On Optimal Protocols for Combinations of Chemo- and Immunotherapy*

Urszula Ledzewicz and Mozhdeh Faraji
Dept. of Mathematics and Statistics,
Southern Illinois University Edwardsville,
Edwardsville, Illinois, USA, 62026-1653,
{uledzew,mfaraji}@siue.edu

Heinz Schättler
Dept. of Electrical and Systems Engineering,
Washington University,
St. Louis, Missouri, USA, 63130-4899,
hms@wustl.edu

***Abstract*— An optimal control problem for combinations of cancer chemotherapy with immunotherapy in form of a boost to the immune system is considered as a multi-input optimal control problem. In the objective, a weighted average of several quantities that describe the effectiveness of treatment is minimized that includes the number of cancer cells at the terminal time, a measure for the immunocompetent cell densities at the terminal point as a negative term, the overall amount of therapeutic agents given as a measure for the side effects of treatment and a small penalty on the terminal time which is free. In the dynamics, a pharmacokinetic model for the concentrations of the pharmaceutical agents is included. The focus of the paper is on the structure of singular arcs. Their local optimality properties will be investigated analytically and then illustrated through numerically obtained results. The resulting geometric structure of optimal controlled trajectories provides some insights into the design of optimal protocols, especially the sequencing of the drugs in these combination treatments.**

I. Introduction

Mathematical models for tumor-immune interactions have a long history dating back at least to Stepanova's classical paper [13] in which a system of two ordinary differential equations was proposed to describe the main interactions between cancer cells and the immune system. Great advances have been made since then in the understanding of the workings of the immune system in connection with research on HIV, yet the main premises of this model remain valid: for small cancer volumes, the immune system can be effective in the control of cancer (*immune surveillance*), but the tumor overwhelms the immune system for large cancer volumes [4], [15]. Tumor-immune system interactions play a significant role in the development of the disease when both a benign (microscopic) and a malignant (macroscopic) stable equilibrium exist. The regions of attractions of these two locally asymptotically stable behaviors are separated by the stable manifold of a saddle point and, geometrically, the aim of therapy can be formulated as to move an initial condition in the region of attraction of the malignant equilibrium point into the region of attraction of the benign equilibrium [8], [9]. In this paper, we consider this problem for a combination of chemo- and immunotherapy when a bilinear pharmacokinetic model for the therapeutic agents is included in the model.

*This material is based upon research supported by the National Science Foundation under collaborative research grants DMS 1008209/1008221.

II. Stepanova's Model for Tumor Immune Interaction

In this paper, we retain Stepanova's original equations, but replace exponential growth for the tumor with a Gompertzian growth model. Stepanova's model gives the advantage of a minimally parameterized model that nevertheless rather accurately models the main aspects of tumor-immune interactions. Let x denote the cancer volume and suppose there exists a fixed carrying capacity $x_\infty < \infty$. Furthermore, let y denote the immunocompetent cell densities, a non-dimensional, order of magnitude quantity related to various types of immune cells (T-cells) activated during the immune reaction. The system then takes the form

$$\dot{x} = -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma x y \tag{1}$$

$$\dot{y} = \mu_I \left(x - \beta x^2\right) y - \delta y + \alpha \tag{2}$$

with all Greek letters denoting constant coefficients. We only briefly indicate the meaning of these coefficients, but refer the reader to [6] for a more detailed discussion.

Equation (2) summarizes the main features of the immune system's reaction to cancer. The coefficient α models a constant rate of influx of T-cells generated through the primary organs and δ is simply the rate of natural death of T-cells. The first term in this equation models the proliferation of lymphocytes. The fact that small tumors stimulate the immune system while large tumors suppress it, is expressed in the model through the inclusion of the factor $(1-\beta x)$ at the term $\mu_I x y$ describing the effects of tumor immune interactions on the immune system. The constant $1/\beta$ thus corresponds to a threshold beyond which the immunological system becomes depressed by the growing tumor. Together, the coefficients μ_I and β are used to calibrate these interactions. Similarly, in the first equation, (1), which models tumor growth employing a Gompertzian function with growth coefficient μ_C, the term $\gamma x y$ describes the elimination effects of the tumor-immune interactions on the cancer volume.

Fig. 1 shows the phase portrait of the system (1) and (2) for the following parameter values: $\alpha = 0.1181$, $\beta = 0.00264$, $\gamma = 1$, $\delta = 0.37451$, $\mu_C = 0.5618$, $\mu_I = 0.00484$, and $x_\infty = 780$. The values for α through δ are taken from the paper by Kuznetsov et al. [4] and the remaining parameters were adjusted to account for Gompertzian growth. The tumor

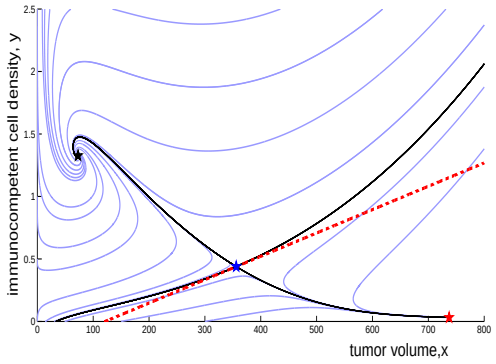

Fig. 1. Phase portrait of the uncontrolled system (1) and (2)

volume x is expressed in terms of multiples of 10^6 cells and y is a dimensionless quantity that describes the immunocompetent cell density as an order of magnitude relative to base value 1. For these parameter values, there exist three equilibria: a *locally asymptotically stable focus* at $(x_b, y_b) = (73.0, 1.327)$ whose region of attraction corresponds to the benign situation, a *saddle point* at $(x_s, y_s) = (356.2, 0.439)$ whose stable manifold is the separatrix between the benign and malignant regions, and an *asymptotically stable node* at $(x_m, y_m) = (737.3, 0.032)$ whose region of attraction defines the malignant situation.

III. Dynamics under Treatment

We consider the system under the action of a chemotherapeutic agent u and a second pharmaceutical agent v that acts on the immune system. We think of the first one as a cytotoxic or killing agent and of the second one as representing rudimentary immunotherapy in the form of an immune boost. Following standard cell-kinetic principles, the so-called *log-kill hypothesis*, we assume that the elimination terms are proportional to the concentrations of the agents and the tumor volume and the immunocompetent cell-densities, respectively. The equations with treatment thus take the form

$$\dot{x} = -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma x y - \kappa_X x c_1, \tag{3}$$

$$\dot{y} = \mu_I \left(x - \beta x^2\right) y - \delta y + \alpha + \kappa_Y y c_2, \tag{4}$$

$$\dot{c}_1 = -\left(\varphi_1 + \theta_1 u\right) c_1 + u, \tag{5}$$

$$\dot{c}_2 = -\left(\varphi_2 + \theta_2 v\right) c_2 + v, \tag{6}$$

where c_1 denotes the concentration of the cytotoxic agent, c_2 the concentration of the immunotherapeutic agent and κ_X and κ_Y are positive coefficients that relate these concentrations to their effect. The dose rates are bounded by $0 \le u \le u_{\max}$ and $0 \le v \le v_{\max}$ with $u_{\max}$ and $v_{\max}$ denoting the maximum rates of the respective agents.

In these equations, the *concentrations* are modeled as the solutions of bilinear differential equations with the *dosage* as input [7]. During application of the drug, the concentration builds up (possibly reaching a saturation plateaux) and then dissipates once the drug is stopped, usually at a lower rate determined by the half-life of the agent. This behavior is captured in the bilinear dynamics through the coefficients φ, the clearance rates of the therapeutic agents, and the coefficients θ that modulate how fast/slow the concentrations build up. For $\theta = 0$ the model reduces to the commonly used linear equations of exponential growth/decay for continuous infusions, but in its bilinear form it allows that concentrations build up to their saturation level at a different (faster) rate from the rate at which the drug is cleared by the system (dissipates). Pharmacologically this is a desired scenario.

Naturally, the model is simplified in many aspects. For example, we did not include a cytotoxic effect of the chemotherapeutic agent on the immune system. Clearly, these exist and the interactions are complex. They might be included as a separate log-kill type term in the equation for $\dot{y}$, but could also be modeled through a factor that reduces the constant influx α of T-cells. This term depends on the bone marrow which is one of the main recipients of the negative side effects of chemotherapeutic drugs. Essentially, in the model above we are assuming that these effects are small and, in a first step towards analyzing such a model, have neglected them. Similarly, implicitly the model assumes that the tumor consists of a homogeneous population of cells that are sensitive to the drug. More generally, however, it is the case that tumors consist of a heterogeneous mixture of sensitive cells and other cells that exhibit various degrees of resistance to the chemotherapeutic agent (Norton-Simon hypothesis). These aspects can be taken into account by augmenting the model with various compartments of partially or fully resistant cancer cells. This leads to a more accurate, but also higher-dimensional and mathematically more challenging system. In a certain sense, the results for the simplified model reported here can be considered a first step towards the analysis of such more realistic models.

IV. Formulation of Treatment as an Optimal Control Problem

The practical aim is to move a given initial state (x_0, y_0) of the system that lies in the region of attraction of the malignant equilibrium point of the uncontrolled system into the region of attraction of the stable, benign equilibrium point while keeping side effects tolerable. In principle, once in the benign region, the uncontrolled dynamics then can take over. We already have described this behavior in the context of chemotherapy only (i.e., for $\kappa_Y = 0$) in [6] and a similar behavior is shown in the context of HIV by Komarova et al. in [3]. Here we want to investigate to what extent the addition of the immune boost can help. In an optimal control formulation, the goal is to make this transfer in an efficient and effective way. Intuitively, this requires to minimize the cancer cells x while not depleting the T-cell density y too strongly. The boundary between the benign and malignant regions consists of the stable manifold of a saddle point and its tangent space, spanned by the stable eigenvector of the saddle point, is easily computed and can serve as a reasonable approximation of the separatrix. This motivates to choose the weights in the objective for the terminal values for

the cancer volume and the immunocompetent cell-densities in the form $Ax(T) - By(T)$ where A and B are positive coefficients given by the stable eigenvector $\mathfrak{v}_s$ of the saddle, $\mathfrak{v}_s = (B, A)^T$. For example, for the parameter values used earlier, normalizing $B = 1$, we have that $A = 0.00192$. Minimizing this quantity thus creates an incentive for the system to move across the separatrix into the benign region.

We only incorporate side effects of the treatment indirectly by adding to the objective to be minimized weighted integral terms $\int_0^T u(t)dt$ and $\int_0^T v(t)dt$ that measure the total amounts of therapeutic agents given. Clearly, side effects are manifold with hematopoietic toxicities that directly effect the parameter α in the model the most common. Here these are all subsumed in the integral of the total dosages and their weights. Finally, we keep the terminal time T free in our problem formulation, but add a small penalty on the terminal time. This makes the problem formulation well-posed (see [6]).

Summarizing, we therefore consider an objective of the following form:

$$J(u) = Ax(T) - By(T) + C\int_0^T u(t)dt + D\int_0^T v(t)dt + ST \tag{7}$$

where A and B are positive coefficients determined by the stable eigenvector $\mathfrak{v}_s = (B, A)^T$ of the saddle and C, D and S are positive weights. This leads to the following optimal control problem in Bolza form:

[OC] for a free terminal time T, minimize the objective (7) over all Lebesgue measurable functions $u : [0, T] \to [0, u_{\max}]$ and $v : [0, T] \to [0, v_{\max}]$ subject to the dynamics (3)–(6).

It is not difficult to see that for positive initial conditions x_0 and y_0 and arbitrary admissible controls u and v, the states x and y remain positive. Thus there is no need to impose positivity as a state-constraint on the variables x and y.

V. Necessary Conditions for optimality

We denote the state by $z = (x, y, c_1, c_2)^T$ and express the dynamics in the form

$$\dot{z} = f(z) + ug_1(z) + vg_2(z) \tag{8}$$

where

$$f(z) = \begin{pmatrix} -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy - \kappa_X x c_1 \\ \mu_I\left(x - \beta x^2\right) y - \delta y + \alpha + \kappa_Y y c_2 \\ -\varphi_1 c_1 \\ -\varphi_2 c_2 \end{pmatrix}$$

is the drift and

$$g_1(z) = \begin{pmatrix} 0 \\ 0 \\ -\theta_1 c_1 + 1 \\ 0 \end{pmatrix} \text{ and } g_2(z) = \begin{pmatrix} 0 \\ 0 \\ 0 \\ -\theta_2 c_2 + 1 \end{pmatrix}$$

are the control vector fields. We call a pair $(z, (u, v))$ consisting of admissible controls u and v and a corresponding solution z of the dynamics (8) with initial condition $z(0) = (x_0, y_0, 0, 0)^T$ a *controlled trajectory*.

First-order necessary conditions for optimality of a pair (u, v) of controls are given by the Pontryagin maximum principle (for some recent texts, see [2], [11]) and we call a controlled trajectory for which there exists a multiplier such that the conditions of the maximum principle are satisfied an *extremal* (pair). It is not difficult to see that in our case the constant multiplier at the objective cannot be zero (extremals are normal) and thus with $H = H(\lambda, z, u, v)$,

$$H = Cu + Dv + S + \langle \lambda, f(z) + ug_1(z) + vg_2(z)\rangle,$$

the (control) Hamiltonian of the problem [OC], these conditions take the following form: if u_* and v_* are optimal controls defined over an interval $[0, T]$ with corresponding trajectory z_*, then there exists a nontrivial absolutely continuous covector, $\lambda : [0, T] \to (\mathbb{R}^4)^*$, that satisfies the adjoint equation

$$\dot{\lambda} = -\frac{\partial H}{\partial z}(\lambda, z_*, u_*, v_*) \tag{9}$$

with terminal condition $\lambda(T) = (A, -B, 0, 0)$ such that for almost every time $t \in [0, T]$, the optimal controls $(u_*(t), v_*(t))$ minimize the Hamiltonian H along $(\lambda(t), x_*(t), y_*(t))$ over the control set $[0, u_{\max}] \times [0, v_{\max}]$ with minimum value given by 0. The terminal condition on the multiplier simply is the transversality condition of the maximum principle.

Since the integral term of the objective does not depend on the state variables x and y, the adjoint equations can succinctly be expressed in the form

$$\dot{\lambda} = -\lambda\left(Df(z_*) + u_* Dg_1(z_*) + v_* Dg_2(z_*)\right) \tag{10}$$

where Df and Dg_i denote the matrices of the partial derivatives of the vector fields f and g, respectively. Since the Hamiltonian is linear in the controls, the minimization condition implies that the controls satisfy the following relations:

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi_1(t) > 0 \\ u_{\max} & \text{if } \Phi_1(t) < 0 \end{cases} \tag{11}$$

and

$$v_*(t) = \begin{cases} 0 & \text{if } \Phi_2(t) > 0 \\ v_{\max} & \text{if } \Phi_2(t) < 0 \end{cases} \tag{12}$$

where Φ_1 and Φ_2 are the corresponding *switching functions* defined by

$$\Phi_1(t) = C + \langle \lambda(t), g_1(z_*(t))\rangle \tag{13}$$

and

$$\Phi_2(t) = D + \langle \lambda(t), g_2(z_*(t))\rangle\,. \tag{14}$$

Thus, whenever one of the switching functions is nonzero, then the corresponding control is locally constant and given by 0 or the maximum dose; we refer to these constant controls as *bang* controls. If $\Phi_i(t) \equiv 0$ on an open interval I, then the corresponding control is called *singular* [2], [11]. Optimal controls generally need to be synthesized from these two classes of candidates.

VI. Singular Controls for Problem [OC]

If the ith control is singular over an open interval I, then all derivatives of the switching function vanish. For model [OC] singular controls are of order 1, i.e., it is possible to determine their structure from the form of the second derivative of the switching function. For the derivatives, the constant terms in the switching function generated by the objective do not matter and since the multiplier λ satisfies the adjoint equation in the form (10), we can compute the derivatives of the switching functions using the following well-known elementary proposition:

Proposition 6.1: Let $z(\cdot)$ be a solution of the dynamics (8) for the controls (u, v) and let λ be a solution of the corresponding adjoint equation (10). For a continuously differentiable vector field h define $\Psi(t) = \langle \lambda(t), h(z(t))\rangle$. Then the derivative of Ψ along an extremal $(z, (u, v), \lambda)$ is given by

$$\dot{\Psi}(t) = \langle \lambda(t), [f + ug_1 + vg_2, h](z(t))\rangle\,, \qquad (15)$$

where $[k, h](z) = Dh(z)k(z) - Dk(z)h(z)$ denotes the Lie bracket of the vector fields k and h. □

A. Singular controls u

Suppose an optimal control u_* is singular on an open interval I so that the switching function Φ_1 and all its derivatives vanish on I. It is easy to see that the control vector fields g_1 and g_2 commute, $[g_1, g_2](z) \equiv 0$, and thus

$$\dot{\Phi}_1(t) = \langle \lambda(t), [f, g_1](z)\rangle \equiv 0. \qquad (16)$$

Applying Proposition 6.1 once more to this formula, it follows that

$$\ddot{\Phi}_1(t) = \langle \lambda(t), [f + ug_1 + vg_2, [f, g_1](z)\rangle \equiv 0 \qquad (17)$$

on I. A direct calculation shows that $[g_2, [f, g_1]](z) \equiv 0$ as well and thus the second control v does not directly affect a singular control. (Obviously, there are indirect effects through the dynamics.) The two second-order brackets appearing in the formula for the second derivative of the switching function are given by

$$[f, [f, g_1]](z) = \begin{pmatrix} \kappa_X x\left(\varphi_1(1 + \theta_1 c_1) + \mu_C(1 - \theta_1 c_1)\right) \\ -\mu_I \kappa_X xy(1 - 2\beta x)(1 - \theta_1 c_1) \\ -\varphi_1^2 \\ 0 \end{pmatrix}$$

and

$$[g_1, [f, g_1]](z) = \begin{pmatrix} -\theta_1 \kappa_X x(1 - \theta_1 c_1) \\ 0 \\ \theta_1 \varphi_1 \\ 0 \end{pmatrix}.$$

Lemma 6.1: It always holds that $\theta_1 c_1(t) < 1$.

Proof. It follows from the pharmacokinetic equation (5) that

$$c_1(t) \le c_{1,\max} = \frac{u_{\max}}{\varphi_1 + \theta_1 u_{\max}}$$

and thus $\theta_1 c_1(t) \le \theta_1 c_{1,\max} < 1$. □

The Lie bracket $[g_1, [f, g_1]]$ lies in the linear span of the vector fields g_1 and $[f, g_1]$. In fact,

$$[g_1, [f, g_1]](z(t)) = \psi_1(t) g_1(z(t)) + \psi_2(t)[f, g_1](z(t) \qquad (18)$$

with

$$\psi_1(t) = \frac{2\varphi_1 c_1(t)}{1 - \theta_1 c_1(t)} \qquad \text{and} \qquad \psi_2(t) \equiv -\theta_1, \qquad (19)$$

and $\psi_1(t)$ is positive. Along a singular control u, we have that $\langle \lambda(t), [f, g_1](z(t))\rangle \equiv 0$ and $\langle \lambda(t), g_1(z(t))\rangle = -C$, and thus it follows that

$$\langle \lambda(t), [g_1, [f, g_1]](z(t))\rangle = -C\psi_1(t) < 0. \qquad (20)$$

Hence *a singular control is of order* 1 *and the Legendre-Clebsch condition for minimality of the singular control is satisfied* [2], [11].

The corresponding singular control is given by

$$u_{\text{sing}}(t) = -\frac{\langle \lambda(t), [f, [f, g_1]](z(t))\rangle}{\langle \lambda(t), [g_1, [f, g_1]](z(t))\rangle}. \qquad (21)$$

In this equation, the multipliers λ_1 and λ_3 are determined by the fact that the switching function and its derivative vanish and the expression determines the singular control as a function dependent on the states and the multiplier λ_2. This multiplier is determined by the structure of the second control v.

B. Singular control v

The computations for a singular control v are analogous. In this case

$$\dot{\Phi}_2(t) = \langle \lambda(t), [f, g_2](z)\rangle \equiv 0 \qquad (22)$$

and

$$\ddot{\Phi}_2(t) = \langle \lambda(t), [f + vg_2, [f, g_2](z)\rangle \equiv 0 \qquad (23)$$

since also $[g_1, [f, g_2]](z) \equiv 0$. (This is a direct consequence of the Jacobi-identity since g_1 and g_2 commute and $[g_2, [f, g_1]](z) \equiv 0$.) Hence the computations are identical, only with the index 1 becoming 2. In particular, for any admissible control it also holds that $\theta_2 c_2(t) < 1$ and the Legendre-Clebsch condition here takes the form

$$\langle \lambda(t), [g_2, [f, g_2]](z(t))\rangle = -D\frac{2\varphi_2 c_2(t)}{1 - \theta_2 c_2(t)} < 0 \qquad (24)$$

and thus again is always satisfied. Now the singular control is given by

$$v_{\text{sing}}(t) = -\frac{\langle \lambda(t), [f, [f, g_2]](z(t))\rangle}{\langle \lambda(t), [g_2, [f, g_2]](z(t))\rangle} \qquad (25)$$

and in this expression the multipliers λ_2 and λ_4 are determined by the fact that the corresponding switching function and its derivative vanish while the multiplier λ_1 depends on the structure of the control u.

C. Totally singular controls u and v

If both controls are singular, all the multipliers are determined and thus these formulas determine the singular controls as feedback functions. In fact, the vector fields g_1, $[f, g_1]$, g_2, and $[f, g_2]$ form a basis and writing the drift vector field f as a linear combination in the form

$$f = \rho_1 g_1 + \rho_2 g_2 + \rho_3 [f, g_1] + \rho_4 [f, g_2],$$

where the ρ_i are smooth functions of the state z, it follows that along an arc where both controls are singular we have

$$\langle \lambda(t), f(z(t)) \rangle = -C\rho_1(z(t)) - D\rho_2(z(t)).$$

Since also

$$H = \langle \lambda(t), f(z(t)) \rangle + u\Phi_1(t) + v\Phi_2(t) + S \equiv 0,$$

in such a case, it follows that

$$C\rho_1(z(t)) + D\rho_2(z(t)) = S. \tag{26}$$

This defines a hypersurface in the state space that supports totally singular controls.

VII. Optimal Controlled Trajectories

We give some examples of optimal controlled trajectories that illustrate typical structures of optimal solutions. For our computations we used the classical ε-approach in which a quadratic penalty term

$$\varepsilon \int_0^T u^2(t) + v^2(t)\ dt$$

is added to the objective and then the optimal controls for the underlying problem are recovered in the limit as $\varepsilon \to 0$ [1].

In all the cases considered below, optimal solutions contain a time interval where the control u is singular. We use identical initial conditions given by $(x_0, y_0) = (600, 0.1)$ in the malignant region. This initial tumor volume is high and for this reason the chemotherapeutic agent is initially given at maximum dose over some small interval $[0, t_1]$. This simply becomes necessary to reduce the large number of cancer cells in a region where immunotherapy is ineffective. Recall that cancer cells are measured in multiples of 10^6 and the variable x ranges in the hundreds while y is a dimensionless normalized to range near 1.

Case 1: Here we take $C = 0.005$, $D = 0.02$, and $S = 0.005$ and the maximum dose rates are equal, $u_{\max} = 2$ and $v_{\max} = 2$. The dose rates of the therapeutic agents along with their concentrations are depicted in the top panel of Figure 2 (chemotherapeutic agent = red, immune boost = green) and the corresponding trajectory is shown in the bottom panel as blue curve. This panel also depicts the stable and unstable submanifolds of the saddle point that generates the separatrix between the benign and malignant regions. For the chemotherapeutic agent, we obtain optimal controls u that qualitatively have the same structure as were observed in [6], [12] when no pharmacokinetic model was included. Following a brief full dose chemotherapy

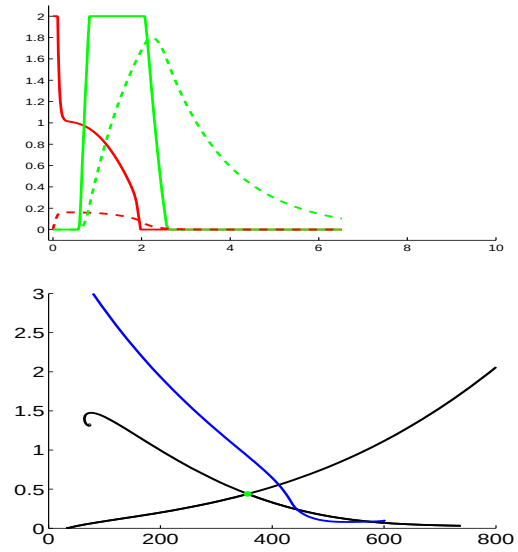

Fig. 2. Examples of optimal controls and concentrations (top) and corresponding controlled trajectories (bottom) with a pharmacokinetic model on both therapeutic agents for "Scenario 1" with coefficients $C = 0.005$, $D = 0.038$, and $S = 0.005$.

treatment, the control u becomes singular and administers chemotherapy at much decreased dose rates as the system approaches the separatrix for the uncontrolled system. In contrast to the model when dose rate and concentration are identified [12], here the dose rates are higher to make up for the smaller concentrations generated by the pharmacokinetic model which diminishes the effects. During the initial phase, the cancer cells decrease only to about 450×10^6. The initial dose thus reduces the number of cancer cells, but by itself does not yet drive the system in the benign region. This is done in combination with a short immune boost that gets activated in a bang-bang switch while the chemotherapeutic agent follows a singular regime. At that time, the trajectory, rather than simply diminishing the cancer cells, also leads to an increase in the value of the immunocompetent cell densities following a more direct route towards the separatrix intersecting it almost orthogonally. The pharmacokinetic parameters for the immune boost are given by $\varphi_1 = \ln(2)$ and $\theta_1 = 0.014$ [14] and have the effect that the concentration c_2 remains significant for quite some time and ensures that the immunocompetent cell densities remain high.

Case 2: For this case, we changed the coefficients in the objective to $C = 0.02$, $D = 0.0335$, and $S = 0.002$. Compared with scenario 1, now chemotherapy has become much more "costly", but overall is used only at slightly lower dose rates. Regardless of the cost imposed on chemotherapy, initially it is always necessary to reduce the high number of cancer cells since immunotherapy simply is not effective in this range. Thus a similar overall picture emerges as in scenario 1. The dosages of the therapeutic agents along with their concentrations again are depicted in the top panel of Figure 3 and the corresponding trajectory is shown in the

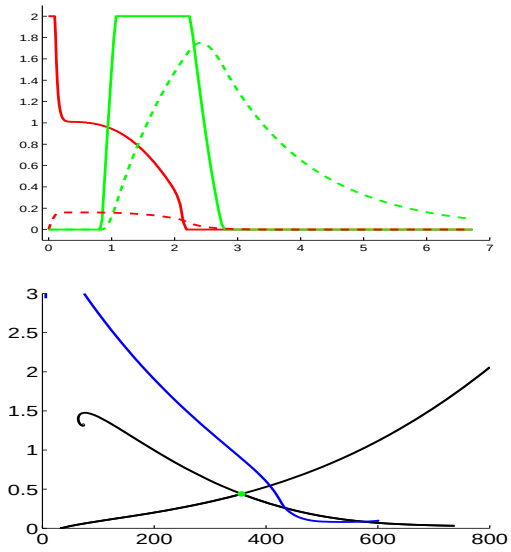

Fig. 3. Examples of optimal controls and concentrations (top) and corresponding controlled trajectories (bottom) with a pharmacokinetic model on both therapeutic agents for "Scenario 2" with coefficients $C = 0.02$, $D = 0.041$, and $S = 0.0025$.

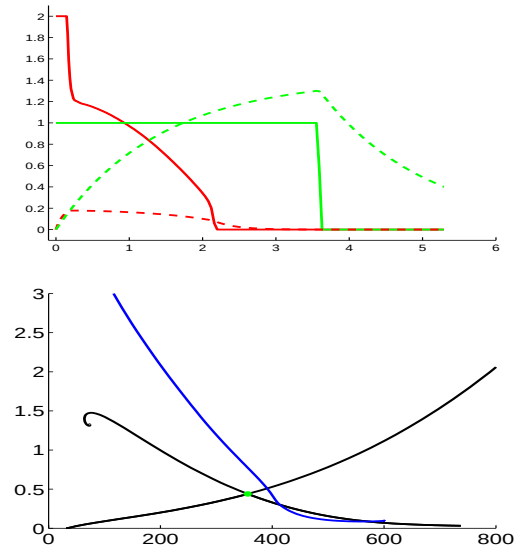

Fig. 4. Examples of optimal controls and concentrations (top) and corresponding controlled trajectories (bottom) with a pharmacokinetic model on both therapeutic agents for "Scenario 3" with coefficients $C = 0.036$, $D = 0.040$, and $S = 0.036$.

bottom panel.

Case 3: The main change in scenario 3 is that we reduced the maximum rate for the immune boost to $v_{\max} = 1$. As a result, the immune boost is given immediately and for much longer duration to make up for a lower maximum concentration. But, once more, similar features emerge, especially if one considers the response of the system shown in the bottom panel of Figure 4.

VIII. Conclusion

We considered a mathematical model for combination of cancer chemotherapy with immunotherapy in form of a boost to the immune system that included pharmacokinetic models for the therapeutic agents as a multi-input optimal control problem. Administrations along intermediate dose rates given by singular controls satisfy the strengthened Legendre-Clebsch condition and thus are expected to be at least locally optimal, but the exact determination of optimal concatenation sequences generally is a challenging problem. In this paper, examples of optimal controls and corresponding trajectories have been computed numerically that confirm optimal administration of the chemotherapeutic agent at dose rates determined by singular controls [5], [6]; in the scenarios considered here, the immune boost is given over a single interval at maximum dose.

References

[1] D.J. Bell and D.H. Jacobson, *Singular Optimal Control Problems*, Academic Press, New York, 1975.

[2] B. Bonnard and M. Chyba, *Singular Trajectories and Their Role in Control Theory*, Mathématiques & Applications, Vol. 40, Springer-Verlag, Paris, 2003.

[3] N.L. Komarova, E. Barnes, P. Klenerman and D. Wodarz, Boosting immunity by anti-viral drug therapy: a simple relationship between timing, efficacy and success, *Proc. Natl. Acad. Sci.*, **100**, (2003), pp. 1855–1860.

[4] V.A. Kuznetsov, I.A. Makalkin, M.A. Taylor and A.S. Perelson, Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis, *Bul. Math. Bio.*, **56**, (1994), 295–321

[5] U. Ledzewicz, M. Naghnaeian and H. Schättler, Dynamics of tumor-immune interactions under treatment as an optimal control problem, Proc. of the 8th AIMS Conf., Dresden, Germany, 2010, pp. 971–980.

[6] U. Ledzewicz, M. Naghnaeian and H. Schättler, Optimal response to chemotherapy for a mathematical model of tumor-immune dynamics, *J. of Mathematical Biology*, DOI 10.1007/s00285-011-0424-6, published online: 08 May 2011, **64**, (2012), pp. 557–577.

[7] U. Ledzewicz and H. Schättler, The influence of PK/PD on the structure of optimal control in cancer chemotherapy models, *Mathematical Biosciences and Engineering (MBE)*, **2**, no. 3, (2005), 561–578,

[8] A. d'Onofrio, A general framework for modeling tumor-immune system competition and immunotherapy: mathematical analysis and biomedical inferences, *Physica D*, **208**, (2005), pp. 220–235

[9] A. d'Onofrio, Tumor-immune system interaction: modeling the tumor-stimulated proliferation of effectors and immunotherapy, *Math. Models and Methods in Applied Sciences*, **16**, (2006), pp. 1375–1401

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

[11] H. Schättler and U. Ledzewicz, *Geometric Optimal Control—Theory, Methods and Examples*, Springer-Verlag, New York, 2012.

[12] H. Schättler, U. Ledzewicz, and M. Faraji, Optimal protocols for a mathematical model of tumor-immune interactions under chemotherapy with immune boost, *Disc. and Cont. Dyna. Syst., Ser. B*, accepted subject to revision.

[13] N.V. Stepanova, Course of the immune reaction during the development of a malignant tumour, *Biophysics*, **24**, (1980), pp. 917–923

[14] T.A. Stoklasek, K.S. Schluns and L. Lefrançois, Combined IL-15/IL-15Ra immunotherapy maximizes IL-15 activity in vivo, *J. of Immunology*, **177**, (2006), pp. 6072–6080.

[15] H.P. de Vladar and J.A. González, Dynamic response of cancer under the influence of immunological activity and therapy, *J. of Theoretical Biology*, **227**, (2004), pp. 335–348