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► **To cite this version:**

Khadija El-Matteli, Ines Abdeljaoued-Tej. Modelling Heterogeneous Tumor Elimination or its Recurrence with ODE. LR16IPT09, Institut Pasteur de Tunis, University Tunis-El-Manar, Tunisia. 2019. hal-04895388

**HAL Id: hal-04895388**

**<https://hal.science/hal-04895388v1>**

Submitted on 18 Jan 2025

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# Modelling Heterogeneous Tumor Elimination or its Recurrence with ODE

Khadija El-Matteli and Ines Abdeljaoued-Tej

BIMS Laboratory, Institute Pasteur of Tunis, University of Tunis El Manar

June 21, 2019

## Abstract

We present a new mathematical model, in the form of a system of ordinary differential equations (ODEs), governing the growth of cancer at the level of the cell population combined with treatment by the immune system or chemotherapy. This model describes the kinetic relationships between different states and cell types. Besides, it will be about presenting a mathematical analyse. The principal objective of this work is to study the recurrence, coexistence, and elimination of cells cancerous, under the assumption of a heterogeneous tumor. Also, we aim to study the influence of cancer stem cells on its dynamics and characterize the subsequent impact on the availability of factors that help tumor growth and resistance to treatment.

**Keywords** Global dynamic of the full system, Competition model, Tumor-Immune dynamic, Stability analysis, Differentiation, Immune system, Chemotherapy.

## 1 Introduction

The cancer stem cell hypothesis is a recent development in cancer dynamics. Tumor is considered as an organ initiated and maintained by a population of tumor cells called cancer stem cells (*CSCs*). These *CSCs* share similar biologic properties to normal adult stem cells [Tan et al., 2006]. *CSCs* are a specialized type of cancer cell that are believed to be responsible for populating tumors, by dividing and producing a large number of cells required for tumor living [Lau et al., 2017]. With the consideration of a heterogeneous cancer, *CSCs* have a very small population in comparison to normal cancer cells because of their specialized function [López-Lázaro, 2018]. Also *CSCs* maintain the cellular hierarchy and store the genetic material throughout tumor life. Furthermore, *CSCs* involvement in developing the vascular network without an endothelial pattern [Shen et al., 2008]. This process is termed Vasculogenic Mimicry, which is independent of angiogenesis and is composed of tumor cells and a basement membrane [Fan et al., 2013]. Blood plasma and red blood cells are able to flow in. Vasculogenic Mimicry allows *CSCs* to express the endothelial phenotype and play a similar functional role to endothelial cells in forming blood vessel-like structures [Li and Li, 2015, Li and Li, 2014].

In this work, we propose a new mathematical model in form of a system of Ordinary Differential Equations (ODE). The ODE system describes the evolution of tumor cells and its interaction with immune cells, and with present or absence of cancer treatment. Indeed, our model is based on and validated by work of [L. G. de Pillis et al., 2009]. In what follows, we will outline the main biological assumptions, which governing tumor evolution and based on *CSCs* hypothesis, as the work of [Molina-Peña and Álvarez, 2012] in order to construct our deterministic hierarchical model. Recently, considerable attention has been paid to use ordinary differential equations to model cancer therapy, the work of [Talkington et al., 2017] have been focused on this issue. Applying this approach, we will study the mathematical proprieties of the model such as its invariance, dissipativity, existence, uniqueness and the equilibrium stability. Also, by following the mathematical approaches of [Abernathy and Burke, 2016, Kogan et al., 2008], we will have mathematically show and determine the conditions of the treatment to ensure moving a large existing tumor to an equilibrium with no tumor cells.

## 2 Ordinary Differential Equations model

This section presents the model which is essentially based on [L. G. de Pillis et al., 2006] model, but we extend the previous work in order to include the heterogeneous populations of tumor in modelling its evolution with or without treatment. Beside, it is clear that for treatment to be effective, we must focus our efforts on eliminating all the type of this heterogeneous populations.

### 2.1 Presentation of the model

**Model Populations** In this model we consider there are interaction between tumor cells population and immune cells. Tumor cells can be classified into: Stem cells (*CSCs*), Progenitor cells ( $P_i$ ) and Differentiated cells ( $D_i$ ), where  $i$  describes the subtype of the progenitor and the differential cells. Cells' subtypes depend on its role in tumor evolution and tumor needs for keeping progressing. *CSCs* produce progenitor cells by the **Trans-differentiation** mechanism [Huang et al., 2015], and they divide into specific type of progenitor cells for maintaining the cancerous tissue growth. Then, when the  $P_i$  cell reached a certain age, it differentiates into  $D_i$  cell with the same subtype of its mother cell by the **Differentiation** mechanism. The *Trans-differentiation* results in changing the *CSCs* genotypes, while the *Differentiation* results in changing the  $P_i$  phenotype and produce  $D_i$ . Therefore,  $P_i$  cells possess intermediate properties between *CSCs* and  $D_i$  cells which have a specific function depends on its phenotype (see Figure 1). On the other hand, immune cells express the immune system response to infected or malignant cells and its defence against cancer [Figueredo et al., 2013]. The immune cells ( $I$ ) is defined as the CD8+T cells, they are a critical subpopulation of T-lymphocytes (small lymphocytes in the peripheral blood) which can be cytotoxic to tumor cells provided previous sensitization has occurred. We hypothesize that *CSCs* can spontaneously form blood vessels or lymphatic vessel in tumor via trans-differentiation into endothelial-like cells. Then, we can categorize  $P_i$  and  $D_i$  cells into three subtypes:

- Tumor cells ( $TC$ ), which are considered the majority of tumor size and they have limited proliferation ability.
- Blood endothelial cells ( $BEC$ ). The principal role of  $D_{BEC}$  is to create tumor vascular network by vasculogenesis for supplying tumor with nutrients. Also they induce cancer metastasis by allowing  $CSCs$  to migrate through the vascular network.
- Lymphatic endothelial cells ( $LEC$ ).  $D_{LEC}$  create tumor lymphatic network by lymphangiogenesis, thus promote tumor metastasis.

Furthermore, after forming the vascular or lymphatic network of the tumor by itself (due to existence of  $D_{BEC}$  and  $D_{LEC}$  cells),  $CSCs$  will have the ability to migrate through these networks, then this cell is referred as migrating cancer stem cell  $MCSC$ , which is the responsible for forming tumors in other sites of the body (Metastasis).

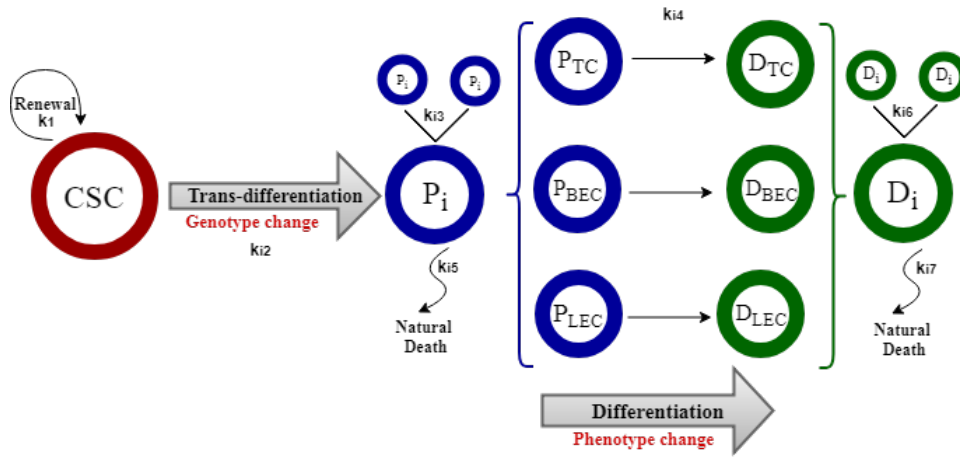


Figure 1: **Basic assumption of the model** Different types of populations found in solid tumors. In the model we consider three main types of cancer cells ( $CSC$  = Cancer Stem Cell,  $P$  = Progenitor cells, and  $D_i$  = Differentiated cells). The cellular division events considered in the model are the symmetrical self-renewal of  $CSC$ , the trans-differentiation of  $CSC$  into  $P_i$  cell and the differentiation of  $P_i$  into  $D_i$  cell. The three subtypes of  $P_i$  and  $D_i$  cells are:  $TC$  = Tumor cells,  $BEC$  = Blood endothelial cells and  $LEC$  = Lymphatic endothelial cells. We consider also that all subtypes of  $P_i$  and  $D_i$  cells can undergo natural cell death.

In the following next sections, in order to simplify the mathematical model, we choose to generalize the hypotheses on all the subtypes of  $P_i$  and  $D_i$ , as they belong to progenitor and differential cells respectively. Therefore, we consider the tumor cells population are only the three main categories: the  $CSCs$ , the progenitor cells  $P$  and the differential cells  $D$ .

**Biological Assumption** We outline the main biological properties of the model in order to obtain feasible and realistic results. Therefore, we present the first list of biological assumptions ( $A1$ ):

1. Tumor is generated from a small number of  $CSCs$ , and all tumor cells grow logistically in the absence of treatment.
2. When the  $CSC$  or  $P$  population is small, they repopulate themselves, but as their population grows, they focus on populating the  $P$  or  $D$  population respectively.

3. Immune cells  $I$  are part of the immune system and they are recruited once tumor cells are presented and target them. The response of immune system depends on the type of cancer cell ( $CSC, P$  or  $D$ ).
4. Chemotherapy drug can kill both cancer and immune cells with different resistance abilities. Knowing that effective chemotherapy kills cancer cells at much higher rates than kills immune cells.
5.  $CSCs$  have the greatest ability to resist cancer treatment.

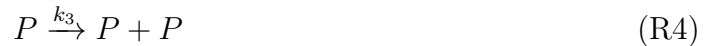
**Methods** In order to establish the model, we follow a classical strategy used in chemical reaction engineering to describe a system of chemical reactions known as pseudo-chemical model. Where the cellular events of all cells types are represented as "chemical reactions". Thus, for each cellular event  $i$ , a reaction rate  $k_i$  can be established.  $CSC$  can undergo the symmetric division, where it divides into two  $CSCs$  with the rate  $k_1$ , this process can expressed as the following reaction (R1):



Otherwise,  $CSC$  may trans-differentiate into  $CSC$  and  $P$  with the rate  $k_2$ , hence we define the trans-differentiation process as (R2):



$P$  may undergo through symmetric division with rate  $k_3$ . Alternatively,  $P$  can differentiates into  $P$  and  $D$  with rates  $k_4$ . Also  $P$  may die due to natural mortality, then it is denoted by naturally dead cell ( $N_d$ ). The last three cellular events can be expressed as:



$D$  can either divide symmetrically with rate  $k_6$ , or undergo natural death with rate  $k_7$ . Thus, we define the cellular events of  $D$  cells as the following reactions:



The ODE model describes the kinetic relationships between the different cellular events of the populations ( $CSCs, P, D$  and  $I$  cells), as well as the chemotherapy drug concentration, using a system of ordinary differential equations. In order to simplify the notations in the ODE system, the populations of cancer stem cells, progenitor cells, differentiated cells, and immune cells at time  $t$  are denoted by  $Y(t), P(t), D(t)$  and  $I(t)$  respectively, and  $M(t)$  represents a specific chemotherapy drug concentration. The ODE system gives the rate of change of the particular cell population in terms of growth, death naturally or

due to chemotherapy, cell-cell kill or cell recruitment. Bringing together all the cellular event and the interaction terms, yields to the full system 1 of ODEs.

$$(1) : \left\{ \begin{array}{l} \frac{dY}{dt} = \overbrace{k_1 Y \left(1 - \frac{Y}{K_Y}\right)}^{r_1(Y)Y} - k_{M_Y}(1 - e^{-M})Y - d_0 Y I \quad (1.1) \\ \frac{dP}{dt} = \overbrace{k_2 \frac{Y}{K_Y} P \left(1 - \frac{P}{K_P}\right)}^{H_1(Y,P)} + \overbrace{k_3 P \left(1 - \frac{P}{K_P}\right)}^{r_2(P)P} - k_5 P - k_{M_P}(1 - e^{-M})P - d_1 P I \quad (1.2) \\ \frac{dD}{dt} = \overbrace{k_4 \frac{P}{K_P} D \left(1 - \frac{D}{K_D}\right)}^{H_2(P,D)} + \overbrace{k_6 D \left(1 - \frac{D}{K_D}\right)}^{r_3(D)D} - k_7 D - k_{M_D}(1 - e^{-M})D - d_2 D I \quad (1.3) \\ \frac{dI}{dt} = s + \frac{\rho N_T}{\alpha + N_T} I - m I - q N_T I - k_{M_I}(1 - e^{-M})I \quad (1.4) \\ \frac{dM}{dt} = -\gamma M + V_d \mathbb{1}_F(t). \quad (1.5) \end{array} \right.$$

Here the terms  $r_1(Y)Y$ ,  $r_2(P)P$  and  $r_3(D)D$  represent the classical logistic growth of  $CSC$ ,  $P$  and  $D$  cells respectively (note that the carrying capacities for  $CSC$ ,  $P$  and  $D$  cells are distinct and they are respectively  $K_Y$ ,  $K_P$  and  $K_D$ ). The term  $H_1(Y, P)$  stands for the  $P$  cells produced by the  $CSC$ s, while  $H_2(P, D)$  stands for  $D$  cells produced by  $P$  cells [Abernathy and Burke, 2016].  $k_{M_Y}$ ,  $k_{M_P}$ ,  $k_{M_D}$  and  $k_{M_I}$  are the rates of killing  $CSC$ s,  $P$ ,  $D$  and  $I$  respectively due to chemotherapy drug, while  $d_0$ ,  $d_1$  and  $d_2$  represent the death rates of  $CSC$ s,  $P$  and  $D$  respectively due to immune system response. In the case of the CD8+T cells, which represent the  $I$  cells, they are recruited by interactions with the total number of tumor cells  $N_T = Y + P + D$  through a Michaelis–Menten dynamic [Kuznetsov et al., 1994], generally used to model kinetic interactions between two cells. Therefore, we use the term  $\frac{\rho N_T}{\alpha + N_T} I$  to represent the  $I$  cells kinetics recruited by tumor cells, where  $\rho$  is the maximum  $I$  cells recruitment rate by tumor cells,  $\alpha$  is Michaelis–Menten recruitment constant for  $I$  cells. The term  $s$  describes an immune treatment or the influx of  $I$  cells directly to the tumor site,  $s$  is considered constant, and it is set equal to 0 in the absence of treatment by recruitment of  $I$  cells.  $m$  stand for  $I$  cells death rate and  $q$  is their inactivation rate by tumor cells. Finally  $\gamma$  is the decay rate of chemotherapy drug and  $V_d$  is the given dose of the drug at the treatment interval  $F$ . The chemotherapy fractional cell kill is reflected by the saturation term  $(1 - e^{-M})$ , which is almost linear if the drug dose is low while it is plateaus in case of high dose. Indeed, we choose that term to model killing tumor cells with chemotherapy with certain rate, knowing that there are other modeling framework which use other function to model the death due to treatment, such as the work of [Nazari et al., 2018].

## 2.2 Basic Mathematical Proprieties

In order to ensure the validation of our model, we study the basic mathematical proprieties of the system (1) and outline its preliminary results. We start by invariance propriety, dissipativity, existence and uniqueness of the solution and finally the stability of tumor elimination and recurrence.

**Invariance** The invariance propriety guarantees that for non-negative initial populations, all populations will remain non-negative. We study this system with non-negative initial data, also we need additional mathematical assumptions besides the assumptions (A1). Therefore, we formulate the second list of the mathematical assumptions (A2):

1. The classical logistic growth terms  $r_1(Y), r_2(P)$  and  $r_3(D)$ , are almost linear, and they are decreasing on  $[0, K_Y]$ ,  $[0, K_P]$  and  $[0, K_D]$  respectively.
2. The logistic growth terms  $H_1(Y, P)$  and  $H_2(P, D)$  are increasing functions.
3. All the growth and death rates  $\{k_1, \dots, k_7\}$  are positive constants. Thus,  $\forall k \in \{k_1, \dots, k_7\}$  and  $\phi > 0$  the function  $f_k(\phi) = k\phi$ , is an increasing, continuous and non-negative function, for  $\phi \in \{Y, P, D\}$ .
4. All the kill rates  $k_M \in \{k_{M_Y}, k_{M_P}, k_{M_D}, k_{M_I}\}$ , due to chemotherapy, are positive constant. Thus,  $\forall k_M$  and  $M > 0$ , the function  $f_{k_M}(M) = k_M(1 - e^{-M})$  is an increasing non-negative function and bounded from above. Hence, we have  $\lim_{M \rightarrow 0} f_{k_M}(M) = 0$  and  $\lim_{M \rightarrow \infty} f_{k_M}(M) = k_M$ .
5. The death rates due to Immunotherapy  $d \in \{d_0, d_1, d_0\}$  are also positive constant, therefore  $\forall d, I$  and  $\phi > 0$ , the function  $f_d(I \cdot \phi) = d\phi I$  is an increasing non-negative function, where  $\phi \in \{Y, P, D\}$ .
6. The recruitment of  $I$  cells into cancer site is a result of immune system response to cancer:  $\rho, \alpha$  are positive constants, and  $\forall N_T > 0$ , the function  $f_r(N_T) = \frac{\rho N_T}{\alpha + N_T}$ , in an increasing non-negative function and bounded from above. Hence, we have  $\lim_{N_T \rightarrow 0} f_r(N_T) = 0$  and  $\lim_{N_T \rightarrow \infty} f_r(N_T) = \rho$ .
7. Increasing the number of tumor cells decreases the activity and the efficacy of  $I$ . The constants  $s, q$  and  $m$  are non-negative.

All the analysis presented further will be done under the set of assumptions (A2). Then, The system (1) is equivalent to the following system (2):

$$(2) : \begin{cases} \frac{dY}{dt} = r_1(Y)Y - f_{k_{M_Y}}(Y) - f_{d_0}(Y \cdot I) & (2.1) \\ \frac{dP}{dt} = H_1(Y, P) + r_2(P)P - f_{k_5}(P) - f_{k_{M_P}}(P) - f_{d_1}(P \cdot I) & (2.2) \\ \frac{dD}{dt} = H_2(P, D) + r_3(D)D - f_{k_7}(D) - f_{k_{M_D}}(D) - f_{d_2}(D \cdot I) & (2.3) \\ \frac{dI}{dt} = s + f_r(N_T)I - mI - qN_T I - f_{k_{M_I}}(I) & (2.4) \\ \frac{dM}{dt} = -\gamma M + V_d \mathbb{1}_F(t). & (2.5) \end{cases}$$

**Theorem 2.1.** *Under the assumptions (A2), the solutions of the system (1) are non-negative for non-negative initial data and they are defined for every  $t \geq 0$ . Hence the system (1) has the invariance propriety.*

*Proof.* We need to search the analytic solution of each equation in the system (1). Knowing that for each first order linear ODE:

$$\frac{du}{dt} = f(t)u + g(t) \quad t \in ]0, t_{max}[, \quad u(0) = u_0 > 0, \quad (3)$$

where  $f$  and  $g$  are continuous functions on  $]0, t_{max}[$ , then the analytic solution is:

$$u(t) = e^{\int_0^t f(\tau)d\tau} u_0 + e^{\int_0^t f(\tau)d\tau} \cdot \int_0^t e^{\int_0^s -f(\tau)d\tau} g(s)ds. \quad (4)$$

According to (3) and (4), the analytic solution of (1.5) is:

$$M(t) = \begin{cases} M_0 e^{-\gamma t} - \frac{V_M}{\gamma} e^{-\gamma t} + \frac{V_M}{\gamma} \geq 0, & \text{if } t \in F. \\ M_0 e^{-\gamma t} \geq 0, & \text{otherwise,} \end{cases} \quad (5)$$

where  $M_0 \geq 0$  is the initial value of the chemotherapy drug. For same, we determine the solution of the equation (1.4) after rearranging it the following form:

$$\frac{dI}{dt} = \overbrace{\left( \frac{\rho N_T}{\alpha + N_T} - m - q N_T - k_{M_I} (1 - e^{-M}) \right)}^{f_0(t)} I + s. \quad (6)$$

for proving the non-negativity of the solution we will use the Property 2.1 mentioned below to ensure the positivity of the integral. Hence,  $\forall t \in ]0, t_{max}[$  and with the initial value of  $I$  cell  $I(0) = I_0 > 0$ , the solution is:

$$I(t) = e^{\phi_0(t)} I_0 + e^{\phi_0(t)} \cdot \int_0^t e^{-\phi_0(\tau)} s d\tau > 0, \quad \text{with } \phi_0(t) = \int_0^t f_0(\tau) d\tau. \quad (7)$$

For searching the analytic solution of the non-linear equations (1.1,1.2 and 1.3) we use method of substitution, which can be applied to change a non-non-linear equation to a linear equation. First, we rearrange the equation 1.1:

$$\frac{dY}{dt} = \overbrace{\left( k_1 - k_{M_Y} (1 - e^{-M}) - d_0 I \right)}^{f_1(t)} Y - \frac{k_1}{K_Y} Y^2, \quad (8)$$

then we multiply 8 by  $(\frac{1}{Y^2})$  and we obtain:

$$\frac{dY}{dt} \cdot \frac{1}{Y^2} = f_1(t) \cdot \frac{1}{Y} - \frac{k_1}{K_Y}. \quad (9)$$

By the substitution method we use the following change of variable and its the derivative:

$$\begin{aligned} y &= Y^{-1} \\ \frac{dy}{dt} &= -\frac{dY}{dt} \cdot Y^{-2} \\ \frac{dy}{dt} &= -f_1(t)y + \frac{k_1}{K_Y}, \end{aligned} \quad (10)$$



then  $\forall t \in ]0, t_{max}[$  and with  $y(0) = y_0 > 0$ :

$$y(t) = e^{-\phi_1(t)} y_0 + \frac{k_1}{K_Y} \cdot e^{-\phi_1(t)} \cdot \int_0^t e^{\phi_1(\tau)} d\tau > 0, \quad \text{with } \phi_1(t) = \int_0^t f_1(\tau) d\tau. \quad (11)$$

According to 10 and with  $Y(0) = Y_0 > 0$ :

$$Y(t) = \frac{1}{y(t)}, \quad Y(t) = \frac{Y_0 e^{-\phi_1(t)}}{1 + Y_0 \frac{k_1}{K_Y} \int_0^t e^{\phi_1(\tau)} d\tau} > 0. \quad (12)$$

Thus, we use the technique for determining the solution of the non-linear ODEs (1.2) and (1.3), which are written as following form:

$$\frac{dP}{dt} = \overbrace{\left( \frac{k_2 Y}{K_Y} + k_3 - k_5 - k_{M_P}(1 - e^{-M}) - d_1 I \right)}^{f_2(t)} P - \overbrace{\left( \frac{k_2 Y}{K_Y K_P} + \frac{k_3}{K_P} \right)}^{g_2(t)} P^2 \quad (13)$$

$$\frac{dD}{dt} = \overbrace{\left( \frac{k_4 P}{K_P} + k_6 - k_7 - k_{M_D}(1 - e^{-M}) - d_2 I \right)}^{f_3(t)} D - \overbrace{\left( \frac{k_4 P}{K_P K_D} + \frac{k_6}{K_D} \right)}^{g_3(t)} D^2. \quad (14)$$

Therefore, by using the substitution method and with  $P(0) = P_0 > 0$ ,  $D(0) = D_0 > 0$  and  $\forall t \in ]0, t_{max}[$ , the analytic solution of equations (13) and (14) are:

$$P(t) = \frac{P_0 e^{-\phi_2(t)}}{1 + P_0 \int_0^t e^{\phi_2(\tau)} g_2(\tau) d\tau} > 0, \quad \text{with } \phi_2(t) = \int_0^t f_2(\tau) d\tau \quad (15)$$

$$D(t) = \frac{D_0 e^{-\phi_3(t)}}{1 + D_0 \int_0^t e^{\phi_3(\tau)} g_3(\tau) d\tau} > 0, \quad \text{with } \phi_3(t) = \int_0^t f_3(\tau) d\tau. \quad (16)$$

Consequently, with the assumptions (A2) imply that all solutions of the system (1) are non-negative for non-negative initial data and they are defined for every  $t \geq 0$ . ■

**Property 2.1.** *let  $f$  be a continuous and positive function on the interval  $X$ , then for all real numbers  $a$  and  $b$  in  $X$ , such as  $a \leq b$  we have:*

$$\int_b^a f(x) dx \geq 0$$

*Proof.* let  $f$  a continuous and positive function on  $X$ , its integral by definition is an area, therefore it is positive. ■

**Dissipativity** The system (1) can be treated as an open system model, with a capability to continuously impose a revolutionary change or transformation in its populations. A dissipative system has a dynamical regimen that is in some sense in a reproducible steady state. This reproducible steady state may be reached by the natural evolution of the system [Brogliato et al., 2007, Willems, 2007]. Studying the dissipativity of an open system [Luhmann, 1995] is equivalent to the stability study of a closed system [Willem, 1972, Forni and Sepulchre, 2013].

**Theorem 2.2.** *The system (1) is dissipative in  $[0, K_Y] \times [0, K_P] \times [0, K_D] \times (\mathbb{R}^+)^2$  under the assumptions (A2).*

*Proof.* Let  $\mathbf{W} = (Y, P, D, I, M)$ . To obtain dissipativity we would like to have  $\nabla \mathbf{W} \cdot F \leq A - \delta \mathbf{W}$ , where  $F$  denotes the right-hand side of equations in system (1),  $A$  and  $\delta$  are positive constants. Note, that  $r_1(Y)Y$  is zero at  $Y = 0$  and at  $Y = K_Y$ , thus we have  $r_1(Y)Y \leq K_Y k_1 - k_1 Y$  on the interval  $[0, K_Y]$ . For same,  $r_2(P)P \leq K_P k_3 - k_3 P$  on the interval  $[0, K_P]$ , and  $r_2(D)D \leq K_D k_6 - k_6 D$  on the interval  $[0, K_D]$ . Also, the process of trans-differentiation and differentiation are estimated by the following inequalities respectively:  $H_1(Y, P) \leq k_2 K_P - k_2 P$  and  $H_2(P, D) \leq k_4 K_D - k_4 D$ . Moreover, we estimate  $(1 - e^{-M}) \leq 1$  and  $f_r(N_T) \leq \rho$ . Hence:

$$\begin{aligned} \nabla \mathbf{W} \cdot F &= k_1 Y \left(1 - \frac{Y}{K_Y}\right) - k_{M_Y} (1 - e^{-M}) Y - d_0 Y I \\ &\quad + k_2 \frac{Y}{K_Y} P \left(1 - \frac{P}{K_P}\right) + k_3 P \left(1 - \frac{P}{K_P}\right) - k_5 P - k_{M_P} (1 - e^{-M}) P - d_1 P I \\ &\quad + k_4 \frac{P}{K_P} D \left(1 - \frac{D}{K_D}\right) + k_6 D \left(1 - \frac{D}{K_D}\right) - k_7 D - k_{M_D} (1 - e^{-M}) D - d_2 D I \\ &\quad + s + \frac{\rho N_T}{\alpha + N_T} I - m I - q N_T I - k_{M_I} (1 - e^{-M}) I \\ &\quad - \gamma M + V_d \mathbb{1}_F(t), \end{aligned}$$

then, according to above estimations and the assumptions (A2):

$$\begin{aligned} \nabla \mathbf{W} \cdot F &\leq k_1 K_Y - (k_1 + k_{M_Y}) Y - d_0 Y I \\ &\quad (k_2 + k_3) K_P - (k_2 + k_3 + k_5 + k_{M_P}) P - d_1 P I \\ &\quad (k_4 + k_6) K_D - (k_4 + k_6 + k_7 + k_{M_D}) D - d_2 D I \\ &\quad + s + \rho I_{max} - (m + q N_T + k_{M_I}) I \\ &\quad - \gamma M + V_d. \end{aligned}$$

$$\nabla \mathbf{W} \cdot F \leq k_1 K_Y + (k_2 + k_3) K_P + (k_4 + k_6) K_D + s + V_d - a_1 Y - a_2 P - a_3 D - a_4 I - \gamma M.$$

Hence we obtain:

$$\nabla \mathbf{W} \cdot F \leq A - \delta \mathbf{W},$$

where  $A = k_1 K_Y + (k_2 + k_3) K_P + (k_4 + k_6) K_D + s + V_d$  and  $\delta = \min\{a_1, a_2, a_3, a_4, \gamma\}$ , where we use the following new constants to simplify the notation:

$$\begin{aligned} a_1 &= k_1 + k_{M_Y}, & a_2 &= k_2 + k_3 + k_5 + k_{M_P}, \\ a_3 &= k_4 + k_6 + k_7 + k_{M_D}, & a_4 &= m - \rho. \end{aligned}$$

■

The dissipativity guarantees all populations remain bounded [Kogan et al., 2008].

**Existence and Uniqueness** We prove the existence and the uniqueness using Cauchy-Lipschitz theorem mentioned in [Driver, 1977] in relation to our problem. First, we define the right hand side of the system (1) by:

$$f(\vec{\psi}) = \begin{pmatrix} k_1 Y(1 - \frac{Y}{K_Y}) - k_{M_Y}(1 - e^{-M})Y - d_0 IY \\ k_2 \frac{Y}{K_Y} P(1 - \frac{P}{K_P}) + k_3 P(1 - \frac{P}{K_P}) - k_5 P - k_{M_P}(1 - e^{-M})P - d_1 IP \\ k_4 \frac{P}{K_P} D(1 - \frac{D}{K_D}) + k_6 D(1 - \frac{D}{K_D}) - k_7 D - k_{M_D}(1 - e^{-M})D - d_2 ID \\ s + \frac{\rho N_T}{\alpha + N_T} I - mI - qIN_T - k_{M_I}(1 - e^{-M})I \\ -\gamma M + V_d \mathbb{1}_F(t) \end{pmatrix},$$

where  $\vec{\psi} = (Y, P, D, I, M)^T$ . Consequently, we can reconsider the system (1) in the form:

$$\vec{\psi}'(t) = F(t, Y(t), P(t), D(t), I(t), M(t)), \quad (17)$$

where  $F : [0, t_{max}] \times [0, K_Y] \times [0, K_P] \times [0, K_D] \times (\mathbb{R}^+)^2 \rightarrow \mathbb{R}^5$  for  $t_{max} > 0$ . Hence, for each  $(t, Y(t), P(t), D(t), I(t), M(t)) \in [0, t_{max}] \times [0, K_Y] \times [0, K_P] \times [0, K_D] \times (\mathbb{R}^+)^2$ ,  $F(t, Y, P, D, I, M)$  is well defined in  $\mathbb{R}^5$ . Now we will use a lemma to obtain a local Lipschitz condition for  $F$ .

**Lemma 2.1.** *If  $f(\vec{\psi})$  has continuous first partial derivatives with respect to all but its first argument, then  $f(\vec{\psi})$  is locally Lipschitz.*

*Proof.* We analyse the first partials of the right hand side of our system. The Jacobian of  $f(\vec{\psi})$  with respect to  $\vec{\psi}$  is:

$$\begin{pmatrix} k_1 - \frac{2k_1}{K_Y} Y - k_{M_Y}(1 - e^{-M}) - d_0 I & 0 & 0 & d_0 Y & -k_{M_Y} e^{-M} Y \\ k_3 \frac{P}{K_Y} (1 - \frac{P}{K_P}) & c_1 - k_{M_P}(1 - e^{-M}) - d_1 I & 0 & d_1 P & -k_{M_P} e^{-M} P \\ 0 & k_4 \frac{D}{K_P} (1 - \frac{D}{K_D}) & c_2 - k_{M_D}(1 - e^{-M}) - d_2 I & d_2 D & -k_{M_D} e^{-M} D \\ \frac{\rho \alpha I}{(\alpha + N_T)^2} & \frac{\rho \alpha I}{(\alpha + N_T)^2} & \frac{\rho \alpha I}{(\alpha + N_T)^2} & \beta_1 - \beta_2 & -k_{M_I} e^{-M} I \\ 0 & 0 & 0 & 0 & -\gamma \end{pmatrix}, \quad (18)$$

where  $c_1 = k_3 - \frac{2k_3}{K_P} P + \frac{k_2 Y}{K_Y} - \frac{2k_2 Y}{K_Y K_P} P - k_5$ ,  $c_2 = k_6 - \frac{2k_6}{K_D} D + \frac{k_4 P}{K_P} - \frac{2k_4 P}{K_P K_D} D - k_7$ ,  $\beta_1 = \frac{\rho N_T}{\alpha + N_T}$  and  $\beta_2 = m + qN_T + k_{M_I}(1 - e^{-M})$ . All the partials in this matrix are continuous on  $[0, K] \times (\mathbb{R}^+)^4$ . Thus  $f(\vec{\psi})$  is locally Lipschitz on  $[0, K] \times (\mathbb{R}^+)^4 \rightarrow \mathbb{R}^5$ . ■

Moreover, since the function  $f$  is locally Lipschitz on  $[0, t_{max}] \times [0, K_Y] \times [0, K_P] \times [0, K_D] \times (\mathbb{R}^+)^2 \rightarrow \mathbb{R}^5$ , then the functional  $F$  mapping  $[0, t_{max}] \times [0, K_Y] \times [0, K_P] \times [0, K_D] \times (\mathbb{R}^+)^2 \rightarrow \mathbb{R}^5$  is locally Lipschitz. It remains to use the following theorem mentioned in [Collins et al., 2010] for obtaining the uniqueness of the solution.

**Theorem 2.3.** *Let  $F(t, Y, P, D, I, M) : [0, t_{max}] \times [0, K_Y] \times [0, K_P] \times [0, K_D] \times (\mathbb{R}^+)^2 \rightarrow \mathbb{R}^5$  be continuous and be locally Lipschitz. If*

$$\|F(t, \psi)\| \leq N_1(t) + N_2(t)\|\psi\| \quad (19)$$

on  $[0, t_{max}] \times [0, K_Y] \times [0, K_P] \times [0, K_D] \times (\mathbb{R}^+)^2$ , where  $N_1(t)$  and  $N_2(t)$  are continuous, positive functions on  $[0, t_{max}]$ ,  $\psi = (Y, P, D, I, M)^T$  and  $\|\cdot\|$  is the Euclidean norm in  $(\mathbb{R}^+)^5$ , then the unique solution exists for all  $t \in [0, t_{max}]$ .

*Proof.*  $F(t, Y, P, D, I, M)$  has already been shown to be locally Lipschitz in Lemma (2.1). As the right hand side of our differential equation system (1) being continuous, then  $F(t, Y, P, D, I, M)$  is a composition of continuous functions and hence is continuous on  $[0, t_{max}]$ . Lastly, we show  $\|F(t, \psi)\| \leq N_1(t) + N_2(t)\|\psi\|$  on the prerequisite domain. We consider supersolutions of  $Y(t), P(t), D(t), I(t)$  as  $Y_{max}, P_{max}, D_{max}$  and  $I_{max}$  respectively. We find from the differential equation (1.5), by determining its analytic solution, then its solution is bounded by:

$$M(t) = \begin{cases} M_0 e^{-\gamma t} - \frac{V_M}{\gamma} e^{-\gamma t} + \frac{V_M}{\gamma}, & \text{if } t \in F. \\ M_0 e^{-\gamma t}, & \text{otherwise.} \end{cases} \quad (20)$$

$$M(t) \leq \begin{cases} M_0 + \frac{V_M}{\gamma} = M_{max}, & \text{if } t \in F. \\ M_0, & \text{otherwise.} \end{cases} \quad (21)$$

where  $M_0 > 0$  is the positive initial value of  $M$ , then the constant  $M_{max} > 0$ . Consequently, a set of supersolutions becomes:

$$\begin{pmatrix} Y_{max} \\ P_{max} \\ D_{max} \\ I_{max} \end{pmatrix}' = \begin{pmatrix} k_1 + k_{M_Y} e^{-M_{max}} & 0 & 0 & 0 \\ k_2 & k_3 + k_{M_P} e^{-M_{max}} & 0 & 0 \\ 0 & k_4 & k_6 + k_{M_D} e^{-M_{max}} & 0 \\ 0 & 0 & 0 & \rho + k_{M_I} e^{-M_{max}} \end{pmatrix} \begin{pmatrix} Y_{max} \\ P_{max} \\ D_{max} \\ I_{max} \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ 0 \\ s \end{pmatrix},$$

note that we use the inequality  $\frac{\rho N_T}{\alpha + N_T} \leq \rho$ , as result of  $\lim_{N_T \rightarrow \infty} f_r(N_T) = \rho$  mentioned above in assumptions (A2). Hence we obtain  $\|F(t, \psi)\| \leq N_1(t) + N_2(t)\|\psi\|$ , where:

$$N_2 = \begin{pmatrix} k_1 + k_{M_Y} e^{-M_{max}} & 0 & 0 & 0 \\ k_2 & k_3 + k_{M_P} e^{-M_{max}} & 0 & 0 \\ 0 & k_4 & k_6 + k_{M_D} e^{-M_{max}} & 0 \\ 0 & 0 & 0 & \rho + k_{M_I} e^{-M_{max}} \end{pmatrix} \quad \text{and} \quad N_1 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ s \end{pmatrix}.$$

Since  $N_1$  and  $N_2$  are both positive and continuous functions under the assumption that the constants are positive, then by application of Cauchy Lipschitz theorem, we have the uniqueness of a existing solution on  $[0, t_{max}]$ .  $\blacksquare$

### 2.3 Stability and bifurcation analysis

In order to study the equilibria of our model and their stability, we now consider the system (2) in the absence of chemotherapy treatment. Then, we eliminate the equation (2.5) and the system is given by:

$$(22) : \begin{cases} \frac{dY}{dt} = r_1(Y)Y - f_{d_0}(Y \cdot I) & (22.1) \\ \frac{dP}{dt} = H_1(Y, P) + r_2(P)P - f_{k_5}(P) - f_{d_1}(P \cdot I) & (22.2) \\ \frac{dD}{dt} = H_2(P, D) + r_3(D)D - f_{k_7}(D) - f_{d_2}(D \cdot I) & (22.3) \\ \frac{dI}{dt} = s + f_r(N_T)I - mI - qN_T I & (22.4) \end{cases} \quad (22.5)$$

All the constant parameters for this system are from Tables 1 and 2 and they are chosen to allow for reasonable simulation outcomes and feasible model solutions with respect to assumptions (A1). Normally in the absence of treatment, the fraction of *CSCs* population is lower than 1% of the total number of tumor cells  $N_T$  [Yanamoto et al., 2011], therefore we set  $CSCs/N_T < 0.01$ . Also, it is well known that total number of *D* cells constitute the majority of tumor cells [Clarke and Fuller, 2006]. Accordingly, we set as constraints the fraction of total number of *P* and *D* cells  $P/N_T \approx 0.3$  and  $D/N_T \approx 0.7$ . In Figure 2, we verify that the chosen parameters (mentioned on Appendix A) fit the model.

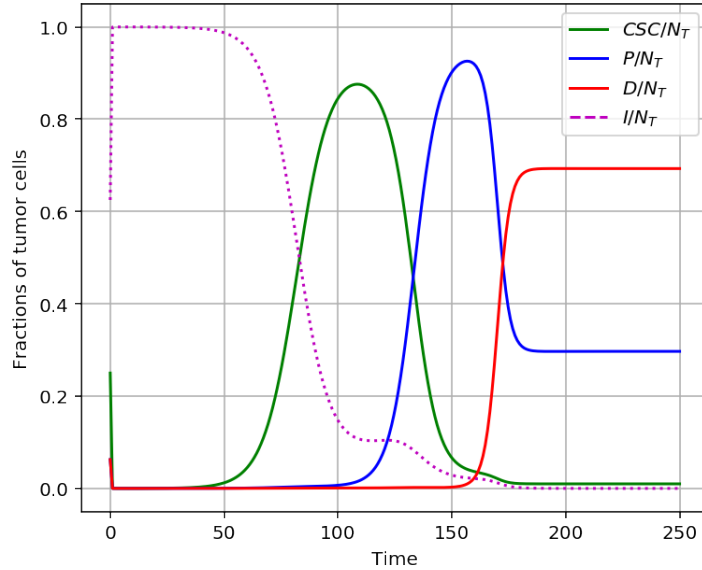


Figure 2: Cells fractions, for each cell population ( $D/N_T$ ; red line), ( $P/N_T$ ; blue line), and ( $CSC/N_T$ ; green line). After 250 time unit (days), all constraints are satisfied; namely,  $CSC/N_T < 0.001$ ,  $P/N_T \approx 0.3$  and  $D/N_T \approx 0.7$ . Note that with weak immune system response, the proliferation of cancer cells decrease the total number of *I* cells ( $I/N_T$ ; pink dashed line). All the used parameters are listed in Tables 1 and 2, except  $d = 1 \times 10^{-9}$ , and the initial populations are  $Y_0 = 4, P_0 = 1, D_0 = 1, I = 10, M_0 = 0$ .

### 2.3.1 Steady states and their stability

Stability of the equilibria are determined by linearizing the system about the calculated values, and by determining the stability of the linearized system. In the physiological point of view, the stability of equilibria is important. If the system is in equilibrium, but the equilibrium point is unstable, a small perturbation from equilibrium will cause the system to move away from that point and evolve toward the stable equilibrium [L. G. de Pillis et al., 2006]. In the following subsections we present an analyse of the steady states stability. We focus on the possible dynamic of elimination of tumor cells, recurrence and coexistence where all type of cancer cells are persisted. For studying its stability, we linearize the system (22) to get the following Jacobian matrix  $J_c(E)$  on the point  $E = (Y, P, D, I)$ :

$$J_c(E) = \begin{pmatrix} k_1 - \frac{2k_1}{K_Y}Y - d_0I & 0 & 0 & d_0Y \\ k_3\frac{P}{K_Y}(1 - \frac{P}{K_P}) & c_1 - d_1I & 0 & d_1P \\ 0 & k_4\frac{D}{K_P}(1 - \frac{D}{K_D}) & c_2 - d_2I & d_2D \\ \frac{\rho\alpha I}{(\alpha+N_T)^2} & \frac{\rho\alpha I}{(\alpha+N_T)^2} & \frac{\rho\alpha I}{(\alpha+N_T)^2} & \beta_1 - \beta_2 \end{pmatrix}. \quad (23)$$

Recall that  $c_1 = k_3 - \frac{2k_3}{K_P}P + \frac{k_2Y}{K_Y} - \frac{2k_2Y}{K_Y K_P}P - k_5$ ,  $c_2 = k_6 - \frac{2k_6}{K_D}D + \frac{k_4P}{K_P} - \frac{2k_4P}{K_P K_D}D - k_7$ ,  $\beta_1 = \frac{\rho N_T}{\alpha + N_T}$  and  $\beta_2 = m + qN_T$ . The stability of the steady states depending on the model parameters.

**Elimination-tumor steady state** The equilibria are determined by finding the simultaneous solutions of system (22). At the elimination-tumor steady state we consider that there is no any type of cancer cells  $Y = P = D = 0$ . The elimination-tumor equilibrium for all four state variables is given by the point  $E_0 = (0, 0, 0, \frac{s}{m})$ . To check stability. We substitute the equilibrium point  $E_0$  in  $J_c(E)$ , we obtain:

$$J_c(E_0) = \begin{pmatrix} k_1 - d_0\frac{s}{m} & 0 & 0 & 0 \\ 0 & k_3 - k_5 - d_1\frac{s}{m} & 0 & 0 \\ 0 & 0 & k_6 - k_7 - d_2\frac{s}{m} & 0 \\ \frac{\rho s}{\alpha m} & \frac{\rho s}{\alpha m} & \frac{\rho s}{\alpha m} & -m \end{pmatrix}. \quad (24)$$

$J_c(E_0)$  is a lower triangular matrix, then the diagonal of a triangular matrix is its set of eigenvalues. Hence, the eigenvalues are:

$$\begin{aligned} \lambda_1 &= k_1 - d_0\frac{s}{m}, & \lambda_2 &= k_3 - k_5 - d_1\frac{s}{m}, \\ \lambda_3 &= k_6 - k_7 - d_2\frac{s}{m}, & \lambda_4 &= -m. \end{aligned}$$

Note that the elimination-tumor equilibrium is stable if and only if all the four previous eigenvalues are negative. Consequently, for obtaining the stability we must have:

$$\lambda_1 = k_1 - d_0\frac{s}{m} < 0 \quad \Leftrightarrow \quad k_1 < d_0\frac{s}{m} \quad (C1)$$

$$\lambda_2 = k_3 - k_5 - d_1\frac{s}{m} < 0 \quad \Leftrightarrow \quad k_3 < k_5 + d_1\frac{s}{m} \quad (C2)$$

$$\lambda_3 = k_6 - k_7 - d_2\frac{s}{m} < 0 \quad \Leftrightarrow \quad k_6 < k_7 + d_2\frac{s}{m}, \quad (C3)$$

Since  $\lambda_4 = -m$  is always negative constant. Subsequently, we substitute the parameter values from Tables 1 and 2 in  $J_c(E_0)$  to determine the values of its eigenvalues. Then, we obtain the set the of eigenvalues  $[-0.02, 0.14, 0.09, 0.07]$ , which are non all negative, then the elimination-tumor equilibrium is unstable. The conditions (C1, C2 and C3)

imply that the stability of elimination-tumor steady state can be accessible and that's depends on proliferation and cell death rates. In other words, it is necessary to have a symmetrical-renewal division rate ( $k_1$ ) of *CSCs* less than the rate of loss due to treatment by immune system. As well for *P* cells, it must have its rate of symmetrical division ( $k_3$ ) less than its rate of death naturally or by treatment. Likewise, the production rate of *D* cells as result of its proliferation ( $k_6$ ), must be less than its death rate.

Therefore, we study the stability near the bifurcations values:  $k_1 = 0.00016$ ,  $k_3 = 0.0003$  and  $k_6 = 0.001$ , where the constant values are taken from Tables 1 and 2. Thus, the elimination-tumor equilibrium is stable if the three conditions:  $k_1 < 0.00016$ ,  $k_3 < 0.0003$  and  $k_6 < 0.001$  are satisfied. By consequences, before the bifurcations values,  $k_1 = 0.00016$ ,  $k_3 = 0.0003$  and  $k_6 = 0.001$  the elimination-tumor equilibrium is stable. This sensitivity to the bifurcations values (shown in Figure 3) implies that this equilibrium loses its stability with some changes in its bifurcations values. Generally, instability means that small changes in the bifurcations (considered as input) will produce large changes in the size of the tumor (considered as output).

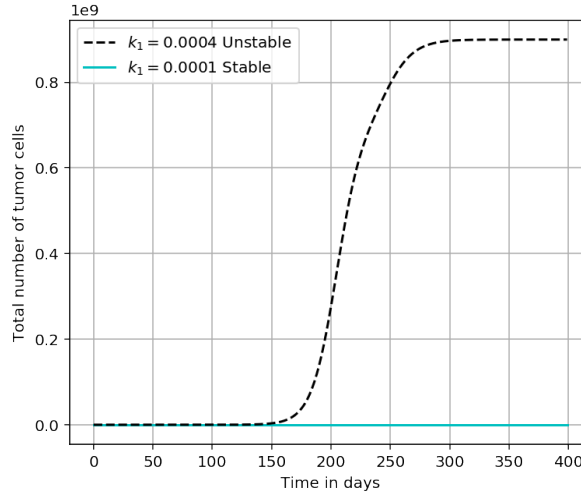


Figure 3: Simulations illustrating system behavior for two values of parameter  $k_1$ . The bifurcation point is  $k_1 = 0.00016$ . Before the bifurcation value  $k_1 = 0.0001$ , the elimination-tumor steady state equilibrium is stable (solid line), with setting  $k_3 = k_4$  at their bifurcation values for ensuring the stability. Conversely after the bifurcation, at  $k_1 = 0.0005$  the tumor grows to its carrying capacity number. In this last case, tumor cells grow to the recurrence-tumor equilibrium (dashed line), that implies the instability of elimination-tumor equilibrium after the bifurcation value. All parameters besides  $k_1$  are from Tables 1 and 2 and the initial populations are  $Y_0 = 4, P_0 = 1, D_0 = 1, I = 10$  for the both two cases.

In other word, The conditions (C1, C2 and C3) imply that for  $s$  large enough the last eigenvalues  $\lambda_1, \lambda_2$  and  $\lambda_3$  are also be negative.

**Corollary 2.1.** *Let  $s$  be large enough, such that*

$$s < \max\left\{\frac{k_1 m}{d_0}, \frac{(k_3 - k_5) m}{d_1}, \frac{(k_6 - k_7) m}{d_2}\right\}$$

. *Then the elimination-tumor steady state ( $E_0$ ) is locally asymptotically stable.*

Corollary 2.1 gives a necessary condition for the treatment to be efficient in tumour elimination. Consequently, if we inject a tumor at its advanced stage with  $s$  large enough, tumor size will decay into 0 like it shown in Figure (4).

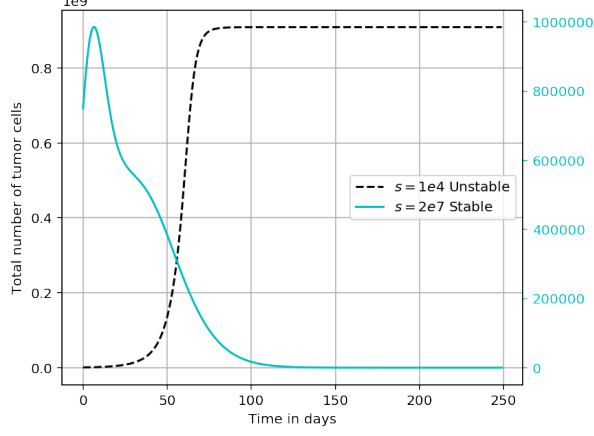


Figure 4: Simulations illustrating system behavior for two immune system treatment injection value. Before the bifurcation value  $s = 1^4$ , the elimination-tumor equilibrium before the bifurcation value is instable, then the pre-existing tumor grows to its carrying capacity number (dashed black line). Conversely after the bifurcation, at  $s = 2^7$  the elimination-tumor steady state equilibrium is stable (solid blue line) and it is decay into 0. All parameters beside  $s$  are from Tables 1 and 2 and the initial populations are  $Y_0 = 5 \cdot 10^4$ ,  $P_0 = 2 \cdot 10^5$ ,  $D_0 = 5 \cdot 10^5$ ,  $I = 10$  for the both two cases.

**Recurrence-tumor steady state** Here, the  $P$  and  $D$  populations are eradicated, but the  $CSC$  population persists. So that, we set the  $P = D = 0$  and see the consequences for the  $CSC$  population steady state. Let  $Y_E \geq 0$ ,  $P_E = 0$ ,  $D_E = 0$  and  $I_E = \frac{s}{\frac{-\rho}{\alpha+Y_E} + m + qY_E}$  be the equilibrium points, then we obtain:

$$\frac{dY}{dt} = r_1(Y_E)Y_E - d_0Y_EI_E = 0, \quad (25)$$

as  $Y_E$  is a steady state then  $Y_E = 0$  or  $r_1(Y_E) = d_0Y_EI_E$ . For further analysis, we denote the two following functions:

$$f(s) = s \quad \text{and} \quad g(Y) = \frac{1}{\frac{-\rho}{\alpha+Y} + m + qY}. \quad (26)$$

Hence, the equation (25) becomes:

$$r_1(Y_E) = d_0f(s)g(Y_E), \quad (27)$$

Then we define:

$$L_s(Y) = r_1(Y) - d_0f(s)g(Y). \quad (28)$$

where  $f(s)$  is increasing in  $s$  and  $r_1(Y_E)$  and  $g(Y_E)$  are both decreasing in  $(Y_E)$ . And with the chosen parameters of the model, we have  $r_1(K_Y) = 0$  and  $g(K_Y) > 0$ . Then  $L_s(K_Y) < 0$  for any  $s > 0$ .

We also know that  $L_s(0) = k_1 - d_0f(s)\frac{\alpha}{m\alpha - \rho}$ . Since  $f(s)$  is an increasing function, its inverse exists and we can define  $s_{min} = \frac{k_1(m\alpha - \rho)}{d_0\alpha}$ . Notice that, for  $s = s_{min}$ ,  $L_s(0) = 0$ . For  $s < s_{min}$ ,  $L_s(0) > 0$ , and  $L_s(K_Y) < 0$ . Therefore, for  $s < s_{min}$ ,  $L_s(Y) = 0$  has at least one solution  $Y_E \in [0, K_Y]$  and, in general, since the function must cross the  $Y$ -axis an odd number of times, there are an odd number ( $n$ ) of solutions,  $Y_{E_1} \cdots Y_{E_n}$ .



We can assume that, for large enough  $t$ :

$$\frac{dY}{dt} = r_1(Y)Y - d_0 f(s)g(Y) = YL_s(Y). \quad (29)$$

For  $s < s_{min}$ , the equilibrium point  $(0, 0, 0, I_E)$  is unstable, since any values of  $Y$  less than 0 will yield a negative value for  $L_s(Y)$ , and any values of  $Y$  between 0 and  $Y_{E_1}$  will yield a positive value for  $L_s(Y)$ . Thus our first stable equilibrium point is at  $(Y_{E_1}, 0, 0, I_E)$ .

In contrast, if  $s$  is large enough so that  $s > s_{min}$ , the equilibrium point  $(0, 0, 0, I_E)$  is locally stable, since for  $s > s_{min}$ ,  $L_s(0) < 0$ . However, it may still exist positive solutions  $Y_E: Y_{E_1} \cdots Y_{E_n}$ , where  $n$  is even. If these solutions are organized in non-decreasing order,  $Y_{E_i}$  is locally stable for even  $i$  and unstable for odd  $i$ , since  $L_s(Y) > 0$  between an odd and even root and  $L_s(Y) < 0$  between an even and odd root. Note that if  $(0, 0, 0, I_E)$  is the only equilibrium point, it is globally asymptotically stable.

**Coexistence-tumor steady state** This case is considered as the disease state, where the existing of all tumor cells (i.e.  $Y > 0, P > 0$  and  $D > 0$ ). Let  $(Y_E, P_E, D_E, I_E)$  denote a coexistence-tumor steady state with  $Y_E > 0$ , then we define:

$$P_E = \frac{k_2 \frac{Y_E}{K_Y} + k_3 - k_5 - d_1 I_E}{\frac{k_2 Y_E}{K_Y K_P} + \frac{k_3}{K_P}} = P_E(I_E) \quad (30.1)$$

$$D_E = \frac{k_4 \frac{P_E}{K_P} + k_6 - k_7 - d_2 I_E}{\frac{k_4 P_E}{K_P K_D} + \frac{k_6}{K_D}} = D_E(I_E) \quad (30.2)$$

We wish to show existence of  $Y_E, P_E, D_E > 0$  and  $I_E > 0$ , so, we have to solve the system:

$$R_1(Y_E) = d_0 I_E \quad (31.1)$$

$$s + \frac{\rho(Y_E + P_E(I_E) + D_E(I_E))}{\alpha + Y_E + P_E(I_E) + D_E(I_E)} I_E - m I_E - q(Y_E + P_E(I_E) + D_E(I_E)) I_E = 0. \quad (31.2)$$

Let us consider equation 31.2, and with  $Y > 0$  we define the auxiliary function:

$$\mathcal{A}_Y(I) = s + \frac{\rho(Y_E + P_E(I) + D_E(I))}{\alpha + Y_E + P_E(I) + D_E(I)} I - m I - q(Y_E + P_E(I) + D_E(I)) I, \quad (32)$$

we notice that for every  $Y > 0$ ,  $\mathcal{A}_Y(0) = s > 0$ . Then, taking the derivative with respect to  $I$ , we obtain:

$$\begin{aligned} \mathcal{A}'_Y(I) &= \frac{\rho(Y_E + P_E(I) + D_E(I))}{\alpha + Y_E + P_E(I) + D_E(I)} + \frac{\alpha \rho(P'_E(I) + D'_E(I))}{(\alpha + Y_E + P_E(I) + D_E(I))^2} \\ &\quad - m - q(Y_E + P_E(I) + D_E(I)) - q(P'_E(I) + D'_E(I)) I \end{aligned} \quad (33)$$

From the model assumptions and parameters, we have  $\mathcal{A}'_Y(I) < 0$ , for a given  $Y$ , then  $\mathcal{A}_Y(I)$  is a decreasing function. Hence, as  $\mathcal{A}_Y(0) > 0$ , there is one positive  $I$  which satisfied  $\mathcal{A}_Y(I) = 0$ , for any given  $Y$ .

Now, we study our stability analysis with consideration of a coexistence steady state. As above in the recurrence-tumor steady state, we expect  $I_E = f(s) \cdot g(Y_E, P_E, D_E)$ , where:

$$f(s) = s \quad \text{and} \quad g(Y_E, P_E, D_E) = \frac{1}{\frac{-\rho}{\alpha + Y_E + P_E + D_E} + m + q(Y_E + P_E + D_E)}, \quad (34)$$

and we can re-write our system as the following:

$$\begin{aligned} \frac{dY}{dt} &= r_1(Y)Y - d_0 f(s)g(Y, P, D)Y = Y \cdot (L_1(Y, P, D)) \equiv Y \cdot N_1(Y, P, D) \\ \frac{dP}{dt} &= r_2(P)P + H_1(Y, P) - k_5 P - d_1 f(s)g(Y, P, D)P \\ &= P \cdot (L_2(Y, P, D) - k_5 + k_2 \frac{Y}{K_Y} (1 - \frac{P}{K_P})) \equiv P \cdot N_2(Y, P, D) \\ \frac{dD}{dt} &= r_3(D)D + H_2(P, D) - k_7 D - d_2 f(s)g(Y, P, D)P \\ &= D \cdot (L_3(Y, P, D) - k_7 + k_4 \frac{P}{K_P} (1 - \frac{D}{K_D})) \equiv D \cdot N_3(Y, P, D). \end{aligned} \quad (35)$$

We define  $s_{min} = \min\{s_{min,Y}, s_{min,P}, s_{min,D}\}$ , where  $s_{min,Y} = \frac{k_1(\frac{-\rho}{\alpha + K_P + K_D}) + m + q(K_P + K_D)}{d_0 \alpha}$ ,  $s_{min,P} = \frac{k_3(m\alpha - \rho)}{d_1 \alpha}$  and  $s_{min,D} = \frac{k_6(m\alpha - \rho)}{d_2 \alpha}$ .

**Proposition 2.1.** *For  $s < s_{min}$  system (35) has a locally stable coexistence steady state if and only if rate of trans-differentiation  $k_3$  and differentiation  $k_4$  is small enough;  $k_3 \approx k_4 \approx 0$ .*

*Proof.* For showing the existence of such a steady state, Without loss of generality, we suppose that  $s_{min} = s_{min,Y}$ . Then for values of  $s < s_{min}$ ,  $N_1(0, P, D) > 0$  and  $N_1(K_Y, P, D) < 0$ , for all values of  $P \in [0, K_P]$  and  $D \in [0, K_D]$ . Therefore, for  $s < s_{min}$ ,  $L_1(Y_E, P, D) = 0$  has at least one solution  $Y_E \in [0, K_Y]$ , for all  $P \in [0, K_P]$  and  $D \in [0, K_D]$ . In general, since the function must cross the  $Y$ -axis an odd number of times, there are an odd number ( $n$ ) of solutions,  $Y_{E_1} \cdots Y_{E_n}$ , such that  $N_1(Y_{E_i}, P, D) = 0$ .

Likewise, by our choice of  $s_{min}$ ,  $N_2(Y, 0, D) > 0$  and  $N_2(Y, K_P, D) < 0$  if and only if  $k_2 \approx 0$ , for all values of  $Y \in [0, K_Y]$  and  $D \in [0, K_D]$ . Thus, for  $s < s_{min}$ ,  $L_2(Y, P_E, D) = 0$  has at least one solution  $P_E \in [0, K_P]$ , for all  $Y \in [0, K_Y]$  and  $D \in [0, K_D]$ . In general, since the function must cross the  $P$ -axis an odd number of times, there are an odd number ( $m$ ) of solutions,  $P_{E_1} \cdots P_{E_m}$ , such that  $N_2(Y, P_{E_j}, D) = 0$ .

A parallel argument works to show that for  $s < s_{min}$ ,  $L_3(Y, P, D_E) = 0$  has at least one solution  $D_E \in [0, K_D]$ , as  $N_3(Y, P, 0) > 0$  and  $N_3(Y, P, K_D) < 0$  if and only if  $k_4 \approx 0$  for all  $Y \in [0, K_Y]$  and  $P \in [0, K_P]$ . And there exist an odd number of solutions  $p, D_{E_1} \cdots D_{E_p}$ , such that  $N_3(Y, P_{E_k}, D) = 0$ .

Then, we can deduce the existence of an equilibrium point  $(Y_E, P_E, D_E)$  in  $[0, K_Y] \times [0, K_P] \times [0, K_D]$  for the system (35). Moreover, notice that while  $(0, 0, 0)$  is an equilibrium point of the system (35), it is unstable since  $N_1(Y, P, D) > 0$  for  $0 \leq Y < Y_E$ ,  $P \in [0, K_P]$

and  $D \in [0, K_D]$ , also  $N_2(Y, P, D) > 0$  for  $0 \leq P < P_E$ ,  $Y \in [0, K_Y]$  and  $D \in [0, K_D]$ , and  $N_3(Y, P, D) > 0$  for  $0 \leq D < D_E$ ,  $Y \in [0, K_Y]$  and  $P \in [0, K_P]$ . In fact, if we denote  $Y_0 = P_0 = D_0 = 0$ , the equilibrium points  $(Y_{E_i}, P_{E_i}, D_{E_\kappa})$  are locally unstable when  $i$  or  $j$  or  $\kappa$  is even and locally stable when  $i$  and  $j$  and  $\kappa$  are odd. ■

We now show that, by increasing the treatment term  $s$ , we will achieve a globally asymptotically stable cure steady state. We conclude our analysis by noting that:

$$\begin{aligned}
\frac{dY}{dt} &= Y \cdot (L_1(Y, P, D)) \\
\frac{dP}{dt} &= P \cdot (L_2(Y, P, D) - k_5 + k_2 \frac{Y}{K_Y K_P} (K_P - P)) \\
&\leq P \cdot (L_2(Y, P, D) + k_2 K_P) \\
\frac{dD}{dt} &= D \cdot (L_3(Y, P, D) - k_7 + k_4 \frac{P}{K_P K_D} (K_D - D)) \\
&\leq D \cdot (L_3(Y, P, D) + k_4 K_D),
\end{aligned} \tag{36}$$

for all  $(Y, P, D) \in [0, K_Y] \times [0, K_P] \times [0, K_D]$ . Hence, for  $s \geq s_{min}$  let us consider the system:

$$\begin{aligned}
\frac{dY}{dt} &= Y \cdot (L_1(Y, P, D)) \\
\frac{dP}{dt} &= P \cdot (L_2(Y, P, D) + k_2 K_P) \\
\frac{dD}{dt} &= D \cdot (L_3(Y, P, D) + k_4 K_D)
\end{aligned} \tag{37}$$

Let  $s_Y$  be the maximum of  $\frac{r_1(Y)}{d_0 f(s_{min, Y}) g(Y, K_P, K_D)}$ , and we choose  $s_{thr, Y}$  such that  $f(s_{thr, Y}) = f(s_{min, Y}) s_Y$ . Similarly, let  $s_P, s_D$  be the maximum of  $\frac{r_2(P) + k_2 K_P}{d_1 f(s_{min, P}) g(K_Y, P, K_D)}$ ,  $\frac{r_3(D) + k_4 K_D}{d_2 f(s_{min, D}) g(K_Y, K_P, D)}$  respectively, and we choose  $s_{thr, P}$  such that  $f(s_{thr, P}) = f(s_{min, P}) s_P$  and  $s_{thr, D}$  such that  $f(s_{thr, D}) = f(s_{min, D}) s_D$ . Let  $s_{cure} = \max\{s_{thr, Y}, s_{thr, P}, s_{thr, D}\}$ .

**Proposition 2.2.** *For  $s > s_{cure}$ ,  $(0, 0, 0)$  is a globally asymptotically stable equilibrium point of system (37).*

*Proof.* For  $s > s_{thr, P}$ ,

$$\begin{aligned}
L_2(Y, P, D) + k_2 K_P &< r_2(P) - f(s_{thr, P}) g(Y, P, D) + k_2 K_P \\
&= r_2(P) - s_P f(s_{min, P}) g(Y, P, D) + k_2 K_P \\
&= r_2(P) + k_2 K_P - \frac{g(Y, P, D)}{g(K_Y, P, K_D)} (r_2(P) + k_2 K_P) \\
&= r_2(P) + k_2 K_P \left(1 - \frac{g(Y, P, D)}{g(K_Y, P, K_D)}\right) \leq 0,
\end{aligned} \tag{38}$$

since  $g$  is decreasing for  $0 \leq P < K_P$ . Then  $L_2(Y, P, D) + k_2 K_P < 0$  for all  $(Y, P, D) \in [0, K_Y] \times [0, K_P] \times [0, K_D]$ . Similarly For  $s > s_{thr, Y}$  and for  $s > s_{thr, D}$ ;  $L_1(Y, P, D) < 0$

and  $L_3(Y, P, D) + k_4 K_D < 0$  respectively, for all  $(Y, P, D) \in [0, K_Y] \times [0, K_P] \times [0, K_D]$ . Therefore,  $(0, 0, 0)$  is the only equilibrium point for system (37) and  $(0, 0, 0)$  is globally asymptotically stable. ■

Now, we will determine the coexistence-tumor equilibrium numerically and check its stability for the model parameters. We set simultaneously the equations of system (22) equal to zero in order to find the equilibria. Therefore, setting (22.1, 22.2, 22.3) and (22.4) to zero respectively yield to:

$$I_{E_1} = \frac{k_1 - \frac{k_1}{K_Y} Y}{d_0} \quad (39.1)$$

$$P_E = \frac{k_2 \frac{Y}{K_Y} + k_3 - k_5 - d_1 I_E}{\frac{k_2 Y}{K_Y K_P} + \frac{k_3}{K_P}} \quad (39.2)$$

$$D_E = \frac{k_4 \frac{P}{K_P} + k_6 - k_7 - d_2 I_E}{\frac{k_4 P}{K_P K_D} + \frac{k_6}{K_D}} \quad (39.3)$$

$$I_{E_2} = \frac{s}{\beta_E - \beta_E}, \quad (39.4)$$

where  $Y > 0$ ,  $\beta_E = \frac{\rho \cdot (Y + P_E + D_E)}{\alpha + N_T}$ ,  $\beta_E = m + q \cdot (Y + P_E + D_E)$  and  $I_{E_1}, I_{E_2}, P_E, D_E$  are the recurrence-tumor equilibrium for the variables  $I, P$  and  $D$ . In this case, the value of the equilibrium  $Y \neq 0$  is determined numerically. Indeed, we vary the value of  $Y$  in the range  $[0, K_Y]$  and we determine the values of the  $D_E$  cells each time. As we can see from the formulas (39.1, 39.2, 39.3 and 39.4), we calculate the value of  $I_{E_1}$  in function of  $Y$ , then the value of  $P_E$  finally  $D_E$  in function of  $Y, P_E$  and  $I_{E_1}$ . With the same way we determine the second values of  $D_E$  but by using the values  $I_{E_2}$ . Therefore, we define the two following function:

$$D_{E_1}(Y) = D_E \circ P_E \circ I_{E_1}(Y) \quad (40)$$

$$D_{E_2}(Y) = D_E \circ P_E \circ I_{E_2}(Y). \quad (41)$$

Hence, we search the positive equilibrium of  $Y$  by plotting the nullclines presented in the following Figure 5:

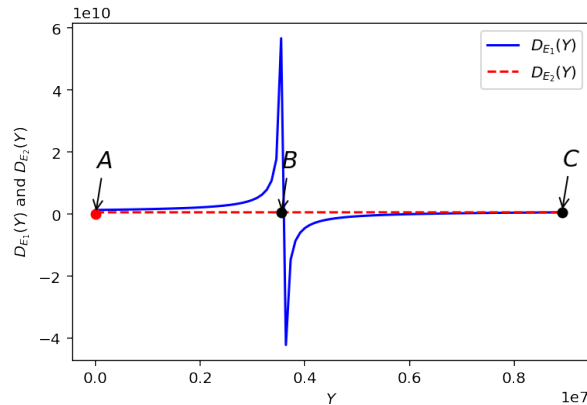


Figure 5: The nullclines intersections of the equationa (40) and (41). The nullclines intersect in 3 points. There is the elimination-tumor equilibrium  $A$ . In addition, the nullclines intersect in two points  $B$  and  $C$ , however there is only one non-zero positive equilibrium  $C$ . The estimated parameter set are taken from Tables 1 and 2.

As a consequence, the positive coexistence-tumor equilibrium points are the intersections of the graphs (shown in Figure 5). We exclude the equilibrium points with negative population, so that we eliminate the point  $B$ . Then, the unique positive equilibrium point, which include the number of  $CSC$ ,  $P$ ,  $D$  and  $I$  cells in equilibrium ( $Y_E, P_E, D_E, I_E$ ) respectively, are approximately:

$$\begin{aligned} A &= (0, 0, 0, 650000) \\ C &= (8 \cdot 10^6, 2 \cdot 10^8, 6 \cdot 10^8, 5 \cdot 10^6) \end{aligned}$$

where  $A$  is the elimination-tumor steady state,  $B$  and  $C$  is the coexistence-tumor steady state. Then, we study the stability of the positive equilibrium  $C$  by substituting its value in the Jacobian matrix (23). Following this, The set of the eigenvalues of the point  $C$  is :  $[-0.3, -0.14, -0.17, -0.2]$ . It's clear that with the chosen parameter of the model, the coexistence-tumor steady state is stable, as all the eigenvalues of the equilibrium  $C$  are non null and negative. At the unstable equilibriums  $A$ , a small perturbation takes place in equilibrium will cause the system moves toward the stable equilibrium  $C$ .

**Conclusion of stability results** We have investigated the behaviour of the model around equilibrium solutions. An equilibrium is considered stable if the system always returns to it after small disturbances. The stability of the coexistence-tumor equilibrium implies that, if treatment is stopped, the system will inevitably return to the coexistence-tumor state, i.e. the tumor will escape from the immune system treatment unless every single tumor cell is killed. Thus, in a case such as ours for which the elimination-tumor equilibrium is unstable, then in order to realistically effect a cure, any treatment must not only reduce the tumor burden, but it must also change the parameters of the system itself.

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## Appendix A Experimental data

Parameter	Estimated value	Units	Description	Reference
$k$	$4.31 \times 10^{-1}$	days <sup>-1</sup>	Tumor growth rate.	[Diefenbach et al., 2001]
$K$	$10^7$	cells	Tumor carrying capacity.	[Turner et al., 2009]
$k_{death}$	$7, 13 \cdot 10^{-10}$	cells <sup>-1</sup> days <sup>-1</sup>	Tumor cells natural death rate.	[Diefenbach et al., 2001]
$k_M$	$9 \times 10^{-1}$	days <sup>-1</sup>	Fractional tumor cells kill by chemotherapy.	[Perry, 2008]
$d$	$1 \times 10^{-7}$	cells <sup>-1</sup> days <sup>-1</sup>	Fractional tumor cells kill by immune cells.	[Kuznetsov et al., 1994]
$\gamma_M$	$1 \times 10^{-1}$	days <sup>-1</sup>	Rate of chemotherapy drug decay.	[L. G. de Pillis et al., 2006]
$V_d$	0	mg/L	Chemotherapy drug infusion rate.	Model-specific parameter
$s$	$1.3 \times 10^4$	cells days <sup>-1</sup>	Immune treatment injection rate into the tumor site.	[Kuznetsov et al., 1994]
$\alpha$	$2.019 \times 10^7$	cells	Steepness coefficient of $I$ cell recruitment.	[Kuznetsov et al., 1994]
$\rho$	0.1245	days <sup>-1</sup>	Maximum $I$ cells recruitment rate.	[Kuznetsov et al., 1994]
$m$	$2 \times 10^{-2}$	days <sup>-1</sup>	$I$ cells death rate	[Kuznetsov et al., 1994]
$q$	$3.42 \times 10^{-10}$	cells <sup>-1</sup> days <sup>-1</sup>	$I$ cells death rate due to interaction with tumor cells.	[Kuznetsov et al., 1994]

Table 1: Parameter values of the model

Parameter	Probability of occurrence ( $p$ )	Estimated value	Units	Description
$K_Y$	0.01	$K \cdot p \approx 9 \cdot 10^6$	Cells	$CSCs$ carrying capacity.
$K_P$	0.3	$K \cdot p \approx 63 \cdot 10^7$	Cells	$P$ cells carrying capacity.
$K_D$	0.7	$K \cdot p \approx 27 \cdot 10^7$	days <sup>-1</sup>	$D$ cells carrying capacity.
$k_1$	$\frac{1}{3}$	$k \cdot p \approx 0.143$	days <sup>-1</sup>	$CSCs$ symmetric division rate
$k_2$	$\frac{3}{3}$	$k \cdot p \approx 0.009$	days <sup>-1</sup>	$CSCs$ trans-differentiation rate
$k_3$	$\frac{1}{3}$	$k \cdot p \approx 0.1$	days <sup>-1</sup>	$P$ proliferation rate
$k_4$	$\frac{3}{4}$	$k \cdot p \approx 0.3$	days <sup>-1</sup>	$P$ differentiation rate
$k_5$	0.5	$k_{death} \cdot p \approx 3, 5 \cdot 10^{-10}$	cells <sup>-1</sup> days <sup>-1</sup>	$P$ natural death rate
$k_6$	$\frac{1}{10}$	$k \cdot p \approx 0.04$	days <sup>-1</sup>	$D$ proliferation rate
$k_7$	1	$k_{death} \cdot p \approx 7, 13 \cdot 10^{-10}$	cells <sup>-1</sup> days <sup>-1</sup>	$D$ natural death rate
$k_{M_Y}$	$\frac{1}{4}$	$k_M \cdot p \approx 0.225$	cells <sup>-1</sup> days <sup>-1</sup>	Fractional $CSCs$ kill by chemotherapy
$k_{M_P}$	$\frac{1}{2}$	$k_M \cdot p \approx 0.45$	cells <sup>-1</sup> days <sup>-1</sup>	Fractional $P$ cells kill by chemotherapy
$k_{M_D}$	1	$k_M \cdot p \approx 0.9$	cells <sup>-1</sup> days <sup>-1</sup>	Fractional $D$ cells kill by chemotherapy
$k_{M_I}$	0.001	$k_M \cdot p \approx 0.0009$	cells <sup>-1</sup> days <sup>-1</sup>	Fractional $I$ cells kill by chemotherapy
$d_0$	$\frac{1}{4}$	$d \cdot p \approx 2.5 \times 10^{-8}$	cells <sup>-1</sup> days <sup>-1</sup>	Fractional $CSCs$ kill by $I$ cells.
$d_1$	$\frac{1}{2}$	$d \cdot p \approx 5 \times 10^{-8}$	cells <sup>-1</sup> days <sup>-1</sup>	Fractional $P$ cells kill by $I$ cells.
$d_2$	1	$d \cdot p \approx 1 \times 10^{-7}$	cells <sup>-1</sup> days <sup>-1</sup>	Fractional $D$ cells kill by $I$ cells.

Table 2: Estimated parameter values of the model

Here in Tables 1 and 2, we list all the parameters used in the model taking into account the biological assumptions of the model. For that, some parameters are estimated specifically for this model but they are based on previous model parameters and experimental studies. So that, we estimate the sets of growth rates  $\{k_1, k_2, k_3, k_4, k_6\}$  from the parameter  $k$ , death rates  $\{k_5, k_7\}$  from  $k_{death}$ , knowing that the natural death rate of tumor cells is increased as cells become more differentiated.  $\{k_{M_Y}, k_{M_P}, k_{M_D}, k_{M_I}\}$  are estimated from  $k_M$  and finally  $\{d_0, d_1, d_2\}$  from  $d$ . These rates can be estimated using a probability value for the occurrence of each process [Wodarz and Komarova, 2014,



Rodriguez-Brenes et al., 2011]. According to the biological assumptions of the model (A1), which based on the model of [Molina-Peña and Álvarez, 2012], we estimate the previous rate on Table 2. Therefore, with this choice of the parameters we assume realistic outcomes shown on Figure 2.