Optimal Control of Multi-input Systems for Cancer Chemotherapy

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Abstract: Cell-cycle specific compartmental models for the growth of cancer cells under combination chemotherapies are considered as optimal control problems with the dose rates of the chemotherapeutic agents as controls. The compartments represent phases of the cell-cycle and allow for a realistic modeling of different actions of the drugs. This is a multi-input optimal control problem over a prescribed therapy horizon with the objective to minimize a weighted average of the cancer cells in the various compartments, both over the course of therapy and at the end of the therapy horizon, while keeping the side effects of the drugs under control. Optimal controls are bang-bang and numerical examples of optimal solutions over longer therapy horizons will be given. The construction of a local field of bang-bang extremals is used to prove the strong local optimality of the computed solutions.

Key–Words: optimal control, multi-input systems, cancer chemotherapy, cell-cycle specific models

1 Introduction

Cancer research has made tremendous progress in the past decades that in turn has led to several novel therapeutic approaches. Many of these involve nontraditional procedures such as, for example, the strive for the development of cancer vaccines, the use of oncolytic adenoviruses that selectively target cancer cells that are deprived of p53, or tumor antiangiogenesis, an indirect cancer treatment approach that targets the vasculature of a developing tumor. While all of these procedures have originally shown promise in in-vivo and even in in-vitro experiments, often their eventual translations into actual therapies have been disappointing. For example, cancer in advanced stages often down regulates proteins that are needed for the adenovirus to enter the cells and this leads to failures in therapy. Anti-angiogenic treatments sometimes only normalize the irregular tumor vasculature eliminating dysfunctional and inefficient vessels and thus may actually lead to improved tumor growth.

Thus the elective forms of cancer treatments still mostly remain surgery (if feasible) and classical chemo- and radiotherapies [1, 6, 7]. In this paper, we consider some cell-cycle specific compartmental models for combination chemotherapies in which a killing agent is combined with a blocking agent and a recruiting agent, respectively. The dynamics of tumor growth under treatment is determined by the various inflows and outflows of the compartments and can be described as a bilinear nonlinear system with the effects of various drugs providing the control inputs [12]. When the question becomes how to optimally schedule these procedures, these become challenging multi-input optimal control systems. In these models, the dimension of the systems increases further if the pharmacokinetics of the therapeutic agents is taken into account. Analyzing these systems with the objective of minimizing the tumor volume while keeping side effects acceptable, allows us to determine the form of the optimal controls and thus give insights into the structure of drug protocols for these treatments. In this paper, we discuss the role of the choice of the objective function as well as the significance of theoretical versus numerical solutions and associated robustness issues.
2 Cell-cycle Specific Models for Combination Chemotherapies

2.1 Biological Background

Each cell passes through a sequence of phases from cell birth to cell division. After an initial growth phase $G_1$, the cell enters a phase $S$ where DNA synthesis occurs. Following a second growth phase $G_2$, the cell prepares for mitosis or phase $M$ that leads to cell division. 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 for optimal control of cancer chemotherapy treat the entire cell cycle as one compartment (e.g. [7, 11]). Multi-compartment models combine phases of the cell cycle into clusters [12] with the purpose of effectively modeling the different types of chemotherapeutic agents used: cytotoxic (killing), cytostatic (blocking) and recruiting agents. Killing agents generally act in the $G_2/M$ phase, since in mitosis $M$ the cell walls become thin and porous and thus the cell is more vulnerable to an attack while there will be a minimal effect on the normal cells. An example of this class is represented by spindle poisons like Vincristine, Vinblastine or Bleomycin [1]. The most commonly used cancer drug, Paclitaxel, also acts in these phases. It binds to tubulin which interferes with the replication and subsequent separation into two daughter-cells thus preventing cell division. Among the blocking drugs we mention Hydroxyurea–HY [6], which is found to synchronize cells by causing brief and invisible inhibition of DNA synthesis in the phase $S$ and holding cells in $G_1$. A recruitment action of cells from the dormant compartment $G_0$ where they are not vulnerable was demonstrated for Granulocyte Colony Stimulating Factors and Interleukin-3. This classification of agents is broad and there clearly exist overlaps in the sense that some drugs have both a cytotoxic and a cytostatic potential. For example, Paclitaxel generally is considered a killing agent since it prevents cell-division and thus does not lead to further cell duplications. But the mechanism arrests cells in the $G_2/M$ phase and does not lead to apoptosis, cell death.

2.2 Bilinear Dynamics

In cell-cycle specific models for cancer therapy, depending on the particular type of cancer that is being considered, an appropriate clustering of the phases of the cell cycle is undertaken. For example, in leukemia cancer cells remain for prolonged times in the dormant stage $G_0$ in which they are not vulnerable and, upon entering the cell cycle, quickly go through cell duplication. Therefore, here recruiting agents become important and in this case the compartment $G_0$ needs to be included. In other models, it plays a minor role and then it becomes more important to synchronize the transition of the cells through the cell cycle to make the killing action more effective in the $G_2/M$ phase. Below we give models for these two examples. The models are based on cell populations and the state $N$ is a vector that gives the average number of cancer cells in the specific compartments with the controls describing the effects of the drug dosages on the respective subpopulation. The transit times of cells through phases of the cell cycle vary, especially in malignant cells. Here, in a first approximation, an exponential distribution is used to model the transit times and the expected number of cells exiting the ith 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 [12]. The controls represent the dose rates of the drug administered with the value 0 corresponding to no treatment and the upper limit corresponding to a maximum dose. Overall, these assumptions lead to a bilinear dynamics of the form

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

with the matrices describing the various in- and out-flows from the compartments.

(A) Combination of a cytotoxic and a cytostatic drug. Here we cluster the cell-cycle into the compartments $G_0/G_1$, $S$, and $G_2/M$ with the killing agent $u_1$ acting in $G_2/M$ and the blocking agent $u_2$ active in the synthesis phase $S$. The matrices in the dynamics (1) are given by

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

and

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

with $a_i$ representing the inverse transit times through the respective compartments and the coefficient 2 arising through cell duplication. It is assumed that the dose rate stands in direct relation to the fraction of cells which are being killed in the $G_2/M$ phase. Therefore only the fraction $1 - u_1$ of the outflow of cells from the last compartment, $-a_3 N_3$, undergoes...
cell division and reenters the first compartment. However, all cells leave compartment $G_2/M$. The blocking agent $u_2$ 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, $a_2 N_2$, is reduced by a factor $1 - v$ to $(1 - v(t))a_2 N_2(t)$, $0 \leq v(t) \leq v_{\text{max}} < 1$. As before, the control $v(t) = 0$ corresponds to no drug being applied while a maximal reduction occurs with a full dose $v_{\text{max}}$.

(B) Combination of a cytotoxic and a recruiting agent. 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 $p_0$ and $p_1$, $p_0 + p_1 = 1$, be the corresponding probabilities with which this happens and now 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 $1 + w$, $0 \leq w \leq w_{\text{max}}$. Again the control $w = 0$ corresponds to no drug being applied while $w = w_{\text{max}}$ occurs with a full dose. For this model the compartments are $G_0$, $G_1$, and $S/G_2/M$ and the matrices for this model are given by

$$A = \begin{pmatrix} -a_0 & 0 & 2p_0 a_2 \\ a_0 & -a_1 & 2p_1 a_2 \\ 0 & a_1 & -a_2 \end{pmatrix},$$

and

$$B_1 = \begin{pmatrix} 0 & 0 & -2p_0 a_2 \\ 0 & 0 & -2p_1 a_2 \\ 0 & 0 & 0 \end{pmatrix}, \quad B_3 = \begin{pmatrix} -a_0 & 0 & 0 \\ a_0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

2.3 Choice of the Objective

The problem of finding an optimal chemotherapy protocol can then be formulated as an optimal control problem over a finite time-interval $[0, T]$, the fixed therapy horizon. The goal is to minimize the number of cancer cells at the end of the therapy session while keeping the toxicity to the normal tissues acceptable. Side effects of the therapy can be included by either explicitly limiting the amounts of drugs to be given a priori (based on medical expertise) or by implicitly limiting their use by including an integral of the control over the therapy interval as a penalty term in the objective so that minimizing controls will have to balance the amount of drugs given with the conflicting objective to kill cancer cells. The choice of the objective is one of the persistent issues in the modeling. Note that the amounts of drugs administered are measured by integrals of the form $\int_0^T u(t) dt$ that are linear in $u$. The form of the objective should be based on the underlying biological situation and not mathematical convenience. It therefore seems questionable to use models that are quadratic in the control. Clearly, these so-called $L_2$-objectives offer mathematical advantages in that the Hamiltonian of the resulting optimal control problem becomes strictly convex with a unique minimum, but they generally lack a biological justification. Therefore we take an objective to be minimized of the following form:

$$J = rN(T) + \int_0^T \left( qN(s) + \sum_{i=1}^m s_i u_i(t) \right) dt \quad (2)$$

The penalty term $rN(T)$ in the objective represents a weighted average of the total number of cancer cells at the end of the therapy interval $[0, T]$ while the term $qN$ in the running cost is included to prevent that the number of cancer cells would increase to unacceptably high levels during the intermediate course of therapy. The number of cancer cells which do not undergo cell division at time $t$ and are considered killed is given by the fraction of ineffective cell divisions. Since the drugs kill healthy cells at a proportional rate, the controls $u_i(t)$ are also used to model the negative effect of the drug on the normal tissue or its toxicity. The coefficients $s_i$ are various nonnegative weights that model the degree of side effects which can be attributed to the specific chemotherapeutic agents. For example, generally a cytotoxic agent is more harmful than a cytostatic drug and thus its coefficient will be higher. All together, the sum in the objective models the cumulative negative effects of the treatment.

2.4 Bang-bang and Singular Controls

Solutions to these models are constructed based on applications of the Pontryagin maximum principle [8], a multiplier type collection of necessary conditions for optimality. For the models formulated here, these conditions indicate so-called bang-bang and singular controls as candidates for optimality [9]. Bang-bang controls correspond to treatment protocols that alternate between maximum doses of chemotherapy with rest periods in between when no drug is administered. Singular controls, on the other hand, correspond to specific time-varying dose rates at less than the maximum rates. For the two models formulated above, it has been been shown analytically that singular controls are not optimal [2, 3]. In fact, the Legendre–Clebsch condition, a necessary condition for optimality of singular controls [9], indicates that these are locally maximizing instead. Thus bang-bang controls become the natural candidates for optimality. However, the maximum principle gives only first order necessary conditions for optimality and thus additional considerations
are needed to ensure at least local optimality. Based on the methods of characteristics [9], it can be shown that the corresponding trajectories remain locally optimal at transversal crossings (the flows corresponding to the two controls involved in the switching cross the switching surface in the state space transversally) while local optimality ceases at a transversal fold (in which case the two flows lie to the same side of the switching surface). The corresponding geometry of the flow is illustrated in Figure 1.

![Figure 1: Transversal crossings and folds for bang-bang trajectories.](image)

An algorithm has been formulated (e.g., see [2]) that allows us to verify which of these types of switchings a flow of bang-bang extremals undergoes. Hence we can determine the local optimality of solutions computed by means of an analysis of the conditions of the maximum principle. This algorithm has been used to establish the local optimality of the bang-bang trajectories shown below for the two examples described above.

For model (A), the inverse cell cycle transit times are taken as \( a_1 = 0.197 \), \( a_2 = 0.395 \) and \( a_3 = 0.107 \) [12] and the coefficients in the objective were taken to be \( r_1 = 1 \), \( r_2 = 0.5 \), \( r_3 = 1 \), \( q_1 = 0.01 \), \( q_2 = 0.2 \), \( q_3 = 0.01 \), and \( s_1 = 100 \), \( s_2 = 0.2 \). The therapy horizon is \([0, 50]\) (in days). Figure 2 shows the optimal cytotoxic and cytostatic agents and the time course of the corresponding bang-bang trajectory for example (A).

![Figure 2: Optimal cytotoxic (top) and cytostatic (middle) agents and time course (bottom) of the corresponding bang-bang trajectory for example (A).](image)

For model (B), the inverse cell cycle transit times are given by \( a_0 = 0.05 \), \( a_1 = 0.5 \) and \( a_2 = 1 \), the probability is given by \( p_0 = 0.9 \), and the coefficients in the objective were taken to be \( r_0 = 2 \), \( r_1 = 1 \), \( r_2 = 1 \), \( q_0 = 3 \), \( q_1 = 1 \), \( q_2 = 1 \), and \( s_1 = 100 \), \( s_2 = 0 \). Again the therapy horizon is \([0, 50]\) (in days) and the initial condition represents the proportions of the steady states for the uncontrolled system. As before, both drugs are given at maximum rates at the beginning to bring down the number of cancer cells and then are turned off as this cell count gets smaller. Towards the end, the number of cells in the dormant compartment \( G_0 \) increases and leads to renewed activation of the recruiting agent.

### 3 Pharmacokinetics of the Drugs

In view of the tremendous complexity of the medical problem that is cancer treatment, for the analysis of mathematical models it makes sense, as it has been done above, to start with simplified models and then...
incorporate increasingly more complex and medically more realistic features into the model. A commonly made simplification in the literature is to identify the drug dosage with its concentration and even more, with its effects. Clearly these are different phenomena and their relations are studied under the names of pharmacokinetics (PK) and pharmacodynamics (PD). Pharmacokinetic equations model the drug’s concentration in the body/plasma (what the body does to the drug) and pharmacodynamics models the effectiveness of the drugs (what the drug does to the body). In short, PK/PD stands for the description of the full process, also known as drug delivery in the medical literature. Thus the question naturally arises whether the structure of optimal controls will change if these more realistic features are included in a model.

3.1 Linear and Bilinear Models for PK

Although almost every drug will have different PK/PD, the general pharmacological features are governed by similar processes. A drug’s concentration is modeled as the solution to a differential equation with the dosage as input. After application of the drug, the concentration builds up (possibly reaching saturation) and then dissipates (usually at a lower rate) once the drug is stopped. A simple 1-compartment linear model for PK takes the form

\[ \dot{c} = -fc + u, \quad c(0) = 0, \quad (3) \]

where the control \( u \) denotes the drug dosage, \( c \) represents the drug’s concentration in the body/plasma and the positive coefficient \( f \) denotes the clearance rate of the drug. More generally, a bilinear system of the form

\[ \dot{c} = -(f + gu)c + hu, \quad c(0) = 0, \quad (4) \]

with an extra \( g \)-term was proposed in [4]. For \( g = 0 \), this model reduces to the standard linear model (3) of exponential growth and decay, but in its full bilinear form with \( g > 0 \) it allows for the feature that concentrations build up to their saturation level at a different (faster) rate than the rate at which the drug is cleared by the system (dissipates) if no additional drugs are given. Pharmacologically this is a desired scenario. Furthermore, such a structure is mathematically compatible with the dynamics (1) and thus easily incorporates into the full model.

3.2 Optimal Controls for Model (A) with a 2-Compartment Linear PK

The most commonly used pharmacokinetic model consists of two linear dynamical systems put in series of the form

\[ \begin{align*}
\dot{c}_1 &= -\alpha c_1 + k_1 c_2 \\
\dot{c}_2 &= -\beta c_2 + k_2 u.
\end{align*} \]

In such a model, the second equation models the concentration of the drug in the blood stream and the first equation models its concentration in the tissue. Below in Figure 4, for the underlying model (A), we show the optimal cytotoxic and cytostatic agents and the time course of the corresponding states when such a 2-compartment model is added as a pharmacokinetic model. The bang-bang property of optimal solutions is not affected by such an addition and again both agents are given at maximum rates from the beginning. But the resulting quantitative changes in the length of the drugs’ administrations are sizable.

4 Conclusion

In any biomedical model, it is of importance to understand the changes that the introduction of a phar-
macokinetic model has on the structure of optimal solutions. For the cell-cycle specific models described above, we have shown that the inclusion of linear 1- and 2-compartment models does not change the qualitative structure of optimal controls [4]. The reason lies with the fact that the optimality status of singular controls is preserved under such an extension [5] and singular controls are not optimal for these models. Thus, it can be argued, that in this case the simplified version of the model suffices to give an accurate structure of optimal protocols although naturally quantitative changes arise. The extent of the quantitative changes clearly depends on the PK parameters. This behavior has to be contrasted with the case when singular controls are optimal, as it is the case for mathematical models for tumor anti-angiogenesis, when qualitative changes arise. In this case, the optimality status of the singular controls is also preserved, but the pharmacokinetic extensions change the so-called order of the singular control (for a definition of this term, e.g., see [9]) leading to more complicated concatenation structures involving chattering arcs [5].

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References