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Stability Analysis Using Nonstandard Finite Difference Method and Model Simulation for Multi-Mutation and Drug Resistance with Immune-Suppression.

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Abstract

We introduced recently a model that takes into account mutation and drug resistance of tumor cells in a case of simple immune system and immune-suppression caused by the resistant cells. The present study is to apply the Nonstandard finite difference method to that model we recently developed in analyzing the stability of non-tumor states to identify under which conditions tumor can be eliminated in the presence of both immunotherapy and chemotherapy. Numerical simulations of the model in the presence of both immunotherapy and chemotherapy are performed with the aid of MATLAB software using *ode45* function and under different treatment strategies to analyze the behavior of both the tumor and immune system cells. The findings of this study indicates that tumor cells can be only eliminated under certain conditions, when a second specific chemotherapy drug that is only toxic to resistant tumor cells is introduced. Moreover, it gives an insight into how tumor and immune system cells evolve when the dynamical system conveys both inherent and drug-induced resistance with immune-suppression, in the presence of both immunotherapy and chemotherapy. Treatment strategies effective are proposed in this case.

Keywords: Cancer Modeling, Drug resistance, Mutation, Immune system, Immunotherapy, Immune-Suppression, Chemotherapy, Nonstandard Finite-Difference Method/Scheme.

AMS Subject Classifications: 37C75; 65L12; 92C37; 68U20.

1 Introduction

To improve the therapeutic approach according to the type and proliferation rate of tumor cells during cancer treatment, many researchers and mathematicians such as Feizabadi & Witten[**1**, **3**, **6**], Kirschner

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& Panetta[**4**], Feizabadi[**2**], and Kirschner & Tsygvintsev[**5**] introduced mathematical models to analyze the evolution of cells. Feizabadi in [**2**] modeled multi-mutation and drug resistance and assessed the response of the time varying cell population under various treatment strategies[**23**]. In [**10**], we added in the model of [**2**] the effect of a basic immune system and the suppression of immunity caused by drug resistant tumor cells[**24**]. The model have been analyzed mathematically and simulated numerically in the presence of only immunotherapy drug to determine its effectiveness.

In this paper which is an extension of our previous work [**10**], we employ the Non-Standard Finite-Difference(NSFD) method proposed by Mikens in [**25**] in our model to analyze the stability of non-tumor states in order to identify under which conditions tumor can be eliminated in the presence of both immunotherapy and chemotherapy. Then, we simulate numerically the model in the presence of both immunotherapy and chemotherapy drug under different treatment strategies to determine the behavior of both tumor and immune system cells[**26**]. Treatment strategies effective are proposed for this purpose.

Introduced by Mickens around 1980, the nonstandard finite difference (NSFD)schemes is chosen for this study because it preserves the important properties of differential equations [**11**, **27**]. At the beginning, the general rules for implementing these schemes were vaguely known[**12**, **28**]. However, Mickens proposed some rules for constructing nonstandard schemes for differential equations[**13**]. Used by many mathematicians such as R. Anguelov et al[**14**]; D.T. Dimitrov et al[**11**]; G. Gabriellini[**15**]; S.M. Garba et al[**16**]; and M.E. Songolo[**17**]; nonstandard finite difference (NSFD) schemes have also a potential to preserve qualitative properties of the original system and to avoid ghost solutions [**17**, **18-22**, **29**].

The following are the organization of the rest of the paper: Section 2 introduce our recent model constructed in [**10**]. In Section 3, we present the NSFD methodology. We construct a NSFD scheme for the model and present a complete stability analysis of non-tumor states considering both immunotherapy and chemotherapy. In section 4, the numerical simulations of the model is done for both immunotherapy and chemotherapy drug and under different treatment strategies[**30**]. Section 5, presents the conclusion of the study.

2 Model of multi-mutation and drug resistance with immune-suppression caused by drug resistance tumor cells

Drug-induced resistance is a signifcant challenge faced by scientists nowadays and is one of the major factors that lead to failure of therapeutic treatment of cancer. During the division of tumor cells there is usually a change in genetics of the cells whereby some cells exhibit inherent resistance to a certain chemotherapy drug. Additionally, some other cells will posses a gene that can transform them into drug-induced resistant cells when the drug is administered[**31**]. These multi-mutation and drug resistance was modeled by Feizabadi in [**2**]. In the previous study[**10**], we extended the model constructed in [**2**] to include the effects of a basic immune system and of immunity-suppression caused by drug resistant tumor cells. we first added the notion of immune system interaction as stated by Kirschner & Panetta in [**4**] and of the immune-suppression established by Feizabadi & Witten in [**1**] to the core model of Feizabadi in [**2**]. Then, we assumed that the immune system can not distinguish between the responsive and the resistance tumor cells, so it acts on all the tumor cells. But those cells that are resistant are not affected by the action of the effector cells. That is the effector cells affect only the drug-sensitive and the mutated tumor cells, but not the resistant tumor cells. Thus the immune-suppression factors was assumed

to be the resistant tumor cells. These resistant tumor cells attack the activated effector cells and lead to a reduction in population of these effector cells which in turn result to a weakening of the immune system. Therefore, the treatment strategy will be that of boosting the immunity (immunotherapy)[**32**]. It should be noted that elimination of tumor population by chemotherapy drugs is dependent on the drug dosage[**7**, **8**]. Also these drugs are cytotoxic to the drug-sensitive tumor cells, effector cells and the normal (body) cells[**1**]. So, in the presence of both immunotherapy and chemotherapy drug, whereby the number of effector and drug-sensitive tumor cells is significantly reduced due to chemotherapy, the dynamics of the tumor, normal and effector cells can be described as follows:

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

Where $T(t), T_R(t), T_M(t), N(t), E(t)$ and $I(t)$ are the total number respectively at a time t; of wild tumor cells, drug-resistant tumor cells, mutated tumor cells, normal cells, effector cells with the unit of cells and the concentration of IL-2[**31**, **33**]. We assume that all of these tumor cells are growing 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 $(time^{-1})$[**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[**1**, **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'[**31**, **33**, **34**]. 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[**34**]. 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[**32**, **35**]. As suggested by Gardner in [**9**] the drug interaction may be structured as $a_\phi(1-e^{-MC})\phi$. Here ϕ is the cell population number.[36] The parameter C is the concentration or amount of the drug at the tumor site at a specific time with the unit $(mg.m^{-2})$[**37**]. 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[**31**]. The function $F(C) = a_\phi(1-e^{-MC})$ is the fraction cell kill for a given amount (concentration) of drug "C"[**36**]. 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[**31**]. Additionally, the immunotherapeutic agent is described by the term $a_{EE}(1-e^{-Mi})E$ and it acts as an immune-boosting agent[**32**].

A solution of (1) is a function $X : t \in J \subset \mathbb{R} \longmapsto X(t) = \begin{pmatrix} T(t) \\ T_R(t) \\ T_M(t) \\ N(t) \\ E(t) \\ I(t) \end{pmatrix} \in \mathbb{R}^6$

Let $F : X \in \mathbb{R}^6 \longmapsto F(X) \in \mathbb{R}^6$ with

$$F(X) = \begin{cases} r_T T\Big(1-\dfrac{T+T_R+T_M}{K_T}\Big) - (\tau_1+\tau_2)T - \dfrac{a_1 ET}{g_2+T} - a_T(1-e^{-MC})T; \\ r_R T_R\Big(1-\dfrac{T+T_R+T_M}{K_R}\Big) + \tau_1 T + \tau_{M\to R}(1-e^{-MC})T_M; \\ r_M T_M\Big(1-\dfrac{T+T_R+T_M}{K_M}\Big) + \tau_2 T - \dfrac{a_2 ET_M}{g_4+T_M} - a_{T_M}(1-e^{-MC})T_M - \tau_{M\to R}(1-e^{-MC})T_M; \\ r_N N\Big(1-\dfrac{N}{K_N}\Big) + k(T+T_R+T_M)\Big(1-\dfrac{T+T_R+T_M}{T^*}\Big) - a_N(1-e^{-MC})N; \\ c(T+T_R+T_M) - \mu_2 E + \dfrac{p_1 EI}{g_1+I} - \alpha E T_R - a_E(1-e^{-MC})E + a_{EE}(1-e^{-Mi})E; \\ \dfrac{p_2 E(T+T_R+T_M)}{g_3+(T+T_R+T_M)} - \mu_3 I; \end{cases} \tag{2}$$

The system (1) becomes:

$$\frac{dX}{dt} = F(X); \qquad X(0) = X_0 = \Big(T_0; T_{R_0}; T_{M_0}; N_0; E_0; I_0\Big)^T. \tag{3}$$

From the existence and uniqueness theorem, F is C^1 and then, first of all, there exists a solution of the initial value problem (3) and, secondly, this is the only such solution. More precisely, there exists an unique global solution which is non negative whenever the initial conditions are non negative.

3 Stability Analysis of Non-tumor states Using Nonstandard Finite difference Schemes

In this section, assuming that the immunotherapy drug is constant, we set $a_{EE}(1-e^{-Mi})E = \beta$ with β a parameter. The non-tumor state is the state defined by $S^* = (T_0^*; T_{R_0}^*; T_{M_0}^*; N_0^*; E_0^*; I_0^*)$ where all the tumor cells are zero. ie $S^* = (0;0;0;N_0^*;E_0^*;0)$ with $N_0^* = K_N - \dfrac{a_N K_N(1-e^{-MC})}{r_N}$ and $E_0^* = \dfrac{\beta}{\mu_2 + a_E(1-e^{-MC})}$. This implies that all the tumor cells can be eliminated by the combination of chemotherapy and immunotherapy drug if S^* is stable. The stability analysis of this state is done in the absence and in the presence of a second specific chemotherapy drug only toxic to T_R. Note that this second chemotherapy drug has been suggested by Feizabadi in [**2**] and expressed by $a_{T_R}(1-e^{-MC_2})T_R$ on resistant tumor cells.
Combining these informattions, the system (1) becomes:

$$\begin{cases} \dfrac{dT(t)}{dt} = r_T T\Big(1 - \dfrac{T+T_R+T_M}{K_T}\Big) - (\tau_1+\tau_2)T - \dfrac{a_1 ET}{g_2+T} - a_T(1-e^{-MC})T; \\ \dfrac{dT_R(t)}{dt} = r_R T_R\Big(1 - \dfrac{T+T_R+T_M}{K_R}\Big) + \tau_1 T + \tau_{M\to R}(1-e^{-MC})T_M - a_{T_R}(1-e^{-MC_2})T_R \\ \dfrac{dT_M(t)}{dt} = r_M T_M\Big(1 - \dfrac{T+T_R+T_M}{K_M}\Big) + \tau_2 T - \dfrac{a_2 ET_M}{g_4+T_M} - a_{T_M}(1-e^{-MC})T_M - \tau_{M\to R}(1-e^{-MC})T_M; \\ \dfrac{dN(t)}{dt} = r_N N\Big(1 - \dfrac{N}{K_N}\Big) + k(T+T_R+T_M)\Big(1 - \dfrac{T+T_R+T_M}{T^*}\Big) - a_N(1-e^{-MC})N; \\ \dfrac{dE(t)}{dt} = c(T+T_R+T_M) - \mu_2 E + \dfrac{p_1 EI}{g_1+I} - \alpha E T_R - a_E(1-e^{-MC})E + \beta; \\ \dfrac{dI(t)}{dt} = \dfrac{p_2 E(T+T_R+T_M)}{g_3+(T+T_R+T_M)} - \mu_3 I; \\ T(0)=T_0,\ T_R(0)=T_{R_0},\ T_M(0)=T_{M_0},\ N(0)=N_0,\ E(0)=E_0,\ I(0)=I_0. \end{cases} \tag{4}$$

To procced, We First define the nonstandard finite difference scheme and present the rules of its construction as proposed by Mickens in [**13**].

3.1 Nonstandard Finite difference Schemes

A numerical scheme with a step size Δt, that approximates the solution $X(t_k)$ of an autonomous system $\dfrac{dX}{dt} = F(X); X(t_0) = X_0$ where F is C^1 can be written in the form:

$$D_{\Delta t}(X_k) = F_{\Delta t}(X_k) \tag{5}$$

where $D_{\Delta t}(X_k) \simeq \dfrac{dX(t_k)}{dt}; X_k \simeq X(t_k); F_{\Delta t}(X_k) \simeq F(X_k)$ and $t_k \simeq t_0 + k\Delta t$ (see, [**11**, **38**, **39**]).

Definition. ***3.1****[**11**, **28**, **39**, **40**]: The scheme (5) is called a nonstandard finite difference scheme if at least one of the following conditions is satisfied:*

1-$D_{\Delta t}(X_k) = \dfrac{X_{k+1} - \psi X_k}{\varphi(\Delta t)}$ *where* ψ *and* φ *are non negative functions depending on the step-size* Δt *and other parameters occurring in the differential equation, and, in addition, satisfies the conditions:* $\psi(\Delta t) = 1 + O(\Delta t)$ *and* $\varphi(\Delta t) = \Delta t + O(\Delta t^2)$.
2-$F_{\Delta t}(X_k) = g(X_k, X_{k+1}, \Delta t)$ *where* g *is a nonlocal approximation of the right-hand side of the system of the differential equation.*

Definition. ***3.2[11, 38, 39]****: The nonstandard finite difference scheme is called elementary stable, if, for any value of the step size, its only fixed points are those of the original differential system, the linear stability properties of each fixed points being the same for both the differential system and the discrete scheme.*

Note 3.1 ([13, 41, 42]): The functions ψ and φ vary from one equation to another and no clear a priori set of guidelines exist for determining them. However, In most applications, ψ is usually selected to be 1; and φ (called the denominator function) is determined as follows: $\varphi(\Delta t) = \dfrac{1 - e^{-R^*\Delta t}}{R^*}$ where $R^* = max\{|R_i|_{i=1;2....}\}$ with $R_i = \left.\dfrac{\partial f}{\partial x_i}\right|_{X=0}$ and $0 < \varphi(\Delta t) < \dfrac{1}{R^*}$
Note also that nonstandard finite difference (NSFD) scheme are topologically equivalent to their original system they approximate (for more details; see [**14**]).
Now, let present the rules for the construction of NSFD schemes as proposed by Mickens in [**13**] and taken into account by [**44**, **45**].

Rule 1: The order of the discrete derivatives must be equal to the order of the corresponding derivatives of the differential equations.
Rule 2: Denominator functions for the discrete derivatives must, in general, be expressed in terms of more complicated functions of the step-sizes than those conventionally used.
Rule 3: Nonlinear terms should, in general, be modeled nonlocally. However, sometimes more general forms may be required, such as $u^2 = 2u^2 - u^2 \longrightarrow 2(u_k)^2 - u_{k+1}u_k$.
Rule 4: Special conditions that hold for the solutions of the differential equations should also hold for the solutions of the finite difference scheme.
Rule 5: The finite difference equations should not have solutions that dont correspond exactly to solutions of the differential equations.

Definition. ***3.3[13]****: A nonstandard finite difference scheme is any discrete representation of a system of differential equations that is constructed according to the above rules.*

3.2 Stability Analysis of the Non-tumor state S^* in the absence of a second specific chemotherapy drug only toxic to T_R

Based on the above definitions and rules, the NSFD scheme of (4) in the absence of the second specific chemotherapy drug only toxic to T_R is given by:

$$\begin{cases} \frac{T^{n+1}-T^n}{\varphi_1(\Delta t)} = r_T T^{n+1}\Big(1-\frac{T^n+T_R^n+T_M^n}{K_T}\Big)-(\tau_1+\tau_2)T^{n+1}-\frac{a_1E^nT^{n+1}}{g_2+T^n}-a_T(1-e^{-MC})T^{n+1};\\ \frac{T_R^{n+1}-T_R^n}{\varphi_2(\Delta t)} = r_R T_R^{n+1}\Big(1-\frac{T^n+T_R^n+T_M^n}{K_R}\Big)+\tau_1T^{n+1}+\tau_{M\to R}(1-e^{-MC})T_M^n;\\ \frac{T_M^{n+1}-T_M^n}{\varphi_3(\Delta t)} = r_M T_M^{n+1}\Big(1-\frac{T^n+T_R^n+T_M^n}{K_M}\Big)+\tau_2T^{n+1}-\frac{a_2E^nT_M^{n+1}}{g_4+T_M^n}-a_{T_M}(1-e^{-MC})T_M^{n+1}-\tau_{M\to R}(1-e^{-MC})T_M^{n+1};\\ \frac{N^{n+1}-N^n}{\varphi_4(\Delta t)} = r_N N^{n+1}\Big(1-\frac{N^n}{K_N}\Big)+k(T^n+T_R^n+T_M^n)\Big(1-\frac{T^n+T_R^n+T_M^n}{T^*}\Big)-a_N(1-e^{-MC})N^{n+1};\\ \frac{E^{n+1}-E^n}{\varphi_5(\Delta t)} = c(T^n+T_R^n+T_M^n)-\mu_2E^{n+1}+\frac{p_1E^nI^n}{g_1+I^n}-\alpha E^{n+1}T_R^n-a_E(1-e^{-MC})E^{n+1}+\beta;\\ \frac{I^{n+1}-I^n}{\varphi_6(\Delta t)} = \frac{p_2E^n(T^n+T_R^n+T_M^n)}{g_3+(T^n+T_R^n+T_M^n)}-\mu_3I^{n+1}; \end{cases} \tag{6}$$

Where: $\varphi_1(\Delta t)=\dfrac{1-e^{-\left(r_T-\tau_1-\tau_2-a_T(1-e^{-MC})\right)\Delta t}}{\left(r_T-\tau_1-\tau_2-a_T(1-e^{-MC})\right)}$; $\varphi_2(\Delta t)=\dfrac{1-e^{-r_R\Delta t}}{r_R}$;

$\varphi_3(\Delta t)=\dfrac{1-e^{-\left(r_M-a_{T_M}(1-e^{-MC})-\tau_{M\to R}(1-e^{-MC})\right)\Delta t}}{\left(r_M-a_{T_M}(1-e^{-MC})-\tau_{M\to R}(1-e^{-MC})\right)}$;

$\varphi_4(\Delta t)=\dfrac{1-e^{-\left(r_N-a_N(1-e^{-MC})\right)\Delta t}}{\left(r_N-a_N(1-e^{-MC})\right)}$; $\varphi_5(\Delta t)=\dfrac{1-e^{-(\mu_2+a_E(1-e^{-MC}))\Delta t}}{\mu_2+a_E(1-e^{-MC})}$;

$\varphi_6(\Delta t)=\dfrac{1-e^{-\mu_3\Delta t}}{\mu_3}$

In explicit form, we have:

$$\begin{cases} T^{n+1} = \dfrac{T^n}{1+(\tau_1+\tau_2-r_T)\varphi_1(\Delta t)+a_T(1-e^{-MC})\varphi_1(\Delta t)+r_T\Big(\frac{T^n+T_R^n+T_M^n}{K_T}\Big)\varphi_1(\Delta t)+\frac{a_1E^n\varphi_1(\Delta t)}{g_2+T^n}};\\ T_R^{n+1} = \dfrac{T_R^n+\tau_1T^{n+1}\varphi_2(\Delta t)+\tau_{M\to R}(1-e^{-MC})T_M^n\varphi_2(\Delta t)}{1-r_R\varphi_2(\Delta t)+r_R\Big(\frac{T^n+T_R^n+T_M^n}{K_R}\Big)\varphi_2(\Delta t)};\\ T_M^{n+1} = \dfrac{T_M^n+\tau_2T^{n+1}\varphi_3(\Delta t)}{1+r_M\Big(\frac{T^n+T_R^n+T_M^n}{K_M}\Big)\varphi_3(\Delta t)+\frac{a_2E^n\varphi_3(\Delta t)}{g_4+T^n}-r_M\varphi_3(\Delta t)+a_{T_M}(1-e^{-MC})\varphi_3(\Delta t)+\tau_{M\to R}(1-e^{-MC})\varphi_3(\Delta t)};\\ N^{n+1} = \dfrac{N^n+k(T^n+T_R^n+T_M^n)\Big(1-\frac{T^n+T_R^n+T_M^n}{T^*}\Big)}{1+r_N\Big(\frac{N^n}{K_N}\Big)\varphi_4(\Delta t)-r_N\varphi_4(\Delta t)+a_N(1-e^{-MC})\varphi_4(\Delta t)};\\ E^{n+1} = \dfrac{c(T^n+T_R^n+T_M^n)\varphi_5(\Delta t)+\frac{p_1E^nI^n\varphi_5(\Delta t)}{g_1+I^n}+\beta\varphi_5(\Delta t)+E^n}{1+\mu_2\varphi_5(\Delta t)+a_E(1-e^{-MC})\varphi_5(\Delta t)+\alpha T_R^n};\\ I^{n+1} = \dfrac{\frac{p_2E^n(T^n+T_R^n+T_M^n)}{g_3+(T^n+T_R^n+T_M^n)}\varphi_6(\Delta t)+I^n}{1+\mu_3\varphi_6(\Delta t)}; \end{cases} \tag{7}$$

With given initial condictions $T(0)=T_0$, $T_R(0)=T_{R_0}$, $T_M(0)=T_{M_0}$, $N(0)=N_0$, $E(0)=E_0$, $I(0)=I_0$.

It is clear that the non-tumor state of (4) is exactly the non-tumor state of (7).

Theorem. ***3.1*** *The non-tumor state S^* is unstable for every value of Δt in the absence of the second specific chemotherapy drug.*

Proof. Linearizing the system (7) about the state S^*, the eigenvalues of the corresponding Jacobian matrix is given by:

$$\lambda = \frac{1}{1+\left[\tau_1+\tau_2-r_T+a_T(1-e^{-MC})+\frac{a_1E_0^*}{g_2}\right]\varphi_1(\Delta t)}, \lambda = \frac{1}{1-r_R\varphi_2(\Delta t)},$$

$$\lambda = \frac{1}{1+\left[-r_M+a_{T_M}(1-e^{-MC})+\tau_{M\to R}(1-e^{-MC})+\frac{a_2E_0^*}{g_4}\right]\varphi_3(\Delta t)},$$

$$\lambda = \frac{1+\left[-r_N+a_N(1-e^{-MC})\right]\varphi_4(\Delta t)}{\left[1+\left(-r_N+a_N(1-e^{-MC})+\frac{r_NN_0^*}{K_N}\right)\varphi_4(\Delta t)\right]^2} = e^{-\left(r_N-a_N(1-e^{-MC})\right)\Delta t},$$

$$\lambda = \frac{1}{1+\left[\mu_2+a_E(1-e^{-MC})\right]\varphi_5(\Delta t)}, \lambda = \frac{1}{1+\mu_3\varphi_6(\Delta t)},$$

Since $0 < \varphi_2(\Delta t) < \frac{1}{r_R}$, then $\left|\frac{1}{1-r_R\varphi_2(\Delta t)}\right| > 1$. Thus, the non-tumor state S^* is unstable for every value of Δt in the absence of the second specific chemotherapy drug. □

3.3 Stability Analysis of the Non-tumor state S^* in the presence of a second specific chemotherapy drug only toxic to T_R

The explicit form of the NSFD scheme of (4) is given by:

$$\begin{cases}
T^{n+1} = \dfrac{T^n}{1+(\tau_1+\tau_2-r_T)\varphi_1(\Delta t)+a_T(1-e^{-MC})\varphi_1(\Delta t)+r_T\left(\frac{T^n+T_R^n+T_M^n}{K_T}\right)\varphi_1(\Delta t)+\frac{a_1E^n\varphi_1(\Delta t)}{g_2+T^n}}; \\
T_R^{n+1} = \dfrac{T_R^n+\tau_1T^{n+1}\varphi_2(\Delta t)+\tau_{M\to R}(1-e^{-MC})T_M^n\varphi_2(\Delta t)}{1-r_R\varphi_2(\Delta t)+a_{T_R}(1-e^{-MC_2})\varphi_2(\Delta t)+r_R\left(\frac{T^n+T_R^n+T_M^n}{K_R}\right)\varphi_2(\Delta t)}; \\
T_M^{n+1} = \dfrac{T_M^n+\tau_2T^{n+1}\varphi_3(\Delta t)}{1+r_M\left(\frac{T^n+T_R^n+T_M^n}{K_M}\right)\varphi_3(\Delta t)+\frac{a_2E^n\varphi_3(\Delta t)}{g_4+T^n}-r_M\varphi_3(\Delta t)+a_{T_M}(1-e^{-MC})\varphi_3(\Delta t)+\tau_{M\to R}(1-e^{-MC})\varphi_3(\Delta t)}; \\
N^{n+1} = \dfrac{N^n+k(T^n+T_R^n+T_M^n)\left(1-\frac{T^n+T_R^n+T_M^n}{T^*}\right)}{1+r_N\left(\frac{N^n}{K_N}\right)\varphi_4(\Delta t)-r_N\varphi_4(\Delta t)+a_N(1-e^{-MC})\varphi_4(\Delta t)}; \\
E^{n+1} = \dfrac{c(T^n+T_R^n+T_M^n)\varphi_5(\Delta t)+\frac{p_1E^nI^n\varphi_5(\Delta t)}{g_1+I^n}+\beta\varphi_5(\Delta t)+E^n}{1+\mu_2\varphi_5(\Delta t)+a_E(1-e^{-MC})\varphi_5(\Delta t)+\alpha T_R^n}; \\
I^{n+1} = \dfrac{\frac{p_2E^n(T^n+T_R^n+T_M^n)}{g_3+(T^n+T_R^n+T_M^n)}\varphi_6(\Delta t)+I^n}{1+\mu_3\varphi_6(\Delta t)};
\end{cases} \tag{8}$$

Where $\varphi_2(\Delta t) = \dfrac{1-e^{-\left|r_R - a_{T_R}(1-e^{-MC_2})\right|\Delta t}}{\left|r_R - a_{T_R}(1-e^{-MC_2})\right|}$ With given initial condictions $T(0) = T_0$, $T_R(0) = T_{R_0}$, $T_M(0) = T_{M_0}$, $N(0) = N_0$, $E(0) = E_0$, $I(0) = I_0$.

Theorem. ***3.2*** *The non-tumor state S^* is locally asymptotically stable for every value of Δt in the presence of the second specific chemotherapy drug if the following condictions hold:*

i) $E_0^* > \dfrac{g_2}{a_1}\left[r_T - \tau_1 - \tau_2 - a_T(1-e^{-MC})\right]$
ii) $a_{T_R}(1-e^{-MC_2}) > r_R$
iii) $E_0^* > \dfrac{g_4}{a_2}\left[r_M - a_{T_M}(1-e^{-MC}) - \tau_{M\to R}(1-e^{-MC})\right]$

Remark 3.1: If one of conditions *i), ii) and iii)* fails, then S^* is unstable.

Proof. Linearizing the system (8) about the state S^*, the eigenvalues of the corresponding Jacobian matrix is given by:

$$\lambda = \frac{1}{1+\left[\tau_1+\tau_2-r_T+a_T(1-e^{-MC})+\dfrac{a_1E_0^*}{g_2}\right]\varphi_1(\Delta t)},$$
$$\lambda = \frac{1}{1+\left[-r_R+a_{T_R}(1-e^{-MC_2}\right])\varphi_2(\Delta t)},$$
$$\lambda = \frac{1}{1+\left[-r_M+a_{T_M}(1-e^{-MC})+\tau_{M\to R}(1-e^{-MC})+\dfrac{a_2E_0^*}{g_4}\right]\varphi_3(\Delta t)},$$
$$\lambda = \frac{1+\left[-r_N+a_N(1-e^{-MC})\right]\varphi_4(\Delta t)}{\left[1+\left(-r_N+a_N(1-e^{-MC})+\dfrac{r_NN_0^*}{K_N}\right)\varphi_4(\Delta t)\right]^2} = e^{-\left(r_N-a_N(1-e^{-MC})\right)\Delta t},$$
$$\lambda = \frac{1}{1+\left[\mu_2+a_E(1-e^{-MC})\right]\varphi_5(\Delta t)}, \lambda = \frac{1}{1+\mu_3\varphi_6(\Delta t)},$$

It follows that the non-tumor state S^* is locally asymptotically stable for every value of Δt in the presence of the second specific chemotherapy drug if the conditions *i), ii) and iii)* hold.

□

Theorem. ***3.3*** *The non-tumor state S^* is globally asymptotically stable for every value of Δt in the presence of the second specific chemotherapy drug if the conditions i), ii) and iii) hold.*

Proof. We must show that the sequence $(T^n, T_R^n, T_M^n, N^n, E^n, I^n)_n$ converge to $S^* = (0,0,0,N_0^*,E_0^*,0)$ for any positive initial conditions when the conditions *i), ii) and iii)* hold for every value of Δt.
The state $S^* = (0,0,0,N_0^*,E_0^*,0)$ is locally asymptotically stable for every value of Δt when the conditions *i), ii) and iii)* hold . Now suppose that for a certain $k > 0$, $(T^k, T_R^k, T_M^k, N^k, E^k, I^k)$ converge to $S^* = (0,0,0,N_0^*,E_0^*,0)$ and show that
$(T^{k+1}, T_R^{k+1}, T_M^{k+1}, N^{k+1}, E^{k+1}, I^{k+1})$ converge also to $S^* = (0,0,0,N_0^*,E_0^*,0)$.

(i) For T^{k+1},

$$T^{k+1} = \frac{T^k}{1 + (\tau_1 + \tau_2 - r_T)\varphi_1(\Delta t) + a_T(1 - e^{-MC})\varphi_1(\Delta t) + r_T\left(\frac{T^k + T_R^k + T_M^k}{K_T}\right)\varphi_1(\Delta t) + \frac{a_1 E^k \varphi_1(\Delta t)}{g_2 + T^k}}$$

Then $T^{k+1} \longrightarrow 0$ when $k \longrightarrow \infty$.

(ii) For T_R^{k+1},

$$T_R^{k+1} = \frac{T_R^k + \tau_1 T^{k+1}\varphi_2(\Delta t) + \tau_{M\to R}(1 - e^{-MC})T_M^k\varphi_2(\Delta t)}{1 - r_R\varphi_2(\Delta t) + a_{T_R}(1 - e^{-MC_2})\varphi_2(\Delta t) + r_R\left(\frac{T^k + T_R^k + T_M^k}{K_R}\right)\varphi_2(\Delta t)}$$

Then $T_R^{k+1} \longrightarrow 0$ when $k \longrightarrow \infty$.

(iii) For T_M^{k+1},

$$T_M^{k+1} = \frac{T_M^k + \tau_2 T^{k+1}\varphi_3(\Delta t)}{1 + r_M\left(\frac{T^k + T_R^k + T_M^k}{K_M}\right)\varphi_3(\Delta t) + \frac{a_2 E^k \varphi_3(\Delta t)}{g_4 + T^k} - r_M\varphi_3(\Delta t) + a_{T_M}(1 - e^{-MC})\varphi_3(\Delta t) + \tau_{M\to R}(1 - e^{-MC})\varphi_3(\Delta t)}$$

Then $T_M^{k+1} \longrightarrow 0$ when $k \longrightarrow \infty$.

(iv) For N^{k+1},

$$N^{k+1} - N_0^* = \frac{N^k + k(T^k + T_R^k + T_M^k)\left(1 - \frac{T^k + T_R^k + T_M^k}{T^*}\right) - N_0^*\left(1 + \frac{r_N N^k}{K_N}\varphi_4(\Delta t) - r_N\varphi_4(\Delta t) + a_N(1 - e^{-MC})\varphi_4(\Delta t)\right)}{1 + \frac{r_N N^k}{K_N}\varphi_4(\Delta t) - r_N\varphi_4(\Delta t) + a_N(1 - e^{-MC})\varphi_4(\Delta t)}$$

Then $N^{k+1} - N_0^* \longrightarrow 0$ when $k \longrightarrow \infty$. Thus, $N^{k+1} \longrightarrow N_0^*$ when $k \longrightarrow \infty$

(v) For E^{k+1},

$$E^{k+1} - E_0^* = \frac{c(T^k + T_R^k + T_M^k)\varphi_5(\Delta t) + \frac{p_1 E^k I^k \varphi_5(\Delta t)}{g_1 + I^k} + \beta\varphi_5(\Delta t) + E^k - E_0^*\left(1 + \mu_2\varphi_5(\Delta t) + a_E(1 - e^{-MC})\varphi_5(\Delta t) + \alpha T_R^k\right)}{1 + \mu_2\varphi_5(\Delta t) + a_E(1 - e^{-MC})\varphi_5(\Delta t) + \alpha T_R^k}$$

Then $E^{k+1} - E_0^* \longrightarrow 0$ when $k \longrightarrow \infty$. Thus, $E^{k+1} \longrightarrow E_0^*$ when $k \longrightarrow \infty$

(vi) For I^{k+1},

$$I^{k+1} = \frac{\frac{p_2 E^k (T^k + T_R^k + T_M^k)}{g_3 + (T^k + T_R^k + T_M^k)}\varphi_6(\Delta t) + I^k}{1 + \mu_3\varphi_6(\Delta t)}$$

Then $I^{k+1} \longrightarrow 0$ when $k \longrightarrow \infty$.

Hence, the non tumor state S_0^* is globally asymptotically stable for every value of Δt in the presence of the second specific chemotherapy drug when the conditions *i), ii) and iii)* hold.

□

4 Numerical simulations under different therapeutic approaches

The numerical simulations of the model (1) is done in MATLAB using *ode45* function. The parameter values used for these simulations are given in Table 1.

Table 1: Description of simulation parameters.

Parameters	Units	Description	Estimated value	Reference Source
r_T	Day^{-1}	Growth rate for wild tumor cells	0.15	[**10**]
r_R	Day^{-1}	Growth rate for resistant tumor cells	0.015	[**10**]
r_M	Day^{-1}	Growth rate for mutated tumor cells	0.1515	[**10**]
r_N	Day^{-1}	Growth rate for the normal cells	0.5	[**2**]
$K_T; K_R; K_M; K_N$	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}	[**10**]
a_1	Day^{-1}	rate of clearance of wild tumor cells	1.5	[**10**]
g_2	Cells	Half-saturation for wild tumor cells clearance	10^5	[**1**]
$\tau_{M\to R}$	Day^{-1}	conversion rate	10^{-4}	[**2**]
a_2	Day^{-1}	rate of clearance of mutated tumor cells	1.5	[**10**]
g_4	Cells	Half-saturation for mutated tumor cells clearance	10^5	[**10**]
k	Day^{-1}	tumor-normal cell interation rate	0.028	[**1**]
T_*	Cells	Critical size of tumor	3×10^5	[**2**]
c	Day^{-1}	Antigenicity	0.5	[**10**]
μ_2	Day^{-1}	Death rate of immune cells	0.003	[**10**]
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}	[**1**]
a_T	Day^{-1}	death rate induced by the chemotherapeutic drug on T	0.15	[**2**]
a_{T_M}	Day^{-1}	death rate induced by the chemotherapeutic drug on T_M	0.10	Assumed
M	$m^2.mg^{-1}$	Pharmacokinetics parameter	1	[**2**]
a_N	Day^{-1}	death rate induced by the chemotherapeutic drug on N	0.05	Assumed
a_E	Day^{-1}	death rate induced by the chemotherapeutic drug on E	0.05	Assumed
a_{EE}	Day^{-1}	Immune boosting rate induced by the immunotherapy drug	0.10	Assumed
i	$mg.m^{-2}$	Concentration of immunotherapy drug	0.2	Assumed

4.1 Constant concentration of the chemotherapy drug ($C = 0.2mg.m^{-2}$) and drug-induced resistance

Assumptions

• The chemotherapy drug is administered at $t = 600$ days.

• The mutation from the group of wild tumor cells T to the group of mutated tumor cells T_M starts at $t = 0$ days.

• As the chemotherapy drug is introduced the conversion from the group of mutated tumor cells T_M to the group of resistant tumor cells T_R starts immediately (ie at $t = 600$ days). Thus the immune-suppression by the resistant tumor cells starts also immediately

Note that the interaction of the chemotherapy drug with the mutated tumor cells partially kills them and partially turns them into drug-resistant tumor cells. Those that remain will grow and create new cells that carry the mutated gene, which potentially can create drug-induced resistance.

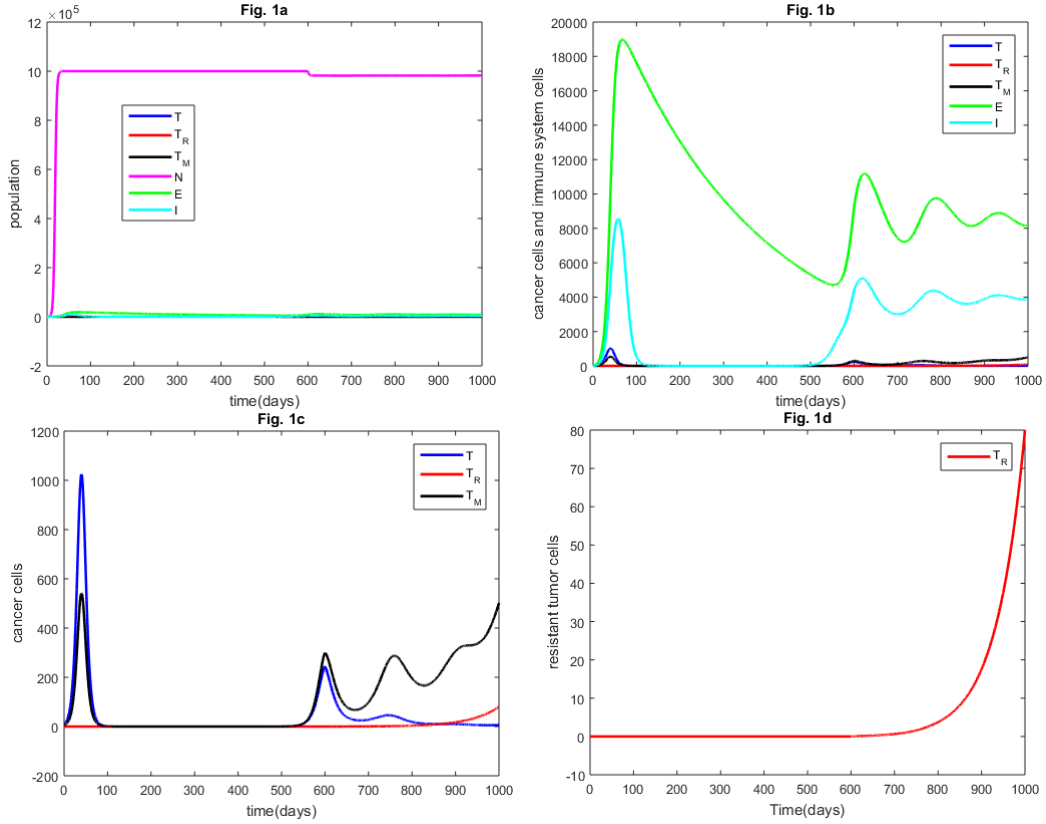

Fig. 1: Simulation results under the therapeutic approach 4.1.

From $t = 100$ days to $t = 500$ days the tumor cells are controlled by the immune system. However from $t = 550$ days these tumor cells started to grow (see Fig. 1a and 1c). After the introduction of the

chemotherapy drug, the wild tumor cells T started to die out from the system. The mutated tumor cells T_M are still in the system by growing. They could be killed by the immune system, but due to the logistic grow of resistant tumor cells which is suppressing the immune system from $t = 600$, they started to grow (see fig. 1c and 1d). The evolution of normal cells can be seen through the figure 1a.

4.2 Constant concentration of the chemotherapy and immunotherapy drug ($C = 0.2mg.m^{-2}$ and $i = 0.2mg.m^{-2}$) and drug-induced resistance.

The assumptions made in the subsection 4.1 are also taken into account here. Moreover, the immunotherapy drug is administered at $t = 800$ days.

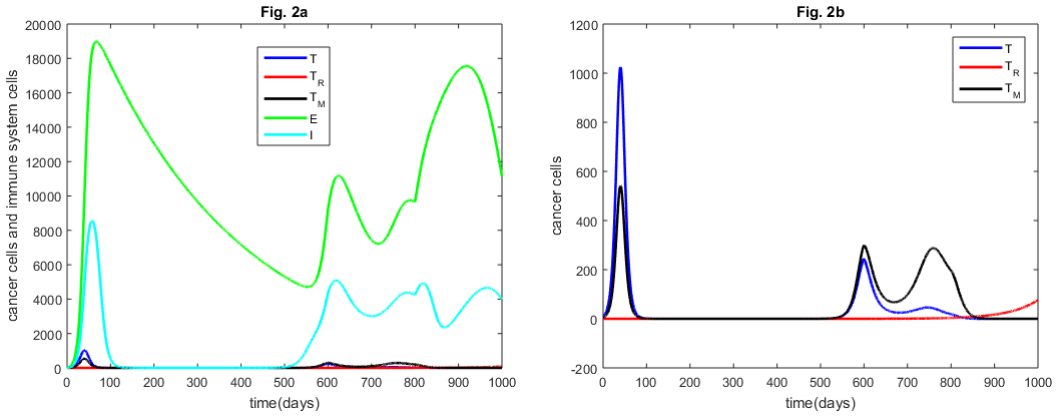

Fig. 2: Simulation results under the therapeutic approach 4.2.

The effectiveness of the immunotherapy drug can be seen with Fig. 2a and 2b. Indeed, the mutated tumor cells that were still growing in the presence of the chemotherapy drug began to die out from $t = 850$ days after the introduction of the immunotherapy drug at $t = 800$ days. Thus, this therapeutic approach is effective on sensitive tumor cells.

4.3 Decreasing concentration of the chemotherapy drug ($C(t) = 0.2\times e^{-10^{-3}t} mg.m^{-2}$), drug-induced resistance and constant concentration of the immunotherapy drug ($i = 0.2mg.m^{-2}$)

The assumptions made in the subsection 4.1 are also taken into account here. However, the concentration of the chemotherapy drug decreases exponentially over time. The immunotherapy drug is administered at $t = 800$ days.

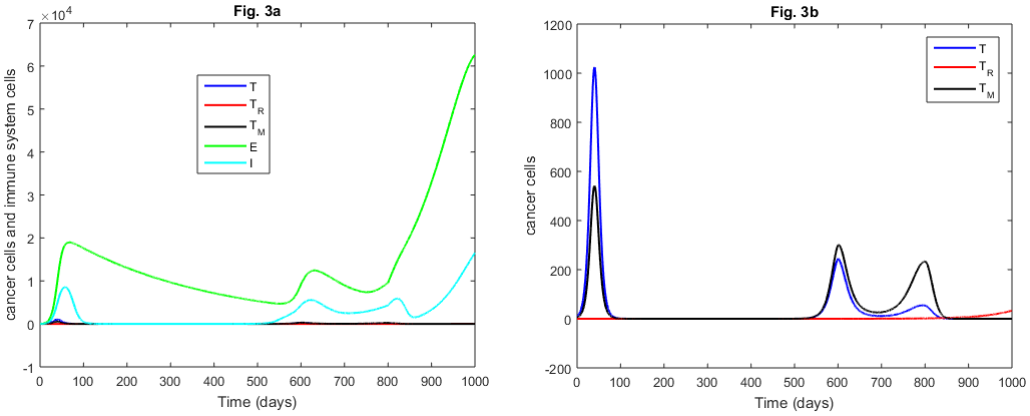

Fig. 3: Simulation results under the therapeutic approach 4.3.

The results of the simulations 3a and 3b are almost similar to those obtained in the therapeutic approach 4.2. All the sensitive tumor cells disappear from the system at the end of the simulation time. However, resistant tumor cells grow more slowly in Fig. 3b than in Fig. 2b. This is due to the decrease in the concentration of the chemotherapeutic drug used.

4.4 Decreasing concentration of the chemotherapy drug ($C(t) = 0.2\times e^{-10^{-3}t} mg.m^{-2}$) and both intrinsic and drug-induced resistance.

Assumptions

• The mutation from the group of wild tumor cells T to the group of resistant tumor cells T_R starts at $t = 0$ days.

• The mutation from the group of wild tumor cells T to the group of mutated tumor cells T_M starts at $t = 0$ days.

• The chemotherapy drug is administered at $t = 650$ days. So, the conversion from the group of mutated tumor cells T_M to the group of resistant tumor cells T_R starts immediately (ie at $t = 650$ days).

As suggested in Ref. 2, We introduce in addition a second chemotherapy drug considered constant over time with a higher dosage $\left(a_{T_R}(1 - e^{-MC_2})T_R \text{ with } a_{T_R} = 0.15 \text{ and } C_2 = 0.6mg.m^{-2}\right)$ that is specifically toxic to drug resistant tumor cells (see Fig. 4c and 4d). This drug is introduced at $t = 850$ days.

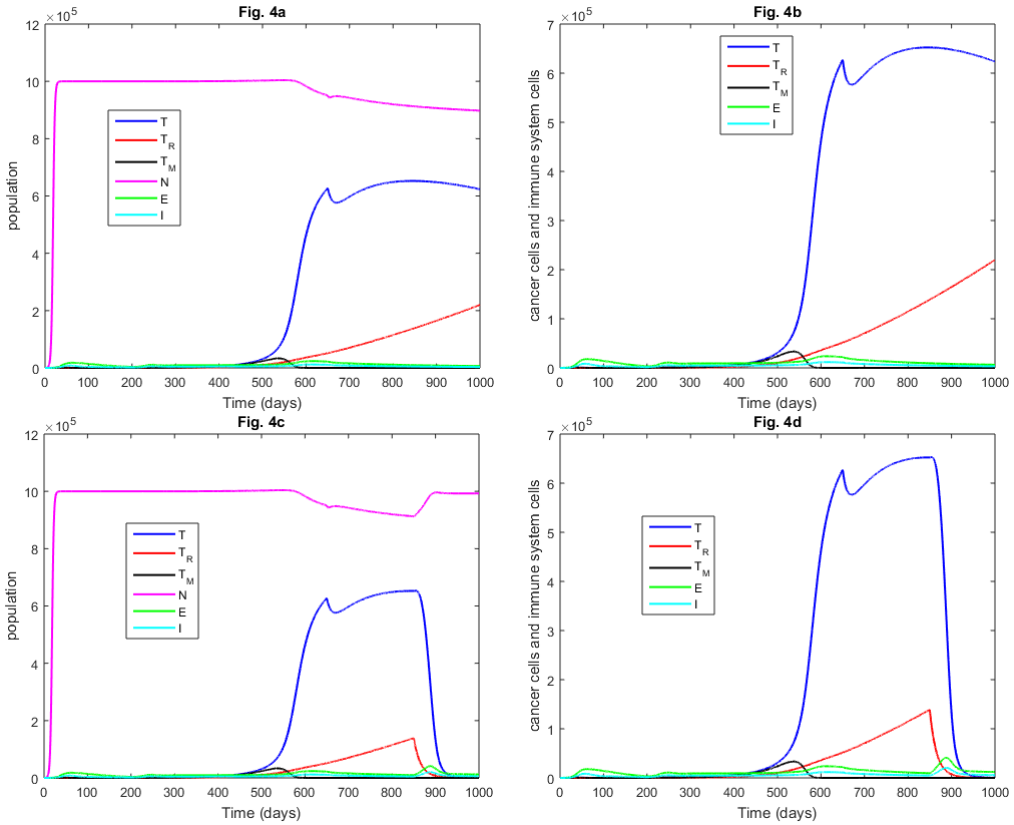

Fig. 4: Simulation results under the therapeutic approach 4.4.

Since the resistant tumor cells started to grow, the immune-suppression also started at the begining of the simulation time. However, the immune system was able to fight the mutated tumor cells. But the wild tumor cells is growing as well and become detectable around $t = 550$ days to the point where the chemotherapy drug administreted at $t = 650$ days was not able to fight the wild tumor cells (see Fig. 4a and 4b).
Through Fig. 4c and 4d, the second chemotherapy drug administreted at $t = 850$ days kill the resistant tumor cells and from that moment the immune system was able to fight the wild tumor cells. It can be concluded that the combination of these two chemotherapy drug is more successful therapeutic approach to control all types of tumor cells.

4.5 Increasing concentration of the chemotherapy drug ($C(t) = 1-e^{-10^{-3}t} mg.m^{-2}$) and both intrinsic and drug-induced resistance.

The assumptions made in the subsection 4.4 are also taken into account here. However, the concentration of the chemotherapy drug increases from 0 to 1 over time.

Also, We introduce in addition a second chemotherapy drug considered constant over time with a higher dosage $\left(a_{T_R}(1-e^{-MC_2})T_R \text{ with } a_{T_R}=0.15 \text{ and } C_2=0.6mg.m^{-2}\right)$ that is only toxic to drug resistant tumor cells specifically (see Fig. 5c and 5d). This drug is introduced at $t=850$ days.

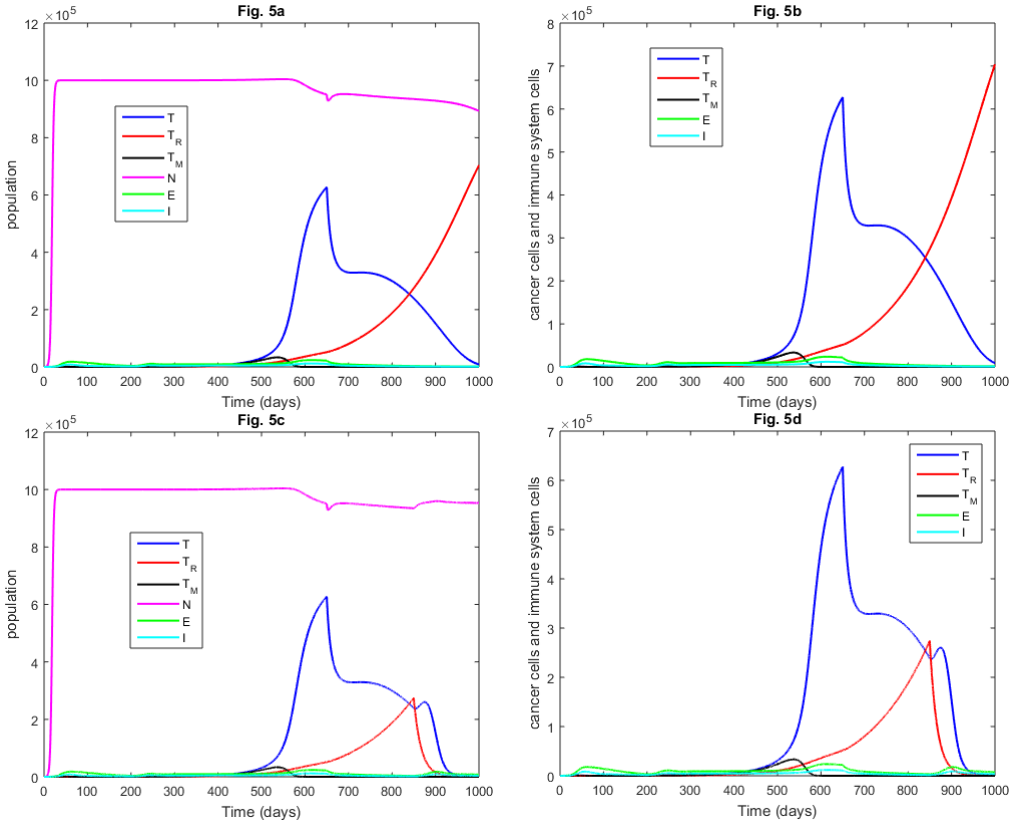

Fig. 5: Simulation results under the therapeutic approach 4.5.

Contrary to the simulation results in Fig. 4a and 4b, here the wild tumor cells disappear from the system at the end of the simulation time. This is due to the increase in the concentration of the chemotherapy drug administreted from $t=650$ days (see Fig. 5a and 5b). Fig. 5c and 5d show that the second chemotherapy drug administreted at $t=850$ days kill the resistant tumor cells. It can be also concluded that the combination of these two chemotherapy drug is more successful therapeutic approach to control all types of tumor cells.

5 Conclusion

In this study, a nonstandard finite difference scheme for our previous multi-mutation and drug resistance model was constructed to analyze the stability of non-tumor state in the presence of both immunotherapy and chemotherapy. Conditions under which tumor can be eliminated was identified. Numerical

simulations of the model in the presence of both immunotherapy and chemotherapy and under different treatment strategies was performed with the aid of MATLAB sofware using*ode45* function. Two differents treatment strategies was proposed when the dynamical system expresses intrinsic and drug induced resistance with immune suppression.

The non-tumor state is stable (ie tumor can be eliminated) under conditions in the presence of both immunotherapy and chemotherapy when a second specific chemotherapy drug only toxic to resistant tumor cells (T_R) is introduced. It can be seen through numerical simulations that the treatment strategies in section 4.4 and 4.5 could be the more successful therapeutic approach to control both the progression of cancer as well as the existing resistance. Some open concerns include whether mutations, the conversion and the infection occur at a constant rate or whether the rates may be affected by the immunotherapy drug and the chemotherapy drug.

Data availability statement

Data supporting this model are from previously published articles and they have been duly cited in this paper. Parameter values taken from published articles are cited at relevant places within the text as references.
MATLAB Codes for simulations are available from the first author.

Conflicts of interest

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

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