# Chemotherapeutic Treatments Involving Drug Resistance and Level of Normal Cells as a Criterion of Toxicity

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## ABSTRACT

A system of differential equations for the control of tumor cells growth in a cycle nonspecific chemotherapy is presented. Drug resistance and toxicity conveyed through the level of normal cells are taken into account in a class of optimal control problems. Alternative treatments for the exponential tumor growth are set forth for cases where optimal treatments are not available.

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## 1. INTRODUCTION

In cancer chemotherapy one aims to control the number of tumor cells in patients, and, for reasons of health safety, some sort of optimal use of the involved drugs would be desirable. However, 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 the drugs, drug resistance, cell growth models, and appropriate criteria for measuring toxicity.

The modeling of the origin and treatment of tumors containing drug resistant cells can be addressed by means of probabilistic models (see [1,2,8–10]) where the parameters possess biological interpretation and their values can be estimated. Therefore, these models can have their predictions tested against clinical data, providing quantitative information for chemotherapeutic protocols.

From another modeling standpoint, in this work (as well as in [3–5]) deterministic models are utilized to describe the evolution and treatment of tumor containing drug resistant cells. Unlike their probabilistic

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counterparts some of their parameters may lack biological interpretation. However, one of the reasons for resorting to them is that they can be seen as an average behavior of the erratic nature of tumor cells growth. Furthermore they may serve as a guide to a qualitative comprehension of the phenomena involved in chemotherapeutic protocols and growth of tumor cells, and may show the relevant aspects captured by the model.

Specifically, the model utilized in this analysis consists of a system of differential equations based on the work of Goldie and Coldman [7, p. 1732] which describes the dynamics of tumor cells (resistant and drug sensitive). Adding to this system a perturbation term to account for the effect of the drug on the tumor cells and an objective function to be optimized, optimal control theory is applied in order to provide chemotherapeutic protocols in qualitative terms. We point out that the first paper to utilize engineering optimal control theory for a chemotherapeutic problem involving a human tumor is found in Swan and Vincent [21], and in Swan [20] there is an extensive review of optimal control theory in cancer chemotherapy.

Some optimal chemotherapeutic treatment were devised in [4] and [5] and the common features of these works were drug resistance and toxicity, where the latter was conveyed through the drug accumulation in the patient's body.

This work attempts to devise optimal treatments in a deterministic setting when drug resistance is taken into account and toxicity is modeled via a minimum level of normal cells which should not be violated. Unlike the toxicity criterion utilized in our previous works [4,5], this criterion in a noncumulative one.

Some authors [13,14,24] utilize normal cells as an indicator of toxicity and their optimal treatments may include rest periods.

As opposed to that, it is shown in this work that the introduction of drug resistance in the model leads to an optimal treatment consisting of maximum allowable drug concentration throughout, and, moreover, although restricted to a set of initial conditions, it is valid for a class of general growth functions and kill rates. For the Malthusian (exponential) cell growth and a linear kill rate, it is shown that under certain conditions, rest periods, albeit not optimal, can be incorporated into alternative treatments.

## 2. OPTIMAL CHEMOTHERAPY WITH NORMAL CELLS

In order to carry out the analysis of tumor growth submitted to chemotherapy some assumptions are made:

(1) The tumor will be viewed as a cell population undergoing homo-

geneous growth, that is, it does not depend on the cell position within the tumor.

(2) The tumor will consist also of drug-resistant cells whose growth rate depends not only on the size of its own population, but on the size of the sensitive cells as well. This latter dependence is due to a randomly spontaneous mutation during mitosis towards drug resistance, which will occur according to a constant probability. In this way no sensitive cell becomes drug resistant during its life time; only their daughter cells may acquire drug resistance by spontaneous mutation during mitosis. A biological validation of this kind of drug resistance was performed by "in vitro" experiments with T-cell lymphoblastic cell line CCRF-CEM. A description of these experiments can be found in Vendite [23]. (The importance of drug resistance in designing chemotherapeutic protocols is also emphasized in Skipper [16]).

(3) The kill rate of the drug (number of cells killed/unit drug concentration) will be considered as a function of the size of the sensitive cells population. As for the normal cells the kill rate will also be a function of their own population size.

The following system is a model for the behavior of tumoral and normal cells submitted to chemotherapy when the assumptions mentioned above are taken into account:

$$\begin{aligned} \frac{dx}{dt} &= xf(y) + \alpha f(y)(y-x), \\ \frac{dy}{dt} &= yf(y) - u(t)g(y-x), \\ \frac{dn}{dt} &= nf_1(n) - u(t)g_1(n), \\ x(0) = x_0, \qquad & y(0) = y_0, \qquad n(0) = n_0. \end{aligned} \tag{2.1}$$

Here, $t \geqslant 0$ represents the elapsed time; $y(t) \in \mathbb{R}$ stands for the total number of tumor cells at time $t$, while $x(t) \in \mathbb{R}$ stands for the number of drug-resistant cells within the tumor and $n(t)$ is the number of normal cells. Clearly, any initial condition $(x_0, y_0)$ is such that $x_0 < y_0$; $f(y)$ and $f_1(n)$ are the specific growth rates for the tumor and normal cells, respectively; $0 < \alpha < 1$ is the fraction per unit of time of the drug sensitive cells that mutates into drug resistant cells; $0 \leqslant u(t) \leqslant u_m$ is the drug concentration at the tumor site (assumed to be limited, i.e., $u_m < +\infty$); $g$ and $g_1$ give the kill rate of the drug per unit of drug concentration as function of the drug-sensitive cells or as a function of the normal cells. As in [5] $f$, $f_1$, $g$, and $g_1$ are taken to be $C^1$-functions and we will be interested in solving the following free end-time optimal control problem associated with (2.1):

Find a time $0 \leqslant t_f^* < +\infty$ and a $BV[0,t_f^*]$-function $u^*\colon [0,t_f^*] \to \mathbb{R}$ (here $BV[0,t_f^*]$ indicates the class of bounded variation functions defined in $[0,t_f^*]$), $0 \leqslant u^*(t) \leqslant u_m$ almost everywhere in $[0,t_f^*]$, that will be the optimal drug concentration in the sense that

$$\begin{aligned} &J_c(u^*(\cdot),t_f^*) \\ &\quad = \text{minimum}\,\{J_c(u,t_f),\, u \in BV[0,t_f],\, t_f > 0;\, 0 \leqslant u(t) \leqslant u_m \text{ a.e.}\} \end{aligned} \tag{2.2}$$

subject to (2.1) and $n(t) \geqslant \beta$ where the functional $J_c$ is defined by

$$J_c(u,t_f) = y(t_f). \tag{2.3}$$

The functional is the number of tumor cells at the end of the treatment, while $\beta$ represents the lowest admissible level of normal cells, indicating a possible measure of toxicity.

As to the functions $f, f_1$ and $g, g_1$ that appear in (2.1), we will consider the following natural assumptions:

$$\begin{aligned} &f, f_1, g, g_1 \text{ are } C^1\text{-functions.} \\ &\text{Moreover, } g(0) = g_1(0) = 0,\ g(s), g_1(s) > 0 \text{ and} \\ &g'(s), g_1'(s) > 0 \text{ when } s > 0 \end{aligned} \tag{2.4}$$

and

$$\begin{aligned} &\text{there exist } y_m > 0 \text{ and } n_m > 0 \\ &\text{such that } f(y_m) = f_1(n_m) = 0, \text{ and} \\ &f(y), f_1(n) > 0 \text{ for } 0 \leqslant y < y_m \text{ and } 0 \leqslant n < n_m \end{aligned} \tag{2.5}$$

or

$$f(y), f_1(n) > 0 \text{ for } y \geqslant 0, n \geqslant 0, f, f_1 \text{ and } g, g_1 \text{ are globally Lipschitz.} \tag{2.6}$$

In (2.4) the two first expressions indicate that the drug effect is strictly related to the existence of sensitive (normal) cells and the third one states that the drug effect increases as the level of sensitive (normal) cells increases.

In (2.5) it is stated that the tumor (normal cells) exhibits a density dependent growth, where $y_m(n_m)$ is the maximum attainable level of tumor (normal) cells.

In (2.6) it is assumed that there is no maximum attainable level of tumor (normal) cells and that the relative increment of kill rate per unit concentration is bounded.

The behavior of system (2.1) without drug injection for all $t(u(t) = 0 \forall t \geqslant 0)$ corresponds to the dynamics obtained in [7, p. 1732] describing the evolution of resistant cells in relation to the number of tumoral cells.

Now we define an open set $\Omega$ in $\mathbb{R}^2$ as

(i) $\Omega = \{(x,y) \in \mathbb{R}^2 \colon 0 < x, 0 < y, x < y\}$
if assumptions (2.4) and (2.6) hold.

(ii) $\Omega = \{(x,y) \in \mathbb{R}^2 \colon 0 < x, 0 < y < y_m, x < y\}$
if assumptions (2.4) and (2.5) hold.

Before proceeding to the analysis of the optimal control problem, we enunciate a lemma that can be proved in exactly the same way as in Lemma 2 in [4]. (It is enough to observe that the first two equations (2.1) are the same as the ones in [4].) This lemma relates the trajectories of system (2.1) with the open set $\Omega$.

*LEMMA 1*

*Consider* $u(t) \geqslant 0$ *a function of bounded variation. The corresponding solution* $(x(t), y(t), n(t))$ *of* (2.1) *with initial conditions* $(x_0, y_0, n_0)$ *satisfying* $(x_0, y_0) \in \Omega$ *is such that its projection on the* $x, y$*-plane, that is* $(x(t), y(t))$, *never touches the boundary of* $\Omega$ *in finite time.*

*This lemma implies in particular that* $0 < x(t) < y(t)$ *for all finite time* $t$.

Before beginning the analysis some comments are in order. A relationship among $u_m$ and the functions $f_1$, $g_1$, and $n$ must be required so that the present problem should not fall exactly in the same frame as that tackled in [4]. In fact, if $dn/dt = nf_1(n) - u_m g_1(n) > 0$ with $n(0) \geqslant \beta$, then $n(t) \geqslant \beta$ for any treatment such that $0 \leqslant u(t) \leqslant u_m$. In this case, the condition $n(t) \geqslant \beta$ is always satisfied and the problem is reduced to the one studied in [4]. To rule out this possibility we will require, in this analysis, that

$$nf_1(n) - u_m g_1(n) < 0 \tag{2.7}$$

for all $n$.

The meaning of the above condition will be made clear in the example in Section 3.

Now we proceed to the study of the optimal control problem formed by (2.1) and (2.2). In clinical terms, the main result of this section states that if an optimal treatment exists, it should consist of maximum allowable drug concentration ($u_m$) at the tumor site throughout and the treatment should be discontinued as soon as the tumor level ($y$) attains its lowest level (i.e., $dy/dt(t_f)=0$, $t_f$-final time) under the condition that the level of normal cells should be higher than $\beta$ all along the treatment, and it could be equal to $\beta$ only at the final time $t_f$. And conversely, if the level of normal cells attains $\beta$ under the maximum allowable drug concentration, the treatment should be immediately discontinued, with the final value of the tumor level determined by this instant, which may not correspond to its lowest level. In this case this treatment is not optimal. We return to this point in Section 3 in order to provide alternative strategies which yield better results than this one.

As for the mathematical analysis, we will follow the procedure of Sage [15] for bounded control and state variables.

Let $z$ and $w$ be slack variables such that

$$z^2=(u_m-u)u$$

and

$$w^2=n-\beta$$

and the augmented functional

$$\begin{aligned}\bar{J}=y(t_0)+\int_{t_0}^{t_f}\{\dot{y}(t_f)+\lambda_1[(xf(y)+\alpha f(y)(y-x)-\dot{x}]\\ +\lambda_2[(yf(y)-u(t)g(y-x))-\dot{y}]+\lambda_3[(nf_1(n)-u(t)g_1(n))-\dot{n}]\\ +p_1(t)[(u_m-u)u-z^2]+p_2(t)[n(t)-\beta-w^2]\}\,dt,\end{aligned}$$

where $\lambda_1,\lambda_2,\lambda_3,p_1,p_2$ are adjoint variables (throughout this work the symbol "$\cdot$" over a variable will denote the time derivative of that variable, "$\cdot$" and "$d/dt$" will be used interchangeably).

Applying the Euler–Lagrange equations to the augmented functional,

$$\begin{aligned}-\dot{\lambda}_1&=\lambda_1 f(y)(1-\alpha)-\lambda_2 u(t)\frac{\partial g(y-x)}{\partial x}\\ -\dot{\lambda}_2&=\lambda_1(xf'(y)+\alpha f'(y)(y-x)+\alpha f(y))\\ &\quad+\lambda_2\left(yf'(y)+f(y)-u(t)\frac{\partial g}{\partial y}(y-x)\right)\\ -\dot{\lambda}_3&=\lambda_3(f_1(m)+nf_1'(n)-u(t)g_1'(n))+p_2(t)\end{aligned}\tag{2.8}$$

$$\lambda_1(t_f)=0;\qquad \lambda_2(t_f)=1;\qquad \lambda_3(t_f)=0\ (\text{transversality conditions}),$$

$$-\lambda_2 g(y-x)-\lambda_3 g_1(n)+p_1(t)(u_m-2u)=0\tag{2.9}$$

$$p_1(t)z(t)=0\tag{2.10}$$

$$p_2(t)w(t)=0\tag{2.11}$$

and the optimal final time $t_f^*$ is given by

$$\frac{dy}{dt}(t_f^*) = 0.$$

*LEMMA 2*

*If there is an optimal strategy $u^*(t)$ on $[0, t_f^*]$, then $u^*(t) = u_m$ in a neighborhood to the left of $t_f$.*

*Proof.* By equation (2.9), $p_1(t_f) \neq 0$ since $\lambda_3(t_f) = 0$ and $\lambda_2(t_f) = 1$. Therefore at $t_f$ the optimal control is $u_m$ or 0. The case $u(t_f) = 0$ is ruled out since we seek to minimize $y(t_f)$. Moreover, by the condition (2.7) this result indicates that the level of normal cells must be strictly above $\beta$ just before the end of the treatment. ■

Next we prove the following lemma.

*LEMMA 3*

*If there exists an optimal strategy $u^*(t)$ for all $t \in [0, t_f^*]$, then the corresponding $n^*(t)$ is such that $n^*(t) > \beta$ for all $t \in [0, t_f^*)$. Thus $n^*(t)$ could be equal to $\beta$ only at the final time $t_f^*$. Moreover, $u^*(t) = u_m$ for $t \in [0, t_f^*]$.*

*Proof.* Suppose by contradiction that $n^*(t)$ is equal to $\beta$ at certain times. Consider $\bar{t}$ as the smallest time in the interval $[0, t_f^*]$ such that for $t \in (\bar{t}, t_f^*], n(t) > \beta$ except on sets of measure zero.

We observe that $0 \leqslant \bar{t} < t_f^*$ because it is known that in a neighborhood of $t_f^*$ the optimal strategy should be $u_m$ and, therefore, $n^*(t)$ should be strictly decreasing (hypothesis (2.7)) in this region. Since $n^*(t_f) \geqslant \beta$ we should have $n(t) > \beta$ for $t$ in a small neighborhood to the left of $t_f^*$. In $[\bar{t}, t_f^*]$ we can apply the version of the Pontryagin's minimum principle for problems with state variables constraints (see Lee and Markus [12, p. 336]). However, as in $[\bar{t}, t_f^*]$ the restrictions $(n \geqslant \beta)$ are active $(n = \beta)$ only on sets of measure zero, we can resort to the usual Pontryagin's minimum principle in order to check whether the proposed strategy is optimal in $[\bar{t}, t_f^*]$.

The state equations are the same as (2.1) and the Hamiltonian [11] is given by

$$\begin{aligned} H = {} & \lambda_1(xf(y) + \alpha f(y)(y - x)) + \lambda_2(yf(y) - u(t)g(y - x)) \\ & + \lambda_3(nf_1(n) - u(t)g_1(n)). \end{aligned}$$

The Hamiltonian yields the same costate equations for $\lambda_1$ and $\lambda_2$ as in (2.8). The transversality conditions $\lambda_1, \lambda_2, \lambda_3$ remain the same. In

$[\bar{t}, t_f^*]\, n(t) \geq \beta$ and equal to $\beta$ only on sets of measure zero. Consequently $w(t) \neq 0$ and $p_2(t) = 0$ in this interval (except on sets of measure zero) ((2.10) and (2.11)). This implies that for $t \in [\bar{t}, t_f^*]$

$$\frac{d\lambda_3}{dt} = \lambda_3\big(u(t)g_1'(m) - f_1(n) - nf_1'(n)\big), \qquad \lambda_3(t_f^*) = 0.$$

Integrating backwards this equation in $[\bar{t}, t_f^*]$ yields $\lambda_3(t) = 0$ in this same interval.

Therefore, in $[\bar{t}, t_f^*]$ the present problems reduces exactly to that one tackled in [4] with the functional $J = y(t_f)$. In this way, we can apply the results that concern $\lambda_1$ and $\lambda_2$ in [4] for $t \in [\bar{t}, t_f^*]$. The following lemmas also hold true here:

*LEMMA 4*

$\lambda_2(t) \geq 0$ *for all* $t \in [\bar{t}, t_f^*]$.

*LEMMA 5*

$\lambda_1(t) > 0$ *for all* $t \in [\bar{t}, t_f^*]$.

The proofs can be found in [4, p. 220–21].

Proceeding accordingly, Theorem 1 stated in [4], which guarantees that the sole optimal strategy is $u(t) = u_m$, is also valid here for all $t \in [\bar{t}, t_f^*]$.

If $\bar{t} = 0$, we have $u(t) = u_m$ for all $t \in [0, t_f^*]$. Thus $n(t)$ is strictly decreasing and since $n(t_f) \geq \beta$, we conclude that $n(t) > \beta$ for all $t \in [0, t_f^*)$, which is a contradiction with the assumption that $n^*(t)$ was equal to $\beta$ at certain times.

If $\bar{t} > 0$, we observe that by its own definition and the continuity of $n^*(t), n^*(t) = \beta$ in an interval $(\bar{\bar{t}}, \bar{t}]$ where $\bar{\bar{t}} < \bar{t}$. But this is a contradiction because it was previously shown that $n(t) > \beta$ for $\bar{t} < t < t_f^*$ ($n(t)$ is strictly decreasing in this interval) and on the other hand $n(t) = \beta$ for $t \in [\bar{\bar{t}}, \bar{t})$. Thus $\lim_{t \to \bar{t}_-} n(t) = \beta$ and $\lim_{t \to \bar{t}_+} n(t) > \beta$ and $n(t)$ could not be continuous. This proves the stated lemma. ■

Hence, if there exists an optimal treatment, the drug concentration at the tumor site should be maintained at its maximum allowable level throughout the treatment. This result holds true for growth functions and kill rates considered at the beginning of this section, including different kill rates for tumor and normal cells.

However there may be initial levels of tumor and normal cells for which the application of $u_m$ till the tumor level attains its minimum (i.e., $dy/dt = 0$) may violate the constraint $n(t) \geq \beta$. In such cases an optimal treatment as defined above is not possible, thus calling for alternative improving strategies.

For instance, should one apply maximum drug concentration until the normal cells attain its lowest allowable level and then discontinue the treatment or is there any treatment after attaining $\beta$ with the application of $u_m$, which will yield better results? This question will be addressed in the next section for the case of exponential growth.

## 3. ALTERNATIVE TREATMENTS IN THE MALTHUSIAN CASE

In the sequel, we proceed to the search of alternative treatments when tumor and normal cells obey a Malthusian (exponential) growth and the kill rate is linearly proportional to the level of sensitive cells.

This model assumes that the specific growth rate of the tumor and normal cells is constant ($f(\cdot) = r$). Its importance is centered on the introduction of the concept of doubling time and, although it does not have a strong physiological basis, it starts with a reasonable assumption [22] (this model is used for modeling cell growth in [6]). The system corresponding to (2.1) has the following form:

$$\begin{aligned} \frac{dx}{dt} &= rx + \alpha r(y - x), \\ \frac{dy}{dt} &= ry - Fu(t)(y - x), \\ \frac{dn}{dt} &= r_1 n - F_1 u(t) n, \\ x(0) = x_0; \qquad & y(0) = y_0; \qquad n(0) = n_0, \end{aligned} \tag{3.1}$$

where the tumor and normal cells have specific growth rates $r$ and $r_1$, respectively. As the drug may act differently on each kind of cell, different constants of proportionality—$F$ and $F_1$—for tumor and normal cells, respectively, were assigned to the kill rates. Moreover, in this analysis condition (2.7) reduces to $r_1 - F_1 u_m < 0$, thus guaranteeing that the problem does not fall in the same frame of [4]. This will be assumed throughout this section.

We start by spotting on the space $x, y, n$ the initial conditions $(x_0, y_0, n_0)$ for which $u^*(t) = u_m$ for all $t \in [0, t_f]$ is really an optimal strategy. The remaining initial conditions in the positive orthant will be the subject of the present analysis.

Since the system (3.1) possesses explicit solutions for $u(t)^* = u_m$, we can calculate the span of time $\Delta t_n$ needed to reach $n = \beta$ for $n(0) = n_0$ when $u^*(t) = u_m$ is applied for all $t$.

From the equation of $dn/dt$ in (3.1)

$$\Delta t_n = \frac{1}{F_1 u_m - r_1} ln \frac{n_0}{\beta}, \tag{3.2}$$

where $\Delta t_n$ is the time needed to attain $n = \beta$ when $n(0) = n_0$ and $u(t) = u_m$ is applied for all $t$. Since an optimal strategy must end at $\dot{y}(t_f^*) = 0$ with $u^*(t_f^*) = u_m$, the span of time $\Delta t_y$ needed to reach $\dot{y}(t_f^*) = 0$ with $u^*(t) = u_m$ for all $t \in [0, t_f^*]$ can be calculated from the equation of $dy/dt$ in (3.1), yielding

$$\Delta t_y = \frac{1}{\alpha r + Fu_m} ln \frac{(r - \alpha r - Fu_m)u_m F(y_0 - x_0)}{ru_m F(y_0 - x_0) - ry_0(\alpha r + Fu_m)}. \tag{3.3}$$

We must require that $\Delta t_y \leqslant \Delta t_n$ in order that $u^*(t) = u_m$ does not violate $n \geqslant \beta$. Therefore, the above inequality involving $\Delta t_y$ and $\Delta t_n$ gives

$$n_0 \geqslant \beta \left( \frac{(r - \alpha r - Fu_m)u_m F(y_0 - x_0)}{ru_m(y_0 - x_0) - ry_0(\alpha r + Fu_m)} \right)^{(F_1 u_m - r_1)/(\alpha r + Fu_m)}. \tag{3.4}$$

The equality in (3.4) determines a helix in the space $x, y, n$ (as depicted in Figure 1).

Any initial condition $(x_0, y_0, n_0)$ on the helix or between it and the plane $n, x$ (see point A in Figure 1 for an example) has an optimal solution $u^*(t) = u_m$ for all $t \in [0, t_f^*]$.

It is worthwhile to remark that in clinical terms the same treatment may have different results. For instance, the inner points have the treatment finished at a higher level of normal cells (i.e., $n^*(t_f^*) > \beta$) than that of the points on the helix, which have the treatment discontinued at $n^*(t_f^*) = \beta$.

According to the results of the previous section, initial conditions between the helix and the plane $n, y$ (see point B in Figure 1) cannot have an optimal solution. Therefore, we seek treatments that, albeit not optimal, may decrease the tumor level with respect to the conspicuous treatment $u(t) = u_m$ for all $t$. For instance, we could try to put forward some cases for which it would be possible to administer drug after the normal cells minimum level has been attained without violating $n(t) \geqslant \beta$. A few cases are depicted in the Figure 1 (trajectories (1) and (2)).

The strategy of maximum drug concentration could be employed till the normal cells attain the level $n = \beta$. Thereafter, a strategy with

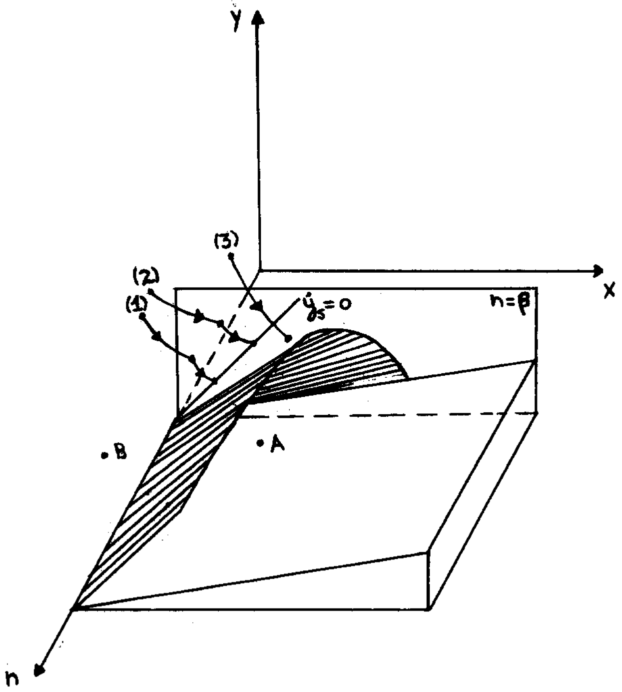

FIG. 1. Helix in the space $x, y, n$.

concentration $u_s = r_1/F_1$, which maintains the normal cells at level $\beta$ (because $\dot{n} = 0$ in this case), could be applied if we guaranteed that it would reduce further the tumor level. This will be so whenever the trajectory of system (3.1) with initial conditions above the helix and with $u(t) = u_m$ hits the plane $n = \beta$ to the left of the isocline $ry - Fu_s(y - x) = 0$ (i.e., $\dot{y} = 0$ for $u = u_s$) itself on the plane $n = \beta$ since $\dot{y} < 0$ for $u(t) = u_s$ in this region. In other words, the initial tumor levels for which it is possible to apply such strategy are determined by the backward integration from the isocline $ry - Fu_s(y - x) = 0$ ($\dot{y} = 0$ for $u(t) = r_1/F_1$) with $u(t) = u_m$ which forms a certain region in the $x, y, n$-space. Any other initial condition outside this region will hit the plane $n = \beta$ to the right of the isocline $\dot{y} = 0$ (for $u_s = r_1/F_1$) on the plane $n = \beta$ and no treatment with $u = u_s$ would reduce the tumor further (see trajectory (3) in Figure 1).

The question that now arises concerns rest periods since it is a common clinical evidence in chemotherapeutic protocols. In the set of alternative treatments we proceed to check whether there are conditions under which rest periods could improve the patient's health.

A possible way of carrying out this analysis consists of choosing an initial condition of the type $(x_0, y_0, \beta)$ and after letting the system evolve with $u = 0$ (rest period) till an arbitrary $(x_1, y_1, n_1)$ with $n_1 > \beta$, apply $u_m$ again till the normal cells attain $\beta$, that is, $(x_2, y_2, \beta)$. Then, it is to be checked if there was any improvement in the tumor level, i.e., if $y_2 < y_0$. Therefore, in the sequel we seek conditions for this improvement in terms of $n_1$. To wit, we try to evaluate how long a rest period should last so that the normal cells be able to recover without, however, letting the tumor become too large for further improvement of the treatment. To achieve this we need expressions that relate the various populations to the interval of rest periods, namely $\Delta_1$, and to the interval of application of $u_m$, namely $\Delta_2$.

In the exponential case, when $u(t) = u_m$ for all $t$ the equation for the tumor dynamics is as follows

$$\frac{dy}{dt} = ry - Fu_m(y - x). \tag{3.5}$$

The sensitive cells $z = y - x$ are governed by the following equation when $u(t) = u_m$ for all $t$

$$\frac{dz}{dt} = (r - Fu_m - \alpha r)z, \tag{3.6}$$

which has an explicit solution

$$z(t) = y(t) - x(t) = z(t_0)\exp[(1 - \alpha)r - Fu_m](t - t_0). \tag{3.7}$$

Substituting (3.7) into (3.5), yields

$$\frac{dy}{dt} = ry - Fu_m z(t_0)\exp[(1 - \alpha)r - Fu_m](t - t_0). \tag{3.8}$$

The solution of (3.8) is given by

$$y(t) = \exp[r(t - t_0)]\Bigg[y(t_0) + \frac{u_m F}{\alpha r + Fu_m}[y(t_0) - x(t_0)] \times [\exp[-(\alpha r + Fu_m)(t - t_0)] - 1]\Bigg]. \tag{3.9}$$

The rest period $\Delta_1$ is given by

$$\Delta_1 = \frac{1}{r_1} ln \frac{n_1}{\beta} \tag{3.10}$$

while $\Delta_2$, the application of $u_m$ till $\beta$ is reached has the following expression:

$$\Delta_2 = \frac{1}{F_1 u_m - r_1} ln \frac{n_1}{\beta}. \tag{3.11}$$

During the rest period the tumor evolves, namely, from $y_0$ to $y_1$ according to

$$y_1 = y_0 e^{r\Delta_1} \tag{3.12}$$

and during $\Delta_2$, it evolves, namely, from $y_1$ to $y_2$ according to (3.9).

Substituting (3.12) into (3.9) and after some cumbersome calculations we get an expression relating the final tumor level $y_2$ to the initial levels $y_0$ and $x_0$, given below:

$$\begin{aligned} y_2 = {} & y_0 \exp r(\Delta_1 + \Delta_2)(1 - k(n_1)\exp(-\alpha r \Delta_1)) \\ & + k(n_1) x_0 \exp r(\Delta_1 + \Delta_2)\exp(-\alpha r \Delta_1), \end{aligned} \tag{3.13}$$

where

$$k = \frac{1 - \exp[-(\alpha r + F u_m)\Delta_2]}{(\alpha r / F u_m + 1)}. \tag{3.14}$$

In order to have $y_2 < y_0$, we must require

$$\begin{aligned} & \exp r(\Delta_1 + \Delta_2)(1 - k(n_1)\exp(-\alpha r \Delta_1)) \\ & \quad + \gamma k(n_1)\exp r(\Delta_1 + \Delta_2)\exp(-\alpha r \Delta_1) < 1, \end{aligned} \tag{3.15}$$

where $\gamma = x_0 / y_0$. Since $\Delta_1$, $\Delta_2$, and $k$ can be written in terms of $n_1$ (equations (3.10),(3.11),(314)), inequality (3.15) can be expressed as a sum of functions of $n_1$, namely, $H_1(n_1) + \gamma H_2(n_1)$, where

$$\begin{aligned} H_1(n_1) &= \exp[r(\Delta_1 + \Delta_2)](1 - k(n_1)\exp(-\alpha r \Delta_1)) \\ &= \left(\frac{n_1}{\beta}\right)^{\theta} \left(1 - \frac{(n_1/\beta)^{-\xi} - (n_1/\beta)^{-\psi}}{\delta}\right) \\ H_2(n_1) &= \exp[r(\Delta_1 + \Delta_2)] k(n_1)\exp(-\alpha r \Delta_1) \\ &= \left(\frac{n_1}{\beta}\right)^{\theta} \left[\frac{(n_1/\beta)^{-\xi} - (n_1/\beta)^{-\psi}}{\delta}\right] \end{aligned}$$

and the constants $\theta, \psi, \xi, \delta$ are all positive and defined as follows:

$$\theta = r\left(\frac{1}{F_1 u_m - r_1} + \frac{1}{r_1}\right), \qquad \psi = \frac{\alpha r}{r_1} + \frac{\alpha r + F u_m}{F_1 u_m - r_1},$$
$$\xi = \frac{\alpha r}{r_1}, \qquad \delta = \frac{\alpha r}{F u_m} + 1. \tag{3.16}$$

Hence, we are searching for conditions that satisfy

$$H_1(n_1) + \gamma H_2(n_1) < 1. \tag{3.17}$$

The rest of the analysis will be carried out for $n_1 \approx \beta$, that is, whether any improvement in the therapy can be achieved by means of rest period when the normal cells level is near the lowest allowable level.

We observe that for $n_1 = \beta$,

$$H_1(n_1) + \gamma H_2(n_1)|_{n_1 = \beta} = 1 \tag{3.18}$$

and

$$\frac{dH_1(n_1)}{dn_1} + \gamma \frac{dH_2(n_1)}{dn_1}\bigg|_{n_1 = \beta} = \frac{\theta}{\beta} + \frac{(1-\gamma)}{\delta}\left[\frac{\xi - \psi}{\beta}\right]. \tag{3.19}$$

For there to be any improvement, we should impose that expression (3.19) be negative so that in the neighborhood of $n_1 = \beta$ inequality (3.17) be satisfied and consequently $y_2 < y_0$.

Substituting $\theta, \psi, \xi, \delta$ in (3.15) for their respective expressions in terms of the original model, we have

$$1 - \frac{rF_1}{r_1 F} > \gamma.$$

Since $0 < \gamma = x_0 / y_0 < 1$ then,

$$0 < \frac{rF_1}{r_1 F} < 1 \tag{3.20}$$

and

$$rF_1 < r_1 F \Rightarrow m = \frac{r}{r_1} < \frac{F}{F_1}. \tag{3.21}$$

In view of (3.21) and assuming that $r > r_1$, rest periods could improve the therapy if the drug effects on normal and tumor cells are differentiated, that is, if $F > F_1$. If they are similar ($F \approx F_1$), the only way to achieve improvement will be the instance where the specific growth of the normal cells is greater than that of the tumor cells (which is not the usual case).

The foregoing analysis provides also an approximate threshold of normal cells for which the rest periods are ineffective. In other words, no improvement can be gained if the level of normal cells after a rest period goes beyond a threshold given by

$$\left(\frac{n_1}{\beta}\right) > \left(\frac{\alpha r/Fu_m}{\alpha r/Fu_m + 1}\right)^{-(r/r_1 + r/(F_1 u_m - r_1))} \tag{3.22}$$

This can be achieved by imposing that the coefficient of $y_0$ in (3.13) be greater than 1. Since the remainder of the right-hand side of (3.13) is nonnegative, this implies that $y_2 > y_0$.

From the inequality (3.22) we can draw some relevant features. The prohibitive range for rest period application varies according to the ratio $\alpha r/Fu_m$—an interplay among drug resistance, tumor growth, and killing effectiveness of the drug. As $\alpha$ and/or $r$ gets smaller or $Fu_m$ gets bigger, the prohibitive region shrinks. Therefore rest periods may be effective if either the rate of mutation to drug-resistant cells and/or the tumor specific growth is low or the killing effect is high.

## 4. DISCUSSION

In this work we attempted to devise an optimal chemotherapeutic treatment that should minimize the tumor cells level at the end of the treatment while maintaining the normal cells above a prescribed level.

The optimal strategy consisted of keeping the maximum drug concentration at the tumor site throughout the treatment. This result holds true for a certain class of growth functions, kill rates, and a specified set of initial levels of tumor and normal cells. This set is determined by the proportion of drug-resistant cells within the tumor and the number of normal cells in the tumor region.

Since the optimal strategy was restricted to a set of initial conditions, we turned to search for alternative strategies. This was carried out for the case of exponential growth with a linear kill rate.

Two alternative strategies were put forward: initially, maximum drug concentration should be applied till the normal cells attained the lowest allowable level $\beta$, then:

(1) the drug concentration should be switched to the value $r_1/F_1$ that keeps the normal cells at a constant level and applied till the tumor attained its minimum level ($\dot{y}(t_f) = 0$);

(2) the treatment should be discontinued since there is no way to reduce the tumor further.

Either strategy (1) or (2) will be applied, depending on the tumor level ($y(t)$) at the time the normal cells attain their lowest allowable level ($\beta$) (that is, it depends on which side of the isocline $\dot{y}=0$ for $u=u_s$ the trajectory hits the plane $n(t)=\beta$) and the switching time will be given by the instant the normal cells attain the level $\beta$.

In the study of the general growth functions and kill rates, it was shown that rest periods were not part of any optimal strategy, though they are known to be used in chemotherapeutic protocols. However, in the context of alternative strategies for the exponential growth and under the assumption that the specific growth rate of the tumor cells is greater than that of the normal cells, rest periods could improve the treatment if: (a) the normal cells level were near its minimum allowable level and (b) the drug affected the tumor cells more effectively than the normal cells.

On the other hand, if the normal cells evolved beyond a specified value (determined by the parameters of the model) during a rest period, no improvement would be obtained by applying the maximum drug concentration again by virtue of the excessive growth of the tumor cells during the interruption of the treatment.

After summarizing the results, some comments are in order. One might expect that a threshold level imposed on the normal cells as a measure of toxicity would engender optimal strategies involving alternated drug concentration and rest periods (see Murray [13, 14] for uncoupled dynamical equations of tumor and normal cells growth without drug resistance). Such strategies did not prove to be optimal in this work.

Our view is that drug resistance plays a prevalent role in determining the optimal treatment. The drug resistant cell population is modeled by a strictly increasing population, whose tendency can only be decreased (but not reversed) through the treatment. Therefore, the maximum drug concentration emerges as the sole possible optimal treatment which minimizes the total tumor population irrespective of the growth functions and kill rates. Therefore, according to this deterministic model, the noncumulative toxicity conveyed by a minimum allowable level of normal cells appears to be not sufficient to override the effects of drug resistance.

This prevalence of maximum drug concentration as an optimal treatment is in part corroborated by the results obtained in probabilistic models. Although in that context the analysis refers to discrete drug application, the results indicate that rapid depletion of sensitive cells is essential and that if low dose therapies are continued over long periods of time, they are unlikely to be successful [1].

Likewise in Harnevo and Agur [8] where the emergence of drug resistance is treated as a dynamic process rather than a single constant, their results provide a formal basis for the conjecture that an effective treatment should entail a high drug concentration. Moreover, they argue that protocols involving frequent low concentration dosing may result in the rapid evolution of large, fully resistant, residual tumors.

Yet it is worthwhile to mention that in the course of our previous work, alternative concentrations as optimal treatments were obtained only for a combination of drug resistance, saturation effect and toxicity (see [5]).

To be in accordance with clinical evidence as regards rest periods, we suggest that a pharmacokinetic equation be adjoined to the model presented in this work. This conjecture is based on the fact that the drug decay rate plays an important role in the determination of optimal treatments as seen in [3]. Another suggestion concerns an alternative modeling of toxicity that would explicitly take into account the patient's recuperation from the side effects of the drug when the treatment is discontinued. This might be accomplished, for instance, by the introduction of the body immunological system's equations in the present models.

However, in spite of the difficulties intrinsic to the biological interpretation of the terms involved in the deterministic description of tumor growth and drug resistance and an appropriate choice for toxicity criterion (see [17–19]), we take the view that such models may shed light on some of the relevant aspects of theoretical chemotherapy and tumor cell growth in order to improve the overall qualitative understanding of cell dynamics and chemotherapeutic protocols.

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