SIAM J. APPL. MATH.
Vol. 60, No. 3, pp. 1059–1072

OPTIMAL CONTROL APPLIED TO CELL-CYCLE-SPECIFIC CANCER CHEMOTHERAPY*

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Abstract. We propose a mathematical model for the growth of cell-cycle-specific dose limiting bone marrow. In an attempt to determine effective methods of treatment without overdestruction of the bone marrow we implement optimal control theory. We design the control functional to maximize both the bone marrow mass and the dose over the treatment interval. Next we show that an optimal control exists for this problem, and then we characterize our optimal control in terms of the solutions to the optimality system, which is the state system coupled with the adjoint system. We show that the optimality system is unique for suitably small time intervals. Finally, we analyze the optimal control and the optimality system using numerical techniques. This allows us to suggest optimal methods of treatment that prevent excessive destruction of the bone marrow based on the specific weights in our objective functional.

Key words. optimal control, cancer, chemotherapy, cell cycle, bone marrow

AMS subject classifications. 49J15, 49K15, 92C50

PII. S0036139998338509

1. Introduction.

Cell-cycle-specific chemotherapy drugs are a common type of drug used in treating cancer. The main action of these drugs works against cells in a specific phase of the cell cycle. That is, all cells go through a well-studied cycle of growth which includes a resting phase, a DNA replication phase, and a cell division (mitosis) phase. For example, the drug Cyclophosphamide acts upon cells in the DNA replication phase of the cycle, while other drugs, such as Taxol, more effectively influence cells in the division phase. These types of drugs do not affect cells in the resting state (i.e., cells that are quiescent). Hence, cells in the quiescent state are thought of as kinetically resistant to these drugs.

Experimental and clinical trials (Hainsworth and Greco [6], Lopes et al. [9], ten Bokkel Huinink, Eisenhauer, and Swenerton [19], and Wilson et al. [22]) and mathematical models (Agur [1], Agur, Arnon, and Schechter [2], Cojocaru and Agur [3], Panetta [14], Panetta and Higgins [15], and Webb [20, 21]) of cell-cycle-specific chemotherapy provide some intriguing results. Agur [1], Agur, Arnon, and Schechter [2], and Cojocaru and Agur [3] use both age-structured and probabilistic models with an "on-off" type drug function (the drug is either active or inactive) to describe the effects of cell-cycle-specific drugs on the bone marrow. They consider only the active phases of the cell-cycle (no resting state). Their main result is that there is reduced toxicity to the bone marrow when the drugs are administered at integer multiples of the bone marrow's mean cell-cycle length. (This is referred to as resonance.) They conclude that short drug pulses at appropriate intervals are less toxic to the bone marrow compared to arbitrary treatment intervals or slowly infused continuous treatments. Similar results are shown in Webb [20, 21], using age- and maturity-structured

*Received by the editors May 11, 1998; accepted for publication (in revised form) March 2, 1999; published electronically March 10, 2000.

http://www.siam.org/journals/siap/60-3/33850.html

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models to describe the effects of the drugs on cancer cells. In a different approach, Panetta [14] and Panetta and Higgins [15] use deterministic systems of ordinary differential equations, which include both the active and resting phases of the cell-cycle, to analyze the effects of cell-cycle-specific chemotherapy. One of the main results is that drug regimens with shorter infusion times (but equivalent doses) destroys fewer bone marrow cells. Similar results are observed in experimental and clinical trials [6, 9, 19, 22].

In the process, the above regimen also destroy fewer cancer cells. This leads to the question, Should the drug infusion time be shortened to reduce toxicity to the bone marrow or should it be increased to destroy more cancer cells? A similar question concerning other important aspects of the treatment regimen, such as the period and dose, create further challenging discussions. The answers to these questions are generally not known. This leads to the following question: How is it possible to minimize destruction of host cells and simultaneously maximize destruction of cancer cells? We will apply the method of optimal control theory to address the issue.

Some mathematical work that has been done in the optimal control setting includes two non-cell-cycle-specific (drugs that are effective in all the phases of the cell cycle) models by Murray [12, 13]. In addition, Swan [17] provides a good review of the role of optimal control in non-cell-cycle-specific cancer chemotherapy. Since we are most interested in optimal control problems as applied to cell-cycle-specific chemotherapy, we will discuss models related to this topic. First, Eisen [4] has designed a system of linear differential equations describing the growth dynamics of the proliferating (drug-sensitive phase) and quiescent (drug-resistant phase) cells. The control reduces the cancer to a fixed level over a given interval while minimizing total drug use. Another work by Swierniak, Polanski, and Kimmel [18] uses optimal control theory on a cell-cycle-specific chemotherapeutic model. They investigate a variety of ways to model the cell-cycle by various groupings of the cell-cycle phases. In each case, they attempt to minimize the total cancer mass at the end of some specified time interval using the least amount of drug possible. Their main results include that optimal solutions are periodic and that the characterization of the solution is insensitive to the particular choice of the model.

By minimizing the dose, these models only indirectly take into account the effects of the drug on the normal tissue, which we consider in this paper as bone marrow. But, the toxicity to the bone marrow is one of the main limiting factors in cell-cycle-specific chemotherapy and should be considered directly. Swierniak, Polanski, and Kimmel [18] along with Swan [17] investigate the effects of the drugs on the normal tissue and use this to limit the drug strength, but only for non-cell-cycle-specific treatment. Therefore, we develop an optimal control problem that will directly determine the effects of cell-cycle-specific treatments on the normal tissue, and we attempt to relate the mathematical results to known clinical information. Since bone marrow produces blood cells, clinicians typically will take a blood cell count from a patient prior to giving further doses of chemotherapy to see if the blood cell count is above some minimum level. If it is too low the clinician will either delay the treatment or give a reduced treatment. They gauge when to give the next treatment based on the constraint of keeping the blood cell count above a fixed level. In this paper, we analyze a system in order to understand better how to effectively treat the cancers so that the blood cell count (and indirectly the bone marrow) can be maintained above this minimum.

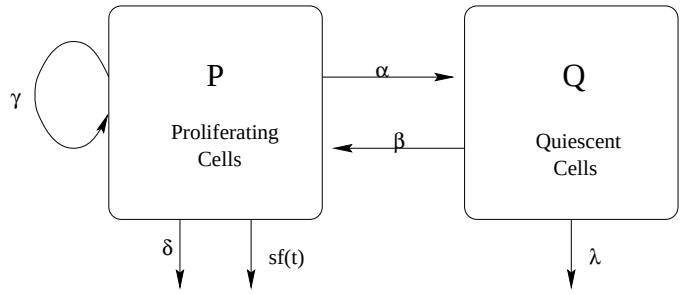

FIG. 2.1. *The cell-cycle.*

2. The model. We analyze the model originally discussed in Panetta [14] which is similar to the state equations in Eisen [4]. It is shown diagrammatically in Figure 2.1 and has the form

$$\frac{dP}{dt} = (\gamma - \delta - \alpha - sf(t))P + \beta Q, \tag{2.1}$$

$$\frac{dQ}{dt} = \alpha P - (\lambda + \beta)Q \tag{2.2}$$

with $P(0) = P_0$ and $Q(0) = Q_0$. P is the proliferating cell mass and Q is the quiescent cell mass in the bone marrow. The parameters are all considered constant, positive, and are defined as follows: γ, cycling cells' growth rate; α, transition rate from proliferating to resting; δ, natural cell death; β, transition rate from resting to proliferating; λ, cell differentiation—mature bone marrow cell leaving the bone marrow and entering the blood stream as various types of blood cells; and s, the strength or effectiveness of the treatment. All the units for the parameters are days^{-1}. The function $f(t)$ is the control describing the effects of the chemotherapeutic treatment only on the proliferating cells. We choose as our control class measurable functions defined on [0,T] with the condition that $0 \leq f(t) \leq 1$. Note that $f(t) = 1$ represents maximal chemotherapy and $f(t) = 0$ represents no chemotherapy. Hence the depiction of the class of admissible controls is

$$U = \{f \text{ measurable } |0 \leq f(t) \leq 1, t \in [0,T]\}. \tag{2.3}$$

In order to properly pose the optimal control problem we must define the goal we wish to maximize (i.e., the objective functional). We would like to give as much drug as possible while not excessively destroying the bone marrow. Therefore we define the objective functional as

$$J(f) = \int_0^T \left[a(P+Q) - \frac{b}{2}(1-f(t))^2\right] dt, \tag{2.4}$$

where the parameters a and b are weights describing the importance of each term in the objective functional. Here we maximize the total amount of bone marrow (first term in (2.4)) and maximize the amount of drug given (second term in 2.4). These two "maximizations" have competing effects because giving large drug doses will lower the amount of bone marrow. This objective functional represents balancing these two effects. Note that as a function of f, the objective functional is increasing and concave down. Also observe that we are assuming the objective functional is a

TABLE 2.1
Bone marrow parameters.

Mean, (Range)	Units = days^{-1}
$\gamma = 1.47, (0.6667 - 2)$	$\delta = 0$
$\alpha = 5.643, (4.92 - 6.12)$	$\beta = 0.48$
$\lambda = 0.164$	

nonlinear function of f, taken to be quadratic here, for the desired increasing and concavity properties. The goal is to characterize the optimal control f^* satisfying

$$\max_{0 \le f \le 1} J(f) = J(f^*). \tag{2.5}$$

It will be seen in sections 6.1 and 6.2 that the weights a and b affect the amount of bone marrow destruction over the interval. Therefore, the weight factors will be chosen such that we obtain an acceptable minimal bone marrow mass.

2.1. Parameter estimation. The basic model parameters for bone marrow are obtained from Mackey [11] and are given in Table 2.1. The treatment interval (T) can either relate to the period of one or multiple treatment regimens. We have used a method involving periodic treatment whereby we consider sequential treatments of period T. In essence, the initial conditions of the current treatment are set to the end conditions of the previous treatment. Moreover, the parameters a and b need not be identical for each period, only within a given period. In treatment of breast or ovarian cancer with the drug Taxol the typical period of one treatment ranges from 7 to 21 days. As mentioned above, a and b relate to the amount of bone marrow destruction and are chosen to prevent overdestruction of the bone marrow tissue. Although the values of a and b may not be specifically measurable from blood cell counts oncologists perform, we can obtain indirect data for these weights by studying the ratio a/b. If the blood cell count is low resulting from a large reduction in bone marrow, then we choose the ratio a/b larger to more heavily weight maximizing bone marrow as opposed to dose. But if the blood cell count is in an acceptable range, then we set a/b smaller, in which case the optimal treatment will allow a larger dose to be given.

3. Existence of optimal control. In this section we examine the existence of an optimal control for the state system. Upper bounds of the state system (2.1)–(2.2) are needed for the existence of an optimal control and are used in the uniqueness proof of the optimality system. Since the state system (2.1)–(2.2) is a linear system in finite time with bounded coefficients, the solution to the state system is uniformly bounded. Utilizing the theory from Fleming and Rishel [5], we prove the existence of an optimal control.

THEOREM 3.1. *There exists an optimal control f^* that maximizes the functional $J(f)$ over the control set U.*

Proof. To prove this theorem, the following conditions must be satisfied:

(i) The class of all initial conditions with a control f in the admissible control set along with the state system being satisfied is not empty.

(ii) The admissible control set U is closed and convex.

(iii) The right-hand side of the state system (2.1)–(2.2) is continuous, is bounded above by a sum of the bounded control and the state, and can be written as a linear function of f with coefficients depending on the time and the state.

(iv) The integrand of the objective functional is concave on U and is bounded above by $c_2 - c_1|f|^\eta$ with $c_1 > 0$, and $\eta > 1$.

First, an existence result in Lukes [10, Theorem 9.2.1] for the state system for bounded coefficients is invoked. Then, by definition, U is closed and convex. We notice that the right-hand side of the state system (2.1)–(2.2) can be written as

$$\begin{pmatrix} (\gamma - \alpha - \delta - sf) & \beta \\ \alpha & -(\beta + \lambda) \end{pmatrix} \begin{pmatrix} P \\ Q \end{pmatrix} = \vec{d}\left(t, \begin{pmatrix} P \\ Q \end{pmatrix}\right) + \vec{h}\left(t, \begin{pmatrix} P \\ Q \end{pmatrix}\right) f(t),$$

where

$$\vec{d}\left(t, \begin{pmatrix} P \\ Q \end{pmatrix}\right) = \begin{pmatrix} (\gamma - \alpha - \delta) & \beta \\ \alpha & -(\beta + \lambda) \end{pmatrix} \begin{pmatrix} P \\ Q \end{pmatrix}$$

$$\text{and } \vec{h}\left(t, \begin{pmatrix} P \\ Q \end{pmatrix}\right) = \begin{pmatrix} -sP \\ 0 \end{pmatrix}.$$

Also, the bound of the right-hand side of the state system is obtained as follows:

$$\begin{vmatrix} (\gamma - \alpha - \delta - sf) & \beta \\ \alpha & -(\beta + \lambda) \end{vmatrix} \begin{vmatrix} P \\ Q \end{vmatrix} \le \begin{vmatrix} \gamma & \beta \\ \alpha & 0 \end{vmatrix} \begin{vmatrix} P \\ Q \end{vmatrix} + |sf| \begin{vmatrix} P \\ Q \end{vmatrix} \le C\left(\begin{vmatrix} P \\ Q \end{vmatrix} + |f|\right),$$

where C incorporates the upper bound of the given constant matrix and the bound on s.

Next we show that the integrand of the functional is concave on U. We suppose that $0 < \epsilon < 1$ and show that for f_1 and $f_2 \in U$

$$(P+Q) - \frac{b}{2}\left(1 - [(1-\epsilon)f_1 + \epsilon f_2]\right)^2 \ge (1-\epsilon)\left[(P+Q) - \frac{b}{2}(1-f_1)^2\right] + \epsilon\frac{b}{2}[(P+Q)(1-f_2)^2]. \tag{3.1}$$

Ultimately, we must show that

$$-\frac{b}{2}\left(1 - [(1-\epsilon)f_1 + \epsilon f_2]\right)^2 + (1-\epsilon)\frac{b}{2}(1-f_1)^2 + \epsilon\frac{b}{2}(1-f_2)^2 \ge 0. \tag{3.2}$$

To obtain concavity we recognize that

$$\left(1 - [(1-\epsilon)f_1 + \epsilon f_2]\right)^2 \le (1-\epsilon)(1-f_1)^2 - \epsilon(1-f_2)^2.$$

Therefore the inequality (3.1) is proven, and the concavity is determined for the integrand of the functional. To complete the proof we see that P and Q are uniformly bounded. Hence, there exists a $B > 0$ such that $|P(t)| < B$ and $|Q(t)| < B$ on [0,T]. Moreover,

$$a(P+Q) - \frac{b}{2}(1-f)^2 \le 2aB - \frac{b}{2} + bf - \frac{b}{2}f^2 \le 2aB + b - \frac{b}{2}f^2.$$

Here, we choose $c_2 = 2aB + b$ and $c_1 = \frac{b}{2}$ with $\eta = 2$. □

4. Characterization of optimal control. Since an optimal control exists for maximizing the functional (2.4) subject to (2.1) and (2.2), then a version of Pontryagin's maximum principle is used to derive necessary conditions for the optimal control (Kamien and Schwartz [7]).

THEOREM 4.1. *Given an optimal control f^* and solutions of the corresponding state system, there exist adjoint variables λ_i for $i = 1, 2$ satisfying the following:*

$$\frac{d\lambda_1}{dt} = -\frac{\partial L}{\partial P} = -\left[a + \lambda_1\left(\gamma - \delta - \alpha - sf\right) + \lambda_2\alpha\right], \tag{4.1}$$
$$\frac{d\lambda_2}{dt} = -\frac{\partial L}{\partial Q} = -\left[a + \lambda_1\beta - \lambda_2(\lambda + \beta)\right],$$

where $\lambda_i(T) = 0$ for $i = 1, 2$. Further, f^* can be represented by

$$f^* = \min\left(1, \left(\frac{b - \lambda_1 sP}{b}\right)^+\right),$$

where the notation is [16]

$$r^+ = \begin{cases} r & \text{if } r > 0, \\ 0 & \text{if } r \le 0. \end{cases} \tag{4.2}$$

Proof. We form the Lagrangian as follows:

$$L(P, Q, f, \lambda_1, \lambda_2, w_1, w_2) = a(P + Q) - \frac{b}{2}(1 - f)^2 + \lambda_1\left((\gamma - \delta - \alpha - sf)P + \beta Q\right)$$
$$+ \lambda_2\left(\alpha P - (\lambda + \beta)Q\right) + w_1(t)f(t) + w_2(t)\left(1 - f(t)\right), \tag{4.3}$$

where $w_1(t) \ge 0$, $w_2(t) \ge 0$ are penalty multipliers satisfying

$$w_1(t)f(t) = 0, \quad w_2(t)\left(1 - f(t)\right) = 0 \tag{4.4}$$

at the optimal f^*. First, the maximum principle gives existence of the adjoint variables satisfying (4.1). To complete the representation for f^* we analyze the optimality condition $\frac{\partial L}{\partial f} = 0$. Upon some algebraic manipulation, the representation of f^* becomes

$$f^*(t) = \frac{b - \lambda_1 sP + w_1(t) - w_2(t)}{b}.$$

To determine an explicit expression for the optimal control, without w_1 and w_2, a standard optimality technique is utilized. We consider three cases:

(i) On the set $\{t | 0 < f^*(t) < 1\}$, $w_1(t) = 0 = w_2(t)$. Hence the optimal control is

$$f^*(t) = \frac{b - \lambda_1 sP}{b}.$$

(ii) On the set $\{t | f^*(t) = 1\}$, $w_1(t) = 0$. Hence,

$$1 = f^*(t) = \frac{b - \lambda_1 sP - w_2(t)}{b}.$$

Furthermore, $\frac{b - \lambda_1 sP}{b} = 1 + \frac{w_2(t)}{b} \ge 1$. Consequently, $1 = f^* \le \frac{b - \lambda_1 sP}{b}$.

(iii) On the set $\{t|f^*(t)=0\}$, $w_2(t)=0$. Hence,

$$0=f^*(t)=\frac{b-\lambda_1 sP+w_1(t)}{b}.$$

Since $w_1(t)\geq 0$, then $\frac{b-\lambda_1 sP}{b}\leq 0$. Notice $\left(\frac{b-\lambda_1 sP}{b}\right)^+=0=f^*(t)$ in this case. Combining these three cases, the optimal control is characterized as

$$f^*(t)=\min\left(1,\left(\frac{b-\lambda_1 sP}{b}\right)^+\right). \tag{4.5}$$

Also it is noted that $f^*(T)=1$ since $\lambda_1(T)=0$.

After obtaining an explicit representation for the control, the adjoint equations coupled with the state equations and the initial and transversality conditions form the optimality system below:

$$\begin{aligned}
\frac{dP}{dt}&=\left[\gamma-\delta-\alpha-s\min\left(1,\left(\frac{b-\lambda_1 sP}{b}\right)^+\right)\right]P+\beta Q, \qquad (4.6)\\
\frac{dQ}{dt}&=\alpha P-(\lambda+\beta)Q,\\
\frac{d\lambda_1}{dt}&=-\frac{\partial L}{\partial P}=-\left[a+\lambda_1\left(\gamma-\delta-\alpha-s\min\left(1,\left(\frac{b-\lambda_1 sP}{b}\right)^+\right)\right)+\lambda_2\alpha\right],\\
\frac{d\lambda_2}{dt}&=-\frac{\partial L}{\partial Q}=-[a+\lambda_1\beta-\lambda_2(\lambda+\beta)]
\end{aligned}$$

with $P(0)=P_0$, $Q(0)=Q_0$, $\lambda_i(T)=0$ for $i=1,2$. □

In addition, the second derivative of the Lagrangian with respect to f is negative, indicating a maximum at f^*.

5. Uniqueness. In order to successively discuss uniqueness of the optimality system we notice that the adjoint system (4.1) is also linear in λ_i for $i=1,2$ with bounded coefficients. Thus, there exists a $D>0$ such that $|\lambda_i(t)|<D$ for $i=1,2$ on $[0,T]$.

THEOREM 5.1. *For T sufficiently small the solution to the optimality system* (4.6) *is unique.*

Proof. To discuss the uniqueness explicitly, we suppose that $(P,Q,\lambda_1,\lambda_2)$ and $(\overline{P},\overline{Q},\overline{\lambda}_1,\overline{\lambda}_2)$ are two distinct solutions to the optimality system (4.6). Let $m>0$ be chosen such that $P=e^{mt}u$, $Q=e^{mt}v$, $\lambda_1=e^{-mt}w$, $\lambda_2=e^{-mt}z$, $\overline{P}=e^{mt}\overline{u}$, $\overline{Q}=e^{mt}\overline{v}$, $\overline{\lambda}_1=e^{-mt}\overline{w}$, and $\overline{\lambda}_2=e^{-mt}\overline{z}$. In addition,

$$f=\min\left(1,\left(\frac{b-swu}{b}\right)^+\right) \tag{5.1}$$

and

$$\overline{f}=\min\left(1,\left(\frac{b-s\overline{wu}}{b}\right)^+\right). \tag{5.2}$$

Consequently, substitution of $P = e^{mt}u$ and $\lambda_1 = e^{-mt}w$ into the first and the third differential equation of the optimality system (4.6) produces

$$\begin{aligned}\dot{u} + mu &= (\gamma - \alpha - \delta - sf)u + \beta v\\ -\dot{w} + mw &= 2e^{2mt}(u+v) + (\gamma - \alpha - \delta - sf)w + \alpha z,\end{aligned}$$

where $u(0) = P_0 e^{-mt}, v(0) = Q_0 e^{-mt}, w(T) = 0$, and $z(T) = 0$. Note that $\dot{u} = \frac{du}{dt}$.

The next step is to subtract the equations for u and $\overline{u}$, v and $\overline{v}$, etc. Then each new equation is multiplied by an appropriate function and integrated from zero to T. Consider the $u - \overline{u}$ equation after multiplying by $u - \overline{u}$ and integrating from zero to the final time.

$$\begin{aligned}&\frac{1}{2}[u(T) - \overline{u}(T)]^2 + m\int_0^T (u-\overline{u})^2 dt\\ &\qquad = (\gamma - \alpha - \delta)\int_0^T (u-\overline{u})^2 - \int_0^T \left(sfu - s\overline{f}\,\overline{u}\right)(u-\overline{u})\,dt\\ &\qquad + \beta\int_0^T (v-\overline{v})(u-\overline{u})dt.\end{aligned}$$

Since bounds on the right-hand sides of the integral equations are necessary, we specifically analyze $-\int_0^T \left(sfu - s\overline{f}\,\overline{u}\right)(u-\overline{u})\,dt$. To obtain this estimate, we use Cauchy's inequality in order to separate the linear terms into quadratic terms. Also, we recognize that $\left|f - \overline{f}\right|^2 \le (w-\overline{w})^2 u^2 + (u-\overline{u})^2 w^2$. Therefore, we obtain

$$\begin{aligned}-\int_0^T \left(sfu - s\overline{f}\,\overline{u}\right)(u-\overline{u})\,dt &\le -\int_0^T \left[s\left(f-\overline{f}\right)u\,(u-\overline{u}) + s\overline{f}\,(u-\overline{u})^2\right]dt\\ &\le Bs\int_0^T \left(f-\overline{f}\right)(u-\overline{u})\,dt\\ &\le C_1\int_0^T (w-\overline{w})^2\,dt + C_2 e^{mT}\int_0^T (u-\overline{u})^2\,dt,\end{aligned}$$

where C_1 depends on B, s, and b, and C_2 depends on B, s, b, and D.

To complete this uniqueness proof, the integral representations of $(u-\overline{u})$, $(v-\overline{v})$, $(w-\overline{w})$, and $(z-\overline{z})$ are combined, and estimates are utilized to obtain the following inequality:

$$\begin{aligned}&\frac{1}{2}[u(T) - \overline{u}(T)]^2 + \frac{1}{2}\left[v(T) - \overline{v}(T)\right]^2 + \frac{1}{2}\left[w(0) - \overline{w}(0)\right]^2 + \frac{1}{2}\left[z(0) - \overline{z}(0)\right]^2\\ &\qquad + m\int_0^T \left[(u-\overline{u})^2 + (v-\overline{v})^2 + (w-\overline{w})^2 + (z-\overline{z})^2\right]dt\\ &\qquad \le (\gamma + \beta + \alpha + C_2 e^{mT})\int_0^T \left[(u-\overline{u})^2 + (v-\overline{v})^2\right]dt + C_1\int_0^T (w-\overline{w})^2\,dt\\ &\qquad + \left(C_5 + C_4 e^{2mT}\right)\int_0^T \left[(u-\overline{u})^2 + (v-\overline{v})^2 + (w-\overline{w})^2 + (z-\overline{z})^2\right]dt\\ &\qquad \le \left(C_6 + C_7 e^{2mT}\right)\int_0^T \left[(u-\overline{u})^2 + (v-\overline{v})^2 + (w-\overline{w})^2 + (z-\overline{z})^2\right]dt,\end{aligned}$$

where C_4 depends on D, s, and b, and C_5, C_6, and C_7 depend on γ, α, s, D, B, b, and β.

Using the nonnegativity of the variable expressions evaluated at the initial and the final time, the inequality is reduced to the following:

$$m\int_0^T \left[(u-\overline{u})^2+(v-\overline{v})^2+(w-\overline{w})^2+(z-\overline{z})^2\right]dt$$
$$\leq \left(C_6+C_7e^{2mT}\right)\int_0^T \left[(u-\overline{u})^2+(v-\overline{v})^2+(w-\overline{w})^2+(z-\overline{z})^2\right]dt.$$

Moreover, the simplification gives

$$\left(m-\left(C_6+C_7e^{2mT}\right)\right)\int_0^T \left[(u-\overline{u})^2+(v-\overline{v})^2+(w-\overline{w})^2+(z-\overline{z})^2\right]dt\leq 0.$$

Hence, m is chosen such that $m-\left(C_6+C_7e^{2mT}\right)>0$. Since the natural logarithm is an increasing function, then

$$\ln\left(\frac{m-C_6}{C_7}\right)>(2m)\,T \tag{5.3}$$

if $m>C_6+C_7$. In essence, this gives that $T<\frac{1}{2m}\ln\left(\frac{m-C_6}{C_7}\right)$. □

Via the uniqueness of the optimality system, the optimal control is thus unique. Hence, the optimal control is completely characterized in terms of λ_1 and P, which are incorporated in the unique solution of the optimality system (4.6).

6. Numerical results. To numerically solve the optimality system (4.6) we use the Fortran subroutine "TWPBVP" written by J. R. Cash and M. H. Wright and available through Netlib. One example of an optimal solution with $a=1$, $b=1$, $s=1$ is seen in Figure 6.1. We observe that the optimal control (4.5) always ends with the treatment at full strength since $\lambda_1(T)=0$. This helps us understand the optimal solution. We are trying to maximize both the total cell mass $(P+Q)$ along with drug $f(t)$ over the interval T. As can be seen in Figure 6.1 this happens when the treatment begins on approximately day 13, thus allowing the bone marrow to stay larger longer. As we will see in the following sections, modifying the weights a and b along with the dose strength parameter s allows us to adjust for an acceptable bone marrow loss for the interval T.

6.1. The effects of *a* and *b*. By changing the weights we can alter the optimal treatment. By increasing the weight b while fixing a (a/b—smaller) we place more importance on maximizing the dose. From Figure 6.2 we observe that as b is increased more drug is used and the bone marrow is decreased. In a similar manner, increasing a with b fixed (a/b—larger) signifies that it is more important to maximize the bone marrow mass rather than the dose.

In general the ratio a/b should be chosen to account for a patient's condition. In patients who have not had any treatment and whose bone marrow is at normal levels, a/b should be small. This means a larger dose may be given. But in a patient who has received several courses of therapy and whose bone marrow is depressed, a/b should be increased to preserve the bone marrow.

One example depicting the changes in the ratio a/b is portrayed in Figure 6.3, where two intervals of $T=7$ are compared to one interval of $T=14$. We attempt to keep $P+Q$ above 50% of the initial bone marrow mass. First we consider two intervals of seven days. For the first period ($0\leq t\leq 7$) we choose $a/b=1/1.5$

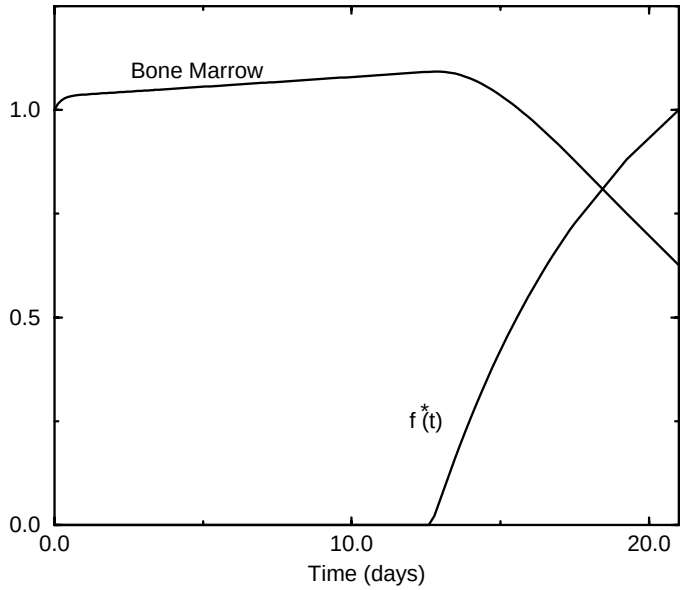

FIG. 6.1. *Optimal solution.* $a = 1$, $b = 1$, $s = 1$, $T = 21$.

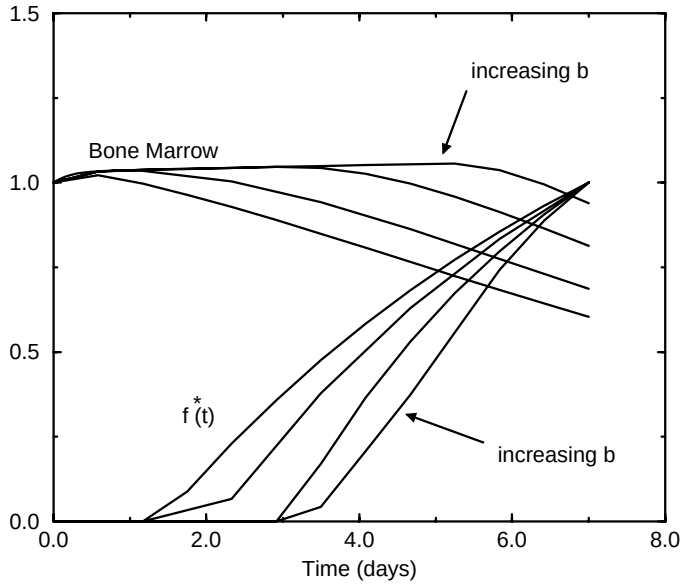

FIG. 6.2. *Optimal solution with* $a = 2$, $s = 1$, $T = 7$ *and with* $0.5 \leq b \leq 2$, *where* b *is incremented by* 0.5 *for each of the four runs. The arrows indicate the direction of increasing* b. *Thus larger* b *allows for a larger dose.*

which allows a larger dose and a larger bone marrow kill. But for the second period ($7 \leq t \leq 14$) we increase a/b to $2.1/1$ since the bone marrow is depressed from the first treatment. Therefore, in this second period, the treatment involves less drug. Hence, the bone marrow remains at acceptable levels. If we instead consider one interval of $T = 14$ with $a/b = 1/1.17$ we obtain an equivalent reduction of the bone

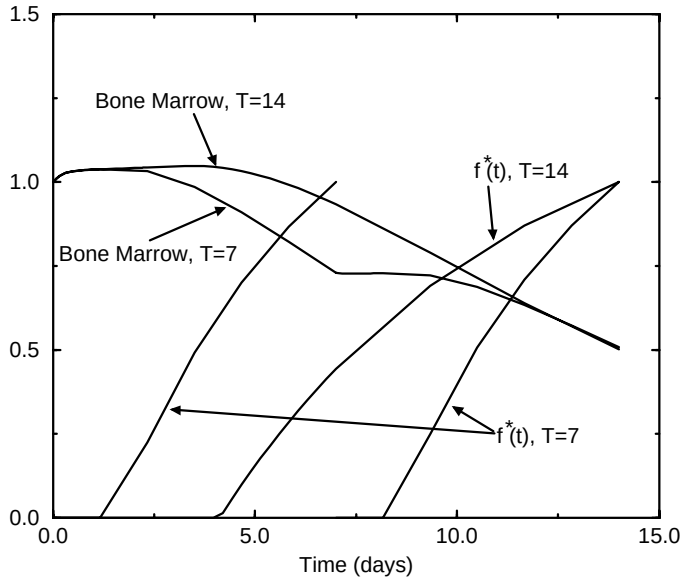

FIG. 6.3. *Optimal solution.* $T = 7$*:* $a = 1$, $b = 1.5$ *for* $0 \le t \le 7$, $a = 2.1$, $b = 1$ *for* $7 \le t \le 14$ *(periodic treatment of period* $2T$*).* $T = 14$*:* $a = 1$, $b = 1.17$*(single period treatment).*

marrow ($P(14) + Q(14)$ is the same as the first case) but in a very different manner. In this case, the bone marrow stays at higher levels since treatment is delayed until day four. Also, the total treatment time is about 1.7 days shorter when $T = 14$ (9.9 days compared to 11.6 days for treatments for two periods of seven days). Finally, we observe in Figure 6.3 that the total dosage (i.e., the integral or AUC (area under the curve) of $f^*(t)$ over the treatment interval) for the one interval of 14 days is 10% less than with two intervals of seven days.

At first, the second option ($T = 14$) appears to be better since there is less bone marrow damage overall (more area under the bone marrow curve). But there are several reasons why this might not be the best choice. First, waiting four days before treating allows the cancer to continue to grow. Since cancer grows faster than the bone marrow, this could be detrimental to the patient. Secondly, we have previously stated that the longer the treatment time (related to $f^*(t)$) and the shorter the treatment period (related to T), the more effective the regimen is at destroying the cancer [14, 15]. This would suggest the treatment described in Figure 6.3 with two treatment intervals of seven days is the better choice since the period is shorter, the total treatment time is longer, and the total dosage is greater.

6.2. The effects of s. Next, if we fix all the parameters except s we can observe how changes in the drug strength affects the optimal treatment. Figure 6.4 shows several interesting facts. First, if a and b are held fixed, the end bone marrow mass ($P(T) + Q(T)$) remains constant as s is varied. This shows that changes in s affect the total bone marrow over the treatment interval (i.e., the integral of $P(t) + Q(t)$ increases as s increases) but not the end amount of bone marrow.

Also, if the stronger drug (larger s) is used, then the total dosage required is smaller. In addition, the bone marrow remains at a higher level for a longer period of time. But this effect is limiting. That is, as s is increased the optimal treatment $f^*(t)$ and the total bone marrow mass approach a limiting function. For example, the

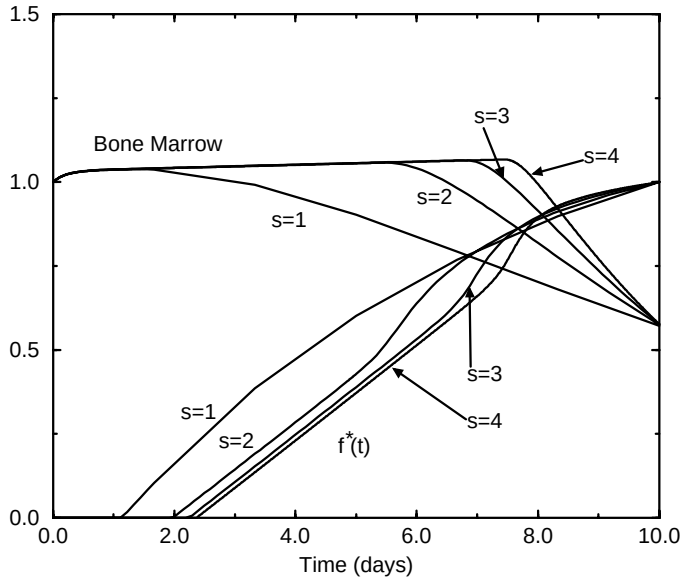

FIG. 6.4. *Optimal solution.* $a = 1$, $b = 1$, $T = 10$. *Larger* s *(a more effective drug) allows for a smaller optimal dose.*

total drug needed for optimal treatment at $s = 3$ is only 3% greater than that needed at $s = 4$ (a 33% increase in the parameter s). Therefore, the stronger drug ($s = 4$) requires about the same total dose as the less effective drug ($s = 3$) to do equivalent damage to the bone marrow. This is because as the strength of the drug is increased, the cell mass sensitive to the drug decreases. Eventually increasing s will not improve cell kill since most of the drug sensitive cells have already been killed. (This effect is seen mathematically in Panetta [14], Panetta and Higgins [15], and experimentally in Liebmann et al. [8].)

7. Conclusions. We have developed a basic model to study effects of a cell-cycle-specific drug on the treatment limiting tissue, bone marrow. In this process we have designed an optimal control problem that will maximize the dose while also maximizing the total bone marrow mass over the treatment interval. First we have shown that an optimal control exists and that it can be characterized in terms of the solution to the optimality system. We also determined that the solution to the optimality system is unique for a suitably small interval. Next, we solved the system numerically in an attempt to understand how to treat cancer more effectively without excessive destruction of bone marrow.

The numerical results show that the weights (a and b) influence the amount of acceptable bone marrow damage in the model. By adjusting them appropriately we prevent excessive destruction of the bone marrow while administering the treatment in an optimal way. We also consider repeated treatments of the optimal control using the final conditions for the previous treatment as the initial conditions of the next treatment. The model shows that treating with repeated shorter periods (T) allows more drug to be given without excess damage to the bone marrow. This result compares well with previous results which show that shorter treatment periods kill more cancer [14, 15]. Finally, we observe that optimal treatment for stronger drugs (larger s) allows for more total bone marrow over the treatment interval. But, this

effect is limiting. After a point increasing s does not allow for an equivalent increase in total bone marrow and decrease in total dose. Similar results are observed in [8, 14] when considering the effects of cell-cycle-specific drugs on cancer cells.

Our work compares to the results in [1, 2, 3, 20, 21] in that we all conclude that shorter periods are less toxic to the bone marrow. But one main difference is that we explicitly consider the resting phase cells. Introducing these cells makes our model more realistic in the clinical setting. This is because a larger percentage of a cancerous mass (around 80–90% in some breast and ovarian cancers) is resting and thus not affected at all by cell-cycle-specific treatments.

This model and variations of it can be useful to experimental and clinical cancer researchers because it gives them possible guidelines for effective methods of treating cancer without excessive side effects to the bone marrow. Currently, we are testing the results of this model experimentally to validate the theoretical results.

Possible future directions include (1) incorporating similar equations for cancer cell growth into the model and then applying optimal control to the new design and (2) utilizing state constraints for the bone marrow cells in an optimal control setting to maintain the normal cells above a certain limit. This would be comparable to the clinician's procedure of analyzing a blood cell count to determine if it is above a fixed level before administering treatment.

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