Optimal Protocols for a Mathematical Model of Tumor-Immune Interactions under Chemotherapy with Immune Boost

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Abstract

An optimal control problem for combination of cancer chemotherapy with immunotherapy in form of a boost to the immune system is considered as a multi-input optimal control problem. The objective to be minimized is chosen as a weighted average of (i) the number of cancer cells at the terminal time, (ii) a measure for the immunocompetent cell densities at the terminal point (included as a negative term), (iii) the overall amount of cytotoxic agents, respectively, (iv) the immune boost given as a measure for the side effects of treatment and (v) a small penalty on the free terminal time that limits the overall therapy horizon. This last term is essential in obtaining a well-posed problem formulation. Both analytical and numerical results about the structures of optimal controls will be presented that provide some insights into the structure of optimal protocols, i.e., the dose rates and sequencing of the drugs in these combination treatments.

1 Introduction

In this paper, we consider a multi-input optimal control problem for combinations of cancer chemotherapy with immunotherapy in form of a boost to the immune system. Mathematical

models for tumor-immune interactions have a long history at least dating back to Stepanova's classical paper [34]. In that paper, a simple system consisting of two ordinary differential equations that describe the main interactions between cancer cell growth and the activity of the immune system during the development of cancer is proposed. The main features of tumor-immune system interactions are aggregated into two principal variables, the tumor volume and immunocompetent cell densities relating to the activities of various kind of T-cells. Tremendous progress has been made in the understanding of the workings of the immune system in the 1990s in connection with research on the HIV-virus and by now the interactions between its various components are well-understood and very detailed models for the workings of the immune system exist. Nevertheless, Stepanova's model, and some of its extensions (e.g, the ones by Kuznetsov, Makalkin, Taylor and Perelson who in [15], employing a logistic model for cancer growth, estimate the parameters based on in vivo data of B-lymphoma BCL_1 in the spleen of mice or the one by de Vladar and González [39], who consider a Gompertz model for cancer growth), in their simplicity, and with a small number of parameters, capture the most important features of tumor-immune interactions: for small cancer volumes, the immune system can indeed be effective in the control of cancer, but for large cancer volumes the dynamics suppresses the immune dynamics and the two systems effectively become separated [39, appendix B]. In the first case, so-called *immune surveillance*, what medically would be considered cancer never develops; in the second one, and while the actions of the immune system may still be helpful in controlling small metastases that develop, for the primary tumor only a therapeutic effect (e.g., chemotherapy, radiotherapy, ...) can stop further cancer growth. But tumor-immune system interactions matter greatly for the case "in between". Mathematically, for all the models mentioned above (i.e., Stepanova [34], Kuznetsov et al. [15], de Vladar and Gonzalez [39], and indeed for a general class of models formulated by d'Onofrio [27, 28] that incorporates all these dynamical models), either both a benign (microscopic) and a malignant (macroscopic) stable equilibrium exist or uncontrolled cancer growth is possible. The underlying models are Morse-Smale systems [12] and indeed the regions of attractions of these two, locally asymptotically stable behaviors, are separated by the stable manifold of an unstable equilibrium point. Thus, the question of curing cancer, mathematically becomes the problem of moving an initial condition that lies in the region of attraction of the malignant equilibrium point, the malignant region, for short, into the region of attraction of the benign equilibrium, the benign region. This requires therapy and can naturally be formulated and analyzed as an optimal control problem. In the paper here, we retain Stepanova's model, but use a Gompertz model for cancer growth (an exponential model was used in the original formulation) and consider a combination of a cytotoxic chemotherapeutic agent with a boost to the immune system. While keeping the model small clearly gives up on modeling accuracy, it has the advantage that analytical methods can be brought in that lead to a robust understanding of the qualitative structure of optimal protocols.

Applications of optimal control to models for cancer chemotherapy have a long history and, in fact, have been among the first topics considered in mathematical biology [8, 35, 36]. Recently there has been significant renewed interest in these methods in connection with novel cancer therapies that also include immunotherapy. In the context of tumor-immune interactions, chemotherapy has been analyzed as an optimal control problem by de Pillis and Radunskaya

[31] who consider a more detailed model and analyze solutions numerically. The optimal bolus type scheduling of dendritic cell transfection has been considered as an optimal control problem by Castiglione and Piccoli in [7]. An optimal control approach to immunotherapy is taken in the papers by Burden, Ernstberger and Fister [6] and by Fister and Hughes Donnelly [10] who build on another classical model for tumor-immune interactions by Kirschner and Panetta [14]. Ledzewicz and Schättler have analyzed mathematical models for tumor anti-angiogenesis, an indirect treatment approach that targets the vasculature of a growing tumor (e.g., [23, 24, 16]) and combinations of these novel therapies with classical approaches such as radio- and chemotherapy also have been considered as optimal control problems, for example, by Ergun, Camphausen and Wein in [9] or by d'Onofrio, Ledzewicz, Maurer and Schättler in [30, 17]. All this attests to a vigorous interest in the subject matter.

In our approach, we are using geometric methods of optimal control theory to obtain qualitative and quantitative information about the structure of optimal protocols. As the objective to be minimized for the problem under consideration, we chose a weighted average of (i) the number of cancer cells at the terminal time, (ii) a measure for the immunocompetent cell densities at the terminal point (included as a negative term), (iii) the overall amount of cytotoxic agents, respectively, (iv) the immune boost given as a measure for the side effects of treatment and (v) a small penalty on the free terminal time that limits the overall therapy horizon. This last term is essential in obtaining a well-posed problem formulation. The motivation for the first two terms lies in the shape of the stable manifold of the saddle point that defines the separatrix between the regions of benign and malignant growth and we choose specific coefficients that reflect this geometry. The mathematical objective thus is strongly motivated by the structure of the underlying dynamical system and ultimately by its biology. We already introduced this idea in earlier papers [18, 20, 21] where we considered optimal protocols for chemotherapy for the same model. In this paper, we make the natural transition to include the action of some immunotherapy in form of an outside immune boost (e.g., provided by some member of the interleukin family such as IL_2) given to the system. For the model with chemotherapy only, we have shown that there exists a locally optimal *singular arc* (the response of the system to a specific time-varying partial dose rate) and that trajectories that are simple concatenations of singular and bang pieces (responses to full or no dose treatment) achieve the underlying objective of moving the state of the system into the benign region. Explicit analytical formulas for this singular arc and its corresponding singular control are given in this earlier work and, based on these formulas, optimal solutions were calculated numerically. In all the cases considered, optimal solutions initially started with a time interval of full dose treatment and then, as the tumor volume decreases, switched to the singular regimen to move the state of the system across the separatrix applying partial dosages. Since we limit the maximum dosage, this structure corresponds to protocols that give an initial burst to reduce the tumor volume and then maintain this volume through lower partial dosages. In the model considered here, where in addition an immune boost is considered, we still see the same qualitative behavior for the chemotherapeutic agent. But contrary to the chemotherapy, the dose rates of the immune boost cannot be singular and are administered in a bang-bang fashion, i.e., as full dose treatments with rest periods. Generally, all the solutions add a short immune boost towards the end of

therapy when the cancer volume already is small while immune boosts are not given for high cancer volumes. Initially always chemotherapy is given to reduce high tumor volumes. However, in some examples, it is then an immune boost that moves the system from the malignant into the benign region once chemotherapy has sufficiently reduced the cancer volume. The precise structure naturally depends on the weights chosen in the objective and in the latter situation the side effects associated with the immune boost are considered less severe than those associated with chemotherapy.

2 Stepanova's Model for Tumor Immune Interaction

In order to keep the paper self-contained, we briefly review Stepanova's model [34] for tumor immune interactions following our exposition in [21]. As in that paper, we replace exponential growth for the tumor with a Gompertz growth model. Other growth functions, such as logistic or generalized logistic growth, are equally realistic depending on a specific situation, but we refer the reader to [21] for a general formulation. Let x denote the cancer volume and suppose there exists a fixed finite 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 T-cells activated during the immune reaction. Stepanova's model with a Gompertz growth function, $F_G(x) = -\ln\left(\frac{x}{x_\infty}\right)$, on the cancer volume 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.

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. For small tumors, it is stimulated by the tumor antigen which can be assumed to be proportional to the tumor volume x. It is argued in [34] that large tumors suppress the activity of the immune system. The reasons for this lie in an inadequate stimulation of the immune forces as well as a general suppression of immune lymphocytes by the tumor (see [34] and the references therein). This feature is expressed in the model through the inclusion of the term $-\beta x^2$. Thus $1/\beta$ corresponds to a threshold beyond which the immunological system becomes depressed by the growing tumor. The coefficients μ_I and β are used to calibrate these interactions and in the product with y collectively describe a state-dependent influence of the cancer cells on the stimulation of the immune system. The first equation, (1), models tumor growth. The coefficient γ denotes the rate at which cancer cells are eliminated through the activity of T-cells and the term $\gamma x y$ thus models the beneficial effect of the immune reaction on the cancer volume. Lastly, μ_C is a tumor growth coefficient.

Figure 1 shows an example of the phase portrait of (1) and (2) for the parameter values given by $\alpha = 0.1181$, $\beta = 0.00264$, $\gamma = 1$, $\delta = 0.37451$, $\mu_C = 0.5618$, $\mu_I = 0.00484$, and $x_\infty = 780$.

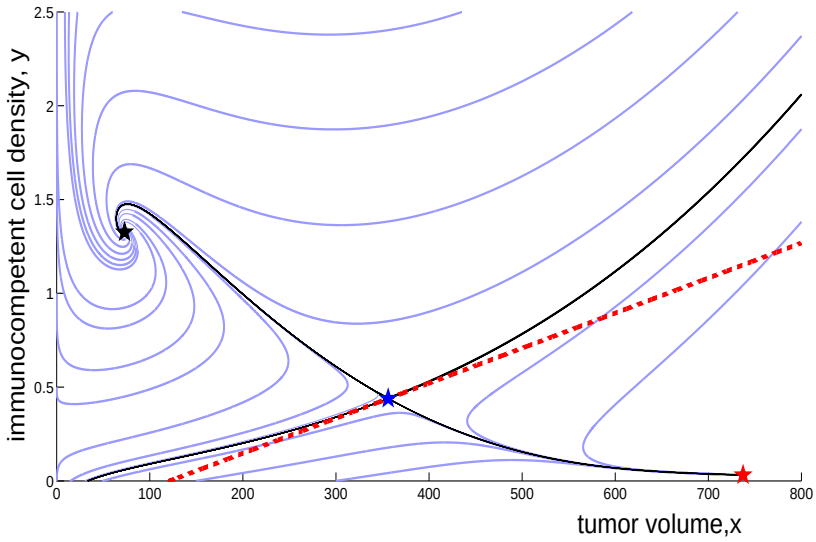

Figure 1: Phase portrait of the uncontrolled system (1) and (2)

Although we have relied on values published in the literature in the choice of these parameters, we emphasize that they are only intended to give numerical illustrations of the results in our paper. The parameters α through δ are taken from the paper by Kuznetsov et al. [15] who estimate these parameters based on in vivo experimental data for B-lymphoma BCL_1 in the spleen of mice. In that paper, a classical logistic term is used for cancer growth and we adjusted the remaining parameters to account for Gompertz growth using linear data fitting. Also, the functional form $\left(x - \beta x^2\right) y$ used in Stepanova's model in equation (2) is a quadratic expansion of the term used in [15]. Following [15], x is given in multiples of 10^6 cells and y is a dimensionless quantity that describes the immuno-competent cell density as an order of magnitude relative to base value 1. The time scale is taken relative to the tumor cell cycle and and is in terms of 0.11 days [15].

For the specified 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 a locally *asymptotically stable node* at $(x_m, y_m) = (737.3, 0.032)$ whose region of attraction defines the malignant situation. From a biological or clinical point of view, the stable focus (of about 10^7 cancer cells with an above normal value for the immunocompetent densities) represents a chronic, but benign state of the cancer in the sense that the activities of the immune system are able to control its growth and prevent that the disease spreads further. The stable node on the other hand represents a ten-fold increase of the cancer cells along with an almost complete depletion of the beneficial activities of the immune system. The tumor has reached a steady-state that over time will be lethal to the host. The saddle point in between is unstable and by itself has no biological meaning except that it defines

the highly critical boundary between the regions of attraction, i.e., the border between benign and malignant tumor behavior. Naturally, this structure depends on the particular parameter values chosen and it is not generally valid for the underlying system. However, for this model it is correct for a large range of values. The parameter values that are used in our numerical computations are summarized in Table 1.

variable/ parameters	interpretation	numerical value	dimension	Reference
x	tumor volume		10^6 cells	[34]
x_0	initial value for x	600	10^6 cells	
y	immuno-competent cell density		orders of magnitude non-dimensional	[34]
y_0	initial value for y	0.10	non-dimensional	
α	rate of influx	0.1181	non-dimensional	[15]
β	inverse threshold for tumor suppression	0.00264	non-dimensional	[15]
γ	interaction rate	1	10^7 cells/day	[15]
δ	death rate	0.37451	non-dimensional	[15]
μ_C	tumor growth parameter	0.5599	10^7 cells/day	
μ_I	tumor stimulated proliferation rate	0.00484	non-dimensional	
x_∞	fixed carrying capacity	780	10^6 cells	
κ	chemotherapeutic killing parameter	1	10^7 cells/day	

Table 1: Variables and parameter values used in numerical computations

3 Formulation of Treatment as an Optimal Control Problem

Different from our approach in [21], we now consider this dynamics (1) and (2) under the action of two independent agents, a chemotherapeutic agent u and an immune boost v. We think of the first as a cytotoxic or killing agent like Paclitaxel and of the second as representing rudimentary immunotherapy in the form of an immune boost provided by the application of a drug based on the interleukin family. Following standard cell-kinetic principles, the so-called *log-kill hypothesis*, we assume that the elimination terms are proportional to the tumor volume and the immunocompetent cell-densities, respectively. If we normalize the maximum dose rates to 1, then, in the absence of a pharmacokinetic model for the drug actions, the equations with

treatment take the form

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

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

where κ_X and κ_Y are positive coefficients that relate the maximum dose rates of the therapeutic agents to their effect. In previous papers [18, 20] we also considered a cytotoxic effect of the chemotherapeutic agent u on the immunocompetent cell densities y with a second elimination term active in the y dynamics. However, this brings in additional complexities and difficulties related to bifurcation phenomena [19] that need to be considered separately. Therefore, as in [21], in this paper we consider the case when the elimination effects on the immunocompetent cells are much smaller than on the tumor cells and for simplicity delete this term. Also, throughout the paper we only consider $\mathbb{R}^2_+ = \{(x, y) : \ x > 0, y > 0\}$, the region of interest for the problem.

Figure 2 shows phase portraits when a constant full or no dose control is applied for either u or v. With a full dose chemotherapy, for $u \equiv 1$ and $v \equiv 0$, the system corresponding to the parameter values specified earlier has a unique, globally asymptotically stable focus $(\bar{x}, \bar{y}) = (11.4, 0.3678)$ (Figure 2(c)) and thus, in principle, it is possible to reduce the cancer volume to a small chronic state using this therapy. If, in addition to chemotherapy, also a full dose immune boost $v \equiv 1$ is given, the y-values of the system approach $+\infty$ while x converges to 0 from the right (Figure 2(d)). However, with a full dose immune boost and no chemotherapy, the malignant equilibrium point is still present and thus for some initial conditions immunotherapy alone is not sufficient to eliminate the cancer (Figure 2(b)). For $u \equiv 0$ and $v \equiv 1$, the same bistable behavior prevails as in the uncontrolled system (Figure 2(a)) and the stable manifold of a saddle at $(x_s, y_s) = (555.1, 0.191)$ still separates a region where the immune system aided by the immune boost can eliminate the cancer (the y-values of the system once more approach $+\infty$ while x converges to 0 from the right) from a region where the cancer eventually will dominate and trajectories converge to the asymptotically stable malignant equilibrium point $(x_m, y_m) = (715.6, 0.048)$.

Obviously, side effects of the drugs need to be taken into account and this invalidates such a simplistic reasoning. The practical aim becomes 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 an optimal control formulation, the aim is to achieve this goal in an efficient and effective way. Intuitively, such a transfer requires to minimize the cancer cells x while not depleting the T-cell density y too strongly. The uncontrolled system is Morse-Smale [12] and the separatrix between the benign and malignant regions consists of a the stable manifold of a saddle point. Generally, it is rather difficult to give explicit analytic expressions for this manifold, but its tangent space, spanned by the stable eigenvector of the saddle point, is easily computed and can serve as a reasonable approximation. For the specified parameter values, the saddle point lies in the intermediate range for the cancer volume that is of particular interest for the problem and indeed the tangent line approximates the manifold very accurately in this range (see Figure 1). Clearly, there may exist parameter values when this no longer is true, but

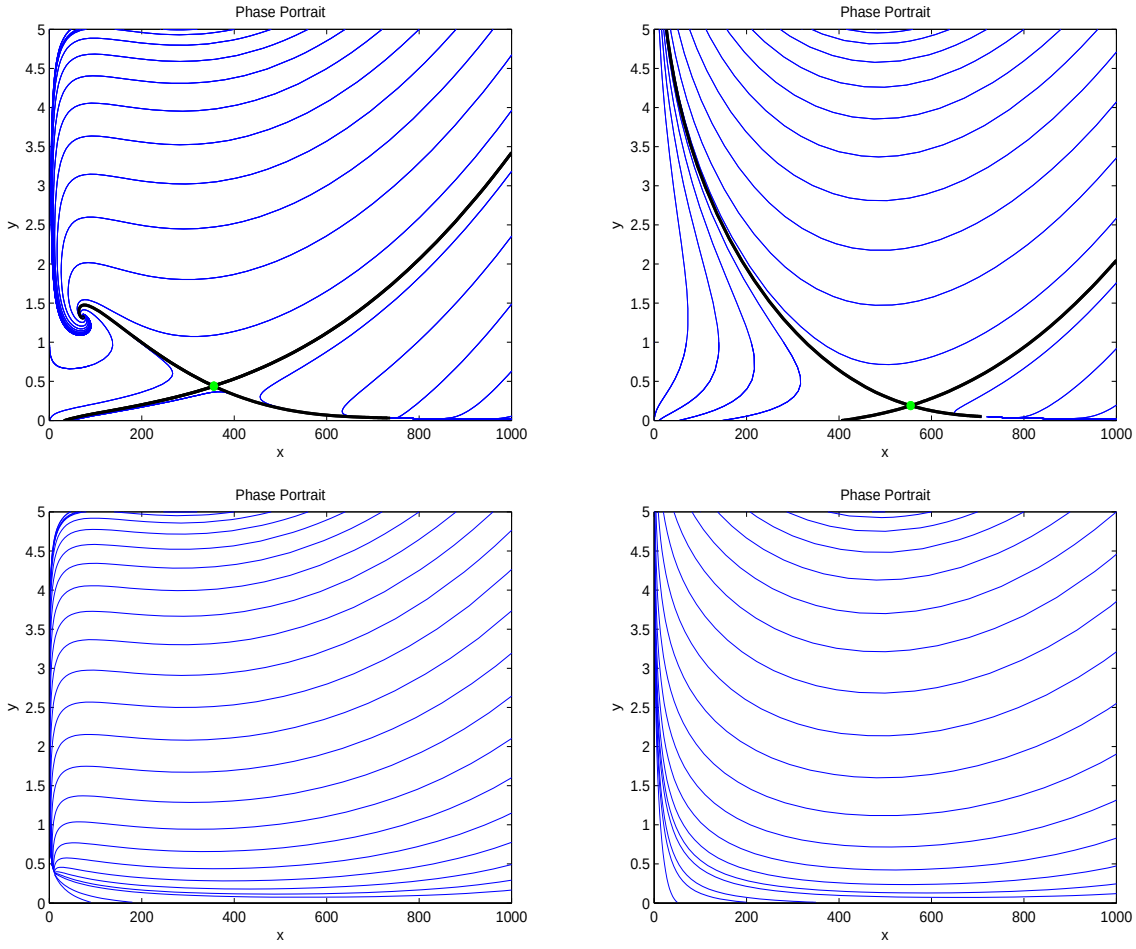

Figure 2: Phase portraits of the controlled system (3) and (4) for (a, top row left) $u = 0$ and $v = 0$, (b, top row right) $u = 0$ and $v = 1$, (c, bottom row left) $u = 1$ and $v = 0$, and (d, top row right) $u = 1$ and $v = 1$.

generally we have seen excellent approximations in our computations that only deteriorate for very small and very large tumor volumes that turn out to be of lesser interest. This motivates to choose the weights in the objective for the terminal values for the cancer volume and the immuno-competent cell-densities in the form $Ax(T) - By(T)$ where A and B are the positive coefficients given by the stable eigenvector $\mathfrak{v}_s$ of the saddle,

$$\mathfrak{v}_s = \begin{pmatrix} B \\ A \end{pmatrix}.$$

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.

But side effects of the treatment need to be taken into account. This model, as a first approximation, does not incorporate a separate compartment comprising healthy cells and tissue and thus these side effects are only taken into account indirectly. It is assumed that chemo- and immunotherapies have a proportional effect on healthy tissue and thus in our formulations we add 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 in the treatment to the objective to be minimized. Generally, the side effects of the immune boosts are less severe, but they depend on the type of the interleukin given and cannot be ignored. Thus both integrals are included in the objective with proper weights. Additionally, based on medical expertise these amounts could be limited a priori and then a minimization problem subject to isoperimetric constraints

$$\int_0^T u(t)dt \leq A \qquad \text{and} \qquad \int_0^T v(t)dt \leq B$$

could be considered. Furthermore, we keep the terminal time T in our problem formulation free and in order to avoid trajectories that use the zero controls over very long time horizons, we also add a small penalty on the terminal time. It has been shown in [20, 21] for the formulation with chemotherapy only that the existence of the asymptotically stable, benign equilibrium point generates controlled trajectories that improve the value $Ax(T) - By(T)$ of the objective along the trivial controls $u = 0$ (and thus also combined with $v \equiv 0$ for the model considered here). These trajectories provide a "free pass" and, by taking a very long time horizon, no minimum may exist in this case. The infimum arises as the control switches to follow $u = 0$ and $v = 0$ when the controlled trajectory intersects the separatrix, then follows the separatrix for an infinite time to the saddle and then again leaves this saddle point along the unstable manifold, once more taking an infinite time. This indeed would be the "optimal" solution for this problem formulation, but it is not an admissible trajectory in our system. For this reason, we include such a penalty term on the final time as well. This gives a well-posed mathematical problem for which the existence of solutions follows from standard theory. From a biological point of view, the addition of this term induces optimal solutions to give more drugs in order to reach the benign equilibrium point faster rather than taking a very long time with a smaller amount of agents. Clearly, it is not desirable for the system to evolve along the border between benign and malignant tumor behavior and it is this term that forces the system into the benign region

more quickly. In view of imprecise and mathematically unmodelled dynamics and other random perturbations, from a system theoretic perspective, the addition of this term provides desired robustness and stability properties for the underlying real system.

Summarizing, we therefore consider an objective of the following form that consists of a weighted average of the penalty term $Ax(T) - By(T)$ that induces the system to move across the separatrix from the malignant into the benign region of the state space, the cumulative side effects of the chemotherapeutic agent and the immune boost, and a small penalty term on the terminal time T:

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

Here 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. We emphasize that these coefficients are variables of choice and typically will be calibrated to tailor the response of the system. The choice of the weights aims at striking a balance between the benefit at the terminal time T, $Ax(T) - By(T)$, and the overall side effects measured by the total amount of drugs given while it guarantees the existence of an optimal solution by also penalizing the free terminal time T. The integrals of the dose rates model the side effects of the therapies on the healthy tissue and if there exist clinical data as to the severity of the drugs, then this should be reflected in the choices for C and D. Naturally, also the specific type of tumor and even the stage of cancer the patient has, may enter into the choice and calibration of these coefficients. In a more advanced stage, higher side effects may need to be tolerated and thus smaller values of C and D need to be taken. Overall, the coefficients C, D and S are variables of choice that can be fine tuned to calibrate the system's optimal response. This leads to the following optimal control problem in Bolza form:

[OC] for a free terminal time T, minimize the objective

$$J(u) = Ax(T) - By(T) + \int_0^T (Cu(t) + Dv(t) + S)\, dt, \tag{5}$$

over all Lebesgue measurable functions $u : [0, T] \to [0, 1]$ and $v : [0, T] \to [0, 1]$ subject to the dynamics (3) and (4),

$$\begin{aligned} \dot{x} &= -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy - \kappa_X xu && x(0) = x_0, \\ \dot{y} &= \mu_I \left(x - \beta x^2\right) y - \delta y + \alpha + \kappa_Y yv && y(0) = y_0. \end{aligned}$$

It is clear that, for positive initial conditions x_0 and y_0 and arbitrary admissible controls u and v, the states x and y remain positive. For, since $x = 0$ is an equilibrium solution of (3), the variable x cannot cross 0 and if $y = 0$, then we always have that $\dot{y} = \alpha > 0$. Thus there is no need to impose positivity as a state-constraint on the variables x and y. Let $z = (x, y)^T$ denote the state and express the dynamics in the compact vector field form

$$\dot{z} = f(z) + ug_1(z) + vg_2(x) \tag{6}$$

where

$$f(z) = \begin{pmatrix} -\mu_C x \ln\left(\dfrac{x}{x_\infty}\right) - \gamma xy \\ \mu_I \left(x - \beta x^2\right) y - \delta y + \alpha \end{pmatrix}, \qquad g_1(z) = \begin{pmatrix} -\kappa_X x \\ 0 \end{pmatrix} \qquad \text{and} \qquad g_2(z) = \begin{pmatrix} 0 \\ \kappa_Y y \end{pmatrix} \tag{7}$$

are the drift and control vector fields, respectively.

4 Necessary Conditions for Optimality

First-order necessary conditions for optimality of the controls u and v are given by the *Pontryagin maximum principle* (for some recent texts, see [4, 5, 33]): for $\lambda_0 \in \mathbb{R}$ and a 2-dimensional row-vector $\lambda = (\lambda_1, \lambda_2)$, define the Hamiltonian $H = H(\lambda_0, \lambda, x, y, u)$ as

$$\begin{aligned} H = \lambda_0 \left(Cu + Dv + S\right) + \lambda_1 \left(-\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy - \kappa_X xu\right) \\ + \lambda_2 \left(\mu_I \left(x - \beta x^2\right) y - \delta y + \alpha + \kappa_Y yv\right), \end{aligned} \tag{8}$$

or, equivalently, in terms of the vector fields f and g_i, as

$$H = \lambda_0 S + \langle \lambda, f(z) \rangle + u \left(\lambda_0 C + \langle \lambda, g_1(z) \rangle\right) + v \left(\lambda_0 D + \langle \lambda, g_2(z) \rangle\right). \tag{9}$$

If (u_*, v_*) is an optimal control defined over an interval $[0, T]$ with corresponding trajectory $z_* = (x_*, y_*)^T$, then, by the Pontryagin maximum principle, there exist a constant $\lambda_0 \geq 0$ and an absolutely continuous covector $\lambda = (\lambda_1, \lambda_2)$ also defined on $[0, T]$, such that the following conditions hold:

(a) λ_0 and $\lambda(t) = (\lambda_1(t), \lambda_2(t))$ do not vanish simultaneously,

(b) λ_1 and λ_2 satisfy the adjoint equations

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial x} = \lambda_1 \left(\mu_C \left(1 + \ln\left(\frac{x}{x_\infty}\right)\right) + \gamma y + u\kappa_X\right) - \lambda_2 \mu_I \left(1 - 2\beta x\right) y \tag{10}$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial y} = \lambda_1 \gamma x - \lambda_2 \left(\mu_I \left(x - \beta x^2\right) - \delta + \kappa_Y v\right) \tag{11}$$

with terminal conditions $\lambda_1(T) = \lambda_0 A$ and $\lambda_2(T) = -\lambda_0 B$,

(c) for almost every time $t \in [0, T]$, the optimal controls $(u_*(t), v_*(t))$ minimize the Hamiltonian H along $(\lambda_0, \lambda(t), x_*(t), y_*(t))$ over the control set $[0, 1] \times [0, 1]$ with minimum value given by 0.

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

$$\dot{\lambda}(t) = -\lambda(t) \left(Df(z_*(t)) + u_*(t) Dg_1(z_*(t)) + v_*(t) Dg_2(z_*(t))\right) \tag{12}$$

where Df and Dg_i denote the matrices of the partial derivatives of the vector fields f and g_i, respectively.

A *controlled trajectory* $((x,y),(u,v))$, consisting of admissible controls (u,v) and corresponding solution (x,y) of the initial value problem (3) and (4), for which there exist multipliers λ_0 and λ such that the conditions of the maximum principle are satisfied is called an *extremal* (pair) and the triple $((x,y),(u,v),(\lambda_0,\lambda))$ is an extremal lift (to the cotangent bundle). If the multiplier $\lambda_0 = 0$, the extremal is called *abnormal* while it is called *normal* if $\lambda_0 > 0$. In this case, by dividing by λ_0, it is always possible to normalize $\lambda_0 = 1$. For our problem, it is easily seen that all extremals are normal. For, if $\lambda_0 = 0$, then the terminal conditions for the adjoint equation are given by $\lambda_1(T) = \lambda_2(T) = 0$ and thus, as solutions of the homogeneous linear differential equations (10) and (11), $\lambda_1(t)$ and $\lambda_2(t)$ vanish identically. But this contradicts condition (a), the nontriviality of the multipliers. Thus extremals are normal and henceforth we normalize $\lambda_0 = 1$.

By condition (c), the optimal controls $u_*(t)$ and $v_*(t)$ minimize the Hamiltonian H along the extremal $(\lambda(t), x_*(t), y_*(t))$ over the control set $[0,1]\times[0,1]$ a.e. on $[0,T]$. Since H is linear in the controls and the control set is a rectangle, these minimizations decouple and can be carried out separately. Defining the *switching function* Φ_1 for u as

$$\Phi_1(t) = C + \langle \lambda(t), g_1(z_*(t))\rangle = C - \lambda_1(t)\kappa_X x_*, \tag{13}$$

it follows that

$$u_*(t) = \begin{cases} 0 & \text{if} \quad \Phi_1(t) > 0, \\ 1 & \text{if} \quad \Phi_1(t) < 0, \end{cases} \tag{14}$$

and with Φ_2 the switching function for v,

$$\Phi_2(t) = D + \langle \lambda(t), g_2(z_*(t))\rangle = D + \lambda_2\kappa_Y y_*, \tag{15}$$

the optimal control v_* satisfies

$$v_*(t) = \begin{cases} 0 & \text{if} \quad \Phi_2(t) > 0, \\ 1 & \text{if} \quad \Phi_2(t) < 0. \end{cases} \tag{16}$$

We refer to the constant controls given by the values 0 and 1 as the *bang* controls. The minimum conditions by themselves do not determine the controls at times when the switching functions vanish, $\Phi_i(\tau) = 0$. But if the time-derivative $\dot\Phi_i(\tau)$ does not vanish, then at such a time the control switches between its extreme values 0 and 1 with the order depending on the sign of $\dot\Phi(\tau)$. Thus also the name of bang-bang controls. In the other extreme, if $\Phi(t) \equiv 0$ on an open interval I, then all derivatives of $\Phi(t)$ must vanish as well and typically this does allow to compute the control. Controls of the second kind are called *singular* [4, 33]. In principle, in a multi-input case, as it is considered here, it is possible that both controls are singular at the same time and in this case the controls are called totally singular. Overall, optimal controls need to be synthesized from these classes of candidates.

5 Singular Controls

It first becomes necessary to compute the singular controls and analyze their local optimality. This is done through the derivatives of the switching functions. The proposition below provides

a simple and efficient formalism for the computation of these derivatives.

Proposition 1 *Let $z(\cdot)$ be a solution of the dynamics (6) for the controls u and v and let λ be a solution of the corresponding adjoint equation (12). For a continuously differentiable vector field h, let*

$$\Psi(t) = \langle \lambda(t), h(z(t)) \rangle \,. \tag{17}$$

The derivative of Ψ is then given by

$$\dot{\Psi}(t) = \langle \lambda(t), [f + ug_1 + vg_2, h](z(t)) \rangle \,, \tag{18}$$

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

Proof. Dropping the argument t, along the solutions of the dynamics and adjoint equation, we have that

$$\begin{aligned}
\dot{\Psi} &= \dot{\lambda} h(z) + \lambda Dh(z)\dot{z} \\
&= -\lambda \left(Df(z) + uDg_1(z) + vDg_2(z) \right) h(z) + \lambda Dh(z) \left(f(z) + ug_1(z) + vg_2(z) \right) \\
&= \lambda \left(Dh(z)f(z) - Df(z)h(z) \right) + u\lambda \left(Dh(z)g_1(z) - Dg_1(z)h(z) \right) \\
&\qquad\qquad + v\lambda \left(Dh(z)g_2(z) - Dg_2(z)h(z) \right) \\
&= \langle \lambda, [f + ug_1 + vg_2, h](z) \rangle \,.
\end{aligned}$$

□

For example, since $[k, k] \equiv 0$ for any vector field k, the derivatives of the switching functions Φ_1 and Φ_2 are thus given by

$$\dot{\Phi}_1 = \langle \lambda(t), [f + vg_2, g_1](z(t)) \rangle$$

and

$$\dot{\Phi}_2 = \langle \lambda(t), [f + ug_1, g_2](z(t)) \rangle \,.$$

A simple computation verifies that $[g_1, g_2] \equiv 0$ for our system and thus the derivatives of the switching functions Φ_i, $i = 1, 2$, take the simple form

$$\dot{\Phi}_i = \langle \lambda(t), [f, g_i](z(t)) \rangle \,, \qquad\qquad i = 1, 2. \tag{19}$$

In particular, these derivatives do not depend on the controls u or v and thus are absolutely continuous functions as well. Using Proposition 1 once more to differentiate $\dot{\Phi}_i$, it follows that

$$\ddot{\Phi}_i = \langle \lambda(t), [f + ug_1 + vg_2, [f, g_i]](z(t)) \rangle \,, \qquad\qquad i = 1, 2.$$

Direct computations verify that

$$[f, g_1](z) = \kappa_X \begin{pmatrix} -\mu_C x \\ \mu_I (1 - 2\beta x) xy \end{pmatrix} \qquad \text{and} \qquad [f, g_2](z) = \kappa_Y \begin{pmatrix} \gamma xy \\ \alpha \end{pmatrix}.$$

Furthermore, the control vector fields g_1 and g_2 also commute with the Lie brackets $[f, g_2]$ and $[f, g_1]$, respectively, i.e.,

$$[g_1, [f, g_2]] \equiv 0, \qquad \text{and} \qquad [g_2, [f, g_1]] \equiv 0.$$

These bracket relations decouple the controls u and v in the first two derivatives of the switching functions and lead to the following simple formulas for their second derivatives:

$$\ddot{\Phi}_1 = \langle \lambda(t), [f + ug_1, [f, g_1]](z(t)) \rangle \tag{20}$$

and

$$\ddot{\Phi}_2 = \langle \lambda(t), [f + vg_2, [f, g_2]](z(t)) \rangle \tag{21}$$

The Legendre-Clebsch condition, a well-known necessary condition for optimality of single-input singular controls [4, 33], therefore directly applies to this situation as well and gives the following necessary condition for optimality of singular controls u and v:

Proposition 2 *If the control u is singular on an open interval I, then it is a necessary condition for optimality that*

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2}\frac{\partial H}{\partial u} = \langle \lambda(t), [g_1, [f, g_1]](z(t)) \rangle \leq 0 \qquad \text{on} \quad I. \tag{22}$$

Similarly, if the control v is singular on an open interval I, then it is a necessary condition for optimality that

$$\frac{\partial}{\partial v}\frac{d^2}{dt^2}\frac{\partial H}{\partial v} = \langle \lambda(t), [g_2, [f, g_2]](z(t)) \rangle \leq 0 \qquad \text{on} \quad I. \tag{23}$$

5.1 Analysis of a singular immune boost v

We show that an optimal control v_* for the immune boost cannot be singular. If the switching function Φ_2 vanishes identically on an open interval I, it follows that

$$\Phi_2(t) = \langle \lambda(t), g_2(z_*(t)) \rangle + D \equiv 0 \qquad \text{and} \qquad \dot{\Phi}_2 = \langle \lambda(t), [f, g_2](z_*(t)) \rangle \equiv 0.$$

The vector fields g_2 and $[f, g_2]$ are linearly independent in the region $P = \{(x, y) : \ x > 0, y > 0\}$ and can therefore be used as a basis for the higher order Lie brackets. We express the second-order Lie bracket $[g_2, [f, g_2]]$ as a linear combination of g_2 and $[f, g_2]$ in the form

$$[g_2, [f, g_2]](z) = \psi_1(z) g_2(z) + \psi_2(z)[f, g_2](z)$$

with smooth functions ψ_1 and ψ_2. A direct computation gives that

$$[g_2, [f, g_2]](z) = \kappa_Y^2 \begin{pmatrix} \gamma xy \\ -\alpha \end{pmatrix}$$

and we therefore need to solve the equations

$$\kappa_Y \begin{pmatrix} \gamma xy \\ -\alpha \end{pmatrix} = \psi_1(z) \begin{pmatrix} 0 \\ y \end{pmatrix} + \psi_2(z) \begin{pmatrix} \gamma xy \\ \alpha \end{pmatrix}$$

which yields

$$\psi_1(z) = -\frac{2\kappa_Y \alpha}{y} \qquad \text{and} \qquad \psi_2(z) = \kappa_Y.$$

Hence along a singular control v it follows that we have

$$\begin{aligned}\langle \lambda(t), [g_2, [f, g_2]](z_*(t))\rangle &= \psi_1(z_*(t))\, \langle \lambda(t), g_2(z_*(t))\rangle + \psi_2(z_*(t))\, \langle \lambda(t), [f, g_2](z_*(t))\rangle \\ &= \psi_1(z_*(t))\, (-D) + \psi_2(z_*(t)) \cdot 0 \\ &= \frac{2D\kappa_Y \alpha}{y_*(t)} > 0\end{aligned}$$

violating the Legendre-Clebsch condition.

Note that this does not yet imply that the control v for the immune boost is bang-bang since, a priori, we only know that the zero set of Φ_2 is a closed subset of the interval $[0, T]$. However, in the absence of a more degenerate behavior, this typically is the case and it holds for the examples considered below.

5.2 Analysis of a singular chemotherapy dose rate u

The situation is different for the chemotherapeutic dose rate u and here singular controls can be optimal. Similarly as above, suppose an optimal control u_* is singular on an open interval I. In this case, we then have that

$$\Phi_1(t) = \langle \lambda(t), g_1\,(z_*(t))\rangle + C \equiv 0$$

and

$$\dot{\Phi}_1(t) = \langle \lambda(t), [f, g_1](z_*(t))\rangle \equiv 0 \tag{24}$$

on I. Recall that

$$g_1(z) = \begin{pmatrix} -\kappa_X x \\ 0 \end{pmatrix} \qquad \text{and} \qquad [f, g_1](z) = \kappa_X \begin{pmatrix} -\mu_C x \\ \mu_I(1 - 2\beta x)xy \end{pmatrix}$$

and a direct calculation verifies that

$$[g_1, [f, g_1]](z) = -\kappa_X^2 xy \begin{pmatrix} 0 \\ \mu_I(1 - 4\beta x) \end{pmatrix}$$

Except for the vertical line $\ell = \{(x, y) : x = \frac{1}{2\beta}\}$, the vector fields g_1 and $[f, g_1]$ are linearly independent and we can express the second-order bracket $[g_1, [f, g_1]]$ as a linear combination of the form

$$[g_1, [f, g_1]](z) = \theta_1(z) g_1(z) + \theta_2(z)[f, g_1](z) \tag{25}$$

with the coefficients θ_1 and θ_2 given by

$$\theta_1(z) = \mu_C \kappa_X \frac{1 - 4\beta x}{1 - 2\beta x} \qquad \text{and} \qquad \theta_2(z) = -\kappa_X \frac{1 - 4\beta x}{1 - 2\beta x}.$$

Thus, if the control u_* is singular on an open interval I, we have that

$$\begin{aligned}\langle \lambda(t), [g_1,[f,g_1]]\,(z_*(t))\rangle &= \theta_1(z_*(t))\,\langle \lambda(t), g_1(z_*(t))\rangle + \theta_2(z_*(t))\,\langle \lambda(t), [f,g_1](z_*(t))\rangle \\ &= \theta_1(z_*(t))\,(-C) + \theta_2(z_*(t))\cdot 0 \\ &= -C\mu_C\kappa_X \frac{1-4\beta x_*(t)}{1-2\beta x_*(t)}.\end{aligned}$$

It follows from the Legendre-Clebsch condition that singular controls u_* are not optimal if the corresponding trajectory lies in the region $\left\{(x,y) : \frac{1}{4\beta} < x < \frac{1}{2\beta}\right\}$, but for $0 < x \leq \frac{1}{4\beta}$ and $x > \frac{1}{2\beta}$ the Legendre-Clebsch condition is satisfied.

Proposition 3 *If an optimal control u_* is singular on an open interval I, then the corresponding trajectory x_* needs to lie in either the interval $(0, \frac{1}{4\beta}]$ or in $[\frac{1}{2\beta}, \infty)$.* □

Explicit formulas for the singular control u_* can be computed from the fact that the second derivative of the switching function Φ_2 vanishes. Simply solving $\ddot{\Phi}_2(t) \equiv 0$ for the control u, we obtain that

$$u_{\sin}(t) = -\frac{\langle \lambda(t), [f,[f,g_1]]\,(z_*(t))\rangle}{\langle \lambda(t), [g_1,[f,g_1]]\,(z_*(t))\rangle}. \tag{26}$$

The vector field $[f,[f,g_1]]$ is given by

$$[f,[f,g_1]](z) = \kappa_X x \begin{pmatrix} -\mu_C^2 + \mu_I\gamma(1-2\beta x)xy \\ -\mu_I(1-4\beta x)\left(\mu_C \ln\left(\frac{x}{x_\infty}\right) + \gamma y\right) y + (\alpha + \mu_C y)\mu_I(1-2\beta x) \end{pmatrix}$$

and, if we express it as a linear combination of g_1 and $[f,g_1]$ in the form

$$[f,[f,g_1]](z) = \varphi_1(z)g_1(z) + \varphi_2(z)[f,g_1](z), \tag{27}$$

then, similarly as above, we obtain that

$$\begin{aligned}\langle \lambda(t), [f,[f,g_1]]\,(z_*(t))\rangle &= \varphi_1(z_*(t))\,\langle \lambda(t), g_1(z_*(t))\rangle + \varphi_2(z_*(t))\,\langle \lambda(t), [f,g_1](z_*(t))\rangle \\ &= -C\varphi_1(z_*(t)).\end{aligned}$$

Hence the singular control is explicitly given as the feedback function

$$u_{\sin}(t) = -\frac{\varphi_1(z_*(t))}{\theta_1(z_*(t))}. \tag{28}$$

However, this singular control cannot be used everywhere. It also follows from the maximum principle that the Hamiltonian H vanishes identically along an optimal controlled trajectory. If the control u is singular on an open interval I and if the other control v is constant given by either $v \equiv 0$ or $v \equiv 1$, then also

$$H = \langle \lambda(t), f(z_*(t)) + v g_2(z_*(t))\rangle + Dv + S \equiv 0$$

on I. Combining this with the identity

$$\langle \lambda(t), g_1(z_*(t)) \rangle + C \equiv 0,$$

we obtain that

$$\langle \lambda(t), C\left[f(z_*(t)) + v g_2(z_*(t))\right] - (Dv + S)\, g_1(z_*(t)) \rangle \equiv 0. \tag{29}$$

Furthermore, from (24) we also have that

$$\langle \lambda(t), [f, g_1](z_*(t)) \rangle \equiv 0.$$

The multiplier λ is nontrivial (since $\lambda(T) \neq 0$), and thus the vector fields $C\,(f + v g_2) - (Dv + S)\, g_1$ and $[f, g_1]$ must be linearly dependent when the control u is singular. The locus of these points is called the corresponding *singular arc* and it can simply be computed as the zero set of the determinant

$$\det\left(C\,(f(z) + v g_2(z)) - (Dv + S)\, g_1(z), [f, g_1](z)\right) = 0 \tag{30}$$

with v given by either 0 or 1.

This expression is a quadratic polynomial in y with coefficients that are functions of x. For $v \equiv 0$ we get

$$\det\left(Cf(z) - S g_1(z), [f, g_1](z)\right) = a_2(x) y^2 + a_1(x) y + a_0(x) \tag{31}$$

with

$$\begin{aligned} a_2(x) &= -C\gamma\mu_I\left(x - 2\beta x^2\right), \\ a_1(x) &= \mu_I(x - 2\beta x^2)\left[S\kappa_X - C\mu_C \ln\left(\frac{x}{x_\infty}\right)\right] + C\mu_C\left[\mu_I(x - \beta x^2) - \delta\right], \\ a_0 &= C\alpha\mu_C > 0. \end{aligned}$$

Thus, for every fixed value x, the singular curve consists of possibly one or two points or no singular arc is possible. For example, since a_0 is a positive constant, for $x < \frac{1}{2\beta}$, the coefficient $a_2(x)$ is negative and thus there exist two real solutions, one positive, one negative. Only the positive one is of interest for the problem and thus the singular arc is the graph of a function over the interval $(0, \frac{1}{2\beta})$. Whether solutions exist for $x > \frac{1}{2\beta}$ depends on the actual parameter values. Analytic formulas for y as a function of x can still be written down, but they get unwieldy.

Similarly, for $v = 1$ we have that

$$\det\left(C\,(f(z) + g_2(z)) - (D + S)\, g_1(z), [f, g_1](z)\right) = 0 \tag{32}$$

and the quadratic polynomial in y now is of the form

$$\det\left(C\,(f(z) + g_2(z)) - (D + S)\, g_1(z), [f, g_1](z)\right) = b_2(x) y^2 + b_1(x) y + b_0 \tag{33}$$

with the coefficients b_2 and b_0 given by a_2 and a_0, respectively, and b_1 slightly modified to

$$b_1(x) = \mu_I(x - 2\beta x^2)\left[(D + S)\,\kappa_X - C\mu_C \ln\left(\frac{x}{x_\infty}\right)\right] + C\mu_C\left[\mu_I(x - \beta x^2) - \delta + \kappa_Y\right].$$

Based on the formulas derived above, the singular arc, the singular control, and their admissible portions can easily be evaluated numerically. As an illustration, Figure 3 gives the singular arcs for the previously used parameter values for the dynamics, for $\kappa_X = 2$ and $\kappa_Y = 1$, and the coefficients $C = 0.036$, $D = 0.007$ and $S = 0.036$ in the objective.

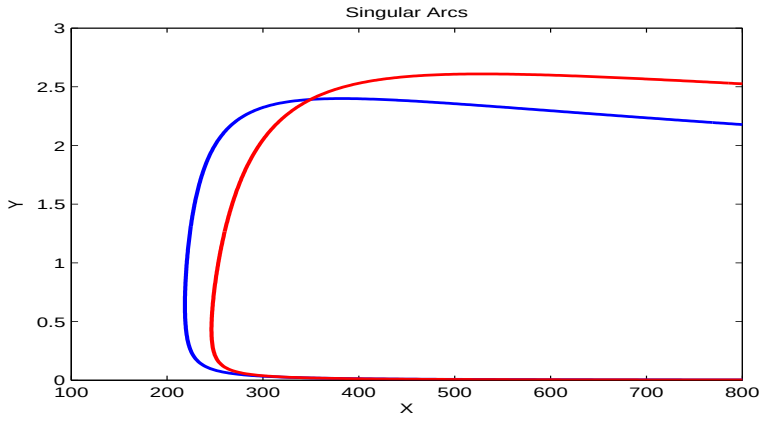

Figure 3: u-singular arcs for the constant controls $v \equiv 0$ (blue curve) and $v \equiv 1$ (red curve)

6 Examples of Optimal Controlled Trajectories

In this section, for the parameter values given in Table 1 and with $\kappa_X = 2$ and $\kappa_Y = 1$ as coefficients that describe the effectiveness of treatments, we give two typical examples of optimal controlled trajectories to illustrate the structure of the solutions. As in [21], we used the classical ε-algorithm approach in which a quadratic penalty term $\varepsilon \int_0^T \left(u^2(t) + v^2(t)\right) dt$ is added to the objective and then the optimal controls for the underlying problem are recovered in the limit as $\varepsilon \to 0$ [1]. The actual computations were done using GPOPS (*G*eneral *P*seudo-spectral *OP*timal *C*ontrol *S*oftware), an open-source MATLAB optimal control software that implements a Gauss hp-adaptive pseudo-spectral method (`http://www.gpops.org/`, [32]). These methods approximate the state using a basis of Lagrange polynomials and collocate the dynamics at the Legendre-Gauss nodes [2, 3, 13]. The continuous-time optimal control problem is then transformed into a finite-dimensional nonlinear programming problem that is solved using well known and standard algorithms.

We want to illustrate the changes in the structure of the optimal controls as the coefficients in the objective change and therefore in both computations we use the same initial condition given by $(x_0, y_0) = (600, 0.1)$. The initial tumor volume x_0 is given as a multiple of some reference value and represents a tumor cell count that is 600 times higher than some chosen base value (10^6 cells); y_0 is a dimensionless, order-of-magnitude quantity that represents a depletion of the immuno-competent cell densities to 10% of a nominal value. Also, the coefficients A and B are not varied and are chosen in accordance with the stable eigenvector of the saddle for the uncontrolled system, i.e., $A = 0.00192$ and $B = 1$. The chosen initial condition lies well within the malignant region and initially in each case the chemotherapeutic agent u is given at full dose. However, depending on the penalty assigned to the side effects, in one of the cases it is chemotherapy that moves the state into the benign region while it is the immune boost in the second.

Scenario 1: In this case we have taken $C = 0.01$, $D = 0.025$ and $S = 0.001$. Recall that

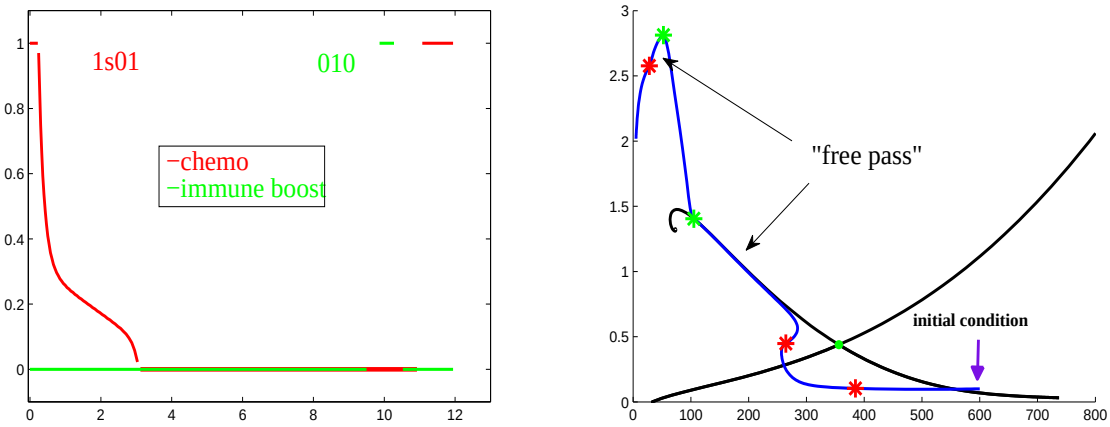

Figure 4: Optimal controls (a, left) and corresponding trajectory (b, right) in Scenario 1. The stars in the panel on the right indicate the points when switchings in the optimal controls occur (red asterisks for switchings in the chemotherapy, green asterisks for switchings in the immunotherapy). The curve gives the response of the system to the optimal controls.

the tumor volume is measured in multiples of 100 while the immuno competent cell densities are on a scale relative to 1. For these weights both the side effects of chemotherapy and an immune boost are significant. Figure 4 shows the computed optimal control on the left (a) and its corresponding trajectory in the state space on the right (b). Since chemotherapy has overall a better effectiveness, it becomes the dominant therapy. After a brief initial full dose segment that moves the system to the singular arc (while $v \equiv 0$), at that point the administration of the cytotoxic drug switches to the singular regimen and the system moves from the malignant into the benign region along the singular arc. The corresponding switching points are indicated on the trajectory by a red asterisk in Figure 4(b). Once a "safe" distance to the separatrix has been established, the controls are switched off ("free pass") and the system follows the uncontrolled trajectory towards the benign stable equilibrium point. This portion of the trajectory closely follows the unstable manifold of the saddle for the uncontrolled system and is labelled as a "free pass" in Figure 4(b). Towards the end, when the cancer volume is already quite small, it becomes beneficial to give an immune boost with the precise timing depending on the penalty S given to the terminal time. In this particular case, another short full dose chemotherapy session reduces the cancer volume further towards the end. Thus for this choice of weights in the objective, chemotherapy becomes the dominant portion and overall has a concatenation structure of the form $1s01$ with 1 and 0 denoting full dose and no dose segments respectively and s denoting an interval along which the optimal control is singular. Here immunotherapy is only used as an additional tool once the cancer volume has become small so that the tumor-immune interactions become significant and here the concatenation structure is 010.

Scenario 2: In this second computation we have increased the side effects of chemotherapy and made the side effects of the immune boost much smaller. The values used in our computation

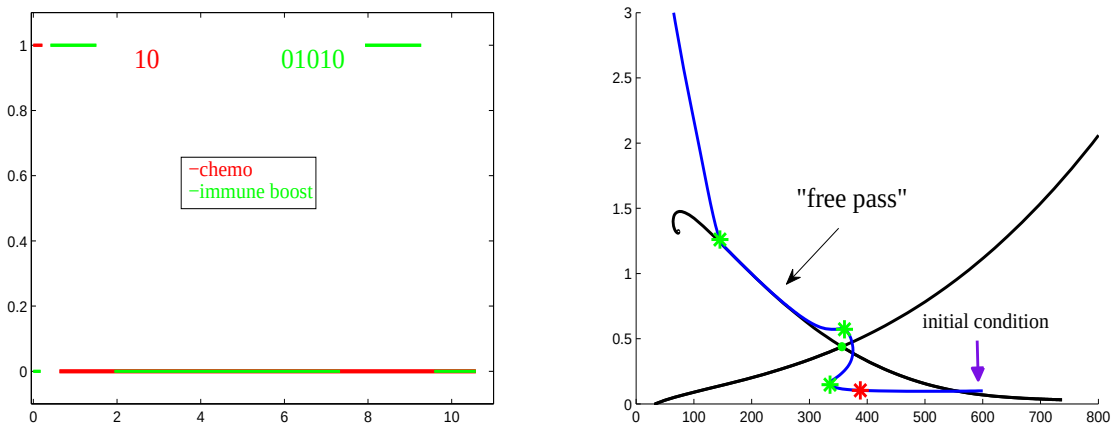

Figure 5: Optimal controls (a, left) and corresponding trajectory (b, right) in Scenario 2. The stars in the panel on the right indicate the points when switchings in the optimal controls occur (red asterisks for switchings in the chemotherapy, green asterisks for switchings in the immunotherapy). The curve gives the response of the system to the optimal controls.

are $C = 0.025$, $D = 0.005$ and $S = 0.0005$. As above, Figure 5 shows the computed optimal control on the left (a) and its corresponding trajectory in the state space on the right (b). Naturally, we expect that the immune boost will thus play a more significant role in this scenario and this is the case. The chosen initial condition still lies in a region where a constant immune boost is not yet able to control the cancer volume. Hence, even though the cost is high, initially full dose chemotherapy must be used to move the state out of the region of attraction of the malignant equilibrium (the one corresponding to the constant controls $(u, v) = (0, 1)$) into the region where an immune boost alone can control the cancer volume. Once there, chemotherapy turns off (the red asterisk on the trajectory) and the immune boost (marked by the green asterisks on the trajectory) moves the state of the system into the benign region. Then, as before, the uncontrolled trajectory ("free pass") becomes the most cost-effective strategy (only paying a small penalty for the time spent along it) until, because of the low cost of the immune boost, it becomes once again beneficial to give an immune boost as the cancer volume becomes small.

The two scenarios described here in a certain sense cover the extreme situations when either chemotherapy or the immune boost become dominant. By varying the weights, more equally distributed therapies can be obtained. However, based on some of our computations, it appears that the structure of the optimal solution is quite sensitive to the weights chosen and the ranges of parameters where these other scenarios arise seem to be small with small bifurcation regions between the two described scenarios.

7 Conclusion

Based on Stepanova's mathematical model of immunological activity during cancer growth, we formulated the problem of how to transfer the system from an initial condition in the malignant region of the state space through therapy into a benign region as an optimal control problem. In this paper, combinations of a chemotherapeutic agent and an immune boost were considered and both qualitative information about the structure of optimal controls and some quantitative illustrations of these solutions were given. Clearly, the model oversimplifies activation and action of the immune system and thus still is far removed from clinical importance. But nevertheless it leads to some interesting practical insights about optimal therapies in the presence of tumor immune interactions. For example, it implies that the action of an immune boost alone may not be sufficient to control the cancer, but that an additional therapeutic agent, like chemotherapy considered here, is needed. Also, the numerical illustrations given show the relative importance of side effects. If the side effects of the immunotherapy are considered significantly smaller than those of chemotherapy, then chemotherapy is only used to reduce large cancer volumes and then immunotherapy would be the preferred option for small cancer volumes. Despite the model's simplicity, the paper thus addresses the important question of how to best schedule therapies over time. In clinical trials, because of the great complexity of the underlying medical problem, the scheduling of drugs is pursued in expensive, exhaustive, medically guided trial-and-error approaches. The results of even simplified mathematical models may be useful to give some guidance. Naturally, the analysis presented here also becomes a first step towards designing treatment protocols for more complex models. It is hoped, that the structure of optimal protocols seen in this simplified model gives an indication about their form for the mathematically more general models.

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