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OPTIMAL CONTROL FOR A CLASS OF COMPARTMENTAL MODELS IN CANCER CHEMOTHERAPY

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We consider a general class of mathematical models P for cancer chemotherapy described as optimal control problems over a fixed horizon with dynamics given by a bilinear system and an objective which is linear in the control. Several two- and three-compartment models considered earlier fall into this class. While a killing agent which is active during cell division constitutes the only control considered in the two-compartment model, Model A, also two three-compartment models, Models B and C, are analyzed, which consider a blocking agent and a recruiting agent, respectively. In Model B a blocking agent which slows down cell growth during the synthesis allowing in consequence the synchronization of the neoplastic population is added. In Model C the recruitment of dormant cells from the quiescent phase to enable their efficient treatment by a cytotoxic drug is included. In all models the cumulative effect of the killing agent is used to model the negative effect of the treatment on healthy cells. For each model it is shown that singular controls are not optimal. Then sharp necessary and sufficient optimality conditions for bang-bang controls are given for the general class of models P and illustrated with numerical examples.

Keywords: compartmental models, cancer chemotherapy, optimal control, necessary and sufficient conditions for optimality

1. Introduction

Mathematical models for cancer chemotherapy have a long history (see, e.g., (Eisen, 1979; Martin, 1992; Swan, 1990)). In the past years there has been renewed interest in these models (Fister and Panetta, 2000; Ledzewicz and Schättler, 2002b), partially due to better modeling capabilities, but also due to a refinement of the techniques which can be used to estimate the necessary control parameters and to analyze the problems. In this paper we consider a specific class of mathematical models based on cell-cycle kinetics which was introduced by Kimmel and Świerniak (Kimmel and Świerniak, 1983; Świerniak and Kimmel, 1984) and has been analyzed in numerous papers (Ledzewicz and Schättler, 2002a; 2002b; Świerniak and Duda, 1995; Świerniak *et al.*, 1992; 1996), from both the numerical and theoretical perspectives. Here we give a review of some of these results, extend them to a broader class of models and outline some open questions.

The model is based on cell-cycle kinetics and treats the cell cycle as the object of control (Świerniak, 1995). The cell cycle is modeled in the form of compartments which describe different cell phases or combine phases of the cell cycle into clusters. Each cell passes through a sequence of phases from cell birth to cell division. The starting point is the growth phase G_1 after which the cell enters the phase S, where the DNA synthesis occurs. Then the 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 offspring cells can either reenter the phase G_1 or may simply lie dormant for some time in a separate phase G_0 until reentering G_1, thus starting the entire process all over again.

The simplest mathematical models which describe the optimal control of cancer chemotherapy treat the entire cell cycle as one compartment (Świerniak, 1994), but solutions to these single compartment models are not very informative due to the over-simplified nature of the model.

Of the more detailed multi-compartment models, the simplest and at the same time most natural ones, are still models which divide the cell cycle into two and three compartments (Świerniak *et al.*, 1996). In these models the G_2 and M phases are combined into one compartment. In the two-compartment model G_0, G_1 and S form another compartment while different three-compartment models arise by separating the synthesis phase S or the dormant stage G_0 for the three-compartment model. The purpose of this division is to effectively model various drugs used in chemotherapy like killing agents, blocking agents or recruiting agents.

The first class is represented by G_2/M specific agents, which include the so-called spindle poisons like Vincristine, Vinblastine or Bleomycin, which destroy a mitotic spindle (Calabresi and Schein, 1993), and Taxol (Fister and Panetta, 2000) or 5-Fluorouracil (Chabner and Longo, 1996), affecting mainly cells during their division. Killing agents also include S specific drugs like Cyclophosphamide (Fister and Panetta, 2000) and Methotraxate (Panetta *et al.*, 2002a), acting mainly in the DNA replication phase, or Cytosine Arabinoside-Ara-C, rapidly killing cells in phase S through the inhibition of DNA polymerase by competition with deoxycytosine triphosphate (Coly *et al.*, 1984). Among the blocking drugs we can distinguish antibiotics like Adriamycin, Daunomycin, Dexorubin, Idarudicin, which cause the progression blockage on the border between the phases G_1 and S by interfering with the formator of the polymerase complex or by hindering the separation of the two polynucleotide strands in the double helix (Alison and Sarraf, 1997). Another blocking agent is Hydroxyurea – HU (Dibrov *et al.*, 1986; Lyss, 1992), which is found to synchronize cells by causing brief and invisible inhibition of the DNA synthesis in the phase S and holding cells in G_1. The recruitment action was demonstrated (Andreef *et al.*, 1992) for Granulocyte Colony Stimulating Factors – G-CSF, Granulocyte Macrophage Colony Stimulating Factors – GM-CSF, Interleukin-3 – Il-3, especially when combined with the Human Cloned Stem Cell Factor – SCF.

This classification of anticancer agents is not quite sharp and there is some controversy in the literature concerning both the site and the role of the action of some drugs. For example, in spite of being active mostly in specific phases, Cyclophosphamide and 5-Fluorouracil kill cells also in other phases of the proliferation cycle, which enables us to treat them as cycle specific agents (Bonadonna *et al.*, 1995; Calabresi and Schein, 1993). On the other hand, some antimitotic agents like curacin A (Kozusko *et al.*, 2001) act by increasing the S phase transition (blocking) and decreasing the M phase transition.

Killing agents which we consider in our model are used in the G_2/M phase, which makes sense from a biological standpoint for a couple of reasons. First, in mitosis M the cell wall becomes very thin and porous. Hence the cell is more vulnerable to an attack, while there will be a minimal effect on the normal cells. Second, chemotherapy during mitosis will prevent the creation of offspring cells. While the killing agent is the only control considered in the two-compartment model A below, in Model B a blocking agent is additionally considered which slows down the development of cells in the synthesis phase S and then releases them at the moment when another G_2/M specific anticancer drug has a maximum killing potential (the so-called synchronization (Brown and Thompson, 1975)). This strategy can have the additional advantage of protecting the normal cells, which would be less exposed to the second agent (e.g., due to a lesser dispersion and a faster transit through G_2/M) (Agur *et al.*, 1988; Dibrov *et al.*, 1985). This cell cycle model includes separate compartments for the G_0/G_1, S and G_2/M phases.

One of the major problems in the chemotherapy of some leukemias is constituted by the large residuum of dormant G_0 cells, which are not sensitive to most cytotoxic agents (Chabner and Longo, 1996; Holmgren *et al.*, 1995; Luzzi *et al.*, 1998). Similar findings for breast and ovarian cancers were reported, e.g., in (Clare *et al.*, 2000; Fister and Panetta, 2000). As indicated by these authors, the insensitivity of dormant cells to the majority of anticancer drugs and the percentage of tumor mass resting is a fact which, if ignored, leads not only to clinical problems but also to some erroneous theoretical findings. Experiments with Ara-C (Coly *et al.*, 1984) indicated that, while double injected during a cell cycle or combined with Adriamycin or anthracyclines, it led to a serious reduction in the leukemic burden without an evident increase in the negative effect on normal tissues. This therapeutic gain was attributed to the specific recruitment inducing effect of Ara-C on leukemic cells in the dormant phase. It became possible to efficiently recruit quiescent cells into the cycle using cytokines (Andreef *et al.*, 1992; Tafuri and Andreeff, 1990) (substances playing a role in the regulation of normal the hemopoiesis) like G-CSF, GM-CSF, and especially Il-3 combined with SCF. Then, a cytotoxic agent like Ara-C or anthracyclines may be used. Model C below uses separate compartments for the G_0, G_1 and $S + G_2/M$ phases and includes such a recruiting agent. Moreover, it also enables an analysis of the alteration of the transit time through the G_0 phase due to the feedback mechanism recruiting the cells into the cycle when chemotherapy is applied. In a similar way, we can model other types of manipulation of the cell cycle as, e.g., the use of triterpenoids to inhibit proliferation and to induce differentiation and apoptosis in leukemic cells (Konopleva *et al.*, 2002).

In Models A–C considered here the problem of finding an optimal cancer chemotherapy protocol is formulated as an optimal control problem over a finite time-interval being the fixed therapy horizon. The state variable is given by the average number of cancer cells and the control is the effect of the drug dosages on the respective subpopulation. The goal is to maximize the number of cancer cells which the agent kills and to appropriately minimize the number of cancer cells at the end of the therapy session, while keeping the toxicity to the normal tissues acceptable. The last aspect is modeled implicitly by including an integral of the control over the therapy interval in the objective so that minimizing controls will have to balance the amount of drugs given with the conflicting objective to kill cancer cells.

In this paper we formulate and analyze a general mathematical model P which has an arbitrary number of compartments. The models mentioned above all fall into this class and other compartmental models whose dynamics arise from balance equations with constant transition rates will fit this class as well. For example, more complicated models involving drug resistance match this framework with the extra compartments representing various levels of drug resistant sub-populations of cancer cells. Analyzing the general model P has the obvious advantage that the mathematics which is common to all these models only needs to be carried out once. But, clearly, for a complete analysis of the problems, specific forms of the data for the models (matrices, parameters, etc.) need to be then taken into account.

Analytical approaches to these models are based on applications of the Pontryagin Maximum Principle (Pontryagin *et al.*, 1964), which results in both bang-bang and singular controls as candidates for optimality. While bang-bang controls corresponds to treatment protocols which alternate maximum doses of chemotherapy with rest periods when no drug is administered, singular controls correspond to applying varying doses at less than their maximum. Bang-bang controls, which are widely used as protocols in medical treatments, are the more natural choice as candidates for optimality, and it even has been observed numerically that singular protocols actually give the worst performance (Duda, 1994; 1997; Świerniak *et al.*, 1996). In the papers (Ledzewicz and Schättler, 2002a; 2002b) singular arcs were indeed excluded from optimality for Models A and B with the use of high-order necessary conditions for optimality. In this paper we extend these results to Model C. This result seems to be important from a practical point of view since it indicates that in the case of cell recruitment bang-bang protocols should be considered as optimal strategies. Once singular controls are excluded from optimality, bang-bang controls become the natural candidate. However, the Maximum Principle only gives first order necessary conditions for optimality and therefore the trajectories it identifies may not be optimal. In fact, some of them, like the singular arcs for Models A–C, are maximizing rather than minimizing ones. In (Ledzewicz and Schättler, 2002a), examples of both optimal and non-optimal bang-bang controls are given for Model A. It is therefore important to further investigate the optimality of these candidates. While the analysis of singular controls in Section 3 depends on the matrices in the dynamics and thus necessarily is model specific, in Section 4 we formulate an algorithm for the general model P which allows us to determine whether or not a bang-bang control which satisfies the conditions of the Maximum Principle is locally optimal, cf. Theorems 2 and 3, respectively. For Models A–C considered in this paper, the general structure simplifies somewhat because of special properties of the matrices in the models and the simplified formulas are given in Corollary 2. The algorithm as presented applies to any model which fits the general class P.

2. Mathematical Models for Cancer Chemotherapy

We formulate a general n-compartment model for cancer chemotherapy as an optimal control problem over a fixed therapy interval with dynamics described by a bilinear system. Let $N = (N_1, \dots, N_n)^T$ denote the state-vector with N_i denoting the number of cancer cells in the i-th compartment, $i = 1, \dots, n$. The control is a vector $u = (u_1, \dots, u_m)^T$ with u_i denoting the drug dosage administered. The control set U is a compact m-dimensional interval of the form $[\alpha_1, \beta_1] \times \cdots \times [\alpha_m, \beta_m]$ with each interval $[\alpha_i, \beta_i] \subset [0, \infty)$. Let A and B_i, $i = 1, \dots, m$, be constant $n \times n$ matrices, let $r = (r_1, \dots, r_n)$ be a row vector of positive numbers and let $s = (s_1, \dots, s_m)$ be a row vector of non-negative numbers. The vectors r and s represent subjective weights in the objective. We then consider the following optimal control problem:

(P) Minimize the objective

$$J = rN(T) + \int_0^T su(t)\,\mathrm{d}t \to \min \tag{1}$$

over all Lebesgue-measurable functions $u : [0, T] \to U$ subject to the dynamics

$$\dot{N}(t) = \Big(A + \sum_{i=1}^{m} u_i B_i\Big) N(t), \quad N(0) = N_0. \tag{2}$$

We briefly recall three two- and three-compartment models which fit into this general class. For a more detailed description of the models we refer the reader to (Świerniak *et al.*, 1996).

Model A: In a two-compartment model the phases G_0, G_1 and S are clustered into the first compartment, G_2 and M are combined into the second compartment, and only a killing agent $u = u_1$ is considered. Thus $n = 2$, $m = 1$, and the matrices A and $B = B_1$ are given by

$$A = \begin{pmatrix} -a_1 & 2a_2 \\ a_1 & -a_2 \end{pmatrix}, \quad B = \begin{pmatrix} 0 & -2a_2 \\ 0 & 0 \end{pmatrix}. \quad (3)$$

The a_i's are positive coefficients related to the mean transit times of cells through the i-th compartment.

Model B: In this three-compartment model a blocking agent $v = u_2$ is additionally considered which is active in the synthesis phase S and thus S is modeled as a separate compartment. Now $n = 3$, $m = 2$, and the matrices are given by

$$A = \begin{pmatrix} -a_1 & 0 & 2a_3 \\ a_1 & -a_2 & 0 \\ 0 & a_2 & -a_3 \end{pmatrix}, \quad (4)$$

and

$$B_1 = \begin{pmatrix} 0 & 0 & -2a_3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & a_2 & 0 \\ 0 & -a_2 & 0 \end{pmatrix}. \quad (5)$$

In both models the control $u = u_1$ represents the dose of the killing agent administered with the value $u = 0$ corresponding to no treatment and $u = 1$ corresponding to a maximum dose. It is assumed that the dose stands in direct relation to the fraction of cells which are being killed in the G_2/M phase. Therefore only the fraction $1 - u$ of the outflow of cells from the last compartment undergoes cell division and reenters the first compartment. However, all cells leave compartment G_2/M. In Model B the blocking agent $v = u_2$ is additionally applied to slow the transit times of cancer cells during the synthesis phase S. As a result, the flow of cancer cells from the second into the third compartment is reduced by a factor of $1-v$ of its original flow to $(1-v(t))a_2N_2(t)$, $0 \le v(t) \le v_{\max} < 1$. Here the control $v(t) = 0$ corresponds to no drug being applied while a maximal reduction occurs with a full dose $v_{\max}$.

Model C: A second three-compartment model can be derived from Model A if the dormant phase G_0 is considered separately. In this case the 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. In addition to that, in this model we also consider a recruiting agent $w = u_3$ which 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 of $1+w$, $0 \le w \le w_{\max}$. Here again the control $w = 0$ corresponds to no drug being applied while $w = w_{\max}$ occurs with a full dose. For this model it is more natural to label the compartments with $i = 0, 1, 2$ and the matrices for this three-compartment model are given by

$$A = \begin{pmatrix} -a_0 & 0 & 2b_0a_2 \\ a_0 & -a_1 & 2b_1a_2 \\ 0 & a_1 & -a_2 \end{pmatrix}, \quad (6)$$

and

$$B_1 = \begin{pmatrix} 0 & 0 & -2b_0a_2 \\ 0 & 0 & -2b_1a_2 \\ 0 & 0 & 0 \end{pmatrix}, \quad B_3 = \begin{pmatrix} -a_0 & 0 & 0 \\ a_0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}. \quad (7)$$

For all three models we take the objective as

$$J = rN(T) + \int_0^T u(t)\,\mathrm{d}t, \quad (8)$$

(i.e., $s_1 = 1$ and $s_2 = s_3 = 0$ in the general formulation (1)). The penalty term $rN(T)$ in the objective represents a weighted average of the total number of cancer cells at the end of an assumed fixed therapy interval $[0, T]$. The number of cancer cells which do not undergo cell division at time t and are killed are given by the portion $u(t)$ of the outflow of the last compartment, i.e., $u(t)$ is proportional to the fraction of ineffective cell divisions. Since the drug kills healthy cells at a proportional rate, the control $u(t)$ 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 treatment. In the three-compartment model B it is assumed that the negative influence of the blocking agent v which does not kill cells is negligible and it is therefore not included in the objective. However, since, as has been mentioned above, some blocking agents exhibit also killing effects, it may be reasonable to include their cytotoxicity on normal tissues. It could easily be incorporated with a small weight s_2 without changing the structure of the results. For the three-compartment model C the only reasonable choice for the recruitment agent is weight $s_3 = 0$.

Returning to the general model P, we also make the assumption that the control system is *internally positive* (Kaczorek, 1998):

(+) The first orthant of the control system is positively invariant, i.e., for any admissible control u, if $N_i(0) > 0$ for all $i = 1, \ldots, n$, then $N_i(t) > 0$ for all $i = 1, \ldots, n$, and all times $t > 0$.

Thus the obvious modeling state-space constraints $N_i(t) \geq 0$ for $i = 0, 1, \ldots, n$, need not be included in our model explicitly, and the analysis simplifies. A simple sufficient condition for $(+)$ to hold (for example, see (Kaczorek, 1998)) is that

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

This condition is natural and will be satisfied for any compartmental model whose dynamics are given by balance equations where the diagonal entries correspond to the outflows from the i-th compartments and the off-diagonal entries represent the inflows from the i-th into the j-th compartment, $i \neq j$. It is satisfied for each of Models A, B and C described above. More generally, if condition $(+)$ were violated, this would be a strong indication that the modeling is inconsistent.

Necessary conditions for optimality are given by the Pontryagin Maximum Principle (Pontryagin *et al.*, 1964): if $u_* = (u_1^*, \ldots, u_m^*)$ is an optimal control, then it follows that there exists an absolutely continuous function λ, which we write as a row vector, $\lambda : [0, T] \to (\mathbb{R}^n)^*$, satisfying the adjoint equation

$$\dot{\lambda} = -\lambda\Big(A + \sum_{i=1}^{m} u_i^* B_i\Big), \qquad \lambda(T) = r, \tag{9}$$

such that the optimal control u_* minimizes the Hamiltonian H over the control set along $(\lambda(t), N_*(t))$,

$$H = \lambda A N + \sum_{i=1}^{m} u_i \left(s_i + \lambda B_i N\right). \tag{10}$$

If the control system satisfies the condition (M), then from the adjoint equation (9) it follows that for any admissible control the first orthant in the λ-space is negatively invariant under the flow of the adjoint system, i.e., if $\lambda_i(T) > 0$ for all $i = 1, \ldots, n$, then $\lambda_i(t) > 0$ for all $i = 1, \ldots, n$, and all times $t \leq T$. In this case, since $N(0)$ and $\lambda(T)$ have positive components, it follows that all states N_i and costates λ_i are positive over $[0, T]$.

Corollary 1. *If the condition (M) is satisfied, then all states N_i and costates λ_i are positive over $[0, T]$.*

Since the control set is a cube, the minimization of the Hamiltonian splits into m separate one-dimensional minimization problems. If we define the i-th switching function as

$$\Phi_i = s_i + \lambda B_i N, \tag{11}$$

then the optimal controls satisfy

$$u_i^*(t) = \begin{cases} \alpha_i & \text{if} \quad \Phi_i(t) > 0, \\ \beta_i & \text{if} \quad \Phi_i(t) < 0. \end{cases} \tag{12}$$

Thus for Models A–C we have

$$u_*(t) = \begin{cases} 0 & \text{if} \quad \Phi_1(t) > 0, \\ 1 & \text{if} \quad \Phi_1(t) < 0, \end{cases} \tag{13}$$

$$v_*(t) = \begin{cases} 0 & \text{if} \quad \Phi_2(t) > 0, \\ v_{\max} & \text{if} \quad \Phi_2(t) < 0, \end{cases} \tag{14}$$

and

$$w_*(t) = \begin{cases} 0 & \text{if} \quad \Phi_3(t) > 0, \\ w_{\max} & \text{if} \quad \Phi_3(t) < 0, \end{cases} \tag{15}$$

where $\Phi_1(t) = 1 + \lambda(t) B_1 N(t)$, $\Phi_2(t) = \lambda(t) B_2 N(t)$ and $\Phi_3(t) = \lambda(t) B_3 N(t)$.

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 candidates.

3. Singular Controls

In this section we show how singular arcs can be excluded from optimality for Models A–C using high-order necessary conditions for optimality. These calculations are model specific and we refer the reader to (Ledzewicz and Schättler, 2002a; 2002b) for the details of calculations for Models A and B, but we give the calculations for Model C. We refer to the killing agent as u, the blocking agent as v, and the recruiting agent as w. If any of these controls are singular on an open interval $I \subset [0, T]$, then the corresponding switching function and all its derivatives must vanish on I. Singular controls are calculated by differentiating the switching functions with respect to time until the control variable explicitly appears in the derivative, say in $\Phi^{(l)}(t)$, and then solving the resulting equation $\Phi^{(l)}(t) \equiv 0$ for the control. For a single-input system which is linear in the control it is known (Krener, 1977) that l must be even, say $l = 2k$, and k is called the order of the singular arc on the interval I. It is a necessary condition for the optimality of a singular arc of order k, the so-called generalized Legendre-Clebsch condition (Krener, 1977), that

$$(-1)^k \frac{\partial}{\partial u} \frac{\mathrm{d}^{2k}}{\mathrm{d}t^{2k}} \frac{\partial H}{\partial u} \geq 0. \tag{16}$$

Note that the term $\partial H / \partial u$ in (16) represents the switching function for the problem. This framework directly applies to the two-compartment model A which has a scalar control. Elementary and direct calculations (Ledzewicz

and Schättler, 2002a) show that in this case singular arcs are of order 1 and that

$$\frac{\partial}{\partial u}\frac{\mathrm{d}^2}{\mathrm{d}t^2}\frac{\partial H}{\partial u} = 4a_1a_2 > 0, \tag{17}$$

violating the Legendre-Clebsch condition. For the three-compartment model B the generalized Legendre-Clebsch condition (16) still applies to the first control u if we freeze the second control v. Assuming that v is constant, it can be shown that a singular control u must be of order 2, but again (16) is violated. Direct, but longer calculations yield

$$\frac{\partial}{\partial u}\frac{\mathrm{d}^4}{\mathrm{d}t^4}\frac{\partial H}{\partial u} = -12a_1a_2a_3^2(1-v)\big(a_1+a_2(1-v)\big) \times\lambda_1(t)N_2(t) < 0. \tag{18}$$

(See (Ledzewicz and Schättler, 2002b), but note that we replaced what was v in this paper with $1-v$. In this way, zero values of the control correspond to no treatment.) Furthermore, if the control v is singular on an interval I, then it can be easily seen that u also must be singular on I. In this case it is a necessary condition for optimality, the so-called Goh condition (Krener, 1977), that on I we have

$$\frac{\partial}{\partial v}\frac{\mathrm{d}}{\mathrm{d}t}\frac{\partial H}{\partial u} \equiv 0. \tag{19}$$

However, a direct calculation gives

$$\frac{\partial}{\partial v}\frac{\mathrm{d}}{\mathrm{d}t}\frac{\partial H}{\partial u} = 2a_2a_3\lambda_1(t)N_2(t) > 0, \tag{20}$$

violating the Goh-condition (Ledzewicz and Schättler, 2002b). Note that these results strongly depend on the fact that states and both multipliers are positive.

We now show how the optimality of singular controls can be excluded for the three-compartment model C. Suppose that the control u is singular on an open interval $I \subset [0,T]$ and consider the system as a single-input optimal control problem with drift $A+wB_3$. For the moment also assume that the control w is constant over I. Then the first two derivatives of the switching function $\Phi_1(t) = 1+\lambda(t)B_1N(t)$ are given by

$$\dot\Phi_1(t) = \lambda(t)[A+wB_3,B_1]N(t), \tag{21}$$

$$\ddot\Phi_1(t) = \lambda(t)\big[A+uB_1+wB_3,[A+wB_3,B_1]\big]N(t), \tag{22}$$

where $[F,G] = GF-FG$ denotes the commutator of matrices. (The opposite sign has been chosen to be consistent with the definition of the Lie-bracket of linear vector fields.) Note that

$$\frac{\partial}{\partial u}\frac{\mathrm{d}^2}{\mathrm{d}t^2}\frac{\partial H}{\partial u} = \lambda(t)\big[B_1,[A+wB_3,B_1]\big]N(t). \tag{23}$$

Direct calculations verify that this double bracket term satisfies the relation

$$\big[B_1,[A+wB_3,B_1]\big] = -4a_1a_2b_1B_1. \tag{24}$$

Hence

$$\frac{\partial}{\partial u}\frac{\mathrm{d}^2}{\mathrm{d}t^2}\frac{\partial H}{\partial u} = -4a_1a_2b_1\lambda(t)B_1N(t) = 4a_1a_2b_1 > 0, \tag{25}$$

violating the Legendre-Clebsch condition. Here, in the last step we use the fact that the switching function vanishes identically on I,

$$\Phi_1(t) = 1+\lambda(t)B_1N(t) \equiv 0. \tag{26}$$

These calculations therefore exclude the optimality of a singular control u when w is constant. It might still be possible, however, that w is not constant over any subinterval $J \subset I$. In this case w must also be singular on I. It turns out that for this example the Goh condition is actually satisfied and thus a further analysis of necessary conditions becomes indispensable. Now we also have on I that

$$\Phi_3(t) = \lambda(t)B_3N(t) = a_0N_0(t)\big(\lambda_1(t)-\lambda_0(t)\big) \equiv 0 \tag{27}$$

and thus $\lambda_1(t) \equiv \lambda_0(t)$. But

$$\dot\lambda_0(t) = a_0\big(\lambda_0(t)-\lambda_1(t)\big)\big(1+w(t)\big) \equiv 0 \tag{28}$$

and thus both λ_0 and λ_1 are constant. Since

$$0 \equiv \dot\lambda_1(t) = a_1\big(\lambda_1(t)-\lambda_2(t)\big), \tag{29}$$

it follows that

$$\lambda_0(t) \equiv \lambda_1(t) \equiv \lambda_2(t) \equiv \mathrm{const} = \bar\lambda > 0. \tag{30}$$

But then the adjoint equation for λ_2 becomes

$$0 \equiv \dot\lambda_2(t) = a_2\big[\lambda_2(t)-2\big(1-u(t)\big)\big(b_0\lambda_0(t)+b_1\lambda_1(t)\big)\big] = a_2\bar\lambda\big(2u(t)-1\big) \tag{31}$$

implying $u(t) \equiv 1/2$. (In particular, this also means that u must be singular if so is w.) Since u is singular, by (26) we also have

$$0 \equiv 1-2a_2N_2(t)\bar\lambda \tag{32}$$

and thus $N_2(t) \equiv \bar N_2 = \mathrm{const}$. But then also

$$0 \equiv \dot N_2(t) = a_1N_1(t)-a_2N_2(t) = a_1N_1(t)-a_2\bar N_2 \tag{33}$$

implying $N_1(t) \equiv \bar N_1 = \mathrm{const}$ as well. Thus

$$0 \equiv \dot N_1(t) = a_0N_0(t)\big(1+w(t)\big) - a_1\bar N_1 + 2b_1a_2\bar N_2\big(1-u(t)\big) = a_0N_0(t)(1+w(t)) - (1-b_1)a_2\bar N_2. \tag{34}$$

But then

$$\dot{N}_0(t) = -a_0 N_0(t)\big(1+w(t)\big) + 2b_0 a_2 \bar{N}_2\big(1-u(t)\big)$$
$$= -a_0 N_0(t)\big(1+w(t)\big) + (1-b_1)a_2\bar{N}_2 \equiv 0 \tag{35}$$

and thus also $N_0(t) \equiv \bar{N}_0 = \text{const}$. In fact, if $u(t) \equiv 1/2$, then the matrix $A + \frac{1}{2}B_1 + wB_3$ has eigenvalue 0 with left-eigenvector $\bar{\lambda} = (1,1,1)$ and right-eigenvector $\bar{N} = (\bar{N}_0, \bar{N}_1, \bar{N}_2)$, which gives an equilibrium for the system and the adjoint equations. But this finally implies

$$\big(1+w(t)\big) = b_0 \frac{a_2\bar{N}_2}{a_0\bar{N}_0} = \text{const}. \tag{36}$$

Thus, if at all admissible, the control w is constant and thus the optimality of the overall control pair (u,w) is excluded by the deliberations above. In summary, neither u nor w can be singular on any subinterval.

Theorem 1. *For Models A–C optimal controls are not singular on any subinterval $I \subset [0,T]$.*

4. Bang-Bang Controls

Once singular controls have been eliminated from optimality, bang-bang controls become the natural candidates. We now state sharp necessary and sufficient conditions for the optimality of bang-bang controls for the general n-compartment model P.

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

$$\dot{\Phi}_i(t) = \lambda(t)\left[A + \sum_{j=1}^{i-1} u_j B_j + \sum_{j=i+1}^{m} u_j B_j, B_i\right] N(t). \tag{37}$$

We then also assume that *(ii) at each switching t_k the derivative of the corresponding switching function Φ_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 the conditions (i) and (ii) are satisfied a *regular strictly bang-bang extremal lift*. We construct a parametrized family of regular strictly bang-bang extremal lifts which contains Γ 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.

The terminal values for the adjoint variables are all the same and are given by the row vector r of weights for the coordinates of the terminal state $N(T)$. Note, however, that the positivity of the trajectories needs to be enforced once we integrate the trajectories backward from a free terminal point p. Choosing the controls $u_i = u_i(t,p)$ to maintain the minimum condition of the Maximum Principle, the system and adjoint equations are thus given by

$$\dot{N}(t,p) = \Big(A + \sum_{i=1}^{m} u_i B_i\Big) N(t,p) \tag{38}$$

and

$$\dot{\lambda}(t,p) = -\lambda(t,p)\Big(A + \sum_{i=1}^{m} u_i B_i\Big),$$

with terminal values

$$N(T,p) = p \quad \text{and} \quad \lambda(T,p) = r. \tag{39}$$

Setting $p_* = N_*(T)$, the controls $u(t,p_*)$ are given by the reference controls u_*, and $N(t,p_*)$ and $\lambda(t,p_*)$ are the reference trajectory and the corresponding multiplier, respectively. It can be shown that there exists a neighborhood W of p_* and continuously differentiable functions τ_k defined on W, $k = 1,\dots,m$, 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 $\Gamma_p = (N(\cdot,p), u(\cdot,p), \lambda(\cdot,p))$ for $p \in W$ are regular strictly bang-bang extremal lifts. This allows us to use field-theoretic concepts to develop sufficient optimality conditions. Essentially, if the system flow is a diffeomorphism away from the switching surfaces and if it crosses the switching surfaces transversally, then using the method of characteristics, a differentiable solution to the Hamilton-Jacobi-Bellman equation can be constructed (Noble and Schättler, 2002). This implies then the optimality of the flow.

Theorem 2. *Let $\Gamma = (N_*, u_*, \lambda_*)$ be a regular strictly bang-bang extremal lift without simultaneous switchings, and let $\Phi_i^*(t) = s_i + \lambda_*(t)B_iN_*(t)$ be the switching function associated with the control u_i, $i = 1,\dots,m$. Denote by t_k, $k = 1,\dots,m$ the switching times of the controls, $0 < t_m < \cdots < t_1 < t_0 = T$ 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 by θ_ι the absolute jump in the control, i.e., $\theta_\iota = \beta_i - \alpha_i$ if $\iota(k) = i$. Set $S_0^- = 0$*

and for $k = 1, \ldots, m$ *define*

$$S_k^+ = \exp\left(\left(A + \sum_{j=1}^{m} u_j^k B_j\right)^T (t_{k-1} - t_k)\right) S_{k-1}^- \times \exp\left(\left(A + \sum_{j=1}^{m} u_j^k B_j\right)(t_{k-1} - t_k)\right), \quad (40)$$

$$G_k = -\frac{\theta_\iota}{|\dot{\Phi}_\iota^*(t_k)|}\left(\lambda_*(t_k)B_\iota + N_*^T(t_k)B_\iota^T S_k^+\right), \quad (41)$$

$$S_k^- = \left(B_\iota^T \lambda_*^T(t_k) G_k + S_k^+\right)\left(Id + \frac{B_\iota N_*(t_k) G_k}{1 - G_k B_\iota N_*(t_k)}\right). \quad (42)$$

If we have

$$\left|\dot{\Phi}_\iota^*(t_k)\right| + \theta_\iota\left(\lambda_*(t_k)B_\iota + N_*^T(t_k)B_\iota^T S_k^+\right)B_\iota N_*(t_k) > 0 \quad (43)$$

for $k = 1, \ldots, m$*, then the matrices* S_k^-*,* $k = 1, \ldots, m$ *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*

$$\sigma : [0, T] \times W \to R,\ (t, p) \mapsto \big(t, x(t, p)\big). \quad (44)$$

A special version of this algorithm was proven for Model A in (Ledzewicz and Schättler, 2002a) and for Model B in (Ledzewicz and Schättler, 2002b). The algorithm here applies to the general model P and differs from those given in (Ledzewicz and Schättler, 2002a; 2002b) in the extra term $\theta_\iota \lambda_*(t_k) B_\iota^2 N_*(t_k)$ in (43). The reason is that for the general dynamics some simplifying properties of these models no longer apply (see Corollary 2 below). The proofs of Theorems 2 and 3 are lengthy and are omitted since they follow the same pattern as in the case of the result proven in (Ledzewicz and Schättler, 2002b), but with the required technical modifications to allow for general n-dimensional dynamics.

Theorem 3. *With the notation of Theorem 2 assume that the transversality condition*

$$\left|\dot{\Phi}_\iota^*(t_k)\right| + \theta_\iota\left(\lambda_*(t_k)B_\iota + N_*^T(t_k)B_\iota^T S_k^+\right)B_\iota N_*(t_k) > 0 \quad (45)$$

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

$$\left|\dot{\Phi}_\iota^*(t_h)\right| + \theta_\iota\left(\lambda_*(t_h)B_\iota + N_*^T(t_h)B_\iota^T S_h^+\right)B_\iota N_*(t_h) < 0. \quad (46)$$

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* $t \leq t_h$*.*

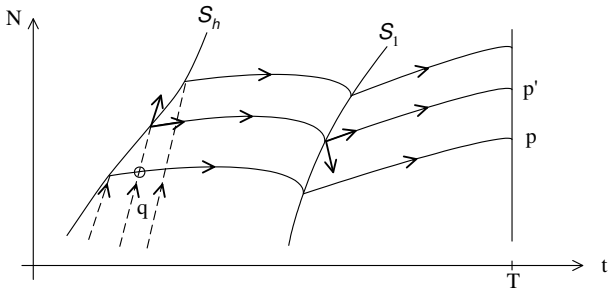

Fig. 1. Optimal and non-optimal switchings.

Figure 1 reflects the geometric meaning of the transversality conditions (45) and (46). If the combined flow crosses the switching surfaces transversally like for the switching surface $\mathcal{S}_1$ (the condition (45) is satisfied), the trajectories cover the time-state space injectively and no local improvements are possible at such a switching. But if the flow reflects off the switching surface like for the switching surface $\mathcal{S}_h$ (the condition (46) holds), then it is possible to do better even locally with exactly one switching less by eliminating the corresponding junction. In this case there exist exactly two trajectories in our parametrization of bang-bang controls which start from points q close to the switching surface $\mathcal{S}_h$. Out of these the one which ends at the terminal point p and does not encounter $\mathcal{S}_h$ satisfies the sufficient optimality conditions given in Theorem 2 and corresponds to a strong local minimum. The trajectory which reflects off $\mathcal{S}_h$ and ends in p' is not optimal by Theorem 3. Intuitively, we can say that we can move down the flow to avoid the transversal fold. The switching surface $\mathcal{S}_h$ exactly acts like an envelope in the Calculus of Variations and the local optimality of the flow ceases there.

Corollary 2. *For the compartmental problems A–C described above, the expressions in (43), (45), and (46) can be simplified to*

$$\left|\dot{\Phi}_\iota^*(t_k)\right| + \theta_\iota N_*^T(t_k)B_\iota^T S_k^+ B_\iota N_*(t_k) > 0 \quad (47)$$

satisfied for $k = 2, \ldots, h-1$*, but*

$$\left|\dot{\Phi}_\iota^*(t_h)\right| + \theta_\iota N_*^T(t_h)B_\iota^T S_h^+ B_\iota N_*(t_h) < 0. \quad (48)$$

Proof. The result follows from special properties of the matrices B_ι which make each of the terms

$\lambda_*(t_k)B_i^2N_*(t_k)$ vanish. For the matrices B_1 in all the models this is trivial since $B_1^2 = 0$. For B_2 and B_3 this holds since we have the relations $B_2^2 = a_2B_2$ and $B_3^2 = -a_0B_3$. This implies

$$\lambda_*(t_k)B_2^2N_*(t_k) = a_2\lambda_*(t_k)B_2N_*(t_k) = -a_2s_2, \quad (49)$$

where the last equality follows since the switching function $\Phi_2 = s_2 + \lambda B_2 N$ vanishes at the switching time t_k. For Model B we have assumed $s_2 = 0$ and thus this term vanishes. Similarly,

$$\lambda_*(t_k)B_3^2N_*(t_k) = -a_0\lambda_*(t_k)B_3N_*(t_k) = a_0s_3, \quad (50)$$

which vanishes since $s_3 = 0$. Furthermore, in these cases we therefore have $S_1^+ = 0$ and thus the condition (47) is trivially satisfied for $k = 1$. ■

5. Numerical Simulations

Examples of both locally optimal and non-optimal bang-bang extremal trajectories for the two-compartment model A were given in (Ledzewicz and Schättler, 2002a). Here we include some new simulations for the three-compartment models B and C. In order to facilitate the computations (which illustrate the mathematical theory) we integrate the systems backward from the terminal time T and take the terminal values of the states as parameters, $p = N(T)$.

The data for Model B with a blocking agent are given by $a_1 = 0.197$, $a_2 = 0.395$ and $a_3 = 0.107$, $v_{\max} = 0.3$, and the weights in r were chosen as $r_1 = 1$, $r_2 = 0.5$ and $r_3 = 1$. The terminal time is $T = 7$ and the parameter values are $p_1 = p_2 = 5$ and $p_3 = 8.5$. For these parameters there are three switchings in the controls and the results are summarized in Table 1 below. Since all transversality conditions are positive, the corresponding controls are locally optimal. The graphs of the corresponding controls and states are given in Figs. 2–4.

The data for model C with a recruiting agent were chosen as $a_0 = 0.05$, $a_1 = 0.5$ and $a_2 = 1$, $w_{\max} = 6$, $b_0 = 0.9 = 1 - b_1$ and the weights in r were as above, $r_0 = 1$, $r_1 = 0.5$ and $r_2 = 1$. Now the terminal time is $T = 4$ and the parameter values are $p_0 = 2.2$, $p_1 = 2.145$ and $p_2 = 1.08$. For these parameters there

Table 1. Data for the switchings for Model B.

switching time	switch in control	transversality condition
$t_1 = 3.56$	v	.1541
$t_2 = 3.28$	u	.2905
$t_3 = 3.09$	v	.1191

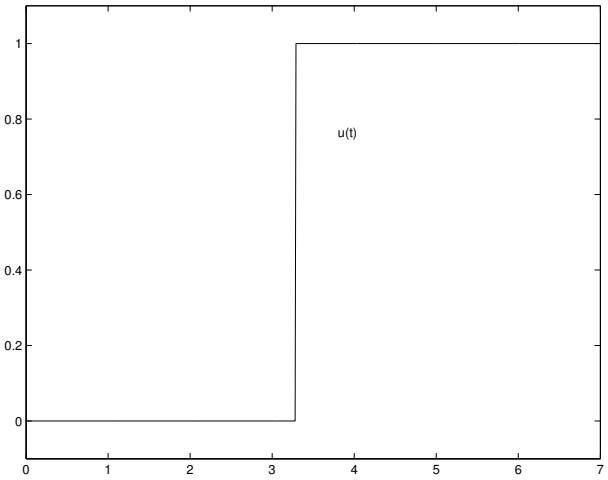

Fig. 2. Killing agent (Model B).

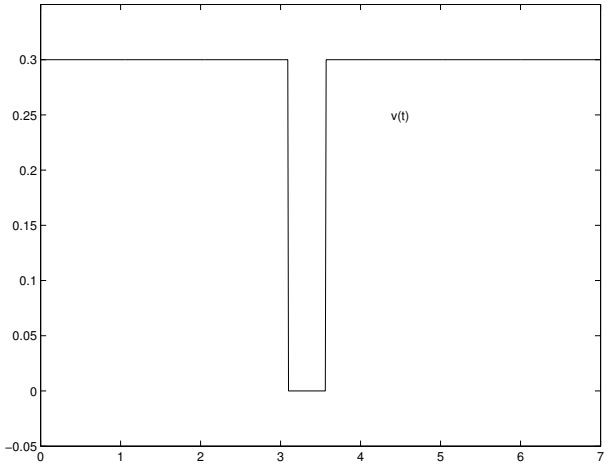

Fig. 3. Blocking agent (Model B).

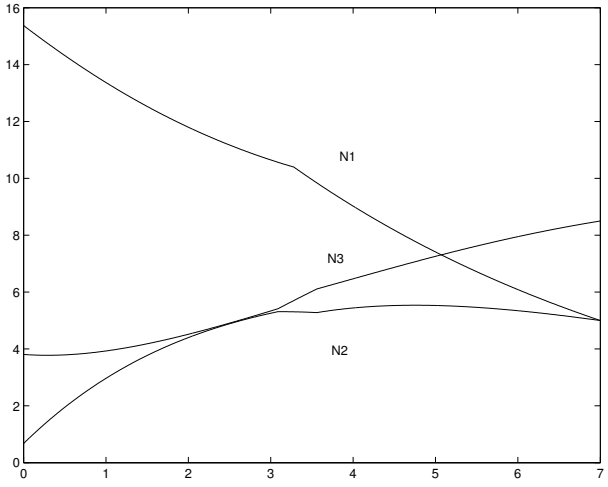

Fig. 4. States (Model B).

Table 2. Data for the switchings for Model C.

switching time	switch in control	transversality condition
$t_1 = 1.96$	u	.7445
$t_2 = 0.28$	w	1.3456

are two switchings in the controls corresponding to the killing and recruiting agents. The results are summarized in Table 2 below. Since all transversality conditions are positive, these controls are also locally optimal. The graphs of the corresponding controls and states are given in Figs. 5–7.

6. Discussion

In this paper we discussed the cell-cycle-phase dependence of cytotoxic drug action in the context of the optimization of cancer chemotherapy. Besides the emergence of drug resistance (see, e.g., (Goldie and Coldman, 1998; Kimmel *et al.*, 1998), the phase sensitivity and the cycle specificity are viewed by many authors, as one of the major obstacles against successful chemotherapy (Chabner and Longo, 1996; Fister and Panetta, 2000).

The simplest cell-cycle-phase dependent models of chemotherapy can be classified based on the number of compartments and the types of drug action modeled. In all these models the attempts at finding optimal controls have been confounded by the presence of singular and periodic trajectories, and multiple solutions. However, in this paper we developed efficient analytical and numerical methods which allow us to overcome the difficulties. In simpler cases, it is possible to eliminate singular protocols as non-optimal and give sufficient conditions for the optimality of bang-bang trajectories. Moreover, we formulated and solved a quite general multicompartment model of chemotherapy which facilitates the discussion of other types of protocols and other phenomena than those considered in the paper.

All possible applications of the mathematical models of chemotherapy are contingent on our ability to estimate their parameters. Recently there has been progress in that direction, concerning particularly precise estimation of drug action in culture and the estimation of cell cycle parameters of tumor cells *in vivo*. The stathmokinetic or "metaphase arrest" technique consists in blocking cell division by an external agent (usually a drug, e.g., vincristine or colchicine). The cells gradually accumulate in mitosis, emptying the postmitotic phase G_1 and with time also the S phases. Flow cytometry allows precise measurements of the fractions of cells residing in a different cell cycle phase. The pattern of cell accumulation in mitosis M depends on the kinetic parameters of the cell

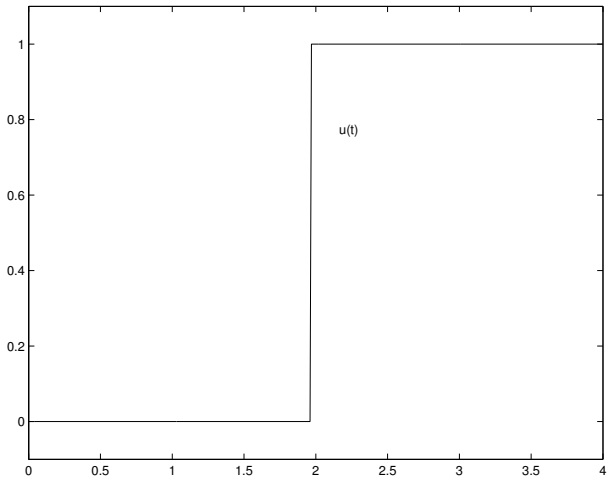

Fig. 5. Killing agent (Model C).

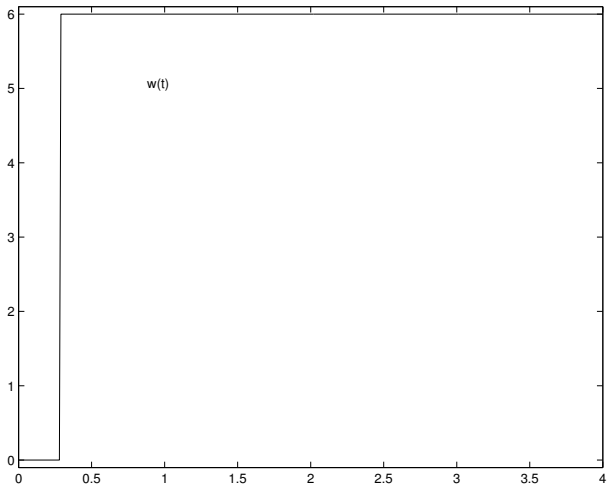

Fig. 6. Recruiting agent (Model C).

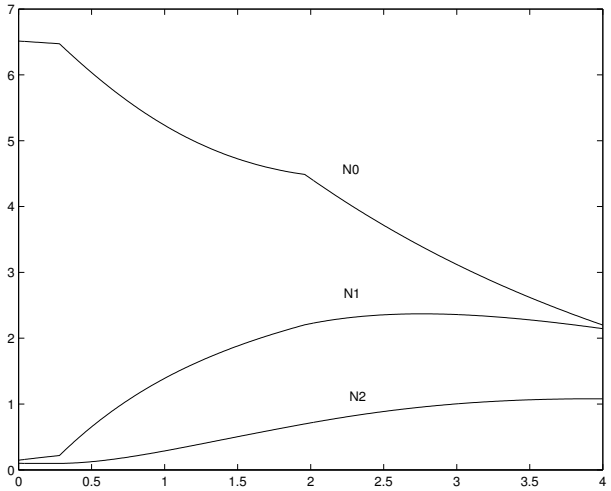

Fig. 7. States (Model C).

cycle and is used for the estimation of these parameters. Exit dynamics from G_1 and transit dynamics through S and G_2 and their subcompartments can be used to characterize very precisely both unperturbed and perturbed cell cycle parameters. A plethora of methods have been developed to analyze the stathmokinetic data. The application of these methods allow the quantification of the cell-cycle-phase action of many agents.

One of the interesting findings was the existence of *after effects* in the action of many cytotoxic agents (Kimmel and Traganos, 1986). The action of these drugs, especially while highly dosed, may extend beyond the span of a single cell cycle. For example, cells blocked in the S-phase of the cell cycle and then released from the block may proceed apparently normally towards mitosis, but then fail to divide, or divide, but not be able to complete the subsequent round of DNA replication. In some experiments it was possible to trace the fates of individual cells and conclude that their nuclear material divided, but the cytoplasmic contents failed to separate. As indicated, e.g., in (Panetta *et al.*, 2002a; 2002b), the after effects due to the accumulation of drugs (in this case methotrexate) result in great interindividual differences in the treatment effectiveness.

A consequence of after effects is that it may be difficult to infer the long-term effects of cytotoxic drugs based on short term experiments like the stathmokinetic experiment. One way of testing this assertion is to carry out both types of experiments, short term and long term, subjecting cells to the action of the same concentration of the same drug. We may then estimate the parameters of the cell cycle and of the drug action based on the short-term experiment, substitute them into a mathematical model and try to predict the results of the long-term experiment. Of course, modeling after effects leads to the growth in the dimension of the system of state equations and makes the explicit results of our models questionable. It seems, however, that it is still possible to place the models in the general model class P discussed in the paper.

The traditional application area of the ideas of cell synchronization, recruitment and rational scheduling of chemotherapy including multidrug protocols is in the treatment of leukemias. It is there where potentially the cell-cycle-phase dependent optimization is especially useful. Moreover, our results could also be applied (with minor modifications) to other types of cell cycle manipulations like the induction of apoptosis and differentiation (Konopleva *et al.*, 2002).

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