

Optimal Control for a Bilinear Model with Recruiting Agent in Cancer Chemotherapy

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Abstract—We consider a general mathematical model for cancer chemotherapy as optimal control problem for a bilinear system and give necessary and sufficient conditions for strong local optimality of bang-bang controls. These results apply to a 3-compartment model which besides a killing agent also includes a recruiting agent, i.e. a drug which acts on the residuum of dormant cells in the cell cycle. For this model it is shown that singular controls are not optimal, in fact singular regimes for the killing agent are locally maximizing with many extremal bang-bang trajectories near the non-optimal singular arc. Our results allow to distinguish between locally optimal and non-optimal bang-bang controls.

I. INTRODUCTION

We consider optimal control problems of Bolza type for bilinear systems which arise in mathematical models for cancer chemotherapy when treatment protocols over a fixed therapy interval are considered. The underlying models are based on cell-cycle dynamics and were originally introduced by Swierniak and Kimmel [9], [12]. Each cell passes through a sequence of phases from cell birth to cell division. Starting point is a growth phase G_1 , after which the cell enters a phase S where DNA synthesis occurs. Then a second growth phase G_2 takes place in which the cell prepares for mitosis or phase M . Here cell division occurs. Each of the two daughter cells can either reenter phase G_1 or for some time may simply lie dormant in a separate phase G_0 until reentering G_1 , thus starting the entire process all over again.

Depending on the medical aspects taken into account, the cell-cycle is divided into compartments which describe the different cell phases or combine phases of the cell cycle into clusters. The simplest and at the same time most natural models divide the cell cycle into two and three compartments, respectively [12], [11]. In these models the phases S , G_2 and M are combined into one compartment. In the two-compartment model G_0 and G_1 form the other compartment while different three-compartment models arise by separating the synthesis phase S or the dormant stage G_0 . The purpose of introducing this compartmental structure is to model the effects of the various drugs used in chemotherapy in the most effective way. These drugs among others consist of killing agents (for example, Taxol, or spindle poisons like Vincristine or Bleomycin which destroy a mitotic spindle), blocking agents (e.g. antibiotics like Adriamycin or Dexorubin which cause progression blockage on the border between the G_1 and S phases or Hydroxyurea which is found to

synchronize cells by causing brief and invisible inhibition of DNA synthesis in the S phase and holding cells in the G_1 phase), or recruiting agents (cytokines, which are substances playing a role in the regulation of normal hemopoiesis, like Interleukin-3.) Killing agents are applied in the G_2/M phase which makes sense from a biological standpoint since the cell wall becomes very thin and porous in mitosis M . Blocking agents slow down the development of cells in the synthesis phase S while recruiting agents effect the large residuum of dormant G_0 cells which are not sensitive to most cytotoxic agents.

In this paper we formulate a general mathematical model for cancer chemotherapy as optimal control problem for a bilinear system. Specific examples of these systems, like the 2- and 3-compartment models considered in [4], [5], exhibit non-optimal (in fact, locally maximizing) singular arcs. Consequently, and although more complicated structures cannot be excluded a priori, bang-bang controls become the prime candidates for optimality. However, due to the presence of locally maximizing 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 this is indeed the case for the problems considered in [4], [5]. It therefore becomes of importance to develop high-order conditions which allow to distinguish between locally optimal and locally non-optimal bang-bang controls. Based on earlier calculations [11] we formulate necessary and sufficient conditions for strong local optimality of bang-bang controls for the general model. We then consider a 3-compartment system which models the recruiting aspect of treatment. For this model we show that singular controls cannot be optimal and then apply our results to analyze bang-bang controls.

II. MATHEMATICAL MODEL

Mathematically the dynamics of these compartmental models can be described by a general n -dimensional bilinear system

$$\dot{N}(t) = (A + \sum_{i=1}^m u_i B_i)N(t), \quad N(0) = N_0, \quad (1)$$

where the components of the state vector $N = (N_1, \dots, N_n)$ denote the average numbers of cancer cells in the respective compartments and the controls are the various drug dosages.

Admissible controls are Lebesgue measurable functions $u = (u_1, \dots, u_m)$ with each component taking values in a given interval $[\alpha_i, \beta_i] \subset [0, \infty)$. In the dynamics A and B_i are constant $n \times n$ matrices which describe the transitions (in- and out-flows, respectively) of cells between the compartments and are such that all the matrices $A + \sum_{i=1}^m u_i B_i$ have negative diagonal and non-negative off-diagonal entries (M -matrices). We make this as a **general assumption**:

- (M) all the matrices $A + \sum_{i=1}^m u_i B_i$, $u \in U$, have negative diagonal entries and non-negative off-diagonal entries.

Condition (M) implies that the first orthant is positively invariant under the flow of any admissible control and therefore no non-negativity constraints need to be imposed on the states.

In earlier papers (e.g. [9], [12], [4], [5], [11]) the problem of cancer chemotherapy has been formulated as an optimal control problem over a fixed interval $[0, T]$ with objective given in Bolza form as

$$J(u) = rN(T) + \int_0^T u_1(t) dt \quad (2)$$

where $r = (r_1, \dots, r_n)$ is a row-vector of positive weights and the penalty term $rN(T)$ gives a weighted average of the total number of cancer cells at the end of the fixed therapy interval $[0, T]$. The control u_1 labels the killing agent. The number of cancer cells which are killed and thus do not undergo cell division at time t is given by the portion $u_1(t)$ of the outflow of the last compartment, i.e. $u_1(t)$ is proportional to the fraction of ineffective cell divisions. Since the drug kills healthy cells at a proportional rate, the control $u_1(t)$ is also used to model the negative effect of the drug on the normal tissue or its toxicity. Thus the integral in the objective models the cumulative negative effects of the killing agent in the treatment. Side effects of blocking and recruiting agents are ignored in this formulation.

In this paper we consider these models for cancer chemotherapy with a more general objective of the form

$$\tilde{J}(u) = rN(T) + \int_0^T qN(t) + su(t) dt. \quad (3)$$

As above $r = (r_1, \dots, r_n)$, $q = (q_1, \dots, q_n)$ and $s = (s_1, \dots, s_n)$ are row-vectors of weights, with r_i all positive while the s_i and q_i are non-negative. The vector $u = (u_1, \dots, u_m)$ of controls represents the various drug dosages. Besides including a measure of possible side effects of blocking and recruiting agents through the term su in the objective, the inclusion of the weighted average qN under the integral has the desirable effect that an optimal therapy will not allow the cancer cells to increase beyond acceptable levels during the therapy. Although the main aim is to have a small number of cancer cells at the end of the therapy session, including cumulative effects has the advantage of implicitly monitoring the growth of the cancer and preventing that it

exceeds unacceptable levels. Another approach to achieve this could be to explicitly set an upper limit on the number of cancer cells and include it as a ‘‘hard’’ limit on the states. However, since typically no further monitoring of growth is done during a fixed chemotherapy session, this seems a less practical approach and a ‘‘soft’’ enforcement of constraints as done in (3) appears more realistic.

III. NECESSARY CONDITIONS FOR OPTIMALITY

First order necessary conditions for optimality are given by the Pontryagin Maximum principle [8]. It is easily seen that all extremals must be normal and therefore, if $u_* = (u_1^*, \dots, u_m^*)$ is an optimal control, then it follows that there exists an absolutely continuous function λ , which we write as row-vector, $\lambda : [0, T] \rightarrow (\mathbb{R}^n)^*$, satisfying the adjoint equation

$$\dot{\lambda} = -\lambda(A + \sum_{i=1}^m u_i^* B_i) - q, \quad \lambda(T) = r, \quad (4)$$

such that the optimal control u_* minimizes the Hamiltonian H ,

$$H = qN + su + \lambda(A + \sum_{i=1}^m u_i^* B_i)N, \quad (5)$$

over the control set along $(\lambda(t), N_*(t))$.

It is easily seen that assumption (M) also implies that the first octant in the dual space $(\mathbb{R}^n)^*$ is negatively invariant under the flow of the adjoint equation.

Lemma 3.1: For any admissible control u , if $\lambda_i(T) > 0$ for $i = 1, \dots, m$, then $\lambda_i(t) > 0$ for all $t \leq T$ and all $i = 1, \dots, m$. \square

Corollary 3.1: All states N_i and costates λ_i are positive over $[0, T]$. \square

Optimal controls u_* satisfy the minimum condition of the Maximum Principle. Since the Hamiltonian is linear in u and the control set is an interval in \mathbb{R}^m , this minimization problem reduces into m separate minimizations and thus, if we define the *switching functions* as

$$\Phi_i(t) = s_i + \lambda(t)B_i N(t), \quad (6)$$

then we have that

$$u_i^*(t) = \begin{cases} \alpha_i & \text{if } \Phi_i(t) > 0 \\ \beta_i & \text{if } \Phi_i(t) < 0 \end{cases}. \quad (7)$$

A priori the controls are not determined by the minimum condition at times where $\Phi_i(t) = 0$. However, if $\Phi_i(t)$ vanishes on an open interval, also all its derivatives must vanish and this may determine the control. Controls of this kind are called *singular* while we refer to piecewise constant controls as *bang-bang* controls. Optimal controls then need to be synthesized from these and other possibly more complicated candidates.

The derivatives of the switching functions are computed using the system and adjoint equations and the relevant relation can be summarized in the basic formula below:

Lemma 3.2: Suppose G is a constant matrix and let $\Psi(t) = \lambda(t)GN(t)$, where N is a solution to the system equation (1) corresponding to the control u and λ is a solution to the corresponding adjoint equation. Then

$$\dot{\Psi}(t) = \lambda(t)[A + \sum_{i=1}^m u_i B_i, G]N(t) - qGN(t), \quad (8)$$

where $[A, G]$ denotes the commutator of the matrices A and G defined as $[A, G] = GA - AG$.

While further differentiation of the first term will lead to additional bracket terms, differentiations of the inhomogeneous term through the dynamics will bring up product terms. Thus the inclusion of the Lagrangian term qN changes the mathematical analysis significantly with regard to singular arcs and it therefore becomes necessary to reevaluate the analysis of singular arcs for each model. However, earlier developed sufficient conditions for optimality of bang-bang trajectories [11] easily adjust with the necessary modifications to the new objective (including qN in the Lagrangian) and we briefly review these results.

IV. SUFFICIENT CONDITIONS FOR STRONG LOCAL OPTIMALITY OF BANG-BANG CONTROLS

Recently there has been significant activity 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 [6]. Here we follow the more geometric approach pursued by Noble and Schättler in [7]. These conditions have been formulated for the model with $q \equiv 0$ in [11], but only minor modification are required for our problem.

Let (N_*, u_*) be a reference extremal pair where all the components of u_* are bang-bang controls with switchings at times t_k , $k = 1, \dots, m$, $0 < t_m < \dots < t_1 < t_0 = T$. Denote the corresponding trajectory and adjoint variable by N_* and λ_* . We assume that (i) *at every switching t_k only one of the components of the control has a switching*. This implies that the switching functions are absolutely continuous functions with derivatives given by

$$\dot{\Phi}_i(t) = \lambda(t) \left[A + \sum_{j=1}^m u_j B_j, B_i \right] N(t) - qB_i N(t). \quad (9)$$

In particular, $\dot{\Phi}_i$ is continuous at t_k if the i^{th} control switches at time t_k . We also assume that (ii) *at each switching t_k the derivative of the corresponding switching function $\dot{\Phi}_i$, $i = i(k)$, does not vanish at t_k , $\dot{\Phi}_i(t_k) \neq 0$* , and we call a triple $\Gamma = (N_*, u_*, \lambda_*)$ along which conditions (i) and (ii) are satisfied a *regular strictly bang-bang extremal lift*. Under these assumptions a parametrized family of regular strictly bang-bang extremal lifts which contains Γ can be constructed

by integrating the dynamics and the adjoint equation backward from the terminal time T with the terminal condition $N(T) = p$ being a free parameter, p varying in a sufficiently small neighborhood of $p_* = N_*(T)$. This allows to use field-theoretic concepts to develop sufficient conditions for optimality. Essentially, since the controls are constant between switchings the flow of the system is a diffeomorphism away from the switching surfaces and thus if the flow crosses the switching surfaces transversally, a differentiable solution to the Hamilton-Jacobi-Bellman equation can be constructed using the method of characteristics [7]. This then implies optimality of the flow. We summarize the main results [11].

Theorem 4.1: Let $\Gamma = (N_*, u_*, \lambda_*)$ be a regular strictly bang-bang extremal lift without simultaneous switchings and let $\Phi_i^*(t) = s_i + \lambda_*(t)B_i N_*(t)$ be the switching function associated with the control u_i , $i = 1, \dots, m$. Denote the switching times of the controls by t_k , $k = 1, \dots, m$, $0 < t_m < \dots < t_1 < t_0 = T$ and let u_i^k denote the constant values of the controls on the interval (t_k, t_{k-1}) . For the k -th switching let $\iota = \iota(k)$ be the indicator of the control that switches and denote the absolute jump in the control by θ_ι , i.e. $\theta_\iota = \beta_i - \alpha_i$ if $\iota(k) = i$. Set $S_0^- = 0$ and for $k = 1, \dots, m$, define

$$S_k^+ = \exp \left(\left(A + \sum_{j=1}^m u_j^k B_j \right)^T (t_{k-1} - t_k) \right) S_{k-1}^- \\ \exp \left(\left(A + \sum_{j=1}^m u_j^k B_j \right) (t_{k-1} - t_k) \right), \quad (10)$$

$$G_k = - \frac{\theta_\iota}{|\dot{\Phi}_\iota^*(t_k)|} (\lambda_*(t_k)B_\iota + N_*^T(t_k)B_\iota^T S_k^+), \quad (11)$$

$$S_k^- = (B_\iota^T \lambda_*^T(t_k)G_k + S_k^+) \left(Id + \frac{B_\iota N_*(t_k)G_k}{1 - G_k B_\iota N_*(t_k)} \right) \quad (12)$$

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

$$\left| \dot{\Phi}_\iota^*(t_k) \right| + \theta_\iota (\lambda_*(t_k)B_\iota + N_*^T(t_k)B_\iota^T S_k^+) B_\iota N_*(t_k) > 0, \quad (13)$$

then all the matrices S_k^- , $k = 1, \dots, m$, are well-defined and u_* is a relative minimum for the n -compartment model. More precisely, there exists a neighborhood W of $N_*(T)$ such that the flow σ restricted to $[0, T] \times W$ defines a field of strictly bang-bang extremals without simultaneous switchings and u_* is optimal relative to any other control whose trajectory lies in the image R of $[0, T] \times W$ under the flow map

$$\sigma : [0, T] \times W \rightarrow R, \quad (t, p) \mapsto (t, x(t, p)). \quad (14)$$

Theorem 4.2: If the transversality condition

$$\left| \dot{\Phi}_l^*(t_k) \right| + \theta_l (\lambda_*(t_k) B_l + N_*^T(t_k) B_l^T S_k^+) B_l N_*(t_k) > 0 \quad (15)$$

is satisfied for $k = 1, \dots, h-1$, but

$$\left| \dot{\Phi}_l^*(t_h) \right| + \theta_l (\lambda_*(t_h) B_l + N_*^T(t_h) B_l^T S_h^+) B_l N_*(t_h) < 0, \quad (16)$$

then there exists a neighborhood W of $p_* = N_*(t)$ such that the flow σ restricted to $D_h = \{(t, p) : t_h < t \leq T, p \in W\}$ defines a field of regular strictly bang-bang extremals without simultaneous switchings and u_* is optimal relative to any other control whose trajectory lies in the image $R_h = \sigma(D_h)$. But u_* is no longer optimal for initial times $t \leq t_h$.

A geometric interpretation of the conditions in Theorem 4.2 is given in Fig. 1.

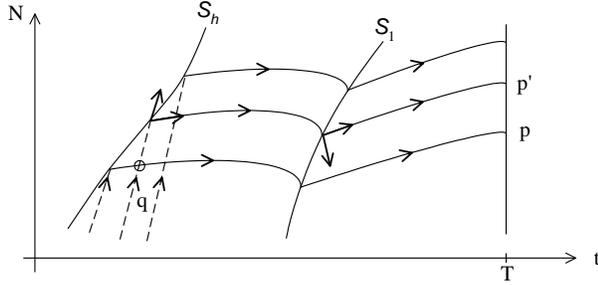


Fig. 1. Optimal and nonoptimal switchings

V. A THREE COMPARTMENT MODEL WITH RECRUITING AGENT

The insensitivity of dormant cells to anti-cancer drugs is a major problem for some kinds of cancer like leucemia or breast cancer [2]. It is possible to recruit dormant cells into the cell cycle using cytokines [13]. Here we consider a mathematical model formulated by Swierniak et al. [12] in which active recruitment of the cells in the dormant stage G_0 through cytokines is modelled. In this case the first compartment consists of G_0 , the second compartment of the first growth phase G_1 , and the third compartment combines synthesis S , the second growth phase G_2 and mitosis M . Now it is more natural to label the states N_0 , N_1 and N_2 . Newly born cells either enter G_1 and immediately start the cell division process or they may enter the dormant stage G_0 . Let b_0 and b_1 , $b_0 + b_1 = 1$, be the corresponding probabilities. A recruiting agent $w = u_2$ is applied to reduce the average sejour time in the quiescent phase. As a result the average transit time through the compartment G_0 is reduced resulting in the outflow being increased by a factor $1 + w$, $0 \leq w \leq w_{\max}$. The control $w = 0$ corresponds to no drug being applied while $w = w_{\max}$ occurs with a full dose. A killing agent $u = u_1$, $0 \leq u \leq 1$, is applied in the third compartment with $u = 1$ corresponding to a maximum dose. The matrices for the corresponding model are given by

$$A = \begin{pmatrix} -a_0 & 0 & 2b_0a_2 \\ a_0 & -a_1 & 2b_1a_2 \\ 0 & a_1 & -a_2 \end{pmatrix}, \quad (17)$$

and

$$B_1 = \begin{pmatrix} 0 & 0 & -2b_0a_2 \\ 0 & 0 & -2b_1a_2 \\ 0 & 0 & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} -a_0 & 0 & 0 \\ a_0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad (18)$$

where the a_i are positive coefficients related to the mean transit times for cancer cells through the compartments. It is easily verified that condition (M) holds for all admissible controls. We take the objective in the form

$$J = rN(T) + \int_0^T qN(t) + u(t)dt, \quad (19)$$

with $r = (r_0, r_1, r_2)$ positive and $q = (q_0, q_1, q_2)$ non-negative. The weights s in the general formulation are chosen as $s_1 = 1$ and $s_2 = 0$. This reflects the fact that from a biological point of view the most reasonable choice for the recruitment agent is weight $s_2 = 0$. Also, since the aim is to eliminate a large residuum of dormant cells, we take q_0 to be positive. This makes perfect sense from a modelling perspective and mathematically it eliminates singular controls from consideration.

Theorem 5.1: Singular controls u are locally maximizing, hence not optimal. If $u \equiv \text{const}$ on an interval $I \subset [0, T]$, then w cannot be singular on I if $q_0 > 0$.

Proof: First suppose u is singular on I and assume that the control w is constant on a subinterval $J \subset I$. It is a necessary condition for local optimality of the singular control u , the so-called Legendre-Clebsch condition [3] that

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} \leq 0 \quad (20)$$

on J along the extremal. Note that

$$\frac{\partial H}{\partial u} = 1 + \lambda B_1 N = \Phi_1.$$

Using Lemma 3.2, it follows that

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} = \lambda [B_1, [A + wB_2, B_1]] N - qB_1^2 N. \quad (21)$$

Direct calculations verify that

$$[B_1, [B_2, B_1]] \equiv 0 \quad (22)$$

$$[B_1, [A, B_1]] = -4a_1a_2b_1B_1 \quad (23)$$

and $B_1^2 = 0$. Thus, and using the fact that $\Phi_1 \equiv 0$ on I , we have that

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} = -4a_1a_2b_1\lambda B_1 N = 4a_1a_2b_1 > 0 \quad (24)$$

violating the Legendre-Clebsch condition. Hence such a singular control u is in fact locally maximizing over J .

Similarly, if the control w is singular on an interval I , then

$$\Phi_2 = \lambda B_2 N = a_0(\lambda_1 - \lambda_0)N_2 \equiv 0 \quad (25)$$

implying $\lambda_0 \equiv \lambda_1$. Using straightforward calculations it then follows from the adjoint equations that

$$\lambda_2 = \lambda_1 + \frac{q_0 - q_1}{a_1} \quad (26)$$

and

$$\frac{q_2 - q_0}{a_2} + \frac{q_1 - q_0}{a_2} = \lambda_0(2u - 1). \quad (27)$$

If there exists a subinterval $J \subset I$ on which the control u is constant equal to 0 or 1, then this equation implies $\lambda_0 = \text{const}$ and thus $0 = \dot{\lambda}_0 = -q_0$ violating our assumption.

Thus the control w can only be singular if u is singular. Fixing the control w , we then have

$$\frac{d}{dt} \frac{\partial H}{\partial u} = \lambda[A + wB_2, B_1] - qB_1N. \quad (28)$$

But

$$[B_2, B_1] = 2a_0a_2b_0 \begin{pmatrix} 0 & 0 & -1 \\ 0 & 0 & 1 \\ 0 & 0 & 0 \end{pmatrix} \quad (29)$$

and thus (since $\lambda_0 \equiv \lambda_1$)

$$\lambda[B_2, B_1] \equiv 0, \quad (30)$$

i.e. the control w does not appear in this derivative. Using Lemma 3.2 it therefore follows again that

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} = \lambda[B_1, [A, B_1]]N - qB_1^2N = 4a_1a_2b_1 > 0.$$

violating the Legendre-Clebsch condition. This proves the result. \square

Once singular controls have been eliminated, bang-bang controls become the natural choice. For this model the necessary and sufficient conditions for optimality of bang-bang controls given in Theorems 4.1 and 4.2 still simplify somewhat.

Corollary 5.1: For the model considered in this section the expressions in (13), respectively (15), and (16) can be simplified to

$$\left| \dot{\Phi}_l^*(t_k) \right| + \theta_l N_*^T(t_k) B_l^T S_k^+ B_l N_*(t_k) > 0 \quad (31)$$

is satisfied for $k = 2, \dots, h - 1$, respectively

$$\left| \dot{\Phi}_l^*(t_h) \right| + \theta_l N_*^T(t_h) B_l^T S_h^+ B_l N_*(t_h) < 0. \quad (32)$$

Proof. This follows from special properties of the matrices B_l which make each of the terms $\lambda_*(t_k) B_l^T N_*(t_k)$ vanish. For the killing agent u this is trivial since $B_1^2 = 0$. For the recruiting agent w we have that $B_2^2 = -a_0 B_2$ and this implies

$$\lambda_*(t_k) B_2^2 N_*(t_k) = -a_0 \lambda_*(t_k) B_2 N_*(t_k) = 0 \quad (33)$$

where the last equality follows since the switching function $\Phi_2 = \lambda B_2 N$ vanishes at the switching time t_k . Furthermore,

we have $S_1^+ = 0$ and thus condition (31) is satisfied for $k = 1$ by our assumption that the derivatives of the switching functions do not vanish at the junctions. \square

Corollary 5.2: In particular, any regular strictly bang-bang extremal which has only one switching is locally optimal.

Figs. 2 and 3 below give the results of a simulation for the model where the algorithm above was used to establish strong local optimality of the control. The data for the model are $a_0 = 0.05$, $a_1 = 0.5$, $a_2 = 1$, $b_0 = 0.9$; the control set for the recruiting agent is defined by $w_{\max} = 6$, and the parameters in the objective were chosen as $T = 4$, $r_0 = 0.5$, $r_1 = r_2 = 0.25$ and $q_0 = 1$, $q_1 = q_2 = .3$. For simplicity the reference trajectory has been generated by integrating the conditions of the maximum principle backward from the terminal condition $p_0 = 1.1$, $p_1 = 1.035$ and $p_2 = .75$. For these data the control w doesn't switch and is constantly on with $w \equiv 6$ and the control u has 1 switching at $t_1 = 3.82$. It follows from Corollary 5.2 that the corresponding control gives a strong local minimum. (The value of the transversality condition (31) at the switching time is given by 1.6612.)

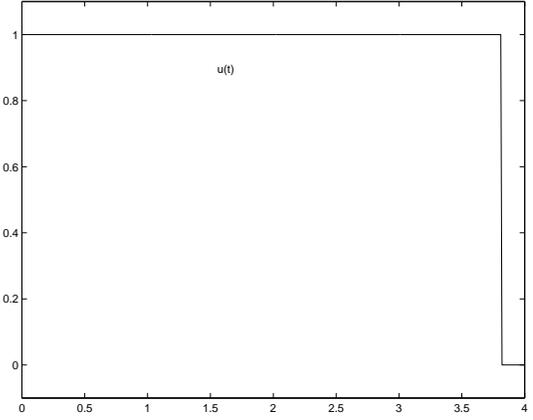


Fig. 2. Killing agent

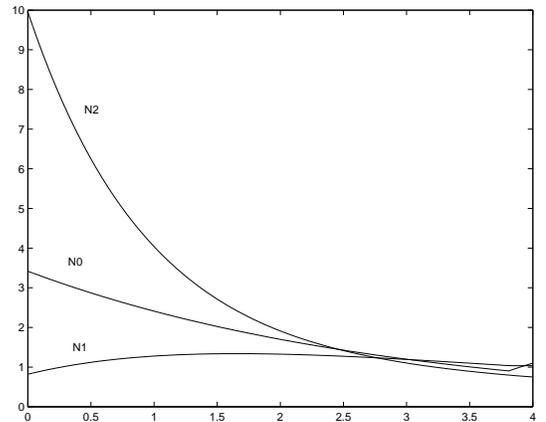


Fig. 3. States

In this run the recruiting agent is always on which is reasonable if a stronger weight is given to the number of cancer cells in the dormant compartment. If this is changed, locally optimal controls which have switchings in the control w as well arise. Figs. 4 and 5 give the recruiting agent w and the states for a run with $r_0 = 0.5$ and $r_1 = r_2 = 1$, but otherwise unchanged parameters. Now the control w switches at time $t_2 = 3.38$ with value 0.0437 for the transversality condition (31) and u switches at $t_1 = 3.90$ with transversality condition given by 1.7797. Thus these controls are locally optimal.

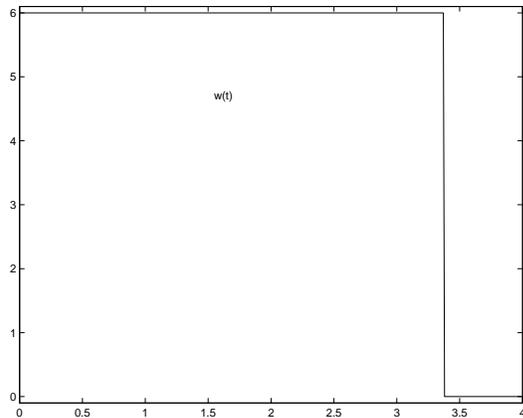


Fig. 4. Recruiting agent

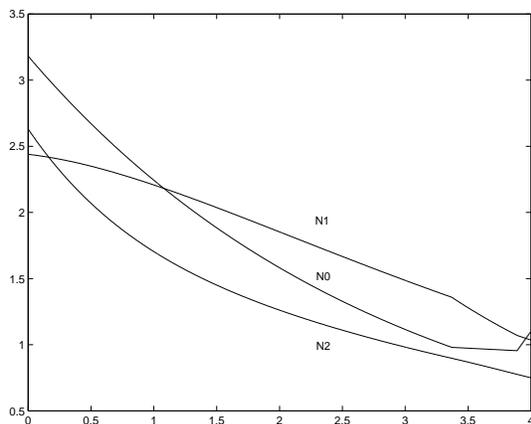


Fig. 5. States

VI. CONCLUSION

In this paper we formulated an algorithm which allows to distinguish between locally optimal and non-optimal bang-bang controls for a class of optimal control problems in cancer chemotherapy. The objective includes a penalty on the states in the Lagrangian term thus trying to limit excessive tumor growth during the therapy interval. These results were

applied to a 3-compartment model with recruiting agent. After showing that singular controls are not optimal, bang-bang extremals were analyzed theoretically and numerically.

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