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Optimal response to chemotherapy for a mathematical model of tumor–immune dynamics

Urszula Ledzewicz · Mohammad Naghnaeian · Heinz Schättler

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Abstract An optimal control problem for cancer chemotherapy is considered that includes immunological activity. In the objective a weighted average of several quantities that describe the effectiveness of treatment is minimized. These terms include (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 given as a measure for the side effects of treatment and (iv) a small penalty on the terminal time that limits the overall therapy horizon which is assumed to be free. This last term is essential in obtaining a well-posed problem formulation. Employing a Gompertzian growth model for the cancer cells, for various scenarios optimal controls and corresponding responses of the system are calculated. Solutions initially follow a full dose treatment, but then at one point switch to a singular regimen that only applies partial dosages. This structure is consistent with protocols that apply an initial burst to reduce the tumor volume and then maintain a small volume through lower dosages. Optimal controls end with either a prolonged

U. Ledzewicz (✉)
Department of Mathematics and Statistics,
Southern Illinois University at Edwardsville,
Edwardsville, IL 62026-1653, USA
e-mail: uledzew@siue.edu

M. Naghnaeian
Department of Mechanical Science and Engineering,
University of Illinois at Urbana Champaign, Urbana,
IL 61801-2906, USA
e-mail: naghnae2@illinois.edu

H. Schättler
Department of Electrical and Systems Engineering,
Washington University, St. Louis, MO 63130-4899, USA
e-mail: hms@wustl.edu

period of no dose treatment or, in a small number of scenarios, this no dose interval is still followed by one more short burst of full dose treatment.

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1 Introduction

Stepanova (1980) proposed a classical mathematical model of two ordinary differential equations that describe the interactions between cancer cell growth and the activity of the immune system during the development of cancer. Despite its simplicity, the few parameters incorporate many medically important features and the underlying equations have been widely accepted as a basic model. There exist numerous extensions and generalizations of this model, most notably the one by Kuznetsov et al. (1994), who, 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 and then analyze both local and global bifurcations for the underlying dynamical system for realistic nearby parameter values. In a paper by de Vladar and González (2004), logistic growth on cancer cells is replaced with a Gompertzian model. In each case, the models exhibit both stable microscopic and macroscopic equilibria and a comprehensive analysis of the dynamic behavior of the underlying systems and its bifurcations is carried out in the respective papers. More recently, d'Onofrio (2005, 2006) formulated and investigated a general class of models that incorporates all these dynamical models. These papers share the following important theoretical findings: while the immune system can be effective in the control of small cancer volumes, for large volumes the cancer dynamics suppresses the immune dynamics and the two systems effectively become separated (de Vladar and González 2004, appendix B). In the first case, so-called *immune surveillance*, what medically would be considered cancer never develops; in the latter one, only a therapeutic effect on the cancer (e.g., chemotherapy, radiotherapy, etc.) needs to be analyzed. However, tumor–immune system interactions matter for the interesting case "in between" when both a benign (microscopic) and a malignant (macroscopic) stable equilibrium exist or uncontrolled cancer growth is seen. The underlying models are Morse–Smale systems (Guckenheimer and Holmes 1983) and the stable manifold of an unstable equilibrium point separates the benign from the malignant region. Thus the question is: how can an initial condition that lies in the malignant region be moved towards and hopefully into the region of benign growth through therapy? This question can naturally be formulated and analyzed as an optimal control problem and this will be the topic of our mathematical analysis here.

In recent years, there has been a strong renewed interest in the application of methods from optimal control to the scheduling of novel cancer therapies. For example, in our own work we have analyzed mathematical models for tumor anti-angiogenesis, an indirect treatment approach that targets the vasculature of a growing tumor (e.g., Ledzewicz and Schättler 2007, 2008; Ledzewicz et al. 2010). Optimal scheduling of anti-angiogenic agents is also considered, for example, by d'Onofrio et al. (2009) or by Swierniak (2008). An example from immunotherapy is the optimal bolus type scheduling of dendritic cell transfection that has been considered as an optimal

control problem by Castiglione and Piccoli (2006). More generally, an optimal control approach to immunotherapy is taken in the papers by Burden, Ernstberger and Fister Burden et al. (2004) and by Fister and Hughes Donnelly (2005) who build on a classical model for tumor–immune interactions by Kirschner and Panetta (1998). 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 et al. (2003) or by d'Onofrio et al. (2009) and Ledzewicz et al. (2009). In the context of tumor–immune interactions, chemotherapy has been analyzed as optimal control problem by de Pillis and Radunskaya (2001). In that paper, a more detailed and complex model for the immune system than the one we shall be employing here was considered and optimal controls were computed numerically.

In this paper, we consider a lower dimensional dynamic model based on Stepanova's (1980) model in which 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. While giving up on some level of modeling accuracy, a small model has the advantage that analytical methods can be brought in yielding qualitatively robust results. In our approach, we are using geometric methods of optimal control theory that have not been applied to these problems before. The motivation for the cost function we propose in the problem is based on the stable manifold of the saddle point that describes the separatrix between the regions of benign and malignant growth. The aim is to move the state of the system across this boundary using chemotherapy with the dosage of a cytotoxic agent as control variable. Our mathematical objective thus is strongly motivated by the underlying structure of the dynamical system and ultimately by its biology. Since this stable manifold rarely can be determined analytically, it becomes necessary to approximate the separatrix by its tangent space. This approximation is generally excellent if very small and very large numbers of cancer cells are excluded. And these are cases when the model does not well represent the underlying biology anyway. Hence we include in our objective a penalty term that induces the system to move across this easily computed tangent line along with an integral term that measures the drug usage and thus indirectly the side effects associated with it.

In earlier papers, we have already introduced this idea (Ledzewicz et al. 2011a,b). It was shown that there exists a locally optimal *singular arc* (the response of the system to specific time-varying partial doses) for the optimal control problem and that trajectories that are concatenations of singular and bang pieces (responses to full or no dose controls) achieve the underlying objective of moving the state of the system into the benign region. However, the existence of a benign, locally asymptotically stable equilibrium point causes a "free pass" phenomenon in the sense that in some cases the trivial control $u = 0$ (no drug given) can be used to improve the value of the objective (while incurring no penalty). This indeed allows for *controlled trajectories*, the system responses to drug dosages, that are defined over arbitrary long time intervals and improve the objective. As a result, while the optimal control approach clearly points in the direction of good treatment schedules that achieve the underlying aim of moving the state of the system from the malignant into the benign region, in some cases *optimal controls do not exist* since the infimum is only realized in the limit as $T \to \infty$. This no longer is possible if we include a small penalty on the terminal time

since this forces the objective to diverge as $T \to \infty$. Hence in this way we obtain a well-posed mathematical problem formulation. Here we consider this formulation and calculate optimal controlled trajectories for various initial conditions based on a theoretical analysis of the singular arc. Explicit formulas that define this singular arc and its corresponding singular control will be given. However, their analytic solutions, although they can still be computed, become rather cumbersome. Thus optimal solutions will be calculated numerically. In all our computations we find optimal solutions that initially follow a full dose treatment, but then at one point switch to the singular regimen that only applies 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. If we increase the allowable maximum dose in the model, then optimal controls precisely will follow such a structure with the burst designed to reach the singular arc. The partial dosages then are determined to follow this special trajectory and optimal protocols end with a prolonged period of no dose treatment, possibly still followed by one more short burst of full dose treatment.

2 Stepanova's model for tumor–immune interaction

We briefly review Stepanova's (1980) model for tumor–immune interactions. While Stepanova uses exponential growth for the tumor, various other models are realistic and have been considered in the literature as well. We therefore use a general growth function of the form $xF(x)$ where x denotes the tumor volume and F is a positive, twice continuously differentiable function defined on an interval $(0, x_\infty)$ with $x_\infty \leq \infty$ denoting a fixed carrying capacity for the cancer. With y representing 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 takes the form

$$\dot{x} = \mu_C x F(x) - \gamma x y, \tag{1}$$

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

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 the 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 Stepanova (1980) that large tumors suppress the activity of the immune system. The reasons lie in a for this case inadequate stimulation of the immune forces as well as a general suppression of immune lymphocytes by the tumor (see Stepanova 1980 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

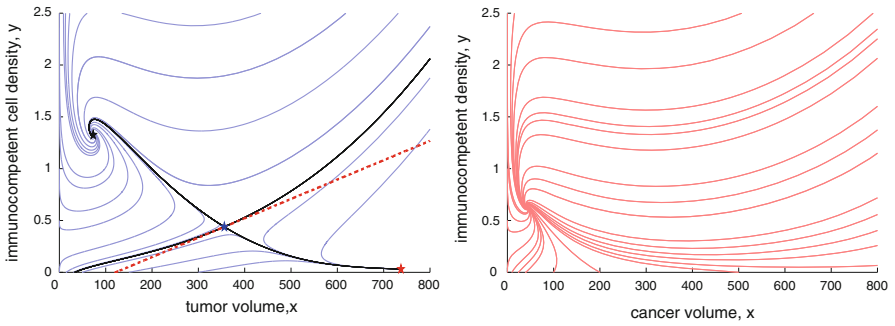

Fig. 1 Phase portraits of the uncontrolled system (1) and (2) (*on the left*) and the fully controlled system (5) and (6) (*on the right*) with $u \equiv 1$ and $\kappa = 1$ for a Gompertzian growth function $F(x) = -\log(\frac{x}{x_\infty})$

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 γxy thus models the beneficial effect of the immune reaction on the cancer volume. Lastly, μ_C is a tumor growth coefficient.

In our formulation F is a functional parameter that allows to specify various growth models for the cancer cells. In Stepanova's original formulation this term F is simply given by $F_E(x) \equiv 1$, i.e., exponential growth of the cancer cells is considered. While there exists a time frame when exponential growth is realistic, over prolonged periods usually saturating models are preferred. For instance, there exists medical evidence that many tumors follow a Gompertzian growth model (Norton and Simon 1977; Norton 1988) in which case the function F is given by $F_G(x) = -\ln(\frac{x}{x_\infty})$ with x_∞ denoting a fixed carrying capacity for the cancer. But also logistic and generalized logistic growth models of the form $F_L(x) = 1 - (\frac{x}{x_\infty})^\nu$ with $\nu > 0$ have been considered for tumor growth (Kuznetsov et al. 1994). We thus formulated the model with a general growth term F only assuming that F is a positive, twice continuously differentiable function defined on the interval $(0, x_\infty)$. While some structural properties of the system will be valid in this generality, to obtain the more detailed results about optimal controls considered in this paper, the function F needs to be specified further and we use a Gompertzian growth model.

Figure 1 (on the left) gives 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 $x_\infty = 780$. The parameters α through δ are directly taken from the paper by Kuznetsov et al. (1994) 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 therefore adjusted the remaining parameters to account for Gompertzian growth using linear data fitting. Also, the functional form $(x - \beta x^2)y$ used in Stepanova's model in Eq. (2) is a quadratic expansion of the term used in Kuznetsov et al. (1994). Following Kuznetsov et al. (1994), x is given in 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. The time scale is taken relative to the tumor cell cycle and and is in terms of

Table 1 Variables and parameter values used in numerical computations

Variable/ parameters	Interpretation	Numerical value	Dimension	Reference
x	Tumor volume		10^6 cells	Stepanova (1980)
x_0	Initial value for x	600	10^6 cells	
y	Immunocompetent cell density		Orders of magnitude Non-dimensional	Stepanova (1980)
y_0	Initial value for y	0.10	Non-dimensional	
α	Rate of influx	0.1181	Non-dimensional	Kuznetsov et al. (1994)
β	Inverse threshold for tumor suppression	0.00264	Non-dimensional	Kuznetsov et al. (1994)
γ	Interaction rate	1	10^7 cells/day	Kuznetsov et al. (1994)
δ	Death rate	0.37451	Non-dimensional	Kuznetsov et al. (1994)
μ_C	Tumor growth parameter	0.5618	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	

0.11 days (Kuznetsov et al. 1994). For the specified parameter values there exist three equilibria: a locally asymptotically stable focus at $(x_b, y_b) = (72.961, 1.327)$ whose region of attraction corresponds to the benign situation, a saddle point at $(x_s, y_s) = (356.174, 0.439)$ whose stable manifold is the separatrix between the benign and malignant regions, and an asymptotically stable node at $(x_m, y_m) = (737.278, 0.032)$ whose region of attraction defines the malignant situation. Clearly such a structure depends on the particular parameter values chosen and it is not generally valid for the underlying system. However, it is correct for a large range of values. Throughout our paper these specific parameter values will be used, but they only serve to illustrate our results and computations numerically. The values are summarized in Table 1.

3 Formulation of treatment as an optimal control problem

We consider this dynamics under the application of a chemotherapeutic agent and, following de Vladar and González (2004), assume that the elimination terms are proportional to the tumor volume (the so-called *log-kill hypothesis*). Hence we subtract a term $\kappa x u$ from the x dynamics. The coefficient κ allows to normalize the control set, i.e., we assume that $0 \leq u \leq 1$ with $u = 1$ representing a full dose treatment and $u = 0$ the uncontrolled system when no chemotherapy is given. In earlier papers (Ledzewicz et al. 2011a,b), we also allowed for a cytotoxic effect of the chemotherapeutic agent on the immunocompetent cell densities with a similar elimination term active on the y dynamics in the form $\varepsilon \kappa y u$ with ε being a parameter. Mathematically, however, this brings in a number of additional complexities and difficulties related to bifurcation

phenomena (Ledzewicz et al. 2010) that need to be considered separately. Therefore, in this paper we focus on the case when the elimination effects on the immunocompetent cells are much smaller than on the tumor cells, $\varepsilon \ll 1$, and for simplicity we then set $\varepsilon = 0$. Also, throughout the paper we only consider $\mathbb{R}^2_+ = \{(x, y) : x > 0, y > 0\}$, the region of interest for the problem.

The right hand side of Fig. 1 shows the phase portrait of the system for a constant full dose therapy ($u = 1$) when $\kappa = 1$. Again, these values are for illustrative purposes only. In this case, the new system has only one globally asymptotically stable equilibrium, a focus, with positive values at $(\bar{x}, \bar{y}) = (43.017, 0.622)$. If a cytotoxic effect on the immunocompetent cell densities were to be considered as well, then the coordinate $\bar{y}$ of the equilibrium would be smaller since the beneficial effect on the cancer volume will be diminished and thus $\bar{x}$ would be larger. But also in this case, in the mathematical model it is in principle (ignoring side effects) possible to reduce the cancer volume to a small enough chronic state.

Obviously, side effects of the drugs invalidate this reasoning and the practical aim is to investigate how an initial condition (x_0, y_0) that lies in the region of malignant cancer growth for the uncontrolled system could be transferred in an efficient and effective way into the region of attraction of the stable, benign equilibrium point. Intuitively, such a transfer requires to minimize the cancer cells x while not depleting the T-cell density y too strongly. The system under consideration is Morse–Smale (Guckenheimer and Holmes 1983) and thus the boundary between the benign and malignant regions consists of a union of smooth curves, the stable manifolds of unstable equilibria. For the classical version of Stepanova's model with exponential growth there exists one saddle point and this separatrix is given by the stable manifold of this saddle. In general, it is not possible to give an analytic description of this manifold. But its tangent space is spanned by the stable eigenvector of the saddle point and this easily computable quantity can serve as a first approximation. In fact, the separatrix shown in Fig. 1 on the left is well approximated by its tangent line in the region where the tumor volume is not too large (otherwise the immune system will mostly be suppressed anyway, de Vladar and González 2004) and also the example shown in Fig. 2 in de Vladar and González (2004) is almost linear. This motivates the choice of an objective function that minimizes a penalty term of the form $ax(T) - by(T)$ where a and b are positive coefficients determined by the stable eigenvector $\mathfrak{v}_s$ of the saddle,

$$\mathfrak{v}_s = \begin{pmatrix} b \\ a \end{pmatrix}. \tag{3}$$

For example, for the parameter values used earlier, normalizing $b = 1$, we have that $a = 0.00192$. Minimizing this objective naturally steers the system towards the benign region.

The formulation so far does not yet take into account side effects of the treatment. There exist various options to do this. In Ledzewicz et al. (2011a) we limited the overall amount of cytotoxic agents u to an a priori given quantity, $\int_0^T u(t)\,dt \le A$, and then analyzed the problem of how this amount can be applied in an optimal way. The time T does not correspond to a therapy horizon, but it merely denotes the time when the minimum for the objective is realized. However, the existence of an

asymptotically stable, benign equilibrium generates controlled trajectories that improve the value $ax(T) - by(T)$ of the objective along the trivial control $u = 0$ by taking a very long time horizon. In some sense, there exist trajectories that provide a "free pass" and can take an arbitrary long time. For this reason, in fact no minimum exists in this problem formulation. There only is an infimum that arises as the control switches to follow $u = 0$ 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. Also, from a practical point of view, it is not desirable at all to have a trajectory that would stay on the boundary of the malignant region. This phenomenon is caused by the dynamic properties of the underlying system and it persists if, rather than limiting the overall amounts of cytotoxic agents a priori, the integral $\int_0^T u(t)\,dt$ is added into the objective to be minimized. Clearly, it is equally possible to improve the value of the objective without incurring any additional cost along $u = 0$ (Ledzewicz et al. 2010). Mathematically, it is preferable to have a well-posed formulation in which optimal controls exist. Therefore, here we introduce a new objective that consists of a weighted average of (i) the penalty term $ax(T) - by(T)$ that induces the system to move from the malignant into the benign region of the state space, (ii) the cumulative effects of the chemotherapeutic agent in the objective and (iii) a penalty term on the terminal time T. We thus aim to minimize an objective of the form

$$J(u) = ax(T) - by(T) + c\int_0^T u(t)\,dt + dT$$

where a and b are positive coefficients determined by the stable eigenvector $\mathfrak{v}_s = (b, a)^T$ of the saddle and c and d are positive weights. Such an objective will strike 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, $\int_0^T u(t)\,dt$, while it guarantees the existence of an optimal solution by also penalizing the free terminal time T. We therefore consider the following optimal control problem in Bolza form:
[OC] for a free terminal time T, minimize the objective

$$J(u) = ax(T) - by(T) + \int_0^T (cu(t) + d)\,dt, \tag{4}$$

over all Lebesgue measurable functions $u : [0, T] \to [0, 1]$ subject to the dynamics

$$\dot{x} = -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy - \kappa xu, \quad x(0) = x_0, \tag{5}$$

$$\dot{y} = \mu_I \left(x - \beta x^2\right) y - \delta y + \alpha, \quad y(0) = y_0. \tag{6}$$

It is easily seen that for positive initial conditions x_0 and y_0 and any admissible control u the states x and y remain positive. For, since $x = 0$ is an equilibrium solution of (5), the variable x cannot cross 0 and if $y = 0$, then we always have that $\dot{y} > 0$. Thus there is no need to impose positivity as a separate state-constraint. We denote the state by $z = (x, y)^T$ and express the dynamics in the form

$$\dot{z} = f(z) + ug(z) \tag{7}$$

where

$$f(z) = \begin{pmatrix} -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy \\ \mu_I \left(x - \beta x^2\right) y - \delta y + \alpha \end{pmatrix} \quad \text{and} \quad g(z) = \begin{pmatrix} -\kappa x \\ 0 \end{pmatrix} \tag{8}$$

are the drift and control vector field, respectively.

4 Necessary conditions for optimality

First-order necessary conditions for optimality of a control u are given by the *Pontryagin Maximum Principle* (for some recent texts, see Bonnard and Chyba 2003; Bressan and Piccoli 2007): For $\lambda_0 \in \mathbb{R}$ and a two-dimensional row-vector $\lambda = (\lambda_1, \lambda_2)$, define the Hamiltonian $H = H(\lambda_0, \lambda, x, y, u)$ as

$$\begin{aligned} H = {} & \lambda_0 (cu + d) + \lambda_1 \left(-\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy - \kappa xu\right) \\ & + \lambda_2 \left(\mu_I (1 - \beta x) xy - \delta y + \alpha\right), \end{aligned} \tag{9}$$

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

$$H = \langle \lambda, f(z) \rangle + u \left(\lambda_0 c + \langle \lambda, g(z) \rangle\right) + \lambda_0 d. \tag{10}$$

If u_* is an optimal control defined over an interval $[0, T]$ with corresponding trajectory $z_* = (x_*, y_*)^T$, then there exist a constant $\lambda_0 \geq 0$ and an absolutely continuous two-dimensional covector λ 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

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial x} = -\lambda_1 \left(-\mu_C \left(1 + \ln\left(\frac{x}{x_\infty}\right)\right) - \gamma y - \kappa u\right) - \lambda_2 \mu_I (1 - 2\beta x)\, y \tag{11}$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial y} = \lambda_1 \gamma x - \lambda_2 \left(\mu_I \left(x - \beta x^2\right) - \delta\right) \tag{12}$$

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 control $u_*(t)$ minimizes the Hamiltonian along $(\lambda_0, \lambda(t), x_*(t), y_*(t))$ over the control set $[0, 1]$ with minimum value given by 0.

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

$$\dot{\lambda}(t) = -\lambda(t)\,(Df(z_*(t)) + u_*(t)Dg(z_*(t))) \tag{13}$$

where Df and Dg denote the matrices of the partial derivatives of the vector fields f and g, respectively.

We call a controlled trajectory $((x, y), u)$ consisting of an admissible control u with corresponding trajectory (x, y) for which there exist multipliers λ_0 and λ such that the conditions of the Maximum Principle are satisfied with an *extremal* (pair) and the triple $((x, y), u, (\lambda_0, \lambda))$ 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 problems all extremals are normal and henceforth we shall set $\lambda_0 = 1$.

Lemma 1 *All extremals are normal.*

Proof If $\lambda_0 = 0$, then the terminal conditions are given by $\lambda_1(T) = \lambda_2(T) = 0$ and thus $\lambda_1(t)$ and $\lambda_2(t)$ vanish identically as solutions of a system of homogeneous linear differential equations. This contradicts condition (a), the nontriviality of the multipliers. □

Lemma 2 *If the optimal control ends with a segment for $u = 0$, then the terminal point $(x(T), y(T))$ lies on the curve*

$$a\left(-\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy\right) - b\left(\mu_I\left(x - \beta x^2\right) y - \delta y + \alpha\right) + d = 0, \tag{14}$$

if it ends with a segment for $u = 1$, then it lies on the curve

$$a\left(-\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy - \kappa x\right) - b\left(\mu_I\left(x - \beta x^2\right) y - \delta y + \alpha\right) + c + d = 0. \tag{15}$$

Proof This follows from the terminal conditions $\lambda_1(T) = a$ and $\lambda_2(T) = -b$ and the fact that H vanishes identically. □

By condition (c), the optimal control $u_*(t)$ minimizes the Hamiltonian $H(\lambda(t), x_*(t), y_*(t), u)$ over the set $0 \le u \le 1$ a.e. on $[0, T]$. Since H is linear in u, and defining the so-called *switching function* Φ as

$$\Phi(t) = c + \langle \lambda(t), g(z_*(t)) \rangle = c - \lambda_1(t)\kappa x_*(t), \tag{16}$$

it follows that

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ 1 & \text{if } \Phi(t) < 0 \end{cases}. \tag{17}$$

We refer to the constant controls $u = 0$ and $u = 1$ as the *bang* controls. The minimum condition by itself does not determine the control at times when $\Phi(\tau) = 0$. If $\dot{\Phi}(\tau) \neq 0$, then at such a time the control switches between $u = 0$ and $u = 1$ depending on the sign of $\dot{\Phi}(\tau)$ and thus also the name of bang-bang controls. However, if $\Phi(t) \equiv 0$ on an open interval I, then also all derivatives of $\Phi(t)$ must vanish and typically this does allow to compute the control. Controls of this kind are called *singular* (Bonnard and Chyba 2003). Optimal controls then need to be synthesized from these two classes of candidates.

This requires to analyze the zero set of the switching function. All we know about the switching function a priori is that it is absolutely continuous and thus in principle its zero set could be any closed subset of $[0, T]$ Golubitsky and Guillemin (1973). However, typically its structure is much simpler and can be determined through an analysis of the derivatives of the switching function. The following well-known elementary proposition summarizes the relevant computations.

Proposition 1 *Let $z(\cdot)$ be a solution of the dynamics (7) for the control u and let λ be a solution of the corresponding adjoint equation (13). For a continuously differentiable vector field h define*

$$\Psi(t) = \langle \lambda(t), h(z(t)) \rangle. \tag{18}$$

Then the derivative of Ψ is given by

$$\dot{\Psi}(t) = \langle \lambda(t), [f + ug, h](z(t)) \rangle, \tag{19}$$

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, we have that

$$\begin{aligned}
\dot{\Psi} &= \dot{\lambda} h(z) + \lambda Dh(z)\dot{z} \\
&= -\lambda \left(Df(z) + uDg(z)\right) h(z) + \lambda Dh(z) \left(f(z) + ug(z)\right) \\
&= \lambda \left(Dh(z) f(z) - Df(z)h(z)\right) + u\lambda \left(Dh(z)g(z) - Dg(z)h(z)\right) \\
&= \langle \lambda, [f + ug, h](z) \rangle.
\end{aligned}$$

□

5 Singular arc and control

Suppose an optimal control u_* is singular on an open interval I. Then the switching function Φ and all its derivatives vanish on I. Especially, we thus have that

$$\Phi(t) = \langle \lambda(t), g\left(z_*(t)\right) \rangle + c \equiv 0$$

and using Proposition 1 with $h = g$ we also get that

$$\dot{\Phi}(t) = \langle \lambda(t), [f, g](z_*(t)) \rangle \equiv 0 \tag{20}$$

on I. The Hamiltonian H can be written in the form

$$H = \langle \lambda(t),\, f(z_*(t))\rangle + \Phi(t)u(t) + d$$

and the fact that H vanishes identically thus also implies that

$$H = \langle \lambda(t),\, f(z_*(t))\rangle + d \equiv 0$$

on I. Hence we have that

$$\langle \lambda(t), cf(z_*(t)) - dg(z_*(t))\rangle \equiv 0. \tag{21}$$

Since λ is nontrivial (otherwise the terminal values on $\lambda(T)$ cannot be satisfied), it follows that the vector fields $cf - dg$ and $[f, g]$ must be linearly dependent when the optimal control is singular. The locus of these points is called a *singular arc* and it can simply be computed as the zero set of the determinant

$$\det\left(cf(z) - dg(z), [f, g](z)\right) = 0. \tag{22}$$

For our system, this expression becomes a quadratic polynomial in y of the form

$$\det\left(cf(z) - dg(z), [f, g](z)\right) = \kappa x \left(a_2(x)y^2 + a_1(x)y + a_0(x)\right) \tag{23}$$

with coefficients that are functions of x. Explicit computations verify that

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

Thus for every value x the singular curve consists of possibly one or two values or no singular arc is possible. For example, since $a_0(x)$ 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 and analytic formulas for y as a function of x can still be written down, but they get unwieldy.

Similar formulas can be derived for the singular control that keeps the singular arc invariant and for the Legendre–Clebsch condition, a necessary condition for optimality of a singular arc (e.g., see Bonnard and Chyba 2003): It follows from Proposition 1 and Eq. (20) that the second derivative of the switching function is given by

$$\ddot{\Phi}(t) = \langle \lambda(t), [f, [f, g]](z_*(t))\rangle + u(t)\langle \lambda(t), [g, [f, g]](z_*(t))\rangle.$$

If $\langle \lambda(t), [g, [f, g]](z_*(t))\rangle$ does not vanish, then it is a necessary condition for optimality of a singular control u_*, the so-called *Legendre–Clebsch (LC) condition*, that

$$\langle \lambda(t), [g, [f, g]](z_*(t))\rangle < 0 \tag{24}$$

holds along the optimal singular arc. In this case the singular control can then formally be expressed as

$$u_{\sin}(t) = -\frac{\langle \lambda(t), [f,[f,g]](z_*(t))\rangle}{\langle \lambda(t), [g,[f,g]](z_*(t))\rangle}. \tag{25}$$

On the set where the vector fields g and $[f,g]$ are linearly independent, we can express the second-order brackets $[f,[f,g]]$ and $[g,[f,g]]$ as linear combinations of this basis, say

$$[f,[f,g]](z) = \varphi_1(z)g(z) + \varphi_2(z)[f,g](z) \tag{26}$$

and

$$[g,[f,g]](z) = \theta_1(z)g(z) + \theta_2(z)[f,g](z). \tag{27}$$

Since we have that $\langle \lambda(t), g(z_*(t))\rangle = -c < 0$ and $\langle \lambda(t), [f,g](z_*(t))\rangle = 0$ along the singular arc, Eq. (27) simplifies to

$$\langle \lambda(t), [g,[f,g]](z_*(t))\rangle = -c\theta_1(z_*(t))$$

and thus the strengthened Legendre–Clebsch condition is satisfied if and only if $\theta_1(z_*(t))$ is positive. Similarly, the singular control can be calculated explicitly as the feedback function

$$\begin{aligned} u_{\sin}(t) &= -\frac{\varphi_1(z_*(t))\langle \lambda(t), g(z_*(t))\rangle + \varphi_2(z_*(t))\langle \lambda(t), [f,g](z_*(t))\rangle}{\theta_1(z_*(t))\langle \lambda(t), g(z_*(t))\rangle + \theta_2(z_*(t))\langle \lambda(t), [f,g](z_*(t))\rangle} \\ &= -\frac{\varphi_1(z_*(t))}{\theta_1(z_*(t))}. \end{aligned} \tag{28}$$

For our system, direct calculations verify that

$$\begin{aligned} [f,g](z) &= Dg(z)f(z) - Df(z)g(z) \\ &= \begin{pmatrix} -\kappa & 0 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy \\ \mu_I(x-\beta x^2)y - \delta y + \alpha \end{pmatrix} \\ &\quad - \begin{pmatrix} -\mu_C\left(1+\ln\left(\frac{x}{x_\infty}\right)\right) - \gamma y & -\gamma x \\ \mu_I(1-2\beta x)\, y & \mu_I\left(x-\beta x^2\right) - \delta \end{pmatrix} \begin{pmatrix} -\kappa x \\ 0 \end{pmatrix} \\ &= \begin{pmatrix} \kappa\mu_C x \ln\left(\frac{x}{x_\infty}\right) + \kappa\gamma xy \\ 0 \end{pmatrix} - \begin{pmatrix} \kappa\mu_C x\left(1+\ln\left(\frac{x}{x_\infty}\right)\right) + \kappa\gamma xy \\ -\kappa\mu_I x(1-2\beta x)\, y \end{pmatrix} \\ &= \kappa x \begin{pmatrix} -\mu_C \\ \mu_I(1-2\beta x)y \end{pmatrix}. \end{aligned}$$

Similar computations show that

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

and

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

The vector fields g and $[f,g]$ are linearly independent unless $x = \frac{1}{2\beta}$ and away from this value we have that

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

Thus we have the simple criterion that a singular arc satisfies the strengthened Legendre–Clebsch condition in the sets $\{(x,y) : 0 < x < \frac{1}{4\beta}\}$ and $\{(x,y) : \frac{1}{2\beta} < x\}$ and it violates it in $\{(x,y) : \frac{1}{4\beta} < x < \frac{1}{2\beta}\}$. Overall, we therefore get the following result:

Proposition 2 *Singular arcs are solutions $y = y(x)$ of the quadratic equation (23), $a_2(x)y^2 + a_1(x)y + a_0(x) = 0$. The singular control that keeps the system on the singular arc is given in feedback form as*

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

where the coefficients φ_1 and θ_1 are defined through the relations (26) and (27). (This control is admissible if and only if its value lies in the interval [0, 1]). *The strengthened Legendre–Clebsch condition is satisfied for $x < \frac{1}{4\beta}$ and $\frac{1}{2\beta} < x$, and it is violated for $\frac{1}{4\beta} < x < \frac{1}{2\beta}$.* □

Based on the formulas derived above, the singular arc, the singular control, and their admissible portions can easily be evaluated numerically. In Fig. 2 we give two graphs that illustrate the structure of the singular curves for two parameter values for which we shall later give the optimal controls.

6 Optimal controlled trajectories

In this section, we give several examples of optimal controlled trajectories for different scenarios that show the typical structure of the solutions. There exists a large literature on algorithms to solve so-called non-singular optimal control problems when the Hamiltonian is quadratic and positive definite in the controls, but numerical methods

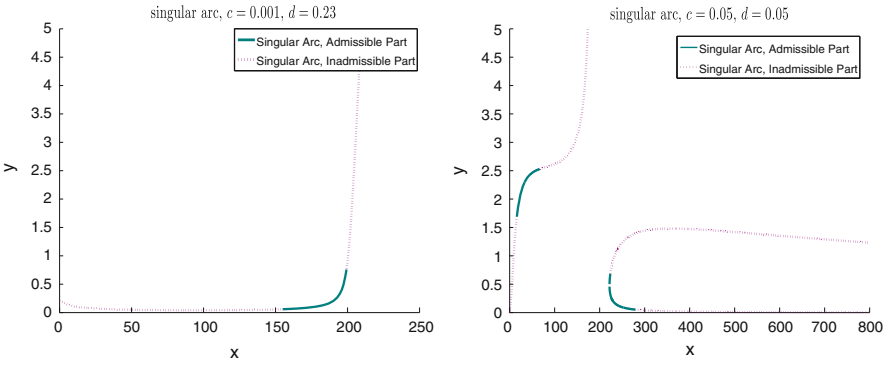

Fig. 2 Examples of singular curves with the admissible portions identified by the solid segments

and software for problems that also include optimal singular arcs are not as developed. Here we used the classical ε-algorithm approach in which a quadratic penalty term

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

is added to the objective and then the optimal controls for the underlying problem are recovered in the limit as $\varepsilon \to 0$ (Bell and Jacobson 1975). For the actual computations we used GPOPS (General Pseudo-spectral OPtimal control Software), an open-source MATLAB optimal controls software that implements the Gauss hp-adaptive pseudo-spectral methods (http://www.gpops.org/, Rao et al. 2008). These methods approximate the state using a basis of Lagrange polynomials and collocate the dynamics at the Legendre-Gauss nodes (Benson 2004; Benson et al. 2006; Huntington 2007). The continuous-time optimal control problem is then transformed into a finite-dimensional nonlinear programming problem that is being solved using well known and standard algorithms. The algorithm generates local minima and, if there exist more than one, a simple comparison of the values is done to obtain the optimal solution. In some simple cases, that essentially are generated by choices c and d of the coefficients in the objective (4) that skew the importance of the side-effects versus the terminal time, optimal controls become constant full-dose regimens. Aside from these scenarios, optimal solutions contain a time interval when the control is singular. The analytic formulas derived above were checked against the numerically found values to verify the accuracy of these solutions.

We want to illustrate the changes in the structure of the optimal controls as the coefficients in the objective change and therefore in our 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 immunocompetent cell densities to 10% of a nominal value. For these initial conditions that lie well within the malignant region, initially in each scenario considered below the control is given by $u \equiv 1$ for some interval $[0, t_1]$.

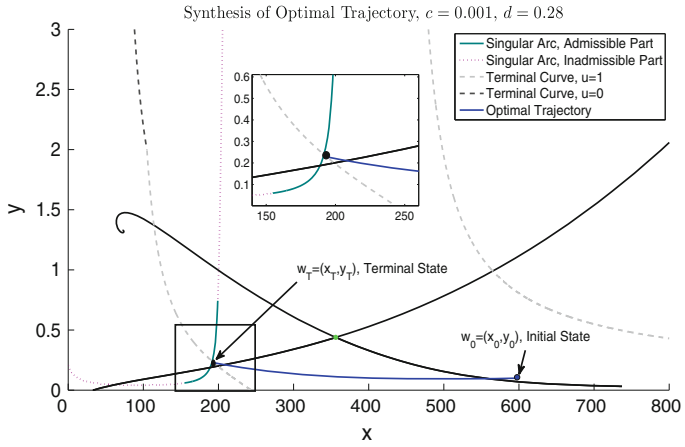

Fig. 3 The initial point $(p_0, q_0) = (600, 0.1)$ is steered optimally with $u = 1$

Scenario 1 If the penalty on the terminal time T is taken large relative to the side-effects of treatment, $d \gg c$, this term becomes dominant and the optimal control is simply constant given by a full dose treatment, $u \equiv 1$. Figure 3 shows an example for this kind of trajectory with $d = 0.28$ and $c = 0.001$. The optimal trajectory barely crosses into the benign region. Yet, assuming the dynamics follows the uncontrolled system after the final time T, the state then converges to the benign equilibrium point. The figure also shows the singular arc which in this range is the graph of a function with its admissible portion identified as the solid green portion. But for these parameter values the optimal solution terminates exactly at the time when the singular arc is reached. The figure, and also the ones given below, also identifies the two curves defined in Eqs. (14) and (15) in Lemma 2 where an optimal control satisfies the required transversality conditions for ending with $u = 0$ and $u = 1$, respectively. The terminal point needs to lie on this curve according to the final value of the control being used.

Scenario 2 For decreasing values of d, the trajectory starts from the initial condition (x_0, y_0) with $u = 1$ until it hits the singular arc. At this time, the control switches to the singular control and follows the singular arc across the separatrix. Then, at a certain time τ the control switches to $u = 0$ and follows the uncontrolled trajectory towards the benign equilibrium point. Because of the small penalty on the amount of drugs used, the control in principle can switch to $u = 1$ once more and push the system further away from the separatrix. We use the notation $1s0$, respectively $1s01$, to label the concatenation sequences of the optimal controls. That is, an $1s01$-trajectory starts with a segment $[0, t_1]$ when the control is at maximum dosage, $u \equiv 1$, followed by an interval $[t_1, \tau]$ where the control is singular and the trajectory follows an admissible singular arc, then switches to an interval $[\tau, \sigma]$ when no drugs are given, $u \equiv 0$, and possibly ends with another full burst of chemotherapy on an interval $[\sigma, T]$.

This leads to the following three-dimensional minimization problem over variables (τ, σ, T) whose numerical solution then defines the optimal control:

- τ denotes the time along the singular arc when the control switches from singular to $u = 0$. At the corresponding point the trajectory leaves the singular arc and follows the trajectory of the uncontrolled system.
- σ denotes the time along the trajectory for the uncontrolled system ($u = 0$) when chemotherapy becomes reactivated. At this time the control switches from $u = 0$ to $u = 1$.
- T denotes the time along this trajectory of the controlled system ($u = 1$) that minimizes the objective (4). The terminal point lies on the curve defined by (15).

Overall, a concatenation sequence for the control of at most the form $1s01$ results. Figure 4 illustrates three examples for $(c, d) = (0.001, 0.23)$, $(c, d) = (0.01, 0.2)$, and $(c, d) = (0.05, 0.2)$. The initial and terminal conditions are labeled as w_0 and w_T, respectively, and the consecutive switching points are w_1, w_2 and w_3. Again, in the relevant range, the singular arc is the graph of a function and the figure identifies its admissible segment.

Scenario 3 The other common structure of optimal controlled trajectories is of the form $1s0$. As the parameter c increases, that is, the penalty on the chemotherapeutic agent is increased, this gives prominent role to the side effects (and this in some sense is the most important case) and then the last segment in the optimal control corresponding to $u = 1$ no longer is present. In this case, the optimal control will be of the form $1s0$ and the optimal trajectory ends on the curve (14) that defines the terminal values for the control $u = 0$. This situation is rather typical and we illustrate it in Fig. 5.

7 Conclusion

Based on Stepanova's mathematical model of immunological activity during cancer growth, we formulated the problem of how to transfer a malignant initial condition into a benign region through therapy as an optimal control problem. Clearly, the model oversimplifies activation and action of the immune system and thus is not practically relevant. But it nevertheless leads to interesting theoretical insights about optimal therapies in the presence of tumor immune interactions. In this paper, by including a penalty term on the final time T, we have given a well-posed formulation for which optimal controls exist. If too much prominence is given to this penalty, optimal controls simply will become constant and be given by the full dose controls $u \equiv 1$. More realistically, as the coefficient at the terminal time is decreased, or, equivalently, the coefficient at the integral of u that measures side-effects is increased, the responses to optimal treatments typically are concatenations that start with a full dose trajectory for $u \equiv 1$ and then are followed by a segment corresponding to partial dose treatments (singular arc). In view of the fact that $u = 1$ denotes the maximum allowable dose in the model, this solution structure agrees with protocols that initially apply a burst of chemotherapy to reduce the tumor volume and then sustain a smaller volume with reduced dosages. At the appropriate time, determined by the optimality conditions, treatment in terms of giving cytostatic agents u ceases and the system follows the uncontrolled trajectory corresponding to $u \equiv 0$ until the minimal value for the objective is reached as the trajectory reaches the curve (14) where the transversality

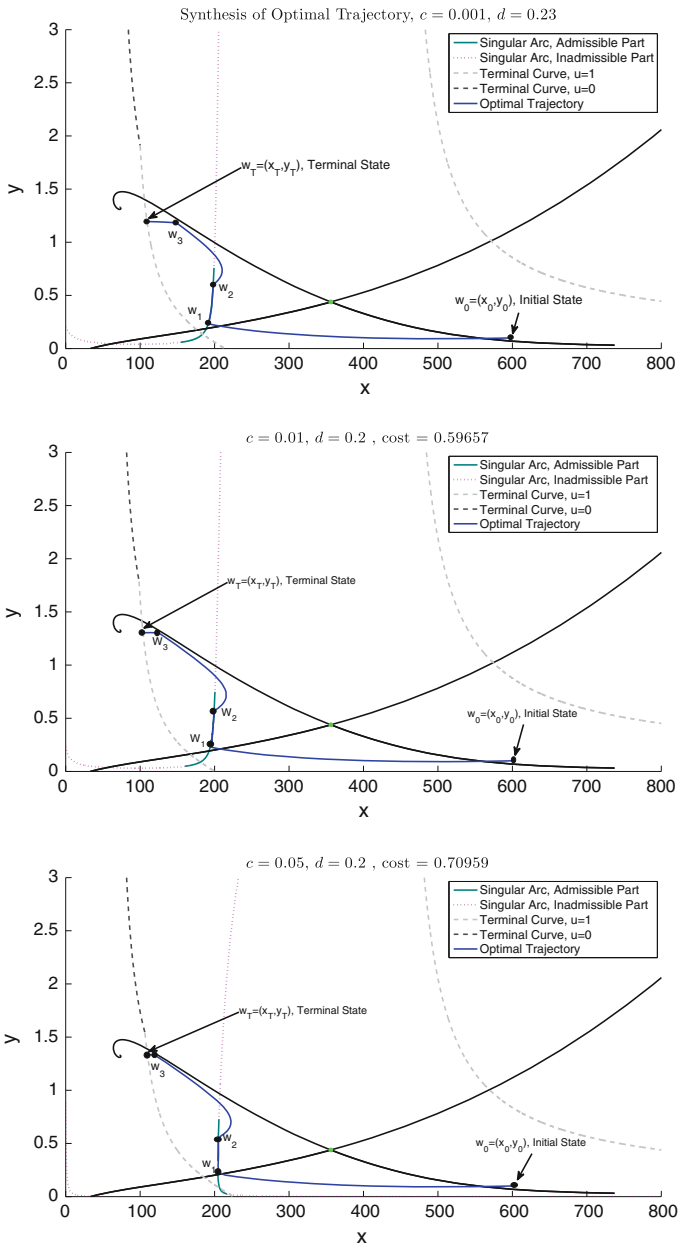

Fig. 4 Examples of optimal controlled trajectories whose controls follow the concatenation structure $1s01$

conditions for ending with $u = 0$ are satisfied. In some cases, depending on the relations between the coefficients c and d in (4) that define the objective, possibly one more short trajectory corresponding to another full dose control segment $u \equiv 1$ at the end is optimal.

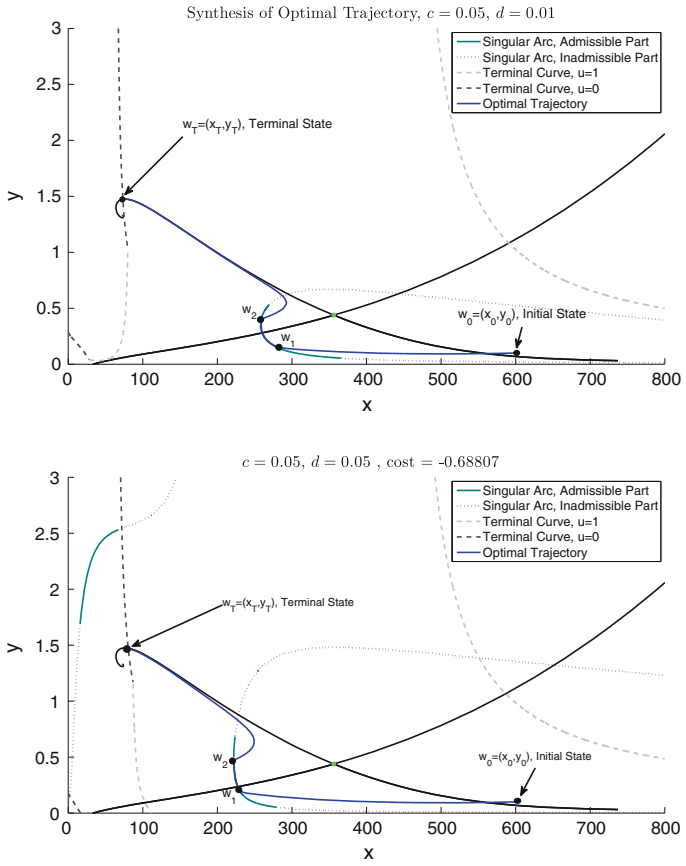

Fig. 5 Examples of optimal controlled trajectories whose controls follow the concatenation structure $1s0$

With the prominent role played by a singular arc, these solutions for model [OC] contrast with optimal controls for cell-cycle specific models for cancer chemotherapy when no tumor–immune system interactions are taken into account and where optimal controls are bang-bang (e.g., Ledzewicz and Schättler 2002; Swierniak et al. 2003). Clearly, the underlying dynamical systems are difficult to compare, but it could be speculated that it is the mitigating influence of the immune system that for smaller tumor volumes leads to the abandonment of the strict bang-bang scheme that is seen in the cell-cycle specific models. For these models the Legendre–Clebsch condition is always violated and thus partial doses will never be optimal. In the model considered here, optimal controls still are given by full dose segments when the tumor volume is large, but then partial doses represented by the singular arc provide better results as the tumor volume shrinks.

Despite the model's simplicity, the paper addresses the important question 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. Hence there exists a strong

opportunity for mathematical techniques to be useful here to give some guidance The analysis presented can be considered 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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