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Drug Kinetics and Drug Resistance in Optimal Chemotherapy

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ABSTRACT

A system of differential equations for the control of tumor cells growth in a cycle nonspecific chemotherapy is presented. First-order drug kinetics and drug resistance are taken into account in a class of optimal control problems. The results show that the strategy corresponding to the maximum rate of drug injection is optimal for the Malthusian model of cell growth (which is a relatively good model for the initial phase of tumor growth). For more general models of cell growth, this strategy proved to be suboptimal under certain conditions.

1. INTRODUCTION

In several practical situations it is necessary to control the growth of certain populations by using some sort of chemical treatment. In cancer chemotherapy, for example, 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, and cell growth models.

The modeling of the origin and treatment of tumors containing drug resistant cells can be addressed by means of probabilistic models (see [2,3,10–12] 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.

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From another modeling standpoint, in this work (as well as in [5, 6]) deterministic models are utilized to describe the evolution and treatment of tumor containing drug resistance cells. Unlike their probabilistic 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 [8, 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 due to Swan and Vincent [16], and in Swan [15] there is an extensive review of optimal control theory in cancer chemotherapy.

The procedure of optimal control theory was taken up in [5], where an optimal chemotherapeutic treatment considering drug resistant cells was devised. There the control variable was cast as the drug concentration at the tumor site. The kill rate of the cells was assumed to be linearly proportional to the drug concentration and within this frame, the optimal strategy was proved to be the administration of the maximum allowed concentration of the drug.

On the other hand, the inclusion of the kill rate of saturation type imparted a much more intricate dynamics as compared to that found in [5]. As a consequence, drug concentrations other than its maximum value proved to be also optimal under certain conditions on the parameters of the problem and the initial tumor levels (see [6]).

In the analysis of the previous models of chemotherapeutic treatment it was assumed that drug injection rate and drug concentration at the tumor site were approximately equal. This assumption implies an instantaneous spreading of the drug and the absence of drug decay in the body.

In practice, however, there is a relationship which describes the behavior of the drug concentration once it enters the body. Such a relationship may be expressed in terms of a proper pharmacokinetic equation for the case of continuous injection, treating the body as one compartment.

The objective of this work is to contribute to a qualitative understanding of the interplay between the drug decay and drug resistance and the influence of this interplay in the determination of an optimal chemotherapeutic treatment.

The equation to be used that relates the drug concentration at the plasma to the actual administered dosage of the drug will consist of a first-order pharmacokinetics dynamics. The drug resistance will be assumed to be acquired by spontaneous mutation, at a certain rate (like in [5,6]; see also the next section for more details).

In Section 2 we formulate the mathematical optimal chemotherapy problem we will work with. We stress that in this work the control variable will be the concentration of drug injection instead of the concentration at the tumor site. Some general preparatory results independent of the specific tumor growth rates used in the model are also presented in this section. They are used in Section 3 to prove that maximum allowed drug injection is the optimal treatment strategy in the case of Malthusian (exponential) model of cell growth (Theorem 3.1). In Section 4 we prove that this strategy is suboptimal (see Section 4 for details) in the case of more general models of cell growth.

In Section 5 the results found in this work are compared with previous ones obtained in [5] and [6] concerning the effect of drug resistance, toxicity, saturation, and pharmacokinetics.

To close this section we point out that throughout this work we did not include in the objective function the cumulative toxicity criterion ($\int_0^t \rho u dt$-used in [5,6]) due to the major difficulties that appear in the mathematical analysis of the problem. This subject is still under investigation and we state some of the related mathematical difficulties also in Section 5.

2. A MATHEMATICAL MODEL WITH DRUG KINETICS

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

(1) The tumor will be viewed as a cell population undergoing homogeneous 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 toward 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 [18] (the importance of drug resistance in designing chemotherapeutic protocols is also emphasized in Skipper [14]).

(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.

(4) The drug concentration at the tumor site is related to the injected drug concentration by means of a first-order kinetics.

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

$$\begin{aligned} \frac{dx}{dt} &= xf(y) + \alpha f(y)(y-x) \\ \frac{dy}{dt} &= yf(y) - c(t)g(y-x) \\ \frac{dc}{dt} &= -\gamma c + u(t) \end{aligned} \tag{2.1}$$

$$x(0) = x_0, \qquad y(0) = y_0, \qquad c(0) = c_0.$$

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; $c(t)$ is the drug concentration at the tumor site; $c_0 \geqslant 0$ is the initial drug concentration at the tumor site. Clearly, any initial condition (x_0, y_0) is such that $0 < x_0 < y_0$; $f(y)$ is the specific growth rate, which can depend on the total number of cells; $0 < \alpha < 1$ 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 injected drug concentration in the body (assumed to be limited, i.e., $u_m < +\infty$); g gives the kill rate of the drug per unit of rate of drug concentration at the tumor site as function of the drug-sensitive cells; $\gamma > 0$ is the decay rate of the drug in the body.

As in [5,6] f and g 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 $u^*: [0,; t_f^*] \to \mathbb{R}$ (here $BV[0, t_f^*]$ indicates the class of bounded variation functions de-

fined 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

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

where the function J_c is defined by

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

This functional represents the number of tumor cells at the end of the treatment.

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

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

and

$$\text{there exists } y_m > 0 \text{ such that } f(y_m)=0 \text{ and } f(y)>0 \text{ for } 0 \leqslant y < y_m \tag{2.5}$$

or

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

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

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

In (2.6) it is assumed that there is no maximum attainable level of tumor 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 $t(c(t) \equiv 0, \forall t \geqslant 0)$ corresponds to the dynamics obtained in [8, p. 1732], describing the evolution of resistant cells in relation to the number of total tumoral cells.

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

(i) $\Omega = \{(x,y) \in \mathbb{R}^2 : 0 < x, 0 < y, x < y\}$
if assumptions (2.4) and (2.6) hold.
(ii) $\Omega = \{(x,y) \in \mathbb{R}^2 : 0 < x, 0 < y < y_m, x < y\}$
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 [5]. (It is enough to observe that the first two equations of (2.1) are the same as the ones in [5] with $u(t)$ replaced by $c(t)$, which is easily seen to be nonnegative). These lemmas relate the trajectories of system (2.1) with the open set Ω.

LEMMA 2.1

Consider $u(t) \geqslant 0$ a function of bounded variation. The corresponding solution $(x(t), y(t), c(t))$ of (2.1) with initial conditions (x_0, y_0, c_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 Ω in finite time.

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

Now we proceed to the study of the optimal control problem formed by (2.1) and (2.2). First of all we introduce the Hamiltonian (Kirk [13])

$$H(x,y,\lambda_1,\lambda_2,c,u) = \lambda_1[xf(y) + \alpha f(y)(y-x)] + \lambda_2[yf(y) - cg(y-x)] + \lambda_3(-\gamma c + u) \quad (2.7)$$

and the costate equations are:

$$\frac{d\lambda_1}{dt} = -\left(\lambda_1 f(y)(1-\alpha) - \lambda_2 c(t)\frac{\partial g(y-x)}{\partial x}\right)$$

$$\frac{d\lambda_2}{dt} = -\left[\lambda_1(xf'(y) + \alpha f'(y)(y-x) + \alpha f(y)) + \lambda_2\left(yf'(y) + f(y) - c(t)\frac{\partial g(y-x)}{\partial y}\right)\right]$$

$$\frac{d\lambda_3}{dt} = \lambda_2 g(y-x) + \lambda_3\gamma$$

with the respective final conditions:

$$\lambda_1(t_f) = \frac{\partial y(t_f)}{\partial x(t_f)}(t_f) = 0, \qquad \lambda_2(t_f) = \frac{\partial y(t_f)}{\partial y(t_f)}(t_f) = 1,$$

$$\lambda_3(t_f) = \frac{\partial y(t_f)}{\partial c(t_f)}(t_f) = 0.$$

According to the Pontryagin's minimum principle [13], the optimal control, $u^*(t)$, must minimize the Hamiltonian for all $t \in [0, t_f]$, and observing that the Hamiltonian is linear in the control variable u, we conclude that the optimal strategy depends on the sign of the coefficient of u (which is λ_3) and is as follows (control law):

$$u^* = \begin{cases} 0 & \text{if } \lambda_3 > 0 \\ u_m & \text{if } \lambda_3 < 0 \\ \text{undetermined} & \text{if } \lambda_3 = 0. \end{cases} \tag{2.8}$$

In the last case ($\lambda_3 = 0$), we say that a situation of *singular control* occurs.

Concerning this, we have the following result:

PROPOSITION 2.1

An optimal solution is such that the corresponding optimal control cannot be singular at any interval.

Proof. Suppose by contradiction that the optimal control is singular in some subinterval of $[0, t_f^*]$. Thus, in this subinterval $\lambda_3 \equiv 0$. By virtue of the equation of $d\lambda_3/dt$, we conclude that $\lambda_2 \equiv 0$ in the same interval (since, according to Lemma 2.1 and the conditions on g, we have $g(y(t) - x(t)) \neq 0$ at any finite time t). As the Hamiltonian is null on an optimal trajectory (this is a free end-time optimal control problem; see [13]), this implies that $\lambda_1 \equiv 0$ in the same interval. Since the costate equations are linear with respect to the costate variables, whose coefficients are bounded function of time on $[0, t_f^*]$, the fact that $\lambda_1 \equiv \lambda_2 \equiv \lambda_3 \equiv 0$ for some interval implies that the same holds for all $t \in [0; t_f^*]$. But $\lambda_2(t_f^*) = 1$, and this is a contradiction. ■

PROPOSITION 2.2

The last control to be applied in an optimal strategy is u_m. That is $u^*(t) = u_m$ for $t \in [t_f^* - \epsilon, t_f^*)$ for some $\epsilon > 0$.

Proof. Since $d\lambda_3/dt(t_f^*) = g(y(t_f^*) - x(t_f^*)) > 0$ because $\lambda_3(t_f^*) = 0$, and $\lambda_3(t_f^*)$ being continuous, we conclude that $\lambda_3(t) < 0$ in a neighborhood of t_f^*. Thus, the optimal control rule (2.8) implies the stated result. ■

The previous two propositions imply

PROPOSITION 2.3

An optimal treatment consists of either continuous drug injection at the highest rate (u_m) *or alternate periods of rest* $(u = 0)$ *and maximum drug injection.*

In view of Proposition 2.3 and the fact that the number of drug resistant cells is a strictly increasing function, another general result is drawn that concerns the performance of the two candidates for the optimal treatment.

COROLLARY 2.3.1

Let $y_m(t)$ *be the level of tumor cells corresponding to the maximum drug injection for all* $t > 0$ *and* $x(t)$ *be the level of drug resistant cells corresponding to the strategy of alternated rest periods* $(u = 0)$ *and maximum drug injection* $(u = u_m)$ *applied in an interval of time* $[0, t_f]$. *Also let* t_f^m *be such that* $(d/dt)y_m(t_f^m) = 0$. *If there exists* $\bar{t} > 0$ *such that* $x(\bar{t}) = y(t_f^m)$, *then the final tumor level for the alternated strategy,* $y(t_f)$ *is such that* $y(t_f) > y_m(t_f^m)$.

Proof. Let $u(t) = u_m$ for all $t \in [0, t_f^m]$ be a treatment where t_f^m is determined by $(d/dt)y(t_f^m) = 0$. Now, let u be a treatment with a finite number of switchings between 0 and u_m in the interval $[0, t_f]$ and $u(t) = u_m$ in the neighborhood of t_f. Suppose that for a certain $\bar{t} \in [0, t_1]$, $t_1 = \min(t_m, t_f)$, one has $x(\bar{t}) = y(t_f^m)$. Since x is a strictly increasing function, $x(t_f) > x(\bar{t}) = y(t_f^m)$ and $y(t) - x(t) > 0$ for all finite t, then $y(t_f) > x(t_f) > y(t_f^m)$. ■

That is to say, if the treatment u allows the drug resistant cells to go beyond the final tumor level of treatment u_m, then the final tumor level of treatment u will be higher than that of u_m. Furthermore, this result indicates that therapies, with switchings between 0 and u_m have a limited time of operation if a better performance than that of u_m is ever to be achieved. The dependence of the performance on this time of operation shows up quite clearly in the analysis of a subsequent section (see Section 4).

In the sequel we will set up the optimal treatment first for the Malthusian (exponential) model of cell growth, and then we analyze the

possibilities for the general model of cell growth, with linear drug kill rate in both cases.

3. THE MALTHUSIAN CASE

This model assumes that the specific growth rate of the cells is constant, that is, $f(\cdot) = r > 0$. 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 [17] (this model is used for modeling cell growth in [7]).

In this case, the equations reduce to the following form:

$$\begin{aligned} \frac{dx}{dt} &= rx + \alpha r(y - x) \\ \frac{dy}{dt} &= ry - Fc(t)(y - x) \\ \frac{dc}{dt} &= -\gamma c + u(t) \end{aligned} \tag{3.1}$$

$$x(t_0) = x_0, \qquad y(t_0) = y_0, \qquad c(t_0) = c_0,$$

where $r > 0$ is the specific growth rate of the cells, and $g(y - x) = (y - x)F$.

Solving the third equation in terms of $u(t)$ yields

$$c(t) = c(t_0)\exp(-\gamma(t - t_0)) + \int_{t_0}^{t} \exp(-\gamma(t - s))u(s)\,ds.$$

From this expression we observe that, if $u_1(t) \geqslant u_2(t)$, then $c_1(t) \geqslant c_2(t)$.

Now, letting $z = y - x$, then

$$z(t) = z(t_0)\exp((1 - \alpha)r(t - t_0))\exp\left(-F\int_{t_0}^{t} c(\tau)\,d\tau\right).$$

And, when $c_1(t) \geqslant c_2(t)$ for $t \in [t_0, t]$, this implies that

$$z_1(t) \leqslant z_2(t) \qquad \text{for } t \in [t_0, t].$$

Let denote $u_1(t) = u_m$ for all t, the strategy of maximum drug injection and $u_2(t)$ be any other strategy such that $u_2(t)$ is either u_m or zero in alternate subintervals of time.

Using the same subscripts for the state variables corresponding to the mentioned strategies, the above observations imply that

$$\frac{dx_1}{dt} = rx_1(t) + \alpha r z_1(t) \leqslant rx_1(t) + \alpha r z_2$$
$$x_1(t_0) = x_0 \tag{3.2}$$

and

$$\frac{dx_2}{dt} = rx_2 + \alpha r z_2$$
$$x_2(t_0) = x_0. \tag{3.3}$$

Comparing (3.2) with (3.3) and resorting to the results of differential inequalities (see Hale [9, p. 30], we have

$$x_1(t) \leqslant x_2(t) \qquad \forall t \in [t_0, t].$$

Since $y_1(t) = x_1(t) + z_1(t) \leqslant x_2(t) + z_2(t) = y_2(t)$, then $y_1(t) \leqslant y_2(t)$ for all $t \in [t_0, t]$ (the strict inequalities also hold true for this analysis).

Therefore, in the exponential cell growth with linear drug kill rate, maximum drug injection will provide lower levels of tumor size at the end of the treatment than its applications with alternated rest periods.

We have thus proved the following:

THEOREM 3.1

In the Malthusian case, the optimal strategy for the optimal control problem given by (2.2), (2.3), (3.1) *is the application of the maximum allowed drug concentration.*

4. A MORE GENERAL CASE

In this section we assume again a linear drug kill rate, but we consider a more general growth rate. Specifically, we assume:

> The specific growth rate f is a *nonincreasing* C^1 function satisfying (2.5) or (2.6). (4.1)

With these assumptions, the model equations reduce to

$$\frac{dx}{dt} = xf(y) + \alpha f(y)(y - x)$$
$$\frac{dy}{dt} = yf(y) - Fc(t)(y - x) \tag{4.2}$$
$$\frac{dc}{dt} = -\gamma c + u(t)$$
$$x(0) = x_0, \qquad y(0) = y_0, \qquad c(0) = c_0.$$

By the same token as in the previous section, inspired on the result of Proposition 2.1, we will compare the performance of the system under the action of two types of strategies: maximum drug injection throughout the treatment and alternating periods of either maximum drug injection or rest.

The main result in this section can be summarized as follows: due to the more difficult nonlinearities, we are not able to prove that the application of maximum injection throughout the treatment is optimal. On the other hand, we demonstrate that it is surely effective under certain conditions (see Theorem 4.1). In better words, under these conditions we prove that the maximum injection strategy is suboptimal in the sense that it is the best in the class of strategies with the same duration and short rest periods.

This result hinges upon a result of integro-differential inequalities given by the following lemma.

LEMMA 4.1

Let Ω *be a connected open set in* $\mathbb{R}^3, w: \Omega \to \mathbb{R}$ *and* $k: \mathbb{R} \to \mathbb{R}$ *be continuous functions such that there is a unique solution in the interval* $[t_0, T]$ *for the initial value problem of the integro-differential equation*

$$\frac{dU}{dt}(t) = w\left(t, U(t), \int_{t_0}^{t} k(U(s))\, ds\right),$$
$$U(t_0) = U_0.$$

Let $V(t)$ *be a continuous function satisfying the corresponding integro-differential inequality in the interval* $[t_0, T]$

$$D_r V(t) \leqslant w\left(t, V(t), \int_{t_0}^{t} k(V(s))\, ds\right),$$
$$V(t_0) = V_0 \tag{4.3}$$

(*here* D_r *denotes the right-hand derivative*).

Suppose that $V_0 \leqslant U_0$, *that* k *is a nonincreasing function, and that* $w(t, W, \xi)$ *is a nonincreasing function in the variable* ξ. *Then* $V(t) \leqslant U(t)$ *for all* $t \in [t_0, T]$.

Proof. For $n \in \mathbb{N} - \{0\}$, we consider the modified integro-differential equation

$$\frac{dU_n}{dt}(t) = w\left(t, U_n(t), \int_{t_0}^{t} k(U_n(s))\, ds\right) + \frac{1}{n}$$
$$U_n(t_0) = U_0.$$

In a standard way it can be proved that, for n large enough, $U_n(t)$ is defined on $[t_0, T]$ and that U_n converges to U uniformly on $[t_0, T]$.

Let us prove that $V(t) \leqslant U_n(t)$ for all $t \in [t_0, T]$. Suppose by contradiction that there are $t_1, t_2 \in [t_0, T]$ such that $V(t) \leqslant U_n(t)$ for $t \in [t_0, t_1]$ and $V(t) > U_n(t)$ for $t \in (t_1, t_2)$.

Then,

$$D_r V(t_1) \geqslant \frac{dU_n}{dt}(t_1) = w\left(t_1, U_n(t_1), \int_{t_0}^{t_1} k(U_n(s))\, ds\right) + \frac{1}{n}$$

$$= w\left(t_1, V(t_1), \int_{t_0}^{t_1} k(U_n(s))\, ds\right) + \frac{1}{n}.$$

But, since $V(s) \leqslant U_n(s)$ for $s \in [t_0, t_1]$, we have $k(V(s)) \geqslant k(U_n(s))$ for $s \in [t_0, t_1]$. Thus,

$$\int_{t_0}^{t_1} k(V(s))\, ds \geqslant \int_{t_0}^{t_1} k(U_n(s))\, ds,$$

and therefore

$$w\left(t_1, V(t_1), \int_{t_0}^{t_1} k(U_n(s))\, ds\right) \geqslant w\left(t_1, V(t_1), \int_{t_0}^{t_1} k(V(s))\, ds\right).$$

Hence,

$$D_r V(t_1) \geqslant w\left(t_1, V(t_1), \int_{t_0}^{t_1} k(V(s))\, ds\right) + \frac{1}{n}$$

$$> w\left(t_1, V(t_1), \int_{t_0}^{t_1} k(V(s))\, ds\right),$$

in contradiction with (4.3), and we conclude that $V(t) \leqslant U_n(t)$ for all $t \in [t_0, T]$. By taking the limit as n goes to infinity, we finally have $V(t) \leqslant U(t)$ for all $t \in [t_0, T]$. ■

To apply the above lemma in our case, we observe that if we call $z(t) = y(t) - x(t)$ (the population of drug sensitive cells) and subtract the first equation from the second one in (4.2), we are left with

$$\frac{dz}{dt} = [(1-\alpha) f(y(t)) - Fc(t)]\, z.$$

Therefore,

$$z(t) = [y(t_0) - x(t_0)] \exp\left[- F \int_{t_0}^{t} c(s)\, ds \right] \exp\left[(1-\alpha) \int_{t_0}^{t} f(y(s))\, ds \right].$$

By using this expression back into the second equation in (4.2), we have

$$\begin{aligned} \frac{dy}{dt}(t) = {} & y(t) f(y(t)) \\ & - F \exp\left[(1-\alpha) \int_{t_o}^{t} f(y(s))\, ds \right] \\ & \times [y(t_0) - x(t_0)] \left\{ c(t) \exp\left[- F \int_{t_0}^{t} c(s)\, ds \right] \right\}, \end{aligned} \tag{4.4}$$

which is an integro-differential equation similar to the one in the above lemma.

Since we want to compare the result of the strategy of maximum injection throughout treatment with the result of the strategy with rest periods, we start with a lemma that considers the behavior of the expression between curly brackets in (4.4) in a simple case.

LEMMA 4.2

Let $t_0 < T$, $0 < \Delta t < T - t_0$, *and* $c_m(t)$ *and* $c(t)$ *be solutions on the interval* $[t_0, T]$ *of the equations*

$$\frac{dc_m}{dt} = - \gamma c_m + u_m(t),$$

$$\frac{dc}{dt} = - \gamma c + u(t),$$

respectively, with initial conditions $c_m(t_0) = c(t_0) = \overline{c_0} > 0$. *Here,* $u_m(t) = u_m > 0$ *for all* $t \in [t_0, T]$ *and* $u(t) = 0$ *for* $t \in [t_0, t_0 + \Delta t)$, $u(t) = u_m$ *for* $t \in [t_0 + \Delta t, T]$.

Then, if $F < \gamma^2 / (\overline{c_0}\gamma + u_m[\exp \gamma T - 1])$ *and* Δt *is small enough, we have for all* $t \in [t_0, T]$

$$c_m(t) \exp\left[- F \int_{t_0}^{t} c_m(s)\, ds \right] \geqslant c(t) \exp\left[- F \int_{t_0}^{t} c(s)\, ds \right].$$

Proof. Since $c(t) \geqslant 0$, to satisfy the above inequality it is enough to have

$$\inf_{t_0 \leqslant t \leqslant T} \frac{c_m(t)}{c(t)} \geqslant \exp F \int_{t_0}^{t} (c_m(s) - c(s))\, ds.$$

By solving the equations for $c_m(t)$ and $c(t)$ we obtain

$$c_m(t) = \overline{c_0} \exp[-\gamma(t-t_0)] + \frac{u_m}{\gamma}\{1 - \exp[-\gamma(t-t_0)]\}$$

and

$$c(t) = \overline{c_0} \exp[-\gamma(t-t_0)] + \frac{u_m}{\gamma}\{1 - \exp[-\gamma(t-t_0)] \exp \gamma \Delta t\}.$$

Thus,

$$h(t) = \frac{c_m(t)}{c(t)} = \frac{(\overline{c_0} - u_m/\gamma) + (u_m/\gamma) \exp \gamma(t-t_0)}{(\overline{c_0} - (u_m/\gamma) \exp \gamma \Delta t) + (u_m/\gamma) \exp \gamma(t-t_0)}$$

and it is easy to verify that $h'(t) < 0$. Therefore,

$$\inf_{t_0 \leqslant t \leqslant T} \frac{c_m(t)}{c(t)} = \frac{(\overline{c_0} + u_m/\gamma) + (u_m/\gamma) \exp \gamma(T-t_0)}{(\overline{c_0} - (u_m/\gamma) \exp \gamma \Delta t) + (u_m/\gamma) \exp \gamma(T-t_0)}.$$

On the other hand, it is also easy to see that

$$\exp\left[F \int_{t_0}^{t} [c_m(s) - c(s)]\, ds\right] \leqslant \exp \frac{F_{u_m}}{\gamma^2} [\exp(\gamma \Delta t) - 1];$$

thus, it is enough to require that

$$\frac{(\overline{c_0} - u_m/\gamma) + (u_m/\gamma) \exp \gamma(T-t_0)}{(\overline{c_0} - (u_m/\gamma) \exp \gamma \Delta t) + (u_m/\gamma) \exp \gamma(T-t_0)} \geqslant \exp \frac{F_{u_m}}{\gamma^2} [\exp(\gamma \Delta t) - 1]. \tag{4.5}$$

For this, we expand both sides of the above inequality in powers of Δt to obtain

$$1 + \frac{u_m \gamma}{\overline{c_0}\, \gamma + u_m [\exp \gamma(T-t_0) - 1]} \Delta t + 0(\Delta t^2) \geqslant 1 + \frac{F_{u_m}}{\gamma} \Delta t + 0(\Delta t^2). \tag{4.6}$$

Hence, if $u_m \gamma / (\overline{c_0} \gamma + u_m [\exp \gamma(T-t_0) - 1]) > F u_m / \gamma$, which is true by hypothesis, and Δt is small enough, we have (4.6) (and therefore (4.5)) satisfied. ∎

Now, we can prove the following

THEOREM 4.1

Let us assume (4.1) *and call* $x_m(t), y_m(t), c_m(t)$ *the solution of* (4.2) *corresponding to maximum drug injection throughout the treatment,* $u(t) = u_m$ *for all time. Let* $T \geqslant 0$ *be the time at which* $y_m(t)$ *reaches its minimum. Let us call* $x(t), y(t), c(t)$ *be any solution of* (4.2) *corresponding to a treatment with a finite number of alternating periods of either maximum drug injection* ($u(t) = u_m$) *or rest* ($u(t) = 0$) *in which the rest periods have a duration less than or equal to a fixed number* Δt.

Then, if $F < \gamma^2/(c_0\gamma + u_m \exp \gamma T)$ *and* Δt *is small enough,* $y_m(t) \leqslant y(t)$ *for all* $t \in [0, T]$.

Proof. Consider initially a $u(t)$ such that it is u_m in a neighborhood of T, that is, there are $0 \leqslant t^{(1)} < \tau^{(1)} < T$, $(\tau^{(1)} - t^{(1)} \leqslant \Delta t)$ such that $u(t) = 0$ for $t \in [t^{(1)}, \tau^{(1)})$ and $u(t) = u_m$ for $t \in [\tau^{(1)}, T]$.

Now, we consider the solution $x^{(1)}(t), y^{(1)}(t), c^{(1)}(t)$ of (4.2) for $u^{(1)}(t) = u(t)$ for $t \in [0, t^{(1)})$ and $u^{(1)}(t) = u_m$ for $t \in [t^{(1)}, T]$, with initial conditions $x(t_0), y(t_0), c(t_0)$.

We observe that $x^{(1)}(t)$, $y^{(1)}(t)$ and $c^{(1)}(t)$ coincide respectively with $x(t)$, $y(t)$ and $c(t)$ in the interval $[0, t^{(1)}]$. Also, from

$$\frac{dc}{dt} = -\gamma c + u(t) \leqslant -\gamma c + u_m,$$

we conclude that $0 \leqslant c(t_0) \leqslant c_0 \exp(-\gamma t_0) + u_m/\gamma[1 - \exp - \gamma t_0] \leqslant c_0 + u_m/\gamma$. Therefore, $F < \gamma^2/(c_0\gamma + u_m \exp \gamma T) \leqslant \gamma^2/(c(t_0)\gamma + u_m[\exp(\gamma T) - 1])$, and if Δt is small enough, we can apply Lemma 4.2 on the interval $[t^{(1)}, T]$ to conclude that $c^{(1)}(t)\exp[-F\int_{t^{(1)}}^{t} c^{(1)}(s)\,ds] \geqslant c(t)\exp[-F\int_{t^{(1)}}^{t} c(s)\,ds]$ on $[t^{(1)}, T]$.

Therefore, the equation corresponding to (4.4) for $y^{(1)}(t)$ in the interval $[t^{(1)}, T]$ satisfies

$$\begin{aligned}
\frac{dy^{(1)}}{dt} &= y^{(1)}(t) f(y^{(1)}(t)) \\
&\quad - F \exp\left[(1-\alpha)\int_{t^{(1)}}^{t} f(y^{(1)}(s))\,ds\right]\left[y(t^{(1)}) - x(t^{(1)})\right] \\
&\quad \times \left\{c^1(t)\exp\left[-F\int_{t^{(1)}}^{t} c^{(1)}(s)\,ds\right]\right\} \\
&\leqslant y^{(1)}(t) f(y^{(1)}(t)) \\
&\quad - F \exp\left[(1-\alpha)\int_{t^{(1)}}^{t} f(y^{(1)}(s))\,ds\right]\left[y(t^{(1)}) - x(t^{(1)})\right] \\
&\quad \times \left\{c(t)\exp\left[-F\int_{t^{(1)}}^{t} c(s)\,ds\right]\right\}.
\end{aligned}$$

On the other hand, the equation corresponding to (4.4) for $y(t)$ in the interval $[t^{(1)}, T]$ is

$$\frac{dy}{dt} = y(t)f(y(t)) - F\exp\left[(1-\alpha)\int_{t^{(1)}}^{t} f(y(s))\,ds\right]\left[y(t^{(1)}) - x(t^{(1)})\right] \times \left\{c(t)\exp\left[-F\int_{t^{(1)}}^{t} c(s)\,ds\right]\right\}.$$

Now, by calling

$$w(t,y,\xi) = yf(y) - F\exp[(1-\alpha)\xi]\left[y(t^{(1)}) - x(t^{(1)})\right] \times \left\{c(t)\exp\left[-F\int_{t^{(1)}}^{t} c(s)\,ds\right]\right\},$$

we have

$$\frac{dy}{dt}(t) = w\left(t, y(t), \int_{t^{(1)}}^{t} f(y(s))\,ds\right),$$

$$\frac{dy^{(1)}}{dt}(t) \leqslant w\left(t, y^{(1)}(t), \int_{t^{(1)}}^{t} f(y^{(1)}(s))\,ds\right)$$

and $y(t^{(1)}) = y^{(1)}(t^{(1)})$.

Now, we have exactly the conditions in Lemma 4.1, and we can conclude that $y^{(1)}(t) \leqslant y(t)$ for $t \in [0,T]$.

If $t^{(1)} = 0$ the stated result is true; otherwise we can repeat the above procedure to obtain a finite sequence $0 = t^{(k)} < t^{(k-1)} < \cdots < t^{(1)} < T$ with corresponding functions $y^{(k)}(t) \leqslant y^{(k-1)}(t) \leqslant \cdots y^{(1)} \leqslant y(t)$ for all $t \in [0,T]$ and $y^{(k)}(t)$ being the solution of (4.2) with $u(t) = u_m$ for all $t \in [0,T]$, that is, $y^{(k)}(t) = y_m(t)$, and we have proved that $y_m(t) \leqslant y(t)$ for all $t \in [0,T]$.

Now, consider the case where $u(t)$ is zero in a neighborhood of T. We take $\bar{t} = T - \epsilon$, with $\epsilon > 0$ small enough in order that $u(t) = 0$ on $[\bar{t}, T]$. Now consider $\bar{u}(t)$ defined by $\bar{u}(t) = u(t)$ for $t \in [0,\bar{t})$, $\bar{u}(t) = u_m$ for $t \in [\bar{t}, T]$.

From the third equation in (4.2) it is easy to obtain that in the interval $[\bar{t}, T]$ the concentrations corresponding to $\bar{u}(t)$ and $u(t)$ are respectively

$$\bar{c}(t) = c(\bar{t})\exp(-\gamma(t-\bar{t})) + \frac{u_m}{\gamma}\left[1 - \exp - \gamma(t-\bar{t})\right]$$

$$c(t) = c(\bar{t})\exp - \gamma(t-\bar{t}).$$

Thus,

$$\frac{\bar{c}(t)}{c(t)} = 1 + \frac{u_m}{\gamma c(\bar{t})}\left[\exp\gamma(t-\bar{t}) - 1\right] = 1 + \frac{u_m}{c(\bar{t})}(t-\bar{t}) + O(t-\bar{t})^2.$$

Also,

$$\exp F\int_{\bar{t}}^{t}\left[\bar{c}(s) - c(s)\right] ds = \exp\frac{F_{u_m}}{\gamma}(t-\bar{t})\exp\frac{-F_{u_m}}{\gamma^2}\left[1 - \exp-\gamma(t-\bar{t})\right]$$
$$= 1 + O(t-\bar{t})^2.$$

Since for $t \in [\bar{t}, T]$, $t - \bar{t} = O(\epsilon)$, by choosing ϵ small enough we can make $\bar{c}(t)/c(t) \geqslant \exp F\int_{\bar{t}}^{t}[\bar{c}(s) - c(s)]ds$ for $t \in [\bar{t}, T]$, that is, in this interval

$$\bar{c}(t)\exp - F\int_{\bar{t}}^{t}\bar{c}(s)\, ds \geqslant c(t)\exp - F\int_{\bar{t}}^{t}c(s)\, ds.$$

Therefore, we can proceed as in the first part of the proof to conclude that the solution of (4.2) corresponding to $\bar{u}(t)$ satisfies $\bar{y}(t) \leqslant y(t)$ for all $t \in [0, T]$. Since $\bar{u}(t)$ is equal to u_m in the neighborhood of T, from the first part we have $y_m(t) \leqslant \bar{y}(t)$, for all $t \in [0, T]$ and therefore $y_m(t) \leqslant y(t)$ in the same interval. ■

5. DISCUSSION

In this work we attempted to derive an optimal chemotherapeutic treatment where the kinetics of the drug is taken into account. In most of the models it is generally assumed that there is an instantaneous mixing of the drug in the plasma and that the drug is delivered to the tumor site with no delay.

Adding a pharmacokinetic equation, the relation between drug concentration at the tumor site and delivered drug concentration was settled. The candidates for the optimal treatment were found to be cyclic (on/off) irrespective of the growth functions and kill rates. Abulesz and Lyberatos [1] arrived at a similar result with the same pharmacokinetic equation, though, in the simpler case of an uncoupled system of equations for tumor and normal cells (without drug resistant cells) and a different performance criterion.

When the specific growth rate is assumed to be constant (e.g., density-independent) and the kill rate linearly proportional to the sensitive cells, maximum allowable drug injection is the optimal treatment, that is, the tumor cells attain its lowest level at the end of the treatment. In this case rest periods are not effective and drug decay does not seem to play an important role.

For density-dependent growth rates, we only proved that the maximum allowable injection is suboptimal in the sense that it is the best in the class of strategies with the same duration and short rest periods (Theorem 4.1). On the other hand, the statement of Theorem 4.1 leads to the conjecture that treatment with rest periods might yield better results if either the rest periods were long enough or the condition in that theorem is not satisfied. Thus, the results found in this work with respect to rest periods seem to be at variance with those obtained in [5] and [6], where maximum allowable drug concentration proved to be optimal (rest periods were not part of any optimal strategy). A very likely cause for this difference may be the fact that instantaneous drug mixing was assumed in those works. This suggests that the inclusion of drug kinetics and density-dependent specific growth rates in chemotherapeutic models may entail optimal treatments containing rest periods under certain conditions, which is in accordance with clinical evidence. The study with the inclusion of the cumulative toxicity criterion ($\int_0^{t_f} \rho u\, dt$) is still under way, but up to now we have been unable to complete the mathematical analysis. This is due, in part, to the fact that the additional term ρu appears in the Hamiltonian ((2.7)) and the switching function in (2.8) changes to $\lambda_3 + \rho$. In turn, these factors may engender a situation of singular control dependent on the penalization term ρ. Consequently, Propositions 2.1 and 2.3 no longer hold. Moreover, it is not clear yet how this situation varies (if ever) in qualitative terms according to the parameter ρ.

Likewise the inclusion of a noncumulative toxicity criterion such a minimum level of normal cells (see [4]) would create similar difficulties due to the increased order of the differential equations system ((2.1) would become a fourth-order system as a result of the additional dynamical equation for the normal cells) and the number of parameters, let alone the inequality constraint on the normal cells. It is very unlikely to draw clear-cut qualitative results from these settings, that is to say, to determine how the chemotherapeutic protocols may vary qualitatively according to the parameters, the initial conditions of the variables and the values taken by the variables as time elapses.

We take the view that all the issues raised in this section await further research and it seems to us that some numerical investigation should be taken up if the search for qualitative results proves to be mathematically intractable.

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