# A Mathematical Model of Cancer Chemotherapy with an Optimal Selection of Parameters

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ABSTRACT

An optimal parameter selection model of cancer chemotherapy is presented which describes the treatment of a tumor over a fixed period of time by the repeated administration of a single drug. The drug is delivered at evenly spaced intervals over the treatment period at doses to be selected by the model. The model constructs a regimen that both minimizes the tumor population at the end of the treatment and satisfies constraints on the drug toxicity and intermediate tumor size. Numerical solutions show that an optimal regimen withholds the bulk of the doses until the end of the treatment period. When a drug used is of either moderate or low effectiveness, an optimal regimen is superior to a schedule that delivers all of the drug at the beginning of the treatment. This study questions whether the current method for the administration of chemotherapy is optimal and suggests that alternative regimens should be considered.

## INTRODUCTION

An early paper by Bahrami and Kim [1] applied optimal control theory to a cancer chemotherapy problem. A discrete model of a cancer cell population was used with an objective function that measured both the final tumor population and the amount of control used to achieve it. The first continuous-time optimal control model of a human tumor was Swan and Vincent [2]. The objective function measured the cumulative drug level; simple constraints on the intermediate drug level and the final tumor size were included. A similar model was used by Swan [3] that considered a variety of objective functions. One function included both a measure of the cumulative drug level and the closeness of the tumor size to some predetermined desired size. No control constraints were used. Sundareshan and

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Fundakowski [4] posed a parameter optimization problem of determining the optimal dose and the optimal period for minimizing the total quantity of drug administered while achieving a predetermined rate of cure. The literature includes comprehensive surveys of cancer therapy models and of optimal control applied to biomedicine [5–6].

This paper constructs a mathematical model describing the action of a single anti-cancer drug repeatedly administered to a tumor. The aim is to find a chemotherapy regimen that both minimizes the tumor population at the end of a fixed treatment period and satisfies given constraints on the drug toxicity and the intermediate tumor size. The model takes the form of an optimal parameter selection problem but due to its special structure gradients it can be constructed analytically, making a numerical solution tractable.

## 1. THE DERIVATION OF THE MATHEMATICAL MODEL

It has been shown [8–11] that the unperturbed growth of a cancer cell population can be modeled by the first-order differential equation

$$\dot{N}(t) = \lambda N(t) \ln\left(\frac{\theta}{N(t)}\right), \tag{1}$$

known as the Gompertz equation (Figure 1). $N(t)$ is the number of cancer cells in the tumor at time $t$, and $\cdot$ indicates a time derivative. The tumor is

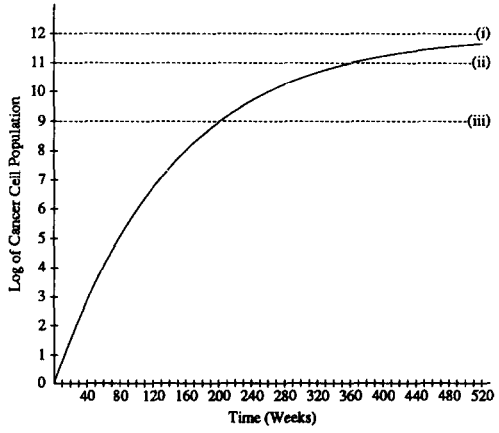


FIG. 1. Plot of $\log_{10} N(t)$ versus time in weeks, assuming that the tumor grew according to the Gompertz differential equation given by Equation (1), starting from a single cell. The limit of clinical detectability (iii) is taken to be $10^9$ cells. If the lethal tumor burden of $10^{11}$ cells (ii) could be evaded, then the tumor size would eventually peak at the plateau population of $10^{12}$ cells (i).

made up of $N_0$ cancer cells at the start of treatment $t = 0$; that is, $N(0) = N_0$. The growth parameter $\lambda$ is assumed to be a positive constant, and $\theta$ is the plateau tumor size, which determines the point of maximum growth rate $N = \theta / e$. An important property of the Gompertz equation is that the rate of increase of the growth rate decreases with increasing $N$. That is, the right-hand side of (1) is concave in $N$.

We now consider the drug concentration at the cancer site, $v(t)$. It is assumed to decay exponentially (with half-life $\ln 2/\gamma$) and to satisfy the equations

$$\dot{v}(t) = u(t) - \gamma v(t), \tag{2}$$

$$v(0) = v_0,$$

where $u(t)$ is the rate of increase of the drug concentration due to infusion of the drug and $v_0$ is the initial drug concentration. A commonly used chemotherapy regimen consists of a series of doses of anti-cancer drugs each separated by a period of rest. The form of $u(t)$ will be chosen to exploit this structure. Only the single drug case will be considered although in practice a number of drugs are often used concurrently. It is assumed that the drug is delivered by infusion, that there is an instantaneous mixing of the drug with the plasma, and that there is an immediate delivery of the drug to the cancer site. These assumptions represent approximations based on the relative amount of time it takes for the above activities to occur with respect to the total amount of time over which treatment is administered.

It is assumed that there are a fixed number of doses administered at evenly spaced intervals over a treatment period of length $t_f$. Suppose that there are $n$ doses, and that the concentration of dose $i$ is $u_i$ and is unknown. Dose $i$ is delivered at the fixed time $t_i = (i-1)t_f / n$. The drug does not have to be administered every week since it is possible for $u_i$ to be zero. Then

$$u(t) = \sum_{i=1}^{n} u_i \delta(t - t_i) \tag{3}$$

A delta function $\delta(t)$ is used to describe an injection since the administration of a dose by infusion typically takes a few hours, whereas the time between doses in a standard treatment is often a week or more. As the number of unknown parameters decreases in any mathematical model, a solution becomes more tractable. In this case, however, a model with few parameters $u_i$ will have long periods between doses thereby excluding a

regimen with frequent doses, which might be a more effective treatment. An explicit form for $v(t)$ may be obtained by substituting (3) into the differential equation describing the change in drug concentration (2).

$$v(t) = \sum_{i=1}^{n} u_i e^{-\gamma(t-t_i)} H(t-t_i). \tag{4}$$

$H(t)$ is the Heaviside step function—

$$H(t-t_i) = \begin{cases} 0 & t < t_i \\ 1 & t \geqslant t_i \end{cases}.$$

The next step in the development of the model is to describe the effect of the drug concentration upon the tumor growth as given in (1). Anti-cancer drugs have been shown to kill by first-order kinetics [12]. That is, a given dose of drug will kill a constant fraction of a population of cells regardless of its size. This implies that the proportion of cells killed per unit time is not a function of $N$. Also, it is known that if the concentration of the drug multiplied by the time of exposure is a constant, then the same degree of cytotoxicity will result [7]. This is true over a wide range of drug concentrations and exposure times and indicates that the proportion of cells killed per unit time is linear in $v(t)$. Therefore, the differential equation describing the growth of the tumor under the influence of the anti-cancer drug is

$$\dot{N}(t) = \lambda N(t) \ln\left(\frac{\theta}{N(t)}\right) - k(v(t) - v_{\text{th}}) H(v(t) - v_{\text{th}}) N(t). \tag{5}$$

Kill terms which are nonlinear functions of the drug concentration $v(t)$ also exist in the literature [2, 3]. The parameter $k$ is the proportion of cells killed per unit time per unit drug concentration and is assumed to be a positive constant. A simple method of calculating $k$ is presented later in this paper. No cancer cells are killed for drug concentrations at or below $v_{\text{th}}$, the therapeutic drug concentration threshold. Norton and Simon [13] have shown that Equation (5) does not agree with the clinical behavior of some tumors whose population lies in the range $\theta/e < N < \theta$. However, experimental evidence suggests that the tumor burden at diagnosis of some cancers is on average an order of magnitude smaller than the plateau tumor population [8]. This means that the tumor population during treatment is well below $\theta/e$.

Anti-cancer drugs are extremely toxic so a valid model must limit the use of the drug. Two measures of drug toxicity are used. First, the intermediate

drug concentration at the cancer site must be below an upper bound $v_{\max}$.

$$0 \leqslant v(t) \leqslant v_{\max} \quad \text{for all } t \in [0, t_f] \tag{6}$$

This is a continuous state constraint. Second, an estimation of the cumulative drug toxicity is bounded above by $v_{\text{cum}}$.

$$\int_0^{t_f} v(s)\, ds \leqslant v_{\text{cum}}. \tag{7}$$

This is an integral constraint that is not necessarily applicable to all drugs used for the treatment of cancer. While agents such as doxorubicin do require dose constraints, other agents may instead be constrained by tumor cell drug resistance. The toxic drug concentration threshold is assumed to be negligible. Making use of Equation (4), Equation (7) may be integrated to give the linear constraint

$$\frac{1}{\gamma} \sum_{i=1}^{n} u_i (1 - e^{-\gamma(t_f - t_i)}) \leqslant v_{\text{cum}}. \tag{8}$$

Given a fixed treatment period and constraints on how the anti-cancer drug is used, a natural measure of success is the tumor size at the end of treatment $N(t_f)$. The smaller $N(t_f)$ the better. Of course there are many ways by which the efficacy of a chemotherapy regimen might be measured, so this performance index is not unique.

It is thought that drug resistance is an important factor in chemotherapeutic failure in human cancers [7]. Moreover it has been shown that both the probability of having drug resistant lines and the proportion of drug resistant cells increases with increasing tumor size [14]. Therefore there is strong motivation for preventing the intermediate tumor size from becoming too large. One way of achieving this is to impose a continuous state constraint of the form

$$N(t) \leqslant N_{\max} \quad \text{for all } t \in [0, t_f]. \tag{9}$$

The upper bound on the tumor population is denoted by $N_{\max}$, which will be taken to be equal to $N_0$, the initial tumor size. The full mathematical statement of the problem may now be summarized as follows:

$$\text{minimize}\{J(u) = N(t_f)\} \tag{10}$$

subject to

$$\dot{N}(t) = \lambda N(t) \ln\left(\frac{\theta}{N(t)}\right) - k(v(t) - v_{\text{th}}) H(v(t) - v_{\text{th}}) N(t), \quad (11)$$

$$N(0) = N_0,$$

$$v(t) = \sum_{i=1}^{n} u_i e^{-\gamma(t-t_i)} H(t - t_i), \quad (12)$$

$$0 \leqslant v(t) \leqslant v_{\max} \quad \text{for all } t \in [0, t_f], \quad (13)$$

$$N(t) \leqslant N_{\max} \quad \text{for all } t \in [0, t_f], \quad (14)$$

$$\frac{1}{\gamma} \sum_{i=1}^{n} u_i (1 - e^{-\gamma(t_f - t_i)}) \leqslant v_{\text{cum}}, \quad (15)$$

over $u = (u_1, \ldots, u_n)^T \in \mathbb{R}^n$. This is an optimal parameter selection problem. Solution methods for problems of this type include gradient restoration and control parameterization [15–21]. The optimal control model of cancer chemotherapy posed by Swan and Vincent [2] minimized the cumulative drug use subject to simple upper and lower bounds on the control, with the tumor size specified at the terminal time. There were no continuous state constraints, and Swan and Vincent were able to derive an analytical closed loop form for the optimal control in terms of the intermediate tumor size. The presence of the continuous state constraints (13) and (14) in the current model precludes an analytical solution.

From clinical studies it is known that some drug concentration half-lives are very short in comparison to the total treatment length. Hence at a relatively short period of time after the delivery of a dose $u_i$, the term in (12) corresponding to $u_i$ will be very small. At any time after this $v(t)$ will be insensitive to changes in $u_i$. That is, $v(t)$ is stiff with respect to the doses $u_i$. This makes the continuous state constraints (13) and (14) difficult to satisfy accurately in a numerical solution with existing software.

## 2. A TRANSFORMATION

If the special structure of the drug concentration $v(t)$ is exploited, the continuous state constraints (13) and (14) can be reduced to linear constraints and nonlinear interior point constraints, respectively. Theorem 1 proves that the resulting model is equivalent to the original, but is more tractable.

*THEOREM 1*

*$0 \leqslant v(t) \leqslant v_{\max}$ and $N(t) \leqslant N_{\max}$ for all $t \in [0, t_f]$ if and only if $0 \leqslant v(t_i) \leqslant v_{\max}$ for $i = 1, \ldots, n$ and $N(t_i) \leqslant N_{\max}$ for $i = 1, \ldots, n+1$.*

*Proof.* $v(t)$ is a nonnegative piecewise continuous function of time over the treatment period $[0, t_f]$. $v(t)$ has jump discontinuities at $t = t_i$, $i = 1$,

$,\ldots,n$, the times at which the doses of anti-cancer drug are administered. Over each subinterval $[t_i, t_{i+1})$, $i=1,\ldots,n$, $v(t)$ is a sum of decaying exponentials and so is infinitely differentiable and monotonically decreasing in $t$. The maximum value of $v(t)$ over $[t_i, t_{i+1})$ occurs at $t=t_i$. Hence $v(t) \leqslant v_{\max}$ for all $t \in [t_i, t_{i+1})$ if and only if $v(t_i) \leqslant v_{\max}$.

$N(t)$ is continuous in time on $[0, t_f]$ and continuously differentiable on $[t_i, t_{i+1})$ [cf. (11)]. If $N(t)$ has a relative maximum in $(t_i, t_{i+1})$ then it satisfies $\dot{N}(t)=0$. $N(t)$ is twice continuously differentiable on $(t_i, t_{i+1})$ with the possible exception of the point at which $v(t)=v_{\text{th}}$. Such a point occurs at most once in $(t_i, t_{i+1})$. If $v \leqslant v_{\text{th}}$ then from (11)

$$\dot{N}(t) = \lambda N \ln\left(\frac{\theta}{N}\right) > 0.$$

so that $N(t)$ cannot have a relative maximum. If $v(t) > v_{\text{th}}$ then

$$\begin{aligned}\ddot{N}(t) &= \dot{N}(t)\left(\lambda \ln\left(\frac{\theta}{N}\right) - \lambda - k(v - v_{\text{th}})\right) + k\gamma v N \\ &= k\gamma v N\end{aligned}$$

since $\dot{N}=0$ at a relative maximum in $(t_i, t_{i+1})$. This establishes that $\ddot{N}$ is positive and therefore $N(t)$ has no relative maximum. Since $N$ is continuous on $[t_i, t_{i+1}]$ the only other possibility is that $N$ is maximized over $t \in [t_i, t_{i+1}]$ at either $t_i$ or $t_{i+1}$. ■

In practice the first and last constraints, given by $N(t_1)=N_0 \leqslant N_{\max}$ and $N(t_{n+1})=N(t_f) \leqslant N_{\max}$, are dropped since the first is independent of the parameter vector $u=(u_1,\ldots,u_n)^T$, and the last absorbed by the objective function (10). As a result of Theorem 1 the problem can now be stated as

$$\text{minimize}\{J(u) = N(t_f)\} \tag{16}$$

subject to

$$\dot{N}(t) = \lambda N(t) \ln\left(\frac{\theta}{N(t)}\right) - k(v(t) - v_{\text{th}}) H(v(t) - v_{\text{th}}) N(t), \tag{17}$$

$$N(0) = N_0$$

$$v(t) = \sum_{i=1}^{n} u_i e^{-\gamma(t-t_i)} H(t - t_i), \tag{18}$$

$$\sum_{i=1}^{j} u_i e^{-\gamma(t_j - t_i)} \leqslant v_{\max} \quad \text{for } j = 1,\ldots,n, \tag{19}$$

$$G_j = N_{\max} - N(t_{j+1}) \geqslant 0 \quad \text{for } j = 1,\ldots,n-1, \tag{20}$$

$$\frac{1}{\gamma} \sum_{i=1}^{n} u_i (1 - e^{-\gamma(t_f - t_i)}) \leqslant v_{\text{cum}}, \tag{21}$$

over $u=(u_1,\ldots,u_n)^T\in\mathbb{R}^n$. A numerical solution of (16)–(21) requires gradients (with respect to the doses $u_i$) of the objective function and the constraints. Because of the specific structure of the problem, analytical gradients can be derived.

For the purposes of calculating gradients, introduce the dimensionless scaling $y(t)=\ln(\frac{\theta}{N(t)})$ (cf. [2]) and let $y_{\min}=\ln(\frac{\theta}{N_{\max}})$. Then the model Equations (16)–(21) become

$$\text{minimize}\{\hat{J}(u)=-y(t_f)\} \tag{22}$$

subject to

$$\dot{y}(t)=-\lambda y(t)+k(v(t)-v_{\text{th}})H(v(t)-v_{\text{th}}) \tag{23}$$

$$y(0)=y_0=\ln\left(\frac{\theta}{N_0}\right),$$

$$v(t)=\sum_{i=1}^{n}u_i e^{-\gamma(t-t_i)}H(t-t_i), \tag{24}$$

$$\sum_{i=1}^{j}u_i e^{-\gamma(t_j-t_i)}\leqslant v_{\max}\quad\text{for } j=1,\ldots,n, \tag{25}$$

$$g_j=y(t_{j+1})-y_{\min}\geqslant 0\quad\text{for } j=1,\ldots,n-1, \tag{26}$$

$$\frac{1}{\gamma}\sum_{i=1}^{n}u_i(1-e^{-\gamma(t_f-t_i)})\leqslant v_{\text{cum}}, \tag{27}$$

over $u=(u_1,\ldots,u_n)^T\in\mathbb{R}^n$. To calculate gradients it is necessary to know the time (if any) in each subinterval $[t_j,t_{j+1})$ at which $v(t)=v_{\text{th}}$. This is denoted by $s_j$. It is possible that $v(t)\neq v_{\text{th}}$ for all $t\in[t_j,t_{j+1})$. Then if $v(t)<v_{\text{th}}$ for all $t\in[t_j,t_{j+1})$ define $s_j=t_j$. If $v(t)>v_{\text{th}}$ for all $t\in[t_j,t_{j+1})$ then let $s_j=t_{j+1}$. If $v(t)=v_{\text{th}}$ for some $s_j\in[t_j,t_{j+1})$, then by (4)

$$s_j=\frac{1}{\gamma}\ln\left(\frac{\sum_{i=1}^{n}u_i H(s_j-t_i)e^{\gamma t_i}}{v_{\text{th}}}\right).$$

That is,

$$s_j=\frac{1}{\gamma}\ln\left(\frac{1}{v_{\text{th}}}\sum_{i=1}^{j}u_i e^{\gamma t_i}\right). \tag{28}$$

The gradients are constructed in Theorem 2:

*THEOREM 2*

*The analytical form of the gradients of* $\hat{J}$ *and* $g_j$, *given in* (22) *and* (26), *are*:

$$\frac{\partial \hat{J}}{\partial u_i} = \frac{k}{\gamma - \lambda} \sum_{m=i}^{n} \{\exp[\gamma(t_i - s_m) - \lambda(t_f - s_m)] - \exp[\gamma(t_i - t_m) - \lambda(t_f - t_m)]\}, \tag{29}$$

$$\frac{\partial g_j}{\partial u_i} = \frac{-k}{\gamma - \lambda} \sum_{m=i}^{j} \{\exp[\gamma(t_i - s_m) - \lambda(t_{j+1} - s_m)] - \exp[\gamma(t_i - t_m) - \lambda(t_{j+1} - t_m)]\}. \tag{30}$$

*Proof.* For each $j = 0, 1, \ldots, n-1$ let $H_j$ be the Hamiltonian function given by $H_j = \psi_j(t)\dot{y}(t)$. The subscript $j = 0$ refers to the objective function, and the subscripts $j = 1, \ldots, n-1$ to the nonlinear constraints. The costate system is given by

$$\dot{\psi}_j(t) = -\frac{\partial H_j}{\partial y},$$

$$\psi_0(t_f) = -1, \text{ and } \psi_j(t_{j+1}) = 1 \quad \text{for } j = 1, \ldots, n-1. \tag{31}$$

The gradients are calculated from

$$\frac{\partial \hat{J}}{\partial u_i} = \int_0^{t_f} \frac{\partial H_0}{\partial u_i} dt, \tag{32}$$

$$\frac{\partial g_j}{\partial u_i} = \int_0^{t_{j+1}} \frac{\partial H_j}{\partial u_i} dt. \tag{33}$$

It follows [cf. (23)] that

$$\dot{\psi}_j(t) = \lambda \psi_j(t) \quad \text{for } j = 0, 1, \ldots, n-1. \tag{34}$$

Integrating (34) using the given boundary conditions gives

$$\psi_0(t) = -e^{\lambda(t - t_f)},$$

$$\psi_j(t) = e^{\lambda(t - t_{j+1})} \text{ for } j = 1, \ldots, n-1.$$

The integrands of (32) and (33) are

$$\frac{\partial H_0}{\partial u_i} = -k\exp\big((\lambda-\gamma)t+\gamma t_i-\lambda t_f\big)H(t-t_i)H\big(v(t)-v_{\text{th}}\big),$$

$$\frac{\partial H_j}{\partial u_i} = k\exp\big((\lambda-\gamma)t+\gamma t_i-\lambda t_{j+1}\big)H(t-t_i)H\big(v(t)-v_{\text{th}}\big)$$

$$\text{for } j=1,\ldots,n-1.$$

Hence the objective function gradient is

$$\begin{aligned}\frac{\partial \hat{J}}{\partial u_i} &= \int_0^{t_f} -k\exp\big((\lambda-\gamma)t+\gamma t_i-\lambda t_f\big)H(t-t_i)H\big(v(t)-v_{\text{th}}\big)\,dt\\ &= \sum_{m=i}^{n}\int_{t_m}^{s_m} -k\exp\big((\lambda-\gamma)t+\gamma t_i-\lambda t_f\big)\,dt \quad \text{by (28)}\\ &= \frac{k}{\gamma-\lambda}\sum_{m=i}^{n}\Big\{\exp\big[\gamma(t_i-s_m)-\lambda(t_f-s_m)\big]\\ &\qquad -\exp\big[\gamma(t_i-t_m)-\lambda(t_f-t_m)\big]\Big\}.\end{aligned}$$

The gradient of the $j$th nonlinear constraint $g_j$ for $j=1,\ldots,n-1$ is

$$\begin{aligned}\frac{\partial g_j}{\partial u_i} &= \int_0^{t_{j+1}} k\exp\big((\lambda-\gamma)t+\gamma t_i-\lambda t_{j+1}\big)H(t-t_i)H\big(v(t)-v_{\text{th}}\big)\,dt\\ &= \sum_{m=i}^{j}\int_{t_m}^{s_m} k\exp\big((\lambda-\gamma)t+\gamma t_i-\lambda t_{j+1}\big)\,dt \quad \text{by (28)}\\ &= \frac{-k}{\gamma-\lambda}\sum_{m=i}^{j}\Big\{\exp\big[\gamma(t_i-s_m)-\lambda(t_{j+1}-s_m)\big]\\ &\qquad -\exp\big[\gamma(t_i-t_m)-\lambda(t_{j+1}-t_m)\big]\Big\}\end{aligned}$$

This completes the proof. ■

Using the simple partial derivative relationship

$$\frac{\partial N}{\partial u_i} = -N\frac{\partial y}{\partial u_i} \tag{35}$$

and Theorem 2, the gradients of $J$ and $G_j$, as given in (16) and (20), are

$$\frac{\partial J}{\partial u_i} = N\frac{\partial \hat{J}}{\partial u_i}, \tag{36}$$

$$\frac{\partial G_j}{\partial u_i} = N\frac{\partial g_j}{\partial u_i}. \tag{37}$$

A method for calculating the parameter $k$ introduced in Section 1 remains to be developed. A simple method of calculating $k$ is via the fractional kill, although this may be inaccurate due to the difficulties in estimating the cancer cell population of a tumor. Suppose a drug of dose $v(t) = v_1$ is delivered at time $t_1 = 0$ to a tumor of size $N_1$. At time $t_2$ the tumor is remeasured at $N_2$. Then the fractional kill $F = (N_1 - N_2)/N_1$ is the proportion of cells killed as measured at time $t_2$. Using the scaling $y(t) = \ln(\theta / N(t))$ the fractional kill becomes

$$F = 1 - e^{y_1 - y_2}, \tag{38}$$

where $y_1 = y(t_1)$ and $y_2 = y(t_2)$. The scaled tumor cell population $y(t)$ is the solution of the first order system (23), namely

$$y(t) = y_0 e^{-\lambda t} + e^{-\lambda t} \int_0^t e^{\lambda w} k(v(w) - v_{\text{th}}) H(v(w) - v_{\text{th}})\, dw. \tag{39}$$

It will be supposed that $v_1 = v(0) > v_{\text{th}}$ and that $v(t) = v_{\text{th}}$ at some $s \in [0, t_2)$. The drug concentration $v(t)$ takes the form $v(t) = v_1 e^{-\gamma t}$ from which the time $s$ can be calculated.

$$s = \frac{1}{\gamma} \ln\left(\frac{v_1}{v_{\text{th}}}\right). \tag{40}$$

For all $t$ satisfying $0 \leqslant t < s$ it is true that $v(t) > v_{\text{th}}$, and so $H(v - v_{\text{th}}) = 1$. Thus at $t = s$ the equation for the state $y(t)$ becomes

$$y(s) = y_0 e^{-\lambda s} + e^{-\lambda s} \int_0^s e^{\lambda w} k(v(w) - v_{\text{th}})\, dw. \tag{41}$$

Substituting $v(t) = v_1 e^{-\gamma t}$ into (41) and integrating gives

$$y(s) = y_0 e^{-\lambda s} - k\left\{\frac{v_{\text{th}}}{\lambda}(1 - e^{-\lambda s}) + \frac{v_1}{\gamma - \lambda}(e^{-\gamma s} - e^{-\lambda s})\right\} \tag{42}$$

On the interval $(s, t_2]$ it is true that $v(t) < v_{\text{th}}$, and therefore

$$y(t_2) = y(s) e^{-\lambda(t_2 - s)}. \tag{43}$$

It can be shown, after substituting Equations (42) and (43) into (38) and rearranging terms, that the fractional kill is given by

$$F = 1 - e^{bk}\left(\frac{\theta}{N_1}\right)^a, \tag{44}$$

where

$$a = 1 - e^{-\lambda t_2},$$
$$b = e^{-\lambda(t_2 - s)}\left\{ \frac{v_{\text{th}}}{\lambda}(1 - e^{-\lambda s}) + \frac{v_1}{\gamma - \lambda}(e^{-\gamma s} - e^{-\lambda s}) \right\}.$$

Equation (44) can be rearranged to give an explicit form for $k$.

$$k = \frac{1}{b} \ln\left[ (1 - F)\left( \frac{N_1}{\theta} \right)^a \right]. \tag{45}$$

The fractional kill is not a constant function of $N_1$, but would be if (1) was replaced by an exponential growth term. For constant $k$,

$$\frac{\partial F}{\partial N_1} = \frac{a}{\theta} e^{bk} \left( \frac{\theta}{N_1} \right)^{a+1}, \tag{46}$$

so that $F$ increases with increasing $N_1$. For $N < \theta/e$ and constant $v(t)$ both the growth term $\lambda N \ln(\theta/N)$ and the kill term $k(v - v_{\text{th}})H(v - v_{\text{th}})N$ in (5) are monotonically increasing functions of $N$. However, the kill term increases faster than the growth term, so that the larger the tumor population the larger the fractional kill. Since the growth and kill terms differ by a factor of $\ln(\theta/N)$ the fractional kill increases very slowly with increasing $N$.

## 3. THE SOLUTION

The problem has been reduced to a standard nonlinear programming form with gradients given by (36) and (37) and can now be solved using standard techniques [22]. A nonstandard feature of the problem is the first order differential equation that is solved at each step in order to evaluate the objective function and the nonlinear constraints. However this is straightforward.

After performing a number of minimizations it became clear that the problem is plagued by a multitude of local minima. Define the set of feasible parameters $\mathbb{U}$ to be the set of all vectors $u = (u_1, \ldots, u_n)^{\mathrm{T}} \in \mathbb{R}^n$ satisfying constraints (18–21). $\mathbb{U}$ is a closed subset of $\mathbb{R}^n$. The objective function $J(u) = N(t_f)$ [cf. (10)] is shown to be monotonically decreasing in $u_i$ for $i = 1, \ldots, n$, as follows. The drug concentration $v(t)$ is monotonically increasing in $u_i$, and the tumor population $N(t)$ is monotonically decreasing in $v(t)$ [cf. (39)]. Hence the larger the dose $u_i$ the smaller the final tumor population $N(t_f)$, therefore $J(u) = N(t_f)$ must be minimized on the boundary of $\mathbb{U}$. However, there are high dimensional subsets in the interior of $\mathbb{U}$ over which the objective function $J(u) = N(t_f)$ is constant. This is due

to the Heaviside function in the right-hand side of Equation (17), the state differential equation. A numerical routine can converge to a point in such a subset since each point satisfies the conditions of a local minimum. This is a major problem since most of these points are clearly not optimal solutions (as an example consider the region $u_i \leqslant \frac{v_{\text{th}}}{2}$ for $i = 1, \ldots, n$).

By means of a mathematical device it is possible to avoid being trapped in these regions. A term is added to the objective function so that it is no longer constant over such a region, but which does not significantly alter the problem. Define an augmented objective function

$$J_\mu(u) = N(t_f) - \mu \sum_{i=1}^{n} u_i^2. \tag{47}$$

The magnitude of the positive parameter $\mu$ controls the influence of the second term of (47) on $J_\mu(u)$. Consider the problem of minimizing (47) subject to Equation (17) over $u \in \mathbb{U}$. Call this problem $P(\mu)$, and the original problem (minimize $J(u) = N(t_f)$ subject to Equation (17) over $u \in \mathbb{U}$) problem $P$. The set $\mathbb{U}$ is not a function of $\mu$. Theorem 3 provides an important relationship between $P(\mu)$ and $P$.

Let $u^{\mu,*}$ be an optimal solution of $P(\mu)$, and $u^*$ an optimal solution of $P$. Suppose that $\{u^{\mu,*}\}$ is a sequence of optimal solutions formed by letting $\mu \to 0$.

*THEOREM 3*

*A subsequence of $\{u^{\mu,*}\}$ converges to an optimal solution of problem $P$.*

*Proof.* $\mathbb{U}$ is closed, and $u_i \leqslant v_{\max}$ for $i = 1, \ldots, n$ [cf. (19)] so that $\mathbb{U}$ is also bounded. That is, $\mathbb{U}$ is a compact subset of $\mathbb{R}^n$. There exists a subsequence of $\{u^{\mu,*}\}$ that without loss of generality is taken to be $\{u^{\mu,*}\}$, which converges to a point of $\mathbb{U}$. Call this feasible solution $u^{0,*}$. It remains to be shown that $u^{0,*}$ is an optimal solution of $P$. For every $\mu > 0$,

$$J_\mu(u^{\mu,*}) \leqslant J_\mu(u^*) \leqslant J(u^*), \tag{48}$$

since $u^{\mu,*}$ is an optimal solution of $P(\mu)$, and $J_\mu(u) \leqslant J(u)$ for any feasible $u$. Then

$$\begin{aligned} \lim_{\mu \to 0} J_\mu(u^{\mu,*}) &= \lim_{\mu \to 0} \left( J(u^{\mu,*}) - \mu \sum_{i=1}^{n} \left(u_i^{\mu,*}\right)^2 \right), \\ &= J(u^{0,*}) \end{aligned}$$

since $\mathbb{U}$ is bounded and $J$ is continuous in $u$. Then by (48) $J(u^{0,*}) \leqslant J(u^*)$.

Since $u^*$ is an optimal solution of $P$, $J(u^*) \leqslant J(u^{0,*})$. In other words $J(u^{0,*}) = J(u^*)$, and so $u^{0,*}$ is an optimal solution of $P$. ■

Theorem 3 shows that a new method of solution of the nonlinear programming problem $P$ is to solve a sequence of subproblems $P(\mu)$ with $\mu$ decreasing to zero. The sign of the second term in (47) is crucial. $J(u) = N(t_f)$ is monotonically decreasing in $u_i$, $i = 1, \ldots, n$, and therefore any term which is added to $J$ must also be monotonically decreasing in $u_i$, otherwise not all of the sub-optimal local minima in the interior of $\mathbb{U}$ will be removed. In general there will still be local minima on the boundary of the feasible region $\mathbb{U}$.

The data which are used to solve the nonlinear programming problem numerically are synthetic. This means that the data have been artificially chosen to represent a generic treatment of a solid tumor by an anti-cancer drug (as opposed to data based upon clinical measurements). The data used are as follows: $t_f = 365$ days, and $n = 52$ (so that the treatment lasts for a real year, with doses given each week). The growth parameter $\lambda$ can be estimated from the tumor doubling time $t_d$ using the relation

$$\lambda = \frac{1}{t_d} \ln \left( \frac{\ln\left(\frac{\theta}{N_0}\right)}{\ln\left(\frac{\theta}{2N_0}\right)} \right). \tag{49}$$

The tumor doubling time is assumed to be five months at $10^{10}$ cells. Sullivan and Salmon [8] used average tumor doubling times in the range of 4–6 months during the clinical phase of the disease, which is based on generally accepted survival data. It follows that $\lambda = 9.9 \times 10^{-4}$ (days)$^{-1}$; $\theta = 10^{12}$ cells; $v_{\text{th}} = 10$ $[D]$ ($[D]$ is the unit of drug concentration); $\gamma = 0.27$ (days)$^{-1}$ (so the half-life of the drug concentration is 2.5 days); $N_0 = 10^{10}$ cells; $v_0 = u_1$, the initial dose; $v_{\max} = 50$ $[D]$; and $N_{\max} = 10^{10}$ cells. The cumulative drug toxicity constraint (7) is assumed to be saturated if maximum doses are administered for the first 26 weeks of treatment, and no drug is given during the final 26 weeks. This gives a value of $v_{\text{cum}} = 4.1 \times 10^3$ $[D]$ days.

Three qualitative drugs are considered.

Drug A: high fractional kill (90%) after one week, with $N_0 = 10^{10}$ cells and $v(0) = v_{\max}$.

Drug B: moderate fractional kill (50%) after one week, with $N_0 = 10^{10}$ cells and $v(0) = v_{\max}$.

Drug C: low fractional kill (10%) after one week, with $N_0 = 10^{10}$ cells and $v(0) = v_{\max}$.

TABLE 1

Calculated values of the proportion of tumor cells killed per unit time per unit drug concentration and of the fractional kill

| Drug | $k$ (days$^{-1}[D]^{-1}$) | $N_0$ (cells) | $F$ |
|---|---|---|---|
| A | $2.7\times10^{-2}$ | $10^{10}$ | 90% |
| | | $10^{2}$ | 88% |
| B | $8.4\times10^{-3}$ | $10^{10}$ | 50% |
| | | $10^{2}$ | 41% |
| C | $1.5\times10^{-3}$ | $10^{10}$ | 10% |
| | | $2.4\times10^{3}$ | 0% |

These values have been used to calculate the parameter $k$ following the method outlined in Section 2. A summary is given in Table 1. While the fractional kills of drugs A and B decrease only marginally over an eight order of magnitude decrease in the initial cell population, drug C is incapable of reducing the tumor size below $2.4\times10^{3}$ cells.

It was evident after performing some numerical minimizations that the problem still has a number of local minima, all of which lie on the boundary of the feasible region $\mathbb{U}$. There is no known method which can guarantee finding a globally optimal control in such a situation. One obvious heuristic method is to run the minimization routine a number of times using randomly chosen starting points, and then select the best resulting solution. This is computationally expensive and is not the best method. Consider the problem of minimizing (16) subject to (17), (18), (19), and (21). That is, the problem without the state constraint (20). Theorem 4 constructs a globally optimal solution to this problem, which is a lower bound on any solution to the full problem [Equations (16)–(21)]. This provides a way of gauging the efficacy of a solution to the full problem. If the value of the objective function of any such solution is close to the lower bound given by Theorem 4 it must be a close approximation to a globally optimal solution to the full problem.

Before proving Theorem 4, two results are established. Define the function $v_1(t)$ as follows. For any $t_i$ satisfying $0 \leqslant t_i \leqslant t_q$, if $t \in [t_i, t_{i+1})$ then $v_1(t) = v_{\max} e^{-\gamma(t-t_i)}$. That is, $v_1(t)$ maximizes the drug concentration $v(t)$ for all $t \in [0, t_{q+1})$.

*LEMMA 1*

*If*

$$\int_0^{t_{q+1}} v_1(t)\,dt \leqslant \int_0^{t_{p+1}} v_2(t)\,dt, \tag{50}$$

*for any* $v_2(t)$ *satisfying* (18) *and* (19), *then*

$$\int_0^{t_{q+1}} (v_1(t) - v_{\text{th}}) H(v_1(t) - v_{\text{th}})\, dt \geq \int_0^{t_{p+1}} (v_2(t) - v_{\text{th}}) H(v_2(t) - v_{\text{th}})\, dt. \tag{51}$$

*Proof.* For $i = 1, \ldots, n$,

$$\int_{t_i}^{t_{i+1}} (v(t) - v_{\text{th}}) H(v(t) - v_{\text{th}})\, dt = \int_{t_i}^{t_i + s_i} (v_i e^{-\gamma(t-t_i)} - v_{\text{th}})\, dt$$
$$= \frac{1}{\gamma}(v_i - v_{\text{th}}) - s_i v_{\text{th}},$$

where $v_i = v(t_i)$ and $s_i = \frac{1}{\gamma} \ln(\frac{v_i}{v_{\text{th}}})$. It is also true that

$$\int_{t_i}^{t_{i+1}} v(t)\, dt = \int_{t_i}^{t_{i+1}} v_i e^{-\gamma(t-t_i)}\, dt$$
$$= \frac{v_i}{\gamma}(1 - e^{-\gamma \Delta t}),$$

where $\Delta t = t_{i+1} - t_i = \dfrac{t_f}{n}$, which is independent of $i$. Then

$$\int_{t_i}^{t_{i+1}} v(t)\, dt = f(v_i) \int_{t_i}^{t_{i+1}} (v(t) - v_{\text{th}}) H(v(t) - v_{\text{th}})\, dt, \tag{52}$$

where $f(v_i)$ is defined by

$$f(v_i) = \frac{v_i(1 - e^{-\gamma \Delta t})}{v_i - v_{\text{th}} - v_{\text{th}} \ln\left(\dfrac{v_i}{v_{\text{th}}}\right)} \tag{53}$$
$$= \frac{a v_i}{v_i - v_{\text{th}} \ln(v_i) + b}.$$

The constants $a$ and $b$ are defined as

$$a = 1 - e^{-\gamma \Delta t}$$
$$b = v_{\text{th}}(\ln(v_{\text{th}}) - 1)$$

The function $f(\cdot)$ is now shown to be monotonically decreasing in $v$ for

$v \in (v_{\text{th}}, v_{\max}]$. Consider the derivative of $f(v_i)$

$$\frac{df(v_i)}{dv_i} = \frac{a(v_i - v_{\text{th}} \ln(v_i) + b) - a(v_i - v_{\text{th}})}{(v_i - v_{\text{th}} \ln(v_i) + b)^2}. \tag{54}$$

The denominator of (54) is positive on $(v_{\text{th}}, v_{\max}]$, while the numerator of (54) is

$$a(v_{\text{th}}(1 - \ln(v_i)) + b) = -av_{\text{th}} \ln\left(\frac{v_i}{v_{\text{th}}}\right) < 0 \quad \text{for } v_i \in (v_{\text{th}}, v_{\max}]$$

Hence $df(v_i)/dv_i$ is strictly negative on $(v_{\text{th}}, v_{\max}]$ and $f(\cdot)$ is monotonically decreasing on $(v_{\text{th}}, v_{\max}]$. Inequality (50) can be rewritten as

$$\sum_{i=1}^{q} \int_{t_i}^{t_{i+1}} v_1(t)\, dt \geqslant \sum_{i=1}^{p} \int_{t_i}^{t_{i+1}} v_2(t)\, dt. \tag{55}$$

Applying result (52) to each integral of inequality (55) and substituting $v_1(t_i) = v_{\max}$ for all $i \leqslant q$ establishes

$$\sum_{i=1}^{q} f(v_{\max}) \int_{t_i}^{t_{i+1}} (v_1(t) - v_{\text{th}}) H(v_1(t) - v_{\text{th}})$$
$$\geqslant \sum_{i=1}^{p} f(v_2(t_i)) \int_{t_i}^{t_{i+1}} (v_2(t) - v_{\text{th}}) H(v_2(t) - v_{\text{th}})\, dt. \tag{56}$$

Since $f(\cdot)$ is monotonically decreasing in $v$ over $(v_{\text{th}}, v_{\max}]$ we have

$$\sum_{i=1}^{q} f(v_{\max}) \int_{t_i}^{t_{i+1}} (v_1(t) - v_{\text{th}}) H(v_1(t) - v_{\text{th}})$$
$$\geqslant \sum_{i=1}^{p} f(v_{\max}) \int_{t_i}^{t_{i+1}} (v_2(t) - v_{\text{th}}) H(v_2(t) - v_{\text{th}})\, dt. \tag{57}$$

Dividing (57) through by the positive quantity $f(v_{\max})$ and rewriting the integrals without summations establishes (51), and this completes the proof. ■

So that the notation in the next lemma is concise, let $f_1 = v_1(s) - v_{\text{th}}$ and $f_2 = v_2(s) - v_{\text{th}}$.

*LEMMA 2*

*If* $t_q \leqslant t_p$ *and*

$$\int_0^{t_q} f_1 H(f_1)\, ds \geqslant \int_0^{t_p} f_2 H(f_2)\, ds, \tag{58}$$

*then for any* $v_2(t)$ *satisfying* (18) *and* (19)

$$\int_0^{t_q} f_1 H(f_1) e^{-\lambda(t_q - s)}\, ds \geqslant \int_0^{t_p} f_2 H(f_2) e^{-\lambda(t_p - s)}\, ds. \tag{59}$$

*Proof.* Rewrite the right-hand side of (58) as follows:

$$\begin{aligned}\int_0^{t_p} f_2 H(f_2)\, ds &= \int_0^{t_p - t_q} f_2 H(f_2)\, ds + \int_{t_p - t_q}^{t_p} f_2 H(f_2)\, ds \\ &= \int_0^{t_p - t_q} f_2 H(f_2)\, ds + \int_0^{t_q} f_3 H(f_3)\, ds, \end{aligned} \tag{60}$$

where $f_3 = v_2(s + t_p - t_q) - v_{\text{th}}$. Substituting (60) into (58) reduces (58) to the inequality

$$\int_0^{t_q} (f_1 H(f_1) - f_3 H(f_3))\, ds \geqslant \int_0^{t_p - t_q} f_2 H(f_2)\, ds. \tag{61}$$

Similarly it can be shown that the right-hand side of (59) may be expressed as

$$\begin{aligned}\int_0^{t_p} f_2 H(f_2) e^{-\lambda(t_p - s)}\, ds &= \int_0^{t_p - t_q} f_2 H(f_2) e^{-\lambda(t_p - s)}\, ds \\ &\quad + \int_0^{t_q} f_3 H(f_3) e^{-\lambda(t_q - s)}\, ds \end{aligned} \tag{62}$$

Using (62) it may be shown that (59) and the following inequality (63) are equivalent.

$$\int_0^{t_q} (f_1 H(f_1) - f_3 H(f_3)) e^{-\lambda(t_q - s)}\, ds \geqslant \int_0^{t_p - t_q} f_2 H(f_2) e^{-\lambda(t_p - s)}\, ds. \tag{63}$$

It remains to be shown that (63) can be derived from (61). Multiply the

right-hand side of (61) by $e^{-\lambda t_q}$.

$$e^{-\lambda t_q}\int_0^{t_p - t_q} f_2 H(f_2)\, ds = \int_0^{t_p - t_q} f_2 H(f_2) \max\{e^{-\lambda(t_p - s)}: s \in [0, t_p - t_q]\}\, ds$$

$$\geqslant \int_0^{t_p - t_q} f_2 H(f_2) e^{-\lambda(t_p - s)}\, ds, \tag{64}$$

which is the right-hand side of (63). Multiply the left-hand side of (61) by $e^{-\lambda t_q}$.

$$e^{-\lambda t_q}\int_0^{t_q} (f_1 H(f_1) - f_3 H(f_3))\, ds$$

$$= \int_0^{t_q} (f_1 H(f_1) - f_3 H(f_3)) \min\{e^{-\lambda(t_q - s)}: s \in [0, t_q]\}\, ds$$

$$\leqslant \int_0^{t_q} (f_1 H(f_1) - f_3 H(f_3)) e^{-\lambda(t_q - s)}\, ds, \tag{65}$$

which is the left-hand side of (63). The last step follows since $v_1(t) \geqslant v_2(t + t_p - t_q)$ for all $t \in [0, t_q]$. Comparing the left- and right-hand sides of (61), in view of (64) and (65), establishes (63), and this completes the proof. ■

Suppose that both

$$v^*(t) = \begin{cases} 0 & \text{for } t \leqslant t_f - t_q \\ v_{\max} & \text{for each } t_i \text{ satisfying } t_f - t_q \leqslant t_i < t_f, \end{cases} \tag{66}$$

and $\int_0^{t_f} v^*(s)\, ds = v_{\text{cum}}$ for some $t_q$. (This last assumption, namely that $v^*$ saturates the cumulative drug toxicity constraint (21), can always be satisfied with just a small change to $v_{\text{cum}}$. This is reasonable since $v_{\text{cum}}$ is only an estimation of the cumulative drug toxicity.) Let $u^*$ be the parameter vector corresponding to the function $v^*(\cdot)$ ($u^*$ is uniquely determined by $v^*$).

*THEOREM 4*

*The parameter vector $u^*$, as defined by* (66), *is a globally optimal solution of the scaled problem without state constraint* (26), *given by Equations* (22)–(25) *and* (27).

*Proof.* Integrating the first order differential equation given by Equation (23) gives

$$y(t_f, u) = y_0 e^{-\lambda t_f} + \int_0^{t_f} (v(s) - v_{\text{th}}) H(v(s) - v_{\text{th}}) e^{-\lambda(t_f - s)}\, ds, \tag{67}$$

The $u_i$ are not functions of time, so that

$$\max_u \big(y(t_f,u)\big) = y_0 e^{-\lambda t_f} + \max_u \left[\int_0^{t_f} \big(v(s)-v_{\text{th}}\big) H\big(v(s)-v_{\text{th}}\big) e^{-\lambda(t_f-s)}\, ds\right]. \quad (68)$$

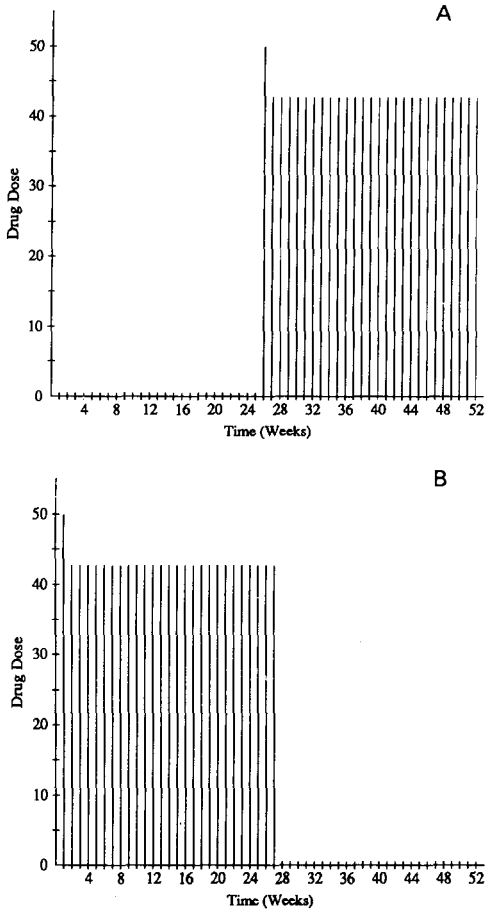


FIG. 2. A globally optimal solution to the problem: minimize $J(u) = N(t_f)$ subject to Equations (17)–(19) and (21) over $u = (u_1, \ldots, u_n)^T \in \mathbb{R}^n$ is shown in A. The state constraint (20) is not included, so that while this solution is a lower bound for the complete problem, it is not a feasible solution to it. The conventional regimen shown in B is an idealization of treatment in which the aim is a cure. All of the drug is delivered towards the beginning of the treatment period. In both cases, the constraint upon the intermediate drug concentration (19) is saturated at each week the drug is administered.

Since both $\int_0^{t_f} v^*(s)\,ds = \int_0^{t_q} v^*(s + t_f - t_q)\,ds$ and $v^*(t_i) = v_{\max}$ for each $t_i$ such that $t_f - t_q \leqslant t_i < t_f$, $v^*(t)$ satisfies the conditions on $v_1(t)$ in Lemmas 1 and 2. But $v^*(t)$ maximizes $\int_0^{t_f} v(s)\,ds$ over all $u$ satisfying constraints (24), (25), and (27), and so by Lemmas 1 and 2 it also maximizes

$$\int_0^{t_f} (v(s) - v_{\text{th}}) H(v(s) - v_{\text{th}}) e^{-\lambda(t_f - s)}\,ds$$

over all such feasible $u$. Then $y(t_f, u^*) \geqslant y(t_f, u)$ for all feasible $u$. The parameter vector $u^*$ is a globally optimal solution of the problem given by Equations (22)–(25) and (27). ■

It follows immediately that $N(t_f, u^*) \leqslant N(t_f, u)$ for any $u$ satisfying (24), (25), and (27). Intuitively the drug regimen represented by $u^*$ delivers all of the drug to the tumor near the end of the treatment period (Figure 2A). The tumor could grow unacceptably large during the first half of the treatment period since no drug is given then, so $u^*$ is not a feasible solution of the problem given by (16)–(21). One regimen currently favored by clinicians delivers all of an anti-cancer drug at the start of a treatment and at the maximum allowable dose. This will be called the conventional regimen (Figure 2B), and will be compared to the optimal regimens derived for drugs A, B, and C. The results are summarized in Table 2. In this table, the objective function $J(u) = N(t_f)$ is denoted by $J$. The lower bound constructed in Theorem 4 may be used to gauge how close the conventional and optimal regimens are to being globally optimal solutions to the full problem given by (16)–(21).

The solution method consisted of solving Equations (16)–(21) numerically with gradients supplied by (36)–(37). The parameter $\mu$ was set to be $\mu = 10^{-2}[D]^{-2}$ during the first iteration, and was progressively decreased to a value of $\mu = 10^{-4}[D]^{-2}$ over several iterations. The starting point for a new iteration was taken to be the solution corresponding to the previous iteration. The value of $\mu = 10^{-4}[D]^{-2}$ gave locally optimal solutions $u^{\mu,*}$ of

TABLE 2

Comparison of the performance of the conventional and optimal regimens for drugs A, B, and C

| Drug | Lower Bound on $J$ (cells) | Conventional Treatment $J$ (cells) | Optimal Treatment $J$ (cells) |
|---|---|---|---|
| A | 0 | $<1$ | $<1$ |
| B | $6.7\times10^2$ | $1.2\times10^4$ | $1.2\times10^3$ |
| C | $1.4\times10^9$ | $2.3\times10^9$ | $1.8\times10^9$ |

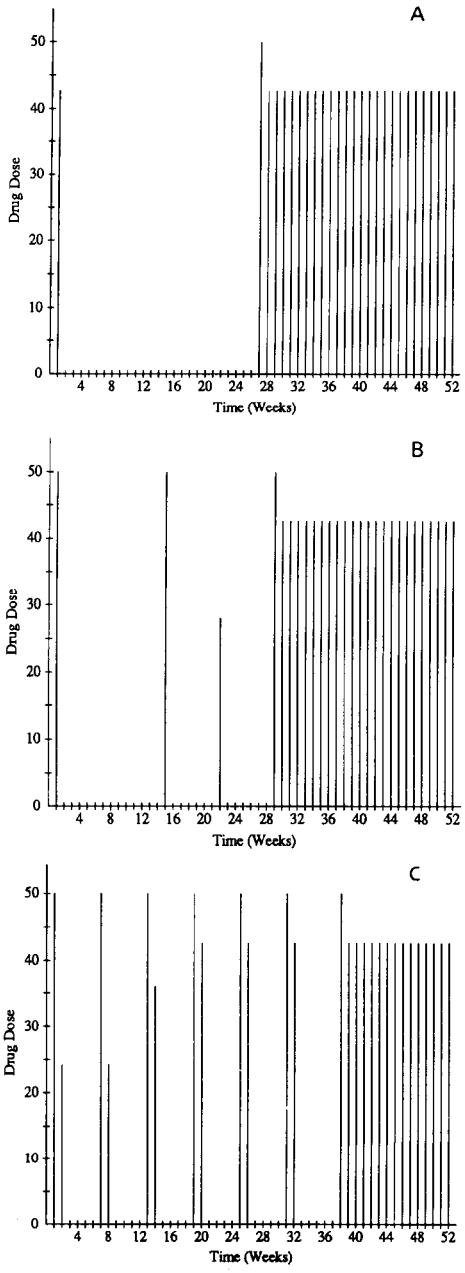


FIG. 3. Optimal regimens for a highly effective (A), moderately effective (B), and poorly effective (C) drug. Treatment commences immediately at relatively low dose intensity in each case to ensure that the intermediate tumor size is controlled. In contrast to the conventional regimen shown in figure 2B, the bulk of drug is administered toward the end of the treatment period.

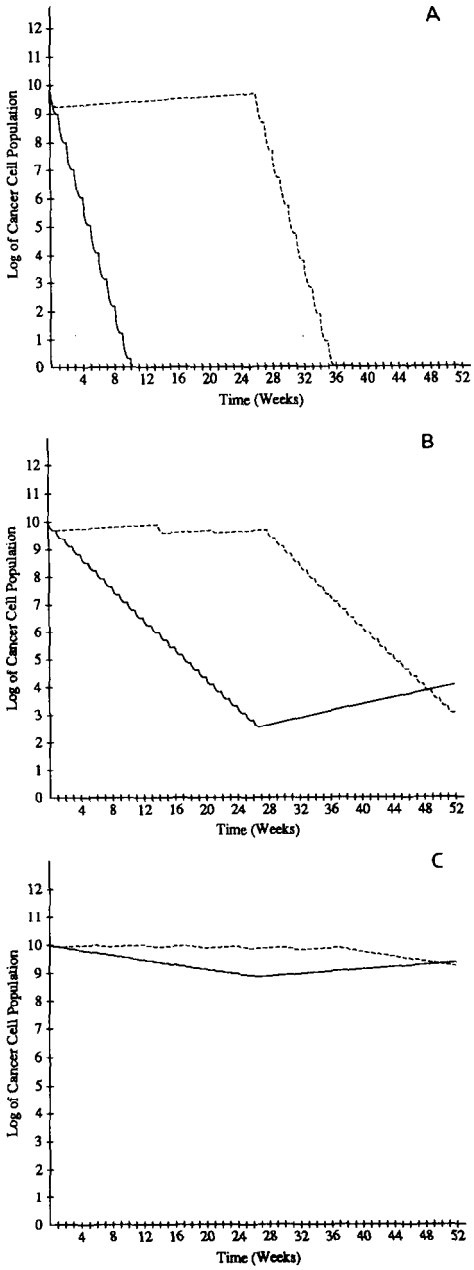


FIG. 4. Plots of $\log_{10} N(t)$ versus time for a tumor treated with the conventional regimen (solid line) and an optimal regimen (dashed line). Both the conventional and optimal regimens destroy the cancer if the drug available is highly effective (A). Although a tumor treated with the moderately effective drug using the conventional regimen reaches a smaller intermediate size (at around 26 weeks), the final tumor burden is an order of magnitude greater than that of the optimally treated tumor (B). When the anti-cancer drug is of low effectiveness (C), the optimal control regimen is only marginally more effective than the conventional regimen in reducing the final tumor burden.

problem $P(\mu)$, which were also local minima for problem $P$ to at least five significant figures accuracy in $J$ in each case.

The resulting optimal regimens (Figure 3) are of the same form for drugs A, B, and C, and are qualitatively different from the conventional regimen. In every case treatment commences immediately at relatively low dose intensity, ensuring that the intermediate tumor size does not exceed $N_{\max}$ [cf. constraint (14)]. The bulk of the doses are delivered towards the end of treatment at high dose intensity. In this way the optimal regimens bear a strong resemblance to the lower bound regimen constructed in Theorem 4. The lower bound regimen, the conventional regimen, and the three optimal regimens all share a common feature: nonzero doses are nearly always given at the highest possible concentration. In other words the drug concentration at the tumor site $v(t)$ is kept as large as possible without exceeding its upper bound $v_{\max}$. This is consistent with the fact that the dose-response curve for most known anti-tumor agents is steep for therapeutic effects.

In the case of the highly effective drug A, both the optimal and conventional treatments predicted a final tumor population smaller than a single cell (Figure 4A). Both treatments destroyed the tumor. (It should be noted at this point that the differential Equation (17) describing the tumor population is only known to be a reasonable approximation when the number of cells is large.) It is not clear that the optimal treatment is preferable, because it delays the delivery of the bulk of the doses. Therefore the final tumor size may not be a satisfactory measure of success when a cure is achievable.

The optimal treatment is clearly superior for drug B, the moderately effective drug. It predicted a final tumor size an order of magnitude smaller than that of the conventional treatment (Figure 4B).

For drug C, the drug of low effectiveness, the optimal treatment was marginally more successful then the conventional treatment (Figure 4C). Both treatments predicted that the initial tumor population could be reduced by about an order of magnitude.

## 4. DISCUSSION

In the present study an optimal control model has been used to test whether the conventional method for treating recurring cancers is necessarily the best. The best regimen is defined to be the one that both minimizes the tumor size at the end of a fixed treatment period and satisfies constraints on the drug toxicity and intermediate tumor population. The principal difference between the conventional regimen and the regimen constructed by our model is that in our model, although chemotherapy commences immediately, the bulk of the treatment is delayed as long as

possible. This is true regardless of the effectiveness of the drug used provided that the intermediate tumor size can be controlled. This concept is consistent with the findings of Swan and Vincent [2] who minimized cumulative drug usage rather than final tumor burden in their optimal control model. It is also consistent with Norton and Simon [13] who argued the case for late-intensity scheduling based upon the phenomenon of kinetic resistance.

A major study published recently [23] has shown that in patients with small-cell lung cancer the best two-year survival was seen using an initial short treatment cycle followed by additional chemotherapy at relapse. Spiro et al. [23] found that withdrawal of patients from treatment was considerably less (29% versus 50%) in the group receiving delayed chemotherapy. It was clear from this study that delaying the administration of chemotherapeutic agents can have a significant clinical benefit. These observations are consistent with the findings in the present study. Because initial chemotherapy in the optimal control regimen is minimal compared to that of the conventional method of administration, adverse side effects are significantly decreased.

Although it is clear that the present model for treating tumors [Equations (10)–(15)] can be improved, the results from this study question the current method for the administration of chemotherapy and suggest that alternative regimens should be considered.

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