Optimal Chemical Control of Populations Developing Drug Resistance

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Abstract: A system of differential equations for the control of the growth of certain populations by the use of chemical treatment is presented. Rather general growth rates and kill rates of drugs, as well as drug resistance, are considered. A class of optimal control problems with a performance criterion depending on a parameter is formulated and shown to admit the same basic optimal strategy. Applications to cycle nonspecific chemotherapy and control of the growth of bacterial population in cellulose medium in paper production plants are described

Keywords: Optimal Control, Chemical Control of Populations, Drug Resistance, Cancer Chemotherapy

1. INTRODUCTION

In several practical situations it is necessary to control the growth of certain populations by using some sort of chemical treatment. Examples of these situations are special types of cancer chemotherapy, in which one aims the control of the number of tumor cells in patients, the control of the growth of bacterial population in cellulose medium in paper industries by using bactericides and the control of pests in agriculture by using pesticides. In all these cases, for reasons of safety and economy, some sort of optimal use of the involved drugs would be desirable, but among the several aspects that make difficult to obtain a satisfactory answer to this problem are the lack of detailed knowledge about the kill rates of drugs, drug resistance and growth models.
In order to understand the interplay between these aspects we considered a simplified compartmental model in which the population to be controlled is composed of drug sensitive and drug resistance individuals; the resistance to drugs being acquired by spontaneous mutation, at a certain rate. The model will be general enough, though, to admit several rates of the previously mentioned aspects. Specifically, we consider the model given by the following system of ordinary differential equations:

\[
\begin{align*}
\frac{dx}{dt} &= xf(y) + \alpha f(y)(y - x), \\
\frac{dy}{dt} &= yf(y) - u(t)g(y - x), \\
x(0) &= x_0, \\
y(0) &= y_0,
\end{align*}
\]

where \( t \geq 0 \) represents the elapsed time; \( y(t) \in \mathbb{R} \) represents the total number of individuals in the population at time \( t \); \( x(t) \in \mathbb{R} \) is the number of drug-resistant individuals; the initial condition \((x_0, y_0)\) is such that \( x_0 < y_0 \); \( f(y) \) is the growth rate, which can depend on the total population; \( 0 < \alpha < 1 \) is the fraction per unit of time of the drug sensitive population that mutates into drug-resistant; \( 0 \leq u(t) \leq u_{\text{max}} \) is the drug concentration in the environment (assumed to be limited, i.e., \( u_{\text{max}} < +\infty \)); \( g \) gives the kill rate of the drug per unit of rate of drug concentration as function of the drug-sensitive population. For simplicity we will assume that \( f \) and \( g \) are \( C^1 \)-functions; other technical assumptions will be described later (Conditions (2.1), (2.2), (2.3), (2.4), in Section 2).

We will be interested in solving the following free end-time Optimal Control Problem associated to (1.1):

We want to find a time \( 0 \leq t_f^* < +\infty \) and a \( BV[0, t_f^*] \)-function \( u^* : [0, t_f^*] \to \mathbb{R} \) (here \( BV[0, t_f^*] \) indicates the class of bounded variation function defined in \([0, t_f^*]\)), \( 0 \leq u^*(t) \leq u_{\text{max}} \) almost everywhere in \([0, t_f^*]\), that will be the optimal drug administration treatment in the sense that

\[
J_c(u^*(\cdot), t_f^*) = \text{minimum} \{ J_c(u, t_f), \ u \in BV[0, t_f], \\
t_f > 0; \ 0 \leq u(t) \leq u_{\text{max}} \ a.e. \},
\]

where the functional \( J_c \) is defined by

\[
J_c(u, t_f) = y(t_f) + c \int_0^{t_f} u(t) dt,
\]
and $c \geq 0$ is a constant, and $(x(t), y(t))$ is solution of (1.1). The pair $(u^*(\cdot), t_f^*)$ is called an optimal strategy to (1.2).

We observe that when $c = 0$ the problem reduces to the one of finding the control that minimizes the total number of individuals at time $t_f^*$. The integral term in (1.3) indicates that an excess of drug is harmful due to side effects (that are not accounted for in (1.1)) in an accumulative way. Thus, $c$ is a measure of how harmful the drug is.

Using the Pontriagin's Minimum Principle (Athans and Falb [1], Kirk [7]), in Section 2 we will prove that the optimal strategy is of the "bang-off-type"; precisely we will prove the following:

**Theorem:** Under the assumptions (2.1), (2.3) and $x_0 \leq y_0$ or assumptions (2.1), (2.2) and $x_0 \leq y_0 \leq y_m$, where $y_m$ is the saturation level of the medium (defined in (2.3)), the optimal strategy is given by $u^*(t) = u_{\text{max}}$, $0 \leq t \leq t_f$, and where $t_f$ is such that if $t_f > 0$ it is given by the condition $\frac{dy}{dt}(t_f) = -cu_{\text{max}}$.

In section 3 we apply this theorem in the case of cycle nonspecific cancer chemotherapy and in control of bacteria population in cellulose medium.

It is noteworthy to point out that (1.1) is a generalization of a model for cancer chemotherapy with drug resistance studied in Vendite [12], [13], [14].

**2. THE GENERAL RESULT**

We will consider the following assumptions concerning the functions $f$ and $g$ that appear in (1.1).

(2.1) $f$, $g$ are $C^1$-functions. Moreover, $g(0) = 0$, $g(s) > 0$ and $g'(s) > 0$ when $s > 0$.

and

(2.2) There exists $y_m > 0$ such that $f(y_m) = 0$ and $f(y) > 0$ for $0 \leq y < y_m$ (where $y_m$ is called the saturation level of the medium).

or

(2.3) $f(y) > 0$ for $y \geq 0$ and $g$ is globally Lipschitz.
Now we define an open set $\Omega$ as

\[
\begin{align*}
\text{i) } \Omega &= \{(x, y) \in \mathbb{R}^2 : 0 < x, 0 < y, x < y\} \\
& \text{if assumptions (2.1) and (2.3) hold.} \\
\text{ii) } \Omega &= \{(x, y) \in \mathbb{R}^2, 0 < x, 0 < y < y_m, x < y\} \\
& \text{if assumptions (2.1) and (2.2) hold.}
\end{align*}
\]

(2.4)

In the Lemmas that follow, we will always assume that the assumptions (2.1) and (2.3) or (2.1) and (2.2) hold, and moreover that $(x_0, y_0) \in \Omega$ (with $\Omega$ defined as (2.4) (i) or (2.4) (ii) accordingly to the set of assumptions taken).

First we consider the system free of control, that is, we take (1.1) with $u(t) \equiv 0$. Then, we have the following lemma.

**Lemma 1**: If $u(t) \equiv 0$, then the set $\Omega$ is positively invariant, and in particular a trajectory starting in $\Omega$ at $t = 0$ will never touch the boundary of $\Omega$ in finite time.

**Proof**: In fact, if assumptions (2.1) (2.3) are taken, it is enough to observe that $x = y, x > 0$ is an integral curve for the system; that $(0, 0)$ is an unstable equilibrium point, that the associated vector field reduces to $(\alpha yf(y), yf(y))$ at points $(0, y)$ of the $y$-axis, having strictly positive horizontal component for $y > 0$; and that the regularity assumptions (2.1) guarantee that the theorem of local existence and uniqueness holds.

In the case of assumptions (2.1), (2.2) it is enough to make the additional observation that the points of form $(x, y_m)$ are equilibrium points.

Now we prove a result similar to the previous one for the controlled system (1.1).

**Lemma 2**: Given $0 \leq u(t)$, a function of bounded variation, then a solution $(x(t), y(t))$ of (1.1) starting in $\Omega$ at $t = 0$ will never touch the boundary of $\Omega$ in finite time.

**Proof**: we will first prove the result for the case of assumptions (2.1), (2.2). Suppose that the result is not true; then we consider the smallest positive time $\bar{t}$ such that $(x(\bar{t}), y(\bar{t})) \in \partial \Omega$ (and so $(x(t), y(t)) \in \Omega$ for $t \in [0, \bar{t})$), and we will
analise the diverse possibilities.

First, suppose that \( x(\overline{t}) = 0 \) and \( 0 < y(\overline{t}) < y_m \). Since \( u(t) \) is of bounded variation, from the first equation we have

\[
\frac{dx}{dt}(\overline{t}-) = 0 \cdot f(y(\overline{t})) + \alpha f(y(\overline{t}))(y(\overline{t}) - 0) > 0.
\]

On the other hand, since \( x(\overline{t}) = 0 \) and \( x(\overline{t} - \varepsilon) > 0 \) for small enough \( \varepsilon > 0 \), we must have \( \frac{dx}{dt}(\overline{t}-) \leq 0 \), in contradiction with the previous result.

Second, suppose \( y(\overline{t}) = y_m \). Since from condition (2.1), \( g(y(t) - x(t)) \geq 0 \) for \( t \in [0, \overline{t}] \), we have for almost every \( t \in [0, \overline{t}] \),

\[
\frac{dy}{dt}(t) = y(t)f(y(t)) - u(t)g(y(t) - x(t)) \leq y(t)f(y(t)).
\]

On the other hand, if \( (x_1(t), y_1(t)) \) denotes the solution to (1.1) with \( u(t) \equiv 0 \) and same initial conditions, we have for every \( t \in [0, \overline{t}] \)

\[
\frac{dy_1}{dt}(t) = y_1(t)f(y_1(t)).
\]

Thus, by result of differential inequalities (see Hale [6], p. 30) we conclude that \( y(t) \leq y_1(t) \) for every \( t \in [0, \overline{t}] \). In particular, \( y_m = y(\overline{t}) \leq y_1(\overline{t}) \), and so \( (x_1(\overline{t}), y_1(\overline{t})) \notin \Omega, \) in contradiction with Lemma 1.

Third, suppose that \( x(\overline{t}) = y(\overline{t}) \). Since \( g \) is \( C^1 \), \( g(0) = 0 \), \( g(s) \geq 0 \) for \( s > 0 \), \( \overline{\Omega} \) is compact, there exists \( M \geq 0 \) such that

\[
g(y - x) = |g(y - x)| \leq M|y - x| = M(y - x)
\]

for all \( (x, y) \in \overline{\Omega} \).

Thus, for almost every \( t \in [0, \overline{t}] \), subtracting the second equation from the first one in (1.1), we conclude

\[
\frac{d}{dt}(y - x)(t) = \left[(1 - \alpha)f(y(t)) - u(t)\frac{g(y(t) - x(t))}{y(t) - x(t)}\right](y(t) - x(t)).
\]

This gives

\[
0 = y(\overline{t}) - x(\overline{t}) = (y_0 - x_0)\exp\int_0^{\overline{t}} \left[(1 - \alpha)f(y(s)) - u(s)\frac{g(y(s) - x(s))}{y(s) - x(s)}\right]ds
\]

which is a contradiction because \( y_0 - x_0 > 0 \) and the integral term is bounded for finite \( \overline{t} \) since \( \left| \frac{g(y(s) - x(s))}{y(s) - x(s)} \right| \leq M \).
Thus the statement of the Lemma is true in the case of assumptions (2.1), (2.2).

The other case is simpler: it is not necessary to consider the second possibility, and in the third one we already have by hypothesis that $g$ is globally Lipschitz and so the same argument is true.

\[\square\]

Now we can start to study the optimal control problem (1.2). For this we introduce the Hamiltonian
\[
H(x, y, \lambda_1, \lambda_2, u) = 
\lambda_1[xf(y) + \alpha f(y)(y - x)] + \lambda_2[yf(y) - ug(y - x)] + cu,
\]

where $\lambda_1$ and $\lambda_2$ are called co-state variables.

Then, if $(u^*, t^*_f)$ is the optimal control and $(x^*(t), y^*(t))$ the corresponding optimal trajectory, the associated optimal trajectory $(\lambda^*_1(t), \lambda^*_2(t))$ in the space of co-state variables must satisfy the two point boundary value problem (see Kirk [7], p. 233)

\[
\begin{align*}
\frac{dx}{dt} &= xf(y) + \alpha f(y)(y - x) \\
\frac{dy}{dt} &= yf(y) - u(t)g(y - x) \\
\frac{d\lambda_1}{dt} &= -\frac{\partial H}{\partial x} = -\lambda_1 f(y)(1 - \alpha) - \lambda_2 u(t)g'(y - x) \\
\frac{d\lambda_2}{dt} &= -\frac{\partial H}{\partial y} = -\lambda_1(xf'(y) + \alpha f'(y)(y - x) + \alpha f(y)) \\
&\quad - \lambda_2(yf'(y) + f(y) - u(t)g'(y - x)) \\
\end{align*}
\]

\[
\begin{align*}
x(0) &= x_0, \quad y(0) = y_0 \\
\lambda_1(t_f^*) &= 0, \quad \lambda_2(t_f^*) = 1
\end{align*}
\]

Moreover, since we are considering a free end-time optimal control problem, we must have
(2.7) \[ H(x^*(t), y^*(t), \lambda^*_1(t), \lambda^*_2(t), u^*(t)) = 0 \] for all \( t \in [0, t_f] \).

Now, if we apply Pontriagyn's Minimum Principle we obtain the following optimal control law:

(2.8) \[
  u^*(t) = \begin{cases} 
    0 & \text{if } c - \lambda^*_2(t)g(y^*(t) - x^*(t)) > 0 \\
    u_{\text{max}} & \text{if } c - \lambda^*_2(t)g(y^*(t) - x^*(t)) < 0 \\
    \text{undetermined} & \text{if } c - \lambda^*_2(t)g(y^*(t) - x^*(t)) = 0
  \end{cases}
\]

Remark: if \( c - \lambda^*_2(t)g(y^*(t) - x^*(t)) = 0 \) in a certain time interval, the associated control at that interval is called singular control.

The lemmas that follow have the objective of preparing for the analysis of the possibilities in (2.8).

**Lemma 3:** The optimal control \( u^* \) is such that \( u^*(t_f) = u_{\text{max}} \).

**Proof:** Suppose that it is not so. Then according to (2.8), we must have \( u^*(t_f) = 0 \) or \( c - \lambda^*_2(t_f)g(y^*(t_f) - x^*(t_f)) = 0 \). In either case, using the expression of the Hamiltonian (2.5) computed at \( t = t_f \), the fact that \( \lambda^*_1(t_f) = 0 \), \( \lambda^*_2(t_f) = 1 \) (see (2.6), and (2.7)), we conclude that \( y^*(t_f) \cdot f(y^*(t_f)) = 0 \).

Now, in the case of assumptions (2.1), (2.3), the last equality gives \( y^*(t_f) = 0 \), which implies \( (x^*(t_f), y^*(t_f)) \in \partial \Omega \), in contradiction with Lemma 2.

In the case of assumptions (2.1), (2.2), we conclude that \( y^*(t_f) = 0 \), which gives the same contradiction as before, or \( f(y^*(t_f)) = 0 \). Thus \( y^*(t_f) \) is a root of \( f \). To prove that \( y^*(t_f) = y_m \) we observe that, since by Lemma 2, \((x^*(t), y^*(t)) \in \Omega \) for all \( t \geq 0 \), we have that \( y^*(t) \leq y_m \). Hence \( \lim_{t \to t_f^-} y^*(t) = y^*(t_f) \leq y_m \) and \( y_m \) is the only root of \( f \) in \([0, y_m]\), so we conclude that \( y^*(t_f) = y_m \). But again this implies that \((x^*(t_f), y^*(t_f)) \in \partial \Omega \) that is in contradiction with Lemma 2.

\( \square \)

**Lemma 4:** \( \lambda^*_2(t) \geq 0 \) for all \( t \in [0, t_f] \).

**Proof:** Again the proof is done by contradiction. Suppose that there exists \( t_0 \in [0, t_f] \) such that \( \lambda^*_2(t_0) < 0 \); \( t_f \) being excluded because by (2.6), \( \lambda^*_2(t_f) = 1 > 0 \). By continuity of \( \lambda^*_2(t) \) we can take the smallest \( t_1 \in (t_0, t_f) \) such that \( \lambda^*_2(t_1) = 0 \).

Since for \( t \in [t_0, t_1] \), \( \lambda^*_2(t) < 0 \), \( c \geq 0 \) and \( g(y^*(t) - x^*(t)) > 0 \), then \( c - \lambda^*_2(t)g(y^*(t) - x^*(t)) > 0 \), and from (2.8) we conclude that \( u^*(t) = 0 \) for \( t \in [t_0, t_1] \).
In this same interval, the Hamiltonian gives

\[ \lambda_1^*(t)[x^*(t)f(y^*(t)) + \alpha f(y^*(t))(y^*(t) - x^*(t))] + \lambda_2^*(t)g(y^*(t)) = 0. \]

Therefore

\[ \lambda_1^*(t) = -\frac{y^*(t)f(y^*(t))}{x^*(t)f(y^*(t)) + \alpha f(y^*(t))(y^*(t) - x^*(t))} \lambda_2^*(t) \]

(2.9) Putting this result into the third equation of (2.6), we conclude that for \( t \in [t_0, t_1] \)

\[ \frac{d\lambda_2^*}{dt} = k(t)\lambda_2^*, \]

where

\[ k(t) = \frac{M(t)y^*(t)f(y^*(t))}{x^*(t)f(y^*(t)) + \alpha f(y^*(t))(y^*(t) - x^*(t))} \]

\[ - y^*(t)f'(y^*(t)) - f(y^*(t)) + u^*(t)g'(y^*(t) - x^*(t)), \]

where

\[ M(t) = [x^*(t)f'(y^*(t)) + \alpha f'(y^*(t))(y^*(t) - x^*(t)) + \alpha f(y^*(t))] \]

From this equation for \( \lambda_2(t) \) we conclude that for small enough \( \varepsilon > 0, \)

\[ \lambda_2(t_1 - \varepsilon) = \lambda_2^*(t_0) \exp \int_{t_0}^{t_1-\varepsilon} k(t)dt \]

(2.10) Now we observe that from Lemma 2, there are positive constants \( d_1, d_2 \) that

\[ f(y^*(t)) \geq d_1, \ y^*(t) - x^*(t) \geq d_2. \]

Thus \( k(t) \) is bounded for \( t \in [t_0, t_1], \) and if we let \( \varepsilon \) tend to zero in (2.10), by the continuity of \( \lambda_2^*(t) \) we conclude

\[ 0 = \lambda_2^*(t_1) = \lambda_2^*(t_0) \exp \int_{t_0}^{t_1} k(t)dt \]

But \( \lambda_2^*(t_0) < 0 \) and \( \int_{t_0}^{t_1} k(t)dt < +\infty, \) and the last equality is a contradiction.

\[ \square \]

**Lemma 5:** \( \lambda_1^*(t) > 0 \) for all \( t \in [0, t_1^*] \)

**Proof:** first we observe that by using Lemma 3, the third equation in (2.6),

\[ \frac{d\lambda_1^*}{dt}(t^*_j-) = -u_{max} g'(y^*(t^*_j) - x^*(t^*_j)) < 0. \]
Thus $\lambda_1^*(t) > 0$ in a neighborhood of $t_f^*$. Suppose that $\lambda_1^*(t)$ is zero for some time $t \in [0, t_f^*)$, and consider $t_0 \in [0, t_f^*)$ to be the closest to $t_f^*$ with this property. Thus, there exists a maximum point $\bar{t} \in (t_0, t_f^*)$ for $\lambda_1^*(t)$, and we have $\lambda_1^*(\bar{t}) > 0$.

Now, using again the third equation in (2.6) to compute the left derivative of $\lambda_1^*$ at $\bar{t}$, since $\bar{t}$ is a maximum point, we conclude

$$0 \leq \frac{d\lambda_1^*(\bar{t}^-)}{dt} = -\lambda_1^*(\bar{t}) f(y^*(\bar{t}))(1 - a) - \lambda_2^*(\bar{t}) u^*(\bar{t}^-) g'(y^*(\bar{t}) - x^*(t)) < 0$$

A contradiction that implies the stated result. □

Remark: An argument similar to the previous one actually proves that $\lambda_1^*(t)$ is strictly decreasing.

Now we are ready to complete the

Proof of the Theorem:

We have to prove that the only possibility in (2.8) is the second. In fact, if for some time $t \in [0, t_f^*)$ the control $u^*(t)$ is zero or singular then (2.5) and (2.8) provide exactly the relationship (2.9) between $\lambda_1^*(t)$ and $\lambda_2^*(t)$.

Moreover, $y^*(t) > 0$, $f(y^*(t)) > 0$, $y^*(t) - x^*(t) > 0$, and by using Lemma 4 and 5, we have

$$0 < \lambda_1^*(t) = -a \lambda_2^*(t) \leq 0,$$

where $a$ is a positive number which is a contradiction.

Thus, $u(t) = u_{max}$ for all $t \in [0, t_f^*)$.

Now we have to characterize $t_f^*$. For this we observe that if $t_f^* > 0$, from the fact that $J_c(u^*(\cdot), t_f^*)$ is a minimum and $t_f^*$ is in the interior of $[0, \infty)$, we conclude that $\frac{\partial J_c}{\partial t_f}(u^*(\cdot), t_f^*) = 0$. So, this conclusion and the definition (1.3) imply:

$$\frac{dy}{dt}(t_f^*) + cu^*(t_f^*) = 0,$$

which proves the stated result. □
3. APPLICATIONS

3.1. Chemotherapy

An example of application of the previous results concerns chemotherapeutic treatment of tumor growth. We will consider a model in which the chemothermal treatment with a single cycle nonspecific agent is assumed to be continuous in time. The clinical support for this kind of procedure and its advantages over the discrete drug dosages can be encountered in Dorr et al [4] and Shepard et al [9].

Moreover, for simplicity, we will assume that the kill rate of the anticancer drug is linearly proportional to its concentration in tumor site, that is, there is no saturation effect of the kill rate.

Another relevant aspect of the model is the development of drug resistance, which was emphasized by Goldie and Coldman [5] (see also Skipper [10]).

According to Vendite [12], [13], a model which includes the characteristics mentioned above is given by

\[
\begin{align*}
\frac{dR}{dt} &= Rr(1 - kN) + \alpha r(1 - kN)(N - R) \\
\frac{dN}{dt} &= Nr(1 - kN) - u(t)F(N - R) \\
R(0) &= R_0; \quad N(0) = N_0;
\end{align*}
\]

(3.1)

where \( R(t) \) is the number of drug resistant cells, \( N(t) \) is the total number of tumor cells, \( u(t) \) is the drug concentration in the tumor site, \( 1/k \) is the maximum tumor size, \( F \) is the effectiveness of the drug and \( \alpha \) is the fraction per unit of time of the drug sensitive cells that mutates into drug resistant cells. \( N(t) - R(t) \) is the number of drug sensitive cells.

A biological validation of this model was performed by “in vitro” experiments with T-cell lymphoblastic cell line CCRF-CEM. A description of these experiments can be found in Vendite [12].

We observe that the system above is a special case of (1.1).

An optimal chemotherapeutic treatment will be defined as the one that minimizes the functional:

\[ J(u(\cdot), t_f) = N(t_f) + c \int_0^{t_f} u(t) dt \]

which is exactly as (1.3).
The correspondence between the above problem and (1.1), (1.3) is listed below

\[ N(t) \equiv y(t) \; ; \; R(t) \equiv x(t) \; ; \; f(y) = r(1 - kN) \; ; \; g(y - x) = F(N - R), \]

where \( F > 0 \) is a constant.

In this case, we notice that the cells growth obeys a logistic dynamics where \( N = \frac{1}{k} \) is the saturation level of the tumor (i.e., \( y_m = \frac{1}{k} \)). Therefore, the present case can be solved by means of the theorem where assumptions (2.1), (2.2) and \( R_0 \leq N_0 \leq \frac{1}{k} \) hold. So, the drug concentration must be kept at its allowable maximum.

The optimal treatment duration \( t_f^* \) is given by

\[ \frac{dN}{dt}(t_f^*) = -cu^*(t_f^*). \]
In other words, the treatment must be interrupted when the growth rate of the tumor cells equals \(-cu_{\text{max}}\). When \(c = 0\), this occurs for \(\frac{dN}{dt}(t^*_f) = 0\), that is, when the level of tumor cells attains its minimum, whereas for \(c > 0\) the same does not occur on account of toxicity effects.

We would like to mention that with respect to toxicity effects, a different approach is to consider the harmful effects of the drugs on the normal cells. This can be modelled, for example, by the introduction of another differential equation describing the dynamics of the normal cells (see, for instance, Murray [8], Zietz and Nicolini [15]).

3.2. Control of bacteria growth in cellulose medium

The second application concerns the control of bacteria growth in cellulose medium where fermentation takes place due to bacterial activity. (Bastin [2], Costa and Bassanezi [3]).

As the levels of bacteria goes beyond a certain threshold, the quality of the final product may become endangered (for example, a yellow dyed paper), resulting in a probably discarding of the material.

Once this level is attained, the whole process is interrupted in order to clean up the reservoirs. In practice the method used to control bacteria growth resorts to bactericide application. Thus, the optimal control problem formulated here involves the application of bactericide (the control) so that the final level of bacteria and the cost of the amount of bactericide employed should be simultaneously minimized.

According to [3], a model for this case is as follows:

\[
\begin{align*}
\frac{dR}{dt} &= rR + \alpha r(B - R) \\
\frac{dB}{dt} &= rB - u(t)F(B - R) \\
R(0) &= R_0, \quad B(0) = B_0,
\end{align*}
\]

(3.2)

where \(R(t)\) is the number of resistant bacteria, \(B(t)\) is the total number of bacteria, \(u(t)\) is the rate of bactericide application, \(F\) is a constant denoting bactericide effectiveness, \(r\) is the bacteria per capita growth rate and \(\alpha\) is the fraction per unit of time of the non-resistant bacteria that mutates into resistant bacteria. \(B(t) - R(t)\) is the number of non resistant bacteria.
The variables corresponding to (1.1) are

\[ B(t) \equiv y(t), \ R(t) \equiv x(t), \ f(y) = r, \ g(y - x) = F(B - R). \]

In this case the bacteria per capita growth rate is constant and equal to \( r \), since it is assumed that during the process the quantity of nutrients is abundant, allowing thus, for unconstrained growth (more precisely, exponential growth).

The functional to be minimized is similar to (1.3).

\[ J(u(\cdot), \ t_f) = B(t_f) + c \int_0^{t_f} u(t) dt. \]

So, the present problem can be solved by means of the theorem where assumptions (2.1), (2.3) hold. Thus, bactericide should be applied at its maximum rate.

The same reasoning employed in the previous application for the optimal time process, \( t_f^* \), holds true here.
4. Discussion

The results obtained in the previous applications were expected, but the main concern of theorem which generated them lies in the fact that the basic optimal strategy is independent of the "natural" growth rates and kill rates of drugs and this, to some extent, justifies what is usually done in several practical circumstances where the degree of uncertainty is high.

For the case $c = 0$, the optimal strategy can be interpreted in the following way: one must administer the drug at the maximum allowable rate ($u_{\text{max}}$) until the number of total population is minimum ($\frac{dy}{dt}(t_f) = 0$); then the treatment must be discontinued. When $c > 0$, it must be discontinued earlier because toxicity effects are accounted for.

We remark that by using numerical calculations, Vendite [12], [14] conjectured the same optimal strategy for $c = 0$. Thus, in this paper we have actually proved a generalization of his conjecture.

Other authors have used optimal Control Theory to study chemotherapeutic treatment (see Swan [11], Murray [8], Zietz and Nicolini [15]), although drug resistance is not taken into account in their models.

Finally we would like to mention that more complex models involving, for example, the use of several drugs or cycle specific drugs could be considered. One could also try an analysis of more complex functionals than (1.3) or of the nondominated-optimality (Pareto-optimal) to balance between the required minimum of total population and, at the same time, reduce the side effects.
4. REFERENCES


