

A MATHEMATICAL JUSTIFICATION FOR METRONOMIC CHEMOTHERAPY IN ONCOLOGY

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Abstract. We mathematically justify metronomic chemotherapy as the best strategy to apply many cytotoxic drugs in oncology for both curative and palliative approaches, assuming the classical pharmacokinetic model together with the Emax pharmacodynamic and the Norton-Simon hypothesis.

From the mathematical point of view, we will consider two mixed-integer nonlinear optimization problems, where the unknowns are the number of the doses and the quantity of each one, adjusting the administration times a posteriori.

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INTRODUCTION

Since the origins of chemotherapy in oncology, the standard and most widely used treatment has been the maximum tolerated dose (MTD): “the higher the dose, the better”, whose rationale seems very intuitive. As everyone knows, the trade-off lies in the side effects due to drug toxicity, which not only diminishes quality of life for the patient (adding more illness to the existing one), but also make it necessary to impose rest periods between cycles of therapy, which compromises a good resolution of the cancer treatment. For this reason, the design of more effective and less toxic chemotherapeutic regimens (by choosing the timing and fractionation of the doses) is a very active area of research in oncology.

A turning point in cancer chemotherapy treatments can be placed in the year 2000, when a revolutionary alternative approach called “metronomic chemotherapy” (MC) was proposed, see [14] and the references therein. According to National Cancer Institute [9], this is the “treatment in which low doses of anticancer drugs are given on a continuous or frequent, regular schedule (such as daily or weekly), usually over a long time. Metronomic chemotherapy causes less severe side effects than standard chemotherapy. Giving low doses of chemotherapy

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may stop the growth of new blood vessels that tumors need to grow". In oncology, this last effect is referred to as "anti-angiogenesis".

The historical controversy between efficacy in tumor killing and lack of toxicity has given rise to numerous studies and experimental trials comparing MTD and MC, the main conclusion of which can be summarized by saying that "the body of experimental and clinical evidence, coupled with theoretical considerations [...] point to MC as a preferred course of action", see [7]. Among the theoretical considerations, in addition to the anti-angiogenesis effect, we can mention that MC can activate anti-tumor immunity and minimize therapeutic resistance.

In this work, we will justify mathematically that MC is the best strategy in oncology for many cytotoxic drugs and both curative and palliative treatments, using simple well-established mathematical models and without taking those additional benefits into account. To that end, we will study two different optimization problems that arise when modeling usual chemotherapy treatments for cancer: to minimize the tumor volume at a fixed final time (curative approach) or to minimize the total cumulative dose that a patient must take during a specific period of time for maintaining the tumor volume below a given threshold (palliative approach). We will assume a Gompertzian type tumor growth and the Norton-Simon hypothesis to represent the growth-inhibitory influence due to the cytotoxic chemotherapy effect (see [11, 15]) with the classical pharmacokinetics and the Emax pharmacodynamic model. As far as we know, the first reference on this topic including some mathematical argumentation is [6], where the efficiency of MC was related with heterogeneous tumor populations (sensitive/resistant cells) assuming the log-kill hypothesis and Skipper's pharmacodynamic model; see also [8] and the references therein.

From the mathematical point of view, the optimization problems under our consideration are nonlinear and of mixed-integer type (where we will have the number of treatment doses as an integer variable, N , and the amount of each individual dose as a continuous variable, d_i). In both cases we will give explicit expressions of the approximated optimal solutions which will lead us to choose treatments corresponding to MC. A posteriori, the administration times can be adjusted (in fact, in several ways) completing the description of the treatment. We will illustrate the utility of our approach with numerical experiments concerning the treatment of some brain tumors that exhibit Gompertzian growth (see [16]) using a cytotoxic drug called Temozolomide. This drug is the subject of many clinical and biological recent studies (see [2, 4, 10, 12] and their references). The origin of this paper was an academic project [13] submitted by the third author under the supervision of the other two authors.

1. ASSOCIATED OPTIMIZATION PROBLEMS

Gompertz's law has often been used to simulate the growth of some untreated tumors (see for instance [1]). In mathematical terms this can be described by the following ordinary differential equation (ODE):

$$L'(t) = \Psi(L(t)), \quad (1)$$

where

$$\Psi(L) = \xi L \log\left(\frac{\theta}{L}\right).$$

In the above equations, $L(t)$ represents the tumor volume (or tumor size) at time t , ξ its growth rate and θ the maximum size it can reach (also called carrying capacity for biological systems). In practice, the parameters ξ and θ can also change with time (due to angiogenesis), but here we will focus on the simpler problem in which they are fixed.

As mentioned before, when using a cytotoxic drug to treat the tumor, we will consider the Norton-Simon hypothesis to model its effect; more precisely, we will assume that the growth-inhibiting effect due to the treatment is proportional to the growth rate of the untreated tumor (see [11, 15]). Mathematically, this can be written as

$$L'(t) = \Psi(L(t))(1 - \rho(t)). \quad (2)$$

Here the term $\Psi(L(t))\rho(t)$ represents the growth-inhibitory influence due to the cytotoxic chemotherapy effect and it reflects both, the level of the therapy at time t , $\rho(t)$, and the tumor's sensitivity to therapy.

First, let us present a general result for the existence and uniqueness of solution for the Cauchy problem associated with (2) (see [5] for the proof). As usual, we will denote by $W^{1,\infty}(0, T)$ the Sobolev space of all functions in $L^\infty(0, T)$ having first order weak derivative (in the distributional sense) also belonging to $L^\infty(0, T)$. It is well known that $W^{1,\infty}(0, T)$ can be identified with $C^{0,1}[0, T]$, the space of Lipschitz continuous functions in $[0, T]$, after a possible redefinition on a set of zero measure.

Theorem 1.1. *Let us assume that ξ , θ , L_0 and T are given positive real numbers, $L_0 \in (0, \theta)$ and $\rho \in L^\infty(0, T)$. Then, there exists a unique solution $L \in W^{1,\infty}(0, T)$ of the following Cauchy problem*

$$L'(t) = \xi L(t) \log \left(\frac{\theta}{L(t)} \right) (1 - \rho(t)), \quad L(0) = L_0, \quad (3)$$

given by

$$L(t) = \theta \exp \left(\log(L_0/\theta) \exp \left(-\xi \int_0^t (1 - \rho(s)) ds \right) \right), \quad \forall t \in [0, T]. \quad (4)$$

Depending on the expression of $\rho(t)$, different pharmacodynamics (PD) can be studied. In this work we consider the classic Emax model:

$$\rho(t) = \frac{k_1 c(t)}{k_2 + c(t)}, \quad (5)$$

where k_1 and k_2 are fixed positive real numbers and $c(t)$ denotes the concentration of the drug in the tumor at time t . More precisely, k_1 represents the maximum effect of the drug on the tumor and k_2 is the half maximal effective concentration, i.e the concentration producing 50% of the maximum effect, usually denoted by EC_{50} . Other choices have been considered in the literature, as the Skipper model where $\rho(t) = k_1 c(t)$. The Emax model seems to be more appropriate from the clinical point of view because it saturates for high concentration values.

Another crucial term is related with the pharmacokinetics (PK). We use the following Cauchy problem to describe the PK of the drug:

$$\begin{cases} c'(t) = -\lambda c(t) + \sum_{i=1}^N \sigma d_i \delta(t - t_i), \\ c(0) = 0. \end{cases} \quad (6)$$

The coefficient λ is the clearance rate and it is related to the half-life of the drug ($t_{1/2}$) by the expression $\lambda = \log(2)/t_{1/2}$. The second term on the right hand of the equation depends on both the specific drug and the way it is administered. We assume that N doses, $\{d_i\}_{i=1}^N$, will be used at N dosage times, $\{t_i\}_{i=1}^N$, such that $0 \leq t_1 < \dots < t_N$. The coefficient σ is determined on the basis of drug-, patient- and tumor-specific parameters. For instance, in the case of brain tumors the drug loss during the transport to the brain has to be taken into account, see [2] and the references therein. In other cases, $\sigma = \frac{\alpha}{V_D \beta}$, where α is the patient's body surface area, V_D is the volume of distribution of the drug (given in l/kg) and β is the patient weight in kg . Finally, $\delta(t - t_i)$ is the Dirac delta distribution concentrated at t_i .

In principle, it seems reasonable to consider the administration times $\{t_i\}_{i=1}^N$ as variables of the optimization problems, as well as N and the doses $\{d_i\}_{i=1}^N$. However, this approach would lead us into serious difficulties because the criterion for deciding a priori the characteristics that determine the feasible protocols may be unknown even to the specialist and in practice, this would make the mathematical approach unfeasible. Instead, after some calculations and under our main hypothesis (15), see below, we will obtain formulations that are independent of the administration times and valid for many cytotoxic drugs. For these cases we propose to consider the administration times set in a first step (patterned or irregularly distributed, as one prefers, but

verifying condition (15)), readjusting them after the optimization process has finished, i.e., once N and the doses $\{d_i\}_{i=1}^N$ have been determined.

In this paper we are interested in the solutions of two optimization problems associated with the Cauchy problem (3) using the Emax model (5) and when the following data are given: the final time T ($T > t_N$) and the levels of effectiveness and the toxicity of each individual dose, d_{min} and d_{max} , respectively. We assume $0 < d_{min} < d_{max}$. To simplify some expressions we will use $t_{N+1} = T$. As we have explained before, the administration times t_i , $i = 1, \dots, N$, are fixed a priori satisfying (15), but the number N of the treatment doses is a variable to be determined.

Firstly, we consider a curative approach with the goal of minimizing the tumor volume at the final time T with a fixed cumulative dose, D , that will be divided into N smaller doses, $\{d_i\}_{i=1}^N$, to be determined. Hence we formulate the following problem with $N + 1$ variables

$$(P_1) \begin{cases} \min L(T), \\ N \in \mathbb{N}, d = (d_1, \dots, d_N) \in \mathbb{R}^N, \\ \text{subject to } \sum_{i=1}^N d_i = D, \\ d_{min} \leq d_i \leq d_{max}, \quad i = 1, \dots, N. \end{cases} \quad (7)$$

Using (4) and the fact that $L_0 < \theta$ (where L_0 is the initial tumor size), we transform (P_1) into the following problem:

$$\begin{cases} \max \int_0^T \rho(s) ds, \\ N \in \mathbb{N}, d = (d_1, \dots, d_N) \in \mathbb{R}^N, \\ \text{subject to } \sum_{i=1}^N d_i = D, \\ d_{min} \leq d_i \leq d_{max}, \quad i = 1, \dots, N. \end{cases} \quad (8)$$

Now, let's formulate the problem related to a palliative approach in which we want to minimize the total dose (determining N and d_i , for $i = 1, \dots, N$) while maintaining the tumor volume at T below a given threshold $L_* > 0$ that is not harmful to the patient, allowing him to have an acceptable quality of life. We consider the same bound constraints on the individual doses as in the previous optimization problem:

$$(P_2) \begin{cases} \min \sum_{i=1}^N d_i, \\ N \in \mathbb{N}, d = (d_1, \dots, d_N) \in \mathbb{R}^N, \\ \text{subject to } L(T) \leq L_*, \\ d_{min} \leq d_i \leq d_{max}, \quad i = 1, \dots, N. \end{cases} \quad (9)$$

Using again (4), it is easy to check the equivalence:

$$L(T) \leq L_* \iff \int_0^T \rho(s) ds \geq T + T_R, \text{ with } T_R = \frac{1}{\xi} \log \left(\frac{\log(L_*/\theta)}{\log(L_0/\theta)} \right). \quad (10)$$

Therefore, we can reformulate the problem (P_2) as follows:

$$\left\{ \begin{array}{l} \min \sum_{i=1}^N d_i, \\ N \in \mathbb{N}, d = (d_1, \dots, d_N) \in \mathbb{R}^N, \\ \text{subject to } \int_0^T \rho(s) ds \geq T + T_R, \\ d_{min} \leq d_i \leq d_{max}, \quad i = 1, \dots, N. \end{array} \right. \quad (11)$$

2. OPTIMAL TREATMENTS

In view of our optimization problems it is convenient to have an explicit formulation for the concentration of the drug.

Proposition 2.1. *The solution of the Cauchy problem (6) is given by*

$$c(t) = \begin{cases} 0, & \text{if } t \in [0, t_1), \\ \sigma e^{-\lambda t} e^{\lambda t_1} d_1, & \text{if } t \in [t_1, t_2), \\ \sigma e^{-\lambda t} (e^{\lambda t_1} d_1 + e^{\lambda t_2} d_2), & \text{if } t \in [t_2, t_3), \\ \vdots & \vdots \\ \sigma e^{-\lambda t} (e^{\lambda t_1} d_1 + \dots + e^{\lambda t_{N-1}} d_{N-1}), & \text{if } t \in [t_{N-1}, t_N), \\ \sigma e^{-\lambda t} (e^{\lambda t_1} d_1 + \dots + e^{\lambda t_N} d_N), & \text{if } t \in [t_N, T). \end{cases} \quad (12)$$

Proof. Applying Laplace transform to problem (6) we get

$$s\mathcal{L}(c)(s) = -\lambda\mathcal{L}(c)(s) + \sum_{i=1}^N \sigma d_i e^{-st_i},$$

and consequently,

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

where

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

This implies that

$$c(t) = \sum_{i=1}^N \sigma d_i g_i(t),$$

which is equivalent to (12). □

We continue by obtaining the expression for the integral term appearing in (8) and (11). In this respect, we present the following result:

Lemma 2.2. *Let us assume that $c(t)$ is given by (12) and $\rho(t)$ by (5). Then, it is verified that*

$$\int_0^T \rho(s) ds = \frac{k_1}{\lambda} \log \left(\frac{(d_1 + \tilde{k}_2) \prod_{i=2}^N \left(\sum_{j=1}^{i-1} d_j e^{\lambda(t_j - t_i)} + d_i + \tilde{k}_2 \right)}{\prod_{i=1}^N \left(\sum_{j=1}^i d_j e^{\lambda(t_j - t_{i+1})} + \tilde{k}_2 \right)} \right), \quad (13)$$

where $\tilde{k}_2 = k_2/\sigma$ and $t_{N+1} = T$.

Proof. Using (12) and the definition of ρ , we derive (13) from the following equalities:

$$\int_{t_1}^{t_2} \frac{c(s)}{k_2 + c(s)} ds = \frac{1}{\lambda} \log \left(\frac{d_1 + \tilde{k}_2}{d_1 e^{\lambda(t_1 - t_2)} + \tilde{k}_2} \right),$$

$$\int_{t_i}^{t_{i+1}} \frac{c(s)}{k_2 + c(s)} ds = \frac{1}{\lambda} \log \left(\frac{d_1 e^{\lambda(t_1 - t_i)} + \dots + d_{i-1} e^{\lambda(t_{i-1} - t_i)} + d_i + \tilde{k}_2}{d_1 e^{\lambda(t_1 - t_{i+1})} + \dots + d_i e^{\lambda(t_i - t_{i+1})} + \tilde{k}_2} \right),$$

for $i = 2, \dots, N-1$ and taking into account that the integral corresponding to the interval $[t_N, T]$ is similar to the previous expression changing t_i by t_N and t_{i+1} by T . \square

2.1. Curative approach

We start by considering the problem (P_1) defined in Section 1 (in which we want to minimize the tumor volume at time T with a fixed cumulative dose D). In this case, using (8), (13), the positivity of k_1/λ and the monotonicity of the logarithm function, we reformulate the problem (P_1) as follows:

$$\left\{ \begin{array}{l} \text{Max } f_1(N, d) = \frac{(d_1 + \tilde{k}_2) \prod_{i=2}^N \left(\sum_{j=1}^{i-1} d_j e^{\lambda(t_j - t_i)} + d_i + \tilde{k}_2 \right)}{\prod_{i=1}^N \left(\sum_{j=1}^i d_j e^{\lambda(t_j - t_{i+1})} + \tilde{k}_2 \right)}, \\ N \in \mathbb{N}, d = (d_1, \dots, d_N) \in \mathbb{R}^N, \\ \text{subject to } \sum_{i=1}^N d_i = D, \\ d_{\min} \leq d_i \leq d_{\max}, \quad i = 1, \dots, N. \end{array} \right. \quad (14)$$

Note that it is a mixed-integer nonlinear optimization problem with an integer variable, N , and N continuous variables, d_i .

In order to simplify the objective function f_1 , along the rest of the work, we will assume the **main hypothesis** that we are considering cytotoxic drugs such that their half maximal effective concentrations (k_2) and their maximum tolerated dose concentrations (σd_{\max}) verify the following condition:

$$\sigma d_{\max} e^{-\lambda s} \ll k_2, \quad (15)$$

where s denotes the minimum of the elapsed time periods; this is

$$s = \min\{t_{i+1} - t_i : i = 1, \dots, N\}.$$

Let us stress that this condition holds (at least) when λ is sufficiently large (or equivalently, the half-life of the drug is sufficiently small). We will show later that many of the common cytotoxic drugs meet this condition, see Table 1 below.

Assuming (15) and recalling that $\tilde{k}_2 = k_2/\sigma$, we have the following approximation for the objective function:

$$f_1(N, d) \approx \prod_{i=1}^N \left(\frac{d_i}{\tilde{k}_2} + 1 \right), \quad (16)$$

that leads to the mixed-integer nonlinear programming problem:

$$(\hat{P}_1) \left\{ \begin{array}{l} \text{Max } \hat{f}_1(N, d) = \prod_{i=1}^N \left(\frac{d_i}{\tilde{k}_2} + 1 \right), \\ N \in \mathbb{N}, d = (d_1, \dots, d_N) \in \mathbb{R}^N, \\ \text{subject to } \sum_{i=1}^N d_i = D, \\ d_{min} \leq d_i \leq d_{max}, \quad i = 1, \dots, N. \end{array} \right. \quad (17)$$

At this point, it is very important to underline that the administration times $\{t_i\}_{i=1}^N$ do not appear in the formulation of (\hat{P}_1) . This is a crucial property that will allow us to break the vicious circle mentioned in the previous section: for many cytotoxic drugs we will first determine N and the doses $\{d_i\}_{i=1}^N$ as the solution of (\hat{P}_1) and then assign appropriate administration times, checking that (15) holds.

Using the bound constraints and the total dose value, in order to have a non-empty set of feasible points, we must assume

$$[D/d_{max}, D/d_{min}] \cap \mathbb{N} \neq \emptyset. \quad (18)$$

In particular, hypothesis (18) implies that only a finite number of values for variable N have to be taken into account to solve the optimization problem. Namely,

$$N \in \{[D/d_{max}], \dots, [D/d_{min}]\}, \quad (19)$$

where $[x]$ denotes the greatest integer less than or equal to x and $\lceil x \rceil$ the least integer greater than or equal to x .

Now, for each fixed feasible value of N , we can formulate the following continuous nonlinear programming problem:

$$(\hat{P}_1^N) \left\{ \begin{array}{l} \text{Max } \hat{f}_1^N(d) = \prod_{i=1}^N \left(\frac{d_i}{\tilde{k}_2} + 1 \right), \\ d = (d_1, \dots, d_N) \in \mathbb{R}^N, \\ \text{subject to } \sum_{i=1}^N d_i = D, \\ d_{min} \leq d_i \leq d_{max}, \quad i = 1, \dots, N. \end{array} \right. \quad (20)$$

It is not difficult to prove that equal-dosage is the optimal solution of the previous problem:

Theorem 2.3. *Let us assume that $d_{min} > 0$ and (18). Then, for each N verifying (19), the problem (\hat{P}_1^N) has a unique optimal solution \hat{d} given by*

$$\hat{d}_i = D/N, \quad \text{for } i = 1, \dots, N.$$

Proof. For any feasible point d , using the relation between the geometric and arithmetic means, we get

$$\sqrt[N]{\prod_{i=1}^N \left(\frac{d_i}{\tilde{k}_2} + 1 \right)} \leq \frac{1}{N} \sum_{i=1}^N \left(\frac{d_i}{\tilde{k}_2} + 1 \right) = \frac{D}{N\tilde{k}_2} + 1,$$

and therefore, $\hat{f}_1^N(d) \leq \left(\frac{D}{N\tilde{k}_2} + 1 \right)^N$. By the hypotheses, $\hat{d} = (D/N, \dots, D/N)$ is a feasible point for (\hat{P}_1^N) such that the corresponding objective function value reaches the above upper bound, so the conclusion of the theorem follows straightforwardly. \square

As a consequence, the optimal solution of the approximate mixed-integer optimization problem (\hat{P}_1) leads to the longest feasible treatment:

Corollary 2.4. *Let us assume that $d_{min} > 0$ and (18). Then the optimal solution of (\hat{P}_1) is given by (\hat{N}, \hat{d}) , with $\hat{N} = \lfloor D/d_{min} \rfloor$ and $\hat{d}_i = D/\hat{N}$, for $i = 1, \dots, \hat{N}$.*

Proof. This can be deduced combining Theorem 2.3 with the fact that the auxiliary function

$$\varphi_1(x) = \left(\frac{1}{x} + 1 \right)^x$$

is strictly increasing in $(0, +\infty)$ and noticing that

$$\hat{f}_1(N, \hat{d}) = \left(\frac{D}{N\tilde{k}_2} + 1 \right)^N = \left(\varphi_1 \left(\frac{N\tilde{k}_2}{D} \right) \right)^{\frac{D}{\tilde{k}_2}}.$$

\square

Furthermore, we can study the dependence of the objective function optimal value with respect to d_{min} . Using previous expressions, we derive

$$\hat{f}_1(\hat{N}, \hat{d}) = \left(\frac{D}{\hat{N}\tilde{k}_2} + 1 \right)^{\hat{N}} \approx \left(\frac{d_{min}}{\tilde{k}_2} + 1 \right)^{\frac{D}{d_{min}}} = \left(\varphi_1 \left(\frac{\tilde{k}_2}{d_{min}} \right) \right)^{\frac{D}{\tilde{k}_2}}.$$

On the one hand, this implies that to increase $\hat{f}_1(\hat{N}, \hat{d})$ (and therefore to decrease the tumor size at the fixed final time) is interesting to take d_{min} as small as possible, in line with the principles of MC. But, on the other hand, from the clinical point of view, it is known that for any drug there is a minimum effective dose (the smallest dose with a discernible useful effect) that must be taken into account. In general, its estimation (and even its definition) remains controversial and this carries over to the determination of the optimal d_{min} in the practice.

Remark 2.5. i) Choosing the Gompertzian law for the untreated tumor growth is not a crucial aspect for deriving our results. Other typical ODEs with sigmoid-type solutions may be reasonable choices, such as (1) with

$$\Psi(L) = \frac{\xi}{\gamma} L \left(1 - \left(\frac{L}{\theta} \right)^\gamma \right),$$

with $\gamma > 0$. For $\gamma = 1$, we recover the well-known logistic ODE, meanwhile for small $\gamma > 0$, this is an approximation of the Gompertz ODE, see [1]. All these options lead to the same results.

- ii) Instead, it can be shown that the Norton-Simon hypothesis is crucial for our argument. There are other classical hypotheses such as the log-kill one. It states that a given dose of chemotherapy kills the same fraction of tumor cells regardless of the size of the tumor at the time of treatment, which leads to the following problem

$$L'(t) = \xi L(t) \log\left(\frac{\theta}{L(t)}\right) - \rho(t)L(t), \quad L(0) = L_0, \quad (21)$$

instead of (3). Although the log-kill hypothesis continues to appear frequently in the literature, it was shown in [11] to be inconsistent with some clinical experiences.

- iii) We have studied a related problem for continuous (non-discrete) drug infusion in [5] (labeled (OP_2) with $G = G_2$). There, it was proved the appearance of a constant maintenance infusion rate (during a fairly long time interval) in the expression of the optimal control. This can be seen as a piecewise continuous version of our previous Corollary 2.4.
- iv) We present Table 1 to illustrate the verification of our main hypothesis (15) for several cytotoxic drugs. The drug name appears in the first column, then two columns show the values of the minimum time interval between doses (s) for the usual monotherapy treatments and the clearance rate (λ) from the data of [3] and finally, the value $exp(-\lambda s)$ appears in the last column. Taking into account these values, we observe that, for our main hypothesis to be fulfilled in all cases, it is sufficient for the half maximal effective concentration (k_2) to be significantly higher than 4% of the concentration associated with the maximum tolerated dose (σd_{max}), which does not seem to be a very demanding condition.

TABLE 1. Parameter values for some cytotoxic drugs.

| Generic Name | s (days) | λ (days ⁻¹) | $exp(-\lambda s)$ |
|--------------|------------|---------------------------------|-------------------|
| Bleomycin | 1 | 8.318e+00 | 2.441e-04 |
| Capecitabine | 0.5 | 3.869e+01 | 3.973e-09 |
| Carboplatin | 28 | 5.545e+00 | 3.709e-68 |
| Cisplatin | 28 | 3.327e+01 | 0 |
| Dacarbazine | 1 | 3.327e+00 | 3.590e-02 |
| Docetaxel | 21 | 1.498e+00 | 2.146e-14 |
| Doxorubicin | 21 | 3.466e-01 | 6.905e-04 |
| Gemcitabine | 7 | 1.060e+01 | 6.136e-33 |
| Melphalan | 1 | 1.331e+01 | 1.660e-06 |
| Methotrexate | 1 | 5.545e+00 | 3.906e-03 |
| Paclitaxel | 21 | 8.235e-01 | 3.084e-08 |
| Pentostatin | 14 | 2.919e+00 | 1.799e-18 |
| Temozolomide | 1 | 9.242e+00 | 9.689e-05 |
| Topotecan | 1 | 5.545e+00 | 3.906e-03 |
| Vinorelbine | 7 | 6.006e-01 | 1.494e-02 |

Among the drugs listed in Table 1, we have chosen Temozolomide (TMZ) for our numerical experiments. TMZ is an oral alkylating agent with antitumor activity in high and low grade gliomas (HGG and LGG, respectively). In the monotherapy phase for adult patients with newly-diagnosed glioblastoma multiforme, TMZ is usually administered consecutively for 5 days of every 28 days (this is denoted by $5/28d$) for a maximum of 6 cycles with individual doses of 150 mg/m^2 in first cycle and 200 mg/m^2 in the others. So, taking into account this usual treatment (UT), we have fixed $T = 210$ days for the final time (approximately two months after the end of UT) and $D = 5,750 \text{ mg/m}^2$ for the cumulative dose.

The parameter values used for our numerical computations are showed in Table 2. The growth rate ξ depends on the type of tumor; the value $\xi = 5.51e-3$ could correspond to an HGG with a volume-doubling time about 126 days (see [16] for growth dynamics of glioblastomas). Following [2], we have used $\sigma = 4e-3$ that corresponds

TABLE 2. Parameter values used for the numerical experiments.

| Parameters | Temozolomide (TMZ) |
|---------------------------|--------------------|
| λ ($days^{-1}$) | 9.242 |
| ξ ($days^{-1}$) | 5.51e-3 |
| k_1 | 60 |
| k_2 (mg/l) | 3.6e-1 |
| σ (m^2/l) | 4e-3 |
| d_{max} (mg/m^2) | 200 |
| T ($days$) | 210 |
| L_0/θ | 2.5e-1 |
| t_1 | 0 |

to a woman with a body surface of $1.6 m^2$ and it takes into account the fraction of TMZ getting to her brain interstitium. We have chosen $k_2 = 3.6e-1 mg/l$, a value that is consistent with predicted peak concentrations of TMZ from [2,12]; also $k_1 = 60$ for illustrative purposes. Let us note that the parameter k_1 does not play any role either in the optimization process of this subsection nor in the main hypothesis (15), but it influences the evaluation of the tumor size. Moreover, let us stress that (15) holds in this case, because

$$\sigma d_{max} e^{-\lambda s} \approx 7.75e-5 \ll k_2 = 3.6e-1,$$

with $s = 1$. Finally, let us underline that the value of θ is unnecessary here, because the initial datum and the results are given rescaled in the form L_0/θ and $L(t)/\theta$, respectively (see Table 2 and all figures).

In Table 3 we present some numerical results to illustrate and compare the optimal treatments of (14) with fixed N (denoted by (P_1^N)) to those associated with (\hat{P}_1^N) in the case of doses between $d_{min} = 100 mg/m^2$ and $d_{max} = 200 mg/m^2$. To solve the problems (P_1^N) , we have used FMINCON (a nonlinear programming solver provided in MATLAB's Optimization Toolbox) with the SQP algorithm and the value $1.e-8$ for the optimality tolerance. Here, we present results only for the feasible values of N , taking into account the length of the treatment interval (210 days) and the number of dosage times for the 5/28d schedule: $N \in [29, 40]$. This number N appears in the first column; then we present two columns with the individual doses of the treatment described in Theorem 2.3 for (\hat{P}_1^N) and the ratio of the final tumor volume to the initial volume, $L(T)/L_0$, for an initial medium size tumor (25% of carrying capacity); the next three columns report results given by FMINCON: the minimum and maximum values reached by the individual doses of each treatment, \bar{d}_{min} and \bar{d}_{max} , and its corresponding ratio $L(T)/L_0$. Let us note at this point that, for each value of N , the individual doses obtained with FMINCON are almost identical and moreover the best solution is reached administering 40 doses. The last line of the table is associated to UT described above using $N = 30$ doses. It is noteworthy that with it the final tumor volume is 91% of the initial volume while the best treatment provides 73%. At the top of Figure 1 we see the evolution of the tumor volume, $L(t)/\theta$, for a selection of treatments of Table 3: UT, the 35-dose treatment and the 40-dose treatment in black, blue and red, respectively. The circles and stars mark the drug administration times (from the 5/28d schedule) used for the graphs. Note that UT is the shortest (it ends in 145 days). To illustrate that the distribution of the dosage times does not influence the final tumor size, we present three treatments with $N = 30$ doses in Figure 2: UT, one with the UT doses equally distributed in time and another with one given at $t_1 = 0$ and the other 29 doses of UT concentrated at the end of the interval (in this case we do not take into account the medical feasibility of the treatments). The tumor size during the last six days is practically the same in all cases (with a difference from the size given by UT less than $4.0558e-5$).

The most relevant results of this section are given in Table 4 and at the top of Figure 3, where we show the influence of the level d_{min} and compare four optimal treatments corresponding to (\hat{P}_1) requiring the same cumulative dose ($D = 5,750 mg/m^2$). The rest of the parameters are given in Table 2. As we have mentioned previously, first d_{min} is fixed and (\hat{P}_1) is solved (using Corollary 2.4) to determine \hat{N} and $\{\hat{d}_i\}_{i=1}^{\hat{N}}$; then, we have

TABLE 3. Results with $D = 5,750 \text{ mg}/\text{m}^2$, $d_{min} = 100 \text{ mg}/\text{m}^2$ and 5/28d schedule.

| N | (\hat{P}_1^N) | | (P_1^N) | | |
|-----------|-----------------|-------------|-----------------|-----------------|-------------|
| | D/N | $L(T)/L_0$ | \bar{d}_{min} | \bar{d}_{max} | $L(T)/L_0$ |
| 29 | 198.28 | 0.93 | 198.26 | 198.32 | 0.93 |
| 30 | 191.67 | 0.91 | 191.65 | 191.71 | 0.91 |
| 31 | 185.48 | 0.89 | 185.47 | 185.54 | 0.89 |
| 32 | 179.69 | 0.87 | 179.67 | 179.72 | 0.87 |
| 33 | 174.24 | 0.85 | 174.23 | 174.28 | 0.85 |
| 34 | 169.12 | 0.83 | 169.10 | 169.15 | 0.83 |
| 35 | 164.29 | 0.81 | 164.27 | 164.32 | 0.81 |
| 36 | 159.72 | 0.79 | 159.71 | 159.77 | 0.79 |
| 37 | 155.41 | 0.77 | 155.39 | 155.43 | 0.77 |
| 38 | 151.32 | 0.76 | 151.30 | 151.34 | 0.76 |
| 39 | 147.44 | 0.74 | 147.42 | 147.46 | 0.74 |
| 40 | 143.75 | 0.73 | 143.74 | 143.78 | 0.73 |
| 30 (UT) | | | 150 | 200 | 0.91 |

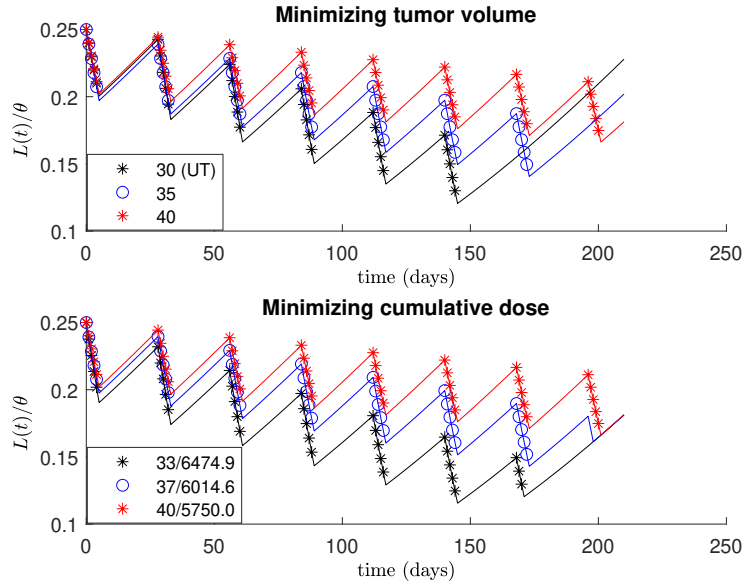


FIGURE 1. Optimization results for TMZ (see Tables 3 and 5).

selected the most appropriate schedules for TMZ considered in some studies, see [10]: the 7/14d with doses of $150 \text{ mg}/\text{m}^2$, the 21/28d with doses of $100 \text{ mg}/\text{m}^2$ and $75 \text{ mg}/\text{m}^2$ and the daily regimen with $50 \text{ mg}/\text{m}^2$ doses. The results of the penultimate column of Table 4 and the graphics of Figure 3 have been calculated with the times given by these schedules. Let us underline that the specific values of the administration times do not affect the optimal solutions (defined by the values of the second and third columns) and the only relevant factor is the maximum number of doses that can be administered with the chosen d_{min} . In the fifth column, we observe that the greatest tumor shrinkage is achieved with the longest treatment which also has the lowest

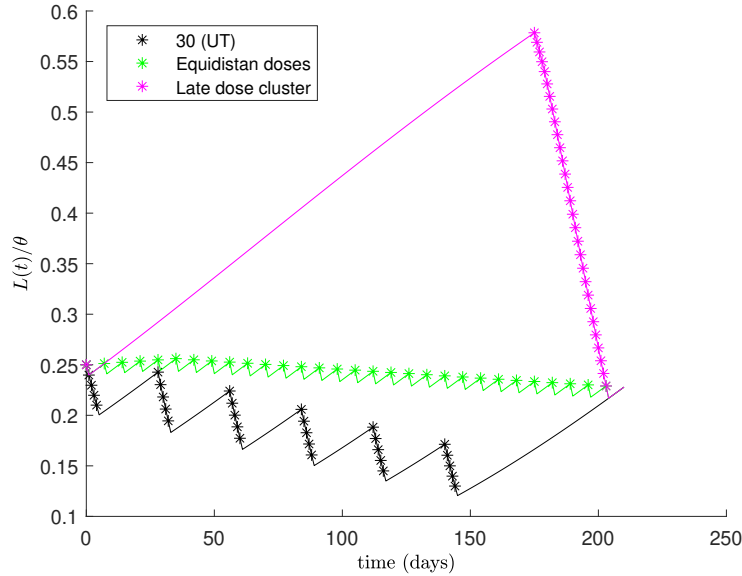


FIGURE 2. Tumor volume evolution with UT doses distributed in three different ways.

TABLE 4. Results for (\hat{P}_1) with $D = 5,750 \text{ mg}/\text{m}^2$ varying d_{min} .

| d_{min} | \hat{N} | D/\hat{N} | Schedule | $L(T)/L_0$ | Dose intensity |
|-----------|-----------|-------------|----------|------------|----------------|
| 150 | 38 | 151.32 | 7/14d | 0.76 | 78.77 |
| 100 | 57 | 100.88 | 21/28d | 0.53 | 80.99 |
| 75 | 76 | 75.66 | 21/28d | 0.41 | 59.28 |
| 50 | 115 | 50.00 | 28/28d | 0.27 | 50.00 |

doses, in line with MC. Moreover, three of the treatments of Table 4 are more effective than the best treatment of Table 3, all of them improving UT. As predicted by the Norton-Simon hypothesis [15], it is apparent that the optimal solution is more “dose-dense” than other feasible protocols, see the top of Figure 3 (the period between cycles is shorter). However, concerning the “dose-intensity” (defined as the total dose administered during a treatment, divided by its duration) it can be seen in the last column of Table 4 that the optimal protocol has the lowest.

2.2. Palliative approach

In this section we are interested in the optimization problem (P_2) , i.e., we want to minimize the total administered dose with a constraint on the tumor size at the final time: $L(T) \leq L_*$, where L_* is a level given in advance. Using (10) and Lemma 2.2, that constraint is equivalent to the following inequality:

$$f_1(N, d) \geq e^{\tilde{T}_R},$$

being f_1 the objective function of problem (14) and

$$\tilde{T}_R \stackrel{def}{=} \frac{\lambda}{k_1}(T + T_R). \quad (22)$$

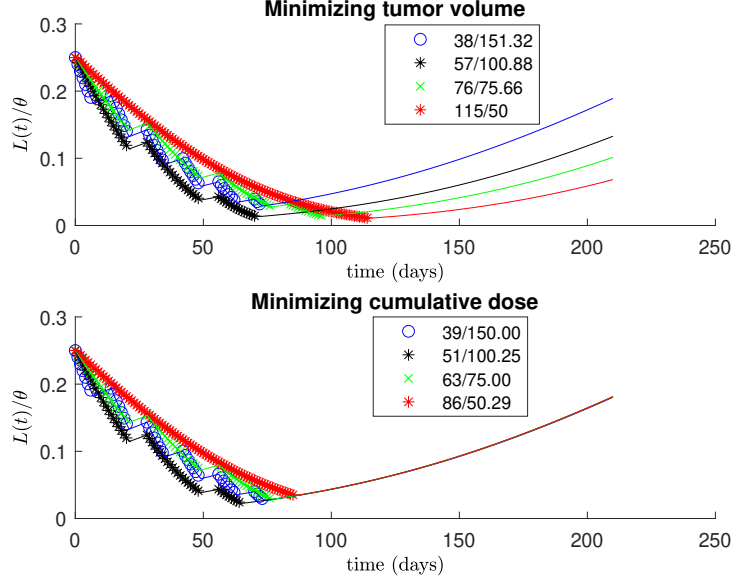


FIGURE 3. Optimization results with TMZ (see Tables 4 and 6).

Let us remember that T_R depends on the data ξ , θ , L_0 and L_* (see (10)). Therefore, through (11), the optimization problem (P_2) can be reformulated as follows:

$$\left\{ \begin{array}{l} \min f_2(N, d) = \sum_{i=1}^N d_i, \\ N \in \mathbb{N}, d = (d_1, \dots, d_N) \in \mathbb{R}^N, \\ \text{subject to } f_1(N, d) \geq e^{\tilde{T}_R}, \\ d_{min} \leq d_i \leq d_{max}, \quad i = 1, \dots, N, \end{array} \right. \quad (23)$$

with $d_{min} > 0$ and $\tilde{T}_R \in \mathbb{R}$ defined in (22). Using the approximation (16) in the nonlinear constraint, we arrive to the following nonlinear programming problem

$$(\hat{P}_2) \left\{ \begin{array}{l} \min f_2(N, d) = \sum_{i=1}^N d_i, \\ N \in \mathbb{N}, d = (d_1, \dots, d_N) \in \mathbb{R}^N, \\ \text{subject to } \hat{f}_1(N, d) \geq e^{\tilde{T}_R}, \\ d_{min} \leq d_i \leq d_{max}, \quad i = 1, \dots, N, \end{array} \right. \quad (24)$$

with \hat{f}_1 defined in (17). As one can see, (\hat{P}_2) is also a mixed-integer nonlinear optimization problem with an integer variable N and N continuous variables, d_i .

In this case, let us remark that the set of feasible values for N is infinite: using the general inequality constraint and the upper bound constraints, the following inequality should be satisfied

$$N \geq \lceil \tilde{T}_R / \log(d_{max}/\tilde{k}_2 + 1) \rceil \stackrel{def}{=} N_{min}.$$

In fact, only a finite subset has practical interest, i.e., those values that also verify

$$N \leq N_{max} \stackrel{def}{=} \lceil \tilde{T}_R / \log(d_{min}/\tilde{k}_2 + 1) \rceil,$$

because at least the pair $(N_{max}, \underbrace{d_{min}, \dots, d_{min}}_{N_{max}})$ is feasible and any other feasible pair with larger value of N will produce a greater value of the objective function f_2 . Therefore, to have a non-empty set of feasible points we will assume

$$[N_{min}, N_{max}] \cap \mathbb{N} \neq \emptyset. \quad (25)$$

Now, as in the previous subsection, we will focus on the associated continuous problems generated when the value of the integer variable N is fixed:

$$(\hat{P}_2^N) \begin{cases} \min & f_2^N(d) = \sum_{i=1}^N d_i, \\ & d = (d_1, \dots, d_N) \in \mathbb{R}^N, \\ \text{subject to} & \hat{f}_1^N(d) \geq e^{\tilde{T}_R}, \\ & d_{min} \leq d_i \leq d_{max}, \quad i = 1, \dots, N, \end{cases} \quad (26)$$

with the function \hat{f}_1^N defined in (20). In the following result we show that the optimal treatment for (\hat{P}_2^N) has also equal doses and moreover, we obtain the explicit formula to determine them:

Theorem 2.6. *Let us assume $d_{min} > 0$ and*

$$N \in [N_{min}, N_{max} - 1]. \quad (27)$$

Then, the optimization problem (\hat{P}_2^N) has a unique solution $\hat{d} = (\hat{d}_1, \dots, \hat{d}_N)$ given by

$$\hat{d}_i = \tilde{k}_2(e^{\tilde{T}_R/N} - 1), \quad \text{for } i = 1, \dots, N. \quad (28)$$

Proof. First of all, it is easy to check that the proposed dose vector is feasible for the problem (\hat{P}_2^N) , if N verifies (27). On the other hand, using once more the relation between the geometric and arithmetic means, the doses of any feasible treatment for (\hat{P}_2^N) verify the following inequalities

$$\frac{1}{N} \sum_{i=1}^N (d_i + \tilde{k}_2) \geq \left(\tilde{k}_2 \hat{f}_1^N(d) \right)^{1/N} \geq \tilde{k}_2 e^{\tilde{T}_R/N},$$

and consequently,

$$\sum_{i=1}^N d_i \geq N \tilde{k}_2 (e^{\tilde{T}_R/N} - 1). \quad (29)$$

Taking into account that the lower bound of (29) is equal to $f_2^N(\hat{d})$, the conclusion follows. \square

Finally, we determine the optimal solution of the approximate mixed-integer optimization problem of the palliative approach.

Corollary 2.7. *Let us assume that $d_{min} > 0$ and (25). Then a global optimal solution of (\hat{P}_2) problem is given by (\hat{N}, \hat{d}) with*

- a) $\hat{N} = N_{max} - 1$ and $\hat{d}_i = d^*$, for $i = 1, \dots, \hat{N}$, if $(N_{max} - 1)d^* \leq N_{max}d_{min}$,
 b) $\hat{N} = N_{max}$ and $\hat{d}_i = d_{min}$, for $i = 1, \dots, \hat{N}$, if $(N_{max} - 1)d^* \geq N_{max}d_{min}$,

where $d^* = \tilde{k}_2(e^{\tilde{T}_R/(N_{max}-1)} - 1)$.

Proof. This can be deduced combining Theorem 2.6 with the fact that the auxiliary function $\varphi_2(x) = x(e^{1/x} - 1)$ is strictly decreasing in $(0, +\infty)$ and

$$f_2(N, \hat{d}) = N\tilde{k}_2(e^{\tilde{T}_R/N} - 1) = \tilde{T}_R\tilde{k}_2\varphi_2\left(\frac{N}{\tilde{T}_R}\right), \quad (30)$$

for $N \leq N_{max} - 1$ and using that $\underbrace{(d_{min}, \dots, d_{min})}_{N_{max}}$ is the solution of $(\hat{P}_2^{N_{max}})$. \square

Remark 2.8.

- i) Let us note that both possibilities presented in Corollary 2.7 can occur in practical situations: for example, it can be observed in Table 6 below that option a) is true for $d_{min} \in \{50, 100\}$, while the option b) holds for $d_{min} \in \{75, 150\}$.
 ii) For the trivial cases we recover the expected solutions. For instance, when $L_* \rightarrow \theta^-$, we derive that $e^{\tilde{T}_R} \rightarrow 0$ and the nonlinear constraint is always verified. Therefore the solution of (\hat{P}_2) is given by $(\hat{N}, \hat{d}) = (1, d_{min})$, as one can expect from the beginning.
 iii) We can also observe that N_{max} is a decreasing function of d_{min} ; in fact, $N_{max} \rightarrow +\infty$ when $d_{min} \rightarrow 0$. Moreover, in case a), we have

$$d_{min} \leq d^* \leq \frac{N_{max}}{N_{max} - 1}d_{min},$$

and $d^* \approx d_{min}$ for N_{max} sufficiently large. From here we deduce that case a) is the prevalent one when d_{min} is small enough.

- iv) Once more, we can now study the dependence of the optimal cumulative dose with respect to d_{min} . Taking (30) and previous remark into account, we conclude that

$$f_2(\hat{N}, \hat{d}) = \tilde{T}_R\tilde{k}_2\varphi_2\left(\frac{N_{max} - 1}{\tilde{T}_R}\right) \approx \tilde{T}_R\tilde{k}_2\varphi_2\left(\frac{1}{\log(d_{min}/\tilde{k}_2 + 1)} - \frac{1}{\tilde{T}_R}\right),$$

and to decrease $f_2(\hat{N}, \hat{d})$ we have to take d_{min} as small as possible. Again, this is in line with the principles of MC.

Tables 5 and 6 together with the plots at the bottom of Figures 1 and 3 are devoted to the palliative approach with TMZ. We have considered the threshold $L_* = 0.1813\theta$ which is associated to the size of the tumor at the final time T with the best treatment of the curative approach in Table 3.

Let us remember that in Figure 1 we are considering treatments with a maximum of 40 doses and $d_{min} = 100$ mg/m². Now, we do the same for Table 5 that presents two kind of optimal solutions: for each value of N , the following three columns are devoted to problems (\hat{P}_2^N) and the last four columns correspond to optimal solutions obtained with FMINCON for problems (P_2^N) , setting the value for N in (23). Columns with labels \bar{d}_{min} and \bar{d}_{max} show the minimum and maximum doses of each treatment given by FMINCON, respectively. Let us note that both values in each row are almost equal. Third and seventh columns (with labels f_2^N and $(f_2^N)_{opt}$) present the total dose associated to each optimal solution. Let us observe that we obtain similar results for both problems and the tumor size level is slightly exceeded by the solutions of (\hat{P}_2^N) . Moreover, we check that the longest treatment is the best from the point of view used in this subsection. The plot at the bottom of Figure 1 shows the evolution of the tumor volume with three of these treatments computed with FMINCON: the best treatment with a red line and asterisk markers for its 40 individual doses, the shortest treatment (with $N = 33$ doses) with a black line and finally, the treatment of 37 doses with a blue line and circle markers. Both

TABLE 5. Results with $L_\star = 0.1813\theta$, $d_{min} = 100 \text{ mg/m}^2$ and 5/28d schedule.

| N | (\hat{P}_2^N) | | | (P_2^N) | | | |
|-----------|-----------------|----------|---------------|------------------|------------------|-----------------|---------------|
| | \hat{d}_i | f_2^N | $L(T)/\theta$ | \bar{d}_{min} | \bar{d}_{max} | $(f_2^N)_{opt}$ | $L(T)/\theta$ |
| 33 | 196.18 | 6,473.84 | 0.18134 | 196.20957 | 196.21000 | 6,474.92 | 0.18130 |
| 34 | 186.60 | 6,344.54 | 0.18134 | 186.63372 | 186.63413 | 6,345.55 | 0.18130 |
| 35 | 177.87 | 6,225.51 | 0.18134 | 177.89874 | 177.89913 | 6,226.46 | 0.18130 |
| 36 | 169.88 | 6,115.59 | 0.18134 | 169.90161 | 169.90211 | 6,116.46 | 0.18130 |
| 37 | 162.54 | 6,013.81 | 0.18134 | 162.55750 | 162.55786 | 6,014.63 | 0.18130 |
| 38 | 155.77 | 5,919.30 | 0.18134 | 155.79148 | 155.79182 | 5,920.08 | 0.18130 |
| 39 | 149.52 | 5,831.32 | 0.18133 | 149.54009 | 149.54041 | 5,832.07 | 0.18130 |
| 40 | 143.73 | 5,749.24 | 0.18133 | 143.74862 | 143.74893 | 5,749.95 | 0.18130 |

TABLE 6. Results for (\hat{P}_2) with $L_\star = 0.1813\theta$ varying d_{min} .

| d_{min} | \hat{N} | \hat{d}_i | $f_2^{\hat{N}}$ | Schedule | $L(T)/\theta$ | Dose intensity |
|-----------|-----------|-------------|-----------------|----------|---------------|----------------|
| 150 | 39 | 150.00 | 5,850.00 | 7/14d | 0.18047 | 79.05 |
| 100 | 51 | 100.25 | 5,112.64 | 21/28d | 0.18133 | 78.66 |
| 75 | 63 | 75.00 | 4,725.00 | 21/28d | 0.18119 | 61.36 |
| 50 | 86 | 50.29 | 4,324.78 | 28/28d | 0.18132 | 50.29 |

in this plot and in the last column of the Table 5 we see that all treatments have the same tumor volume at the final observation time ($T = 210$) reaching the threshold L_\star/θ .

Last but not least, in Table 6 and at the bottom of Figure 3 we show the influence of the level d_{min} corresponding to the palliative approach. Again, once we have fixed d_{min} and solved (\hat{P}_2) , using Corollary 2.7 to determine \hat{N} and $\{\hat{d}_i : i = 1, \dots, \hat{N}\}$, we have selected the more appropriated schedules used for TMZ. All the treatments in the table keep the tumor below or very close to the given L_\star level, and the longest treatment (that also has the lowest doses) is the best because it has the lowest cumulative dose. These results are also consistent with MC. The corresponding tumor volumes, $L(t)/\theta$, for a medium-sized initial tumor (25% of carrying capacity) with the treatments in Table 6 are shown in the plot at the bottom of Figure 3. The final parts of the four curves are graphically indistinguishable. Specifically, from day 86 onwards, the L^∞ norm of the numerical differences between their values is less than $2.1447e-03$. This is surprising because the total doses administered during the four treatments are quite different, but it is a clear evidence of the superiority of MC and the plot accurately reflects what is happening.

The computations were performed on a 3.9 GHz Core i5-8265U machine, with 8 GB RAM running under the 64-bit version of Windows 10 and MATLAB R2019b.

3. CONCLUSIONS

Throughout this work we have given a mathematical justification supporting metronomic chemotherapy (MC) as the best option for many cytotoxic drugs (i.e., when the main hypothesis (15) holds) for both curative and palliative approaches in oncology. First, we have obtained explicit expressions of global optimal solutions of (\hat{P}_1) and (\hat{P}_2) problems (given by Corollaries 2.4 and 2.7) that are approximations of (P_1) and (P_2) , respectively. Once more, we emphasize that the administration times do not appear in the formulation of (\hat{P}_1) and (\hat{P}_2) and for both cases the optimal solutions lead to the longest feasible treatments with equal doses, which are in line with MC. We further deduce mathematically that it is convenient to take the effectiveness level d_{min} as small as possible (above the minimum effective dose). Numerical experiments with TMZ support the high

quality of the solutions of (\hat{P}_1) and (\hat{P}_2) with respect to those of (P_1) and (P_2) , respectively, and illustrate the theoretical results. Moreover, the optimal treatments calculated for both curative and palliative approaches are quite similar. Finally, with our method, the administration times are adjusted a posteriori (once the number of doses and the individual doses of the treatment are determined).

In our work we have used a simple mathematical model being crucial the Norton-Simon hypothesis, the Emax model, the PK of the drug given by (6) and the main hypothesis (15). In the future, we would like to analyze several generalizations and extensions from a mathematical point of view, including some relevant factors such as drug resistance and anti-angiogenesis effect or the case when (15) fails. We think that both theoretical and numerical results would be very useful for clinical purposes.

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