Optimal Control for a Class of Compartmental Models in Cancer Chemotherapy

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Abstract

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 objective 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 is 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 recruiting agent, respectively. In model (B) a blocking agent which slows down the growth of the cells during synthesis enabling in consequence synchronization of 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 conditions for optimality of bang-bang controls are given for the general class of models (P) and illustrated with numerical examples.

1 Introduction

Mathematical models for cancer chemotherapy have a long history (see, for instance, [14, 29, 34]). In the past years there has been renewed interest in these models [15, 26], partially due to better models, 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 Swierniak [21, 37] and has been analyzed in numerous papers since (e.g. [38, 39, 40, 25, 26]), both from numerical as well as theoretical perspectives. Here we give a review of some of these results, extend them onto a broader class of models and outline some still open questions.

The model is based on cell-cycle kinetics and treats the cell cycle as the object of control [36]. The cell cycle is modelled in the form of compartments which describe the 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 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.

The simplest mathematical models which describe optimal control of cancer chemotherapy treat the entire cell cycle as one compartment (e.g. [35]), 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 still are models which divide the cell cycle into two and three compartments, respectively [38]. 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 the other compartment while different three-compartment models arise by separating, respectively 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 [6] and Taxol [15] or 5-Fluorouracil [7] affecting mainly cells during their division. Killing agents also include S specific drugs like Cyclophosphamide [15] or Metatraxate [31] acting mainly in the DNA replication phase, Cytosine Arabinoside - Ara-C, rapidly killing cells in phase S through inhibition of DNA polymerase by competition with deoxycytosine triphosphate [9]. Among the blocking drugs we can mention 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 [2]. Another blocking agent is Hydroxyurea - HU [28], [11] which is found to synchronize cells by causing brief and invisible inhibition of DNA synthesis in the phase S and holding cells in G_1. The recruitment action was demonstrated [3] for Granulocyte Colony Stimulating Factors - G-CSF, Granulocyte Macrophage Colony Stimulating Factors - GM-CSF, Interleukin-3 - Il-3, specially when combined with 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 action of some drugs. For example, although mostly active in specific phases Cyclophosphamide and 5-Fluorouracil kill cells also in other phases of the proliferation cycle that enables to encounter them to cycle specific agents [6], [5]. On the other hand some antimitotic agents like curacin A [23] act by increasing the S phase transition (blocking) and decreasing the M phase transition.

Killing agents which we consider in our model are applied in the G_2/M phase which makes sense from a biological standpoint for a couple of reasons. First, in mitosis M the cell 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 daughter cells. While the killing agent is the only control considered in the two-compartment model (A) below, in model (B) in addition a blocking agent is 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 maximum killing potential (so-called synchronization [4]). This strategy may have the additional advantage of protecting the normal cells which would be less exposed to the second agent (e.g. due to less dispersion and faster transit through G_2/M) [10], [1]. 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 chemotherapy of some leukemias is constituted by the large residuum of dormant G_0 cells which are not sensitive to most cytotoxic agents [7], [17], [27]. Similar findings for breast and overian cancers were reported, e.g. in [15, 8]. As indicated by these authors the insensitivity of dormant cells to the majority of anticancer drugs and percentage of tumor mass resting is a fact which, if ignored, leads not only to clinical problems but also to some erronomous theoretical considerations. Experiments with Ara-C [9], indicated that while double injected during cell cycle or combined with Andriamycin or anthracyclines led to serious reduction of leukemic burden without an evident increase of 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 [41], [3] (substances playing a role in the regulation of normal 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 enables also analysis of the alteration of the transit time through G_0 phase due to the feedback mechanism that recruits the cells into the cycle when chemotherapy is applied. In a similar way we may model other types of manipulation of the cell cycle as for example the use of triterpenoids to inhibit proliferation and induce differentiation and apoptosis in leukemic cells [20].

In the 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, 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, respectively minimize the number of cancer cells at the end of the therapy session, while keeping the toxicity to the normal tissues acceptable. The latter aspect is modelled 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 arises 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, the specific forms of the data for the models (matrices, parameters etc.) then need to be taken into account.

Analytical approaches to these models are based on applications of the Pontryagin Maximum Principle [33] which results in both bang-bang and singular controls as candidates for optimality. While bang-bang controls correspond 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 [38, 12, 13]. In the papers [25, 26] 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 candidates. 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 the models (A)-(C), are maximizing rather than minimizing. In [25] 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 to determine whether bang-bang controls which satisfy the conditions of the Maximum Principle are locally optimal (Theorem 4.1) or not (Theorem 4.2). For the 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 4.1. 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

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

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

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

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 [38].

Model (A): In a 2-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

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

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

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

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

and

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

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) in addition the blocking agent $v = u_2$ is 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 $1 - v$ of its original flow to $(1 - v(t))a_2N_2(t)$, $0 \leq v(t) \leq v_{\max} < 1$. 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 3-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 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 $1 + w$, $0 \leq w \leq w_{\max}$. 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 $i = 0, 1, 2$ and the matrices for this 3-compartment model are given by

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

and

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

For all three models we take as objective

$$J = rN(T) + \int_0^T u(t)dt, \tag{8}$$

(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 3-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 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 3-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* [18]:

(+) The first orthant of the control system is positively invariant, that is 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 modelling 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 [18]) 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. have negative diagonal entries, but non-negative off-diagonal entries.

This condition is natural and will be satisfied for any compartmental model whose dynamics is 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 the models (A), (B) and (C) described above. More generally, if condition (+) were violated, this is a strong indication that the modelling is inconsistent.

Necessary conditions for optimality are given by the Pontryagin Maximum Principle [33]: 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 row-vector, $\lambda : [0, T] \to (\mathbb{R}^n)^*$, satisfying the adjoint equation

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

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 condition (M), then it follows from the adjoint equation (9) that for any admissible control the first orthant in 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 2.1 *If 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 optimal controls satisfy

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

Thus for models (A)-(C) we have

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

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

and

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

where $\Phi_1(t) = 1 + \lambda(t)B_1N(t)$, $\Phi_2(t) = \lambda(t)B_2N(t)$ and $\Phi_3(t) = \lambda(t)B_3N(t)$.

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 the models (A)-(C) using high-order necessary conditions for optimality. These calculations are model specific and we refer the reader to [25] and [26] 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 in time until the control variable explicitly appears in the derivative, say in $\Phi^{(r)}(t)$, and then solving the resulting equation $\Phi^{(r)}(t) \equiv 0$ for the control. For a single-input system which is linear in the control it is known [24] that r must be even, say $r = 2k$, and k is called the order of the singular arc on the interval I. It is a necessary condition for optimality of a singular arc of order k, the so-called generalized Legendre-Clebsch condition [24], that

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

Note that the term $\frac{\partial H}{\partial u}$ in (16) represents the switching function for the problem. This framework directly applies to the 2-compartment model (A) which has a scalar control. Elementary and direct calculations [25] show that in this case singular arcs are of order 1 and that

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

violating the Legendre-Clebsch condition. For the 3-compartment model (B) the generalized Legendre-Clebsch condition (16) still applies to the first control u if we freeze the second control v. Assuming 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 verify that

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

(See [26], but note that we replaced what was v in this paper with $1-v$. 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 easily be seen that u also must be singular on I. In this case it is a necessary condition for optimality, the so-called Goh condition [24], that on I we have

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

However, a direct calculation gives

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

violating the Goh-condition [26]. Note that these results strongly depend on the fact that states and also multipliers are positive.

We now show how the optimality of singular controls can be excluded for the 3-compartment model (C). Suppose 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

$$\dot{\Phi}_1(t) = \lambda(t)[A + wB_3, B_1]N(t) \tag{21}$$

$$\ddot{\Phi}_1(t) = \lambda(t)[A + uB_1 + wB_3, [A + wB_3, B_1]]N(t) \tag{22}$$

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

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

Direct calculations verify that this double bracket term satisfies the relation

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

Hence

$$\begin{aligned}\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} &= -4a_1a_2b_1\lambda(t)B_1N(t)\\ &= 4a_1a_2b_1 > 0\end{aligned} \tag{25}$$

violating the Legendre-Clebsch condition. Here, in the last step we use 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 singular controls u when w is constant. It might still be possible, however, that w is singular and not constant over any subinterval $J \subset I$. In this case w also must 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 necessary. Now we also have on I that

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

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

$$\dot{\lambda}_0(t) = a_0(\lambda_0(t) - \lambda_1(t))(1 + w(t)) \equiv 0 \tag{28}$$

and thus both λ_0 and λ_1 are constant. Since thus

$$0 \equiv \dot{\lambda}_1(t) = a_1(\lambda_1(t) - \lambda_2(t)), \tag{29}$$

it indeed follows that

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

But then the adjoint equation for λ_2 becomes

$$\begin{aligned} 0 \equiv \dot{\lambda}_2(t) &= a_2\left[\lambda_2(t) - 2(1 - u(t))(b_0\lambda_0(t) + b_1\lambda_1(t))\right] \\ &= a_2\bar{\lambda}\,(2u(t) - 1) \end{aligned} \tag{31}$$

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

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

and thus $N_2(t) \equiv \bar{N}_2 = const$. 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 $N_1(t) \equiv \bar{N}_1 = const$ as well. Thus

$$\begin{aligned} 0 \equiv \dot{N}_1(t) &= a_0N_0(t)(1 + w(t)) - a_1\bar{N}_1 + 2b_1a_2\bar{N}_2(1 - u(t)) \\ &= a_0N_0(t)(1 + w(t)) - (1 - b_1)a_2\bar{N}_2. \end{aligned} \tag{34}$$

But then

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

and thus also $N_0(t) \equiv \bar{N}_0 = const.$ In fact, if $u(t) \equiv \frac{1}{2}$, 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 adjoint equations. But this finally implies that

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

Thus, if at all admissible, this control w is constant and thus the optimality of the overall control pair (u, w) is excluded by the considerations above. In summary, neither of the controls u or w can be singular on any subinterval. Summarizing we have:

Theorem 3.1 *For models (A)-(C) optimal controls are not singular on any subinterval* $I \subset [0,T]$. $\square$

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 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, $k = 1, \ldots, m$, $0 < t_m < \cdots < t_1 < t_0 = T$ and N_* is the corresponding trajectory. Denote the corresponding adjoint variable by 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

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

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 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 positivity of the trajectories needs to be enforced once we integrate 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 equation are thus given by

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

and

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

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 corresponding multiplier. It can be shown that there exists a neighborhood W of p_* and continuously differentiable functions τ_k defined on W, $k = 1,\ldots,m$, 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 to use field-theoretic concepts to develop sufficient conditions for optimality. Essentially, if the flow of the system 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 [30]. This then implies optimality of the flow.

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, $i = 1,\ldots,m$. Denote the switching times of the controls by t_k, $k = 1,\ldots,m$, $0 < t_m < \cdots < t_1 < t_0 = T$ 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 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 $k = 1, \ldots, m$, define

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

$$\exp\left(\left(A + \sum_{j=1}^{m} u_j^k B_j\right)(t_{k-1} - t_k)\right), \tag{41}$$

$$G_k = -\frac{\theta_\iota}{\left|\dot{\Phi}_\iota^*(t_k)\right|}\left(\lambda_*(t_k)B_\iota + N_*^T(t_k)B_\iota^T S_k^+\right), \tag{42}$$

$$S_k^- = \left(B_\iota^T \lambda_*^T(t_k) G_k + S_k^+\right)\left(Id + \frac{B_\iota N_*(t_k) G_k}{1 - G_k B_\iota N_*(t_k)}\right) \tag{43}$$

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

$$\left|\dot{\Phi}_\iota^*(t_k)\right| + \theta_\iota\left(\lambda_*(t_k)B_\iota + N_*^T(t_k)B_\iota^T S_k^+\right) B_\iota N_*(t_k) > 0, \tag{44}$$

then all 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

$$\sigma : [0, T] \times W \to R, \ (t, p) \mapsto (t, x(t, p)). \tag{45}$$

A special version of this algorithm has been proven for model (A) in [25] and for model (B) in [26]. The algorithm here applies to the general model (P) and differs from those given in [25] and [26] in the extra term $\theta_\iota \lambda_*(t_k) B_\iota^2 N_*(t_k)$ in (44). The reason is that for the general dynamics some simplifying properties of these models no longer apply (see Corollary 4.1 below). The proofs of Theorem 4.1 and Theorem 4.2 below are lengthy and are omitted since they follow the same pattern as for the result proven in [26], but with the required technical modifications to allow for a general n-dimensional dynamics.

Theorem 4.2 *With the notation of Theorem 4.1 assume that the transversality condition*

$$\left|\dot{\Phi}_\iota^*(t_k)\right| + \theta_\iota\left(\lambda_*(t_k)B_\iota + N_*^T(t_k)B_\iota^T S_k^+\right) B_\iota N_*(t_k) > 0 \tag{46}$$

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

$$\left|\dot{\Phi}_\iota^*(t_h)\right| + \theta_\iota\left(\lambda_*(t_h)B_\iota + N_*^T(t_h)B_\iota^T S_h^+\right) B_\iota N_*(t_h) < 0. \tag{47}$$

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 $t \leq t_h$.

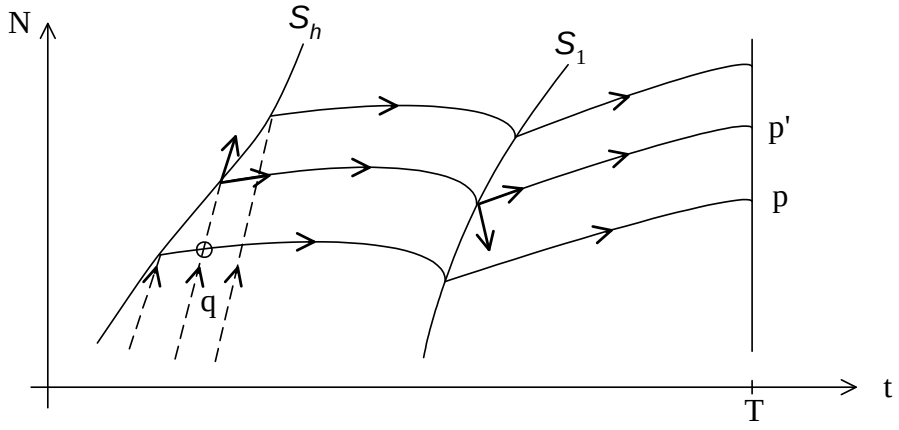

Figure 1: Optimal and non-optimal switchings

Figure 1 visualizes the geometric meaning of the transversality conditions (46) and (47). If the combined flow crosses the switching surfaces transversally like for the switching surface $\mathcal{S}_1$ (condition (46)) 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 $\mathcal{S}_h$ (condition (47) 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 $\mathcal{S}_h$. Of these the one which ends at the terminal point p and does not encounter $\mathcal{S}_h$ satisfies the sufficient conditions for optimality given in Theorem 4.1 and gives a strong local minimum. The trajectory which reflects off $\mathcal{S}_h$ and ends in p' is not optimal by Theorem 4.2. 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 local optimality of the flow ceases there.

Corollary 4.1 *For the compartmental problems (A)-(C) described above, the expressions in (44), respectively (46), and (47) can be simplified to*

$$\left|\dot{\Phi}^*_\iota(t_k)\right| + \theta_\iota N_*^T(t_k) B_\iota^T S_k^+ B_\iota N_*(t_k) > 0 \tag{48}$$

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

$$\left|\dot{\Phi}^*_\iota(t_h)\right| + \theta_\iota N^T_*(t_h) B^T_\iota S^+_h B_\iota N_*(t_h) < 0. \tag{49}$$

Proof. This follows from special properties of the matrices B_ι which make each of the terms $\lambda_*(t_k) B^2_\iota N_*(t_k)$ vanish. For the matrices B_1 in all the model this is trivial since $B_1^2 = 0$. For B_2 and B_3 this holds since we have the relations $B_2^2 = a_2 B_2$ and $B_3^2 = -a_0 B_3$. This implies

$$\lambda_*(t_k) B_2^2 N_*(t_k) = a_2 \lambda_*(t_k) B_2 N_*(t_k) = -a_2 s_2 \tag{50}$$

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

$$\lambda_*(t_k) B_3^2 N_*(t_k) = -a_0 \lambda_*(t_k) B_3 N_*(t_k) = a_0 s_3 \tag{51}$$

which vanishes since $s_3 = 0$. Furthermore, in these cases we have therefore $S_1^+ = 0$ and thus condition (48) 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) have been given in [25]. 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 have been 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. Graphs of the corresponding controls and states are given in Figures 2-4.

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

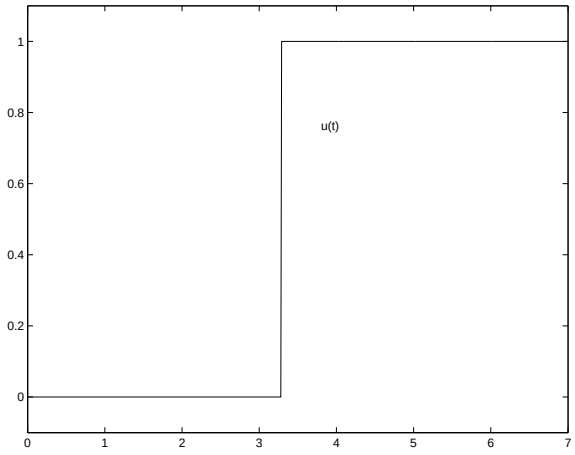

Figure 2: Killing agent

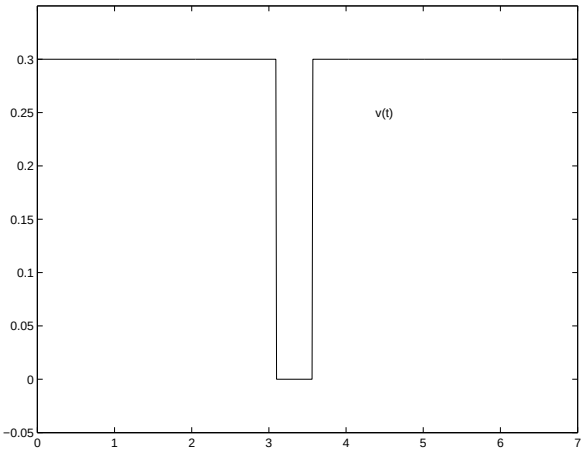

Figure 3: Blocking agent

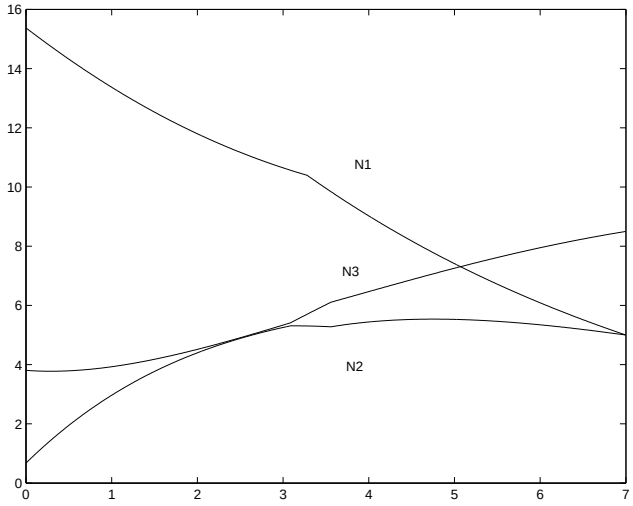

Figure 4: States

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 are two switchings in the controls, one each for the killing and recruiting agent. The results are summarized in Table 2 below. Since all transversality conditions are positive, these controls are also locally optimal. Graphs of the corresponding controls and states are given in Figures 5-7.

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

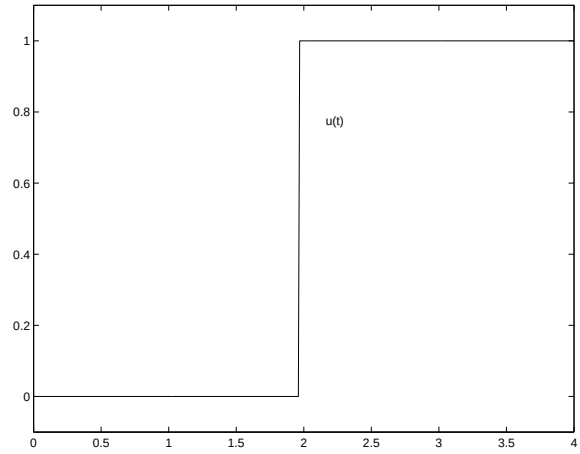

Figure 5: Killing agent

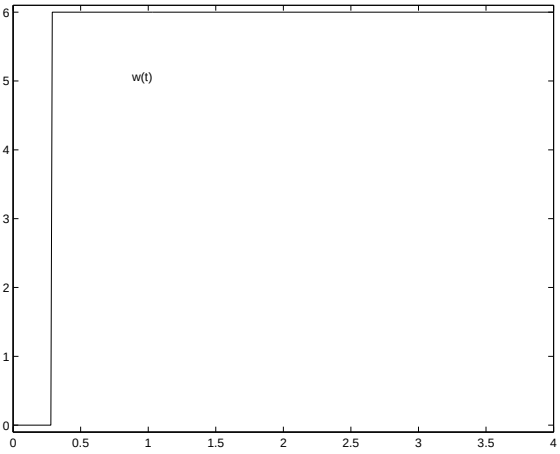

Figure 6: Recruiting agent

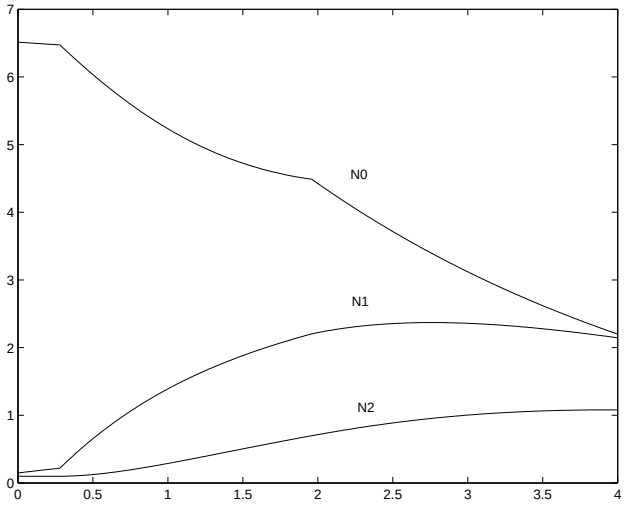

Figure 7: States

6 Discussion

In this paper we discussed the cell-cycle-phase dependence of cytotoxic drug action in the context of optimization of cancer chemotherapy. By many authors, besides the emergence of drug resistance (see, e.g. [16] [22]), phase sensitivity and cycle specificity are viewed as one of the major obstacles against successful chemotherapy [15], [7].

The simplest cell-cycle-phase dependent models of chemotherapy can be classified based on the number of compartments and types of drug action modelled. 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 have developed efficient analytical and numerical methods which enable to overcome the difficulties. In simpler cases, it is possible to eliminate singular protocols as non-optimal and give sufficient conditions for optimality of bang-bang trajectories. Moreover, we have formulated and solved a quite general multicompartment model of chemotherapy which enables 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, particularly concerning precise estimation of drug action in culture and estimation of cell cycle parameters of tumor cells *in vivo*. The stathmokinetic or "metaphase arrest" technique consists of 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 different cell cycle phase. The pattern of cell accumulation in mitosis M depends on the kinetic parameters of the cell cycle and is used for 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 true arsenal of methods have been developed to analyze the stathmokinetic data. Application of these methods allow 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 [19]. The action of these drugs especially while high 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 for example in [31], [32], the after effects due to

accumulation of drugs (in this case methatrexate) result in great interindividual differences of the effectiveness of treatment.

The consequence of the 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 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 modelling the after effects leads to the growth of the dimension of the system of state equations and makes the explicit results of our models questionable. It seems, however, that it still is possible to place the models in the general model class (P) discussed in the paper.

The traditional area of application of 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 small modification) to other types of cell cycle manipulations like induction of apoptosis and differentiation [20].

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