Mathematical Biosciences and Engineering

http://www.aimspress.com/journal/MBE

MBE, 18(2): 1845–1863.
DOI: 10.3934/mbe.2021096
Received: 19 December 2020
Accepted: 01 February 2021
Published: 22 February 2021

Research article

Analysis of the effectiveness of the treatment of solid tumors in two cases of drug administration

Lorand Gabriel Parajdi[1,*], Radu Precup[1,*], Marcel-Adrian Şerban[1] and Ioan Ştefan Haplea[2]

[1] Department of Mathematics, Babeş-Bolyai University, Cluj-Napoca 400084, Romania
[2] Department of Internal Medicine, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca 400012, Romania

* **Correspondence:** Email: r.precup@math.ubbcluj.ro, lorand@cs.ubbcluj.ro.

Abstract: A complete stability analysis of the equilibrium solutions of a system modeling tumor chemotherapy is performed in two cases of administration of the treatment, by continuous infusion and by periodic infusion. Several numerical simulations illustrate and complement the theory.

Keywords: generalized logistic model; solid tumor; stability; equilibrium point; numerical simulation; dynamic system

1. Introduction

Applied mathematics did not only appear because of an objective purpose, but also thanks to the human desire of always getting to know more. It is known that a quantitative description of a phenomenon observed with the formulation of laws is not enough if it does not make a qualitative study of the model along with the corresponding phenomenon. Mathematical modeling of a real problem is sometimes a difficult, long-term and very detailed process. An effective or at least close to an effective solution represents the final target of any problem. The theory of differential equations and some software packages are important tools for solving several actual problems from different real-world domains.

There are known various contributions to the investigation of solid tumor growth and chemotherapeutic scenarios. Thus, the effects of drug administration in chemotherapy are studied in the papers of R.B. Martin et al. [1] and S.T.R. Pinho et al. [2]; the fail of chemotherapy, in S.T.R. Pinho et al. [3] and D.S. Rodrigues et al. [4]; problems of optimal control of drug administration, in J.C. Panetta and K.R. Fister [5], L.G. de Pillis and A. Radunskaya [6], L.G. de Pillis et al. [7], A. D'Onofrio et al. [8]; multi-scale simulations, in G.S. Stamatakos et al. [9]; Monte Carlo models, in L.G. Marcu and E. Bezak [10]; models based on ordinary differential equations, in S.T.R. Pinho et al. [11], D.S.

Rodrigues and P.F. de Arruda Mancera [12], M. Mamat et al. [13], J. Malinzi [14] and P. Unni and P. Seshaiyer [15]; and stochastic dynamic models, in W. L. Duan [16], W. L. Duan and H. Fang [17] and W. L. Duan et al. [18]. For some reviews on mathematical models for tumor growth and treatment, we refer the reader to P.M. Altrock et al. [19], A. Fasano et al. [20] and A. Yin et al. [21].

In paper [22], the mathematical model for solid tumors has been the self-limiting equation

$$N'(t) = \frac{aN(t)}{1 + bN(t)} - cN(t)$$

involving three positive parameters a, b, c. The same equation has been used in [23–25] for modeling cell proliferation in leukemias.

Alternatively, one can use the generalized logistic equation or Richards' growth model [26],

$$N'(t) = rN(t)\left(1 - \left(\frac{N(t)}{K}\right)^{\theta}\right). \tag{1.1}$$

Such an approach is given by H.M. Byrne in [27], where the following dynamic system is suggested as a model for tumor chemotherapy:

$$\begin{cases} N'(t) = rN(t)\left(1 - \left(\frac{N(t)}{K}\right)^{\theta}\right) - \mu A(t)N(t) \\ A'(t) = \alpha(t) - \lambda A(t) - \gamma A(t)N(t). \end{cases} \tag{1.2}$$

We will adopt this model for the study which follows. In this model, $N(t)$ represents the number of the tumor cell population from a solid tumor that changes in time, $A(t)$ is the drug concentration within the tumor at time t, and $\alpha(t)$ represents the rate at which the drug is injected in the body.

Parameter r represents the nonrestrictive growth rate of the tumor cell population giving the proliferative capacity of the cells, K stands for the tumor carrying capacity, θ measures how quickly the tumor reaches its carrying capacity, μ is the rate at which the drug kills malignant cells, λ represents the decreasing rate of the concentration of the drug, and γ gives the rate at which the drug is consumed significantly within the tumor. We emphasize the role of the parameter θ for the adequacy of the logistic equation to the real clinical data obtained on each type of tumor. A method for determining the value of this parameter is described in paper [28], where the criterion of best fit was the mean square error between the observed and predicted tumor values. For breast cancer, the best overall fit to the clinical data was obtained with $\theta = 1/4$.

According to the clinical practice, two cases have to be considered: (a) the case of continuous infusion, when $\alpha(t)$ is a constant α_∞, and (b) case of periodic infusion, when the drug is delivered as a series of interrupted continuous infusions, and thus $\alpha(t)$ is only piecewise constant.

The scope of this paper is to perform a complete analysis of the stability of the equilibrium or stationary solutions of the Eq (1.2), as a theoretical basis of the chemotherapeutic protocols. Our results extend to a general exponent θ and some of the conclusions established in [27, Chapter 4]. The theory is illustrated and complemented by a number of numerical simulations with MATLAB and MAPLE software, using real data from the medical literature. A part of the numerical simulations was carried out on the Kotys HPC (High Performance Computing) infrastructure of Babeş-Bolyai University, Cluj-Napoca [29].

2. The generalized logistic growth model for a solid tumor

Before starting to discuss the model of chemotherapy given by the Eq (1.2), in this first section, for comparative purposes, we remind the reader of some well-known basic results regarding the generalized logistic Eq (1.1) here considered as a model for tumor cell dynamics and the stability of its equilibrium solutions.

The solution of Eq (1.1) satisfying the initial condition $N(0) = N_0$ can be given explicitly, namely

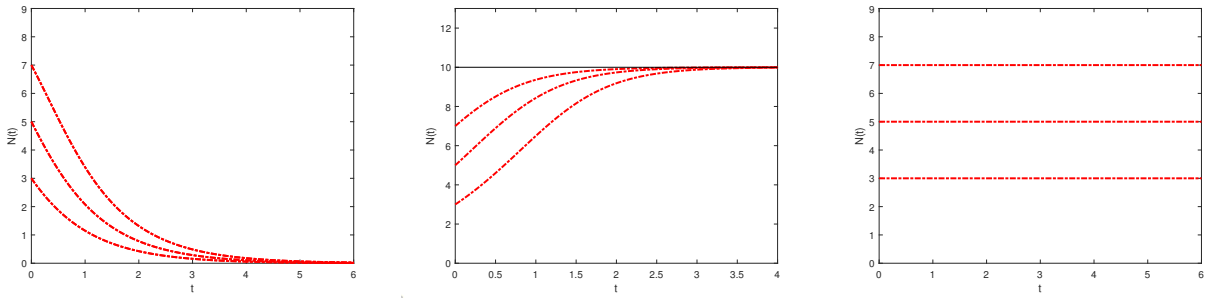
$$N(t) = \frac{1}{\left(K^{-\theta} + e^{-r\theta t}\left(N_0^{-\theta} - K^{-\theta}\right)\right)^{\frac{1}{\theta}}}.$$

The equation admits two equilibrium solutions, $N_1^* = 0$ and $N_2^* = K$. Their stability properties can be easily established and are given by the next result.

Theorem 2.1. (a) *If $r < 0$ and $N_0 < K$, then $N(t) \to 0$ as $t \to +\infty$, thus $N_1^* = 0$ is the only one equilibrium solution which is locally asymptotically stable.*

(b) *If $r > 0$, then $N(t) \to K$ as $t \to +\infty$, thus $N_2^* = K$ is the only one equilibrium solution which is locally asymptotically stable.*

(c) *If $r = 0$, then $N(t) \equiv N_0$, thus the solution $N(t)$ remains constantly equal with the initial value N_0.*



(a) Tumor cell population behavior when $r = -1$, $\theta = 2$ and $K = 10$.

(b) Tumor cell population behavior when $r = 1$, $\theta = 2$ and $K = 10$.

(c) Tumor cell population behavior when $r = 0$, $\theta = 2$ and $K = 10$.

Figure 1. The dynamics of the generalized logistic model.

From a biological point of view, we can say that in the case of a negative nonrestrictive growth rate, as in situation (a) from the previous theorem, the population of tumor cells will be eliminated in time, see Figure 1(a). On the contrary, in the case of a positive nonrestrictive growth rate, as in situation (b), the population of tumor cells reaches its carrying capacity K, see Figure 1(b). In the case when the nonrestrictive growth rate is equal to zero, as in situation (c), the population of tumor cells remains constant in time, see Figure 1(c).

The aim of this paper is to study the influence of chemotherapy over the dynamics of the tumor cell population, in the case $r > 0$, when, in the absence of the treatment, the tumor cell population approaches K. We are looking for conditions for the treatment to be effective, i.e. to make the transition from the bad situation $N(t) \to K$ to the good one $N(t) \to 0$ as $t \to +\infty$.

3. Treatment of homogeneous solid tumors

Consider that a tumor grows according to the generalized logistic model, where $r > 0$, that a drug is used to destroy the malignant cells, and that the mathematical model of the therapeutic dynamics is given by Eq (1.2).

We take into consideration two methods of treatment administration: by continuous infusion and by periodic infusion.

3.1. Continuous infusion

When the tumor is in a continuously mode exposed to cytostatic medicine, the concentrations of tumor cells and of the drug can evolve to equilibrium values. To study the impact produced by the continuous infusion of the drug, we will find and classify the equilibrium solutions of the Eq (1.2), by taking into consideration how they both depend on α_∞ and therefore on the amount of medicine administered.

We consider two cases: Case I of continuous infusion when the medicine keeps its efficiency effect (which means is not consumed within the tumor), that is $\gamma = 0$; Case II of continuous infusion when the drug does not keep its efficiency effect (which means is consumed significantly within the tumor), that is $\gamma \neq 0$.

Case I: Assume that the drug keeps its efficiency effect, that is, $\gamma = 0$. Then Eq (1.2) has the following form

$$\begin{cases} N'(t) = rN(t)\left(1 - \left(\frac{N(t)}{K}\right)^\theta\right) - \mu A(t)N(t) = f_1(N, A) \\ A'(t) = \alpha_\infty - \lambda A(t) = f_2(N, A). \end{cases} \tag{3.1}$$

The equilibrium points are the solutions of the algebraic system

$$\begin{cases} rN\left(1 - \left(\frac{N}{K}\right)^\theta\right) - \mu AN = 0 \\ \alpha_\infty - \lambda A = 0. \end{cases}$$

By direct calculation, we find two equilibrium points $X_1\left(N_1^*, A^*\right)$ and $X_2\left(N_2^*, A^*\right)$, where

$$A^* = \frac{\alpha_\infty}{\lambda}, \quad N_1^* = 0 \quad \text{and} \quad N_2^* = K\left(1 - \frac{\mu\alpha_\infty}{r\lambda}\right)^{\frac{1}{\theta}}. \tag{3.2}$$

We say that an equilibrium point is *admissible* (from a biological point of view) if its components are nonnegative. The discussion which follows is about the admissibility and local stability of the above equilibrium points.

Clearly, the equilibrium X_1 is admissible. As regards X_2, observe that if $r > \frac{\mu\alpha_\infty}{\lambda}$, then $N_2^* > 0$, that is the equilibrium point X_2 is admissible, while if $r < \frac{\mu\alpha_\infty}{\lambda}$, then $N_2^* < 0$ and so X_2 is not admissible, without biological relevance.

Next, by the method of the first approximation (for details about the method see [30,31]), we study the stability of the equilibrium solutions. The Jacobian matrix associated to Eq (3.1) is

$$J_{f=(f_1,f_2)}(N, A) = \begin{pmatrix} \frac{\partial f_1}{\partial N}(N, A) & \frac{\partial f_1}{\partial A}(N, A) \\ \frac{\partial f_2}{\partial N}(N, A) & \frac{\partial f_2}{\partial A}(N, A) \end{pmatrix}$$

$$= \begin{pmatrix} r - \frac{r}{K^\theta}(\theta+1)N^\theta - \mu A & -\mu N \\ 0 & -\lambda \end{pmatrix}.$$

For $X_1\left(N_1^*, A^*\right)$ we have

$$J_f\left(N_1^*, A^*\right) = \begin{pmatrix} r - \frac{\mu\alpha_\infty}{\lambda} & 0 \\ 0 & -\lambda \end{pmatrix}$$

and its eigenvalues are

$$\eta_1 = r - \frac{\mu\alpha_\infty}{\lambda}, \quad \eta_2 = -\lambda < 0.$$

Hence, if $r < \frac{\mu\alpha_\infty}{\lambda}$, then the equilibrium solution $X_1\left(0, \frac{\alpha_\infty}{\lambda}\right)$ is locally asymptotically stable, while if $r > \frac{\mu\alpha_\infty}{\lambda}$, then it is unstable.

For $X_2\left(N_2^*, A^*\right)$, the Jacobian matrix is

$$J_f\left(N_2^*, A^*\right) = \begin{pmatrix} r - \frac{(\theta+1)(r\lambda-\mu\alpha_\infty)-\mu\alpha_\infty}{\lambda} & -\mu K\left(\frac{r\lambda-\mu\alpha_\infty}{\lambda}\right)^{\frac{1}{\theta}} \\ 0 & -\lambda \end{pmatrix}$$

and its eigenvalues are

$$\eta_1 = r - \frac{(\theta+1)(r\lambda-\mu\alpha_\infty)-\mu\alpha_\infty}{\lambda}, \quad \eta_2 = -\lambda < 0.$$

Hence, if $r\lambda - (\theta+1)(r\lambda - \mu\alpha_\infty) < \mu\alpha_\infty$, or equivalently $r > \frac{\mu\alpha_\infty}{\lambda}$, then the equlibrium point $X_2\left(N_2^*, A^*\right)$ is locally asymptotically stable, while if $r < \frac{\mu\alpha_\infty}{\lambda}$, then it is unstable.

If we put together the above results, we can state the following theorem about the local asymptotic stability of the equilibrium points of Eq (3.1).

Theorem 3.1. *Let $r, K, \theta, \mu, \alpha_\infty$ and λ be positive parameters. Then Eq* (3.1) *has the following admissible equilibrium points:*

(a) *If $r < \frac{\mu\alpha_\infty}{\lambda}$, then there is only one admissible equilibrium point $X_1\left(N_1^*, A^*\right)$ which is locally asymptotically stable.*

(b) *If $r > \frac{\mu\alpha_\infty}{\lambda}$, then there are two admissible equilibrium points: $X_1\left(N_1^*, A^*\right)$ unstable, and $X_2\left(N_2^*, A^*\right)$ locally asymptotically stable.*

From a medical point of view, conclusion (a) of the above theorem says that the treatment is successful leading to the elimination of the cancer cells provided that the amount α_∞ of drug infused is large enough as the inequality $\alpha_\infty > \frac{r\lambda}{\mu}$ shows. If on the contrary $\alpha_\infty < \frac{r\lambda}{\mu}$, then the treatment can only guarantee a reduction of the limit value for the tumor cell population from K to $K\left(1 - \frac{\mu\alpha_\infty}{r\lambda}\right)^{\frac{1}{\theta}}$.

Numerical simulations in Case I of continuous infusion

The results of our study cover all the positive values of the parameters. For clinical applications, however, it is necessary to determine the specific values of these parameters. This aspect is intensely analyzed in the literature (see, for example [15,32–34]) and is not the subject of our research. Here, for the numerical simulations, we use the values of the parameters presented in Table 1.

Next, we simulate numerically the Eq (3.1) to investigate the behavior of the tumor cell population after the continuous infusion of the chemotherapy treatment when the drug is not consumed within the tumor, that is when $\gamma = 0$.

The initial number of tumor cells N_0 was calculated by dividing up the initial tumor volume to the individual volume of a typical tumor cell. For the initial tumor volume, we took the median value of all breast tumor volumes $V_t = 407\ mm^3$ as estimated by mammography in a series of 448 patients see J.A. Spratt et al. [28]. The individual volume of a tumor cell $V_c = 1760\ \mu m^3$ was taken from M.P. Gamcsik et al. [35], which measured breast cancer cells in culture. It appears reasonable to approximate the size of actual tumor cells in *vivo* by the size of the lab-grown cells. This leads to an initial number of cells equal to:

$$\frac{V_t}{V_c} = \frac{407\ mm^3}{1760\ \mu m^3} = \frac{4.07 \times 10^{11}\ \mu m^3}{1760\ \mu m^3} = 2.31 \times 10^8.$$

We chose a value for γ such as the consumption of the drug within the tumor ($-\gamma NA$) equals the elimination of the drug by first-order kinetics such as excretion via kidneys ($-\lambda A$), when the tumor is large (N approaches the carrying limit K). That is, $\lambda = \gamma K$, or

$$\gamma = \frac{\lambda}{K} = \frac{4.16\ \text{day}^{-1}}{1.1 \times 10^{12}\ \text{cells}} = 3.78 \times 10^{-12}\ \text{day}^{-1}/\text{cell}.$$

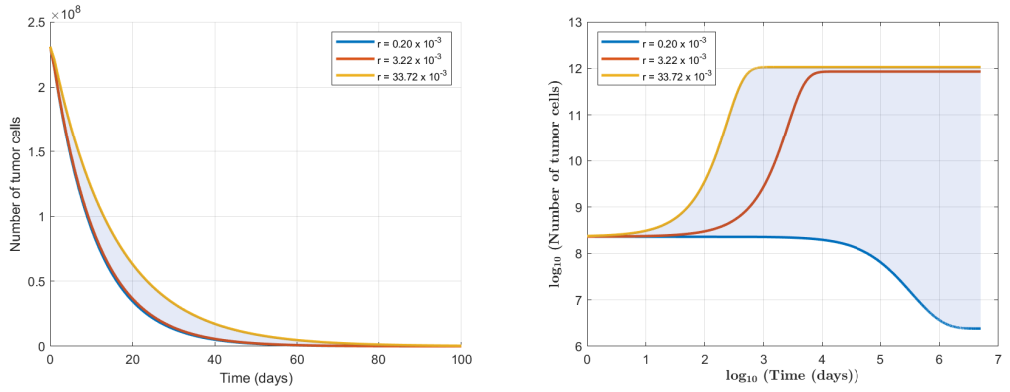
Table 1. Parameter values for simulations.

Parameters	Values	Units	Comments / References
r	$\left[0.2 \times 10^{-3},\ 33.72 \times 10^{-3}\right]$	day^{-1}	see J.A. Spratt et al. [28]
K	1.1×10^{12}	$cells$	see J.A. Spratt et al. [28]
θ	$1/4$	$-$	see J.A. Spratt et al. [28]
μ	8×10^{-2}	day^{-1}	$\mu > r$ / assumed condition, see R.N. Buick [36]
α_∞	$[0.01,\ 5]$	$mg\ day^{-1}$	continuous infusion / see L. Edelstein-Keshet [37]
λ	4.16	day^{-1}	see S.T.R Pinho et al. [2], D.S. Rodrigues et al. [12]
γ	3.78×10^{-12}	$day^{-1}/cell$	$\gamma = \lambda/K$ / calculated value
τ	0.5	day	assumed value
N_0	2.31×10^8	$cells$	calculated value

In a previous study on a sample of 448 patients diagnosed with breast tumors, see J.A. Spratt et al. [28], the growth rate r was calculated for each individual case by regression analysis. Centrality (the median, 3.22×10^{-3}/day) and dispersion measures (1% and 99% percentiles, 0.2×10^{-3}/day, and 33.72×10^{-3}/day, respectively) were then computed for the set of growth rates. We have employed these three values for r across all our simulations. They characterize synthetically the spectrum of disease severity, spanning from the slowest growing tumors (low r) to the most aggressive (high r). The shaded area between the curves in the simulations using time-series representations corresponds to values of r between the above limits.

Case I of continuous infusion: In this case, the drug is not consumed within the tumor, that means $\gamma = 0$. Figure 2(a) shows the behavior in time ($t = 100$ days) of the breast tumor cell population for the corresponding parameter values from Table 1, values that correspond to treatment success,

when $r < \mu\alpha_\infty/\lambda$. The breast tumor cell population $N(t)$ and the drug concentration $A(t)$ becomes arbitrarily close to the values $N_1^* = 0$ and $A^* = \alpha_\infty/\lambda$, that means the equilibrium point $X_1\left(N_1^*, A^*\right)$ is locally asymptotically stable. Figure 2(b) shows the behavior in time ($t = 5 \times 10^6$ days) of the breast tumor cell population for the corresponding parameter values from Table 1, values that correspond to treatment failure, when $r > \mu\alpha_\infty/\lambda$. The breast tumor cell population $N(t)$ and the drug concentration $A(t)$ tend toward N_2^* and A^*, respectively. In this case, the equilibrium $X_1\left(N_1^*, A^*\right)$ is unstable and $X_2\left(N_2^*, A^*\right)$ is locally asymptotically stable.



(a) Treatment success (b) Treatment failure

Figure 2. Behavior of breast tumor cell population according to Eq (3.1). For this time-series representations we chose the cytostatic drug dose α to be: $\alpha = 5\ mg\ day^{-1}$ in the case of treatment success (a), and $\alpha = 0.01\ mg\ day^{-1}$ in the case of treatment failure (b). The values for all the other parameters are listed in Table 1. Initial conditions for both (a) and (b) are: $N(0) = 2.31 \times 10^8$ and $A(0) = 0$.

Case II: Assume that the drug does not keep its efficiency effect. Then $\gamma \neq 0$ and for the determination of the equilibrium points of the Eq (1.2), we need to solve the algebraic system

$$\begin{cases} rN\left(1 - \left(\frac{N}{K}\right)^\theta\right) - \mu AN = 0 \\ \alpha_\infty - \lambda A - \gamma AN = 0. \end{cases}$$

Direct calculation yields the equilibrium point

$$X_1\left(N_1^*, A_1^*\right), \quad N_1^* = 0, \ \ A_1^* = \frac{\alpha_\infty}{\lambda}$$

and possible additional equilibrium points of the form $X\left(N^*, A^*\right)$, where $\left(N^*, A^*\right)$ solves the system

$$\begin{cases} A = \frac{\alpha_\infty}{\lambda + \gamma N} \\ r\left(1 - \left(\frac{N}{K}\right)^\theta\right) - \mu A = 0, \end{cases}$$

and consequently, N^* is a solution of the equation

$$r\left(1 - \left(\frac{N}{K}\right)^\theta\right) = \frac{\mu\alpha_\infty}{\lambda + \gamma N}. \tag{3.3}$$

To discuss the solvability of Eq (3.3) and the number of its solutions, it is convenient to look at the functions $\varphi_1, \varphi_2 : [0, +\infty) \to \mathbb{R}$,

$$\varphi_1(N) = r\left(1 - \left(\frac{N}{K}\right)^{\theta}\right), \quad \varphi_2(N) = \frac{\mu\alpha_\infty}{\lambda + \gamma N}.$$

Both functions are decreasing and

$$\begin{aligned} \varphi_1(0) &= r, \quad \varphi_1(K) = 0, \quad \lim_{N\to+\infty} \varphi_1(N) = -\infty, \\ \varphi_2(0) &= \frac{\mu\alpha_\infty}{\lambda}, \quad \lim_{N\to+\infty} \varphi_2(N) = 0. \end{aligned}$$

In addition, the function φ_2 is convex, while φ_1 is concave if $\theta > 1$, and convex if $\theta < 1$. Then, elementary geometric considerations yield the following conclusions about Eq (3.3):

(a) If $r > \frac{\mu\alpha_\infty}{\lambda}$, then Eq (3.3) has a unique solution $N^* \in (0, K)$ and Eq (1.2) admits the equilibrium point $X\left(N^*, \frac{\alpha_\infty}{\lambda+\gamma N^*}\right)$.

(b) If $r < \frac{\mu\alpha_\infty}{\lambda}$, then Eq (3.3) may have no positive solution, one positive solution, or two positive solutions, and any positive solution belongs to the interval $(0, K)$.

(c) If $r\left(1 + \frac{\gamma K}{\lambda}\right) \le \frac{\mu\alpha_\infty}{\lambda}$, then Eq (3.3) has no solution in $(0, K)$.

We can prove assertion (c) assuming the contrary, i.e., the existence of a solution N in $(0, K)$. Then we would have

$$r > r\left(1 - \left(\frac{N}{K}\right)^{\theta}\right) = \frac{\mu\alpha_\infty}{\lambda + \gamma N} > \frac{\mu\alpha_\infty}{\lambda + \gamma K},$$

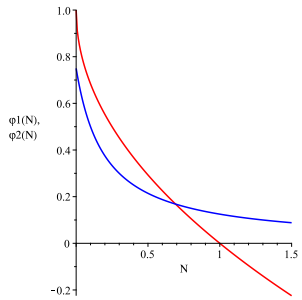
or equivalently

$$r\left(1 + \frac{\gamma K}{\lambda}\right) > \frac{\mu\alpha_\infty}{\lambda},$$

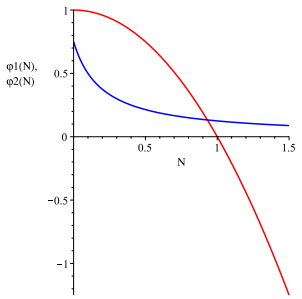
which yields a contradiction.

Numerical simulations for Eq (3.3)

Figures 3(a)–(b), 4(a)–(c) and 5(a)–(c) illustrate the number of solutions of Eq (3.3).

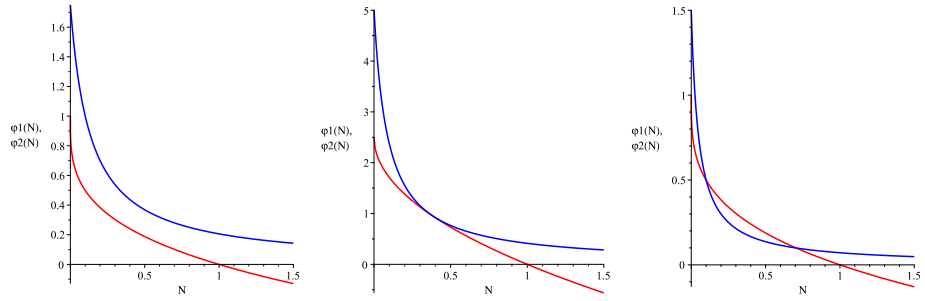


(a) Eq (3.3) has a unique solution.



(b) Eq (3.3) has a unique solution.

Figure 3. Graphs functions φ_1 (red solid line) and φ_2 (blue solid line) in the case when $r > \mu\alpha_\infty/\lambda$. In both cases (a) and (b), Eq (3.3) has a unique solution $N^* \in (0, K)$ for the following values: Case (a) $r = 1,\ K = 1,\ \theta = 0.5\ (\theta < 1), \mu = 0.5,\ \alpha_\infty = 0.3,\ \lambda = 0.2,\ \gamma = 1$ and Case (b) $r = 1,\ K = 1,\ \theta = 2\ (\theta > 1), \mu = 0.5,\ \alpha_\infty = 0.3,\ \lambda = 0.2,\ \gamma = 1$.

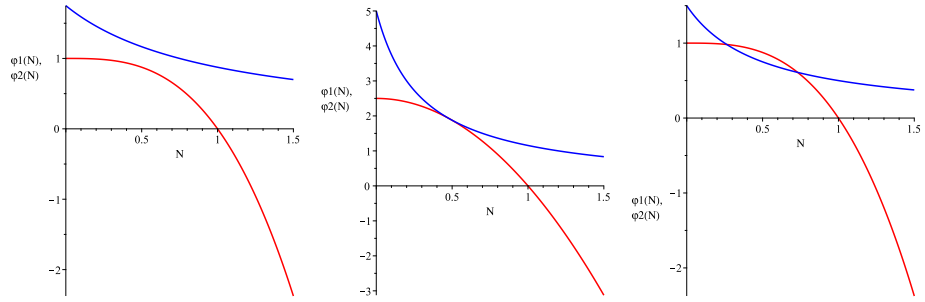


(a) Eq (3.3) has no positive solution.

(b) Eq (3.3) has one positive solution.

(c) Eq (3.3) has two positive solutions.

Figure 4. Graphs functions φ_1 (red solid line) and φ_2 (blue solid line) in the case when $r < \mu\alpha_\infty/\lambda$ for $\theta < 1$. In Case (a), Eq (3.3) has no positive solution, in Case (b), has one positive solution and in Case (c), has two positive solutions for the following values: Case (a) $r = 1,\ K = 1,\ \theta = 0.3,\ \mu = 0.7,\ \alpha_\infty = 0.5,\ \lambda = 0.2,\ \gamma = 1.5$, Case (b) $r = 2.5,\ K = 1,\ \theta = 0.5,\ \mu = 0.5,\ \alpha_\infty = 1,\ \lambda = 0.1,\ \gamma = 1.109016994$, and Case (c) $r = 1,\ K = 1,\ \theta = 0.3,\ \mu = 0.5,\ \alpha_\infty = 0.3,\ \lambda = 0.1,\ \gamma = 2$.



(a) Eq (3.3) has no positive solution.

(b) Eq (3.3) has one positive solution.

(c) Eq (3.3) has two positive solutions.

Figure 5. Graphs functions φ_1 (red solid line) and φ_2 (blue solid line) in the case when $r < \mu\alpha_\infty/\lambda$ for $\theta > 1$. In Case (a), Eq (3.3) has no positive solution, in Case (b), has one positive solution and in Case (c), has two positive solutions for the following values: Case (a) $r = 1,\ K = 1,\ \theta = 3,\ \mu = 0.7,\ \alpha_\infty = 0.5,\ \lambda = 0.2,\ \gamma = 0.2$, Case (b) $r = 2.5,\ K = 1,\ \theta = 2,\ \mu = 0.5,\ \alpha_\infty = 1,\ \lambda = 0.1,\ \gamma = 0.3330190676$, and Case (c) $r = 1,\ K = 1,\ \theta = 3,\ \mu = 0.5,\ \alpha_\infty = 0.3,\ \lambda = 0.1,\ \gamma = 0.2$.

We now go to study the stability of the equilibrium solutions. The Jacobian matrix is in this case

$$J_f(N, A) = \begin{pmatrix} r - \frac{r}{K^\theta}(\theta+1)N^\theta - \mu A & -\mu N \\ -\gamma A & -\lambda - \gamma N \end{pmatrix}.$$

For $X_1\left(0, \frac{\alpha_\infty}{\lambda}\right)$, one has

$$J_f\left(0, \frac{\alpha_\infty}{\lambda}\right) = \begin{pmatrix} r - \frac{\mu\alpha_\infty}{\lambda} & 0 \\ -\gamma\frac{\alpha_\infty}{\lambda} & -\lambda \end{pmatrix}$$

and the eigenvalues are

$$\eta_1 = r - \frac{\mu\alpha_\infty}{\lambda}, \quad \eta_2 = -\lambda < 0.$$

Therefore, the equilibrium point $X_1\left(0, \frac{\alpha_\infty}{\lambda}\right)$ is locally asymptotically stable if $r < \frac{\mu\alpha_\infty}{\lambda}$, and unstable if $r > \frac{\mu\alpha_\infty}{\lambda}$. Notice the same stability behavior of the equilibrium point $X_1\left(0, \frac{\alpha_\infty}{\lambda}\right)$ as in the case $\gamma = 0$.

Assume now that there exists a solution $N^* \in (0, K)$ of the Eq (3.3). Then

$$J_f(N^*, A^*) = \begin{pmatrix} r - \frac{r}{K^\theta}(\theta+1)(N^*)^\theta - \mu A^* & -\mu N^* \\ -\gamma A^* & -\lambda - \gamma N^* \end{pmatrix}$$

and using the equality

$$r\left(1 - \left(\frac{N^*}{K}\right)^\theta\right) = \mu A^*$$

we obtain

$$J_f(N^*, A^*) = \begin{pmatrix} -r\theta\left(\frac{N^*}{K}\right)^\theta & -\mu N^* \\ -\frac{\gamma r}{\mu}\left(1 - \left(\frac{N^*}{K}\right)^\theta\right) & -\lambda - \gamma N^* \end{pmatrix}.$$

The corresponding characteristic polynomial is

$$\eta^2 + \left(\lambda + \gamma N^* + r\theta\left(\frac{N^*}{K}\right)^\theta\right)\eta + r\left(\left(\frac{N^*}{K}\right)^\theta(\theta\lambda + N^*\gamma(\theta+1)) - N^*\gamma\right) = 0.$$

From the Hurwitz principle, we have that $Re\ \eta < 0$ if and only if all coefficients of the characteristic polynomial are positive. Thus, the equilibrium point $X(N^*, A^*)$ is locally asymptotically stable if and only if

$$\left(\frac{N^*}{K}\right)^\theta(\theta\lambda + N^*\gamma(\theta+1)) - N^*\gamma > 0. \tag{3.4}$$

Replacing

$$\left(\frac{N^*}{K}\right)^\theta = 1 - \frac{\mu A^*}{r} \quad \text{and} \quad N^*\gamma = \frac{\alpha_\infty}{A^*} - \lambda$$

we obtain the equivalent condition in terms of A^*, namely

$$r\theta\alpha_\infty - \mu\alpha_\infty(\theta+1)A^* + \mu\lambda(A^*)^2 > 0. \tag{3.5}$$

We can summarize the conclusions about the local asymptotic stability of the equilibrium points of Equation (1.2) in this case as follows.

Theorem 3.2. *Let $r, K, \theta, \mu, \alpha_\infty, \lambda$ and γ be positive parameters. Then Eq* (1.2) *has the following admissible equilibrium points:*

(a) *If $r > \frac{\mu\alpha_\infty}{\lambda}$, then there are two admissible equilibrium points: $X_1\left(0, \frac{\alpha_\infty}{\lambda}\right)$ unstable, and $X(N^*, A^*)$ locally asymptotically stable if and only if condition Eq* (3.4) *or equivalently Eq* (3.5) *holds.*

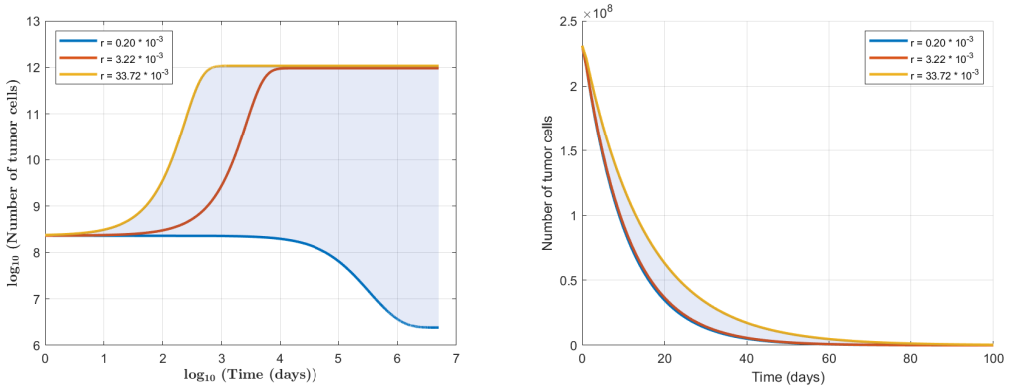
(b) *If $r < \frac{\mu\alpha_\infty}{\lambda}$, then there is at least one admissible equilibrium point, namely $X_1\left(0, \frac{\alpha_\infty}{\lambda}\right)$ which is locally asymptotically stable. Additionally, one or two other equilibrium points of the form $X(N^*, A^*)$ could exist depending on the number of positive solutions of Eq* (3.3)*, and they are locally asymptotically stable provided that condition Eq* (3.4) *or equivalently Eq* (3.5) *holds.*

In the case of one equilibrium point, the treatment succeeds, but in the case of multiple equilibrium points the dynamics is sensitive to the initial conditions since it is possible that one of the equilibrium points $X(N^*, A^*)$ is locally asymptotically stable if the condition Eq (3.4) (or Eq (3.5)) is satisfied. So, to make sure that the treatment succeeds, it is necessary to have $r < \frac{\mu\alpha_\infty}{\lambda}$ and that the Eq (3.3) has no positive solution.

Numerical simulations in Case II of continuous infusion

In the following, we will simulate numerically the Eq (1.2) in order to investigate the behavior of the tumor cell population after the continuous infusion of the chemotherapy treatment when the drug is consumed significantly within the tumor, that is when $\gamma \neq 0$. For the numerical simulations, we use the values of the parameters presented in Table 1.

Case II of continuous infusion: In this case, the drug is consumed significantly within the tumor, that means $\gamma \neq 0$. Figure 6(a) shows the behavior in time ($t = 5 \times 10^6$ days) of the breast tumor cell population for the corresponding parameter values from Table 1, values that correspond to treatment failure, when $r > \mu\alpha_\infty/\lambda$. The breast tumor cell population $N(t)$ and the drug concentration $A(t)$ tend toward N^* and A^*, respectively. In this case, there exists two admissible equilibrium $X_1\left(0, \frac{\alpha_\infty}{\lambda}\right)$ unstable and $X(N^*, A^*)$ locally asymptotically stable. Figure 6(b) shows the behavior in time ($t = 100$ days) of the breast tumor cell population for the corresponding parameter values from Table 1, values that correspond to treatment success, when $r < \mu\alpha_\infty/\lambda$. The breast tumor cell population $N(t)$ and the drug concentration $A(t)$ becomes arbitrarily close to the values $N_1^* = 0$ and $A_1^* = \alpha_\infty/\lambda$. In this case the Eq (3.3) has no positive solution, so $X_1\left(0, \frac{\alpha}{\lambda}\right)$ is locally asymptotically stable. This case is similar to the Case I when $\gamma = 0$, see the treatment success from the Figure 2(a).

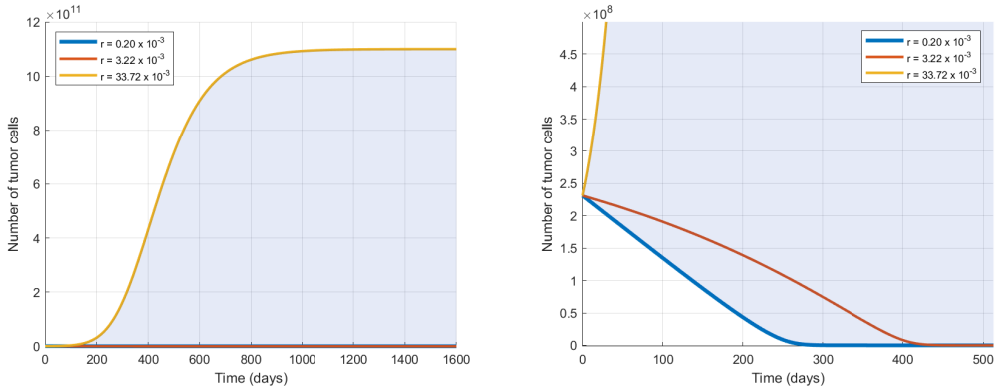


(a) Treatment failure (b) Treatment success

Figure 6. Behavior of breast tumor cell population according to Eq (1.2). For this time-series representations we chose the cytostatic drug dose α to be: $\alpha = 0.01\ mg\ day^{-1}$ in the case of treatment failure (a), and $\alpha = 5\ mg\ day^{-1}$ in the case of treatment success (b). The values for all the other parameters are listed in Table 1. Initial conditions for both (a) and (b) are: $N(0) = 2.31 \times 10^8$ and $A(0) = 0$.

In the Figure 7(a), (b) (enlarged Figure 7(a)), we can see the behavior in time ($t = 1600$ days

respectively $t = 500$ days) of the breast tumor cell population for the corresponding parameter values from Table 1. Under the condition $r < \mu\alpha_\infty/\lambda$, both treatment success and treatment failure are possible outcomes. As we can see, for the value of the nonrestrictive growth rate $r = 33.72 \times 10^{-3}$ the breast tumor cell population $N(t)$ and the drug concentration $A(t)$ tend toward N_3^* and A_3^*, respectively. For the values $r = 3.22 \times 10^{-3}$ and $r = 0.2 \times 10^{-3}$ of the growth rate, the breast tumor cell population $N(t)$ and the drug concentration $A(t)$ become arbitrarily close to the values $N_1^* = 0$ and $A_1^* = \alpha_\infty/\lambda$. In this case the Eq (3.3) has two positive solutions N_2^* and N_3^*, so $X_1\left(0, \frac{\alpha_\infty}{\lambda}\right)$ is locally asymptotically stable, $X_2\left(N_2^*, \frac{\alpha_\infty}{\lambda+\gamma N_2^*}\right)$ is unstable and $X_3\left(N_3^*, \frac{\alpha_\infty}{\lambda+\gamma N_3^*}\right)$ is locally asymptotically stable.



(a) Treatment failure for $r = 33.72 \times 10^{-3}$ and is successful for $r = 0.2 \times 10^{-3}$ and $r = 3.22 \times 10^{-3}$

(b) in large figure of (*a*)

Figure 7. Behavior of breast tumor cell population according to Eq (1.2). For this time-series representation we chose the rate at which the drug is consumed within the tumor $\gamma = 3.78 \times 10^{-7}\ day^{-1}/cell$, and the cytostatic drug dose α to be: $\alpha = 5\ mg\ day^{-1}$. The values for all the other parameters are listed in Table 1. Initial conditions are: $N(0) = 2.31 \times 10^8$ and $A(0) = 0$.

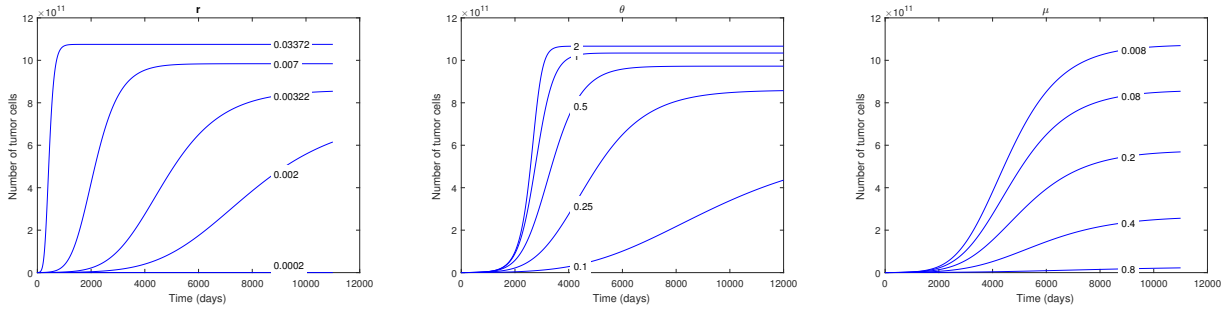
Numerical simulations of the dependence on parameters

To illustrate the dependency of solution on the parameters, we have performed numerical sweeps for each of the six system parameters: r, θ, μ, α_∞, λ and γ, see Figures 8 and 9. We have excluded from the analysis the carrying capacity K, as it has only a trivial effect on the solution (scaling). Except for the swept parameter, the fixed values are: $r = 3.22 \times 10^{-3}$, $\theta = 0.25$, $\mu = 8 \times 10^{-2}$, $\alpha_\infty = 0.01$, $\lambda = 4.16$, $\gamma = 0$, $K = 1.1 \times 10^{12}$. The initial conditions are: $N_0 = 2.31 \times 10^8$, $A_0 = 0$.

3.2. Periodic infusion

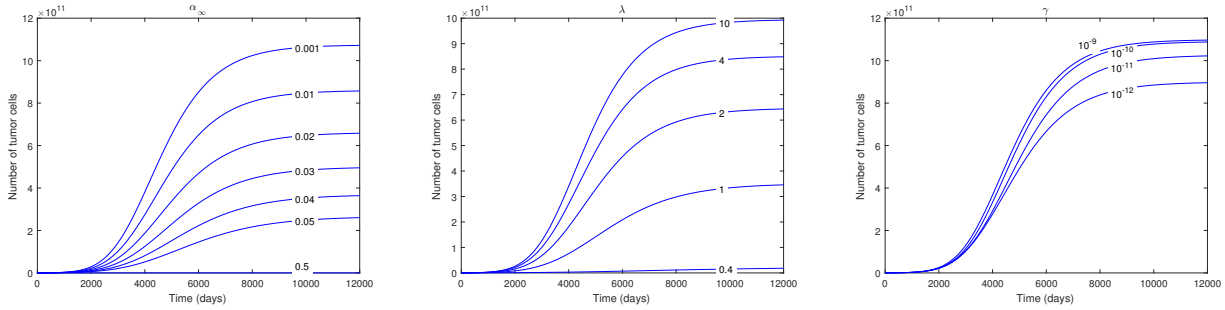
In real situations, secondary effects reveal that continuous infusion is not usually considered a viable method to administrate the drug. Administered systematically, the drug can have an adverse effect on the vital organs (i.e., the liver). As a result, the chemotherapeutic drug is usually delivered as a series of continuous infusions, so that the health of the patient's organs can recover between the successive treatments. Unfortunately, this kind of method can have as a result the regeneration of the tumor.

Next, we will investigate the impact of periodic infusion considering that the tumor cell population



(a) Dependence of solution on the parameter r (b) Dependence of solution on the parameter θ (c) Dependence of solution on the parameter μ

Figure 8. Dependence of solution on the parameters r, θ and μ.



(a) Dependence of solution on the parameter α_∞, (b) Dependence of solution on the parameter λ (c) Dependence of solution on the parameter γ

Figure 9. Dependence of solution on the parameters α_∞, λ and γ.

grows according to the generalized logistic model with a nonrestrictive growth rate $r > 0$. Thus, we assume that the cell population develops under treatment according to the model

$$\begin{cases} N'(t) = rN(t)\left(1 - \left(\frac{N(t)}{K}\right)^{\theta}\right) - \mu A(t)N(t) \\ N(0) = N_0 \end{cases}, \ t \geq 0 \tag{3.6}$$

where this time the function which describes the chemotherapeutic drug infusion $A(t)$ is only piecewise continuous, more exactly it has the form

$$A(t) = \begin{cases} \alpha_\infty & \text{for } n \leq t < n + \tau \\ 0 & \text{for } n + \tau \leq t < n + 1. \end{cases} \tag{3.7}$$

Here, τ denotes the duration of each period of treatment in which the drug is administered, and it is assumed that $\tau < 1$. Therefore, on a time interval $[n; n + \tau]$, the drug is continuously infused at the constant rate α_∞, while on the time interval $[n + \tau; n + 1]$, no drug is administered. By integration, we find the expression of $N(t)$ on $[n, n + 1]$, namely

$$N(t) = \begin{cases} \left(\frac{K^\theta \Lambda N_n^\theta}{N_n^\theta + [K^\theta \Lambda - N_n^\theta]e^{-r\theta\Lambda(t-n)}}\right)^{\frac{1}{\theta}}, & n \leq t < n + \tau \\ \left(\frac{K^\theta N_{n+\tau}^\theta}{N_{n+\tau}^\theta + \left[K^\theta - N_{n+\tau}^\theta\right]e^{-r\theta(t-n-\tau)}}\right)^{\frac{1}{\theta}}, & n + \tau \leq t < n + 1 \end{cases}$$

where $\Lambda = 1 - \frac{\mu\alpha_\infty}{r}$ and $N_t := N(t)$. Then

$$N_{n+\tau} = N(n+\tau) = \left(\frac{K^\theta \Lambda N_n^\theta}{N_n^\theta + [K^\theta \Lambda - N_n^\theta] e^{-r\theta\Lambda\tau}} \right)^{\frac{1}{\theta}}$$

and we find that the values N_n satisfy the following recurrence relation

$$N_{n+1} = h(N_n), \tag{3.8}$$

where h is the function

$$h(x) = \left(\frac{K^\theta \Lambda x^\theta}{\Lambda x^\theta + \left[(1-\Lambda) x^\theta + (K^\theta \Lambda - x^\theta) e^{-r\theta\Lambda\tau}\right] e^{-r\theta(1-\tau)}} \right)^{\frac{1}{\theta}}, \quad x > 0.$$

The equilibrium points of the discrete dynamic process Eq (3.8), that is the solutions N_∞ of the equation $N_\infty = h(N_\infty)$ are $N_\infty^1 = 0$ and

$$N_\infty^2 = \left(\frac{\Lambda \left(1 - e^{-r\theta(1-\tau+\Lambda\tau)}\right) K^\theta}{\Lambda + e^{-r\theta(1-\tau)} - e^{-r\theta(1-\tau)}\Lambda - e^{-r\theta(1-\tau+\Lambda\tau)}} \right)^{\frac{1}{\theta}}$$

in case that $r - \tau\mu\alpha_\infty > 0$. Obviously, if the initial condition is $N(0) = N_\infty^1 = 0$, then $N(t) \equiv 0$ meaning that tumor cannot develop in the absence of cancer cells. By contrary, if the initial condition is $N(0) = N_\infty^2$, then $N(t)$ becomes a nontrivial periodic function N_{per} because $N_{n+1} = h(N_n) = N_\infty^2$, see the Figure 10.

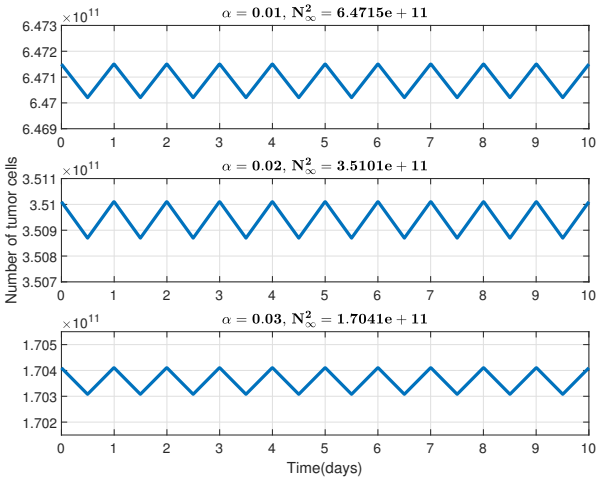


Figure 10. Breast tumor cell population behavior when $N(t)$ is a periodic solution for the following values $r = 3.22 \times 10^{-3}$, $K = 1.1 \times 10^{12}$, $\theta = 0.25$, $\mu = 8 \times 10^{-2}$, $\tau = 0.5$ and three different values for alpha: $\alpha = 0.01$, $\alpha = 0.02$ and $\alpha = 0.03$.

We now study the stability of the equilibrium points for the discrete dynamic process Eq (3.8). One has

$$h'\left(N_\infty^1\right) = e^{r-\tau\mu\alpha_\infty} \quad \text{and} \quad h'\left(N_\infty^2\right) = e^{\theta(\tau\mu\alpha_\infty - r)}.$$

Therefore, we can state the following theorem.

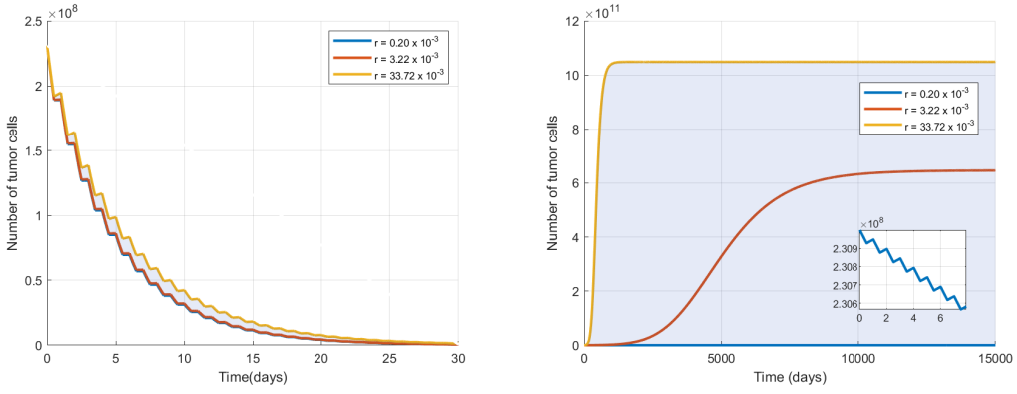
Theorem 3.3. (a) *If* $r-\tau\mu\alpha_\infty < 0$, *then* $h'\left(N_\infty^1\right) < 1$, *which implies that* $N_\infty^1 = 0$ *is locally asymptotically stable; so if* N_0 *is in a neighbourhood of* N_∞^1 *then* $N_n \to N_\infty^1 = 0$ *as* $n \to +\infty$ *and therefore* $N(t) \to 0$ *as* $t \to +\infty$.

(b) *If* $r - \tau\mu\alpha_\infty > 0$, *then* $h'\left(N_\infty^1\right) > 1$ *and* $h'\left(N_\infty^2\right) < 1$, *which implies that* $N_\infty^1 = 0$ *is unstable and* N_∞^2 *is locally asymptotically stable, so if* N_0 *is in a neighbourhood of* N_∞^2 *then* $N_n \to N_\infty^2$ *as* $n \to +\infty$ *and therefore* $N(t) \to N_{per}(t)$ *as* $t \to +\infty$.

Under the conditions of the previous theorem, in case (a), we have $N(t) \to 0$ as $t \to +\infty$, which means that the malign cells are eliminated in time, and so the treatment succeeds; in case (b), we have $N(t) \to N_{per}(t)$, which shows that the graph of tumor cell population stabilizes at the graph of a periodic function. Thus, when a periodic infusion takes place, the system can develop to a nontrivial periodic solution for which $N(t) = N(1+t)$. Applying numerical simulation, we will see how N_∞^2 and the limit function N_{per} depend on the drug dose. In the simulations, the graphs show us the way that N_∞^2 decreases as the drug dose α_∞ increases. If the drug dose is high enough, then the eradication of the tumor occurs. Obviously, with periodic infusion, the dose required to achieve eradication is greater than that required for continuous infusion. This conclusion holds because with periodic infusion, tumor cells are exposed to chemotherapy for short periods of time.

Numerical simulations in the case of periodic infusion

Next, we will simulate numerically the Eq (3.6) when the chemotherapeutic drug infusion $A(t)$, given by Eq (3.7) is a piecewise continuous function, in order, to investigate the behavior of the tumor cell population after the periodic infusion of the chemotherapy treatment. For the numerical simulations, we use the values of the parameters presented in Table 1.



(a) Treatment success

(b) Treatment failure for $r = 33.72 \times 10^{-3}$ and $r = 3.22 \times 10^{-3}$ and is successful for $r = 0.2 \times 10^{-3}$

Figure 11. Behavior of breast tumor cell population according to the Eq (3.6), after the periodic infusion of the drug, where $A(t)$ given by Eq (3.7), is a piecewise continuous function. For this time-series representations we chose the cytostatic drug dose α to be: $\alpha = 5\ mg\ day^{-1}$ in the case of treatment success (a), and $\alpha = 0.01\ mg\ day^{-1}$ in the case of treatment failure and is successful (b). The values for all the other parameters are listed in Table 1. The initial condition for both (a) and (b) is $N(0) = 2.31 \times 10^8$.

In Figure 11(a) we can see the behavior in time ($t = 30$ days) of the breast tumor cell population after the periodic infusion of the drug, for the corresponding parameter values from Table 1, values that correspond to treatment success, when $r - \tau\mu\alpha_\infty < 0$. The breast tumor cell population $N(t)$ becomes arbitrarily close to the values $N_\infty^1 = 0$, that means the equilibrium N_∞^1 is locally asymptotically stable. Figure 11(b) shows the behavior in time ($t = 15000$ days) of the breast tumor cell population for the corresponding parameter values from Table 1, values that correspond to treatment failure, when $r - \tau\mu\alpha_\infty > 0$ and to treatment success, when $r - \tau\mu\alpha_\infty < 0$. As we can see, when the treatment fails, for the values of the nonrestrictive growth rate $r = 33.72 \times 10^{-3}$ and $r = 3.22 \times 10^{-3}$ the breast tumor cell population $N(t)$ tend toward a periodic solution N_{per}. For the value $r = 0.2 \times 10^{-3}$ of the growth rate, the breast tumor cell population $N(t)$ becomes arbitrarily close to the value $N_\infty^1 = 0$. In the case when the treatment fails, the equilibrium points of the equation with differences Eq (3.8) are $N_\infty^1 = 0$ unstable and N_∞^2 locally asymptotically stable, and when the treatment is successful, the only admissible equilibrium point is $N_\infty^1 = 0$, locally asymptotically stable.

4. Conclusions

It is natural that due to the limitations imposed by the biological environment, the mathematical models of the growth of homogeneous solid tumors should be based on self-limited equations, particularly on the logistic equation. In this paper, we worked with the generalized logistic equation of Richards. Without any medical intervention, if the nonrestrictive growth rate is positive ($r > 0$), the tumor cell population will tend to the carrying capacity constant K. In order to destroy the tumor a medical treatment is necessary.

We study the dynamics of the tumor cell population in two cases of chemotherapy, the case of continuous infusion when the medicine keeps its efficiency ($\gamma = 0$) and when the medicine does not keep its efficiency ($\gamma \neq 0$), and the case when the chemotherapeutic drug is administrated as a series of continuous infusions, so that the health of the patient's organs can recover between successive treatments. The mathematical model is given by the dynamic Eq (1.2), where $\alpha_\infty(t)$ is constant in case of continuous infusion of the drug and piecewise continuous when the drug administration is periodic. In the first case the system is autonomous, while in the second case it is nonautonomous.

From the stability analysis of the equilibrium solutions of the system, it turns out that it is necessary that the parameters satisfy the condition $r < \frac{\mu\alpha_\infty}{\lambda}$ in order to have a successful treatment, but in the case when the medicine does not keep its efficiency this is not sufficient. In addition, it is necessary that the value of $\frac{\mu\alpha_\infty}{\lambda}$ to be big enough - more exactly $\frac{\mu\alpha_\infty}{\lambda} \geq r\left(1 + \frac{\gamma K}{\lambda}\right)$ - so that the system has only one positive equilibrium point $X_1\left(0, \frac{\alpha_\infty}{\lambda}\right)$, i.e.. Eq (3.3) has no positive solutions. If Eq (3.3) has a positive solution N^*, then it is possible that the corresponding equilibrium point $X\left(N^*, \frac{\alpha_\infty}{\lambda+\gamma N^*}\right)$ be asymptotically stable, and the cell dynamics becomes sensitive to the initial conditions: if the initial value is in the attraction basin of X_1, then the treatment succeeds, while if it is in the attraction basin of X, then the treatment fails.

A more realistic chemotherapy treatment is that when the drug is administrated as a series of continuous infusions separated by rest periods. Then the dynamics is described by a nonautonomous system. In this case, in addition to the trivial null periodic solution, a non trivial periodic solution appears, which biologically means that the tumor cells can remain in the body. However, if the null periodic solution is asymptotically stable, then the treatment succeeds. Our result is that this happens

if the condition $r < \tau\mu\alpha_\infty$ holds. Otherwise, i.e., if $r > \tau\mu\alpha_\infty$, then the non trivial periodic solution is asymptotically stable and the treatment proves unsuccessful.

It is noteworthy that the conditions for successful treatment never depend on the exponent θ. That is, from a treatment standpoint, the generalized logistic model behaves exactly like a plain logistic variant. In biological terms, the speed of tumor cell proliferation may modify the growth curve towards the plateau phase of tumor growth, but has no bearing whatsoever on the success or failure of chemotherapy. This interesting and counterintuitive finding may have implications for adjuvant antiangiogenic therapy, even modeled without an explicit description of tumor vascular network. However, our study highlights a certain dependence on the parameter θ, namely the value of N representing residual cancer (in the case of incomplete elimination of the disease). Therefore, we can conclude that, for the same dose, the size of the residual cancer also depends on the speed of proliferation of the tumor cells.

The mathematical analysis performed provides the necessary conditions for the success of chemotherapy, in the form of precise mathematical relationships given in terms of system parameters. Practically, the determination by theoretical and laboratory methods of the values of these parameters becomes essential for anticipating the effectiveness of treatment.

Acknowledgments

The authors would like to express their gratitude to the three anonymous reviewers for their time and effort for a careful reading of the manuscript and valuable comments and suggestions which have led to an improved version of the article.

Conflict of interest

The authors declare that they have no conflicts of interest.

References

1. R. B. Martin, M. E. Fisher, R. F. Minchin, K. L. Teo, Low-intensity combination chemotherapy maximizes host survival time for tumors containing drug-resistant cells, *Math. Biosc.*, **110** (1992), 221–252.
2. S. T. R. Pinho, D. S. Rodrigues, P. F. de A. Mancera, A mathematical model of chemotherapy response to tumor growth, *Can. Appl. Math. Q.*, **4** (2011), 369–384.
3. S. T. R. Pinho, F. S. Bacelar, R. F. S. Andrade, H. I. Freedman, A mathematical model for the effect of anti-angiogenic therapy in the treatment of cancer tumours by chemotherapy, *Nonlin. Anal.: Real World Appl.*, **14** (2013), 815–828.
4. D. S. Rodrigues, S. T. R. Pinho, P. F. de A. Mancera, Um modelo matemático em quimioterapia, *TEMA Tend. Mat. Appl. Comput.*, **13** (2012), 1–12.
5. J. C. Panetta, K. R. Fister, Optimal control applied to competing chemotherapeutic cell-kill strategies, *SIAM J. Appl. Math.*, **63** (2003), 1954–1971.
6. L. G. de Pillis, A. Radunskaya, A mathematical tumor model with immune resistance and drug therapy: An optimal control approach, *J. Theor. Med.*, **3** (2001), 79–100.

7. L. G. de Pillis, W. Gu, K. R. Fister, T. Head, K. Maples, A. Murugan, et al., Chemotherapy for tumors: An analysis of the dynamics and a study of quadratic and linear optimal controls, *Math. Biosc.*, **209** (2007), 292–315.
8. A. D'Onofrio, U. Ledzewicz, H. Maurer, H. Schättler, On optimal delivery of combination therapy for tumors, *Math. Biosc.*, **222** (2009), 13–26.
9. G. S. Stamatakos, E. A. Kolokotroni, D. D. Dionysiou, E. C. Georgiadi, C. Desmedt, An advanced discrete state-discrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study, *J. Theor. Biol.*, **266** (2010), 124–139.
10. L. G. Marcu, E. Bezak, Neoadjuvant cisplatin for head and neck cancer: Simulation of a novel schedule for improved therapeutic ratio, *J. Theor. Biol.*, **297** (2012), 41–47.
11. S. T. R. Pinho, H. I. Freedman, F. Nani, A chemotherapy model for the treatment of cancer with metastasis, *Math. Comp. Model.*, **36** (2002), 773–803.
12. D. S. Rodrigues, P. F. de A. Mancera, Mathematical analysis and simulations involving chemotherapy and surgery on large human tumours under a suitable cell-kill functional response, *Math. Biosci. Eng.*, **10** (2013), 221–234.
13. M. Mamat, K. A. Subiyanto, A. Kartono, Mathematical model of cancer treatments using immunotherapy, chemotherapy and biochemotherapy, *Appl. Math. Sci.*, **7** (2013), 247–261.
14. J. Malinzi, Mathematical analysis of a mathematical model of chemovirotherapy: Effect of drug infusion method, *Comput. Math. Methods Med.*, **2019** (2019), 7576591.
15. P. Unni, P. Seshaiyer, Mathematical modeling, analysis, and simulation of tumor dynamics with drug interventions, *Comput. Math. Methods Med.*, **2019** (2019), 4079298.
16. W. L. Duan, The stability analysis of tumor-immune responses to chemotherapy system driven by Gaussian colored noises, *Chaos Solitons Fractals*, **141** (2020), 110303.
17. W. L. Duan, H. Fang, The unified colored noise approximation of multidimensional stochastic dynamic system, *Phys. A*, **555** (2020), 124624.
18. W. L. Duan, H. Fang, C. Zeng, The stability analysis of tumor-immune responses to chemotherapy system with gaussian white noises, *Chaos Solitons Fractals*, **127** (2019), 96–102.
19. P. M. Altrock, L. L. Liu, F. Michor, The mathematics of cancer: integrating quantitative models, *Nat. Rev. Cancer*, **15** (2015), 730–745.
20. A. Fasano, A. Bertuzzi, A. Gandolfi, Mathematical modelling of tumour growth and treatment, *Complex Syst. Biomed.*, 2006.
21. A. Yin, D. J. A. R. Moes, J. G. C. van Hasselt, J. J. Swen, H. J. Guchelaar, A Review of mathematical models for tumor dynamics and treatment resistance evolution of solid tumors, *CPT Pharmacometrics Syst. Pharmacol.*, **8** (2019), 720–737.
22. L. Parajdi, Modeling the treatment of tumor cells in a solid tumor, *J. Nonlinear Sci. Appl.*, **7** (2014), 188–195.
23. A. Cucuianu, R. Precup, A hypothetical-mathematical model of acute myeloid leukaemia pathogenesis, *Comput. Math. Methods Med.*, **11** (2010), 49–65.

24. D. Dingli, F. Michor, Successful therapy must eradicate cancer stem cells, *Stem. Cells*, **24** (2006), 2603–2610.
25. L. G. Parajdi, R. Precup, E. A. Bonci, C. Tomuleasa, A mathematical model of the transition from normal hematopoiesis to the chronic and accelerated-acute stages in myeloid leukemia, *Mathematics*, **8** (2020), 376.
26. F. J. Richards, A flexible growth function for empirical use, *J. Exp. Bo.*, **10** (1959), 290–301.
27. L. Preziosi, Cancer modelling and simulation, *Chap. Hall/CRC*, 2003.
28. J. A. Spratt, D. A Fournier, J. S. Spratt, E. E. Weber, Decelerating growth and human breast cancer. *Cancer*, **71** (1993), 2013–2019.
29. D. Bufnea, V. Niculescu, G. Silaghi, A. Sterca, Babeş-Bolyai University's High Performance Computing Center, *Stud. Univ. Babeş-Bolyai, Inf.,* **61** (2016), 54–69.
30. E. A. Coddington, N. Levinson, Theory of Ordinary Differential Equations, *Tata McGraw-Hill*, New Delhi, 1972.
31. D. Kaplan, L. Glass, *Understanding Nonlinear Dynamics*, Springer, New York, 1995.
32. G. Lillacci, M. Khammash, Parameter estimation and model selection in computational biology, *PLoS Comput. Biol.*, **6** (2010), 1000696.
33. M. Quach, N. Brunel, F. d'Alché-Buc, Estimating parameters and hidden variables in non-linear state-space models based on ODEs for biological networks inference, *Bioinformatics*, **23** (2007), 3209–3216.
34. A. Tarantola, Inverse problem theory and methods for model parameter pstimation, *SIAM*, 2005.
35. M. P. Gamcsik, K. K. Millis, O. M. Colvin, Noninvasive detection of elevated glutathione levels in MCF-7 cells resistant to 4-hydroperoxycyclophosphamide, *Cancer Res.*, **55** (1995), 2012–2016.
36. R. N. Buick, Cellular basis of chemotherapy in cancer chemotherapy handbook, *Appl. Lange*, (1994), 9.
37. L. E. Keshet, Mathematical models in biology, *Soc. Ind. Appl. Math.*, 2005.

AIMS Press