Facultad de Ciencias

Analysis and optimization of a mathematical model for the growth and treatment of cancerous tumors including angiogenesis

(Análisis y optimización de un modelo matemático para el crecimiento y tratamiento de tumores cancerígenos incluyendo angiogénesis)

Trabajo de Fin de Grado
para acceder al

Grado en Matemáticas

Autora: María Peña Fernández

Director: Luis Alberto Fernández Fernández

Fecha: Junio 2022

Agradecimientos

En primer lugar, agradecer a Luis Alberto todo el tiempo que ha dedicado a enseñarme y guiarme para que este trabajo saliese adelante. Gracias también a mis padres y a mi hermano, por apoyarme durante estos años y comprender los noes que recibían por respuesta a muchos de los planes que sugerían. A Abram, por estar siempre ahí, en las buenas y en las no tan buenas. A Ana y a Constanza, por ayudarme a entender lo que pasaba por mi cabeza cuando ni yo misma lo hacía. En general, gracias a todo aquel que, de una manera u otra, ha colaborado para que hoy yo esté aquí.

Abstract

Angiogenesis is the natural physiological process of new blood vessel formation and plays a fundamental role in the growth of cancerous tumors. In this work, we study a mathematical model of pharmacodynamics (introduced in 1999 by P. Hahnfeldt et al.) that includes this effect. It consists of a system of two nonlinear ODEs whose asymptotic behavior we analyze. In addition, the model allows the inclusion of a term for the antiangiogenic treatment, whose antitumor action can be optimized using mathematical techniques. We further assume that tumor growth is of the Gompertz type.

We study an optimization related problem where the number of doses applied in the treatment, as well as their quantity and the time of administration, are variables. We also perform some approaches to this problem that, as far as we know, have not been published yet, and show examples to contrast with the theory.

Several numerical experiments using MATLAB for three commonly used antiangiogenic drugs with different properties are also included. These are Angiostatin, Endostatin and TNP-470. With them, it is evidenced that metronomic type of therapies are more suitable for treating tumors under this approach in most cases.

Key words: Metronomic therapy, Hahnfeldt et al. model, angiogenesis, optimization problem

Resumen

La angiogénesis es el proceso fisiológico natural de formación de nuevos vasos sanguíneos y desempeña un papel fundamental en el crecimiento de los tumores cancerígenos. En este trabajo estudiamos un modelo matemático de farmacodinámica (introducido en 1999 por P. Hahnfeldt y sus colaboradores) que incluye este efecto. Consiste en un sistema de dos EDO no lineales cuyo comportamiento asintótico analizamos. Además, el modelo permite incluir un término para el tratamiento antiangiogénico, cuya acción antitumoral se puede optimizar utilizando técnicas matemáticas. Suponemos además que el crecimiento del tumor es de tipo Gompertz.

Estudiamos un problema de optimización relacionado, donde el número de dosis aplicadas en el tratamiento, al igual que su cantidad y el tiempo de administración son variables. Realizamos además varios enfoques de este problema que, por lo que sabemos, no han sido publicados antes, y mostramos ejemplos para contrastar con la teoría.

Se incluyen también algunos experimentos numéricos utilizando MATLAB para tres fármacos antiangiogénicos de uso común con diferentes propiedades. Estos son Angiostatina, Endostatina y TNP-470. Con ellos queda evidenciado que las terapias de tipo metronómico son las adecuadas para tratar tumores con este enfoque en la mayoría de los casos.

Palabras clave: Terapia metronómica, modelo de Hahnfeldt et al., angiogénesis, problema de optimización

Index

1 Introduction **1**
1.1 A mathematical approach to cancer therapy 1
1.2 Structure of the work 2

2 Tumor dynamics **3**
2.1 Tumor dynamics without drug administration 3
2.2 Pharmacodynamics 9

3 Drug concentration **17**
3.1 Formulating the drug concentration function 17
3.2 Keeping the drug concentration in a steady state 18
3.2.1 Having a fixed ideal constant concentration 22
3.2.2 Looking for the optimal constant drug level 26
3.2.2.1 Considering a large elimination rate 28
3.2.3 Using the total cumulative dose to choose an ideal concentration level . . 33

4 Simulations **37**
4.1 Palliative therapy 37
4.1.1 Keeping the cumulative dose constant 37
4.1.2 Varying the initial tumor size 42
4.2 Curative therapy 44
4.2.1 Keeping the cumulative dose constant 44
4.2.2 Testing with alternative treatments combination 46

5 Conclusions **49**

Bibliography **51**

A Glossary **53**

Chapter 1

Introduction

In 2020, nearly 20 million people were diagnosed with cancer worldwide. The International Agency for Research on Cancer[3] further estimates that this number will continue to increase in the coming years. One of the factors favoring the uncontrolled proliferation and spread of cells is angiogenesis. It is the process of formation of new blood vessels that provide nutrients and oxygen to the body's tissues they reach. It is a vital physiological process in body growth and development, but it also supplies the blood tumors need to thrive, grow and metastasize.

Most of these diagnosed people undergo treatments like chemotherapy, radiotherapy, and immunotherapy. The treatment's purpose varies depending on both the tumor characteristics and the patient's conditions. It can be curative, in case the tumor stage allows it to be eliminated, or palliative, if a reduction of the malignant tumor is sought when it is already very advanced.

In addition, there are different treatment regimens to achieve these objectives. Among the most common are the following:

- Maximum Tolerated Dose (MTD) therapy: the doses applied are the highest ones that can be administered to a patient before unacceptable toxic effects appear. It is required a low dosing frequency so that the drug concentration in the blood is eliminated before each application. They target dividing tumor cells, i.e., they have a cytotoxic effect.

- Metronomic (MN) therapy: doses below the MTD are applied frequently to maintain the plasma concentration quasi-constant. It is less toxic than MTD therapy, and it aims to control tumors by targeting angiogenesis. Very recently, it has been shown that for most cytotoxic drugs it is also the most recommended therapy, even without taking into account their antiangiogenic effect (see [5]).

Therefore, to describe a treatment properly, the doses administered, as well as the amount of them and the time of application should be detailed.

1.1. A mathematical approach to cancer therapy

Mathematical models allow us to describe many of the processes that we observe in our daily lives. In particular, models using differential equations (those that establish relationships between variables and their derivatives) are used to study, for example, population dynamics, the mechanics of particles or the diffusion of substances in our body.

The evolution of a tumor can be considered as a process involving a large number of chemical reactions, which can also be studied from a mathematical point of view. Among other advantages, it makes it possible to predict the impact of drugs on the tumor before the application in a patient and to establish the cancer treatments that will work best for their target.

Among the differential equation models that we can use, we will consider the Gompertz model, one of the most widely used to deal with the tumor size evolution, but many others can be also used (Bertalanffy, logistic, ...). In addition, we will consider the effect of administering an angiogenesis inhibitor through an expression first introduced in 1999 by Hahnfeldt et al. (see [6]). Although it was described more than 20 years ago, its significance makes it interesting to be studied yet (see [10], [4]).

1.2. Structure of the work

In this work, we will conduct a study based on Hahnfeldt et al.'s article, expanding on what appears there with innovative approaches. We will also study the drug concentration of the cancer treatment applied within the body, formulating a complex nonlinear optimization problem with several variables. We will analyze particular cases of this problem to obtain the best treatments in different circumstances of significant clinical interest. To the best of our knowledge, there are mathematical studies that have considered them, but using a different point of view (see [1]).

Along this work, we will face with results from other areas of mathematics such as algebra, and we will argument from the heuristic point of view as a way to simplify mathematical results. We will also use MATLAB software to perform simulations that will allow us to reinforce what we have studied theoretically and to solve the particular cases of the complex system mentioned above. For these examples, we will use the drugs studied by Hahnfeldt et al. in their article[6], whose variety of characteristics allows us to cover the particular cases analyzed theoretically.

The work is divided into five chapters, the first of which is the current introduction. They include the following content:

- **Chapter 2** presents the Cauchy system that models tumor dynamics both in the presence of a drug and in the untreated case. The existence and uniqueness of solution in both situations is studied together with its asymptotic behavior.
- **Chapter 3** contains the study of the concentration of the drug in the patient's body. It presents both the expression of the concentration and the optimization problem with its variants.
- **Chapter 4** presents practical examples of the theoretical aspects analyzed above. We will analyze the effect of both curative and palliative therapy and show that the optimal treatment with an angiogenesis inhibitor is the metronomic type one in most cases.
- **Chapter 5** reviews the results obtained in the previous chapters, proposing new lines of research that will allow the continuation of this study.

Chapter 2

Tumor dynamics

In this chapter, we will study the tumor's development and progression in the body. We will start by considering that the cancer is not being treated, and we will prove the existence and uniqueness of the solutions of a particular Cauchy problem under these hypotheses in two different cases. Afterward, we will analyze the case in which a drug is being administered, introducing a piecewise continuous and time-dependent function representing its concentration into the previously formulated Cauchy problem. We will also study the existence and uniqueness of solution under this circumstance.

2.1. Tumor dynamics without drug administration

Among the different mathematical models that can be utilized to study the tumor cells proliferation rate[2] [11], we will consider the Gompertzian growth one. It establishes that

$$V'(t) = -\lambda_1 V(t) \log\left(\frac{V(t)}{V_{\max}}\right), \tag{2.1}$$

where $\lambda_1 > 0$ is the growth rate, $V(t)$ the tumor size or volume at time $t > 0$, and $V_{\max} > 0$ the so-called carrying capacity, i.e., the maximum volume a tumor can reach.

However, this last quantity is not fixed in time, as it depends on biological processes that affect vascular growth. Therefore, we can replace it by a variable $K(t)$, where the change rate $K'(t)$ we consider in this dissertation is the one proposed by Philip Hahnfeldt et al. in 1999[6] (with no treatment first):

$$K'(t) = -\lambda_2 K(t) + S(V(t), K(t)) - I(V(t), K(t)) = -\lambda_2 K(t) + bV(t) - dK(t)V(t)^{2/3}, \tag{2.2}$$

with $\lambda_2 \geq 0$ being the intrinsic loss rate and b and d being the weights of the vascular growth stimulating and inhibiting processes, respectively.

Remark 2.1.1. As we are dealing with a chemical process involving the diffusion of inhibitory and stimulatory substances, it can be modeled using the following reaction-diffusion partial differential equation:

$$\frac{\partial n}{\partial t}(x, y, z, t) = \tilde{D}^2 \Delta n(x, y, z, t) - cn(x, y, z, t) + s_0 \mathbb{1}_{[0, r_0^2)}(x^2 + y^2 + z^2),$$

where we assume that the tumor is a spheroid of radius r_0, $c > 0$ describes the clearance rate of stimulators, $\tilde{D}^2 > 0$ is the constant diffusion coefficient and $n(x, y, z, t)$ is the stimulator/inhibitor concentration at time t in position (x, y, z). Finally, the last term describes the rate of

stimulator secretion, which takes the value s_0 inside the tumor, and is null outside it. Through this equation it is possible to justify the form of both the inhibitor ($I(V,K) = bV$) and the stimulation ($S(V,K) = dKV^{2/3}$) factors of Equation (2.2).

We further assume that the tumor is in a quasi-steady state, i.e., $\frac{\partial n}{\partial t}(x,y,z,t) = 0$, and that it has radial symmetry. It allows us to reduce the number of parameters of n, such that $n(x,y,z) = n(r)$, with r being the distance from the center of the tumor to the origin.

Thus, the above expression is reduced to the following second-order ordinary differential equation:

$$n''(r) + \frac{2}{r}n'(r) - \frac{c}{\tilde{D}^2}n(r) + \frac{s_0 \mathbb{1}_{[0,r_0)}(r)}{\tilde{D}^2} = 0. \tag{2.3}$$

Let us take $c_1 = \frac{\sqrt{c}}{\tilde{D}}$. Now, we can distinguish between two cases:

- If $r > r_0$, then the ODE is homogeneous. By using the change of unknown function $v(r) = rn(r)$, the general solution of $n(r)$ is

$$n(r) = k_1\frac{e^{c_1 r}}{r} + k_2\frac{e^{-c_1 r}}{r}, \qquad \text{with } k_1, k_2 \in \mathbb{R}. \tag{2.4}$$

  As $n(r) \longrightarrow 0$ if $r \longrightarrow +\infty$ (i.e. we are assuming that the inhibitory/stimulatory effect occurs near the tumor), then $k_1 = 0$ and the solution becomes

$$n(r) = k_2\frac{e^{-c_1 r}}{r}, \qquad \text{with } k_2 \in \mathbb{R}.$$

- If $r \leq r_0$, the resulting expression is analogous to the previous one, excepting for an additional term that makes it inhomogeneous. We now have $n(r) = \frac{s_0}{c}$ as a particular constant solution of this inhomogeneous equation, while the solution of the homogeneous equation is (2.4). Therefore, as the sum of solutions is also a solution, then, when $r \leq r_0$, the general solution of Equation (2.3) is as follows

$$n(r) = \tilde{k_1}\frac{\sinh(c_1 r)}{r} + \tilde{k_2}\frac{\cosh(c_1 r)}{r} + \frac{s_0}{c}, \qquad \text{with } \tilde{k_1}, \tilde{k_2} \in \mathbb{R}.$$

  where we have expressed the exponential functions in terms of hyperbolic functions. Now, note that $n(r)$ has to be bounded when $r \longrightarrow 0$, so $\tilde{k_2} = 0$, and

$$n(r) = \tilde{k_1}\frac{\sinh(c_1 r)}{r} + \frac{s_0}{c}, \qquad \text{with } \tilde{k_1} \in \mathbb{R}.$$

Therefore, by continuity of both $n(r)$ and $n'(r)$ at the point $r = r_0$, we can obtain the expressions of $\tilde{k_1}$ and k_2, such that the unique solution of $n(r)$ is as follows

$$n(r) = \begin{cases} \dfrac{s_0}{c}\left(1 - \dfrac{1 + r_0 c_1}{c_1}\dfrac{\sinh(c_1 r)}{r}e^{-c_1 r_0}\right), & \text{if } r \leq r_0, \\ \dfrac{s_0}{c}\left(r_0\cosh(c_1 r_0) - \dfrac{\sinh(c_1 r_0)}{c_1}\right)\dfrac{e^{-c_1 r}}{r}, & \text{if } r > r_0. \end{cases}$$

We now need to distinguish between tumor inhibitors and stimulators. In the first case, it is assumed that c (stimulator clearance rate) is small ($c \approx 0$), such that the exact solution can be approximated as

$$n_I(r) = \begin{cases} \dfrac{s_0}{\tilde{D}^2}\dfrac{3r_0^2 - r^2}{6}, & \text{if } r \leq r_0, \\ \dfrac{s_0 r_0^3}{3\tilde{D}^2 r}, & \text{if } r > r_0. \end{cases}$$

Then, we can calculate the total concentration of inhibitors inside the tumor, such that

$$I(r_0) = v_1 \int_0^{r_0} n_I(r) r^2 dr = v_1 \int_0^{r_0} \frac{s_0(3r_0^2 - r^2)}{6\tilde{D}^2} r^2 dr = \frac{2v_1 s_0}{15\tilde{D}^2} r_0^5,$$

where v_1 is a constant that comes from expressing the integral in spherical coordinates. Assuming that $I(V,K)$ is proportional to $I(r_0)$, and having that $I(r_0)$ is proportional to r_0^5, a reasonable proposal is to take $I(V,K) = dKV^{2/3}$, because both $KV^{2/3}$ and r_0^5 have the same 'units'.

In the case of the stimulation factor, c is considered to be large ($c >> 0$), so under this assumption $n(r)$ is approximated by $\frac{s_0}{c}$ inside the tumor, and therefore:

$$S(r_0) = \tilde{v_1} \int_0^{r_0} n_S(r) r^2 dr = \tilde{v_1} \int_0^{r_0} \frac{s_0}{c} r^2 dr = \frac{\tilde{v_1} s_0}{3c} r_0^3,$$

where $\tilde{v_1}$ is also a constant. Arguing in the same way as before, and assuming that $S(V,K)$ is proportional to $S(r_0)$, we can take $S(V,K) = bV$ since V and r_0^3 have 'units of volume'.

It is noteworthy to mention that these are not the only options we can choose. Following the criterion of the units and taking into account that V and K tend to move together, we can also have $S(V,K) = bK$ and $I(V,K) = dK^\alpha V^\beta$, where $\alpha + \beta = 5/3$.

Note that neither (2.1) nor (2.2) depend explicitly on time. As a consequence, we can write equations (2.1) and (2.2) together as a time-constant Cauchy problem:

$$\begin{cases} V' = -\lambda_1 V \log\left(\frac{V}{K}\right), \\ K' = -\lambda_2 K + bV - dKV^{2/3}, \\ V(0) = V_0 > 0,\ K(0) = K_0 > 0, \end{cases} \tag{2.5}$$

where K_0 should be larger than V_0, as we are considering that when a tumor is firstly detected, its volume can still be larger.

Theorem 2.1.1. *Let us consider the system* (2.5) *and* $b > \lambda_2$. *Let* $0 < V_0 < K_0$. *There exists a unique solution* $(V(t), K(t))$ *of the system for all* $t > 0$. *In addition,* $(V(t), K(t)) \longrightarrow (V_c, K_c)$ *as* $t \longrightarrow \infty$, *where*

$$(V_c, K_c) = \left(\left(\frac{b - \lambda_2}{d} \right)^{3/2}, \left(\frac{b - \lambda_2}{d} \right)^{3/2} \right)$$

is a critical point.

Proof. Let

$$f_1(V,K) = -\lambda_1 V \log\left(\frac{V}{K}\right), \qquad f_2(V,K) = -\lambda_2 K + bV - dKV^{2/3}.$$

Let $\Omega = \{(V,K) \in \mathbb{R}^2 : V > 0, K > 0\}$ be the domain of both functions due to biological reasons. Let us note that $f_1(V,K)$ is not defined at the origin (see Remark 2.1.2).

As problem (2.5) does not depend explicitly on time, we can represent its solutions in a VK phase portrait[13]. In Figure 2.1.a. we can observe the evolution of some solutions (blue, orange, purple, and yellow curves) of the problem with respect to time for different initial points (not-filled points of the figure).

The first step that has to be done is the proof of the existence and uniqueness of local solution. To do so, we have to check whether $f_1(V,K)$ and $f_2(V,K)$ and their partial derivatives are continuous in the Ω subset (i.e. that f_1 and f_2 are C^1 functions in Ω).

The expressions of the partial derivatives are as follows:

$$\frac{\partial f_1}{\partial V}(V,K) = -\lambda_1\left[\log\left(\frac{V}{K}\right)+1\right], \qquad \frac{\partial f_2}{\partial V}(V,K) = b - \frac{2}{3}\frac{dK}{V^{1/3}},$$
$$\frac{\partial f_1}{\partial K}(V,K) = \frac{\lambda_1 V}{K}, \qquad \frac{\partial f_2}{\partial K}(V,K) = -\lambda_2 - dV^{2/3}.$$

We can see that all the expressions, as well as $f_1(V,K)$ and $f_2(V,K)$ are continuous, as they are compositions of continuous functions (remember that (0,0) $\notin \Omega$). Then, there exists only one solution for each initial point (V_0, K_0) in some interval $[0,h]$. It is reflected in the phase portrait as a lack of bifurcations in the solution curves in that interval.

Before proving the existence of a global solution, we need to ensure that the solution will remain in the domain Ω for all $t > 0$, and that any of its components tends to infinity or to the Ω's boundary as time tends towards infinity. To do so, we can make use of the VK phase portrait of Figure 2.1.a., and the different regions that we can divide it in according to the sign of both V' and K'.

Let us obtain first the conditions that should fulfill V and K so that $V' > 0$:

$$f_1(V,K) = V' > 0 \iff \log\left(\frac{V}{K}\right) < 0 \iff V < K \tag{2.6}$$

where we have to remember that V, K, and λ_1 are positive and non-zero. On the other hand, if we desire that $K' > 0$ (with λ_2, $d > 0$), then:

$$f_2(V,K) = K' > 0 \iff bV > K(\lambda_2 + dV^{2/3}) \iff \frac{bV}{\lambda_2 + dV^{2/3}} > K \tag{2.7}$$

The so-called nullclines are the curves that make $f_1(V,K) = 0$ and $f_2(V,K) = 0$, and they separate the VK phase portrait into four different regions according to the sign of K' and V'. In Figure 2.1.a. we can also observe the nullclines of the system drawn in dark blue (which makes $f_1(V,K) = 0$) and brown (where $f_2(V,K) = 0$). We can distinguish the following cases:

i) Let us suppose $K < \min\left\{V, \frac{bV}{\lambda_2+dV^{2/3}}\right\}$. Here we have that $V' < 0$ and $K' > 0$, which indicate that the solution of the system (2.5) should move up and leftwards.

ii) If $K \in \left[V, \frac{bV}{\lambda_2+dV^{2/3}}\right]$, then $K', V' > 0$. The solution in this region moves both to the right and top.

iii) When $K > \max\left\{V, \frac{bV}{\lambda_2+dV^{2/3}}\right\}$, K' is negative and V' is positive. As a result, the solution should go to the right and down.

iv) If $K \in \left[\frac{bV}{\lambda_2+dV^{2/3}}, V\right]$ both K' and V' are negative. It implies that the solution moves down and leftwards.

Each of the curves representing the evolution of the solutions with respect to time of Figure 2.1.a. has its initial point located in one of the mentioned regions. For instance, the orange curve starts in the i) region, so it goes slightly to the left and the top until it crosses the dark

blue nullcline, where it turns to the right. At first, it is a subtle right movement, but once it is close to the brown nullcline, it follows its path tending to the critical point, represented by a red dot. The blue and the yellow curves start in the ii) and iv) regions, respectively, and they follow the movement established by them, tending to the equilibrium point, too. Finally, the purple curve starts in the iii) region, so the solution evolves moving down and to the right. When it crosses the brown nullcline, the curve starts going up, keeping close to this zero-growth isocline and tending to the critical point.

As a result, we have also proved that neither of the solutions can have a negative or a tending-to-infinity component because of the behavior they should have in each region.

Once we have checked how solutions behave for all $t > 0$, we have to extend the reasoning followed to prove the local existence to all $t > 0$, in order to prove the global existence. As we have observed, both V and K are positive at all times. In particular, they are positive at time h, so $(V(h), K(h)) \in \Omega$. Thus, there exists a solution in some interval $[h, h + h']$, with $h' > 0$.

This process is repeated iteratively until we demonstrate the existence of solution for all $t > 0$. Moreover, it is unique because the partial derivatives are continuous in all Ω.

Critical points (V_c, K_c) satisfy that $f_1(V_c, K_c) = f_2(V_c, K_c) = 0$, i.e, they are the intersection between nullclines. In our biological framework, it is where the tumor size reaches the carrying capacity, which is the worst situation for the patient. By using Equations (2.6) and (2.7), we get

$$V_c = K_c = \left(\frac{b - \lambda_2}{d}\right)^{3/2}. \tag{2.8}$$

which we know that exists because of the theorem's hypothesis $b > \lambda_2$.

As we have noticed, all solutions converge to that point, regardless of the starting point. As a result, we have proved globally that it is asymptotically stable. □

Remark 2.1.2. As we have mentioned before, $f_1(V, K)$ can not be defined at the origin. If it were, then $f_1(V, K)$ and $f_2(V, K)$ would be continuous in (0,0), or at least have a removable discontinuity in that point. We have that $f_2(0, 0) = 0$. However, $f_1(V, K)$ is not continuous at the origin because of the terms inside the logarithm. What is more, we can not solve this discontinuity by taking the value of the limit of $f_1(V, K)$ when $(V, K) \longrightarrow$ (0,0) because it does not exist. We have that

$$\lim_{(V,K)\to(0,0)} f_1(V, K) = \lim_{(V,K)\to(0,0)} -\lambda_1 V \log(V) + \lim_{(V,K)\to(0,0)} \lambda_1 V \log(K), \tag{2.9}$$

where the first term's limit exists. By applying L'Hôpital's rule:

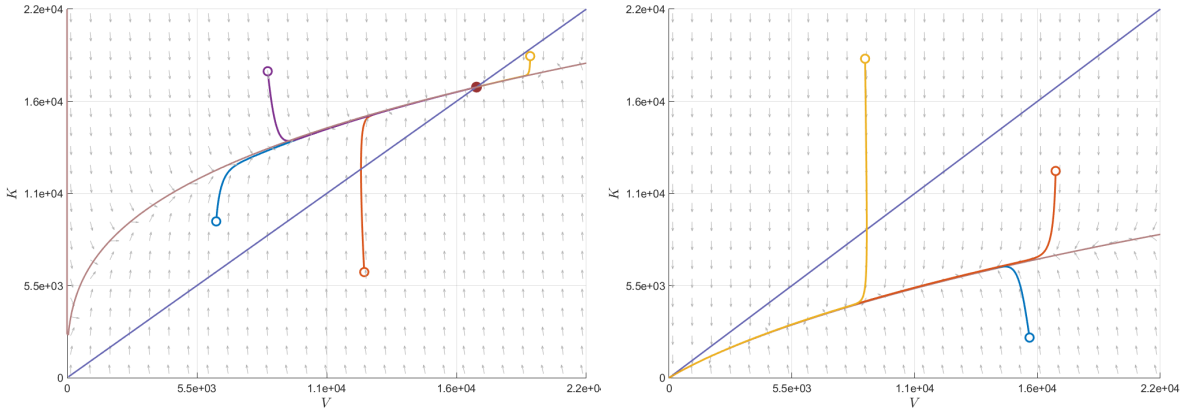
$$\lim_{(V,K)\to(0,0)} -\lambda_1 V \log(V) = \lim_{(V,K)\to(0,0)} -\lambda_1 \frac{\log(V)}{1/V} = \lim_{(V,K)\to(0,0)} \lambda_1 V = 0.$$

Nevertheless, we can not compute the second term of the expression (2.9). We can take two sequences tending to the origin such that this limit takes two different values. Let us take:

$$(V_n, K_n) = \left(\frac{1}{n}, e^{-n}\right) \xrightarrow[n\longrightarrow+\infty]{} (0, 0) \Longrightarrow \lim_{(V,K)\to(0,0)} \lambda_1 V_n \log(K_n) = -\lambda_1,$$

and by taking other sequence we have:

$$(V_n, K_n) = \left(\frac{1}{n}, e^{-n^2}\right) \xrightarrow[n\longrightarrow+\infty]{} (0, 0) \Longrightarrow \lim_{(V,K)\to(0,0)} \lambda_1 V_n \log(K_n) = -\infty.$$



(a) Case $b > \lambda_2$.

(b) Case $b \leq \lambda_2$.

Figure 2.1: VK phase portrait with the nullclines (brown and dark blue curves), the critical point in red and some solutions of system (2.5) for different initial points. They were obtained with a MATLAB toolbox called *PhasePlane*.

Theorem 2.1.2. *Let $(V(t), K(t))$ be a solution of system (2.5) in $t > 0$ and $b \leq \lambda_2$. Then, $(V(t), K(t)) \longrightarrow (0, 0)$ as $t \longrightarrow +\infty$, independently of the starting point (V_0, K_0), with $0 < V_0 < K_0$.*

Proof. As we have showed in Theorem 2.1.1, nullclines can divide a VK phase portrait into a certain number of regions according to the sign of both V' and K'. Unlike the previous theorem, nullclines now do not intersect in $\Omega = (0, +\infty) \times (0, +\infty)$, because $b \leq \lambda_2$. As a result, we just can divide the VK portrait into three regions, as it can be observed in Figure 2.1.b..

Using the same reasoning as before, we can further distinguish between:

i) If $K < \min\left\{V, \frac{bV}{\lambda_2 + dV^{2/3}}\right\}$, then we have that $V' < 0$ and $K' > 0$. Here, the the solution of the system (2.5) should move to the left and the top.

ii) When $K > \max\left\{V, \frac{bV}{\lambda_2 + dV^{2/3}}\right\}$, $K' < 0$ and $V' > 0$, so the solution should go rightwards and down.

iii) If $K \in \left[\frac{bV}{\lambda_2 + dV^{2/3}}, V\right]$ both K' and V' are negative, so the solution should move down and to the left.

In Figure 2.1.b. we have represented the trajectories of some solutions, each of them starting in a different region. The blue curve starts in region i), so it moves to the left and up until it reaches the nonlinear nullcline. Then, it continues its path tending to the origin. The orange curve's starting point is in the ii) region. As a result, it moves slightly to the left and down, and once it is close to the brown nullcline, it follows its path tending to (0,0). Finally, the yellow one starts in the iii) region, and it goes slightly to the right and down until it crosses the blue nullcline. Then, it moves as it does the orange curve.

Arguing as before, we can prove that a solution of system (2.5) exists for all $t > 0$ and tends to the origin as $t \longrightarrow +\infty$, for any starting point (V_0, K_0) that satisfies $0 < V_0 < K_0$. What is more, we can ensure that none of the solution trajectories will tend neither to infinity nor to another $\mathbb{R}^2$ quadrant because of the regions' rules. □

2.2. Pharmacodynamics

Neither (2.1) nor (2.2) equations take into account unnatural external stimuli like cancer treatments, whose aim is to reduce the tumor size in order to maintain it in a non-toxic volume or even, if possible, to eliminate it. If we add the effect of cancer drugs, then those expressions change. They can be divided into two groups according to the type of cells they target: cytotoxic and antiangiogenic drugs. In this dissertation, we will focus on the second ones.

Antiangiogenic drugs block the nutrients and oxygen necessary for a tumor for its development, by inhibiting the growth of new vasculature. We formulate their effect in Equation (2.2) as an additional term, such that

$$K' = -\lambda_2 K + bV - dKV^{2/3} - eKc(t), \tag{2.10}$$

where $e > 0$ is the factor that quantifies the consequence of applying the $c(t)$ concentration of antiangiogenic drugs in the carrying capacity.

The Cauchy problem can now be rewritten as:

$$\begin{cases} V' = -\lambda_1 V \log\left(\frac{V}{K}\right), \\ K' = -\lambda_2 K + bV - dKV^{2/3} - eKc(t), \\ V(0) = V_0 > 0,\ K(0) = K_0 > 0, \end{cases} \tag{2.11}$$

where all constants have already been specified. Note that the system now depends on time, unless $c(t) \equiv c_d$. If it were, we could distinguish between the following two cases:

- If $b > \lambda_2 + ec_d$, then we are under the hypotheses of Theorem 2.1.1, where the critical point $(\tilde{V_c}, \tilde{K_c})$ is now
$$\tilde{V_c} = \tilde{K_c} = \left(\frac{b - \lambda_2 - ec_d}{d}\right)^{3/2}. \tag{2.12}$$
As we have that ec_d is a positive quantity, it can be observed that applying a treatment reduces the maximum volume a tumor can reach. It is related to palliative treatments.

- If $b \leq \lambda_2 + ec_d$, then we can apply Theorem 2.1.2, where the final volume can be reduced to zero. It is the case of a curative treatment.

Let us see an example in which we apply a drug, and we want to see the maximum volume a tumor could reach when it is applied. We will consider that there is a minimum constant concentration and a maximum one, and observe the changes they produce in $\tilde{V_c}$:

Example 2.2.1. *Let $b = 5.85$ day^{-1}, $\lambda_2 = 0$ day^{-1}, $e = 0.15$ mg^{-1} L day^{-1} and $d = 0.00873$ day^{-1} mm^{-2} [6]. If we do not consider any treatment, then $V_c \approx 17346$ mm^3 (see Equation (2.8)). In case we suppose that the patient is being treated, by considering $c_d = 10$ mg/L we get $\tilde{V_c} = \tilde{K_c} = 11123$ mm^3, with $c_d = 20$ mg/L we obtain $\tilde{V_c} = 5899$ mm^3, and if $c_d = 30$ mg/L, $\tilde{V_c} = \tilde{K_c} = 1923$ mm^3 (see Equation (2.12)). As we could expect, the effects of the treatment on the tumor volume increase with c_d. However, biologically it is not always possible to apply the amount of drug we would desire.*

In Figure 2.2 we can see the effect of the different drug concentrations both in the volume and in the carrying capacity. Note that the carrying capacity K is always above the tumor volume V, which is consistent with the biological meaning of both quantities, and that they both move

together. In addition, we can see that the effect of the concentration is not only on the maximum possible tumor volume but also on the time it takes to reach it. When we only apply 10 mg/L of the drug, it takes approximately 80 days to reach the maximum. Nevertheless, in the second situation, it takes around 100 days to reach it, and it enlarges to 150 days in the third one.

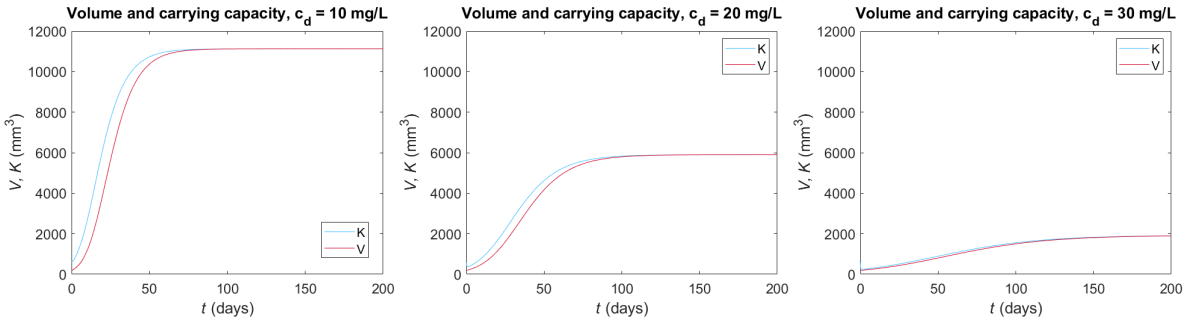


Figure 2.2: Tumor volume (V) and carrying capacity (K) when c_d takes values 10 (left), 20 (center) and 30 mg/L (right).

The phase portraits resulting from the three cases of the example are represented as follows:

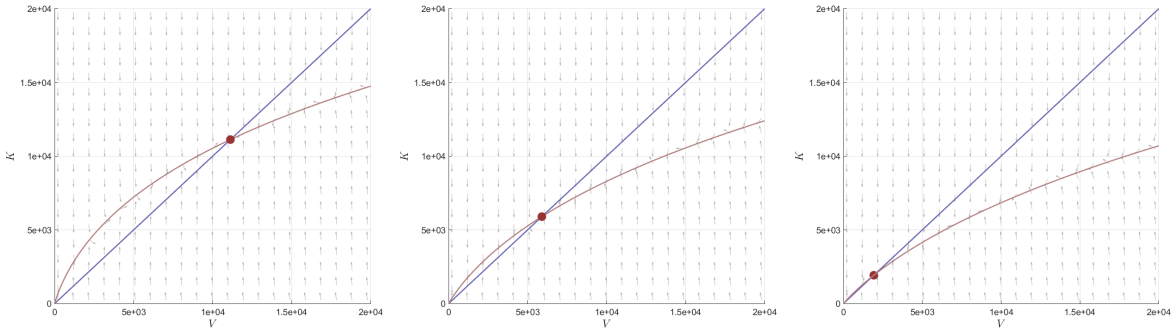


Figure 2.3: VK phase portraits with the nullclines (brown and dark blue curves) and the critical point in red, when the constant drug concentration c_d takes values 10 (left), 20 (center) and 30 mg/L (right).

Notice that the critical point moves down the blue nullcline as the drug concentration increases. Moreover, its coordinates coincide with those calculated from Equation (2.12) *in each case.*

Nevertheless, when a drug is administered in doses, it is not possible to maintain a constant concentration in the body. Since this varies with time, being also a piecewise continuous function, it is not possible to use the standard arguments to prove the existence and uniqueness of the solution (those used in the previous section). Let us see, however, that we can make use of a similar argument to prove it if there is a finite number of jump discontinuities. The following example shows how we have to proceed when we have a piecewise continuous function:

Example 2.2.2. *Let us take the following ODE:*

$$x'(t) = \begin{cases} x(t), & \text{if } t < 0, \\ tx(t), & \text{if } t \geq 0, \end{cases}$$

with the condition $x(0) = 5$.

We can solve first the equation in each interval, such that

$$x(t) = \begin{cases} c_1 e^t, & \text{if } t < 0, \\ c_2 e^{t^2/2}, & \text{if } t \geq 0 \end{cases}$$

where c_1 *and* c_2 *are real constants.*

If we ask it to be continuous not only in each of the intervals where it is defined but also in the connection points, then $c_1 = c_2 = 5$ *(as they should also satisfy that* $x(0) = 5$*). Therefore, the solution obtained exists for all* $t \in \mathbb{R}$*, and it is unique.*

Note that when $t = 0$ *it is not derivable, because* $x'(0^-) = 5 \neq 0 = x'(0^+)$.

In view of this example, we can observe that if we have a function $x'(t)$ with a finite number of jump discontinuities $t_1, ..., t_N$, function $x(t)$ will not be derivable at those points, although it will be continuous for the whole domain. Therefore, the classical theory about the existence and uniqueness of solution for Cauchy problems can be extended to the case where the function defining the ODE is only piecewise continuous with respect to t and C^1 with respect to x, just pasting the solutions at the finite number of points where the function has such a discontinuity with respect to t (see Chapter 3 of [7]).

Theorem 2.2.1. *Let* $c : [0, +\infty) \longrightarrow [0, +\infty)$ *be a piecewise continuous function in* $[0, +\infty)$ *with (at most) a finite number of jump discontinuity points. Let* $c_1, c_2 > 0$*, such that* $0 < c_1 < c(t) < c_2$*, for all* $t > 0$*, and* $0 < V_0 < K_0$*. Then, there exists a unique solution* $(V(t), K(t))$ *of the Cauchy problem* (2.11) *defined in* $[0, +\infty)$*. It verifies that* $V(t) > 0$ *and* $K(t) > 0$*, for all* $t > 0$*, and*

i) if $b > \lambda_2 + ec_2$*,*

$$0 < \left(\frac{b - \lambda_2 - ec_2}{d}\right)^{3/2} \leq \liminf_{t \to +\infty} V(t) \leq \limsup_{t \to +\infty} V(t) \leq \left(\frac{b - \lambda_2 - ec_1}{d}\right)^{3/2},$$
$$0 < \left(\frac{b - \lambda_2 - ec_2}{d}\right)^{3/2} \leq \liminf_{t \to +\infty} K(t) \leq \limsup_{t \to +\infty} K(t) \leq \left(\frac{b - \lambda_2 - ec_1}{d}\right)^{3/2}.$$

ii) if $b \leq \lambda_2 + ec_1$*, we have that*

$$\lim_{t \to +\infty} V(t) = \lim_{t \to +\infty} K(t) = 0.$$

Proof. Let

$$\tilde{f}_1(V, K) = -\lambda_1 V \log\left(\frac{V}{K}\right), \qquad \tilde{f}_2(t, V, K) = -\lambda_2 K + bV - dKV^{2/3} - eKc(t).$$

Note that $\tilde{f}_1(V, K) = f_1(V, K)$, and $\tilde{f}_2(t, V, K) = f_2(V, K) - eKc(t)$, where $f_1(V, K)$ and $f_2(V, K)$ were defined in the proof of Theorem 2.1.1.

Let us prove first the existence and uniqueness of solution $(V(t), K(t))$ of the Cauchy problem (2.11) for all $t \in [0, +\infty)$. Be $\{t_1, ..., t_N\} \subset [0, +\infty)$ the jump discontinuity points of function c, such that $0 \leq t_1 < t_2 < ... < t_N$. Let us take the interval $[0, t_1)$, so that we can ensure that function c is continuous there. Let us suppose $(V(0), K(0)) \in \Omega = \{(V, K) \in \mathbb{R}^2 : V > 0, K > 0\}$,

where $(V(0), K(0)) = (V_0, K_0)$ is the initial point of problem (2.11). We have to prove that $\tilde{f}_1(V, K)$ and $\tilde{f}_2(t, V, K)$ are continuous in $[0, t_1) \times \Omega$. The first function is C^1 in Ω, as we had proved in Theorem 2.1.1. The second function is also continuous in all Ω, because the new term $-eKc(t)$ added to the C^1 function $f_2(V, K)$ of Theorem 2.1.1 is continuous when $t \in [0, t_1)$. In addition, the partial derivatives of $\tilde{f}_2(t, V, K)$ are also continuous in $[0, t_1) \times \Omega$:

$$\frac{\partial \tilde{f}_2}{\partial V}(t, V, K) = b - \frac{2}{3}\frac{dK}{V^{1/3}}, \qquad \frac{\partial \tilde{f}_2}{\partial K}(t, V, K) = -\lambda_2 - dV^{2/3} - ec(t).$$

Therefore, there exists a unique solution for each initial point (V_0, K_0) in the interval $[0, h]$, for some $h > 0$, such that $h < t_1$. Here again, the solution neither diverges nor tends to Ω's boundary. As c is continuous in $[0, t_1)$, and $(V(h), K(h)) \in \Omega$ by continuity, we can repeat this process iteratively to prove the existence of a unique solution in $t \in [0, t_1)$.

We can follow the same reasoning with the intervals $[t_i, t_{i+1})$, where $i \in \{1, ..., N-1\}$, and with $[t_N, +\infty)$, and prove the existence of a unique solution in each of those intervals pasting the different branches as explained above. Then, we can prove the existence and uniqueness of solution for all $t > 0$.

In order to prove the inequalities stated in the theorem, let $(V_1(t), K_1(t))$ and $(V_2(t), K_2(t))$ be the solutions of the following Cauchy problems, respectively:

$$(C_1)\begin{cases} V' = -\lambda_1 V \log\left(\frac{V}{K}\right), \\ K' = -\lambda_2 K + bV - dKV^{2/3} - eKc_1, \\ V(0) = V_0 > 0,\ K(0) = K_0 > 0, \end{cases} \qquad (C_2)\begin{cases} V' = -\lambda_1 V \log\left(\frac{V}{K}\right), \\ K' = -\lambda_2 K + bV - dKV^{2/3} - eKc_2, \\ V(0) = V_0 > 0,\ K(0) = K_0 > 0. \end{cases}$$

By using the comparison Theorem 2.2.2, we get that

$$0 < V_2(t) \leq V(t) \leq V_1(t), \qquad 0 < K_2(t) \leq K(t) \leq K_1(t), \tag{2.13}$$

for all $t \geq 0$. If $b > \lambda_2 + ec_2$, by taking into account Theorem 2.1.1 we know that

$$\begin{aligned} \lim_{t\to+\infty} V_1(t) &= \lim_{t\to+\infty} K_1(t) = \left(\frac{b - \lambda_2 - ec_1}{d}\right)^{3/2}, \\ \lim_{t\to+\infty} V_2(t) &= \lim_{t\to+\infty} K_2(t) = \left(\frac{b - \lambda_2 - ec_2}{d}\right)^{3/2}. \end{aligned} \tag{2.14}$$

As a result, we can prove the theorem's statement *i)* by taking the limit $t \longrightarrow +\infty$, and substituting expressions (2.14) into inequalities (2.13). It is noteworthy to mention that the solutions of problem (2.11) heavily oscillate as $t \longrightarrow +\infty$ (see figures of Chapter 4), and that is the reason why we have to distinguish between the limit superior and inferior.

On the other hand, if we have $b \leq \lambda_2 + ec_1$, then $\lim_{t\to+\infty} V_1(t) = \lim_{t\to+\infty} K_1(t) = 0$, as it is stated in Theorem 2.1.2. By taking limits and using the sandwich rule in expressions (2.13) we can finally prove statement *ii)*. □

Remark 2.2.1. Function c will represent the drug concentration in the patient's body.

As we have mentioned, the above theorem bases its reasoning on the so-called comparison theorem. Before stating it, we have to introduce the Chaplygin Lemma:

Lemma 2.2.1. *Let $f_1, f_2 \in C^1(\Omega)$, where $\Omega \subset \mathbb{R}^2$ is an open set. Let x_1, x_2, y_1, y_2 continuous functions in $[0, T_f]$, such that $(x_1(t), x_2(t)) \in \Omega$, and $(y_1(t), y_2(t)) \in \Omega$, $\forall t \in [0, T_f]$. Let us suppose that they verify*

$$\begin{cases} x_1'(t) = f_1(x_1(t), x_2(t)), \\ x_2'(t) = f_2(x_1(t), x_2(t)), \\ x_1(t_0) = x_{10},\ x_2(t_0) = x_{20}, \end{cases} \qquad \begin{cases} y_1'(t) < f_1(y_1(t), y_2(t)), \\ y_2'(t) < f_2(y_1(t), y_2(t)) - f_3(t), \\ y_1(t_0) < x_{10},\ y_2(t_0) < x_{20}, \end{cases}$$

with $(x_{10}, x_{20}) \in \Omega$. *If*

$$\frac{\partial f_1}{\partial x_2}(x_1, x_2) \geq 0, \qquad \frac{\partial f_2}{\partial x_1}(x_1, x_2) \geq 0, \quad \forall (x_1, x_2) \in \Omega,$$

then $y_1(t) \leq x_1(t)$ *and* $y_2(t) \leq x_2(t),\ \forall t \in [0, T_f]$.

Proof. We will prove it by contradiction. Let us assume that there is a $t^* \in (0, T_f)$ and $i \in \{1, 2\}$ such that $y_i(t^*) > x_i(t^*)$. Let us consider the set

$$A = \{t \in [0, T_f] : y_i(t) > x_i(t) \text{ for some } i \in \{1, 2\}\}.$$

Note that A is bounded from below by 0, and it is not empty because $t^* \in A$. By the infimum axiom, we know that there exists a $t_1 \in [0, T_f]$ such that $t_1 = \inf(A)$.

Let us assume $i = 1$, so $y_1(t_1) = x_1(t_1)$ and $x_2(t_1) \geq y_2(t_1)$: if $t_1 \in A$ or $x_2(t_1) < y_2(t_1)$ then, by continuity of y_1, y_2, x_1 and x_2, t_1 would not be the infimum of the set. Therefore, we have

$$\begin{aligned} f_1(x_1(t_1), x_2(t_1)) - f_1(y_1(t_1), y_2(t_1)) &= f_1(x_1(t), x_2(t_1)) - f_1(x_1(t_1), y_2(t_1)) \\ &= \frac{\partial f_1}{\partial x_2}(x_1(t_1), \theta x_2(t_1) + (1-\theta) y_2(t_1))(x_2(t_1) - y_2(t_1)) \geq 0, \end{aligned} \tag{2.15}$$

where we have used the Mean Value Theorem, with $\theta \in (0, 1)$ and the partial derivative hypothesis of the lemma.

As $t_1 = \inf(A)$, there exists an element $\delta > 0$ such that $y_1(t_1 + \Delta) > x_1(t_1 + \Delta)$, where $\Delta \in (0, \delta)$. Therefore,

$$\frac{y_1(t_1 + \Delta) - y_1(t_1)}{\Delta} > \frac{x_1(t_1 + \Delta) - x_1(t_1)}{\Delta}$$

and if we consider $\Delta \longrightarrow 0$, then it is obtained that $f_1(y_1(t_1), y_2(t_1)) > y_1'(t_1) \geq x_1'(t_1) = f_1(x_1(t_1), x_2(t_1))$, which contradicts (2.15).

If $i = 2$, the process can be repeated by considering $x_2(t_1) = y_2(t_1)$ and $x_1(t_1) \geq y_1(t_1)$. □

Now, we can present the comparison theorem, whose proof is based on the Chaplygin Lemma:

Theorem 2.2.2. *Let* $f_1, f_2 \in C^1(\Omega)$, *where* $\Omega \subset \mathbb{R}^2$ *is an open set. Let* $f_3 \geq 0$, *piecewise continuous in the interval* $[0, T_f]$. *Let us consider the following ODE systems:*

$$\begin{cases} x_1'(t) = f_1(x_1(t), x_2(t)), \\ x_2'(t) = f_2(x_1(t), x_2(t)), \\ x_1(0) = x_{10},\ x_2(0) = x_{20}, \end{cases} \qquad \begin{cases} y_1'(t) = f_1(y_1(t), y_2(t)), \\ y_2'(t) = f_2(y_1(t), y_2(t)) - f_3(t), \\ y_1(0) = x_{10},\ y_2(0) = x_{20}, \end{cases}$$

with $(x_{10}, x_{20}) \in \Omega$. *If the following conditions are fulfilled:*

i) $(x_1(t), x_2(t))$ *exists* $\forall t \in [0, T_f]$, *and* $(x_1(t), x_2(t)) \in \Omega,\ \forall t \in [0, T_f]$,

ii) $(y_1(t), y_2(t))$ *exists* $\forall t \in [0, T_f]$, *and* $(y_1(t), y_2(t)) \in \Omega$, *for all* $t \in [0, T_f]$,

iii) $\dfrac{\partial f_1}{\partial x_2}(x_1, x_2) \geq 0$ *and* $\dfrac{\partial f_2}{\partial x_1}(x_1, x_2) \geq 0$, $\forall (x_1, x_2) \in \Omega$,

then, $y_1(t) \leq x_1(t)$ *and* $y_2(t) \leq x_2(t)$, $\forall t \in [0, T_f]$.

Proof. Let us take $\varepsilon > 0$. We will consider that $(y_{1\varepsilon}(t), y_{2\varepsilon}(t))$ as the solution of the following Cauchy problem:

$$\begin{cases} y'_{1\varepsilon}(t) = f_1(y_{1\varepsilon}(t), y_{2\varepsilon}(t)) - \varepsilon, \\ y'_{2\varepsilon}(t) = f_2(y_{1\varepsilon}(t), y_{2\varepsilon}(t)) - f_3(t) - \varepsilon, \\ y_{1\varepsilon}(0) = x_{10} - \varepsilon, \ y_{2\varepsilon}(0) = x_{20} - \varepsilon. \end{cases}$$

If ε is small enough, then $(y_{1\varepsilon}(t), y_{2\varepsilon}(t)) \in \Omega$, and it is defined in $[0,T_f]$. Moreover,

$$(y_{1\varepsilon}(t), y_{2\varepsilon}(t)) \longrightarrow (y_1(t), y_2(t)) \ \forall t \in [0, T_f], \text{ when } \varepsilon \longrightarrow 0^+.$$

By applying the Chaplygin Lemma we obtain that $y_{1\varepsilon}(t) \leq x_1(t)$ and $y_{2\varepsilon}(t) \leq x_2(t)$, for all $t \in [0, T_f]$, and for all $\varepsilon > 0$ small enough.

To get the final result of the theorem it is enough to take the limit when $\varepsilon \longrightarrow 0^+$. □

Under the hypotheses of Theorem 2.2.1, and considering $x_1 = V$, and $x_2 = K$, we can prove $V(t) \leq V_1(t)$ and $K(t) \leq K_1(t)$ if we take:

$$\begin{aligned} f_1(V, K) &= -\lambda_1 V \log\left(\frac{V}{K}\right), \\ f_2(V, K) &= bV - \lambda_2 K - dKV^{2/3} - eKc_1, \\ f_3(t) &= eK(t)(c(t) - c_1) \geq 0 \end{aligned}$$

By using Theorems 2.1.1 and 2.2.1 we know that conditions *i)* and *ii)* of the comparison theorem are satisfied. Let us see what happens with the third hypothesis:

$$\begin{aligned} &\frac{\partial f_1}{\partial K}(V, K) = \frac{\lambda_1 V}{K} > 0 \Longleftrightarrow V, K < 0 \text{ or } V, K > 0, \\ &\frac{\partial f_2}{\partial V}(V, K) = b - \frac{2}{3} d \frac{K}{V^{1/3}} > 0 \Longleftrightarrow \frac{K}{V^{1/3}} < \frac{3}{2}\frac{b}{d}. \end{aligned}$$

We have already observed that the first condition is attained in Ω. In the case of the second condition, note that it includes in that region the nonlinear nullcline described in Theorem 2.1.1:

$$K = \frac{bV}{\lambda_2 + dV^{2/3}} \leq \frac{b}{d} V^{1/3} \leq \frac{3}{2}\frac{b}{d} V^{1/3}.$$

We should remember that solutions evolve with time following the same path as the previously mentioned nullcline. As a result, we can ensure that the condition is met if the starting point is already in that region.

If we want to prove $V_2(t) \leq V(t)$ and $K_2(t) \leq K(t)$, we will consider the alternative $-V(t) \leq -V_2(t)$ and $-K(t) \leq -K_2(t)$, and then

$$\begin{aligned} f_1(V, K) &= \lambda_1 V \log\left(\frac{V}{K}\right), \\ f_2(V, K) &= -bV + \lambda_2 K + dKV^{2/3} + eKc_2, \\ f_3(t) &= eK(t)(c_2 - c(t)) \geq 0 \end{aligned}$$

where the hypothesis of the comparison theorem are satisfied as before.

Now, we will show an example where we can observe how the limit of the tumor volume is kept between the limits expressed in Theorem 2.2.1.

Example 2.2.3. *Let us take $c(t)$ whose expression are obtained in the following chapter (see (3.2)), with $\lambda = 0.38$ days^{-1}. We study three cases, that take different N, $d = (d_1, ..., d_N)$ and $t = (t_1, ..., t_N)$ values. We also consider the maximum and minimum values of $c(t)$ in each situation. They are all displayed in the following table:*

Treatment	N	Δt **(days)**	d **(mg/kg)**	c_{min} **(mg/L)**	c_{max} **(mg/L)**
1	53	(1.96, 2.61,..., 2.61)	(12.46, 10,..., 10)	5.74	15.74
2	106	(1.12, 1.32,..., 1.32)	(23.45, 10,..., 10)	15.32	25.32
3	135	(0.97, 1.03,..., 1.03)	(30, 10,... 10)	20.74	30.74

Table 2.1: Different treatments according to the quantities N, d and t for $c(t)$. It is also included both the superior and the inferior levels of $c(t)$.

Note that we have written the values of Δt instead of the t vector, but it is just for simplicity reasons. We take $t_1 = 0$, and then $t_2 = \Delta t_1$, $t_3 = \Delta t_1 + \Delta t_2$,..., $t_N = \sum_{i=1}^{N-1} \Delta t_i$. This criterion is used throughout the whole work.

The following graphs represent the drug concentration in the body for the different treatments presented above. Note that the maximum and minimum values are the ones included in Table 2.1:

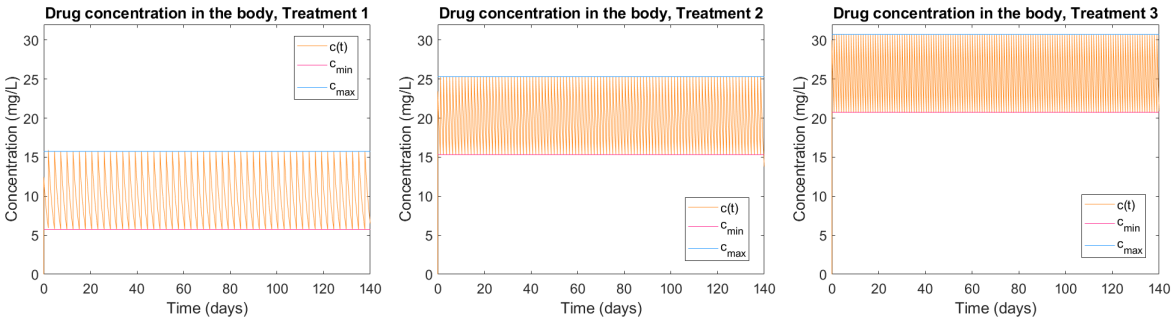


Figure 2.4: Drug concentration in the body $c(t)$ with c_{min} and c_{max} limits for the treatments presented in Table 2.1.

Although it may not seem so, let us note that $c(t)$ is a piecewise continuous function, with finite jump discontinuities at each t_i.

Now, let us substitute $c(t)$ into the Cauchy problem (2.11), and c_{min} and c_{max} into Equation (2.12), where b, d, e and λ_2 take the values expressed in Example 2.3, for each treatment. We can observe the evolution of the tumor's volume with the three concentrations in each case.

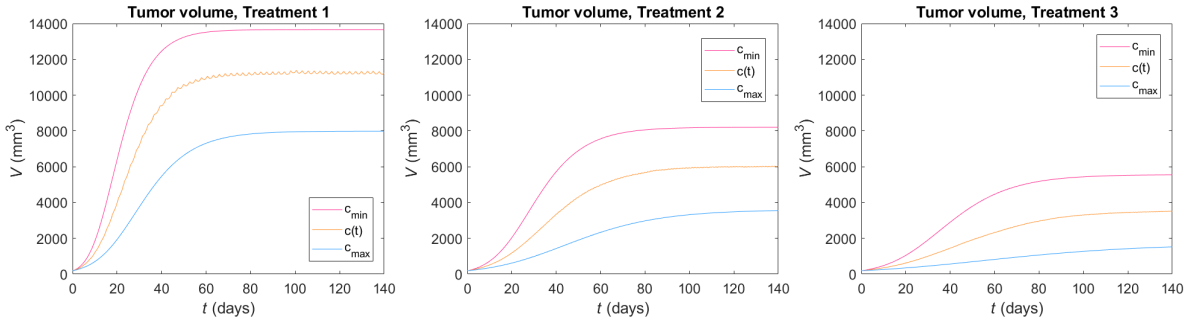


Figure 2.5: Evolution of the tumor's volume with time when the drug concentration $c(t)$ is between c_{min} and c_{max} limits for the treatments presented in Table 2.1.

In Figure 2.5, we have illustrated an example of case i) of Theorem 2.2.1, because we can observe that there is no limit for the volume and that both the superior and inferior limits are between the values expressed there.

Moreover, if we decrease the elapsed times between doses while having fixed the dosages and the final day of treatment (in this case day 140th), there is a noticeable decrease in the final tumor's volume. It is consistent with the fact that we are applying a higher quantity of drug in the same period of time.

Chapter 3

Drug concentration

Once we have studied the dynamics of the tumor under treatment, it is necessary to formulate the expression of the drug concentration in the body. To avoid large fluctuations in the tumor volume, we will obtain the schedules of the treatments that would keep it in a quasi-steady state through an optimization problem. We will also study different particular cases of significant practical interest.

3.1. Formulating the drug concentration function

Once a drug is administered to a patient, its body interacts with it by activating drug-elimination biological processes. As a result, the concentration of the drug c varies with time. In addition, when a patient undergoes a treatment, it usually consists in the application of certain (let's suppose $N > 0$) number of doses $\{d_i\}_{i\in\{1,\dots,N\}} \subset [0, +\infty)$ at times $\{t_i\}_{i\in\{1,\dots,N\}} \subset [0, +\infty)$, respectively, which should also be considered when formulating the drug concentration in the body. Then, we will consider the following Cauchy problem:

$$\begin{cases} c'(t) = -\lambda c(t) + \sigma \displaystyle\sum_{i=1}^{N} d_i \delta(t - t_i), \\ c(0) = 0 \end{cases} \tag{3.1}$$

where $\lambda > 0$ represents the clearance or elimination rate, i.e., the rate at which the body eliminates the drug, and the second term considers each drug administration, with $\sigma > 0$. The coefficient σ depends on the drug itself, the patient, and the tumor. In this case, $\sigma = \frac{\beta}{V_D}$, where V_D is the volume of distribution of the drug (in L) and β is the patient weight (in kg). For the sake of simplicity and without loss of generality, throughout this work we will consider $\sigma = 1$ kg/L. In the general case, expressions where d_i appears should be replaced by σd_i. Once more, let us note that the concentration is not a continuous function and that (3.1) is formulated in the sense of distributions due to the presence of Dirac deltas.

In order to solve the Cauchy problem, we can apply both the definition and some properties of Laplace transforms. Firstly, by applying Laplace transform, we get[5]

$$s\mathcal{L}[c(t)](s) = -\lambda \mathcal{L}[c(t)](s) + \sum_{i=1}^{N} d_i e^{-st_i} \mathcal{L}[\delta(t - t_i)](s),$$

where

$$\mathcal{L}[\delta(t - t_i)](s) = \int_0^{\infty} e^{-st} \delta(t - t_i) dt = e^{-st_i}.$$

Once we rearrange the terms and substitute the latest result we get

$$\mathcal{L}[c(t)](s) = \frac{1}{s+\lambda}\sum_{i=1}^{N} d_i e^{-st_i} = \sum_{i=1}^{N} d_i e^{-st_i}\mathcal{L}[e^{-\lambda t}](s) = \sum_{i=1}^{N} d_i \mathcal{L}[g_i(t)](s),$$

where

$$g_i(t) = \begin{cases} 0 & 0 \leq t \leq t_i, \\ e^{-\lambda(t-t_i)} & t > t_i. \end{cases}$$

By applying inverse Laplace transform we finally obtain

$$c(t) = \sum_{i=1}^{N} d_i e^{-\lambda(t-t_i)} = \begin{cases} 0 & t \in [0, t_1), \\ e^{-\lambda t} d_1 e^{\lambda t_1} & t \in [t_1, t_2), \\ e^{-\lambda t}(d_1 e^{\lambda t_1} + d_2 e^{\lambda t_2}) & t \in [t_2, t_3), \\ \vdots & \vdots \\ e^{-\lambda t}(d_1 e^{\lambda t_1} + d_2 e^{\lambda t_2} + ... + d_N e^{\lambda t_N}) & t > t_N. \end{cases} \tag{3.2}$$

3.2. Keeping the drug concentration in a steady state

We would desire to reach a steady-state for the concentration of the drug in the patient. It would help to have the upper and lower limits of both the volume and the carrying capacity inside a shorter interval, as we got in Theorem 2.2.1. Therefore, we could get some guidance about how much the maximum tumor volume can be reduced if the drug is applied and how much time it would take to reach it.

The next problem is presented in order to determine the minimization of the integral of the quadratic difference between the concentration function $c(t)$ and an ideal constant one c_d in an interval of time $[0, T_f]$[1]. We have a fixed maximum total dose $D > 0$, which has to be divided (it is not necessary to use the total D quantity) into N doses $\{d_i\}_{i=1}^{N}$. Each of these doses has to be larger than a quantity $d_{min} > 0$ and smaller than $d_{max} > 0$, both for treatment effectiveness and toxicity reasons, respectively. As a result, we have an upper bound in the number of doses N, such that $N \leq \frac{D}{d_{min}}$.

In addition, all these doses have to be taken in times $0 \leq t_1 < t_2 < ... < t_N \leq T_f$ whose elapsed times of application should be larger than γ days, as it is more practical for the patient and also to avoid toxic effects. The value of γ can be fixed in each treatment.

$$(P_1) \begin{cases} \min\limits_{N\in\mathbb{N},\{d_i\}_{i=1}^{N},\{t_i\}_{i=1}^{N}\subset\mathbb{R}^+} & J(N, d_1, ..., d_N, t_1, ...t_N) \\ \text{subject to} & t_i + \gamma \leq t_{i+1}, \ \forall i \in \{1, ...N-1\} \\ & t_N \leq T_f \\ & d_{min} \leq d_i \leq d_{max}, \ \forall i \in \{1, ...N\} \\ & \sum\limits_{i=1}^{N} d_i \leq D \end{cases}$$

where the objective function J is described as follows,

$$J(N, d_1, ..., d_N, t_1, ...t_N) = \int_0^{T_f} (c(t) - c_d)^2 dt = \int_0^{T_f} c^2(t)dt - 2c_d \int_0^{T_f} c(t)dt + c_d^2 T_f.$$

Note that the constant desired drug level c_d should take a reasonable value. If it is too high, then we are limited by the maximum total and individual dose limits, D, d_{max}, and d_{min} (see Example 3.2.1).

We have to calculate each integral in order to get an expression that can be used to formulate the objective function of (P_1) in terms of its variables. To do so, we will proceed with inductive processes.

Firstly, we will expand the integral of the quadratic concentration function. To do so, let us suppose we have $N = 2$, i.e, the treatment only consists of two doses, applied at t_1 and $t_2 < T_f$. Then,

$$\begin{aligned}\int_0^{T_f} c^2(t)dt &= \int_{t_1}^{t_2} e^{-2\lambda(t-t_1)}d_1^2dt + \int_{t_2}^{T_f} e^{-2\lambda t}(d_1e^{\lambda t_1} + d_2e^{\lambda t_2})^2dt \\ &= \frac{1}{2\lambda}\left[\left(d_1^2e^{2\lambda t_1}\right)\left(e^{-2\lambda t_1} - e^{-2\lambda t_2}\right) + \left(d_1^2e^{2\lambda t_1} + d_2^2e^{2\lambda t_2} + 2d_1d_2e^{\lambda(t_1+t_2)}\right)\cdot\right. \\ &\quad \left.\cdot\left(e^{-2\lambda t_2} - e^{-2\lambda T_f}\right)\right] \\ &= \frac{1}{2\lambda}\left[d_1^2(1 - e^{2\lambda(t_1-T_f)}) + d_2^2(1 - e^{2\lambda(t_2-T_f)}) + 2d_1d_2(e^{\lambda(t_1-t_2)} - e^{\lambda(t_1+t_2-2T_f)})\right].\end{aligned}$$

If we consider $N = 3$, then we have

$$\begin{aligned}\int_0^{T_f} c^2(t)dt &= \int_{t_1}^{t_2} e^{-2\lambda(t-t_1)}d_1^2dt + \int_{t_2}^{t_3} e^{-2\lambda t}(d_1e^{\lambda t_1} + d_2e^{\lambda t_2})^2dt + \int_{t_3}^{T_f} e^{-2\lambda t}(d_1e^{\lambda t_1} + \\ &\quad + d_2e^{\lambda t_2} + d_3e^{\lambda t_3})^2dt \\ &= \frac{1}{2\lambda}\left[\left(d_1^2e^{2\lambda t_1}\right)\left(e^{-2\lambda t_1} - e^{-2\lambda t_2}\right) + \left(d_1^2e^{2\lambda t_1} + d_2^2e^{2\lambda t_2} + 2d_1d_2e^{\lambda(t_1+t_2)}\right)\cdot\right. \\ &\quad \cdot\left(e^{-2\lambda t_2} - e^{-2\lambda T_f}\right) + (d_1^2e^{2\lambda t_1} + d_2^2e^{2\lambda t_2} + d_3^2e^{2\lambda t_3} + 2d_1d_2e^{\lambda(t_1+t_2)} + 2d_1d_3\cdot \\ &\quad \left.\cdot e^{\lambda(t_1+t_3)} + 2d_2d_3e^{\lambda(t_2+t_3)})(e^{-2\lambda t_3} - e^{-2\lambda T_f})\right] \\ &= \frac{1}{2\lambda}\left[d_1^2(1 - e^{2\lambda(t_1-T_f)}) + d_2^2(1 - e^{2\lambda(t_2-T_f)}) + d_3^2(1 - e^{2\lambda(t_3-T_f)}) + 2d_1d_2\cdot\right. \\ &\quad \cdot(e^{\lambda(t_1-t_2)} - e^{\lambda(t_1+t_2-2T_f)}) + 2d_1d_3(e^{\lambda(t_1-t_3)} - e^{\lambda(t_1+t_3-2T_f)}) + 2d_2d_3(e^{\lambda(t_2-t_3)} - \\ &\quad \left.- e^{\lambda(t_2+t_3-2T_f)})\right].\end{aligned}$$

So then, for a general N we have

$$\int_0^{T_f} c^2(t)dt = \frac{1}{2\lambda}\left[\sum_{i=1}^{N} d_i^2(1 - e^{2\lambda(t_i-T_f)}) + 2\sum_{k=1}^{N-1}\sum_{j=k+1}^{N} d_jd_k(e^{\lambda(t_k-t_j)} - e^{\lambda(t_j+t_k-2T_f)})\right].$$

We will use the same method to expand the integral of the concentration function. Now, considering N=2:

$$\begin{aligned}\int_0^{T_f} c(t)dt &= \int_{t_1}^{t_2} e^{-\lambda(t-t_1)}d_1dt + \int_{t_2}^{T_f} e^{-\lambda t}(d_1e^{\lambda t_1} + d_2e^{\lambda t_2})dt \\ &= \frac{1}{\lambda}\left[d_1e^{\lambda t_1}\left(e^{-\lambda t_1} - e^{-\lambda t_2}\right) + \left(d_1e^{\lambda t_1} + d_2e^{\lambda t_2}\right)\left(e^{-\lambda t_2} - e^{-\lambda T_f}\right)\right] \\ &= \frac{1}{\lambda}\left[d_1(1 - e^{\lambda(t_1-T_f)}) + d_2(1 - e^{\lambda(t_2-T_f)})\right].\end{aligned}$$

If we suppose the treatment consists of three doses:

$$\begin{aligned}\int_0^{T_f} c(t)dt &= \int_{t_1}^{t_2} e^{-\lambda(t-t_1)}d_1dt + \int_{t_2}^{t_3} e^{-\lambda t}(d_1e^{\lambda t_1} + d_2e^{\lambda t_2})dt + \int_{t_3}^{T_f} e^{-\lambda t}(d_1e^{\lambda t_1}+ \\ &\quad + d_2e^{\lambda t_2} + d_3e^{\lambda t_3})dt \\ &= \frac{1}{\lambda}\left[d_1e^{\lambda t_1}\left(e^{-\lambda t_1} - e^{-\lambda t_2}\right) + \left(d_1e^{\lambda t_1} + d_2e^{\lambda t_2}\right)\left(e^{-\lambda t_2} - e^{-\lambda t_3}\right) + (d_1e^{\lambda t_1}+ \right. \\ &\quad \left. + d_2e^{\lambda t_2} + d_3e^{\lambda t_3})(e^{-\lambda t_3} - e^{-\lambda T_f})\right] \\ &= \frac{1}{\lambda}\left[d_1(1 - e^{\lambda(t_1-T_f)}) + d_2(1 - e^{\lambda(t_2-T_f)}) + d_3(1 - e^{\lambda(t_3-Tf)})\right].\end{aligned}$$

Proceeding inductively, for a general N we obtain:

$$\int_0^{T_f} c(t)dt = \frac{1}{\lambda}\sum_{i=1}^{N} d_i(1 - e^{\lambda(t_i-T_f)}).$$

Therefore, we get the following expression for the objective function of (P_1):

$$\begin{aligned}J(N, d_1, ..., d_N, t_1, ...t_N) = \frac{1}{2\lambda}\left[\sum_{i=1}^{N} d_i^2(1 - e^{2\lambda(t_i-T_f)}) + 2\sum_{k=1}^{N-1}\sum_{j=k+1}^{N} d_jd_k(e^{\lambda(t_k-t_j)}- \right. \\ \left. -e^{\lambda(t_j+t_k-2T_f)})\right] - \frac{2c_d}{\lambda}\sum_{i=1}^{N} d_i(1 - e^{\lambda(t_i-T_f)}) + c_d^2T_f,\end{aligned} \tag{3.3}$$

which can also be expressed in matrix form as

$$J = \frac{1}{2\lambda}d^THd - \frac{2c_d}{\lambda}p^Td + c_d^2T_f, \tag{3.4}$$

where $d = (d_1, d_2, ..., d_N)^T$ and p is a vector whose components are $p(i) = 1 - r_i$, with $r_i = e^{\lambda(t_i-T_f)}$, $\forall i \in \{1, ..., N\}$. Moreover, H is a symmetric matrix, where

$$H(i, j) = \frac{r_i}{r_j} - r_ir_j, \quad H(j, i) = H(i, j), \quad \forall i, j \text{ such that } i \leq j \leq N. \tag{3.5}$$

H matrix is included in the class of generator representable semiseparable matrices. They are those symmetric matrices whose upper and lower triangular parts are given by the product of two vectors. These matrices have a surprising property: their inverses are tridiagonal matrices, where both the superdiagonal and the subdiagonal have the same values. See [14] for a proof of this fact.

Let us explore an example by considering different elimination rates so that we can observe the importance of taking an adequate c_d in each case.

In order to solve numerically the optimization system (P_1^N) and those that will be presented throughout the work, MATLAB programs have been developed. In particular, we have used the *fmincon* function to solve them. It is a nonlinear programming solver that attempts to find the minimum of a multivariate function under certain equality, inequality, and boundary constraints by giving an initial value. Note that in this case, although the objective function is quadratic, we cannot use the *quadprog* function because time variables are within exponential terms.

Example 3.2.1. *Given $D = 300$ mg/kg, $d_{min} = 10$ mg/kg, $d_{max} = 30$ mg/kg, $\gamma = 0.3$ days and $T_f = 30$ days. We will solve (P_1) for different elimination rates λ.*

We will start by considering a very short elimination rate, i.e., a situation in which the drug administered remains in the patient's body almost in its totality. The results with ideal constant concentration of $c_d = 100$, 200 and 300 mg/L, respectively, are graphically expressed as follows:

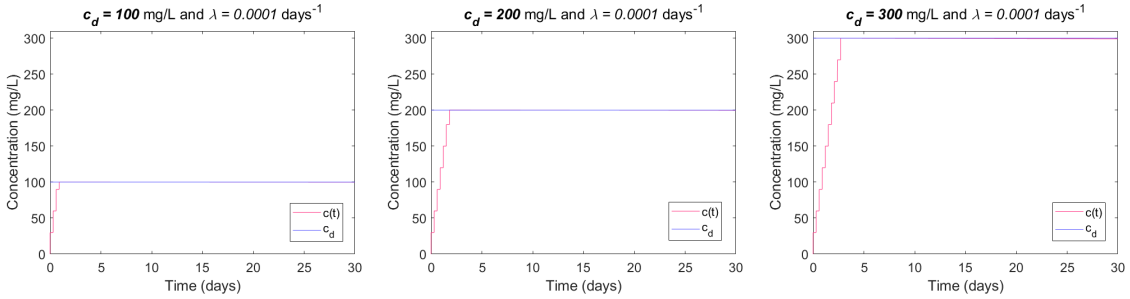


Figure 3.1: Drug concentration in the body with $\lambda = 0.0001$ days^{-1} for different c_d.

Note that in this case, c_d can take the value of the maximum cumulative dosage D, and the concentration in the body is able to reach that quantity. The best strategy in order to reduce the difference between the concentration in the body and the ideal one is to administer all the doses at the start of the treatment, with the minimum elapsed time γ. They take the maximum individual dose value d_{max} until $c_d - c(t) < 30$ mg/L, and then the last dose is equal to the difference between both quantities. Moreover, as the elimination rate is almost null, once c_d is reached, there is no need to take more doses. Therefore, the total dosage administered corresponds to c_d in each case, so if we have an ideal constant concentration larger than 300 mg/L, the concentration in the body will not be able to reach it as it has already consumed the maximum cumulative dosage.

Let us now consider the opposite situation in which the patient eliminates the drug very fast ($\lambda = 10$ days^{-1}). The following figure represents three cases, with $c_d = 10$, 12 and 14 mg/L, respectively:

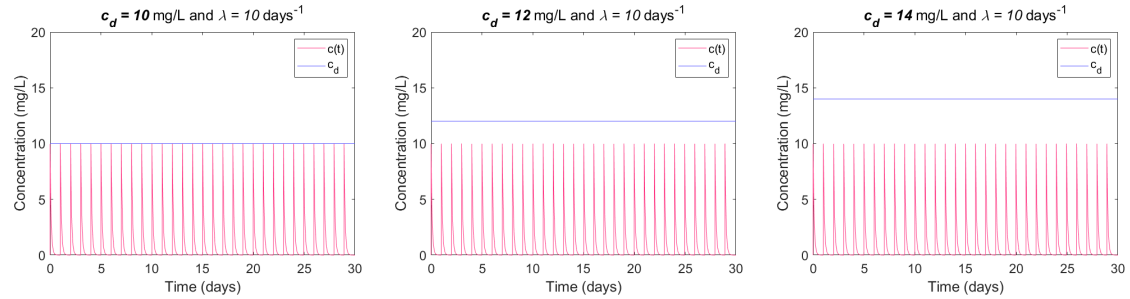


Figure 3.2: Drug concentration in the body with $\lambda = 10$ days^{-1} for different c_d.

Now, we can observe that there is no constant concentration over 10 mg/L such that the drug concentration in the body can be around it (considering a c_d below 10 mg/L could have no notorious effect on the patient's tumor). In the three cases the best option is to administer the maximum number of d_{min} doses possible (we are limited by the quantity $\frac{D}{d_{min}}$) and equally spaced along the 30 days of treatment. It is noteworthy to mention that it is spent the whole cumulative dosage possible in order to reach the ideal concentration level, but λ makes it not possible.

Finally, if we consider an intermediate elimination rate of $\lambda = 0.38$ days^{-1}, the graphs of Figure 3.3 are obtained with $c_d = 20$, 30 and 40 mg/L.

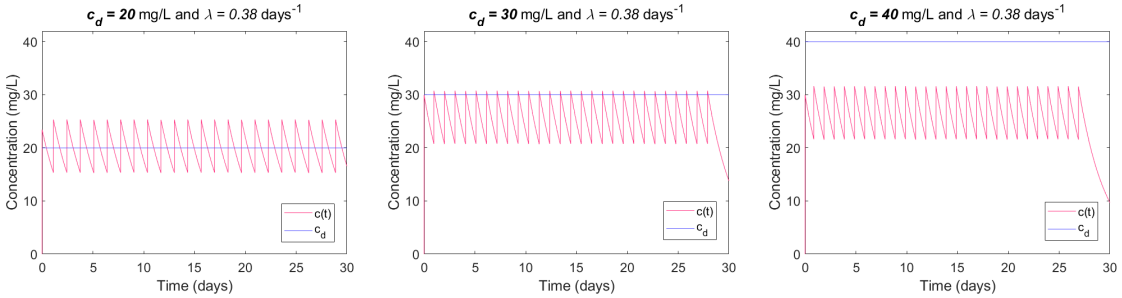


Figure 3.3: Drug concentration in the body with $\lambda = 0.38$ days^{-1} for different c_d.

By looking at the graphs, we can observe that the most efficient treatment consists of taking an initial large dose so that a high concentration is reached and then keeping it constant. In the case of $c_d = 20$ mg/L, the concentration is kept around the ideal level, but when c_d increases, it is not possible to reach it, and a tail appears. It is larger as c_d increases.

In view of Example 3.2.1, we can see that c_d can take values from d_{min}, considering this level as the minimum possible to observe changes in the tumor, to D. However, the value should be reasonable according to the drug we are dealing with.

Along the following subsections, we will analyze different situations related to the choice of the ideal concentration level.

3.2.1. Having a fixed ideal constant concentration

We will first consider that the ideal constant concentration c_d is fixed, and we will observe the behavior of both the dosage time spacing and the doses when the number of doses $N \in \left[1, \frac{D}{d_{min}}\right] \cap \mathbb{N}$ is fixed. Note that the problem we want to solve now is not (P_1) but a particular case of it:

$$(P_1^N) \begin{cases} \min\limits_{\{d_i\}_{i=1}^N, \{t_i\}_{i=1}^N \subset \mathbb{R}^+} & J^N(d_1, ..., d_N, t_1, ...t_N) = \displaystyle\int_0^{T_f} (c(t) - c_d)^2 dt \\ \text{subject to} & t_i + \gamma \leq t_{i+1}, \ \forall i \in \{1, ...N-1\} \\ & t_N \leq T_f \\ & d_{min} \leq d_i \leq d_{max}, \ \forall i \in \{1, ...N\} \\ & \displaystyle\sum_{i=1}^N d_i \leq D \end{cases}$$

Theorem 3.2.1. *There exists at least one solution for problem (P_1^N).*

Proof. Let's consider K the set of restrictions of (P_1^N), such that

$$K = \Bigg\{ (d,t) \in \mathbb{R}^{2N} : \sum_{i=1}^N d_i - D \leq 0, d_{min} \leq d_i \leq d_{max}, \forall i \in \{1, ..., N\}, \\ t_i + \gamma \leq t_{i+1} \ \forall i \in \{1, ...N-1\}, t_1 \geq 0, t_N \leq T_f \Bigg\}.$$

Be the linear, and therefore continuous functions:

$$\begin{aligned}
g_i : \mathbb{R}^{2N} &\longrightarrow \mathbb{R} \text{ such that } g_i(d,t) = d_i, \ \forall i \in \{1,...,N\},\\
g_{N+1} : \mathbb{R}^{2N} &\longrightarrow \mathbb{R} \text{ such that } g_{N+1}(d,t) = \sum_{i=1}^{N} d_i - D,\\
\tilde{g}_i : \mathbb{R}^{2N} &\longrightarrow \mathbb{R} \text{ such that } \tilde{g}_i(d,t) = t_{i+1} - t_i, \ \forall i \in \{1,...,N-1\},\\
\tilde{g}_{N+1} : \mathbb{R}^{2N} &\longrightarrow \mathbb{R} \text{ such that } \tilde{g}_{N+1}(d,t) = t_1,\\
\tilde{g}_{N+2} : \mathbb{R}^{2N} &\longrightarrow \mathbb{R} \text{ such that } \tilde{g}_{N+2}(d,t) = t_N.
\end{aligned}$$

Set K can be written then as

$$K = \left[\bigcap_{i=1}^{N} g_i^{-1}([d_{min}, d_{max}])\right] \bigcap g_{N+1}^{-1}((-\infty, 0]) \bigcap \left[\bigcap_{i=1}^{N-1} \tilde{g}_i^{-1}([\gamma, +\infty))\right] \bigcap \bigcap \tilde{g}_{N+1}^{-1}([0, +\infty)) \bigcap \tilde{g}_{N+2}^{-1}((-\infty, T_f]).$$

Since the preimage of continuous functions on a closed set is closed, then so it is K because it is the intersection of closed sets. Moreover, all the variables of the problem are bounded, so K is bounded too. Finally, as the objective function of (P_1^N), J^N, is continuous, and K is compact, we are under the hypotheses of the Weierstrass' theorem, so there is at least one solution of problem (P_1^N). □

As there exists a solution of problem (P_1^N), with $N \in \left[1, \frac{D}{d_{min}}\right] \cap \mathbb{N}$, then there should be at least one N in this finite set that makes J minimal. In order to observe this fact, we have depicted the next figure, which represents the objective function J^N for each N in the interval $N \in [10, 30] \cap \mathbb{N}$, when c_d takes values 12, 20 and 28 mg/L. The other quantities of problem (P_1^N) are those stated in Example 3.2.2.

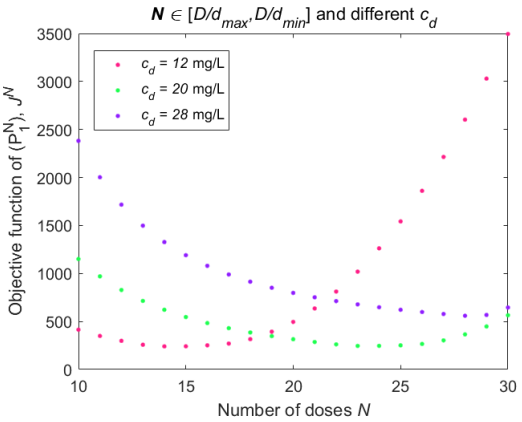


Figure 3.4: Objective function of (P_1^N) as a function of the number of doses N, when $c_d = 12$, 20 and 28 mg/L.

Note that in these particular cases, there is only one N that makes J^N minimal for each c_d. In addition, N increases as it does c_d. In particular, when c_d takes the smallest value, the minimum value of the objective function is reached when $N = 14$. In this case, the J^N function takes low values when N is small, and once it increases, the function increases as it is easy to surpass the ideal constant concentration with many doses.

By contrast, when c_d takes the highest value, we have the minimum value of the objective function when the number of doses is 28. Moreover, J^N increases notably as the N decreases because with fewer doses, it is not possible to reach the steady-state around the ideal constant concentration. Finally, when $c_d = 20$ mg/L, the situation is similar to the previous one, but it is less steep.

The next example shows the solutions of problem (P_1^N) for different fixed N in the particular case of $c_d = 20$ mg/L. Instead of displaying the times, we show the elapsed times between dosages, as we explained in Example 2.2.3.

Example 3.2.2. *Be $D = 300$ mg/kg the maximum total dosage, $d_{min} = 10$ mg/kg and $d_{max} = 30$ mg/kg. Be $c_d = 20$ mg/L and $\lambda = 0.38$ day^{-1}. Let us assume that the treatment can last 30 days at most, and the elapsed time between doses should be at least $\gamma = 0.3$ days. Then, we can study the effect of the number of doses of a treatment on (P_1^N) problem.*

Treatment	$\boldsymbol{J^N}$ **(days mg^2 L^{-2})**	$\boldsymbol{\Delta t}$ **(days)**	**Doses (mg/kg)**
18 doses	385.66	(1.67, 1.67,..., 1.67)	(26.13, 12.26,..., 12.26)
21 doses	286.27	(1.43, 1.43,..., 1.43)	(25.30, 10.60,..., 10.60)
22 doses	261.51	(1.36, 1.36,..., 1.37)	(25.07, 10.14,..., 10.14)
23 doses	**245.28**	**(1.12, 1.32,..., 1.32)**	**(23.45, 10,..., 10)**
24 doses	246.12	(1.10, 1.32,..., 1.32)	(23.29, 10,..., 10)
25 doses	251.24	(0.30, 1.26,1.31,..., 1.31)	(16.97, 10,..., 10)
27 doses	303.22	(0.30, 0.83, 1.25,..., 1.25, 0.93, 0.30)	(13.89, 10,..., 10)

Table 3.1: Results of the minimization of (P_1^N) for different number of doses N with $c_d = 20$ mg/L and $t_1 = 0$.

As we can observe from Table 3.1, the solution usually has a loading dose larger than the rest of them, which allows the concentration to reach the level of the ideal constant concentration c_d. Then, the optimal strategy is to keep the doses constant, and they are d_{min} when the number of doses is high enough. We can also see that the number of doses that makes the objective function J minimal is 23. When it happens, the elapsed time between dosages is smaller at first, and then it gets a constant higher value. It is also the case of the treatment of 24 doses. Before that number of doses is reached, the elapsed time always takes the same value, and when the number of doses is too high for $c_d = 20$ mg/L, which happens with $N = 27$, the elapsed time's strategy changes to try to minimize the problem.

Once we have studied the behavior of both the elapsed times and the doses, we can try to guess those values and also the number of doses (heuristic solution) in the problems in which we already know d_{min}, T_f, λ and c_d. It will allow us to obtain an approximated solution without needing to use a mathematical software.

Let us start by finding a formula for the maximum possible number of doses. We have the constraint of the maximum total administered drug and the minimum dose, and also the one of the minimum elapsed time and T_f. Therefore,

$$N_{max} = \min\left\{ \left\lfloor \frac{D}{d_{min}} \right\rfloor, \left\lceil \frac{T_f}{\gamma} \right\rceil \right\}.$$

Before guessing N, we have to observe its behavior when c_d, T_f, λ and d_{min} vary. Let us take the following example:

Example 3.2.3. *Under the hypothesis of Example 3.2.2, we can analyze the effect of some quantities in the optimal N by changing only one of them in each case:*

i) If we consider $\lambda = 0.25$ days^{-1}, then $N = 15$, and if $\lambda = 0.38$ days^{-1}, $N = 23$.

ii) Let us take $c_d = 10$ mg/L and $c_d = 20$ mg/L. In the first case we get $N = 12$, while in the second one, $N = 23$.

iii) We get $N = 46$ if we suppose that $d_{min} = 5$ mg/kg, and $N = 29$ if $d_{min} = 8$ mg/kg.

iv) Be $T_f = 20$ days, and also $T_f = 24$ days. In the first variant, N took value 17, and in the second one, $N = 20$.

We can observe that the ratio of λ, T_f, and c_d to N is kept constant (considering a small discrepancy because of the integer constraint of N) when the values of the first quantities are changed. In the case of d_{min} it is the product with N the constant quantity. Therefore, we can already establish that

$$N = \max\left\{\min\left\{\frac{\lambda T_f c_d}{d_{min}}, N_{max}\right\}, 1\right\}. \tag{3.6}$$

Once we have obtained our estimation of N, and we consider constant doses equal to d_{min} except for the first one (if λ and c_d take reasonable values), that is higher than c_d, and certain constant elapsed times, we can compare it with the results obtained numerically. If we take different values of c_d and the rest of the quantities are as expressed in Example 3.2.2, we can complete the following table:

	$c_d = 10$ mg/L	$c_d = 20$ mg/L
Estimated	295.26	268.84
Numerically	238.13	245.28

Table 3.2: Values taken by the objective function of (P_1), J (in days mg^2 L^{-2}), for different c_d when the number of doses, the doses themselves and the dosage elapsed time were both estimated and calculated numerically.

The concentration of the drug in the body by calculating the optimal treatment with both methods are represented in Figure 3.5.

When $c_d = 10$ mg/L and $c_d = 20$ mg/L, the objective function has a lower value if the treatment is calculated numerically. Nevertheless, we can see that the difference between both methods is not very notorious.

However, when if c_d is too high, the solutions that we propose could be not admissible (for example, because the total dosage quantity exceeds the maximum possible one). In this situation, we can add additional constraints to our heuristic reasoning to get closer to the original problem.

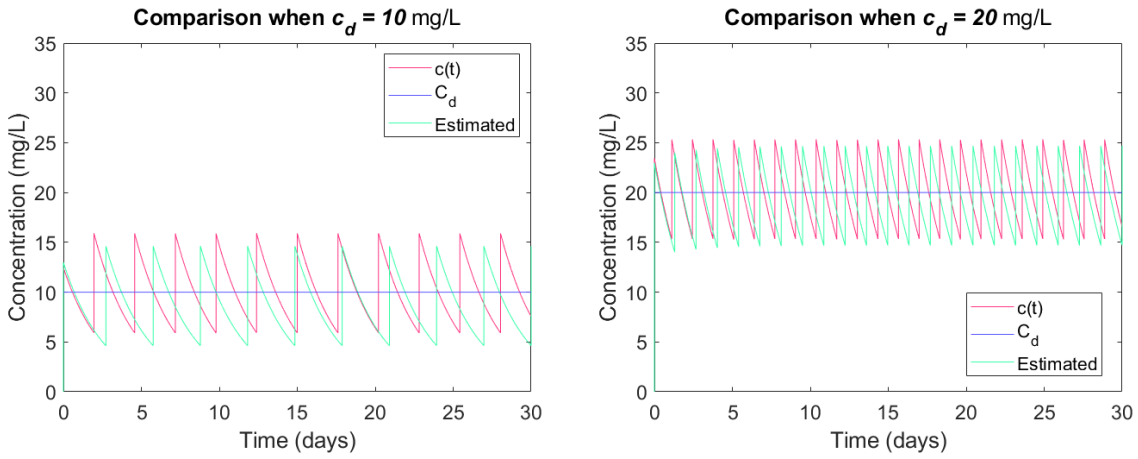


Figure 3.5: Concentration as a function of time when the treatment is estimated (green) and also when it is calculated numerically (red).

To sum up, the solution to problem (P_1) can be acceptably estimated with our method, but in general, it will not be the optimal one. In addition, the results obtained are better when there is no extra condition that we should consider, which happens when the constant ideal concentration c_d is too high.

3.2.2. Looking for the optimal constant drug level

Note that J, expressed in Equation (3.4), has a quadratic expression with respect to the variable c_d. If we fix N, the doses $\{d_i\}_{i\in\{1,\dots,N\}}$ and the times $\{t_i\}_{i\in\{1,\dots,N\}}$, we can look for the c_d that makes J minimum. It is important in order to get a concentration as closer to as constant as possible, which will reduce the final fluctuations in the characteristics of the tumor:

$$\frac{\partial J}{\partial c_d} = 2c_d T_f - \frac{2}{\lambda} p^T d = 0 \quad \Longrightarrow \quad c_d^{min} = \frac{1}{T_f \lambda} \sum_{i=1}^{N} d_i (1 - e^{\lambda(t_i - T_f)}). \tag{3.7}$$

We can ensure that function J has a minimum for that c_d^{min} because the second derivative of J with respect to c_d is positive $(2T_f > 0)$.

Now, by substituting expression (3.7) into Equation (3.3), we get

$$\begin{aligned} J_{c_d^{min}}(N, d_1, \dots, d_N, t_1, \dots t_N) = \frac{1}{2\lambda} \Bigg[\sum_{i=1}^{N} d_i^2 (1 - e^{2\lambda(t_i - T_f)}) + 2 \sum_{k=1}^{N-1} \sum_{j=k+1}^{N} d_j d_k (e^{\lambda(t_k - t_j)} - \\ - e^{\lambda(t_j + t_k - 2T_f)}) \Bigg] - \frac{1}{\lambda^2 T_f} \left(\sum_{i=1}^{N} d_i (1 - e^{\lambda(t_i - T_f)}) \right)^2, \end{aligned} \tag{3.8}$$

which can be formulated matricially as

$$J_{c_d^{min}} = \frac{1}{2\lambda} d^T \left(H - \frac{2}{\lambda T_f} \tilde{H} \right) d,$$

where matrix H has already been defined and $\tilde{H}$ is such that

$$\tilde{H}(i,j) = (1 - r_i)(1 - r_j), \quad \forall i, j \in \{1, \dots, N\}.$$

Let us focus again on the objective function $J_{c_d^{min}}$ of the general case (Equation (3.8)), and we fix N, as we did in the previous section, such that

$$(P^N_{1,c_d^{min}}) \begin{cases} \min\limits_{\{d_i\}_{i=1}^N,\{t_i\}_{i=1}^N \subset \mathbb{R}^+} & J^N_{c_d^{min}}(d_1,...,d_N,t_1,...t_N) \\ \text{subject to} & t_i + \gamma \leq t_{i+1},\ \forall i \in \{1,...N-1\} \\ & t_N \leq T_f \\ & d_{min} \leq d_i \leq d_{max},\ \forall i \in \{1,...N\} \\ & \sum\limits_{i=1}^{N} d_i \leq D \end{cases}$$

The objective $J^N_{c_d^{min}}$ function is continuous (the expression is $J_{c_d^{min}}$ but with N fixed), as it is composed of sums and products of continuous functions. In addition, the restriction set is compact, as we have proved in Theorem 3.2.1. Therefore, there exist at least one solution to this problem.

We can look now for solutions of problem $(P^N_{1,c_d^{min}})$ for different number of doses. As a result, we will be able to check which treatment would be the optimum one among a list of them that have the same conditions of d_{min}, d_{max}, D, λ, and T_f. In each case, we will provide the ideal constant concentration obtained by using Equation (3.7).

However, it is not the right criterion to choose the optimum treatment just by comparing the objective functions of $(P^N_{1,c_d^{min}})$. When we are considering very low Ns, the optimum constant concentration will also be low, which would automatically imply a smaller $J^N_{c_d^{min}}$. For that reason, it is better to compare the different options by using relative errors E_R, such that $E_R = J^N_{c_d^{min}}/(c_d^{min})^2$.

Example 3.2.4. *Let us take D, d_{min}, d_{max}, λ, T_f and γ as expressed in Example 3.2.2. We can observe the effect of the number of doses in the objective function of $(P^N_{1,c_d^{min}})$ in Figure 3.6. We have also performed the optimum constant concentration in each case by using Equation* (3.7)*, so that we could plot the relative errors for each N.*

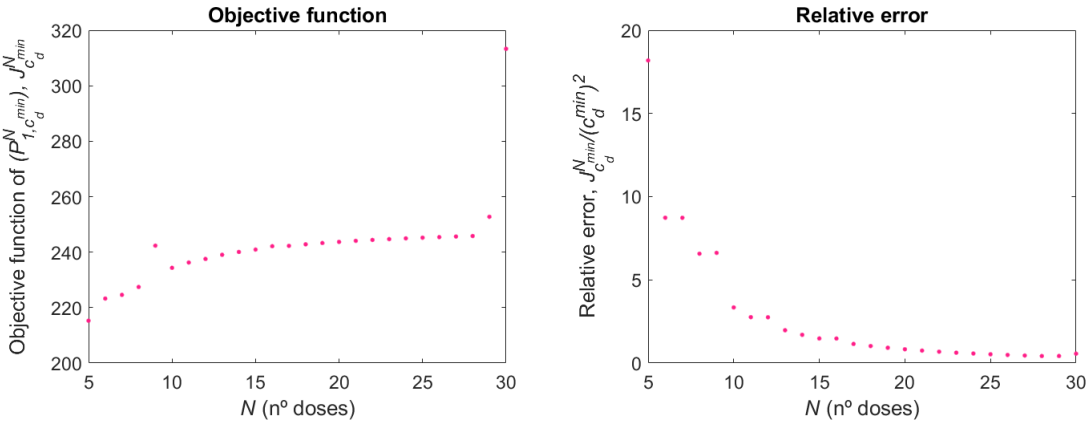


Figure 3.6: Objective function of $(P^N_{1,c_d^{min}})$, $J^N_{c_d^{min}}$ (left) and relative error (right), as a function of the number of doses N.

Some of those treatments are also presented in the following table:

Treatment	c_d^{min} (mg/L)	$J^N_{c_d^{min}}$ (days mg^2 L^{-2})	E_R (days)
5 doses	3.44	215.28	18.19
13 doses	11.02	239.04	1.970
20 doses	17.16	243.70	0.827
27 doses	23.31	245.62	0.452
28 doses	**24.19**	**245.81**	**0.420**
29 doses	24.39	252.74	0.424
30 doses	23.57	313.32	0.564

Table 3.3: Results of the minimization of $(P^N_{1,c_d^{min}})$ for different number of doses, the optimum concentration c_d^{min} and the relative error E_R in each case.

By looking at both Figure 3.6 and Table 3.3, we can observe that the minimum value of the objective function is reached at the smallest N value. However, the optimum constant concentration is low (c_d^{min} = 3.44 mg/L), so that we can not reach a steady-state because we have d_{min} = 10 mg/kg and it is impossible to get the concentration centered in the ideal constant one. In addition, c_d^{min} is too low to get a significant reduction both in the final volume and carrying capacity of the tumor (Example 2.3), so it is not reasonable to consider it due to biological reasons. When we compute the relative error, we can see that taking 5 doses is the worst option. Here we can see the importance of using this criterion to compare the different treatments.

On the other hand, if we look at the column of the relative error of the table, 28 doses seem to be the best option. Furthermore, the constant concentration looks reasonable. In fact, if we take a look at the heuristic formula we got in the previous section (Equation 3.6), under the hypothesis of this example we get c_d = 24.56 mg/L if N = 28. We have to take into consideration that by this method we did not find the optimal solution to the problem, so the obtained constant concentration could not be the one we got now. However, both results are very similar.

Moreover, we can distinguish two different cases with the c_d^{min} expression (Equation (3.7)) according to the value of the elimination rate λ:

- If $\lambda >> 0$, then $(1 - e^{\lambda(t_i - T_f)}) \approx 1$. Consequently, $c_d^{min} \approx \dfrac{1}{T_f\lambda}\displaystyle\sum_{i=1}^{N} d_i \leq \dfrac{D}{T_f\lambda}$. It is the maximum value that this quantity can reach, as $e^{\lambda(t_i - T_f)} \in (0, 1)$.
- If $\lambda \approx 0$, by using infinitesimals we get $(1 - e^{\lambda(t_i - T_f)}) \approx \lambda(T_f - t_i)$. As a result, $c_d^{min} \approx \displaystyle\sum_{i=1}^{N} d_i \left(1 - \frac{t_i}{T_f}\right) \leq D - \sum_{i=1}^{N} d_i \frac{t_i}{T_f}$.

3.2.2.1. Considering a large elimination rate

Let us study first the consequences of applying a drug with a large elimination rate. As $\lambda >> 0$, we are in the first case of the previous distinction, so $c_d \approx \dfrac{1}{T_f\lambda}\displaystyle\sum_{i=1}^{N} d_i$. By substituting it in (3.3) we get

$$J_{max}(N, d) = \frac{1}{2\lambda}\sum_{i=1}^{N} d_i^2 - \frac{1}{T_f\lambda^2}\left(\sum_{i=1}^{N} d_i\right)^2, \tag{3.9}$$

where we have considered that the negative exponential functions are approximately null.

As a result, if we consider a fixed number of doses $N \leq \frac{D}{d_{min}}$, which makes the problem easier because otherwise, it would have both natural and real variables, we have the next alternative optimization problem:

$$(P^N_{1,max}) \begin{cases} \min\limits_{d \in \mathbb{R}^N} & J^N_{max}(d) = \frac{1}{2}\sum\limits_{i=1}^{N} d_i^2 - \frac{1}{T_f \lambda}\left(\sum\limits_{i=1}^{N} d_i\right)^2 \\ \text{subject to} & d_{min} \leq d_i \leq d_{max},\ \forall i \in \{1, ...N\} \\ & \sum\limits_{i=1}^{N} d_i \leq D \end{cases}$$

For simplicity, we have also removed a $\lambda > 0$ from expression (3.9). This has no effect on the problem being minimized.

Note that if the elimination rate is much larger than one, then the times when the doses are applied do not have an influence on the value of the objective function J^N. Let us observe it in a numerical example:

Example 3.2.5. *Be $N = 10$, $d = (10, ...10)$, T_f= 30 days and c_d = 4 mg/L. Let's suppose $t = (0, 3, 6, 9, 12, 15, 18,\ 21, 24, 27)$, and $t' = (0, 1, 2, 3, 4, 5, 6, 7, 8, 9)$. Then:*

- *If we consider a drug with $\lambda = 10.1$ days^{-1}, we obtain $J^N(d) = 450.30$ days mg^2 L^{-2} independently on the times when the doses are applied.*
- *When we use a drug with an elimination rate of $\lambda = 0.38$ days^{-1}, we obtain $J^N = 815.87$ days mg^2 L^{-2} using t, and $J^N = 3622.93$ days mg^2 L^{-2}, with t'. We can observe that when $\lambda \approx 0$, the times at which doses are applied have a strong influence on the objective function.*

Theorem 3.2.2. *Problem $(P^N_{1,max})$ has, at least, a solution.*

Proof. Let's consider K the set of restrictions of $(P^N_{1,max})$, such that

$$K = \left\{ d \in \mathbb{R}^N : \sum_{i=1}^{N} d_i - D \leq 0, d_{min} \leq d_i \leq d_{max}, \forall i \in \{1, ..., N\} \right\},$$

and the following continuous functions:

$$g_i : \mathbb{R}^N \longrightarrow \mathbb{R} \text{ such that } g_i(d) = d_i,\ \forall i \in \{1, ..., N\},$$
$$g_{N+1} : \mathbb{R}^N \longrightarrow \mathbb{R} \text{ such that } g_{N+1}(d) = \sum_{i=1}^{N} d_i - D.$$

Then, we can represent the set K as:

$$K = \left[\bigcap_{i=1}^{N} g_i^{-1}([d_{min}, d_{max}]) \right] \bigcap g_{N+1}^{-1}((-\infty, 0]).$$

K is compact because it is a bounded and closed set. In addition, J^N_{max} is a continuous function, so by using the Weierstrass' theorem, we can conclude that there exists at least one solution to problem $(P^N_{1,max})$. □

Note that the function of problem $(P^N_{1,max})$ can be written matricially as $J^N_{max}(d) = \frac{1}{2} d\hat{H}d$, where

$$\hat{H} = \begin{pmatrix} 1 & \dots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \dots & 1 \end{pmatrix}_{N\times N} - \rho \begin{pmatrix} 1 & \dots & 1 \\ \vdots & \ddots & \vdots \\ 1 & \dots & 1 \end{pmatrix}_{N\times N} = \begin{pmatrix} 1-\rho & -\rho & \dots & -\rho \\ -\rho & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & -\rho \\ -\rho & \dots & -\rho & 1-\rho \end{pmatrix}_{N\times N},$$

with $\rho = \frac{2}{T_f \lambda}$. Thus, we have the following property:

Proposition 3.2.1. *$\hat{H}$ is a symmetric and positive-definite matrix if $N < \frac{\lambda T_f}{2}$. In fact, the eigenvalues are 1 (with multiplicity $N-1$) and 1-$N\rho$.*

Proof. Let us prove first that 1 and 1-$N\rho$ are the eigenvalues of matrix $\hat{H}$.

If 1 is an eigenvalue it should be satisfied that $(\hat{H} - \mathbb{I})x{=}0$, for a certain $x \in \mathbb{R}^N \backslash (0, ...0)$. Note that

$$\hat{H} - \mathbb{I} = \begin{pmatrix} -\rho & \dots & -\rho \\ \vdots & \ddots & \vdots \\ -\rho & \dots & -\rho \end{pmatrix}_{N\times N} \sim \begin{pmatrix} -\rho & \dots & -\rho \\ 0 & \dots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \dots & 0 \end{pmatrix}_{N\times N},$$

where $\sim$ denotes that both matrices are equivalent.

Therefore, $x = (x_1, ..., x_N)$ should fulfill that $\sum_{i=1}^{N} x_i = 0$. The equation has $N-1$ degrees of freedom, which implies that 1 is an eigenvalue of $\hat{H}$ and it has multiplicity $N-1$.

Reasoning in a similar way with eigenvalue 1-$N\rho$ we have that $(\hat{H} - (1-N\rho)\mathbb{I})x{=}0$, with $x \in \mathbb{R}^N \backslash (0, ...0)$ is satisfied if $(N-1)x_i - \sum_{j=1, j\neq i}^{N} x_j = 0$, $\forall i \in \{1, ..., N\}$. Now, there is only one possible solution, $x_i = \frac{1}{N}$ $\forall i \in \{1, ..., N\}$, which implies that $1 - N\rho$ is an eigenvalue of $\hat{H}$ with multiplicity 1.

In order to prove that $\hat{H}$ is definite-positive, we need to check whether the eigenvalues are positive. Once we have proved their form, note that they are all positive if and only if

$$1 - N\rho > 0 \iff 1 - \frac{2N}{\lambda T_f} > 0 \iff N < \frac{\lambda T_f}{2}.$$

Finally, the property of symmetry of this matrix can be easily proved, as it is a linear combination of two symmetric matrices (a matrix of ones and an identity one). □

Therefore, if $N < \frac{\lambda T_f}{2}$, we have that J^N_{max} is convex. This property will be utilized in the following theorem.

Theorem 3.2.3. *Let us fix quantities D, N, $\lambda >> 0$ and T_f, all of them positive and with $N \in \left[1, \frac{D}{d_{min}}\right] \cap \mathbb{N}$. If $N < \frac{\lambda T_f}{2}$, then the solution of problem $(P^N_{1,max})$ is $\bar{d} = (d_{min}, ..., d_{min})$.*

Proof. Be the function $J^N_{max} : \mathbb{R}^N \longrightarrow \mathbb{R}$ and

$$g_i : \mathbb{R}^N \longrightarrow \mathbb{R} \text{ such that } g_i(d) = d_i - d_{max},\ \forall i \in \{1, ..., N\},$$
$$\tilde{g}_i : \mathbb{R}^N \longrightarrow \mathbb{R} \text{ such that } \tilde{g}_i(d) = d_{min} - d_i,\ \forall i \in \{1, ..., N\},$$
$$\hat{g} : \mathbb{R}^N \longrightarrow \mathbb{R} \text{ such that } \hat{g}(d) = \sum_{i=1}^{N} d_i - D.$$

We have that the set of restrictions K, such that

$$K = \left\{ d \in \mathbb{R}^N : \hat{g}(d) \leq 0, g_i(d) \leq 0, \tilde{g}_i(d) \leq 0, \forall i \in \{1, ..., N\} \right\},$$

is convex, because all the restrictions included in the set are linear. We also have that the objective function is strictly convex, so the first-order necessary optimality conditions are also sufficient.

Then, we can prove that $\bar{d}$ is a solution of the system, if it is a Kuhn-Tucker point, i.e., if it satisfies the following the Lagrange multipliers' conditions:

1. $$\begin{pmatrix} \bar{d_1} - \frac{2}{T_f \lambda} \sum_{i=1}^{N} \bar{d_i} \\ \vdots \\ \bar{d_N} - \frac{2}{T_f \lambda} \sum_{i=1}^{N} \bar{d_i} \end{pmatrix} + \begin{pmatrix} \bar{\mu_1} \\ \vdots \\ \bar{\mu_N} \end{pmatrix} - \begin{pmatrix} \tilde{\mu_1} \\ \vdots \\ \tilde{\mu_N} \end{pmatrix} + \begin{pmatrix} \hat{\mu} \\ \vdots \\ \hat{\mu} \end{pmatrix} = \begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}.$$

2. $\bar{\mu_i}(\bar{d_i} - d_{max}) = 0, \quad \tilde{\mu_i}(d_{min} - \bar{d_i}) = 0,\ \forall i \in \{1, ..., N\}, \quad \text{and} \quad \hat{\mu}\left(\sum_{i=1}^{N} \bar{d_i} - D \right) = 0.$

3. $\bar{d_i} - d_{max} \leq 0, \quad d_{min} - \bar{d_i} \leq 0,\ \forall i \in \{1, ..., N\}, \quad \text{and} \quad \sum_{i=1}^{N} \bar{d_i} - D \leq 0.$

where $\{\bar{\mu_i}\}_{i \in \{1,...N\}}, \{\tilde{\mu_i}\}_{i \in \{1,...N\}} \subset [0, +\infty)$ and $\hat{\mu} \in [0, +\infty)$.

Let us demonstrate that there are Lagrange multipliers satisfying the conditions if $\bar{d_i} = d_{min}\ \forall i \in \{1, ...N\}$.

By using condition 2, we already know that $\bar{\mu_i} = 0,\ \forall i \in \{1, ...N\}$, because $d_{min} \neq d_{max}$, and we can take $\hat{\mu} = 0$. In addition, condition 3 is also fulfilled with $\bar{d_i} = d_{min}$. Therefore, from the first condition, and considering these facts, we get that

$$\tilde{\mu_i} = d_{min}\left(1 - \frac{2N}{T_f \lambda}\right),\ \forall i \in \{1, ...N\}.$$

$\tilde{\mu_i}$ should be positive, and it occurs if $N < \frac{\lambda T_f}{2}$, which is satisfied by hypothesis.

As a result, $\bar{d} = (d_{min}, ..., d_{min})$ is a Kuhn-Tucker point, so it is the solution of $(P^N_{1,max})$.

□

Now, as the solution $\bar{d}$ of Problem $(P^N_{1,max})$ under the hypotheses of Theorem 3.2.3 has all the doses equal to the minimum dosage d_{min}, we can rewrite expressions (3.7) and (3.9), respectively, as follows:

$$c_d^{min} \approx \frac{N d_{min}}{T_f \lambda}, \qquad J_{max}(N, \bar{d}) \approx \left(\frac{1}{2} - \frac{1}{T_f \lambda} N\right) \frac{N d_{min}^2}{\lambda}.$$

We can observe that the concentration c_d^{min} that makes (P_1) minimum when a large-elimination-rate drug is applied is directly proportional to N and d_{min}, so it is constant if the product between N and d_{min} is too. Moreover, the objective function of our initial optimization problem is directly proportional to the product $N d_{min}^2$. Let us look at a numerical example to check these statements:

Example 3.2.6. *Be $\lambda = 10.1$ $days^{-1}$, and $T_f = 50$ days. We can solve $(P^N_{1,c_d^{min}})$ and then obtain c_d^{min}. This last quantity can be introduced in problem (P_1^N) to get the value of the objective function J^N:*

- *We obtain $c_d^{min} = 0.198$ mg/L if $N = 10$ and $d_{min} = 10$ mg/kg, and also in the cases $N = 20$ and $d_{min} = 5$ mg/kg, and if $N = 50$ and $d_{min} = 2$ mg/kg. We can observe that if $N d_{min}$ is constant, then c_d^{min} keeps constant too. Moreover, the objective function of problem (P_1) decreases its value as d_{min} decreases. Its values are $J^N = 47.544$, 22.792 and 7.941 days mg^2 L^{-2}, respectively. This is consistent with the fact that the concentration function is closer to a constant as shorter the doses are.*

- *Now, we keep the product $N d_{min}^2$ constant to observe the behavior of the objective function of (P_1^N). Let $N = 8$ and $d_{min} = 4$ mg/kg. Then $c_d^{min} = 0.0063$ mg/L, and $J^N = 6.300$ days mg^2 L^{-2}. If we consider $N = 16$ and $d_{min} = 2.83$ mg/kg, we obtain $c_d^{min} = 0.009$ mg/L, and $J^N = 6.267$ days mg^2 L^{-2}. Finally, if $N = 32$ and $d_{min} = 2$ mg/kg, then we get $c_d^{min} = 0.253$ mg/L and $J^N = 6.331$ days mg^2 L^{-2}. Note that the objective function is constant, which is consistent with the approximations we have obtained theoretically in the lines preceding this example.*

We can proceed with a similar reasoning in case $N > \frac{\lambda T_f}{2}$. Nevertheless, we should notice that now the objective function of $(P^N_{1,max})$ is not convex, so we have to study the necessary conditions for optimality and not the sufficient ones.

Theorem 3.2.4. *Be D, $\lambda >> 0$ and T_f, as in the previous theorem. Let us take a number of doses satisfying that $N \in \left[1, \frac{D}{d_{min}}\right] \cap \mathbb{N}$ and also $N > \frac{\lambda T_f}{2}$. Under these hypotheses, the solution of problem $(P^N_{1,max})$ is constant, i.e. $\bar{d} = (d_c, ...d_c)$, where $d_c = \frac{D}{N}$, if $\frac{D}{N} \leq d_{max}$, and $d_c = d_{max}$, otherwise.*

Proof. Given g_i, $\tilde{g}_i$, $\forall i \in \{1, ..., N\}$ and $\hat{g}$ as defined in Theorem 3.2.3, all of them C^1 functions. Let us consider the Kuhn-Tucker conditions expressed in the previous theorem.

Let us prove the theorem without distinguishing whether $\sum_{i=1}^{N} d_i = D$ or not. The only difference would be that in the second case $\hat{\mu}$ is null, but it does not make any difference in our reasoning. By using the first Kuhn Tucker's condition we have:

$$d_i - \frac{2}{T_f \lambda} \sum_{i=1}^{N} d_i + \bar{\mu}_i - \tilde{\mu}_i + \hat{\mu} = 0, \qquad \forall i \in \{1, ..., N\}. \tag{3.10}$$

We prove that the solution of the problem is constant arguing by contradiction. Let us assume $\bar{d}$ has at least two different doses $d_i, d_j \in [d_{min}, d_{max}]$, such that $d_i \neq d_j$. We can distinguish the following cases:

i) Let us suppose that $d_i, d_j \notin \{d_{min},\, d_{max}\}$, so by using condition 2, $\bar{\mu}_i = \tilde{\mu}_i = \bar{\mu}_j = \tilde{\mu}_j = 0$. Then, by using Equation (3.10) we get that

$$d_i - \frac{2}{T_f\lambda}\sum_{k=1}^{N} d_k + \hat{\mu} = 0 \qquad\qquad d_j - \frac{2}{T_f\lambda}\sum_{k=1}^{N} d_k + \hat{\mu} = 0,$$

which is satisfied only if $d_i = d_j$.

ii) If $d_i = d_{min}$ then $\bar{\mu}_i = 0$, and $\tilde{\mu}_i = d_{min} - \frac{2}{T_f\lambda}\sum_{k=1}^{N} d_k + \hat{\mu} \geq 0$. If $d_j \notin \{d_{min},\, d_{max}\}$, it results that $d_j - \frac{2}{T_f\lambda}\sum_{k=1}^{N} d_k + \hat{\mu} = 0$, which implies that $d_{min} > d_j$ and it contradicts the previous statement.

iii) If we take $d_j = d_{max}$ ($\tilde{\mu}_j = 0$) and $d_i \notin \{d_{min},\, d_{max}\}$, we are in a situation similar to the previous one, because we get that

$$-\bar{\mu}_j = d_{max} - \frac{2}{T_f\lambda}\sum_{k=1}^{N} d_k + \hat{\mu} \leq 0 \qquad\qquad d_i - \frac{2}{T_f\lambda}\sum_{k=1}^{N} d_k + \hat{\mu} = 0.$$

It is not possible either to have this situation because $d_{max} > d_i$.

iv) Finally, we can suppose that $d_i = d_{min}$ and $d_j = d_{max}$. By using the values of both $\tilde{\mu}_i$ and $\bar{\mu}_j$, from cases ii) and iii), respectively, we know that it is not possible to have this situation because $d_{max} > d_{min}$.

As a consequence, the treatment must have only one type of doses, so $\bar{d}_i = d_c,\ \forall i \in \{1, ..., N\}$. Therefore, we can write the objective function of problem $(P^N_{1,max})$ as follows:

$$J^N_{max} = \left(\frac{1}{2} - \frac{1}{T_f\lambda}N\right) N d_c^2,$$

which is a negative quantity by hypothesis. As a result, $d_c = d_{max}$ if $N < \frac{D}{d_{max}}$, and $d_c = \frac{D}{N}$, otherwise.

□

3.2.3. Using the total cumulative dose to choose an ideal concentration level

Finally, we can also study the situation in which we have to use the total cumulative dose available when the number of doses is fixed. This approach can help us to obtain the highest level that the drug concentration can reach and keep a steady state. Therefore, we will deal now with the following problem:

$$(P^N_{1,D}) \begin{cases} \min\limits_{\{d_i\}_{i=1}^N, \{t_i\}_{i=1}^N \subset \mathbb{R}^+} & J^N(d_1, ..., d_N, t_1, ...t_N) = \displaystyle\int_0^{T_f} (c(t) - c_d)^2 dt \\ \text{subject to} & t_i + \gamma \leq t_{i+1}, \ \forall i \in \{1, ...N-1\} \\ & t_N \leq T_f \\ & d_{min} \leq d_i \leq d_{max}, \ \forall i \in \{1, ...N\} \\ & \displaystyle\sum_{i=1}^N d_i = D. \end{cases}$$

As we are considering the condition of consuming the total cumulative dosage, the number of doses N has both upper and lower bounds, such that $N \in \left[\frac{D}{d_{max}}, \frac{D}{d_{min}}\right] \cap \mathbb{N}$.

Theorem 3.2.5. *There is at least one solution of Problem* $(P^N_{1,D})$.

Proof. The proof is similar to the one considered in Theorem 3.2.1, but instead of considering the restriction $\displaystyle\sum_{i=1}^N d_i - D \leq 0$, we have to consider $\displaystyle\sum_{i=1}^N d_i - D = 0$. The set of restrictions is still compact, and we already know that J^N is continuous. Therefore, by using the Weierstrass' theorem we can conclude that there exists a solution of Problem $(P^N_{1,D})$. □

In addition, we take c_d as higher as possible such that the effect on the tumor is optimized while we keep the concentration in the body in a steady state along the duration of the treatment (i.e., we want to avoid the tails that appear in Example 3.2.1 when c_d is too high).

However, there are some cases in which the ideal concentration level that produces this effect is very similar to the one obtained in the previous sections, where the sum of the doses could be lower than the cumulative dosage. We have already seen in Example 3.2.1 that when the elimination rate is too high ($\lambda = 10$ days^{-1}), the results obtained suggest that the best strategy is to apply the maximum number of d_{min} doses possible, $\frac{D}{d_{min}}$. As a result, the maximum cumulative dosage was used.

When $\lambda = 0.38$ days^{-1}, we have already explore an example where we found the optimum concentration level when it was not needed to consume all the amount of drug (see Example 3.2.4). We now see which is the best c_d when $\displaystyle\sum_{i=1}^N d_i = D$.

Example 3.2.7. *Let us consider D = 300 mg/kg, d_{min} = 10 mg/kg, d_{max} = 30 mg/kg, γ = 0.3 days and T_f = 30 days. Given λ = 0.38 days^{-1}, the maximum c_d that can be reached without detecting a tail in the drug concentration in the body is approximately 25 mg/L. In Example 3.2.4 we saw that the optimum c_d when we solved Problem $(P^N_{1,c_d^{min}})$ was 24.19 mg/L. In Figure 3.7, we represent the drug concentration in the body with the treatment provided by the solution of Problem $(P^N_{1,D})$ when c_d = 24.19 mg/L and 25 mg/L, respectively.*

When c_d = 24.19 mg/L, the concentration $c(t)$ at the end of the treatment (day 30th), is not as low as the minimum value reached during the previous days (around 20 mg/L). It is the opposite of getting a tail, so we decided to increase c_d until 25 mg/L. It is the highest possible level to keep a steady-state.

It is noteworthy to mention that with c_d = 25 mg/L, the objective function J^N takes value 255.02 days mg^2 L^{-2}. As expected, this value is higher than the one obtained in Example 3.2.4 (245.81 days mg^2 L^{-2}) because the restrictions now are more stringent.

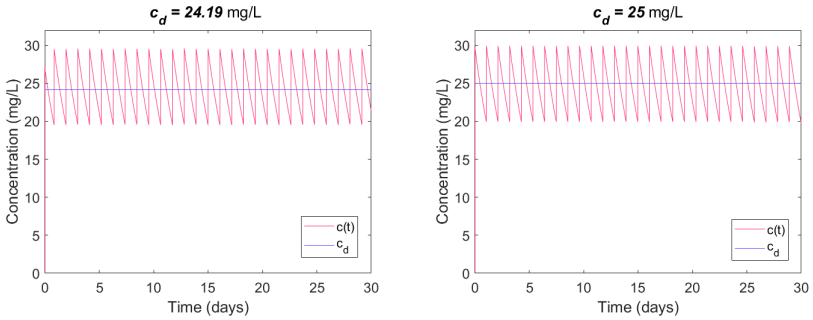


Figure 3.7: Drug concentration in the body when the maximum cumulative dose is reached, with $c_d = 24.19$ mg/L (left) and $c_d = 25$ mg/L (right).

In view of Example 3.2.7, we could think that the concentration level we aim to reach in this subsection is similar to the optimum constant concentration we could obtain with the previous subsection approach. However, it is not always true. In the following example we represent a situation in which, under the same hypotheses, the results of c_d^{min} and c_d with $\sum_{i=1}^{N} d_i = D$ vary notably.

Example 3.2.8. *Let us take D, d_{min}, d_{max}, γ and T_f as in the previous example. We will suppose now that the administered drug has an elimination rate of $\lambda = 0.1$ days^{-1}. Given $N = 22$, we can distinguish then the following situations:*

- *The solution provided by $(P^N_{1,c_d^{min}})$ makes that the objective function takes value $J^N_{c_d^{min}} = 547.8$ days mg^2 L^{-2}. The optimum c_d in this situation, computed using Equation (3.7) is 59.18 mg/L.*
- *When we want to use the maximum cumulative dosage, the highest c_d we can require to get a steady state of the drug concentration in the body is approximately 77 mg/L. The objective function of Problem $(P^N_{1,D})$ takes value $J^N = 1027.3$ days mg^2 L^{-2}.*

In Example 3.2.8, it is clear the difference between both approaches. There is a variation not only in the concentration level but also in the objective function of each problem. It would imply more fluctuations in both the volume and the carrying capacity of the tumor, but at the same time, the effect of the second treatment on the tumor would be greater.

Chapter 4

Simulations

In this chapter, we will show the effects produced by three angiogenesis inhibitors which have a different impact on the tumor dynamics and clearance. They are Angiostatin, Endostatin, and TNP-470, included in the analysis of Hahnfeldt et al. (see [6]). We will distinguish between treatments that aim to keep the tumor volume constant (palliative therapy) and those that expect to eliminate cancer (curative therapy). We will also simulate different situations of each case, which will provide us with evidence of the aspects we have already explored in the previous chapters.

Let us describe first the three drugs that we will consider in this chapter. TNP-470[8] is the first angiogenesis inhibitor discovered, in 1992. It is a synthetic drug created as an alternative to an antibiotic called *Fumagillin* to avoid the side effects it causes. It can reduce the growth and vascularization not only of primary tumors but also in metastatic cancers. Nowadays, it is one of the most used antiangiogenic drugs, and it is utilized to treat patients with breast, ovarian, and prostate cancer, among others. It has a large elimination rate ($\lambda = 10.1$ days^{-1}), i.e., its half-life is about 1.65 hours.

The second is Angiostatin[12], which also produces the blocking of tumor growth and neovascularization. However, unlike TNP-470, it is not synthetic, but it is generated from fragments of a protein called *Plasminogen*. It was the first antiangiogenic peptide discovered (in 1994, by O'Reilly et al.). Its clearance is $\lambda = 0.38$ days^{-1}, noticeably lower than the previous one.

Finally, Endostatin[12], also discovered by O'Reilly et al. in 1997, is an inhibitor similar to Angiostatin but with a higher elimination rate ($\lambda = 1.3$ days^{-1}). It is a product of a specific type of collagen and can be applied to treat different types of cancer.

4.1. Palliative therapy

When cancer is in an advanced stage, it is usually not possible to cure it. However, a patient in these circumstances can receive treatment to relieve the symptoms of the illness and even increase its survival if possible. We will provide here some examples of this type, in which the therapy is taken to slow the growth of the tumor that is causing the pain or shrink it.

4.1.1. Keeping the cumulative dose constant

As we have proved in Chapter 3, when we want to keep the concentration in a steady state, the best option is to take doses equal to the minimum individual dose d_{min} during the whole

treatment except for the first ones, that usually take a higher value.

In this subsection, we will see the effect of the variation of d_{min} in the fluctuations of both the tumor volume and the carrying capacity. To do so, we keep the cumulative dose constant. Note that it would imply that the number of doses of each treatment has to be also changed.

We will analyze the following treatments:

	d_{min} (mg/kg)	Δt (days)	Number of doses N
Treatment 1.a.	5	0.6	1000
Treatment 1.b.	10	1.2	500
Treatment 1.c.	15	1.8	333
Treatment 1.d.	20	2.4	250

Table 4.1: Different options of treatments to observe the effect of the doses. In all cases, $t_1 = 0$.

Before considering the three different inhibitors of the Hahnfeldt et al. article (see [6]), we observe their concentration in the body when Treatment 1.a. is applied, such that we can know in advance the limits of the final constant volume ('set point'). Those concentrations are represented as follows:

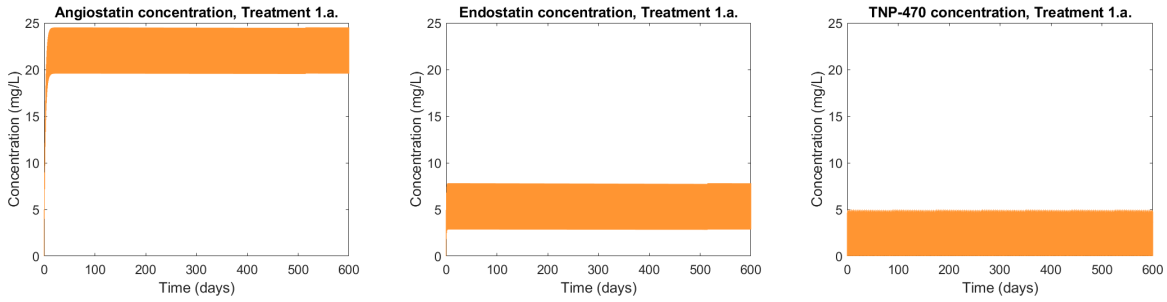


Figure 4.1: Drug concentration in the body with the different inhibitors by considering Treatment 1.a.

The elimination rates are $\lambda = 0.38$ days^{-1} for Angiostatin, $\lambda = 1.7$ days^{-1} in the case of Endostatin and $\lambda = 10.1$ days^{-1} for TNP-470.

Let us analyze both the effect of the concentration in the body and the treatment administered with each inhibitor separately. The figures that appear represent the solutions of the Cauchy problem (2.11), where $b = 5.85$ day^{-1}, $\lambda_2 = 0$ day^{-1}, and $d = 0.00873$ day^{-1} mm^{-2} (taken from [6]). If no drug is applied, the set point is approximately 17300 mm^3 (see Example 2.2.1). Quantity e, which measures the impact of the treatment on the dynamics of the carrying capacity, depends on the drug used. Moreover, we will consider that the initial points are $V_0 = 1000$ mm^3 and $K_0 = 1025$ mm^3.

Angiostatin

In view of Figure 4.1, we can see that when Angiostatin is administered, the concentration in the body can reach certain quasi-constant value, limited by the amount of dose administered. It moves around $c_1 = 19.5$ mg/L minimum and $c_2 = 24.5$ mg/L maximum. Now, we can make use of Equation (2.12) to obtain an estimation of the limits of the set point, with $e = 0.15$ mg^{-1}

L day^{-1}. Using Theorem 2.2.1, as $5.85 = b > \lambda_2 + ec_2 = 3.68$, we get that both for the volume and the carrying capacity will be between 3932.5 and 6132.9 mm^3.

Note that even though the cumulative dose is kept constant with the four treatments, the level reached by the concentration could be slightly different. When Treatment 1.d. is applied, this level is between 14 and 34 mg/L approximately. As a result, the final tumor volume will be in the range of 796.3 and 8902.8 mm^3.

As both treatments 1.a. and 1.d. are the extremes of the ones considered, we expect that in all cases, the maximum volume would stay between both limits. Let us show the figures representing those situations:

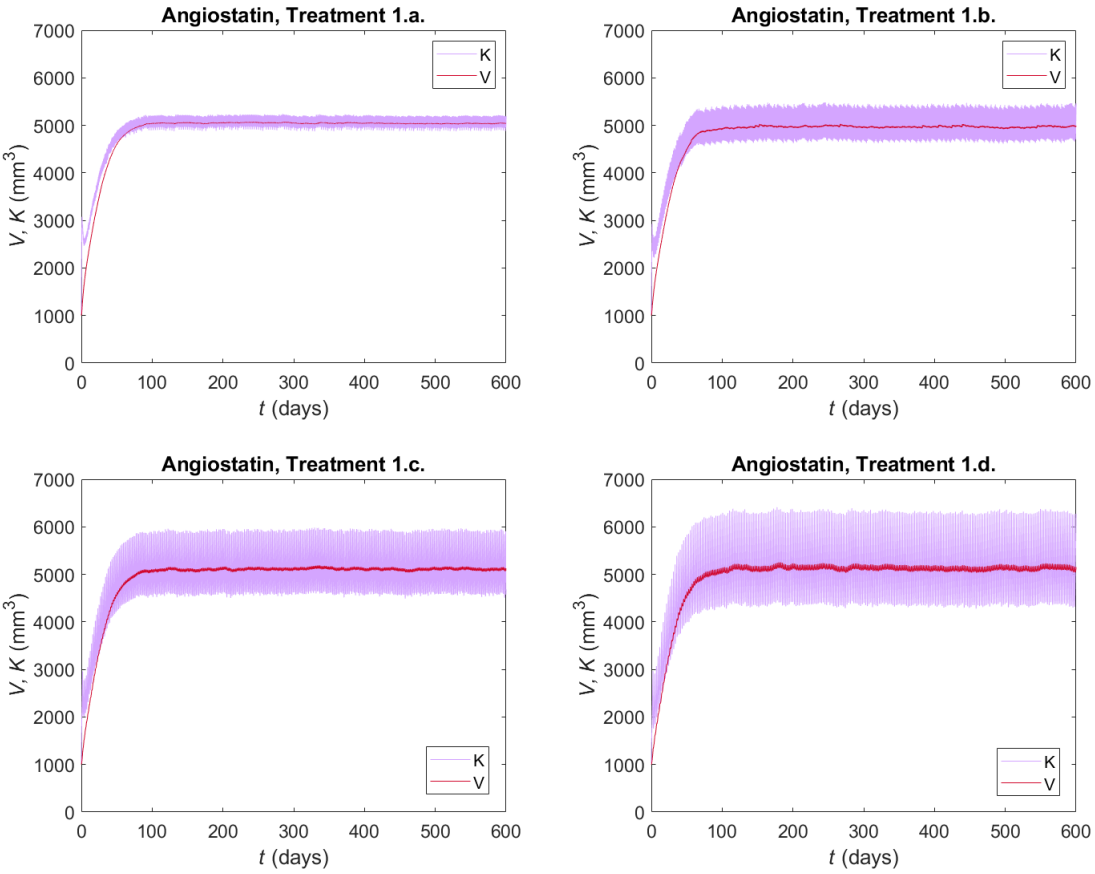


Figure 4.2: Evolution of the tumor volume (V) and carrying capacity (K) when the treatments of Table 4.1 are applied with Angiostatin.

The most notorious aspect we can observe from the figures is the large fluctuations of the carrying capacity compared to the ones of the tumor volume. Nevertheless, it should not be surprising, as we are applying an angiogenesis inhibitor, which affects the environment that makes the tumor grow but does not affect it directly. In addition, we see that the fluctuations increase as they do the doses, which is consistent with what we studied in Chapter 3 that when looking for a steady-state in concentration, it is better to apply small doses. Thus, when these are large, the fluctuations in concentration translate into substantial variations in the carrying capacity K and the tumor volume V.

Last but not least, note that the maximum volume that is reached by the tumor is between

the ranges of values we expected. Moreover, it barely varies when the different treatments are applied, as it seemed to do according to the theoretical estimations made.

Endostatin

In the case of Endostatin, it seems that the concentration of the drug is in a range of 2.5 and 7.5 mg/L approximately (see Figure 4.1). Now, by using Equation (2.12), where $e = 0.66$ mg^{-1} L day^{-1}, and Theorem 2.2.1 (we are under the hypothesis of case i)) we get that the set point will be between 1046.7 and 10552.4 mm^3 for Treatment 1.a..

When Treatment 1.d. is applied, the quasi-constant concentration level is between $\tilde{c_1} = 0.5$ and $\tilde{c_2} = 20.5$ mg/L.

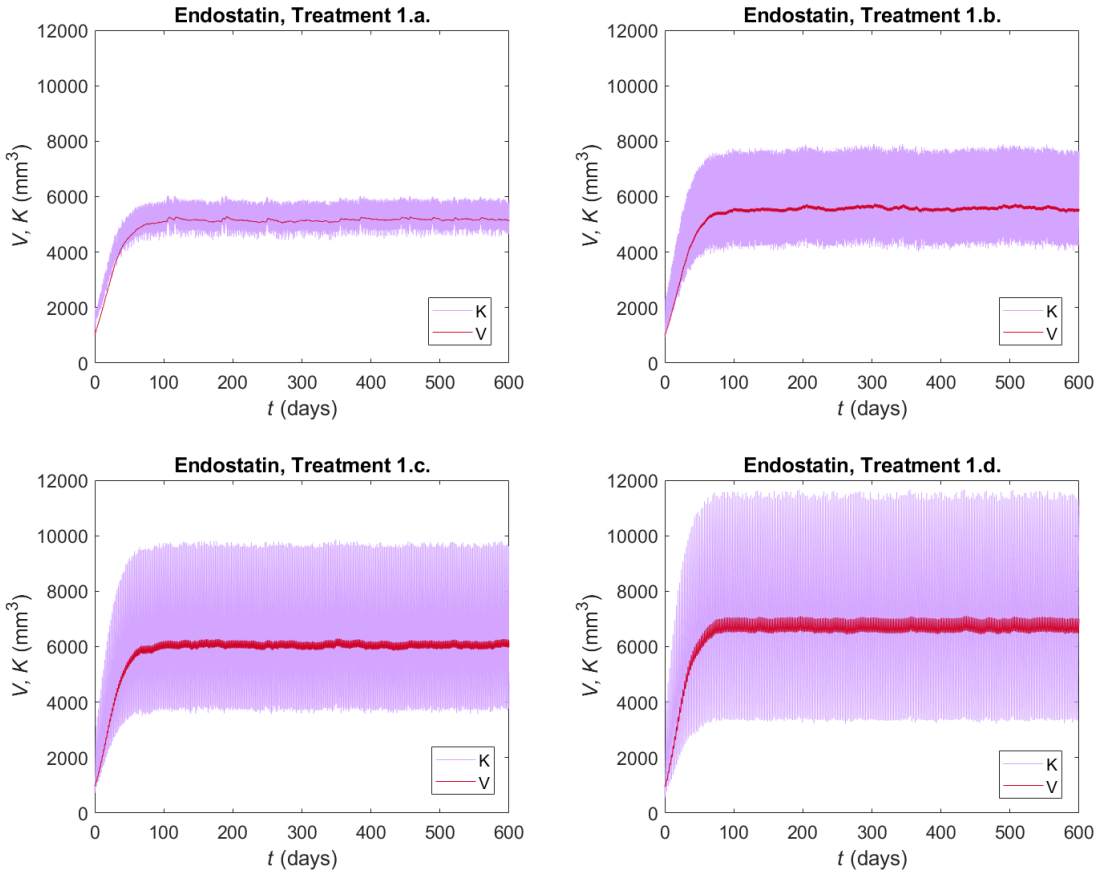


Figure 4.3: Evolution of the tumor volume (V) and carrying capacity (K) when the treatments of Table 4.1 are applied with Endostatin.

In Figure 4.3, we observe that the tumor is reduced until a quasi-constant that increases with the doses quantities, from around 5500 to 6750 mm^3. It can be seen then that increasing them makes the impact on tumor shrinkage minor.

Moreover, note that the fluctuations now are much greater than in the case of Angiostatin for any of the treatments used. It is because the effect of Endostatin on both the tumor volume and the carrying capacity is greater than when Angiostatin is used, so any variation in the concentration has a major impact on these quantities. Finally, as before, increasing the quantity of

the doses applied causes the variation of K and V to be greater, again being larger in the case of the first quantity.

TNP-470

Finally, note that the drug TNP-470, which has a large elimination rate, can not be used to keep a high concentration in the body (Figure 4.1). We have already detected this situation in Example 3.2.1. As a result, when we increase the dosage applied, for instance, by taking Treatment 1.b., we will observe that the concentration moves only from 0 to 10 mg/L. As the concentration varies quickly because of the high clearance, we could not expect the tumor volume to be highly reduced compared to the case in which we do not apply any treatment.

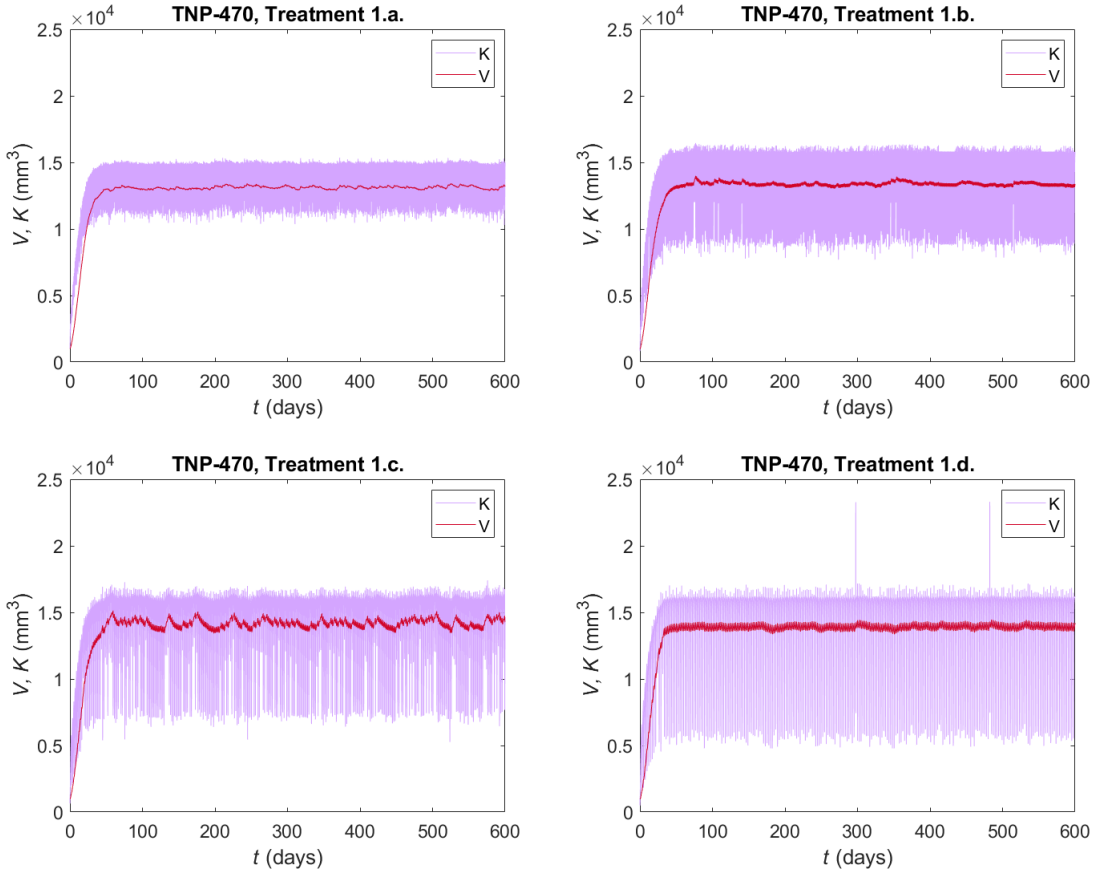


Figure 4.4: Evolution of the tumor volume (V) and carrying capacity (K) when the treatments of Table 4.1 are applied with TNP-470.

In fact, by looking at Figure 4.4 we can observe that the level reached with all treatments is approximately 13500 mm^3, which is much larger than with Angiostatin and Endostatin. The fluctuations now are even more notorious than before, but we have to take into consideration that in this case, $e = 1.3\ \text{mg}^{-1}\ \text{L day}^{-1}$, i.e., the effect of the drug concentration in the tumor is greater. The two highest peaks in the graph of Treatment 1.d. seem to be due to MATLAB numerical limitations.

Furthermore, note that when we increase the dosage, K seems to be asymmetrical compared

to the volume, and the maximum value reached is around 17000 mm^3. It is approximately the value of the set point when we are considering that no drug is applied. It is consistent with the fact that the inferior bound of the concentration is zero (see Theorem 2.2.1, case i) with $c_1 = 0$).

To sum up, regardless of the drug used, it seems that the optimal strategy consists of using many small doses spaced over a short time interval so that fluctuations in concentrations are not transmitted to the tumor's properties. Moreover, it is with the smaller dose treatment that the greatest benefit is obtained in terms of tumor shrinkage. Therefore, we have shown that it is better to apply a metronomic type therapy rather than a maximum tolerated dose one.

Note that by using the palliative treatment condition $b > \lambda_2 + ec_d$ (see Section 2.2) we can find the upper bounds of the ideal constant concentration for each drug. Taking b and λ_2 as presented in this subsection, and the value e of each drug, we get $c_{A,d}^{max} = 39$ mg/L for Angiostatin, $c_{E,d}^{max} = 8.86$ mg/L for Endostatin, and for TNP-470 we obtain $c_{T,d}^{max} = 4.5$ mg/L. As can be seen, there is a big difference between the maximum concentration levels that can be reached for a palliative treatment by each drug.

4.1.2. Varying the initial tumor size

In the previous subsection, we have considered in all cases the same tumor volume and carrying capacity at which the treatment is initialized. Nevertheless, looking at Equation (2.12), we observe that the set point attained does not depend on the characteristics of the tumor at the beginning of the treatment.

Here, we verify that the set point is independent of the initial properties of the tumor. We do this with two of the angiogenesis inhibitors previously mentioned, as the impact of the drug on the tumor depends on them. We suppose that the treatment applied is Treatment 1.b. of Table 4.1, which we have already seen that is insufficient to eliminate completely the tumor.

Angiostatin

For Angiostatin, Treatment 1.b. had a set point of about 5000 mm^3, both for V and K. Thus, we have decided to start the treatment with an initial tumor volume of 2000, 5000, and 7000 mm^3, respectively (see Figure 4.5). Regarding the carrying capacity, taking into account that it has to be higher, we have decided that for this inhibitor as well as for Endostatin it will be 25 mm^3 higher than the initial volume in each case.

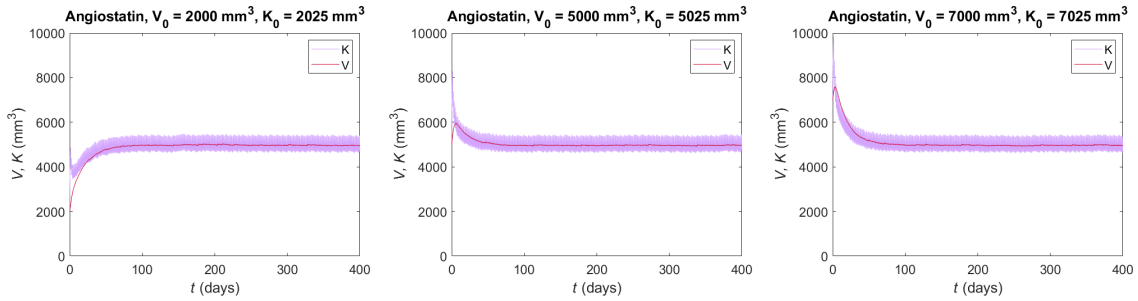


Figure 4.5: Evolution of the tumor volume (V) and carrying capacity (K) when Treatment 1.b. is applied with Angiostatin for different initial points.

By starting the treatment with a tumor size below the set point, it can be seen that it tends to rise to the set point value and remains there for the duration of the therapy. Nevertheless, the behavior of the tumor when treatment is initiated if its size is similar or larger than the set point is different. In these situations, an increase in tumor size is observed during the first few days of therapy, followed by an asymptotic decrease until reaching the same quasi-constant level as in the previous case.

It is reasonable to think that this rise and fall is due to the fact that the concentration takes several days to reach its maximum quasi-constant value, as can be seen in Figure 4.1 with Treatment 1.a. As a result, during those days, the impact of the doses on the tumor is lower so that the tumor increases above the set point first.

Endostatin

Now, we proceed as before, but in this case, the set point is approximately 5500 mm^3. Thus, we take as the initial tumor size of treatment 2000, 5500, and 9000 mm^3, respectively.

Note that when using Endostatin as an angiogenesis inhibitor, the concentration needs less days to reach the quasi-constant value than with Angiostatin. It could imply that the initial peak does not appear in this case.

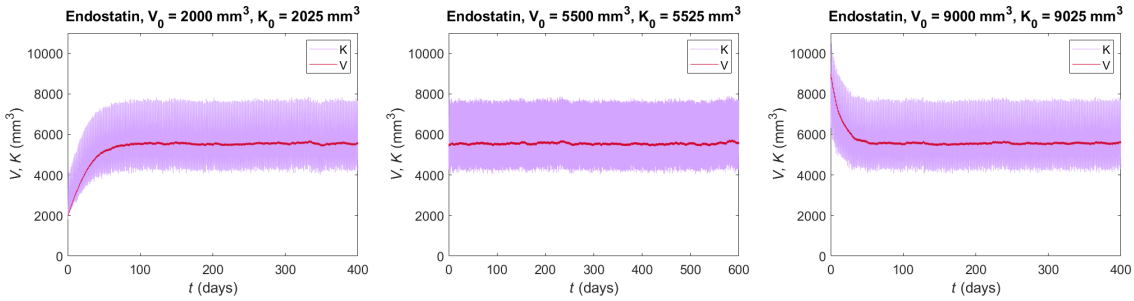


Figure 4.6: Evolution of the tumor volume (V) and carrying capacity (K) when Treatment 1.b. is applied with Endostatin for different initial points.

Given the results in Figure 4.6, we see that if the treatment starts when the size is already 5500 mm^3, it is maintained at that value, and no increase is seen in the first days. Nor is a peak observed when the treatment starts with larger tumor size, as expected. In this case, the treatment shrinks the tumor to the asymptotic set point (note that the tumor does not reach a size beyond that point).

Therefore, when applying this treatment with Endostatin, the effect of the drug concentration in the body before reaching the constant level does not have an impact on tumor dynamics.

Finally, TNP-470 provides a very similar result to the previous case because its clearance rate is large ($\lambda = 10.1$ $days^{-1}$) as the one of Endostatin. We do not add this case to avoid repeating it.

In summary, we have numerically verified that the set point does not depend on tumor size when treatment begins for any of the inhibitors analyzed. However, if clearance is slow, the treatment will take longer to take effect, which translates into a peak in tumor volume at onset in the cases where V_0 is equal to or greater than the set point.

4.2. Curative therapy

There is another type of therapy that can be carried out if the tumor we have to deal with, and the patient's own situation allows it. It is the curative therapy whose objective is to eradicate cancer. In this section, we will look at different strategies included in this therapy for the three inhibitors we are working with. The initial size of the tumor $V_0 = 1000$ mm^3 will be the same during the whole section. Note that we are now under the hypothesis of the case ii) of Theorem 2.2.1.

4.2.1. Keeping the cumulative dose constant

Let us now consider that the cumulative dose is kept constant so that we can see the effect of applying different doses, as we did before. In this case, we consider specific treatments for each drug because the variation in their clearance rates causes them to behave very distinctively when trying to eliminate the tumor.

Angiostatin

First of all, we are going to analyze Angiostatin treatments. Due to its short clearance, we know that it is not necessary to apply doses very frequently to achieve a high level of concentration in the body. We then plan the following curative treatments so that the cumulative dose remains at $D = 9000$ mg/kg.

	d_{min} (mg/kg)	Δt (days)	Number of doses N
Treatment 2.a.	10	0.66	900
Treatment 2.b.	15	1	600
Treatment 2.c.	20	1.33	450

Table 4.2: Different options of treatments with Angiostatin to observe the effect of the doses when we want to eliminate the tumor. In all cases, $t_1 = 0$.

Solving system (2.11) again with the same hypotheses of Subsection 4.1.1, and the treatments of Table 4.2, we obtain the results provided below:

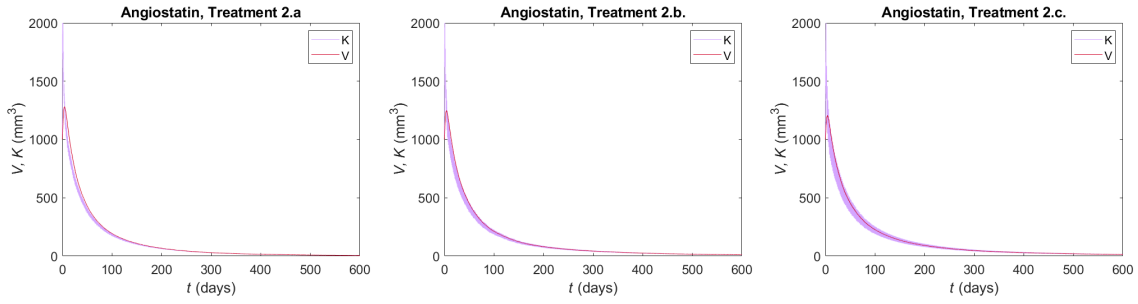


Figure 4.7: Evolution of the tumor volume (V) and carrying capacity (K) when treatments of Table 4.2 are applied.

We can see the initial peak in both volume and carrying capacity due to the low elimination rate of Angiostatin as before. The height reached by the summit decreases as d increases because

the concentration reaches the quasi-constant level earlier.

It can also be appreciated that now the fluctuations that occur, which increase as it does d, are much smaller than those that occurred in palliative therapy for the same dose values. Moreover, at day 100th of treatment, there is still tumor to be reduced, while in Subsection 4.1.1 the maximum tumor size value was already reached at that time.

Endostatin

Now, we study the case of Endostatin, where the time between doses must be shorter than for Angiostatin if we want to eradicate the tumor since the clearance is now larger. The following treatments are proposed for analysis so that the cumulative dose is now $D = 10000$ mg/kg:

	d_{min} (mg/kg)	Δt (days)	Number of doses N
Treatment 3.a.	10	0.6	1000
Treatment 3.b.	15	0.9	666
Treatment 3.c.	20	1.2	500

Table 4.3: Different options of treatments with Endostatin to observe the effect of the doses when we want to eliminate the tumor. In all cases, $t_1 = 0$.

Figure 4.8 represents the evolution of V and K for the above treatments. Now, fluctuations are more noticeable than with Angiostatin, as we had before because the impact of the drug on the carrying capacity is greater.

It is noteworthy to mention that it takes about 400 days to remove the tumor with any treatment applied. It takes less time than with Angiostatin, but we have to take into account that now, the cumulative dose is higher.

As expected from what we saw in the previous section, in this case, there is no initial peak but rather a continuous decline until it is eradicated.

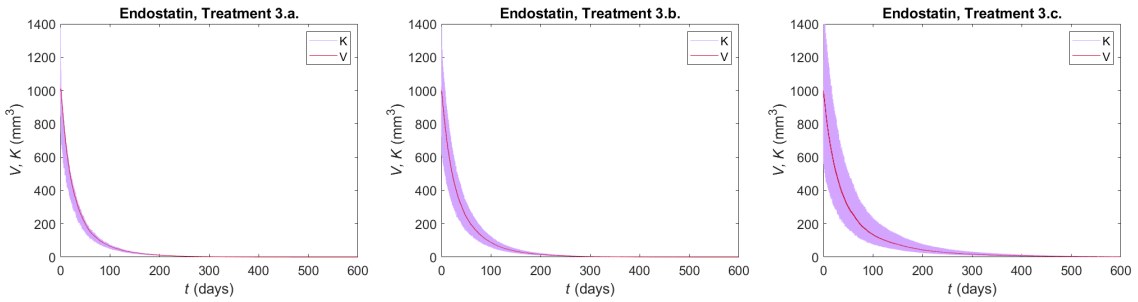


Figure 4.8: Evolution of the tumor volume (V) and carrying capacity (K) when treatments of Table 4.3 are applied.

TNP-470

Lastly, if we want to use TNP-470 as the angiogenesis inhibitor, we have to take into account its large elimination rate. We have seen that it is difficult to reach a high concentration of the drug in the body that is capable of significantly reducing the tumor size. Therefore, in order to eliminate it, it is necessary that the treatment doses are applied within a very short period of

time between doses so that the drug is not completely eliminated from the organism during the time interval between doses.

	d_{min} (mg/kg)	Δt (days)	Number of doses N
Treatment 4.a.	10	0.2	3000
Treatment 4.b.	15	0.3	2000
Treatment 4.c.	20	0.4	1500

Table 4.4: Different options of treatments with TNP-470 to observe the effect of the doses when we want to eliminate the tumor. In all cases, $t_1 = 0$.

The treatments to be analyzed are those shown in the table above. Note the difference in Δt compared to the previous cases. In addition, the sum of all treatment doses results in $D = 30000$ mg/kg, tripling the ones of Angiostatin and Endostatin.

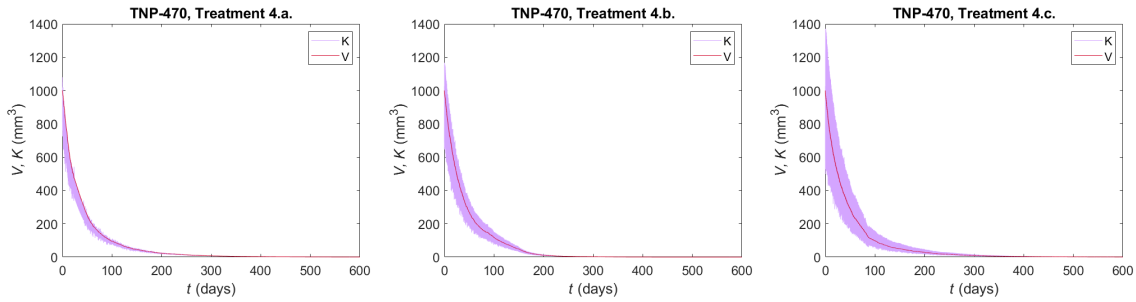


Figure 4.9: Evolution of the tumor volume (V) and carrying capacity (K) when treatments of Table 4.4 are applied.

The graphs observed with TNP-470 are very similar to the ones of Endostatin (Figure 4.8). The only difference is that, in this case, the descent is not so homogeneous, having irregular fluctuations until the tumor is eradicated. They may be due to the inhibitor's difficulty in maintaining the necessary concentration level in the body to eliminate the tumor.

Given the obtained results, it seems that TNP-470 is not an appropiate drug to perform curative therapy. We see that the tumor evolution is the same as that of Endostatin, but the patient will be subjected to a higher total dose, which may be more harmful to him. Angiostatin also allows tumor elimination without needing to use so much drug, although it takes a little longer to eradicate it. The administration of one or other drug will depend on their particular characteristics and the patient's situation.

4.2.2. Testing with alternative treatments combination

We have mentioned the possibility that treatments may be harmful or toxic to the patient. In this subsection, we analyze the effect of reducing the cumulative dose of curative treatments applied during a certain time. We do this only for the case of Angiostatin because the results are similar to the rest of the inhibitors.

In all treatments, we start with an initial dose of 10 mg/kg, which is increased in constant steps Δd of 0.015, 0.0125, and 0.01 mg/kg, respectively (see Figure 4.10). The application time between them is 1.2 days. Thus, the cumulative dose is 17500, 16250, and 15000 mg/kg in each

case. However, in the first 600 days, we will apply 8696, 8246, and 7797 mg/kg, unlike the 9000 mg/kg applied in the previous subsection.

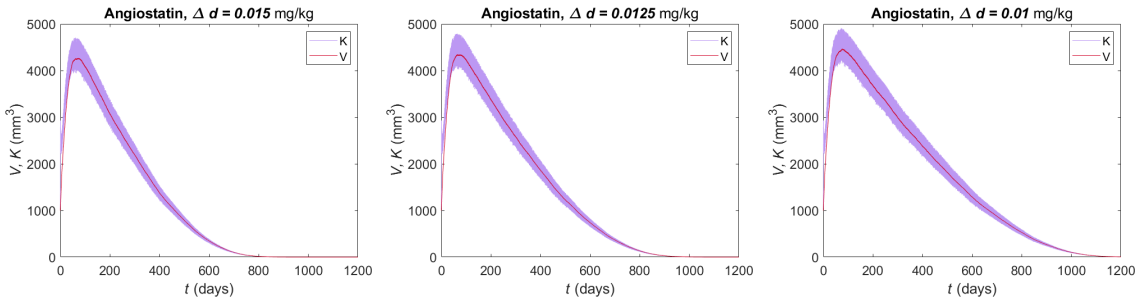


Figure 4.10: Evolution of the tumor volume (V) and carrying capacity (K) when alternative curative treatments are applied with Angiostatin.

We see that under these regimens, it is also possible to eradicate the tumor, although, in the first 100 days, its volume increases to a bit more than 4000 mm^3. The largest size is reached when Δd takes the smallest value since it takes longer to achieve a high drug concentration in the body. Moreover, unlike before, when it took about 600 days to cure cancer, now it takes 800 days if $\Delta d = 0.015$ mg/kg, and even this time is doubled if the increase between doses is 0.01 mg/kg. All of the situations are examples of the case ii) of Theorem 2.2.1. The final decision will depend on the physician, but we have shown that it is not necessary to have so much cumulative dose to achieve its elimination, and it may involve fewer side effects for the patient.

Chapter 5

Conclusions

This study allows us to predict the results that can be expected from antiangiogenic treatments, depending on the type of tumor, the drug used, the total dose administered, the way it is administered, the total duration of treatment, etc...

In the work, an optimization problem has been studied to try to maintain the drug concentration in the patient's body in a steady-state. It has been used for the subsequent analysis of a pharmacodynamic model that includes angiogenesis, which we have proved that has a unique solution for all $t > 0$ (see Chapter 2).

Through the analysis carried out in Chapter 3, we have considered three different approaches to select the ideal concentration level to be achieved in the body by solving the corresponding optimization problem. Along this work, we have assumed $\sigma = 1$ kg/L in (3.1), for simplicity. In the general case, expressions where d_i appears should be replaced by σd_i, for example, in Table 5.1.

Example 3.2.1 shows the importance of selecting a good constant concentration c_d to be achieved and the differences that exist when using one or the other drug. It also illustrates that the ideal concentration can take very low values when the drug used has a high value of λ (this means, the drug is eliminated very quickly from the body), and reach up to the value of the cumulative dose D when $\lambda \approx 0$.

In the general case, it can be noticed that the optimal strategy to achieve a reasonable quasi-steady state of the drug in the body is to take constant doses equispaced throughout most of the treatment. Only the initial doses (loading doses) may vary depending on the drug to be applied and the ideal concentration level to be considered. If λ is not too large, the number of initial doses different to the maintenance ones is one if $c_d \in [d_{min}, d_{max}]$, such that it takes a similar value to the concentration level to be reached. On the other hand, if $c_d > d_{max}$, then as many maximum doses d_{max} as necessary will be taken in the shortest possible time, i.e. equispaced by γ, until the drug concentration is at a distance less than d_{max} from c_d. At that point, a dose d^* sufficient to reach the constant concentration level could be taken.

In addition, in Subsection 3.2.1 we have seen that if we fix the dose concentration to be achieved at a reasonable level, we can predict quite accurately the best treatment for each drug by first estimating the number of doses that can be applied and utilizing the minimum individual dose d_{min} as the maintenance ones. Moreover, we have seen that if we use a drug with a high clearance rate, it would be best that all doses are constant. They should be the minimum possible (d_{min}) if the number of doses is less than $\frac{\lambda T_f}{2}$, with T_f being the last possible day of treatment (see Theorem 3.2.3). We can summarize the results seen in the following table, where

$\tilde{t} \in [\gamma, \frac{T_f}{N}]$ and $t^* \in [\gamma, \tilde{t}]$. Once more, we remark that $t_1 = 0$ in all cases:

Type of drug	**Optimal treatment dosage**	**Optimal treatment interval times**
$\boldsymbol{\lambda \approx 0}$ & **intermediate** $\boldsymbol{\lambda}$	$(d_{max}, ..., d_{max}, d^*, d_{min}, ..., d_{min})$ if $c_d > d_{min}$ $(d^*, d_{min}, ..., d_{min})$ if $c_d \leq d_{min}$	$(\gamma, ..., \gamma, t^*, \tilde{t}, ..., \tilde{t})$ $(t^*, \tilde{t}, ..., \tilde{t})$
$\boldsymbol{\lambda >> 0}$	$(d_{min}, ..., d_{min})$ if $N < \frac{\lambda T_f}{2}$ $(\frac{D}{N}, ..., \frac{D}{N})$ if $N > \frac{\lambda T_f}{2}$ and $N \geq \frac{D}{d_{max}}$ $(d_{max}, ..., d_{max})$ if $N > \frac{\lambda T_f}{2}$ and $N < \frac{D}{d_{max}}$	$(\tilde{t}, ..., \tilde{t})$

Table 5.1: Summary of the results obtained in Chapter 3 for problem (P_1).

The last question we have discussed in the chapter on drug concentration is to find the ideal level when using the entire available dosage D. Although it is not the treatment that is considered optimal to problem (P_1), this is an interesting approach, since it would help to know the maximum concentration level that can be reached with a drug. Example 3.2.8 shows that this level varies significantly if a short-clearance inhibitor is considered, while there is hardly any difference in other cases (Example 3.2.7).

On the other hand, in Chapter 4 we perform simulations to study the effect of different treatments (with a scheme similar to those presented in Table 4) on the volume and carrying capacity considered in the pharmacodynamic model. For this purpose, we have used three inhibitors that have a different impact on the tumor, as well as a distinct clearance rate. We have observed that if we take higher doses, the great fluctuations in the drug concentration are transferred to the tumor size. We have seen, for example, that for TNP-470, with $\lambda >> 0$ and a high impact on the tumor carrying capacity, the maximum volume hardly decreases with respect to the case in which the patient is not under treatment, unlike Angiostatin, and that fluctuations are greater. These observations have been made for both curative and palliative therapies. For the first case we have also seen that it is possible to use less cumulative dose to eliminate the tumor, although it will take longer to do so (see Subsection 4.2).

Previous study has allowed us to show that the most recommended treatments are mainly metronomic, ahead of MTD therapy, providing greater stability in the concentration of the drug in the body, and translating into greater stability in tumor size (and carrying capacity) at the time of treatment.

To continue with this research, and considering what has been studied in this thesis, we suggest that it could be interesting to establish an optimization problem that encompasses the approach of Subsection 3.2.3 to obtain the largest c_d that is reasonable, and that was beyond the scope of this work. We have also left unanalyzed the case of $\lambda \approx 0$ when looking for the optimal c_d in Subsection 3.2.2.

Bibliography

[1] R. Bellman. "Topics in Pharmacokinetics III: Repeated Dosage and Impulse Control". In: *Mathematical Biosciences* 12 (1971), pp. 1–5.

[2] S. Benzekry, C. Lamont, A. Beheshti, A. Tracz, J. Ebos, L. Hlatky, and P. Hahnfeldt. "Classical Mathematical Models for Description and Prediction of Experimental Tumor Growth". In: *PLoS Computational Biology* 10 (2014), pp. 1–19.

[3] *Cancer Today. International Agency for Research on Cancer*. `https://gco.iarc.fr/today/online-analysis-table`. Accessed: 2022-05-12.

[4] A. D'Onofrio and A. Gandolfi. "Tumour eradication by antiangiogenic therapy: Analysis and extensions of the model by Hahnfeldt et al. (1999)". In: *Mathematical Biosciences* 191 (2004), pp. 159–184.

[5] L. A. Fernández, C. Pola, and J. Sáinz-Pardo. "A mathematical justification for metronomic chemotherapy in oncology". In: *Math. Model. Nat. Phenom.* 17 (2022). Article 12.

[6] P. Hahnfeldt, D. Panigrahy, J. Folkman, and L. Hlatky. "Tumor Development under Angiogenic Signaling A Dynamical Theory of Tumor Growth, Treatment Response, and Postvascular Dormancy". In: *Cancer Research* 59 (1999), pp. 4770–4775.

[7] H.K. Khalil. *Nonlinear Systems*. Prentice Hall, (1996).

[8] J. Mauriz, P. Linares, P. González, and J. Culebras. "Tratamiento antiangiogénico del cáncer". In: *Cirugia Española - CIR ESPAN* 78 (2005), pp. 3–11.

[9] *National Cancer Institute*. `https://www.cancer.gov/`. Accessed: 2022-03-31.

[10] J. Poleszczuk and U. Forys. *Derivation of the Hahnfeldt et al. model tumor angiogenesis model*. Proceedings of the Sixteenth National Conference on Application of Mathematics in Biology and Medicine, (2010).

[11] R. Sachs, L.R. Hlatky, and P. Hahnfeldt. "Simple ODE models of tumor growth and anti-angiogenic or radiation treatment". In: *Mathematical and Computer Modelling* 33 (2001), pp. 1297–1305.

[12] B. Sim, N. MacDonald, and E. Gubish. "Angiostatin and Endostatin: Endogenous Inhibitors of Tumor Growth". In: *Cancer Metastasis Reviews* 19 (2000), pp. 181–90.

[13] H.L. Smith and P. Waltman. *The Theory of the Chemostat*. Cambridge University Press, (1995), pp. 261–263.

[14] R. Vandebril, M. Van Barel, and N. Mastronardi. "A note on the representation and definition of semiseparable matrices". In: *Numerical Linear Algebra with Applications* 12 (2005), pp. 839 –858.

Appendix A

Glossary

Some definitions explored during the work are presented here. They are taken from the National Cancer Institute (see [9]).

- Angiogenesis: process of formation of new blood vessels, that provide nutrients and oxygen to the body's tissues they reach. It's a vital physiological process in body growth and development, but it also supplies the blood that tumors need to thrive, grow and metastasize.
- Antiangiogenic effect: it is the block of nutrients and oxygen needed by a tumor for its development, by inhibiting the growth of new vasculature.
- Carrying capacity: the maximum volume a tumor can reach.
- Clearance λ: elimination rate, i.e. the rate at which the body eliminates the drug.
- Half-life $t_{1/2}$: the time required to reduce the drug concentration to one-half its initial value. In pharmacology, it is considered that the drug is fully eliminated from the organism once the elapsed time since it was applied is five times $t_{1/2}$, where $t_{1/2} = \frac{\ln(2)}{\lambda}$.
- Loading dose: it is the initial dose applied in a treatment, and it is also the largest one. The required drug concentration is quicker achieved if the loading dose is applied.
- Maximum Tolerated Dose (MTD) therapy: the doses applied are the highest ones that can be administered to a patient before unacceptable toxic effects appear. It is required a low dosing frequency so that the drug concentration in the blood is eliminated before each application. They target dividing tumor cells, i.e., they have a cytotoxic effect.
- Metronomic (MN) therapy: doses below the MTD are applied frequently, to maintain the plasma concentration constant. It is less toxic than MTD therapy, and it aims to control tumors by targeting angiogenesis.
- Pharmacodynamics (PD): it is the study of the effects the drugs cause in the body and also their mechanisms of action that produce the therapeutic response. It is 'what the drug does to the body'.
- Steady-state: situation in which the amount of drug administered is equal to the amount of drug eliminated in that same period.