MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **1**, Number **1**, June **2004**

http://math.asu.edu/~mbe/

pp. **95–110**

CONTROLLING A MODEL FOR BONE MARROW DYNAMICS IN CANCER CHEMOTHERAPY

Urszula Ledzewicz
Department of Mathematics and Statistics
Southern Illinois University at Edwardsville
Edwardsville, Illinois, 62026-1653

Heinz Schättler
Department of Electrical and Systems Engineering
Washington University
St. Louis, Missouri, 63130-4899

(Communicated by Yang Kuang)

Abstract. This paper analyzes a mathematical model for the growth of bone marrow cells under cell-cycle-specific cancer chemotherapy originally proposed by Fister and Panetta [8]. The model is formulated as an optimal control problem with control representing the drug dosage (respectively its effect) and objective of Bolza type depending on the control linearly, a so-called L^1-objective. We apply the Maximum Principle, followed by high-order necessary conditions for optimality of singular arcs and give sufficient conditions for optimality based on the method of characteristics. Singular controls are eliminated as candidates for optimality, and easily verifiable conditions for strong local optimality of bang-bang controls are formulated in the form of transversality conditions at switching surfaces. Numerical simulations are given.

1. **Introduction.** Mathematical models for cancer chemotherapy treatments have a long history (for a survey of early efforts see, for example [7, 23]) and attracted extensive research in the eighties and nineties (for example, [5, 15, 25]). While biomedical research concentrates on the development of new drugs and experimental (in vitro) and clinical (in vivo) determinations of their treatment schedules, analysis of mathematical models can assist in testing various treatment strategies and searching for optimal ones. Considerable research has been done in this direction analytically (for example, [2, 3, 4, 5, 27]) as well as experimentally and clinically (for example, [9, 14, 26]). However, the few existing realistic models for specific diseases are very complex and with a large number of variables and parameters, typically are analyzed on a computational or simulation level [21]. Usually only simpler models with a small number of variables can be analyzed theoretically. Although they may be medically unrealistic, nevertheless their analysis can further our understanding of some simplified aspects of the overall system, a necessary step toward the goal of analyzing more medically relevant models.

A major problem in the design of actual chemotherapy protocols is the assessment of the negative side effects of the therapeutic agents. In clinical studies, these

2000 *Mathematics Subject Classification.* 49J15,92C50.

Key words and phrases. optimal control, cancer chemotherapy, singular controls, bang-bang controls.

are determined experimentally: drug dosages are tested by increasing the dosage until limiting side effects occur. Because most models for cancer chemotherapy focus, for obvious reasons, on the dynamics of the cancer cells, automatically less emphasis is put on the effect therapy has on healthy cells. For example, in compartmental models considered in [25, 12, 13, 24] the dynamics represents the numbers of cancer cells at various stages of the cell cycle, and the aim is to minimize the number of these cells at the end of a fixed therapy interval. The negative effects on the healthy cells are represented only indirectly by also minimizing the drug dosage in the objective. For this, however, many nonequivalent formulations exist, with no apparent clear-cut biological favorite (see also section 3.2). Other models distinguish normal and tumor populations and include loss-functions to model the effects of the drugs [16]. These and other efforts indicate that the complexity of the underlying biological processes is difficult to capture in a mathematical framework.

In this paper, we analyze a model for cancer chemotherapy in which the negative effects of the drug are central. For many drugs the limiting tissue is hemopoietic (related to blood cell formulation). Blood cell counts are routinely taken in clinical practice and if the results are too low, treatment will be delayed or a lower dose will be administered. Thus the blood count becomes a deciding factor in designing treatment. Mature cells of these renewing tissues are formed through differentiation from the self-renewing stem-cell population in the bone marrow and it is generally accepted that "ideal cancer treatment would aim to bring about minimal normal stem cell kill "[10]. Toxicity to the bone marrow thus is one of the main limiting factors in chemotherapy. The model considered here, introduced in the nineties by Panetta [19] and analyzed by Fister and Panetta in [8], focuses on this aspect by directly modelling the dynamic behavior of the number of bone marrow cells. The purpose of its analysis is to find strategies for chemotherapy treatments of cancer where the bone marrow and thus, indirectly, the blood cell count are kept above a minimum level. An analysis of this model as an optimal control problem was given in [8] with an objective of Lagrange type (no terminal payoff) which was quadratic in the control, a so-called L^2-objective. The analysis led to protocols, which starting from no dose gradually increased achieving a full dose at the end of the therapy. On the other hand, both experimental and clinical trials as well as preliminary analysis of models led to the general conclusion that "short drug pulses at appropriate intervals are less toxic to the bone marrow compared to arbitrary treatment intervals or slowly infused continuous treatments"[8, 27]. Researchers suggested the use of "on-off" type drug functions (the drug is either active or not active) to describe the effect of the cell-cycle-specific drugs on the bone marrow. Such a treatment corresponds to bang-bang controls, which also appeared in our work on other chemotherapy models [12, 13, 24], with an objective, that was linear in the control; that is, a so-called L^1-type objective. Combining these suggestions and experiences, in this paper we analyze the bone marrow dynamics with an L^1-objective containing also a terminal payoff term representing the total count of the bone marrow cells at the end of the therapy.

We review the underlying model in section 2. To establish the steady state behavior of the system, we start with the analysis of the uncontrolled dynamics. Then the application of the Maximum Principle to the optimal control problem in section 3 leads to two types of controls: singular controls (with values in the interior of the control set corresponding to partial drug dosages) and bang-bang controls

(which take values in the boundary of the control set corresponding to alternating full-dose and no-dose periods). Further analysis of both classes of controls is performed using high-order conditions. The Legendre-Clebsch condition is used to eliminate singular controls and bang-bang controls are analyzed with the use of the method of characteristics. The results are supported by numerical simulations which are presented in Section 4. Simulations of trajectories and controls are compared for initial conditions from the steady state and away from it. Comparisons of the results obtained with an L^2-objective case and remarks on future directions of research conclude the paper.

2. **Mathematical Model.** The model for cancer chemotherapy considered below assesses the negative side-effects of chemotherapy on healthy tissue, which is taken as bone marrow. The effects of the drugs on cancer cells are not modelled in the dynamics, but will be taken into account indirectly in the objective for the optimal control problem.

2.1. **The dynamics of the uncontrolled model.** We briefly review the underlying model which originally was proposed by Panetta in [19] and then analyzed as an optimal control problem with an objective which was quadratic in the control by Fister and Panetta in [8].

In the model, proliferating cells P and quiescent (or dormant) cells Q are distinguished in the bone marrow. The growth rate of the proliferating cells is denoted by γ, and the transition rates from proliferating to quiescent cells and vice versa are denoted by α and β respectively. The rate at which bone marrow enters the blood stream is denoted by ρ, and the natural death rate of the proliferating cells is called δ. It is assumed that all these parameters governing the cell cycle remain constant over the time horizon considered. Thus, the overall dynamics of the uncontrolled system is described by

$$\dot{P} = (\gamma - \delta - \alpha)P + \beta Q, \qquad P(0) = P_0, \tag{1}$$

$$\dot{Q} = \alpha P - (\rho + \beta)Q, \qquad Q(0) = Q_0, \tag{2}$$

with all initial conditions positive. It is easy to see (c.f. Lemma 2.1 below) that all states remain positive if the initial conditions are positive.

In steady state, this corresponds to a model of exponential growth of the overall bone marrow at a fixed rate ξ given by

$$\xi = \omega\bar{x} - \rho, \qquad \omega = \gamma - \delta + \rho > 0, \tag{3}$$

where $\bar{x}$ is the unique positive root of the quadratic equation

$$-\omega x^2 + (\omega - \alpha - \beta)x + \beta = 0. \tag{4}$$

For, if

$$x = \frac{P}{P+Q} \qquad \text{and} \qquad y = \frac{Q}{P+Q} = 1 - x \tag{5}$$

denote the portions of the cells in the respective compartments, then x satisfies the scalar Riccati equation

$$\dot{x} = -\omega x^2 + (\omega - \alpha - \beta)x + \beta, \tag{6}$$

which has a locally asymptotically stable equilibrium at $\bar{x}$ in the open interval $(0, 1)$ that contains the closed interval $[0, 1]$ in its region of attraction. Thus, in terms of P and Q the region of attraction contains all possible initial conditions.

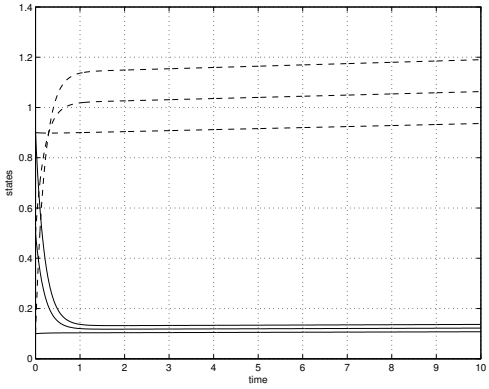

FIGURE 1. Evolution of the uncontrolled system.

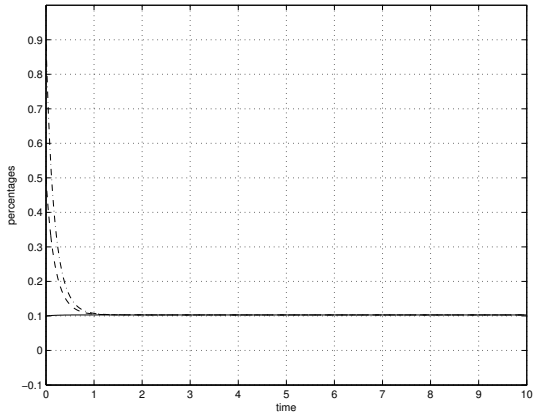

FIGURE 2. Evolution of $x = \frac{P}{P+Q}$.

For our simulations, we use the parameters from [8] given by $\alpha = 5.643$, $\beta = 0.48$, $\gamma = 1.47$, $\delta = 0$, and $\rho = 0.164$. In this case, we have $\bar{x} = 0.1031$ and $\xi = 0.0044$. In particular, in steady state only about 10% of the bone marrow cells are in their proliferating state and the total bone marrow mass is quite stagnant. Figs. 1 and 2 give the graphs of trajectories of the system for various initial conditions (the percentages of cells in the proliferating compartment are 10%, 50% and 90%, respectively, with the total bone-marrow cells normalized to 1 initially). These simulations show how quickly the steady state behavior is reached for the percentages. While the total number of bone-marrow cells grows slowly as the steady state is reached, note, however, that higher initial numbers of proliferating cells produce significantly higher total numbers of bone marrow cells. The reason is the high transition rate α from proliferating to quiescent cells. Not only the total initial bone marrow cells, but also their distribution as proliferating and dormant cells– i.e., the initial condition of (1)-(2)–determines the total number of bone marrow cells. This transition effect would not be captured in a scalar exponential growth model alone.

2.2. **The controlled dynamics.** Drug treatment is modelled by a bounded measurable function u, which takes values in the compact interval $[0,1]$ and represents the drug dosage with $u=1$ corresponding to a full dose and $u=0$ standing for no control being applied. It is assumed that the drug effects are instantaneous, i.e., pharmacokinetic equations are not modelled. This is a reasonable assumption for fast-acting drugs, and in this paper we want to focus on the role of the objective in the model. Simple linear models for pharmacokinetics can be included in the model and will not change the analysis. Also a simple case of pharmacodynamics is assumed where the effect of the drug is proportional to the dosage u, with a factor s, $0<s\leq 1$. Then as in [8], the overall dynamics can be described as

$$\dot{P} = (\gamma - \delta - \alpha - su(t))P + \beta Q, \qquad P(0) = P_0, \tag{7}$$

$$\dot{Q} = \alpha P - (\rho + \beta)Q, \qquad Q(0) = Q_0. \tag{8}$$

If we set $N=(P,Q)^T$, then the general form of the dynamics is given by the bilinear system

$$\dot{N}(t) = (A + uB)N(t), \quad N(0) = N_0, \tag{9}$$

where A and B are (2×2)-matrices given by

$$A = \begin{pmatrix} \gamma - \delta - \alpha & \beta \\ \alpha & -(\rho+\beta) \end{pmatrix} \text{ and } B = \begin{pmatrix} -s & 0 \\ 0 & 0 \end{pmatrix} \tag{10}$$

Note that for any admissible control the norm of matrix $A+uB$ is bounded over the interval $[0,T]$ and thus the right-hand side of the differential equation (9) is linearly bounded. Hence it follows from well-known results about ordinary differential equations that the corresponding trajectory (i.e., solution to the dynamics) exists on all of $[0,T]$. Furthermore, only states $N(t)$ for which each component is positive are meaningful, but it is not necessary to add this condition as extra state-space constraint since it is easily seen that the first quadrant $\mathbb{P}=\mathbb{R}^2_+=\{N\in\mathbb{R}^2 : P,Q>0\}$ in the state-space is positively invariant; that is, if each coordinate of $N(t_0)$ is positive, then all coordinates of $N(t)$ remain positive for all times $t\geq t_0$. This follows directly from the fact that the off-diagonal terms in the matrix $A+uB$ are positive for all $u\in[0,1]$.

LEMMA 2.1. *If $N(t_0)\in\mathbb{P}$, then $N(t)\in\mathbb{P}$ for all $t\geq t_0$.*

Proof: Let $\tau=\inf\{t>0 : P(t)<0\}$ and let $\sigma=\inf\{t>0 : Q(t)<0\}$. Nothing needs to be shown if both τ and σ are infinite. Thus, assume at least one is finite and without loss of generality suppose $\tau<\sigma\leq\infty$. (Since the differential equations are homogeneous, P and Q cannot vanish simultaneously.) But then we have $\dot{P}(\tau)=\beta Q(\tau)>0$, and thus P is positive for $t>\tau$, t sufficiently close to τ. But this contradicts the definition of τ. □

2.3. **Objective.** While there is underlying biology for modelling the dynamics even in simplified form, there are no real biological or medical indications for how the objective should be structured mathematically except for the obvious: the aim is to kill as many cancer cells possible without causing too much damage to healthy cells. There seems to be consensus that depending on the type of cells that are directly modelled (such as bone marrow cells here, or cancer cells in other models [25, 24]), terms representing these cells should be in the objective either at the terminal time, under the integral, or both. Different approaches arise when the overall drug given is measured in different norms. This term typically represents

the influence on the "other" types of cells not directly included in the model and thus is open to interpretation. Commonly used models are linear (L^1-type) or quadratic (L^2-type) and each has its advantage and disadvantage. Quadratic objectives are easier mathematically since the associated Hamiltonian will be strictly convex in the control with a unique minimum; on the other hand, they lower the role of partial doses somewhat by squaring the control. Linear objectives typically lead to more difficult mathematical models, but they are consistent with a linear relation for the effect of the drug on the modelled cells (as in (7)). Since both approaches lead to different classes of optimal controls it seems worthwhile to analyze the problems in both scenarios and compare the results.

In [8], Fister and Panetta maximize an objective with a quadratic control term,

$$J = \int_0^T a(P(t) + Q(t)) - \frac{b}{2}(1 - u(t))^2 dt \to \max, \tag{11}$$

over the class $\mathcal{U}$ of all Lebesgue measurable functions that take values in the control set $U = [0, 1]$; a and b are positive constants. It is shown in [8] that for T sufficiently small a unique optimal control exists and is continuous on $[0, T]$. However, only at the terminal time T does the optimal control take the maximum value $u = 1$; otherwise it is strictly smaller than one, $u(t) < 1$ for $t < T$. In all the simulations in [8], the optimal controls are first given by $u = 0$, and from a certain time the drug dosages strictly increase to reach level 1 at the terminal time. This leads to a depletion of bone marrow toward the end, which is natural since the later values have a much smaller influence in the objective.

In this paper, we chose the performance index with a linear control term in the form to maximize

$$J = r_1 P(T) + r_2 Q(T) + \int_0^T q_1 P(t) + q_2 Q(t) + bu(t) dt \to \max, \tag{12}$$

where r_1, r_2 , q_1 and q_2 are positive weights and b is a positive constant. We assume that *at least one of* r_1 *or* q_1 *and one of* r_2 *or* q_2 *is positive*, so that no compartment would be left out completely in the objective. As in [8] we have incorporated a term $q_1 P(t) + q_2 Q(t)$ in the Lagrangian, in an effort to keep the number of bone-marrow cells high. Rather than requiring an absolute lower bound, this so-called "soft" constraint implicitly maximizes the bone marrow. In addition, we have added a terminal term $r_1 P(T) + r_2 Q(T)$ which represents a weighted average of the total bone marrow at the end of an assumed fixed therapy interval $[0, T]$. This term is included to prevent the possibility that the bone marrow would be depleted excessively toward the end of the therapy interval. Like for the L^2-model the effectiveness of the treatment (i.e., the killing effect on the cancer cells) has to be taken into account indirectly, since the cancer cells are not modelled in the dynamics. To kill a large number of cancer cells, one wants to maximize the dosage. In the dynamics, the side-effects of the drug on the proliferating bone marrow cells are described by $-su(t)P(t)$; that is, the drug dosage $u(t)$ is proportional to the number of proliferating bone marrow cells killed. Using the same reasoning for the objective, the dosage is also proportional to the number of cancer cells killed; thus, a linear term $\int_0^T u(t)dt$ represents a measure for the total number of cancer cells killed over the therapy interval.

Writing $r = (r_1, r_2)$ and using $q = (q_1, q_2)$, the objective therefore can be formulated mathematically as to maximize

$$J(u) = rN(T) + \int_0^T qN(t) + bu(t)dt \tag{13}$$

over all Lebesgue measurable functions u which take values in $[0, 1]$, subject to the dynamics (9) and given initial condition $N(0)$.

3. **Analysis of Extremals.** First-order necessary conditions for optimality are given by the Pontryagin Maximum Principle [20], which for this model can be stated as follows: If u_* is an optimal control with corresponding trajectory N_*, then there exists an absolutely continuous function λ, which we write as row-vector, $\lambda : [0, T] \to (\mathbb{R}^2)^*$, satisfying the adjoint equation with transversality condition,

$$\dot{\lambda} = -\lambda(A + uB) - q, \qquad \lambda(T) = r, \tag{14}$$

with the property that an optimal control maximizes the Hamiltonian

$$H = qN + bu + \lambda(A + uB)N \tag{15}$$

over the control set $[0, 1]$ along $(\lambda(t), N_*(t))$. We call a pair (x, u) consisting of an admissible control u and corresponding trajectory for which there exists a multiplier λ such that the conditions of the Maximum Principle are satisfied an *extremal* (pair), and the triple (x, u, λ) is an *extremal lift* (to the cotangent bundle).

While the first quadrant in the state-space is positively invariant, the first quadrant in the dual space becomes negatively invariant under the adjoint flow (14). Even a bit stronger, it holds that if $\lambda_i(T) \geq 0$ for $i = 1, 2$, then $\lambda_i(t) > 0$ for all $t < T$. This result, which will be important in the further analysis of the problem, again easily follows from the fact that the off-diagonal elements in the matrix defining the dynamics, α and β, are positive.

LEMMA 3.1. *If $\lambda_i(T) \geq 0$ for $i = 1, 2$, then $\lambda_i(t) > 0$ for all $t < T$.*

Proof: We first note that there exists an $\varepsilon > 0$ such that both components $\lambda_i(t)$, $i = 1, 2$, are positive on $[T - \varepsilon, T)$. This is trivial for λ_i if $r_i = \lambda_i(T) > 0$. If $r_1 = 0$, then $\dot{\lambda}_1(T) = -r_2\alpha - q_1 \leq -q_1 < 0$, and if $r_2 = 0$, then $\dot{\lambda}_2(T) = -r_1\beta - q_2 \leq -q_2 < 0$. Thus, in either case λ_i is positive on a small interval before the terminal time T. Now let $\tau = \sup\{0 \leq t \leq T : \lambda_1(t) < 0\}$ and $\sigma = \sup\{0 \leq t \leq T : \lambda_2(t) < 0\}$. Thus $\lambda_1(\tau) = 0$ and $\lambda_2(\sigma) = 0$. If $\tau = \sigma$, then q_1 and q_2 cannot both be zero since otherwise $\lambda(t) \equiv 0$. If, say $q_1 > 0$, then $\dot{\lambda}_1(\tau) = -q_1 < 0$ and thus λ_1 is negative for times $t > \tau$, contradicting the definition of τ. If $\tau < \sigma$, then $\dot{\lambda}_2(\sigma) = -\lambda_1(\sigma)\beta - q_2 < 0$, and again λ_2 is negative for times $t > \sigma$, contradicting the definition of σ. Similarly, if $\tau > \sigma$, then $\dot{\lambda}_1(\tau) = -\lambda_2(\tau)\alpha - q_1 < 0$, leading to the same contradiction. □

Summarizing, since $N_0 \in \mathbb{P}$ we have shown that

PROPOSITION 3.1. *All states N_i are positive over $[0, T]$ and the costates λ_i are positive over $[0, T)$ with the possible exception of the endpoints if $r_i = 0$.*

3.1. **Switching function.** Optimal controls u_* maximize the Hamiltonian H, i.e.

$$(b + \lambda(t)BN(t))u_*(t) = \max_{0 \leq u \leq 1} (b + \lambda(t)BN(t))u. \tag{16}$$

Thus, if we define the so-called switching function Φ by $\Phi(t) = b + \lambda(t)BN(t)$, then the optimal controls are given as

$$u_*(t) = \begin{cases} 1 & \text{if } \Phi(t) > 0 \\ 0 & \text{if } \Phi(t) < 0 \end{cases} . \tag{17}$$

A priori the control is not determined by the maximum condition at times when $\Phi(t) = 0$. However, if $\Phi(t) \equiv 0$ on an open interval, then all its derivatives vanish as well and this may determine the control. Controls of this kind are called *singular*, while we refer to the constant controls as *bang* controls. Optimal controls then need to be synthesized from these candidates.

The structure of optimal controls is determined by the switching function and its derivatives. For instance, if $\Phi(t) = 0$, but $\dot{\Phi}(t) \neq 0$, then the control has a switch at time t. To analyze the structure of the optimal controls, we therefore need to analyze the switching function and its derivatives. The following lemma, which is verified by a direct calculation, allows one to calculate first and higher order derivatives of the switching function simply by calculating commutators of matrices.

LEMMA 3.2. *Let M be a constant matrix and let $\Psi(t) = \lambda(t)MN(t)$, where N is a solution to the system equation (9) for control u and λ is a solution to the corresponding adjoint equation. Then*

$$\dot{\Psi}(t) = \lambda(t)[A + uB, M]N(t) - qMN(t), \tag{18}$$

where $[A, M]$ denotes the commutator of the matrices A and M defined as $[A, M] = MA - AM$. □

Note that we have chosen the order in the commutator to be consistent with the Lie derivative of the linear vector fields $f(N) = AN$ and $g(N) = MN$. For,

$$[f, g](N) = Dg(N)f(N) - Df(N)g(N) = MAN - AMN = [A, M]N. \tag{19}$$

Proof: The Lemma is verified by a direct computation, which we include for the reader's convenience. Using the dynamics and adjoint equation we obtain

$$\begin{aligned} \dot{\Psi}(t) &= \dot{\lambda}(t)MN(t) + \lambda(t)M\dot{N}(t) \\ &= \left(-\lambda(t)(A + uB) - q\right) MN(t) + \lambda(t)M(A + uB)N(t) \\ &= \lambda(t)[A + uB, M]N(t) - qMN(t). \end{aligned}$$

3.2. **Singular Controls.** We will show that singular controls in fact are locally minimizing instead of maximizing; hence not optimal. Suppose a control u is singular on a non-empty open interval I. Thus the switching function vanishes identically on I, and we obtain

$$\dot{\Phi}(t) = \lambda(t)[A, B]N(t) - qBN(t) \equiv 0. \tag{20}$$

Differentiating once more yields

$$\ddot{\Phi}(t) = \lambda(t)[A + u(t)B, [A, B]]N(t) - q\left([A, B] + B(A + uB)\right)N(t) \equiv 0. \tag{21}$$

The coefficient multiplying the control u is given by the expression

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} = \lambda[B, [A, B]]N - qB^2N \tag{22}$$

evaluated along the extremal lift of the singular control. The singular control is of order 1 on the interval I if this quantity does not vanish on I. In this case the equation (21) can formally be solved for the control, and if the corresponding

control value is admissible (i.e., has a value between 0 and 1), this defines the singular control. Otherwise the singular arc is not admissible. It is a second-order necessary condition for optimality of a singular arc of order one, the so-called generalized Legendre-Clebsch condition [11], that for the case of maximizing the Hamiltonian

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u}(\lambda(t), x(t), u(t)) \geq 0. \tag{23}$$

Since $B^2 = -sB$ and $\dot{\Phi} \equiv 0$ along a singular arc, for this model we find that

$$qB^2N = -sqBN = -s\lambda[A, B]N. \tag{24}$$

Thus (all quantities are evaluated along the singular lift):

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} = \lambda\left([B, [A, B]] + s[A, B]\right)N. \tag{25}$$

Direct calculations show that

$$[A, B] = s\begin{pmatrix} 0 & -\beta \\ \alpha & 0 \end{pmatrix}, \qquad [B, [A, B]] = -s^2\begin{pmatrix} 0 & \beta \\ \alpha & 0 \end{pmatrix}, \tag{26}$$

and thus

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} = s^2\lambda\begin{pmatrix} 0 & -2\beta \\ 0 & 0 \end{pmatrix}N = -2s^2\beta\lambda_1 Q < 0, \tag{27}$$

violating the Legendre-Clebsch condition. Thus all singular arcs locally minimize the objective. Hence we have:

PROPOSITION 3.2. *Singular controls are not optimal.* □

3.3. **Bang-bang Controls.** Although more complicated structures (like for example chattering arcs, which would have an infinite number of switchings), cannot be excluded a priori, bang-bang controls with only a finite number of switchings become the prime candidates for optimality. However, because of the presence of nonoptimal singular arcs, one expects that there exist bang-bang extremals with an arbitrary large number of switchings in a vicinity of this non-optimal singular arc, and it therefore becomes important to develop high-order conditions that distinguish between locally optimal and locally nonoptimal bang-bang controls. In this section we formulate such an algorithm based on an earlier construction by Noble and Schättler [18] specifically tailored to the type of problems under consideration. Recently significant activity has focused on the question of high-order necessary and sufficient conditions for optimality of bang-bang controls, specifically the papers by Agrachev, Stefani and Zezza [1] and by Maurer and Osmolovskii [17]. Either of these constructions could equally well be employed in the further analysis, but we use the more geometric approach pursued in [18]. We have the following theorem about optimality of bang-bang controls:

THEOREM 3.1. *Let u_* be a bang-bang control with switchings at times t_i, $i = 1, \ldots, m$, $0 < t_m < \cdots < t_1 < t_0 = T$, and denote the values of the control on the interval (t_i, t_{i-1}) by u_i. Let N_* be the corresponding trajectory and suppose $\Gamma = (N_*, u_*)$ is an extremal pair (control and trajectory) with corresponding multiplier λ_*. Assume that the derivative $\dot{\Phi}_*(t_i)$ of the switching function $\Phi_*(t) = b + \lambda_*(t)BN_*(t)$ does not vanish at the switching times t_i, $i = 1, \ldots, m$.*

Set $R_0^- = 0$, *and for* $i = 1, \dots, m$, *inductively define*

$$R_i^+ = \exp\left((A + u_i B)^T (t_{i-1} - t_i)\right) R_{i-1}^- \exp\left((A + u_i B)(t_{i-1} - t_i)\right), \tag{28}$$

$$G_i = \frac{1}{\left|\dot{\Phi}_*(t_i)\right|} \left(\lambda_*(t_i) B + N_*^T(t_i) B^T R_i^+\right), \tag{29}$$

$$R_i^- = \left(B^T \lambda_*^T(t_i) G_i + R_i^+\right) \left(Id + \frac{B N_*(t_i) G_i}{1 - G_i B N_*(t_i)}\right). \tag{30}$$

Here we have $G_i B N_*(t_i) \neq 1$ *if and only if*

$$\left|\dot{\Phi}_*(t_i)\right| \neq sb + N_*^T(t_i) B^T R_i^+ B N_*(t_i). \tag{31}$$

If for $i = 1, \dots, m$, *we have that*

$$\left|\dot{\Phi}_*(t_i)\right| > sb + N_*^T(t_i) B^T R_i^+ B N_*(t_i), \tag{32}$$

then u_* *is a strong relative minimum. If the transversality condition*

$$\left|\dot{\Phi}_*(t_i)\right| > sb + N_*^T(t_i) B^T R_i^+ B N_*(t_i), \tag{33}$$

is satisfied for $i = 1, \dots, \ell - 1$, *but*

$$\left|\dot{\Phi}_*(t_\ell)\right| < sb + N_*^T(t_\ell) B^T R_\ell^+ B N_*(t_\ell), \tag{34}$$

then u_* *is optimal for initial times* $t > t_\ell$, *but is no longer optimal for initial times* $t \leq t_\ell$.

The proof of this theorem is rather lengthy. The calculations are based on the results in [18] for a general system, and the arguments are similar to those in [12] for a model for cancer chemotherapy, but with several minor modifications due to the structure of the equations. Thus here we only *outline* the *proof* and illustrate the geometry of the construction (Fig. 3), referring the reader to [12] and [18] for the general arguments.

Since the derivative of the switching function does not vanish at the switching times for the reference trajectory, it is possible to construct a family of bang-bang extremal lifts (that is, triples consisting of an extremal control and the corresponding trajectory and adjoint variable) around the reference trajectory by parametrizing the extremals through their endpoint in a sufficiently small neighborhood W of $p_* = N_*(T)$. Specifically, for p in a neighborhood W of p_*, integrate the equations

$$\dot{N}(t, p) = (A + u(t, p) B) N(t, p), \qquad N(T, p) = p, \tag{35}$$

$$\dot{\lambda}(t, p) = -\lambda(t, p)(A + u(t, p) B) - q, \qquad \lambda(T, p) = r, \tag{36}$$

backward from time T while choosing the control $u = u(t, p)$ to maintain the maximum condition of the maximum principle. Thus $u(t, p_*)$ is given by the reference control u_* and $N(t, p_*)$ and $\lambda(t, p_*)$ are the reference trajectory and corresponding multiplier, respectively. Integration is done backward, since the transversality condition (14) specifies the terminal condition for the multiplier λ, whereas the initial condition is unknown. Then we have, analogous to [12, Lemma 5.1]:

LEMMA 3.3. *There exists a neighborhood* W *of* p_* *and continuously differentiable functions* τ_i *defined on* W, $i = 1, \dots, m$, *such that for* $p \in W$ *the controls* $u(\cdot, p)$ *are bang-bang with switchings in the same order as the reference control at the times* $0 < \tau_m(p) < \cdots < \tau_1(p) < T$ *and the corresponding triples* $\Gamma_p = (N(\cdot, p), u(\cdot, p), \lambda(\cdot, p))$

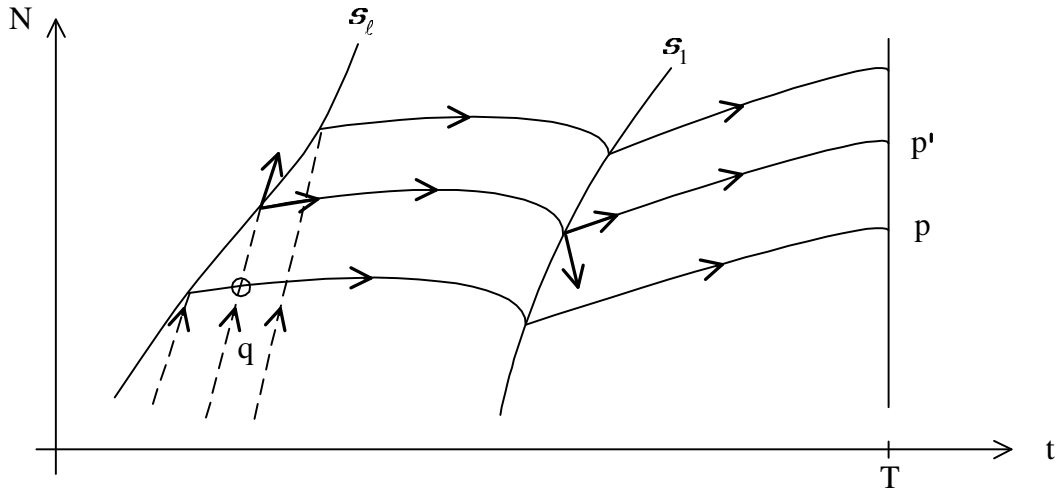

FIGURE 3. Optimal and non-optimal switchings.

for $p \in W$ are extremal lifts with the property that the derivatives of the switching function $\Phi(t,p) = b + \lambda(t,p)BN(t,p)$ do not vanish at all switching times.

The issue then becomes whether the flow map σ of the trajectories,

$$\begin{aligned} \sigma :&[0,T] \times W \to [0,T] \times \mathbb{P}, \\ &(t,p) \mapsto \sigma(t,p) = (t, N(t,p)) \end{aligned} \tag{37}$$

defines a field; that is, whether the corresponding curves cover a neighborhood of the reference trajectory injectively. This is checked with the algorithm formulated in the theorem. The matrices $R_i^{\pm}$ denote the left- and right-hand limits of the matrix

$$R(t,p) = \frac{\partial \lambda^T}{\partial p}(t,p) \left(\frac{\partial N}{\partial p}(t,p) \right)^{-1} \tag{38}$$

evaluated along the reference trajectory at times $t = t_i$. Since the controls are constant over the intervals (t_i, t_{i-1}) these matrices are easily propagated over the intervals (equation (28)), but the matrices become discontinuous at the switching surfaces, and (29) and (30) compute the required jumps. Condition (31) guarantees that the matrix $\frac{\partial N}{\partial p}$ remains invertible. The geometric interpretation of condition (32) is that the flow σ crosses the corresponding switching surfaces transversally. This implies that the flow covers the state-space injectively in a neighborhood of the reference trajectory and thus locally defines a field of broken extremals (see Fig. 3). A differentiable solution to the Hamilton-Jacobi-Bellman equation can then be constructed, implying the strong local optimality of the controls [18, Cors. 2.13 and 2.14]. If condition (34) is satisfied, however, the flow σ reflects off the ℓ^{th} switching surface generating an overlap. The ℓ^{th} switching surface becomes a surface of conjugate points and local optimality of the flow ceases there. This can be verified for example with an envelope argument as in [12, Thm. 5.3] Thus the algorithm (28)-(30) calculates the first conjugate point, but, following the spirit of [18], integrating backward.

Fig. 3 illustrates the idea of the proof; that is, the embedding of the extremal in a parametrized flow and the two types of transversal behavior at the switching

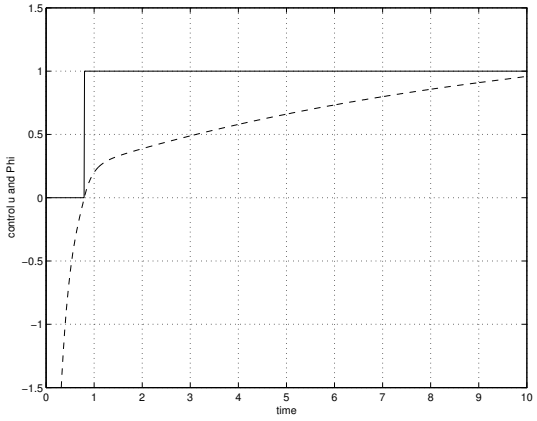

FIGURE 4. Control for $p_0 = 0.9$, $b = 1$.

surfaces: transversal crossings where the transversality is preserved and transversal folds where the flow loses optimality. The algorithm (28)-(30) along with (32) can easily be used in the numerical simulations to analyze local optimality of bang-bang extremals at the switchings.

4. **Simulations and Comparisons.** Using a version of the gradient method for the calculation of extremal bang-bang controls developed earlier by Duda [6], we ran simulations for the model presented here for a therapy interval of length $T = 10$ with the following parameter values taken from [8]: $\alpha = 5.643$, $\beta = 0.48$, $\gamma = 1.47$, $\delta = 0$, and $\rho = 0.164$. In the simulations we report on below, we set $s = 1$, $r_1 = r_2 = 1$, and also $q_1 = q_2 = 1$. We do vary the parameter b multiplying the control in the objective.

For $b = 1$ and initial conditions (p_0, q_0) chosen as the steady state of the uncontrolled system with these parameters, the optimal control is $u \equiv 1$. As the initial conditions are changed to $(p_0, q_0) = (.5, .5)$, the control has one switch from $u = 0$ to $u = 1$ which occurs at $\tau_0 = 0.54$. Even as the initial conditions are changed to $(p_0, q_0) = (.9, .1)$, the switching in the control still happens quickly at $\tau_0 = 0.80$. The control (and switching function as dashed line) for this simulation is given in Fig. 4, and the corresponding states are shown in Fig. 5. The dashed line in the graphs of the states gives the evolution of the cells in the quiescent compartment while the regular line gives the evolution of the cells in the proliferating stage. For a control with only one switching, we have $R_1^+ = 0$ in (32) and thus this condition reduces to $trans = |\dot{\Phi}(t_1)| - bs > 0$. For this case $trans = 0.525$, and thus the corresponding control is locally optimal. In all these cases, for $u \equiv 0$ the system quickly settles into steady state, and then the optimal control becomes $u \equiv 1$ for the remaining time.

This behavior changes if a different weight is used for the control in the objective. If the weight b at the integral of the control is decreased to $b = .5$, trajectories in these simulations still have exactly one switch, from $u = 0$ to $u = 1$, but now the switches occur much later. For initial conditions corresponding to the uncontrolled steady state, the switching now is at $\tau_0 = 5.02$. This is consistent with the fact that more "weight" put on the bone marrow cells count delays the time at which the full

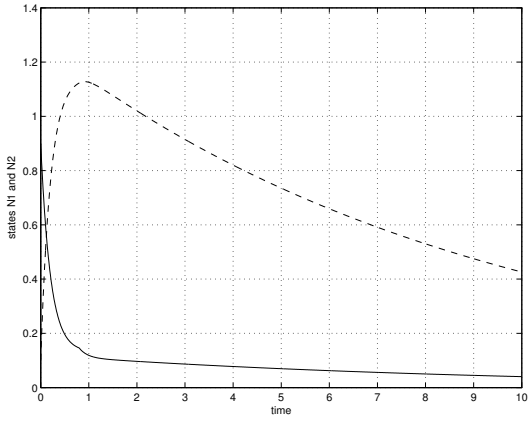

FIGURE 5. States for $p_0 = 0.9$, $b = 1$.

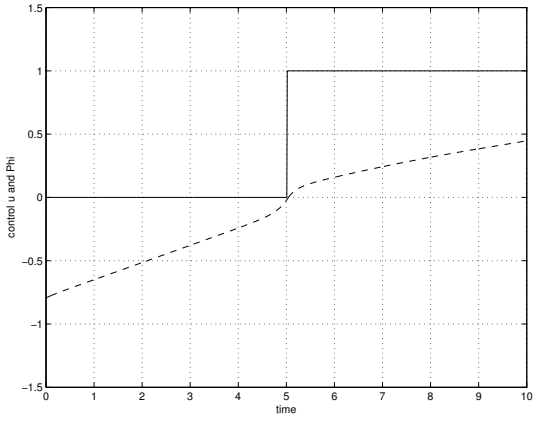

FIGURE 6. Control from steady state, $b = 0.5$.

dose can be applied. Figs. 6 and 7 give the graphs for steady state initial conditions, and Figs. 8 and 9 give the graphs for $(p_0, q_0) = (.9, .1)$. The corresponding values of the transversality condition are given by $trans = 0.013$ for initial conditions in steady state and by $trans = 0.100$ for $p_0 = .9$; thus, each control is locally optimal.

5. **Comparisons and Conclusions.** In this paper we analyzed a model for cancer chemotherapy proposed earlier by Fister and Panetta [19, 8], which aims at minimizing the damage to bone marrow cells during chemotherapy with an objective linear in the control (L^1-type). The analysis shows that partial doses are not optimal and that optimal controls alternate between chemotherapy sessions of full dose and rest-periods. While the model is specified through a number of cell-cycle specific parameters, this analysis does not depend on the actual values of these parameters, and so this conclusion is generally valid. In fact, even if the parameters in the model are allowed to vary in time, (which seems reasonable under chemotherapy), it can be shown that singular controls are not optimal. In all simulations we ran (for various coefficients in the objective, but keeping the medically motivated

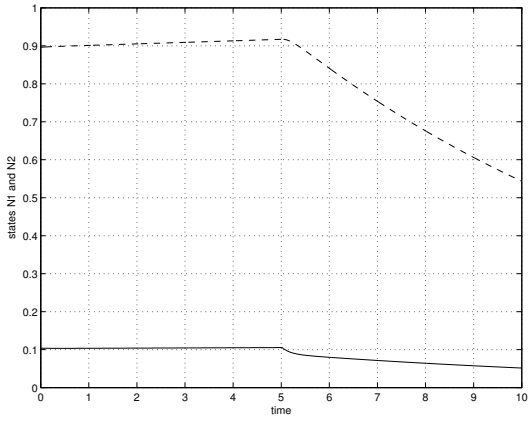

FIGURE 7. States from steady state, $b = 0.5$.

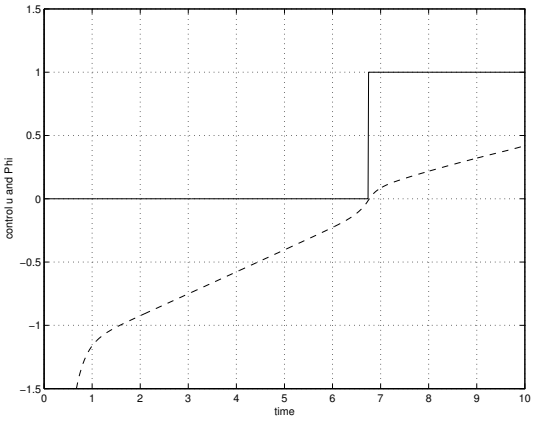

FIGURE 8. Control for $p_0 = 0.9$, $b = 0.5$.

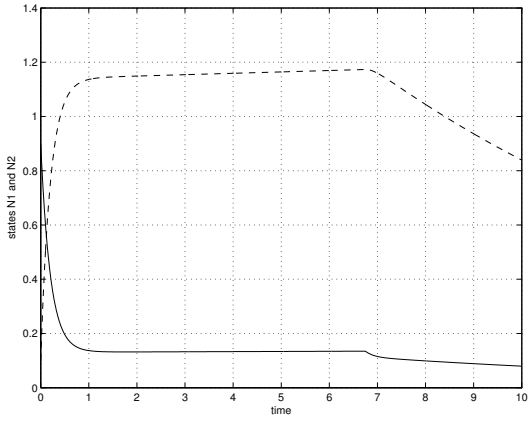

FIGURE 9. States for $p_0 = 0.9$, $b = 0.5$.

values for the parameters in the dynamics), the results had only one switching in the control. But there does not seem to be a straightforward way of proving such a result analytically. In principle, convexity properties of the switching functions seen in some simulations (especially if we set $q = 0$) allow for more switchings. But this also strongly depends on the parameter values in the dynamics and objective. It is clear that putting less weight on the control (drug dosage) in the objective makes it more beneficial to give less drug overall since thus the bone marrow cells automatically are measured with relatively higher coefficients.

The simulations above exhibit both differences and similarities to the ones obtained with the use of an L^2-objective. The main difference, of course, lies in the class of controls: bang-bang controls for an L^1-objective versus continuous controls for L^2. On the other hand, although the controls come from different classes, they exhibit similar overall behavior. In all the simulations for the L^1-objective, optimal controls exhibit only one switch from $u = 0$ to $u = 1$. Also, in runs performed for the same time interval as in [8] (which are not included here), the solutions in both cases start with a no-dose period that lasts longer in the case of an L^1-objective, but then the control switches to the full dose, whereas the control starts earlier in the L^2-objective case increasing slowly to a full dose only at the terminal time. Thus, in the case of an L^1-objective analyzed here, a full dose is applied more than just at the final time and partial doses are not optimal. This would agree with experimental and clinical data on the model, but only to some extent. All the controls we obtained in our simulations have only one switching which means that in one therapy interval there is only one "full-dose session" rather than "short drug pulses at appropriate intervals"as clinical data indicate. However, we believe that one should be able to achieve the desired effect by combining several short therapy intervals. Another approach would be to maximize an objective which measures the bone marrow not just at the final time, but at some intermediate times as well. All of this will be pursued in future research on the topic.

Another important change in the model would be the inclusion of pharmacokinetics/pharmacodynamics (PK/PD) where the distinction of the drug dosage u and the drug concentration c is made and the effects of the drug concentration on the bone marrow and/or cancer cells are modelled through a more realistic function $s = s(c)$ (rather than just an effectiveness coefficient s as it was done here.) If this function saturates at certain upper and lower concentrations, then we expect the optimal solutions have several switchings, but this research currently is still in progress.

Acknowledgements. This material is based upon work supported by the National Science Foundation under grant Nos. 0205093 and 0305965. U. Ledzewicz is supported in part by SIUE Summer Research Fellowship 2003 and SIUE Hoppe Research Professor Award.

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Received on Feb. 27, 2004. Revised on March 15, 2004.

E-mail address: uledzew@siue.edu
E-mail address: hms@wustl.edu