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# A model for cancer chemo-immunotherapy treatment schedules

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***Abstract:*** **This work constructs a generic model for chemo-immunotherapy of cancer in a healthy tissue. The main interests are the modeling and computer study of chemotherapy, immunotherapy and the advantages in their combined applications. It describes the dynamics of Healthy, Immune, and Cancer cells when chemotherapy and immunotherapy are applied, either separately or combined. The analysis of the model shows that its solutions exist, are bounded and nonnegative on each finite time interval, and thus are biologically feasible. The model simulations describe the development of the disease without intervention, when only chemotherapy or immunotherapy are administered periodically, when the two modalities are combined. In this manner, once validated, the model can be used to design treatment schedules for improved outcomes.**

***Keywords:*** **dynamical system model, cancer, chemotherapy, immunotherapy, simulations**

***MSC2020:*** **34A12, 37C20, 49K15, 49K40, 92C17, 92C60**

## I. Introduction

Every year, cancer causes the deaths of millions of people around the world. Moreover, the death rate has been increasing year after year, as has the disease morbidity. The WHO World Cancer Report [1] provides very recent information on the prevalence and trends of cancer in the world. Although considerable progress has been achieved in the understanding and treatment of cancer, the current limitations of the scheduling of chemotherapy and immunotherapy treatments are quite noticeable. Indeed, they are being dictated by the results of field drug testing, which are very expensive and time consuming and usually do not address the very different possible combinations of treatments. The main aim of this work is to provide a tool, in the form of a mathematical model, for the scheduling of cancer chemotherapy and immunotherapy treatments.

More generally, it is a contribution to the growing field of mathematical modeling of various aspects of the disease. Indeed, such a mathematical model and its computer simulations allow for the study of alternative scenarios, which cannot be performed in the field, and thus open the ways for possible optimization of treatments and improvement of the outcomes. The new mathematical model is within the theory of dynamical systems and includes chemotherapy and immunotherapy. This model, once validated by comparison with field data, can be used to optimize cancer chemotherapy



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and immunotherapy schedules. The model, in addition to its predictive aspects, can be used to better understand the disease dynamics.

In recent years, mathematical models have become an integral part of the study of biological systems and, what is relevant here, the dynamics of cancer; see, e.g., [2–5] and the host of references therein. Indeed, these are powerful tools for both obtaining a mechanistic understanding of the processes involved in cancer and possible quantitative predictions of the treatments' outcomes. In this way, mathematical modeling contributes to the insight into the underlying mechanisms and can provide quantitatively validated predictions. The application of mathematical models to systems such as these are broad and varied.

The monograph [2] employs tools and methods from the theories of dynamical systems and optimal control to analyze the populations of cancer cells and elements of the tumor micro-environment undergoing anticancer therapies. An extensive survey of optimization of mathematical models for chemotherapy treatments can be found in [5].

The works [6, 7] develop and analyze mathematical models for cancer growth at the cell-level and its treatments by combination of immune, vaccine and chemotherapy. The model is similar to the one here, and the work [8] uses pulsed chemotherapy as we do. Another model similar to the one constructed here can be found in [9]. There, the conditions for the local stability of all the equilibrium points and global stability condition for the tumor-free equilibrium point, including the feasibility of the solution, are studied. However, when dealing with cancer, it seems to us that the stability of disease-free or endemic equilibria is of less interest.

A model for the interactive dynamics between effector-tumor-normal cells can be found in [10], where the growth of cancer, when immunotherapy is applied, is presented. Their numerical simulations show that the optimal regimens eradicate the tumor load in less time than the other treatments. We also mention some of the mathematical models constructed recently to deal with chemotherapy or immunotherapy or a combination of both are [11–17], and the references therein. We employ strategies similar to these sources; specifically concerning chemotherapy, immunotherapy and combinations of both treatments, to better understand each treatment, as well as how they interact with one another to eliminate cancer from the system.

Following this introduction, Section II constructs our mathematical model. As mentioned above, it is similar to those in [9, 10]. It consists of a coupled nonlinear system of ordinary differential equations (ODEs). We explain the assumptions underlying the model and the various terms in the rate equations. The model describes the dynamics of Healthy, Immune and Cancer cell populations and of the chemo-and-immunotherapies. In particular, we allow for the pulse-like administration of the chemo drug or immunotherapy.

Section III presents the analysis of the model; we show that the solutions exist and are bounded on every finite time interval, and if the initial conditions are nonnegative the solutions remain nonnegative.

Section IV deals with the analysis of the system's steady states and their stability. There, we determine the basic stability number $\mathcal{R}_0$ for the Disease-Free Equilibrium (DFE).

Section V describes an algorithm for the numerical simulations of the model and depicts a few representative model solutions. It indicates that combined chemotherapy and immunotherapy can lead to better outcomes than each one separately.

The paper concludes in Section VI, where we summarize the results and comment on some near-future research directions.

## II. Mathematical model

We develop a 'generic' model for the combined chemotherapy and immunotherapy of a cancer tumor. In the process, a chemotherapeutic drug and white platelets are administered to the tumor to eliminate it. The model allows us to study the effects of each treatment on its own and of the outcomes of combined treatments.

The model deals with total numbers, assumes that the numbers of the cells are large, so we may use continuous methods and that ODEs may be applied. We let the total number of normal or healthy cells be $H(t)$, immune cells $I(t)$, cancer tumor cells $K(t)$, and the amount of chemotherapy drug $D(t)$, all in the tumor and its immediate surroundings, at time $t$. We measure time in days, and the time interval of interest is $0 \le t \le T$, for some $T > 0$.

For mathematical reasons, which we explain below, we introduce the Heaviside or *cutoff function* $\chi_a$, for $a \ge 0$, defined as

$$\chi_a(X) = \begin{cases} 0, & 0 \le X \le a, \\ 1, & a < X. \end{cases}$$

The model we propose deals with the rates of change of the four variables as follows.

**Model 1** (*Model for Chemotherapy and Immunotherapy of a Cancer Tumor*)**.** *Find four functions* $H, I, K, D : [0, T] \to \mathbb{R}^+$*, such that:*

$$\frac{dH}{dt} = \alpha_1 H(1 - \alpha_H H) - \gamma_1 KH - \mu_1 DH - \mu_H H, \quad (1)$$

$$\frac{dI}{dt} = q + \psi + \alpha_2 I(1 - \alpha_I I) - \gamma_2 KI - \mu_2 DI - \mu_I I, \quad (2)$$

$$\frac{dK}{dt} = \alpha_3 K(1 - \alpha_K K)\chi_1(K) - \gamma_3 IK - \gamma_4 HK - \mu_3 DK - \mu_K K, \quad (3)$$

$$\frac{dD}{dt} = \varphi - \beta_1 ID - \beta_2 HD - \beta_3 KD - \mu_D D. \quad (4)$$

*Together with the initial conditions,*

$$H(0) = H_0,\ I(0) = I_0,\ K(0) = K_0,\ D(0) = D_0.$$

In the model, the rates are per day, $H, I, K$ are measured as populations, that is, the number of individuals, while the units of $D$ are arbitrary, and the various terms have the correct units, so that $\beta_3 KD$ or $\varphi$ have the units of drug/day, while $q$ and $\psi$ have units of cell/day.

Equation (1) describes the rate of change of the normal cell population, which is assumed to grow logistically, with growth rate $\alpha_1$ and carrying capacity $1/\alpha_H$. The second term, $\gamma_1 KH$, represents the loss rate due to interaction with tumor cells. The term $\mu_1 DH$ is the death rate caused by the drug, and $\mu_H H$ is the cell's natural death rate, in the absence of the chemo drug.

Equation (2) describes the immune cells rate of change in the tumor and its vicinity. The natural supply rate of immune cells from internal growth and from outside or the rest of the body is $q = q(t)$, and the function $\psi = \psi(t)$ represents the immunotherapy process in which white platelets are added to the tumor, thus increasing the number of immune cells. The tumor-specific immune response is also regulated by logistic growth, which is the rate at which the number of immune cells grows, with rate coefficient $\alpha_2$ and $1/\alpha_I$ the carrying capacity. The terms $\gamma_2 IK$ and $\mu_2 DI$ describe the rate at which immune cells die because of their interaction with tumor cells and that caused by the drug, respectively. Finally, $\mu_I I$ represents their natural mortality rate.

We note that mathematically, we could combine $q$ and $\psi$ into one function. However, we choose to separate them because the first is organic and the second represents the medical intervention.

The rate of change in the number of tumor cells is described by equation (3). The logistic term controls the growth rate, where $\alpha_3$ and $1/\alpha_K$ denote the growth rate constant and the carrying capacity of tumor cells, respectively. When the population of cancer cells is above carrying capacity, the cells die out. The second and third terms on the right-hand side, $\gamma_3 IK$, $\gamma_4 KH$, represent the loss rate caused by interactions with immune and normal cells, and $\mu_3 CK$ represents the rate at which the drug kills tumor cells. The last term describes their natural death rate, where $\mu_K$ is likely to be a very small number. The introduction of $\chi_1(K)$ is for the following reasons.

**Remark 1.** Whereas the logistic term in (3) makes biological sense in describing the growth of cancer cells up to the carrying capacity of the system, it has a mathematical drawback in that even for exceedingly small $K << 1$, once drug administration is stopped, cancer rebounds and $K$ grows to its carrying capacity, which defeats the purpose of the model. Therefore, we introduce the cutoff function $\chi_a$, which turns off the growth term once the population of cancer cells is below the threshold $a$. For the sake of simplicity we choose $a = 1$. In real situations, there may be a small number of cancer cells that survive the treatments but are of no concern, because the body can take care of them without the treatments.

It is assumed that the chemotherapy drug kills all types of cells, but at different rates. Indeed, $\mu_1 DH$, $\mu_2 DI$, $\mu_3 DK$ refer to the death rates of immune, tumor, and normal cells, respectively, caused by chemotherapy treatment.

Equation (4) describes the dynamics of the chemotherapy drug. The first term, $\varphi = \varphi(t)$, represents the rate at which the drug is administered, while the drug amount decreases because of the interactions with the immune, cancer, and normal cells. The rates are given by $\beta_1 DI$, $\beta_2 DH$, and $\beta_3 DK$, respectively. The natural decay of the drug in vivo is $\mu_D D$.

We note that whereas the amount of chemotherapy drug is represented by an equation, we add the immunotherapy into the equation for the immune cells, since it seems more natural to consider them as a part of the immune system.

To complete the model, we prescribe in (4) the initial cell populations and the initial drug amount. For the sake biological sense, we assume below that

$$H(0) = H_0 \in (0, 1/\alpha_H), \quad I(0) = I_0 \in (0, 1/\alpha_I),$$
$$K(0) = K_0 \in (1, 1/\alpha_K), \quad D(0) = D_0 > 0. \quad (5)$$

We note that the model is rather complex, with nonlinear interactions and 21 rate constants, three, possibly

time dependent, input functions $q$, $\varphi$ and $\psi$ and four initial conditions.

## III. Existence, positive invariance, and boundedness

We proceed with the mathematical analysis. Since the right-hand sides are locally Lipschitz continuous, the system (1)–(4) has a local solution. Using the initial conditions (5) it follows that there exists $0 < t_0$ such that the solution exists on the time interval $[0, t_0]$, and it is nonnegative and bounded. Let $C^*$ denote the bound of all the variables on $[0, t_0]$.

To show global solvability, we first show that the model is *biologically feasible*, that is, if we start with nonnegative initial conditions all the solutions remain nonnegative. Moreover, we also show that all the solutions are bounded on arbitrary finite time intervals. These two facts allow us to establish the global solvability on every finite time interval.

**Proposition 1.** *Assume that the initial conditions satisfy (5) and $q$, $\varphi$ and $\psi$ are Lipschitz, nonnegative and bounded functions, say $0 \le q, \varphi, \psi \le M$. Then, every solution of system (1)–(4) satisfies the estimates:*

$$0 < H \le H_0 e^{\alpha_1 T}, \tag{6}$$

$$0 < I \le \frac{1}{\alpha_2}(I_0 e^{\alpha_2 T} + 2MT), \tag{7}$$

$$0 \le K \le K_0 e^{\alpha_3 T}, \tag{8}$$

$$0 < D \le D_0 + MT, \tag{9}$$

*on every interval $[0, T]$, for $0 < T < \infty$.*

We conclude that the *feasible region* $\Delta$ is

$$\Delta = \big\{(H, I, K, D) \in R^4_+ :\ H \le H_0 e^{\alpha_1 T}, \\ I(t) \le \frac{1}{\alpha_2}(I_0 e^{\alpha_2 T} + 2MT), \\ K(t) \le K_0 e^{\alpha_3 T},\ D(t) \le D_0 + MT\big\},$$

which is positively invariant for the system (1)–(4).

*Proof:* First, since the initial conditions are positive by the continuity of the solutions there is a time interval $[0, t_0]$, $t_0 > 0$, on which the solutions are nonnegative and bounded by some positive constant $C^*$. It follows from (1) that

$$H' \le \alpha_1 H.$$

Then, it follows from Gronwall's Lemma that

$$H(t) \le H_0 e^{\alpha_1 T}.$$

Next, since $H_0 > 0$, because of the continuity and local boundedness of the solutions, it follows from (1) that

$$H' > -(\alpha_1 \alpha_H C^* + \gamma_1 C^* + \mu_1 C^* + \mu_H) H \ge -c_* H,$$

where $c_* > 0$, and this implies that

$$H(t) \ge H_0 e^{-c_* t} > 0.$$

This establishes estimate (6).

Estimate (8) is derived similarly. The introduction of the cutoff function $\chi$ does not change the estimates, actually makes it slightly easier.

To obtain (7) we proceed in the same way. Indeed, (2) implies that

$$I' \le q + \alpha_2 I \le M + \alpha_2 I,$$

hence

$$\frac{\alpha_2 I'}{M + \alpha_2 I} \le \alpha_2 t,$$

and then we find

$$I \le \frac{1}{\alpha_2}(M + I_0 e^{\alpha_2 t}).$$

Considering the other inequality,

$$\frac{dI}{dt} \ge -(\alpha_2 \alpha_I + \gamma_2 K + \mu_2 D + \mu_I) I \ge -c_{**} I,$$

thus,

$$I(t) \ge I_0 e^{-c_{**} t} > 0.$$

These establish (7).

Finally, we turn to (9). It follows from (4) that

$$D' \le M,$$

therefore

$$D(t) \le D_0 + MT.$$

Furthermore,

$$D' \ge -(\beta_1 I + \beta_2 H + \beta_3 K + \mu_D) D,$$

and so

$$D(t) \ge D_0 e^{-c_1 t} \ge 0.$$

This completes the proof. ∎

This result shows that the system is Lipschitz on every arbitrary finite time interval. Therefore, we have the following global existence result.

**Theorem 1** (Global Existence)**.** *Assume that the initial conditions satisfy (5) and $q$ and $\varphi$ are positive, bounded and Lipschitz continuous functions. Then, system (1)–(4) has a unique smooth solution on every finite time interval $[0, T]$.*

## IV. Equilibrium points and their stability

Equilibrium points are found by equating the derivatives to zero. Denoting $(\bar{H}, \bar{I}, \bar{K}, \bar{D})$ the equilibrium values and omitting the bars, we have

$$\begin{aligned}\alpha_1 H(1-\alpha_H H) - \gamma_1 KH - \mu_1 DH - \mu_H H = 0,\\ q + \psi + \alpha_2 I(1-\alpha_I I) - \gamma_2 IK - \mu_2 DI - \mu_I I = 0,\\ \alpha_3 K(1-\alpha_K K)\chi_1(K) - \gamma_3 IK - \gamma_4 KH\\ -\mu_3 DK - \mu_K K = 0,\\ \varphi - \beta_1 DI - \beta_2 DH - \beta_3 DK - \mu_D D = 0.\end{aligned}$$

For biological reasons, we assume everywhere below that the growth rate constants are larger than the death rate constants,

$$\alpha_1 > \mu_H, \quad \alpha_2 > \mu_I, \quad \alpha_3 > \mu_K. \tag{10}$$

### A. Disease free equilibria

To study the DFEs, we observe that we need to have $K = 0$ and $\psi = \varphi = 0$, hence $D = 0$, since neither the drug nor the immunotherapy are needed. Moreover, $q = const. > 0$. Thus, we have the reduced system,

$$\begin{aligned}\alpha_1 H(1-\alpha_H H) - \mu_H H = 0,\\ q + \alpha_2 I(1-\alpha_I I) - \mu_I I = 0.\end{aligned}$$

The first equation has the two solutions

$$H_1 = \frac{(\alpha_1 - \mu_H)}{\alpha_1 \alpha_H}, \quad H_2 = 0.$$

The second equation has two solutions

$$I_{1,2} = \frac{(\alpha_2 - \mu_I) \pm \sqrt{(\alpha_2 - \mu_I)^2 + 4\alpha_2 \alpha_I q}}{2\alpha_2 \alpha_I}.$$

We note that the solution $I_1$ is positive, since $\alpha_2 > \mu_I$, while $I_2$ is negative, which we discard as a mathematical artifact. Indeed, since the solutions are nonnegative, Proposition 1, the negative solution cannot be reached as a long-time limit, starting with nonnegative initial conditions.

Therefore, we find four DFE solutions $(H, I, K, D)$, however the two solutions with $H_2 = 0$ are of no interest and neither is $I_2$. Hence, we consider the only feasible solution

$$(H_1, I_1, 0, 0). \tag{11}$$

The stability of these DFE points is studied below.

In the numerical simulations, in the case of convergence to a DFE, it was found that

$$(H, I, K, D) = (600, 958, 0, 0).$$

To study the stability of the DFE, we computed the Jacobian of the system, given by

$$J(H,I,K,D) = \begin{bmatrix} J_{11} & 0 & -\gamma_1 H & -\mu_1 H \\ 0 & J_{22} & -\gamma_2 I & -\mu_2 I \\ -\gamma_4 K & -\gamma_3 K & J_{33} & -\mu_3 K \\ -\beta_2 D & -\beta_1 D & -\beta_3 D & J_{44} \end{bmatrix}$$

where the terms $J_{11}, J_{22}, J_{33}$ and $J_{44}$ are:

$$J_{11} = \alpha_1(1 - 2\alpha_H H) - \gamma_1 K - \mu_1 D - \mu_H, \tag{12}$$
$$J_{22} = \alpha_2(1 - 2\alpha_I I) - \gamma_2 K - \mu_2 D - \mu_I, \tag{13}$$
$$J_{33} = \alpha_3(1 - 2\alpha_K K) - \gamma_3 I - \gamma_4 H - \mu_3 D - \mu_K, \tag{14}$$
$$J_{44} = -\beta_1 I - \beta_2 H - \beta_3 K - \mu_D. \tag{15}$$

Then, in the DFE, we have

$$\begin{aligned} J_{11} &= (\alpha_1 - \mu_H) - 2\alpha_1 \alpha_H H = -(\alpha_1 - \mu_H) < 0,\\ J_{22} &= (\alpha_2 - \mu_I) - 2\alpha_2 \alpha_I I\\ &= -\sqrt{(\alpha_2 - \mu_I)^2 + 4\alpha_2 \alpha_I q} < 0,\\ J_{33} &= (\alpha_3 - \mu_K) - \gamma_3 I - \gamma_4 H\\ &= (\alpha_3 - \mu_K) - \gamma_4 \frac{(\alpha_1 - \mu_H)}{\alpha_1 \alpha_H}\\ &\quad - \gamma_3 \frac{(\alpha_2 - \mu_I) + \sqrt{(\alpha_2 - \mu_I)^2 + 4\alpha_2 \alpha_I q}}{2\alpha_2 \alpha_I},\\ J_{44} &= -\beta_1 I - \beta_2 H - \mu_D = -\beta_2 \frac{(\alpha_1 - \mu_H)}{\alpha_1 \alpha_H} - \mu_D\\ &\quad - \beta_1 \frac{(\alpha_2 - \mu_I) + \sqrt{(\alpha_2 - \mu_I)^2 + 4\alpha_2 \alpha_I q}}{2\alpha_2 \alpha_I} < 0. \end{aligned}$$

Hence,

$$J(H,I,0,0) = \begin{bmatrix} J_{11} & 0 & -\gamma_1 H & -\mu_1 H \\ 0 & J_{22} & -\gamma_2 I & -\mu_2 I \\ 0 & 0 & J_{33} & 0 \\ 0 & 0 & 0 & J_{44} \end{bmatrix}.$$

Since $J_{11} < 0$, $J_{22} < 0$ and $J_{44} < 0$ the stability of the DFE depends on the sign of $J_{33}$. We conclude that:

**Proposition 2.** *Assume that (10) holds. Then, the DFE is stable and attracting when*

$$\begin{aligned}(\alpha_3 - \mu_K) < \gamma_3 \frac{(\alpha_2 - \mu_I) + \sqrt{(\alpha_2 - \mu_I)^2 + 4\alpha_2 \alpha_I q}}{2\alpha_2 \alpha_I}\\ + \gamma_4 \frac{(\alpha_1 - \mu_H)}{\alpha_1 \alpha_H}.\end{aligned}$$

*When equality holds, the DFE is only stable. When the inequality is reversed, the DFE is unstable.*

We conclude that the *basic stability number* is

$$\mathcal{R}_0 = \Big(2\alpha_1\alpha_H\alpha_2\alpha_I(\alpha_3-\mu_K)\Big)/ \Big(\gamma_3\alpha_1\alpha_H\big((\alpha_2-\mu_I)+\sqrt{(\alpha_2-\mu_I)^2+4\alpha_2\alpha_I q}\big) + 2\gamma_4\alpha_2\alpha_I(\alpha_1-\mu_H)\Big). \quad (16)$$

Using the baseline simulations, we find that $\mathcal{R}_0 = 0.3208$, thus, the DFE is stable and attracting.

### B. Endemic equilibrium

The main interest of this work is the eradication of cancer cells; hence, the endemic equilibrium is of no interest here. However, for the sake of completeness, we provide the following brief description.

To find the endemic equilibria (EE), we assume that $q = const. > 0$, and $\varphi = const. > 0$, since it is necessary to use the chemo to keep the cancer at a steady nonzero level, but $\psi = 0$. The system now is the full system, indeed,

$$\begin{aligned} \alpha_1(1-\alpha_H H) - \gamma_1 K - \mu_1 D - \mu_H &= 0,\\ q+\psi+\alpha_2 I(1-\alpha_I I) - \gamma_2 IK - \mu_2 DI - \mu_I I &= 0,\\ \alpha_3(1-\alpha_K K) - \gamma_3 I - \gamma_4 H - \mu_3 D - \mu_K &= 0,\\ \varphi - \beta_1 DI - \beta_2 DH - \beta_3 DK - \mu_D D &= 0. \end{aligned}$$

Simple manipulations, using the fact that $H > 0$ and $K > 1$, otherwise $K = 0$, hence $\chi_1(K) = 1$, yield

$$\begin{aligned} \alpha_1\alpha_H H + \gamma_1 K + \mu_1 D &= \alpha_1 - \mu_H,\\ q+\psi+\alpha_2 I(1-\alpha_I I) - \gamma_2 IK - \mu_2 DI - \mu_I I &= 0,\\ \alpha_3\alpha_K K + \gamma_3 I + \gamma_4 H + \mu_3 D &= \alpha_3 - \mu_K,\\ \varphi - \beta_1 DI - \beta_2 DH - \beta_3 DK - \mu_D D &= 0. \end{aligned}$$

Therefore,

$$\begin{aligned} H &= \frac{1}{\alpha_1\alpha_H}\left(\alpha_1 - \mu_H - \gamma_1 K - \mu_1 D\right),\\ I &= \frac{1}{\alpha_2\alpha_I}\Big((\alpha_2 - \gamma_2 K - \mu_2 D - \mu_I) + \sqrt{(\alpha_2 - \gamma_2 K - \mu_2 D - \mu_I)^2 + 4\alpha_2\alpha_I(q+\psi)}\Big),\\ K &= \frac{1}{\alpha_3\alpha_K}\left(\alpha_3 - \mu_K - \gamma_3 I - \gamma_4 H - \mu_3 D\right), \end{aligned}$$

and finally, the amount of chemo needed to maintain EE is

$$D = \frac{\varphi}{\beta_1 I + \beta_2 H + \beta_3 K + \mu_D}.$$

Clearly, the system is highly nonlinear and is not easy to solve explicitly. Indeed, using symbolic algebra leads to very convoluted expressions.

## V. Numerical algorithm and simulations

To obtain insight into the model solutions, that is, to compute approximate solutions of the model, we constructed an explicit time-stepping algorithm and wrote the program in MATLAB. The purpose of the simulations is to show a typical behavior of the model, and then to compare the results when only chemotherapy is administered, only immunotherapy is used, and when both are applied.

We discretized the time interval $T$ into $N$ subintervals of length $\Delta t = T/N$. Typically, in the simulations, we use $\Delta t = 4.5872 \times 10^{-4}$. Denoting the value of a function $f$ at time $t_n = n\Delta t$ by $f^n$, we consider the discretized system, for $n = 0, 1, \ldots N-1$,

$$H^{n+1} = H^n + \Big(\alpha_1 H^n(1-\alpha_H H^n) - \gamma_1 K^n H^n - \mu_1 D^n H^n - \mu_H H^n\Big)\Delta t, \quad (17)$$

$$I^{n+1} = I^n + \Big(q^n + \psi^n + \alpha_2 I^n(1-\alpha_I I^n) - \gamma_2 K^n I^n - \mu_2 D^n I^n - \mu_I I^n\Big)\Delta t, \quad (18)$$

$$K^{n+1} = K^n + \Big(\alpha_3 K^n(1-\alpha_K K^n)\chi_1(K^n) - \mu_K K^n - \gamma_3 I^n K^n - \gamma_4 H^n K^n - \mu_3 D^n K^n\Big)\Delta t, \quad (19)$$

$$D^{n+1} = D^n + \Big(\varphi^n - \beta_1 I^n D^n - \beta_2 H^n D^n - \beta_3 K^n D^n - \mu_D D^n\Big)\Delta t. \quad (20)$$

Together with the initial conditions,

$$H^0 = H_0,\ I^0 = I_0,\ K^0 = K_0,\ D^0 = D_0. \quad (21)$$

Using the above discretization of the model equations, we have the following algorithm.

**Algorithm 1** Explicit time-stepping.

Set $H^0$, $I^0$, $K^0$ and $D^0$ using (21).
**for** $n = 0$ **to** $N-1$ **do**
  Calculate $H^{n+1}, I^{n+1}, K^{n+1}$ and $D^{n+1}$ according to (17)–(20).
**end for**

Since the model is new and generic, we experimented with the values of the various parameters, using 'reasonable' values, to obtain the different possible types of behavior of the system. Since our main interest is to eradicate the disease, we do not dwell on the EE equilibrium, nor on the various other types of behavior generated by the code.

| Par. | Value | Description |
|---|---|---|
| $q$ | 20 | rate of supply of immune cells |
| $\varphi$ | 10 | rate at which drug is administered (variable) |
| $\alpha_1$ | 0.05 | maximal growth rate constant of healthy cells |
| $\alpha_2$ | 0.1 | maximal growth rate constant of immune cells |
| $\alpha_I$ | 0.001 | reciprocal of immune cell carrying capacity |
| $\alpha_H$ | 0.001 | reciprocal of healthy cell carrying capacity |
| $\alpha_3$ | 0.3 | maximal growth rate constant of tumor cells |
| $\alpha_K$ | 0.002 | reciprocal of tumor cell carrying capacity |
| $\gamma_1$ | 0.0005 | loss rate of healthy cells due to tumor cells |
| $\gamma_2$ | 0.002 | loss rate of immune cells due to tumor cells |
| $\gamma_3$ | 0.0005 | loss rate of cancer cells due to immune cells |
| $\gamma_4$ | 0.0005 | loss rate of cancer cells due to normal cells |
| $\mu_1$ | 0.0005 | death rate of healthy cells due to drug |
| $\mu_H$ | 0.02 | natural mortality rate of healthy cells |
| $\mu_2$ | 0.0005 | rate at which drug kills immune cells |
| $\mu_I$ | 0.025 | natural death rate of immune cells |
| $\mu_3$ | 0.001 | death rate of cancer cells due to drug |
| $\mu_K$ | 0.05 | natural death rate of cancer cells |
| $\mu_D$ | 0.075 | natural decay in vivo of the drug |
| $\beta_1$ | 0.0002 | drug decrease due to immune cells |
| $\beta_2$ | 0.001 | drug decrease due to cancer cells |
| $\beta_3$ | 0.005 | drug decrease due to normal cells |

Table 1: Symbols and the values of the baseline parameters.

| Parameter | Weekly chemo | Weekly immunotherapy |
|---|---|---|
| $q$ | 40 | 4 |
| $\psi$ | 0 | 9850 |
| $\varphi$ | 3200 | 0 |
| $\alpha_1$ | 0.1 | 0.1 |
| $\alpha_2$ | 0.2 | 0.2 |
| $\alpha_3$ | 0.5 | 0.5 |
| $\alpha_K$ | 0.001 | 0.001 |
| $\gamma_1$ | 0.001 | 0.001 |
| $\gamma_2$ | 0.025 | 0.025 |
| $\gamma_3$ | 0.015 | 0.0178 |
| $\gamma_4$ | 0.001 | 0.001 |
| $\mu_1$ | 0.001 | 0.001 |
| $\mu_H$ | 0.0005 | 0.0005 |
| $\mu_2$ | 0.001 | 0.001 |
| $\mu_I$ | 0.01 | 0.01 |
| $\mu_3$ | 0.45 | 0.45 |
| $\mu_K$ | 0.001 | 0.001 |
| $\mu_D$ | 0.1 | 0.1 |
| $\beta_1/\beta_2/\beta_3$ | 0.01/0.5/0.01 | 0.01/0.5/0.01 |

Table 2: Symbols and values of the parameters in the simulations of weekly administer chemotherapy and weekly administered immunotherapy.

### A. Baseline – DFE

First, we describe the baseline simulations that correspond to a DFE. Table 1 provides the system coefficients in this case. Using these parameter values together with the initial values $H_0 = 500$, $I_0 = 250$, $K_0 = 100$, and $D_0 = 100$, we obtain the results depicted in Figure 1. However, to obtain the DFE we truncate the chemo source function $\varphi$ and set it to zero at times $t \geq 30$. Healthy and immune cells initially decrease, stabilize and then increase monotonically to their steady state values, predicted in (11), which are

$$\bar{H} = 600, \quad \bar{I} = 958.$$

It is seen that cancer cells, and therefore the disease, vanish after 50 days. Here, we used the cutoff function $\chi_1$ and set $K = 0$ when its value was below $K = 1$.

We conclude that the model predicts the healing from the disease under these conditions. Substituting the parameter values into the expression (16) yield $\mathcal{R}_0 = 0.3208$, which shows that the DFE is, indeed, stable and attracting (asymptotically stable).

For completeness, Figure 2 shows the behavior of the system using the same parameters, but without the chemo drug. It is clear that cancer cells grow to their steady state, at the expense of healthy and immune cells. Thus, without the chemo drug, the DFE is unstable, and the model makes treatments necessary.

### B. Weekly chemotherapy or immunotherapy

We turn to the main interest of this work, namely, the simulations of weekly cancer treatments. The choice of weekly administration of the chemo drug and immunotherapy was based on information we received from cancer specialists. However, it is only one regimen of many possible time scheduling found in the literature.

The first case is when only chemotherapy is administered weekly, and the second case is when only immunotherapy is administered weekly. The parameters used in these two simulations are given in Table 2. The difference is that in the first case $\psi = 0$ and in the second case $\varphi = 0$. Moreover, $q$ and $\gamma_3$ are slightly modified to obtain clearer figures.

*1) Effects of chemotherapy alone:* We assume that the chemo drug is administered on day 8, and once every week afterwards, for four consecutive times,

$$\varphi = \begin{cases} 3200, & t = 8, 15, 22, 29, \\ 0, & \text{otherwise.} \end{cases}$$

As was noted in Section II, the units of $\varphi$ are drug quantity/day.

For mathematical reasons, we may consider an appropriate Lipschitz continuous approximation of $\varphi$, to have smooth solutions.

The simulation results are shown in Figure 3. Immediately after each of the first two applications the

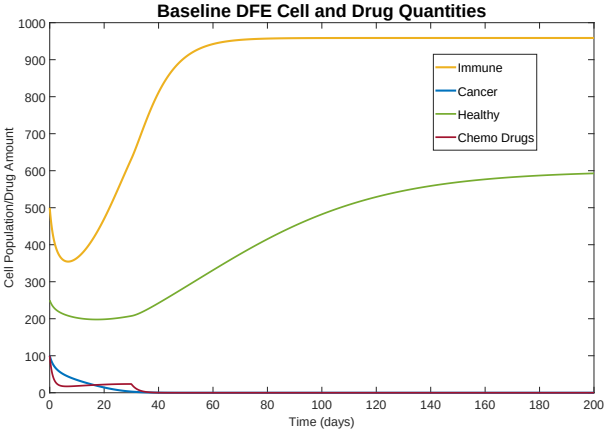


Fig. 1: The baseline (DFE), data in Table 1. The chemo was discontinued ($\varphi = 0$) after 30 days. Cancer vanishes ($K < 1$ hence $K = 0$) close to day $t = 50$. The vertical axis is population/drug amount, the horizontal axis is time in days.

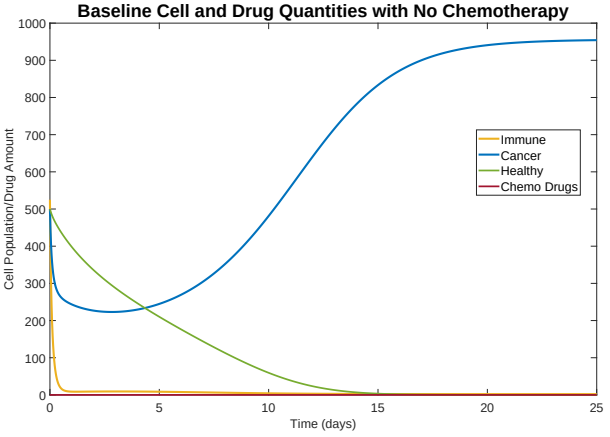


Fig. 2: The baseline case, Table 1, but without the chemo drug ($D = 0$). At $t = 25$ cancer reaches close to the carrying capacity and stays there, while the other cell populations collapse.

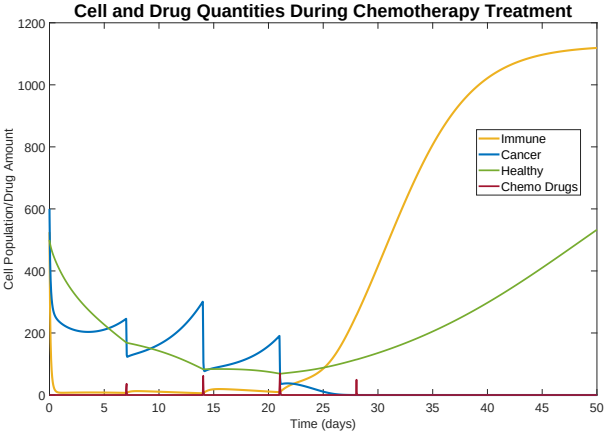


Fig. 3: Weekly administered chemo drug (red). Cancer (blue) vanished ($K < 1$) after the third dose; then the healthy and immune cell populations increase monotonically towards their steady states.

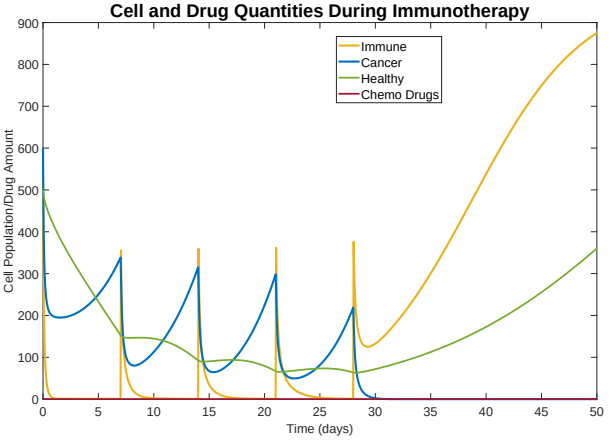


Fig. 4: Weekly administered immunotherapy; without the chemo drug, $D = 0$. Cancer dies out ($K < 1$) after the fourth dose, and then the other populations increase toward their steady states.

number of cancer cells drops sharply and then resumes their growth. In addition, there is a considerable decrease in the number of healthy and immune cells due to their interactions with cancer cells. However, after the third installment of the chemo treatment, on day 22, the cancer decreases sharply and then dies out a short time before day $t = 28$. Once cancer disappears with its negative effects on the other cells, immune and healthy cell populations rebound and monotonically approach their steady-state levels of $\bar{H} = 995$ and $\bar{I} = 1127$.

*2) Effects of immunotherapy alone:* Next, we simulate the case of weekly treatment with immunotherapy. We note that while the dynamics of the chemo drug are represented by $\varphi$ in equation (4), the administration of immunotherapy $\psi$ is included in the dynamics of the immune cell population.

We follow a similar pattern as above and assume that the immunotherapy is administered once a week, starting on day $t = 8$, for four consecutive weeks, until day $t = 29$,

$$\psi = \begin{cases} 9850, & t = 8, 15, 22, 29, \\ 0, & \text{otherwise.} \end{cases}$$

As was noted in Section II, the units are cell/day.

The simulation results are shown in Figure 4. After each immunotherapy dose, the number of cancer cells

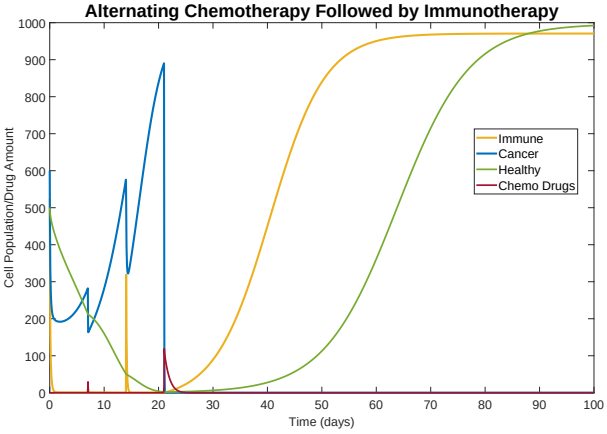


Fig. 5: Weekly alternately administered chemotherapy and immunotherapy, beginning with chemotherapy. Cancer reaches zero after the two doses of chemotherapy and one immunotherapy treatment; then the other populations increase toward their steady states.

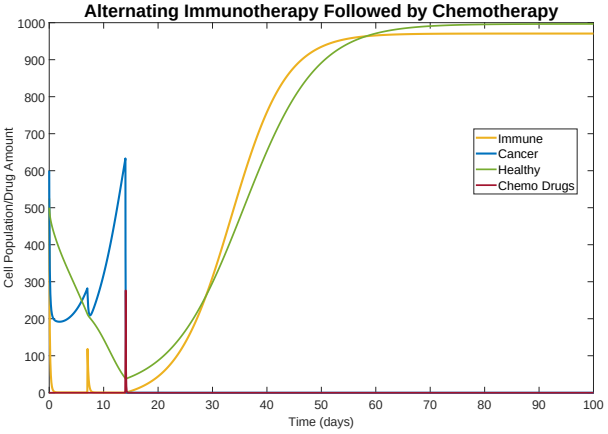


Fig. 6: Weekly alternately administered chemotherapy and immunotherapy, beginning with immunotherapy. Cancer dies out after one immunotherapy and one chemotherapy treatments; then the other populations increase toward their steady states.

decreases sharply due to the treatment, but afterwards, it grows following the first three applications. The number approaches zero after the fourth application. A decrease in the number of healthy cells is evident as a result of their interaction with cancer cells. Once cancer disappears, immune and healthy cell populations recover and approach monotonically their steady-state levels of $\bar{H} = 995$ and $\bar{I} = 971$.

*3) Combined chemotherapy and immunotherapy:* We now describe three computer experiments of the effects of the combined treatments. The first experiment, shown in Figure 5, deals with weekly administration of alternate chemotherapy and immunotherapy, beginning with chemotherapy, using the same source functions $\varphi$ and $\psi$ as above. Cancer dies out after the two doses of chemotherapy and one immunotherapy treatment and then, as above, the other populations recover and grow to their steady-state values.

However, it is seen that the level of cancer reaches much higher peaks, before disappearing following the third treatment (the second chemotherapy). Figure 6 shows the experiment when immunotherapy is administered first and then chemotherapy. It is found that cancer disappears after the second treatment (the first chemotherapy). Cancer peaks higher than in the cases of single therapy, but less than when chemotherapy was used before immunotherapy. Finally, Figure 7 shows when both chemotherapy and immunotherapy are administered on the same day. It is very interesting that the model predicts that a single application of both therapies at the same time kills the cancer population.

We conclude that this model predicts that using both therapies on the same day leads to much better outcomes. However, the model does not include any levels of randomness in the coefficients, drug toxicity, or patient variability, etc., and needs to be validated by field data before the conclusion is found reliable. However, it may point to important ways to improve the treatments.

## VI. Conclusions

This work presents a novel generic dynamical systems model for the treatment of a cancer tumor using chemotherapy, immunotherapy, or combinations of both. The model consists of four ODE rate equations for the Healthy, Immune and Cancer cell populations, and for the effects of the chemo drug on these cells. The model (actually a family of models) provides insight into and possible quantitative estimates of the effects of the two therapies administered alone or in combination. It is meant to be a tool for computer experiments to improve treatment schedules. Once validated, the model can be used to optimize therapy schedules, therefore saving time, effort, and money while improving the outcomes. Furthermore, the model can be easily extended to include other treatment modalities and more complex and realistic settings.

The model is constructed in Section II, and its analysis is provided in Section III, where the positive invariance, boundedness, and existence of the solutions can be found. The steady states are studied in Section IV where an explicit expression for the basic stability

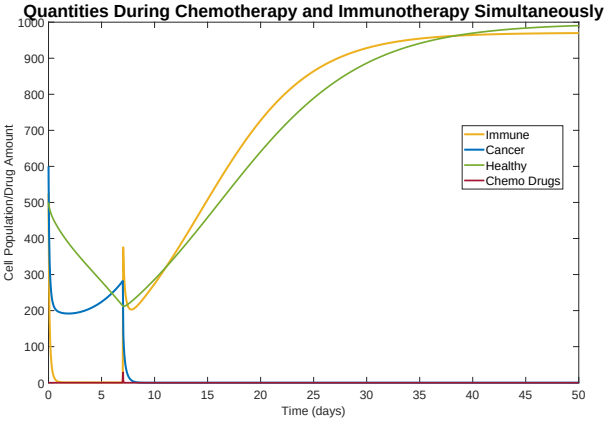


Fig. 7: Weekly administered both chemotherapy and immunotherapy. Cancer vanished after the first dose, the other populations increase toward their steady states.

number $\mathcal{R}_0$ is given in (16). However, in our setting, the stability of the disease-free equilibrium (DFE) is of little interest, since the intention is to find conditions that *drive* the system to the DFE as fast as possible.

In Section V we construct and use a relatively simple explicit finite-differences algorithm for the model simulations. The results show the value of the model, since it predicts the dynamics of chemo or immunotherapies, and the conditions for the eradication cancer. In the simulations, we study first the baseline case, Figure 1, which seems to be typical, in which cancer is eventually eradicated. Then, the continuous administration of the chemo drug is discontinued. After an initial decrease, the healthy and immune cell populations converge monotonically to their steady-states values. In this case we may say that the DFE is stable and attracting, indeed, $\mathcal{R}_0 = 0.3208 < 1$. For completeness, we also provide in Figure 2 the simulation with the same data but in the absence of the chemo treatment ($D = 0$). It is seen that without treatment, cancer reaches close to its carrying capacity value at the expense of the other cell populations that collapse.

Next, we study the effects of the application of chemotherapy or immunotherapy or their combinations. Figure 3 shows the effects of a weekly application of chemotherapy, in which cancer vanishes after three applications. Figure 4 shows the case where immunotherapy is used and in this case it disappears after four applications.

The next three experiments deal with the combined administration of the chemo drug and immunotherapy. We chose chemotherapy first, then immunotherapy and then chemotherapy again, Figure 5. The disease vanishes after the second chemotherapy treatment. When immunotherapy is first followed by chemotherapy, Figure 6, cancer disappears following the chemotherapy treatment. When immunotherapy and chemotherapy are applied at the same time, cancer is eradicated after one single dose of both treatments. These three results show the advantages of the model and open the way for optimizing treatment schedules.

We conclude, tentatively based on the model predictions, that by itself chemotherapy eradicates cancer in about 28 days, and immunotherapy in 32 days, their combined application eradicates it in 10 days. This result must be taken with caution, as the model is not yet validated. This, when validated, opens the way to considerable improvement in treatment outcomes in terms of patient care, cost, time, and overall use of medical facilities. Indeed, the model may suggest different, more effective and shorter periods of treatments, possibly with lower doses of the therapies. The steps needed to validate the model consist of comparing its solutions with real field data and adjusting the coefficients accordingly.

This work opens the door to a host of related models and their computer experiments. Moreover, some of the questions of interest are as follows:

- Perform more extensive simulations of chemotherapy and immunotherapy treatments and their interactions. Use different schedules for the administration of the treatments.
- Add other possible treatments, modalities and methods, such as radiation or virotherapy.
- Perform parameter sensitivity analysis, to find which are the more important parameters.
- Conduct partial optimization of system outcomes.
- Add randomness to the system, to make it more realistic, and study its effects. Use randomness to find the bands in which solutions exist.
- Study the attractors in the system and find if the model supports chaos.

We believe that the model, and its variants, will find ways to be applied in the real world and improve cancer treatments.

## Statement on Authors Contributions

First author (TK Dutta): Conceptualization, methodology and writing; Second Author (J Moore): Software development, computer simulation and analysis; Third author (M Shillor): Model development, analysis and writing; Fourth author (SA Sangma): Some formal analysis and investigation.

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