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Singular controls and chattering arcs in optimal control problems arising in biomedicine*†

by

Urszula Ledzewicz[1] and Heinz Schättler[2]

[1] Department of Mathematics and Statistics,
Southern Illinois University Edwardsville
Edwardsville, Illinois, 62026-1653, USA

[2] Department of Electrical and Systems Engineering,
Washington University
St. Louis, Missouri, 63130-4899, USA

e-mail: uledzew@siue.edu, hms@wustl.edu

Abstract: We consider an optimal control problem of the Mayer-type for a single-input, control affine, nonlinear system in small dimension. In this paper, we analyze effects that a modeling extension has on the optimality of singular controls when the control is replaced with the output of a first-order, time-invariant linear system driven by a new control. This analysis is motivated by an optimal control problem for a novel cancer treatment method, tumor anti-angiogenesis, when such a linear differential equation, which represents the pharmacokinetics of the therapeutic agent, is added to the model. We show that formulas that define a singular control of order 1 and its associated singular arc carry over verbatim under this model extension, albeit with a different interpretation. But the intrinsic order of the singular control increases to 2. As a consequence, optimal concatenation sequences with the singular control change and the possibility of optimal chattering arcs arises.

Keywords: optimal control, singular controls, biomedical models, anti-angiogenesis.

1. Introduction

Applications of optimal control to mathematical models in biomedical problems have a long history with some early research in the seventies (see Eisen's monograph, 1979), and several seminal papers on cancer chemotherapy in the eighties

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and early nineties (e.g., Swierniak, 1988 and 1995, Swan, 1988 and 1990, Martin, 1992). A number of models have been, and still are being formulated that describe the dynamics of cancer and normal cells under the action of various chemotherapeutic agents, most importantly cytotoxic drugs. Since these drugs equally destroy healthy cells, the side effects of treatment need to be balanced with its therapeutic effects. It is natural to formulate questions like: *how to apply chemotherapy in the most effective way*, as optimal control problems with the drug dosage playing the role of the control. Efforts to model and analyze various aspects of this problem (e.g., drug resistance, drug delivery, etc.) have continued until now (e.g., Swierniak, Polanski and Kimmel, 1996; Fister and Panetta, 2000; Ledzewicz and Schättler, 2002a,b; Swierniak et al., 2003; Ledzewicz and Schättler, 2007b), including some of our own work. For many of these models optimal controls turn out to be bang-bang if a Mayer-type objective (i.e., only a penalty term at the endpoint) or a Lagrangian function that is linear in control is being used. Bang-bang controls represent sessions of full dose treatments with rest periods in between and thus correspond to standard medical practice. On the other hand, singular controls, which typically would define treatment schedules with feedback type time-varying partial doses, are not optimal in most of these models.

More recently, methods of optimal control also have intensively been applied to the analysis of models that represent new directions of medical research. Topics include HIV-infection (e.g., Kirschner, Lenhart and Serbin, 1997) as well as novel treatment approaches to cancer such as immunotherapy (e.g., de Pillis and Radunskaya, 2001; Castiglione and Piccoli, 2006) and tumor anti-angiogenesis (e.g., Swierniak, d'Onofrio and Gandolfi, 2006; Ledzewicz and Schättler, 2007 and 2009; Swierniak, 2008). In the latter problem, the therapeutic components are mostly biological agents that need to be grown in a laboratory and are very expensive and limited. Once more, it thus becomes important to optimize the scheduling of agents over time in order to achieve best possible usage. For these newer approaches, the fact that anti-angiogenic agents are still only in medical trials and thus no guidelines for their scheduling have been established, adds further incentive to undertake a mathematical analysis of optimal solutions. Even for only one agent, it is prohibitively expensive to test all reasonable protocols in a laboratory setting. Thus, the issue how to design an optimal protocol is particularly important for these novel therapies.

Tumor anti-angiogenesis, already proposed by Folkman in the seventies (Folkman, 1972), but only enabled by medical research in the nineties, is a treatment approach for cancer that aims at depriving a tumor of its network of blood vessels and capillaries that it needs for its supply of nutrients and oxygen. In an initial stage of avascular growth, a tumor gets sufficient supply of oxygen and nutrients from the surrounding host blood vessels to allow for cell duplication and tumor growth. However, at the size of about $1-2$ mm in diameter, this no longer is true and most tumor cells enter the dormant stage in the cell cycle. These cells then produce vascular endothelial growth factor (VEGF) (Klagsburn

and Soker, 1993) initiating the process of *tumor angiogenesis*. During this stage of tumor development, surrounding mature host blood vessels are recruited to develop the capillaries the tumor needs for its supply of nutrients. The lining of these newly developing blood vessels consist of endothelial cells that are stimulated by VEGF. Surprisingly, the tumor also produces inhibitors that at times are used to suppress this process (Folkman, 1995, Davis and Yancopoulos, 1999). Anti-angiogenic treatments rely on these mechanisms by bringing in external anti-angiogenic agents (e.g., endostatin) that disrupt the growth and migration of endothelial cells and thus indirectly halt the growth of the tumor. This treatment targets genetically stable healthy cells, not fast duplicating and continuously mutating cancer cells. As a consequence, and contrary to traditional chemotherapy, no drug resistance has been observed in experimental cancer (Boehm et al., 1997). For this reason the therapy has been called a new hope for the treatment of tumors (Kerbel, 1997).

Mathematical models for tumor anti-angiogenesis that have been formulated can broadly be divided into two groups: those that try to accurately reflect the biological processes, (e.g., Anderson and Chaplain, 1998; Arakelyan, Vainstain and Agur, 2002), and those that aggregate variables into low-dimensional dynamical systems, (e.g., Hahnfeldt, Panigrahy, Folkman and Hlatky, 1999; Ergun, Camphausen and Wein, 2003; d'Onofrio and Gandolfi, 2004). While the former allow for realistic, large-scale simulations, the latter enable a theoretical mathematical analysis. The biological motivation for this paper is the well-recognized model by Hahnfeldt et al. (1999), a group of researchers then at Harvard Medical School. In this 2-dimensional model the growth of the primary tumor and endothelial cells supporting the vasculature is described under the action of anti-angiogenic agents, whose dosage represents the control in the problem. In previous research, we have addressed the question of how to schedule a given amount of inhibitors to achieve the maximum tumor reduction. Mathematically, this becomes an optimal control problem of Mayer-type with control-affine nonlinear dynamics. In Ledzewicz and Schättler (2007), we obtained a full synthesis of optimal controlled trajectories. Contrary to the cancer chemotherapy problems mentioned above, now optimal controls consist of concatenations of bang and singular portions. Not only do optimal singular arcs exist, but, in fact, the singular arc becomes the centerpiece for the optimal synthesis in the sense that for a large region of realistic initial conditions every optimal controlled trajectory contains an interval along which the control is singular.

This problem formulation, however, did not include a mathematical model for drug delivery. Rather, the control identified the dosage with the concentration of the anti-angiogenic agents and their effect. In reality, these are different concepts that are linked through pharmacokinetics (PK) and pharmacodynamics (PD). In its simplest and most often used form, PK is described by a time-invariant linear ordinary differential equation. An extension of the model for anti-angiogenesis that incorporates such a PK-model is accomplished, from a control theoretic point of view, through the addition of a linear system to the

original dynamics which generates this concentration as state with the dosage as input while the control of the original system is replaced with this state in the extended model. In this paper, we shall analyze such an extension in a general framework and shall discuss how such an extension effects the structure of solutions, especially, the properties of optimal singular arcs. For the model of tumor anti-angiogenesis, the result of this analysis will answer the question of how the structure of optimal protocols is effected if the model is made more realistic by incorporating the pharmacokinetics of the drug. This is of importance from the modeling perspective where clearly some biological accuracy has to be compromised to enable mathematical analysis of the model.

2. Optimal control with linear dynamics for the control

While the theory below will be developed for a general 2-dimensional dynamics of the form

$$\Sigma : \qquad \dot{x} = f(x) + ug(x), \qquad 0 \leq u \leq a, \qquad x \in \mathbb{X} \subset \mathbb{R}^2, \tag{1}$$

it has been motivated by a model for tumor anti-angiogenesis that was developed and biologically validated by Hahnfeldt et al. (1999). We briefly describe this model that we also shall use to illustrate our results. It is a two-dimensional system of ordinary differential equations for the interactions between the primary tumor volume, p, and the carrying capacity of the vasculature, q. The latter is the maximum tumor volume sustainable by the vascular network that supports the tumor with nutrients and it largely depends on the volume of endothelial cells. The control u is the dosage of an exogenously administered vessel disruptive agent. Tumor growth is described by a Gompertzian growth function of the form

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right) \tag{2}$$

with ξ a growth parameter and variable carrying capacity q. The dynamics for q consists of a balance between stimulatory and inhibitory effects given by

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}} + \gamma u\right) q. \tag{3}$$

The term bp represents stimulation of the vasculature by the tumor and is taken proportional to the tumor volume. The three terms with negative signs represent different types of inhibition. Loss of vascular support through natural causes is modeled as μq. Generally, μ is small and often this term is negligible compared to the other factors. The second term, $dp^{\frac{2}{3}}q$, represents endogenous inhibition due to the fact that the tumor also produces inhibitors that impact on its vascular support. These inhibitors are released through the tumor surface (hence the scaling of the tumor volume p to its surface area $p^{\frac{2}{3}}$) and interact

with the endothelial cells. The last term γuq models loss of vascular support due to outside inhibition. It corresponds to the angiogenic dose rate with γ a constant that represents the anti-angiogenic killing parameter. It can be shown that, given positive initial conditions p_0 and q_0 and any Lebesgue measurable function $u : [0, T] \to [0, a]$, solutions to (2) and (3) exist and remain positive for all times $t \geq 0$ (d'Onofrio and Gandolfi, 2004). Thus, the state space $\mathbb{X} = ((p, q) : p > 0, q > 0\}$ is positive invariant. Given an a priori specified amount of inhibitors,

$$\int_0^T u(t)dt \leq A, \tag{4}$$

following Ergun et al. (2003), we then consider the optimal control problem how to schedule the inhibitors in order to maximize the tumor reduction achievable, or, equivalently, for a free terminal time T, we minimize the tumor volume $p(T)$ achievable at time T.

Mathematically, the dynamics is thus given by a 2-dimensional system of the form Σ with $x = (p, q)$,

$$f(x) = \begin{pmatrix} -\xi p \ln\left(\frac{p}{q}\right) \\ bp - \left(\mu + dp^{\frac{2}{3}}\right) q \end{pmatrix} \qquad \text{and} \qquad g(x) = \begin{pmatrix} 0 \\ -\gamma q \end{pmatrix}.$$

If the isoperimetric constraint (4) is added as a third variable to the dynamics, the optimal control problem then becomes a Mayer-type problem of the following form:

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

$$J(u) = \varphi(x(T)) \tag{5}$$

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

$$\dot{x} = f(x) + ug(x) \qquad x(0) = x_0, \tag{6}$$

$$\dot{y} = u, \qquad y(0) = 0, \tag{7}$$

and terminal constraint $y(T) \leq A$.

In this formulation, the dosage of the anti-angiogenic agent and its concentration in the plasma are identified, i.e., pharmacokinetics of the inhibitors is neglected. Given the background of the model, the obvious question arises to what extent the structure of optimal controls and trajectories is preserved if the dynamics is refined to include these relations. For the most commonly used model of exponential growth and decay, this leads to the following extension of the optimal control problem [OC]:

[OCwLDC] for a free terminal time T, minimize the objective $J(u) = \varphi(x(T))$ over all Lebesgue measurable functions $u : [0, T] \to [0, a]$ subject to the dynamics

$$\begin{aligned} \dot{x} &= f(x) + cg(x) & x(0) &= x_0, \\ \dot{c} &= -kc + u & c(0) &= 0, \\ \dot{y} &= u, & y(0) &= 0, \end{aligned} \tag{8}$$

and the terminal constraint $y(T) \leq A$.

Thus, here the control u of formulation $[OC]$ has been replaced by the state of a first-order linear system. In equation (8), k is a positive constant, the so-called clearance rate of the agent. The control limit a still denotes the maximal allowable dosage. Mathematically, it would be redundant to include another coefficient at the control u in equation (8) and therefore this term has been normalized. These coefficients determine the limits for the achievable concentration, $0 \leq c(t) \leq c_{\max} = \frac{a}{k}$. The coefficient γ in the original equation (3) represents a simple model for the pharmacodynamics of the agent and is retained.

Both formulations are single-input, control affine systems and it is well-known (see also section 3 below) that the main candidates for optimality are the constant controls $u = 0$ and $u = a$, the so-called *bang* controls, and *singular* controls. The latter typically correspond to time-varying controls that take values in the interior of the control set. For a class of models for cancer chemotherapy that also have this general structure Σ and were analyzed earlier (e.g., Swierniak, 1988, 1995; Swierniak, Polanski and Kimmel, 1996; Ledzewicz and Schättler, 2002a,b), optimal controls are bang-bang and in Ledzewicz and Schättler (2005), we have shown that this property of optimal controls is preserved under the addition of a linear PK-model of the form (8). In Ledzewicz and Schättler (2007), we constructed the optimal synthesis for problem $[OC]$ for the model for tumor anti-angiogenesis by Hahnfeldt et al. (1999), and in this case optimal controls generally contain a segment where the control is singular of order 1. The same holds for the modification of this model by Ergun et al. (2003), that was analyzed in Ledzewicz, Munden and Schättler (2009). Since singular controls are inherently defined through nonlinear relationships, it is a priori not evident whether their optimality will be preserved under such a modeling extension. In this paper we show that in a certain sense this actually is true for a planar system. *All equations that define an order* 1 *singular control and its optimality status carry over verbatim from the optimal control problem* $[OC]$ *to the model* $[OCwLDC]$. At the same time, however, the order of the singular arc increases from 1 to 2 and this does have significant implications for the concatenation structures of optimal trajectories. Direct concatenations of the optimal singular control with the bang controls $u = 0$ and $u = a$ are no longer optimal and now this transition can only be accomplished by means of chattering controls (see, e.g., Zelikin and Borisov, 1994) or possibly even more complicated control schemes. Thus, while essential features are preserved under

the modeling extension considered here, the structure of the optimal synthesis does change.

3. Order 1 singular controls for model $[OC]$

We briefly describe the Lie-bracket based formulas for an optimal singular arc and its corresponding singular control in dimension 2. These computations are well-known in the framework of differential geometric methods for optimal control (see, e.g., Sussmann et al., 1983, H. Sussmann's work on time-optimal control for planar systems in Sussmann, 1982, 1987, or the research monographs by Bonnard and Chyba, 2003, or Boscain and Piccoli, 2004). These relations are essential for the construction of a synthesis of optimal controls for problem $[OC]$ and will then be connected to the singular arc for the extended model $[OCwLDC]$ in the next section.

If $u_* : [0,T] \to [0,a]$ is an optimal control for problem $[OC]$ with corresponding trajectory x_*, then, by the Pontryagin maximum principle, there exist a constant $\lambda_0 \geq 0$, an absolutely continuous co-vector, $\lambda : [0,T] \to (\mathbb{R}^2)^*$ (which we write as row-vector), and a constant ν such that (i) $(\lambda_0, \lambda(t), \nu) \neq (0,0,0)$ for all $t \in [0,T]$, (ii) λ satisfies the adjoint equations

$$\dot{\lambda}(t) = -\lambda(t)\left(Df(x_*(t) + u_*(t)Dg(x_*(t))\right), \qquad \lambda(T) = \lambda_0 \varphi_x(x(T)), \quad (9)$$

and (iii) the optimal control $u_*(t)$ minimizes the Hamiltonian H,

$$H = \lambda\left(f(x) + ug(x)\right) + \nu u \quad (10)$$

along $(\lambda(t), \nu, x_*(t))$ over the interval $[0,a]$, and the minimum value is given by 0. The trivial y dynamics only enters the Hamiltonian H and gives rise to the extra multiplier ν, but otherwise can mostly be taken out from the explicit formulation of the conditions of the Maximum principle.

We call a pair $((x,y),u)$ consisting of an admissible control u and corresponding trajectory (x,y) an *extremal* (pair) if there exist multipliers $(\lambda_0, \lambda, \nu)$ such that the conditions of the Maximum Principle are satisfied; the triple $((x,y),u,(\lambda_0,\lambda,\nu))$ including the multipliers is an extremal lift (to the cotangent bundle). Extremals with $\lambda_0 = 0$ are called abnormal, while those with a positive multiplier λ_0 are called normal. For problem $[OC]$, except for degenerate solutions when $u \equiv 0$ would be optimal (and these are not realistic for the underlying biological problem we are interested in), all extremals are normal, and we henceforth assume $\lambda_0 = 1$.

The minimum condition (iii) is equivalent to minimizing the so-called *switching function* Φ,

$$\Phi(t) = \nu + \lambda(t)g(x_*(t)), \quad (11)$$

over the interval $[0,a]$ and optimal controls thus satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ a & \text{if } \Phi(t) < 0 \end{cases}. \quad (12)$$

A priori, the control is not determined by the minimum condition at times when $\Phi(t) = 0$. Clearly, if the derivative of Φ does not vanish at a zero τ, then the value of the control switches between $u = 0$ and $u = a$ at τ and we refer to the constant controls $u = 0$ and $u = a$ as *bang* controls. On the other hand, if Φ vanishes on an open interval I, then also all derivatives of Φ must vanish and this may determine the control. Controls of this kind are called *singular*. These two classes of controls are the natural candidates for optimal controls and there exists a wealth of literature, both classical and modern, analyzing their optimality status. (For some recent references, see Stefani, 2003; Felgenhauer, 2003; Bonnard and Chyba, 2004; or Maurer et al., 2005.) Derivatives of the switching function are a key tool in analyzing optimal controls and the following well-known lemma shows how to calculate these derivatives efficiently in terms of Lie brackets.

PROPOSITION 3.1 *Let h be a continuously differentiable vector field and define*

$$\Psi(t) = \langle \lambda(t), h(x(t)) \rangle \,. \tag{13}$$

The derivative of Ψ along a solution x to the system equation (6) for control u and a solution λ to the corresponding adjoint equation (9) is given by

$$\dot{\Psi}(t) = \langle \lambda(t), [f + ug, h](x(t)) \rangle \,, \tag{14}$$

where $[k, h]$ denotes the Lie bracket of the vector fields k and h. In local coordinates the Lie bracket is given by

$$[k, h](x) = Dh(x)k(x) - Dk(x)h(x)$$

with Dh and Dk denoting the matrices of the partial derivatives. □

Suppose an optimal control is singular on an open interval I. Since $\nu = const$, it follows that

$$\dot{\Phi}(t) = \langle \lambda(t), [f, g](x(t)) \rangle \equiv 0, \tag{15}$$

$$\ddot{\Phi}(t) = \langle \lambda(t), [f + ug, [f, g]](x(t)) \rangle \equiv 0. \tag{16}$$

It is a necessary condition for optimality of the singular control, the so-called *Legendre-Clebsch condition* (e.g., Bryson and Ho, 1975; Bonnard and Chyba, 2003), that

$$\langle \lambda(t), [g, [f, g]](x(t)) \rangle \leq 0. \tag{17}$$

The singular control is said to be of *order 1* on I if everywhere on the interval this quantity does not vanish. Singular controls of higher order arise if the term $\langle \lambda(t), [g, [f, g]](x(t)) \rangle$ does vanish on some subintervals. If the singular control is of order 1 on I, then we necessarily have that

$$\langle \lambda(t), [g, [f, g]](x(t)) \rangle < 0, \tag{18}$$

i.e., the so-called *strengthened Legendre-Clebsch condition* is satisfied. This inequality indeed implies some *local* optimality properties of the singular control. For example, we refer the reader to the classical paper by Gardner-Moyer (1973), where a local embedding of the corresponding singular arc, respectively surface, into a family of extremals is constructed in $\mathbb{R}^3$, or to the more recent paper by Stefani (2003), in which strong minimality of a singular extremal is proven if I is the full interval $(0, T)$. But generally, for any particular problem, it will become necessary to combine the singular arc(s) with other extremal trajectories to construct a so-called regular synthesis to actually prove optimality (Boltyansky, 1966; Piccoli and Sussmann, 2000). For an order 1 singular control, equation (16) can formally be solved for u as

$$u_{\sin}(t) = -\frac{\langle \lambda(t), [f,[f,g]](x(t))\rangle}{\langle \lambda(t), [g,[f,g]](x(t))\rangle} \tag{19}$$

and this formula determines the singular control as a function of the state $x(t)$ and the multiplier $\lambda(t)$. Thus the computation of singular controls and the analysis of their local optimality requires the computations of the Lie brackets $[f,[f,g]]$ and $[g,[f,g]]$ and their inner products with the multiplier λ.

Special situations arise in dimension 2 (and also 3) if the vector field $[f,[f,g]]$ can be written as a linear combination of lower order Lie brackets. In these cases, it is often possible to simplify the expression (19) further and obtain the singular control as a feedback control $u_{\sin}(x)$. In the models for tumor anti-angiogenesis that are of interest to us, the vector fields $[f,g]$ and $[g,[f,g]]$ are linearly independent and thus $[f,[f,g]]$ can be written as a linear combination of this basis with coefficients that are smooth functions of the state x,

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

For a singular extremal $\langle \lambda(t), [f,g](x(t))\rangle$ vanishes and thus

$$\langle \lambda(t), [f,[f,g]](x(t))\rangle = -\psi(x(t)) \cdot \langle \lambda(t), [g,[f,g]](x(t))\rangle\,.$$

Hence, if the the strengthened Legendre-Clebsch condition is satisfied, the term $\langle \lambda(t), [g,[f,g]](x(t))\rangle$ cancels and the singular control is given as a feedback function by $u_{\sin}(t) = \psi(x(t))$. Clearly, whether this feedback is admissible, that is, whether it takes values in the control set $[0, a]$, needs to be determined for each problem under consideration and cannot be asserted in general. Even when admissible, this feedback does not define a singular control everywhere, but only on a thin subset. The conditions of the Maximum principle need to be satisfied and the extra condition that $H \equiv 0$ requires that also

$$\langle \lambda(t), f(x(t))\rangle = 0 \qquad \text{for all} \quad t \in I. \tag{20}$$

Since $\lambda(t) \neq 0$ (otherwise we once more have the trivial case of $u \equiv 0$), it follows that the vector fields f and $[f,g]$ must be linearly dependent along the singular

arc and thus the singular control is only defined on the curve

$$\mathcal{S} = \{x \in \mathbb{R}^2 : \Delta(x) = \det\left(f(x), [f,g](x)\right) = 0\}.$$

Summarizing, we have the following well-known statement (Sussmann, 1982 and 1987; Bonnard and Chyba, 2003; Boscain and Piccoli, 2004):

PROPOSITION 3.2 *Suppose the vector fields* $[f,g]$ *and* $[g,[f,g]]$ *are linearly independent and*

$$[f,[f,g]](x) = \varphi(x)[f,g](x) - \psi(x)[g,[f,g]](x). \tag{21}$$

Then the singular control is given in feedback form as

$$u_{\sin}(t) = \psi(x(t)) \tag{22}$$

and the singular arc is defined by

$$\Delta(x) = \det\left(f(x), [f,g](x)\right) = 0. \tag{23}$$

Furthermore, if the strengthened Legendre-Clebsch condition is satisfied along these arcs, and if the singular control takes values in the interior of the control set, then it is a classical result that the singular control can be concatenated at every time with the bang controls $u = a$ or $u = 0$ without violating the conditions of the Maximum principle. That is, if $(\tau - \varepsilon, \tau + \varepsilon)$ is a small interval with the property that the optimal control is singular on $(\tau - \varepsilon, \tau)$ or $(\tau, \tau + \varepsilon)$ and constant on the complementary interval, $u = 0$ or $u = a$, then the conditions of the Maximum Principle are satisfied. To see this, recall that by Proposition 3.1, for any control u that is continuous from the left $(-)$ or right $(+)$, the second derivative of the switching function is given by

$$\ddot{\Phi}(t_\pm) = \langle \lambda(t), [f,[f,g]](x(t))\rangle + u(t_\pm)\,\langle \lambda(t), [g,[f,g]](x(t))\rangle \tag{24}$$

and it vanishes identically on I along the singular control. Since the strengthened Legendre-Clebsch condition is satisfied, we have $\langle \lambda(t), [g,[f,g]](x(t))\rangle < 0$. If the singular control takes values in the interior of the control set $[0,a]$, then $\langle \lambda(t), [f,[f,g]](x(t))\rangle > 0$. Hence, for $u = 0$ we get $\ddot{\Phi}(t) > 0$ and for $u = a$ we have $\ddot{\Phi}(t) < 0$. These signs are consistent with entry and exit from the singular arc for each control, i.e., for example, if $u = 0$ on an interval $(\tau - \varepsilon, \tau)$, then Φ is positive over this interval, consistent with the choice $u = 0$ as minimizing control. This allows to construct a local synthesis of extremals around $\mathcal{S}$ by integrating the constant controls $u = 0$ or $u = a$ forward and backward from the singular arc. These trajectories indeed are locally optimal over a neighborhood covered by the trajectories in this construction (see, for instance, Gardner-Moyer, 1973, or Sussmann, 1982). For the models for tumor anti-angiogenesis which we considered in Ledzewicz and Schättler (2007 and 2009), in fact the global optimality of these singular controls can be established in this way.

4. Singular controls for model $[OCwLDC]$

We now show that all the formulas defining the singular arc and its control carry over (albeit with a different interpretation) if a linear dynamics is added to the model for the control, i.e., if we replace u with c where

$$\dot{c} = -kc + u, \qquad c(0) = 0.$$

We write $z = (x, c)$ and, as before, keep the variable y that keeps track of the isoperimetric constraint separate since it does not participate in the computations of the Lie brackets. The dynamical equations now form a single input, control-affine system of the form

$$\dot{z} = F(z) + uG \tag{25}$$

with 3-dimensional state vector z, drift F, and a constant control vector field G given by

$$F(z) = \begin{pmatrix} f(x) + cg(x) \\ -kc \end{pmatrix}, \qquad G(z) = \begin{pmatrix} 0 \\ 1 \end{pmatrix}. \tag{26}$$

We denote the corresponding adjoint variable by $\Lambda = (\hat{\lambda}, \hat{\mu})$ and the adjoint equations and transversality conditions are

$$\dot{\hat{\lambda}} = -\hat{\lambda}\left(Df(x) + cDg(x)\right), \qquad \hat{\lambda}(T) = \varphi_x(x(T)) \tag{27}$$

$$\dot{\hat{\mu}} = -\hat{\lambda}g(x) + k\hat{\mu}, \qquad \hat{\mu}(T) = 0. \tag{28}$$

The Hamiltonian for the problem $[OCwLDC]$ is

$$\hat{H} = \hat{\lambda}\left(f(x) + cg(x)\right) + \hat{\mu}(-kc + u) + \hat{\nu}u \tag{29}$$

with $\hat{\nu}$ again a constant, the multiplier associated with the isoperimetric constraint. The switching function now is given by

$$\Psi(t) = \hat{\mu}(t) + \hat{\nu} = \langle \Lambda(t), G(z(t)) \rangle + \hat{\nu}. \tag{30}$$

As before, we need to calculate the derivatives of the switching function. The control vector field G is a coordinate vector field and we simply have that

$$[F, G](z) = -\frac{\partial F}{\partial c}(z) = -\begin{pmatrix} g(x) \\ -k \end{pmatrix} \tag{31}$$

and the higher order Lie brackets with G all vanish identically: if we write $ad_G^n(F) = ad_G \circ ad_G^{n-1}(F)$ with $ad_G(F)$ defined by $ad_G(F) = [G, F]$, then for $n \geq 2$

$$ad_G^n(F)(z) = \frac{\partial^n F}{\partial c^n}(z) \equiv 0. \tag{32}$$

In particular, $[G,[F,G]](z(t)) \equiv 0$. The derivatives of the switching function therefore are now given by

$$\dot{\Psi}(t) = \langle \Lambda(t), [F,G](z(t)) \rangle \equiv 0, \tag{33}$$

$$\ddot{\Psi}(t) = \big\langle \Lambda(t), ad_F^2(G)(z(t)) \big\rangle \equiv 0, \tag{34}$$

$$\dddot{\Psi}(t) = \big\langle \Lambda(t), ad_F^3(G)(z(t)) \big\rangle \equiv 0, \tag{35}$$

and the control only enters the fourth derivative,

$$\Psi^{(4)}(t) = \big\langle \Lambda(t), [F+uG, ad_F^3(G)](z(t)) \big\rangle \equiv 0. \tag{36}$$

A singular control of this type is said to be of *intrinsic order* 2 (Zelikin and Borisov, 1994). Note that, for a general problem, it need not follow that the third derivative of the switching function vanishes on an interval I if only the inner product $\langle \Lambda(t), [G,[F,G]](z(t)) \rangle$ vanishes on I, (see, e.g., Bonnard and Chyba, 2003). But this is true if $[G,[F,G]] \equiv 0$ as it is the case here. The adjective 'intrinsic' is used to distinguish these cases. Thus, in this case, if the control u is singular on an open interval I, then Λ must vanish against the vector fields F (since $\hat{H} \equiv 0$), G, and their Lie brackets $[F,G]$, $ad_F^2(G)$ and $ad_F^3(G)$. Generically, in low dimensions, these are too many conditions to be met simultaneously. But in our case there exist relations between these vector fields that guarantee that all these conditions can be satisfied. Note that

$$F(z) = \begin{pmatrix} f(x) \\ 0 \end{pmatrix} - c[F,G](z) \tag{37}$$

and direct computations verify that

$$ad_F^2 G(z) = -\begin{pmatrix} [f,g](x) \\ 0 \end{pmatrix} + k[F,G](z), \tag{38}$$

$$ad_F^3 G(z) = -\begin{pmatrix} [f+cg,[f,g]](x) \\ 0 \end{pmatrix} + k ad_F^2 G(z) \tag{39}$$

and

$$[G, ad_F^3(G)](z) = -\begin{pmatrix} [g,[f,g]](x) \\ 0 \end{pmatrix}. \tag{40}$$

The multiplier Λ is nonzero (otherwise we again have the trivial solution $u \equiv 0$) and thus the condition that Λ vanishes against the vector fields F, $[F,G]$ and $ad_F^2(G)$ is equivalent to the statement that these vector fields are linearly dependent:

$$\begin{aligned} 0 &= \det \big[\ F(z), \quad [F,G](z), \quad ad_F^2(G)(z)\ \big] \\ &= \det \left[\begin{pmatrix} f(x)+cg(x) \\ -kc \end{pmatrix}, \begin{pmatrix} -g(x) \\ k \end{pmatrix}, \begin{pmatrix} -[f,g](x) - kg(x) \\ k^2 \end{pmatrix} \right] \\ &= -\det \left[\begin{pmatrix} f(x) \\ 0 \end{pmatrix}, \begin{pmatrix} -g(x) \\ k \end{pmatrix}, \begin{pmatrix} [f,g](x) \\ 0 \end{pmatrix} \right] = k\Delta(x). \end{aligned} \tag{41}$$

Hence this equation reduces to relation (23) that defines the singular arc for the model $[OC]$. Now, however, this relation, which does not depend on the new variable c, only defines a vertical surface in (x,c)-space on which singular arcs need to lie. But $\Lambda(t)$ also vanishes against the vector field $ad_F^3(G)$ and the linear dependence of the vector fields $ad_F(G)$, $ad_F^2(G)$ and $ad_F^3(G)$ determines c:

$$\begin{aligned}
0 &= \det\left[\ [F,G](z), \quad ad_F^2(G)(z), \quad ad_F^3(G)(z)\ \right] \\
&= \det\left[\ [F,G](z), \quad ad_F^2(G)(z), \right. \\
&\qquad\qquad \left. - \begin{pmatrix} [f+cg,[f,g]](x) \\ 0 \end{pmatrix} + k ad_F^2(G)(z)\right] \\
&= -\det\left[\ [F,G](z), \quad -\begin{pmatrix} [f,g](x) \\ 0 \end{pmatrix} + k[F,G](z), \right. \\
&\qquad\qquad \left. \begin{pmatrix} [f+cg,[f,g]](x) \\ 0 \end{pmatrix}\right] \\
&= \det\left[\ -\begin{pmatrix} g(x) \\ -k \end{pmatrix}, \quad \begin{pmatrix} [f,g](x) \\ 0 \end{pmatrix}, \quad \begin{pmatrix} [f+cg,[f,g]](x) \\ 0 \end{pmatrix}\ \right] \\
&= k \det\left[\ [f,g](x), \quad [f+cg,[f,g]](x)\ \right]. \qquad (42)
\end{aligned}$$

Using the relation (21) to express $[f,[f,g]]$ as a linear combination of $[f,g]$ and $[g,[f,g]]$, we thus get that

$$\begin{aligned}
0 &= \det\left[\ [f,g](x), \quad [f+cg,[f,g]](x)\ \right] \\
&= \det\left[\ [f,g](x), \quad \varphi(x)[f,g](x) + (-\psi(x)+c)[g,[f,g]](x)\ \right] \\
&= (c-\psi(x)) \det\left[\ [f,g](x), \quad [g,[f,g]](x)\ \right].
\end{aligned}$$

The linear independence of $[f,g]$ and $[g,[f,g]]$ implies that c is given by

$$c = \psi(x), \qquad (43)$$

the same function that defines the optimal control in the model $[OC]$.

Overall, *the singular arc of the model $[OC]$ in x-space is preserved as a vertical surface in (x,c)-space and the equation, which for problem $[OC]$ defines the singular control, now defines the new state variable c. The graph of this function intersects the singular surface in a unique curve, the new singular arc.* The control that keeps this arc invariant is calculated by implicit differentiation of this relation, i.e.,

$$\begin{aligned}
u &= \dot{c} + kc = D\psi(x)\dot{x} + kc \\
&= kc + D\psi(x)\left(f(x) + cg(x)\right).
\end{aligned}$$

If u is singular of intrinsic order 2, then the necessary condition for minimality is that

$$\frac{\partial}{\partial u}\left(\frac{d^4}{dt^4}\Psi(t)\right) = \left\langle \Lambda(t), [G, ad_F^3(G)](z(t))\right\rangle \geq 0.$$

This is known as the Kelley condition (Kelley, 1964; Kelley et al., 1967; Zelikin and Borisov, 1994), but is also called the generalized Legendre-Clebsch condition in Bryson and Ho (1975), or in Knobloch (1981). For a singular control that is of intrinsic order k, this necessary condition for minimality can compactly be expressed as

$$(-1)^k \frac{\partial}{\partial u}\frac{d^k}{dt^k}\frac{\partial H}{\partial u} \geq 0. \tag{44}$$

For problem [OCwLDC], by (40) we have that

$$\left\langle \Lambda(t), [G, ad_F^3(G)](z(t)) \right\rangle = -\left\langle \hat{\lambda}(t), [g,[f,g]](x(t)) \right\rangle. \tag{45}$$

Therefore, if we can identify $\hat{\lambda}$ with λ over an interval I when the control is singular, then the strengthened Legendre-Clebsch condition for the singular control of problem [OC] implies that the strengthened version of the Kelley condition is satisfied for problem $[OCwLDC]$. This indeed can be done: since (i) the singular arc $\mathcal{S}$ is preserved and (ii) the extra variable c is defined by the same feedback function of x, it follows that λ and $\hat{\lambda}$ satisfy the same differential equation on I. Furthermore, by (34) and (38) we also have that $\left\langle \hat{\lambda}(t), [f,g](x(t)) \right\rangle = 0$. The fact that the switching function Φ for problem $[OC]$ vanishes on I implies that

$$\langle \lambda(t), g(x(t)) \rangle = -\nu \tag{46}$$

while the fact that the switching function Ψ and its derivative vanish for problem $[OCwLDC]$ imply that $\hat{\mu}(t) \equiv -\hat{\nu}$ and $\left\langle \hat{\lambda}(t), g(x(t)) \right\rangle = k\hat{\mu}(t)$. Hence

$$\left\langle \hat{\lambda}(t), g(x(t)) \right\rangle = -k\hat{\nu}. \tag{47}$$

Thus, if we take $\lambda(t) = \hat{\lambda}(t)$ and $\nu = k\hat{\nu}$, then these multipliers satisfy the conditions of the Maximum Principle for a singular control on I. Hence the status of the necessary condition for optimality of a singular control carries over from problem $[OC]$ to $[OCwLC]$.

However, the fact that the Kelley condition is now satisfied with a positive sign, has significant implications on possible concatenations between the singular control and bang controls. If the singular control takes a value in the interior of the control set, $0 < u_{sin}(z(t)) < a$, then it is no longer optimal to concatenate the singular control at time t with any of the two bang controls $u = 0$ or $u = a$. For example, suppose that for some $\varepsilon > 0$ the control is singular over the interval $(\tau - \varepsilon, \tau)$ and is given by $u = 0$ over the interval $(\tau, \tau + \varepsilon)$. We now have that

$$\Phi^{(4)}(\tau+) = \left\langle \lambda(\tau), ad_F^4(G)(z(t)) \right\rangle < 0 \tag{48}$$

and thus the switching function has a local maximum for $t = \tau$, i.e., is negative over the interval $(\tau, \tau+\varepsilon)$. But then, the minimization property of the Hamiltonian implies that the control must be $u = a$. The analogous contradiction arises

for other types of concatenations. Thus *an optimal singular control of order* 2 *that takes values in the interior of the control set cannot be concatenated with a bang control*. However, transitions onto the singular arc are still possible by means of chattering arcs, i.e., through controls that switch infinitely often between the controls $u = 0$ and $u = a$ on any interval $(\tau, \tau + \varepsilon)$. For a single-input control-affine system, Zelikin and Borisov (1994), Zelikin and Zelikina (1998) give conditions, under which a canonical family of chattering extremals does exist in the cotangent bundle, but for these controls to be optimal (like it is the case in the Fuller problem), a bijective projection into the state space must exist (also, see Chyba and Haberkorn, 2003). Nevertheless, in all these cases, chattering controls appear to provide the only realistic control scheme that would allow to connect with the singular arc.

5. Example: optimal control for tumor anti-angiogenesis

For the mathematical model for tumor anti-angiogenesis from Hahnfeldt et al. (1999), the optimal control problem [OC] under consideration is to minimize the tumor volume $p(T)$ over all Lebesgue measurable functions $u : [0, T] \to [0, a]$ subject to the dynamics (2) and (3) and terminal condition $y(T) \leq A$. In this case there exists an optimal singular arc which determines the optimal synthesis and we briefly describe both, but refer to Ledzewicz and Schättler (2007a), for the mathematical analysis.

PROPOSITION 5.1 *(Ledzewicz and Schättler, 2006, 2007a) For problem [OC] there exists a locally minimizing singular arc $\mathcal{S}$ in (p, q)-space which, using a blow-up of the form $r = \frac{p}{q}$, can be parameterized in the form*

$$\mathcal{S}: \qquad dp^{\frac{2}{3}} = br(1 - \ln r) - \mu \tag{49}$$

with $r \in (r_1^*, r_2^*)$, where r_1^* and r_2^* are the unique zeroes of the equation

$$br(1 - \ln r) - \mu = 0$$

and satisfy $0 < r_1^* < 1 < r_2^* < e$. The singular control keeps $\mathcal{S}$ invariant and is given as a feedback function of p and q as

$$\begin{aligned} u_{\sin}(t) &= \psi(p(t), q(t)) \\ &= \frac{1}{\gamma}\left(\xi \ln\left(\frac{p(t)}{q(t)}\right) + b\frac{p(t)}{q(t)} + \frac{2}{3}\xi\frac{d}{b}\frac{q(t)}{p^{\frac{1}{3}}(t)} - \left(\mu + dp^{\frac{2}{3}}(t)\right)\right). \end{aligned} \tag{50}$$

Using the relation (49), the singular control can equivalently be expressed as a function of r alone in the form

$$u_{\sin}(t) = \frac{1}{\gamma}\left[\left(\frac{1}{3}\xi + br(t)\right)\ln r(t) + \frac{2}{3}\xi\left(1 - \frac{\mu}{br(t)}\right)\right]. \tag{51}$$

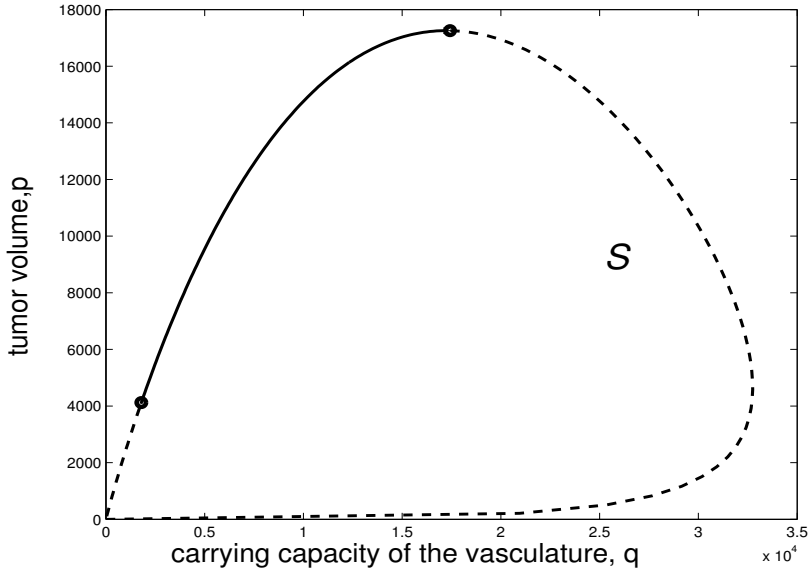

Figure 1. Singular arc and its admissible part

There exists exactly one connected arc on the singular curve $\mathcal{S}$, along which the singular control is admissible, i.e., satisfies the bounds $0 \leq u_{\sin}(r) \leq a$. *This arc is defined over an interval* $[r_\ell^*, r_u^*]$ *where* r_ℓ^* *and* r_u^*, *respectively, are the unique solutions to the equations* $u_{\sin}(r_\ell^*) = 0$ *and* $u_{\sin}(r_u^*) = a$ *and these values satisfy* $r_1^* < r_\ell^* < 1 < r_u^* < r_2^*$.

This structure is fully robust and only requires that we have $\gamma a > b - \mu > 0$, natural conditions for the problem. Fig. 1 gives the graph of the singular curve defined by (49) with the admissible portion marked as solid curve. For the parameter values for this illustration we used the following data from Hahnfeldt et al. (1999): $\xi = \frac{0.192}{\ln 10} = 0.084$ per day (this value is adjusted to the natural logarithm), $b = 5.85$ mm per day, $d = 0.00873$ per mm per day, $\gamma = 0.15$ kg per mg of dose. For the upper limit a on the dosage we selected $a = 75$ and for illustrative purposes we also set $\mu = 0.02$.

The admissible singular arc becomes the centerpiece for the synthesis of optimal solutions shown in Fig. 2. The important curves are the admissible portions of the singular arc S (solid curve), portions of trajectories corresponding to the constant controls $u = 0$ and $u = a$ (dash-dotted and solid almost horizontal line-like curves), and the line $p = q$ (dotted line) where the trajectories achieve the maximum tumor reduction. This diagram represents the optimal trajectories as a whole and each of the different curves gives a different optimal trajectory depending on the actual initial condition. The thick curves in the graph mark one specific such trajectory. In this case the initial value p_0 for the tumor vol-

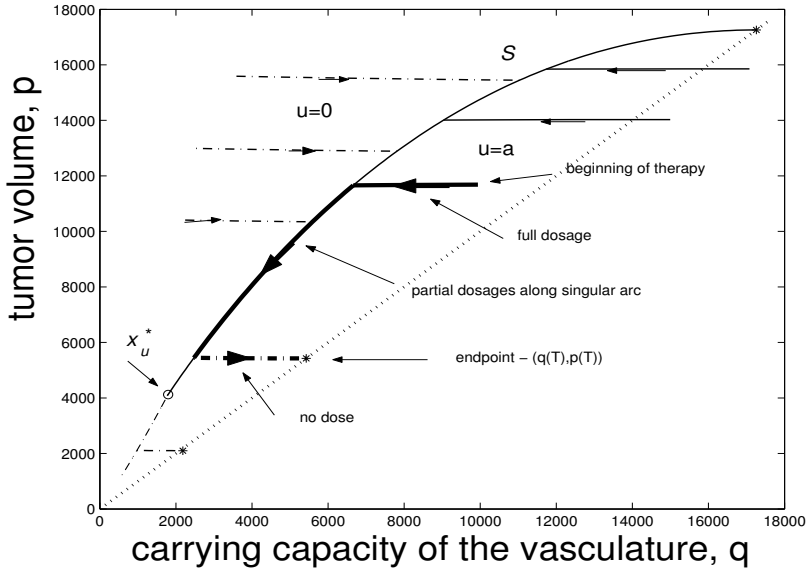

Figure 2. Synthesis of optimal trajectories for problem [OC] for a model for tumor anti-angiogenesis (Hahnfeldt et al., 1999)

ume and q_0 for the carrying capacity are high and require an immediate start of the treatment. The optimal trajectory, therefore, initially follows the curve corresponding to the control $u = a$. Note that, although inhibitors are given at full dose along this curve, this shows very little effect on the number of the cancer cells in a sense of decrease. During this period the inhibitors drive down the carrying capacity q and in this way prevent the further growth of the tumor that otherwise, enabled by ample vascular support, would have occurred. Once the trajectory corresponding to the full dose hits the singular arc $\mathcal{S}$, it is no longer optimal to give full dose and the optimal controls here switch to the singular control. The optimal trajectory then follows the singular arc until all inhibitors are exhausted. At this time therapy is over, but there still are the after effects of treatment. Since the singular curve $\mathcal{S}$ lies in the region $p > q$ where we always have $\dot{p} < 0$, even along $u = 0$, the tumor volume is still decreasing and the maximum tumor reduction is only realized as the trajectory for the control $u = 0$ crosses the diagonal $p = q$. The corresponding time then is the optimal free end-time T considered in the problem formulation $[OC]$. We only remark that the scenario described here assumes that no saturation occurs along the singular arc. If that were the case, then optimal controls no longer follow the singular regimen until saturation, but, in fact, optimal trajectories leave the singular arc with the control $u = a$ prior to the saturation point (see also Schättler and Jankovic, 1993, or Bonnard and de Morant, 1995). Simply

continuing the control with $u = a$ is not optimal (Ledzewicz and Schättler, 2007).

When a linear model for pharmacokinetics is added, the model being $[OCwLDC]$, the singular curve is preserved as a vertical surface in (p, q, c)-space, Fig. 3, and now the singular arc is defined as the intersection with the graph of the function $c = \psi(p, q)$, see Fig. 4.

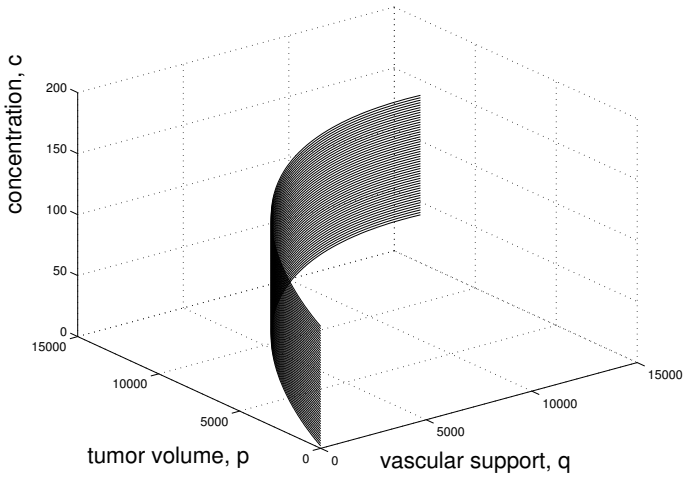

Figure 3. Vertical singular surface in (p, q, c)-space for problem [OCwLDC]

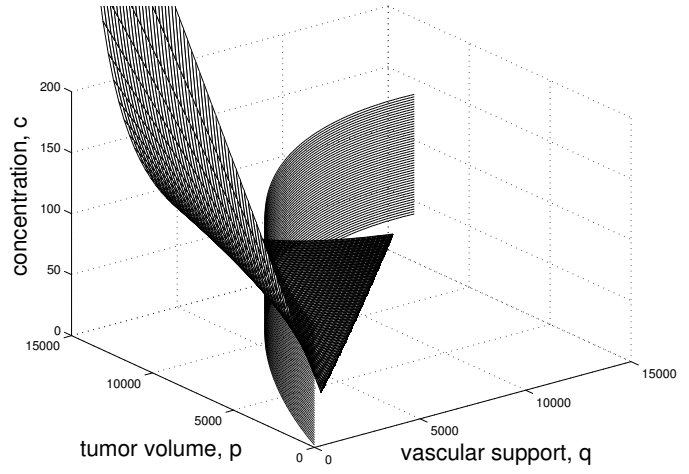

Figure 4. Singular arc in (p, q, c)-space for problem [OCwLDC]

Chattering arcs now become the prime candidates for the optimal transitions to and from the singular arc. The precise structure of these optimal controls, however, has not yet been worked out. From a practical point of view, for the underlying application chattering controls are not realistic. The real significance of knowing the optimal solution lies rather in establishing a benchmark value with which other, simple and realizable strategies can be compared. In fact, even for problem [OC], the optimal singular controls are defined by time-varying feedback controls and thus are not medically realizable. In Ledzewicz, Marriott, Maurer and Schättler (2009), we have shown for this problem (for both the original model by Hahnfeldt et al., 1999, and its modification by Ergun, Camphansen and Wein, 2003) that simple piecewise constant controls with two dosages - easily practically realizable protocols - provide excellent suboptimal approximations to the optimal controls that consistently give values that come within 1% of the theoretically optimal values. These dosages are not of the bang type, but rather give lower dosages over specified time intervals that mimick the time-varying optimal singular control in its behavior. It is hoped that similar results can be established for the problem [$OCwLDC$] when a linear pharmacokinetic model is added and that simple, non-optimal concatenations with bang controls will provide satisfactory suboptimal approximations. Thus, it would not only be of theoretical interest to establish an optimal synthesis of controlled trajectories for this problem.

6. Conclusion

We considered a Mayer optimal control problem for a single-input, control affine system in dimension 2 when control is replaced by the state of a first order time-invariant linear system. We showed that the fundamental formulas that define and characterize the optimality of singular controls and their corresponding trajectories are preserved verbatim under such an extension. However, the intrinsic order of the singular arc increases from 1 to 2. If the Kelley condition is satisfied and the singular control takes values in the interior of the control set, then this precludes concatenations between the singular and bang controls from being optimal and now chattering arcs become the prime candidates to effect the transitions to and from the singular arc.

For an application of these results to the problem of minimizing the tumor size for a model of tumor anti-angiogenesis, establishing the structure of an optimal synthesis would provide valuable information about the extent, to which the pharmacokinetics of anti-angiogenic agents would need to be included in the modeling of the problem. In this regard, the important question is how close to optimal protocols simple realizable ones can come and how the optimal values for the two problem formulations [OC] and [$OCwLDC$] compare. Thus, if there is little difference in the tumor volumes achievable with realizable protocols, this gives credence to a modeling approach that neglects the pharmacokinetic model.

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