OPTIMAL CONTROL PROBLEMS FOR THE GOMPERTZ MODEL UNDER THE NORTON-SIMON HYPOTHESIS IN CHEMOTHERAPY

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ABSTRACT. We study a collection of problems associated with the optimization of cancer chemotherapy treatments, under the assumptions of Gompertzian-type tumor growth and that the drug killing effect is proportional to the rate of growth for the untreated tumor (Norton-Simon hypothesis). Classical pharmacokinetics and different pharmacodynamics (Skipper and $E_{max}$) are considered, together with a toxicity limit or the penalization of the accumulated drug effect. Existence and uniqueness of the optimal control is proved in some cases, while in others the total amount of drug is the unique relevant aspect to take into account and the existence of an infinite number of optimal controls is shown. In all cases, explicit expressions for the solutions are derived in terms of the problem data. Finally, numerical results of illustrative examples and some conclusions are presented.

1. Introduction. It is a widespread opinion that mathematical modelling can help to cure cancer in a relevant way ([10],[19]), an idea that arose about fifty years ago (see [5], [12], [18] and the references therein).

In 1964, Skipper, Schabel and Wilcox were the first to introduce theoretical concepts in cancer chemotherapy claiming that the tumor growth is exponential (using the L1210 mouse leukemia) and that the growth rate inhibiting effect of a treatment is proportional to the tumor volume (log-kill hypothesis), see for instance [15]. It is known that this simple model also applies to some few human neoplasms, but most solid tumors follow a Gompertzian type growth ([15]) and for them, there are clinical observations contradicting the log-kill hypothesis. In 1977, an alternative consistent with these experimental results was proposed by Norton and Simon in their famous paper [14] hypothesizing that “chemotherapy results in a rate of regression in tumor volume that is proportional to the growth of an unperturbed tumor of that size”, [17]. This hypothesis (named after them) was a major breakthrough in oncology history (Chapter 2 of [15] is devoted exclusively to this topic). One of the main implications of this approach is to predict the superiority of densified dosing regimen that have been confirmed in several clinical trials over the last years (see for instance [2], [15] and the references therein). However, the majority opinion is that we are still far from optimizing the chemotherapy strategies. Using
Norton’s own words: “I have a suspicion that we are using almost all the cancer drugs in the wrong way”, see [10]. For this reason, the design of more effective and less toxic chemotherapeutic regimens continues to be a very active research area in the medical field. Of course, in recent decades, new and outstanding theoretical concepts have been proposed (metronomic chemotherapy, adaptive therapy, personalized treatments,...), but the Norton-Simon hypothesis is still a very influential concept in modern oncology (see for example [2],[17],[20], among others).

In the mid-1970s, the optimal control theory was first used in cancer chemotherapy, see for instance [18] and the references therein. Since then, most of the mathematical works are still assuming the log-kill hypothesis, and very few the Norton-Simon hypothesis (one example is [9]). In our opinion there is no a complete rigorous and detailed study from the mathematical point of view that can be used for comparison purposes. This is the aim of this paper, where we study a collection of optimal control problems related with the cancer chemotherapy treatment under the Norton-Simon hypothesis, varying the pharmacokinetics, the pharmacodynamics and the form in which the side effects are taken into account in the model (as constraints or through a penalty term). In some cases we are able to determine explicitly the unique optimal control in terms of the problem data, all of them having a simple piecewise constant structure. For other problems, we prove that the total amount of drug is the unique relevant aspect to take into account, and furthermore there exists an infinite number of solutions that are also characterized. In fact, we will see that the infinite-dimensional optimal control problems can be transformed into an equivalent 1d (or 2d) optimization problem. Apart from recover the “dose-dense chemotherapy”, we highlight the appearance of a constant maintenance infusion rate during a quite long time interval, that it has not been reported previously in this context, as far as we know. Moreover, we emphasize that one of the problems studied in this work (specifically, problem ($OP_4$) with $G = G_1$) was previously considered in [9], but the singular case was excluded there, meanwhile we show here that this case really comes up, see Theorem 8.1 and Remark 8 below. This paper is a continuation of [8] where similar problems where addressed under the log-kill hypothesis and without including any penalty term.

The paper is organized as follows: in Section 2, we study a general Gompertz-type ODE and prove some estimates for their solutions. Also we describe some optimal control problems (with an integral constraint modelling the toxicity limit), showing the existence of optimal controls for each one. In Sections 3 - 5, we derive the detailed expressions of these solutions (when they are unique) in terms of the problem parameters, by using the classical Pontryagin’s Maximum Principle. In Section 6, some elementary results in one variable are proved, that will be essential along the rest of the paper. In Section 7, we formulate another more realistic optimal control problems with a penalty term on the accumulated drug effect and we state their relation with the optimal control problems previously considered. In Sections 8 - 10, we obtain the explicit expressions of their solutions depending on the value of the penalty parameter. Finally, in Section 11, we present some numerical experiments to illustrate the therapy results depending on the chosen model, providing in Section 12 the comparison with the results obtained in [8] and some conclusions of our work.

2. The optimal control problems ($OP_1$)-($OP_3$). As we have mentioned, the Gompertz ODE has been widely used to simulate the growth of certain tumors, although other possibilities have been also considered such as the logistic equation,
Denoting by $L(t)$ the tumor volume (or the tumor cell population) at time $t$, it can be written as follows:

$$L'(t) = \xi L(t) \log \left( \frac{\theta}{L(t)} \right) \overset{\text{def}}{=} \psi(L(t)). \quad (1)$$

It contains two parameters: the growth rate $\xi$ and the greatest size of the tumor $\theta$ (also called carrying capacity for biological systems) that can be different from case to case and must be estimated. In practice, they can also change with time; for $\theta$, this question is related with the angiogenesis process (i.e. the recruitment of surrounding host blood vessels in order to facilitate the supply of nutrients for the tumor) and it has led to important changes in the anticancer therapy, such as the metronomic concept (see for instance [2] or [7]). This situation will not be considered here.

Let us present a general version of the Gompertz ODE (including a loss term that will vary with the pharmacodynamics) together with the basic result for the existence and uniqueness of solution and some useful estimates that we will need later. 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 2.1.** Let us assume that $\xi$, $\theta$, $L_0$ and $T$ are given positive real numbers, with $L_0 \in (0,\theta)$ 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

$$L'(t) = \xi L(t) \log \left( \frac{\theta}{L(t)} \right) \rho(t), \quad L(0) = L_0, \quad (2)$$

given by

$$L(t) = \theta \exp \left( \log \left( \frac{L_0}{\theta} \right) \exp \left( -\xi \int_0^t \rho(s) \, ds \right) \right), \quad \forall t \in [0,T]. \quad (3)$$

In particular, it is verified

$$0 < \theta \exp \left( \log \left( \frac{L_0}{\theta} \right) \exp \left( -\xi T \rho_\infty \right) \right) \leq L(t) \leq \theta \exp \left( \log \left( \frac{L_0}{\theta} \right) \exp \left( -\xi T \rho_\infty \right) \right), \quad (4)$$

for all $t \in [0,T]$, where $\rho_\infty = \|\rho\|_{L^\infty(0,T)}$.

**Proof.** Expression (3) can be easily derived by using the well known change of function for the Gompertz type equation (see for instance [18])

$$x(t) = \log \left( \frac{L(t)}{\theta} \right), \quad (5)$$

that transforms the problem (2) into the linear one

$$x'(t) = -\xi x(t) \rho(t), \quad x(0) = \log \left( \frac{L_0}{\theta} \right). \quad (6)$$

Taking into account that $x$ is given by

$$x(t) = \log \left( \frac{L_0}{\theta} \right) \exp \left( -\xi \int_0^t \rho(s) \, ds \right), \quad \forall t \in [0,T], \quad (7)$$

the identity (3) follows immediately.

Estimates (4) are a simple consequence of (3) and the fact that $-\rho_\infty \leq \rho(t) \leq \rho_\infty$ for $t \in [0,T]$, noticing that $\log \left( \frac{L_0}{\theta} \right) < 0$, because $L_0 < \theta$. \qed
In the first part of this work we are interested in the solutions of the following three optimal control problems associated with the Gompertz ODE. In all of them, the main objective is to minimize the volume of the tumor at the final time $T$ (chosen a priori) under some constraints to take into account the toxicity of the treatment. The control variable, denoted by $u$, will represent the infusion rate of the chemotherapy drug and will be a function taken in $L^\infty(0, T)$, because the continuous drug delivery method has proved its superiority over the discrete dosage regimen from the therapeutic view point (see for instance [18]) and it is feasible (the modern pumps allow to deliver the anticancer agent, even using portable programmable devices, endowing the patient with autonomy for several weeks).

The first problem concerns the case in which the chemotherapy infusion rate is identified with its concentration. This is a usual (although unrealistic) assumption in many papers (see for instance [18]) and leads to the following formulation:

\[
\begin{aligned}
\text{(OP1)} \quad \min_{u \in U^1_{ad}} & \ J(u) = L(T), \\
\end{aligned}
\]

where $L$ is the solution of the Cauchy problem

\[
\begin{aligned}
L'(t) = \psi(L(t))(1 - G(u(t))), & \quad L(0) = L_0, \quad t \in [0, T], \\
\end{aligned}
\]

with $\psi$ defined in (1), $L_0 \in (0, \theta)$ and the set of admissible controls given by

\[
U^1_{ad} = \{ u \in L^\infty(0, T) : 0 \leq u(t) \leq u_{max}, \ a.e. \ t \in (0, T), \ \int_0^T u(t) dt \leq y_{max} \},
\]

where $u_{max}$ and $y_{max}$ are known positive real numbers.

Depending on the expression of the term $G$, different pharmacodynamics can be studied. In this paper, two classical situations will be considered:

$G_1(u) = k_1 u$, \hspace{1cm} (Skipper model), \hspace{1cm} (11)

and

$G_2(u) = \frac{k_1 u}{k_2 + u}$, \hspace{1cm} (E_{max} model), \hspace{1cm} (12)

where $k_1$ and $k_2$ are given positive real numbers. The main difference between them is that the second one will saturate for high values of $u$. For that reason it seems to be more appropriate from the clinical point of view (see [13] and [18]). Other choices have been considered in the literature, see for instance [9] and [12].

In the second and third optimal control problems, the typical pharmacokinetics first-order equation for the drug concentration will be taken into account combined with the previous pharmacodynamics terms. The only difference between them is the constraint that will concern the integral of the drug infusion rate (representing the total amount of chemotherapy drug used during the whole process) for (OP2) or the integral of the concentration (usually called “AUC” in the medical terminology) for (OP3). More precisely,

\[
\begin{aligned}
\text{(OP2)} \quad \min_{u \in U^1_{ad}} & \ J(u) = L(T), \\
\end{aligned}
\]

where $(L, c)$ is the solution of the Cauchy problem

\[
\begin{aligned}
L'(t) = \psi(L(t))(1 - G(c(t))), & \quad L(0) = L_0, \quad t \in [0, T], \\
c'(t) = -\lambda c(t) + u(t), & \quad c(0) = 0, \\
\end{aligned}
\]

\[
\begin{aligned}
\end{aligned}
\]
with $G \in \{G_1, G_2\}$, $L_0 \in (0, \theta)$, $\lambda$ being the positive value of the drug decay rate, and

$$\min J(u) = L(T),$$

where $(L, c)$ is the solution of the Cauchy problem (14) and the set of admissible controls is given by

$$U_{ad}^2 = \{u \in L^\infty(0, T) : 0 \leq u(t) \leq u_{max}, \text{a.e. } t \in (0, T), \quad \int_0^T c(t)dt \leq y_{max}\}. \quad (16)$$

Let us now present the result on the existence of solution for these problems:

**Theorem 2.2.** Under previous assumptions, each one of the optimal control problems $(OP_1), (OP_2)$ and $(OP_3)$ has (at least) an optimal control, with $G \in \{G_1, G_2\}$.

**Proof.** It is a consequence of the corresponding explicit expressions for the solutions of the state equation derived from (3). More precisely, the unique solution in $W^{1, \infty}(0, T)$ of the problem (9) for each $u \in L^\infty(0, T)$ is given by

$$L_u(t) = \theta \exp \left(\log (L_0/\theta) \exp (-\xi t + \xi \int_0^t G(u(s))ds)\right), \quad \forall t \in [0, T], \quad (17)$$

and the unique pair $(L_u, c_u) \in C^1[0, T] \times W^{1, \infty}(0, T)$ that is solution of the system (14) for each nonnegative $u \in L^\infty(0, T)$ is given by

$$c_u(t) = \exp (-\lambda t) \int_0^t u(s) \exp (\lambda s)ds, \quad \forall t \in [0, T], \quad (18)$$

and

$$L_u(t) = \theta \exp \left(\log (L_0/\theta) \exp (-\xi t + \xi \int_0^t G(c_u(s))ds)\right), \quad \forall t \in [0, T]. \quad (19)$$

The first important observation is that the sets of admissible controls $U_{ad}^1$ and $U_{ad}^2$ are non-empty bounded convex closed subsets of $L^2(0, T)$. Taking a minimizing sequence, $\{u_n\}_n$ for each optimal control problem, the usual argumentation allows us to conclude that (after taking a subsequence, if necessary), there exists an admissible control $\bar{u}$ such that $u_n \rightarrow \bar{u}$ weakly in $L^2(0, T)$ and also *-weakly in $L^\infty(0, T)$, as $n \rightarrow +\infty$. Now, using (17)-(19) it is standard to deduce for $(OP_1)$ (with $G = G_1$), $(OP_2)$ and $(OP_3)$ (with $G \in \{G_1, G_2\}$) that $L_{u_n}(T) \rightarrow L_{\bar{u}}(T)$ as $n \rightarrow +\infty$, and therefore, $\bar{u}$ is an optimal control for the corresponding problem. For $(OP_1)$ with $G = G_2$ the argumentation is not so obvious, due to the nonlinear character of the function $G_2$ and the fact that the control appears directly (not through the concentration): since $G_2$ is a concave function and $f(r) = \exp (-\exp (r))$ is a decreasing and convex one for $r \geq 0$, we can derive that $J$ is a convex function, too; moreover, $J$ is also continuous on $U_{ad}^1 \subset L^2[0, T]$ (for the strong topology) and, consequently, the existence of an optimal control holds, thanks to classical results (see for instance [3, Corollaries III.8 and III.20]).

**Remark 1.** Taking into account the explicit formula (17), we can deduce very easily that $\bar{u}$ is an optimal control for the problem $(OP_1)$ if and only if $\bar{u}$ is a solution of the optimization problem

$$\left\{\begin{array}{l}
\max \varphi(u) = \int_0^T G(u(t))dt.
\quad (20)
\end{array}\right. \quad u \in U_{ad}^1$$
Lemma 2.3. Under previous assumptions, if \( u_1(t) \leq u_2(t) \) for a.e. \( t \in [0, T] \), then \( J(u_2) \leq J(u_1) \) for problems \((OP_1),(OP_2)\) and \((OP_3)\).

Proof. For \((OP_1)\), this is a consequence of (17), that \( G_1, G_2 \) are increasing functions and \( \log (L_0/\theta) < 0 \). For \((OP_2)\) and \((OP_3)\), the same argumentation can be used with (19), because if \( u_1(t) \leq u_2(t) \) for a.e. \( t \in [0, T] \), then \( c_{u_1}(t) \leq c_{u_2}(t) \) for all \( t \in [0, T] \).

\[ \Box \]

Remark 2. Clearly, the solution for our optimal control problems is \( \bar{u} \equiv u_{\text{max}} \) if it is an admissible control. This is called the “Maximum tolerated dose” (MTD) paradigm in the specialized literature. But, in most practical situations, \( u_{\text{max}} \) will not satisfy the integral constraint, due to undesired side effects. Along the Sections 3 – 5 we will assume that \( u_{\text{max}} \) is not an admissible control (this assumption will be denoted \((H_1)\)), that is equivalent to

\[ Tu_{\text{max}} > y_{\text{max}}, \tag{21} \]

for \((OP_1)\) and \((OP_2)\) (see (10) for the definition of \( U_{\text{ad}}^1 \)) and to the condition

\[ (\lambda T + \exp (-\lambda T) - 1)u_{\text{max}} > \lambda^2 y_{\text{max}}, \tag{22} \]

for \((OP_3)\) (see (16) for the definition of \( U_{\text{ad}}^2 \) and (18)).

3. Optimal controls for \((OP_1)\). In order to derive the first order optimality conditions and later to identify the solutions for our optimal control problems (see Theorem 2.2), we are going to transform them into a more convenient form to deal with the integral constraint. More precisely, by taking the new functions

\[ x_1(t) = L(t), \quad x_2(t) = \int_0^t u(s)ds, \tag{23} \]

the problem \((OP_1)\) can be written equivalently as

\[ \big(\hat{OP}_1\big) \left\{ \begin{array}{l} \min J(u) = x_1(T), \\ u \in \hat{U}_{\text{ad}} \end{array} \right. \tag{24} \]

where the pair \((x_1, x_2) \in (W^{1,\infty}(0, T))^2\) is the unique solution of the Cauchy problem

\[ \left\{ \begin{array}{l} x'_1(t) = \psi(x_1(t))(1 - G(u(t))), \quad x_1(0) = L_0, \quad t \in [0, T], \\ x'_2(t) = u(t), \quad x_2(0) = 0, \end{array} \right. \tag{25} \]

with \( G \in \{G_1, G_2\} \), and the set of admissible controls is given by

\[ \hat{U}_{\text{ad}} = \{ u \in L^{\infty}(0, T) : 0 \leq u(t) \leq u_{\text{max}}, \text{ a.e. } t \in (0, T), \quad x_2(T) \leq y_{\text{max}} \}. \tag{26} \]

By using the Pontryagin’s Maximum Principle, we derive the following result:

Theorem 3.1. Let us assume \((H_1)\) and \( L_0 \in (0, \theta) \). Then, any function \( \bar{u} \) satisfying \( \bar{u}(t) \in [0, u_{\text{max}}] \) a.e. \( t \in [0, T] \) and

\[ \int_0^T \bar{u}(t)dt = y_{\text{max}} \tag{27} \]

is an optimal control for problem \((OP_1)\) with \( G = G_1 \).
Remark 3. Proof. Let us assume that \( \bar{\psi} \) is an optimal control of the problem \((\tilde{OP}_1)\) with \( u = \bar{u} \). We introduce the classical Hamiltonian function

\[
H(x_1, x_2, t, p_1, p_2) = p_1 \psi (x_1)(1 - G_2(u)) + p_2 u.
\]

Thanks to the Pontryagin’s Maximum Principle (see for instance [4, Theorem 4.2.i, p. 162]) we deduce the existence of a pair of adjoint states \((p_1, p_2)\) with \( u = \bar{u} \). We introduce the classical Hamiltonian function

\[
H(x_1, x_2, t, p_1, p_2) = p_1 \psi (x_1)(1 - G_2(u)) + p_2 u.
\]

Together with the transversality condition \( \mu (\bar{x}_2(T) - y_{max}) = 0 \) and

\[
H(\bar{x}_1(t), \bar{x}_2(t), \bar{u}(t), p_1(t), p_2(t)) \leq H(\bar{x}_1(t), \bar{x}_2(t), u, p_1(t), p_2(t)),
\]

for all \( u \in [0, u_{max}] \), a.e. \( t \in [0, T] \). This relation can be re-written as

\[
p_1(t)\psi (\bar{x}_1(t))(G_2(\bar{u}(t)) - G_2(u)) + p_2(t)(u - \bar{u}(t)) \geq 0,
\]

for all \( u \in [0, u_{max}] \), a.e. \( t \in [0, T] \).

It is easy to check that \( p_2(t) \equiv \mu \) and the relevant fact that \( p_1(t)\psi (\bar{x}_1(t)) \) is constant in \([0, T]\), because

\[
(p_1(t)\psi (\bar{x}_1(t)))' = p_1(t)\psi (\bar{x}_1(t)) + p_1(t)\psi' (\bar{x}_1(t))\bar{x}_1'(t).
\]
$= p_1(t)(G_2(\bar{u}(t)) - 1)\psi'(\tilde{x}_1(t))\psi(\bar{x}_1(t)) + p_1(t)\psi'(\tilde{x}_1(t))\psi(\bar{x}_1(t))(1 - G_2(\bar{u}(t))) = 0.$

Hereafter we will denote $\gamma = p_1(t)\psi(\bar{x}_1(t))$ for a.e. $t \in [0, T]$. Solving explicitly the first ODE of (32) we get the following expression

$$p_1(t) = \exp \left( \int_t^T \psi'(\tilde{x}_1(s))(1 - G_2(\bar{u}(s)))ds \right).$$

In particular, since $\psi(\bar{x}_1(t)) > 0$ we deduce that $\gamma > 0$ and the inequality (34) reduces to

$$\gamma(G_2(\bar{u}(t)) - G_2(u)) + \mu(u - \bar{u}(t)) \geq 0,$$

for all $u \in [0, u_{\text{max}}]$, a.e. $t \in [0, T]$.

From (35), the case $\mu = 0$ leads us to the condition $G_2(\bar{u}(t)) \geq G_2(u)$, for all $u \in [0, u_{\text{max}}]$, a.e. $t \in [0, T]$. Since $G_2$ is an increasing function, we conclude that $\bar{u} \equiv u_{\text{max}}$, but this case is excluded by (H1). Consequently, it must be $\mu > 0$ and the transversality relation implies that $\tilde{x}_2(T) = y_{\text{max}}$, i.e. (27).

Taking $u = \bar{u}(t) + \epsilon(v - \bar{u}(t))$ in (35), with $\epsilon \in (0, 1)$, dividing the inequality by $\epsilon$ and letting $\epsilon$ goes to 0, we get

$$(\mu - \gamma G'_2(\bar{u}(t))) (v - \bar{u}(t)) = \left( \mu - \frac{\gamma k_1 k_2}{(k_2 + u_{\text{max}})^2} \right) (v - \bar{u}(t)) \geq 0,$$

for all $v \in [0, u_{\text{max}}]$, a.e. $t \in [0, T]$.

Therefore, we have that

$$\bar{u}(t) = \begin{cases} u_{\text{max}}, & \text{if } \frac{\gamma k_1 k_2}{(k_2 + u_{\text{max}})^2} > \mu, \\ 0, & \text{if } \frac{\gamma k_1 k_2}{(k_2 + u_{\text{max}})^2} < \mu. \end{cases} = \begin{cases} u_{\text{max}}, & \text{if } \frac{\gamma k_1 k_2}{(k_2 + u_{\text{max}})^2} > \mu, \\ 0, & \text{if } \frac{\gamma k_1 k_2}{k_2} < \mu. \end{cases}$$

Once more, the trivial constant cases $\bar{u} \equiv 0$ and $\bar{u} \equiv u_{\text{max}}$ are excluded by (27) and (H1), respectively. Furthermore, both possibilities can not appear at the same time, because (recalling that $\gamma > 0$)

$$\frac{\gamma k_1 k_2}{(k_2 + u_{\text{max}})^2} < \frac{\gamma k_1}{k_2}.$$ 

Hence, the only possibility for (36) being valid is the singular case

$$\frac{\gamma k_1 k_2}{(k_2 + u(t))^2} = \mu, \text{ a.e. } t \in [0, T].$$

This implies that $\bar{u}$ should be constant in $[0, T]$ and its value can be determined by using (27). We emphasize that $u_{\text{max}} \in (0, u_{\text{max}})$ due to (H1) (see (21)).

4. Optimal control for $(OP_2)$. In this case, we will use the functions

$$x_1(t) = L(t), \quad x_2(t) = \int_0^t u(s)ds, \quad x_3(t) = c(t),$$

(38)

to transform the problem $(OP_2)$ into

$$(\hat{OP}_2) \left\{ \begin{array}{l} \min J(u) = x_1(T), \\ u \in \hat{U}_{ad} \end{array} \right\}
$$

(39)

where the triplet $(x_1, x_2, x_3) \in C^1[0, T] \times (W^{1,\infty}(0, T))^2$ is the unique solution of the system

$$\begin{cases} x'_1(t) = \psi(x_1(t))(1 - G(x_3(t))), & x_1(0) = L_0, \quad t \in [0, T], \\ x'_2(t) = u(t), & x_2(0) = 0, \\ x'_3(t) = -\lambda x_3(t) + u(t), & x_3(0) = 0, \end{cases}
$$

(40)
with \( G \in \{G_1, G_2\} \), and \( \hat{U}_{ad} \) is still defined by (26).

First order necessary optimality conditions for this problem lead us to the following characterization:

**Theorem 4.1.** Let us assume \((H_1)\), \( L_0 \in (0, \theta) \) and \( G = G_1 \). Then, the unique optimal control of the problem \((OP_2)\) is given by

\[
\bar{u}(t) = \begin{cases} 
  u_{\text{max}}, & \text{if } t \in [0, t^*], \\
  0, & \text{if } t \in (t^*, T],
\end{cases}
\]

with \( t^* = \frac{u_{\text{max}}}{u_{\text{max}}} \in (0, T) \).

**Proof.** In this case, the Hamiltonian function is as follows:

\[
H(x_1, x_2, x_3, u, p_1, p_2, p_3) = p_1 \psi(x_1)(1 - G(x_3)) + p_2 u + p_3 (u - \lambda x_3).
\]

Using the classical Pontryagin’s Maximum Principle (see for instance [4, Theorem 4.2.i, p. 162]) we deduce the existence of a triplet of adjoint states \((p_1, p_2, p_3) \in (C^1[0, T])^3\) (not identically zero) and \( \mu \geq 0 \) satisfying

\[
\begin{aligned}
  &p_1'(t) = p_1(t) \psi'(\bar{x}_1(t))(G(\bar{x}_3(t)) - 1), \\
  &p_2'(t) = 0, \\
  &p_3'(t) = \lambda p_3(t) + p_1(t) \psi(\bar{x}_1(t))G'(\bar{x}_3(t)),
\end{aligned}
\]

for all \( u \in [0, u_{\text{max}}] \), a.e. \( t \in [0, T] \).

The same argumentation than in the proof of Theorem 3.2 allows us to conclude that \( p_1(t) \psi(\bar{x}_1(t)) \equiv \gamma \) for all \( t \in [0, T] \), for some \( \gamma > 0 \). Moreover, \( p_2 \equiv \mu \), and

\[
p_3(t) = -\gamma \exp(\lambda t) \int_{t}^{T} G'(\bar{x}_3(s)) \exp(-\lambda s)ds,
\]

where the previous identity has been taken into account. Hence, (43) can be rewritten as

\[
(\mu + p_3(t))(u - \bar{u}(t)) \geq 0,
\]

for all \( u \in [0, u_{\text{max}}] \), a.e. \( t \in [0, T] \).

From (44) and the fact that \( p_3(t) < 0 \) for all \( t \in [0, T] \), the case \( \mu = 0 \) leads us to the condition \( \bar{u} \equiv u_{\text{max}} \), but this is excluded by \((H_1)\). Consequently, it must be \( \mu > 0 \) and the transversality relation implies that \( \bar{x}_2(T) = y_{\text{max}} \). Moreover,

\[
\bar{u}(t) = \begin{cases} 
  0, & \text{where } p_3(t) > -\mu, \\
  u_{\text{sin}}(t), & \text{where } p_3(t) = -\mu, \\
  u_{\text{max}}, & \text{where } p_3(t) < -\mu,
\end{cases}
\]

where \( u_{\text{sin}} \) denotes the singular part of \( \bar{u} \) that remains undefined at this moment, except that \( u_{\text{sin}}(t) \in [0, u_{\text{max}}] \).

Since \( G = G_1 \), we have

\[
p_3(t) = \frac{\gamma k_1}{\lambda} (\exp(\lambda (t - T) - 1),
\]

and consequently \( p_3'(t) > 0 \) for all \( t \in [0, T] \). Let us show that the singular part can not appear in this case:

i) If \( p_3(0) \geq -\mu \), we have \( p_3(t) > -\mu \) for all \( t \) and hence, \( \bar{u} = 0 \), which contradicts the fact that \( \bar{x}_2(T) = y_{\text{max}} \).
ii) If $p_3(0) < -\mu$, since $p_3(T) = 0$ there must exist a unique $t^* \in (0,T)$ where $p_3(t^*) = -\mu$ and therefore we arrive to (41). The value of $t^*$ is a consequence of the transversality relation.

**Theorem 4.2.** Let us assume (H1), $L_0 \in (0,\theta)$ and $G = G_2$. Then, an optimal control of the problem (OP2) has one of the following forms:

$$
\bar{u}(t) = \begin{cases} 
    u_{\text{max}}, & \text{if } t \in [0,t^*), \\
    0, & \text{if } t \in (t^*,T]
\end{cases}
$$

with $t^* = \frac{y_{\text{max}}}{u_{\text{max}}}$ or

$$
\bar{u}(t) = \begin{cases} 
    u_{\text{max}}, & \text{if } t \in [0,t_1), \\
    u_{\text{sin}}, & \text{if } t \in (t_1,t_2), \\
    0, & \text{if } t \in (t_2,T]
\end{cases}
$$

with $0 < t_1 < t_2 < T$, $u_{\text{sin}} = u_{\text{max}}(1 - e^{-\lambda t_1})$ and $(t_1,t_2)$ being a pair solution of the system of nonlinear equations

$$
\begin{align*}
    u_{\text{max}}(t_2 + (t_1 - t_2)e^{-\lambda t_1}) &= y_{\text{max}}, \\
    u_{\text{max}}(1 - e^{-\lambda t_1})(e^{\lambda(T-t_2)} - 2) &= k_2\lambda,
\end{align*}
$$

(48)

that depend only on the parameters defining (OP2).

**Proof.** We arrive to (45) exactly as in the proof of Theorem 4.1. The argumentation to get (46) or (47) is a little bit more technical, because the explicit form of $p_3$ is not completely known: here, we have that

$$
p_3(t) = -k_1k_2 \gamma \exp(\lambda t) \int_t^T \frac{\exp(-\lambda s)}{(k_2 + \bar{x}_3(s))^2} ds.
$$

The first observation is that $p_3(t) < 0$ for all $t \in [0,T)$. The second one is that the singular part of the control (if exists) must be constant: assuming that $p_3(t) = -\mu$ for all $t$ belonging to some open interval $I$, it follows that $p_3'(t) = 0$, for all $t \in I$. Taking into account that the ODE satisfied by $p_3$ is given by

$$
p_3'(t) = \lambda p_3(t) + \frac{\gamma k_1 k_2}{(k_2 + \bar{x}_3(t))^2},
$$

(49)

see (42), we conclude that

$$
\frac{\gamma k_1 k_2}{(k_2 + \bar{x}_3(t))^2} = \lambda \mu, \quad \forall t \in I,
$$

and therefore

$$
\bar{x}_3(t) = \sqrt{\frac{\gamma k_1 k_2}{\lambda \mu}} - k_2, \quad \forall t \in I.
$$

Now, taking into account the ODE for $\bar{x}_3$ (see (40)), we arrive to

$$
\bar{u}(t) = \lambda \bar{x}_3(t) = \sqrt{\frac{\lambda \gamma k_1 k_2}{\mu}} - \lambda k_2, \quad \forall t \in I.
$$

Now, we will explore the existing possibilities for the optimal control. In a first step, we claim that the following configuration is not admissible
\[ \bar{u}(t) = \begin{cases} \vdots \quad & t \in (t_2, t_3), \\ u_{\text{max}}, & t \in (t_2, t_3), \\ \vdots \end{cases} \]  

(50)

with \(0 < t_2 < t_3 < T\). Let us argue by contradiction. Combining (45), previous considerations and the continuity of \(p_3\), we know that \(p_3(t) \geq -\mu\) for all \(t \in (t_1, t_2) \cup (t_3, t_4)\), \(p_3(t) < -\mu\) for all \(t \in (t_2, t_3)\) and \(p_3(t_2) = p_3(t_3) = -\mu\) for \(0 < t_1 < t_2 < t_3 < t_4 < T\). Hence, \(p_3\) should achieve a local minimum at some point \(\tilde{t} \in (t_2, t_3)\) and using now that \(p_3 \in C^2(t_2, t_3)\), it is verified that \(p_3'(\tilde{t}) = 0\) and \(p_3''(\tilde{t}) \geq 0\). Differentiating (49), the ODE satisfied by \(p_3\), with respect to \(t\), we deduce that

\[
p_3''(t) = \frac{2\gamma k_1 k_2 \bar{x}_3'(t)}{(k_2 + \bar{x}_3(t))^3}, \quad t \in (t_2, t_3),
\]

and therefore we arrive to the contradiction

\[
p_3''(\tilde{t}) = \frac{2\gamma k_1 k_2 \bar{x}_3'(\tilde{t})}{(k_2 + \bar{x}_3(\tilde{t}))^3} < 0,
\]

because \(\gamma > 0\) and \(\bar{x}_3'(\tilde{t}) > 0\), due to the fact that \(\bar{u} = u_{\text{max}}\) in \((t_2, t_3)\).

In a second step, we will show that the following configuration is also not admissible:

\[ \bar{u}(t) = \begin{cases} \vdots \quad & t \in (t_2, t_3), \\ 0, & t \in (t_2, t_3), \\ \vdots \end{cases} \]

(51)

with \(0 < t_2 < t_3 < T\). Arguing once more by contradiction, it must hold that \(p_3(t) \leq -\mu\) for all \(t \in (t_1, t_2) \cup (t_3, t_4)\), \(p_3(t) > -\mu\) for all \(t \in (t_2, t_3)\) and \(p_3(t_2) = p_3(t_3) = -\mu\) for \(0 < t_1 < t_2 < t_3 < t_4 < T\). Here, \(p_3\) should achieve a local maximum at some point \(\tilde{t} \in (t_2, t_3)\) and the argumentation follows analogously.

Since \(p_3(T) = 0\) and \(p_3\) is a continuous function in \([0, T]\), we know that there exists \(t_2 \in (0, T)\) such that \(\bar{u} = 0\) in \((t_2, T]\). Taking into account that the case \(\bar{u} \equiv 0\) is excluded by the transversality relation, previous considerations imply (46) or (47), because the configuration

\[ \bar{u}(t) = \begin{cases} 0, & t \in [0, t_1], \\ u_{\text{sin}}, & t \in (t_1, t_2), \\ 0, & t \in (t_2, T], \\ \vdots \end{cases} \]

can be excluded by using the continuity of \(\bar{x}_3\) at \(t_1\) and the expression

\[ \bar{x}_3(t) = \begin{cases} 0, & t \in [0, t_1], \\ \frac{u_{\text{sin}}}{\lambda}, & t \in [t_1, t_2], \\ \vdots \end{cases} \]

It remains to explain how to get the values \(t_1\) and \(t_2\) in (47). It is easy to derive from the ODE for the concentration \(\bar{x}_3\) (see (40)) that

\[ \bar{x}_3(t) = \begin{cases} \frac{u_{\text{max}}}{\lambda} (1 - \exp(-\lambda t)), & t \in [0, t_1], \\ \frac{u_{\text{max}}}{\lambda}, & t \in [t_1, t_2], \\ \frac{u_{\text{max}}}{\lambda} \exp(-\lambda (t - t_2)), & t \in [t_2, T]. \end{cases} \]

(52)

Since \(\bar{x}_3\) is continuous at \(t = t_1\), we get that \(u_{\text{sin}} = u_{\text{max}} (1 - \exp(-\lambda t_1))\), that it is an admissible control. Once more, by the transversality condition we arrive
to the first equation of (48). For getting the second identity, we can use condition $p_3'(t_2) = 0$. Hence, we have
\[
\lambda \int_{t_2}^{T} \exp(-\lambda s) \frac{(k_2 + \bar{x}_3(s))^2}{(k_2 + \bar{x}_3(t))^2} \, ds = \exp(-\lambda t_2) \frac{(k_2 + \bar{x}_3(t))^2}{(k_2 + \bar{x}_3(t))^2}.
\]
By using (52) this can be written equivalently as
\[
\lambda \int_{t_2}^{T} \exp(-\lambda s) \frac{(k_2 + \frac{u}{\sin \lambda} \exp(-\lambda(s - t_2)))^2}{(k_2 + \frac{u}{\sin \lambda})^2} \, ds = \exp(-\lambda t_2) \frac{(k_2 + \frac{u}{\sin \lambda})^2}{(k_2 + \frac{u}{\sin \lambda})^2}.
\]
Now, the integral on the left hand side can be calculated explicitly and by elementary (but tedious) calculations we derive the second equation of (48). Alternatively we could get this second equation starting from the equality $p_3(t_1) = p_3(t_2)$.

**Remark 4.** Optimal control (46) has a simple bang-bang structure that appears in many problems. On the other hand, the optimal control (47) is of bang-singular-bang type, where the singular part is constant and it can be viewed as a maintenance infusion rate. As far as we know, this configuration has not been reported in the literature in this context until now, although it appeared in a different context under the log-kill hypothesis, see [13]. In the sequel and for brevity, we will denote these structures by $u_{\max}/0$ and $u_{\max}/u_{\sin}/0$, respectively.

5. **Optimal controls for** $(OP_3)$. Here we select the functions
\[
x_1(t) = L(t), \quad x_2(t) = \int_0^t c(s) \, ds, \quad x_3(t) = c(t),
\]
(53) to transform the problem (15) into
\[
(\hat{OP}_3) \left\{ \begin{array}{l}
\min J(u) = x_1(T), \\
u \in \hat{U}_{ad}
\end{array} \right. \tag{54}
\]
where now the triplet $(x_1, x_2, x_3) \in (C^1[0, T])^2 \times W^{1, \infty}(0, T)$ is the unique solution of the system
\[
\begin{aligned}
x_1'(t) &= \psi(x_1(t))(1 - G(x_3(t))), \quad x_1(0) = L_0, \quad t \in [0, T], \\
x_2'(t) &= x_3(t), \quad x_2(0) = 0, \\
x_3'(t) &= -\lambda x_3(t) + u(t), \quad x_3(0) = 0,
\end{aligned} \tag{55}
\]
with $G \in \{G_1, G_2\}$, and the set of admissible controls $\hat{U}_{ad}$ given by (26).

Let us stress that problem $(\hat{OP}_3)$ differs from $(\hat{OP}_2)$ only in the second ODE of the system (compare (55) with (40)).

**Theorem 5.1.** Let us assume $(H_1)$ and $L_0 \in (0, \theta)$. Then, any function $\bar{u}$ satisfying $\bar{u}(t) \in [0, u_{\max}]$ a.e. $t \in [0, T]$ and
\[
\int_0^T \bar{u}(t)(1 - \exp(\lambda(t - T))) \, dt = \lambda y_{\max} \tag{56}
\]
is an optimal control for problem $(OP_3)$ with $G = G_1$.

**Proof.** It follows from (19) by introducing the real variable
\[
r = \int_0^T c(t) \, dt, \tag{57}
\]
Let us assume Theorem 5.2. in the following detailed form:

\[ u \]

Theorem 5.2. Let us assume \((OP_3)\) for \(G = G_1\) in the form (29) and arguing as for Theorem 3.1. Denoting \(\hat{c} = c_w\), we arrive to (56) thanks to Fubini’s Theorem and (18):

\[
y_{\text{max}} = \int_0^T \hat{c}(t) dt = \int_0^T \exp(-\lambda s) \left( \int_0^s \bar{u}(t) \exp(\lambda t) dt \right) ds = \int_0^T \bar{u}(t) \exp(\lambda t) \left( \int_0^T \exp(-\lambda s) ds \right) dt = \frac{1}{\lambda} \int_0^T \bar{u}(t) (1 - \exp(\lambda(t - T))) dt.
\]

\[ (58) \]

**Remark 5.**

i) Again, from a practical point of view, this means that the total AUC of the drug concentration is the relevant aspect to pay attention for \((OP_3)\) with \(G = G_1\), and this can be expressed as a condition over the amount of drug used during the treatment, but this has not influence on the form in which it is the drug administered.

ii) Once more, it is clear that there exists an infinite number of optimal controls for \((OP_3)\) with \(G = G_1\): for instance, we can consider \(\bar{u}_2(t) = \frac{\lambda y_{\text{max}}}{\alpha_T + \exp(-\lambda T) - 1} \) that belongs to \(U_{ad}^2\) thanks to \((\text{H}_1)\) (in this case meaning (22)) and

\[
\bar{u}_2(t) = \begin{cases} u_{\text{max}}, & \text{if } t \in [0, t^*), \\ 0, & \text{if } t \in (t^*, T], \end{cases}
\]

where \(t^*\) is the unique solution in \((0, T)\) of the nonlinear equation

\[
\lambda t^* + \frac{1 - \exp(\lambda t^*)}{\exp(\lambda T)} = \frac{\lambda^2 y_{\text{max}}}{u_{\text{max}}}. \tag{59}
\]

Any convex combination of \(\bar{u}_1\) and \(\bar{u}_2\) will be also an optimal control in this case.

We can describe the unique optimal control of the problem \((OP_3)\) with \(G = G_2\) in the following detailed form:

**Theorem 5.2.** Let us assume \((\text{H}_1)\), \(L_0 \in (0, \theta)\) and \(G = G_2\). Then, the unique optimal control of the problem \((OP_3)\) is given by

\[
\bar{u}(t) = \begin{cases} u_{\text{max}}, & \text{if } t \in [0, t^*), \\ u_{\text{in}}, & \text{if } t \in (t^*, T], \end{cases} \tag{60}
\]

where \(u_{\text{in}} = u_{\text{max}}(1 - \exp(-\lambda t^*))\) and \(t^*\) is the unique solution in \((0, T)\) of the nonlinear equation

\[
\lambda^2 y_{\text{max}} = u_{\text{max}}(\lambda T - 1 + \exp(-\lambda t^*)1 + \lambda(t^* - T))), \tag{61}
\]

that depends only on the parameters defining \((OP_3)\).

**Proof.** Using again the classical Pontryagin’s Maximum Principle (see [4]) we deduce the existence of a triplet of adjoint states \((p_1, p_2, p_3) \in (C^1[0, T])^3\) (not identically zero) and \(\mu \geq 0\) satisfying

\[
\begin{align*}
p_1'(t) &= p_1(t) \psi' \bar{x}_1(t)(G_2 \bar{x}_3(t) - 1), & p_1(T) &= 1, \\
p_2'(t) &= 0, & p_2(T) &= \mu, \\
p_3'(t) &= \lambda p_3(t) - p_2(t) + p_1(t) \psi(\bar{x}_1(t))G_2 \bar{x}_3(t), & p_3(T) &= 0,
\end{align*}
\]

\[ (62) \]

together with the transversality condition \(\mu(\bar{x}_2(T) - y_{\text{max}}) = 0\) and

\[
p_3(t)(u - \bar{u}(t)) \geq 0, \tag{63}
\]

for all \(u \in [0, u_{\text{max}}]\), a.e. \(t \in [0, T]\).
Arguing as in the proof of Theorem 3.2 we deduce the existence of a positive constant $\gamma$ such that $p_1(t)\psi(x_1(t)) \equiv \gamma$ for all $t \in [0,T]$. Moreover, from (62) we get that $p_2 \equiv \mu$ and

$$p_3(t) = \exp(\lambda t) \int_t^T \left( \mu - \frac{\gamma k_1 k_2}{(k_2 + \bar{x}_3(s))^2} \right) \exp(-\lambda s)ds =$$

$$\frac{\mu}{\lambda} \left( 1 - \exp(\lambda(t-T)) \right) - \gamma \frac{k_1 k_2}{(k_2 + \bar{x}_3(T))^2} \int_t^T \exp(-\lambda s) \left( k_2 + \bar{x}_3(s) \right)^2 ds.$$

If $\mu = 0$, inequality (63) implies that $\bar{u} \equiv u_{max}$, but this is excluded by (H1). Consequently, the transversality condition involves $\bar{x}_2(T) = y_{max}$. Using the same argumentations than in the proof of Theorem 4.2 one can conclude that:

i) The singular part of the optimal control $u_{sin}$ must be a constant, belonging to the interval $(0,u_{max})$.

ii) The general structure of the optimal control is given by

$$\bar{u}(t) = \begin{cases} 
0, & \text{where } p_3(t) > 0, \\
 u_{sin}, & \text{where } p_3(t) = 0, \\
 u_{max}, & \text{where } p_3(t) < 0.
\end{cases}$$

iii) The following configurations are not admissible

$$\bar{u}(t) = \begin{cases} 
\vdots \ , \ u_{max}, & \text{and } \bar{u}(t) = \begin{cases} 
\vdots \\
 0, \end{cases} \\
\vdots, \end{cases}$$

iv) Additionally, taking into account that here $p_3(T) = 0$, we can deduce that the next configurations are not admissible either

$$\bar{u}(t) = \begin{cases} 
\vdots, \ t \in (t_2,T) \text{ and } \bar{u}(t) = \begin{cases} 
\vdots \\
 0, \ t \in (t_2,T).
\end{cases}
\end{cases}$$

Combining previous information it becomes clear that the only possible configurations are given by (60) and

$$\bar{u}(t) = \begin{cases} 
0, & \text{if } t \in [0,t^*], \\
 u_{sin}, & \text{if } t \in [t^*,T].
\end{cases}$$

But this last one can be excluded once more by using the continuity of $\bar{x}_3$ at $t^*$ and the expression

$$\bar{x}_3(t) = \begin{cases} 
0, & \text{if } t \in [0,t^*], \\
 \frac{u_{max}}{\lambda}, & \text{if } t \in [t^*,T].
\end{cases}$$

Consequently, (60) is the unique valid configuration for $\bar{u}$. Again, the value of $u_{sin} = u_{max}(1 - \exp(-\lambda t^*))$ can be deduced from the continuity of the corresponding $\bar{x}_3$ at $t^*$:

$$\bar{x}_3(t) = \begin{cases} 
\frac{u_{max}}{\lambda}, & \text{if } t \in [0,t^*], \\
 \frac{u_{max}(1 - \exp(-\lambda t))}{\lambda}, & \text{if } t \in [t^*,T].
\end{cases}$$

(64)

Equation (61) for determining the value of $t^*$ can be obtained combining the transversality condition $\bar{x}_2(T) = y_{max}$ with (64):

$$y_{max} = \int_0^T \bar{x}_3(t)dt = \frac{u_{max}}{\lambda} \left( t^* + \frac{\exp(-\lambda t^*) - 1}{\lambda} + (T - t^*)(1 - \exp(-\lambda t^*)) \right).$$

(65)
The existence of a solution $t^*$ for (61) in $(0, T)$ can be deduced by considering the continuous auxiliary function 

$$
\tilde{F}(t) = u_{\text{max}}(\lambda T - 1 + \exp(-\lambda t)(1 + \lambda(t - T))) - \lambda^2 y_{\text{max}}, \quad t \in [0, T],
$$

checking that $\tilde{F}(0) = -\lambda^2 y_{\text{max}} < 0$, $\tilde{F}(T) > 0$ (by ($H_1$), see (22)) and using Bolzano’s Theorem. Uniqueness is a consequence of the fact that $\tilde{F}$ is a strictly increasing function in $[0, T]$.

Remark 6.  

i) In Theorem 5.2, we can give an a priori lower estimate of the interval length where the control is singular in terms of the data as follows:

using the second order Taylor approximation of $\tilde{F}$ centered at $t^*$, we know

$$
\tilde{F}(T) = \tilde{F}(t^*) + \tilde{F}'(t^*)(T - t^*) + \frac{\tilde{F}''(\chi)}{2}(T - t^*)^2 < \tilde{F}'(t^*)(T - t^*), \quad \text{for some } \chi \in (t^*, T),
$$

because $\tilde{F}(t^*) = 0$ and $\tilde{F}''(t) < 0$ for all $t \in [0, T]$. This yields

$$
\lambda T - 1 + \exp(-\lambda T) - \frac{\lambda^2 y_{\text{max}}}{u_{\text{max}}} < \lambda^2 \exp(-\lambda t^*)(T - t^*)^2 < \lambda^2(T - t^*)^2,
$$

and therefore

$$
|T - t^*| > \sqrt{\frac{T}{\lambda} + \frac{\exp(-\lambda T) - 1}{\lambda^2} - \frac{y_{\text{max}}}{u_{\text{max}}}}.
$$

(66)

For the numerical examples in Section 11, this lower bound takes an approximate value of $T/2$, which means that more than half the time, the control is singular (see also Table 3).

iii) Conclusions of Theorems 3.1, 3.2, 4.1, 4.2, 5.1 and 5.2 remain valid (exactly with the same proofs) for any other model similar to (1), but with different function $\psi$, just satisfying the sign condition $\psi(L) > 0$ for all $L \in (0, \theta)$: for instance, for the logistic model, where $\psi(L) = \xi L (\theta - L)$. Here the key point is the Norton-Simon hypothesis.

iv) Furthermore, it is very surprising that the optimal controls in all these theorems do not depend neither on the initial size of the tumor $L_0$ either on the greatest size of the tumor $\theta$. This makes us believe that this formulation of the problems (with the toxicity limit) is not very adequate in this framework. In a slightly different context, the same conclusion was reached in [13], under the log-kill hypothesis. For that reason, we think that it is interesting to study now some related optimal control problems where the integral constraint for the accumulated drug effect is penalized, see Section 7.

6. Some technical results. Previously, we collect some elementary results concerning real functions in one variable, that will be needed in Section 7.

Lemma 6.1.  

Let us consider the following optimization problem in one variable:

$$
(P_{\beta}) \quad \left\{ \begin{array}{l}
\min F_{\beta}(r) = F(r) + \beta r,
\end{array} \right.
\quad r \in [0, R],
$$

where $\beta \geq 0$ and $F \in C^2[0, R]$ verifying $F'(r) < 0$ for all $r \in [0, R]$. Let us denote by $r_{\beta} \in [0, R]$ a solution for $(P_{\beta})$. 

a) (Strictly convex case) If $F''(r) > 0$ for all $r \in (0,R)$, then
\[ r_\beta = \begin{cases} 
R, & \text{for } \beta \in [0,-F'(R)], \\
\text{Unique solution in } (0,R) \text{ of } F'(r) = -\beta, & \text{for } \beta \in (-F'(R),-F'(0)), \\
0, & \text{for } \beta \in [-F'(0),+\infty). 
\end{cases} \] (68)

b) (Strictly concave case) If $F''(r) < 0$ for all $r \in [0,R]$, then
\[ r_\beta = \begin{cases} 
R, & \text{for } \beta \in \left[0, \frac{F(0)-F(R)}{R}\right], \\
0, & \text{for } \beta \in \left[\frac{F(0)-F(R)}{R},+\infty\right). 
\end{cases} \] (69)

c) (Mixed concave-convex case) If $F''(r) < 0$ for all $r \in [0,R_1)$ and $F''(r) > 0$ for all $r \in (R_1,R]$, there are two possibilities:

\[ c1) \text{ When } F'(R) \leq \frac{F(R)-F(0)}{R}, \text{ the relation (69) still holds.} \]
\[ c2) \text{ When } F'(R) > \frac{F(R)-F(0)}{R}, \text{ then} \]
\[ r_\beta = \begin{cases} 
R, & \text{for } \beta \in [0,-F'(R)], \\
\text{Unique solution in } (R^*,R) \text{ of } F'(r) = -\beta, & \text{for } \beta \in (-F'(R),-F'(R^*)), \\
0, & \text{for } \beta \in [-F'(R^*),+\infty), 
\end{cases} \] (70)

where $R^* \in (R_1,R)$ is the unique value satisfying $F'(R^*) = \frac{F(R^*)-F(0)}{R^*}$.

Proof. It is well known that the following necessary condition for $r_\beta$ holds:
\[ (F'(r_\beta) + \beta)(r-r_\beta) \geq 0, \forall r \in [0,R], \]
which implies
\[ \begin{align*}
F'(0) &\geq -\beta, & \text{if } r_\beta = 0, \\
F'(r_\beta) &\leq -\beta, & \text{if } r_\beta \in (0,R). \text{ Moreover, } F''(r_\beta) \geq 0, \\
F'(R) &\leq -\beta, & \text{if } r_\beta = R.
\end{align*} \] (71)

In general, these conditions are not sufficient, except for strictly convex functions $F$. This is case a). For item b), it is clear that the option $r_\beta \in (0,R)$ does never hold (because $F''(r) < 0$ for all $r$), so $r_\beta \in \{0,R\}$ and the equivalence
\[ F_\beta(R) > F_\beta(0) \iff \beta > \frac{F(0)-F(R)}{R} \]
provides the result. It is clear that for $\beta = \frac{F(0)-F(R)}{R}$, both possibilities $r_\beta = 0$ and $r_\beta = R$ are valid.

Let us prove the most interesting case c). First, we observe that when $r_\beta \notin \{0,R\}$ it should be $r_\beta \in (R_1,R)$ with $-\beta \in F(R_1,R) = \{F'(R_1),F'(R)\}$, thanks to the assumptions for $F''$.

Here, we will introduce the auxiliary function $G(r) = F(r) - rF'(r)$, that clearly satisfies $G \in C[0,R]$ with $G'(r) = -rF''(r)$. Hence, by hypothesis,
\[ G'(r) > 0, \forall r \in [0,R_1), \quad G'(r) < 0, \forall r \in (R_1,R]. \]
In case c1) we will argue by contradiction: let us assume that \( r_\beta \not\in \{0, R\} \). 
Therefore, since \( F'(r_\beta) = -\beta \) (see (71)) and \( F'_\beta(r_\beta) \leq F_\beta(0) \) we deduce that 
\( G(r_\beta) \leq G(0) = F(0) \). Using now that \( r_\beta \in [R_1, R] \) and \( G \) is strictly decreasing in \( (R_1, R) \) we have \( G(R) < G(r_\beta) \leq G(0) \). This implies \( F'(R) > \frac{F(R) - F(0)}{R} \)
which contradicts the specific hypothesis for c1). Once it is known that \( r_\beta \in \{0, R\} \)
the proof can be finished as for a).

In case c2), we know by the hypotheses that \( G(R) < G(0) < G(R_1) \) and consequently, there exists a unique \( R^* \in (R_1, R) \) satisfying \( G(R^*) = G(0) \).

On the other hand, when \( r_\beta \not\in \{0, R\} \) arguing as before, we deduce that \( G(r_\beta) \leq G(0) \) and we conclude that \( r_\beta \in [R^*, R) \) with \( -\beta \in [F'(R^*), F'(R)) \). Taking into
account these facts, we can distinguish the following possibilities:

- For \( \beta > -F'(R^*) \), since \( -\beta \not\in [F'(R^*), F'(R)) \) and \( F'(R) + \beta > 0 \), it holds \( r_H = 0 \), thanks to (71).

- For \( \beta \leq -F'(R) \), we have again that \( -\beta \not\in [F'(R^*), F'(R)) \) and then \( r_\beta \in \{0, R\} \). Furthermore, here \( -\beta \leq F'(R) > \frac{F(R) - F(0)}{R} \), which implies \( F'_\beta(R) < F_\beta(0) \) and then \( r_\beta = R \).

- For \( \beta \in (-F'(R), -F'(R^*)) \), there exists a unique \( \tilde{r}_\beta \in [R^*, R) \) such that \( F'(\tilde{r}_\beta) = -\beta \). Since \( G \) is strictly decreasing in \( (R_1, R] \), we know that \( G(\tilde{r}_\beta) < G(R^*) = F(0) \). This fact is equivalent to \( F_\beta(\tilde{r}_\beta) < F_\beta(0) \). Moreover, \( F'(R) + \beta > 0 \) still holds. Therefore, using again (71), we conclude that \( r_\beta = \tilde{r}_\beta \).

\[ \square \]

**Remark 7.** Let us show that both possibilities mentioned in the item c) can appear in practice. For example, we can consider the function \( F(r) = \exp(-\exp(r)/10) \) with \( r \in [0, R] \) and different values of \( R \). For \( R = 2.6 \) it is easily verified that \( F'(R) \approx -0.35 < -0.248 \approx \frac{F(R) - F(0)}{R} \), i.e. c1). On the other hand, for \( R = 4 \) it is satisfied that \( \frac{F(R) - F(0)}{R} \approx -0.225 < -0.023 \approx F'(R) \), that belongs to the case c2); here we can check that \( R_1 = \log(10) \approx 2.3 \) and \( R^* \approx 3.0452 \).

**Lemma 6.2.** Given the real function \( F(r) = \exp(-\delta \exp(\tilde{H}(r))) \) with \( \delta > 0 \) and \( \tilde{H} \in C^2[0, R] \), it is verified that

i) \( F'(r) < 0 \) if and only if \( \tilde{H}'(r) > 0 \).

ii) \( F''(r) < 0 \) if and only if \( \left( \delta \exp(\tilde{H}(r)) - 1 \right) (\tilde{H}'(r))^2 \tilde{H}''(r) \).

**Proof.** Item i) is a straightforward consequence of the identity

\[ F'(r) = -\delta F(r) \exp(\tilde{H}(r)) \tilde{H}'(r). \]

Analogously, item ii) holds thanks to

\[ F''(r) = \delta F(r) \exp(\tilde{H}(r)) \left[ \left( \delta \exp(\tilde{H}(r)) - 1 \right) (\tilde{H}'(r))^2 - \tilde{H}''(r) \right]. \]

\[ \square \]

**7. The optimal control problems \((OP_3)-(OP_6)\).** In the second part of this work we are interested in the solutions of some optimal control problems related with the previous ones \((OP_1)-(OP_3)\), but without assuming any a priori integral constraint. In all cases, the objective to be minimized is a combination of the volume of the tumor at the final time \( T \) with some penalty integral term. The control variable (still denoted by \( u \)) will represent the infusion rate of the chemotherapy drug and will be a function taken in \( L^\infty(0, T) \), as before.
Once more, in the first problem of this section the chemotherapy infusion rate is identified with its concentration:

\[
\begin{align*}
\min J_\alpha(u) &= L(T) + \alpha \left( \int_0^T u(t) \, dt \right),
\end{align*}
\]

where \(\alpha \geq 0\) is the penalty parameter, \(L\) is the solution of the Cauchy problem

\[
\begin{align*}
L'(t) &= \psi(L(t))(1 - G(u(t))), \quad L(0) = L_0, \quad t \in [0, T],
\end{align*}
\]

recall that \(\psi\) is defined in (1) and the set of admissible controls is given by

\[
U_{ad} = \{ u \in L^\infty(0, T) : 0 \leq u(t) \leq u_{max}, \ a.e. \ t \in (0, T) \},
\]

where \(u_{max}\) is a positive given number.

Again, we will consider two classical pharmacodynamics, depending on the expression of the term \(G\): the Skipper and the \(E_{\text{max}}\) models (see (11)-(12)).

In the second and third optimal control problems of this part of the paper, we will introduce the typical pharmacokinetics first-order equation for the concentration combined with the previous pharmacodynamics terms. The only difference between them is the penalized term that will concern the integral of the drug infusion rate (the total amount of chemotherapy drug used during the process) for \((OP_5)\) or the integral of the concentration ("AUC") for \((OP_6)\). More precisely,

\[
\begin{align*}
\min J_\alpha(u) &= L(T) + \alpha \left( \int_0^T u(t) \, dt \right),
\end{align*}
\]

where \(\alpha \geq 0\) and \((L, c)\) is the solution of the Cauchy problem

\[
\begin{align*}
\begin{cases}
L'(t) &= \psi(L(t))(1 - G(c(t))), \quad L(0) = L_0, \quad t \in [0, T], \\
c'(t) &= -\lambda c(t) + u(t), \quad c(0) = 0,
\end{cases}
\end{align*}
\]

with \(G \in \{G_1, G_2\}\), \(\lambda\) being the positive value of the drug decay rate, and

\[
\begin{align*}
\min J_\alpha(u) &= L(T) + \alpha \left( \int_0^T c(t) \, dt \right),
\end{align*}
\]

where \(\alpha \geq 0\) and \((L, c)\) is the solution of the Cauchy problem (76) and the set of admissible controls is given by \(U_{ad}\) (see (74)).

The choice of the penalty parameter \(\alpha\) will differ depending on practical considerations: for instance, small values for \(\alpha\) can correspond to low cost treatments and/or to patients in good physical condition, while large values of \(\alpha\) will be selected for expensive treatments and/or when the patient is very weak physically.

The existence of solution for these problems relies on classical argumentations:

**Theorem 7.1.** Under previous assumptions, each one of the optimal control problems \((OP_4), (OP_5)\) and \((OP_6)\) has (at least) an optimal control, with \(G \in \{G_1, G_2\}\).

**Proof.** It follows exactly by using the same technicalities than the proof of Theorem 2.2, the explicit expressions derived for the solutions of the state equation (73) (see (17)) and the system (76) (see (18)-(19)). Again it is crucial that the set of admissible controls \(U_{ad}\) is a non-empty bounded convex closed subset of \(L^2(0, T)\).

There exists a close relationship between the problems \((OP_4) - (OP_6)\) and the previous ones that is shown in the next result:
Lemma 7.2.

i) If \( \bar{u} \) is an optimal control for \((OP_1)\) for some value \( \alpha \geq 0 \), then \( \hat{u} \) is an optimal control for \((OP_1)\) with \( y_{max} = \int_0^T \bar{u}(t) dt \).

ii) If \( \bar{u} \) is an optimal control for \((OP_2)\) for some value \( \alpha \geq 0 \), then \( \hat{u} \) is an optimal control for \((OP_2)\) with \( y_{max} = \int_0^T \bar{u}(t) dt \).

iii) If \( \bar{u} \) is an optimal control for \((OP_3)\) for some value \( \alpha \geq 0 \), then \( \hat{u} \) is an optimal control for \((OP_3)\) with \( y_{max} = \int_0^T \bar{u}(t) dt \).

Proof. Let us show that i) holds. By hypothesis, we know that \( \hat{J}_\alpha(v) \leq \bar{J}_\alpha(v) \) for all \( v \in U_{ad} \). Now, let us take any \( v \in U_{ad} \) such that \( \int_0^T v(t) dt \leq y_{max} \). Previous inequality gives us

\[
L_{\bar{u}}(T) + \alpha \left( \int_0^T \bar{u}(t) dt \right) \leq L_v(T) + \alpha \left( \int_0^T v(t) dt \right) \leq L_v(T) + \alpha y_{max},
\]

which implies that

\[
L_{\bar{u}}(T) \leq L_v(T),
\]

as desired. In all other cases the argumentation is similar. \( \square \)

8. Optimal controls for \((OP_4)\). Now, we are in conditions to combine the previous results and derive the following characterizations for the optimal controls of these problems:

Theorem 8.1. Let us assume \( L_0 \in (0, \theta) \) and that \( \bar{u} \) is an optimal control for problem \((OP_4)\) with \( G = G_1 \) for some value \( \alpha \geq 0 \). Consider the auxiliary function

\[
F(r) = \theta \exp \left( \log \left( \frac{L_0}{\theta} \right) \exp \left( \xi(k_1 r - T) \right) \right),
\]

(78)

that depends only on the parameters defining the control problem.

Then, there exist positive real values \( \alpha_1 \) and \( \alpha_2 \) (with \( \alpha_1 \leq \alpha_2 \)) such that:

Case 1. If \( \alpha_1 < \alpha_2 \), the following conclusions hold:

1. i) For \( \alpha \in [0, \alpha_1] \), the unique optimal control is given by \( \bar{u} \equiv u_{max} \).

1. ii) For \( \alpha \in [\alpha_2, +\infty) \), the unique optimal control is given by \( \bar{u} \equiv 0 \).

1. iii) For \( \alpha \in (\alpha_1, \alpha_2) \), there is an infinite number of optimal controls. In fact, any of them is a function \( \bar{u} \) verifying \( \bar{u}(t) \in [0, u_{max}] \) for a.e. \( t \in [0, T] \) and \( \int_0^T \bar{u}(t) dt = r_\alpha \), where \( r_\alpha \in (0, Tu_{max}) \) is the unique solution of the equation \( F'(r_\alpha) = -\alpha \).

Case 2. If \( \alpha_1 = \alpha_2 \), the following conclusions hold:

2. i) For \( \alpha \in [0, \alpha_1] \), the unique optimal control is given by \( \bar{u} \equiv u_{max} \).

2. ii) For \( \alpha \in (\alpha_1, +\infty) \), the unique optimal control is given by \( \bar{u} \equiv 0 \).

2. iii) For \( \alpha = \alpha_1 \), there are two optimal controls given by \( \bar{u} \equiv 0 \) and \( \bar{u} \equiv u_{max} \).

Depending on the parameters, the values \( \alpha_1 \) and \( \alpha_2 \) are the following:

a) When \( \exp (\xi T) \leq \log (\theta/L_0) \), we have \( \alpha_1 = -F'(Tu_{max}) \) and \( \alpha_2 = -F'(0) \).

b) When \( \exp (\xi T) > \log (\theta/L_0) \) and \( F'(Tu_{max}) \leq \frac{F(Tu_{max}) - F(0)}{Tu_{max}} \), we have \( \alpha_1 = \alpha_2 = \frac{F(0) - F(Tu_{max})}{Tu_{max}} \).

c) When \( \exp (\xi T) > \log (\theta/L_0) \) and \( F'(Tu_{max}) > \frac{F(Tu_{max}) - F(0)}{Tu_{max}} \), we have \( \alpha_1 = -F'(Tu_{max}) \) and \( \alpha_2 = -F'(T^*) \), where \( T^* \in (0, Tu_{max}) \) is the unique value satisfying

\[
F'(T^*) = \frac{F(T^*) - F(0)}{T^*}.
\]
Proof. As we did for \((OP_1)\) (see (28)), introducing the new variable

\[ r = \int_0^T u(t) dt \]  \hspace{1cm} (79)

and using (17) we can write the optimal control problem \((OP_4)\) with \(G = G_1\) in the following equivalent form:

\[ \left\{ \begin{array}{l}
\min_{r \in [0,Tu_{\text{max}}]} F_{\alpha}(r) = F(r) + \alpha r \\
\end{array} \right. \]  \hspace{1cm} (80)

with the function \(F\) defined in (78).

Now we can apply Lemma 6.2 with \(\delta = \log \left(\theta/L_0\right) \exp(-\xi T)\) and \(\tilde{H}(r) = \xi k_1 r\) to verify that \(F''(r) < 0\) for all \(r\) and moreover:

a) When \(\exp(\xi T) \leq \log \left(\theta/L_0\right)\), it holds that \(F''(r) > 0\) for all \(r > 0\) (strictly convex case).

b) When \(\exp(\xi T) > \log \left(\theta/L_0\right)\), we consider the value \(R_1 > 0\), given by

\[ R_1 = \frac{\xi T - \log \left(\log \left(\theta/L_0\right)\right)}{\xi k_1}. \]  \hspace{1cm} (81)

There are two possibilities: \(Tu_{\text{max}} \leq R_1\) or \(R_1 < Tu_{\text{max}}\). In the first case, we know that \(F''(r) < 0\) for all \(r \in [0,Tu_{\text{max}}]\) (strictly concave case); in the second one, \(F''(r) < 0\) for all \(r \in [0,R_1]\) and \(F''(r) > 0\) for all \(r \in (R_1,Tu_{\text{max}}]\) (mixed concave-convex case).

The conclusions of the theorem follow directly from Lemma 6.1. \(\square\)

Remark 8. Problem \((OP_4)\) with \(G = G_1\) was studied in [9, Section 4] and the optimal control was characterized there by using the adjoint state, without detailing its explicit expression in terms of the data, see [9, Theorem 4.4]. Moreover, during the proof of their result the authors claim that “we can exclude the singular case” and the optimal control can only take the values 0 and/or \(u_{\text{max}}\). Contrarily, we have seen (as in Theorem 3.1) that this case really comes up, see Remark 3-ii).

Theorem 8.2. Let us assume \(L_0 \in (0,\theta)\) and that \(\bar{u}\) is an optimal control for problem \((OP_4)\) with \(G = G_2\) for some value \(\alpha \geq 0\). Then, there exists \(r_\alpha \in [0,u_{\text{max}}]\) such that

\[ \bar{u}(t) = r_\alpha. \]  \hspace{1cm} (82)

Moreover, the value \(r_\alpha \in [0,u_{\text{max}}]\) can be determined as the solution of the following optimization problem in one variable:

\[ \left\{ \begin{array}{l}
\min_{r \in [0,u_{\text{max}}]} F_{\alpha}(r) = F(r) + \alpha Tr, \\
\end{array} \right. \]  \hspace{1cm} (83)

where

\[ F(r) = \theta \exp \left( \log \left(\theta/L_0\right) \exp \left(\xi T \left( \frac{k_1 r}{k_2 + r} - 1 \right) \right) \right), \]  \hspace{1cm} (84)

that depends only on the parameters defining the control problem.

More precisely, there exist positive real values \(\alpha_1\) and \(\alpha_2\) (with \(\alpha_1 \leq \alpha_2\)) such that:

Case 1. If \(\alpha_1 < \alpha_2\), the following conclusions hold:

1.i) For \(\alpha \in [0,\alpha_1]\), the unique optimal control is given by \(\bar{u} \equiv u_{\text{max}}\).

1.ii) For \(\alpha \in [\alpha_2,\infty)\), the unique optimal control is given by \(\bar{u} \equiv 0\).

1.iii) For \(\alpha \in (\alpha_1,\alpha_2)\), the unique optimal control is given by \(\bar{u} \equiv r_\alpha\), where \(r_\alpha \in (0,u_{\text{max}}]\) is the unique solution of the equation \(F'(r_\alpha) = -\alpha T\).
Case 2. If $\alpha_1 = \alpha_2$, the following conclusions hold:

2.i) For $\alpha \in [0, \alpha_1)$, the unique optimal control is given by $\bar{u} = u_{\max}$.
2.ii) For $\alpha \in (\alpha_1, +\infty)$, the unique optimal control is given by $\bar{u} \equiv 0$.
2.iii) For $\alpha = \alpha_1$, there are two optimal controls given by $\bar{u} \equiv 0$ and $\bar{u} \equiv u_{\max}$.

Depending on the parameters, the values $\alpha_1$ and $\alpha_2$ are the following:

a) When $\exp(\xi T) \left(1 - \frac{2}{k_1 T} \right) \leq \log(\theta/L_0)$, we have $\alpha_1 = -F'(u_{\max})/T$ and $\alpha_2 = -F'(0)/T$.

b) When $\exp(\xi T) \left(1 - \frac{2}{k_1 T} \right) > \log(\theta/L_0)$ and $F'(u_{\max}) \leq \frac{F(u_{\max}) - F(0)}{u_{\max}}$, we have $\alpha_1 = \alpha_2 = \frac{F(0) - F'(u_{\max})}{T u_{\max}}$.

c) When $\exp(\xi T) \left(1 - \frac{2}{k_1 T} \right) > \log(\theta/L_0)$ and $F'(u_{\max}) > \frac{F(u_{\max}) - F(0)}{u_{\max}}$, we have $\alpha_1 = -F'(u_{\max})/T$ and $\alpha_2 = -F'(R^*)/T$, where $R^* \in (0, u_{\max})$ is the unique value satisfying $F'(R^*) = \frac{F(R^*) - F(0)}{R^*}$.

Proof. Combining Theorem 3.2 with Lemma 7.2-i) we deduce that $\bar{u}$ must be a constant function (i.e. (82)). To determine its value, using (17) we can reduce the optimal control problem (OP2) with $G = G_2$ to the form (83), where $r = \bar{u}$ and the function $F$ is given by (84), because we can restrict our search among the constant controls.

Now we can apply Lemma 6.2 with $\delta = \log(\theta/L_0) \exp(-\xi T)$ and $\tilde{H}(r) = \frac{\xi T k_1 r}{k_2 + r}$ to deduce that $F'(r) < 0$ for all $r$ and $F''(r) > 0$ if and only if

$$\varphi(r) > k_1 k_2 \xi T \log(\theta/L_0),$$

with

$$\varphi(r) = \exp \left( \xi T \left( 1 - \frac{k_1 r}{k_2 + r} \right) \right) \left( 2(k_2 + r) - \xi T k_1 k_2 \right).$$

(86)

Let us recall that inequality (85) is always satisfied for $r \geq k_2(k_1 \xi T - 2)/2$, because the right hand side is negative, meanwhile the left hand side is non-negative in that case. It is easy to check that $\varphi$ is an strictly increasing function. Hence, relation (85) holds for all $r > 0$ if and only if $\varphi(0) \geq k_1 k_2 \xi T \log(\theta/L_0)$. This is equivalent to say that $F$ is strictly convex in $(0, u_{\max})$ if and only if $\exp(\xi T) \left(1 - \frac{2}{R_{\xi T}}\right) \leq \log(\theta/L_0)$.

When this is not the case, we can consider the unique value $R_1 > 0$ satisfying $\varphi(R_1) = k_1 k_2 \xi T \log(\theta/L_0)$. Again, there are two possibilities: $u_{\max} \leq R_1$ or $R_1 < u_{\max}$. As before, the first case, corresponds to the concave case and the second one, to the mixed concave-convex case. We conclude the proof once more from Lemma 6.1 with $\beta = \alpha T$.

9. Optimal controls for (OP3).

Theorem 9.1. Let us assume $L_0 \in (0, \theta)$ and that $\bar{u}$ is an optimal control for problem (OP3) with $G = G_1$ for some value $\alpha \geq 0$. Then, there exists $t_\alpha \in [0, T]$ such that

$$\bar{u}(t) = \begin{cases} u_{\max}, & \text{if } t \in [0, t_\alpha), \\ 0, & \text{if } t \in (t_\alpha, T]. \end{cases}$$

(87)
Moreover, the value $t_\alpha \in [0,T]$ can be determined as the solution of the following optimization problem in one variable:

$$\min F_\alpha(t) = F(t) + \alpha u_{\max} t,$$

where

$$F(t) = \theta \exp \left( \log \left( \frac{L_0}{\theta} \right) \exp \left( -\xi T + \frac{\xi k_1 u_{\max}}{\lambda} \left( t + 1 - \exp(\lambda t) \right) \right) \right),$$

that depends only on the parameters defining the control problem.

More precisely, there exist positive real values $\alpha_1$ and $\alpha_2$ (with $\alpha_1 \leq \alpha_2$) such that:

Case 1. If $\alpha_1 < \alpha_2$, the following conclusions hold:

1.i) For $\alpha \in [0,\alpha_1]$, the unique optimal control is given by $\bar{u} \equiv u_{\max}$.

1.ii) For $\alpha \in (\alpha_2, +\infty)$, the unique optimal control is given by $\bar{u} \equiv 0$.

1.iii) For $\alpha \in (\alpha_1, \alpha_2)$, the unique optimal control is given by (87) where $t_\alpha \in (0,T)$ is the unique solution of the equation $F'(t_\alpha) = -\alpha u_{\max}$.

Case 2. If $\alpha_1 = \alpha_2$, the following conclusions hold:

2.i) For $\alpha \in [0,\alpha_1]$, the unique optimal control is given by $\bar{u} \equiv u_{\max}$.

2.ii) For $\alpha \in (\alpha_1, +\infty)$, the unique optimal control is given by $\bar{u} \equiv 0$.

2.iii) For $\alpha = \alpha_1$, there are two optimal controls given by $\bar{u} \equiv 0$ and $\bar{u} \equiv u_{\max}$.

An algorithm to determine the values $\alpha_1$ and $\alpha_2$ can be explicitly specified, just using the values of the control problem.

Proof. In this case, combining Theorem 4.1 with Lemma 7.2-ii) we deduce that $\bar{u}$ has the structure (87), for some $t_\alpha \in [0,T]$. It remains only to determine the value $t_\alpha$. Taking into account (87) and (18) it is straightforward (see (65)) to derive that

$$\bar{c}(t) = \bar{c}_u(t) = \begin{cases} \frac{u_{\max}}{\lambda} \left( 1 - \exp(-\lambda t) \right), & \text{if } t \in [0,t_\alpha], \\ \frac{u_{\max}}{\lambda} \left( \exp(\lambda t_{\alpha}) - 1 \right) \exp(-\lambda t), & \text{if } t \in [t_\alpha,T], \end{cases}$$

and

$$\int_0^T \bar{c}(t) dt = \frac{u_{\max}}{\lambda} \left( t_\alpha + 1 - \exp(\lambda t_{\alpha}) \right).$$

Using now (19) and (90)-(91) we can reduce the optimal control problem (OP$\tilde{g}$) with $\bar{G} = G_1$ to the form (88), with the function $F$ given by (89), because we can restrict our search among the controls with the structure (87).

Now we can apply Lemma 6.2 with $\delta = \log(\theta/L_0) \exp(-\xi T)$ and

$$\tilde{H}(t) = \hat{\rho} \left( t + 1 - \exp(\lambda t) \right),$$

with $\hat{\rho} = \frac{\xi k_1 u_{\max}}{\lambda}$ to deduce that $F''(t) < 0$ for all $t \in [0,T]$ and $F'''(t) > 0$ if and only if

$$\varphi(t) < 0,$$

with

$$\varphi(t) = \frac{\hat{\rho}}{\lambda} \left( 1 + \log(\theta/L_0) \exp(-\xi T + \hat{\rho} \left( t + 1 - \frac{e^\lambda}{(1-e^\lambda)(1-e^{-\lambda T})} \right)) \right) (1 - e^{\lambda(t-T)})^2 - e^{\lambda(t-T)}.$$

Let us recall that inequality (92) is satisfied (at least) for $t$ close to $T$. 

Since it seems complicated to argue directly through $\varphi$, we prefer to transform it by taking $a = -\log \left( \frac{L_0}{\theta} \right) \exp \left( (\hat{\rho} - \xi)T + \frac{\hat{\xi}}{\lambda e^T} \right) > 0$, $b = \frac{\xi}{\lambda} > 0$ and the new variable $z = e^{\lambda(t-T)} \in [e^{-\lambda T}, 1] \subset (0, 1]$. Then we arrive to the inequality

$$\tilde{\varphi}(z) \overset{\text{def}}{=} b(1 - az^b e^{-bz})(1 - z)^2 - z < 0,$$

(94) which it is equivalent to (92). It is easy to check that $\tilde{\varphi}(0) = b > 0$ and $\tilde{\varphi}(1) = -1 < 0$. By the continuity of the function $\tilde{\varphi}$ and Bolzano’s Theorem, we conclude that there exists (at least one point) $z_1 \in (0, 1)$ such that $\tilde{\varphi}(z_1) = 0$. Let us now deduce that $z_1$ is unique, showing that $\tilde{\varphi}(z) < 0$ for all $z \in (z_1, 1]$. To that end we will utilize the auxiliary functions

$$\psi_1(z) = 1 - az^b e^{-bz}, \quad \psi_2(z) = \frac{z}{(1 - z)^2}.$$  

(95) It is easy to check that $\psi_1$ is an strictly decreasing function in $(0, 1)$, meanwhile $\psi_2$ is an strictly increasing function in $(0, 1)$. Using these facts and that $\tilde{\varphi}(z_1) = 0$, we have that for every $z \in (z_1, 1]$

$$\tilde{\varphi}(z) < b(1 - az_1^b e^{-bz_1})(1 - z)^2 - z = \frac{z_1}{(1 - z_1)^2} (1 - z)^2 - z < 0.$$  

Consequently, relation (92) holds for all $t \in (T_1, T]$ with $T_1 = T + \frac{\log (z_1)}{\lambda}$.

Here again there are two possibilities: $T_1 \leq 0$ or $T_1 > 0$. The first case corresponds to the convex case and the second one, to the mixed concave-convex case. We conclude the proof once more with the help of Lemma 6.1, recalling than here we must take $\beta = \alpha u_{\max}$. The algorithm for determining the values $\alpha_1$ and $\alpha_2$ follows the same argumentation than in previous theorems:

a) When $T_1 \leq 0$, we have $\alpha_1 = -\frac{F'(T)}{u_{\max}}$ and $\alpha_2 = -\frac{F'(0)}{u_{\max}}$.

b) When $T_1 > 0$ and $F'(T) \leq \frac{F(T) - F(0)}{T}$, we have $\alpha_1 = \alpha_2 = \frac{F(0) - F(T)}{T_{\max}}$.

c) When $T_1 > 0$ and $F'(T) > \frac{F(T) - F(0)}{T}$, we have $\alpha_1 = -\frac{F'(T)}{u_{\max}}$ and $\alpha_2 = -\frac{F'(T^*)}{u_{\max}}$, where $T^* \in (T_1, T)$ is the unique value satisfying

$$F'(T^*) = \frac{F(T^*) - F(0)}{T^*}.$$

\[\square\]

**Theorem 9.2.** Let us assume $L_0 \in (0, \theta)$ and that $\bar{u}$ is an optimal control for problem $(OP_5)$ with $G = G_2$ for some value $\alpha \geq 0$. Then, there exist $t_{1a}, t_{2a} \in [0, T]$ such that $t_{1a} \leq t_{2a}$ and

$$\bar{u}(t) = \begin{cases} u_{\max}, & \text{if } t \in [0, t_{1a}), \\ u_{\max}(1 - e^{-\lambda t_{1a}}), & \text{if } t \in (t_{1a}, t_{2a}), \\ 0, & \text{if } t \in (t_{2a}, T]. \end{cases}$$

(96)

Moreover, the pair $(t_{1a}, t_{2a}) \in [0, T]^2$ can be determined as the solution of the following optimization problem in two variables:

$$\left( \widehat{OP}_{52} \right) \begin{cases} \min_{t_1, t_2} F_\alpha(t_1, t_2), \\ 0 \leq t_1 \leq t_2 \leq T, \end{cases}$$

(97) where
\[ F_\alpha(t_1, t_2) = \theta \exp \left( \log \left( \frac{L_0}{\theta} \right) \exp \left( \xi(k_1 \tilde{H}(t_1, t_2) - T) \right) \right) + \alpha u_{\text{max}} (t_2 + e^{-\lambda t_1} (t_1 - t_2)), \]  

(98)

\[ \tilde{H}(t_1, t_2) = t_1 - \frac{k_2}{\lambda k_2 + u_{\text{max}}} \log \left( \frac{(\lambda k_2 + u_{\text{max}}) e^{\lambda t_1} - u_{\text{max}}}{\lambda k_2} \right) + \frac{(t_2 - t_1) u_{\text{max}} (1 - e^{-\lambda t_1})}{k_2 \lambda + u_{\text{max}} (1 - e^{-\lambda t_1})} - \frac{1}{\lambda} \log \left( \frac{\lambda k_2 + u_{\text{max}} (1 - e^{-\lambda t_1}) e^{-\lambda (T - t_2)}}{\lambda k_2 + u_{\text{max}} (1 - e^{-\lambda t_1})} \right), \]  

(99)

that depend only on the parameters defining the control problem.

**Proof.** Once more, combining Theorem 4.2 with Lemma 7.2-ii) we deduce that \( \bar{u} \) has the structure (96), eventually with \( t_{1\alpha} = t_{2\alpha} \), see (46)-(47). To determine the values of \( t_{1\alpha} \) and \( t_{2\alpha} \), taking into account (96) and

\[ \bar{c}(t) = \begin{cases} \frac{u_{\text{max}}}{\lambda} (1 - e^{-\lambda t}), & \text{if } t \in [0, t_{1\alpha}], \\ \frac{u_{\text{max}}}{\lambda} (1 - e^{-\lambda t_{1\alpha}}), & \text{if } t \in [t_{1\alpha}, t_{2\alpha}], \\ \frac{u_{\text{max}}}{\lambda} (1 - e^{-\lambda t_{1\alpha}}) e^{-\lambda (t - t_{2\alpha})}, & \text{if } t \in [t_{2\alpha}, T], \end{cases} \]  

(100)

we can explicitly derive (after some long and tedious calculations) that

\[ \int_0^T \frac{c(t)}{k_2 + c(t)} dt = \tilde{H}(t_{1\alpha}, t_{2\alpha}) \]  

(101)

with \( \tilde{H} \) given by (99). Using now (90) and (101) we can write the optimal control problem \( (O_{P_6}) \) with \( G = G_2 \) in the equivalent form (97), with the function \( F_\alpha \) given by (98).

**Remark 9.** Clearly, in the particular case \( t_{1\alpha} = t_{2\alpha} \), the singular part of the optimal control does not appear and its form reduces to the typical bang-bang one

\[ \bar{u}(t) = \begin{cases} u_{\text{max}}, & \text{if } t \in [0, t_{1\alpha}], \\ 0, & \text{if } t \in (t_{1\alpha}, T]. \end{cases} \]  

(102)

**10. Optimal controls for \( (O_{P_6}) \).**

**Theorem 10.1.** Let us assume \( L_0 \in (0, \theta) \) and that \( \bar{u} \) is an optimal control for problem \( (O_{P_6}) \) with \( G = G_1 \) for some value \( \alpha \geq 0 \). Consider the auxiliary function

\[ F(r) = \theta \exp \left( \log \left( \frac{L_0}{\theta} \right) \exp \left( \xi(k_1 r - T) \right) \right), \]  

(103)

that depends only on the parameters defining the control problem.

Then, there exist positive real values \( \alpha_1 \) and \( \alpha_2 \) (with \( \alpha_1 \leq \alpha_2 \)) such that:

**Case 1.** If \( \alpha_1 < \alpha_2 \), the following conclusions hold:

1. For \( \alpha \in [0, \alpha_1] \), the unique optimal control is given by \( \bar{u} \equiv u_{\text{max}} \).

2. For \( \alpha \in [\alpha_2, +\infty) \), the unique optimal control is given by \( \bar{u} \equiv 0 \).

3. For \( \alpha \in (\alpha_1, \alpha_2) \), there is an infinite number of optimal controls. In fact, any of them is a function \( \bar{u} \) verifying \( \bar{u}(t) \in [0, u_{\text{max}}] \) for a.e. \( t \in [0, T] \) and

\[ \int_0^T c(t) dt = r_\alpha, \]  

(104)

where \( r_\alpha \in (0, R) \) with \( R = \frac{u_{\text{max}}}{\lambda} \left( T + e^{\lambda T} \right) \), is the unique solution of the equation \( F'(r_\alpha) = -\alpha \).
Case 2. If $\alpha_1 = \alpha_2$, the following conclusions hold:

2.i) For $\alpha \in [0, \alpha_1)$, the unique optimal control is given by $\bar{u} \equiv u_{\text{max}}$.
2.ii) For $\alpha \in (\alpha_1, +\infty)$, the unique optimal control is given by $\bar{u} \equiv 0$.
2.iii) For $\alpha = \alpha_1$, there are two optimal controls given by $\bar{u} \equiv 0$ and $\bar{u} \equiv u_{\text{max}}$.

Depending on the parameters, the values $\alpha_1$ and $\alpha_2$ are the following:

a) When $\exp(\xi T) \leq \log(\theta/L_0)$, we have $\alpha_1 = -F'(R)$ and $\alpha_2 = -F'(0)$.

b) When $\exp(\xi T) > \log(\theta/L_0)$ and $F'(R) \leq \frac{F(R) - F(0)}{R}$, we have $\alpha_1 = \alpha_2 = \frac{F(0) - F(R)}{F(0) - F(\bar{R})}$.

c) When $\exp(\xi T) > \log(\theta/L_0)$ and $F'(R) > \frac{F(R) - F(0)}{R}$, we have $\alpha_1 = -F'(R)$ and $\alpha_2 = -F'(R^*)$, where $R^* \in (0, R)$ is the unique value satisfying

$$F'(R^*) = \frac{F(R^*) - F(0)}{R^*}.$$

Proof. In this case, it is clear that the objective to be minimized depends only on the term $\int_0^T c_u(t)dt$. Using (18) and Fubini’s Theorem it can be written in the equivalent form (see (58))

$$\int_0^T c_u(t)dt = \frac{1}{\lambda} \int_0^T u(t)(1 - e^{\lambda(T-t)})dt. \tag{105}$$

So, here we will introduce the new variable

$$r = \int_0^T c_u(t)dt, \tag{106}$$

and using (105) we can reduce the optimal control problem $(\widehat{OP}_0)$ with $G = G_1$ to the following form:

$$(\widehat{OP}_{61}) \begin{cases} \min_{r \in [0, R]} F_{\alpha}(r) = F(r) + \alpha r \\ \end{cases}, \tag{107}$$

with the function $F$ defined in (103). The right extreme $R$ of the interval is calculated by taking $u \equiv u_{\text{max}}$ in (105).

Problem $(\widehat{OP}_{61})$ is exactly the same than problem $(\widehat{OP}_{41})$ (see (80)) with the unique difference that $r$ is moving in the interval $[0, R]$, instead of $[0, T_{\text{u_{max}}}]$. Hence, the conclusions of Theorem 10.1 are exactly the same than for Theorem 8.1 with this change.

**Theorem 10.2.** Let us assume $L_0 \in (0, \theta)$ and that $\bar{u}$ is an optimal control for problem $(\widehat{OP}_0)$ with $G = G_2$ for some value $\alpha \geq 0$. Then, there exists $t_\alpha \in [0, T]$ such that

$$\bar{u}(t) = \begin{cases} u_{\text{max}}, & \text{if } t \in [0, t_\alpha), \\ u_{\text{max}}(1 - e^{-\lambda t}), & \text{if } t \in (t_\alpha, T]. \end{cases} \tag{108}$$

Moreover, the value $t_\alpha \in [0, T]$ can be determined as the solution of the following optimization problem in one variable:

$$(\widehat{OP}_{62}) \begin{cases} \min_{t \in [0, T]} F_{\alpha}(t) = F(t) + \alpha G(t), \\ \end{cases}, \tag{109}$$

where $F$ is given by

$$F(t) = \theta \exp \left( \log \left( \frac{L_0}{\theta} \right) \exp \left( \xi(k_1 \bar{H}(t) - T) \right) \right). \tag{110}$$
\[ \hat{H}(t) = t - \frac{k_2}{\lambda k_2 + u_{\max}} \log \left( \frac{(\lambda k_2 + u_{\max}) e^{\lambda t} - u_{\max}}{\lambda k_2} \right) + \frac{(T - t) u_{\max} (1 - e^{-\lambda t})}{\lambda k_2 + u_{\max} (1 - e^{-\lambda t})}, \]  

and

\[ G(t) = \frac{u_{\max}}{\lambda^2} \left( e^{-\lambda t} (1 + \lambda (t - T)) + \lambda T - 1 \right), \]  

that depend only on the parameters defining the control problem.

**Proof.** It follows by using the same argumentations than in the other cases, thanks to (91), (101) and Lemma 7.2-iii).

11. **Numerical results.** In this section, we present some numerical experiments to illustrate and compare the therapy results depending on the chosen model. Taking into account Lemma 7.2, we only consider the penalized problems \((\mathcal{O}P_i)\) for \(i = 4, 5, 6\). In order to circumvent the presence of the carrying capacity \(\theta\), we will use the transformation \((5)\). Consequently, our numerical results will refer to \(L(t)/\theta\) (see Figures 1-4), instead of \(L(t)\) directly. More precisely, we will consider the following three formulations:

\[
(\tilde{\mathcal{O}P}_4) \quad \left\{ \begin{array}{l}
\min \hat{J}_\alpha(u) = \exp(x(T)) + \hat{\alpha} \int_0^T u(t) dt,
\end{array} \right.
\]

where \(x\) is the solution of the Cauchy problem

\[ x'(t) = \xi x(t)(G(u(t)) - 1), \quad x(0) = \log \left( \frac{L_0}{\theta} \right), \quad t \in [0, T], \]  

\[
(\tilde{\mathcal{O}P}_5) \quad \left\{ \begin{array}{l}
\min \hat{J}_\alpha(u) = \exp(x(T)) + \hat{\alpha} \int_0^T u(t) dt,
\end{array} \right.
\]

\[
(\tilde{\mathcal{O}P}_6) \quad \left\{ \begin{array}{l}
\min \hat{J}_\alpha(u) = \exp(x(T)) + \hat{\alpha} \int_0^T c(t) dt,
\end{array} \right.
\]

where, for both problems, \((x, c)\) is the solution of the Cauchy problem

\[
\begin{cases}
x'(t) = \xi x(t)(G(c(t)) - 1), \quad x(0) = \log \left( \frac{L_0}{\theta} \right), \quad t \in [0, T], \\
c'(t) = -\lambda c(t) + u(t), \quad c(0) = 0.
\end{cases}
\]

In all cases the set of admissible controls, \(U_{\text{ad}}\), is given by (74) and \(\hat{\alpha} \geq 0\) is the penalty parameter. Let us note that \((\tilde{\mathcal{O}P}_i)\) is an equivalent formulation to \((\mathcal{O}P_i)\) for \(i = 4, 5, 6\) with \(\hat{\alpha} = \alpha/\theta\), being \(\alpha\) the penalty parameter in the above sections.

For solving numerically these problems, we have used GPOPS (General Pseudospectral OPtimal control Software, http://www.gpops.org/), that implements a Radau hp adaptive pseudospectral method ([6] and [16]). In each iteration the optimal control problem is transformed into a nonlinear programming problem by approximating the state and control with Lagrange polynomials and collocating the differential-algebraic equations using nodes obtained from the Legendre-Gauss-Radau quadrature. The time interval is divided into several subintervals and a different Lagrange polynomial is used in each one. The number of subintervals, their widths and the degree of the polynomial on each subinterval is determined iteratively in order to reach a specified solution accuracy. The iterative procedure stops when the dynamic constraints and the bounds on the state and control are satisfied within the specific tolerance, \(\varepsilon\), in all the subintervals. We have used GPOPS
version 5.0 with SNOPT to solve the large nonlinear programming problems arising from the discretization. We chose $\varepsilon = 1.e-4$ and the values $1.e-9$ and $2.e-9$ for the optimality and feasibility tolerances for the NLP solver, respectively.

As expected, the structures of the optimal controls (in case of having uniqueness) determined by GPOPS agree with the ones showed in previous theorems. In some cases to compute the switching times with higher precision than GPOPS we have solved a small nonlinear programming problem (based in the particular underlying structure) where the unknowns are these switching times. For instance, for the $E_{max}$ model, we have solved (97) using fmincon with the option SQP and (109) using fminbnd. In both cases we chose the value $1.e-12$ for the termination tolerances. All computations were performed on a 3.3 GHz Core i5-2500 machine, with 8 GB RAM running under the 64-bit version of Windows 7 and MATLAB R2014b.

We present six tables and four figures with a selection of our numerical results. Figures show the tumor volumes, $L(t)/\theta$, or the optimal controls, $\bar{u}$, using a solid blue line, a dash-dot red line and a dash-dash black line for the three problems, $(\bar{OP}_4)$, $(\bar{OP}_5)$ and $(\bar{OP}_6)$, respectively. The controls correspond to cases for which the uniqueness is guaranteed. The values for the equations’ parameters were chosen for illustrative purposes and they are not based on biological data.

Table 1, plots on the left of Figure 1 and Figure 3 are devoted to the Skipper model, meanwhile Table 2 and plots on the right of Figure 1 and Figures 2 and 4 are associated with the $E_{max}$ model. For each example we use a code word starting with the letter $E$ followed by one of these capital letters: S (small), M (midsized) or L (large), two numbers to identify the problem (the first one is equal to $i$ for $(\bar{OP}_i)$ and the second one is equal to 1 for $G = G_1$ or equal to 2 for $G = G_2$), a lowercase letter related to the penalty parameter (the letters a, b and c indicate the item of the corresponding theorem of Sections 8-10 and the letter o is used for other case) and, finally, a number that classifies the example inside its category. Hence, $ES_{4.1.a2}$ refers to the second example of $(\bar{OP}_4)$ with the pharmacodynamics model defined by $G = G_1$, the switching values of the penalty parameter corresponding to case $a$ in Theorem 8.1 and a small initial tumor volume.

In Tables 1 and 2 the example code appears in the first column, then four columns show some parameters and, finally, the main numerical results appear in the other columns. The parameter set given in the tables are the tumor growth parameter, $\xi$, the value of the drug decay rate, $\lambda$ (except for problem $(\bar{OP}_4)$ because this parameter does not appear in its description), the final time, $T$, and the penalty parameter, $\hat{\alpha}$. We arrange the results taking into account the initial tumor volume, distinguishing between three groups in the penultimate column: a small tumor (5% of carrying capacity), a midsized tumor (50% of carrying capacity) and, finally, a large tumor (75% of carrying capacity). For each initial tumor volume the results are grouped under three categories depending on the problem that has been solved. The examples corresponding to the same problem are ranked in order of the total amount of drug used in the treatment (showed in the sixth column). We have taken $u_{max} = 2.4$ for the maximum infusion rate of the chemotherapeutic agent in all the examples. The seventh column only presents numerical results for $(\bar{OP}_4)$ because it is the unique problem that uses the integral of the drug concentration in its formulation. Moreover, the last column reports the ratio of the final tumor volume to the initial volume (of course, multiplying the values of $L(T)/L_0$ and $L_0/\theta$ we can get $L(T)/\theta$, if desired). For completeness of information for the cases where
the optimal control is unique and it could have a singular part (see Theorems 9.2 and 10.2), Table 3 shows the structure, the switching times and the value of the singular part of the computed controls. At this point it is remarkable that the constant singular value can be interpreted as a maintenance infusion rate that is used most of the time (in the examples between 72% and 84%, see (66) for a general lower bound) with a low value, compared with the maximum infusion rate (in the examples between 14% and 31%).

Tables 1 and 2 start with nine examples for a small initial tumor (5% of the carrying capacity). For each problem \( (\hat{OP}_i), i = 4, 5, 6 \), we present numerical results of three examples corresponding to different values for the penalty parameter \( \hat{\alpha} \). In the fifth column we show the computational values chosen for this parameter in order to obtain controls with different structures. The first value is associated with the maximum infusion rate therapy, \( \bar{u} \equiv u_{\text{max}} \), (see in both Tables that \( \int_0^T \bar{u}(t)dt = 2.4 \) for this case) and the last one is devoted to zero-therapy. Those penalty parameter values correspond to \( \alpha_1 \) and \( \alpha_2 \) of previous sections' theorems. For the other six examples, we have chosen the same intermediate value (3 \( e^{-2} \)). As one could expect, the larger the penalty parameter value, the greater the volume reached by the tumor. Moreover, if we compare the tumor volume of the examples with maximum infusion rate therapy (\( ES_{41a1}, ES_{51a1} \) and \( ES_{61a1} \) on one hand and \( ES_{42a1}, ES_{52a1} \) and \( ES_{62a1} \) on the other) we observe the effects of including the equation for the concentration. Let us note at this point that for \( ES_{41a2} \) and \( ES_{61a2} \) there is an infinite number of optimal controls, all of them taking the same values in columns six and seven, respectively. In Table 2 (with numerics for \( E_{\text{max}} \) model and \( k_2 = 0.25 \)) for those nine examples related to a small initial tumor we observe

| Example | \( \xi \) | \( \lambda \) | \( T \) | \( \hat{\alpha} \) | \( \int_0^T \bar{u}(t)dt \) | \( \int_0^T \bar{c}(t)dt \) | \( L_0/\theta \) | \( L(T)/L_0 \) |
|---------|--------|--------|--------|-----------|----------------|----------------|--------------|--------------|
| ES_{41a1} | 0.1 | 1 | 3.0e-02 | 9.5e-01 | 5.0e-02 | 3.8e-01 |
| ES_{41a2} | 0.1 | 1 | 7.3e-02 | 0 | 5.0e-02 | 1.3e+00 |
| ES_{41a3} | 0.1 | 1 | 9.0e-05 | 2.4e+00 | 5.0e-01 | 3.9e-01 |
| EM_{41a1} | 0.1 | 1 | 1.2e-01 | 2.4e+00 | 5.0e-01 | 3.9e-01 |
| EM_{41a2} | 0.1 | 1 | 1.4e-01 | 1.9e+00 | 5.0e-01 | 5.2e-01 |
| EM_{41a3} | 0.1 | 1 | 1.5e-01 | 0 | 5.0e-01 | 1.0e+00 |
| EL_{41a1} | 0.1 | 1 | 1.1e-01 | 2.4e+00 | 7.5e-01 | 6.8e-01 |
| EL_{41a2} | 0.1 | 1 | 1.2e-01 | 0 | 7.5e-01 | 1.0e+00 |
| EL_{41a3} | 0.1 | 1 | 1.4e-01 | 2.4e+00 | 1.1e+00 | 7.6e-01 |
CONTROL UNDER NORTON-SIMON HYPOTHESIS 2605

Table 2. Parameters and numerical results with $G = G_2$, $k_1 = 4$ and $k_2 = 0.25$.

| Example | $\xi$ | $\lambda$ | $T$ | $\hat{\alpha}$ | $\int_0^T \hat{u}(t)dt$ | $\int_0^T \hat{c}(t)dt$ | $L_0/\theta$ | $L(T)/L_0$ |
|---------|-------|-----------|-----|-----------------|------------------------|------------------------|--------------|-------------|
| $ES_{42o1}$ | 0.1  | 1         | 5.0e-02 | 1.1e-03          | 2.4e+00                | 5.0e-02                | 4.1e-01     |
| $ES_{42o2}$ | 0.1  | 1         | 3.0e-02 | 3.6e-01          | 5.0e-02                | 6.5e-01                |
| $ES_{42o3}$ | 0.1  | 1         | 2.9e-01 | 0               | 5.0e-02                | 1.3e+00                |
| $ES_{52o1}$ | 0.1  | 0.27     | 1      | 5.2e-07          | 2.4e+00                | 5.0e-02                | 5.2e-01     |
| $ES_{52o2}$ | 0.1  | 0.27     | 1      | 3.0e-02          | 3.4e-01                | 5.0e-02                | 7.1e-01     |
| $ES_{52o3}$ | 0.1  | 0.27     | 1      | 2.4e-01          | 0                      | 5.0e-02                | 1.3e+00     |
| $ES_{62o1}$ | 0.1  | 0.27     | 1      | 1.7e-03          | 2.4e+00                | 5.0e-02                | 5.2e-01     |
| $ES_{62o2}$ | 0.1  | 0.27     | 1      | 3.0e-02          | 4.6e-01                | 5.0e-02                | 6.7e-01     |
| $ES_{62o3}$ | 0.1  | 0.27     | 1      | 2.9e-01          | 0                      | 5.0e-02                | 1.3e+00     |
| $EM_{42o1}$ | 0.1  | 5         | 5.0e-01 | 2.7e-03          | 1.2e+01                | 5.0e-01                | 1.5e-01     |
| $EM_{42o2}$ | 0.1  | 5         | 4.0e-03 | 1.0e+01          | 5.0e-01                | 1.7e-01                |
| $EM_{42o3}$ | 0.1  | 5         | 4.5e-01 | 0               | 5.0e-01                | 1.3e+00                |
| $EM_{52o1}$ | 0.1  | 0.27     | 5      | 4.4e-10          | 1.2e+01                | 5.0e-01                | 1.5e-01     |
| $EM_{52o2}$ | 0.1  | 0.27     | 5      | 4.0e-03          | 5.6e+00                | 5.0e-01                | 1.7e-01     |
| $EM_{52o3}$ | 0.1  | 0.27     | 5      | 4.5e-02          | 1.9e+00                | 5.0e-01                | 2.8e-01     |
| $EM_{62o1}$ | 0.1  | 0.27     | 5      | 4.2e-04          | 1.2e+01                | 5.0e-01                | 1.5e-01     |
| $EM_{62o2}$ | 0.1  | 0.27     | 5      | 4.0e-03          | 4.7e+00                | 5.0e-01                | 1.9e-01     |
| $EL_{42o1}$ | 0.1  | 5         | 7.5e-01 | 5.2e-03          | 1.2e+01                | 7.5e-01                | 4.6e-01     |
| $EL_{42o2}$ | 0.1  | 5         | 2.4e-01 | 0               | 7.5e-01                | 1.1e+00                |
| $EL_{52o1}$ | 0.1  | 0.27     | 5      | 8.8e-10          | 1.2e+01                | 7.5e-01                | 4.6e-01     |
| $EL_{52o2}$ | 0.1  | 0.27     | 5      | 4.0e-03          | 6.9e+00                | 7.5e-01                | 4.7e-01     |
| $EL_{52o3}$ | 0.1  | 0.27     | 5      | 4.5e-02          | 2.2e+00                | 7.5e-01                | 5.6e-01     |
| $EL_{62o1}$ | 0.1  | 0.27     | 5      | 7.8e-4           | 1.2e+01                | 7.5e-01                | 4.6e-01     |
| $EL_{62o2}$ | 0.1  | 0.27     | 5      | 4.0e-03          | 6.0e+00                | 7.5e-01                | 4.8e-01     |

Table 3. Switching times with $G = G_2$, $k_1 = 4$ and $k_2 = 0.25$.

| Example | Structure | $S_{\text{times}}$ | $u_{\text{sin}}$ |
|---------|-----------|--------------------|-----------------|
| $ES_{52o1}$ | $u_{\text{max}}/0$ | 1.4e-01            |                |
| $EM_{52o1}$ | $u_{\text{max}}/0$ | 2.3e+00            |                |
| $EM_{52o2}$ | $u_{\text{max}}/u_{\text{sin}}/0$ | 5.6e-01            | 3.4e-01         |
| $EL_{52o2}$ | $u_{\text{max}}/0$ | 2.9e+00            |                |
| $ES_{52o3}$ | $u_{\text{max}}/u_{\text{sin}}/0$ | 6.8e-01            | 4.0e-01         |
| $EM_{52o3}$ | $u_{\text{max}}/0$ | 1.6e-01            | 9.9e-02         |
| $EM_{62o2}$ | $u_{\text{max}}/u_{\text{sin}}/0$ | 1.0e+00            | 5.6e-01         |
| $EL_{62o2}$ | $u_{\text{max}}/u_{\text{sin}}/0$ | 1.4e+00            | 7.5e-01         |

that the final tumor volumes with a nonzero therapy are bigger than those of the Skipper model (see Table 1), again as expected. The numerical results with the same penalty parameter, $3e - 2$, show that a smaller amount of drug is needed for the $E_{\text{max}}$ model (see sixth columns of both tables); moreover, for these examples we see in Figure 1 a similar behavior in the tumor evolution (with three different ways
of administering the drug). In case of zero therapy, the same sizes are obtained, but for different values of $\hat{\alpha}$.

The rest of the rows in Tables 1 and 2 correspond to examples with an initial tumor volume equal to 50% or 75% of the carrying capacity. Here we only present the zero-therapy example for problem $(\hat{OP}_4)$. In Table 1 we show numerical results obtained with the penalty parameter value associated with $\alpha_1$ and, if $\alpha_1 < \alpha_2$, we also consider the corresponding value to $(\alpha_1 + \alpha_2)/2$. For many of these examples, the final tumor volume is larger or equal than 67.6% of the initial tumor volume even at the maximum infusion rate. On the other hand, in Table 2 numerical results for midsized and large tumors are obtained with a longer therapy time, $T = 5$, to better observe their reduction. Hence, the numerical results associated with the maximum infusion rate therapy satisfy $\int_0^T \bar{u}(t) dt = 1.2e + 01$. Moreover, we show numerical results for the same penalty value $(\hat{\alpha} = 4.0e - 03)$ in these last examples (except for $EL_{42a1}$, where $\hat{\alpha}_1 = 5.2e - 03$ and therefore the results also correspond to $\hat{\alpha} = 4.0e - 03$). For problem $(\hat{OP}_{52})$ we present three examples for each initial volume, as many as different structures of nonzero optimal control the concerned problem has (see also Table 3).

![Figure 1](image1.png)

**Figure 1.** Optimization results for Skipper model on the left (see Table 1) and for the $E_{\text{max}}$ model on the right (see Table 2).

Figure 2 corresponds to the $E_{\text{max}}$ model and shows two plots of the tumor volume at the top and the corresponding optimal controls at the bottom. On the left the graphics correspond to the examples with the same penalty parameter value, $\hat{\alpha} = 4.0e - 3$, and with large initial tumor volume (see Table 2). There are not big differences between the graphics for the tumor volume, but this is not the case for the optimal controls: one of them is related with a constant maximum dosage, another consists in supplying the maximum infusion rate at the beginning.
Figure 2. Some optimization results for $E_{\text{max}}$ model (see Table 2).

followed by a period without medication and the third one consists in starting with a maximum infusion rate and continuing with a maintenance one (the total amount of drug corresponding to this case is half of the first one). Furthermore, on the right of the figure, the plots show the tumor volume and the corresponding optimal controls (all in red) obtained for $(\hat{O}P_5)$ with two different penalty parameter values for a mid-sized initial tumor volume (see Table 2).

Figures 3 and 4 show the evolution of tumor volume corresponding to trivial controls for some examples in Tables 1 and 2. Hence the plot at the top right of both figures shows the tumor volume corresponding to zero-therapy and the other three plots were obtained with maximum dosage for different initial sizes.

Numerical results for the maximum infusion rate therapy can be useful to take decisions about the dosage planning. We are going to quantify the contribution of the control theory in such decisions. With this aim, fixed the amount of drug (or the AUC for the concentration) to be used along the therapy, we consider the maximization of the tumor volume at the final time to find the worst therapy in these conditions. More precisely, we have solved the following problems:

$$(\hat{O}P_{2\text{MAX}}) \left\{ \begin{array}{l} \max_{u \in \hat{U}_{ad}^2} \hat{J}(u) = \exp(x(T)) \\ (118) \end{array} \right.$$  

where $(x,c)$ is the solution of the Cauchy problem (117), the set of admissible controls is given by

$$\hat{U}_{ad}^2 = \{ u \in L^\infty(0,T) : 0 \leq u(t) \leq u_{\max}, \ a.e. \ t \in (0,T), \ \int_0^T u(t)dt = y_{\max} \}.$$  

(119)
Figure 3. Tumor volume with trivial controls for Skipper model (see Table 1).

Figure 4. Tumor volume with trivial controls for $E_{\text{max}}$ model (see Table 2).
with \( y_{\text{max}} = \int_0^T \tilde{u}(t)dt \), \( \tilde{u} \) being a solution of \((\overline{OP}_5)\) for a given \( \hat{\alpha} \), and

\[
(\overline{OP}_{3\text{MAX}}) \quad \max \hat{J}(u) = \exp (x(T)) \quad \text{subject to} \quad u \in \hat{U}_{ad}^3
\]

where again \((x,c)\) is the solution of the Cauchy problem (117),

\[
\hat{U}_{ad}^3 = \{ u \in L^\infty((0,T]) : 0 \leq u(t) \leq u_{\text{max}}, \text{ a.e. } t \in (0,T), \quad \int_0^T c(t)dt = y_{\text{max}} \}
\]

and \( y_{\text{max}} = \int_0^T \hat{c}(t)dt \), with \( \hat{c} \) corresponding to a solution of \((\overline{OP}_6)\) for a given \( \hat{\alpha} \).

Table 4 is devoted to the Skipper model for a midsized initial tumor, meanwhile Tables 5 and 6 are associated with the \( E_{\text{max}} \) model for a small and a midsized tumor, respectively. The first four columns present numerical results obtained by solving problems \((\overline{OP}_5)\) and \((\overline{OP}_6)\) and the rest correspond to maximization problems \((\overline{OP}_{2\text{MAX}})\) and \((\overline{OP}_{3\text{MAX}})\). Tables 4 and 5 show that the final tumor size with the worst dosage planning can be more than twice the size obtained by solving \((\overline{OP}_5)\), using the same total amount of drug; consequently, the form of the drug administration is very important in this case. On the other hand, the final tumor size is the same for \((\overline{OP}_6)\) and \((\overline{OP}_{3\text{MAX}})\) for Skipper model, meanwhile the total used drug corresponding to the maximization problem is bigger than that for \((\overline{OP}_6)\).

| Problem   | \( \hat{\alpha} \) | \( L(T)/L_0 \) | \( \int_0^T \tilde{u}(t)dt \) | Problem   | \( L(T)/L_0 \) | \( \int_0^T \tilde{u}(t)dt \) |
|-----------|---------------------|-----------------|-----------------|-----------|-----------------|-----------------|
| \((\overline{OP}_5)\) | 7.e-2               | 2.3e-01         | 2.9e+00         | \((\overline{OP}_{3\text{MAX}})\) | 6.9e-01         | 2.9e+00         |
| \((\overline{OP}_6)\) | 7.e-2               | 1.3e-01         | 4.7e+00         | \((\overline{OP}_{3\text{MAX}})\) | 1.3e-01         | 4.7e+00         |
| \((\overline{OP}_5)\) | 9.e-2               | 2.8e-01         | 2.6e+00         | \((\overline{OP}_{2\text{MAX}})\) | 7.7e-01         | 2.6e+00         |
| \((\overline{OP}_6)\) | 9.e-2               | 1.9e-01         | 3.8e+00         | \((\overline{OP}_{3\text{MAX}})\) | 1.9e-01         | 4.5e+00         |

In the second rows of Tables 5 and 6, we obtain the same results for both problems, because they are using the maximum infusion rate therapy, \( \tilde{u} \equiv u_{\text{max}} \). For the other cases, it repeats the fact that, using the same or greater amount of drug, the tumor at the final instant increases significantly with respect to the minimizing therapy.

| Problem   | \( \hat{\alpha} \) | \( L(T)/L_0 \) | \( \int_0^T \tilde{u}(t)dt \) | Problem   | \( L(T)/L_0 \) | \( \int_0^T \tilde{u}(t)dt \) |
|-----------|---------------------|-----------------|-----------------|-----------|-----------------|-----------------|
| \((\overline{OP}_5)\) | 1.e-3               | 3.8e-01         | 7.9e+00         | \((\overline{OP}_{2\text{MAX}})\) | 6.7e-01         | 7.9e+00         |
| \((\overline{OP}_6)\) | 1.e-3               | 3.7e-01         | 9.6e+00         | \((\overline{OP}_{3\text{MAX}})\) | 3.7e-01         | 9.6e+00         |
| \((\overline{OP}_5)\) | 5.e-3               | 5.4e-01         | 4.9e+00         | \((\overline{OP}_{2\text{MAX}})\) | 1.5e+00         | 4.9e+00         |
| \((\overline{OP}_6)\) | 5.e-3               | 7.2e-01         | 4.3e+00         | \((\overline{OP}_{3\text{MAX}})\) | 9.3e-01         | 6.8e+00         |
Table 6. Comparison Min, Max therapies with $G = G_2$, $k_1 = 4$, $k_2 = 4$, $\lambda = 0.27$, $\xi = 0.1$, $T = 8$ and $L_0 = 0.5\theta$.

| Problem | $\hat{\alpha}$ | $L(T)/L_0$ | $\int_0^T \bar{u}(t) \, dt$ |
|---------|----------------|-------------|-----------------|
| $(OP_5)$ | 1.6e-3 | 3.6e-01 | 1.9e+01 |
| $(OP_6)$ | 1.6e-3 | 3.6e-01 | 1.9e+01 |

12. Comparison and conclusions. Let us summarize the results that we have obtained along this work. First, we have checked that the solution for the optimal control problems $(OP_1)$–$(OP_3)$ is $\bar{u} \equiv u_{max}$, when it is admissible. Next, we can focus on the most interesting case, when $(H_1)$ holds.

Table 7. Catalog for Skipper model ($G = G_1$) under $(H_1)$

| Problem | Optimal control |
|---------|----------------|
| $(OP_5)$ | $u_{max}/0$ (*) |
| $(OP_6)$ | $u_{max}/0$ |
| $(OP_3)$ | $u_{max}/0$ (*) |

Table 8. Catalog for $E_{max}$ model ($G = G_2$) under $(H_1)$

| Problem | Optimal control |
|---------|----------------|
| $(OP_5)$ | $u_{sin}$ |
| $(OP_2)$ | $u_{max}/0$, $u_{max}/u_{sin}$ |
| $(OP_3)$ | $u_{max}/u_{sin}$ |

Comparing our results with those obtained in [8] (under the log-kill hypothesis), the following remarks are in order:

a) For the Skipper model associated to $(OP_5)$ and $(OP_3)$, we found in [8] that a unique non-trivial configuration appears $(0/u_{max})$, while we have proved here that the total amount of drug is the unique relevant aspect (not the form in which it is administered) and hence, there exists an infinite number of (singular) optimal controls. This is indicated in Table 7 with the asterisk (*), together with one of the possible structures. These qualitative similarities between the cases identifying (and without identifying) the drug infusion rate with its concentration was remarked in [19]. For $(OP_2)$, the optimal control is of type $u_{max}/0$, that also appeared in [8], jointly with $0/u_{max}/0$.

b) For the $E_{max}$ model, we have seen that there are four possible structures for the optimal control, all of them very simple (constant, of bang-bang or bang-singular-bang type, see Table 8), having at most two switching times. Compared with [8], the number of possible configurations have significantly reduced: for instance, for $(OP_2)$ we found eight possibilities in [8], but now there are only two. Moreover, the structures are simpler here (piecewise constant) than in [8], because the singular control is of exponential type there. Finally, there are no optimal controls for the $E_{max}$ model with zero-therapy at the beginning as it was the case sometimes in [8].
As we have highlighted in Remark 6, it is very surprising that the optimal controls in Theorems 3.1, 3.2, 4.1, 4.2, 5.1 and 5.2 do not depend neither on the initial size of the tumor $L_0$ nor on the greatest size of the tumor $\theta$ and remain valid (with the same proofs) for any other model similar to (1), such as the logistic model. This makes us think that the formulation of problems $(OP_1) - (OP_3)$ (with the toxicity integral constraint) is not adequate in this framework. Consequently, we have studied some other closely related optimal control problems $(OP_4) - (OP_6)$, where the integral term for the accumulated drug effect is penalized.

Depending on the value of the penalty parameter $\alpha$, the results of Theorems 8.1, 8.2, 9.1, 9.2, 10.1 and 10.2 can be summarized as follows:

a) For small values of $\alpha$, the unique optimal control is the maximum infusion rate therapy $\bar{u} \equiv u_{\text{max}}$. In practical terms, this could happen for instance, for low cost treatments or if the patient is in good physical condition.

b) For very large values of $\alpha$, the unique optimal control is the zero-therapy. This could be the case in the opposite situations to those mentioned in the previous paragraph, i.e. when the treatment is very expensive or the patient is very weak physically.

c) For intermediate values of $\alpha$, the number of optimal controls can be one, two or infinite. In the first cases, we have determined explicitly the optimal control in terms of the problem data, showing again that it has a simple piecewise constant structure with the maximum loading infusion rate at the beginning of the treatment (“dose-dense chemotherapy”) and the possible appearance of a constant maintenance infusion rate in some cases, for instance, for $(OP_6)$ with $E_{\text{max}}$ model (from our point of view the most realistic problem among the studied ones). As far as we know, this last fact has not been reported previously in this context. On the other hand, we have characterized the problems with an infinite number of optimal controls, showing that they can be transformed into an equivalent finite-dimensional optimization problem.

In the future, we would like to analyze several generalizations and extensions of the problems considered here from the mathematical point of view, including relevant factors such as drug resistance and the anti-angiogenesis effect, see [7], [11] and [19], among others. Both theoretical and numerical results would be very useful for clinical purposes.

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