Structure of Optimal Controls for a Cancer Chemotherapy Model with PK/PD

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***Abstract*— A mathematical model for cancer chemotherapy treatment with a single G_2/M specific killing agent is considered as an optimal control problem. The control represents the drug dosage of a single chemotherapeutic agent and the drug dosage enters the objective linearly. In this paper pharmacokinetic equations (PK) which model the drug's plasma concentration and various pharmacodynamic models (PD) in terms of functions representing the concentration effects are included. It is shown that geometric properties of the PK and PD equations determine the qualitative properties of the optimal solution. Here for various models we analyze the local optimality of singular controls which correspond to treatment schedules with varying dosages at less than maximum rate.**

I. Introduction

Mathematical models for cancer chemotherapy treatments have a long history (for a survey of the early efforts see, for example [4], [11]) and have been extensively researched in the eighties and nineties (e.g. [3], [8], [9], [14], [15], [16]). However, the complexity of the underlying biological processes is difficult to capture in a mathematical framework and in many cases our understanding of the dynamics still is incomplete, especially in multi-drug treatments, and/or it may be impossible to determine relevant parameters etc. An important problem in the design of actual chemotherapy protocols is the assessment of the negative side effects of the therapeutic agents. In clinical studies these are determined experimentally: drug dosages are tested by increasing the dosage until the patient experiences limiting side effects. Due to a lack of knowledge of the actual biological mechanisms these side effects therefore can often only be included implicitly in mathematical models. One approach is to aim at minimizing the number of cancer cells at the end of a fixed therapy interval and represent the negative effects on the healthy cells only indirectly by also minimizing the drug dosage in the objective.

More recent models for cancer chemotherapy are cell-cycle specific and treat the cell cycle as the object of control [12]. 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 where 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. 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 wall becomes very thin and porous in mitosis M and thus the cell is more vulnerable to an attack. Clearly drug treatment influences the cell cycle in many possible ways, but here only the most fundamental aspect is considered, *cell-killing*.

In this paper we consider a mathematical model for cancer chemotherapy treatment with a single G_2/M specific killing agent. It is therefore 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. The underlying model is probabilistic [12] and the *state* of the system is given by the average *number of cancer cells* in these compartments and the *control* is the *drug dosage*. The active ingredient in the drug is a cytostatic agent which kills cancer cells and healthy cells alike. The medical goal is to maximize the number of cancer cells which the agent kills while keeping the toxicity to the normal tissue acceptable. The mathematical model which forms the basis of our study here was proposed and originally analyzed as an optimal control problem by Swierniak [12] and then reconsidered by us in [7] with the objective to minimize the number of cancer cells at the end of a fixed therapy interval. However, in the model it is assumed that drug dosage equals its concentration and its effects are instantaneous (or, for that matter, the control variable is considered as the *effect* of the drug). In this paper we augment the underlying model

by introducing a pharmacokinetic (PK) equation which models the time evolution of the drug's concentration in the body/plasma and acts as a controller for the system. We consider a general one-dimensional bilinear model which contains the more standard linear model as special case. But we want to illustrate that nonlinearities influence the character of solutions. For example, the optimality status of singular arcs is preserved under in fact any linear (even higher order) controller and singular controls are not optimal (i.e. treatment schedules with varying dosages at less than maximum rate are not optimal). But for the bilinear model the non-linear term decides the optimality of singular arcs. We also consider several commonly used models for pharmacodynamics (a linear model, the so-called $E_{\max}$ model and sigmoidal functions) which represent the effect of the concentration on the body and we show that geometric properties of these functions (convexity vs. concavity) are essential in determining the optimality of singular arcs. While the model is specified through a number of cell-cycle specific parameters, our results do not depend on the actual values of these parameters, but only on the choice of the PK/PD model.

II. A Two-Compartment Model for Chemotherapy including PK/PD

In this section we describe the underlying model and augment it by pharmacokinetic and pharmacodynamic equations. Then an optimal control problem is formulated for minimizing the number of cancer cells at the end of an assumed fixed therapy interval.

A. The dynamics of the uncontrolled model

This model was originally introduced in [12]. Two compartments are distinguished which combine G_0, G_1 and S and G_2 and M respectively. Let $N_i(t)$, $i = 1, 2$, denote the average 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:

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

In *steady-state* this corresponds to a model of exponential growth of the overall cancer cells $N(t) = N_1(t) + N_2(t)$ at a fixed rate ξ given by the unique positive root of the quadratic equation

$$-x^2 - (a_1 + a_2)x + a_1 a_2 = 0. \tag{3}$$

For, if

$$x = \frac{N_2}{N} \qquad \text{and} \qquad y = \frac{N_1}{N} = 1 - x \tag{4}$$

denote the portions of the cells in the respective compartments, then x satisfies the scalar Riccati equation

$$\dot{x} = -a_2 x^2 - (a_1 + a_2)x + a_1. \tag{5}$$

This equation has a locally asymptotically stable equilibrium at $\bar{x}$ in the open interval $(0, 1)$ which contains the closed interval $[0, 1]$ in its region of attraction and $\xi = a_2\bar{x}$. For example, for the parameters from [12] given by $a_1 = .197$ and $a_2 = .356$ we have that $\bar{x} = 0.2988$ and $\xi = 0.1064$. In particular, in steady state about 30% of the cancer cells are in G_2/M and the cancer cells would be doubling every 6.51 units of time.

B. A model for pharmacokinetics

Drug treatment is represented by a bounded measurable function u which takes values in the compact interval $[0, 1]$. In the model as it was initially considered by Swierniak (e.g. [12]) this variable u actually did not stand for the drug dosages, but the effects of the chemotherapeutic treatment with $u = 1$ representing maximal chemotherapy and $u = 0$ corresponding to no chemotherapy. Pharmacokinetic equations describe how the concentration of the drug builds up in the body and we extend the model by including a simple model for pharmacokinetics. Let u denote the drug dosage with $u = 1$ corresponding to a maximal dose and $u = 0$ denoting no treatment. Typical models in the literature [11], [9] use a first-order linear system of the form

$$\dot{c} = -fc + hu, \qquad c(0) = 0, \tag{6}$$

to represent the dynamics for the drug concentration c in the plasma were f and h are positive constants. The model itself is one of exponential growth/decay as it is commonly used for continuous infusions. Here we change it slightly to a bilinear system of the form

$$\dot{c} = -(f + ug)c + hu, \qquad c(0) = 0. \tag{7}$$

with g another constant (without sign restrictions). 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. For a constant drug dose $\bar{u}$ the maximum concentration is given by

$$c_{\max}(\bar{u}) = \frac{h\bar{u}}{(f + \bar{u}g)}$$

which is attained asymptotically. The parameters f and g can easily be related to standard pharmacokinetic data in terms of the times it takes for the concentration to reach 50% effectiveness by simple algebraic relations. Note that for admissible controls u with values in $[0, 1]$ the concentration will always take values in the interval $[0, h/(f+g))$.

C. Models for pharmacodynamics

Pharmacodynamic equations describe the effect the drug concentration c has on the cancer cells. It is assumed in the model that the effectiveness e of the drug is proportional to the number of ineffective cell-divisions in the G_2/M phase. 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. The effectiveness is given by a function s, for simplicity defined on the interval $[0,\infty)$ with values in the interval $[0,1]$. Depending on the choice of this function qualitatively different models arise. A standardly used model is to simply assume (a) a linear relation

$$s_1(c) = sc \tag{8}$$

where s is a constant, $0 < s \leq 1$. However this is only reasonable over a range of concentration; it is typically not a valid model for a low and high concentration. The so-called (b) $E_{\max}$ model [2] of the form

$$s_2(c) = \frac{E_{\max}c}{EC_{50}+c} \tag{9}$$

more accurately approximates the effectiveness for high concentrations. But it assumes that drugs become effective immediately and thus is only a reasonable model for fast acting drugs. More generally (c) sigmoidal functions [5] capture saturation behavior at both lower and higher concentrations. Commonly used models are

$$s_3(c) = E_{\min} + \frac{E_{\max}-E_{\min}}{1+10^{n(\log ED_{50}-c)}} \tag{10}$$

or its approximation

$$s_4(c) = \frac{E_{\max}c^n}{EC_{50}^n+c^n} \tag{11}$$

where n is a positive integer greater than 1.

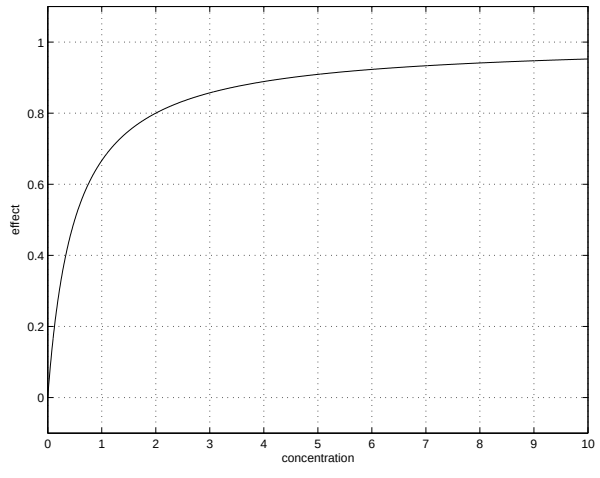

Fig. 1. $E_{\max}$ pharmacodynamics s_2

For our analysis below we only **assume** that s is a *strictly increasing, twice continuously differentiable* function and

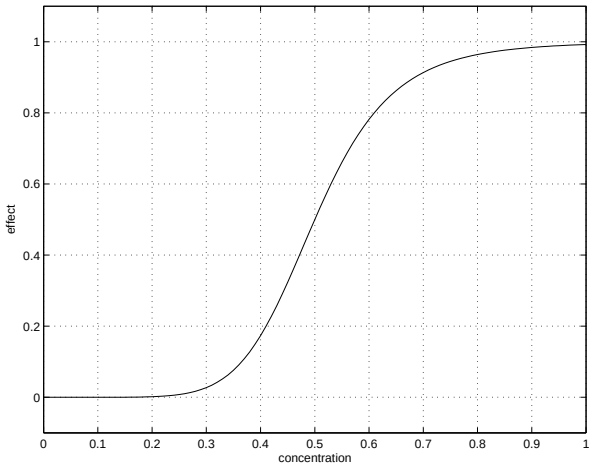

Fig. 2. Sigmoidal pharmacodynamics s_4

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. For a linear function like s_1 or other unbounded models this can be guaranteed by appropriately choosing the model parameters in (7).

D. The controlled dynamics with PK/PD

Adding pharmacokinetic and pharmacodynamic models to the uncontrolled model (1) and (2) we thus obtain

$$\dot{N}_1 = -a_1N_1 + 2(1-s(c))a_2N_2, \quad N_1(0) = N_{10}, \tag{12}$$
$$\dot{N}_2 = a_1N_1 - a_2N_2, \quad N_2(0) = N_{20}, \tag{13}$$
$$\dot{c} = -(f+ug)c + hu, \quad c(0) = 0, \tag{14}$$

with $N_1(0)$ and $N_2(0)$ positive. Setting $N = (N_1, N_2)$, the general form of the dynamics for the number of cancer cells is given by

$$\dot{N} = (A + s(c)B)N, \quad N(0) = N_0, \tag{15}$$

where A and B are the (2×2)-matrices

$$A = \begin{pmatrix} -a_1 & 2a_2 \\ a_1 & -a_2 \end{pmatrix} \quad \text{and} \quad B = \begin{pmatrix} 0 & -2a_2 \\ 0 & 0 \end{pmatrix} \tag{16}$$

Since s takes values in the interval $[0,1]$ it is easily seen that for any control u and corresponding concentration c the trajectory N exists on all of $[0,T]$ and that each coordinate of $N(t)$ remains positive for all times $t \geq t_0$ (c.f. Prop. 3.1 below).

E. Objective

In this paper we consider a performance index in the form

$$J = rN(T) + \int_0^T qN(t) + bu(t)dt \to \min \tag{17}$$

where $r = (r_1, r_2)$ and $q = (q_1, q_2)$ are row-vectors with $r_i > 0$, $q_i \geq 0$ and b is a positive constant. 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. 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 $[0,T]$. 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. Rather than requiring an absolute upper bound, this so-called "soft" constraint implicitly minimizes the cancer cells. 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. This linearity, although it complicates the mathematical analysis, is consistent with the control appearing linearly in the dynamics. This is biologically motivated by identifying cell kill with the number of ineffective cell divisions. It also is appropriate to use the drug dosage u rather than the concentration c as a measure of toxicity since the drug's side effects are manifold and cannot all be measured in terms of cell kill alone.

III. Analysis of the Model with PK/PD Equations

A. Necessary conditions for optimality

First-order necessary conditions for optimality are given by the *Pontryagin Maximum Principle* [10], [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, $\lambda : [0,T] \to (\mathbb{R}^2)^*$, $\mu : [0,T] \to \mathbb{R}^*$, satisfying the adjoint equations with transversality condition,

$$\dot\lambda = -\lambda(A + s(c)B) - q, \qquad \lambda(T) = r, \tag{18}$$

$$\dot\mu = \mu(f + ug) - s'(c)\lambda BN, \qquad \mu(T) = 0, \tag{19}$$

such the optimal control u_* minimizes the Hamiltonian H,

$$H = qN + bu + \lambda(A + s(c)B)N + \mu\left(-(f + ug)c + hu\right), \tag{20}$$

over the control set $[0,1]$ along $(\lambda(t), \mu(t), N_*(t), c_*(t))$.

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 3.1: All states N_i and costates λ_i, $i = 1,2$, are positive over the interval $[0,T]$. The concentration c is zero on some initial interval $[0,\tau]$ if no control is applied and then it is positive and the multiplier μ is negative for $t < T$.

Proof: Clearly for any admissible control u the concentration c takes non-negative values and will be positive once controls are applied. Since the values of s lie in the interval $[0,1]$ it follows that for any value of c the matrix $A + s(c)B$ is an M-matrix (it has negative diagonal and non-positive off-diagonal entries). It easily follows that the states $N_1(t)$ and $N_2(t)$ remain positive for all times (for example, see [7, Prop. 3.1]). Furthermore, $\lambda_i(T) = r_i > 0$ by assumption. Let $\tau = \sup\{t \in [0,T] : \lambda_1(t) \le 0\}$ and $\sigma = \sup\{t \in [0,T] : \lambda_2(t) \le 0\}$. Thus $\lambda_1(\tau) = 0$ and $\lambda_2(\sigma) = 0$. If $\tau = \sigma$, then $\dot\lambda_1(\tau) = -q_1 \le 0$ and $\dot\lambda_2(\tau) = -q_2 \le 0$. If both q_1 and q_2 are zero, then it follows from (18) that $\lambda(t) \equiv 0$ violating the terminal conditions at time T. Hence, at least one of them, say q_1, is positive. But then $\lambda_1(t) < 0$ for $t > \tau$ close to τ contradicting the definition of τ. If $\tau < \sigma$, then $\lambda_1(\sigma) > 0$ and thus $\dot\lambda_2(\sigma) = -\lambda_1(\sigma)2a_2(1 - s(c)) - q_2 < 0$ and again λ_2 is negative for times $t > \sigma$ contradicting the definition of σ. Similarly, if $\tau > \sigma$, then $\dot\lambda_1(\tau) = -\lambda_2(\tau)a_2 - q_1 < 0$ leading to the same contradiction. In particular, it thus follows that

$$\begin{aligned}\lambda(t)BN(t) &= (\lambda_1(t), \lambda_2(t)) \begin{pmatrix} 0 & -2a_2 \\ 0 & 0 \end{pmatrix} N(t) \\ &= -2a_2\lambda_1(t)N_2(t) < 0. \end{aligned} \tag{21}$$

Hence, whenever $\mu(\tau) = 0$, then

$$\dot\mu(\tau) = -s'(c(\tau))\lambda(\tau)BN(\tau) > 0. \tag{22}$$

Since $\mu(T) = 0$, this implies that μ is negative for all earlier times. □

B. Switching function

Optimal controls u_* minimize the Hamiltonian H, i.e.

$$\left[b + \mu(t)(h - gc(t)\right] u_*(t) = \min_{0 \le v \le 1} \left[b + \mu(t)(h - gc(t))\right] v. \tag{23}$$

Thus, if we define the *switching function* Φ by

$$\Phi(t) = b + \mu(t)(h - gc(t), \tag{24}$$

then optimal controls are given as

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ 1 & \text{if } \Phi(t) < 0 \end{cases}. \tag{25}$$

In particular, since $\Phi(T) = b > 0$, optimal controls always end with an interval where $u(t) \equiv 0$. (Intuitively, the addition of a pharmacokinetic model generates a delay in the effectiveness of the control and thus since there are no benefits, but still negative side effects, it is not optimal to administer drugs until the very end of therapy.) A priori the control is not determined by the minimum condition at times when $\Phi(t) = 0$. However, if $\Phi(t) \equiv 0$ on an open interval, then also all derivatives of $\Phi(t)$ 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 $\dot\Phi(\tau) \ne 0$, then the control has a switch at time τ. In order to analyze the structure of the optimal controls we therefore need to analyze the switching function and its derivatives. In this paper we only consider one aspect, namely optimality properties of singular arcs. These properties always are central to establishing a synthesis of solutions.

C. Singular extremals

Assume the control u is singular on some open interval I, i.e. the switching function Φ vanishes on I. In this case the minimum condition (23) does not determine the value of the control. Instead singular controls can be computed by differentiating the switching function in time until the control variable explicitly appears in the derivative, say in $\Phi^{(r)}(t)$, and then solving the resulting equation $\Phi^{(r)}(t) \equiv 0$ for the control. If the corresponding control value is admissible, i.e. has a value between 0 and 1, this defines the singular control. Otherwise the singular arc is not admissible. For a single-input system which is linear in the control it is well-known [6] that r must be even, say $r = 2k$, 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 optimality of a singular arc of order k, the so-called generalized Legendre-Clebsch condition [6], [1], that

$$(-1)^k \frac{\partial}{\partial u} \frac{d^{2k}}{dt^{2k}} \frac{\partial H}{\partial u} \geq 0 \tag{26}$$

along the extremal. Note that the term $\frac{\partial H}{\partial u} = \Phi$ in (26) represents the switching function for the problem.

Differentiating $\Phi = b + \mu(h - gc)$ gives

$$\dot{\Phi} = \mu f h - s'(c)(h - gc)\lambda BN \equiv 0 \tag{27}$$

and thus

$$\begin{aligned} \frac{\partial}{\partial u}\ddot{\Phi} = &\left(\frac{\partial}{\partial u}\dot{\mu}\right) fh - s''(c)\left(\frac{\partial}{\partial u}\dot{c}\right)(h - gc)\lambda BN \\ &+ s'(c)g\left(\frac{\partial}{\partial u}\dot{c}\right)\lambda BN \\ &- s'(c)(h - gc)\frac{\partial}{\partial u}\left(\frac{d}{dt}\lambda BN\right). \end{aligned} \tag{28}$$

But

$$\frac{d}{dt}(\lambda BN) = \lambda[A, B]N - qBN \tag{29}$$

(where $[A, B] = BA - AB$) does not depend on the control and thus it follows from the dynamics and adjoint equations that

$$\begin{aligned} \frac{\partial}{\partial u}\ddot{\Phi} &= \mu g f h - s''(c)(h - gc)^2\lambda BN \\ &\quad + s'(c)g(h - gc)\lambda BN \\ &= g\left(\mu f h + s'(c)(h - gc)\lambda BN\right) \\ &\quad - s''(c)(h - gc)^2\lambda BN. \end{aligned} \tag{30}$$

But $\dot{\Phi} \equiv 0$ along the singular arc and therefore using (27) we get

$$\begin{aligned} \frac{\partial}{\partial u}\ddot{\Phi} &= (h - gc)\lambda BN\left[2gs'(c) - s''(c)(h - gc)\right] \\ &= (h - gc)\lambda BN\left[g\left(2s'(c) + cs''(c)\right) - hs''(c)\right]. \end{aligned} \tag{31}$$

It follows from $\Phi \equiv 0$ that $h - gc > 0$ and by Proposition 3.1 λBN is negative. Hence we have

Proposition 3.2: A singular control of order 1 satisfies the Legendre-Clebsch condition (26) if and only if

$$g\left(2s'(c) + cs''(c)\right) > hs''(c). \tag{32}$$

□

Corollary 3.1: For the case of a linear PD-equation ($g = 0$) singular controls are not optimal in regions where s is strictly convex. □

In particular, for a linear PK-model and a sigmoidal PD-equation, singular controls are not optimal for low concentrations, but the Legendre-Clebsch condition is satisfied and thus feasible singular arcs are expected to be locally optimal at high-concentrations. Singular controls do always satisfy the Legendre-Clebsch condition for the $E_{\max}$-model.

Corollary 3.2: For $g \neq 0$ and a linear PK-model $s(c) = sc$ singular arcs are not optimal if $g < 0$, but they satisfy (26) if $g > 0$. □

A special case arises for a linear PK-model ($g = 0$) in combination with a linear PD-equation $s(c) = sc$, a case often considered in the literature. Here the singular arc is of higher order. For this case the equations above simplify to

$$\Phi = b + h\mu \equiv 0, \tag{33}$$

$$\dot{\Phi} = h\left(\mu f - s\lambda BN\right) \equiv 0, \tag{34}$$

$$\begin{aligned} \ddot{\Phi} &= h\left(f\left(\mu f - s\lambda BN\right) - s\left(\lambda[A, B]N - qBN\right)\right) \\ &= -sh\left(\lambda[A, B]N - qBN\right) \equiv 0. \end{aligned} \tag{35}$$

Differentiating once more gives

$$\begin{aligned} \dddot{\Phi} = -sh\big(&\lambda[A + scB, [A, B]] - q[A, B]N \\ &-qB(A + scB)N\big) \equiv 0. \end{aligned} \tag{36}$$

Since only $\dot{c}$ explicitly depends on the control, it follows that

$$\frac{\partial}{\partial u}\Phi^{(4)} = -s^2 h\left(\frac{\partial \dot{c}}{\partial u}\right)\left(\lambda[B, [A, B]]N - qB^2N\right). \tag{37}$$

But $B^2 = 0$ and a direct computation verifies that

$$[B, [A, B]] = -4a_1a_2B. \tag{38}$$

Hence using (34) we have

$$\begin{aligned} \frac{\partial}{\partial u}\Phi^{(4)} &= 4s^2h^2a_1a_2\lambda BN \\ &= 4sfh^2a_1a_2\mu < 0 \end{aligned} \tag{39}$$

violating (26). Thus in this case singular controls are not optimal in agreement with the results in [7]. Summarizing we thus have:

Proposition 3.3: Singular controls are not optimal for the case of a linear PK-model with linear PD-equation. □

In fact, the following result can be shown with similar calculations:

Proposition 3.4: For the case of a linear PD-equation singular controls are not optimal for any order linear PK-model. □

IV. Conclusion

In this paper we initiated the analysis of optimal controls for a simple model of cancer chemotherapy when pharmacokinetic and pharmacodynamic models are included. Our results show that the geometric properties of these models have a direct influence on the type of controls which are optimal. Singular arcs are not optimal if linear models are used, but 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 (typically this holds for low concentrations), the optimality status changes as s becomes concave (as it typically is 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. Research in the direction of analyzing the structure of optimal controls is still ongoing.

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