Annals of the Academy of Romanian Scientists
Series on Mathematics and its Applications
ISSN 2066 - 6594 Volume 3, Number 2 / 2011

TWO OPTIMAL CONTROL PROBLEMS IN CANCER CHEMOTHERAPY WITH DRUG RESISTANCE*

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Abstract

We investigate two well-known basic optimal control problems for chemotherapeutic cancer treatment modified by introducing a time-dependent "resistance factor". This factor should be responsible for the effect of the drug resistance of tumor cells on the dynamical growth for the tumor. Both optimal control problems have common point-wise but different integral constraints on the control. We show that in both models the usually practised bang-bang control is optimal if the resistance is sufficiently strong. Further, we discuss different optimal strategies in both models for general resistance.

MSC 2000: 49 J 15; 49 K 15; 92 C 50.

Keywords: Cancer chemotherapy, optimal control, drug resistance.

1 Introduction

Optimal control problems based on mathematical models for cancer chemotherapy have a long history and obtained a renewed interest in the last years

*Accepted for publication on March 13, 2011.

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‡Lothar von Wolfersdorf passed away on November 30, 2010.

(cf. [2-6, 10-26]). There are further recent papers on mathematical models for immunotherapy and mixed immunotherapy and chemotherapy starting with papers by A. Kuznetsov and coworkers in the nineties (cf. [19,20], for instance) but which are not in our focus here. Instead the present paper follows the two pioneering papers by J.M. Murray in 1990 [16,17] (see also [24]) whose basic problems are modified in the following.

One difficulty in applying the considered optimal control problems in cancer chemotherapy is the occurance of optimal solutions which are seldom or not used in medical practice. A desired optimal solution by the physician is the bang-bang control consisting of a starting interval with maximal dose of drug followed by an interval of zero-therapy till the end of treatment (considering one cycle of the chemotherapeutic treatment). In particular, the therapy should theoretically end with an interval of zero-therapy to have the required minimum of the tumor cells population also somewhat later than at the practical end of treatment. To obtain optimal solutions of this type often a suitable choice of the objective functions is proposed (cf. [14, 17, 19, and 24]).

The aim of the present paper is to circumvent this difficulty taking into account the resistance of the tumor cells against drug (and further using the size of the tumor cells population at the final time as the natural objective function). Acquired and intrinsic resistance of the tumor cells against drug is an important but very complex phenomen in tumor therapy (cf. [8, 12]) and related deterministic models [4, 12, 14] and stochastic ones [2, 3] in dealing with it are developed recently. In our highly simplified model we only consider a summarizing effect of resistance by introducing a time-dependent "resistance factor" in front of the loss function of the tumor cells in the deterministic differential equation for the tumor growth. In particular, we do not distinguish between drug sensitive and resistant tumor cells like in [4, 12, 14].

Further, we deal with two basic problems where in each problem we have two restrictions, namely the usual pointwise inequality for the control function (which is in the dose of the drug administered per unit of time) and an integral inequality for the loss function of the normal cells in the first problem and for the drug dose itself in the second problem. To keep the mathematical analysis simple other restrictions like the pointwise limit for the size of the population of the normal cells like in [15, 17, and 24] are not taken into consideration. There is only one dynamic equation for the growth and suppression of the tumor cells and no one for the normal cells (but which could be easily supplemented).

Both optimal control problems show the desired effect that for (properly defined) "strong resistance" the above-named bang-bang control is the unique optimal control (cp. with the results in [3, 26], for instance). With respect to general resistance we have another picture. In the first problem in case of "weak resistance" the optimal control is the non desired "opposite" bang-bang control with starting interval of zero-therapy and final interval of maximal drug dose. On the other hand, in the second problem for general resistance an optimal control similar to the desired bang-bang control starting and ending with a subinterval of zero-therapy is to be expected as an example with Gompertzian growth show (cp. with other forms of optimal solutions in [14, 17], for instance). So, especially with respect to weak resistance the second problem seems preferable to the first problem.

The plan of the paper is as follows. After performing the mathematical modelling in Section 2 we investigate the first optimal control problem in Section 3 and the second optimal control problem with the example for Gompertzian growth in Section 4.

2 Mathematical Models

We denote the time-dependent number of cancer cells in the tumor by a function $T = T(t)$, $t \in I\!R_+$, which we assume to be differentiable with derivative $\dot{T}(t)$. The temporal development of the tumor cells population $T(t)$ in a given interval $[0, t_f]$ is governed by the differential equation

$$\dot{T}(t) = [f(T(t)) - \varphi(t)L(M(t))]T(t),\ t \in [0, t_f], \tag{2.1}$$

with the initial condition

$$T(0) = T_0 > 0. \tag{2.2}$$

The function $f = f(t), T \geq 0$ describes the dynamics of the tumor population $F(T) = f(T)T$ if there is no administration of drugs. We assume $f \in C^1(I\!R_+)$ with $f(T) > 0$, $f'(T) < 0$ for all relevant $T \geq 0$. This is fulfilled for many of the commonly used dynamics as Gompertz, logistic (Verhulst-Pearl) and other growth laws in an interval $[0, \theta]$ with maximal tumor population θ (cf. [5, 10, 16, 22, 24]).

By $L = L(M)$, $M \geq 0$ we denote the destruction rate of the drug level M. We assume that this loss function $L \in C^2(I\!R_+)$ satisfies $L(0) = 0$ and $L'(M) > 0$ for all relevant $M \geq 0$. This is fulfilled, for instance, for linear and fractional linear ("saturated") function L (cf. [10, 16, 24]). The drug level function $M = M(t)$ obeys the linear differential equation

$$\dot{M}(t) = -\delta M(t) + V(t), \ t \in [0, t_f], \tag{2.3}$$

and the initial condition

$$M(0) = 0 \tag{2.4}$$

with a positive drug decay rate δ where $V(t)$ denotes the drug dose that is administered per unit of time at time $t \in [0, t_f]$. In the following we assume $\delta \geq 0$, thus including the mathematical limit case $\delta = 0$ of no drug decay.

The drug dosis $V = V(t)$ per unit of time is considered as the control function in the model. We assume it to be a bounded measurable function, i.e. $V \in L^\infty(0, t_f)$, and to satisfy the pointwise condition

$$0 \leq V(t) \leq A \ \text{ for a.a. } \ t \in [0, t_f] \tag{2.5}$$

where $A > 0$ is a prescribed constant, the maximum drug dosis per unit of time. Further, below we require additionally an integral condition which we regard as responsible for the compatibility of the treatment.

The new feature in this model is the introduction of the function $\varphi = \varphi(t)$, $t \in [0, t_f]$, which is assumed to be in $C^1[0, t_f]$ satisfying $\varphi(t) > 0$ in $[0, t_f)$ and normed by $\varphi(0) = 1$. The factor φ in Eq. (2.1) should - in a most simple way - describe the total effect of inner influences (like drug resistance) and other ones (like accompanying therapies) on the destruction rate of the tumor cells by the drug during the treatment. Especially, the influence of the drug resistance of the tumor cells will be expressed by a function $\varphi \in C^1[0, t_f]$ with $\varphi(0) = 1$, $\dot{\varphi}(t) \leq 0$ in $[0, t_f]$ and $\varphi(t) > 0$ in $[0, t_f]$. (We call such a function a "resistance factor" in the following).

The integral condition in *problem 1* now reads

$$\int_0^{t_f} \varphi_0(t) L_0(M(t)) dt \leq B \tag{2.6}$$

with a prescribed constant $B > 0$ where $L_0(M)$ is the destruction rate of the normal cells for which we assume the same properties as for the loss function $L(M)$ of the tumor cells above and $\varphi_0 \in C^1[0, t_f]$ with $\varphi_0(t) > 0$ in $[0, t_f)$, $\varphi_0(0) = 1$ is a weight function possessing the analogous meaning for the normal cells as φ for the tumor cells. In *problem 2* we simply require that

$$\int_0^{t_f} V(t) dt \leq B \tag{2.7}$$

with a given constant $B > 0$.

The aim of chemotherapeutic treatment is to make the tumor cells population $T(t_f)$ at the end of the treatment as small as possible. In view of Eq. (2.1) this can be written in the usual form of the minimum condition

$$\int_0^{t_f} [f(T(t)) - \varphi(t) L(M(t))] T(t) dt \to \min . \tag{2.8}$$

We further remark that for a given $V \in L^\infty(0, t_f)$ the solution of (2.3), (2.4) has the form

$$M(t) = M[V](t) = \int_0^t e^{\delta(s-t)} V(s) ds, t \in [0, t_f]$$

which implies $M \in C[0, t_f]$. By our assumptions on f, φ, L we then have $T \in C^1[0, t_f]$ for the corresponding solution $T = T[V]$ of Eq. (2.1).

Our *optimal control problems* are now defined by the minimum condition (2.8) for the state equations (2.1) - (2.4) with the constraints (2.5), (2.6) (*problem 1*) or (2.5), (2.7) (*problem 2*). Here the integral constraints (2.6) and (2.7) can be taken, respectively, in the form

$$Q(t_f) \leq B \text{ or } U(t_f) \leq B \tag{2.9}$$

where the additional state functions $Q = Q(t)$ and $U = U(t)$ are given by the integrals

$$Q(t) = \int_0^t \varphi_0(s) L_0(M(s) ds \text{ and } U(t) = \int_0^t V(s) ds,$$

respectively, or equivalently by the additional state equations

$$\dot{Q}(t) = \varphi_0(t) L_0(M(t)),\ t \in [0, t_f] \tag{2.10}$$

with $Q(0) = 0$ and

$$\dot{U}(t) = V(t), t \in [0, t_f] \tag{2.11}$$

with $U(0) = 0$, respectively.

These optimal control problems always have solutions as follows by adapting the *existence proof* by J.M. Murray in [16] on the basis of Theorem 5.4.4 in [1] (taking into account that for the admissible control $V(t) = 0$ in $[0, t_f]$ the state equation (2.1) has a continuous solution $T(t)$ in $[0, t_f]$ with finite $T(t_f)$ and because of the finite interval $[0, t_f]$ also the parameter $\delta = 0$ in Eq. (2.3) is possible).

Finally, we simplify the mathematical analysis for our problems slightly by applying the usual substitution $y = \ell n T$ for $T > 0$. Then the differential equation (2.1) is transformed into

$$\dot{y}(t) = f(e^{y(t)}) - \varphi(t) L(M(t)), t \in [0, t_f] \tag{2.12}$$

and the initial condition (2.2) reads

$$y(0) = y_0 = \ell n T_0. \tag{2.13}$$

The minimum condition (2.8) takes the form

$$\int_0^{t_f} [f(e^{y(t)}) - \varphi(t)L(M(t))]dt \to \text{ Min.} \tag{2.14}$$

The optimal control problems to be solved are then given by the minimum condition (2.14) for the state equations (2.12), (2.13), (2.3), (2.4), and (2.10) or (2.11), respectively, under the constraints (2.5), (2.9).

3 Solutions of the first problem

We determine optimal solutions of problem (2.12 - 2.14), (2.5), (2.9), (2.10) as usual with the aid of the maximum principle [9]. The Hamiltonian of the problem is given by

$$\begin{aligned} &H(t, y, M, Q, V, p_1, p_2, p_3, \lambda_0) \\ &= (f(e^y) - \varphi(t)L(M))(p_1 - \lambda_0) \\ &+(V - \delta M)p_2 + \varphi_0(t)L_0(M)p_3 \end{aligned} \tag{3.1}$$

with the parameter λ_0 and the adjoint state functions p_k, $k = 1, 2, 3$. If $(\hat{y}, \hat{M}, \hat{Q}, \hat{V})$ is an optimal quadruple there exist a number $\lambda_0 \geq 0$ and three functions $p_k \in C^1[0, t_f]$, $k = 1, 2, 3$ with $(\lambda_0, p_1, p_2, p_3) \neq (0, 0, 0, 0)$ satisfying the differential equations

$$\dot{p}_1(t) = -f'(e^{\hat{y}(t)})e^{\hat{y}(t)}(p_1(t) - \lambda_0) \tag{3.2}$$

$$\dot{p}_2(t) = \varphi(t)L'(\hat{M}(t))(p_1(t) - \lambda_0) + \delta p_2(t) - \varphi_0(t)L_0'(\hat{M}(t))p_3(t) \tag{3.3}$$

$$\dot{p}_3(t) = 0 \tag{3.4}$$

in $[0, t_f]$ and the transversality conditions in t_f

$$p_1(t_f) = 0, p_2(t_f) = 0, \text{ and } p_3(t_f) \leq 0, p_3(t_f)(\hat{Q}(t_f) - B) = 0 \tag{3.5}$$

such that for a.a. $t \in [0, t_f]$ the maximum condition

$$\hat{V}(t)p_2(t) = \max_{0 \leq V \leq A}[Vp_2(t)] \tag{3.6}$$

is valid. From (3.4) and (3.5) it follows that p_3 is a nonpositive constant which vanishes if $\hat{Q}(t_f) < B$.

We define $\tilde{p}_1(t) = p_1(t) - \lambda_0$ and

$$g(t) = -f'(e^{\hat{y}(t)})e^{\hat{y}(t)} > 0, \ t \in [0, t_f]. \tag{3.7}$$

Then from (3.2) we have $\dot{\tilde{p}}_1(t) = g(t)\tilde{p}_1(t)$ which gives

$$\tilde{p}_1(t) = \tilde{p}_1(0)\exp\left(\int_0^t g(s)ds\right), \ t \in [0, t_f]. \tag{3.8}$$

From $p_1(t_f) = 0$ we obtain

$$\tilde{p}_1(t_f) = \tilde{p}_1(0)\exp\left(\int_0^{t_f} g(t)dt\right) = -\lambda_0 \leq 0 \tag{3.9}$$

which shows that $\tilde{p}_1(t) \leq 0$ for all $t \in [0, t_f]$.

We further put

$$h(t) = \varphi(t)L'(\hat{M}(t))\tilde{p}_1(t) - \varphi_0(t)L_0'(\hat{M}(t))p_3. \tag{3.10}$$

From (3.3) we get

$$\dot{p}_2(t) = \delta p_2(t) + h(t), \ t \in [0, t_f] \tag{3.11}$$

which yields $p_2(t) = e^{\delta t}H(t)$ with

$$H(t) = p_2(0) + \int_0^t e^{-\delta s}h(s)ds, \ t \in [0, t_f]. \tag{3.12}$$

In view of $p_2(t_f) = 0$ we have

$$p_2(0) = -\int_0^{t_f} e^{-\delta t} h(t)dt \tag{3.13}$$

which implies

$$p_2(t) = -e^{\delta t} \int_t^{t_f} e^{-\delta s} h(s)ds, \ t \in [0, t_f]. \tag{3.14}$$

Now we distinguish the two cases

$$B \geq Q_A(t_f) \equiv \int_0^{t_f} \varphi_0(t) L_0(M_A(t))dt \tag{3.15}$$

where

$$M_A(t) = \frac{A}{\delta}[1 - e^{-\delta t}] \text{ if } \delta > o, At \text{ if } \delta = 0$$

is the solution of (2.3), (2.4) for $V(t) = A$ a.e. in $[0, t_f]$, and

$$B < Q_A(t_f) \equiv \int_0^{t_f} \varphi_0(t) L_o(M_A(t))dt. \tag{3.16}$$

If (3.15) is fulfilled we have the optimal solution $\hat{V}(t) = A$ a.e. in $[0, t_f]$. So we can assume (3.16) in the following. In this case the equality

$$\hat{Q}(t_f) \equiv \int_0^{t_f} \varphi_0(t) L_0(\hat{M}(t))dt = B \tag{3.17}$$

for the optimal solutions must hold. We prove this by contradiction. If $\hat{Q}(t_f) < B$ we have $p_3 = 0$. In the anormal case $\lambda_0 = 0$ by (3.9), (3.8) and (3.10), (3.14) this implies $p_1(t) = \tilde{p}_1(t) = 0$ and $p_2(t) = 0$ in $[0, t_f]$ which contradicts the condition $(\lambda_0, p_1, p_2, p_3) \neq (0, 0, 0, 0)$. In the normal case $\lambda_0 > 0$ by (3.8) we would have $\tilde{p}_1(t) < 0$ and hence by (3.10) also $h(t) < 0$ in $[0, t_f]$ which by (3.14) yields $p_2(t) > 0$ in $[0, t_f]$. The maximum condition (3.6) then would give $\hat{V}(t) = A$ for a. a. $t \in [0, t_f]$. This implies $Q_A(t_f) = \hat{Q}(t_f) < B$, a contradiction to (3.16). Therefore, (3.17) and $p_3 < 0$ hold true.

We further show because of the condition (3.17) the abnormal case $\lambda_0 = 0$ cannot occur. Namely, from $\lambda_0 = 0$ as before we obtain $\tilde{p}_1(t) = p_1(t) = 0$ in $[0, t_f]$ implying

$$h(t) = -\varphi_0(t) L_0'(\hat{M}(t)) p_3 > 0,\ t \in [0, t_f]$$

from (3.10). By (3.14) it follows that $p_2(t) < 0$ in $[0, t_f]$. Then (3.6) yields $\hat{V}(t) = 0$ for a.a. $t \in [0, t_f]$ which by (2.3), (2.4) leads to $\hat{M}(t) = 0$ in $[0, t_f]$ and by $L(0) = 0$ to $\hat{Q}(t_f) = 0$, a contradiction to (3.17). Summing up, in the case (3.16) equality (3.17) is valid and we have $\lambda_0 > 0$, $\tilde{p}_1(t) < 0$ in $[0, t_f]$ and $p_3 < 0$.

We introduce the functions

$$q(t) = \frac{L_0'(\hat{M}(t))}{L'(\hat{M}(t))}, \Delta(t) = \varphi(t)\tilde{p}_1(t) - \varphi_0(t) q(t) p_3 \tag{3.18}$$

so that by (3.10) we have $h(t) = L'(\hat{M}(t))\Delta(t)$ with $sign h(t) = sign \Delta(t)$. Now we make the *assumption* that Δ is a strictly increasing function in $[0, t_f]$ which is fulfilled if

$$\frac{d}{dt}\Delta(t) \equiv \frac{d}{dt}[\varphi(t)\tilde{p}_1(t) - \varphi_0(t) q(t) p_3] > 0 \text{ in } (0, t_f). \tag{3.19}$$

We distuingish the three cases

(i) $\Delta(0) \geq 0$

(ii) $\Delta(0) < 0, \Delta(t_f) \leq 0$

(iii) $\Delta(0) < 0, \Delta(t_f) > 0$.

In case (i) we have $\Delta(t) > \Delta(0) \geq 0$ in $[0, t_f]$ implying $h(t) > 0$ in $(0, t_f]$ and $p_2(t) < 0$ in $[0, t_f)$ by (3.14). The condition (3.6) then yields the solution $\hat{V}(t) = 0$ a.e. in $[0, t_f]$ which is not possible.

In case (ii) we have $\Delta(t) < \Delta(t_f) \leq 0$ in $[0, t_f]$ which gives $h(t) < 0$ in $[0, t_f]$ and $p_2(t) > 0$ in $[0, t_f]$ by (3.14) again. In view of (3.6) then $\hat{V}(t) = A$ a.e. in $[0, t_f]$ which is also not allowed in the case of (3.16).

It remains the case (iii). By the strict monotonicity of Δ there exists exactly one $t_1 \in (0, t_f)$ with $\Delta(t_1) = 0$, $\Delta(t) < 0$ in $[0, t_1)$, and $\Delta(t) > 0$ in $(t_1, t_f]$. This implies the analogous inequalities for h. Therefore the function H in (3.12) is strictly decreasing from $H(0) = p_2(0)$ to $H(t_1) < p_2(0)$ and then strictly increasing from $H(t_1)$ to $H(t_f) = 0$. If now $p_2(0) \le 0$ were true we would get $H(t) < 0$ and hence $p_2(t) < 0$ in $(0, t_f)$. This would imply $\hat{V}(t) = 0$ a.e. in $[0, t_f]$ again. Therefore, it must be $p_2(0) > 0$. Then there exists exactly one $t_0 \in (0, t_1)$ with $H(t_0) = 0$, $H(t) > 0$ in $[0, t_0)$ and $H(t) < 0$ in $(t_0, t_f]$ which implies $p_2(t) > 0$ in $[0, t_0)$ and $p_2(t) < 0$ in $(t_0, t_f]$. The maximum condition (3.6) yields the unique optimal solution

$$\hat{V}(t) = \begin{cases} A & \text{for a.a.} \quad t \in [0, t_0) \\ 0 & \text{for a.a.} \quad t \in (t_0, t_f] \end{cases} \tag{3.20}$$

where $t_0 \in (0, t_f)$ can be defined as the (unique) solution of the equation

$$\int_0^{t_f} \varphi_0(t) L_0(\hat{M}(t))dt = B \tag{3.21}$$

with

$$\hat{M}(t) = \begin{cases} \frac{A}{\delta}[1 - \bar{e}^{\delta t}] & \text{if} \quad \delta > 0, At \quad \text{if} \quad \delta = 0 \quad \text{for} \quad t \in [0, t_0] \\ \frac{A}{\delta}[e^{\delta t_0} - 1]\bar{e}^{\delta t} & \text{if} \quad \delta > 0, At_0 \quad \text{if} \quad \delta = 0 \quad \text{for} \quad t \in (t_0, t_f] \end{cases}$$

following from (3.17) and (2.3), (2.4) with (3.20).

We summarize the result in

THEOREM 3.1

(i) Let (3.15)be fulfilled. Then problem 1 has the unique optimal solution $\hat{V}(t) = A$ a.e. in $[0, t_f]$.

ii) Let (3.16) be fulfilled and the function Δ in (3.18) strictly increasing. Then problem 1 has the unique optimal solution (3.20) with (3.21).

REMARKS. The monotonicity assumption on Δ in Theorem 3.1 is an implicit condition on φ (and φ_0) since the functions $\tilde{p}_1$by (3.8) and q by (3.18) in general depend on the optimal solution $\hat{V}$ of the problem with the function

φ in (2.1) (and φ_0 in (2.6)). But this dependence can be well derived from (3.20) with (3.21) and Eqs. (2.1), (2.3). Moreover, in the important particular case $L = cL_0$ with a constant $c > 0$ and $L_0 \in C^1(I\!R_+)$ (cf. [16, 17]) we have $q(t) = c$ and for $\varphi_0(t) = 1$ in $[0, t_f]$ the sufficient condition (3.19) reduces to the simple condition

$$\dot{\varphi}(t) + g(t)\varphi(t) < 0 \text{ in } (0, t_f) \tag{3.22}$$

with the positive function $g = -f'(\hat{T})\hat{T}$ by (3.7). Further, in the special case of Gompertzian growth $f(T) = \lambda \ell n \frac{\theta}{T} (\lambda, \theta > 0)$ we have $g = \lambda$, a constant which is independent of the optimal solution $\hat{V}$.

Condition (3.22) is for instance satisfied, if

$$\varphi(t) = \exp(-(\int\limits_0^t g(s)ds + \gamma t)),\ t \in [0, t_f],$$

for some $\gamma > 0$.

In general, it remains the dependence of Δ on the (negative) parameter p_3 or equivalently on the (positive) quotient $p_3/\tilde{p}_1(0)$ which are not directly expressed by the optimal solution $\hat{V}$. To avoid this dependence we derive a further sufficient criterion for the optimal solution (3.20) in the sequel.

LEMMA 3.2
Under the conditions (3.16) and

$$\frac{d}{dt}[\rho(t)p_2(t)] < 0 \text{ in } (0, t_f) \tag{3.23}$$

with a nonnegative function $\rho \in C^1(0, t_f)$ the optimal solution of problem 1 is uniquely determined and has the form (3.20).

Proof. Because of (3.23) the optimal solution cannot contain singular parts in subintervals where $\dot{p}_2(t) = p_2(t) = 0$ and parts of the form

$$\hat{V}(t) = \begin{cases} 0 & \text{a.e. in} \quad [t_1, \tau) \\ A & \text{a.e. in} \quad (\tau, t_2] \end{cases}$$

with $0 \le t_1 < \tau < t_2 \le t_f$ where $p_2(t) \le 0$ in (t_1, τ), $p_2(\tau) = 0$, $p_2(t) \ge 0$ in (τ, t_2) and $\dot{p}_2(\tau) \ge 0$. Further, the solutions $\hat{V}(t) = 0$ a.e. in $[0, t_f]$ and

$\hat{V}(t) = A$ a.e. in $[0, t_f]$ are not possible in view of (3.16) with (3.17). This proves the lemma.

In view of (3.11) the condition (3.23) can be written in the form

$$[\dot{\rho}(t) + \delta g(t)]p_2(t) + \rho(t)h(t) < 0 \text{ in } (0, t_f) \tag{3.24}$$

with h defined in (3.10). Taking

$$\rho(t) = \exp(\int_0^t \mu(s)ds),\ \mu \in C(0, t_f)$$

and $r(t) = \mu(t) + \delta \in C(0, t_f)$ condition (3.24) simply writes

$$r(t)p_2(t) + h(t) < 0 \text{ in } (0, t_f).$$

By (3.10) and (3.14) this means

$$\Delta_1(t) + p_3\Delta_2(t) < 0 \text{ in } (0, t_f) \tag{3.25}$$

where

$$\begin{aligned}
\Delta_1(t) &= \varphi(t)L'(\hat{M}(t))\tilde{p}_1(t) - r(t)\int_t^{t_f} e^{\delta(t-s)}\varphi(s)L'(\hat{M}(s))\tilde{p}_1(s)ds, \\
\Delta_2(t) &= r(t)\int_t^{t_f} e^{\delta(t-s)}\varphi_0(s)L_0'(\hat{M}(s))ds - \varphi_0(t)L_0'(\hat{M}(t)).
\end{aligned}$$

We now choose $r \in C(0, t_f)$ such that $\Delta_2(t) = 0$ in $(0, t_f)$, i.e.

$$r(t) = \frac{e^{-\delta t}\varphi_0(t)L_0'(\hat{M}(t))}{\int_t^{t_f} e^{-\delta s}\varphi_0(s)L_0'(\hat{M}(s))ds}.$$

Then (3.25) simplifies to the condition $\Delta_1(t) < 0$ in $(0, t_f)$ or defining further the quotient

$$q_1(t) = \frac{\tilde{p}_1(t)}{\tilde{p}_1(0)} = \exp(-\int_0^t f'(\hat{T}(s))\hat{T}(s)ds) > 0 \tag{3.26}$$

by (3.7), (3.8) to the *integral inequality*

$$\begin{aligned} & q_1(t)\varphi(t) \int_t^{t_f} e^{-\delta s}\varphi_0(s)L_0'(\hat{M}(s))ds \\ & > q(t)\varphi_0(t) \int_t^{t_f} e^{-\delta s}\varphi(s)L'(\hat{M}(s))q_1(s)ds \end{aligned} \tag{3.27}$$

in $(0, t_f)$ where q is defined in (3.18). A sufficient condition for (3.27) is the *differential condition*

$$\begin{aligned} & \tfrac{d}{dt}[q_1(t)\varphi(t)] \int_t^{t_f} e^{-\delta s}\varphi_0(s)L_0'(\hat{M}(s))ds \\ & < \tfrac{d}{dt}[q(t)\varphi_0(t)] \int_t^{t_f} e^{-\delta s}\varphi(s)L'(\hat{M}(s))q_1(s)ds \text{ in } 0, (t_f). \end{aligned} \tag{3.28}$$

Summing up we obtain

THEOREM 3.2

i) *Let (3.16) and (3.27) with (3.18), (3.26) be fulfilled. Then problem 1 has the unique optimal solution (3.20) with (3.21).*

ii) *The integral condition (3.27) is satisfied if the differential condition (3.28) is valid.*

REMARKS. The conditions (3.27) and (3.28) do not contain the unknown parameters p_3 and $\tilde{p}_1(0)$. In the particular case $L = cL_0$ with $\varphi_0(t) = 1$ from (3.28) we get the condition (3.22) again.

Finally, we briefly deal with the cases where in Theorem 3.1 the function Δ is strictly decreasing and the inequalities (3.19) and (3.27) in Theorems 3.1 and 3.2, respectively, are fulfilled with the opposite signs. In particular, this is the case if $L = cL_0$ and $\varphi(t) = \varphi_0(t) = 1$ on $[0, t_f]$. Then the above analysis shows that the unique optimal solution of problem 1 is

$$\hat{V}(t) = \begin{cases} 0 & \text{for} \quad a.a.t \in [0, t_*) \\ A & \text{for} \quad a.a.t \in (t_*, t_f] \end{cases} \tag{3.29}$$

where $t \in (0, t_f)$ is the (unique) solution of the equation

$$\int_{t_*}^{t_f} \varphi_0(t) L_0(\hat{M}(t)) dt = B$$

with $\hat{M}(t) = 0$ for $t \in [0, t_*]$ and

$$\hat{M}(t) = \frac{A}{\delta}[d^{\delta(t_* - t} - 1] \text{ if } \delta > 0,\ A(t - t_*) \text{ if } \delta = 0$$

for $t \in [t_*, t_f]$ following from (3.17) and (2.3), (2.4) with (3.29) again.

In case of the conditions (3.19) or (3.27), (3.28) for a resistance factor φ (with some associated φ_0) we say that we have *strong resistance* of the tumor cells against the drug, and in case of these conditions with the opposite sign *weak resistance*.

4 Solutions of the second problem

Problem (2.12 - 2.14), (2.5), (2.9), (2.11) possesses the Hamiltonian

$$\begin{aligned} &H(t, y, M, U, V, p_1, p_2, p_3, \lambda_0) \\ &= (f(e^y) - \varphi(t)L(M))(p_1 - \lambda_0) + (V - \delta M)p_2 + Vp_3 \end{aligned} \tag{4.1}$$

with the parameter λ_0 and the adjoint state functions $p_k, k = 1, 2, 3$. If $(\hat{y}, \hat{M}, \hat{U}, \hat{V})$ is an optimal quadruple, by the maximum principle [9], there exist a number $\lambda_0 \geq 0$ and three functions $p_k \in C^1[0, t_f]$, $k = 1, 2, 3$ with $(\lambda_0, p_1, p_2, p_3) \neq (0, 0, 0, 0)$ satisfying the differential equations

$$\dot{p}_1(t) = -f'(e^{\hat{y}(t)})e^{\hat{y}(t)}(p_1(t) - \lambda_0) \tag{4.2}$$

$$\dot{p}_2(t) = \varphi(t)L'(\hat{M}(t))(p_1(t) - \lambda_0) + \delta p_2(t) \tag{4.3}$$

$$\dot{p}_3(t) = 0 \tag{4.4}$$

in $[0, t_f]$ and the transversality conditions in t_f

$$p_1(t_f) = 0, p_2(t_f) = 0, \text{ and } p_3(t_f) \leq 0, p_3(t_f)(\hat{U}(t_f) - B) = 0 \tag{4.5}$$

such that for a.a. $t \in [0, t_f]$ the maximum condition

$$\hat{V}(t)(p_3(t) + p_3) = \max_{0 \leq V \leq A} [V(p_2(t) + p_3)] \tag{4.6}$$

holds. By (4.4), (4.5) p_3 is a nonpositive constant which vanishes if $\hat{U}(t_f) < B$.

We remark that in the limit case $\delta = 0$ in view of (2.3), (2.4) and (2.11) the quantities U and M coincide. Hence U, p_3 could be omitted and formally $p_2(t) + p_3$ replaced by a new $p_2(t)$.

We define the functions $\tilde{p}_1$ and g as in problem 1 with the relations (3.7) - (3.9). Further we have the relations (3.11) - (3.14) for p_2 if we replace the function h in (3.10) by

$$h_0(t) = \varphi(t) L'(\hat{M}(t), \tilde{p}_1(t), \; t \in [0, t_f]. \tag{4.7}$$

Discussing the optimal solutions of problem 2 we distinguish the two cases $B \geq t_f A$ and $B < t_f A$. For $B \geq T_f A$ the obvious solution is $\hat{V}(t) = A$ for a.a. $t \in [0, t_f]$. For $B < t_f A$ we have the equality

$$\hat{U}(t_f) = \int_0^{t_f} \hat{V}(t) dt = B \tag{4.8}$$

and the inequalities $p_3 < 0$, $\lambda_0 > 0$, and $\tilde{p}_1(t) < 0$ in $[0, t_f]$ which can be shown as above in problem 1. By (4.7) this implies $h_0(t) < 0$ in $[0, t_f]$ which by (3.11) and (3.14) gives

$$\dot{p}_2(t) - \delta p_2(t) < 0, p_2(t) > 0 \text{ in } [0, t_f). \tag{4.9}$$

If additionally $\varphi(t_f) > 0$ then also $h_0(t_f) < 0$ and consequently $\dot{p}_2(t_f) < 0$.

From (4.9) we obtain a first result about the form of the optimal solutions in the case $B < t_f A$.

LEMMA 4.1

For $B < t_f A$ the optimal solutions of problem 2 do not contain a solution part of the form

$$\hat{V}(t) = A \text{a.e. for } t \in [\tau, t_f], \tau \in [0, t_f) \tag{4.10}$$

and if $\varphi(t_f) > 0$ they do not contain singular parts in intervals of the form $[\tau, t_f]$ with $\tau \in [0, t_f)$.

Proof: The assertion (4.10) for $\tau = 0$ follows from (4.14). For $\tau > 0$ we have $p_2(t) + p_3 \geq 0$ in $(\tau, t_f]$ and $p_2(\tau) + p_3 = 0$ implying $\dot{p}_2(\tau) \geq 0$, but since $p_2(\tau) = -[p_2(t_f) + p_3] \leq 0$ by (4.9) it must be $\dot{p}_2(\tau) < \delta p_2(\tau)$ and $\dot{p}_2 < 0$.

The proof for the singular parts is a consequence of the condition $\dot{p}_2(t) = 0$ in $[\tau, t_f]$ which leads to a contradiction to $\dot{p}_2(t_f) < 0$ from (4.9).

Lemma 4.1 shows that the optimal solutions of problem 2 end with an interval of zero-therapy if $\varphi(t_f) > 0$.

We now give a *sufficient condition* for the optimal solutions being of the (in practice desired) bang-bang control type.

LEMMA 4.2

Under the conditions $B < t_f A$ and

$$\dot{p}_2(t) < 0 \text{ in } (0, t_f) \tag{4.11}$$

the optimal solution of problem 2 is uniquely determined and has the form

$$\hat{V}(t) = \begin{cases} A & \text{for a.a.} \quad t \in [0, t_0) \\ 0 & \text{for a.a.} \quad t \in (t_0, t_f] \end{cases} \tag{4.12}$$

where $t_0 = B/A \in (0, t_f)$.

Proof. Since $\dot{p}_2(t) \neq 0$ in $(0, t_f)$ the optimal solution does not contain singular parts. Further, it does not contain parts of the forms

$$\hat{V}(t) = 0 \text{ for a.a. } t \in [0, \tau], \tau \in (0, t_f]$$

and

$$\hat{V}(t) = \begin{cases} 0 & \text{for a.a.} \quad t \in (t_1, \tau) \\ A & \text{for a.a.} \quad t \in (\tau, t_2) \end{cases} \quad (0 \leq t_1 < \tau < t_2 \leq t_f)$$

The first one is impossible for $\tau = t_f$ because of (4.8) and for $\tau < t_f$ since we could have $p_2(t) + p_3 \leq 0$ in $(0, \tau)$ and $p_2(\tau) + p_3 \geq 0$ implying $\dot{p}_2(\tau) \geq 0$. For the second one we obtain $p_2(t) + p_3 \leq 0$ in (t_1, τ) and $p_2(t) + p_3 \geq 0$ in (τ, t_2) yielding $\dot{p}_2(\tau) \geq 0$ again. This proves the form (4.12) of the optimal solution $\hat{V}$ with unique value t_0 following from (4.8).

The proof can also be given directly by using the fact that (4.11) implies $p_2(t) > 0$ for all $t \in [0, t_f)$ and discussing the two cases $p_2(0) + p_2 \leq 0$ and $p_2(0) + p_3 > 0$.

By equations (3.11) and (4.7) the condition (4.11) is equivalent to

$$\delta p_2(t) < \phi(t) \text{ in } (0, t_f)$$

where

$$\phi(t) = -h_0(t) = -\varphi(t) L'(\hat{M}(t)\tilde{p}_1(t) > 0 \text{ in } [0, t_f) \tag{4.13}$$

with $\phi(t_f) \geq 0$ and by (3.14) equivalent to the *integral inequality*

$$\psi(t) \equiv \phi(t) - \delta \int_t^{t_f} e^{\delta(t-s)} \phi(s) ds > 0 \text{ in } (0, t_f). \tag{4.14}$$

If (4.14) holds the optimal solution is given by (4.12). In particular, this is fulfilled for all positive functions φ in the limit case $\delta = 0$ suggesting that (4.14) is not a too strong condition on φ for sufficiently small $\delta > 0$.

This can be underlined in the simple case of Gompertz growth (cf. [7, 10, 17, 23 - 25]) where

$$f(T) = \lambda \ell n \frac{\theta}{T}, T > 0, (\lambda > 0, \theta > 0)$$

and a linear loss function

$$L(M) = kM, M \geq 0, (k > 0).$$

In this case we find that

$$g(t) = -f'(e^{\hat{y}(t)}) e^{\hat{y}(t)} = \lambda, h_0(t) = k\varphi(t)\tilde{p}_1(0) e^{\lambda t}, t \in [0, t_f],$$

and (4.14) turns out to be equivalent with

$$\varphi(t)e^{(\lambda-\delta)t} - \delta \int_t^{t_f} \varphi(s)e^{(\lambda-\delta)s}ds > 0 \text{ for all } t \in (0, t_f). \tag{4.15}$$

If we put

$$\varphi(t) = e^{-(\lambda-\delta)t}, t \in [0, t_f],$$

and assume that $\lambda > \delta$, then it follows that $\varphi \in C^1[0, t_f]$,

$$\varphi(0) = 1, \dot{\varphi}(t) < 0 \text{ and } \varphi(t) > 0 \text{ for all } t \in [0, t_f].$$

Further (4.15) turns out to be equivalent to

$$(1 - \delta(t_f - t) > 0 \text{ for all } t \in (0, t_f)) \Longleftrightarrow \delta t_1 < 0.$$

This shows that (4.15) can be satisfied for sufficiently small $\delta > 0$ and a suitable choice of φ.

The inequality (4.14) is fulfilled if we have

$$\dot{\phi}(t) < 0 \text{ in } (0, t_f), \tag{4.15}$$

since integration by parts of the integral in (4.14) yields

$$\psi(t) = e^{\delta t}[e^{-\delta t_f}\phi(t_f) - \int_t^{t_f} e^{-\delta s}\dot{\phi}(s)ds] > 0 \text{ in } (0, t_f)$$

due to $\phi(t_f) \geq 0$ and (4.15). Differentiating (4.13) and using $\dot{\tilde{p}}_1 = g\tilde{p}_1$ we further have

$$\dot{\phi}(t) = -\tilde{p}_1(t)L'(\hat{M}(t))[\dot{\varphi}(t) + \{g(t) + m(t)\}\varphi(t)]$$

where

$$m(t) = \frac{1}{L'(\hat{M}(u)}\frac{d}{dt}[L'(\hat{M}(t))] = \frac{L''(\hat{M}(u)\dot{\hat{M}}(t)}{L'(\hat{M}(t))}. \tag{4.16}$$

Therefore, in view of $\tilde{p}_1(t) < 0$ in $[0, t_f]$ and $L'(M) > 0$, condition (4.15) is equivalent to the *differential inequality*

$$\dot{\varphi}(t) + [g(t) + m(t)]\varphi(t) < 0 \text{ in } (0, t_f) \tag{4.17}$$

where $m = m(t)$ is given by (4.16) and $g = g(\hat{T})$ by (3.17), i.e.

$$g(t) = -f'(\hat{T}(t))\hat{T}(t) < 0, t \in [0, t_f]. \tag{4.18}$$

Condition (4.17) has the same form as condition (3.22) and is like this in general an implicit condition on φ.

Summing up, by Lemma 4.2 and (4.14) - (4.18) we obtain

THEOREM 4.3

(i) *Under the conditions $B < t_f A$ and (4.14) the optimal solution of problem 2 is uniquely determined and has the form (4.12).*

ii) *Asumption (4.14) is satisfied if the condition (4.17) with (4.18) and (4.16) holds true.*

REMARKS. For a linear loss function L we have $m(t) = 0$ in $[0, t_f]$ and the condition (4.17) reduces to (3.22). As for problem 1 we say in case of (4.14) for a resistance factor φ that there is a *strong resistance* of the tumor cells against the drug.

We conclude the paper working out the simple case of Gompertz growth (cf. [7, 10, 17, 23 - 25])

$$f(T) = \lambda \ell n \frac{\theta}{T} (\lambda > 0, \theta > 0) \tag{4.19}$$

with a linear loss function $L(M) = kM$ $(k > 0)$ as an example for what can happen for general resistance.

In this case we have for $y = \ell n T$ the explicit expression

$$\begin{aligned} y(t) &= \ell n T_0 \cdot e^{-\lambda t} + \lambda \ell n \theta [1 - e^{-\lambda t}] \\ &- k \int_0^t e^{-\lambda(t-s)} \varphi(s) M(s) ds \end{aligned}$$

and the minimum condition for $y(t_f)$ leads to the maximum condition

$$\int_0^{t_f} e^{\lambda s}\varphi(s)M(s)ds \longrightarrow \max$$

which can be written in the form

$$\int_0^{t_f} p(t)V(t)dt \longrightarrow \max \tag{4.20}$$

where

$$p(t) = e^{\delta t}\int_0^{t_f} e^{(\lambda-\delta)s}\varphi(s)ds. \tag{4.21}$$

The maximum problem (4.20) where $V \in L^\infty(0,t_f)$ satisfies the restrictions (2.5) and (2.7) is a linear problem of the form of the Neyman-Pearson lemma and can be solved in explicit form. Let be $B < t_f A$. For (4.19) the condition (4.17) is equivalent to the inequality

$$\frac{d}{dt}[e^{\lambda t}\varphi(t)] < 0 \text{ in } (0,t_f).$$

If this is fulfilled the problem has the solution (4.12). We consider further the opposite case that

$$\frac{d}{dt}[e^{\lambda t}\varphi(t)] > 0 \text{ in } (0,t_f) \tag{4.22}$$

incorporating the limit case of non-resistance that $\varphi(t) \equiv 1$ on $[0,t_f]$. For $\delta > 0$ the function (4.21) has the derivative

$$\dot{p}(t) = e^{\delta t}[F(t) - C], t \in [0,t_f]$$

where

$$C = e^{(\lambda-\delta)t_f}\varphi(t_f), F(t) = \int_t^{t_f} e^{-\delta s}\frac{d}{ds}[e^{\lambda s}\varphi(s)]ds.$$

Under the assumption (4.22) the function F is strictly decreasing in $[0, t_f]$ from the value

$$F(0) = \int_0^{t_f} e^{-\delta s} \frac{d}{ds}[e^{\lambda s}\varphi(s)]ds > 0$$

to $F(t_f) = 0$. Hence we have two cases (i) $F(0) \le C$ where $\dot{p}(t) < 0$ in $(0, t_f)$ so that $p(t)$ is strictly decreasing in $[0, t_f]$ and (ii) $F(0) > C$ where there exists a unique $t_0 \in (0, t_f)$ such that $p(t)$ is strictly increasing in $[0, t_0]$ and strictly decreasing in $[t_0, t_f]$ till $p(t_f) = 0$. In case (i) the optimal solution is given by (4.12). In case (ii) the optimal solution has the form

$$\hat{V}(t) = \begin{cases} 0 & \text{a.e. in} \quad [0, t_1) \quad \text{and} \quad (t_2, t_f] \\ A & \text{a.e. in} \quad (t_1, t_2) \end{cases} \tag{4.23}$$

where t_1, t_2 with $0 < t_1 < t_0 < t_2 < t_f$ are uniquely determined by the equations

$$A(t_2 - t_1) = B, p(t_1) = p(t_2).$$

In the particular case $\varphi(t) = 1$ on $[0, t_f]$ we have

$$p(t) = \begin{cases} (e^{(\lambda-\delta)t_f} - e^{(\lambda-\delta)t})e^{\delta t} \text{ if } \lambda > \delta \\ (t_f - t)e^{\delta t} \text{ if } \lambda = \delta \\ (e^{(\lambda-\delta)t} - e^{(\lambda-\delta)t_f})e^{\delta t} \text{ if } \lambda < \delta \end{cases}$$

and

$$C = e^{(\lambda-\delta)t_f}, F(0) = \begin{cases} \frac{\lambda}{\lambda-\delta}[e^{(\lambda-\delta)t_f} - 1] \text{ if } \lambda \neq \delta \\ \lambda t_f \text{ if } \lambda = \delta. \end{cases}$$

Therefore, case (i) occurs if $\lambda t_f \le 1$ for $\lambda = \delta$, $\delta e^{(\lambda-\delta)t_f} \le \lambda$ for $\lambda > \delta$, and $\lambda e^{(\delta-\lambda)t_f} \le \delta$ for $\lambda < \delta$, and case (ii) under the opposite inequalities.

We remark hat the optimal solution (4.23) in case (ii) starts and ends with an interval of zero-therapy.

References

[1] F.H. Clarke, Optimization and Nonsmooth Analysis, Wiley, New York, 1983.

[2] A.J. Coldman, J.H. Goldic, A model for the resistance of tumor cells to cancel chemotherapeutic agents, Math. Biosci. 65 (1983) 291-307.

[3] A. J. Coldman, J.M. Murray, Optimal control for a stochastic model of cancer chemotherapy, Math. Biosci. 168 (2000) 187-200.

[4] M.I.S. Costa, J.M. Boldrini, and R.C. Bassanezi, Drug kinetics and drug resistance in optimal chemotherapy, Math. Biosci. 125 (1995) 191-209.

[5] M. Eisen, Mathematical Models in Cell Biology and Cancer Chemotherapy, Lecture Notes in Biomathematics, Vol. 30, Springer-Verlag, Berlin-Heidelberg-New York, 1979.

[6] K.R. Fister, J.C. Panetta, Optimal control applied to competing chemotherapeutic cell-kill strategies, SIAM J. Appl. Math. 63 (2003) 1954-1971.

[7] C.L. Frenzen, J.D. Murray, A cell kinetics justification for Gompertz' equation, SIAM J. Appl. Math. 46 (1986) 614-629.

[8] J.H. Goldie, Drug resistance in cancer: A perspective, Cancer and Metastasis Reviews 20 (2001) 63-68.

[9] A.D. Joffe, V.M. Tichomirov, Theorie der Extremalaufgaben, Deutscher Verlag der Wissenschaften, Berlin, 1979.

[10] W. Krabs, S.W. Pickl, Modelling, Analysis and Optimization of Biosystems, Springer-Verlag, Berlin–Heidelberg–New York, 2007.

[11] U. Ledzewicz, T. Brown and H. Schüttler, Comparison of optimal controls for a model in cancer chemotherapy with L_1- and L_2-type objectives, Optimization Methods and Software 19 (2004) 339-350.

[12] U. Ledzewicz, H. Schüttler, Drug resistance in cancer chemotherapy as an optimal control problem, Discrete and Continuous Dynamical Systems, Ser. B 6 (2006) 129-150.

[13] R.B. Martin, M.E. Fisher, R.F. Minchin, and K.L. Teo, A mathematical model of cancer chemotherapy with an optimal selection of parameters, Math. Biosci. 99(1990)205-230.

[14] R.B. Martin, M.E. Fisher, R.F. Minctin, and K.L. Teo, Low-intensity combination chemotherapy maximizes host survival time for tumors containing drug-resistant cells, Math. Biosci. 110 (1992) 221-252.

[15] A.S. Matveev, A.V. Savkin, Application of optimal control theory to analysis of cancer chemotherapy regimes, Systems and Control Letters 46 (2002) 311-321.

[16] J.M. Murray, Optimal control for a cancer chemotherapy problem with general growth and loss functions, Math. Biosci. 98 (1990) 273-287.

[17] J.M. Murray, Some optimal control problems in cancer chemotherapy with a toxicity limit, Math. Biosci. 100 (1990) 49-67.

[18] J.M. Murray, Optimal drug regimes in cancer chemotherapy for single drugs that block progression through the cell cycle, Math. Biosci. 123 (1994) 183-193.

[19] L.G. de Pillis, W. Gu, K.R. Fister, T. Head, K. Maples, A. Murugan, T. Neal, and K. Yoshida, Chemotherapy for tumors: An analysis of the dynamics and a study of quadratic and linear optimal controls, Math. Biosci. 209 (2007) 292-315.

[20] L.G. de Pillis, A. Radunskaya, A mathematical tumor model with immune resistance and drug therapy: An optimal control approach, J. Theor. Medicine 3 (2001), 79-100.

[21] L.G. de Pillis, A. Radunskaya, The dynamics of an optimally controlled tumor model: A case study, Math. Comput. Modelling 37 (2003) 1221-1244.

[22] G.W. Swan, Optimal control analysis of a cancer chemotherapy problem, IMA J. Math. Appl. Med. Biol. 4 (1987) 171-184.

[23] G.W. Swan, Applications of Optimal Control Theory in Biomedicine, Marcel Dekker Inc., New York – Basel 1984.

[24] G.W. Swan, Role of Optimal Control Theory in Cancer Chemotherapy, Math. Biosci. 101 (1990) 237-284.

[25] G.W. Swan, T.L. Vincent, Optimal control analysis in the chemotherapy of IgG multiple myeloma, Bull. Math. Biology 39 (1977) 317-337.

[26] A. Swierniak, U. Ledzewicz, and H. Schättler, Optimal control for a class of compartmental models in cancer chemotherapy, Int. J. Appl. Math. Comput. Sci. 13 (2003) 357-368.