

Bifurcation of Singular Arcs in an Optimal Control Problem for Cancer Immune System Interactions under Treatment

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Abstract—A mathematical model for cancer treatment that includes immunological activity is considered as an optimal control problem. In the uncontrolled system there exist both a region of benign and of malignant cancer growth separated by the stable manifold of a saddle point. The aim of treatment is to move an initial condition that lies in the malignant region into the region of benign growth. In our formulation of the objective a penalty term is included that approximates this separatrix by its tangent space and minimization of the objective is tantamount to moving the state of the system across this boundary. In this paper, for various values of a parameter that describes the relative effectiveness of the killing action of a cytotoxic drug on cancer cells and the immunocompetent cell density, the existence and optimality of a singular arc is analyzed. The question of existence of optimal controls and the structure of near-optimal protocols that move the system into the region of attraction of the benign stable equilibrium is discussed.

I. INTRODUCTION

We consider a mathematical model for cancer-immune system interactions under chemotherapy as an optimal control problem. For the underlying dynamics we use the classical model by Stepanova [13], a system of two ordinary differential equations that model 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 incorporates many medically important features and the underlying equations have been widely accepted as a basic model. There exist numerous extensions and generalizations including the ones by Kuznetsov, Makalkin, Taylor and Perelson [12] who also estimate growth parameters and the one by de Vladar and González [5] who use different cancer growth models. D’Onofrio formulates and investigates a general class of models [6] that incorporates all these dynamical models. In these papers an extensive analysis of the dynamical properties of the underlying systems has been carried out with the following important common 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 [5, appendix B]. In the first case what medically would be considered cancer never develops, so-called *immune surveillance*; in the latter one only a therapeutic effect on the cancer (e.g., chemotherapy, radiotherapy, ...) needs to be analyzed. However, tumor-immune system interactions matter for the interesting case “in the middle” when a benign (microscopic or macroscopic) stable equilibrium exists, but uncontrolled cancer growth is possible as well. In this case, an unstable equilibrium point and its stable manifold separate the benign region from the malignant region of uncontrolled cancer growth. Through therapy it may then be possible to move an initial condition that lies in the malignant region towards and hopefully into the region of benign growth and thus control the cancer.

In this paper, for a slight modification of Stepanova’s model, we formulate this treatment objective as an optimal control problem. 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. The key novel idea is to approximate the separatrix, more generally, the stable manifolds of the unstable equilibria that form the boundaries between these regions of qualitative different growth, by their tangent spaces and include in the objective a penalty term that induces the system to move across this manifold. Contrary to the full manifolds, these linear approximations are easily computed. In [7], [8] we have already considered this problem for chemotherapy when the effect of the cytotoxic agent on the immunocompetent cell densities that formulate the immune system reaction was neglected. Essentially, in this case there exists a locally optimal singular arc that lies in the biologically relevant region and optimal controlled trajectories follow this path from the malignant into the benign region. In this paper we include a cytotoxic effect on the cells of the immune system and investigate the existence and optimality of this singular arc as a 1-dimensional parameter that reflects the strength of this effect is varied.

II. STEPANOVA'S MODEL [13] FOR CANCER IMMUNE RESPONSE AS AN OPTIMAL CONTROL PROBLEM [8]

In a slightly more general form, the dynamical equations are given by

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

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 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 μ_I and β are used to calibrate these interactions and in the product with y collectively describe a state-dependent influence of the cancer cells on the stimulation of the immune system.

The first equation, (1), models tumor growth. The coefficient γ denotes the rate at which cancer cells are eliminated through the activity of T -cells and the term 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 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 period in the tumor's growth when exponential growth is realistic, over prolonged periods saturating growth models are preferred. There exists medical evidence that some tumors follow a Gompertzian growth model [10], [11], i.e., the function F is given by $F_G(x) = -\ln\left(\frac{x}{x_\infty}\right)$ with x_∞ denoting a fixed carrying capacity for the cancer. But also logistic and generalized logistic growth models of the form $F_L(x) = 1 - \left(\frac{x}{x_\infty}\right)^\nu$ 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 the uncontrolled dynamics is shown in Fig. 1. For our numerical illustration we use a Gompertzian growth model with $x_\infty = 780$ and the following parameter values: $\mu_C = 0.5618$, $\gamma = 1$, $\mu_I = 0.00484$, $\beta = 0.00264$, $\delta = 0.37451$, $\alpha = 0.1181$. These values are based on the paper by Kuznetsov et al. [12], with some adjustments made for the Gompertzian growth model.

For these data there are three equilibria, a stable focus at $(72.961, 1.327)$, a saddle point at $(356.174, 0.439)$ and a stable node at $(737.278, 0.032)$. The region of attraction of the stable focus represents the benign area while the region of attraction of the stable node is the malignant area. The stable manifold of the saddle separates these two regions.

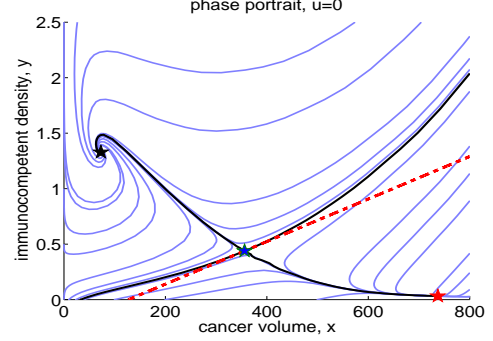


Fig. 1. Phase portrait of the uncontrolled system

We consider this dynamics under the application of a chemo-therapeutic agent. Following [5], we 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 are chosen to normalize the control values to $0 \leq u \leq 1$. Fig. 2 shows the phase portrait of the system under constant full-dosage control $u = 1$ for $(\kappa_X, \kappa_Y) = (1, 0)$ and $(\kappa_X, \kappa_Y) = (1, 1)$. Setting $\kappa_Y = \varepsilon \kappa_X$ we shall study the system dynamics as a function of the parameter ε . Note that for $u \equiv 1$ the system has one benign, globally asymptotically stable equilibrium point. Hence at least in principle it would be possible to control the cancer if an unlimited amount of cytotoxic agents could be administered. This is of course not feasible because of side effects and thus an optimal control problem arises.

The aim is to move an initial condition (x_0, y_0) in the region of uncontrolled (malignant) cancer growth into the region of attraction of the stable, benign equilibrium point of the uncontrolled system. 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 and 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 exactly one saddle point if

$$\mu_C \left(\delta - \frac{\mu_I}{4\beta} \right) < \alpha \gamma \quad (3)$$

and then this separatrix is given by the unstable manifold of this saddle [5]. In general, however, 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 thus is easily computable and can serve as a first

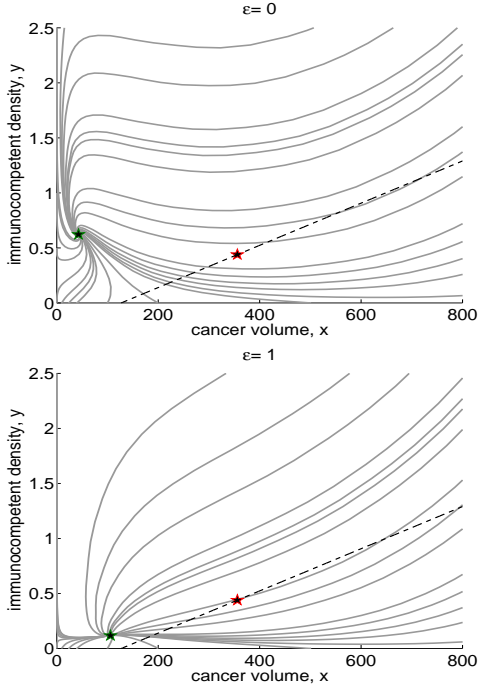


Fig. 2. Phase portraits of the system with $\kappa_X = 1$ for $\varepsilon = 0$ (top) and $\varepsilon = 1$ (bottom).

approximation. In fact, the separatrix shown in Fig. 1 or also the one in Fig. 2 of [5] are almost lines. It thus is a reasonable strategy to include a penalty term of the form $ax(T) - by(T)$ in the objective where a and b are positive coefficients determined by the stable eigenvector $v_s = (b, a)^T$ of the saddle. For example, normalizing $b = 1$, for the parameter values given earlier we have that $a = 0.00192$. Minimizing this penalty term naturally directs the system towards the benign region.

But side effects of the treatment need to be taken into account. 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

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

with some $c > 0$. 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. This is the approach we take here. The problem can be considered both for a fixed or for a free terminal time T . In the first case, T denotes some a priori determined therapy horizon; in the second one it merely denotes the time when the minimum for the objective is realized. The necessary conditions for optimality for these two formulations are closely related, but here, for definiteness sake, we consider

the problem for a free final time T .

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

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

(a , b and c positive coefficients), subject to the dynamics

$$\dot{x} = \mu_C x F(x) - \gamma xy - \kappa_X x u, \quad x(0) = x_0, \quad (5)$$

$$\dot{y} = \mu_I (x - \beta x^2) y - \delta y + \alpha - \varepsilon \kappa_Y y u, \quad y(0) = y_0, \quad (6)$$

over all Lebesgue measurable functions $u : [0, T] \rightarrow [0, 1]$.

It is easily seen that for any admissible control u all variables remain non-negative and thus there is no need to impose this as a state-constraint. Also, we denote the state by $z = (x, y)^T$ and express the dynamics in the form $\dot{z} = f(z) + ug(z)$ where

$$f(z) = \begin{pmatrix} \mu_C x F(x) - \gamma xy \\ \mu_I (x - \beta x^2) y - \delta y + \alpha \end{pmatrix} \quad (7)$$

and

$$g(z) = \begin{pmatrix} -\kappa_X x \\ -\kappa_Y y \end{pmatrix}. \quad (8)$$

are the drift and control vector field, respectively.

III. 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 [1], [2]). It is easily seen that all extremals for this problem are normal, i.e., that the multiplier at the objective cannot vanish. We already incorporate this into our formulation and, for a row-vector $\lambda = (\lambda_1, \lambda_2) \in (\mathbb{R}^2)^*$, define the Hamiltonian $H = H(\lambda, x, y, u)$ as

$$H = cu + \lambda_1 (\mu_C x F(x) - \gamma xy - \kappa_X x u) + \lambda_2 (\mu_I (x - \beta x^2) y - \delta y + \alpha - \kappa_Y y u), \quad (9)$$

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

$$H = \langle \lambda, f(z) \rangle + u (c + \langle \lambda, g(z) \rangle). \quad (10)$$

If u_* is an optimal control defined over an interval $[0, T]$ with corresponding trajectory $z_* = (x_*, y_*)^T$, then there exists an absolutely continuous co-vector, $\lambda : [0, T] \rightarrow (\mathbb{R}^2)^*$, such that the following conditions hold:

(a) λ_1 and λ_2 satisfy the adjoint equations

$$\dot{\lambda}_1 = -\lambda_1 (\mu_C (F(x) + x F'(x)) - \gamma y - \kappa_X u) - \lambda_2 \mu_I (1 - 2\beta x) y \quad (11)$$

$$\dot{\lambda}_2 = \lambda_1 \gamma x - \lambda_2 (\mu_I (x - \beta x^2) - \delta - \kappa_Y u) \quad (12)$$

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.

Defining the so-called *switching function* Φ as

$$\Phi(t) = c + \langle \lambda(t), g(z_*(t)) \rangle, \quad (13)$$

the Hamiltonian can be written in the form

$$H = \langle \lambda(t), f(w(t)) \rangle + \Phi(t)u(t).$$

Since H is linear in u , the minimum is realized for $u_*(t) = 0$ if $\Phi(t) > 0$ and $u_*(t) = 1$ if $\Phi(t) < 0$ and 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 $\Phi(t) = 0$. 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]. Optimal controls then need to be synthesized from these candidates. 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 $\dot{\Phi}(\tau)$. Thus derivatives of the switching function matter in this analysis. These computations simplify significantly within the framework of geometric optimal control theory. The adjoint equations then simply read

$$\dot{\lambda}(t) = -\lambda(t) (Df(z_*(t)) + u_*(t)Dg(z_*(t))) \quad (14)$$

with Df and Dg denoting the matrices of the partial derivatives of the vector fields which are evaluated along the reference trajectory $z_*(t)$. The derivatives of the switching function can easily be computed. Since the objective does not contain a Lagrangian term that depends on the state, for problem [OC] a direct calculation verifies the following well-known formula.

Proposition 3.1: Let $z(\cdot)$ be a solution to the dynamics for control u and let λ be a solution of the corresponding adjoint equations. For a continuously differentiable vector field h define $\Psi(t) = \langle \lambda(t), h(z(t)) \rangle$. Then the derivative of Ψ is given by

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

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

The first two derivatives of the switching function Φ are thus given by

$$\dot{\Phi}(t) = \langle \lambda(t), [f, g](z(t)) \rangle, \quad (15)$$

and

$$\ddot{\Phi}(t) = \langle \lambda(t), [f, [f, g]](z(t)) \rangle + u(t) \langle \lambda(t), [g, [f, g]](z(t)) \rangle. \quad (16)$$

For our system, direct calculations give the required Lie brackets and, for example, we have that

$$[f, g](z) = \kappa_X \begin{pmatrix} \mu_C x^2 F'(x) - \varepsilon \gamma x y \\ \mu_I (x - 2\beta x^2) y - \varepsilon \alpha \end{pmatrix}, \quad (17)$$

and

$$[g, [f, g]](z) = -\kappa_X^2 \begin{pmatrix} \mu_C x^2 (F'(x) + xF''(x)) \\ \mu_I (1 - 4\beta x) xy \end{pmatrix} + \kappa_X^2 \varepsilon^2 \begin{pmatrix} \gamma xy \\ -\alpha \end{pmatrix} \quad (18)$$

The formula for $[f, [f, g]]$ is quite complex and will not be stated here.

If an optimal control u_* is singular over an open interval I , then $\Phi \equiv 0$ and thus $\langle \lambda(t), g(z_*(t)) \rangle = -c < 0$. Moreover, from (10), the Hamiltonian along I reduces to

$H = \langle \lambda, f(z_*) \rangle \equiv 0$. Since the derivative of the switching function vanishes on I as well,

$$\langle \lambda(t), [f, g](z_*) \rangle \equiv 0, \quad (19)$$

it follows that the vector fields f and $[f, g]$ are linearly dependent along z_* on I . (The multiplier $\lambda(t)$ is a nontrivial solution to a homogeneous linear differential equation and thus nonzero.) For our system the determinant of f and $[f, g]$ is a quadratic polynomial in y with coefficients that are functions of x of the form

$$\det(f(z), [f, g](z)) = a_2(x)y^2 + a_1(x)y + a_0(x), \quad (20)$$

with

$$\begin{aligned} a_0(x) &= -\alpha \mu_C (xF'(x) + \varepsilon F(x)), \\ a_1(x) &= \mu_I \mu_C (x - 2\beta x^2) F(x) + 2\alpha \gamma \varepsilon \\ &\quad - \mu_I \mu_C (x - \beta x^2) xF'(x) + \delta \mu_C xF'(x), \end{aligned}$$

and

$$a_2(x) = -\mu_I \gamma (x - 2\beta x^2) + \varepsilon \gamma [\mu_I (x - \beta x^2) - \delta].$$

It is a necessary condition for optimality of a singular control u_* , the so-called Legendre Clebsch (LC) condition, that

$$\langle \lambda(t), [g, [f, g]](z_*) \rangle \leq 0 \quad (21)$$

holds along an optimal singular arc. If we actually have $\langle \lambda(t), [g, [f, g]](z_*) \rangle < 0$, i.e., the strict LC-condition is satisfied, then, since the second derivative of the switching function vanishes, the singular control can be computed from $\ddot{\Phi}(t) = 0$ as

$$u_{\text{sin}}(t) = -\frac{\langle \lambda(t), [f, [f, g]](z_*) \rangle}{\langle \lambda(t), [g, [f, g]](z_*) \rangle}. \quad (22)$$

In the region R 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

$$[f, [f, g]](z) = \zeta_1(z)g(z) + \zeta_2(z)[f, g](z) \quad (23)$$

and

$$[g, [f, g]](z) = \xi_1(z)g(z) + \xi_2(z)[f, g](z).$$

Along a singular arc λ vanishes against $[f, g]$ and is negative against g . Hence, the strengthened Legendre-Clebsch condition is satisfied if and only if $\xi_1(z_*(t))$ is positive and the singular control is given by

$$u_{\text{sin}}(t) = -\frac{\zeta_1(z_*(t))}{\xi_1(z_*(t))}. \quad (24)$$

Once more, explicit calculations show that ξ_1 has the form

$$\xi_1(x, y) = \kappa_X \frac{p_2(x)y^2 + p_1(x)y + p_0(x)}{q_2(x)y^2 + q_1(x)y + q_0(x)}, \quad (25)$$

with

$$\begin{aligned} p_0(x) &= -\varepsilon \alpha \mu_C [(1 + \varepsilon) F'(x) + xF''(x)] x, \\ p_1(x) &= \mu_I \mu_C [F''(x) + 2\beta (F'(x) - xF''(x))] x^3 + 2\varepsilon^3 \alpha, \\ p_2(x) &= \varepsilon \mu_I \gamma x [(1 - \varepsilon) (1 - 2\beta x) - 2\beta x], \end{aligned}$$

and

$$\begin{aligned} q_0(x) &= -\varepsilon\alpha, & q_2(x) &= \varepsilon^2\gamma, \\ q_1(x) &= \mu_I(1 - 2\beta x)x - \varepsilon\mu_C F'(x)x. \end{aligned}$$

These formulas simplify considerably if $\varepsilon = 0$, i.e., when we assume that there is no or only a negligible influence of the cytotoxic agent on the immunocompetent cell densities, $\kappa_Y = 0$ [8]. In this case the functions p_0 , p_2 , q_0 and q_2 all vanish. For the remaining computations and our numerical calculations we now *assume* a *Gompertzian growth model*, $F_G(x) = -\ln\left(\frac{x}{x_\infty}\right)$. For $\varepsilon = 0$ equation (25) then reads

$$\xi_1(x, y) = \kappa_X \frac{p_1(x)}{q_1(x)} = \kappa_X \frac{\mu_C [1 - 4\beta x]}{(1 - 2\beta x)}$$

which is positive for $x > \frac{1}{2\beta}$ or $x < \frac{1}{4\beta}$. 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 control the cancer, the medically more interesting region is $\mathbb{G} = \{(x, y) : x > \frac{1}{2\beta}\}$ where the cancer volume is large. In this region the strengthened Legendre-Clebsch condition is satisfied. For $\varepsilon > 0$ the numerator and denominator of $\xi_1(x, y)$ are quadratic functions in y provided that $p_2(x) \neq 0$. For $(x, y) \in \mathbb{G}$ it can be shown that $p_2(x)$ is positive and thus, for example, both numerator and denominator of $\xi_1(x, y)$ are positive if y is larger than the largest real root of numerator and denominator. In general, however, it is now no longer possible to determine the form of the singular arc analytically. Similarly, whether it satisfies the Legendre-Clebsch condition and whether the singular control is admissible (i.e., takes values in the control set $[0, 1]$) can only be determined numerically. But the formulas given above allow to make these numerical computations. In Fig. 3, for a Gompertzian growth model and the parameter values given earlier, we include several graphs that illustrate the evolution of the singular arc and the corresponding Legendre-Clebsch condition as ε varies from 0 to 1. In the figure we graph ξ_1 so that the Legendre-Clebsch condition is satisfied when the function is positive.

For $\varepsilon = 0$ the singular set contains a closed loop in \mathbb{G} and two more curves for small cancer volumes (that are not of practical interest to this problem). As the parameter ε increases, the two branches on the left coalesce (not shown) to one curve (see Fig. 3 with $\varepsilon = 0.70$). As ε is increased further, this curve moves to the right and eventually bifurcates (i.e., merges and separates with a qualitatively different shape) with the loop in \mathbb{G} for some value in the interval $[0.87, 0.89]$ to form one curve. The Legendre-Clebsch condition is consistently satisfied for the medically interesting branch lying in \mathbb{G} to the right.

IV. ON THE STRUCTURE OF OPTIMAL AND NEAR-OPTIMAL CONTROLS

The admissible portion of the singular arc in \mathbb{G} is essential in steering the system across the separatrix of the uncontrolled system. Recall that the aim in the problem is to move an initial condition in the malignant region into the region

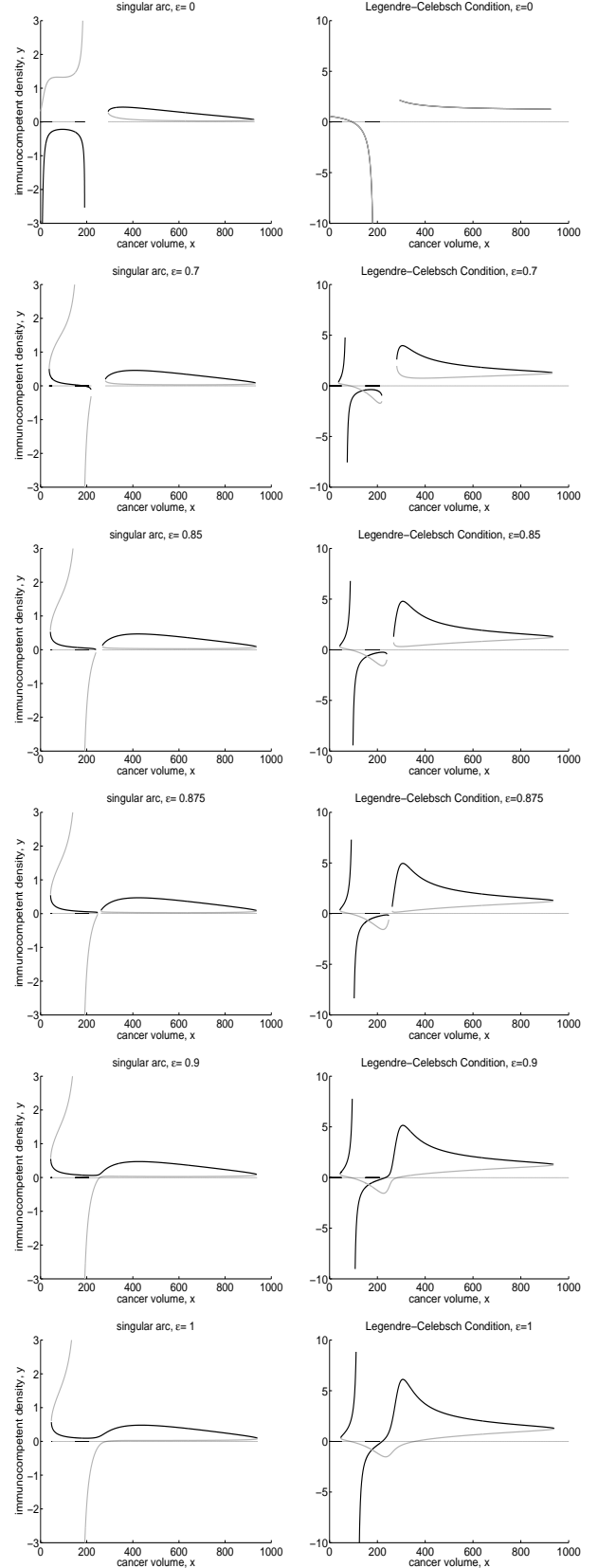


Fig. 3. Singular curves (left) and Legendre-Clebsch condition (right)

of attraction of the benign equilibrium. Optimal control is only the framework employed to realize this underlying objective. For $\varepsilon = 0$ a realistic initial condition lies to the right of the singular arc and initially optimal controls are constant given by $u = 1$ until the trajectory hits the singular arc. At this junction, and assuming the singular control is admissible, the control becomes singular. Assuming a sufficient amount of drugs is available, the trajectory now follows the singular arc across the separatrix. Once this has happened, in principle the control could switch to $u = 0$ and follow the uncontrolled trajectory towards the benign equilibrium point. This trajectory provides a “free pass” since it does not incur any additional cost in the sense of increasing the value of the objective as long as the linear penalty term $ax(t) - by(t)$ keeps decreasing. Depending on geometric properties of the uncontrolled system near the benign equilibrium (a stable focus), optimal times τ when to leave the singular arc and σ of when to restart chemotherapy at maximum dose then need to be computed numerically. Overall, a concatenation sequence of the form **1s01** (that is, initial treatment with a full dose followed by a singular segment, then a rest period, and one final full dose treatment interval) is expected to be a close-to-optimal strategy.

However, the existence of “free pass” trajectories coupled with a free terminal time T raises the possibility that for some parameter values optimal controls actually do not exist. In fact, the junction points $x(\tau)$ when the controls leave the singular arc may converge to the intersection point of the singular arc with the stable manifold of the saddle point that defines the separatrix to generate better values for the second junction point $x(\sigma)$. In this case we only have an infimum, not a minimum. From a practical point of view, however, this is irrelevant since the real objective only is to move the initial condition into the region of attraction of the benign equilibrium point. This is accomplished by any of the **1s01**-type controls that are indicated by the necessary conditions for optimality and we call these controls *near optimal*. Another approach that would make the problem formulation well-posed is to add a penalty term on the terminal time T , say dT with d some positive constant, to the objective. This is being developed in [9].

V. CONCLUSION

Based on Stepanova’s mathematical model of immunological activity during cancer growth, we considered the problem of how to transfer a malignant initial condition into a benign region through therapy. We turn this into an optimal control problem by approximating a separatrix between regions of benign and cancerous growth with its tangent space at the corresponding saddle point and including this term as penalty term in our objective. Consequently a minimization of the objective realizes the desired transfer. Necessary condition for optimality suggest as optimal concatenations of the form **1s01**. Even when the existence of an optimal control is not guaranteed, this structure provides near optimal controls that achieve the main aim of the underlying problem formulation.

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