotherapeutic drug [2]. These are the mutated tumor cells that are also responsive to the chemotherapy drug, but carry a mutated gene that causes drug resistance as they interact with the chemotherapy drug. They are denoted by T_M. The methods by which therapeutic approaches need to be revised in the occurrence of drug-induced resistance are still being explored. Because of that, Feizabadi & Witten [6] previously modified the model of [3] in order to make only a distinction between tumor cells that are responsive to chemotherapy and those that may show intrinsic drug resistance. Feizabadi [2] expanded the last model to include terms that can express both intrinsic drug

resistance and drug-induced resistance (multi-mutations). He analyzed the response of the cell population according to different treatment strategies and discussed the results. The effects of a simple immune system and of the immune-suppression caused by drug resistant tumor cells are not yet considered in [2]. Therefore, in this paper a model that take into account these multi-mutations and effects is proposed and an efficient treatment strategy in this case is identified. The rest of the paper is organized as follows. Section 2 presents the model formulation. Section 3 presents a mathematical analysis and the numerical simulations of the corresponding tumor-immunotherapy model, to determine the effectiveness of the immunotherapy. Section 4, presents the conclusion of the study.

2. Model Formulation

Here, we add the concepts of the interaction of the immune system established by [4] and of the immune-suppression established by [1] to the core model of [2]. As explained in [4], two variables are considered to be the main immune system components: the activated immune-system cells (effector cells) including T-cells and other immune cells that are cytotoxic to tumor cells, denoted by E and the concentration of IL-2, which is the main cytokine responsible for T-cells activation, growth and differentiation at the tumor site. This variable is denoted by I. While in [1] the immune-suppression factors was the viruses, In this study we assume that the immune system cannot distinguish between the responsive and the resistance tumor cells, so it acts on all the tumor cells. However the resistant tumor cells are not affected by the action of the effector cells. That is the effector cells affect only the drug-sensitive tumor cells and the mutated tumor cells, but not the resistant tumor cells. Thus the immune-suppression factors are assumed to be the resistant tumor cells. These resistant tumor cells infect the activated immune cells. As a result of this infection, the population of activated immune cells decrease and this leads to a weakened immune system. In such a case, the treatment will consist of immune boosting drugs (immunotherapy). Indeed, many approaches can be implemented to control cancer progression, among them chemotherapy, immunotherapy or some combination of both. The enhancement of the immune system by immunotherapeutic agents that directly boost the number of effector cells has a key role in the reduction of the number of tumor cells. Chemotherapeutic agents can kill the tumor population in a dose-dependent manner [7, 8]. Chemotherapeutic agents are cytotoxic not only to responsive tumor cells, but also to normal and activated-effector cells as well [1]. All of the tumor cells are assumed to grow under the logistic law. The schematic view of the system describing the interations between the immune system cells (E) and (I), wild tumor cells (T), mutated tumor cells (T_M), drug resistant tumor cells (T_R) and normal cells (N) is expressed in figure 1.

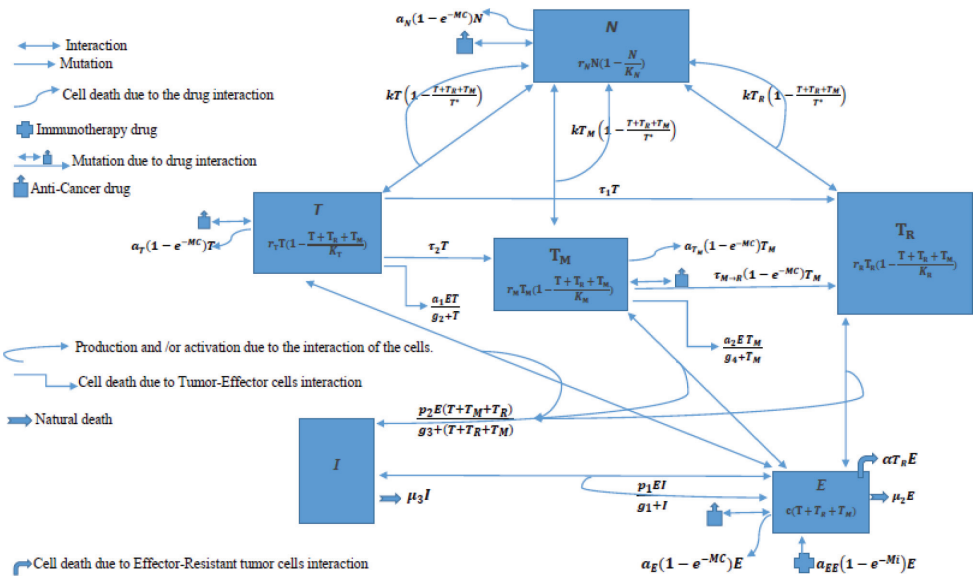


Figure 1: The schematic view of the system interactions. The system includes 5 types of cells: normal cells (N), wild tumor cells (T), mutated tumor cells (T_M), drug resistant tumor cells (T_R), and effector cells (E). (I) represents the concentration of IL-2. The population of normal, wild tumor, mutated tumor and effector cells decreases as they interact with the chemotherapy drug. As the wild tumor cells divide, they can create mutated tumor cells and/or resistant tumor cells. As the mutated tumor cells interact with the chemotherapy drug, they can partially die and partially be transformed to resistant cells induced by the utilized anti-cancer drug. The population of effector cells decreases as they interact with the Resistant tumor cells. This leads to a weakened immune system and in such a case, the treatment consists of immune boosting drugs (immunotherapy). The population of wild tumor, mutated tumor cells decreases as they interact with the effector cells. The effector cells are activated as they interact with the IL-2. Also IL-2 are activated as the effector cells interact with the tumor cells. Naturally, some of immune system cells die.

The dymanic of the system (proposed model) can be expressed as follow:

$$
\begin{aligned}
\frac{dT(t)}{dt} &= r_T T\big(1-\frac{T+T_R+T_M}{K_T}\big)-(\tau_1+\tau_2)T-\frac{a_1 ET}{g_2+T}-a_T(1-e^{-MC})T;\\
\frac{dT_R(t)}{dt} &= r_R T_R\big(1-\frac{T+T_R+T_M}{K_R}\big)+\tau_1 T+\tau_{M\to R}(1-e^{-MC})T_M;\\
\frac{dT_M(t)}{dt} &= r_M T_M\big(1-\frac{T+T_R+T_M}{K_M}\big)+\tau_2 T-\frac{a_2 ET_M}{g_4+T_M}-a_{T_M}(1-e^{-MC})T_M-\tau_{M\to R}(1-e^{-MC})T_M;\\
\frac{dN(t)}{dt} &= r_N N\big(1-\frac{N}{K_N}\big)+k(T+T_R+T_M)\big(1-\frac{T+T_R+T_M}{T^*}\big)-a_N(1-e^{-MC})N;\\
\frac{dE(t)}{dt} &= c(T+T_R+T_M)-\mu_2 E+\frac{p_1 EI}{g_1+I}-\alpha ET_R-a_E(1-e^{-MC})E+a_{EE}(1-e^{-Mi})E;\\
\frac{dI(t)}{dt} &= \frac{p_2 E(T+T_R+T_M)}{g_3+(T+T_R+T_M)}-\mu_3 I;\\
T(0) &= T_0,\ T_R(0)=T_{R_0},\ T_M(0)=T_{M_0},\ N(0)=N_0,\ E(0)=E_0,\ I(0)=I_0.
\end{aligned}
\tag{1}
$$

Where $N(t), T(t), T_M(t)$ and $T_R(t)$ are respectively the total number at a time t; of normal cells, wild tumor cells, mutated tumor cells and drug-resistant tumor cells with the unit of cells. All of these tumor cells are assumed to grow under the logistic law. Also, K_N, K_T, K_M and K_R are the carrying capacity of normal cells and the three types of tumor cells with the unit of cells. The per capita growth rate for the drug-responsive tumor cells, mutated tumor cells, drug-resistant tumor cells, and normal cells are expressed by r_T, r_M, r_R, r_N with the unit of $(time^{-1})$. The T^* is the critical size of the collection of tumor cells with the unit of cells. The second term in the fourth equation represents the interaction between tumor and normal cells. This interaction is chosen as a logistic growth function [3]. In this term k with the units of $(time^{-1})$ represent the tumor-normal cell interaction rate. The term $\tau_1 T$ in first two equations expresses the transition of wild tumor cells (responsive tumor cells) to intrinsically resistant tumor cells with a mutation rate of $\tau_1(time^{-1})$. The term $\tau_2 T$ in the first and the third equations represents the transition of wild tumor cells to mutated tumor cells with a mutation rate of $\tau_2(time^{-1})$. The effector cells are stimulated to grow based on two terms: One is a recruitment term $c(T+T_R+T_M)$ due to the direct presence of the tumor, where the parameter c models the antigenicity of the tumor. Antigenicity can be thought of as a measure of how different the tumor is from 'self'. The second is due to the presence of IL-2 hormones and is given by the term $\frac{p_1 EI}{g_1 + I}$ [4]. This is of Michaelis-Menten form to indicate the saturated effects of immune reponse. p_1 is the proliferation rate of immune cells and g_1 is the half-saturation for the proliferation term. To express the natural death of effector cells, the term $-\mu_2 E$ is added. In this term μ_2 is the death rate of the immune cells. The change in concentration of IL-2 is expressed as: $\frac{p_2 E(T + T_R + T_M)}{g_3 + (T + T_R + T_M)}$, which is the activation due to the presence of the tumor. In this term, p_2 is the production rate of the effector molecules and g_3 is the half-saturation of production. $-\mu_3 I$, is the natural loss of IL-2 by the rate of μ_3. The infection of the effector cells by the resistant tumor cells reduce the size of the populations of the effector cells. This is expressed as: $-\alpha E T_R$ with α the infection rate. The loss of tumor cells, due to the immune-effector cells can be characterized with the Michaelis-Menten interaction terms: $\frac{a_1 ET}{g_2 + T}$ on wild tumor cells [1] and $\frac{a_2 ET_M}{g_4 + T_M}$ on mutated tumor cells . Here, a_1 is the rate of clearance of wild tumor cells as a result of these two populations and g_2 is the half-saturation for wild tumor cells clearance. a_2 is the rate of clearance of mutated tumor cells as a result of these two populations and g_4 is the half-saturation for mutated tumor cells clearance. As suggested by Gardner [9] the drug interaction may be structured as $a_\phi(1 - e^{-MC})\phi$. Here ϕ is the cell population number. The parameter C is the concentration or amount of the drug at the tumor site at a specific time with the unit $(mg.m^{-2})$. M is associated to the drug pharmacokinetics and known as the drug efficiency coefficient with the unit of $(m^2.mg^{-1})$. The coefficient a_ϕ when $\phi = N, T, T_M$ and E with the unit of $(time^{-1})$ expresses the death rate induced by the administered chemotherapeutic drug. The function $F(C) = a_\phi(1 - e^{-MC})$ is the fraction cell kill for a given amount (concentration) of drug "C". Thus the toxic effect of the administered drug, which leads to the reduction in populations of cells, has been

expressed by $a_T(1-e^{-MC})T$ on wild tumor cells, by $a_N(1-e^{-MC})N$ on normal cells and by $a_E(1-e^{-MC})E$ on effector cells. The interaction of the drug with the mutated tumor cells partially kills them and partially turns them into drug-resistant tumor cells. The toxic effect of the drug on the mutated tumor cells has been expressed as $a_{T_M}(1-e^{-MC})T_M$. The term that expresses the conversion of mutated tumor cells to drug-resistant tumor cells has been expressed by $\tau_{M\to R}(1-e^{-MC})T_M$. In this term $\tau_{M\to R}$ with the unit of $(time^{-1})$ expresses the conversion rate from mutated tumor cells to resistant tumor cells due to interaction with the drug. Additionally, the immunotherapeutic agent is described by the term $a_{EE}(1-e^{-Mi})E$ and it acts as an immune-boosting agent.

Results and discussion

3. Mathematical analysis and numerical simulations of the corresponding tumor-immunotherapy model

Taking the model (1) without its fourth equation and without all the chemotherapy terms as well as the third term of its second equation, we obtain the corresponding tumor-immunotherapy model of (1) as follows:

$$\left.\begin{aligned}
\frac{dT(t)}{dt} &= r_T T\big(1-\frac{T+T_R+T_M}{K_T}\big)-(\tau_1+\tau_2)T-\frac{a_1ET}{g_2+T};\\
\frac{dT_R(t)}{dt} &= r_R T_R\big(1-\frac{T+T_R+T_M}{K_R}\big)+\tau_1 T;\\
\frac{dT_M(t)}{dt} &= r_M T_M\big(1-\frac{T+T_R+T_M}{K_M}\big)+\tau_2 T-\frac{a_2ET_M}{g_4+T_M};\\
\frac{dE(t)}{dt} &= c(T+T_R+T_M)-\mu_2E+\frac{p_1EI}{g_1+I}-\alpha ET_R+a_{EE}(1-e^{-Mi})E;\\
\frac{dI(t)}{dt} &= \frac{p_2E(T+T_R+T_M)}{g_3+(T+T_R+T_M)}-\mu_3 I;\\
T(0)&=T_0,\ T_R(0)=T_{R_0},\ T_M(0)=T_{M_0},\ E(0)=E_0,\ I(0)=I_0.
\end{aligned}\right\} \tag{2}$$

3.1. Existence and uniqueness of the solution

Definition 3.1. [10] A function $F:\mathbb{R}^n\longmapsto\mathbb{R}^n$ is said to be continuously differentiable at $a\in\mathbb{R}^n$, if all the partial dervatives of F exist near and at a, and each is continuous at a. If F is continuously differentiable at each point in its domain, then we say simply that ' F is continuously differentiable ' (or ' C^1 ' for short).

- All the polynomial functions are C^1 in their domain.
- If f_1 and f_2 are C^1 in U and $\forall a\in U;\ f_2(a)\neq 0$, then $\dfrac{f_1}{f_2}$ is C^1 in U

The Existence and Uniqueness Theorem [10]: Consider the initial value problem $\frac{dX}{dt} = F(X); X(t_0) = X_0$ where $X_0 \in \mathbb{R}^n$. Suppose that $F : \mathbb{R}^n \longmapsto \mathbb{R}^n$ is C^1. Then, first of all, there exists a solution of this initial value problem and, secondly, this is the only such solution. More precisely, there exists an $\eta > 0$ and an unique solution $X : (t_0 - \eta; t_0 + \eta) \longmapsto \mathbb{R}^n$ of this differential equation satisfying the initial condition $X(t_0) = X_0$.

A solution of (2) is a function $X : t \in J \subset \mathbb{R} \longmapsto X(t) = \begin{pmatrix} T(t) \\ T_R(t) \\ T_M(t) \\ E(t) \\ I(t) \end{pmatrix} \in \mathbb{R}^5$

Let $F : X \in \mathbb{R}^5 \longmapsto F(X) \in \mathbb{R}^5$ with

$$F(X) = \begin{cases} r_T T\big(1 - \dfrac{T + T_R + T_M}{K_T}\big) - (\tau_1 + \tau_2)T - \dfrac{a_1 E T}{g_2 + T} \\ r_R T_R\big(1 - \dfrac{T + T_R + T_M}{K_R}\big) + \tau_1 T \\ r_M T_M\big(1 - \dfrac{T + T_R + T_M}{K_M}\big) + \tau_2 T - \dfrac{a_2 E T_M}{g_4 + T_M} \\ c(T + T_R + T_M) - \mu_2 E + \dfrac{p_1 E I}{g_1 + I} - \alpha E T_R + a_{EE}(1 - e^{-Mi})E \\ \dfrac{p_2 E(T + T_R + T_M)}{g_3 + (T + T_R + T_M)} - \mu_3 I \end{cases}$$

The system (2) becomes $\frac{dX}{dt} = F(X); X(0) = X_0 = \big(T_0; T_{R_0}; T_{M_0}; E_0; I_0\big)^T$.

F is C^1 in its domain. Then, first of all, there exists a solution of this initial value problem and, secondly, this is the only such solution. More precisely, there exists an unique solution of this differential equation satisfying the initial condition $X(0) = X_0$.

3.2. Positivity and boundedness of the solution

Let $T_0; T_{R_0}; T_{M_0}; E_0$ and I_0 be non negative. Since $T(t); T_R(t); T_M(t); E(t)$ and $I(t)$ are respectively the number of cells and the concentration of IL-2 at time t, then, $T(t); T_R(t); T_M(t); E(t)$ and $I(t)$ are non negative for all $t > 0$.

Lemma 3.2. If $T_0; T_{R_0}; T_{M_0}; E_0$ and I_0 are non negative, then $T(t); T_R(t); T_M(t); E(t)$ and $I(t)$ are non negative for all $t > 0$.

Lemma 3.3. Let $K = max\{K_T; K_R; K_M\}$ and $r = max\{r_T; r_R; r_M\}$. All feasible solutions of the system (2) are bounded and enter the region:

$$\Omega = \Big\{\big(T(t); T_R(t); T_M(t); E(t); I(t)\big) \in \mathbb{R}^5_+ : E(t) \leqslant 3K;$$
$$T(t) + T_R(t) + T_M(t) + E(t) + I(t) \leqslant \frac{3K(r + c + 2\mu_3 + p_1 + p_2 + a_{EE} - \mu_2)}{\mu_3}\Big\}$$

Proof. Let $P(t) = T(t) + T_R(t) + T_M(t) + E(t) + I(t), K = max\{K_T; K_R; K_M\}, r = max\{r_T; r_R; r_M\}$ and $\big(T(t); T_R(t); T_M(t); E(t); I(t)\big) \in \mathbb{R}^5_+$ be any solution with positive initial condition.

- Taking the fourth equation of the model (2), we have:

$$\begin{aligned}
\frac{dE(t)}{dt} &= c(T + T_R + T_M) - \mu_2 E + \frac{p_1 EI}{g_1 + I} - \alpha E T_R + a_{EE}(1 - e^{-Mi})E \\
&\leqslant c(K_T + K_R + K_M) + p_1 E + a_{EE} E \\
&\leqslant 3cK + (p_1 + a_{EE})E \\
&\leqslant 3K + (p_1 + a_{EE})E,
\end{aligned}$$

because $0 < c < 1$.
Integrating and applying the initial condition $E(0) = E_0$ result to $E(t) \leqslant 3K - (3K - E_0)e^{(p_1 + a_{EE})t}$.
Since $3K - E_0 > 0$, then we get that $E(t) \leqslant 3K$.

- Adding the five equations of the model (2), we have:

$$\begin{aligned}
\frac{dP(t)}{dt} &= r_T T\big(1 - \frac{T + T_M + T_R}{K_T}\big) + r_R T_R\big(1 - \frac{T + T_R + T_M}{K_R}\big) \\
&\quad + r_M T_M\Big(1 - \frac{T + T_R + T_M}{K_M}\Big) \\
&\quad + c(T + T_R + T_M) + \frac{p_1 EI}{g_1 + I} + \frac{p_2 E(T + T_R + T_M)}{g_3 + (T + T_R + T_M)} \\
&\quad + a_{EE}(1 - e^{-Mi})E - \Big(\frac{a_1 ET}{g_2 + T} + \frac{a_2 ET_M}{g_4 + T_M} + \mu_2 E + \alpha E T_R + \mu_3 I\Big) \\
&\leqslant r_T T + r_R T_R + r_M T_M + c(T + T_R + T_M) + p_1 E + p_2 E \\
&\quad + a_{EE} E - (\mu_2 E + \mu_3 I) \\
&= (r + c + \mu_3)(T + T_R + T_M) + (p_1 + p_2 + a_{EE} - \mu_2 + \mu_3)E - \mu_3 P \\
&\leqslant 3K(r + c + 2\mu_3 + p_1 + p_2 + a_{EE} - \mu_2) - \mu_3 P(t)
\end{aligned}$$

It follows that

$$\begin{aligned}
0 < P(t) &\leqslant \frac{3K(r + c + 2\mu_3 + p_1 + p_2 + a_{EE} - \mu_2)}{\mu_3} \\
&\quad + \big(P(0) - \frac{3K(r + c + 2\mu_3 + p_1 + p_2 + a_{EE} - \mu_2)}{\mu_3}\big)e^{-\mu_3 t},
\end{aligned}$$

where $P(0)$ represents initial value of the total population. Thus $0 < P(t) \leqslant \frac{3K(r + c + 2\mu_3 + p_1 + p_2 + a_{EE} - \mu_2)}{\mu_3}$ as $t \longrightarrow \infty$. Therefore all feasible

solutions of system (2) enter the region

$$\Omega = \Big\{\big(T(t); T_R(t); T_M(t); E(t); I(t)\big) \in \mathbb{R}^5_+ : E(t) \leqslant 3K;$$
$$T(t) + T_R(t) + T_M(t) + E(t) + I(t) \leqslant \frac{3K(r + c + 2\mu_3 + p_1 + p_2 + a_{EE} - \mu_2)}{\mu_3}\Big\}$$

i.e. any trajectory of the system (2) starting from an initial state in Ω remains in Ω. Also, existence, uniqueness and continuation results for system (2) hold in this region.

3.3. Stability analysis and numerical results of tumor-immunotherapy model

$aEE(1-e^{-Mi})E$ is a treatment term (immunotherapy) that represents an external source of effector cells. In this section, assuming that the immunotherapy drug is constant, we set $aEE(1-e^{-Mi})E = \beta$ with β a parameter. First, we shall present the numerical results of the model (2) in the absence of immunotherapy term, to show how resistant tumor cells are weakening the immune system. Then the stability analysis of the non-tumor states and the numerical simulations of the tumor-immunotherapy model is presented. Our aim here is to see whether the immunotherapy drug is effective.

3.3.1 No immunotherapy case ($\beta = 0$)

The first equilibruim is the trivial state defined by $S_0 = (T_0^*; T_{R_0}^*; T_{M_0}^*; E_0^*; I_0^*)$ where all the populations are zero, ie $S_0 = (0; 0; 0; 0; 0)$. Evaluating the Jacobian matrix of (2) at S_0 gives:

$$J_{S_0} = \begin{pmatrix} r_T - \tau_1 - \tau_2 & 0 & 0 & 0 & 0 \\ \tau_1 & r_R & 0 & 0 & 0 \\ \tau_2 & 0 & r_M & 0 & 0 \\ c & c & c & -\mu_2 & 0 \\ 0 & 0 & 0 & 0 & -\mu_3 \end{pmatrix}$$

- J_{S_0} is a triangular matrix. So its eigenvalues are: $r_T - \tau_1 - \tau_2$; r_R; r_M; $-\mu_2$; $-\mu_3$. At least one eigenvalue has negative real part and one positive real part. Therefore, S_0 is always a locally unstable saddle point.

Now, we present the numerical simulation results for no immunotherapy case under the following four scenarios: Scenario 1: Presence of wild tumor cells (T), drug resistant tumor cells (T_R) and mutated tumor cells (T_M) (ie the system expresses both intrinsic and drug induced resistance). Scenario 2: Presence of wild tumor cells (T) and drug resistant tumor cells (T_R) (ie the system expresses only intrinsic resistance). Scenario 3: Presence of wild tumor cells (T) and mutated tumor cells (T_M) (ie the system expresses only drug induced resistance). Scenario 4: Presence of wild tumor cells (T) only (ie the system expresses neither intrinsic nor drug induced resistance).

Table 1: Description of simulation parameters of the model (2).

Parameters	**Units**	**Description**	**Estimated value**	**Reference Source**
r_T	Day^{-1}	Growth rate for wild tumor cells	0.15	Assumed
r_R	Day^{-1}	Growth rate for resistant tumor cells	0.015	Assumed
r_M	Day^{-1}	Growth rate for mutated tumor cells	0.1515	Assumed
$K_T; K_R; K_M$	Cells	Carrying capacity of cells	10^6	[2]
τ_1	Day^{-1}	Mutation rate	10^{-4}	[2]
τ_2	Day^{-1}	Mutation rate	10^{-5}	Assumed
a_1	Day^{-1}	rate of clearance of wild tumor cells	1.5	Assumed
g_2	Cells	Half-saturation for wild tumor cells clearance	10^5	[1]
a_2	Day^{-1}	rate of clearance of mutated tumor cells	1.5	Assumed
g_4	Cells	Half-saturation for mutated tumor cells clearance	10^5	Assumed
c	Day^{-1}	Antigenicity	0.5	Assumed
μ_2	Day^{-1}	Death rate of immune cells	0.003	Assumed
μ_3	Day^{-1}	Death rate of IL-2	10	[1]
p_1	Day^{-1}	Proliferation rate of immune cells	0.1245	[1]
g_1	$Cells$	Half-saturation for the proliferation	2×10^7	[1]
p_2	Day^{-1}	Production rate of IL-2	5	[1]
g_3	$Cells$	Half-saturation of production	30	[1]
α	Day^{-1}	Effector-Resistant tumor cells interation rate	3×10^{-4}	Assumed

The outcome of the simulation expressed in (2a) and (2d) shows that the population of mutated tumor cells (T_M) have been successfully controled by the immune system in the time frame of simulation ($t = 700days$). The wild tumor cells (T) and the drug resistant tumor cells (T_R) have started to grow as well. Around ($t = 580days$) the wild tumor cells can be detectable. It can be seen through the figure (2c) that when the drug resistant tumor cells have started to grow, the immune system cells have started to decrease from 600th day. This is due to the effects of the drug resistance tumor cells on the effector

Scenario 1.

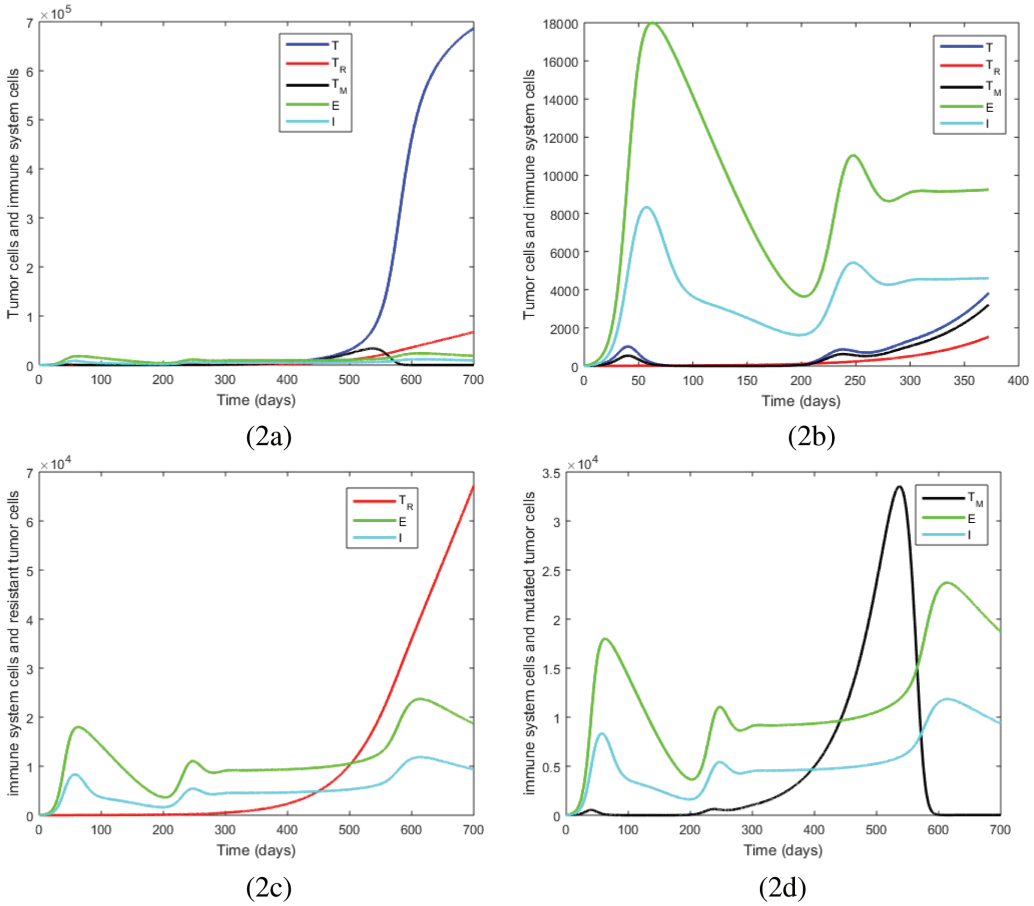
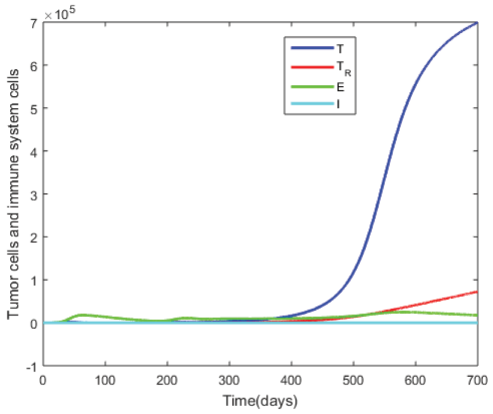


Figure 2: (2a) The behavior of tumor cells and immune system cells in the absence of immunotherapy, (2b) is a zoom of (2a) for $0 \leq t \leq 375$, (2c) The behavior of the immune system cells and resistant tumor cells in the absence of immunotherapy, (2d) The behavior of Mutated tumor cells and of effector cells in the absence of immunotherapy, when the system expresses both intrinsic and drug-induced resistance.

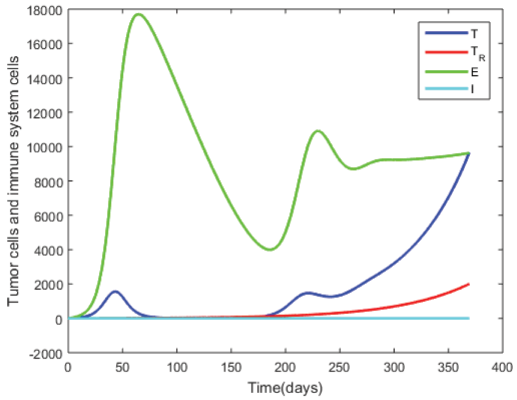
cells to make the immune system weak. The figure (2b) shows that as the tumor cells started to grow, the immune system cells started to grow as well and this happened from the begining of simulation time up to 350th day. It can be seen that between 50 days and 200 days the wild tumor cells and the mutated tumor cells have been controlled by the immune system. Note that the drug resistant tumor cells have started to grow well from 250th day.

The figures (3a) and (3b)show that as the wild tumor cells started to grow, the effector cells started to grow also and this happened up to 285th day. It can be seen that the wild tumor cells are controlled by the effector cells between 75th day and 185th day. From 150th day the drug resistant tumor cells started to grow (see figure (3c)). This has started

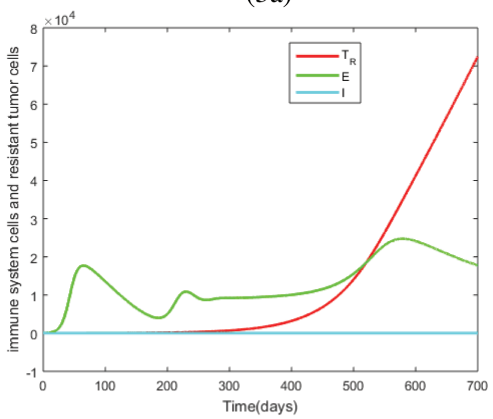
Scenario 2.



(3a)



(3b)



(3c)

Figure 3: (3a) The behavior of tumor cells and immune system cells in the absence of immunotherapy, (3b) is a zoom of (3a) for $0 \leq t \leq 375$, (3c) The behavior of the immune system cells and resistant tumor cells in the absence of immunotherapy, when the system expresses only intrinsic resistance.

to reduce the population of the effector cells. This reduction of effector cells allowed the wild tumor cells to grow logistically from 285th day up to the end of the simulation time ($t = 700days$). They become detectable around $t = 543days$. Due to the high mortality rate of IL-2, the concentration of IL-2 is negligible.

In the figure (4a) and (4b) it can be seen that the wild tumor cells and the mutated tumor cells have been controlled by the immune system. This happened because of the absence of the resistant tumor cells which suppress the immune system. Through the figures (4c), (4d), (4e), (4f) the state $(T_1^*, T_{M_1}^*, E_1^*, I_1^*)$ for coexistence is stable with $4 \times 10^{-9} < T_1^* < 6 \times 10^{-9}$, $\quad 60 < T_{M_1}^* < 61$, $\quad 10^4 < E_1^* < 1.2 \times 10^4$.

The wild tumor cells have been controlled by the immune system through the figures (5a) and (5b). Moreover the state (T_2^*, E_2^*, I_2^*) for coexixtence is stable with $60 < T_2^* <$

Scenario 3.

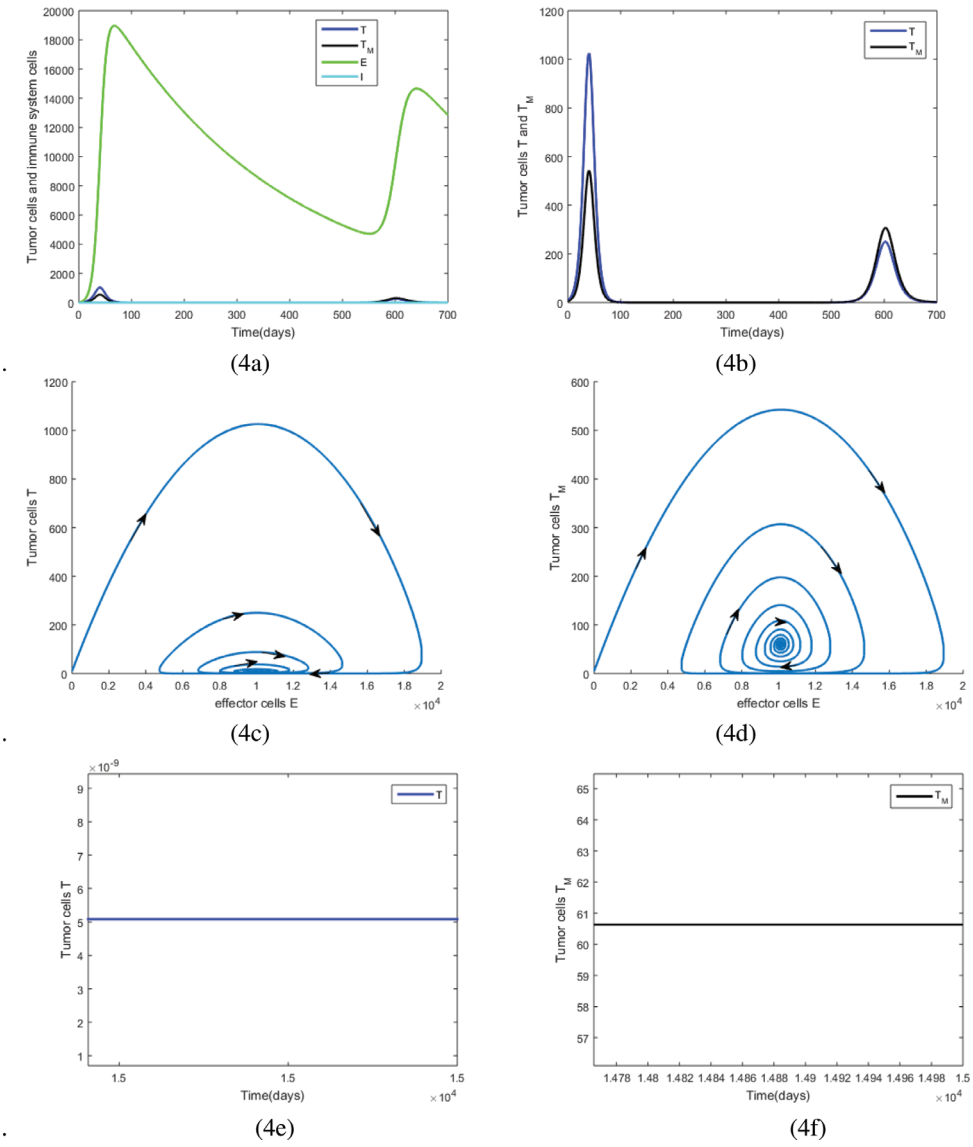


Figure 4: (4a) The behavior of tumor cells and immune system cells in the absence of immunotherapy, (4b) A zoom of (4a) into the behavior of tumor cells T and T_M in the absence of immunotherapy, (4c) Phase diagram relating T and E in the absence of immunotherapy, (4d) Phase diagram relating T_M and E in the absence of immunotherapy, (4e) Zoom into the behavior of tumor cells T after the simulation time in the absence of immunotherapy, (4f) Zoom into the behavior of tumor cells T_M after the simulation time in the absence of immunotherapy, when the system expresses only drug-induced resistance.

Scenario 4.

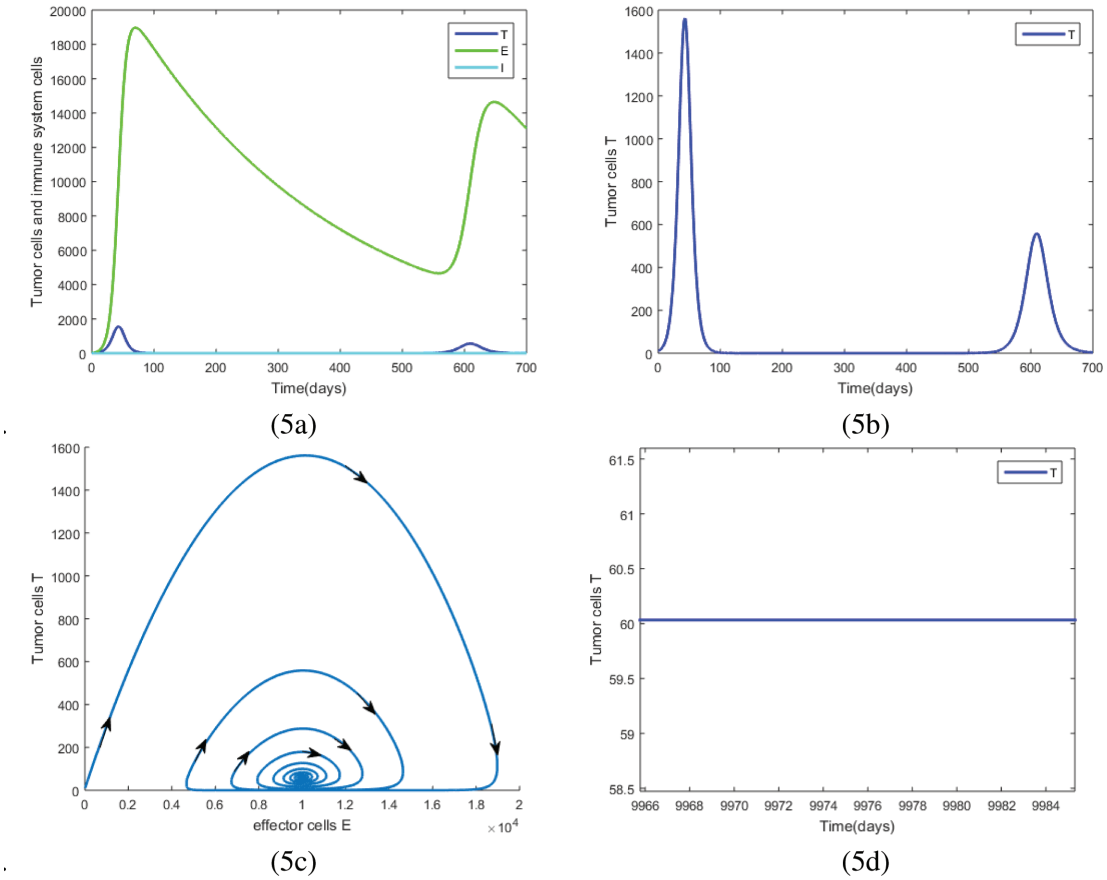


Figure 5: (5a) The behavior of tumor cells and immune system cells in the absence of immunotherapy, (5b) The behavior of tumor cells T in the absence of immunotherapy, (5c) Phase diagramm relating T and E in the absence of immunotherapy, (5d) Zoom into the behavior of tumor cells T after the simulation time in the absence of immunotherapy, when the system expresses neither intrinsic nor drug-induced resistance.

61, $10^4 < E_2^* < 1.2 \times 10^4$ (see figures (5c) and (5d)).

3.3.2 Immunotherapy case ($\beta > 0$)

For this case, we have the non-tumor states, where $E^\sharp = \dfrac{\beta}{\mu_2}$ and $I^\sharp = 0$. This implies that the tumor can be eliminated by effector cells if these equilibrium points are stable.

- The Jacobian matrix of (2) evaluated at the state denoted by $S_{E^\sharp_{R;M}} = (0; 0; 0; E^\sharp; 0)$

when the system expresses both intrinsic and drug induced resistance is:

$$J_{S_{E^{\sharp}_{R;M}}} = \begin{pmatrix} r_T - \tau_1 - \tau_2 - \dfrac{\beta a_1}{\mu_2 g_2} & 0 & 0 & 0 & 0 \\ \tau_1 & r_R & 0 & 0 & 0 \\ \tau_2 & 0 & r_M - \dfrac{\beta a_2}{\mu_2 g_4} & 0 & 0 \\ c & \dfrac{c\mu_2 - \alpha\beta}{\mu_2} & c & -\mu_2 & \dfrac{\beta p_1}{\mu_2 g_1} \\ \dfrac{\beta p_2}{\mu_2 g_3} & \dfrac{\beta p_2}{\mu_2 g_3} & \dfrac{\beta p_2}{\mu_2 g_3} & 0 & -\mu_3 \end{pmatrix}$$

The eigenvalues are: $r_T - \tau_1 - \tau_2 - \dfrac{\beta a_1}{\mu_2 g_2}; r_R; r_M - \dfrac{\beta a_2}{\mu_2 g_4}; -\mu_2; -\mu_3$. From analying the eigenvalues, at least one has negative real part and one positive real part. Thus the state $S_{E^{\sharp}_{R;M}}$ is unstable saddle. This implies that the immunotherapy drug can not eliminate all the tumor cells when the system expresses both intrinsic and drug-induced resistance.

The following are the numerical simulation results for immunotherapy case under the scenario 5 in the presence of wild tumor cells (T), drug resistant tumor cells (T_R) and mutated tumor cells (T_M) (ie the system expresses both intrinsic and drug induced resistance). The immunotherapy drug is introduced by setting $\beta = 75000$ cells at $t \geq 500 days$ for the figures (6a), (6b), (6c) and at $t \geq 200 days$ for the figures (6d), (6e), (6f).

The effectiveness of the immunotherapy can be seen through the figures (6a) and (6c). Unlike the figures (2a) and (2c), here the wild tumor cells and the mutated tumor cells started to die out from the date that the immunotherapy drug is introduced. But it can be seen that in the end of the simulation time, those two populations started to grow again. Thus a periodic immunotherapy can eliminate the responsive tumor cells. Of course, through the figure (6b) the immune system cells started to decrease when the resistant tumor cells started to grow. We can conclude that a periodic immunotherapy and a specifique chemotherapy drug on the resistant tumor cells can clear the tumor. So far, it can be seen that the state $(0, 0, T^{\sharp}_{R_1}, E^{\sharp}_1, I^{\sharp}_1)$ is stable when the immunotherapy drug is introduced at the early stage ($t = 200 days$) (see figures (6d), (6e), (6f)).

Two treatment strategies can be proposed in this case: Periodic and constant immunotherapy drug starting around $t = 500 days$ and a specific chemotherapy drug on the resistant tumor cells, or constant immunotherapy drug at the early stage (around $t = 200 days$) and a specific chemotherapy drug on the resistant tumor cells.

- The immunotherapy drug can not also eliminate all the tumor cells in the case where the system expresses only intrinsic resistance.

Indeed, the eigenvalues of the Jacobian matrix for the state $S_{E^{\sharp}_R} = (0; 0; E^{\sharp}; 0)$ when the system expresses only intrinsic resistance are: $r_T - \tau_1 - \dfrac{\beta a_1}{\mu_2 g_2}; r_R; -\mu_2; -\mu_3$. Thus the state $S_{E^{\sharp}_R}$ is unstable saddle.

Scenario 5.

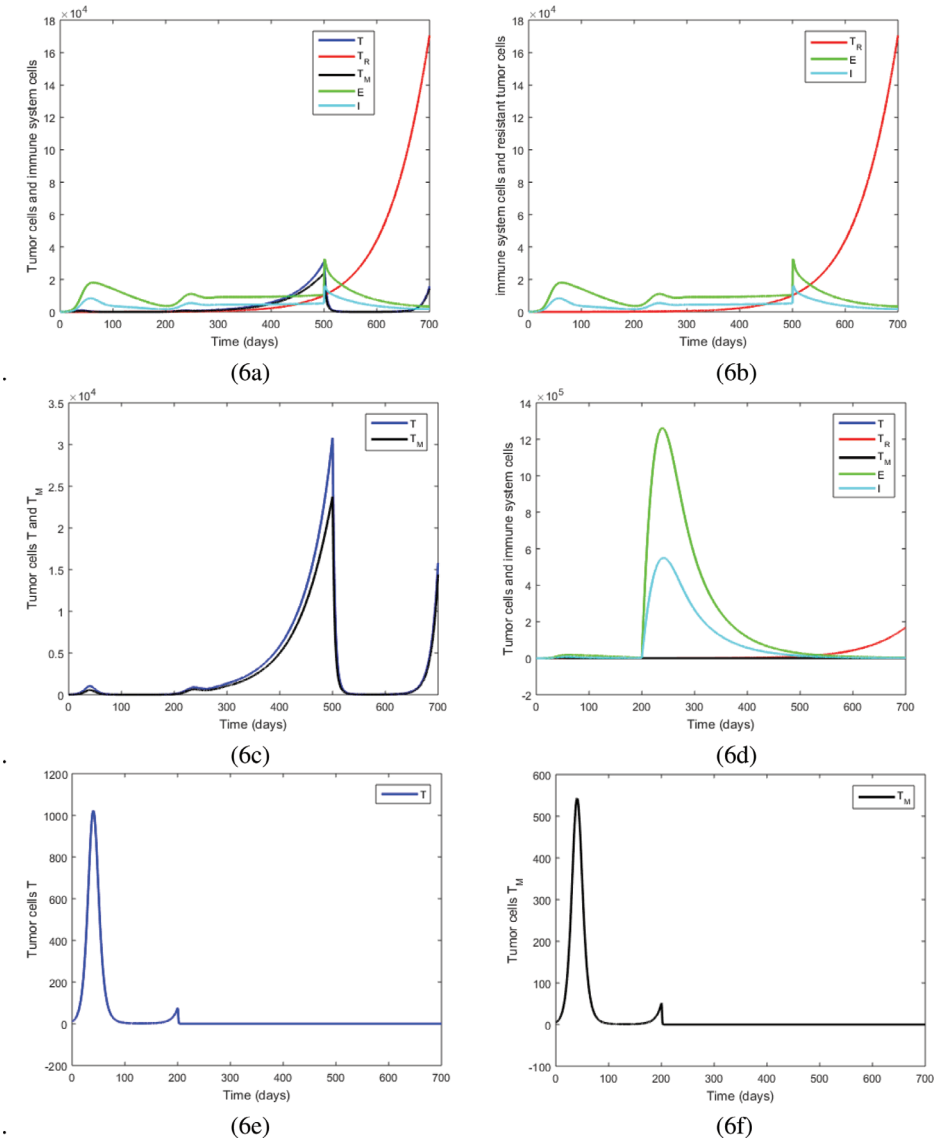


Figure 6: (6a) The behavior of tumor cells and immune system cells in the presence of immunotherapy, (6b) The behavior of the immune system cells and resistant tumor cells in the presence of immunotherapy, (6c) The behavior of tumor cells T and T_M in the presence of immunotherapy, (6d) The behavior of tumor cells and immune system cells in the presence of immunotherapy (introduced at $t = 200days$), (6e) The behavior of tumor cells T in the presence of immunotherapy (introduced at $t = 200days$), (6f) The behavior of tumor cells T_M in the presence of immunotherapy (introduced at $t = 200days$), when the system expresses both intrinsic and drug-induced resistance.

Scenario 6.

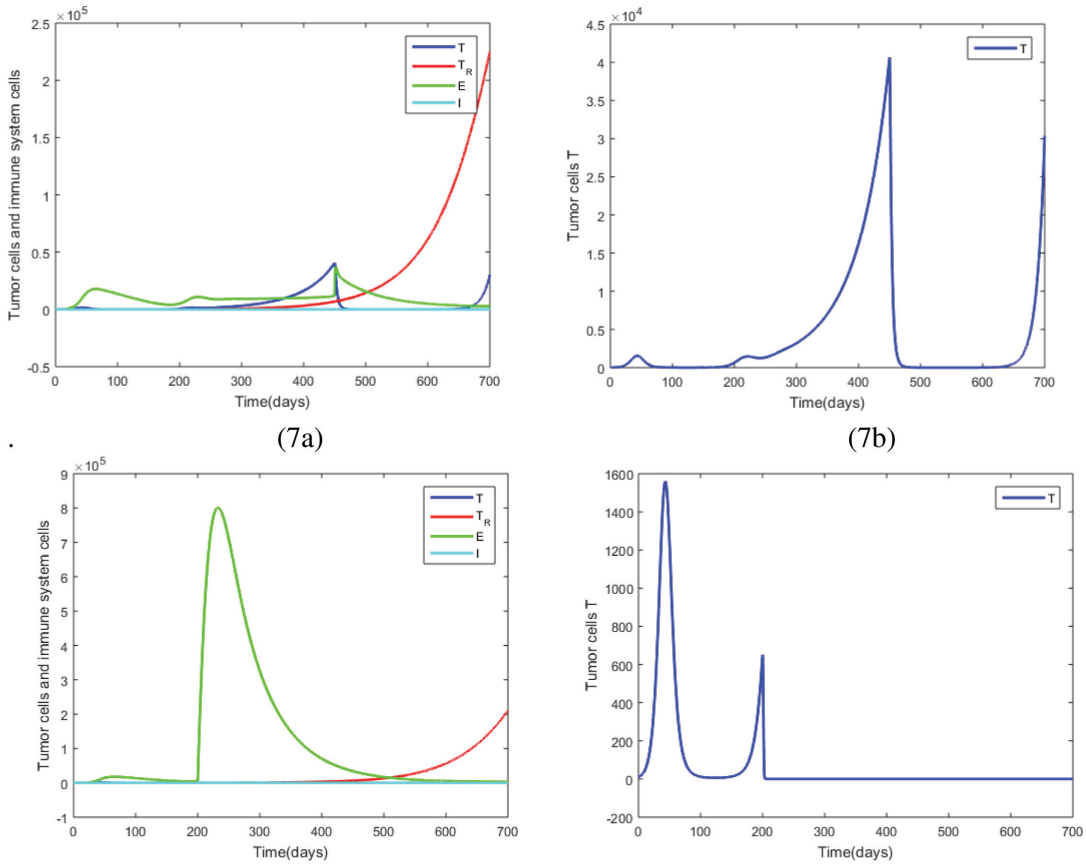


Figure 7: (7a) The behavior of tumor cells and immune system cells in the presence of immunotherapy, (7b) The behavior of tumor cells T in the presence of immunotherapy, (7c) The behavior of tumor cells and immune system cells in the presence of immunotherapy (introduced at $t = 200days$), (7d) The behavior of tumor cells T in the presence of immunotherapy (introduced at $t = 200days$), when the system expresses only intrinsic resistance.

The following are the numerical simulation results for immunotherapy case under the scenario 6 in the presence of wild tumor cells (T) and drug resistant tumor cells (T_R) (ie the system expresses only intrinsic resistance). The immunotherapy drug is introduced by setting $\beta = 60000$ cells at $t \geq 450days$ for the figures (7a), (7b) and at $t \geq 200days$ for the figures (7c), (7d).

The effectiveness of the immunotherapy can be seen through the figures (7a) and (7b). The wild tumor cells started to die out from the date that the immunotherapy drug is introduced and started to grow again in the end of the simulation time. Thus, here

also a periodic immunotherapy can eliminate the responsive tumor cells. Of course, through the figure (7a) the immune system cells started to decrease when the resistant tumor cells started to grow. We can conclude here also that a periodic immunotherapy and a specifique chemotherapy drug on the resistant tumor cells can clear all the tumor. So far, the figures (7c) and (7d) show that the state $(0, T_{R_2}^\sharp, E_2^\sharp, I_2^\sharp)$ is stable when the immunotherapy drug is introduced at the early stage ($t = 200days$).

So the two treatment strategies proposed in the case where the system expresses both intrinsic and drug-induced resistance are also proposed here.

- When the system expresses only drug-induced resistance, the eigenvalues of the Jacobian matrix for the state $S_{E_M^\sharp} = (0; 0; E^\sharp; 0)$ are: $r_T - \tau_2 - \frac{\beta a_1}{\mu_2 g_2}; r_M - \frac{\beta a_2}{\mu_2 g_4}; -\mu_2; -\mu_3$. From analyzing, this state is locally stable (that is the immunotherapy drug can eliminate the tumor) if $\beta > \frac{\mu_2 g_2(r_T - \tau_2)}{a_1}$ and $\beta > \frac{r_M \mu_2 g_4}{a_2}$. If one of those conditions is not satisfied, $S_{E_M^\sharp}$ is unstable.
  (The value of $\frac{\mu_2 g_2(r_T - \tau_2)}{a_1} = 29.998$ and the value of $\frac{r_M \mu_2 g_4}{a_2} = 30.3$ for the parameter values in Table 1.)

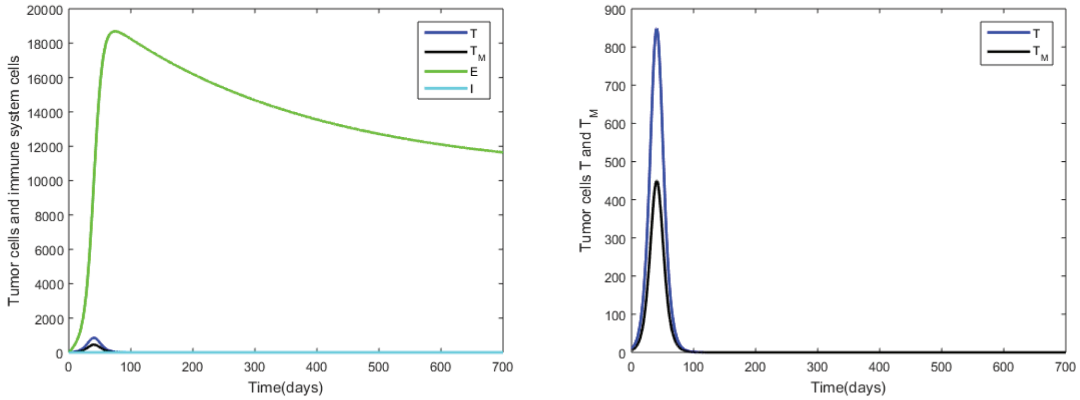
The following are the numerical simulation results for immunotherapy case under the scenario 7 in the presence of wild tumor cells (T) and mutated tumor cells (T_M) (ie the system expresses only drug induced resistance). The immunotherapy drug is administered at the begining of the simulation time (ie $t \geq 0$) and $\beta = 31$ cells.

The figures (8a) and (8b) show that the state $S_{E_M^\sharp} = (0; 0; E^\sharp; 0)$ which was locally stable for $\beta > \frac{\mu_2 g_2(r_T - \tau_2)}{a_1}$ and $\beta > \frac{r_M \mu_2 g_4}{a_2}$ is globally stable, since all the tumor cells are eliminated by the immunotherapy drug from 100th day. We can conclude that the introduction of the immunotherapy drug at the begining of the desease can save the patients when the system expresses only drug induced resistance.

- When the system expresses neither intrinsic nor drug-induced resistance, the eigenvalues of the Jacobian matrix for the state $S_{E^\sharp} = (0; E^\sharp; 0)$ are: $r_T - \frac{\beta a_1}{\mu_2 g_2}; -\mu_2; -\mu_3$. From analyzing the eigenvalues, this state is locally stable (that is the immunotherapy drug can eliminate the tumor) if $\beta > \frac{r_T \mu_2 g_2}{a_1}$ and unstable if $\beta < \frac{r_T \mu_2 g_2}{a_1}$
  (The value of $\frac{r_T \mu_2 g_2}{a_1} = 30$ for the parameter values in Table 1.)

The following are the numerical simulation results for immunotherapy case under the scenario 8 in the presence of wild tumor cells (T) only (ie the system expresses neither

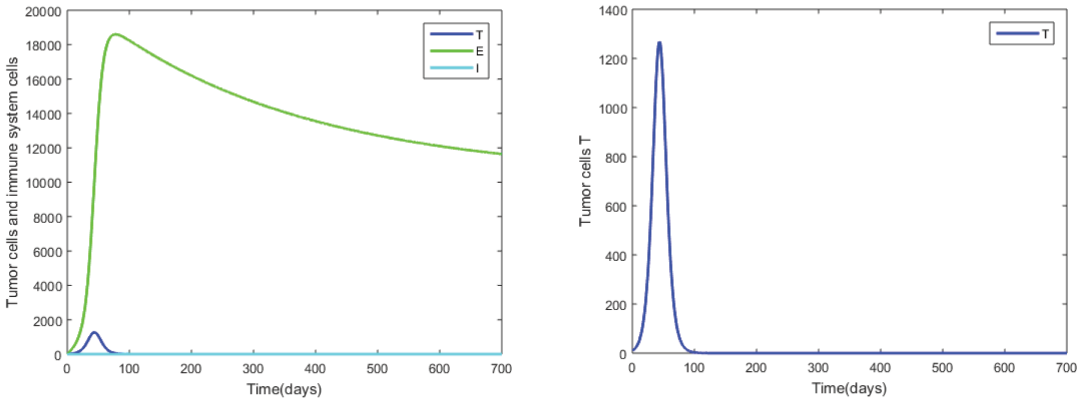
Scenario 7.



(8a) (8b)

Figure 8: (8a) The behavior of tumor cells and immune system cells in the presence of immunotherapy, (8b) The behavior of tumor cells T and T_M in the presence of immunotherapy, when the system expresses only drug-induced resistance.

Scenario 8.



(9a) (9b)

Figure 9: (9a) The behavior of tumor cells and immune system cells in the presence of immunotherapy, (9b) The behavior of tumor cells T in the presence of immunotherapy, when the system expresses neither intrinsic nor drug-induced resistance.

intrinsic nor drug-induced resistance.). The immunotherapy drug is administered at the begining of the simulation time (ie $t \geq 0$) and $\beta = 31$ cells.

Here also, all the tumor cells are eliminated by the immunotherapy drug from 100th day (see the figures (9a) and (9b)). So the state $S_{E^\sharp} = (0; E^\sharp; 0)$ is globally stable. This implies that the introduction of the immunotherapy drug at the begining of the desease can save the patients when the system expresses neither intrinsic nor drug-induced resistance.

4. Conclusion

In this paper, a model that take into account multi-mutation and drug resistance in a case of simple immune system and immuno-suppression caused by drug resistant tumor cells was proposed to understand the dynamic of wild tumor cells (T), drug resistant tumor cells (T_R), mutated tumor cells (T_M), Normal cells (N) and immune system cells (E) and (I). A mathematical analysis of the corresponding tumor-immunotherapy model was carried out to show the exitence, the uniqueness, and the boundedness of its solution. Also the stability of the non-tumor state, when the dynamical system expresses both intrinsic and drug induced resistance, only intrinsic resistance, only drug induced resistance, and neither intrinsic nor drug induced resistance was discussed in the presence of the immunotherapy drug. Then a detailed numerical analysis of the corresponding tumor-immunotherapy model was done to identify an efficient treatment strategie in each case.

Two treatment strategies were proposed when the dynamical system expresses both intrinsic and drug induced resistance (presence of wild tumor cells (T), drug resistant tumor cells (T_R) and mutated tumor cells (T_M)), or only intrinsic resistance (presence of wild tumor cells (T) and drug resistant tumor cells (T_R)): Periodic and constant immunotherapy drug starting around $t = 500days$ and a specific chemotherapy drug on the resistant tumor cells, or constant immunotherapy drug at the early stage (around $t = 200days$) and a specific chemotherapy drug on the resistant tumor cells.

In the case where the dynamical system expresses only drug induced resistance (presence of wild tumor cells (T) and mutated tumor cells (T_M))or neither intrinsic nor drug induced resistance (presence of wild tumor cells (T) only), the introduction of the immunotherapy drug at the begining of the desease was observed to be effective in treating the cancer. Due to the high mortality rate of IL-2, we observed in scenario 2, 3, 4 and 6 that concentration of IL-2 is negligible.

With this paper, we can safely say that the state of the patient's immune system plays an important role in making decisions about the impact of therapy. Some open concerns include whether mutations occur at a constant rate or whether the rate may be affected by the immunotherapy drug. Our next article will study the behavior of each population of the above model, in the presence of only chemotherapy and in the presence of both immunotherapy and chemotherapy.

Conflicts of interest

The authors declare that there is no conflicts of interest regarding the publication of this paper.

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