

# An Optimal Control Approach to Cancer Treatment under Immunological Activity\*

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## 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 the optimal synthesis is described.

## 1 Introduction

In 1980, Stepanova [11] 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., [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. For example, de Vladar and González analyze Stepanova's model in [5] and d'Onofrio formulates and investigates a general class of models in [6]. Among the more

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important common theoretical findings are the following ones: while under certain conditions the immune system can be effective in the 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 then may 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 problem as an optimal control problem and describe the structure of optimal controls for a Gompertzian growth function on the cancer cells. Optimal control approaches have been considered previously in the context of cancer immune interactions (for example, the papers by de Pillis et al. [3, 4]), but our approach differs from those in the selection of an objective that is strongly determined by geometric properties of the underlying uncontrolled system.

## 2 Stepanova’s Mathematical Model for Cancer Immune Response

In a slightly modified form, the dynamical equations are given by

$$\dot{x} = \mu_C x F(x) - \gamma xy, \quad (1)$$

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

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  $\alpha$  models a constant rate of influx of  $T$ -cells generated through the primary organs and  $\delta$  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 can be 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  $\mu_I$  and  $\beta$  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  $\gamma$  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,  $\mu_C$  is a tumor growth coefficient. In our formulation above,  $F$  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 growth models are preferred. For instance, there exists some medical evidence that many tumors follow a Gompertzian growth model [9, 10] in which case the function  $F$  is given by  $F_G(x) = -\ln\left(\frac{x}{x_\infty}\right)$  where  $x_\infty$  denotes a fixed carrying capacity for the cancer. But also logistic and generalized logistic growth models of the form  $F_L(x) = 1 - \left(\frac{x}{x_\infty}\right)^\nu$  with  $\nu > 0$  have been considered as models for tumor growth. We here thus consider the model with a general growth term  $F$  only assuming that  $F$  is a positive, twice continuously differentiable function defined on the interval  $(0, \infty)$ .

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 in the caption and are based on the data in [8] with some adjustments made to account for a Gompertzian growth model. In this case 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).

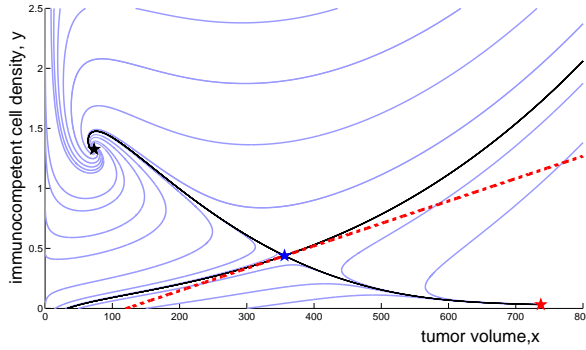


Figure 1: Phase portrait of the system given by equations (1) and (2) where  $\mu_c = 0.5618$ ,  $x_\infty = 780$ ,  $\gamma = 1$ ,  $\mu_I = 0.00484$ ,  $\beta = 0.00264$ ,  $\delta = 0.37451$  and  $\alpha = 0.1181$ .

### 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  $\kappa_X$  and  $\kappa_Y$  are chosen 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  $u = 1$ . In this case the system has only one equilibrium which is a globally asymptotically stable focus at (43.017, 0.622). Hence, in principle it would always be possible (ignoring side effects) to reduce the cancer volume to a small enough chronic state.

Side effects of the drugs clearly invalidate such an approach and thus our aim is to investigate

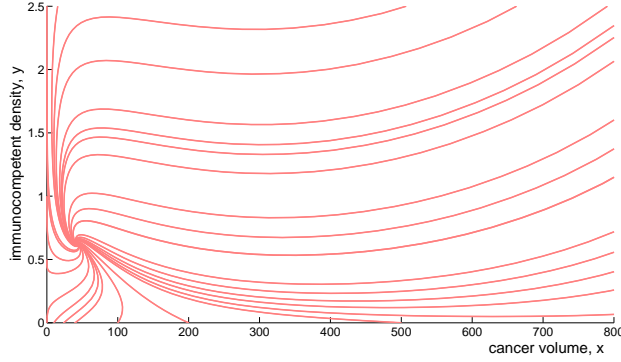


Figure 2: Phase portrait of the system with Gompertzian growth and  $u = 1$ .

how an initial condition  $(x_0, y_0)$  in the region of malignant cancer growth for the uncontrolled system could be transferred in an optimal way into the region of attraction of the stable, benign equilibrium point. Such a transfer typically requires to minimize 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 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

$$\mathbf{v}_s = \begin{pmatrix} b \\ a \end{pmatrix}$$

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

Naturally, 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

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

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 therefore is sometimes a more useful approach to limit a priori the overall amount of

cytotoxic agents to be given,

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

and then to ask the question how this amount can best be applied. This is the approach we take here. In such a formulation the time  $T$  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  $A$ , then an appropriate therapy interval can 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 as a third variable  $z$ , we thus consider the following optimal control problem:

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

$$J(u) = ax(T) - by(T), \quad (3)$$

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

$$\begin{aligned} \dot{x} &= \mu_C x F(x) - \gamma xy - \kappa_X xu, & x(0) &= x_0, \\ \dot{y} &= \mu_I (x - \beta x^2) y - \delta y + \alpha - \kappa_Y yu, & y(0) &= y_0, \\ \dot{z} &= u, & z(0) &= 0, \end{aligned}$$

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

$$\mathbb{G} = \{(x, y, z) : x > \frac{1}{2\beta}, y > 0\} \quad (4)$$

where the cancer volume is reasonably large. Furthermore, while we derive some properties in general, we also 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

$$H = \lambda_1 (\mu_C x F(x) - \gamma xy - \kappa_X xu) + \lambda_2 (\mu_I (x - \beta x^2) y - \delta y + \alpha - \kappa_Y yu) + \lambda_3 u. \quad (5)$$

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  $\lambda_0$  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)  $\lambda_3$  is constant, and  $\lambda_1$  and  $\lambda_2$  satisfy the adjoint equations

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial x} = -\lambda_1 (\mu_C (F(x) + xF'(x)) - \gamma y - \kappa_X u) - \lambda_2 \mu_I (1 - 2\beta x) y \quad (6)$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial y} = \lambda_1 \gamma x - \lambda_2 (\mu_I (x - \beta x^2) - \delta - \kappa_Y u) \quad (7)$$

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  $\lambda_1$  is positive and  $\lambda_2$  is negative on the closed interval  $[0, T]$ .*

*Proof.* The adjoint equations (6) and (7) form a homogeneous system of linear ODE's and thus  $\lambda_1$  and  $\lambda_2$  cannot vanish simultaneously. It follows from the terminal conditions that  $\lambda_1(T) > 0$  and  $\lambda_2(T) < 0$ . Suppose now  $\lambda_2$  has a zero in the interval  $[0, T]$  and, if there are more than one, let  $\tau$  be the last one. This zero cannot be of order 2 (otherwise  $\lambda_2$  and  $\lambda_1$  vanish identically) and therefore  $\dot{\lambda}_2(\tau) = \lambda_1(\tau)\gamma x(\tau)$  must be negative implying that  $\lambda_1(\tau) < 0$ . But then  $\lambda_1$  must have a zero in  $(\tau, T)$  and, once more taking  $\sigma$  as the last one, we have that  $\dot{\lambda}_1(\sigma) = -\lambda_2(\sigma)\mu_I [1 - 2\beta x(\sigma)] y(\sigma) > 0$ . But  $\lambda_2(\sigma) < 0$  and in the region  $\mathbb{G}$  also  $1 - 2\beta x(\sigma) < 0$ . Contradiction. Thus  $\lambda_2$  has no zero in the interval  $[0, T]$ . The reasoning just given then also implies that  $\lambda_1$  cannot have a zero.  $\square$

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*  $\Phi$  as

$$\Phi(t) = \lambda_3 - \lambda_1(t)\kappa_X x_*(t) - \lambda_2(t)\kappa_Y y_*(t), \quad (8)$$

it follows that

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ 1 & \text{if } \Phi(t) < 0 \end{cases} . \quad (9)$$

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 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 to analyze 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

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

where

$$f(w) = \begin{pmatrix} \mu_C x F(x) - \gamma xy \\ \mu_I (x - \beta x^2) y - \delta y + \alpha \\ 0 \end{pmatrix} \quad \text{and} \quad g(w) = \begin{pmatrix} -\kappa_X x \\ -\kappa_Y y \\ 1 \end{pmatrix}. \quad (10)$$

The adjoint equations then simply read

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

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

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

and its derivatives can easily be computed using the following well-known result that can be verified by a direct calculation.

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

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

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

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

$$\dot{\Phi}(t) = \langle \lambda(t), [f, g](w(t)) \rangle. \quad (11)$$

For the system considered here, direct calculations verify that

$$[f, g](w) = \kappa_X \begin{pmatrix} \mu_C x^2 F'(x) \\ \mu_I (1 - 2\beta x) xy \\ 0 \end{pmatrix} - \kappa_Y \begin{pmatrix} \gamma xy \\ \alpha \\ 0 \end{pmatrix}. \quad (12)$$

Setting  $\kappa_Y = 0$  we thus get that

$$\dot{\Phi}(t) = \kappa_X (\lambda_1(t) \mu_C x(t)^2 F'(x(t)) + \lambda_2(t) \mu_I (1 - 2\beta x(t)) x(t) y(t)). \quad (13)$$

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

**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 one switching from  $u = 1$  to  $u = 0$ .  $\square$*

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

For a *Gompertzian growth model*,  $F_G(x) = -\ln\left(\frac{x}{x_\infty}\right)$ , we have that  $x^2 F'_G(x) = -x$  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 that

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

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

$$\langle \lambda(t), [g, [f, g]](w(t)) \rangle = -\lambda_2(t) \kappa_X^2 \mu_I [1 - 4\beta x(t)] x(t) y(t) < 0, \quad (14)$$

i.e., the strengthened Legendre-Clebsch condition for minimality is satisfied. Hence the second derivative of the switching function,

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

can be solved for  $u$  as

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

Expressing  $[f, [f, g]]$  in the form

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

since  $\dot{\Phi}(t) = \langle \lambda(t), [f, g](w(t)) \rangle = 0$ , the singular control is thus given as a feedback function of  $w$  by

$$u_{\sin}(w) = \psi(w) = \frac{1}{k_X} \left[ \mu_C \ln\left(\frac{x}{x_\infty}\right) + \gamma y - \frac{1 - 2\beta x}{1 - 4\beta x} \left( \frac{\alpha}{y} + \gamma \frac{\mu_I}{\mu_C} (1 - 2\beta x) xy \right) \right]. \quad (15)$$

A direct calculation then verifies that the dynamics along the singular arc takes the form

$$\dot{x} = -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy - \kappa_X x \psi(w) = -x \frac{1 - 2\beta x}{1 - 4\beta x} \left( \frac{\alpha}{y} + \gamma \frac{\mu_I}{\mu_C} (x - 2\beta x^2) y \right). \quad (16)$$

The Hamiltonian  $H$ ,

$$H = \langle \lambda(t), f(w(t)) \rangle + u(t) \langle \lambda(t), g(w(t)) \rangle, \quad (17)$$

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. Furthermore, also the derivative of the switching function is



identically zero along a singular arc,  $\dot{\Phi}(t) = \langle \lambda(t), [f, g](w(t)) \rangle \equiv 0$ . Since the multiplier  $\lambda$  is non-zero, the vector fields  $f$ ,  $g$  and their Lie bracket  $[f, g]$  must be linearly dependent along a singular arc. For the system under consideration here, 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 set is given by

$$0 = -\gamma\mu_I(1 - 2\beta x)xy^2 + \mu_C \left( -\mu_I \ln\left(\frac{x}{x_\infty}\right) (x - 2\beta x^2) + \mu_I(x - \beta x^2) - \delta \right) y + \alpha\mu_C. \quad (18)$$

If we write this equation in the form

$$a_2(x)y^2 + a_1(x)y + a_0 = 0, \quad (19)$$

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  $x$  generally there are no, one or two positive solutions  $y = y_{\sin}(x)$  that define the singular curve. For the numerical values we are using in this article, we have  $\frac{1}{2\beta} = 189.68$  and in the region  $\mathbb{G}$  there exist no positive solutions for  $\frac{1}{2\beta} < x < 292.82$  and  $x > 927.47$ , exactly one for  $x = 292.82$  and  $x = 927.47$  and two positive solutions for  $292.82 < x < 927.47$ , (see Fig. 3). Summarizing, for a Gompertzian growth model we thus have the following result:

**Proposition 4** *For the model with Gompertzian growth function (i.e.,  $F_G(x) = -\ln\left(\frac{x}{x_\infty}\right)$ ), there exists a singular curve defined as the zero-set of equation (18). Along the singular curve the strengthened Legendre-Clebsch condition for minimality is satisfied and the corresponding singular dynamics is defined by (16).  $\square$*

## 5 Towards a Synthesis of Optimal Controlled Trajectories

We briefly describe (without proof) some aspects of the structure of optimal controls. Our objective is to move an initial condition in the malignant region into the region of attraction of the benign equilibrium. Typically such an initial condition will lie to the right of the singular arc and initially the optimal 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. (Note that for each initial condition this construction also allows 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. For the optimal control problem the remaining drugs can be used to improve the value of the objective. This leads to the following three-dimensional minimization problem over variables  $(\tau, \sigma, \alpha)$  whose numerical solution defines the optimal control:

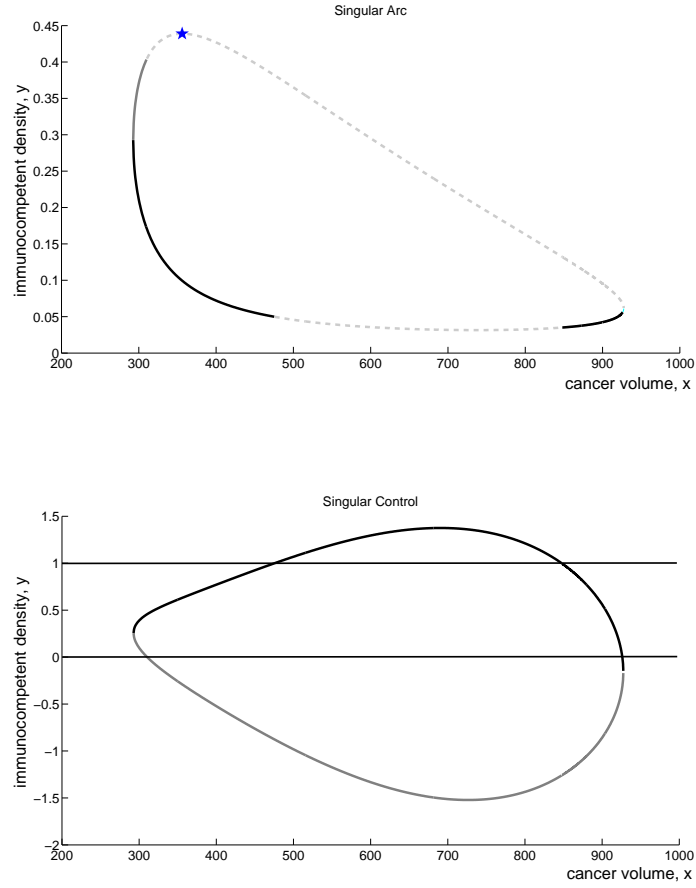


Figure 3: The figure shows the singular curve (top) and the singular control (bottom). The solid portions correspond to segments where the singular control is admissible and the dashed pieces correspond to inadmissible segments. The singular control is negative on the top portion of the singular curve.

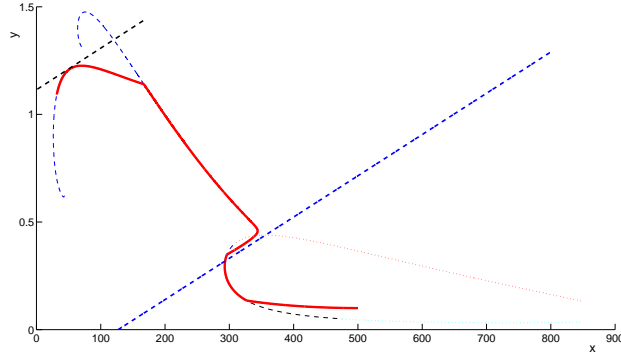


Figure 4: Example of a trajectory of the type **1s01**

- $\tau$  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.
- $\sigma$  denotes a subsequent time when chemotherapy becomes reactivated. At this time the control switches from  $u = 0$  to  $u = 1$ .
- $\alpha$  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 (3). Note that we may actually have that  $\alpha < A$ .

Thus the overall concatenation sequence for the optimal control is of the form **1s01** and the exact values of the switching times can be obtained as the solution of a straightforward low-dimensional optimization problem. Fig. 4 illustrates this procedure and the red curve gives one particular (non-optimal) trajectory corresponding to a specific choice of parameters  $(\tau, \sigma, \alpha)$ .

## 6 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 optimal controls for the case when the effects of the cytotoxic agents on immunocompetent cells is much smaller than on the tumor cells,  $\kappa_Y \ll \kappa_X$ , and in this case optimal controls typically 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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