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PROBLEMAS DE OPTIMIZACIÓN ASOCIADOS A MODELOS DE ECUACIONES DIFERENCIALES PARA QUIMIOTERAPIA
(Optimization Problems Associated with Differential Equation Models for Chemotherapy)

Trabajo de Fin de Grado
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Abstract

This report includes our study of some optimization problems that arise when modeling the usual chemotherapy treatments for cancer. Gompertz-type tumor growth is considered and that the effect of the drug is proportional to the growth rate of the untreated tumor (Norton-Simon hypothesis). Also, we use classical pharmacokinetics and two pharmacodynamics: Skipper and Emax.

We study optimization problems for initially fixed dosage times, and we find explicit expressions for their solutions. We show examples that contrast this theoretical study. As far as we know, these are results that have not been published previously.

In addition, we present several numerical results made with MATLAB for two types of drugs used in chemotherapy: one with a long half-life (Cabazitaxel) and another with a short half-life (Temozolomide).

Key words: Optimization problems, chemotherapy, Norton-Simon hypothesis, Skipper model, Emax model.

Resumen

Esta memoria recoge un estudio propio de algunos problemas de optimización que surgen al modelizar los tratamientos habituales de quimioterapia para el cáncer. Se considera el crecimiento tumoral de tipo Gompertz y que el efecto del fármaco es proporcional a la tasa de crecimiento del tumor no tratado (hipótesis de Norton-Simon). Además, utilizamos la farmacocinética clásica y dos farmacodinámicas: Skipper y Emax.

Estudiamos los problemas de optimización con tiempos de dosificación fijos inicialmente, y hallamos expresiones explícitas para sus soluciones. Mostramos ejemplos que contrastan el estudio teórico. Hasta donde nosotros sabemos, son resultados que no han sido publicados previamente.

Además, presentamos varios resultados numéricos realizados con MATLAB para dos tipos de fármacos usados en quimioterapia: uno de vida media larga (Cabazitaxel) y otro de vida media corta (Temozolomide).

Palabras clave: Problemas de optimización, quimioterapia, hipótesis de Norton-Simon, modelo Skipper, modelo Emax.

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Chapter 1

Introduction

1.1 Chemotherapy: history, purpose and use

Cancer is a process of uncontrolled cell growth and spread. There are many types of treatment for this disease, depending on the type and stage of the cancer (how advanced it is, the size of the tumor...). The most common treatments today are surgery, immunotherapy, radiation therapy, and chemotherapy. Chemotherapy is a type of cancer treatment that uses drugs to kill cancer cells. Chemotherapy treatments began to be developed in the early 20th century, and it began to be used to treat cancer in the 1940s.

Depending on the type of tumor and its condition, chemotherapy can have two principal purposes:

- Curative: Its aim is to cure the disease, when it is in a suitable phase. Chemotherapy can reduce the size of a tumor before surgery or radiation therapy. Also, another of its purposes may be to help other treatments work better.
- Palliative: If the state of the tumor is very advanced, chemotherapy can be used in order to control the symptoms produced by it, reduce pain, and in some cases, increase the patient's survival.

There are different ways of administering chemotherapy: intravenous (the most common), oral (for drugs that can be absorbed through the stomach or intestine), or directly in an hospital if important safety measures are needed.

1.2 Metronomic chemotherapy and MTD therapy

The most common therapies in cancer treatments with chemotherapy are MTD therapy and metronomic chemotherapy:

- **MTD (Maximum Tolerated Dose) therapy** consists on administering the maximum tolerated dose with longer rest periods. Its goal is to be as harmful as possible with cancer cells. However, the damage that this type of therapy can cause to healthy cells near the tumor tissue must be taken into account (see [10]).
- **Metronomic chemotherapy** consists of the administration of low doses of the drug over long periods of time and with the minimum possible spacing between doses. By administering the drug in low doses, it is hoped to reduce the toxic effects of the treatment. In addition, being long lasting treatments it is expected to improve the overall effect of the treatment

(see for instance [16]). This therapy is relatively recent (in 2007 there was a talk of it as a new therapeutic strategy for the treatment of breast cancer, see [6]).

1.3 Mathematics in chemotherapy

There are numerous studies that highlight the importance of mathematical models (based on differential equations) in the development of better schedules for chemotherapy treatments (through optimization problems), as well as to predict the effect of certain drugs on patients (see for instance [3] and [12]).

In the mid-1970s, the optimal control theory for chemotherapy treatments was first applied, assuming the log-kill hypothesis, which will be explained in Chapter 2. Therefore, many articles highlight the usefulness of mathematical models to find more effective and less toxic treatments (see [8]).

We can consider different ODE models, such as: exponential, logistic, Bertalanffy for the untreated tumor, which are studied in [1]. In this study we will consider the problems that arise when modeling usual chemotherapy treatments under the assumptions of Gompertz-type tumor growth and the Norton-Simon hypothesis (the effect of the drug is proportional to the growth rate of the untreated tumor). That seem to provide a more precise and realistic framework for chemotherapy (see [8]). In addition we will consider the classical pharmacokinetics and two pharmacodynamics: Skipper and Emax (see Chapter 2).

1.4 Contribution and structure of the work

The interest of this work lies in the fact that it is an innovative study that has not been reported previously, as far as we know. As we have already mentioned, we have based the line of research on the Norton-Simon hypothesis. Most of the mathematical works we have found in this area are restricted to a simpler framework (such as the log-kill hypothesis). However, we have not found any in-depth mathematical studies using Norton-Simon's hypothesis, nor any that reach the results which we have achieved.

The complexity of this work is also illustrated by the fact that the optimization problems studied are mixed, nonlinear, and with numerous variables. In most cases we have obtained explicit expressions of the solutions based on the initial data. For the practical cases, we have carried out numerous programs in MATLAB that have allowed us to make simulations to contrast the theoretical results and, in some cases, to study problems which are complex in their theoretical analysis. We have selected two drugs for the numerical simulations, which we have chosen after analyzing different possibilities, because they were those that gave us more variety in the results as they had very different characteristics. At the same time, both drugs are very used in the clinical practice.

With this work we want to contribute to the study of the theory of optimization in chemotherapy bringing unpublished results and leaving open lines to continue the research.

This report is divided into five chapters. After this introduction, in Chapter 2 we will present the pharmacokinetics and pharmacodynamics models used, and the optimization problems which will

be studied in the following. In Chapters 3 and 4 we will study the above optimization problems for Skipper and Emax models, respectively, their solution and other characteristics, also providing examples to illustrate the theoretical results. Also, in those chapters we will make some numerical simulations for two different drugs, which have different half-life: Temozolomide and Cabazitaxel. Finally, Chapter 5 reviews the results obtained in the previous chapters following the investigations carried out, and proposes new lines to continue the research.

Chapter 2

The optimization problems

The objective of this chapter is to give the general formulation of the optimization problems that we are going to study. For this purpose, we will first deal with some aspects related to pharmacology[1]: pharmacodynamics (PD) and pharmacokinetics (PK). Pharmacodynamics is the study of the biochemical and physiological effects of drugs and their mechanisms of action on the organism. On the other hand, pharmacokinetics studies the processes a drug undergoes from the time it is administered until it is eliminated by the body. As an intuitive idea, we can say that pharmacodynamics can be defined as "what a drug does to the body" and pharmacokinetics as "what the body does to a drug".

As for the drugs used in chemotherapy, we are going to introduce two concepts: the volume of distribution of a drug (V_D) is the theoretical volume (studied in pharmacology) that would be necessary to ensure that all organs or compartments have the same concentration of the drug as in the blood plasma (see [24]). Depending on the type of drug, its units can be L or L/kg if it depends on the patient's weight. Also, many of these drugs are administered according to the patient's body surface area (BSA) which (on average) for men is 1.9 m^2 and for women is 1.6 m^2 (see, for instance [20]).

2.1 Pharmacokinetics

Let $c(t)$ be the concentration of the drug in the body at the instant of time t. The simplest pharmacokinetics model that we can consider is that the body does not interact with the drug, but it is unrealistic although in some works this simplification is used. Instead, let's consider the following first-order Cauchy problem:

$$\begin{cases} c'(t) = -\lambda c(t) + u(t) \\ c(0) = 0 \end{cases}.$$

The term $-\lambda c(t)$ represents that the body is eliminating the drug, and the function $u(t)$ depends on the drug and the way it is administered. In our work, taking into account that N doses $\{d_i\}_{i=1}^N$ are given at the different instants of time $0 \leq t_1 < t_2 < \ldots < t_N$, and considering $\sigma = \dfrac{\alpha}{V_D \beta}$, where β is the patient weight (in kg) if V_D is given in L/kg and α its BSA, we can write:

$$u(t) = \sum_{i=1}^{N} \sigma d_i \delta(t - t_i),$$

[1] Pharmacology is the study of drugs and their action.

where $\delta(t-t_i)$ is the Dirac delta distribution concentrated at t_i.

Therefore, the term $u(t)$ represents that a d_i dose of the drug is given at the instant t_i. Then, the Cauchy problem takes the following form:

$$\begin{cases} c'(t) = -\lambda c(t) + \sum_{i=1}^{N} \sigma d_i \delta(t-t_i) \\ c(0) = 0 \end{cases}, \tag{2.1}$$

To solve problem (2.1), we must do it separately in each interval and we get the following results:

- In $[0,t_1)$, $\begin{cases} c'(t) = -\lambda c(t) \\ c(0) = 0 \end{cases}$ and therefore we get that $c(t) = 0$.
- In $[t_1,t_2)$: $\begin{cases} c'(t) = -\lambda c(t) \\ c(t_1^+) = \sigma d_1 \end{cases}$ and we get that $c(t) = \sigma d_1 e^{\lambda(t_1-t)}$.
- In $[t_2,t_3)$: $\begin{cases} c'(t) = -\lambda c(t) \\ c(t_2^+) = \sigma(d_1 e^{\lambda(t_1-t_2)} + d_2) \end{cases}$ and then $c(t) = \sigma e^{-\lambda t}(d_1 e^{\lambda t_1} + d_2 e^{\lambda t_2})$.
- Proceeding inductively, we obtain the following values for $c(t)$:

$$c(t) = \begin{cases} 0 & t \in [0,t_1) \\ \sigma e^{-\lambda t} d_1 e^{\lambda t_1} & t \in [t_1,t_2) \\ \sigma e^{-\lambda t}(d_1 e^{\lambda t_1} + d_2 e^{\lambda t_2}) & t \in [t_2,t_3) \\ \vdots & \vdots \\ \sigma e^{-\lambda t}(d_1 e^{\lambda t_1} + d_2 e^{\lambda t_2} + \cdots + d_{N-1} e^{\lambda t_{N-1}}) & t \in [t_{N-1},t_N) \\ \sigma e^{-\lambda t}(d_1 e^{\lambda t_1} + d_2 e^{\lambda t_2} + \cdots + d_N e^{\lambda t_N}) & t > t_N \end{cases}. \tag{2.2}$$

2.2 Pharmacodynamics

In the following equations, $L(t)$ represents the volume of the tumor at time t, ξ is its growth rate and, θ the maximum size it can reach. In practice θ can change over time, but we will focus on the problem in which θ is fixed. Also, we are going to consider $\theta = 1$ as the maximum size of the tumor, therefore, if the volume of the tumor is 0.2, we are meaning that it is 20% of the maximum size.

Although several mathematical models can be considered for the study of tumor growth, such as the logistic or exponential, in this case we will use the Gompertzian one, which has been considered recently in numerous studies (see [1]). It is given by the ODE:

$$L'(t) = \xi L(t) \log\left(\frac{\theta}{L(t)}\right). \tag{2.3}$$

There are different models to formulate the effect of chemotherapy on the volume of the tumor, the most basic one is known as log-kill hypothesis:

$$L'(t) = \xi L(t) \log\left(\frac{\theta}{L(t)}\right) - L(t)\tilde{\rho}(t). \tag{2.4}$$

The log-kill hypothesis establishes that a given dose of drug on a chemotherapy treatment kills the same fraction of tumor cells regardless of the size of the tumor at the time of treatment [13]. Note that $\tilde{\rho}(t)$ is related to the level of therapy and the two classic expressions are:

- **Skipper**: $\tilde{\rho}(t) = k_1 c(t)$, with $k_1 \in \mathbb{R}$, $k_1 > 0$.
- **Emax**: $\tilde{\rho}(t) = \dfrac{k_1 c(t)}{k_2 + c(t)}$, with $k_1, k_2 \in \mathbb{R}$, $k_1, k_2 > 0$.

In both cases, k_1 and k_2 are constants that are experimentally estimated. In this study we are going to consider the Norton-Simon hypothesis [8]. It states that the rate of cancer cell death due to the treatment is directly proportional to the tumor growth rate at the time of treatment. That is, we will consider the following Cauchy problem:s

$$\begin{cases} L'(t) = \xi L(t) \log\left(\dfrac{\theta}{L(t)}\right)(1 - \tilde{\rho}(t)) \\ L(0) = L_0 \end{cases}. \tag{2.5}$$

Now let's get the expression of the solution to problem (2.5). We solve the first order separable ODE:

$$\frac{L'(t)}{L(t)\log\left(\dfrac{\theta}{L(t)}\right)} = \xi\,(1 - \tilde{\rho}(t)).$$

We integrate to reach the solution:

$$\text{For any } k \in \mathbb{R},\ \log\left(\log\left(\frac{\theta}{L(t)}\right)\right) = k - \xi \int_0^t (1 - \tilde{\rho}(s))ds \overset{L(0)=L_0}{\Longrightarrow}$$

$$\Longrightarrow \boxed{L(t) = \theta\, exp\left(\log\left(\frac{L_0}{\theta}\right) exp\left(-\xi \int_0^t (1 - \tilde{\rho}(s))ds\right)\right)}. \tag{2.6}$$

Note that the volume of the tumor $L(t)$ depends on the value of $\displaystyle\int_0^t (1 - \tilde{\rho}(s))ds$. We are interested in calculating $L(T)$ (the tumor size at T, the final time to study, fixed a priori, with $T \geq t_N$). As the value of $\tilde{\rho}(s)$ depends on the model considered (Skipper or Emax), $L(T)$ varies according to the model under study:

$$\boxed{L(T) = \theta\, exp\left(\log\left(\frac{L_0}{\theta}\right) exp\left(-\xi\left(T - \int_0^T \tilde{\rho}(s)ds\right)\right)\right)}. \tag{2.7}$$

2.3 Associated optimization problems

We are going to study two different optimization problems that arise when modeling the usual chemotherapy treatments for cancer, under the assumptions of tumor growth of the Gompertz model and the Norton-Simon hypothesis, considering the classical pharmacokinetic and the Skipper or Emax pharmacodynamic in each case. Be the times in which the doses are given $0 \leq t_1 < \ldots < t_N \leq T$, fixed during all this work. In addition, each given dose must be between a maximum dose, d_{max}, (for reasons of toxicity), and above a minimum dose, $d_{min} > 0$, so that the treatment is effective.

- In the first problem, the goal is to minimize the volume of the tumor, subject to a total dose, $D > 0$, which is divided into N doses, $\{d_i\}_{i=1}^N$ in the treatment period. Hence we consider the following problem with $N + 1$ variables:

$$(P_1)\begin{cases} Min\ \ L(T) \\ N \in \mathbb{N}, d \in \mathbb{R}^N \\ \text{subject to } \displaystyle\sum_{i=1}^N d_i = D, \\ \qquad\qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1, \ldots, N\}, \end{cases}, \tag{2.8}$$

As we saw in (2.7), the volume of the tumor $L(T)$ depends on the value of $\int_0^T \tilde{\rho}(s)ds$. Also, as $L_0 < \theta$ (because L_0 is the initial tumor volume and θ is its maximum volume), $\log\left(\frac{L_0}{\theta}\right) < 0$, so (P_1) is equivalent to the following problem:

$$(\hat{P}_1)\begin{cases} Max \int_0^T \tilde{\rho}(s)ds \\ N \in \mathbb{N}, d \in \mathbb{R}^N \\ \text{subject to } \sum_{i=1}^N d_i = D, \\ \qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1, \dots, N\}, \end{cases}, \tag{2.9}$$

- Now, let's present the problem in which we want to maintain the tumor volume under a level that is not harmful to the patient, allowing him to lead a normal life (formulations considered, for example, in [4] and [9]). Then, be L_* the maximum tumor size allowed at the final time T. We are going to minimize the total dose that a patient should take for a specified period of time so that the volume of the tumor at T does not exceed L_*. We consider the same restrictions on doses as in the previous case:

$$(P_2)\begin{cases} Min \sum_{i=1}^N d_i \\ N \in \mathbb{N}, d \in \mathbb{R}^N \\ \text{subject to } L(T) \leq L_* \\ \qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1, \dots, N\}, \end{cases}, \tag{2.10}$$

with $L_* \in (0, 1)$.
Let's see a condition equivalent to $L(T) \leq L_*$:

$$\begin{aligned} L(T) \leq L_* &\iff \theta\, exp\left(\log\left(\frac{L_0}{\theta}\right) exp\left(-\xi\left(T - \int_0^T \tilde{\rho}(s)ds\right)\right)\right) \leq L_* \iff \\ &\iff \log\left(\frac{L_0}{\theta}\right) exp\left(-\xi\left(T - \int_0^T \tilde{\rho}(s)ds\right)\right) \leq \log\left(\frac{L_*}{\theta}\right) \iff \\ \iff T - \int_0^T \tilde{\rho}(s)ds &\leq -\frac{1}{\xi}\log\left(\frac{\log\left(\frac{L_*}{\theta}\right)}{\log\left(\frac{L_0}{\theta}\right)}\right) \iff \boxed{\int_0^T \tilde{\rho}(s)ds \geq T + \tilde{\gamma}}, \end{aligned} \tag{2.11}$$

with $\tilde{\gamma} = \frac{1}{\xi}\log\left(\frac{\log\left(\frac{L_*}{\theta}\right)}{\log\left(\frac{L_0}{\theta}\right)}\right)$.
We can therefore reformulate the problem (P_2) as follows:

$$(\hat{P}_2)\begin{cases} Min \sum_{i=1}^N d_i \\ N \in \mathbb{N}, d \in \mathbb{R}^N \\ \text{subject to } \int_0^T \tilde{\rho}(s)ds \geq T + \tilde{\gamma} \\ \qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1, \dots, N\}. \end{cases}. \tag{2.12}$$

In Chapters 3 and 4 we are going to consider these two problems, $(\hat{P}_1)$ and $(\hat{P}_2)$ for the two pharmacodynamic models under study: Skipper and Emax, so we must calculate $\int_0^T \tilde{\rho}(s)ds$ for each case.

Chapter 3

Skipper model

In this chapter we consider (2.5) with the Skipper model for the level of therapy, in which $\tilde{\rho}(t) = k_1 c(t)$, with $k_1 > 0$ a given constant and $c(t)$ as we have defined in (2.2).

We are interested in the formulation that takes in this case the two optimization problems raised in the previous chapter: $(\hat{P}_1)$ and $(\hat{P}_2)$. Then, let's calculate $\int_0^T c(s)ds$. Using (2.2):

$$\begin{aligned}
\int_{\mathbf{0}}^{\mathbf{T}} \boldsymbol{c(s)ds} = &\int_{t_1}^{t_2} \sigma e^{-\lambda s} d_1 e^{\lambda t_1} ds + \int_{t_2}^{t_3} \sigma e^{-\lambda s}(d_1 e^{\lambda t_1} + d_2 e^{\lambda t_2}) ds + \cdots + \\
&\int_{t_{N-1}}^{t_N} \sigma e^{-\lambda s}(d_1 e^{\lambda t_1} + \cdots + d_{N-1} e^{\lambda t_{N-1}}) ds + \int_{t_N}^{T} \sigma e^{-\lambda s}(d_1 e^{\lambda t_1} + \cdots + d_N e^{\lambda t_N}) ds = \\
&\sigma\left(-\frac{d_1}{\lambda} e^{\lambda(t_1 - t_2)} + \frac{d_1}{\lambda}\right) + \sigma\left(-\frac{d_1}{\lambda} e^{\lambda(t_1 - t_3)} - \frac{d_2}{\lambda} e^{\lambda(t_2 - t_3)} + \frac{d_1}{\lambda} e^{\lambda(t_1 - t_2)} + \frac{d_2}{\lambda}\right) + \cdots + \\
&+ \sigma\left(-\frac{d_1}{\lambda} e^{\lambda(t_1 - t_N)} - \cdots - \frac{d_{N-1}}{\lambda} e^{\lambda(t_{N-1} - t_N)} + \frac{d_1}{\lambda} e^{\lambda(t_1 - t_{N-1})} + \cdots + \frac{d_{N-1}}{\lambda}\right) + \\
&+ \sigma\left(-\frac{d_1}{\lambda} e^{\lambda(t_1 - T)} - \cdots - \frac{d_N}{\lambda} e^{\lambda(t_N - T)} + \frac{d_1}{\lambda} e^{\lambda(t_1 - t_N)} + \cdots + \frac{d_N}{\lambda}\right) = \\
&= \sigma\left(\frac{d_1}{\lambda}\left(1 - e^{\lambda(t_1 - T)}\right) + \frac{d_2}{\lambda}\left(1 - e^{\lambda(t_2 - T)}\right) + \cdots + \frac{d_N}{\lambda}\left(1 - e^{\lambda(t_N - T)}\right)\right) = \\
&= \boxed{\frac{\sigma}{\lambda} \sum_{i=1}^{N} d_i \left(1 - e^{\lambda(t_i - T)}\right)}.
\end{aligned} \tag{3.1}$$

Then, we get the following expression for $L(T)$:

$$L(T) = \theta \, exp\left(\log\left(\frac{L_0}{\theta}\right) exp\left(-\xi\left(T - \frac{k_1 \sigma}{\lambda} \sum_{i=1}^{N} d_i \left(1 - e^{\lambda(t_i - T)}\right)\right)\right)\right). \tag{3.2}$$

3.1 Minimizing the tumor volume with a fixed cumulative dose

We will start by considering the problem $(\hat{P}_1)$ defined in Section 2.3, in which we want to minimize the tumor volume at time T. Using (3.1), $\sigma, \lambda > 0$, we reformulate the problem $(\hat{P}_1)$ as follows:

$$(P_{1S}) \begin{cases} Max \;\; f(N,d) = \sum_{i=1}^{N} \left(1 - e^{\lambda(t_i - T)}\right) d_i \\ N \in \mathbb{N}, d \in \mathbb{R}^N \\ \text{subject to} \quad \sum_{i=1}^{N} d_i = D, \\ \qquad\qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1, \ldots, N\}, \end{cases}.$$

Note that (P_{1S}) is a mixed optimization problem, that is, it has N continuous variables, d, and an integer variable, N. In order to have a non-empty set of feasible points, N must take a finite number of values ($N \in [\frac{D}{d_{max}}, \frac{D}{d_{min}}] \cap \mathbb{N}$). We are interested in solving this problem for each of these values. Furthermore, by setting the value of N, we are going to solve the following problem:

$$(P_{1S}^N) \begin{cases} Max \;\; f_1^N(d) = \sum_{i=1}^{N} w_i d_i \\ d \in \mathbb{R}^N \\ \text{subject to} \quad \sum_{i=1}^{N} d_i = D, \\ \qquad\qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1, \ldots, N\} \end{cases}.$$

with $0 < w_N < \ldots < w_2 < w_1 < 1$. In the two following theorems we consider a general array w, so they are valid for a more general problem where the coefficients of the objective function verify the previous inequality. Later, when we come back to (P_{1S}) resolution, we will take $w_i = 1 - e^{\lambda(t_i - T)}$ (remember that $\{t_i\}_{i=1}^N$ are fixed and verify $0 \leq t_1 < t_2 < \ldots < t_N \leq T$).

Theorem 3.1.1. *If $d_{min} > 0$ and $N \in \left[\frac{D}{d_{max}}, \frac{D}{d_{min}}\right] \cap \mathbb{N}$, then the problem (P_{1S}^N) has, at least, a solution.*

Proof. Be K_1 the set of restrictions of the problem (P_{1S}^N), as $N \in \left[\frac{D}{d_{max}}, \frac{D}{d_{min}}\right] \cap \mathbb{N}$, then $K_1 \neq \emptyset$. Let's consider the following continuous functions:

- $g_1 : \mathbb{R}^N \longrightarrow \mathbb{R}$ such as $g_1(d) = \sum_{i=1}^{N} d_i - D$.
- $\hat{g}_i : \mathbb{R}^N \longrightarrow \mathbb{R}$ such as $\hat{g}_i(d) = d_i$, $\forall i \in \{1, \ldots, N\}$.

Now we can represent the set of restrictions of problem (P_{1S}^N), K_1, as follows:

$$K_1 = g_1^{-1}(\{0\}) \cap \left(\bigcap_{i=1}^{N} \hat{g}_i{}^{-1}([d_{min}, d_{max}]) \right).$$

K_1 is closed because it is an intersection of closed sets. Furthermore, as all the variables are bounded, K_1 is compact. Since K_1 is compact and the function f_1^N is continuous, there is at least a global solution to the problem (P_{1S}^N) (see Appendix A). □

Theorem 3.1.2. *Under the hypothesis of the previous theorem, the solution of problem (P_{1S}^N) is:*

1. $(d_{min}, \ldots, d_{min})$ *if* $N = \dfrac{D}{d_{min}} \in \mathbb{N}$.
2. $(d_{max}, \ldots, d_{max})$ *if* $N = \dfrac{D}{d_{max}} \in \mathbb{N}$.

3. $(d_{max}, \ldots, d_{max}, d^*, d_{min}, \ldots, d_{min})$ *if* $\frac{D}{d_{max}} < N < \frac{D}{d_{min}}$, $N \in \mathbb{N}$, *with* d^* *verifying* $d_{min} \leq d^* \leq d_{max}$ *and* $d^* = D - (j_0 - 1)d_{max} - (N - j_0)d_{min}$, *where* $j_0 = max\{j \in \{1, \ldots, N\} : (j_0 - 1)d_{max} + (N - j_0 + 1)d_{min} \leq D\}$.

Proof. Let's study the different possible cases:

1. If $D = Nd_{min}$ with $N \in \mathbb{N}$, then $\overline{d} = (d_{min}, \ldots, d_{min})$ it is the solution of the problem because is the unique feasible point.

2. If $D = Nd_{max}$ with $N \in \mathbb{N}$, then $\overline{d} = (d_{max}, \ldots, d_{max})$ is the unique feasible point.

3. If $D \in (Nd_{min}, Nd_{max})$ with $N \in \mathbb{N}$:

   - If $D \in [(N-1)d_{max} + d_{min}, Nd_{max})$, $\overline{d} = (d_{max}, \ldots, d_{max}, d^*)$ is the solution with $d^* = D - (N-1)d_{max}$. Indeed, using $w_1 > w_2 > \ldots > w_N$, $f(\overline{d}) > f(d)$, $\forall d \in \mathbb{R}^N$, d being a feasible point.
   - If $D \in [(N-2)d_{max} + 2d_{min}, (N-1)d_{max} + d_{min})$, $\overline{d} = (d_{max}, \ldots, d_{max}, d^*, d_{min})$ is the solution with $d^* = D - (N-2)d_{max} - d_{min}$. Again, using $w_1 > w_2 > \ldots > w_N$, $f(\overline{d}) > f(d)$, $\forall d \in \mathbb{R}^N$, d being a feasible point.
   - If $D \in [(j_0 - 1)\, d_{max} + (N - j_0 + 1)\, d_{min}, j_0\, d_{max} + (N - j_0)\, d_{min})$, following the pattern of the two previous cases, $\overline{d} = (\underbrace{d_{max}, \ldots, d_{max}}_{j_0 - 1}, d^*, \underbrace{d_{min}, \ldots, d_{min}}_{N - j_0})$ is the solution of (P_{1S}^N), with $d^* = D - (j_0 - 1)d_{max} - (N - j_0)d_{min}$, $d_{min} \leq d^* \leq d_{max}$ and with $j_0 = max\{j \in \{1, \ldots, N\} : (j_0 - 1)d_{max} + (N - j_0 + 1)d_{min} \leq D\}$.

□

In Theorem 3.1.2 we have seen that the solution of (P_{1S}^N) does not depend on the values of w_i against what might seem intuitively (although the value of the objective function depends on them). Note that only the strictly decreasing order of these values has been used.
Now, we know how to solve (P_{1S}^N) for each value of $N \in \mathbb{N}$, $\frac{D}{d_{max}} \leq N \leq \frac{D}{d_{min}}$. Then, to try to solve (P_{1S}) we propose the following strategy:

- First, we can consider $N = \lceil \frac{D}{d_{max}} \rceil$, where $\lceil x \rceil$ denotes the smallest integer that is not less than x. Then, we solve the problem (P_{1S}^N) to get $\overline{d}^{(N)}$. To evaluate the objective function $f_1^N(\overline{d}^{(N)})$ we need to know the coefficients $\{w_i\}_{i=1}^N$ from the pre-set values of $\{t_i\}_{i=1}^N$ (according to the specialists' criteria).

- Then, we can repeat this process for $N = \lceil \frac{D}{d_{max}} \rceil + k$, $k \in \mathbb{N}$, verifying $N \leq \frac{D}{d_{min}}$.

Then, a solution of (P_{1S}) is each tuple $(N, \overline{d}^{(N)})$ which maximizes $\{f_1^N(\overline{d}^{(N)}) : N \in \left[\frac{D}{d_{max}}, \frac{D}{d_{min}}\right] \cap \mathbb{N}\}$.

To illustrate this procedure, let's see an example (only for mathematical purposes) where we consider the times fixed and solve (P_{1S}^N) for each feasible value of N.

Example 3.1.1. *Be* $D = 1050\ mg/m^2$, $d_{min} = 100\ mg/m^2$, $d_{max} = 200\ mg/m^2$, $T = 28$, $\lambda = 0.1$ *and the times fixed for each value of* N: $t_1 = 0$ *and* $t_{i+1} = 2 + t_i\ \forall i \in \{1, \ldots, N-1\}$. *The values have been chosen for illustrative purposes and they are not based on clinical practice. In order to solve problem* (P_{1S}) *with these data, we have to solve* (P_{1S}^N) *for* $N \in [5.25, 10.50] \cap \mathbb{N}$:

- *If* $N = 6$, *be* $\overline{t}^{(6)} = (0, 2, 4, 6, 8, 10)$. *Then,* $\overline{d}^{(6)} = (200, 200, 200, 200, 150, 100)$, *and* $f_1^6(\overline{d}^{(6)}) = 945.85$.
- *If* $N = 7$, *be* $\overline{t}^{(7)} = (0, 2, 4, 6, 8, 10, 12)$. *Then* $\overline{d}^{(7)} = (200, 200, 200, 150, 100, 100, 100)$ *and* $f_1^7(\overline{d}^{(18)}) = 937.97$.
- *If* $N = 8$, *then* $\overline{d}^{(8)} = (200, 200, 150, \underbrace{100, \ldots, 100}_{5})$ *and* $f_1^8(\overline{d}^{(8)}) = 923.38$.
- *If* $N = 9$, *then* $\overline{d}^{(9)} = (200, 150, \underbrace{100, \ldots, 100}_{7})$ *and* $f_1^9(\overline{d}^{(9)}) = 901.51$.
- *If* $N = 10$, *then* $\overline{d}^{(10)} = (150, \underbrace{100, 100, \ldots, 100}_{9})$ *and* $f_1^{10}(\overline{d}^{(10)}) = 871.48$.

Finally, the solution for (P_{1S}) *in this case is the tuple* $(6, \overline{d}^{(6)})$ *because we get that* $max\{f_1^N(\overline{d}^{(N)}), N \in \{6, \ldots, 10\}\} = f_1^6(\overline{d}^{(6)})$.

Once the general scheme for the resolution of the problem (P_{1S}) is clear, note that the coefficients of the objective function depend on λ, so we can distinguish two cases depending on the type of drug used:

- If $\lambda >> 0$, then $\left(1 - e^{\lambda(t_i - T)}\right) \approx 1$, and as a consequence the influence of dosing times is hardly noticeable and only total dose $\sum_{i=1}^{N} d_i = D$ matters. For example, this would be the case of short-lived drugs, whose treatments are carried out for long periods of time. Let's go back to the Example 3.1.1, and now consider the case of Temozolomide, where $\lambda = 9.242$:

  Example 3.1.2. *With the data of the Example 3.1.1 and* $\lambda = 9.242$, *we obtain five solutions for* (P_{1S}): $\bar{d}^{(N)}$ *for* $N \in \{6, 7, 8, 9, 10\}$. *In all these cases the numerical result* $f_1^N(\bar{d}^{(N)}) = 1050$ *is obtained.*

  Also, in Table 3.1 in Section 3.3 we see that treatments 2 and 3 described in Figure 3.1 achieve the same objective (in both the same total dose is given). From the computational point of view there are an infinite number of solutions in this case.

- If the value of λ or λT is not big, then the terms $\sum_{i=1}^{N} d_i \left(1 - e^{\lambda(t_i - T)}\right)$ and $\sum_{i=1}^{N} d_i$ behave differently, so the dosing time influence the value of the objective function in the solution. In Table 3.4 in Section 3.4 we will see an example of this situation for the drug Cabazitaxel, with the treatments of 20 mg/m^2 dose every 3 week and 10 mg/m^2 dose once a week (in both the same cumulative dose is given but the final tumor size is different).

To conclude this section, let's look at an example of the influence of times on results, considering the same doses:

Example 3.1.3. *Be* $N = 6$, $\bar{d} = (200, 200, 200, 200, 200, 200)$, *and* $\tilde{t} = (1, 2, 3, 4, 5, 28)$, $\hat{t} = (1, 6, 11, 16, 21, 26)$, $T = 29$:

- *If* $\lambda = 9.242$, *with both* $\tilde{t}$ *and* $\hat{t}$, $f_1^N(\bar{d}) = 1200$. *In this case, we can see that there is no influence of the time on the value of the objective function in* $\bar{d}$.
- *If* $\lambda = 0.1$, *with* $\tilde{t}$, $f_1^N(\bar{d}) = 944.01$ *and with* $\hat{t}$, $f_1^N(\bar{d}) = 842.19$. *We observe that in this case, the dosing times influence the value of the objective function in* $\bar{d}$, *giving a better result than the one obtained with* $\tilde{t}$.

3.2 Minimizing the cumulative dose and keeping the tumor size below a level

As in (2.10), we are interested in minimizing the given drug dose, but with a constraint on the tumor size at the final time: $L(T) \leq L_*$, where L_* is a given level beforehand. Using (2.11), the Skipper model and (3.1), that constraint is equivalent to the following inequality:

$$\sum_{i=1}^{N} d_i \left(1 - e^{\lambda(t_i - T)}\right) \geq \gamma, \text{ with } \gamma = \frac{\lambda}{k_1 \sigma} \left(T + \tilde{\gamma}\right). \tag{3.3}$$

Remember that as we defined $\tilde{\gamma}$ in Section 2.3, this constant depends on the data ξ, θ, L_0 and L_*. Therefore the optimization problems (P_2) and $(\hat{P}_2)$ can be reformulated as follows:

$$(P_{2S}) \begin{cases} Min \;\; \tilde{f}(N, d) = \sum_{i=1}^{N} d_i \\ N \in \mathbb{N}, d \in \mathbb{R}^N \\ \text{subject to } \sum_{i=1}^{N} d_i \left(1 - e^{\lambda(t_i - T)}\right) \geq \gamma, \\ \qquad\qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1, \ldots, N\}. \end{cases}.$$

with $d_{min} > 0$ and $\gamma \in \mathbb{R}$ defined as in (3.3). This problem is a mixed optimization problem, because it has continuous variables, d, and an integer variable, N. In this case, let us note that there is an infinite set of feasible N values, but only a finite subset of them has practical interest. First of all, using $d_i < d_{max}$ we have the bound $\gamma \leq \sum_{i=1}^{N} d_{max} \left(1 - e^{\lambda(t_i - T)}\right)$. On the other hand, there should be a $\hat{N}$ large enough so that $\sum_{i=1}^{\hat{N}} d_{min} \left(1 - e^{\lambda(t_i - T)}\right) \geq \gamma$. Once we find that value, it doesn't make sense to take a higher value, since if $N > \hat{N}$, then $\tilde{f}(\hat{N}, \hat{d}) = \hat{N} d_{min} < \tilde{f}(N, d)$ for $\hat{d} = (d_{min}, \ldots, d_{min})$ and for all (N, d) feasible for (P_{2S}). If we fix the value of N we get the following problem of N variables:

$$(P_{2S}^N) \begin{cases} Min \;\; f_2^N(d) = \sum_{i=1}^{N} d_i \\ d \in \mathbb{R}^N \\ \text{subject to } \sum_{i=1}^{N} w_i d_i \geq \gamma, \\ \qquad\qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1, \ldots, N\} \end{cases}.$$

with $w_i = 1 - e^{\lambda(t_i - T)}$, $0 < w_i < 1$, $\forall i \in \{1, \ldots, N\}$ and $w_1 > w_2 > \ldots > w_N$. Note that this problem can be interpreted similarly to the knapsack problem [1].

Theorem 3.2.1. *If $\gamma \leq \sum_{i=1}^{N} w_i d_{max}$, then there is, at least, a solution for (P_{2S}^N).*

Proof. Be K_2 the set of restrictions of the problem (P_{2S}^N). If $\gamma \leq \sum_{i=1}^{N} w_i d_{max}$, then $K_2 \neq \emptyset$. From $K_2 = g_2^{-1}((-\infty, 0]) \cap \left(\bigcap_{i=1}^{N} \hat{g}_i^{-1}([d_{min}, d_{max}])\right)$ with $g_2(d) = -w^T d + \gamma$ and $\hat{g}_i$ the same as that of

[1] It models a situation analogous to minimize the weight of the backpack contents with the restriction that the contents provide a minimum level of nutrition. [22]

problem (P_{1S}^N), we deduce that K_2 is a closed and bounded set. As in addition f_2^N is a continuous function, we conclude that there is a global solution to the problem (P_{2S}^N) (see Appendix A).

□

Theorem 3.2.2. *Under the hypotheses of the above theorem, the solution of the problem* (P_{2S}^N) *is given by:*

1. $(d_{max}, \dots, d_{max})$ *if* $\gamma = \sum_{i=1}^{N} w_i d_{max}$.
2. $(d_{min}, \dots, d_{min})$ *if* $\gamma \leq \sum_{i=1}^{N} w_i d_{min}$.
3. $(d_{max}, \dots, d_{max}, d^*, d_{min}, \dots, d_{min})$ *in other case, where* d^* *verifies:* $d_{min} \leq d^* \leq d_{max}$, $d^* = \left(\gamma - \sum_{i=1}^{j_0-1} w_i d_{max} - \sum_{i=j_0+1}^{N} w_i d_{min}\right) / w_{j_0}$, *with* $j_0 = min\left\{ j \in \{1, \dots, N\} : \gamma \leq \sum_{i=1}^{j} w_i d_{max} + \sum_{i=j+1}^{N} w_i d_{min} \right\}$.

Proof. Let's study the three cases:

1. If $\gamma = \sum_{i=1}^{N} w_i d_{max}$, then $(d_{max}, \dots, d_{max})$ is the solution of (P_{2S}^N), because it's the unique feasible point.
2. If $\gamma \leq \sum_{i=1}^{N} w_i d_{min}$, then $(d_{min}, \dots, d_{min})$ is the solution of (P_{2S}^N) due to the components are the lower bound for d_i, $\forall i \in \{1, \dots, N\}$.
3. Now let us assume that $\gamma \in \left(\sum_{i=1}^{N} w_i d_{min}, \sum_{i=1}^{N} w_i d_{max}\right)$. First let us note that (P_{2S}^N) is a linear programming problem and the necessary and sufficient optimally conditions for $\bar{d}$ being a solution of (P_{2S}^N), are given by the Kuhn-Tucker conditions (see [2]):
   1. $\begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix} - \begin{pmatrix} w_1\mu \\ \vdots \\ w_N\mu \end{pmatrix} + \begin{pmatrix} \overline{\mu_1} \\ \vdots \\ \overline{\mu_N} \end{pmatrix} - \begin{pmatrix} \hat{\mu_1} \\ \vdots \\ \hat{\mu_N} \end{pmatrix} = \begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}$.
   2. $\overline{\mu_i}(\overline{d}_i - d_{max}) = 0$, $\overline{\mu_i} \geq 0$, $\forall i \in \{1, \dots, N\}$.
      $\hat{\mu_i}(-\overline{d}_i + d_{min}) = 0$, $\hat{\mu_i} \geq 0$, $\forall i \in \{1, \dots, N\}$.
      $\mu(-w^T\overline{d} + \gamma) = 0$, $\mu \geq 0$.
   3. $\bar{d}$ must also be feasible.

   Moreover, let us show that those conditions imply that the general linear constraint is active at $\bar{d}$. If $w^T\overline{d} > \gamma$, using conditions 2 and 1 above, we get $\mu = 0$, $1 + \overline{\mu}_i - \hat{\mu}_i = 0$, $\forall i \in \{1, \dots, N\}$ and then $\hat{\mu}_i > 0$ and $\overline{d}_i = d_{min}$, $\forall i \in \{1, \dots, N\}$, which contradicts the fact that $\gamma > \sum_{i=1}^{N} w_i d_{min}$.

   Now, we can distinguish several subcases:

- If $\gamma \in \left(\sum_{i=1}^{N} w_i d_{min}, w_1 d_{max} + \sum_{i=2}^{N} w_i d_{min} \right]$, then $\overline{d} = (d^*, d_{min}, \ldots, d_{min})$, with $d^* = \left(\gamma - \sum_{i=2}^{N} w_i d_{min} \right) / w_1 \in (d_{min}, d_{max}]$ verifies the optimality conditions above with $\overline{\mu}_1, \hat{\mu}_1 = 0$, $\overline{\mu}_i = 0$, $\hat{\mu}_i = 1 - \frac{w_i}{w_1}$, $\forall i \in \{2, \ldots, N\}$ and $\mu = \frac{1}{w_1}$. Let us note that, using $w_i < w_1$, $\forall i \in \{2, \ldots, N\}$, we get $\hat{\mu}_i \geq 0$.
- If $\gamma \in \left(w_1 d_{max} + \sum_{i=2}^{N} w_i d_{min}, (w_1 + w_2) d_{max} + \sum_{i=3}^{N} w_i d_{min} \right]$, taking $\bar{d}_1 = d_{max}$ and arguing as in the previous subcase, we get that $\bar{d} = (d_{max}, d^*, d_{min}, \ldots, d_{min})$ is solution of the problem (P_{2S}^N) with d^* verifying $d^* = \left(\gamma - w_1 d_{max} - \sum_{i=3}^{N} w_i d_{min} \right) / w_2 \in (d_{min}, d_{max}]$. It is enough to take in Kuhn-Tucker conditions the values: $\bar{\mu}_1 = -1 + \frac{w_1}{w_2}$, $\hat{\mu}_1 = 0$, $\bar{\mu}_2 = \hat{\mu}_2 = 0$, $\bar{\mu}_i = 0$, $\hat{\mu}_i = 1 - \frac{w_i}{w_2}$ for $i > 2$ and $\mu = \frac{1}{w_2}$.
- If $\gamma \in \left(\sum_{i=1}^{j_0 - 1} w_i d_{max} + \sum_{i=j_0}^{N} w_i d_{min}, \sum_{i=1}^{j_0} w_i d_{max} + \sum_{i=j_0+1}^{N} w_i d_{min} \right]$, we obtain that the solution $\overline{d}$ is given by:

$$\overline{d}_i = \begin{cases} d_{max} & \text{if } i < j_0 \\ d^* & \text{if } i = j_0 \\ d_{min} & \text{if } i > j_0 \end{cases},$$

where $d^* \in (d_{min}, d_{max}]$, $d^* = \left(\gamma - \sum_{i=1}^{j_0 - 1} w_i d_{max} - \sum_{i=j_0+1}^{N} w_i d_{min} \right) / w_{j_0}$, and

$$j_0 = min \left\{ j \in \{1, ..., N\} : \gamma \leq \sum_{i=1}^{j} w_i d_{max} + \sum_{i=j+1}^{N} w_i d_{min} \right\}.$$

Finally let's prove the uniqueness of solution: using the inequalities of the $\{w_i\}_{i=1}^N$ and that the general inequality constraint is active in $\bar{d}$, $f_2^N(\bar{d}) < f_2^N(d)$ for any other feasible point d. □

From Theorem 3.2.2 we know the structure of the solution of problem (P_{2S}^N), so we have carried out a program in MATLAB that solves it following the scheme of the theorem's proof. Let's see an example in which we set the values of N, w, d_{min}, d_{max} and vary γ:

Example 3.2.1. *Be* $N = 10$, $w_i = \dfrac{1}{(i+1)^2}$, $d_{min} = 10\ mg/m^2$ *and* $d_{max} = 20\ mg/m^2$.

- *If* $\gamma = 5$, *then* $\gamma < d_{min} \sum_{i=1}^{N} w_i$, *so we obtain* $\overline{d} = (\underbrace{10, \ldots, 10}_{N})$.
- *If* $\gamma = 10$, *then we get as a solution* $\overline{d} = (\underbrace{20, 20, 20}_{3}, 14.59, \underbrace{10, \ldots, 10}_{6})$, *with the value* $d^* = 14.59\ mg/m^2$ *in the fourth position.*
- *If* $\gamma = 11$, *we get as a solution* $\overline{d} = (\underbrace{20, \ldots, 20}_{8}, 12.20, 10)$, *with* $d^* = 12.20\ mg/m^2$ *in the ninth position.*
- *If* $\gamma = 12$, *there are no feasible points because* $\gamma > \sum_{i=1}^{N} w_i d_{max}$.

In the previous example we can see the usefulness of the theorem 3.2.2. As we know the structure of the solution of the problem (P_{2S}^N), we can quickly calculate it. Also, in order to solve (P_{2S}) we have to do it for the different values of N with interest in the clinical practice which are also conditioned by the desired duration of the treatment.

3.3 Temozolomide

Temozolomide (Temodar and Temodal) is an oral chemotherapy drug, used for the treatment of refractory anaplastic astrocytoma, which is a type of cancerous brain tumor. Its half life[2] is about 1.8 hours, and its volume of distribution (V_D) is 0.4 L/kg (this information is available at [17]). In Figure 3.1 we show the structure of the usual treatments which we will describe below:

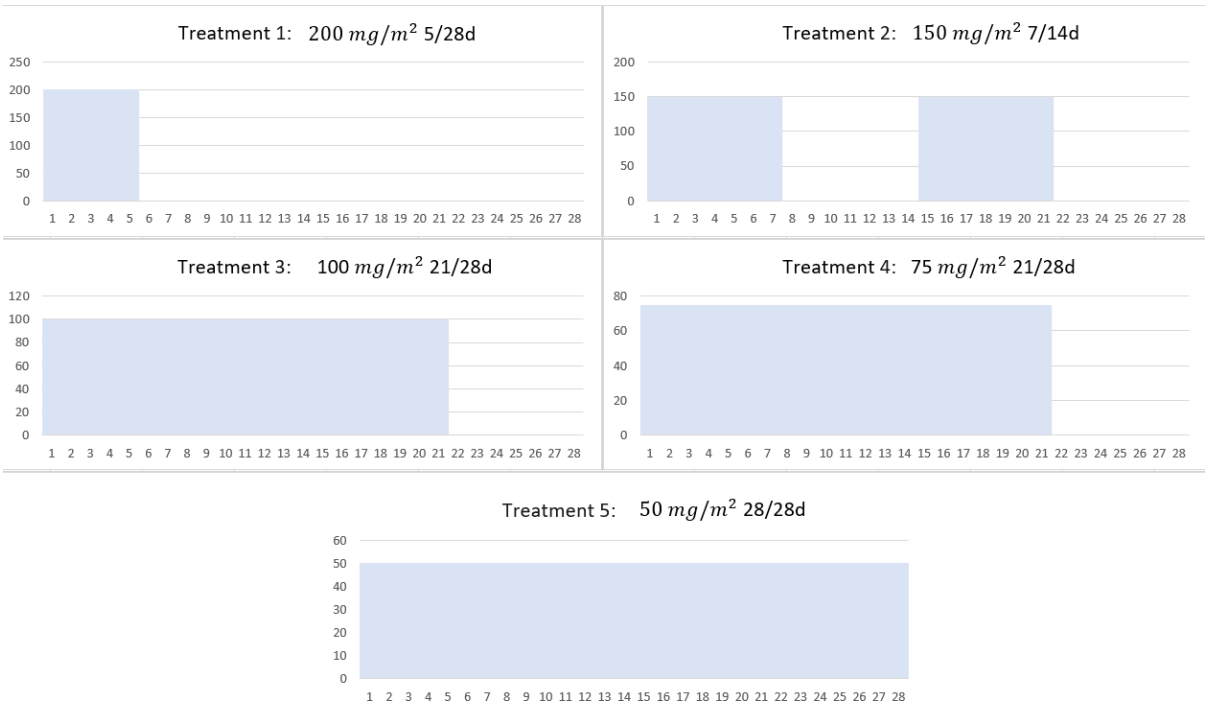

Figure 3.1: Usual treatments with Temozolomide.

- **Treatment 1:** 28 days of treatment, in which the first 5 days a dose of 200 mg/m^2 is given, and the other 23 days no dose is given.
- **Treatment 2:** 28 days of treatment, in which the first 7 days doses of 150 mg/m^2 are given, the next 7 days (between the 8 and the 14) no dose is given, the next 7 days (between 15 and 21) 150 mg/m^2 day dose, and the last 7 days no dose is administrated.
- **Treatment 3:** 28 days of treatment, in which the first 21 days doses of 100 mg/m^2 are administrated, and the other 7 days no dose is given.
- **Treatment 4:** 28 days of treatment, in which the first 21 days doses of 75 mg/m^2 are given, and the other 7 days no dose is administrated.
- **Treatment 5:** 28 days of treatment in which daily doses of 50 mg/m^2 are given.

[2]The half-life of a drug is the time it takes to reduce to half the amount of agent present in the body, through various elimination processes. This is a fundamental parameter for knowing the intervals of application of this drug (see, for instance, [19]).

First of all, we are going to estimate the value of λ of (2.1) using that the half-life of the Temozolomide is about 1.8 hours ($\tilde{t} = 0.075$ days):

$$c'(t) = -\lambda c(t) \Longrightarrow c(t) = c_0 e^{-\lambda t} \Longrightarrow c(\tilde{t}) = \frac{c_0}{2} = c_0 e^{-\lambda \tilde{t}} \Longrightarrow \lambda = \frac{\log(2)}{\tilde{t}} \approx 9.2419 \text{ days}^{-1}.$$

Let's see how can we estimate the value of the parameter ξ of (2.3):
Without medication, $L(t) = \theta \left(\frac{L(0)}{\theta}\right)^{exp(-\xi t)}$ (see (2.7) with $\tilde{\rho} = 0$). If we take $\theta = 1$ as the maximum tumor volume and $L(t^*) = 2L(0)$, we get:

$$L(t^*) = 2L(0) = (L(0))^{exp(-\xi t^*)} \Longrightarrow \log(2L(0)) = exp(-\xi t^*)\log(L(0)) \Longrightarrow$$
$$\Longrightarrow exp(-\xi t^*) = \frac{\log(2L(0))}{\log(L(0))} \Longrightarrow \boxed{\xi = -\frac{1}{t^*}\log\left(\frac{\log(2L(0))}{\log(L(0))}\right)}.$$

The value of t^* depends on the type of tumor and it is calculated experimentally. Taking $L(0) = 0.03$, we can make different estimations depending on the value of t^*, for example, for $t^* = 40$ days, $\xi \approx 0.00551$, for $t^* = 10$ days, $\xi \approx 0.022$, and for $t^* = 2$ days, $\xi \approx 0.11$. In this work we are going to consider $\xi = 0.00551$ (also, see [7]).

Note that the given doses depend on whether the patient is male or female. In each treatment, we estimate the mg of drug that must be given for m^2, and we consider the average BSA which for men is 1.9 m^2 and for women is 1.6 m^2 (see, for instance [20]). For the analysis of Temozolomide, we are going to estimate the constant k_1 of the Skipper model as an academic value to illustrate the theoretical results (its estimation is in itself a complex problem). Let's consider the minimum dose that is applied in treatments, 50 mg/m^2, and 2 mg/m^2 as a dose that has no effect on the body. Then, considering the male's and women's BSA, and the distribution volume ($V_D = 0.4$ L/kg), we can make the following reasoning:

Be c the concentration of the drug in the body at the instant of time t_1, and d_1 the dose given at t_1. Let's consider a man with a weight $\beta = 80$ kg. If the tumor volume decreases with doses of 50 mg/m^2, then by (2.5), $(1 - k_1 c) < 0$. Note that by (2.2) we get that $c = d_1\sigma = \frac{d_1\alpha}{v_D\beta} = 2.96875 \approx 3$ mg/L (σ defined in Section 2.1). So in this case $k_1 > \frac{1}{c} = \frac{1}{3}$. In the same way, if the volume of the tumor increases with doses of 2 mg/m^2, by (2.5), $(1 - k_1 c) > 0$. Now, as $c = \frac{d_1\alpha}{v_D\beta} = 0.11875$ mg/L, in this case $k_1 < \frac{1}{0.11875} \approx 8.42$. Then we get the following interval: $k_1 \in (0.33, 8.42)$. For the case of a woman ($\beta = 60$ kg) we can make an analogous reasoning, so in this case we get: $k_1 \in (0.3, 7.5)$. Finally, for our numerical experiments we will take $k_1 = 3$.

We are going to study what is the total dose given in each usual treatment of Temozolomide, and what is the final size of the tumor at time T, considering a study period of 28 days (from 0 to 27), $T = 29$ (two days after the end of the treatment), $L_0 = 0.03$ and that the patient is a woman (so the final total dose given is always multiplied by 1.6). As an illustration, we are going to compare the results for each treatment taking $k_1 = 3$ and $\xi = 0.00551$. In Table 3.1 we show the results obtained, and in Figure 3.2 the graphic representation of the evolution of the tumor with each treatment.

	L(T)	Total dose
Treatment 1	0.0345	1000 mg/m^2
Treatment 2	0.0215	2100 mg/m^2
Treatment 3	0.0215	2100 mg/m^2
Treatment 4	0.0272	1575 mg/m^2
Treatment 5	0.0293	1400 mg/m^2

Table 3.1: Results obtained for each treatment of Temozolomide and the Skipper model.

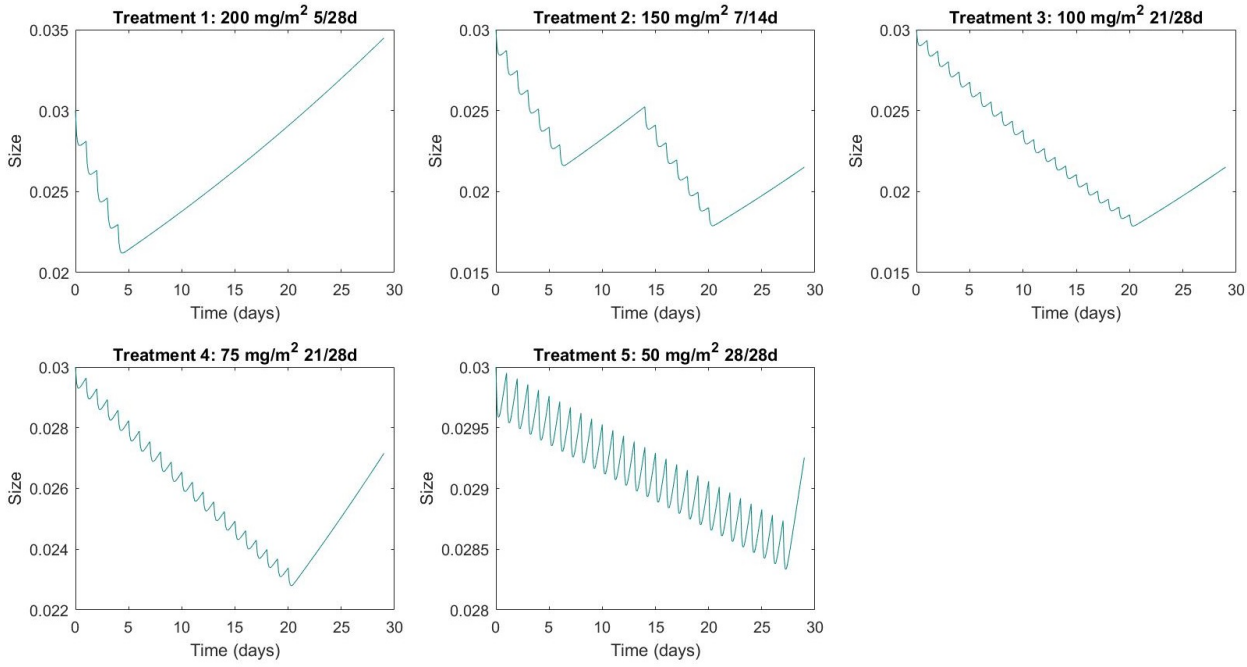

Figure 3.2: Tumor's size evolution with the five treatments.

Note that in treatments 2 and 3, the same total dose is given, and the tumor volume has been reduced to the same size (see rows 2 and 3 of Table 3.1). This exemplifies what was seen in Section 3.1, because in this case $\lambda >> 0$. Furthermore, there is not a great reduction in the volume of the tumor, because if k_1 is small, it means that the human organism has a high resistance to the drug.

In relation to problem $(\hat{P}_2)$ defined in (2.10), assuming that times have no influence, and using what we saw while studying problem (P_{2S}), we have used the total dose so that the bound γ is satisfied in two different ways, with the five treatments considered for Temozolomide. Experimentally we have made the calculations assuming that the patient is a woman of 60 kg, the initial size of the tumor is 0.3 and we do not want it to be greater than 0.5 at the final time $T = 365$. We have also consider $k_1 = 3$ and $\xi = 0.00551$. Let's estimate the bound γ calculated in (3.3): In this specific case, $\tilde{\gamma} = \dfrac{1}{\xi}\log\left(\dfrac{\log\left(\frac{L_*}{\theta}\right)}{\log\left(\frac{L_0}{\theta}\right)}\right) = -100.2068$ and $\sigma = \dfrac{1.6}{24}$. Then, $\gamma = \dfrac{\lambda}{k_1\sigma}\left(T + \tilde{\gamma}\right) = 12236.09$.

- **CASE 1:** Fixed the final time of treatment T and a maximum tumor volume that we do not want to exceed (L_*) we are going to compare the possible treatments, with $d_i = d$, $\forall i \in \{1, ..., N\}$. In this way we are going to study how often each dose of Temozolomide

should be given ($d = 200$, 150, 100, 75 or 50 mg/m^2).

To this end we are going to take into account that the sum of the doses $\{d_i\}_{i=1}^{N}$ must be greater or equal than $\gamma = 12236.09$. As an example, if all doses are of 200 mg/m^2, $N \geq \lceil 12236.09/200 \rceil = 62$. Since we are interested in minimizing the total dose, we take $N = 62$. As the time period under study is 365 days, each dose should be given every $\lfloor 365/62 \rfloor = 5$ days (where $\lfloor x \rfloor$ denotes the largest integer that does not exceed x). We proceed in the same way with the other possible doses, and obtain the results of the second column of Table 3.2, Also, in that table we show the results obtained: the total dose given and the value of $L(T)$, and in Figure 3.3 we can see the evolution of the tumor size for each case.

Dose	**Frequency**	**Total dose**	**L(T)**
200 mg/m^2	62 doses given, every 5 days	12400 mg/m^2	0.4913
150 mg/m^2	82 doses given, every 4 days	12300 mg/m^2	0.4954
100 mg/m^2	123 doses given, every 2 days	12300 mg/m^2	0.4954
75 mg/m^2	164 doses given, every 2 days	12300 mg/m^2	0.4954
50 mg/m^2	245 doses given, every day	12250 mg/m^2	0.4975

Table 3.2: Results obtained for each treatment in CASE 1 with Temozolomide.

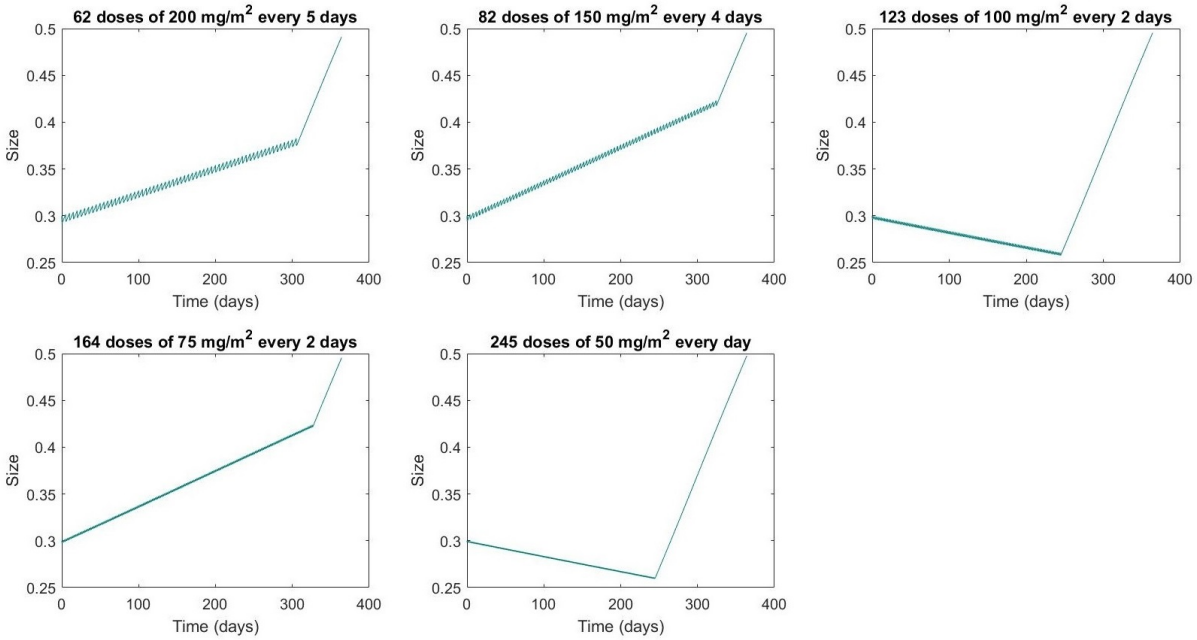

Figure 3.3: Evolution of the tumor size for each case of Table 3.2.

Conclusions: In the first row of Table 3.2, 200 mg/m^2 doses are given every five days during 62 cycles, and the tumor reaches the smallest volume. However this case is not very safe in terms of toxicity: we know that a usual treatment in which 200 mg/m^2 dose are given is carried out for 5 days in a row, and with 23 days off, so it is not clear that it is safe to give that dose it every 5 days. On the other hand, the most reasonable treatment seems to be the fifth, because the maximum allowed tumor size is not exceeded and 50 mg/m^2 dose will be given every day during a period of 245 days with 120 days off (metronomic chemotherapy),

which is reasonable in regards to toxicity because usually, in treatment 5, 50 mg/m^2 dose are given daily. In this instance the final tumor size would be 0.4979. Furthermore, Table 3.2 shows that the reduction in size of the tumor only depends on the total dose given: the higher the total dose, the lower the final tumor size. Also, we can see that in those cases where the same total dose is given (see the rows 2, 3 and 4 of the Table 3.2), the same value of $L(T)$ is reached.

- **CASE 2:** In this case, we are going to estimate how long each treatment should be carried out minimizing the dose given, but without exceeding the maximum tumor volume at the time T, $L_* = 0.5$.

Now let's consider the treatments in Figure 3.1 and the number of doses exposed in the second column of Table 3.2. If we use Treatment 1, taking into account that we need to give 62 doses of 200 mg/m^2 to satisfy the restriction, and that 5 doses are given in each cycle, then 12 cycles and 2 more days (338 days) are needed. Proceeding in a similar way with the rest of the treatments, we obtain the duration of each one of them so that $L(T) \leq L_*$. We show the results in the last column of Table 3.3.

	Dose	**Duration**
Treatment 1	200 mg/m^2	338 days
Treatment 2	150 mg/m^2	152 days
Treatment 3	100 mg/m^2	158 days
Treatment 4	75 mg/m^2	213 days
Treatment 5	50 mg/m^2	245 days

Table 3.3: Results obtained in CASE 2 with Temozolomide.

Conclusions: In Table 3.3 we observe that when the doses given are between 100 and 150 mg/m^2 we get the shortest treatment times. In this case, these two seem the most interesting, since they respect toxicity criteria (being treatments that are commonly used), verify that the volume $L_* = 0.5$ of the tumor is not exceed, and they are the ones which require less treatment time. It is therefore noted that in this case the therapy that seems to be most recommended is not MTD therapy, but smaller doses with less spacing.

3.4 Cabazitaxel

The drug Cabazitaxel is used to treat people with prostate cancer. It belongs to a group of anticancer drugs known as taxanes. These types of drugs prevent cell growth by stopping the cells from dividing. Its half life is about 95 hours and its volume of distribution (V_D) is 4.864 L (see [17]). It is administered intravenously, and the dose varies depending on the patient's body surface, as in the case of Temozolomide. There are numerous studies on the dose that should be administered, and there are three common treatments which depend on the possible adverse reactions that may occur (see [15]):

- **Treatment 1:** 25 mg/m^2 administered for 1 hour intravenously every 3 weeks. It is the most common treatment.
- **Treatment 2:** 20 mg/m^2 administered for 1 hour intravenously every 3 weeks. This treatment is administered in case of adverse reactions.

- **Treatment 3:** 15 mg/m^2 administered for 1 hour intravenously every 3 weeks. This treatment is administered in case the adverse reactions continue after treatment 2.

As we have seen, its half-life is 95 hours (3.96 days), which we can use to estimate the value λ of (2.1) as follows:

$$c'(t) = -\lambda c(t) \Longrightarrow c(t) = c_0 e^{-\lambda t} \Longrightarrow c(\tilde{t}) = \frac{c_0}{2} = c_0 e^{-\lambda \tilde{t}} \Longrightarrow \lambda = \frac{\log(2)}{\tilde{t}} \approx 0.175 \text{ days}^{-1}.$$

In a similarly way to the case of Temozolomide, we are going to take $\xi = 0.00551$ on equation (2.3). Also, we have taken this value based on the one calculated in experimental studies for drugs with long half-life. See, for example [11], where a value $\xi = 0.0075$ is obtained for a drug with long half-life: Bevacizumab.

In order to estimate the value of the constant k_1 of the Skipper model, note that there is not usual to give doses of less than 10 mg/m^2. Then, considering that the minimum dose that is applied in treatments is 10 mg/m^2 and 2 mg/m^2 as a dose that has no effect on the body, and making a reasoning analogous to that of Temozolomide, we take as theoretical value $k_1 = 1.2$ for women and $k_1 = 1$ for men.

We are going to study the 3 treatments exposed previously, and another case that although it's not medically used, serves us to check the results of the Section 3.1 numerically. We want to compare two different treatments but in which the same total dose is given. Therefore, we introduce a fourth treatment in which 10 mg/m^2 dose is administrated every week, so in this treatment the same cumulative dose is given as in treatment 2. Then, let's consider a period of time of 28 days, $T = 29$, $L_0 = 0.03$, and that the patient is a male (so the total dose given will be multiplied by 1.9 and $k_1 = 1$). In Figure 3.4 and in Table 3.4 we can see the comparison of these 4 treatments.

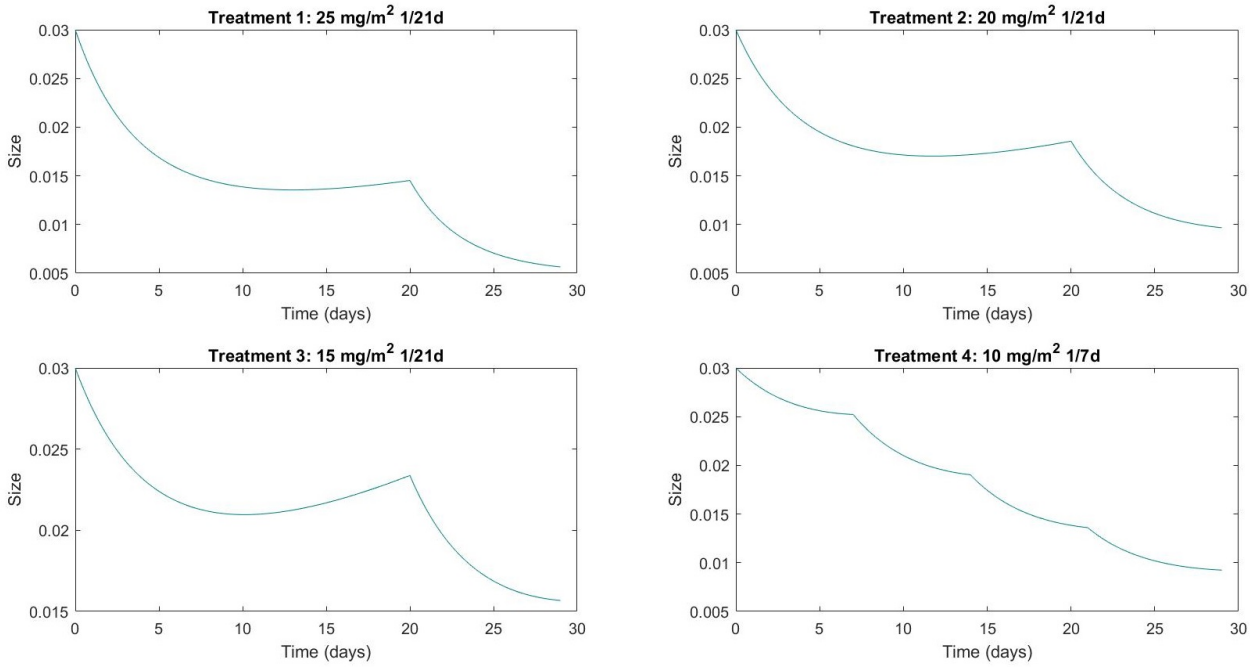

Figure 3.4: Tumor volume evolution with the four treatments of Cabazitaxel.

Dose	Frecuency	Total dose	L(T)
25 mg/m^2	Every 3 weeks	50 mg/m^2	0.0056
20 mg/m^2	Every 3 weeks	40 mg/m^2	0.0097
15 mg/m^2	Every 3 weeks	30 mg/m^2	0.0157
10 mg/m^2	Once a week	40 mg/m^2	0.0092

Table 3.4: Results obtained for each treatment of Cabazitaxel with the Skipper model.

In the case of this drug, in which the value of λ is small ($\lambda = 0.175$), and taking $T = 29$, a small value for λT is obtained. Then, we can observe (as we saw in Section 3.1) that although the total dose given in treatments 2 and 4 is the same, we don't get the same value for the final volume of the tumor (see rows 2 and 3 of Table 3.4).

Now, let's study the problem $(\hat{P}_2)$ by considering the same two cases which we studied for the Temozolomide. Again we are going to assume that the times have no influence. Be $L_0 = 0.3$, $L_* = 0.5$, $k_1 = 1$ (considering that the patient is a male), $\xi = 0.00551$, and $T = 365$, then $\gamma = 118.63$.

- **CASE 1:** For the 3 possible doses, 25, 20 and 15 mg/m^2, we are going to see how many and how often they should be administered during a year so that the final volume of the tumor is less than $L_* = 0.5$. To this end, we have carried out a process analogous to that of the Temozolomide case. In Figure 3.5 we can see the evolution of the volume of the tumor in each case and in the Table 3.5 the results obtained.

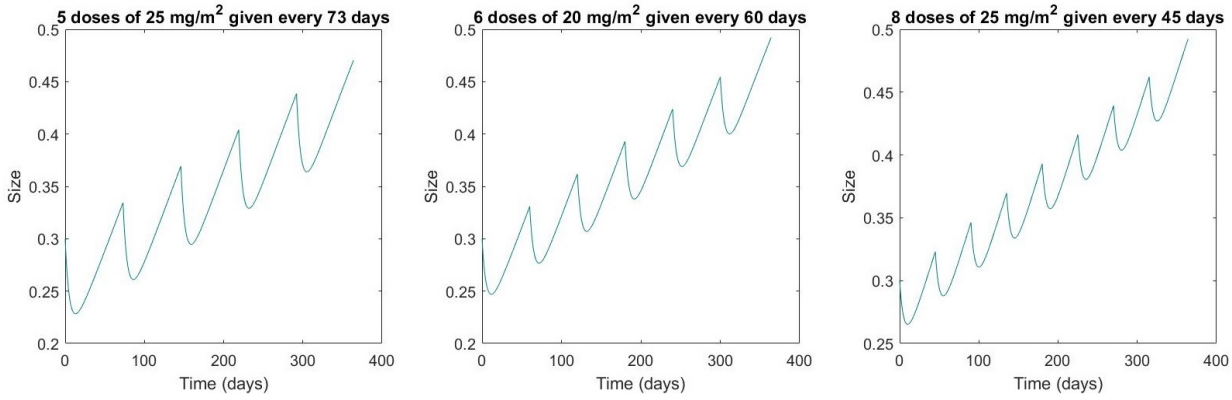

Figure 3.5: Evolution of the tumor size for each treatment of Cabazitaxel using the assumptions of case 1.

Dose	Frequency	Total dose	L(T)
25 mg/m^2	5 doses given, every 73 days	125 mg/m^2	0.47057
20 mg/m^2	6 doses given, every 60 days	120 mg/m^2	0.49221
15 mg/m^2	8 doses given, every 45 days	120 mg/m^2	0.49222

Table 3.5: Results obtained for each treatment in CASE 1 with Cabazitaxel.

Conclusions: As expected, the case that produces the best results is the one in which the total dose administered is higher (see the first row of Table 3.5). On the other hand,

we cannot be sure that these three treatments are effective in practice due to the spacing between doses. Therefore, the treatment that produces the best results is a dose of 25 mg/m^2 every 73 days (only 5 mg/m^2 more are given in total respect the other two cases). Note that now, although the value of λ is small, $\lambda T >> 0$, so there is a great similarity in the final result ($L(T)$) of the two cases where the same total dose is given (see rows 2 and 3 of Table 3.5).

- **CASE 2:** For the 3 possible treatments, we're going to study what the duration of these would be so that the final size of the tumor at $T = 365$ is less than $L_* = 0.5$. Note that in all the cases, a dose is given every 3 weeks. Figure 3.6 represents the evolution of the size of the tumor over a year, and Table 3.6 shows the duration of each treatment and the results obtained.

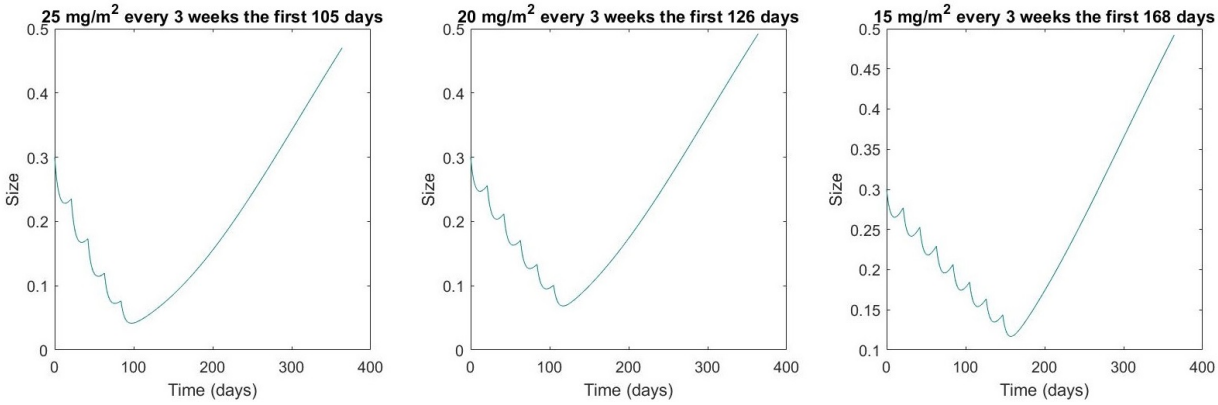

Figure 3.6: Tumor size evolution for each treatment of Cabazitaxel with the assumptions of the case 2.

	Dose	**Duration**	**L(T)**
Treatment 1	25 mg/m^2	105 days	0.47057
Treatment 2	20 mg/m^2	126 days	0.49221
Treatment 3	15 mg/m^2	168 days	0.49221

Table 3.6: Results obtained for each treatment in CASE 2 with Cabazitaxel.

Conclusions: Again, the treatment that produces the best results is the one in which a higher total dose is given and it is also which finishes earlier (first row of Table 3.6). Although λ is small, as $\lambda T >> 0$, in both approaches to the problem we arrive to similar values of $L(T)$. It is also observed that the best results are not produced by the treatment that ends later (the same as in the case of Temozolomide).

To conclude this chapter, let's see why we have decided to consider in the numerical simulations $t_1 = 0$ with a simple two variable example. As in all the cases under study, let's consider $0 \leq t_1 < t_2 \leq T$, and let's assume the following problem:

$$\begin{cases} Max \;\; d_1\left(1 - e^{\lambda(t_1 - T)}\right) + d_2\left(1 - e^{\lambda(t_2 - T)}\right) \\ d \in \mathbb{R}^2 \\ \text{subject to} \;\; d_1 + d_2 = D, \\ \qquad\qquad d_{min} \leq d_1, d_2 \leq d_{max}, \end{cases} \iff \begin{cases} Max \;\; D - e^{-\lambda T}\left(d_1 e^{\lambda t_1} + d_2 e^{\lambda t_2}\right) \\ d \in \mathbb{R}^2 \\ \text{subject to} \;\; d_{min} \leq d_1, d_2 \leq d_{max}, \end{cases} \iff$$

$$\iff \begin{cases} Min \;\; d_1 e^{\lambda t_1} + d_2 e^{\lambda t_2} \\ d \in \mathbb{R}^2 \\ \text{subject to} \;\; d_{min} \leq d_1, d_2 \leq d_{max}, \end{cases} \overset{t_1=0}{\iff} \begin{cases} Min \;\; d_1 + (D - d_1) e^{\lambda t_2} \\ d_1, d_2 \in [d_{min}, d_{max}] \cap [D - d_{max}, D - d_{min}] \end{cases}.$$

Note that in the last equivalence we are taking $t_1 = 0$ the minimum possible value, since our interest is to reduce the volume of the tumor as much as possible.

On the other hand, let's see an example in which the conclusions of Theorem 3.1.2 are not true in the case where the values of the times $\{t_i\}_{i=1}^N$ are not fixed from the beginning. This does not contradict the theorem, since in the hypotheses that led us to state it, we counted on fixed times. With Example 3.4.1 we want to emphasize why we had fixed them initially:

Example 3.4.1. *Be $N = 2$, $\lambda = 1$, $d_{min} = 1\ mg/m^2$, $d_{max} = 9\ mg/m^2$, $D = 10\ mg/m^2$. Let's solve the problem (P_{1S}) without considering the times initially fixed.*

From Theorem 3.1.2, we would consider taking $\overline{d} = (9, 1)$. As in this case we do not consider fixed times, we must estimate $\overline{t}_1$ and $\overline{t}_2$. From what was seen before $\overline{t}_1 = 0$, and as the dose $\overline{d}_1$ is big, we can consider, for example, $\overline{t}_2 = 3$ (3 days between each dose), and the cost functional of the problem would be approximately 29.

Let's consider the case where we start with the lowest dose. That is, $\overline{d} = (1, 9)$. Again we take $\overline{t}_1 = 0$, but now, as the first dose is small, we could consider that one day of spacing is enough, and therefore $\overline{t}_2 = 1$. In this way the cost functional of the problem becomes approximately 25.5.

This shows that the hypothesis of having fixed times is absolutely necessary in Theorem 3.1.2.

Chapter 4

Emax model

For the Emax model, we consider $\tilde{\rho}(t) = \dfrac{k_1 c(t)}{k_2 + c(t)}$ in (2.5), with given $k_1, k_2 > 0$, and $c(t)$ as we have defined in (2.2).

In order to study the problems presented in Section 2.3, using (2.2) and considering $\hat{k}_2 = \dfrac{k_2}{\sigma}$, let's calculate $\displaystyle\int_0^T \frac{c(s)}{k_2 + c(s)} ds$:

$$
\begin{aligned}
\int_0^{\mathbf{T}} \frac{\boldsymbol{c(s)}}{\boldsymbol{k_2 + c(s)}} \boldsymbol{ds} &= \int_{t_1}^{t_2} \frac{e^{-\lambda s} d_1 e^{\lambda t_1}}{\hat{k}_2 + e^{-\lambda s} d_1 e^{\lambda t_1}} ds + \int_{t_2}^{t_3} \frac{e^{-\lambda s}(d_1 e^{\lambda t_1} + d_2 e^{\lambda t_2})}{\hat{k}_2 + e^{-\lambda s}(d_1 e^{\lambda t_1} + d_2 e^{\lambda t_2})} ds + \cdots + \\
&+ \int_{t_{N-1}}^{t_N} \frac{e^{-\lambda s}(d_1 e^{\lambda t_1} + \cdots + d_{N-1} e^{\lambda t_{N-1}})}{\hat{k}_2 + e^{-\lambda s}(d_1 e^{\lambda t_1} + \cdots + d_{N-1} e^{\lambda t_{N-1}})} ds + \\
&+ \int_{t_N}^{T} \frac{e^{-\lambda s}(d_1 e^{\lambda t_1} + \cdots + d_N e^{\lambda t_N})}{\hat{k}_2 + e^{-\lambda s}(d_1 e^{\lambda t_1} + \cdots + d_N e^{\lambda t_N})} ds = \\
&= -\frac{1}{\lambda} \log\left(\frac{d_1 e^{\lambda(t_1 - t_2)} + \hat{k}_2}{d_1 + \hat{k}_2} \right) - \frac{1}{\lambda} \log\left(\frac{d_1 e^{\lambda(t_1 - t_3)} + d_2 e^{\lambda(t_2 - t_3)} + \hat{k}_2}{d_1 e^{\lambda(t_1 - t_2)} + d_2 + \hat{k}_2} \right) - \cdots - \\
&- \frac{1}{\lambda} \log\left(\frac{d_1 e^{\lambda(t_1 - t_N)} + \cdots + d_{N-1} e^{\lambda(t_{N-1} - t_N)} + \hat{k}_2}{d_1 e^{\lambda(t_1 - t_{N-1})} + \cdots + d_{N-2} e^{\lambda(t_{N-2} - t_{N-1})} + d_{N-1} + \hat{k}_2} \right) - \\
&- \frac{1}{\lambda} \log\left(\frac{d_1 e^{\lambda(t_1 - T)} + \cdots + d_N e^{\lambda(t_N - T)} + \hat{k}_2}{d_1 e^{\lambda(t_1 - t_N)} + \cdots + d_{N-1} e^{\lambda(t_{N-1} - t_N)} + d_N + \hat{k}_2} \right) = \\
&= \boxed{\frac{1}{\lambda} \log\left(\frac{(d_1 + \hat{k}_2) \cdots (d_1 e^{\lambda(t_1 - t_N)} + \cdots + d_{N-1} e^{\lambda(t_{N-1} - t_N)} + d_N + \hat{k}_2)}{(d_1 e^{\lambda(t_1 - t_2)} + \hat{k}_2) \cdots (d_1 e^{\lambda(t_1 - T)} + \cdots + d_N e^{\lambda(t_N - T)} + \hat{k}_2)} \right)} \\
&= F(N, d)
\end{aligned}
\tag{4.1}
$$

Then, using (2.7) we get the following expression for $L(T)$:

$$
L(T) = \theta \, exp\left(\log\left(\frac{L_0}{\theta} \right) exp\left(-\xi \left(T - k_1 F(N, d) \right) \right) \right). \tag{4.2}
$$

4.1 Minimizing the tumor volume with a fixed cumulative dose

As in the case of the Skipper model, first of all we want to minimize the tumor volume: problem $(\hat{P}_1)$ defined in Section 2.3. As we saw in that section, it is equivalent to maximize $F(N, d)$:

$$(P_{1E}) \begin{cases} Max \;\; F(N,d) \\ N \in \mathbb{N}, d \in \mathbb{R}^N \\ \text{subject to } \sum_{i=1}^{N} d_i = D, \\ \qquad\qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1,\dots,N\}, \end{cases} . \tag{4.3}$$

In this problem, we have $N+1$ variables to determine: N, d_i, $\forall i \in \{1,\dots,N\}$. As in the previous cases, the values of T, D, d_{min} d_{max} and t_i, $\forall i \in \{1,\dots,N\}$ are fixed. Also, the objective function is nonlinear. To study (P_{1E}) we are going to consider two cases: $\lambda >> 0$ and $\lambda \approx 0$.

4.1.1 Case 1: $\lambda >> 0$

Let's start by studying a simple case, in which $\lambda >> 0$ (for example the case of Temozolomide). Here, the times t_i do not seem to play a relevant role, because as $T > t_i$, $\forall i \in \{1,\dots,N\}$, $\lambda T >> 0$, then $e^{\lambda(t_i - T)} \approx 0$ and $e^{\lambda(t_i - t_j)} \approx 0$, $\forall i,j \in \{1,\dots,N\}, j > i$. Therefore, we can take:

$$F(N,d) \approx \frac{1}{\lambda}\left(\log\left(\prod_{i=1}^{N}(d_i + \hat{k}_2)\right) - \log(\hat{k}_2^N)\right).$$

To maximize $F(N,d)$, as $\hat{k}_2 > 0$ is constant and log is a strictly increasing function , it is equivalent to maximize $\prod_{i=1}^{N}(d_i + \hat{k}_2)$, so we get the problem $(\overline{P}_{1E})$:

$$(\overline{P}_{1E}) \begin{cases} Max \;\; f_3(N,d) = \prod_{i=1}^{N}(d_i + \hat{k}_2) \\ N \in \mathbb{N}, d \in \mathbb{R}^N \\ \text{subject to } \sum_{i=1}^{N} d_i = D, \\ \qquad\qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1,\dots,N\}. \end{cases} .$$

Once more, this is a mixed nonlinear optimization problem, and we have to determine the value of $N+1$ variables: N and $\{d_i\}_{i=1}^{N}$.

Theorem 4.1.1. *If $d_{min} > 0$ and $N \in \left[\frac{D}{d_{max}}, \frac{D}{d_{min}}\right] \cap \mathbb{N}$, then there is a solution for $(\overline{P}_{1E})$.*

Proof. It is enough to consider values of N in the interval $\left[\frac{D}{d_{max}}, \frac{D}{d_{min}}\right] \cap \mathbb{N}$. Then, fixed the value of N, the set of restrictions of the problem is nonempty and compact (it's the same of problem (P_{1S}^N), see the proof of Theorem 3.1.2). Then, as the function f_3 is continuous in the variable d (for N fixed) there is a global solution to the problem $(\overline{P}_{1E})$ (see Appendix A). □

It is a well known result the following relation between the geometric and arithmetic means:

Proposition 4.1.1. *The arithmetic mean of a set of positive numbers ($d_i \in \mathbb{R}^+, i \in \{1,\dots,N\}$) is always equal to or greater than the geometric mean. Therefore, the following inequality is verified:*

$$\sqrt[N]{\prod_{i=1}^{N} d_i} \leq \frac{1}{N}\sum_{i=1}^{N} d_i. \tag{4.4}$$

We only obtain the equality when $d_i = d_j$, $\forall i,j \in \{1,\dots,N\}$.

Proof. See Proposition B.0.1 in Appendix B. □

Using Proposition 4.1.1 for problem $(\overline{P}_{1E})$, we get:

$$\sqrt[N]{\prod_{i=1}^{N}(d_i+\hat{k}_2)} \leq \frac{\sum_{i=1}^{N}(d_i+\hat{k}_2)}{N} = \frac{D}{N}+\hat{k}_2 \Longrightarrow \prod_{i=1}^{N}(d_i+\hat{k}_2) \leq \left(\frac{D}{N}+\hat{k}_2\right)^N. \tag{4.5}$$

Therefore, by (4.5) the maximum of $(\overline{P}_{1E})$ with N fixed is reached when $d_i = \dfrac{D}{N}$, $\forall i \in \{1,\ldots,N\}$. Now we want to study the dependence on N. To do this we are interested in studying the function f_4 defined below. In the following we will write x instead of N, but we are only interested in the values of $x \in \mathbb{N}$.

For simplicity, we will consider the case where D is a natural multiple of d_{min} and d_{max}, that is: $D = N_1\, d_{max} = N_2\, d_{min}$, with $d_{min} > 0$ and $N_1, N_2 \in \mathbb{N}$.

$$(P_4)\begin{cases} Max \;\; f_4(x) = \left(\dfrac{D}{x}+\hat{k}_2\right)^x \\ \text{subject to} \quad x \in [N_1, N_2] \cap \mathbb{N}. \end{cases}.$$

Let's study the growth of the function $f_4(x)$ for different values of $\hat{k}_2$. By hypothesis of the Emax model, we know that it must be $\hat{k}_2 > 0$. Moreover, it is easy to get the derivative:

$$f_4'(x) = \left(\frac{D}{x}+\hat{k}_2\right)^x \left(\log\left(\frac{D}{x}+\hat{k}_2\right) - \frac{D}{D+\hat{k}_2\, x}\right).$$

To see the behavior of function f_4, in Figure 4.1 we represent its graph for $D = 100$ and $\hat{k}_2 \in [0.3, 0.5]$, $\hat{k}_2 \in [1, 1.2]$:

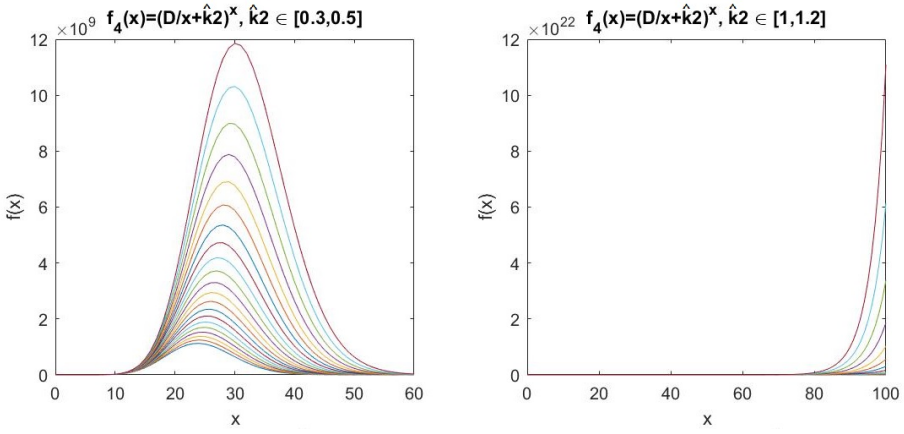

Figure 4.1: Graphic of $f_4(x)$ for different values of $\hat{k}_2$.

Let's study the positive roots of $f_4'(x)$:

$$f_4'(x) = 0 \Longleftrightarrow \log\left(\frac{D}{x}+\hat{k}_2\right) = \frac{D}{D+\hat{k}_2 x} \Longleftrightarrow \log\left(\frac{D}{x}+\hat{k}_2\right)(D+\hat{k}_2 x) = D \Longleftrightarrow$$

$$\Longleftrightarrow \log\left(\frac{D}{x}+\hat{k}_2\right)\left(\frac{D}{x}+\hat{k}_2\right) = \frac{D}{x} \Longleftrightarrow \left(\log\left(\frac{D}{x}+\hat{k}_2\right)-1\right)\left(\frac{D}{x}+\hat{k}_2\right) = -\hat{k}_2 \Longleftrightarrow$$

$$\Longleftrightarrow \left(\log\left(\frac{D}{x}+\hat{k}_2\right)-1\right) e^{\log\left(\frac{D}{x}+\hat{k}_2\right)-1} = -\frac{\hat{k}_2}{e} \overset{\hat{k}_2 \in (0,1)}{\Longleftrightarrow} \log\left(\frac{D}{x}+\hat{k}_2\right) - 1 = W(-\hat{k}_2/e) \Longleftrightarrow$$

$$\iff \frac{D}{x} + \hat{k}_2 = e^{W(-\hat{k}_2/e)+1} \iff \boxed{x = \frac{D}{e^{W(-\hat{k}_2/e)+1} - \hat{k}_2}}, \tag{4.6}$$

where W is the Lambert W function (see Appendix C). Let's see what branch of Lambert's W function we should consider:

$$x > 0 \iff e^{W(-\hat{k}_2/e)+1} > \hat{k}_2 \iff W(-\hat{k}_2/e) > \log(\hat{k}_2/e) \overset{r=\hat{k}_2/e}{\iff} W(-r) > \log(r)$$

In Figure 4.2 we show the graphs of $W(-r)$ and $\log(r)$, and we see that $W(-r) > \log(r)$ if and only if $r \in (0, 1/e)$ (so, as $r = \hat{k}_2/e$, $\hat{k}_2 \in (0, 1)$), then with W we represent the branch W_0 of the W Lambert function:

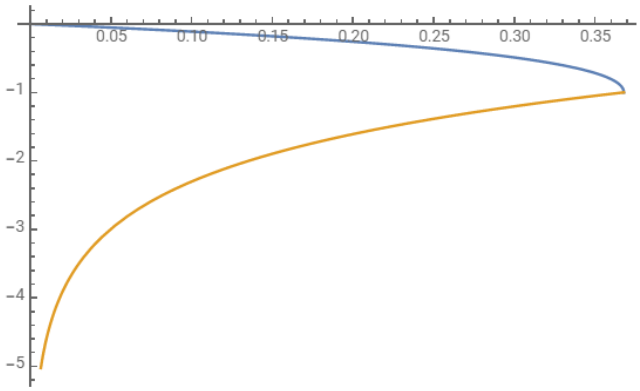

Figure 4.2: Graphs of $W(-r)$ and $\log(r)$.

Then, we distinguish two cases:

- $\hat{k}_2 \geq 1$. As $x > 0$ and $D > 0$, the function f_4 is strictly increasing because it has no real roots for $x > 0$ (see Figure 4.1) and $\lim_{x\to+\infty} \log\left(\frac{D}{x} + \hat{k}_2\right) = \log(\hat{k}_2)$ and $\lim_{x\to+\infty} \frac{D}{D + \hat{k}_2\, x} = 0 < \log(\hat{k}_2)$.

  Then, the solution of (P_4) is $N_2 = \frac{D}{d_{min}}$, and $(N_2, \underbrace{(d_{min}, \ldots, d_{min})}_{N_2})$ is the solution of $(\overline{P}_{1E})$ (Metronomic chemotherapy).

- $0 < \hat{k}_2 < 1$. As $x > 0$, $f_4'(x)$ has one positive root $\overline{x} = \frac{D}{e^{W(-\hat{k}_2/e)+1} - \hat{k}_2}$ then:
  - If $x < \bar{x}$ the function f_4 increases.
  - If $x > \bar{x}$ the function f_4 decreases.

  As the maximum of f_4 is reached at $\bar{x} = \frac{D}{e^{W(-\hat{k}_2/e)+1} - \hat{k}_2}$ let's study the solution of (P_4) and $(\overline{P}_{1E})$:

  - If $e^{W(-\hat{k}_2/e)+1} - \hat{k}_2 \geq d_{max}$, then $N_1 = \frac{D}{d_{max}}$ is the solution of (P_4), and the solution of $(\overline{P}_{1E})$ is $(N_1 \underbrace{(d_{max}, \ldots, d_{max})}_{N_1})$ (MTD therapy).
  - If $e^{W(-\hat{k}_2/e)+1} - \hat{k}_2 \leq d_{min}$, then $N_2 = \frac{D}{d_{min}}$ is the solution of (P_4), and the solution of $(\overline{P}_{1E})$ is $(N_2, \underbrace{(d_{min}, \ldots, d_{min})}_{N_2})$ (Metronomic chemotherapy).

– If $d_{min} \leq e^{W(-\hat{k}_2/e)+1} - \hat{k}_2 \leq d_{max}$ then $N_3 \in \mathbb{N}$ such as $f_4(N_3) \geq f_4(N)$ for each $N \in [N_1, N_2] \cap \mathbb{N}$ is the solution of (P_4), and $\left(N_3, \underbrace{\left(\frac{D}{N_3}, \ldots, \frac{D}{N_3}\right)}_{N_3}\right)$ is the solution of $(\overline{P}_{1E})$, where $N_3 = \lfloor \bar{x} \rfloor$ or $N_3 = \lceil \bar{x} \rceil$.

Let's see an example where we can observe the variation in the solution of the problem $(\overline{P}_{1E})$ according to the value of $\hat{k}_2$:

Example 4.1.1. *Let's set a value for D, d_{min}, d_{max} and vary the value of $\hat{k}_2$ to see how the optimal treatment changes according to the value of this constant. Be $z = e^{W(-\hat{k}_2/e)+1} - \hat{k}_2$:*

a) Be $D = 1000\ mg/m^2$, $d_{min} = 50\ mg/m^2$ and $d_{max} = 200\ mg/m^2$. This is a realistic example for the case of the Temozolomide.

- *If $\hat{k}_2 = 0.2$, $z = 2.31 < d_{min}$, so $N = 20$, $d_i = d_{min} = 50\ mg/m^2$, $i = 1, \ldots, N$.*
- *If $\hat{k}_2 = 0.5$, $z = 1.66 < d_{min}$, so $N = 20$, $d_i = d_{min} = 50\ mg/m^2$, $i = 1, \ldots, N$.*
- *If $\hat{k}_2 \geq 1$, $f_4'(x)$ has no real roots, so we get that again $N = 20$, $d_i = d_{min} = 50\ mg/m^2$, $i = 1, \ldots, N$.*

In view of the treatment 1 defined in Figure 3.1, in the three cases $t = (1, 2, 3, \ldots, 20)$, so the treatment that seems most reasonable is metronomic chemotherapy.

b) Be $D = 100\ mg/m^2$, $d_{min} = 2\ mg/m^2$ and $d_{max} = 10\ mg/m^2$. This is not a realistic example.

- *If $\hat{k}_2 = 0.2$, $z \in (d_{min}, d_{max})$, so $N = 43$, $d_i = 2.33\ mg/m^2$, $i = 1, \ldots, N$.*
- *If $\hat{k}_2 = 0.5$, $z < d_{min}$, so $N = 50$, $d_i = d_{min} = 2\ mg/m^2$, $i = 1, \ldots, N$.*
- *If $\hat{k}_2 \geq 1$, $f_4'(x)$ has no real roots, so $N = 50$ and $d_i = d_{min} = 2\ mg/m^2$, $i = 1, \ldots, N$.*

In this example, when $\hat{k}_2 \geq 0.5$ the treatment that seems to be most effective is metronomic chemotherapy. Note that taking into account the interpretation of $\hat{k}_2$ (whih will be explained in Section 4.3), usually $\hat{k}_2 > 1$.

4.1.2 Case 2: $\lambda \approx 0$

$$\text{Be } h(\lambda) = \log\left(\frac{d_1 + \hat{k}_2}{d_1 e^{\lambda(t_1 - t_2)} + \hat{k}_2}\right) + \log\left(\frac{d_1 e^{\lambda(t_1 - t_2)} + d_2 + \hat{k}_2}{d_1 e^{\lambda(t_1 - t_3)} + d_2 e^{\lambda(t_2 - t_3)} + \hat{k}_2}\right) + \cdots + \\ + \log\left(\frac{d_1 e^{\lambda(t_1 - t_N)} + \cdots + d_N + \hat{k}_2}{d_1 e^{\lambda(t_1 - T)} + \cdots + d_N e^{\lambda(t_N - T)} + \hat{k}_2}\right).$$

Let's consider the case of drugs with long half-life ($\lambda \approx 0$). By (4.1), $\lim_{\lambda \to 0} F(N, d) = \lim_{\lambda \to 0} \frac{h(\lambda)}{\lambda} = \frac{0}{0}$ and let's apply L'Hopital's rule:

$$\begin{aligned}\lim_{\lambda \to 0} h'(\lambda) =& (t_2 - t_1)\frac{d_1}{d_1 + \hat{k}_2} - (t_2 - t_1)\frac{d_1}{d_1 + d_2 + \hat{k}_2} + (t_3 - t_1)\frac{d_1}{d_1 + d_2 + \hat{k}_2} + \\ &+ (t_3 - t_2)\frac{d_1 + d_2}{d_1 + d_2 + \hat{k}_2} + \cdots + \frac{d_1(t_1 - t_N) + \cdots + d_{N-1}(t_{N-1} - t_N)}{d_1 + \cdots + d_N + \hat{k}_2} - \\ &- \frac{d_1(t_1 - T) - \cdots - d_N(t_N - T)}{d_1 + \cdots + d_N + \hat{k}_2} = \\ =& \boxed{(t_2 - t_1)\frac{d_1}{d_1 + \hat{k}_2} + (t_3 - t_2)\frac{d_1 + d_2}{d_1 + d_2 + \hat{k}_2} + \cdots + (T - t_N)\frac{d_1 + \cdots + d_N}{d_1 + \cdots + d_N + \hat{k}_2}}.\end{aligned}$$

Therefore, we can consider the following optimization problem to minimize $L(T)$, with N variable:

$$(\tilde{P}_{1E}) \begin{cases} Min \;\; \tilde{f}_5(N,d) = -\dfrac{(t_2-t_1)d_1}{d_1+k_2} - \dfrac{(t_3-t_2)(d_1+d_2)}{d_1+d_2+k_2} - \cdots - \dfrac{(T-t_N)(d_1+\cdots+d_N)}{d_1+\cdots+d_N+k_2} \\ N \in \mathbb{N}, d \in \mathbb{R}^N \\ \text{subject to } \displaystyle\sum_{i=1}^{N} d_i = D, \\ \qquad\qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1,...,N\}. \end{cases}.$$

For simplicity, let us begin by stating the problem $(\tilde{P}_{1E})$ in the case $N = 3$ fixed, and considering $w_i = (t_{i+1} - t_i)$, $i \in \{1, 2\}$. We can reduce it to a 2 variable problem because as $w_3 = (T - t_3)$ and $d_1 + d_2 + d_3 = D$, then the last term is constant. Also, using the equality constraint, we get:

$$(\tilde{P}^3_{1E}) \begin{cases} Min \;\; f^3_5(d) = -\dfrac{w_1 d_1}{d_1+\hat{k}_2} - \dfrac{w_2(d_1+d_2)}{d_1+d_2+\hat{k}_2} \\ d \in \mathbb{R}^2 \\ \text{subject to } D - d_{max} \leq d_1 + d_2 \leq D - d_{min} \\ \qquad\qquad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1,2\}. \end{cases}.$$

Let's see that the function f^3_5 is strictly convex:

$$\nabla^2 f^3_5(d) = \frac{2w_1\hat{k}_2}{(d_1+\hat{k}_2)^3}\begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix} + \frac{2w_2\hat{k}_2}{(d_1+d_2+\hat{k}_2)^3}\begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix}.$$

As $w_1, w_2, \hat{k}_2 > 0$ and $d_1, d_2 > 0$, then $z^T[\nabla^2 f^3_5(d)]z > 0$, $\forall z \in \mathbb{R}^2 \backslash \{0\}$, and $\nabla^2 f^3_5(d)$ is a positive definite matrix. Therefore, as $f^3_5(d)$ is strictly convex and the set of restrictions is convex (because the restrictions are linear), the problem $(\tilde{P}^3_{1E})$ has only one solution (see, for instance [2]).

Let's see in Figure 4.3 an example of the graphical representation of this problem, with $w_1, w_2 = 1$, $\hat{k}_2 = 1$, $d_{min} = 1$, $d_{max} = 3$ and $D = 4$.

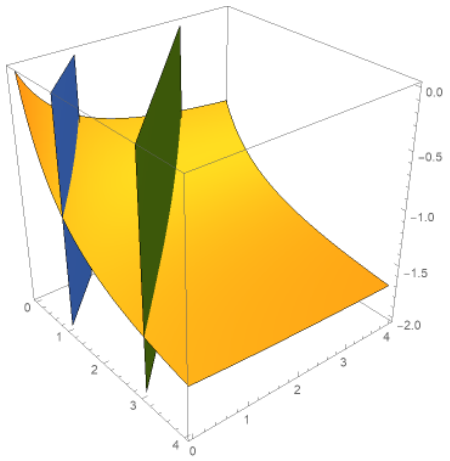

Figure 4.3: Example of problem $(\tilde{P}^3_{1E})$.

Let's come back to problem $(\tilde{P}_{1E})$ and now, we are going to study it in the case of N fixed and

with $w_i = (t_{i+1} - t_i)$, $i \in \{1, \dots, N-1\}$, $w_N = (T - t_N)$:

$$(\tilde{P}_{1E}^N) \begin{cases} Min \;\; f_5(d) = -\dfrac{w_1 d_1}{d_1 + \hat{k}_2} - \dfrac{w_2(d_1+d_2)}{d_1+d_2+\hat{k}_2} - \cdots - \dfrac{w_{N-1}(d_1+\cdots+d_{N-1})}{d_1+\cdots+d_{N-1}+\hat{k}_2} - \dfrac{w_N(d_1+\cdots+d_N)}{d_1+\cdots+d_N+\hat{k}_2} \\ d \in \mathbb{R}^N \\ \text{subject to } \displaystyle\sum_{i=1}^{N} d_i = D, \\ \qquad\qquad d_{min} \le d_i \le d_{max}, \quad \forall i \in \{1, \dots, N-1\}. \end{cases}$$

Also, we can reduce this problem to a $N-1$ variable problem because as $w_N = (T - t_N)$ is fixed and $\displaystyle\sum_{i=1}^{N} d_i = D$, the term $\dfrac{w_N(d_1+\cdots+d_N)}{d_1+\cdots+d_N+\hat{k}_2}$ is constant:

$$(\tilde{P}_{1E}^{N-1}) \begin{cases} Min \;\; f_5(d) = -\dfrac{w_1 d_1}{d_1 + \hat{k}_2} - \dfrac{w_2(d_1+d_2)}{d_1+d_2+\hat{k}_2} - \cdots - \dfrac{w_{N-1}(d_1+\cdots+d_{N-1})}{d_1+\cdots+d_{N-1}+\hat{k}_2} \\ d \in \mathbb{R}^{N-1} \\ \text{subject to } D - d_{max} \le \displaystyle\sum_{i=1}^{N-1} d_i \le D - d_{min}, \\ \qquad\qquad d_{min} \le d_i \le d_{max}, \quad \forall i \in \{1, \dots, N-1\}. \end{cases}$$

However, for simplicity, in order to study the existence of a unique solution and its structure, we are going to consider the problem $(\tilde{P}_{1E}^N)$.

Theorem 4.1.2. *If $d_{min} > 0$ and $N \in \left[\dfrac{D}{d_{max}}, \dfrac{D}{d_{min}}\right] \cap \mathbb{N}$, then there is a unique solution for $(\tilde{P}_{1E}^N)$.*

Proof. The proof of the existence of solution is analogous to the proof of Theorem 3.1.1. The uniqueness of the solution follows from the fact that f_5 is strictly convex. □

Theorem 4.1.3. *Under the hypotheses of Theorem 4.1.2, the unique solution to the problem $(\tilde{P}_{1E}^N)$ is given by:*

1. $(d_{min}, \dots, d_{min})$ *if* $N = \dfrac{D}{d_{min}} \in \mathbb{N}$.
2. $(d_{max}, \dots, d_{max})$ *if* $N = \dfrac{D}{d_{max}} \in \mathbb{N}$.
3. $(d_{max}, \dots, d_{max}, d^*, d_{min}, \dots, d_{min})$ *if* $\frac{D}{d_{max}} < N < \frac{D}{d_{min}}$, $N \in \mathbb{N}$. *with d^* verifying $d_{min} \le d^* \le d_{max}$. The number of d_{min} and d_{max} doses can be between 0 and $N-1$. If m is the number of d_{min}, then $d^* = D + (d_{max} - d_{min})m - (N-1)d_{max}$.*

Proof. Let's study the different possible cases:

1. If $N = \frac{D}{d_{min}} \in \mathbb{N}$, then $\overline{d} = (d_{min}, \dots, d_{min})$ is the solution of the problem because it's the unique feasible point.
2. If $N = \frac{D}{d_{max}} \in \mathbb{N}$, then $\overline{d} = (d_{max}, \dots, d_{max})$ is the solution of the problem because it's the unique feasible point.

3. If $N \in \left(\frac{D}{d_{max}}, \frac{D}{d_{min}}\right) \cap \mathbb{N}$:
   Be $j_0 = N - m$ the position of $d^* \in [d_{min}, d_{max}]$, then $\overline{d} = (\underbrace{d_{max}, \dots, d_{max}}_{N-m-1}, d^*, \underbrace{d_{min}, \dots, d_{min}}_{m})$ is a Kuhn-Tucker point (see [2]):

   1. $\nabla f_5(\overline{d}) + \overline{\lambda} \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix} + \begin{pmatrix} \overline{\mu_1} \\ \vdots \\ \overline{\mu}_N \end{pmatrix} - \begin{pmatrix} \hat{\mu}_1 \\ \vdots \\ \hat{\mu}_N \end{pmatrix} = \begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}$.
   2. $\overline{\mu_i}(\overline{d}_i - d_{max}) = 0$, $\forall i \in \{1, \dots, N\}$.
      $\hat{\mu}_i(-\overline{d}_i + d_{min}) = 0$, $\forall i \in \{1, \dots, N\}$.
      $\overline{\mu_i}, \hat{\mu}_i \geq 0$, $\forall i \in \{1, \dots, N\}$.
   3. The point verifying the two previous conditions must also be feasible.

   In this case we can take $\overline{\lambda} = -(\nabla f_5(\overline{d}))_{j_0}$ ($\overline{\lambda}$ is positive), and taking in account that $(\nabla f_5(\overline{d}))_i - (\nabla f_5(\overline{d}))_j > 0$ if $i > j$:

   - If $i < j_0$, $\hat{\mu}_i = 0$ and $\overline{\mu}_i = -(\nabla f_5(\overline{d}))_i - \overline{\lambda} > 0$.
   - If $i = j_0$, $\hat{\mu}_i = 0$ and $\hat{\mu}_i = 0$.
   - If $i > j_0$, $\overline{\mu}_i = 0$ and $\hat{\mu}_i = (\nabla f_5(\overline{d}))_i + \overline{\lambda} > 0$.

   Let's calculate m: Using $D = m\, d_{min} + (N - m - 1)d_{max} + d^*$, it follows that $d_{min} \leq d^* = D + (d_{max} - d_{min})m - (N-1)d_{max} \leq d_{max}$, then:

$$\frac{N d_{max} - D}{d_{max} - d_{min}} - 1 \leq m \leq \frac{N d_{max} - D}{d_{max} - d_{min}} \tag{4.7}$$

   Therefore, m is the greater integer which verifies (4.7).

Finally, as f_5 is strictly convex and the set of restrictions is convex, then if $\overline{d}$ is a Kuhn-Tucker point it is the solution to $(\tilde{P}_{1E}^N)$ (see [2]). □

Let's see an example in which we solve $(\tilde{P}_{1E}^N)$ using the previous theorem for different values of N:

Example 4.1.2. *Be $D = 1050\ mg/m^2$, $d_{min} = 100\ mg/m^2$, $d_{max} = 200\ mg/m^2$. Then, let's solve $(\tilde{P}_{1E}^N)$ for $N \in [6, 10]$:*

- *If $N = 6$, $m \in [0.5, 1.5]$ and we take $m = 1$. Then, $\overline{d} = (200, 200, 200, 200, 150, 100)$.*
- *If $N = 7$, $m \in [2.5, 3.5]$ and we take $m = 3$, so $\overline{d} = (200, 200, 200, 150, \underbrace{100, 100, 100}_{3})$.*
- *If $N = 8$, $m \in [4.5, 5.5]$ so $m = 5$, and $\overline{d} = (200, 200, 150, \underbrace{100, \dots, 100}_{5})$.*
- *If $N = 9$, $m \in [6.5, 7.5]$ so $m = 7$, and $\overline{d} = (200, 150, \underbrace{100, \dots, 100}_{7})$.*
- *If $N = 10$, $m \in [8.5, 9.5]$ so $m = 9$, and $\overline{d} = (150, \underbrace{100, \dots, 100}_{9})$.*

Note that in all the previous cases, there is a dose $d^* = 150\ mg/m^2$ in the position $N - m$. Finally, in order to solve the problem $(\tilde{P}_{1E})$ we need to know the times (fixed a priori) and the value of $\hat{k}_2$ and keep the tuple (N, d) which minimizes $\tilde{f}_5(N, d)$.

4.2 Minimizing the cumulative dose and keeping the tumor size below a level

We will start by considering the problem $(\hat{P}_2)$ defined in Section 2.3. In this problem we want to minimize the total dose given but preserving the volume of the tumor at time T not to exceed an established bound L_*.

As we are studying the Emax model, $\int_0^T \tilde{\rho}(t)dt = k_1 F(N,d)$, with F given in (4.1). Then, we have to preserve the following lower bound:

$$\log\left(\frac{(d_1+\hat{k}_2)\cdots(d_1e^{\lambda(t_1-t_N)}+\cdots+d_{N-1}e^{\lambda(t_{N-1}-t_N)}+d_N+\hat{k}_2)}{(d_1e^{\lambda(t_1-t_2)}+\hat{k}_2)\cdots(d_1e^{\lambda(t_1-T)}+\cdots+d_{N-1}e^{\lambda(t_{N-1}-T)}+d_Ne^{\lambda(t_N-T)}+\hat{k}_2)}\right)\geq\gamma, \quad (4.8)$$

with $\gamma = \frac{\lambda}{k_1}(T+\tilde{\gamma})$, $\tilde{\gamma}$ defined in Section 2.3. Therefore let's consider the following optimization problem:

$$(P_{2E})\begin{cases} Min\ \ \tilde{f}(N,d)=\sum_{i=1}^{N} d_i \\ N\in\mathbb{N}, d\in\mathbb{R}^N \\ \text{subject to} \quad \frac{(d_1+\hat{k}_2)\cdots(d_1e^{\lambda(t_1-t_N)}+\cdots+d_N+\hat{k}_2)}{(d_1e^{\lambda(t_1-t_2)}+\hat{k}_2)\cdots(d_1e^{\lambda(t_1-T)}+\cdots+d_Ne^{\lambda(t_N-T)}+\hat{k}_2)}\geq e^{\gamma}, \\ \qquad\qquad d_{min}\leq d_i\leq d_{max}, \quad \forall i\in\{1,\ldots,N\}. \end{cases}.$$

with γ as defined above. Again, in this problem both N and each d_i are variables. As in Section 4.1, we are going to distinguish 2 cases to study this problem: $\lambda >> 0$ and $\lambda \approx 0$.

4.2.1 Case 1: $\lambda >> 0$

Let's start by studying the case in which $\lambda >> 0$. Then, as $T > t_i$, $\forall i \in \{1,\ldots,N\}$, $e^{\lambda(t_i-T)} \approx 0$ and $e^{\lambda(t_i-t_j)} \approx 0$, $\forall i,j \in \{1,\ldots,N\}, j > i$. Be $\gamma = \frac{\lambda}{k_1}(T+\tilde{\gamma})$, therefore, we get:

$$L(T)\leq L_* \iff \frac{(d_1+\hat{k}_2)\cdots(d_{N-1}+\hat{k}_2)(d_N+\hat{k}_2)}{\hat{k}_2^N}\geq e^{\gamma}.$$

Then the problem (P_{2E}) is formulated as follows:

$$(\overline{P}_{2E})\begin{cases} Min\ \ \tilde{f}(N,d)=\sum_{i=1}^{N} d_i \\ N\in\mathbb{N}, d\in\mathbb{R}^N \\ \text{subject to} \quad \prod_{i=1}^{N}(d_i+\hat{k}_2)\geq e^{\gamma}\,\hat{k}_2^N \\ \qquad\qquad d_{min}\leq d_i\leq d_{max}, \quad \forall i\in\{1,\ldots,N\}. \end{cases}.$$

First, note that the set of feasible N values is infinite, but only a finite number of N have practical interest: There is a value $\hat{N}\in\mathbb{N}$ large enough so that $(d_{min}+\hat{k}_2)^{\hat{N}} \geq e^{\gamma}\,\hat{k}_2^{\hat{N}}$. Of course, there is no point in considering larger values, since if $N > \hat{N}$, then $\tilde{f}(\hat{N},\hat{d}) = \hat{N}d_{min} < \tilde{f}(N,d)$ for $\hat{d} = (d_{min},\ldots,d_{min})$ and for all (N,d) feasible for $(\overline{P}_{2E})$. Using $d_i \leq d_{max}$, $\forall i \in \{1,\ldots,N\}$, we get the following lower bound for N:

$$\prod_{i=1}^{N}(d_{max}+\hat{k}_2)\geq\prod_{i=1}^{N}(d_i+\hat{k}_2)\geq e^{\gamma}\hat{k}_2^N \iff \left(\frac{d_{max}+\hat{k}_2}{\hat{k}_2}\right)^N\geq e^{\gamma}\iff N\geq\frac{\gamma}{\log\left(\frac{d_{max}+\hat{k}_2}{\hat{k}_2}\right)}.$$

Using the inequality between the arithmetic and geometric means (see Proposition 4.1.1), we get:

$$\frac{1}{N}\sum_{i=1}^{N}(d_i+\hat{k}_2)=\hat{k}_2+\frac{1}{N}\sum_{i=1}^{N}d_i\geq\left(\prod_{i=1}^{N}(d_i+\hat{k}_2)\right)^{1/N}\geq e^{\gamma/N}\hat{k}_2\Longleftrightarrow\boxed{\sum_{i=1}^{N}d_i\geq N\hat{k}_2(e^{\gamma/N}-1)}.$$

Then, the minimum of $(\overline{P}_{2E})$ is reached when $\sum_{i=1}^{N}d_i = N\hat{k}_2(e^{\gamma/N}-1)$ and $d_i = d_j$, $\forall i,j \in \{1,\dots,N\}, i\neq j$, by Proposition 4.1.1, and $\bar{d}_i = \hat{k}_2(e^{\gamma/N}-1)$, $\forall i\in\{1,\dots,N\}$, when this point is feasible.

Imposing that $\bar{d}_i \geq d_{min}$, $\forall i\in\{1,\dots,N\}$, then $e^{\gamma/N}\geq\dfrac{d_{min}+\hat{k}_2}{\hat{k}_2}$ and $N\leq\dfrac{\gamma}{\log\left(\frac{d_{min}+\hat{k}_2}{\hat{k}_2}\right)}$.

Therefore, let's consider the following optimization problem in one variable in order to estimate the optimum value of N. We will write x instead of N for simplicity, but we are only interested in the values of $x\in\mathbb{N}$. Also, be $N_1=\dfrac{\gamma}{\log\left(\frac{d_{max}+\hat{k}_2}{\hat{k}_2}\right)}$ and $N_2=\dfrac{\gamma}{\log\left(\frac{d_{min}+\hat{k}_2}{\hat{k}_2}\right)}$:

$$(P_6)\begin{cases} Min\ \ f_6(x)=x\hat{k}_2(e^{\gamma/x}-1) \\ \text{subject to}\ \ x\in[N_1,N_2]\cap\mathbb{N}. \end{cases}.$$

The function $f_6(x)$ is strictly decreasing for $x>0$, let's see its graphic for $\gamma=5>1$, $\gamma=0.5<1$ and in both cases $\hat{k}_2=100$:

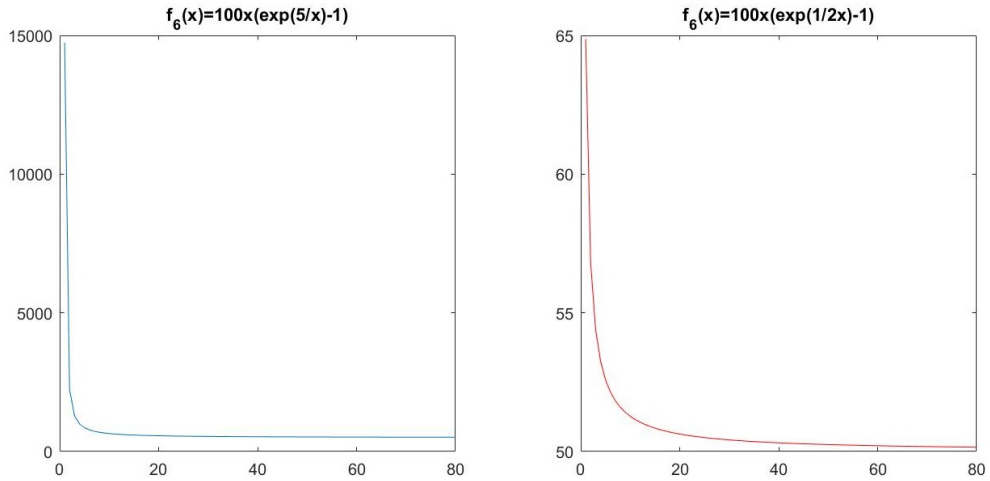

Figure 4.4: Graphic of $f_6(x)$ for $\hat{k}_2=100$ and $\gamma=5$ (left), $\gamma=0.5$ (right).

Note that $f_6'(x)=\dfrac{\hat{k}_2}{x}(e^{\gamma/x}(x-\gamma)-x)$ has no real roots for $x>0$, and $f_6'(x)<0$, $\forall x>0$:

$$f_6'(x)=0\Longleftrightarrow x=e^{\gamma/x}(x-\gamma)\Longleftrightarrow 1=\left(1-\frac{\gamma}{x}\right)e^{\gamma/x}\Longleftrightarrow -\frac{1}{e}=\left(\frac{\gamma}{x}-1\right)e^{\gamma/x-1}$$
$$\Longleftrightarrow \frac{\gamma}{x}-1=W\left(-\frac{1}{e}\right),$$

where W is the Lambert function (see Appendix C). However, $W\left(-\dfrac{1}{e}\right)=-1$ (see Appendix C), so it must be $\dfrac{\gamma}{x}=0$, and we get a contradiction because $\gamma>0$. Then, as $f_6'(x)$ has no real roots

for $x > 0$, and $f_6'(1) < 0$, we get that $f_6'(x) < 0$, $\forall x > 0$. Therefore, $f_6(x)$ is strictly decreasing for all $x > 0$, so the solution to (P_6) will be $x = \lfloor N_2 \rfloor$.

Coming back to problem $(\overline{P}_{2E})$, as we want to minimize the cumulative dose, we will take $\overline{d} = (\underbrace{\hat{k}_2(e^{\gamma/N} - 1), \ldots, \hat{k}_2(e^{\gamma/N} - 1)}_{N})$ with $N = \left\lfloor \frac{\gamma}{\log\left(\frac{d_{min}+\hat{k}_2}{\hat{k}_2}\right)} \right\rfloor$.

Let's look at an example where we check that the expected result is obtained:

Example 4.2.1. *Be $\gamma = 6$, $\hat{k}_2 = 100$, $d_{min} = 75$ mg/m^2 and $d_{max} = 200$ mg/m^2. Let's solve $(\overline{P}_{2E})$.*

In this conditions, $3^N \geq e^6$, so $N \geq 5.46$. Also, $N \leq \frac{\gamma}{\log\left(\frac{d_{min}+\hat{k}_2}{\hat{k}_2}\right)} = \frac{6}{\log(1.75)} = 10.72$. Note that there are 5 possible values of N : $6, 7, 8, 9, 10$:

- *If $N = 6$, $\overline{d}^{(6)} = (\underbrace{171.83, \ldots, 171.83}_{6})$ and $\tilde{f}(6, \overline{d}^{(6)}) = 1030.98$.*
- *If $N = 7$, $\overline{d}^{(7)} = (\underbrace{135.64, \ldots, 135.64}_{7})$ and $\tilde{f}(7, \overline{d}^{(7)}) = 949.48$.*
- *If $N = 8$, $\overline{d}^{(8)} = (\underbrace{111, 70, \ldots, 111, 70}_{8})$ and $\tilde{f}(8, \overline{d}^{(8)}) = 893.60$.*
- *If $N = 9$, $\overline{d}^{(9)} = (\underbrace{94.77, \ldots, 94.77}_{9})$ and $\tilde{f}(9, \overline{d}^{(9)}) = 852.93$.*
- *If $N = 10$, $\overline{d}^{(10)} = (\underbrace{82.21, \ldots, 82.21}_{10})$ and $\tilde{f}(10, \overline{d}^{(10)}) = 822.11$.*

As we already knew, the solution of $(\overline{P}_{2E})$ is reached when $N = \left\lfloor \frac{\gamma}{\log\left(\frac{d_{min}+\hat{k}_2}{\hat{k}_2}\right)} \right\rfloor = \left\lfloor \frac{6}{\log(1.75)} \right\rfloor = 10$ and $d_i = \hat{k}_2(e^{\gamma/N} - 1) = 100(e^{6/10} - 1) = 82.21$, $\forall i \in \{1, \ldots, 10\}$.

4.2.2 Case 2: $\lambda \approx 0$

Now let's consider the case in which $\lambda \approx 0$. Then, $e^{\lambda(t_i - T)} \approx 1$ and $e^{\lambda(t_i - t_j)} \approx 1$, $\forall i, j \in \{1, \ldots, N\}, j > i$. We are going to consider the same function $h(\lambda)$ as in subsection 4.1.2. Again: $\lim_{\lambda \to 0} F(N, d) = \lim_{\lambda \to 0} \frac{h(\lambda)}{\lambda} = \frac{0}{0}$, and applying L'Hopital's rule we know that:

$$\lim_{\lambda \to 0} h'(\lambda) = (t_2 - t_1)\frac{d_1}{d_1 + \hat{k}_2} + (t_3 - t_2)\frac{d_1 + d_2}{d_1 + d_2 + \hat{k}_2} + \cdots + (T - t_N)\frac{d_1 + \cdots + d_N}{d_1 + \cdots + d_N + \hat{k}_2}.$$

Therefore, combining (2.12) and (4.8) we get

$$L(T) \leq L_* \iff \frac{(t_2 - t_1)d_1}{d_1 + \hat{k}_2} + \frac{(t_3 - t_2)(d_1 + d_2)}{d_1 + d_2 + \hat{k}_2} + \cdots + \frac{(T - t_N)(d_1 + \cdots + d_N)}{d_1 + \cdots + d_N + \hat{k}_2} \geq \overline{\gamma}, \tag{4.9}$$

with $\overline{\gamma} = \frac{1}{k_1}\left(T + \frac{1}{\xi}\log\left(\frac{\log\left(\frac{L_*}{\theta}\right)}{\log\left(\frac{L_0}{\theta}\right)}\right)\right)$.

In this case the problem (P_{2E}) is formulated as follows for N fixed:

$$(\tilde{P}_{2E}^N)\begin{cases} Min \;\; f_2^N(d) = \sum_{i=1}^{N} d_i \\ d \in \mathbb{R}^N \\ \text{subject to} \;\; \dfrac{(t_2-t_1)d_1}{d_1+\hat{k}_2} + \dfrac{(t_3-t_2)(d_1+d_2)}{d_1+d_2+\hat{k}_2} + \cdots + \dfrac{(T-t_N)(d_1+\cdots+d_N)}{d_1+\cdots+d_N+\hat{k}_2} \geq \overline{\gamma} \\ \qquad\quad d_{min} \leq d_i \leq d_{max}, \quad \forall i \in \{1,\ldots,N\}. \end{cases}.$$

In general, we think that this problem is very complex to be solved explicitly; however, the fact of having it formulated helps us to be able to compare several treatments: check if they are admissible under the conditions of the problem, and which would produce better results. Let's look at an example:

Example 4.2.2. *Be* $N = 10$, $\overline{\gamma} = 25$, $\hat{k}_2 = 5$, $T = 28$. *Be* $g(t,d) = \dfrac{(t_2-t_1)d_1}{d_1+\hat{k}_2} + \dfrac{(t_3-t_2)(d_1+d_2)}{d_1+d_2+\hat{k}_2} + \cdots + \dfrac{(T-t_N)(d_1+\cdots+d_N)}{d_1+\cdots+d_N+\hat{k}_2}$. *We want to study the following three treatments:*

- ***Treatment 1:*** $\tilde{t} = (0,1,2,\ldots,9)$ *and* $\tilde{d} = (10,10,10,\ldots,10)$. *We can check that* $g(\tilde{t},\tilde{d}) = 25.96 \geq \overline{\gamma}$, *and* $f_2^N(\tilde{d}) = 100$.
- ***Treatment 2:*** $\hat{t} = (0,1,2,\ldots,9)$ *and* $\hat{d} = (7,7,7,\ldots,7)$. *We can check that* $g(\hat{t},\hat{d}) = 25.23 \geq \overline{\gamma}$, *and* $f_2^N(\hat{d}) = 70$.
- ***Treatment 3:*** $\overline{t} = (10,11,\ldots,19,20)$ *and* $\overline{d} = (10,10,10,\ldots,10)$. *We can check that* $g(\overline{t},\overline{d}) = 16.44 < \overline{\gamma}$, *so this treatment is not feasible under the conditions of the statement and the problem* $(\tilde{P}_{2E}^N)$.

In view of Example 4.2.2 we can see all the useful practical information that we can obtain just from the formulation of the problem. Among the admissible treatments, we can observe which one minimizes the total dose given (in this case, the second one) verifying the conditions of the problem. In addition, we can discard those treatments that do not verify the desired conditions (in this case, treatment 3), without the need for clinical or experimental verification.

4.3 Temozolomide

As we know, Temozolomide is a drug with short half-life, equivalently $\lambda >> 0$. Therefore, we are going to use this drug to check what has been studied in the problems $(\overline{P}_{1E})$ and $(\overline{P}_{2E})$. That is, we are going to study the problems $(\hat{P}_1)$ and $(\hat{P}_2)$ in the case of the Emax model and $\lambda >> 0$. Also, we will study the evolution of the tumor volume with the 5 treatments of Temozolomide exposed in Section 3.3. In order to perform these tasks let's begin by estimating the value of the parameters k_1 and k_2 for this model:

- Note that $\lim_{c\to\infty} \dfrac{k_1 c}{k_2+c} = k_1$, so we can define the parameter k_1 as the maximum effect of the drug on the body.
- Regarding the constant k_2, it can be viewed as the concentration that produces 50% of the maximum effect of the drug. Let's check it out:

$$\frac{k_1\hat{c}}{k_2+\hat{c}} = \frac{k_1}{2} \Longrightarrow 2\hat{c} = k_2+\hat{c} \Longrightarrow \hat{c} = k_2.$$

  It is usually noted $k_2 = EC_{50}$ (see, for instance [10]).

In order to contrast previous results, let's consider the theoretical values $k_1 = 45$ and $k_2 = 9$. In Figure 4.5 we can see the graphical comparison between $3c$ (see Section 3.3) and $\frac{45c}{9+c}$.

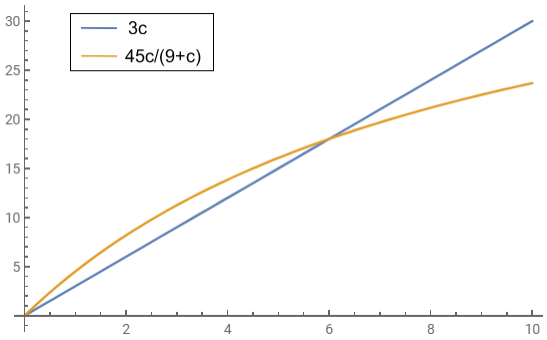

Figure 4.5: Graphical comparison between $3c$ and $\frac{45c}{9+c}$.

Let's start studying the different value of $L(T)$ obtained with each treatment. As an example, we consider that the patient is a woman, $L_0 = 0.03$, $N = 28$, $T = 29$, $k_1 = 9$, $k_2 = 45$ and $\xi = 0.00551$ (the last value is the same as in Section 3.3). In Table 4.1 we can see the results obtained with each treatment (note that the total dose is multiplied by 1.6 when the patient is a woman), and in Figure 4.6 the graphic representation of the evolution of the tumor.

	L(T)	**Total dose**
Treatment 1	0.0342	1000 mg/m^2
Treatment 2	0.0191	2100 mg/m^2
Treatment 3	0.0168	2100 mg/m^2
Treatment 4	0.0216	1575 mg/m^2
Treatment 5	0.0227	1400 mg/m^2

Table 4.1: Results obtained for each treatment with Temozolomide.

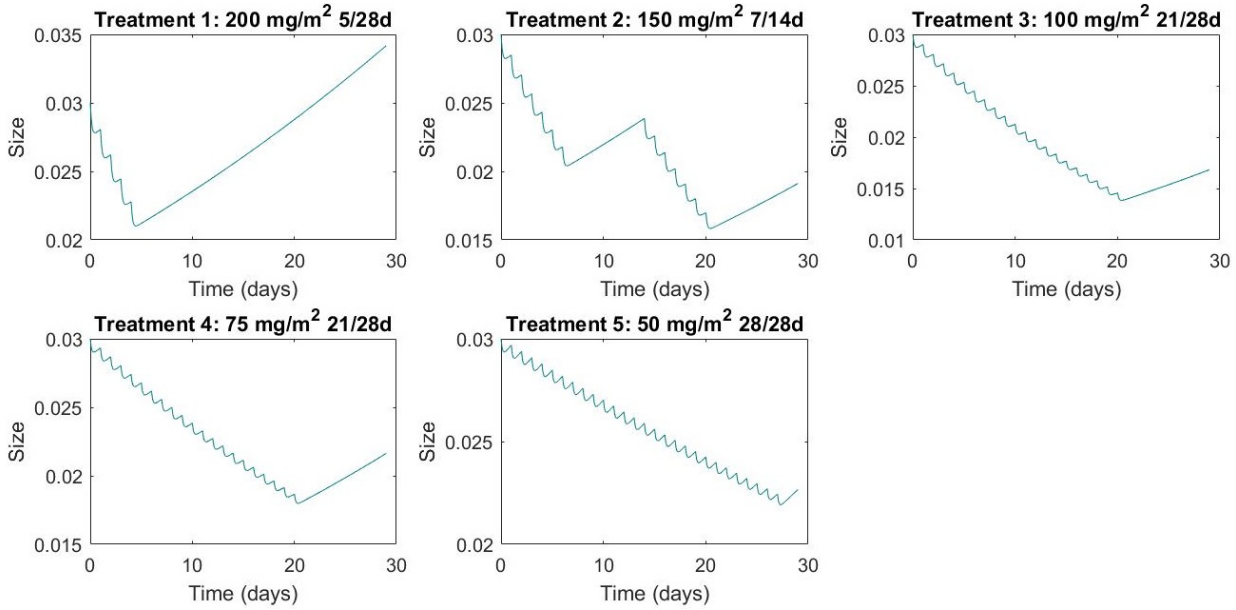

Figure 4.6: Tumor's size evolution with the five treatments of Temozolomide.

Now to study the problem $(\hat{P}_1)$ in the case of the Emax model and $\lambda >> 0$, we take $D = 600$ mg/m^2, $d_{min} = 50$ mg/m^2 and $d_{max} = 200$ mg/m^2 (as these values are the maximum and minimum dose that are administered in the treatments exposed above). We will also consider $T = 25$ and that the study period consists on 24 days. We are going to study different types of treatments with the 5 most common doses, that is, d_i can be 50, 75, 100, 150 or 200 mg/m^2, and $d_i = d_j, \forall i, j \in \{1, \ldots, N\}, i \neq j$. As an example we have assumed again that the patient is a woman, $L_0 = 0.03$, $k_1 = 45$ and $k_2 = 9$. In Table 4.2 we can see the results obtained: the total number of doses given, and the frequency with which each dose is given:

Dose	**Frecuency**	**Number of doses**	**L(T)**
200 mg/m^2	Every 8 days	3	0.0374
150 mg/m^2	Every 6 days	4	0.0365
100 mg/m^2	Every 4 days	6	0.0354
75 mg/m^2	Every 3 days	8	0.0348
50 mg/m^2	Every 2 days	12	0.0340

Table 4.2: Results obtained for each treatment with Temozolomide.

As we saw when we studied the problem $(\overline{P}_{1E})$, in this case as $\lambda >> 0$ and $k_2 > 1$, the best results are obtained using metronomic chemotherapy (lower doses with less spacing), see the last row of Table 4.2.

In order to study problem $(\hat{P}_2)$, let's use the theoretical results obtained for problem $(\overline{P}_{2E})$. As is Section 3.3, for these experiments we're going to consider that the patient is a woman, $L_0 = 0.3$, $L_* = 0.5$, a period of a year and $T = 365$. Again we get that $\tilde{\gamma} = -100.2068$, and then, using $k_1 = 45$, $\gamma = 54.3826$. As the patient is woman, and considering $k_2 = 9$ we get $\hat{k}_2 = 135$. For the 5 usual treatments, we are going to study how many doses should be given and what's the cumulative dose in each case. For example, for the case in which doses of 50 mg/m^2 are given, $\left(\frac{50+135}{135}\right)^N \geq e^{\gamma}$, so $N \geq 172.60$. Then, 173 doses of 50 mg/m^2 should be given during 365 days. Proceeding in the same way with the other treatments we get the following results:

Dose	**Number of doses given**	**Cumulative dose**
200 mg/m^2	60	12000 mg/m^2
150 mg/m^2	73	10950 mg/m^2
100 mg/m^2	99	9900 mg/m^2
75 mg/m^2	124	9300 mg/m^2
50 mg/m^2	173	8650 mg/m^2

Table 4.3: Possible treatments of Temozolomide to get $L(T) \leq L_*$.

Again, we can note here that the treatment which minimize the cumulative dose is the one in which the minimum dose is given (metronomic chemotherapy). The time at which the doses will be given, which should be fixed, will vary the value of $L(T)$ obtained, but it will be in any case less than L_* as seen in Subsection 4.2.1.

From a different point of view, for the five usual treatments of Temozolomide, we have developed a program in MATLAB that allows us to know the minimum number of complete cycles that must

be carried out to get $L(T) < L_*$, and the value of $L(T)$ obtained for each case. In Table 4.4 we can see the results obtained, and we can note that, once more, the treatment which minimize the dose given is that in which lower doses are given (metronomic chemotherapy), as we have proved in Subsection 4.2.1.

	Number of cycles	**Cumulative dose**	**L(T)**
Treatment 1	12	12000 mg/m^2	0.4987
Treatment 2	6	12600 mg/m^2	0.4198
Treatment 3	5	12600 mg/m^2	0.4640
Treatment 4	6	11025 mg/m^2	0.4880
Treatment 5	7	9800 mg/m^2	0.4297

Table 4.4: Usual treatments of Temozolomide and number of cycles to get $L(T) \leq L_*$.

4.4 Cabazitaxel

To illustrate the theoretical results obtained with respect to drugs with a long half-life, as in the case of the Skipper model, we will analyze the case of Cabazitaxel. Along this study we have to consider that the patient is a male.

First of all, we are going to study the 4 treatments which we studied in Section 3.4. To do this, we have taken a period under study of 4 weeks, with $T = 29$, $k_1 = 16$, $k_2 = 8$, $L_0 = 0.03$, and that the patient is a male, so the total dose given will be multiplied by 1.9. In Figure 4.7 we show the tumor evolution with each treatment and in Table 4.5 the results obtained.

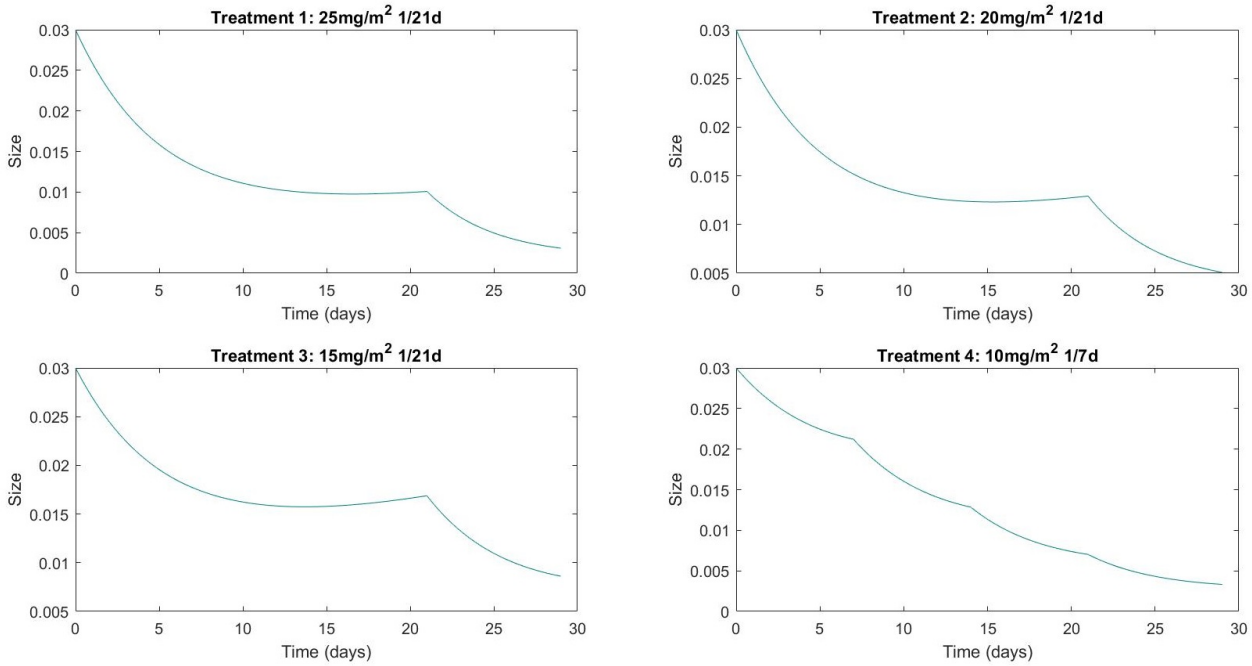

Figure 4.7: Tumor volume evolution with the four treatments of Cabazitaxel with Emax model.

Dose	**Frecuency**	**Total dose**	**L(T)**
25 mg/m^2	Every 3 weeks	50 mg/m^2	0.0031
20 mg/m^2	Every 3 weeks	40 mg/m^2	0.0051
15 mg/m^2	Every 3 weeks	30 mg/m^2	0.0086
10 mg/m^2	Once a week	40 mg/m^2	0.0033

Table 4.5: Results obtained for each treatment of Cabazitaxel with the Emax model.

Here, we can appreciate that the best results are obtained the higher the total dose administered. However, in treatments 2 and 4, the same total dose is given (see rows 2 and 4 of Table 4.5), but the best results are obtained for the treatment where the doses are given less spaced, that is, a metronomic treatment.

Now, let's study some examples as an illustration in order to see what kind of therapy produces the best results (the lowest value for $L(T)$) when the same total dose is given (problem $(\tilde{P}_{1E})$). First of all, we have taken the same parameters as in the previous example: $k_1 = 16$, $k_2 = 8$, $L_0 = 0.03$ but with a period of time of 6 weeks and $T = 43$. In this case, we consider 3 types of treatments, where in all of them the total dose administered is 50 mg/m^2. In the first one, 2 doses of 25 mg/m^2 are given, in the second one 3 doses of 16.67 mg/m^2 and in the third one 4 doses of 12.5 mg/m^2. We want to estimate what the optimal dose spacing would be for this example.

In Figure 4.8 we can see the graphic representation of the value of $L(T)$ according to the time spacing between each given dose. We know that under these conditions the minimum value for $L(T)$ is reached when all doses are equal, and furthermore we expect that as $k_2 > 1$, the best result will be obtained for the lowest dose and with the shortest time spacing (as it can be seen in Figure 4.8).

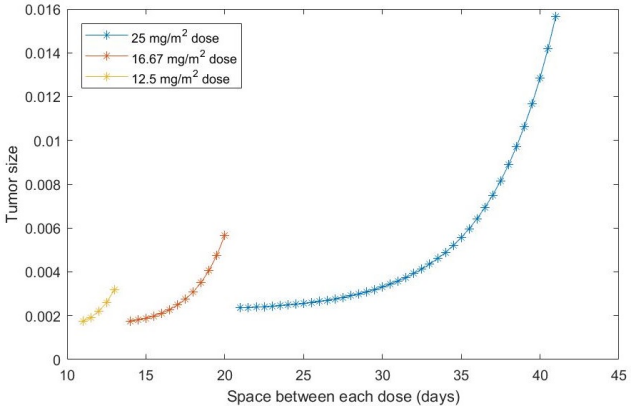

Figure 4.8: Tumor's size at T according to the time spacing between each given dose.

Now, let's consider that doses of 25 mg/m^2 are given during 6 weeks (42 days), every 21 days. Then, 1 mg/m^2 is given every 0.84 days. As the most common doses are 25, 20 and 15 mg/m^2, we are going to study the following cases:

- **Treatment 1:** 25 mg/m^2 every 21 days.
- **Treatment 2:** 20.24 mg/m^2 every 17 days.
- **Treatment 3:** 15.48 mg/m^2 every 13 days.

In Figure 4.9 we can observe the graphical comparison of these three treatments, and in table 4.6 each value of $L(T)$.

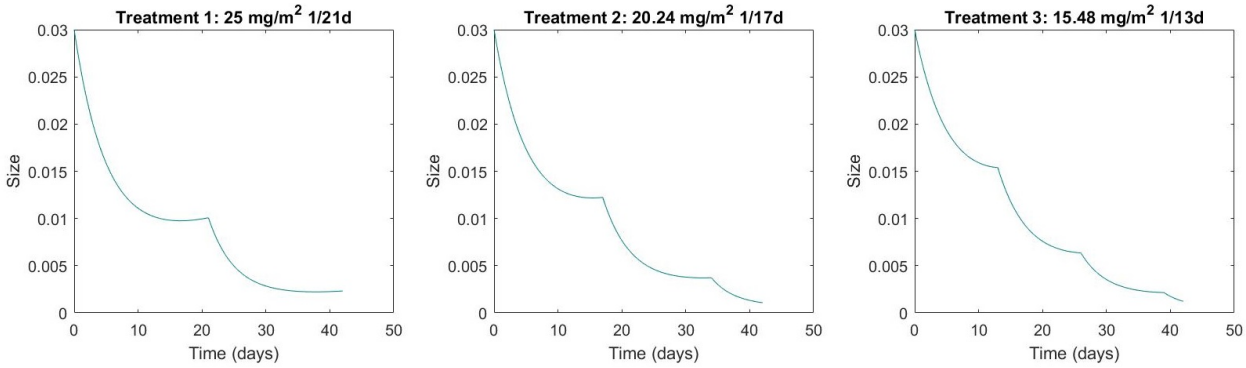

Figure 4.9: Graphic comparison of Cabazitaxel treatments 1,2,3.

Treatment	**L(T)**
25 mg/m^2 every 21 days	0.0023
20.24 mg/m^2 every 17 days	0.0011
15.48 mg/m^2 every 13 days	0.0012

Table 4.6: Results obtained for each treatment with Cabazitaxel.

The treatments in which lower doses are given, produce the best results (see rows 2 and 3 of Table 4.6).

We are going to end up looking at the problem $(\hat{P}_2)$. We know 3 types of treatments (see Section 3.4), so we are going to study how many doses should be given in each case so that after one year of treatment, if $L_0 = 0.3$, the tumor size does not exceed $L_* = 0.5$. In the 3 treatments exposed in Section 3.4, the spacing between doses is 21 days. In addition, the same dose is given in each of them during the whole cycle. Let's take $t_{i+1} - t_i = 21$, $\forall i \in \{1, \ldots, N-1\}$. Using MATLAB, we are going to check what is the minimum number of doses that should be given in order to have $L(T) < L_*$. In Figure 4.10 we can see the graphic representation of the tumor evolution with $N = 1, 2, \ldots$ to the minimum N verifying the previous condition.

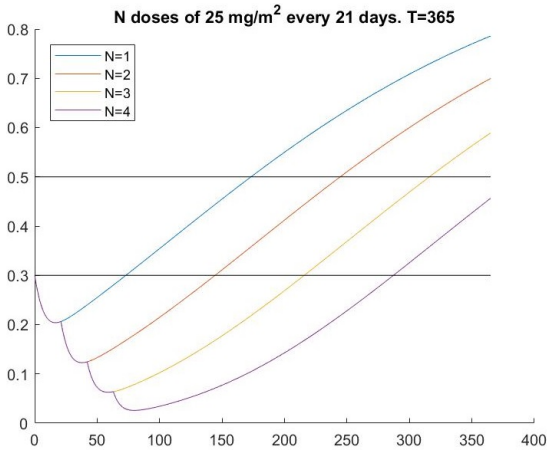

Figure 4.10: Tumor size evolution with N doses of 25 mg/m^2 given every 21 days.

It is noted that the lowest value of N so that $L(T) < L_*$ is 4. That is, 4 doses of 25 mg/m^2 should be given every 21 days. In total, 100 mg/m^2 are given and $L(T) = 0.4566$.

If the doses are of 20 mg/m^2, then the lowest feasible N is 5 and $L(T) = 0.4168$, again the cumulative dose is 100 mg/m^2. If the dose is 15 mg/m^2, $N = 6$, $L(T) = 0.4351$ and the total dose given is 90 mg/m^2. Figure 4.11 shows the graphic representation of the volume of the tumor for these two cases:

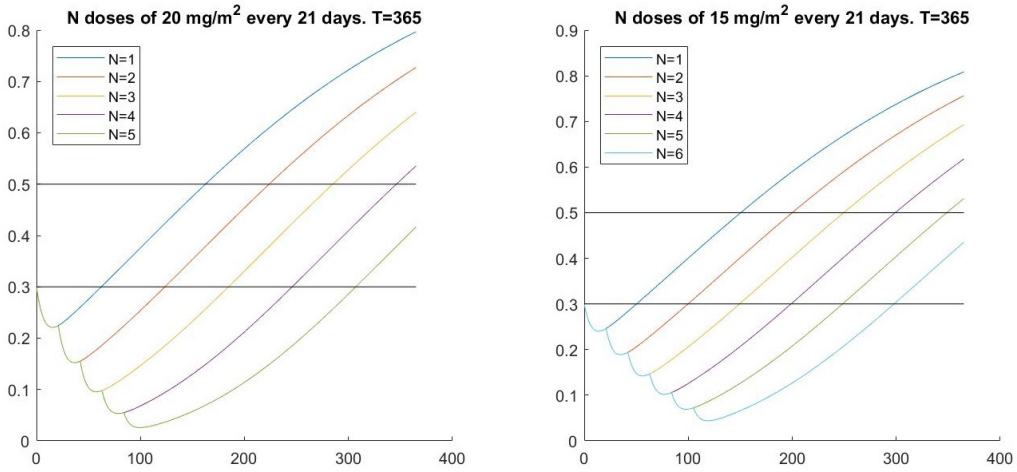

Figure 4.11: Tumor size evolution with N doses of 20 mg/m^2 given every 21 days (left) and doses of 15 mg/m^2 (right).

In Table 4.7 we can see a summary of the results obtained in this case for each usual treatment.

Treatment	**L(T)**	**Total dose**
25 mg/m^2 every 21 days	0.4566	100 mg/m^2
20 mg/m^2 every 21 days	0.4170	100 mg/m^2
15 mg/m^2 every 21 days	0.4354	90 mg/m^2

Table 4.7: Results obtained for problem $(\hat{P}_2)$ with Cabazitaxel.

In this case, the third treatment seems to be the best in relation to the problem we want to solve, as it minimizes the total dose. On the other hand, we can observe that in those treatments where the same accumulated dose is given (rows 2 and 3 of Table 4.7), the best results are obtained when lower doses are given but a greater number of them. Finally, let us note that it is more effective to give many smaller doses, but a greater number of them, than few larger doses. This is observed in rows 1 and 3 of Table 4.7, where results are better when 6 doses of 15 mg/m^2 are given than when 4 doses of 25 mg/m^2 are given, although in the second case the total dose is higher than in the first one.

Chapter 5

Conclusions

To conclude this study, let's go back to the two optimization problems we have analyzed: (P_1) and (P_2), which we introduced in Chapter 2. We have studied them for the two most common models in pharmacodynamics: Emax and Skipper. Also. we have observed that the optimal treatment depends on the type of drug administered, mainly if it has a long or short half-life.

With the Skipper model, for both problems and both types of drugs, the optimal treatment consists of doses administrated following the scheme: $(d_{max}, \ldots, d_{max}, d^*, d_{min}, \ldots, d_{min})$, with $d_{min} \leq d^* \leq d_{max}$, as we explained in Theorems 3.1.2 and 3.2.2. However, we have noted that for the problem (P_1), if the drug is short-lived, only the total sum of the doses administered influences the value of $L(T)$ (this doesn't happen if it's a long-life drug). In Table 5.1 we show a summary of the most recommendable treatments for each case and each type of drug, which in this case is always the same.

Problems (P_1) and (P_2), Skipper model	
Type of drug	Optimal treatment
Short-life	$(d_{max}, \ldots, d_{max}, d^*, d_{min}, \ldots, d_{min})$
Long-life	$(d_{max}, \ldots, d_{max}, d^*, d_{min}, \ldots, d_{min})$

Table 5.1: Summary of the results obtained for problems (P_1) and (P_2) with the Skipper model.

For the usual treatments of the drugs under study, the same dose is always given throughout the cycle. For this reason, we have contrasted the results of Table 5.1 using the Examples 3.1.1 and 3.1.2 for the problem (P_1) and the Example 3.2.1 for the problem (P_2).

On the other hand, for the Emax model, to study the problem (P_1), both the type of drug and the value of the constant $\hat{k}_2$ has influence. In Table 5.2 we can see the optimal treatment for the problem (P_1) depending on the type of drug and the value of $\hat{k}_2$.

Problem (P_1), Emax model		
Type of drug	$\hat{k}_2$	Optimal treatment
Short-life	$\hat{k}_2 \in (0,1)$	Depends on the value of d_{min} and d_{max}
	$\hat{k}_2 \geq 1$	Metronomic chemotherapy
Long-life	$\hat{k}_2 > 0$	$(d_{max}, \ldots, d_{max}, d^*, d_{min}, \ldots, d_{min})$

Table 5.2: Summary of the results obtained for problem (P_1) and Emax model.

In the case of drugs with short-life and $\hat{k}_2 \in (0,1)$, the optimal treatment depends on the value of d_{min} and d_{max}, and can be MTD therapy, metronomic chemotherapy, or another type of treatment as explained in Subsection 4.1.1, but all of them verifying that all the doses administered are equal (still, remember that in most cases $\hat{k}_2 > 1$). As in the Skipper case, for short half-life drugs, we obtain again that the optimal treatment is: $(d_{max}, \dots, d_{max}, d^*, d_{min}, \dots, d_{min})$, with $d_{min} \leq d^* \leq d_{max}$.

Regarding the problem (P_2) for the Emax case, if the drug has a short half-life, we have obtained that the most recommendable treatment is the metronomic one, with all doses being equal. However, the resolution of this problem for long half-life drugs is more complex. Although we have not explicitly solved it for that case, as we have formulated $(\tilde{P}_{2E}^N)$, we can compare several treatments that are reasonable (exposed by specialists), and decide which one will give better results in theory. The fact that we have formulated the problem allows us to reduce the number of treatments to be studied, since those that are not feasible can quickly be discarded. This can greatly facilitate clinical practice by reducing it to those treatments that have been proven to give the best results.

To support these theoretical results, we have performed numerical simulations for both models and both problems for a short half-life drug, Temozolomide, and for a long half-life one, Cabazitaxel. With the numerical experiments carried out for these drugs we have also found that, in many cases, the treatment which gives the best results is metronomic chemotherapy.

There are certain biological processes that make metronomic chemotherapy work better than MTD therapy, such as angiogenesis. However, we have not taken into account this type of process (as we have always considered θ fixed, while if we consider angiogenesis this parameter should grow with the tumor size). We want to emphasize that even so, following mathematical reasoning, there are many cases in which we obtain that metronomic chemotherapy gives better results than MTD therapy. Differentiating the advantages of these two therapies is a frequent discussion in the oncological field (see, for instance [5]), and with this study we want to provide a mathematical view of the problem, which in most cases leads us to choose as the best option metronomic chemotherapy.

As for future lines of research, it may be interesting to study these problems by leaving the times at which doses are administered as variables. We have tried to carry out this study but it is really complex because clinical knowledge is needed to know how much time should pass between one dose and another, both for reasons of effectiveness and toxicity of the treatment. In addition, it is also pending to study the characteristics of the problem (P_{2E}) for the case $\lambda \approx 0$.

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Appendix A

Weierstrass extreme value theorem

Be $K \subset \mathbb{R}^N$, $K \neq \emptyset$, $f : K \longrightarrow \mathbb{R}$, and the problem (P):

$$(P) \begin{cases} Min \ \ f(x) \\ \text{subject to } x \in K \end{cases} .$$

Theorem A.0.1. *([2]). If f is a continuous function and K is a compact set, then exists at least a global solution for (P) .*

Proof. Be $\mu = inf\{f(x) : x \in K\}$. We know that there is a minimizing sequence $(x^{(k)})_{k\in\mathbb{N}}$ such as

$$\begin{cases} (x^{(k)})_{k\in\mathbb{N}} \subset K \\ f(x^{(k)}) \longrightarrow \mu, \ \text{when } k \to +\infty \end{cases} . \tag{A.1}$$

As K is compact, it's bounded in $\mathbb{R}^N$, so there is a convergent subsequence $(x^{(k')})_{k'\in\mathbb{N}} \subset (x^{(k)})_{k\in\mathbb{N}}$ such as $x^{(k')} \longrightarrow \overline{x} \in K$ (K is closed) when $k' \to +\infty$. As f is continuous, $f(x^{(k')}) \longrightarrow f(\overline{x})$ when $k' \to +\infty$. Also, by (A.1), $f(x^{(k')}) \longrightarrow \mu$, when $k' \to +\infty$. Therefore, because of the uniqueness of the limit in $\mathbb{R}$, $f(\overline{x}) = \mu$.

Finally, as $\mu = inf\{f(x) : x \in K\}$, $\overline{x} \in K$ and $f(\overline{x}) = \mu$, then $\overline{x}$ is a global solution of (P). □

Appendix B

Inequality of arithmetic and geometric means

Definition B.0.1. *a) The **arithmetic mean** of the positive numbers $d_i \in \mathbb{R}^+, i \in \{1, \dots, N\}$ is defined as* $\frac{1}{N}\sum_{i=1}^{N} d_i$.

*b) The **geometric mean** of the positive numbers $d_i \in \mathbb{R}^+, i \in \{1, \dots, N\}$ is defined as* $\sqrt[N]{\prod_{i=1}^{N} d_i}$.

Proposition B.0.1. *([21]). The arithmetic mean of a set of positive numbers ($d_i \in \mathbb{R}^+, i \in \{1, \dots, N\}$) is always equal to or greater than the geometric mean. Therefore, the following inequality is verified:*

$$\sqrt[N]{\prod_{i=1}^{N} d_i} \leq \frac{1}{N}\sum_{i=1}^{N} d_i. \tag{B.1}$$

Moreover, the equality is only obtained when $d_i = d_j$, $\forall i, j \in \{1, \dots, N\}$.

Proof. First of all, it's trivial that if $d_i = d_j$, $\forall i, j \in \{1, \dots, N\}$, then $\sqrt[N]{d_1^N} = \frac{d_1 N}{N}$ and we get the equality in the equation (B.1). Now, let's prove (B.1) by induction:

- If $N = 2$:
$$\frac{d_1 + d_2}{2} \geq \sqrt{d_1 d_2} \Longrightarrow d_1^2 + d_2^2 - 2d_1 d_2 = (d_1 - d_2)^2 \geq 0.$$
Here we can note that we get the equality if and only if $d_1 = d_2$.

- Now let's suppose that (B.1) holds for $k \in \mathbb{N}$ (and the equality is only obtained for $d_1 = \dots = d_k$), and let's prove it for $2k$.
$$\frac{d_1 + \dots + d_{2k}}{2k} = \frac{1}{2}\left(\frac{d_1 + \dots + d_k}{k} + \frac{d_{k+1} + \dots + d_{2k}}{k}\right).$$
Knowing that (B.1) is verified for $N = 2$ and for k:
$$\frac{1}{2}\left(\frac{d_1 + \dots + d_k}{k} + \frac{d_{k+1} + \dots + d_{2k}}{k}\right) \geq \sqrt[2]{\sqrt[k]{d_1 \dots d_k}\sqrt[k]{d_{k+1} \dots d_{2k}}} = \sqrt[2k]{d_1 \dots d_{2k}}. \tag{B.2}$$
Note that the equality is only given if $d_1 = \dots = d_k$ and $d_{k+1} \dots = d_{2k}$ (by the hypothesis about k). In this case we get:
$$\frac{d_1 + d_{k+1}}{2} \geq \sqrt[2]{\sqrt[k]{d_1^k}\sqrt[k]{d_{k+1}^k}} = \sqrt{d_1 d_{k+1}},$$

and by the case $N = 2$, the equality is only fulfilled if $d_1 = d_{k+1}$, and then in (B.2) we get the equality if and only if $d_1 = \ldots = d_{2k}$.

- We assume (B.1) for k (inductive hypothesis), and let's prove it for $k-1$:
  We're going to apply the inductive hypothesis to $d_1, d_2, \ldots, d_{k-1}$ and its arithmetic mean:

$$\frac{d_1 + \ldots + d_{k-1}}{k-1} = \frac{d_1 + \ldots d_{k-1} + \frac{d_1+\ldots+d_{k-1}}{k-1}}{k} \geq \sqrt[k]{d_1 \ldots d_{k-1} \left(\frac{d_1 + \ldots + d_{k-1}}{k-1}\right)} \Longrightarrow$$

$$\Longrightarrow \frac{d_1 + \ldots + d_{k-1}}{k-1} \geq (d_1 \ldots d_{k-1})^{\frac{1}{k}} \left(\frac{d_1 + \ldots + d_{k-1}}{k-1}\right)^{\frac{1}{k}} \Longrightarrow$$

$$\Longrightarrow \left(\frac{d_1 + \ldots + d_{k-1}}{k-1}\right)^{\frac{k-1}{k}} \geq (d_1 \ldots d_{k-1})^{\frac{1}{k}} \Longrightarrow \frac{d_1 + \ldots + d_{k-1}}{k-1} \geq \sqrt[k-1]{d_1 \ldots d_{k-1}}.$$

  By the inductive hypothesis, in the first inequality we only get the equality if $d_1 = \ldots = d_{k-1} = \frac{d_1 + \ldots + d_{k-1}}{k-1}$, so the last equality is only fulfilled if $d_1 = \ldots = d_{k-1}$.

□

Appendix C

Lambert W function

Lambert W function (*omega function or product logarithm*) is defined as the inverse of the function $f(w) = w\,e^w$, with $w \in \mathbb{R}$ (see [23]). This function is usually represented by W. In Figure C.1 we show the graphic representation of the function $f(w) = w\,e^w$ for $w \in [-5, 2]$:

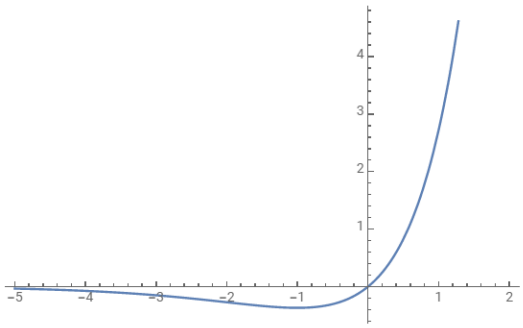

Figure C.1: $f(w) = w\,e^w$.

Note that this function is not injective. If the argument is real, Lambert W function is only defined for $z \geq -1/e$, and also for $z \in (-1/e, 0)$, because there are two branches. The principal branch is known as W_0, for which we know some values: $W_0(-1/e) = -1$, $W_0(0) = 0$, $W_0(e) = 1$...

Each function $W_k(z)$ is injective, and all of then have disjointed ranges. For example, in Figure C.2 we see the graphic of the branch $W_0(z)$ for $z \in [-1/e, 10]$, and in Figure C.3, that of the branch $W_{-1}(z)$ for $z \in [-1/e, 1]$.

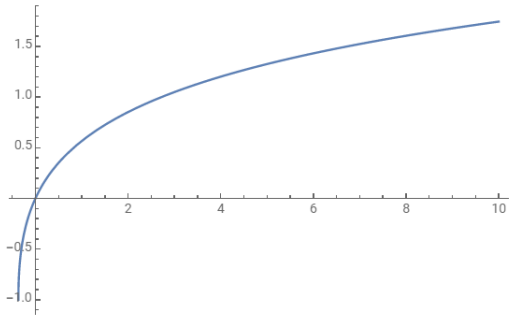

Figure C.2: $W_0(z)$

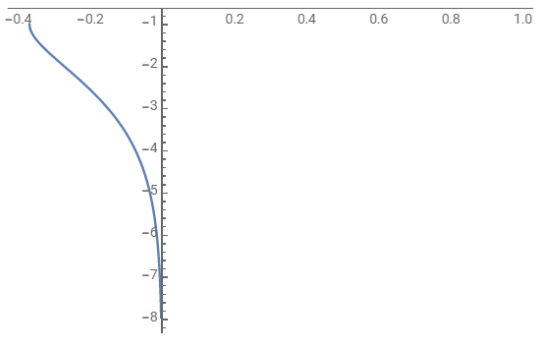

Figure C.3: $W_{-1}(z)$