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AN OPTIMAL CONTROL APPROACH TO CANCER TREATMENT UNDER IMMUNOLOGICAL ACTIVITY

Abstract. Mathematical models for cancer treatment that include immunological activity are considered as an optimal control problem with an objective that is motivated by a separatrix of the uncontrolled system. For various growth models on the cancer cells the existence and optimality of singular controls is investigated. For a Gompertzian growth function a synthesis of controls that move the state into the region of attraction of a benign equilibrium point is developed.

1. Introduction. In 1980, Stepanova [12] proposed a mathematical model of two ordinary differential equations for the interactions between cancer cell growth and the activity of the immune system during the development of cancer. Despite its simplicity, depending on the parameter values, this model allows for various medically observed features. By now the underlying equations have been widely accepted as a basic model and have become the basis for numerous extensions and generalizations (e.g., [8, 5, 6] and the references therein). An extensive analysis of the dynamical properties of mathematical models including tumor immune-system interactions has been carried out in the literature. Kuznetsov et al. [8] give a bifurcation analysis and estimate parameters based on in vivo experimental data. De Vladar and González [5] further analyze Stepanova's model, and d'Onofrio [6] formulates and investigates a general class of models. Among the more important common theoretical findings are the following ones: while under certain conditions the immune system can be effective in the

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control of small cancer volumes (and in these cases what actually is medically considered cancer never develops), so-called immune surveillance, for large volumes the cancer dynamics suppresses the immune dynamics and the two systems effectively become separated [5, Appendix B]. Consequently, in this case only a therapeutic effect on the cancer (e.g., chemotherapy, radiotherapy, ...) needs to be analyzed. There is, however, the interesting case “in the middle” when both a benign (microscopic or macroscopic) stable equilibrium exists and uncontrolled growth is possible as well. In this case, there also exists an unstable equilibrium point and its stable manifold becomes a separatrix between the benign region and the malignant region of uncontrolled cancer growth. It may then be possible to shift an initial condition of the system from the region of uncontrolled growth into the region of attraction of the benign equilibrium through therapy and thus control the cancer. In this paper, for Stepanova’s model we formulate this aim as an optimal control problem and, based on necessary conditions for optimality, derive a structure of controls that achieves this objective when cancer growth is modeled by a Gompertzian growth function.

Optimal control approaches have been considered previously in the context of cancer immune interactions, for example, in the work by de Pillis et al. [3, 4]. In these papers, for a larger and more detailed model of the tumor immune system interactions, optimal controls are computed numerically for an a priori specified time horizon. In contrast, our approach is analytical and the final time is free with the overall amount of therapeutic agents to be given specified. But the main difference of our formulation considered here lies in the selection of an objective that is determined by geometric properties of the underlying uncontrolled system. Preliminary research in this direction has been presented in [9].

2. Stepanova’s mathematical model for cancer immune response. In a slightly modified form, the dynamical equations are given by

$$\begin{aligned} (1) \quad & \dot{x} = \mu_C x F(x) - \gamma xy, \\ (2) \quad & \dot{y} = \mu_I (x - \beta x^2) y - \delta y + \alpha, \end{aligned}$$

where x denotes the tumor volume and y represents the immunocompetent cell densities related to various types of T -cells activated during the immune reaction; all Greek letters denote constant coefficients.

Equation (2) summarizes the main features of the immune system’s reaction to cancer in a one-compartment model with the T -cells as the most important indicator. 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 anti-

tumor antigen which is assumed to be proportional to the tumor volume x . But large tumors predominantly suppress the activity of the immune system and this is expressed 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 this term thus models the beneficial effect of the immune reaction on the cancer volume. Lastly, μ_C is a tumor growth coefficient. In our formulation above, F is a functional parameter that allows one 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 growth models are preferred. For instance, there exists medical evidence that some tumors follow a Gompertzian growth model [11, 10] in which case the function F is given by $F_G(x) = -\ln(x/x_\infty)$ with x_∞ denoting a fixed carrying capacity for the cancer. But also logistic and generalized logistic growth models of the form $F_L(x) = 1 - (x/x_\infty)^\nu$ with $\nu > 0$ have been considered as models for tumor growth. We here thus mostly consider the model with a general growth term F only assuming that F is a positive, twice continuously differentiable function defined on the interval $(0, x_\infty)$.

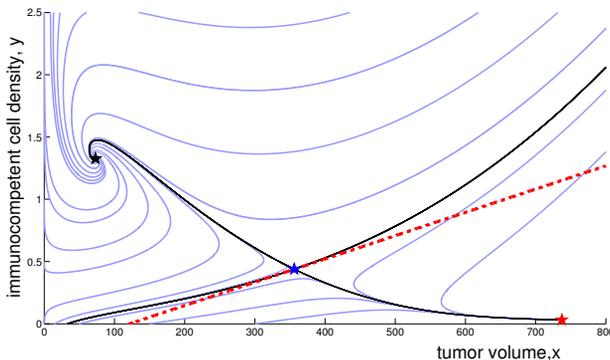


Fig. 1. Phase portrait of the system given by equations (1) and (2) with a Gompertzian growth function

An example of the phase portrait of this system for a Gompertzian growth function is shown in Fig. 1. The parameter values that were used

to generate this figure are 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 [8] by Kuznetsov et al. who estimate parameters based on in vivo experimental data for B-lymphoma BCL_1 in the spleen of mice. In that paper a classical logistic growth model is used to model cancer growth and we therefore adjusted the remaining parameters to account for a Gompertzian growth model using linear data fitting. Also, the functional form $(x - \beta x^2)y$ used in Stepanova's model in equation (2) is a quadratic expansion of the term used in [8]. The specified parameter values only serve to illustrate our results and computations numerically. There exist three equilibria, an asymptotically stable focus at $(72.961, 1.327)$, a saddle point at $(356.174, 0.439)$ and an asymptotically stable node at $(737.278, 0.032)$. Clearly this structure depends on the parameter values chosen and it is not generally valid for the underlying system. However, it is correct for a large range of close-by values.

3. Formulation of the optimal control problem. We consider this dynamics under the application of a therapeutic agent and, following [5], assume that the elimination terms are proportional to tumor volume and immunocompetent cell densities (the so-called *log-kill hypothesis*). Hence we subtract terms $\kappa_X x u$, respectively $\kappa_Y y u$, from the x and y dynamics. The coefficients κ_X and κ_Y allow us to normalize the control set, i.e., we assume that $0 \leq u \leq 1$. Fig. 2 shows the phase portrait of the system when $u = 1$

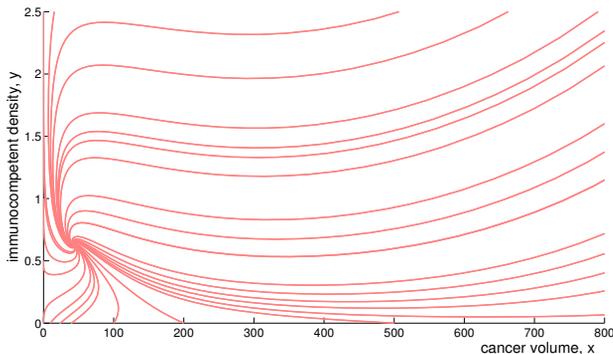


Fig. 2. Phase portrait of the system with Gompertzian growth and $u = 1$ and $(\kappa_X, \kappa_Y) = (1, 0)$

and $(\kappa_X, \kappa_Y) = (1, 0)$. Again these values are for illustrative purposes only. In this case the system has only one equilibrium with positive values at $(\bar{x}, \bar{y}) = (43.017, 0.622)$, which is a globally asymptotically stable focus for the region $\mathbb{R}_+^2 = \{(x, y) : x > 0, y > 0\}$, the region of interest. For $\kappa_Y > 0$

the y -coordinate \bar{y} of the equilibrium will be smaller, but the beneficial effect on the cancer volume will be diminished and thus \bar{x} will be larger. But for any values of (κ_X, κ_Y) it is in principle possible (ignoring side effects) to reduce the cancer volume to a small enough chronic state.

Naturally, side effects of the drugs invalidate this reasoning and our aim is to investigate how an initial condition (x_0, y_0) 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. Such a transfer requires minimizing the cancer cells x while not depleting the T -cell density y too strongly. The system under consideration is Morse–Smale [7] and thus the boundary between these two types of behaviors 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 is well approximated by its tangent line in the region where the tumor volume is not too large (otherwise the immune system will not be very effective anyway [5]) and also the one of Fig. 2 in [5] is almost linear. It thus becomes a reasonable strategy to minimize an objective of the form $ax - by$ where a and b are positive coefficients determined by the stable eigenvector

$$(3) \quad \mathbf{v}_s = \begin{pmatrix} b \\ a \end{pmatrix}$$

of the saddle that determines the boundary between the two stable behaviors of the system. For example, for the parameter values used earlier, normalizing $b = 1$ we have $a = 0.00192$.

Side effects of the treatment still need to be taken into account and there exist various options of modeling them. For example, if u denotes a cytotoxic agent, one can include its cumulative effects in the objective and aim to minimize a weighted average of the form

$$(4) \quad J(u) = ax(T) - by(T) + \varepsilon \int_0^T u(t) dt$$

with some $\varepsilon > 0$. Such an objective will strike a balance between the benefit at the terminal time T and the overall side effects measured by the total amount of drugs given. However, it is still possible that this amount far exceeds any tolerable limits in order to gain the “optimal” benefit. It is therefore sometimes a more useful approach to limit the overall amount of

cytotoxic agents to be given a priori,

$$(5) \quad \int_0^T u(t) dt \leq A,$$

and then to ask how this amount can best be applied. This is the approach we take here. In such a formulation, T does not correspond to a therapy horizon, but it merely denotes the time when the minimum for the objective is realized. Based on a solution to this optimal control problem, possibly for various values of the overall amount A , an appropriate therapy interval can then be determined. In any case, the necessary conditions for optimality for these two formulations are closely related and thus it can be expected that the structure of optimal solutions is similar.

Adjoining the isoperimetric constraint (5) as a third variable z , we thus consider the following optimal control problem:

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

$$(6) \quad J(u) = ax(T) - by(T),$$

$a > 0, b > 0$, subject to the dynamics

$$(7) \quad \dot{x} = \mu_C x F(x) - \gamma xy - \kappa_X xu, \quad x(0) = x_0,$$

$$(8) \quad \dot{y} = \mu_I(x - \beta x^2)y - \delta y + \alpha - \kappa_Y yu, \quad y(0) = y_0,$$

$$(9) \quad \dot{z} = u, \quad z(0) = 0,$$

over all Lebesgue measurable functions $u : [0, T] \rightarrow [0, 1]$ for which the corresponding trajectory satisfies $z(T) \leq A$.

It is not difficult to see that for positive initial conditions x_0 and y_0 and for any admissible control u all states remain positive and thus there is no need to impose this condition as a state-space constraint. Since we are interested in the case when the immune activity can have some influence, but, on the other hand, by itself is not able to suppress the cancer, here we only consider trajectories that lie in the region

$$(10) \quad \mathbb{G} = \{(x, y) : x > 1/(2\beta), y > 0\}$$

where the cancer volume is not too small. If the initial condition (x_0, y_0) lies in the malignant region, but outside of \mathbb{G} , the phase portrait of the uncontrolled system (see Fig. 1) shows that the tumor volume increases for $u \equiv 0$ and thus also in this case the system will eventually enter the region \mathbb{G} if no actions are taken and then our analysis will apply. Of course, it is not claimed that it would be an optimal strategy to let the tumor grow to the size $1/(2\beta)$, but in principle this allows us to reduce the problem mathematically to considering the region \mathbb{G} only. Also, while we derive some properties of optimal controls in general, in this paper we restrict our core analysis to the

case when the elimination effects on the immunocompetent cells are much smaller than on the tumor cells, $\kappa_Y \ll \kappa_X$, and for simplicity we then set $\kappa_Y = 0$.

4. Necessary conditions for optimality. First-order necessary conditions for optimality of a control u are given by the *Pontryagin Maximum Principle* (some recent textbooks on the topic are [1, 2]): For a row-vector $\lambda = (\lambda_1, \lambda_2, \lambda_3) \in (\mathbb{R}^3)^*$, we define the Hamiltonian $H = H(\lambda, x, y, u)$ as

$$(11) \quad H = \lambda_1(\mu_C x F(x) - \gamma x y - \kappa_X x u) \\ + \lambda_2(\mu_I(x - \beta x^2)y - \delta y + \alpha - \kappa_Y y u) + \lambda_3 u.$$

Ignoring one trivial situation when the optimal control is constant and is given by $u = 1$ over the full interval, we can restrict our analysis to so-called normal extremals when the multiplier λ_0 corresponding to the objective is non-zero and we normalize $\lambda_0 = 1$. Hence, if u_* is an optimal control defined over the interval $[0, T]$ with corresponding trajectory (x_*, y_*, z_*) , then there exists an absolutely continuous co-vector, $\lambda : [0, T] \rightarrow (\mathbb{R}^3)^*$, such that the following conditions hold:

(a) λ_3 is constant, and λ_1 and λ_2 satisfy the adjoint equations

$$(12) \quad \dot{\lambda}_1 = -\frac{\partial H}{\partial x} \\ = -\lambda_1(\mu_C(F(x) + xF'(x)) - \gamma y - \kappa_X u) - \lambda_2\mu_I(1 - 2\beta x)y,$$

$$(13) \quad \dot{\lambda}_2 = -\frac{\partial H}{\partial y} = \lambda_1\gamma x - \lambda_2(\mu_I(x - \beta x^2) - \delta - \kappa_Y u),$$

with terminal conditions $\lambda_1(T) = a$ and $\lambda_2(T) = -b$,

(b) for almost every time $t \in [0, T]$, the optimal control $u_*(t)$ minimizes the Hamiltonian along $(\lambda(t), x_*(t), y_*(t))$ over the control set $[0, 1]$ with minimum value given by 0.

The following properties of the multipliers directly follow from these conditions:

PROPOSITION 1. *If an optimal trajectory x entirely lies in the region \mathbb{G} , then λ_1 is positive and λ_2 is negative on the closed interval $[0, T]$.*

Proof. The adjoint equations (12) and (13) form a homogeneous system of linear ODE's and thus λ_1 and λ_2 cannot vanish simultaneously. It follows from the terminal conditions that $\lambda_1(T) > 0$ and $\lambda_2(T) < 0$. Suppose now λ_2 has a zero in the interval $[0, T)$ and, if there are more than one, let τ be the last one. This zero must be simple (otherwise λ_2 and λ_1 vanish identically) and therefore $\dot{\lambda}_2(\tau) = \lambda_1(\tau)\gamma x(\tau)$ is negative, implying that $\lambda_1(\tau) < 0$. But then λ_1 must have a zero in (τ, T) and, once more taking σ as the last one,

we have $\dot{\lambda}_1(\sigma) = -\lambda_2(\sigma)\mu_I[1 - 2\beta x(\sigma)]y(\sigma) > 0$. But $\lambda_2(\sigma) < 0$ and in the region \mathbb{G} also $1 - 2\beta x(\sigma) < 0$. Contradiction. Thus λ_2 has no zero in the interval $[0, T]$. The reasoning just given then also implies that λ_1 cannot have a zero. ■

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

$$(14) \quad \Phi(t) = \lambda_3 - \lambda_1(t)\kappa_X x_*(t) - \lambda_2(t)\kappa_Y y_*(t),$$

it follows that

$$(15) \quad u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0, \\ 1 & \text{if } \Phi(t) < 0. \end{cases}$$

The minimum condition by itself does not determine the control at times when $\Phi(t) = 0$. However, if $\Phi(t) \equiv 0$ on an open interval, then also all derivatives of $\Phi(t)$ must vanish and this typically allows one to compute the control. Controls of this kind are called *singular* [1] while we refer to the constant controls $u = 0$ and $u = 1$ as the *bang* controls. For example, if $\Phi(\tau) = 0$, but $\dot{\Phi}(\tau) \neq 0$, then the control switches between $u = 0$ and $u = 1$ depending on the sign of $\dot{\Phi}(\tau)$.

Optimal controls need to be synthesized from these candidates. This requires analyzing the switching function and its derivatives. The computations of the derivatives of the switching function simplify significantly within the framework of geometric optimal control theory. We define the state vector as $w = (x, y, z)^T$ and express the dynamics in the form

$$(16) \quad \dot{w} = f(w) + ug(w)$$

where

$$(17) \quad f(w) = \begin{pmatrix} \mu_C x F(x) - \gamma xy \\ \mu_I(x - \beta x^2)y - \delta y + \alpha \\ 0 \end{pmatrix} \quad \text{and} \quad g(w) = \begin{pmatrix} -\kappa_X x \\ -\kappa_Y y \\ 1 \end{pmatrix}.$$

The adjoint equations then simply read

$$(18) \quad \dot{\lambda}(t) = -\lambda(t)(Df(w(t)) + u_*(t)Dg(w(t)))$$

with Df and Dg denoting the matrices of the partial derivatives of the vector fields which are evaluated along $w(t)$. In this notation the switching function becomes

$$(19) \quad \Phi(t) = \lambda(t)g(w(t)) = \langle \lambda(t), g(w(t)) \rangle.$$

The derivatives of Φ can easily be computed by invoking a well-known direct calculation.

PROPOSITION 2. Let $w(\cdot)$ be a solution to the dynamics for control u and let λ be a solution to the corresponding adjoint equation. For a continuously differentiable vector field h define $\Psi(t) = \langle \lambda(t), h(w(t)) \rangle$. Then the derivative of Ψ is given by

$$(20) \quad \dot{\Psi}(t) = \langle \lambda(t), [f + ug, h](w(t)) \rangle,$$

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

Proof. Dropping the argument t , we have

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

The derivative of the switching function Φ thus does not depend on the control variable u and is given by

$$(21) \quad \dot{\Phi}(t) = \langle \lambda(t), [f, g](w(t)) \rangle.$$

For the system considered here, direct calculations verify that

$$(22) \quad [f, g](w) = \kappa_X \begin{pmatrix} \mu_C x^2 F'(x) \\ \mu_I (1 - 2\beta x) xy \\ 0 \end{pmatrix} - \kappa_Y \begin{pmatrix} \gamma xy \\ \alpha \\ 0 \end{pmatrix}.$$

Setting $\kappa_Y = 0$ we thus get

$$(23) \quad \dot{\Phi}(t) = \kappa_X (\lambda_1(t) \mu_C x(t)^2 F'(x(t)) + \lambda_2(t) \mu_I (1 - 2\beta x(t)) x(t) y(t)).$$

In the case of an *exponential growth model* we have $F'(x) \equiv 0$ and thus by Proposition 1 the switching function is increasing in the region \mathbb{G} . Hence we have

PROPOSITION 3. For the model with exponential growth (i.e., $F_E(x) = 1$), optimal controls u for trajectories x that entirely lie in the region \mathbb{G} are bang-bang with at most one switching from $u = 1$ to $u = 0$. \blacksquare

Hence for this model a full dose therapy is used to move the system across the separatrix (if the total amount A allows one to do so) and then the uncontrolled dynamics takes over to steer the system towards the benign equilibrium point.

5. Problem [OC] with a Gompertzian growth model $F(x) = -\ln(x/x_\infty)$. For a *Gompertzian growth model*, $F_G(x) = -\ln(x/x_\infty)$, we have $x F'_G(x) = -1$ and in this case $\dot{\Phi}(t)$ consists of a positive and a negative

term. In fact, now the derivative $\dot{\Phi}(t)$ can be made identically zero and a singular control exists. With $\kappa_Y = 0$ we get

$$(24) \quad [g, [f, g]](w) = -\kappa_X^2 \mu_I (1 - 4\beta x) xy \begin{pmatrix} 0 \\ 1 \\ 0 \end{pmatrix}$$

and thus for trajectories lying in \mathbb{G} ,

$$(25) \quad \langle \lambda(t), [g, [f, g]](w(t)) \rangle = -\lambda_2(t) \kappa_X^2 \mu_I [1 - 4\beta x(t)] x(t) y(t) < 0,$$

i.e., the strengthened Legendre–Clebsch condition for minimality is satisfied.

Hence the equation for the second derivative of the switching function,

$$(26) \quad \ddot{\Phi}(t) = \langle \lambda(t), [f, [f, g]](w(t)) \rangle + u(t) \langle \lambda(t), [g, [f, g]](w(t)) \rangle \equiv 0,$$

can be solved for u as

$$(27) \quad u_{\text{sin}}(t) = -\frac{\langle \lambda(t), [f, [f, g]](w(t)) \rangle}{\langle \lambda(t), [g, [f, g]](w(t)) \rangle}.$$

For the Gompertzian growth model the vector fields g , $[f, g]$ and $[g, [f, g]]$ are everywhere linearly independent on \mathbb{G} and thus form a basis. Hence the second-order bracket $[f, [f, g]]$ can be expressed as a linear combination of these vector fields with coefficients that are smooth functions of w . It is easily seen that the third coordinate of $[f, [f, g]]$ is zero and therefore the coefficient at the vector field g is zero. We therefore have a relation of the form

$$(28) \quad [f, [f, g]](w) = \varphi(w)[f, g](w) - \psi(w)[g, [f, g]](w)$$

with φ and ψ easily obtained as solutions of the linear equations defined by (28).

The switching function and its derivative vanish along a singular control and thus we have $\dot{\Phi}(t) = \langle \lambda(t), [f, g](w(t)) \rangle = 0$. Substituting (28) into (27) we obtain

$$(29) \quad u_{\text{sin}}(t) = -\frac{\langle \lambda(t), \varphi(w(t))[f, g](w(t)) - \psi(w(t))[g, [f, g]](w(t)) \rangle}{\langle \lambda(t), [g, [f, g]](w(t)) \rangle}$$

$$(30) \quad = -\varphi(w(t)) \frac{\langle \lambda(t), [f, g](w(t)) \rangle}{\langle \lambda(t), [g, [f, g]](w(t)) \rangle} + \psi(w(t)) = \psi(w(t)).$$

Direct calculations verify that

$$(31) \quad \psi(w) = -\frac{1}{k_X} \left[\mu_C \ln \left(\frac{x}{x_\infty} \right) + \gamma y - \frac{1 - 2\beta x}{1 - 4\beta x} \left(\frac{\alpha}{y} + \gamma \frac{\mu_I}{\mu_C} (1 - 2\beta x) xy \right) \right].$$

Clearly, it depends on the actual parameter values whether this control is admissible (i.e., its values lie in the control set $[0, 1]$) or not. For this model this property cannot be guaranteed a priori and generally the admissible portions of the singular control need to be calculated numerically. Note that

the first two terms in (31) cancel the x -dynamics of the system and thus along a singular control we have

$$(32) \quad \begin{aligned} \dot{x} &= -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy - \kappa_X x \psi(w) \\ &= -x \frac{1 - 2\beta x}{1 - 4\beta x} \left(\frac{\alpha}{y} + \gamma \frac{\mu_I}{\mu_C} (x - 2\beta x^2) y \right). \end{aligned}$$

Furthermore, the Hamiltonian H ,

$$(33) \quad H = \langle \lambda(t), f(w(t)) \rangle + u(t) \langle \lambda(t), g(w(t)) \rangle,$$

also vanishes identically along an optimal control. Along a singular arc $\langle \lambda(t), g(w(t)) \rangle \equiv 0$ and thus $\langle \lambda(t), f(w(t)) \rangle$ vanishes as well. Since the derivative of the switching function vanishes along a singular arc, that is, $\dot{\Phi}(t) = \langle \lambda(t), [f, g](w(t)) \rangle \equiv 0$, the multiplier $\lambda(t)$ vanishes along f , g and $[f, g]$. By Proposition 1, λ is non-zero and thus these vector fields must be linearly dependent along the singular arc. For this system the control vector field g is always independent of f and $[f, g]$, and therefore this condition is equivalent to the linear dependence of the vector fields f and $[f, g]$. This reduces to the following relation:

$$(34) \quad 0 = -\gamma \mu_I (x - 2\beta x^2) y^2 + \mu_C \left(-\mu_I \ln\left(\frac{x}{x_\infty}\right) (x - 2\beta x^2) + \mu_I (x - \beta x^2) - \delta \right) y + \alpha \mu_C.$$

If we write this equation in the form

$$(35) \quad a_2(x)y^2 + a_1(x)y + a_0 = 0,$$

then a_2 is positive on \mathbb{G} and a_0 is a positive constant. Thus positive solutions y can only exist for $a_1(x) < 0$. Depending on the value of x there exist no, one or two positive solutions $y = y_{\text{sin}}(x)$ that define the singular curve. For the numerical values given earlier we have $1/(2\beta) = 189.68$ and in the region \mathbb{G} there exist no positive solutions for $1/(2\beta) < x < 292.82$ and $x > 927.47$, exactly one for $x = 292.82$ and $x = 927.47$, and two positive solutions for $292.82 < x < 927.47$. This singular curve is shown in the top portion of Fig. 3, and the bottom portion gives the values of the singular control $u_{\text{sin}}(t) = \psi(w(t))$ as $w(t)$ varies along the singular curve; the admissible control set $[0, 1]$ is marked as well. For these parameter values there exist two connected segments when the singular control is admissible, separated by two inadmissible segments. The admissible segments are identified by a solid curve, while the inadmissible segments are shown as a dotted curve in Fig. 3. Note that the upper and lower portions on these two graphs are in an inverted relation to each other, i.e., the upper portion of the singular curve corresponds to the lower portion of the singular control and vice versa.

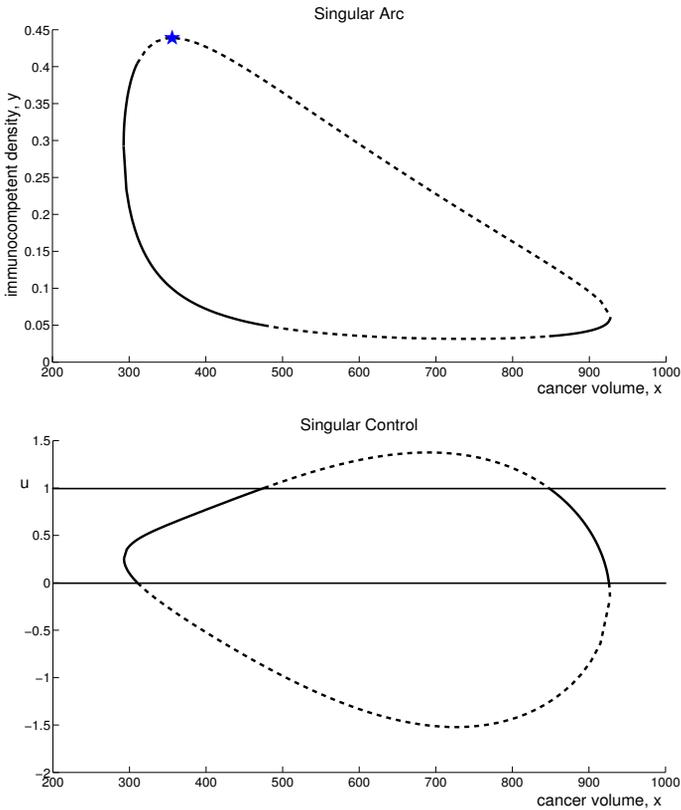


Fig. 3. The singular curve (top) and the singular control (bottom)

Summarizing, for a Gompertzian growth model we thus have the following result:

PROPOSITION 4. *For the model with Gompertzian growth function (i.e., $F_G(x) = -\ln(x/x_\infty)$), there exists a singular curve defined as the zero-set of equation (34). Along the singular curve the strengthened Legendre–Clebsch condition for minimality is satisfied and the corresponding singular dynamics is defined by (32). ■*

6. Towards a synthesis of solutions. We briefly describe (informally and without proofs) some aspects of the structure of extremal controls derived above. Recall that the underlying aim is to move an initial condition in the malignant region into the region of attraction of the benign equilibrium and that the optimal control formulation [OC] only provides the means for achieving this objective. Typically an initial condition will lie to the right of the singular arc and initially an extremal control will be constant given

by $u = 1$ until the trajectory hits the singular arc. At the junction with the singular arc, and assuming the singular control is admissible, the control switches to the singular control. Assuming enough drugs are available, the trajectory now follows the singular arc across the separatrix. (For each initial condition this construction thus allows one to compute the total amount A of the drug that is needed to move the system into the region of attraction of the benign equilibrium point.) After the trajectory has crossed the separatrix, in principle the control could switch to $u = 0$ and then follow the uncontrolled trajectory towards the benign equilibrium point. However, it seems prudent to establish an adequate security margin and move the state of the system as far away as possible from the separatrix. The remaining drugs can be used to achieve this objective. This leads to the following three-dimensional minimization problem over variables (τ, σ, α) whose numerical solution then defines the optimal control:

- τ denotes the time along the singular curve 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 this trajectory of the uncontrolled system ($u = 0$) when chemotherapy becomes reactivated. At this time the control switches from $u = 0$ to $u = 1$.
- α denotes the total amount of the drug that is being used so that the state at the terminal time T minimizes the objective given in (6). Note that we may actually have $\alpha < A$.

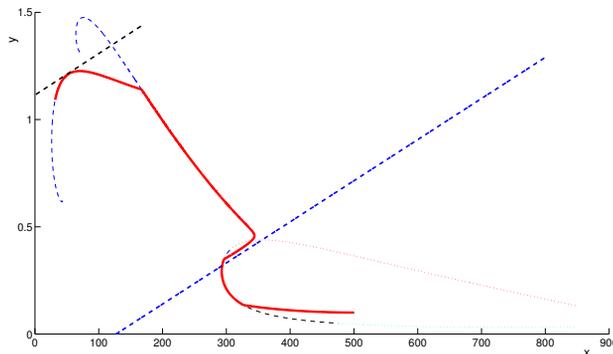


Fig. 4. Example of a trajectory of the type **1s01**

Overall, a concatenation sequence for the control of the form **1s01** results. The solid curve in Fig. 4 gives an example of a trajectory computed

for specific values of (τ, σ, α) . Initially the control is taken as $u = 1$ until the singular curve is reached. The curved dotted portion for low values of y represents other points on the singular curve. At the junction point of the trajectory for $u = 1$ with the singular curve the singular control is admissible, and now the solid curve follows the singular curve across the separatrix. The dash-dotted line represents the tangent line to this separatrix at the saddle point. At time τ the control switches to $u = 0$ and the trajectory follows this trajectory towards the benign equilibrium point. Once more we show the continuation of this trajectory as a dotted curve, while the solid curve then represents a switch to the control $u = 1$ at time σ .

The presence of the trajectory corresponding to $u = 0$ actually has important implication on the structure of optimal controls, and in fact, optimal controls need not exist in all cases. The reason is that this trajectory provides a “free pass” (i.e., does not incur a penalty), but can take an infinite time. It seems clear from the geometric properties of the phase portrait (and numerical simulations bear this out) that these calculations only give an infimum, but not a minimum. This infimum arises as the controls switch from the singular control to $u = 0$ as the singular arc intersects the stable manifold of the saddle that defines the separatrix, then follow the separatrix for an infinite time to the saddle and then again leave this saddle point along the unstable manifold again taking an infinite time. It seems intuitively clear that this would be the best solution in the sense of using the least amounts of inhibitors. But it is not an admissible trajectory in our system. While the question of the existence of an optimal control thus becomes a non-trivial one, as far as the underlying objective is concerned, this does not matter. The controls of the type **1s01** that are identified from the conditions of the Maximum Principle indeed accomplish this objective.

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. For a Gompertzian growth model on the cancer volume we described the structure of a class of controls that accomplish this objective for the case when the effects of the cytotoxic agents on immunocompetent cells is much smaller than on the tumor cells, $\kappa_Y \ll \kappa_X$. These controls are concatenations of an initial bang arc (given by $u = 0$ or $u = 1$) followed by a singular portion and a final bang-bang sequence of the form **01**.

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