Application of Control Theory in Modelling Cancer Chemotherapy

Urszula Ledzewicz* and Heinz Schättler**

*Department of Mathematics and Statistics, Southern Illinois University at Edwardsville, Edwarsville, Il, 62026, USA,
(Tel: +1-618-650-2361; Email:uledzew@siue.edu)

**Department of Electrical and Systems Engineering, Washington University, St. Louis, Mo, 63130 USA
(Tel: +1-314-935-6019; Email:hms@wustl.edu)

Abstract: Phase specific models for cancer chemotherapy are described as optimal control problems. We review earlier 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. In this paper we discuss how to incorporate more realistic medical aspects which hitherto have been neglected in the models. They include pharmacokinetic equations (PK) which model the drug's plasma concentration and various pharmacodynamic models (PD) which describe the effect the concentrations have on cells. We also briefly discuss the important medical issue of drug resistance.

Keywords: optimal control, mathematical models for cancer chemotherapy, pharmacokinetics and pharmacodynamics, drug resistance

1. Introduction

Mathematical models for cancer chemotherapy treatments have a long history (for a survey of the early efforts see, for example [6], [22]) and have been extensively researched in the eighties and nineties (e.g. [4], [19], [20], [23]). While biomedical research concentrates on the development of new drugs and experimental (in vitro) and clinical (in vivo) determinations of their treatment schedules, the analysis of models can assist in testing various treatment strategies and searching for optimal ones. But the complexity of the underlying biological processes is still difficult to capture. In many cases our understanding of the dynamics is incomplete, especially in multi-drug treatments when synergistic relations may not be known, or it may be impossible or too difficult to determine relevant parameters. While mathematical models thus necessarily still are crude, their analysis can further our understanding of some simplified aspects of the overall system, a necessary step towards developing and analyzing a medically relevant model.

Mathematically, cancer chemotherapy can be viewed as a control system with the *state* of the system, N, given by the *number of cancer cells* and the *control*, u, as the *drug dosage* or 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. This naturally can be formulated as an optimal control problem. In section 2 we describe the underlying phase specific models for cancer chemotherapy as optimal control problems. But in view of the complexity of the real medical problem, it makes sense to start with simplified models and then add increasingly more complex and medically more realistic features to the model. Thus our starting point is a simplified formulation where the drug dosage is identified with the drug effects or, equivalently, it is assumed that the drugs act instantaneously. We review existing results for this class of models. In section 3 we then add to the model the more realistic feature that there is some delay in terms of the drug's effectiveness, that is, we add extra dynamical equations which model the drug's concentration in the body plasma, so-called *pharmacokinetic equations* (PK). We also allow for *pharmacodynamic* (PD) effects in modelling the effectiveness of the drugs. Thus, in principle, the dynamics of drug delivery and effectiveness can formally be incorporated in the models. Another important issue is to model developing drug resistance of the cancer cells [2], [3]. This is one of the main reasons why many actual chemotherapy treatments fail and has been called "probably the most important - and certainly the most frustrating - of these limitating factors" [10, pg. 335]. Realistic models of cancer chemotherapy therefore need to take developing drug resistance into account. In section 4 we formulate such a model for phase specific chemotherapy.

This research was supported by NSF grant DMS 0305965 and collaborative research grants DMS 0405827/0405848; U. Ledzewicz's research also was supported by SIUE Hoppe Research Scholar Award and 2004 Summer Research Fellowship

2. Phase specific models for cancer chemotherapy as optimal control problems

Recent models for cancer chemotherapy are cell-cycle specific and treat the cell cycle as the object of control [23], [25]. 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. These distinctions are important since most drugs are active in a specific phase of the cell-cycle. For example, so-called spindle poisons like Vincristine, Vinblastine or Bleomycin which destroy a mitotic spindle are active in mitosis. Depending on the type of drug modelled and the degree of detail in mathematical models

the phases of the cell cycle are then combined into clusters. Drug treatment influences the cell cycle in many possible ways. The most fundamental aspect is cell-killing, but also *blocking* and *recruitment agents* play important roles. Blocking agents slow down the transitions of the cells through the cell cycle and thus impede on the tumor's growth while recruiting agents make cancer cells leave the dormant stage G_0 where they are not susceptible to any chemotherapy. In this paper, however, we mostly focus on *killing agents*. In the modelling often G_2 and M are combined into one compartment since the boundaries between these phases are difficult to establish and many killing agents like for example Paclitaxel (Taxol) mainly affect cells during their division and thus are G_2/M specific. This makes sense biologically since the cell walls become very thin and porous in mitosis M and thus the cell is more vulnerable to an attack during this phase. On the other hand, cells which lie in the dormant phase G_0 are too stable and essentially cannot be killed.

Depending on the number and types of chemotherapeutic 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 number of compartments defines the dimension of the system and the *dynamics* describes the in- and out-flows between the compartments in the presence of the control, that is under therapy.

2.1. Example: a 2-compartment model with a single G_2/M specific killing agent

In a mathematical model for cancer chemotherapy treatment with a single G_2/M specific killing agent [23], [13] 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. Let $N_i(t)$, $i = 1, 2$, denote the number of cancer cells in the i-th compartment at time t. The transit times of cells through phases of the cell cycle vary, particularly in malignant cells. In the simplest models an exponential distribution is used to model the transit times and the expected number of cells exiting the i-th compartment is given by $a_i N_i(t)$, where a_i is the parameter of the exponential distribution related to the inverse of the transit time. Assuming that no external stimuli are present, the inflow of the second compartment equals the outflow of the first and thus we have

$$\dot{N}_2(t) = -a_2 N_2(t) + a_1 N_1(t). \tag{1}$$

Cell division is represented by a factor 2 in the equation which describes the flow from the second into the first compartment,

$$\dot{N}_1(t) = -a_1 N_1(t) + 2a_2 N_2(t).$$

Admissible controls are Lebesgue measurable functions $u : [0, T] \to [0, 1]$ with values in the closed interval $[0, 1]$ here representing the *effects* of the dose of the drug administered with $u = 0$ corresponding to no treatment and $u = 1$ corresponding to a maximum dose, i.e. it is assumed that drug effects are instantaneous; pharmaco-kinetic equations are not modelled. This is a reasonable assumption for fast-acting drugs. It is assumed that the effectiveness of the drug is proportional to the number of ineffective cell-divisions in the G_2/M phase with a factor s, $0 < s \leq 1$. Therefore while all cells $a_2 N_2$ leave the compartment G_2/M, only a fraction $(1 - su)a_2 N_2$ of cells reenters phase G_1/S and undergoes cell division. Thus the controlled mathematical model becomes

$$\dot{N}_1 = -a_1 N_1 + 2(1 - su)a_2 N_2, \qquad N_1(0) = N_{10}, \tag{2}$$

$$\dot{N}_2 = a_1 N_1 - a_2 N_2, \qquad N_2(0) = N_{20}, \tag{3}$$

with all initial conditions positive. Note that for $s \leq \frac{1}{2}$ the total number of cancer cells cannot be reduced and thus we will generally also assume that $s > \frac{1}{2}$. If we set $N = (N_1, N_2)^T$, then the general form of the dynamics is is described by a single-input bilinear system of the form

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

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

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

Clearly only states $N(t)$ for which each coordinate is positive are meaningful. It is easily seen that if each coordinate of $N(t_0)$ is positive, then all coordinates of $N(t)$ remain positive for all times $t \geq t_0$ [13, Prop. 3.1]. It is therefore not necessary to add this positivity condition as state-space constraint.

2.2. The general dynamics

More generally, if more compartments and multi-drug treatments are consider, under these modelling assumptions a bilinear system of the form

$$\dot{N} = (A + \sum_{i=1}^{m} u_i B_i)N, \quad N(0) = N_0, \tag{6}$$

arises where again A and the B_i are $n \times n$ matrices and n is the number of compartments. (See [23], [14], [15], [16]) for other specific models of this form.) The controls u_i represent the drug dosages of various drugs and all take values in compact intervals $[\alpha_i, \beta_i] \subset [0, \infty)$. An obvious state space constraint for these models then is that the number of cells remains positive. A simple sufficient condition for this to hold is that (M) 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 negative diagonal entries, but non-negative off-diagonal entries (i.e are so-called M-matrices.) In cell-cycle specific compartmental models for cancer chemotherapy this condition is always satisfied since there are only outflows from the i^{th} compartment, but no direct return flows into the i^{th} 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 [15].

2.3. Objective

The active ingredients in the drugs are cytostatic agents which kill cancer cells and healthy cells alike. The aim of any

treatment is to kill the cancer or at a minimum to curtail its further spread while keeping the toxicity to the normal tissue acceptable. Mathematically there are many (non-equivalent) ways of modelling this. The model which forms the basis of our study here was proposed and originally analyzed as an optimal control problem by Swierniak [23] and then reconsidered in [13] with the objective to minimize the number of cancer cells at the end of a fixed therapy interval. The negative effects on the healthy cells are represented only indirectly by also minimizing the drug dosage in the objective. We consider a linear (L_1-type) objective of the form

$$J = rN(T) + \int_0^T qN(t) + bu(t)dt \to \min \tag{7}$$

where $r = (r_1, \ldots, r_n)$, $q = (q_1, \ldots, q_n)$ and $b = (b_1, \ldots, b_m)$ are non-zero row-vectors of non-negative coefficients $r_i \geq 0$, $q_i \geq 0$, $b_i \geq 0$. While some of the components may be zero (this would hold for the component of b corresponding to a recruiting agent), the components of b corresponding to killing agents should be positive. 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 we have added the term $qN(t)$ in the Lagrangian to prevent that the number of cancer cells would rise to unacceptably high levels at intermediate times. Side effects of treatment (toxicity) are only modelled indirectly through the last term which is linear in the control generating an L_1-type objective. In this formulation of cancer chemotherapy we do not yet take into account pharmaco-kinetic equations or pharmacodynamics nor do we consider drug resistant subclasses of cells. Thus the optimal control problem is to

(P) choose a Lebesgue measurable function $u : [0, T] \to U$ that minimizes the objective (7) subject to the dynamics (6).

2.4. Brief summary of existing results

In earlier research we have analyzed both specific models of this class [13], [14], [16] and the structure of its solutions in the general case [15], [24]. The necessary conditions for optimality for these models given by the Pontryagin Maximum Principle [21] have been analyzed. In general they do not sufficiently restrict the class of controls, although they single out *bang-bang* and *singular* controls [1], [12] as the prime candidates. The first class corresponds to protocols where a full dose is administered separated by rest-periods in between when no dose is given. The second class, singular controls, corresponds to all type of protocols when time varying partial doses are allowed. In our research we have eliminated singular controls for specific models as in fact locally maximizing rather than minimizing [13], [14] using high order necessary conditions for optimality like the generalized Legendre-Clebsch condition or the Goh condition [12]. Also, using the method of characteristics we have given easily verifiable sufficient conditions for local optimality of bang-bang trajectories [13], [24]. These results confirm the medical practice of giving full dose chemotherapy sessions with complete rest-periods in between. Continuously varying partial doses as they would occur for singular arcs are in fact not optimal under the objective (7).

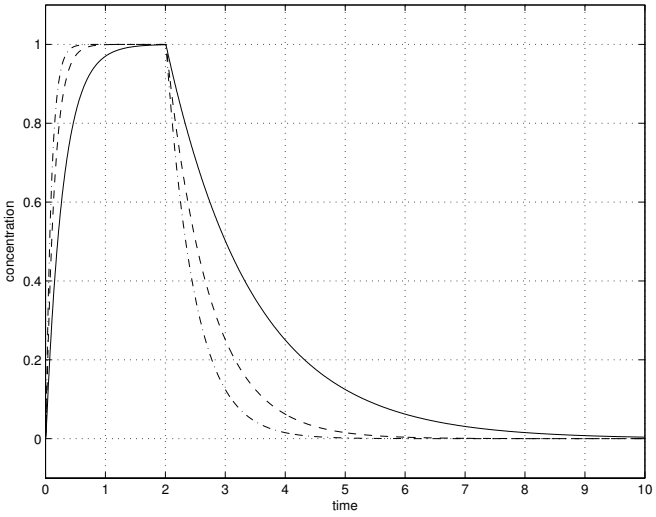

Fig. 1. Bilinear model for PK

3. Models including pharmacokinetics and pharmacodynamics (PK/PD)

In this section we augment the model (6) with a pharmacokinetic (PK) equation which models the drug's concentration in the body and also add a function $e = s(c)$ as model for pharmacodynamics (PD). These are important aspects and make the models more medically relevant and realistic. However, for simplicity of exposition we only consider the single-input case (4) of one active chemotherapeutic agent. In multi-control models, which have been analyzed without PK/PD in [14], [24], additional equations and functions would need to be added for each drug.

3.1. Pharmacokinetics

In (4), as in many other models, the relations between the drug dosage and the effects of the drugs are simply considered instantaneous, that is, modelled by a zero-order controller. We first augment the class of compartmental models for cancer chemotherapy defined by (4) with pharmacokinetic (PK) equations which model the time evolution of the drug's concentration in the body/plasma. These equations act like a controller for the system. 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/decay as it is commonly used for continuous infusions. Here more generally we consider a bilinear system of the form

$$\dot{c} = -(f + ug)c + hu, \qquad c(0) = 0, \tag{8}$$

where f and h are positive constants, but g is arbitrary. This model has the advantage that it allows for different rates at which the concentrations build up to their maximum level and decay if no drugs are given. In the case of $g = 0$ this reduces to the linear system. Trajectories for some different values of g are shown in Fig. 1.

Thus the combined dynamics becomes

$$\dot{N} = (A + cB)N, \qquad N(0) = N_0, \tag{9}$$

$$\dot{c} = -(f + ug)c + hu, \qquad c(0) = 0; \tag{10}$$

the objective remains unchanged. Our mathematical analysis in [17] shows that the introduction of a linear pharmacokinetic equation (e.g. $g = 0$) as exponential growth and decay does *not* change the qualitative structure of the solution - partial doses still are not optimal and, in principle, optimal controls alternate between chemotherapy sessions of full dose and rest-periods, exactly as in the model where PK was not present. However, 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 for $g > 0$ singular controls satisfy the necessary conditions for optimality. Intuitively, once the drug's concentration is built up, in this case 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 does not depend on the actual values of these parameters, but it is the type of PK-model which determines the class of optimal controls. Overall, this raises the issue about the proper choice of pharmacokinetics in the cancer chemotherapy problems. This aspect, which is often neglected in mathematical models, therefore becomes an essential item in the modelling of cancer chemotherapy.

3.2. Pharmacodynamics

A related and equally important aspect is the question of pharmacodynamic models for the effect the drug concentration c has on the cancer cells. For example, in the 2-compartment model described above, 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, i.e. $e = su$ with s called the effectiveness of the drug. Therefore, 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. This is the most basic way of modelling pharmacodynamics. More generally, the effect can be modelled by a function s defined on the interval $[0, \infty)$ with values in the interval $[0, 1]$. Depending on the choice of this function qualitatively different models arise. Two commonly used models in practice are the so-called $E_{\max}$ model [5] of the form

$$s_1(c) = \frac{E_{\max} c}{EC_{50} + c} \tag{11}$$

and sigmoidal functions [11] like

$$s_2(c) = \frac{E_{\max} c^n}{EC_{50}^n + c^n} \tag{12}$$

where n is a positive integer greater than 1. In the $E_{\max}$ model it is assumed that the drug becomes effective very quickly, but then saturates at high concentrations while the sigmoidal models more accurately approximate the effectiveness at both lower and higher concentrations.

Overall we therefore arrive at a dynamics of the form

$$\dot{N} = (A + s(c)B)N, \qquad N(0) = N_0, \tag{13}$$

$$\dot{c} = -(f + ug)c + hu, \qquad c(0) = 0. \tag{14}$$

In the model we only *assume* that s is a *strictly increasing, twice continuously differentiable* function and that the parameters have been normalized so that the values of s lie in the interval $[0, 1]$ possibly only reaching level 1 asymptotically as $c \to \infty$ for full dose.

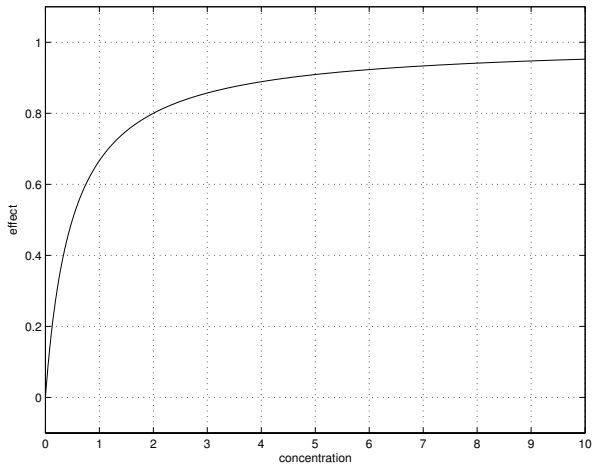

Fig. 2. $E_{\max}$ model for pharmacodynamics

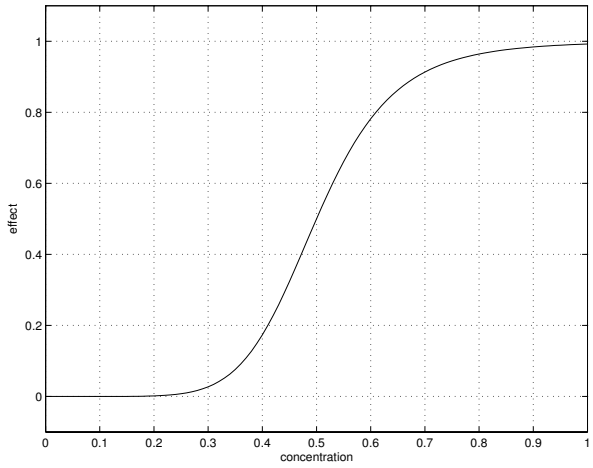

Fig. 3. Sigmoid model for pharmacodynamics

In [17] we carried out the analysis of optimal controls for the two-compartment model of cancer chemotherapy when both pharmacokinetic and pharmacodynamic models were included. Our results show that the geometric properties of these functions have a direct influence on the type of controls which are optimal. While singular arcs are not optimal if linear models are used, for more general PK-models and PD-functions s this does not necessarily hold. While it is still true for regions where s is strictly convex (low concentrations), the optimality status of singular controls changes as s becomes concave (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.

4. Mathematical models for cancer chemotherapy with a single killing agent under evolving drug resistance

Probably the single most important obstacle to successful chemotherapy lies in acquired drug resistance [10] and it is therefore of utmost importance to include this in the mod-

elling. Cancer cells are genetically highly unstable and due to mutational events and gene amplification during cell division, cells can acquire genes which as a result make them more resistant to certain drugs, for example by addition of genes which aid removal or metabolization of the drug. The more copies of such a gene will be present, the more resistant the cells become to even higher concentrations of the drug. In this section we discuss a mathematical models that describes a type of drug resistance based on a *one-copy forward gene amplification model* (see [7], [8], [9]). The basic assumption is that in cell division at least one of the two daughter cells will be an exact copy of the mother cell while the second one with some positive probability undergoes gene amplifications.

4.1. The basic structure

We consider two compartments consisting of drug sensitive and resistant cells and denote the numbers of cells in the sensitive and resistant compartments by S and R, respectively. If a sensitive cell undergoes cell division, the mother cell dies and one of the daughters will remain sensitive. The other daughter with probability q, $0 < q < 1$, changes into a resistant cell. Similarly, if a resistant cell undergoes cell division, then the mother cell dies, and one of the daughters remains resistant. However, for cancer cells (and different from viral infections like HIV) it is possible that a resistant cell may mutate back into a sensitive cell. This phenomenon is well-documented in the medical literature where experiments have shown that the resistant cell population decreases in a drug free medium. We therefore include a probability $r \geq 0$ that one of the daughters of a resistant cell may become sensitive. Generally r will be small. The case $r = 0$ where this is excluded is called *stable gene amplification* while *unstable gene amplification* refers to the phenomenon $r > 0$. We denote the inverses of the transit times of cells through the sensitive and resistant compartments by a and c, respectively, and assume that the cytostatic agent kills the sensitive cells. Let u denote the drug dose, $0 \leq u \leq 1$, with $u = 0$ corresponding to no drug being used and $u = 1$ corresponding to a full dose. (In order to focus on the aspect of drug resistance, here we do not include PK and PD in the model.) It is assumed that the drug kills a fixed proportion u of the outflow of the sensitive cells, $aS(t)$, at time t and therefore only the remaining fraction $(1-u)aS(t)$ of cells undergoes cell division. Of these new cells then $(2-q)(1-u)aS(t)$ remain sensitive, while a fraction $q(1-u)aS(t)$ mutates to resistant cells. Thus overall the controlled dynamics can be represented as

$$\dot{S} = -aS + (1-u)(2-q)aS + rcR, \tag{15}$$

$$\dot{R} = -cR + (2-r)cR + (1-u)qaS. \tag{16}$$

Here the first terms on the right hand sides account for the deaths of the mother cells, the second terms describe the return flows into the compartments and the third terms give the cross-over flows.

4.2. The model with phase sensitivity in the sensitive compartment

Most common killing agents are G_2/M specific agents and thus as above, we consider a the corresponding two-compartment model for the sensitive cells. We denote the number of cancer cells in these compartments by S_1 and S_2, respectively, and denote the corresponding inverse transit times of cells through these compartments by a_1 and a_2. The cells are killed in the second compartment, i.e. all cells leave, but only the surviving ones reenter the first compartment. The dynamics of the resistant compartment is not changed. Thus we get

$$\dot{S}_1 = -a_1 S_1 + (1-u)(2-q)a_2 S_2 + rcR, \tag{17}$$

$$\dot{S}_2 = -a_2 S_2 + a_1 S_1, \tag{18}$$

$$\dot{R} = -cR + (2-r)cR + (1-u)qa_2 S. \tag{19}$$

More general structures of models are developed in [18].

4.3. Mathematical structure of the models with a single killing agent under evolving drug resistance

Both these models are single-input bilinear systems. If, similarly as it is done in [26] more compartments are added to further differentiate the levels of drug resistance, or if blocking and/or recruiting agents (without additional killing effects) are modelled as well, then as above multi-input bilinear systems of the form (6) arise. Thus again this becomes an optimal control problem of the form (P). However, there exist qualitative differences in the underlying models. Now positive invariance of the system is not guaranteed apriori and needs to be established separately. The optimality of possible singular controls needs to be investigated on a case-by-case basis and it is intended to perform such an analysis, possibly investigating whether there exist common features in the models described above and possibly more general models which would allow to give a broader criterion. Preliminary computations show that the optimality of singular controls depends on the relative portion of resistant cells, but further analysis needed. These models lead to mathematically more challenging structures which become even more complicated as interactions between different killing agents are modelled [18]. This, however, is a very important aspect of the overall development of a realistic model since it corresponds to current medical practice of treating patients with a cocktail of two or three drugs simultaneously. The rational behind this is precisely to counter developing drug resistance to one specific drug in this way. Thus it becomes of interest to investigate these kind of models.

5. Conclusion

In this paper we reviewed some results about mathematical models for phase specific cancer chemotherapy. Starting with models when drug actions are assumed instantaneous, we augmented these formulations with models for pharmacokinetics and pharmacodynamics. While these models become increasingly more complex, analytical results can still be obtained and it are geometric properties of the defining

PK/PD functions which determine the structure of optimal controls [17]. We also briefly discussed the medically important issue of evolving drug resistance under chemotherapy. If drug resistance is taken into account, the mathematical models become high dimensional since various degrees of drug resistance give rise to new compartments. This therefore naturally produces more difficult problems, but any results towards establishing the structure of optimal protocols would be of interest and significance for as of now for many types of cancer drug resistance is the main obstacle for developing an effective treatment or even a cure.

References

[1] A.E. Bryson and Y.C. Ho, *Applied Optimal Control*, Hemisphere Publishing, 1975

[2] A.J. Coldman and J.H. Goldie, "A model for the resistance of tumor cells to cancer chemotherapeutic agents", *Mathematical Biosciences*, **65**, pp. 291-307, 1983

[3] M.I.S. Costa, J.L. Boldrini and R.C. Bassanezi, "Drug kinetics and drug resistance in optimal chemotherapy", *Mathematical Biosciences*, **125**, pp. 191-209, 1995

[4] B.F. Dibrov, A.M. Zhabotinsky, Yu.A. Neyfakh, M.P. Orlova and L.I. Churikova, "Mathematical model of cancer chemotherapy. Periodic schedules of phase-specific cytotoxic-agent administration increasing the selectivity of therapy", *Mathematical Biosciences*, **73**, pp. 1-31, 1985

[5] H. Derendorf, The general concept of Pharmacokinetics, 4th ISAP Educational Workshop, Pharmacokinetics and Pharmacodynamics in 2001, http://www.isap.org/2001/Workshop-Istanbul

[6] M. Eisen, *Mathematical Models in Cell Biology and Cancer Chemotherapy*, Lecture Notes in Biomathematics, Vol. 30, Springer Verlag, 1979

[7] L.E. Harnevo and Z. Agur, "The dynamics of gene amplification described as a multitype compartmental model and as a branching process", *Mathematical Biosciences*, **103**, pp. 115-138, 1991

[8] L.E. Harnevo and Z. Agur, "Drug resistance as a dynamic process in a model for multistep gene amplification under various levels of selection stringency", *Cancer Chemotherapy and Pharmacology*, **30**, pp. 469-476, 1992

[9] M. Kimmel and D.E. Axelrod, "Mathematical models of gene amplification with applications to cellular drug resistance and tumorigenicity", *Genetics*, **125**, pp. 633-644, 1990

[10] R.S. Kerbel, "A cancer chemotherapy resistant to resistance", *Nature*, **390**, pp. 335-336, 1997

[11] J.D. Knudsen, General concepts of pharmacodynamics, 4th ISAP Educational Workshop, Pharmacokinetics and Pharmacodynamics in 2001, http://www.isap.org/2001/Workshop-Istanbul

[12] A. Krener, "The high-order maximal principle and its application to singular controls", *SIAM J. Control and Optimization*, **15**, pp. 256-293, 1977

[13] U. Ledzewicz and H. Schättler, "Optimal bang-bang controls for a 2-compartment model in cancer chemotherapy", *Journal of Optimization Theory and Applications - JOTA*, **114**, pp. 609-637, 2002

[14] U. Ledzewicz and H. Schättler, "Analysis of a cell-cycle specific model for cancer chemotherapy", *J. of Biological Systems*, **10**, pp. 183-206, 2002

[15] U. Ledzewicz and H. Schättler, "Analysis of a class of optimal control problems arising in cancer chemotherapy", Proceedings of the American Control Conference, Anchorage, Alaska, pp. 3460-3465, 2002

[16] U. Ledzewicz and H. Schättler, "Optimal control for a bilinear model with recruiting agent in cancer chemotherapy", Proceedings of the 42nd IEEE Conference on Decision and Control (CDC), Maui, Hawaii, December 2003, pp. 2762-2767, 2003

[17] U. Ledzewicz and H. Schättler, "A two-compartment model for cancer chemotherapy with PK/PD Equations", Proceedings of the 43rd IEEE Conference on Decision and Control (CDC), Nassau, The Bahamas, December 2004, 2004, to appear

[18] U. Ledzewicz, H. Schättler and A. Swierniak, "Finite dimensional models of drug resistant and phase specific cancer chemotherapy", *J. of Medical Information Technology*, 2004, to appear

[19] R.B. Martin, "Optimal control drug scheduling of cancer chemotherapy", *Automatica*, **28**, pp. 1113-1123, 1992

[20] J.M. Murray, "Optimal drug regimens in cancer chemotherapy for single drugs that block progression through the cell cycle", *Mathematical Biosciences*, **123**, pp. 183-193, 1994

[21] L.S. Pontryagin, V.G. Boltyanskii, R.V. Gamkrelidze and E.F. Mishchenko, *The Mathematical Theory of Optimal Processes*, MacMillan, New York, 1964

[22] G.W. Swan, "Role of optimal control in cancer chemotherapy, *Mathematical Biosciences*, **101**, pp. 237-284, 1990

[23] A. Swierniak, "Cell cycle as an object of control", *Journal of Biological Systems*, **3**, pp. 41-54, 1995

[24] A. Swierniak, U. Ledzewicz and H. Schättler, "Optimal control for a class of compartmental models in cancer chemotherapy", *International J. of Applied Mathematics and Computer Science*, **13**, pp. 357-368, 2003

[25] A. Swierniak, A. Polanski and M. Kimmel, "Optimal control problems arising in cell-cycle-specific cancer chemotherapy", *Cell proliferation*, **29**, pp. 117-139, 1996

[26] A. Swierniak and J. Smieja, "Cancer chemotherapy optimization under evolving drug resistance", *Nonlinear Analysis*, **47**, pp. 375-386, 2000