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Optimal control problems for differential equations applied to tumor growth: state of the art.

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## Abstract

In this manuscript, we shall apply the tools and methods from optimal control to analyze various minimally parameterized models that describe the dynamics of populations of cancer cells and elements of the tumor microenvironment under different anticancer therapies. In spite of their simplicity, the analysis of these models that capture the essence of the underlying biology sheds light on more general scenarios and, in many cases, leads to conclusions that confirm experimental studies and clinical data. We focus on four applications: optimal control applied to compartmental models, brain tumors, drug resistance and antiangiogenic treatment.

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## 1 Introduction

In this paper, we shall focus on topics where methods from optimal control theory will be applied to biomedical problems arising from cancer treatments. Specifically, we will focus on optimal control problems for systems of differential equations. Optimal control for partial differential equations, stochastic differential equations, discrete difference equations and so on are not considered in this document.

There exists a vast literature in which optimal control methods are applied to cancer treatment. The early literature on applications of optimal control to cancer treatment is almost exclusively on cancer chemotherapy (see references [14, 32, 45]). Much of this work is on cell-cycle nonspecific mathematical models and focusing on different growth models [32]. The monograph [31] by Martin and Teo is entirely devoted to such models, but including increasingly more comprehensive medical conditions such as single and multi-drug resistance.

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Later, a greater emphasis in research has been put on cell-cycle specific models. In reference [10], the authors considered phase-specific administration of cytotoxic agents to increase the selectivity of therapy. Reference [46] models the proliferation cycle of leukemia. Eisen [14] also gives some introductory discussion of cell-cycle specific chemotherapy and compartmental models (distinguishing between proliferating and quiescent cells), but mostly in the context of pharmacokinetics and clearly the emphasis is more on modeling than on analysis.

After that, a great effort was done to study the development and analysis of compartmental models which describe and analyze the actions of drugs on specific compartments from a control theory point of view [49–51]. In these models, the emphasis is on the cancerous cells and side effects are only measured indirectly through the total dose of drugs administered.

Thus, from the mathematical point of view, the modeling of chemotherapy for cancer using the optimal control theory has 40 years of history. Different frameworks have been considered in the literature, depending on the study approach, from macroscopic levels [45] to microscopic levels [25,26], including systems of differential equations (v. [9,11,16,40] and their references) and equations in partial derivatives (v. [45] and their references). Normally, the control variable represents the dose of the drug and the state variables represent the tumor cells. In general, the main objective is to determine the optimal application of the drugs that minimizes the number of tumor cells at the end of treatment, while maintaining the toxic effects of the drug at an acceptable level. To reduce the toxicity of the anticancer drug, which also affects normal cells, it is customary to add some control restrictions, isoperimetric or state. There are different types of restrictions depending on the assumptions of the model, mainly punctual or integral. For example, a maximum rate is prescribed at which the chemotherapeutic drug is administered at each time or a limit is imposed on the total dose of the drug in the therapy interval (see [9,12,27]).

On the other hand, mathematical modeling of tumor growth in general is very important when it comes to having a model that fits the biology of the problem [35]. There are many mathematical models that deal with the different aspects of the growth of a tumor. They use ordinary differential equations [2,6,13,54], partial differential equations [1,3,34], stochastic processes [38], game theory [52], etc.

In this review, we focus on 4 applications of the control theory to the growth of tumors:

1. The first is referred to the application of the theory of optimal control to compartmental models.
2. The second deals with the theory of optimal control of brain tumors.
3. The third deals with a topic that is becoming more and more important: the resistance in tumors to different treatments and, therefore, to optimize such kind of treatments.
4. The latest studies the application of optimal control to antiangiogenic and chemotherapeutic treatments.

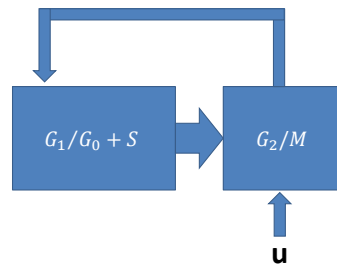
Section 2 shows several compartmental models, which have been useful in the understanding of the application of optimal control theory to the growth of tumors.

Another topic of great importance is the study of the administration of chemotherapy in brain tumors [6,20,37]. Thus, in this review we study a model developed in the reference [40] based on a work by Ribba [37]. This revision can be found in Section 3.

Next topic is the drug administration in presence of multi-drug resistance cells. There exists a vast literature on optimal administration of chemotherapeutic drugs in the presence of drug resistance [7,8,18,26,33]. A model of sensitive and resistant cells to the treatment can be found in Section 4.

Optimal control is useful as a methodology in response to mathematical models for novel cancer treatments as anti-angiogenic treatments [27,39]. A mathematical model with anti-angiogenic and chemotherapeutic treatment can be found in Section 5.

Finally, the review ends with some Conclusions in Section 6.



**Fig. 1** A 2-compartment model with  $G_2/M$ -specific cytotoxic agent.

## 2 Cell-cycle specific cancer chemotherapy

In this section, we analyze a set of differential equations for a class of cell-cycle specific compartmental models for cancer chemotherapy.

Each cell goes through a sequence of phases from birth to cell division:  $G_1 \rightarrow G_0 \rightarrow S \rightarrow G_2 \rightarrow M$ . While the simplest mathematical models for the treatment of cancer with chemotherapy, applying the theory of optimal control, treat the complete cycle as a compartment, the multicompartmental models group the phases of the cell cycle with the purpose of representing the action of the different types of chemotherapeutic agents used. Cytotoxic agents generally act in the phase  $G_2/M$  because the cell walls become thin and porous in mitosis  $M$  and, therefore, the cell is more vulnerable to attack. The cytostatic agents aim to synchronize the transitions of cells through the cell cycle causing a brief and invisible inhibition of the DNA synthesis in the  $S$  phase and the retention of the cells in the  $G_1$  phase. Recruitment agents cause the cells to leave the inactive  $G_0$  compartment where they are not vulnerable to attacks by any chemotherapeutic drug. This classification is general, being able to find agents that have more than one effect depending on their concentration [43]. Depending on the specific type of tumor that is considered, and the drugs that are administered, an appropriate grouping of the phases of the cell cycle is carried out.

### 2.1 A 2-compartment model with a cytotoxic agent

This model deals with the application of a single cytotoxic agent that is activated in the  $G_2/M$  phase of the cell cycle. Taking into account the sensitivity of the drug to the phase, the cell cycle is divided into two compartments, one combining the second growth phase  $G_2$  and the mitosis  $M$  and the other formed by the rest of the phases. The state of the system is described by a two-dimensional vector where  $N_1(t)$  represents the mean number of cancer cells in the first compartment at time  $t$  (composed of the phases  $G_0, G_1$  and  $S$ ) and  $N_2(t)$  the average number of carcinogenic cells in the second compartment at time  $t$  (composed of  $G_2$  and  $M$ ). The equation for the second compartment has the form

$$\dot{N}_2(t) = -a_2N_2(t) + a_1N_1(t) \tag{1}$$

where  $a_i > 0$  is the average inverse transit time through the  $i$ -th compartment. The equation for the first compartment becomes

$$\dot{N}_1(t) = -a_1N_1(t) + 2a_2N_2(t). \tag{2}$$

In matrix form, the system given by the equations (1) and (2) can be expressed as  $\dot{N} = AN$  where  $N = (N_1, N_2)^T$  and  $A \in \mathbb{R}^{2 \times 2}$  with

$$A = \begin{pmatrix} -a_1 & 2a_2 \\ a_1 & -a_2 \end{pmatrix}.$$

Now, we consider a cytotoxic agent whose concentration in blood is represented by the function  $u$  acting in the  $G_2/M$  phase. It is assumed that all cells are sensitive to treatment (homogeneous population). According to

the log-kill hypothesis, it is assumed that the concentration of the drug  $u(t)$  kills a fraction of the output flow  $a_2N_2(t)$  of cells of the  $G_2/M$  compartment and, therefore, the number of cells dead is given by  $\phi u(t)a_2N_2(t)$ ,  $\phi$  being a parameter of constant chemotherapeutic death. The control set is a compact interval  $[0, u_{\max}]$ , with  $u_{\max}$  the maximum dose rate or the maximum concentration. In the model, the  $u$  control always appears together with the constant  $\phi$  and so, in order to keep the number of free parameters as low as possible, it is combined with the maximum dose rate in an amount represented as  $u_{\max}$  under the assumption that  $u_{\max} \leq 1$ . If the concentration is high enough, then really  $u_{\max} = 1$  is realistic: almost all the cancer cells in that compartment can be killed. The cells that die in  $G_2/M$  leave this compartment, that is, they are counted as outputs from the second compartment, but they no longer enter the first compartment. In this sense, it is considered to kill the cell even if apoptosis is not induced. The remaining fraction  $(1 - u)a_2N_2$  suffers cell division and therefore the controlled mathematical model becomes

$$\dot{N}_1(t) = -a_1N_1(t) + 2(1 - u)a_2N_2(t), \quad N_1(0) = N_{10}, \tag{3}$$

$$\dot{N}_2(t) = a_1N_1(t) - a_2N_2(t), \quad N_2(0) = N_{20}. \tag{4}$$

The matrix expression for the system has the form [41]

$$\dot{N}(t) = (A + uB)N(t), \quad N(0) = N_0, \tag{5}$$

where  $A$  and  $B$  are

$$A = \begin{pmatrix} -a_1 & 2a_2 \\ a_1 & -a_2 \end{pmatrix}, \quad B = \begin{pmatrix} 0 & -2a_2 \\ 0 & 0 \end{pmatrix}. \tag{6}$$

Consider now as a functional objective

$$J = rN(T) + \int_0^T qN(t) + su(t)dt \rightarrow \min \tag{7}$$

where  $T$  is the final fixed time,  $r = (r_1, r_2)$  is a positive vector of weights and  $q = (q_1, q_2)$  is a vector row of weights not negative. The penalty term  $rN(T) = r_1N_1(T) + r_2N_2(T)$  represents an average weight of the total number of cancer cells at the end of treatment and the term  $qN(t) = q_1N_1(t) + q_2N_2(t)$  measures the volume of the tumor during treatment. Side effects of the treatment are only indirectly included in the model through the minimization of the total dose,  $\int_0^T u(t)dt$ . The positive coefficient  $s$  in this integral is redundant since it could be absorbed by the other weights. Recall that the number of cancer cells that do not undergo cell division at time  $t$  and that are consider eliminated is given by  $u(t)a_2N_2$ , that is,  $u(t)$  is proportional to the fraction of inefficient divisions. Since the drug kills healthy cells at a similar rate, the integral  $\int_0^T u(t)dt$  represents the cumulative negative effects of the treatment on the normal tissue or its toxicity. The aim is to minimize tumor volume in both compartments at the end of treatment, but taking into account the tumor volume in both compartments during treatment, while minimizing side effects. Thus, the following optimal control problem arises:

**Problem 1.** For a fixed time  $T > 0$ , minimize  $J$  subject to the system of equations

$$\dot{N}(t) = (A + uB)N(t), \quad N(0) = N_0, \tag{8}$$

for all measurable functions Lebesgue (respectively, piecewise continuous)  $u : [0, T] \rightarrow [0, u_{\max}]$  with  $A$  and  $B$  given by equation (6), [41, 47].

The necessary conditions for optimality for Problem 1 are given by the Pontryagin maximum principle [28, 36, 42]. The main necessary conditions for optimality is the statement that optimal controls minimize (respectively, maximize) the Hamiltonian function

$$H = H(\lambda, N, u) = qN + su + \lambda(A + uB)N, \tag{9}$$

over the control set  $[0, u_{\max}]$  pointwise along the optimal controlled trajectory  $(N_*, u_*)$  and the multipliers  $\lambda$ . The conditions of the Pontryagin maximum principle for our optimal control problem are

**Theorem 1.** *If  $u_*$  is an optimal control with corresponding trajectory  $N_*$  then there exist a continuous function  $\lambda : [0, T] \rightarrow (\mathbb{R}^2)^*$  called the adjoint function, such the following conditions are satisfied:*

1. *Nontriviality:  $\lambda(t) \neq 0$  for all  $t \in [0, T]$ .*
2. *Adjoint equations and transversality conditions: the multiplier  $\lambda$  is a solution to the terminal value problem*

$$\dot{\lambda} = -\frac{\partial H}{\partial N}(\lambda, N_*, u_*) = -q - \lambda(A + u_*B), \quad \lambda(T) = r, \tag{10}$$

*i.e.,*

$$\begin{aligned} \dot{\lambda}_1 &= -q_1 + \lambda_1 a_1 - \lambda_2 a_1, & \lambda_1(T) &= r_1, \\ \dot{\lambda}_2 &= -q_2 - 2(1 - u_*)\lambda_1 a_2 + \lambda_2 a_2, & \lambda_2(T) &= r_2. \end{aligned}$$

3. *Minimum condition: the optimal control minimizes the Hamiltonian  $H$  pointwise over the control set  $[0, u_{max}]$  along the optimal controlled trajectory and the multiplier  $\lambda(t)$ , i.e.,*

$$H(\lambda(t), N_*(t), u_*(t)) = \min_{u \in [0, u_{max}]} H(\lambda(t), N_*(t), u(t)), \tag{11}$$

*and the minimum value is constant over the interval  $[0, T]$ ,*

$$H(\lambda(t), N_*(t), u_*(t)) = \text{const}. \tag{12}$$

The switching function  $\Phi$  for this problem is

$$\Phi(t) = \frac{\partial H}{\partial u} = s + \lambda(t)BN_*(t). \tag{13}$$

Then, the optimal controls are given by

$$u_*(t) = \begin{cases} u_{max} & \text{if } \Phi(t) < 0, \\ u_{sing} & \text{if } \Phi(t) = 0, \\ 0 & \text{if } \Phi(t) > 0. \end{cases} \tag{14}$$

For control-affine problems as is our case, the best candidates for optimal controls turn out to be finite concatenations of bang and singular control. The precise concatenation sequences need to be determined through an analysis of the switching function. Then, it is straightforward, although somewhat complicated and tedious, to calculate the singular control [22]. It is given by

$$u_{sing} = 1 - \frac{a_1 s}{2a_2} - q_1 N_1(t) + \frac{1}{2a_1} (a_1 q_2 + a_2 q_1) N_2(t). \tag{15}$$

However, singular controls are not necessarily minimizing, but they can also be maximizing. Now, if we use the Legendre-Clebsch condition, a higher-order necessary condition for optimality of singular controls [42], allows us to distinguish between these two classes. For the case of a minimizing control  $u$ , the Legendre-Clebsch condition states that

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u}(\lambda(t), N_*(t), u_*(t)) \leq 0, \quad \forall t \in I. \tag{16}$$

In our problem, such Legendre-Clebsch condition becomes

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u}(\lambda(t), N_*(t), u_*(t)) = 4a_1 a_2 s > 0. \tag{17}$$

Hence, the Legendre-Clebsch condition for minimality of a singular control is violated. Thus, singular controls are locally maximizing for this problem. This brings us to the next result

**Table 1** Numerical values for the coefficients and parameters used in numerical computations for the optimal control problem 1, extracted from [41].

Coefficient	Interpretation	Numerical value
$a_1$	Inverse transit time through $G_0/G_1 + S$	0.197
$a_2$	Inverse transit time through $G_2/M$	0.356
$N_{10}$	Initial condition for $N_1$	0.7012
$N_{20}$	Initial condition for $N_2$	0.2988
$u_{max}$	Maximum dose rate/concentration effectiveness of the drug	0.90
$s$	Penalty/weight for the total dose of cytotoxic agent	0.50
$q_1$	Penalty/weight in the objective for the average number of cancer cells in $G_0/G_1 + S$ during therapy	0.10
$q_2$	Penalty/weight in the objective for the average number of cancer cells in $G_2/M$ during therapy	0.10
$r_1$	Penalty/weight in the objective for the average number of cancer cells in $G_0/G_1 + S$ at the end of therapy	3
$r_2$	Penalty/weight in the objective for the average number of cancer cells in $G_2/M$ at the end of therapy	3
$T$	Therapy horizon	$T = 7, 21, 60$

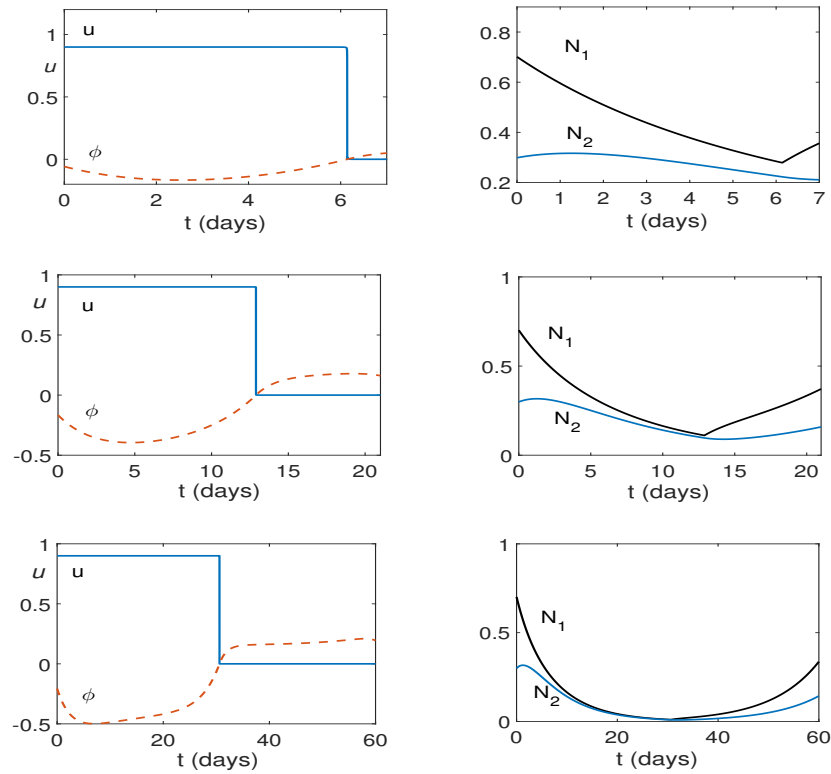
**Theorem 2.** *If  $(N_*, u_*)$  is an optimal controlled trajectory for problem 1, then there does not exist an interval on which the control  $u_*$  is singular.*

We show some examples of extremal bang-bang controls that have been computed using the values in Table 1, which are shown in Figure 2.

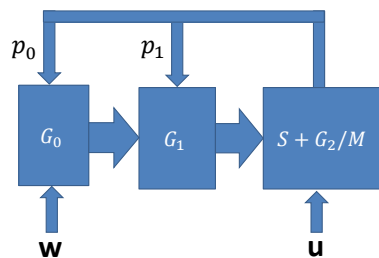
## 2.2 A 3– compartment model with a cytotoxic and recruiting agent

This model was originally formulated by Swierniak et al. [47], where a cytotoxic agent, which can act in  $S$  or  $G_2/M$  phases, is combined with a recruitment agent, which attracts inactive cells in the  $G_0$  compartment to re-enter the active cell cycle and thus be attacked by the cytotoxic agent. One of the biggest problems in the chemotherapeutic treatment of some leukemias is a large residue of inactive cells in the  $G_0$  phase, which are not sensitive to most of the cytotoxic agents. This problem has also been reported in breast and ovarian cancer. In this model, three compartments are considered:  $G_0$ ,  $G_1$  and  $S + G_2/M$ . The state space is thus the first orthant  $P$  in  $\mathbb{R}^3$ . The variables  $N_0$ ,  $N_1$  and  $N_2$  represent the states. The newborn cells initiate the process of cell division, but they can remain dormant and remain in the quiescent stage  $G_0$ . Let  $p_0$  and  $p_1$  be positive numbers, with  $p_0 + p_1 = 1$ , representing the probabilities that the daughter cells will pass through the first growth phase without obstacles ( $p_1$ ) or fall into the state of quiescence ( $p_0$ ). A recruiting agent is applied to reduce the average transit time through the  $G_0$  compartment, resulting in a higher outflow from  $G_0$ . If  $w$  represents the concentration of the recruitment agent, it is assumed that the outflow is increased by a factor of  $1 + w$ ,  $0 \leq w \leq w_{max}$ , where  $w = 0$  represents that no drug is being applied and  $w_{max}$  corresponds to a full dose treatment. A cytotoxic agent  $u$ ,  $0 \leq u \leq u_{max}$ , is applied in the third compartment, where  $u_{max}$  corresponds to the maximum dose (see Figure 3). The combination of these drugs with the standard characteristics of cell division and cell death (and under the log-kill hypothesis), results in a bilinear control system, of the form

$$\dot{N}(t) = (A + uB_1 + wB_2)N(t), \quad N(0) = N_0, \quad (18)$$



**Fig. 2** Examples of locally optimal controls (left) and their corresponding trajectories (right) for  $T = 7$  (top),  $T = 21$  (middle) and  $T = 60$  (bottom) for the parameter values given in Table 1.



**Fig. 3** A 3-compartment model with cytotoxic and recruiting agent.

where the matrices  $A, B_1, B_2$  are

$$A = \begin{pmatrix} -a_0 & 0 & 2p_0a_2 \\ a_0 & -a_1 & 2p_1a_2 \\ 0 & a_1 & -a_2 \end{pmatrix}, \quad B_1 = \begin{pmatrix} 0 & 0 & -2p_0a_2 \\ 0 & 0 & -2p_1a_2 \\ 0 & 0 & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} -a_0 & 0 & 0 \\ a_0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}. \tag{19}$$

As in the 2– compartment model considered earlier, the  $a_i$  are positive coefficients related to the inverse transit times of the cancer cells through the compartments.

Thus, we consider the following optimal control problem:

**Problem 2.** For a fixed therapy horizon  $[0, T]$ , minimize the objective

$$J = rN(T) + \int_0^T qN(t) + s_1u(t) + s_2w(t)dt$$

over all Lebesgue-measurable (respectively, piecewise continuous) functions  $(u, w) : [0, T] \rightarrow [0, u_{max}] \times [0, w_{max}]$ ,  $u_{max} \neq \frac{1}{2}$ , subject to equations [47]

$$\dot{N}(t) = \begin{pmatrix} -(1+w)a_0 & 0 & 2p_0(1-u)a_2 \\ (1+w)a_0 & -a_1 & 2p_1(1-u)a_2 \\ 0 & a_1 & -a_2 \end{pmatrix} N(t), \quad N(0) = N_0.$$

Using the Pontryagin maximum principle, the adjoint equation is given by

$$\dot{\lambda} = -\lambda(A + uB_1 + wB_2) - q, \quad \lambda(T) = r,$$

which, in terms of its components can be written as,

$$\dot{\lambda}_0 = (1+w)a_0(\lambda_0 - \lambda_1) - q_0, \quad \lambda_0(T) = r_0, \tag{20}$$

$$\dot{\lambda}_1 = a_1(\lambda_1 - \lambda_2) - q_1, \quad \lambda_1(T) = r_1, \tag{21}$$

$$\dot{\lambda}_2 = -2a_2(1-u)(p_0\lambda_0 + p_1\lambda_1) + a_2\lambda_2 - q_2, \quad \lambda_2(T) = r_2. \tag{22}$$

The switching functions for the controls  $u$  and  $w$  are, respectively

$$\Phi_1(t) = s_1 + \lambda(t)B_1N(t) = s_1 - 2a_2\{p_0\lambda_0(t) + p_1\lambda_1(t)\}N_2(t), \tag{23}$$

$$\Phi_2(t) = s_2 + \lambda(t)B_2N(t) = s_2 - a_0\{\lambda_0(t) - \lambda_1(t)\}N_0(t). \tag{24}$$

The following theorem shows that the optimal control for the cytotoxic agent  $u$  can not be singular:

**Theorem 3.** Suppose  $(N_*, u_*, w_*)$  is an optimal controlled trajectory for problem 2. Then there does not exist an interval on which the control  $u_*$  is singular, i.e., the cytotoxic agent is not given at partial dose rates/concentrations.

The proof of this theorem can be found in [47].

The following theorem establishes what the behavior of the recruiting agent  $w$  should be:

**Theorem 4.** Let  $(N_*, u_*, w_*)$  be an optimal controlled trajectory for problem 2. If the weight  $s_2$  in the Lagrangian for the recruiting agent  $w$  is zero,  $s_2 = 0$  then there does not exist an interval on which the control  $w_*$  is singular. However, if this coefficient is positive,  $s_2 > 0$ , then the Legendre-Clebsch condition for optimality of a singular control  $w$  is satisfied.

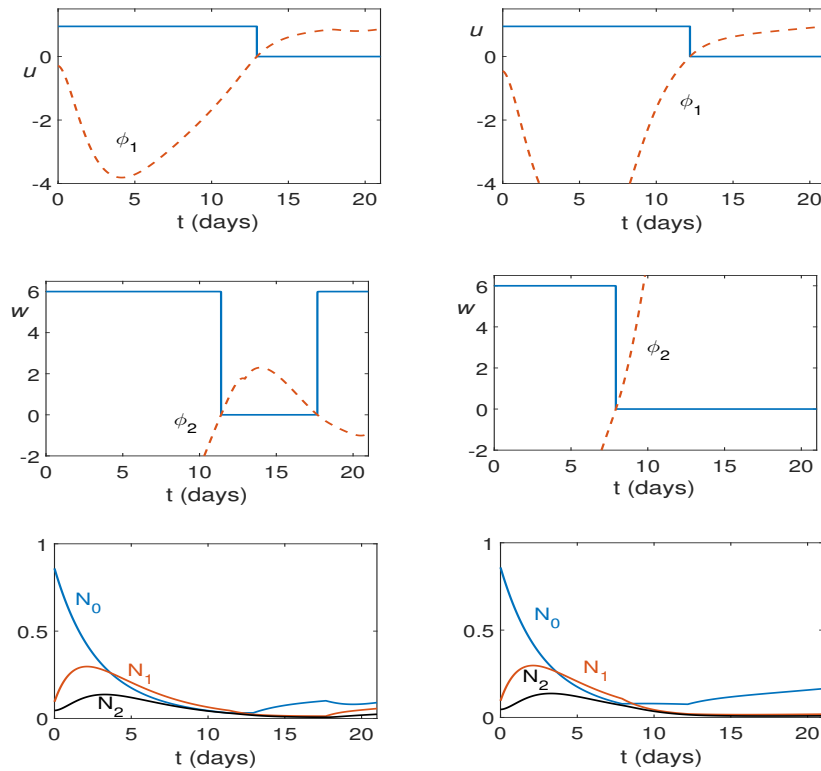
The proof of this theorem can be found again in [47].

For small positive weights  $s_2$ , and this is the important case for this model, bang-bang controls are optimal. Figure 4 shows the graphs of such controls  $u$  and  $w$  and their corresponding trajectories when the weight  $s_2$  in the Lagrangian is chosen as  $s_2 = 0$  and  $s_2 = 0.1$  for parameter values specified in Table 2.

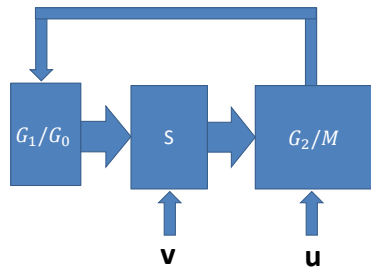


**Table 2** Numerical values for the coefficients and parameters used in numerical computations for the optimal control problem 2 with cytotoxic and recruitment agents, extracted from [41].

Coefficient	Interpretation	Numerical value
$a_0$	Inverse transit time through $G_0$	0.05
$a_1$	Inverse transit time through $G_1$	0.5
$a_2$	Inverse transit time through $S + G_2/M$	1
$p_0$	Probability that cells enter $G_0$	0.9
$p_1 = 1 - p_0$	Probability that cells enter $G_1$	0.1
$N_0(0)$	Initial condition for $N_0$	0.8589
$N_1(0)$	Initial condition for $N_1$	0.0954
$N_2(0)$	Initial condition for $N_2$	0.0456
$u_{max}$	Maximum dose rate/concentration effectiveness	0.95
$w_{max}$	Maximum dose rate/concentration effectiveness	6
$s_1$	Penalty/weight at the cytotoxic agent	1
$s_2$	Penalty/weight at the recruiting agent	0, 0.1
$q_0$	Penalty/weight in the objective for the average number of cancer cells in $G_0$ during therapy	3
$q_1$	Penalty/weight in the objective for the average number of cancer cells in $G_1$ during therapy	1
$q_2$	Penalty/weight in the objective for the average number of cancer cells in $S + G_2/M$ during therapy	1
$r_0$	Penalty/weight in the objective for the average number of cancer cells in $G_0$ at the end of therapy	3
$r_1$	Penalty/weight in the objective for the average number of cancer cells in $G_1$ at the end of therapy	1
$r_2$	Penalty/weight in the objective for the average number of cancer cells in $S + G_2/M$ at the end of therapy	1
$T$	Therapy horizon	$T = 21$



**Fig. 4** Examples of locally optimal controls  $u$  (citotoxic agent, top),  $w$  (recruiting agent, middle) and their corresponding trajectories (bottom) for weights  $s_2 = 0$  (left) and  $s_2 = 0.1$  (right). The parameter values are given in Table 2.



**Fig. 5** A 3-compartment model with cytostatic agent  $v$  and cytotoxic agent  $u$ .

**2.3 A 3– compartment model with a cytotoxic and blocking agent**

In this model the combination of two drugs is considered: a cytotoxic agent  $u$ , which is responsible for killing tumor cells and acts in the  $G_2/M$  phase, and a blocking agent  $v$  (cytostatic), which slows the development of tumor cells in the  $S$  phase, preventing them from passing into the cell division phase [48]. Therefore, three compartments are considered: the first formed by the phases  $G_0$  and  $G_1$ , the second by the  $S$  phase and the third is formed by the phases  $G_2$  and  $M$ . The space of states is the first orthant  $P$  in  $\mathbb{R}^3$ , being  $N_i(t)$ ,  $i = 1, 2, 3$ , the number of cancer cells in the  $i$ -th compartment at time  $t$ .

As a result, the flow of tumor cells from the second compartment to the third is reduced by a factor given by  $v(t)$ , from a value of  $a_2 N_2(t)$  to  $(1 - v(t)) a_2 N_2(t)$ , where  $0 \leq v(t) \leq v_{\max} < 1$ . The value  $v(t) = 0$  represents that the treatment is not being applied, while  $v_{\max}$  represents a complete dose. The control  $u$  represents the

dose of cytotoxic agent administered with  $u = 0$  indicating the absence of treatment and  $u = 1$  the maximum dose (see Figure 5). Under all assumed conditions for the previous compartmental models (homogenous tumor population, constituted by cells sensitive to therapy and under the log-kill hypothesis), we get back to a bilinear system again of the form (18), but now the matrices involved have the form

$$A = \begin{pmatrix} -a_1 & 0 & 2a_3 \\ a_1 & -a_2 & 0 \\ 0 & a_2 & -a_3 \end{pmatrix}, \quad B_1 = \begin{pmatrix} 0 & 0 & -2a_3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & a_2 & 0 \\ 0 & -a_2 & 0 \end{pmatrix}.$$

We thus have the following optimal control problem

**Problem 3.** For a fixed therapy horizon  $[0, T]$ , minimize the objective

$$J = rN(T) + \int_0^T qN(t) + s_1u(t) + s_2v(t)dt \rightarrow \min$$

over all Lebesgue-measurable (respectively piecewise continuous) functions  $(u, v) : [0, T] \rightarrow [0, u_{max}] \times [0, v_{max}]$  subject to the dynamics

$$\dot{N}(t) = \begin{pmatrix} -a_1 & 0 & 2(1-u)a_3 \\ a_1 & -(1-v)a_2 & 0 \\ 0 & (1-v)a_2 & -a_3 \end{pmatrix} N(t), \quad N(0) = N_0.$$

We again write out the fundamental necessary condition for optimality for this system. In terms of components, the adjoint equations read as

$$\begin{aligned} \dot{\lambda}_1 &= a_1(\lambda_1 - \lambda_2) - q_1, & \lambda_1(T) &= r_1, \\ \dot{\lambda}_2 &= (1-v)a_2(\lambda_2 - \lambda_3) - q_2, & \lambda_2(T) &= r_2, \\ \dot{\lambda}_3 &= a_3(\lambda_3 - 2(1-u)\lambda_1) - q_3, & \lambda_3(T) &= r_3, \end{aligned}$$

and the switching functions for the controls  $u$  and  $v$  are given by

$$\Phi_1(t) = s_1 - 2a_3\lambda_1(t)N_3(t),$$

and

$$\Phi_2(t) = s_2 + a_2\{\lambda_2(t) - \lambda_3(t)\}N_2(t),$$

respectively. Once again, we analyze the optimality properties of singular controls, starting with the cytostatic agent [47].

**Theorem 5.** If  $(N_*, u_*, v_*)$  is an optimal controlled trajectory for problem 3, then there does not exist an interval on which the control  $v_*$  is singular.

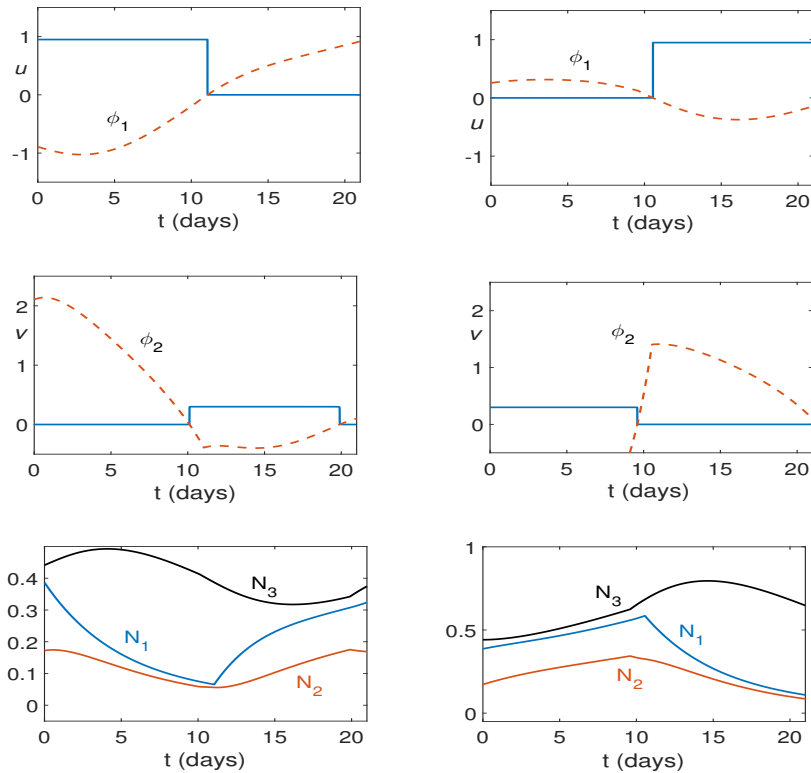
For this model we can no longer assert in general that the cytotoxic agent  $u$  can not be singular, but need to impose an inequality relation on the inverse transit times in the cell cycle and the maximum reduction  $v_{max}$  that the cytostatic agent can achieve.

**Theorem 6.** Suppose that

$$a_1 + a_2(1 - v_{max}) - 2a_3 \geq 0. \tag{25}$$

If  $(N_*, u_*, v_*)$  is an optimal controlled trajectory for problem 3, there also does not exist an interval on which the control  $u_*$  is singular.

We close this section with some numerical experiments of locally optimal controls for problem 3. The parameter values are given in Table 3 and condition (25) is satisfied. Figure 6 shows two different scenarios.



**Fig. 6** Examples of locally optimal controls  $u$  (cytotoxic agent) (top),  $v$  (cytostatic agent) (middle) and their corresponding trajectories (bottom) for different weights  $r = (1, 1, 1)$  and  $q = (1, 1, 1)$  on the left and  $r = (8.25, 8.25, 8.25)$  and  $q = (0.1, 0.1, 0.1)$  on the right. The parameter values are given in Table 3.

### 3 Low grade glioma and chemotherapy

In this section, we consider a low grade glioma (LGG), which is a term denoting a set of primary progressive brain tumor of astrocytic or oligodendroglial origin characterized by slow and continuous growth preceding the anaplastic transformation [30]. Such model was considered by Ribba and coloborators [37] and assumes that a LGG is composed of proliferative  $P$  and nonproliferative quiescent tissue  $Q$ . The chemotherapy treatment  $u(t)$  eliminates proliferative cells and the quiescent cells are also affected by the treatment and become damaged quiescent cells  $Q_p$ . Damaged quiescent cells, when re-entering the cell cycle, be able to repair their DNA and become proliferative once again or can die because of unrepaired damages. For simplicity, here it is assumed that the dosage, the concentration and the effect of the drug are equal. Thus, it is assumed that the drug kills a proportion of  $u$  of proliferating cells,  $\gamma u P$ , and damages a proportion of  $u$  of quiescent cells,  $\gamma u Q$ . Therefore, the system of differential equations that describes the proliferative, non-proliferative and damaged cells and the effect of chemotherapy on these populations is given by [40]

$$\frac{dP}{dt} = c_p P \left(1 - \frac{N}{K}\right) + c_{QP} Q_p - c_{PQ} P - \gamma P u, \quad P(0) = P_0, \tag{26}$$

$$\frac{dQ}{dt} = c_{PQ} P - \gamma Q u, \quad Q(0) = Q_0, \tag{27}$$

$$\frac{dQ_p}{dt} = \gamma Q u - c_{QP} Q_p - \delta_{QP} Q_p, \quad Q_p(0) = 0, \tag{28}$$

**Table 3** Numerical values for the coefficients and parameters used in computations for the optimal control problem 3 with cytostatic and cytotoxic agents, extracted from [41].

Coefficient	Interpretation	Numerical value
$a_1$	Inverse transit time through $G_1/G_0$	0.197
$a_2$	Inverse transit time through $S$	0.395
$a_3$	Inverse transit time through $G_2/M$	0.107
$N_1(0)$	Initial condition for $N_1$	0.3866
$N_2(0)$	Initial condition for $N_2$	0.1722
$N_3(0)$	Initial condition for $N_3$	0.4412
$u_{max}$	Maximum dosage/concentration/effectiveness of cytotoxic agent	0.95
$v_{max}$	Maximum blocking effect of cytostatic agent	0.30
$s_1$	Penalty/weight at the cytotoxic agent	1
$s_2$	Penalty/weight at the cytostatic agent	0.01
$q_1$	Penalty/weight in the objective for the average number of cancer cells in $G_1/G_0$ during therapy	1, resp. 0.1
$q_2$	Penalty/weight in the objective for the average number of cancer cells in $S$ during therapy	1, resp. 0.1
$q_3$	Penalty/weight in the objective for the average number of cancer cells in $G_2/M$ during therapy	1, resp. 0.1
$r_1$	Penalty/weight in the objective for the average number of cancer cells in $G_1/G_0$ at the end of therapy	1, resp. 8.25
$r_2$	Penalty/weight in the objective for the average number of cancer cells in $S$ at the end of therapy	1, resp. 8.25
$r_3$	Penalty/weight in the objective for the average number of cancer cells in $G_2/M$ at the end of therapy	1, resp. 8.25
$T$	Therapy horizon	$T = 21$

where  $N = P + Q + Q_p$  is the total number of cells and  $P, Q, Q_p \geq 0$ . Consider now the following functional objective

$$J_w(u) = (1 - w)(P(T) + Q(T)) + w \int_0^T (P(t) + Q(t))dt, \quad w \in [0, 1], \tag{29}$$

where  $w$  is a weight parameter. We obtain two different functionals with biological relevance for  $w = 0$  and  $w = 1$ . Thus, for  $w = 0$  we obtain a functional in the form of Mayer that focuses on the tumor cells at the end of the treatment,

$$J_0(u) = P(T) + Q(T),$$

while for  $w = 1$  we obtain a functional in the form of Lagrange that takes into account the tumor cells throughout the dynamic process:

$$J_1(u) = \int_0^T P(t) + Q(t)dt.$$

In addition, we introduce a restriction for additional control by imposing a limit on the total dose of the drug:

$$\int_0^T u(t)dt \leq M. \tag{30}$$

Thus, we have the following optimal control problem:

**Problem 4.** For a fixed time  $T > 0$ , minimize  $J_w(u)$  subject to the system of equations (26) for all measurable functions Lebesgue (respectively, piecewise continuous)  $u : [0, T] \rightarrow [0, u_{max}]$  and satisfying the constraint (30).

First of all, existence of optimal controls are proved:

**Theorem 7.** Suppose that the initial conditions of the control system (26) satisfy  $P(0) = P_0 > 0$ ,  $Q(0) = Q_0 > 0$ ,  $Q_p(0) = 0$  and  $N(0) = P_0 + Q_0 + Q_{p0} < K$ . Then there is an optimal control for the function  $J_w(u)$ ,  $0 \leq w \leq 1$ , in (29).

The proof of this theorem can be found in [40]. On the other hand, system (26) can be written in a matrix form as

$$\dot{x} = f(x) + g(x)u, \tag{31}$$

where  $x = (P, Q, Q_p, z)^t$  and

$$f(x) = \begin{pmatrix} c_p P \left(1 - \frac{N}{K}\right) + c_{QP} Q_p - c_{PQ} P \\ c_{PQ} P \\ -c_{QP} Q_p - \delta_{QP} Q_p \\ 0 \end{pmatrix}, \quad g(x) = \begin{pmatrix} -\gamma P \\ -\gamma Q \\ \gamma Q \\ 1 \end{pmatrix}. \tag{32}$$

Defining the attached variable  $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ , the Hamiltonian is given by

$$H(x, \lambda, u) = w(P + Q) + \lambda_1 \left[ c_p P \left(1 - \frac{N}{K}\right) + c_{QP} Q_p - c_{PQ} P - \gamma P u \right] + \lambda_2 [c_{PQ} P - \gamma Q u] + \lambda_3 [\gamma Q u - c_{QP} Q_p - \delta_{QP} Q_p] + \lambda_4 u.$$

The adjoint equation becomes

$$\dot{\lambda} = -a - \lambda(Df(x) + u^* Dg(x)), \quad \lambda(T) = m,$$

where  $a = (w, w, 0, 0)^t$ ,  $m = (1 - w, 1 - w, 0)^t$  and  $Df$ , resp.,  $Dg$  represent the matrices of partial derivatives of the vectors  $f$ , resp.,  $g$ .

The switching function  $\Phi$  for this problem is

$$\Phi(t) = \lambda_4 - \gamma(\lambda_1 P + \lambda_2 Q - \lambda_3 Q). \tag{33}$$

Then, the optimal controls are given by

$$u_*(t) = \begin{cases} u_M & \text{if } \Phi(t) < 0, \\ 0 & \text{if } \Phi(t) > 0. \end{cases} \tag{34}$$

The control is not determined a priori by the minimum condition when  $\Phi(t) = 0$ . Thus, we consider two cases:

- If the switching function  $\Phi(t)$  has only a finite number of zeros in an interval  $I_b \subset [0, T]$ , the control  $u_*$  is called bang-bang over  $I_b$ . In this case we have  $u_*(t) \in \{0, u_M\}$  for all  $t \in I_b$ .
- If  $\Phi(t) \equiv 0$  is maintained over a time interval  $I_s = [t_1, t_2]$ ,  $0 \leq t_1 < t_2 \leq T$ , we say that  $u_*$  is singular about  $I_s$ .

For the optimal control problems that are linear in the control, it is typical that the optimal solutions are concatenations of bang-bang and singular controls, but this does not derive directly from the necessary conditions. In principle, since the controls are measurable Lebesgue, more degenerate situations can not be excluded a priori.

As in the previous section, we can use the strict Legendre-Clebsch condition as a necessary condition for the existence of singular controls. Thus, if we assume that the strict Legendre-Clebsch condition is satisfied

$$-\frac{\partial}{\partial u} \frac{d^2}{dt^2} \phi(t) = -N(x(t), \lambda(t)) > 0, \quad \forall t \in I_s, \tag{35}$$

where

$$N(x(t), \lambda(t)) = \gamma^2 \lambda_1 \left[ \frac{c_p}{K} P^2 - c_{QP}(Q + Q_p) \right] - \gamma^2 \lambda_3 L_4 - \gamma^2 w(P + Q),$$

with

$$L_4 = c_{PQ}P + (c_{QP} + \delta_{QP})Q,$$

the relation  $\frac{d^2}{dt^2} \phi(t) = 0$  gives rise to the following formula for singular control in terms of the state variable  $x$  and the adjoint variable  $\lambda$ :

$$u_{\text{sing}}(x, \lambda) = -\frac{M(x, \lambda)}{N(x, \lambda)}, \tag{36}$$

where

$$M(x, \lambda) = \gamma \lambda_1 \left[ L_5 - 2 \frac{c_p}{K} P L_1 + L_2 L_3 - \left( c_{QP} - \frac{c_p}{K} P \right) L_4 \right] + \gamma w (L_1 + L_3 + c_{PQ}P) + \gamma \lambda_2 c_{PQ} L_3 + \gamma \lambda_3 [c_{PQ}L_1 + (c_{QP} + \delta_{QP})(c_{PQ}P + L_4)],$$

and

$$\begin{aligned} L_1 &= c_p P \left( 1 - \frac{N}{K} \right) + c_{QP} Q_p - c_{PQ} P, \\ L_2 &= c_p \left( 1 - \frac{N}{K} \right) - \frac{c_p}{K} P - c_{PQ}, \\ L_3 &= \frac{c_p}{K} P^2 + c_{QP} Q_p + c_{QP} Q, \\ L_4 &= c_{PQ} P + (c_{QP} + \delta_{QP}) Q, \\ L_5 &= c_{QP} (c_{QP} + \delta_{QP}) Q_p - c_{QP} c_{PQ} P. \end{aligned}$$

Thus, the strict Legendre-Clebsch condition (35) requires checking if the inequality

$$-\lambda_1 \left( \frac{c_p}{K} P^2 - c_{QP}(Q + Q_p) \right) + \lambda_3 (c_{PQ}P + (c_{QP} + \delta_{QP})Q) + w(P + Q) > 0 \tag{37}$$

is satisfied on the singular interval  $I_s$ .

### 3.0.1 Numerical solutions

We solve the optimal control problem 4 using AMPL software [19], which is linked to the IPOPT Interior Point optimization code. We use a high number  $N \in [3000, 10000]$  of grid points and implement the trapezoidal integration scheme [5].

The objective of this section is to calculate a standard chemotherapy protocol for a LGG, where the total amount of TMZ dose is  $M = 5$  and the treatment time is  $T = 1$  (30 days). We use the parameters of Table 4 and the initial conditions

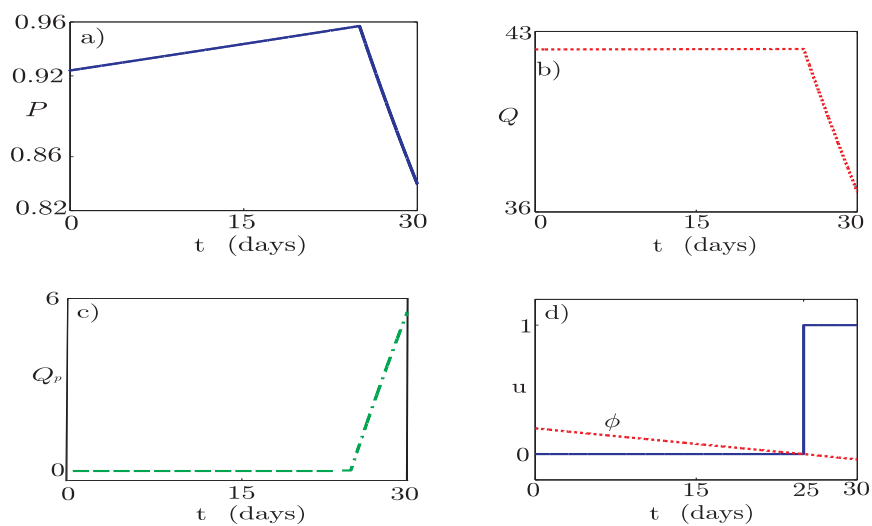
$$P(0) = 0.924, \quad Q(0) = 42.3, \quad Q_p(0) = 0.$$

1.  $w = 0$ . The state variables, the optimal control and the change function are shown in Figure 7. The optimal treatment consists of DMT therapy. Initially, the dose level is zero and then jump to the maximum tolerated dose (DMT) for 5 days. Initially, the proliferative and quiescent cells are growing, but after applying the chemotherapy, both types of cells are drastically decreasing until the end of the treatment period. We obtain the objective value and terminal states

$$J_0(u^*) = 37.0623, \quad P(T) = 0.8396, \quad Q(T) = 36.7801, \quad Q_p(T) = 5.5286.$$

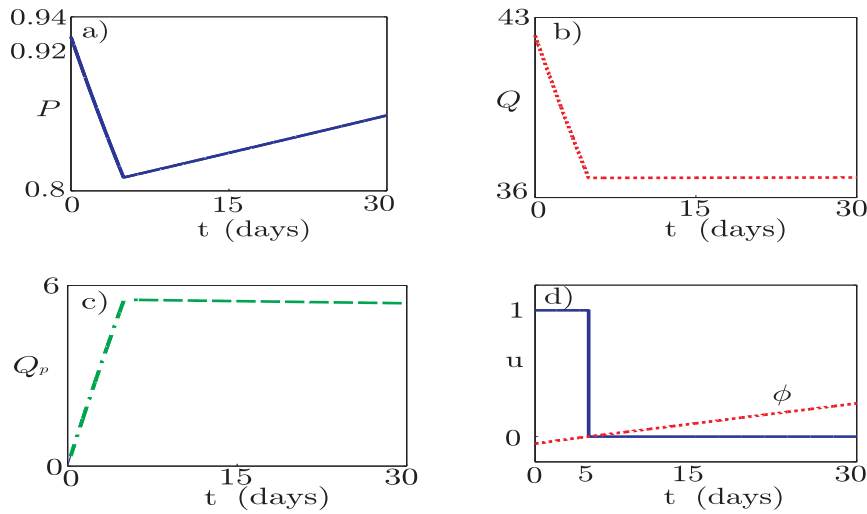
**Table 4** Values of the biological parameters in the model of LGG evolution.

Variable	Value (Units)
$P_0$	0.924 mm
$Q_0$	42.3 mm
$Q_{p0}$	0 mm
$K$	100 mm
$c_p$	$0.114 \text{ mo}^{-1}$
$c_{PQ}$	$0.0226 \text{ mo}^{-1}$
$c_{QP}$	$0.0045 \text{ mo}^{-1}$
$\delta_{QP}$	$0.0214 \text{ mo}^{-1}$
$\gamma$	0.842



**Fig. 7** Optimal solution for functional  $J_w(u)$  in (29) with  $w = 0$  and total dose  $M = 5$ ; the time horizon is 30 days. *Top row:* a) proliferative cells  $P$ , b) nonproliferative quiescent cells  $Q$ ; *Bottom row:* c) damaged quiescent cells  $Q_p$ , d) optimal control  $u^*(t)$  and switching function  $\phi$ .





**Fig. 8** Optimal solution for functional  $J_w(u)$  in (29) with  $w = 1$  and total dose  $M = 5$ ; the time horizon is 30 days. *Top row:* a) proliferative cells  $P$ , b) nonproliferative quiescent cells  $Q$ ; *Bottom row:* c) damaged quiescent cells  $Q_p$ , d) optimal control  $u^*(t)$  and switching function  $\phi$ .

- $w = 1$ . Figure 8 shows the optimal control and the state variables for the weight  $w = 1$  in the objective (29). The optimal treatment is based on DMT therapy, but now, in contrast to the solution for  $w = 0$ , the initial dose is the maximum dose until the total dose  $M = 5$  is reached. Subsequently, no dose is administered. We get the following final value for the objective and the state variables

$$J_1(u^*) = 38.0623, \quad P(T) = 0.8607, \quad Q(T) = 36.7804, \quad Q_p(T) = 5.4084.$$

- $w = w_s = 0.004067$ . For this value, the optimal control is given by

$$0 \leq w < w_s : u^*(t) = \begin{cases} 0 & \text{for } 0 \leq t \leq 25 \\ 1 & \text{for } 25 < t \leq 30 \end{cases} \quad (38)$$

$$w_s < w \leq 1 : u^*(t) = \begin{cases} 1 & \text{for } 0 \leq t \leq 5 \\ 0 & \text{for } 5 < t \leq 30 \end{cases} \quad (39)$$

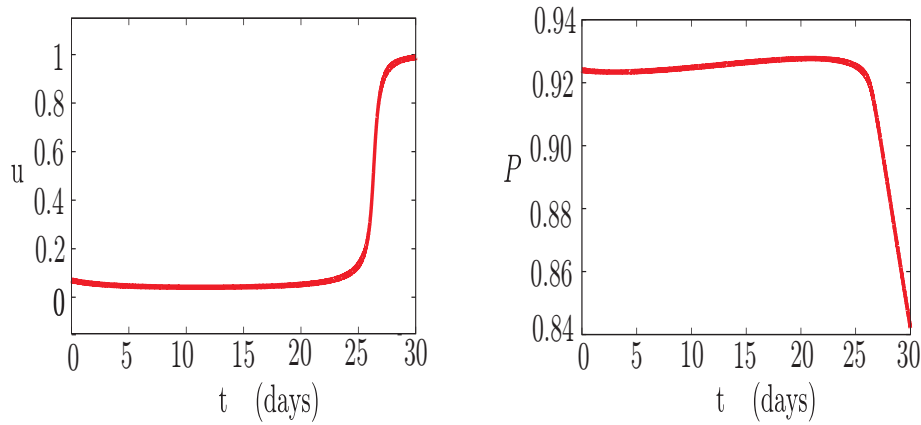
Therefore, for  $w \neq w_s$  all controls are bang-bang with a single switching that occurs at the time when the total amount of dose,  $M = 5$ , has been administered. But the structure of the control "switch" in the weight  $w_s = 0.004067$  being, for this value, a totally singular optimal control.

Figure 9 show this fact.

Now, we solve the optimal control problem (29) for  $T = 30$  months.

- $w = 0$ . In this case, we get control with the bang-singular-bang structure:

$$u^*(t) = \begin{cases} 0 & \text{for } 0 \leq t < t_1, \\ u_{\text{sing}}(x(t), \lambda(t)) & \text{for } t_1 \leq t \leq t_2, \\ 1 & \text{for } t_2 < t \leq 30. \end{cases} \quad (40)$$

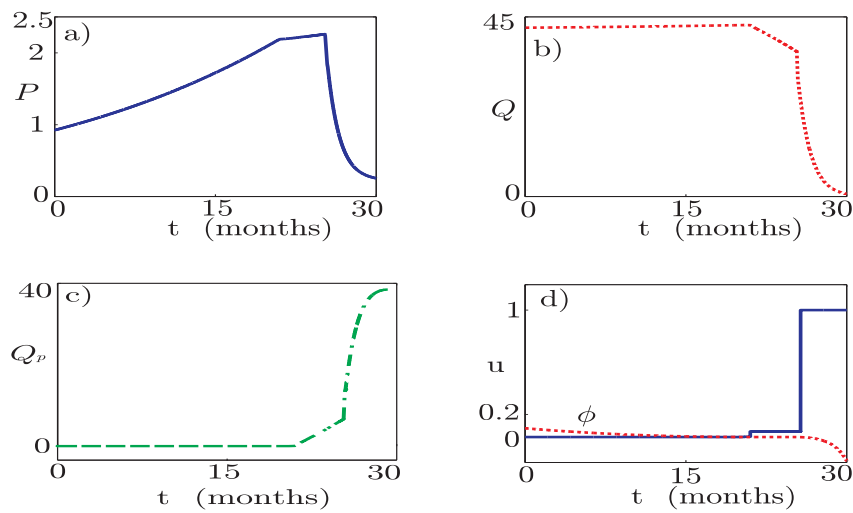


**Fig. 9** Optimal solution for functional  $J_w(u)$  in (29) with  $w = w_s = 0.004067$  and total dose  $M = 5$ ; the time horizon is 30 days. (left) optimal control  $u^*(t)$  which is totally singular on  $[0, 1]$ , (right) proliferative cells  $P$ .

The singular control  $u_{\text{sing}}$  is obtained in (36). On the other hand, we can obtain the change times  $t_1 = 20.1$  and  $t_2 = 25.2$ . The control and state variables are shown in Figure 10. We get the following final value for the objective and the state variables

$$J_0(u^*) = 0.9059, \quad P(T) = 0.2545, \quad Q(T) = 0.6514, \quad Q_p(T) = 38.2335.$$

Here, the treatment starts with zero doses, then jumps to a single dose with fairly small values followed by a total dose at the end of the treatment.



**Fig. 10** Optimal solution for functional  $J_w(u)$  in (29) with  $w = 0$  and total dose  $M = 5$ ; the time horizon is  $T = 30$  months. *Top row*: a) proliferative cells  $P$ , b) nonproliferative quiescent cells  $Q$ ; *Bottom row*: c) damaged quiescent cells  $Q_p$ , d) optimal control  $u^*(t)$  and switching function  $\phi$ ; the switching function  $\phi(t)$  is zero on the singular arc  $[t_1, t_2]$ .

2.  $w = 1$ . Here, we consider the functional

$$J_1(u) = \int_0^T (P(t) + Q(t))dt,$$

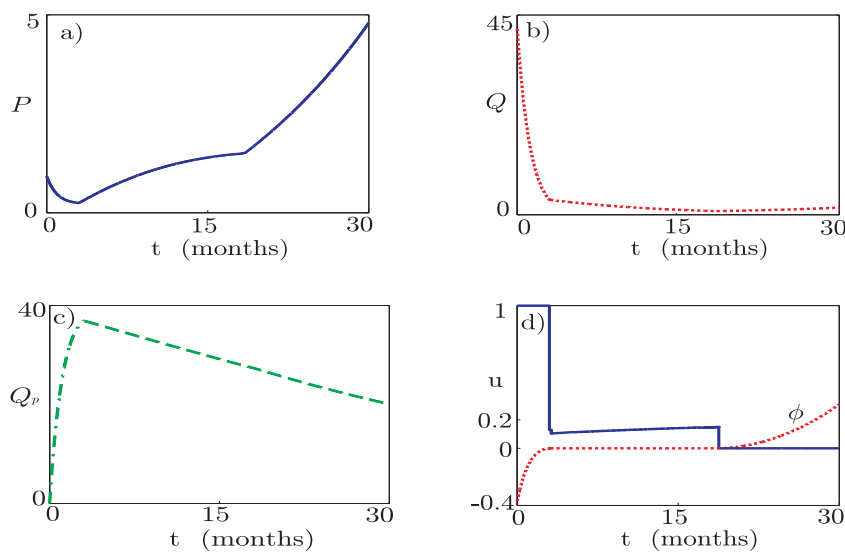
and we find again the control structure bang-singular-bang

$$u^*(t) = \begin{cases} 1 & \text{for } 0 \leq t < t_1, \\ u_{\text{sing}}(x(t), \lambda(t)) & \text{for } t_1 \leq t \leq t_2, \\ 0 & \text{for } t_2 < t \leq 30. \end{cases} \quad (41)$$

The switching times for are  $t_1 = 3.00$  and  $t_2 = 18.4$  showing a fairly long singular arc. We get the following final value for the objective and the state variables

$$J_1(u^*) = 139.31, \quad P(T) = 4.7982, \quad Q(T) = 1.6042, \quad Q_p(T) = 20.0689.$$

Figure 11 shows the state variable and the optimal control.



**Fig. 11** Optimal solution for functional  $J_w(u)$  in (29) with  $w = 1$  and total dose  $M = 5$ ; the time horizon is  $T = 30$  months. *Top row*: a) proliferative cells  $P$ , b) nonproliferative quiescent cells  $Q$ ; *Bottom row*: c) damaged quiescent cells  $Q_p$ , d) optimal control  $u^*(t)$  and switching function  $\phi$ ; the switching function  $\phi(t)$  is zero on the singular arc  $[t_1, t_2]$ .

#### 4 Cancer chemotherapy and drug resistance

Resistance to drugs is one of the most important problems in the treatment of cancer, causing a high number of deaths. There are several probabilistic models for the development of drug resistance [8, 53]. The amplification of a gene is an increase in the number of copies of that gene present in the cell after cell division, the depletion corresponds to a decrease in its number of copies. The hypothesis of amplification of a gene to a copy establishes that in cell division at least one of the two daughter cells will be an exact copy of the mother cell while the second, with some positive probability, will undergo genetic amplifications. Next, we present a model studied by Ledzewicz et al. in [26].

##### 4.1 A 2– compartment model with sensitive and resistant subpopulations

Here, we consider two compartments consisting of drug sensitive and resistant cells, and we denote the numbers of cells in the sensitive and resistant compartments by  $S$  and  $R$ , respectively. Within the one copy

forward gene amplification model, once a sensitive cell undergoes cell division, the mother cell dies and one of the daughters will remain sensitive. The other daughter, with probability  $q$ ,  $0 < q < 1$ , changes into a resistant cell. Similarly, if a resistant cell undergoes cell division, then the mother cell dies, and one of the daughters remains resistant. However, for cancer cells it is possible that a resistant cell may mutate back into a sensitive cell. This phenomenon is well-documented in the medical literature where experiments have shown that the resistant cell population decreases in a drug free medium [44]. We therefore include a probability  $r \geq 0$  that one of the daughters of a resistant cell may become sensitive. Generally  $r$  will be small.

Thus, the controlled dynamics can be represented as

$$\dot{S} = -aS + (1 - u)(2 - q)aS + rcR, \tag{42}$$

$$\dot{R} = -cR + (2 - r)cR + (1 - u)qaS, \tag{43}$$

and the initial condition is given by positive numbers  $S_0$  and  $R_0$  at time  $t = 0$ . Setting  $N = (S, R)^T$ , the dynamics is described again by a bilinear system

$$\dot{N} = (A + uB)N, \tag{44}$$

where

$$A = \begin{pmatrix} (1 - q)a & rc \\ qa & (1 - r)c \end{pmatrix}, \quad B = a \begin{pmatrix} q - 2 & 0 \\ -q & 0 \end{pmatrix}. \tag{45}$$

The problem that we want to solve is to delay the onset of the time when drugs are no longer effective. Mathematically, we consider the problem to minimize an objective of the form

$$J = kN(T) + \int_0^T (lN(t) + u(t))dt \rightarrow \min \tag{46}$$

where  $k$  and  $l$  are row-vectors of weights with the components of  $k$  positive and those of  $l$  non-negative. The penalty term  $kN(T)$  represents a weighted average of the total number of cancer cells at the end of an assumed fixed therapy interval  $[0, T]$  and the term  $lN(t)$  models cumulative effects during the therapy. The control term  $u(t)$  in the Lagrangian models the negative side effects of the drugs, measured in the  $L_1$  norm. The parameters  $k$  and  $l$  can also be used to put a stronger emphasis on the number of cancer cells since it can be argued that a duplication of the cancer or the drug dose is more hazardous than a duplication of the objective would represent.

Thus, the optimal control problem has the form

**Problem 5.** For a fixed therapy interval  $[0, T]$ , minimize the objective  $J$  (46), over all Lebesgue measurable functions (respectively, piecewise continuous)  $u : [0, T] \rightarrow [0, u_{\max}]$  subject to the equations (42) and (43).

Using the Pontryagin Maximum Principle, there exists a continuous function  $\lambda$  satisfying the adjoint equation

$$\dot{\lambda} = -\lambda(A + u^*B) - l, \quad \lambda(T) = k,$$

such that the optimal control  $u^*$  minimizes the Hamiltonian  $H$ ,

$$H = lN + u + \lambda(A + u^*B)N \tag{47}$$

over the control set  $[0, u_{\max}]$  along  $(\lambda(t), N^*(t))$ . Since the Hamiltonian is linear in  $u$  and the control set is an interval, defining the switching function  $\Phi$  by

$$\Phi(t) = 1 + \lambda(t)BN(t) \tag{48}$$

and, therefore, we have

$$u^*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0, \\ u_{\text{sing}}(x(t), \lambda(t)) & \text{if } \Phi(t) \equiv 0, \\ u_{\max} & \text{if } \Phi(t) < 0. \end{cases} \tag{49}$$

Thus, the singular control can be computed and to get

$$u_{\text{sing}} = - \frac{\lambda(t)[A, [A, B]]N(t) - I[A, B]N(t) - IBAN(t)}{\lambda(t)[B, [A, B]]N(t) - IB^2N(t)}. \tag{50}$$

Whether the singular control will be admissible, i.e., whether it will obey the control bounds  $0 \leq u \leq u_{\text{max}}$ , will depend on the parameter values, but also on the region in the state space where the state  $(S, R)^T$  lies and cannot be answered in general. In this case the singular control is called of order 1 and it is again where we have to use the generalized Legendre-Clebsch condition as before we did:

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} < 0.$$

Thus, we get

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} = 2a^2rc \{ (2 - q)\lambda_0 + q\lambda_1 \} (qS - (2 - q)R). \tag{51}$$

Since  $(2 - q)\lambda_0 + q\lambda_1 > 0$  the generalized Legendre-Clebsch condition therefore implies:

**Proposition 8.** *Singular controls are not optimal in regions of the state space where  $qS > (2 - q)R$ .*

This holds as long as the resistant population is very small and then optimal controls will be bang-bang, i.e., correspond to sessions of full dose chemotherapy with rest periods interlaced. However, as the portion of resistant cells  $R$  increases, the Legendre-Clebsch condition will be satisfied and if admissible, there are mathematical reasons to suspect that it indeed will be the optimal control in this case. It is also quite intuitive that a full dose may do more harm than good once resistance builds up and thus the optimal strategy may switch to give partial doses, i.e., use singular controls.

## 5 Cancer chemotherapy and antiangiogenic treatment

Cancer is fundamentally a genetic disease: it arises as a consequence of pathological changes in the information contained in the DNA. That is, the uncontrolled growth of the cells is the result of alterations or mutations in the genetic material. These mutations lead to a process of altering the cell division and the inability to undergo programmed cell death (or apoptosis). The growth of a single cancer (or primary cancer) does not usually lead to the death of the organism. However, some cancer cells can acquire the ability to enter the bloodstream, travel to another part of the body and begin to grow in a different organ. This process is known as metastasis. Generally, metastatic growth is what kills the body. When a cancer cell is created, it can multiply and lead to a tumor of small size without the need for blood supply. At this stage, the growth of an avascular tumor stops. Subsequently, to continue growing, since the tumor needs oxygen and nutrients to grow, provided by the blood, the tumor sends out chemical signals called promoters. This induces the blood vessels to grow towards the tumor and leads to the complete vascularization of the tumor, which allows it to increase in size. The formation of new blood vessels is called angiogenesis. The understanding of the role of angiogenesis in the development of cancer has advanced significantly due to the studies conducted by Folkman [17]. We now know that without angiogenesis, the size of most primary tumors does not exceed 3 mm. One type of very important promoters are the so-called Vascular Endothelial Growth Factors (VEGF). These factors stimulate cellular responses joining the tyrosine kinase receptors (a type of enzyme) on the surface of the endothelial cells and stimulate their proliferation and migration to the tumor. Other pro-angiogenic factors are PDGF, PIGF or FGF. Therefore, anti-angiogenic therapies are important in the treatment of certain cancers. But, by itself, the antiangiogenic treatment only prevents the tumor from developing its support of blood vessels and does not directly destroy the cancer cells. In fact, the benefits of using anti-angiogenic therapies alone are, at best, transient and are followed by the restoration of tumor growth and progression [4]. As a consequence, it is common not to limit the treatment to a body, but to

**Table 5** Values of the biological parameters in the model.

Variable	Description	Value (Units)
$\xi$	Tumor growth parameter	0.084 day <sup>-1</sup>
$b$	Tumor-induced stimulation parameter	5.85 day <sup>-1</sup>
$d$	Tumor-induced inhibition parameter	0.00873 mm <sup>-2</sup> day <sup>-1</sup>
$\mu$	Loss of vascular support	0.02 day <sup>-1</sup>
$\chi$	Maduration of unstable vessels parameter	0.025 day <sup>-1</sup>
$\gamma$	Anti-angiogenic elimination parameter	0.15 kg/mg day <sup>-1</sup>
$\varphi$	Cytotoxic killing parameter for the tumor	0.1 kg/mg day <sup>-1</sup>

combine different treatments in the hope of achieving a synergistic effect. In this way, antiangiogenic treatment should be combined with other treatments, such as radiotherapy or chemotherapy. In this section, we combine antiangiogenic therapy with chemotherapy.

The mathematical model studied in [39] is

$$\frac{dp}{dt}(t) = -\xi p(t) \log\left(\frac{p(t)}{s(t)}\right) - \varphi v(t)p(t), \tag{52}$$

$$\frac{ds}{dt}(t) = \chi q(t) - \mu s(t), \tag{53}$$

$$\frac{dq}{dt}(t) = -\chi q(t) + bp(t) - dp(t)^{2/3}q(t) - \gamma u(t)q(t), \tag{54}$$

where  $p(t)$  is the size of the tumor,  $s(t)$  is the number of stable vessels,  $q(t)$  is the number of unstable vessels and  $u(t)$  and  $v(t)$  are the antiangiogenic and cytotoxic agents respectively. Table 5 shows the values of the parameters of the model.

Thus, the problem that we want to solve is to minimize the size of the tumor  $p(t)$ :

$$J(u) = p(T) \tag{55}$$

for a free final time  $T$  and subject to the constraints

$$\int_0^T u(t)dt \leq M, \quad \int_0^T v(t)dt \leq N, \tag{56}$$

where the set of admissible controls is given by

$$u \in U = \{u(t) \mid 0 \leq u(t) \leq u_M, \forall t \in [0, T]\},$$

$$v \in V = \{v(t) \mid 0 \leq v(t) \leq v_M, \forall t \in [0, T]\}.$$

Thus, we have the following problem:

**Problem 6.** For a free final time  $T$ , minimize the objective  $J$ , equation (55), over all Lebesgue measurable functions (respectively, piecewise continuous)  $u : [0, T] \rightarrow [0, u_M]$  and  $v : [0, T] \rightarrow [0, v_M]$  subject to the equations (52), (53) and (54) and the constraints (56).

As was done in previous problems, the switching functions can be calculated to get

$$\phi_1(t) = \lambda_4 - \gamma\lambda_3q, \tag{57}$$

$$\phi_2(t) = \lambda_5 - \varphi\lambda_1p, \tag{58}$$

and then, the optimal controls satisfy

$$u^*(t) = \begin{cases} 0, & \text{if } \phi_1(t) > 0, \\ u_{\text{sing}}, & \text{if } \phi_1(t) \equiv 0, \\ u_M, & \text{if } \phi_1(t) < 0, \end{cases} \tag{59}$$

and

$$v^*(t) = \begin{cases} 0, & \text{if } \phi_2(t) > 0, \\ v_{\text{sing}}, & \text{if } \phi_2(t) \equiv 0, \\ v_M, & \text{if } \phi_2(t) < 0, \end{cases} \tag{60}$$

and the adjoint equations are

$$\begin{aligned} \dot{\lambda}_1 &= \lambda_1 \left( \xi \log\left(\frac{p}{s}\right) + \xi + \varphi v \right) - \lambda_3 \left( b - \frac{2}{3} dp^{-1/3} q \right), & \lambda_1(T) &= 1, \\ \dot{\lambda}_2 &= -\lambda_1 \xi \frac{p}{s} + \mu \lambda_2, & \lambda_2(T) &= 0, \\ \dot{\lambda}_3 &= -\chi \lambda_2 + \lambda_3 (\chi + dp^{2/3} + \gamma u), & \lambda_3(T) &= 0, \\ \dot{\lambda}_4 &= 0, \\ \dot{\lambda}_5 &= 0. \end{aligned}$$

The generalized Legendre-Clebsch condition

$$(-1)^q \frac{\partial}{\partial u} \frac{d^{2q}}{dt^{2q}} \geq 0,$$

for our problem becomes

$$-\frac{\partial}{\partial u} \frac{d^2}{dt^2} \phi_1(t) = 2b\gamma^2 \lambda_3(t) p(t). \tag{61}$$

Therefore, the generalized Legendre-Clebsch condition is satisfied if  $\lambda_3(t) > 0, \forall t \in I$ . We have then the following proposition:

**Proposition 9.** *If the optimal control  $u^*$  is singular over an interval  $I = (a, b)$ , then  $\lambda_2, \lambda_3, \lambda_4, \lambda_5 > 0$ . In addition, the control  $u^*$  ends in an interval  $(t_1, T)$  where  $u^* = 0$ .*

Then, we suppose the control  $u$  is singular and let's calculate that control. After some tedious calculations, we get the following singular optimal control

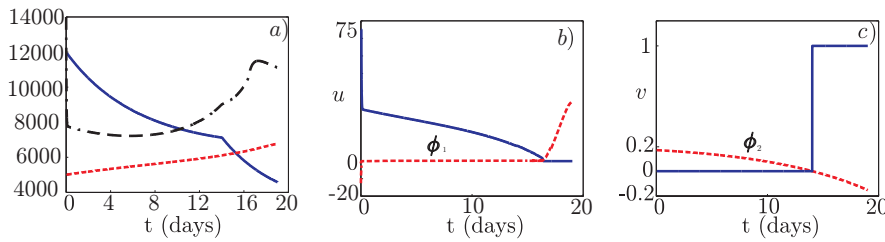
$$u_{\text{sing}}^* = \frac{\lambda_1 \psi_1 + \lambda_2 \psi_2 + \lambda_3 (\varphi b v + \psi_3)}{2b\gamma \lambda_3}, \tag{62}$$

where

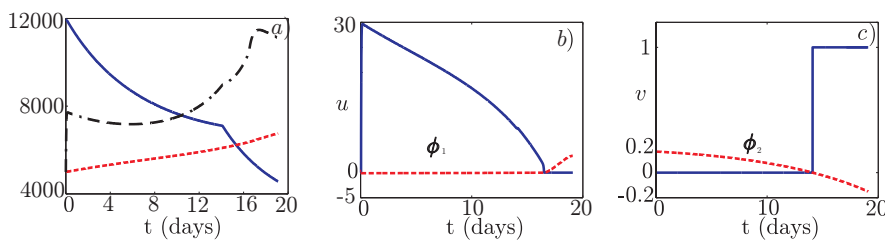
$$\begin{aligned} \psi_1(p, q, s) &= -\chi \frac{\xi q}{s}, \\ \psi_2(p, q, s) &= 2\chi b + \chi \frac{q}{p} (\mu - \chi) - dp^{-1/3} q \chi, \\ \psi_3(p, q, s) &= b \left[ \xi \log\left(\frac{p}{s}\right) - \chi - dp^{2/3} \right]. \end{aligned}$$

Regarding to the control  $v$ , analytically it is complicated to characterize it for what the numerical methods are used. Thus, in all the numerical simulations,  $\dot{\phi} < 0$  and thus the control  $v$  is of the bang-bang type.

Some numerical solutions are shown in Figure 12 and Figure 13.



**Fig. 12** [Color Online]. a) Evolution of the solutions to Eqs. (52), (53) and (54),  $p$  (solid line),  $s$  (dotted line), and  $q$  (solid-dot line) with the initial conditions  $(p_0, s_0, q_0) = (12000, 5000, 14000)$  b) Optimal control  $u(t)$  (solid line) and switching function  $\phi_1$  (dotted line) for  $M = 300$  doses and  $u_M = 75$  c) Optimal control  $v(t)$  (solid line) and switching function  $\phi_2$  (dotted line) for  $N = 5$  doses and  $v_M = 1$ .



**Fig. 13** [Color Online]. a) Evolution of the solutions to Eqs. (52), (53) and (54),  $p$  (solid line),  $s$  (dotted line), and  $q$  (solid-dot line) with the initial conditions  $(p_0, s_0, q_0) = (12000, 5000, 5000)$  b) Optimal control  $u(t)$  (solid line) and switching function  $\phi_1$  (dotted line) for  $M = 300$  doses and  $u_M = 75$  c) Optimal control  $v(t)$  (solid line) and switching function  $\phi_2$  (dotted line) for  $N = 5$  doses and  $v_M = 1$ .

## 6 Conclusions

In this survey, a series of problems of optimal control theory applied to cancer treatments have been addressed. First of all, a class of cell cycle specific compartmental models for cancer chemotherapy was analyzed. By considering the phases of the cell cycle separately, it is possible to appropriately model the different actions of various drugs involved. A common characteristic of the models analyzed in the second section is that it is implicitly assumed that the cancer population is homogeneous and consists of cells that are sensitive to the chemotherapy applied. If we then minimize a weighted average of the tumor population and the total dose of chemotherapy given over a fixed therapy interval, it will be seen that in this scenario it indeed is optimal to give chemotherapy in one full dose session upfront at the beginning of the therapy interval. These results are fully consistent with and confirm as optimal the classical MTD (maximum tolerated dose) regimen. Essentially, the underlying scenario in these models is one where cancer is growing rapidly at a critical level, but sensitive to chemotherapeutic agents. The intuitive optimal solution then is to hit it as hard as possible, as soon as possible.

In the third section, low grade glioma, a type of brain tumor, together with the action of a cytotoxic agent, as the temozolomide, is studied [39]. For this problem, the optimal control solutions depend on the treatment time. If the treatment time is long enough ( $T = 30$  months), the optimal control will be unique. On the other hand, if the treatment time is  $T = 30$  days, the control will be of the bang-bang type.

Many tumors consist of heterogeneous agglomerations of subpopulations of cells that show widely varying sensitivities toward the actions of a particular chemotherapeutic agent [15, 29]. Coupled with the fact that growing tumors also exhibit considerable evolutionary ability to enhance cell survival in an environment that is becoming hostile, this leads to multi-drug resistance of some strains of the cells. Naturally, it makes sense to combine drugs with different activation mechanisms to reach a larger population of the tumor cells-and this is what is being done-but the sad fact remains that some cells develop multi-drug resistance to a wide variety



of even structurally unrelated drugs. There may even exist subpopulations of cells that are not sensitive to the treatment from the beginning (ab initio, intrinsic resistance). For certain types of cancer cells, there are simply no effective agents known. We have explored this aspect in section four, studying a 2– compartment model with sensitive and resistant populations.

Finally, we have considered tumor's microenvironment. One of the most important component of a tumor's microenvironment is its vasculature. In order to grow beyond a small size, a growing tumor needs to develop its own network of blood vessels and capillaries that will provide it with nutrients and oxygen. This process is called angiogenesis and was already pointed out as a therapeutic target by J. Folkman in the early 1970s [23,24]. Antiangiogenic treatments aim at depriving the tumor of this needed vasculature by either disrupting the signaling process that the tumor uses to recruit surrounding, mature, host blood vessels or by directly inhibiting the growth of endothelial cells that form the lining of the newly developing blood vessels and capillaries. We have studied this kind of treatment together with the chemotherapy [39] which is based on this model by Hahnfeldt et al. [21].

We hope that this survey will be useful in understanding the optimal treatment protocols in tumors. Mathematical models need to be developed to aid in our understanding of how to implement this work and hopefully to show how to develop new optimal treatment strategies.

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