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THE INFLUENCE OF PK/PD ON THE STRUCTURE OF OPTIMAL CONTROLS IN CANCER CHEMOTHERAPY MODELS

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Abstract. Mathematical models for cancer chemotherapy as optimal control problems are considered. Results on scheduling optimal therapies when the controls represent the effectiveness of chemotherapeutic agents, or, equivalently, when the simplifying assumption is made that drugs act instantaneously, are compared with more realistic models that include pharmacokinetic (PK) equations modelling the drug's plasma concentration and various pharmacodynamic (PD) models for the effect the concentrations have on cells.

1. **Introduction.** Mathematical modelling of cancer chemotherapy has more than four decades of history (e.g., [2, 5, 17, 18, 22, 23]) and has contributed to the development of several qualitative ideas for chemotherapy scheduling. But the more difficult part of this research lies in generating quantitative practical results. The reasons for this lie in both biomedicine and mathematics. On the biological side, important cell processes still are not fully understood, since the complexity of the underlying biological processes is difficult to capture. Thus our understanding of the dynamics is incomplete, especially in multidrug treatments when synergistic or antagonistic relations may not be clear. Another problem is that crucial parameters in the modeling may not be known or may simply vary too much from case to case so that data are not readily transferable. On the mathematical side, the only feasible approach for dealing with realistic (and thus necessarily high-dimensional, complicated, and intricate) models is through numerical simulation studies relying on computational power (as for the model underlying [21]). But if there is high uncertainty or a large range of relevant parameter values from patient to patient, then in chemotherapy simulations inherently are of limited quantitative practical value as well. As Goldie has observed, "The best average treatment may be the poorest option for a particular patient" [7]. Theoretical analysis, on the other hand, is limited to small and hence overly simplified models whose results are not applicable quantitatively. Nevertheless, their analysis can further our understanding of some simplified aspects of the overall system, a necessary step toward the goal

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of analyzing more medically relevant models. For example, these investigations can point out how sensitive some protocols are with respect to specific parameters and thus indicate the relevant and less relevant medical parameters in quantitative approaches.

Mathematically, cancer chemotherapy can be viewed as a control system with the state of the system, N, given by the numbers of cells of various type in specific compartments. The number of compartments determines the dimension n of the system. For example, the compartments can correspond to the phases of the cell cycle or some clusters of these, and the components of N give the average number of cancer cells in these compartments as in the models in [23, 25]. If the emphasis is on healthy cells rather than on cancer cells, the state might consist of the number of bone marrow cells as in [6]. The control, u, typically represents the drug dosage or, in simplified models, the effect the drugs have on normal and cancer cells. Since chemotherapeutic agents affect normal cells as well as cancer cells, the objective becomes to minimize the number of cancer cells over a fixed therapy interval while keeping the toxicity to the normal tissue at an acceptable level. In such a formulation, side effects typically are modeled implicitly only by minimizing the total amount of drugs given. If the side effects are more in the focus of the model, the objective may be to maximize the bone marrow cells while trying to administer as much drugs as possible. Either way, these approaches naturally can be formulated as optimal control problems.

In view of the complexity of the real medical problem, it makes sense to start with the analysis of simplified models and then add increasingly complex and medically more realistic features to the model. In this sense, a commonly made simplification is to identify the drug dosage with its concentration or even with its effects. In reality, these clearly are different phenomena and their relationships are studied under the names of *pharmacokinetics* (PK) and *pharmacodynamics* (PD). In this paper, we consider a general mathematical model for cancer chemotherapy described by a bilinear system, but add pharmacokinetic equations that model the drug's concentration in the body plasma and also allow for pharmacodynamic effects in modeling the effectiveness of the drugs. Thus, in principle, the dynamics of drug delivery and effectiveness can formally be incorporated in the models. But the models used here are still small and clearly are not comprehensive. For example, the important aspect of drug resistance is not included.

In section 2, a general mathematical model with the dynamics given by a bilinear system is formulated that is then augmented by models for PK and PD in section 3. An analysis of optimal controls using the Maximum principle is given in section 4, and the optimality of singular controls is investigated. These results are illustrated for two simple two-dimensional models in section 5. For these examples, it is shown that the optimality status of singular controls does not change under the addition of linear PK and PD models. For both models, which have been initially analyzed in [14] and [16], singular controls are not optimal when linear PK and PD models are added. However, with nonlinearities in the PK/PD equations, singular controls become viable candidates for optimality.

2. A general compartmental model for cancer chemotherapy as optimal control problem.

2.1. **Dynamics.** Many models for cancer chemotherapy considered in the literature have an underlying dynamics described by a bilinear system of the form

$$\Sigma_0 : \qquad \dot{N} = (A + \sum_{i=1}^{m} u_i B_i)N, \quad N(0) = N_0, \tag{1}$$

where A and B_i are $n \times n$ matrices, $B_i \neq 0$, and n is the number of compartments. (For example, see [6, 12, 13, 23].) The components of the vector N denote the number of cancer (or other) cells in the compartments, and the controls u_i often represent the drug dosages of various drugs and take values in compact intervals $[\alpha_i, \beta_i] \subset [0, \infty)$ with $\alpha_i = 0$ in these cases. Initially all components of N_0 are positive. An obvious state space constraint for these models is that the number of cells remains positive. However, with correct modeling this constraint should not need to be imposed.[1] Mathematically, a simple sufficient condition for this to hold, which often can easily be verified, is that all the matrices $A + \sum_{i=1}^{m} u_i B_i$, $u_i \in [\alpha_i, \beta_i]$, $i = 1, \ldots, m$, have nonnegative off-diagonal entries.

PROPOSITION 2.1. *Suppose all the matrices* $A + \sum_{i=1}^{m} u_i B_i$, $u \in U = [\alpha_1, \beta_1] \times \ldots \times [\alpha_m, \beta_m]$, *have nonnegative off-diagonal entries. Then all states* N_i, $i = 1, \ldots, n$, *are positive over the interval* $[0, T]$.

Proof. For any control u defined on $[0, \infty)$, (1) is a linear system with bounded coefficients, and thus solutions exist over $[0, \infty)$. Define τ as the supremum over all times η such that all components $N_i(t)$ are positive on $[0, \eta]$:

$$\tau = \sup\{\eta \geq 0 : N_i(t) > 0 \text{ for } 0 \leq t \leq \eta \text{ and all } i\}. \tag{2}$$

Since all components of N_0 are positive, $\tau > 0$. If $\tau < \infty$, then let ρ denote one of the components i of N for which $N_i(\tau) = 0$. Then ρ satisfies a first-order ordinary differential equation (ODE) of the form $\dot{\rho} = \alpha\rho + \beta$ with $\rho(0) > 0$ and $\beta(t) \geq 0$ for $0 \leq t \leq \tau$. Hence,

$$\rho(\tau) = \exp\left(\int_0^\tau \alpha(s)ds\right)\left[\rho(0) + \int_0^\tau \exp\left(-\int_0^s \alpha(r)dr\right)\beta(s)ds\right] > 0.$$

Contradiction. □

In the cell-cycle-specific compartmental models for cancer chemotherapy developed in [23], this condition is always satisfied since there are outflows only from the ith compartment but no direct return flows into the ith compartment. Thus, 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 $t > 0$. Therefore the physical state-space constraints $N_i(t) \geq 0$ for $i = 1, \ldots, n$ of our model will never be active and need not be stated explicitly. We therefore henceforth assume that the system Σ_0 is positive invariant in this sense.

2.2. **Objective.** The aim of any treatment is to kill the cancer or at a minimum to curtail its further spread while keeping the side effects of treatment on the normal tissue acceptable. Mathematically there are many (nonequivalent) ways of modeling this. In this paper, we consider a linear (L_1-type) objective of the form

$$J = rN(T) + \int_0^T qN(t) + \ell u(t)dt, \tag{3}$$

[1] If the state variables can turn negative, the modeling is faulty.

where $r = (r_1, \ldots, r_n)$ and $q = (q_1, \ldots, q_n)$ are row vectors of positive coefficients and $\ell = (\ell_1, \ldots, \ell_m)$ is a nonzero row vector of nonnegative coefficients, $\ell_i \geq 0$. While some of the components of ℓ may be zero (for example, this would be natural for the weight ℓ_i of a drug that has minimal or no significant side effects, such as recruiting agents), the weights in ℓ corresponding to killing agents must be positive. Depending on the specific model and the actual meaning of the vector N, we may want to minimize J (in the case of cancer cells) or maximize J (in the case of bone-marrow cells). For example, for a model where N represents the number of cancer cells, the terminal term $rN(T)$ represents a weighted average of the total number of cancer cells at the end of an assumed fixed therapy interval $[0, T]$, and the term $qN(t)$ in the Lagrangian measures the number of cancer cells over the therapy period and is added to prevent the number of cancer cells from rising to unacceptably high levels at intermediate times. Side effects of treatment (e.g., toxicity to healthy tissue) are modeled only indirectly here through the last term, which is taken as linear in the control generating an L_1-type objective. Clearly, other choices for modeling side effects are also possible. A linear integral term has the advantage that it gives a measure proportional to the overall dosage (this would be distorted by a quadratic or other nonlinear term), and since side effects can be manifold, and are not always easily quantifiable, this appears reasonable. At the moment, we do not yet take into account pharmacokinetic equations or pharmacodynamics. Thus the optimal control problem is to

($P_{\min\,/\,\max}$)**:** choose a Lebesgue measurable function $u : [0, T] \to U$ that minimizes (or maximizes) the objective (3) subject to dynamics (1).

While the choice of Lebesgue measurable functions as controls may appear unrealistic in their generality, this choice guarantees some basic mathematical properties, such as the existence of an optimal control.[2]

2.3. **Example 1: Phase-specific models for cancer cells.** 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 may either reenter phase G_1 or simply lie dormant in a separate phase G_0 for some time until reentering G_1, thus starting the entire process all over again. These distinctions are important, because most drugs are active in a specific phase of the cell cycle. For example, so-called spindle poisons destroy a mitotic spindle and are active in mitosis. In the modeling, G_2 and M often are combined into one compartment, since the boundaries between these phases are difficult to establish and many killing agents, such as paclitaxel (Taxol), mainly affect cells during their division and thus are G_2/M specific. The reason for this is that the cell walls become very thin and porous in mitosis M, and so the cell is more vulnerable to an attack during this phase. Drug treatment influences the cell cycle in many other ways besides cell-killing; blocking and recruitment agents also play important roles. Blocking agents slow the transitions of the cells through the cell cycle and thus impede the tumor's growth, while recruiting agents make cancer cells leave the dormant stage G_0, where they typically are not susceptible to any chemotherapy.

[2]No such statement can be made a priori, for example, with controls given by piecewise continuous functions, although often optimal controls do in fact belong to this class.

Taking into account phase specificity naturally leads to compartmental models for cancer chemotherapy. One class of probabilistic models of this type was developed in [23, 25]. Depending on the number and types of therapeutic agents considered, the phases of the cell cycle are clustered into compartments, with the state representing the average number of cells in each compartment and the control representing the dosages or effects of the various drugs. The dynamics describes the in- and outflows between the compartments in the presence of the control, that is, under therapy. The transit times of cells through phases of the cell cycle vary, particularly in malignant cells. If an exponential distribution is used to model the transit times, then for the averages, a bilinear system of the type Σ_0 arises, with the parameters of the matrices related to the inverse of the expected transit times [23].

The simplest model arises when a single G_2/M-specific killing agent is considered. Then it is natural to combine the dormant phase G_0, the first growth phase G_1 and the synthesis phase S into the first compartment, while the second consists of the second growth phase G_2 and mitosis M. If $N_i(t)$, $i = 1, 2$, denote the number of cancer cells in the ith compartment at time t, then a single-input two-dimensional system of the form

$$\dot{N}(t) = (A + uB)N(t), \quad N(0) = N_0, \tag{4}$$

arises with

$$A = \begin{pmatrix} -a_1 & 2a_2 \\ a_1 & -a_2 \end{pmatrix}, \; B = \begin{pmatrix} 0 & -2a_2 \\ 0 & 0 \end{pmatrix} \tag{5}$$

and control constraint $0 \le u \le 1$. The coefficients a_i represent the inverse mean transit times of the cells through the ith compartment [23].

If additional drugs are considered, the numbers of controls and compartments increases as in examples including blocking agents [12], recruiting agents, or both [13]. For example, the insensitivity of dormant cells to anticancer drugs is a major problem for leukemia. A mathematical model in which active recruitment of the cells in the dormant stage G_0 through cytokines [26] is modeled distinguishes the dormant phase G_0 from the first growth phase G_1 and combines the remaining phases S, G_2, and M. This leads to a three-dimensional system of the form

$$\dot{N}(t) = (A + u_1B_1 + u_2B_2)N(t), \quad N(0) = N_0, \tag{6}$$

where

$$A = \begin{pmatrix} -a_0 & 0 & 2b_0a_2 \\ a_0 & -a_1 & 2b_1a_2 \\ 0 & a_1 & -a_2 \end{pmatrix} \tag{7}$$

and

$$B_1 = \begin{pmatrix} 0 & 0 & -2b_0a_2 \\ 0 & 0 & -2b_1a_2 \\ 0 & 0 & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} -a_0 & 0 & 0 \\ a_0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}. \tag{8}$$

The control u_1, $0 \le u_1 \le 1$, represents the killing agent, and a recruiting agent u_2 is applied to reduce the average sejour time in the quiescent phase. As a result, the average transit time through the compartment G_0 is reduced, increasing the outflow by a factor $1 + u_2$, $0 \le u_2 \le w_{\max}$. The control $u_2 = 0$ corresponds to no drug being applied, while $u_2 = w_{\max}$ occurs with a full dose. It is assumed that newly born cells either enter G_1 and immediately start the cell division process or that they enter the dormant stage G_0 with probabilities b_0 and b_1, $b_0 + b_1 = 1$.

2.4. **Example 2: Models for bone-marrow cells.** A different type of model that goes back to Eisen [5] and fits the same mathematical pattern was considered by Panetta [19]. For many drugs, the limiting tissue is hemopoietic (i.e., related to blood-cell formulation). Mature cells of these renewing tissues are formed through differentiation from the self-renewing stem-cell population in the bone marrow, and it is generally accepted that "ideal cancer treatment would aim to bring about minimal normal stem cell kill" [9]. Toxicity to the bone marrow thus is one of the main limiting factors in chemotherapy and should be taken into account. This model focuses on this aspect of treatment.

The model distinguishes proliferating cells P from quiescent (or dormant) cells Q in the bone marrow. The growth rate of the proliferating cells is denoted by γ, and the transition rates from proliferating to quiescent cells and vice versa are denoted by α and β, respectively. The rate at which bone marrow enters the blood stream is denoted by ρ, and the natural death rate of the proliferating cells is called δ. It is assumed that all these parameters governing the cell cycle remain constant over the time horizon considered and that chemotherapy kills proliferating cells but that quiescent cells are not affected by the agent. The overall dynamics of the controlled system is described by

$$\dot{P} = (\gamma - \delta - \alpha - u)P + \beta Q, \qquad P(0) = P_0, \tag{9}$$

$$\dot{Q} = \alpha P - (\rho + \beta)Q, \qquad Q(0) = Q_0, \tag{10}$$

with all initial conditions positive. If we set $N = (P, Q)$, the general form of the dynamics is given by the bilinear system

$$\dot{N} = (A + uB)N, \quad N(0) = N_0, \tag{11}$$

with

$$A = \begin{pmatrix} \gamma - \delta - \alpha & \beta \\ \alpha & -(\rho + \beta) \end{pmatrix} \qquad \text{and} \qquad B = \begin{pmatrix} -1 & 0 \\ 0 & 0 \end{pmatrix}. \tag{12}$$

2.5. **Brief summary of existing results.** In earlier research, we have analyzed both specific models from the class Σ_0 [11, 12, 13] as well as the structure of its solutions in the general case [24]. The necessary conditions for optimality for these models given by the Pontryagin maximum principle [20] single out bang-bang and singular controls [1, 10] as the prime candidates, although they do not fully restrict the candidates for optimal controls in general. Bang-bang controls correspond to protocols in which a full dose is administered separated by rest periods when no dose is given. Singular controls correspond to specific types of protocols with time-varying partial doses. However, with the aid of high-order necessary conditions for optimality, such as the generalized Legendre-Clebsch condition or the Goh condition [10], it has been shown for each of the specific models considered that singular controls are not optimal. In fact, for all models considered falling into the type of Example 1, singular controls are locally maximizing rather than minimizing [11, 12], and they also are not optimal for the bone-marrow model of Example 2. For all these models, easily verifiable sufficient conditions for local optimality of bang-bang trajectories [11, 24] have been developed using the method of characteristics. These results agree with medical practice of giving full-dose chemotherapy sessions with complete rest periods in between. Giving continuously varying partial doses as they would occur for singular arcs is in fact not optimal for problem $(P_{\min\,/\,\max})$.

3. **Models including pharmacokinetics and pharmacodynamics (PK/PD).** In these earlier models, the drug's dosage is identified with its concentration and effects. Here we investigate whether and to what extent the qualitative results about optimal controls will change if more generally one augments model (1) with PK equations that model the drug's concentration in the body and also adds functions $e = s(c)$ as a model for PD. These are important aspects and make the models more medically relevant and realistic.

3.1. **Pharmacokinetics.** In (1), as in most other models, the variable u actually represents the effects of the drugs. Mathematically equivalent, the relations between the drug dosage and the effects of the drugs are considered instantaneous. We augment the class of compartmental models for cancer chemotherapy defined by (1) with PK equations that model the time evolution of the drug's concentration. We first consider a single chemotherapeutic agent. Simple models considered in the literature use a first-order linear system to represent the dynamics for the drug concentration c in the plasma. The model itself is one of exponential growth and decay as it is commonly used as the model for continuous infusions. Here, we more generally consider a bilinear system of the form

$$\dot{c} = -(f + ug)c + hu, \qquad c(0) = 0, \tag{13}$$

where f and h are positive constants, but g is arbitrary. This model introduces some mild nonlinearities and allows for the feature that concentrations build up to their maximum level at a different rate from that at which the drug is cleared by the system if no additional drugs are given. This makes sense because these are physiologically different procedures. For example, if $c(\tau) = \bar{c}$ and a constant control $u(t) \equiv \bar{u}$ is used for $t > \tau$, then

$$c(t) = \exp(-(f + \bar{u}g)(t - \tau))\bar{c} + \frac{h\bar{u}}{f + \bar{u}g}\left(1 - \exp(-(f + \bar{u}g)(t - \tau)\right).$$

For a linear system ($g = 0$) the concentrations therefore build up to their maximal value exponentially in the same way that they decay when no drug is given, namely, at rate f. For the bilinear model in the absence of additional drugs given, the concentration still decays exponentially at rate f, but it is possible to differentiate the speed of the build up to $f + \bar{u}g$. Thus $g > 0$ implies a faster buildup of the concentration than the eventual clearance of the drug. Figure 1 illustrates the different behaviors for a system of the form $\dot{c} = -(1+ug)c+hu$ for $g = 0, 1, 2, 3$ when an initial dose $u \equiv 1$ is given on the interval $[0, 2]$. The normalization $h = 1 + g$ has been made to set the maximal achievable concentration to $c = 1$ for all cases. The linear system $g = 0$ corresponds to the lower solid line for which the concentration grows to less than 90%, while the curves for $g = 1$ (dash-dot), $g = 2$ (dash), and $g = 3$ (upper solid curve) show an acceleration in the buildup of the concentration. After the drug has been stopped, the decay follows the same exponential law in all the cases, and the curves for positive g are very close to each other. We only note that the dynamic response can also be tailored to bolus injections by properly choosing the parameters simply with the understanding that the time interval of application is very small.

The bilinear model (13) represents a first attempt at introducing nonlinearities into the PK model and could be replaced with more complicated nonlinear structures. But then our analysis in section 4 below would need to be adjusted and

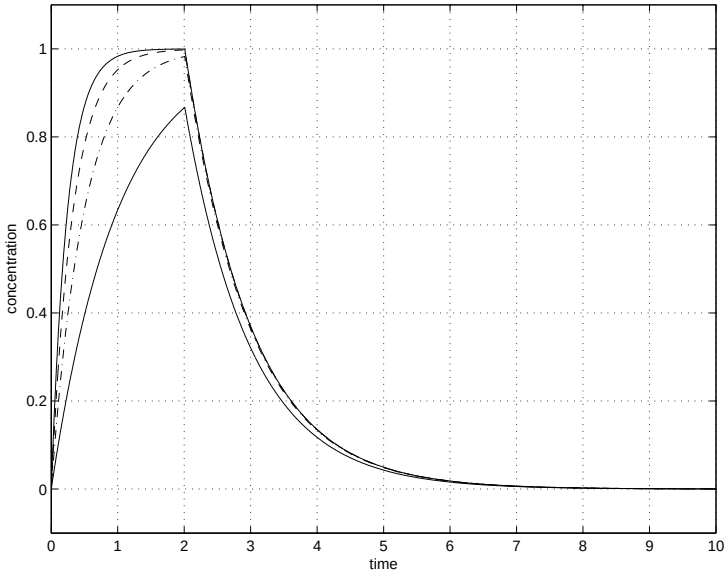

Figure 1. Bilinear model for PK.

carried out anew. In this paper, our interest is to explore the effect of nonlinearities on the structure of optimal solutions, and for this the model (13) is a good starting point.

For multidrug treatments it is still a reasonable first-order approximation to assume that the concentrations of the different drugs build up independently. Thus if we add an equation of the type (13) for each of the drugs and replace the drug dosage in the dynamics by its concentration, then the combined dynamics becomes

$$\dot{N} = (A + \sum_{i=1}^{m} c_i B_i)N, \qquad N(0) = N_0, \tag{14}$$

$$\dot{c}_i = -(f_i + u_i g_i)c_i + h_i u_i, \qquad c_i(0) = 0; \tag{15}$$

the objective remains unchanged.

3.2. **Pharmacodynamics.** However, (14) does not properly account for the effect e the drug concentration c has on the cancer cells. For instance, in the models of Example 1, it is assumed that the effect e of the drug is proportional to the number of ineffective cell divisions in the G_2/M phase; that is, $e = sc$ and s is called the effectiveness of the drug. Thus, for the two-compartment model, while all cells a_2N_2 leave the compartment G_2/M, only a fraction $(1 - e)a_2N_2$ of cells reenters phase G_1/S and undergoes cell division. The same model is used for the bone-marrow model of Example 2 [6]. This is the most elementary way of modeling pharmacodynamics, but it is only reasonable over a range of concentration and often is not a valid model for low or high concentrations. More generally, the effect of a single chemotherapeutic agent can be modeled by a function s defined on the interval $[0, \infty)$ with values in some interval $[0, \bar{s}]$. Depending on the choice of this function, qualitatively different models arise. Commonly used forms are a Michaelis-Menton or $E_{\max}$ type model [3] of the form

$$s(c) = \frac{E_{\max} c}{EC_{50} + c}, \tag{16}$$

which more accurately describes the effectiveness for high concentrations and sigmoidal functions [8] try to capture the behavior at both lower and higher concentrations. Examples of these are

$$s(c) = E_{\min} + \frac{E_{\max} - E_{\min}}{1 + 10^{n(\log EC_{50} - c)}} \tag{17}$$

or its approximation

$$s(c) = \frac{E_{\max} c^n}{EC_{50}^n + c^n}, \tag{18}$$

where n is a positive integer greater than 1. In these equations, $E_{\max}$ and $E_{\min}$ denote the maximum and minimum effects, respectively, and EC_{50} denotes the concentration at half the maximum effect; these are commonly used parameters in pharmacology. The $E_{\max}$ model is reasonable for fast-acting drugs, which then saturate at high concentrations while the sigmoidal models more accurately approximate the effectiveness at both lower and higher concentrations.

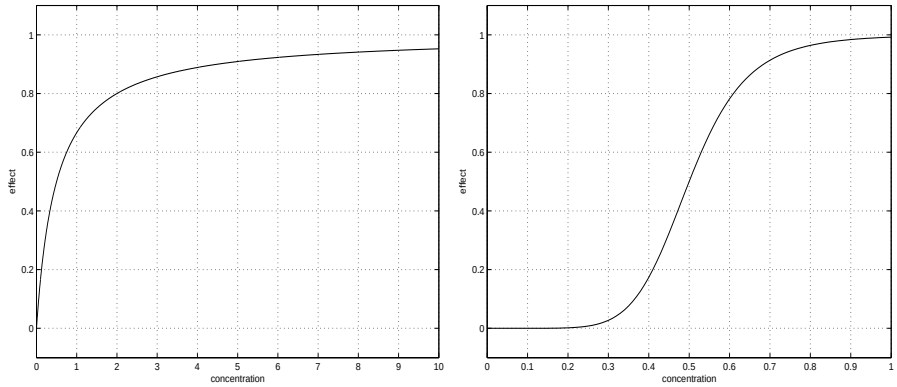

Figure 2. (a) $E_{\max}$ model; (b) sigmoidal model.

In our analysis below we only assume that the functions s_i satisfy $s_i(0) = 0$, are strictly increasing and twice continuously differentiable with values in intervals $[0, \bar{s}_i]$, $0 < \bar{s}_i < \infty$, possibly only reaching level $\bar{s}_i$ asymptotically for full dose. For a linear function or other unbounded models, this can be guaranteed by appropriately choosing the model parameters in (13).

In a multidrug treatment, however, these formulations are only applicable if the drugs act in different ways. Clearly, if there are two or more killing drugs that essentially act in the same phase of the cell cycle, their combined effectiveness depends on the concentrations of all of them and all their possible synergistic properties. To the best of our knowledge, these types of interactions are not well understood even for the most commonly used drugs, and therefore usually similarly acting drugs are bundled into one control in mathematical models. In the model below this is assumed, or equivalently, the controls correspond to qualitatively different drugs (e.g., killing agents versus recruiting agents) that act in different compartments in the model. Then we can formulate the overall dynamics as

$$\dot{N} = (A + \sum_{i=1}^{m} s_i(c_i) B_i) N, \qquad N(0) = N_0, \tag{19}$$

$$\dot{c}_i = -(f_i + u_i g_i) c_i + h_i u_i, \qquad c_i(0) = 0. \tag{20}$$

Since side effects of drugs are manifold and not necessarily restricted to the killing agents, we retain the drug dosage u as a measure in the integral of the objective. Thus, overall the problem now becomes:

($Q_{\min\,/\,\max}$)**:** choose a Lebesgue measurable function $u : [0,T] \to U$ that minimizes (or maximizes) objective (3) subject to dynamics (19) and (20).

4. **Analysis of the model with PK/PD equations.**

4.1. **Necessary conditions for optimality.** First-order necessary conditions for optimality are given by the Pontryagin maximum principle [20, 1]. It is easily seen that extremals are normal and therefore these conditions reduce to the following statement: If u_* is an optimal control with corresponding trajectory (N_*, c_*), then there exist absolutely continuous functions λ and μ, which we write as row vectors, $\lambda : [0,T] \to (\mathbb{R}^n)^*$, $\mu : [0,T] \to (\mathbb{R}^m)^*$, satisfying the adjoint equations with transversality condition,

$$\dot{\lambda} = -\lambda(A + \sum_{i=1}^{m} s_i(c_i)B_i) - q, \qquad \lambda(T) = r, \tag{21}$$

$$\dot{\mu}_i = \mu_i(f_i + u_i g_i) - s_i'(c_i)\lambda B_i N, \qquad \mu_i(T) = 0, \tag{22}$$

such the optimal control u_* minimizes (or maximizes) the Hamiltonian H,

$$H = qN + \sum_{i=1}^{m} \ell_i u_i + \lambda(A + \sum_{i=1}^{m} s_i(c_i)B_i)N + \sum_{i=1}^{m} \mu_i \left((h_i - g_i c_i)u_i - f_i c_i\right), \tag{23}$$

over the control set $U = [\alpha_1, \beta_1] \times \ldots \times [\alpha_m, \beta_m]$ along $(\lambda(t), \mu(t), N_*(t), c_*(t))$. For the sake of definiteness, we henceforth consider the minimization problem.

We call a pair $((N,c),u)$ consisting of an admissible control u with corresponding trajectory (N,c) for which there exist multipliers (λ,μ) such that the conditions of the maximum principle are satisfied an extremal (pair), and the triple $((N,c),u,(\lambda,\mu))$ is an extremal lift (to the cotangent bundle).

PROPOSITION 4.1. *Suppose all the matrices* $A + \sum_{i=1}^{m} s_i B_i$, $s \in \bar{S} = [0, \bar{s}_1] \times \ldots \times [0, \bar{s}_m]$, *have nonnegative off-diagonal entries. Then all states* N_i *and costates* λ_i, $i = 1, \ldots, n$, *are positive over the interval* $[0,T]$.

Proof. For any admissible control u_i the function s_i takes values in the interval $[0, \bar{s}_i]$, and thus it follows from Proposition 2.1 that all components of N remain positive. Similarly, as the solution to a linear ODE, the adjoint variable exists over the full interval. Let σ denote the infimum over all times η such that all components λ_i are positive on $[\eta, T]$:

$$\sigma = \inf\{\eta \leq T : \lambda_i(t) > 0 \text{ for } \eta \leq t \leq T \text{ for all } i\}.$$

Since the components of r are positive, we have $\sigma < T$. If $\sigma > -\infty$, let ρ denote one of the components i of λ for which $\lambda_i(\sigma) = 0$. Again ρ satisfies a first-order ODE of the form $\dot{\rho} = \alpha\rho + \beta$ with $\rho(T) > 0$, but now $\beta(t) \leq 0$ for $\tau \leq t \leq T$. Hence

$$\rho(\tau) = \exp\left(-\int_\tau^T \alpha(s)ds\right)\left[\rho(T) - \int_\tau^T \exp\left(\int_s^T \alpha(r)dr\right)\beta(s)ds\right] > 0.$$

Contradiction. □

We henceforth assume that all states N and costates λ are positive. Sign properties of the multipliers μ_i depend on the coefficients of the matrix B_i. If τ is a zero of μ_i, then

$$\dot{\mu}_i(\tau) = -s_i'(c_i(\tau))\lambda(\tau)B_iN(\tau). \tag{24}$$

Since s_i is strictly increasing, for example, we have the following proposition.

PROPOSITION 4.2. *If all entries of the matrix B_i are nonpositive (resp. nonnegative), then the multiplier μ_i is negative (resp. positive) for $t < T$.*

Proof. We only consider the case when the entries are nonpositive. Then, since $B_i \neq 0$, at least one entry must be negative, and thus $\lambda(t)B_iN(t) < 0$ for all t. Therefore, $\dot{\mu}_i(\tau) > 0$ whenever $\mu_i(\tau) = 0$. Since $\mu_i(T) = 0$, it follows that μ_i is negative for $t < T$. □

More generally, similar results can be proven if it can be asserted that $\lambda(\tau)B_iN(\tau) < 0$ whenever $\mu_i(\tau) = 0$. The conditions of the maximum principle in some instances allow to do this.

4.2. **Bang-bang and singular controls.** The Hamiltonian H of the optimal control problem is of the form

$$H = \Phi_0 + \sum_{i=1}^{m} u_i\Phi_i \tag{25}$$

with

$$\Phi_i(t) = \ell_i + \mu_i(t)(h_i - g_ic_i(t)) \tag{26}$$

and

$$\Phi_0(t) = qN(t) + \lambda(A + \sum_{i=1}^{m} s_i(c_i)B_i)N - \sum_{i=1}^{m} \mu_i f_i c_i. \tag{27}$$

Since the control set is an interval, $U = [\alpha_1, \beta_1] \times \ldots \times [\alpha_m, \beta_m]$, the minimization condition is equivalent to m scalar minimization problems for each control u_i, and thus we have

$$u_i^*(t) = \begin{cases} \alpha_i & \text{if } \Phi_i(t) > 0, \\ \beta_i & \text{if } \Phi_i(t) < 0. \end{cases} \tag{28}$$

The functions Φ_i are called the corresponding *switching functions*. Note that $\Phi_i(T) = \ell_i \geq 0$, and thus optimal controls will always end with an interval where $u_i(t) \equiv \alpha_i$ if a positive weight is put on the corresponding drug. Intuitively this is clear, since the addition of a pharmacokinetic model generates a delay in the effectiveness of the control, and thus because since side effects still are measured instantaneously in the model in terms of the drug dosage, it is not optimal to give drugs until the very end of therapy.

A priori, the controls are not determined by the minimum condition at times when $\Phi_i(t) = 0$. However, if $\Phi_i(t) \equiv 0$ on an open interval, then all derivatives of $\Phi_i(t)$ also must vanish, and this may determine the control. Controls of this kind are called *singular*, while we refer to the constant controls as *bang* controls. Optimal controls then need to be synthesized from these candidates through an analysis of the switching function. For example, if $\Phi(\tau) = 0$ but $\dot{\Phi}(\tau) \neq 0$, then the control has a switch at time τ and must be bang-bang near τ. To analyze the structure of the optimal controls, we therefore need to analyze the switching function and its derivatives. A simple direct computation shows that these derivatives are given by

$$\dot{\Phi}_i(t) = \mu_i(t)f_ih_i - s_i'(c_i(t))[h_i - g_ic_i(t)]\lambda(t)B_iN(t). \tag{29}$$

This allows for $\dot{\Phi}_i(\tau)$ to vanish at points where $\Phi_i(\tau) = 0$. For example, if the entries of B_i are nonpositive, then $\lambda(\tau)B_iN(\tau) < 0$, $\mu_i(\tau) < 0$ and $h_i - g_ic_i(\tau) > 0$. Since $s_i' > 0$, we always have a difference of negative terms, which allows for the possibility of singular arcs.

If the control u_i is singular on some open interval I (i.e., if the switching function Φ_i vanishes on I), minimization of the Hamiltonian (23) is inconclusive and does not determine the value of the control. However, in this case all derivatives of the switching function also vanish identically on I. Typically the singular controls can be computed by differentiating the switching function in time until the control variable explicitly appears in the derivative, say in $\Phi_i^{(d)}(t)$, and then solving the resulting equation $\Phi_i^{(d)}(t) \equiv 0$ for the control. If the corresponding control value is admissible (i.e., has a value in the interval $[\alpha_i, \beta_i]$), this defines the singular control. Otherwise the singular arc is not admissible. For a single-input system that is linear in the control, it is well known [10] that d must be even, say $d = 2k$, and k is called the order of the singular arc. In principle, this order can vary with time over the interval I. If it is constant on the interval I, then it is a necessary condition for minimality of a singular arc of order k, the so-called generalized Legendre-Clebsch condition [10, 1], that

$$(-1)^k \frac{\partial}{\partial u} \frac{d^{2k}}{dt^{2k}} \frac{\partial H}{\partial u} \geq 0 \tag{30}$$

along the extremal. Note that the term $\frac{\partial H}{\partial u} = \Phi$ in (30) represents the switching function for the problem. The situation becomes more complicated in the multi-input case, but in our model the controls are sufficiently decoupled so that the single-input results suffice.

Differentiating (29) once more and looking for singular arcs of order 1, we compute

$$\begin{aligned} \frac{\partial}{\partial u_i}\ddot{\Phi}_i = &\left(\frac{\partial}{\partial u_i}\dot{\mu}_i\right) f_ih_i - s_i''(c_i)\left(\frac{\partial}{\partial u_i}\dot{c}_i\right)(h_i - g_ic_i)\lambda B_iN \\ &+ s_i'(c_i)g_i\left(\frac{\partial}{\partial u_i}\dot{c}_i\right)\lambda B_iN - s_i'(c_i)(h_i - g_ic_i)\frac{\partial}{\partial u_i}\left(\frac{d}{dt}(\lambda B_iN)\right). \end{aligned} \tag{31}$$

For later use, we state the following formula that follows by a direct computation.

LEMMA 4.1. *For any $n \times n$ matrix R, the derivative of $\Psi(t) = \lambda(t)RN(t)$ along solutions N of (19) and λ of (21) is given by*

$$\dot{\Psi} = \lambda\left[A + \sum_{i=1}^{m} s_i(c_i)B_i, R\right]N - qRN \tag{32}$$

where $[A, B] = BA - AB$ denotes the commutator (or Lie-bracket) of A and B. □

Hence

$$\frac{d}{dt}(\lambda B_iN) = \lambda[A + \sum_{j\neq i} s_j(c_j)B_j, B_i]N - qB_iN \tag{33}$$

does not depend on the control. It therefore follows from the dynamics and adjoint equations that

$$\begin{aligned} \frac{\partial}{\partial u_i}\ddot{\Phi}_i &= \mu_ig_if_ih_i - s_i''(c_i)(h_i - g_ic_i)^2\lambda B_iN + s_i'(c_i)g_i(h_i - g_ic_i)\lambda B_iN \\ &= g_i\left(\mu_if_ih_i + s_i'(c_i)(h_i - g_ic_i)\lambda B_iN\right) - s_i''(c_i)(h_i - g_ic_i)^2\lambda B_iN. \end{aligned} \tag{34}$$

But $\dot{\Phi} \equiv 0$ along the singular arc, and therefore using (29) we get

$$\frac{\partial}{\partial u_i}\ddot{\Phi}_i = (h_i - g_i c_i)\lambda B_i N \left[g_i(2s_i'(c_i) + c_i s_i''(c_i)) - h_i s_i''(c_i))\right], \tag{35}$$

and for the minimization problem, it is a necessary condition of optimality of the singular arc that this quantity is nonpositive. Further analysis of this condition depends on the signs of $\lambda B_i N$ and the multiplier μ_i and needs to be done on a case-by-case basis. Here, as an example, we consider the scenario when all entries of B_i are nonpositive. This applies to both the two-compartment cancer model defined by (5) and the model for bone-marrow depletion in (12). In this case, by Propositions 4.1 and 4.2, it follows that both $\lambda B_i N$ and μ_i are negative. Using $\dot{\Phi} \equiv 0$, this implies that $h_i - g_i c_i$ is positive along a singular arc. Summarizing, we have the following proposition.

PROPOSITION 4.3. *Suppose* ***(A)*** *all entries of B_i are nonpositive and all the matrices $A + \sum_{i=1}^m s_i B_i$, $s \in \bar{S} = [0, \bar{s}_1] \times \ldots \times [0, \bar{s}_m]$, have nonnegative off-diagonal entries. Then a singular control of order* 1 *satisfies the Legendre-Clebsch condition (35) for minimality of a singular arc if and only if*

$$g_i \left(2s_i'(c_i) + c_i s_i''(c_i)\right) \geq h_i s_i''(c_i). \tag{36}$$

For the case of a linear PK equation ($g_i = 0$), singular controls are not optimal in regions where s_i is strictly convex. □

In particular, under Assumption (A) with a linear PK model and a sigmoidal PD equation for drug i, singular controls u_i are not optimal for low concentrations, but the Legendre-Clebsch condition is satisfied, and thus feasible singular arcs in fact can be expected to be locally optimal at high concentrations. Singular controls do always satisfy the Legendre-Clebsch condition for the $E_{\max}$ model in this case.

COROLLARY 4.1. *Suppose* ***(A)*** *holds. For $g_i \neq 0$ and a linear PD model, $s(c_i) = s_i c_i$, singular arcs are not optimal if $g_i < 0$, but they satisfy (36) if $g_i > 0$.* □

A special case arises for a linear PK model ($g_i = 0$) in combination with a linear PD equation, $s_i(c_i) = s_i c_i$, a case often considered in the literature. In this case, (35) is satisfied trivially, and the singular arc is of higher order. While having simple PK and PD, this case nevertheless becomes more involved now since interactions between the drugs and their concentrations come into play. We briefly give the relevant computations. Again, it is assumed that Φ_i and thus also all its derivatives vanish on some open interval I:

$$\Phi_i = \ell_i + h_i \mu_i \equiv 0, \qquad \dot{\Phi}_i = h_i \left(\mu_i f_i - s_i \lambda B_i N\right) \equiv 0, \tag{37}$$

$$\begin{aligned}\ddot{\Phi}_i &= f_i \dot{\Phi}_i - s_i h_i \left(\frac{d}{dt}\lambda B_i N\right) = -s_i h_i \left(\frac{d}{dt}\lambda B_i N\right) \\ &= -s_i h_i \left(\lambda \left[A + \sum_{j \neq i} s_j(c_j) B_j, B_i\right] N - q B_i N\right) \equiv 0.\end{aligned} \tag{38}$$

Since the second derivative does not explicitly depend on the control u_i, the singular arc is of higher order. What makes the computation still manageable is that this derivative also does not depend on the particular concentration c_i of the drug dose

u_i, which is singular. Differentiating once more gives

$$\Phi_i^{(3)} = -s_i h_i \left(\lambda \left[A + \sum_{k=1}^{m} s_k(c_k) B_k, \left[A + \sum_{j \neq i} s_j(c_j) B_j, B_i \right] \right] N \right.$$
$$+ \sum_{j \neq i} s_j'(c_j) \dot{c}_j \lambda [B_j, B_i] N - q \left[A + \sum_{j \neq i} s_j(c_j) B_j, B_i \right] N \qquad (39)$$
$$\left. -qB_i \left(A + \sum_{j=1}^{m} s_j(c_j) B_j \right) N \right).$$

In the fourth derivative formally, derivatives of the other controls u_j, $j \neq i$, also are needed, and we assume they exist (e.g., bang-bang or itself differentiable singular controls). Differentiating once more, however, any term arising from the second and third term in (39) does not depend on u_i, and overall we get the following necessary condition for optimality of the singular arc:

$$\frac{\partial}{\partial u_i} \Phi_i^{(4)} = -s_i^2 h_i^2 \left(\lambda \left[B_i, \left[A + \sum_{j \neq i} s_j(c_j) B_j, B_i \right] \right] - q B_i^2 \right) N \geq 0. \qquad (40)$$

For a single-input system this simplifies to

$$\frac{\partial}{\partial u} \Phi^{(4)} = -s^2 h^2 \left(\lambda [B, [A, B]] - q B^2 \right) N \geq 0. \qquad (41)$$

5. **Simulations and comparisons.** We include some brief simulations for the two-compartment model in Example 1 and the bone-marrow model in Example 2 to show that the addition of linear PK and PD models does not change the qualitative structure of solutions: solutions are bang-bang with one switching, and linear PK and PD models only shift the location of the switching.

5.1. **A two-compartment model for cancer cells.** For this model, the original control set is $0 \leq u \leq 1$, and we therefore take $\bar{s} \leq 1$. Hence, Assumption (A) of Proposition 4.3 holds and singular controls are of order 2. From (5), we see that $B^2 = 0$ and $[B, [A, B]] = -4a_1 a_2 B$ so that

$$\frac{\partial}{\partial u} \Phi^{(4)} = 4s^2 h^2 a_1 a_2 \lambda B N = 4sfh^2 a_1 a_2 \mu < 0, \qquad (42)$$

violating (41). Thus, in this case, singular controls are not optimal, and optimal controls still are bang-bang, as in the model without PK equations [11].

Using a version of the gradient method for the calculation of extremal bang-bang controls developed by Duda [4], we computed the locally optimal controls shown below. (The local optimality of each run can be established using the algorithm developed in [11], but this will not be discussed here.) The length of the therapy interval is $T = 10$, and as parameter values we used $a_1 = 0.197$ and $a_2 = 0.356$. In the objective, we set $r_1 = r_2 = 1$, $q_1 = q_2 = 1$ and picked $\ell = 1$; in the linear PD equation, we set $s = 1$. The initial condition was chosen as the steady-state value of the uncontrolled system. For these parameter values with the total number of cells normalized to 1, about 70% of the cancer cells are in the first compartment and about 30% are in the second compartment [14]. Figure 3a shows the control and corresponding switching function for the model without PK while Figure 3b show these data for runs with a linear PK equation of the form $\dot{c} = -c + u$. By

choosing $h = f$ in this equation, we normalize the maximum concentration to 1 in agreement with the choice $s = 1$ for the model without PK and PD; otherwise results are not comparable. In all the figures, the optimal controls are given by the solid line, and the corresponding switching functions are given by a dashed line.

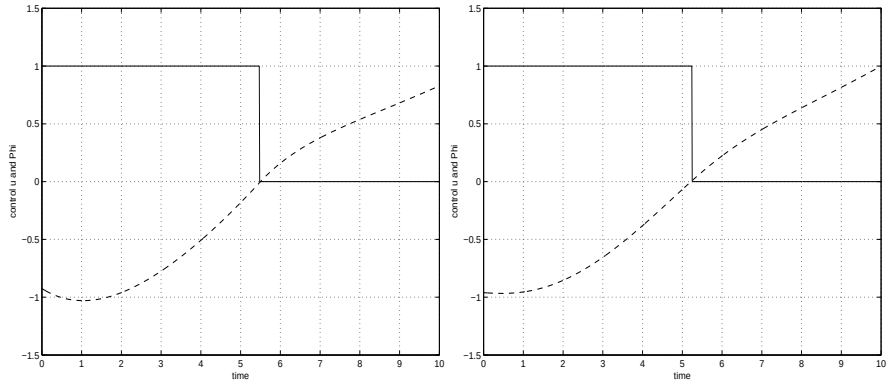

Figure 3. Controls (a) without PK, $\tau = 5.48$; (b) with PK, $f = 1$, $\tau = 5.25$.

Optimal controls are bang-bang, with one switching from $u = 1$ to $u = 0$. As linear PK and PD equations are added, the qualitative behavior of the solutions remains the same, but the switching occurs slightly earlier, which is caused by the delay type effect of PK. The slower the PK dynamics is, the more pronounced this effect becomes.

5.2. **A two-compartment model for bone-marrow cells.** As in the example above, Assumption (A) of Proposition 4.3 holds, and singular controls are of order 2. But since Example 2 is a maximization problem, the signs in the Legendre-Clebsch condition are reversed, and now it is a necessary condition for optimality of a singular arc that

$$\frac{\partial}{\partial u}\Phi^{(4)} = -s^2h^2\left(\lambda\,[B,[A,B]] - qB^2\right)N \le 0. \tag{43}$$

Using (12), we have $B^2 = -B$, and since also $\ddot{\Phi} \equiv 0$ along a singular arc, we get

$$qB^2N = -qBN = -\lambda s[A,B]N. \tag{44}$$

Hence (all quantities are evaluated along the singular lift)

$$\frac{\partial}{\partial u}\Phi^{(4)} = -s^2h^2\lambda\left([B,[A,B]] + [A,B]\right)N. \tag{45}$$

Direct calculations show that

$$[A,B] = \begin{pmatrix} 0 & -\beta \\ \alpha & 0 \end{pmatrix}, \qquad [B,[A,B]] = -\begin{pmatrix} 0 & \beta \\ \alpha & 0 \end{pmatrix}. \tag{46}$$

Thus

$$\frac{\partial}{\partial u}\Phi^{(4)} = -s^2h^2\lambda\begin{pmatrix} 0 & -2\beta \\ 0 & 0 \end{pmatrix}N = 2s^2\beta\lambda_1 Q > 0 \tag{47}$$

also violating the Legendre-Clebsch condition. Hence, all singular arcs locally minimize the objective.

Again using the version of the gradient method for the calculation of extremal bang-bang controls developed by Duda [4], we computed the locally optimal controls shown below. (The local optimality of each run can be established using the algorithm developed in [15] and is not discussed here.) The length of the therapy interval is $T = 10$, and we used the following parameter values taken from [6]: $\alpha = 5.643$, $\beta = 0.48$, $\gamma = 1.47$, $\delta = 0$, and $\rho = 0.164$. In the simulations, we set $s = 1$, $r_1 = r_2 = 1$, and $q_1 = q_2 = 1$ and picked $\ell = 0.5$. As above, the initial condition was chosen as the steady-state value of the uncontrolled system when about 10% of the bone-marrow cells are in their proliferating state [16]. Figures 4a and 4b show optimal controls and corresponding switching functions for the models without PK and a linear PK equation of the form $\dot{c} = -c + u$, respectively. As above, choosing $h = f$ in this equation normalizes the maximum concentration to 1 in agreement with the choice $s = 1$.

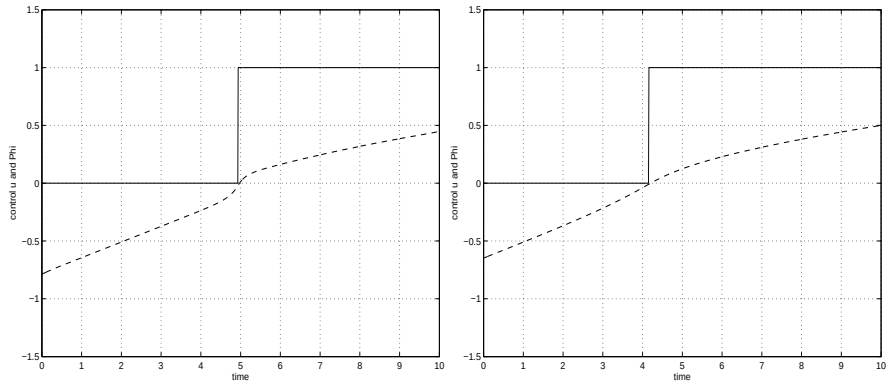

Figure 4. Controls (a) without PK, $\tau = 4.94$; (b) with linear PK, $f = 1$, $\tau = 4.16$.

In each case, the control is bang-bang with one switching from $u = 0$ to $u = 1$. Since the objective now is maximized and the effect is described in terms of the bone marrow, the negative effects of the drug are delayed by the PK equation, and thus the optimal control now—contrary to the cancer model above—ends with a full dose. This delay effect also accounts for the fact that the controls switch earlier, since the negative effects lag behind. The faster the concentrations build up, however, the smaller this effect is, and for $f = 5$ (not shown), it is almost negligible.

6. **Conclusion.** In this paper, we initiated the analysis of optimal controls for a class of models of cancer chemotherapy when pharmacokinetics and pharmacodynamics of the drugs are included. Our results show that the geometric properties of these models have a direct influence on the type of controls that are optimal. For the examples considered here, singular arcs remain not optimal if linear PK models and PD functions s are used and only small quantitative changes in the switching times of bang-bang controls are generated, but no qualitative changes occur. For more general PK models and PD functions s, this does not necessarily hold. Although singular controls are still not optimal for regions where s is strictly convex (typically this holds for low concentrations), the optimality status changes as s becomes concave (as is typically the case for high concentrations). This suggests a structure of optimal controls, which provide a quick initial boost in terms of bang-bang controls and then regulate the concentration through slowly varying

infusions. Similarly, in the case of a bilinear (or more generally nonlinear) PK equation, the structure changes and singular controls representing protocols with partial doses can be optimal. For the bilinear model, the sign of the parameter g matters, and depending on whether the problem is formulated as minimization or maximization for $g > 0$, respectively, $g < 0$ singular controls satisfy the necessary conditions for optimality. Intuitively, in this case, once the drug's concentration is built up, the injection of smaller time-varying doses can be used to maintain a high effectiveness of the drug, which by itself slowly decays. Although the model is characterized through a number of cell-cycle-specific parameters, our analysis for these examples does not depend on the actual values of these parameters, but it is the type of PK and PD model that determines the class of optimal controls. Research in the direction of analyzing the structure of optimal controls, especially when singular arcs become candidates, is still ongoing.

In conclusion, although linear PK and PD models do not change the qualitative structure of optimal controls and, at least in the models considered here, lead only to small quantitative changes, allowing for more complex nonlinear forms for PK and PD in the model introduces singular controls as viable candidates for optimality. Their analysis, especially a synthesis with bang-bang controls, is a mathematically much more difficult problem and still needs to be addressed in further research.

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