

# Minimization of Tumor Volume and Endothelial Support for a System Describing Tumor Anti-Angiogenesis

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*Abstract:* Anti-angiogenic therapy is a novel treatment approach for cancer that aims at preventing a tumor from developing its own network of blood vessels that it needs for its supply of nutrients and thus indirectly inhibits the growth of the tumor. In this paper a mathematical model for anti-angiogenic treatment is analyzed as a 3-dimensional optimal control problem with the aim of minimizing a convex combination of tumor volume and endothelial support. The latter represents a measure for the size of the tumor's vasculature. The results are compared with the solutions for the problem when only the tumor volume is minimized.

*Key-Words:* Optimal control, singular controls, cancer treatments, tumor anti-angiogenesis

## 1 Introduction

Anti-angiogenic therapy is a novel treatment approach for cancer that aims at preventing a tumor from developing its own network of blood vessels [12, 19]. After going through a state of avascular growth, at the size of about 2 mm in diameter a primary solid tumor starts the process of *angiogenesis* to recruit surrounding, mature, host blood vessels in order to develop capillaries needed for its own supply of nutrients. The lining of these newly developing blood vessels consist of endothelial cells and the tumor produces vascular endothelial growth factor (VEGF) to stimulate their growth [20] as well as inhibitors to suppress it [13]. Overall this process is based on a bi-directional signaling that can be viewed as a complex balance of tightly regulated stimulatory and inhibitory mechanisms [14, 8]. Anti-angiogenic treatments rely on these mechanisms by bringing in external angiogenic inhibitors (e.g., endostatin) targeting the endothelial cells and thus blocking their growth. This indirectly effects the tumor which, ideally, deprived of necessary nutrition, would regress. Since the treatment does not target cancer cells, but healthy cells instead, no occurrence of drug resistance has been reported in lab studies [4]. For this reason tumor anti-angiogenesis has been called a therapy "resistant to resistance" that provides a new hope for the treatment of tumor type cancers [18]. Naturally, as such it became an active area of research in the last ten years not only in medicine but also in modeling and mathematical biology.

In mathematical modeling several models de-

scribing the dynamics of angiogenesis have been proposed. Some of these aim at fully reflecting the complexity of the biological processes, (e.g., [1, 2]), and allow for large scale simulations while other models emphasize the spatial aspects of the problem [22]. However, because of the dimensionality of these systems a theoretical analysis often is difficult. On the other hand, if the dimensions are small analytical techniques from such fields as dynamical systems or optimal control theory can be applied to study the problem. Applications of optimal control to mathematical models arising in biomedical problems have a long history going back to Eisen's monograph [9] and some of the classical papers by Swan [34, 35]. The early focus was on models in connection with cancer chemotherapy and these efforts have continued to the present day (e.g., [36, 11, 23, 24]). The problem of optimal dosages of drugs has also been addressed using some alternative numerical techniques like, for example, genetic algorithms (e.g., [3]).

In this paper we consider the question how to schedule an a priori given amount of angiogenic inhibitors as an optimal control problem. The underlying model was formulated and biologically validated by Hahnfeldt, Panigrahy, Folkman and Hlatky (then at Harvard Medical School) in [16]. Mathematically it is described by a two-dimensional dynamical system with the volume of primary tumor cells,  $p$ , and the carrying capacity of the endothelial cells,  $q$ , as variables. The latter is defined as the maximum tumor volume sustainable by the vascular network and henceforth

we also refer to this as the endothelial support of the tumor for short. Based on this model and the underlying spatial analysis carried out in the research by Hahnfeldt et al. [16] two modifications of the original model have been formulated since, one by d’Onofrio (at the European Institute of Oncology in Milan) and Gandolfi (at the National Research Council in Rome, Italy) [7], the other by Ergun, Camphausen and Wein (at the Cancer Research Institute at NIH) [10]. In each formulation a Gompertzian model with variable carrying capacity  $q$  is chosen to model tumor growth, but the dynamics for the endothelial support differ in their inhibition and stimulation terms.

In earlier research we have analyzed the problem how to schedule given amounts of angiogenic inhibitors in order to minimize the cancer volume (see [27, 28, 29] for the original model of Hahnfeldt et al., [25] for the modification by Ergun et al., and [30] for the modification by d’Onofrio and Gandolfi). Sub-optimal controls were explored in [31] with an emphasis on medically realizable protocols. In this paper we modify the objective to include the level of endothelial support. More precisely, here we consider the problem of how to schedule an a priori given amount of anti-angiogenic inhibitors in order to minimize a convex combination

$$\theta p(T) + (1 - \theta)q(T), \quad 0 \leq \theta \leq 1 \quad (1)$$

while our earlier results were for the special case  $\theta = 1$ . Several aspects of the overall solution remain unaltered under this modification. For example, in either case the synthesis of optimal solutions is largely determined by an optimal singular arc  $\Gamma$  whose equation naturally is not effected by this change in the objective. But the value of  $\theta$  determines the behavior near the optimal terminal time  $T$ . We shall show that there is an interval  $(\theta^*, 1]$ , generally small for biologically realistically parameter values, such that for  $\theta \in (\theta^*, 1]$  the typical optimal control is a concatenation of the type  $\text{as0}$ , that is, consists of an initial segment where inhibitors are given at maximum dose  $u = a$  until the optimal singular arc  $\Gamma$  is reached, then follow the optimal singular arc until all inhibitors are exhausted, but then still have another short time interval along which the optimal control is  $u = 0$  and on which the value of the objective still decreases due to after effects. However, for  $\theta < \theta^*$ , it is no longer optimal to stay on the singular arc until all inhibitors have been exhausted and in these cases optimal controls are concatenations of the form  $\text{bsa}$  where, depending on the initial condition  $\mathbf{b}$  denotes an interval either with  $u = 0$  or  $u = a$ .

## 2 A Mathematical Model for Tumor Anti-Angiogenesis [16]

The mathematical model considered here was developed and biologically validated by Hahnfeldt, Panigrahy, Folkman and Hlatky in [16]. Its principal variables are the primary tumor volume,  $p$ , and the carrying capacity or the endothelial support of the vasculature,  $q$ , that is the maximum tumor volume sustainable by the vasculature. The dynamics describes the time evolution of these quantities. Tumor growth is modelled by a Gompertzian growth function with variable carrying capacity represented by  $q$ , that is the rate of change in the volume of primary tumor cells is given by

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

where  $\xi$  denotes a tumor growth parameter. Other growth models, like for example logistic growth considered in [7] or general growth functions considered in [15] are equally plausible, but lead to different computations and the corresponding optimal control problems would need to be analyzed separately. Here we retain the original modeling. The dynamics of the endothelial support consists of a balance between stimulatory and inhibitory effects and is taken of the following form in [16]

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

In this equation  $bp$  represents the stimulation term which is taken proportional to the tumor volume. The terms  $\mu q$  and  $Guq$ , respectively, model loss to the endothelial cells through natural causes (death etc.) and loss of endothelial cells due to additional outside inhibition. The variable  $u$  denotes the control in the system and corresponds to the angiogenic dose rate while  $G$  is a constant that represents the anti-angiogenic killing parameter. Generally  $\mu$  is small and often this term is negligible compared to the other factors and thus in the literature sometimes  $\mu$  is set to 0 in this equation. The other inhibition term  $dp^{\frac{2}{3}}q$  represents the fact that the tumor also produces inhibitors that impact endothelial cells in a way that grows like volume of cancer cells to the power  $\frac{2}{3}$ . The exponent  $\frac{2}{3}$  arises through the interplay of the surface of the tumor through which the inhibitor needs to be released with the volume of endothelial cells [16].

The problem how to administer a given amount of inhibitors to achieve the “best possible” effect arises naturally and leads to optimal control problems. One possible formulation, considered first in [10] and then taken up by us in [25, 27, 29, 30], is to minimize the tumor volume or, equivalently, maximize the tumor

reduction possible with an a priori given amount of inhibitors. In this paper, since both tumor volume and its carrying capacity determine the overall behavior, we modify the objective to minimize a convex combination of tumor volume and endothelial support. Thus here we consider the following optimal control problem:

**[OC]** For a free terminal time  $T$ , minimize the value

$$J_\theta(u) = \theta p(T) + (1 - \theta)q(T), \quad 0 \leq \theta \leq 1,$$

over all piecewise continuous (more generally, Lebesgue measurable) functions

$$u : [0, T] \rightarrow [0, a] \quad (4)$$

that satisfy a constraint on the total amount of anti-angiogenic inhibitors to be administered,

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

subject to the dynamics (2), (3) with initial conditions  $p_0$  and  $q_0$ .

The upper limit  $a$  in the definition of the control set  $U = [0, a]$  is a previously determined maximum dose at which inhibitors can be given. Note that in this formulation the time  $T$  does not correspond to a therapy horizon, but instead the solution to this problem gives the maximum reduction possible for the weighted average  $J_\theta$  of tumor volume and endothelial support with an overall amount  $A$  of inhibitors available and  $T$  is the time when this minimum is being realized. Mathematically it is more convenient to adjoin the constraint as third variable and define the problem in  $\mathbb{R}^3$  which overall leads to the following dynamical equations:

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right), \quad p(0) = p_0, \quad (6)$$

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}}\right)q - Guq, \quad q(0) = q_0, \quad (7)$$

$$\dot{y} = u, \quad y(0) = 0, \quad (8)$$

Naturally, from their definition all the state variables need to be positive. It was shown in [7] that this condition is ensured by the dynamics and need not be imposed as a separate constraint.

**Proposition 1** [7] *For any admissible control  $u$  and arbitrary positive initial conditions  $p_0$  and  $q_0$ , the corresponding solution  $(p, q)$  exists for all times  $t \geq 0$  and both  $p$  and  $q$  remain positive.  $\square$*

Since we consider problem [OC] for arbitrary initial conditions, in this formulation degenerate cases are included that we want to exclude for our analysis. They all are related to the fact that the initial condition may be skewed heavily in favor of the endothelial support, that is,  $q$  is much larger than  $p$ . In this case it may simply not be possible to lower the value  $\theta p(t) + (1 - \theta)q(t)$  below its initial value  $\theta p_0 + (1 - \theta)q_0$  since for any admissible control the function

$$J_{\theta,u}(t) = \theta p(t) + (1 - \theta)q(t) \quad (9)$$

is increasing in the region where the initial condition lies and the overall amount  $A$  of inhibitors is too small to reach a region where this function would have a lower value than

$$J_{\theta,u}(0) = \theta p_0 + (1 - \theta)q_0. \quad (10)$$

In such a case the (mathematically) optimal time  $T$  is  $T = 0$  since the overall available amount of inhibitors is too small to reach a point  $(p(t), q(t))$  that would have a lower  $J_\theta$ -value than the initial condition. It is only possible to slow down the tumor's growth. Indeed, a good way of doing this is to give the full dose  $u = a$  until all inhibitors run out - this is implied by the structure of optimal controls to be shown later - but mathematically this is not the "optimal" solution for problem [OC]. This one is simply to do nothing and take  $T = 0$ . Clearly for these initial conditions the mathematical formulation considered here is not adequate and we wish to exclude these degenerate scenarios from our analysis. We thus make the following definition:

**Definition 1** *We say an initial condition  $(p_0, q_0)$  is well-posed if the optimal final time  $T$  is positive.*

Clearly whether an initial condition is well-posed depends on the overall available amount  $A$  of inhibitors and the location of  $(p_0, q_0)$ . In this paper we only consider well-posed initial conditions.

### 3 The Maximum Principle and Optimal Controls

First-order necessary conditions for optimality of a control  $u$  for problem [OC] are given by the *Pontryagin Maximum Principle* [32, 6]: If  $u_*$  is an optimal control defined over an interval  $[0, T]$  with corresponding trajectory  $(p_*, q_*, y_*)^T$ , then there exist a constant  $\lambda_0 \geq 0$  and an absolutely continuous co-vector,  $\lambda : [0, T] \rightarrow (\mathbb{R}^3)^*$ , (which we write as row-vector) such that

(a)  $(\lambda_0, \lambda(t)) \neq (0, 0)$  for all  $t \in [0, T]$ ,

(b) the adjoint equations hold

$$\dot{\lambda}_1 = \xi \lambda_1 \left( \ln \left( \frac{p_*(t)}{q_*(t)} \right) + 1 \right) + \lambda_2 \left( \frac{2}{3} d \frac{q_*(t)}{p_*^{\frac{1}{3}}(t)} - b \right), \quad (11)$$

$$\dot{\lambda}_2 = -\xi \lambda_1 \frac{p_*(t)}{q_*(t)} + \lambda_2 \left( \mu + d p_*^{\frac{2}{3}}(t) + Gu \right), \quad (12)$$

$$\dot{\lambda}_3 = 0, \quad (13)$$

with transversality conditions

$$\lambda_1(T) = \lambda_0 \theta, \quad \lambda_2(T) = \lambda_0 (1 - \theta), \quad (14)$$

and

$$\lambda_3(T) = \begin{cases} 0 & \text{if } y(T) < A \\ \text{free} & \text{if } y(T) = A \end{cases} \quad (15)$$

and

(c) the optimal control  $u_*$  minimizes the Hamiltonian  $H$ ,

$$H = -\lambda_1 \xi p \ln \left( \frac{p}{q} \right) + \lambda_3 u + \lambda_2 \left( bp - \left( \mu + d p^{\frac{2}{3}} \right) q - Guq \right), \quad (16)$$

along  $(\lambda(t), p_*(t), q_*(t))$  over the control set  $[0, a]$  with minimum value given by 0.  $\square$

We call a pair  $((p, q, y), u)$  consisting of an admissible control  $u$  with corresponding trajectory  $(p, q, y)$  an *extremal* (pair) if there exist multipliers  $(\lambda_0, \lambda)$  such that the conditions of the Maximum Principle are satisfied and the triple  $((p, q, y), u, (\lambda_0, \lambda))$  is an extremal lift (to the cotangent bundle). Extremals with  $\lambda_0 = 0$  are called *abnormal* while those with a positive multiplier  $\lambda_0$  are called *normal*. In this case it is possible to normalize  $\lambda_0 = 1$ .

The following Lemmas summarize some elementary properties of optimal controls and extremals for well-posed initial conditions.

**Lemma 1** *Extremals are normal. The multipliers  $\lambda_1$  and  $\lambda_2$  cannot vanish simultaneously;  $\lambda_2$  has only simple zeroes. The multiplier  $\lambda_3$  is constant and non-negative.*

*Proof.* The multipliers  $\lambda_1$  and  $\lambda_2$  satisfy the homogeneous linear system (11) and (12) and thus they vanish identically if they vanish at some time  $t$ . This is equivalent to  $\lambda_0 = 0$ . In this case the nontriviality of  $(\lambda_0, \lambda(t))$  then implies that the multiplier  $\lambda_3$ , which is constant, is not zero. The condition  $H \equiv 0$  on the

Hamiltonian therefore gives  $u \equiv 0$ , i.e., the initial condition is ill-posed. Thus, without loss of generality we may assume that  $\lambda_0 = 1$  and hence  $\lambda_1$  and  $\lambda_2$  cannot vanish simultaneously. In particular, whenever  $\lambda_2(t) = 0$ , then  $\dot{\lambda}_2(t) \neq 0$  and thus  $\lambda_2$  has only simple zeroes.

Using

$$J_{\theta, u}(t) = \theta p(t) + (1 - \theta)q(t),$$

the condition  $H(T) = 0$  at the terminal time can be written in the form

$$\begin{aligned} H(T) &= -\theta \xi p \ln \left( \frac{p}{q} \right) + \lambda_3 u \\ &+ (1 - \theta) \left( bp - \left( \mu + d p^{\frac{2}{3}} \right) q - Guq \right) \\ &= \frac{dJ_{\theta}}{dt}(T) + \lambda_3 u = 0. \end{aligned} \quad (17)$$

Along an optimal solution the derivative  $\frac{dJ_{\theta}}{dt}(T)$  cannot be positive. For, if  $\frac{dJ_{\theta}}{dt}(T) > 0$ , then the function  $J_{\theta}(t)$  is strictly increasing over some interval  $[T - \varepsilon, T]$  and it would have been better to stop already at time  $T - \varepsilon$ . Hence we must have  $\lambda_3 u(T) \geq 0$ . For  $u(T) > 0$  this already implies  $\lambda_3 \geq 0$ . If  $u(T) = 0$ , then it follows from the minimization property (c) that  $\lambda_3 - \lambda_2(T)Gq_*(T) \geq 0$  and this also implies  $\lambda_3 \geq \lambda_2(T)Gq_*(T) = (1 - \theta)Gq_*(T) \geq 0$ .  $\square$

The function

$$\Phi(t) = \lambda_3 - \lambda_2(t)Gq_*(t), \quad (18)$$

determines the structure of the optimal control  $u_*$  through the minimization property (c) on the Hamiltonian  $H$  and is called the *switching function* of the problem. Optimal controls satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ a & \text{if } \Phi(t) < 0 \end{cases}. \quad (19)$$

A priori the control is not determined by the minimum condition at times when  $\Phi(t) = 0$ . If  $\Phi(\tau) = 0$ , but  $\dot{\Phi}(\tau) \neq 0$ , then the control switches between  $u = 0$  and  $u = a$  depending on the sign of  $\dot{\Phi}(\tau)$ . On the other hand, if  $\Phi(t)$  vanishes identically on an open interval, then the minimization property in itself gives no information about the control. However, in this case also all derivatives of  $\Phi(t)$  must vanish and this may and typically does determine the control. Controls of this kind are called *singular* [5] while we refer to the constant controls as *bang* controls. Optimal controls then need to be synthesized from these candidates through an analysis of the switching function and its derivatives. For example, we have

**Lemma 2** *If  $\lambda_3 = 0$ , then optimal controls are bang-bang with at most one switching.*

*Proof.* For  $\lambda_3 = 0$  the switching function can be re-defined to be  $\tilde{\Phi}(t) = \lambda_2(t)$  and the optimal control is given by  $u_*(t) = 0$  if  $\lambda_2(t) < 0$  and  $u_*(t) = a$  if  $\lambda_2(t) > 0$ . Since we have  $H \equiv 0$ , it follows that whenever  $\lambda_2(t) = 0$ , then we must have that  $p_*(t) = q_*(t)$ , i.e., switchings are only possible when the system state is on the diagonal  $p = q$ . The uncontrolled system ( $u = 0$ ) has a unique globally asymptotically stable equilibrium  $(\bar{p}, \bar{q})$  at the point

$$\bar{p} = \left( \frac{b - \mu}{d} \right)^{\frac{3}{2}} = \bar{q} \quad (20)$$

and the biologically relevant region is contained in the square domain

$$\mathcal{D} = \{(p, q) : 0 < p < \bar{p}, 0 < q < \bar{q}\}. \quad (21)$$

It is shown in [29] that this region is positively invariant and thus without loss of generality we may assume that our system lives in  $\mathcal{D}$ . A direct computation verifies that on the diagonal  $p = q$  the system dynamics points into  $p < q$  for  $u = 0$  and into  $p > q$  for  $u = a$ . This implies that there can be at most one switching since trajectories cannot return to the diagonal.  $\square$

The case  $\lambda_3 = 0$  also includes degenerate cases when optimal controls end with  $u = a$  and all available inhibitors have not been exhausted, i.e.,  $y_*(T) < A$ . This is possible when the function  $J_{\theta, u=a}(t)$  reaches a local minimum along the control  $u = a$  before all inhibitors have been exhausted. In this case the minimal value is realized at that time. These kind of degenerate situations no longer arise if the multiplier  $\lambda_3$  is positive.

**Lemma 3** *If  $\lambda_3 > 0$ , then all available inhibitors are exhausted along the corresponding trajectory, i.e.,  $y_*(T) = A$ .*

*Proof.* Suppose inhibitors are still available  $y_*(T) < A$ . If  $\lambda_3 u_*(T) > 0$ , then it follows from (17) that  $\frac{dJ_\theta}{dt}(T) < 0$ . But then the value of the objective could be lowered further by adding a small interval  $[T, T + \epsilon]$ . Similarly, if  $u_*(T) = 0$ , then also  $\frac{dJ_\theta}{dt}(T) = 0$  along the final segment  $u = 0$ . But then again switching to the control  $u = a$  on a sufficiently small interval  $[T, T + \epsilon]$  would turn  $\frac{dJ_\theta}{dt}(T)$  negative and thus again a lower value could be achieved.  $\square$

We henceforth always assume that  $\lambda_3 > 0$ .

## 4 Optimal Solution for the case $\theta = 1$

In earlier research [29] we gave a complete solution for the optimal control problem [OC] in form of a *synthesis* of optimal controls for the case when  $\theta = 1$ , i.e., the cancer volume  $J_1(u) = p(T)$  was minimized. A synthesis provides a full “road map” of how optimal protocols look like depending on the initial condition in the problem, both qualitatively and quantitatively. We briefly summarize the general structure of optimal trajectories for this case and then proceed to a precise description of the optimal controls.

**Theorem 1** [29] *Given a well-posed initial condition  $(p_0, q_0)$ , optimal controls are at most concatenations of the form  $\mathbf{0asa0}$  where  $\mathbf{0}$  denotes an interval along which the optimal control is given by a constant control  $u = 0$ , that is no inhibitors are given,  $\mathbf{a}$  denotes an interval along which the optimal control is given by the constant control  $u = a$  at full dose, and  $\mathbf{s}$  denotes an interval along which the optimal control follows a time-varying singular feedback control. This control is only optimal while the system follows a particular curve  $\mathcal{S}$  in the  $(p, q)$ -space, the optimal singular arc. Depending on the initial condition  $(p_0, q_0)$ , not all of these intervals need to be present in a specific solution. For the biologically most relevant initial conditions typically optimal controls have the form  $\mathbf{bs0}$  where  $\mathbf{b}$  stands for an interval along which the optimal control is given by either  $u = a$  or  $u = 0$  depending on the initial condition.*

Despite their name, which is related to some classical control literature from the sixties (e.g., [5, 6, 21]), singular controls and the corresponding singular curves are to be expected in a synthesis of optimal controls for a problem of the type [OC] for nonlinear models. The singular control and the geometry of the singular curve  $\mathcal{S}$  are an essential part of the design of the optimal protocol and in order to construct a full synthesis of solutions, the formulas for singular controls and corresponding singular trajectories given below are essential. A full derivation of these formulas is given in [29].

**Proposition 2** *Using a blow-up of the form  $x = \frac{p}{q}$  the singular curve  $\mathcal{S}$  can be parameterized in the form*

$$\mu + dp^{\frac{2}{3}} = bx(1 - \ln x) \quad (22)$$

with  $x \in (x_1^*, x_2^*)$  where  $x_1^*$  and  $x_2^*$  are the unique zeroes of the equation

$$\varphi(x) = \frac{b}{d}x(\ln x - 1) + \frac{\mu}{d} = 0 \quad (23)$$

and satisfy  $0 < x_1^* < 1 < x_2^* < e$ . The singular control keeps the system on the singular curve and is given as a feedback function of  $x$  in the form

$$u_{\text{sin}}(x) = \frac{1}{G} \left[ \left( \frac{1}{3}\xi + bx \right) \ln x + \frac{2}{3}\xi \left( 1 - \frac{\mu}{bx} \right) \right]. \quad (24)$$

There exists exactly one connected arc on the singular curve  $\mathcal{S}$  along which the singular control is admissible, i.e., satisfies the bounds  $0 \leq u_{\text{sin}}(x) \leq a$ . This arc is defined over an interval  $[x_\ell^*, x_u^*]$  where  $x_\ell^*$  and  $x_u^*$  are the unique solutions to the equations  $u_{\text{sin}}(x_\ell^*) = 0$  and  $u_{\text{sin}}(x_u^*) = a$  and these values satisfy  $x_1^* < x_\ell^* < 1 < x_u^* < x_2^*$ .

The two graphs given in Fig. 1 and in Fig. 2 illustrate the proposition for the following parameter values taken from [16]: The variables  $p$  and  $q$  are volumes measured in  $mm^3$ ;  $\xi = \frac{0.192}{\ln 10} = 0.084$  per day (adjusted to the natural logarithm),  $b = 5.85$  per day,  $d = 0.00873$  per  $mm^2$  per day,  $G = 0.15$  kg per mg of dose per day, and for illustrative purposes we chose a small positive value for  $\mu$ ,  $\mu = 0.02$  per day. For the control limits we have taken  $a = 75$  and  $A = 300$ . Fig. 1 shows the plot for the singular control defined by (24) also indicating the values  $x_\ell^*$  and  $x_u^*$  where the control saturates at  $u_{\text{sin}}(x) = 0$  and  $u_{\text{sin}}(x) = a$ . Fig. 2 shows the graph of the singular curve given by formula (22). In all our figures we plot  $p$  vertically and  $q$  horizontally since this easier visualizes tumor reductions. Saturation of the singular control at  $x_\ell^*$  and  $x_u^*$  restricts the admissible part of this petal-like curve to the portion lying between the lines  $p = x_\ell^*q$  and  $p = x_u^*q$ . This portion is marked with a solid line in Fig. 2. The qualitative structures shown in these figures are generally valid for arbitrary parameter values, both for the control and the singular curve. Only with decreasing values for the upper control limit  $a$  the admissible portion shrinks until it disappears for  $a = 0$ .

The admissible singular arc becomes the essential piece for the synthesis of optimal solutions that is depicted in Fig. 3. The important curves for the synthesis are the admissible portions of the singular curve (solid blue curve), portions of trajectories corresponding to the constant controls  $u = 0$  (dash-dotted green curves) and  $u = a$  (solid green curves), and the line  $p = q$  (dotted black line) where the trajectories achieve the maximum tumor reduction. These diagrams represent 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 lines in the graphs mark one specific such trajectory. In each case the initial value  $p_0$  for the tumor volume and  $q_0$  for the endothelial support are high and require to immediately start with

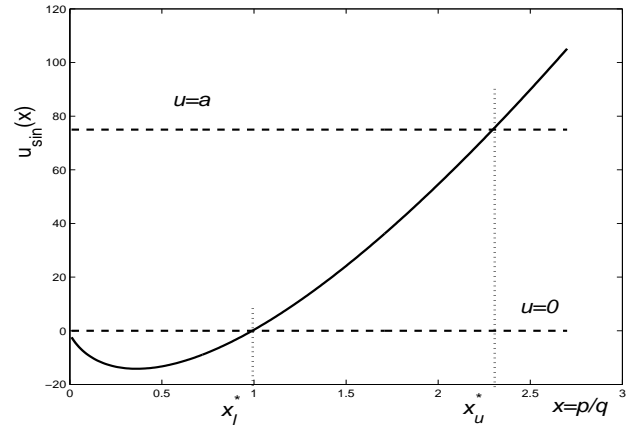


Figure 1: Singular control

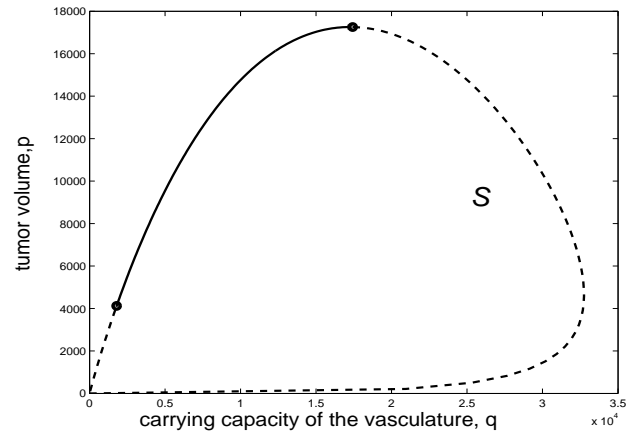


Figure 2: Admissible singular arc

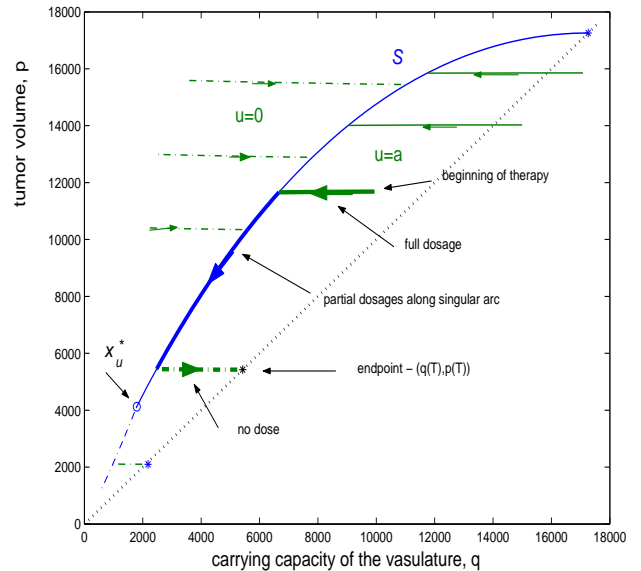


Figure 3: Synthesis of optimal trajectories for  $\theta = 1$

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. 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 and the optimal trajectory follows the singular arc until all inhibitors are exhausted according to the condition that  $y(T) = A$ . When the inhibitors have been exhausted, therapy is over, but due to after effects the maximum tumor reduction is only realized as the trajectory for the control  $u = 0$  crosses the diagonal  $p = q$ . The corresponding time  $T$  then is the limit of the horizon 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 control until saturation, but in fact optimal trajectories leave the singular with the control  $u = a$  prior to the saturation point. Simply continuing the control with  $u = a$  is not optimal [29].

Figs. 4 and 5 give an example of the optimal control and its corresponding trajectory for the initial conditions  $(p_0, q_0) = (12,000 \text{ mm}^3; 15,000 \text{ mm}^3)$ . For this example the concatenation sequence is **as0**: first the optimal control is given at full dosage  $u = a = 75$  until the singular curve  $\mathcal{S}$  is reached at time  $t_1 = 0.09$  days. Then administration follows the time-varying singular control until inhibitors are exhausted at time  $t_2 = 6.56$  days. Due to after effects the maximum tumor reduction is realized along a trajectory for control  $u = 0$  at the optimal terminal time  $T = 6.73$  days when the trajectory reaches the diagonal  $p = q$ .

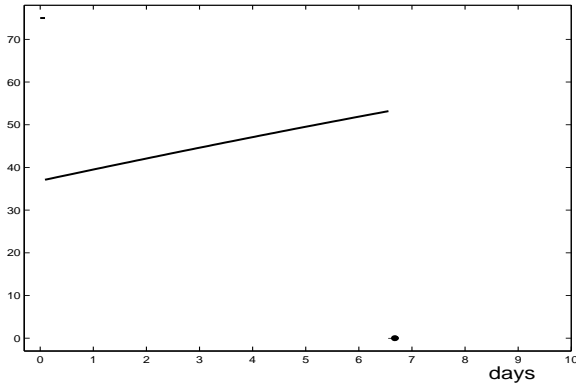


Figure 4: Optimal control for  $(p_0, q_0) = (12,000 \text{ mm}^3; 15,000 \text{ mm}^3)$

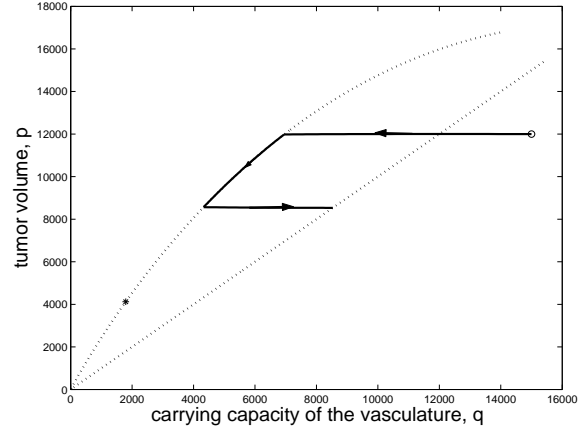


Figure 5: Optimal trajectory for  $(p_0, q_0) = (12,000 \text{ mm}^3; 15,000 \text{ mm}^3)$

## 5 Optimal Solution for the case $\theta < 1$

In the case  $\theta < 1$  many qualitative features of the solution for the case  $\theta = 1$  are retained. Clearly, all the vector fields defining the dynamics are unchanged and thus all the calculations of singular arcs and singular controls from [29] remain valid and as before the singular arc  $\mathcal{S}$  defined in (22) is the center piece of the synthesis. However, the change in the objective enters into the terminal conditions for the multipliers  $\lambda_1$  and  $\lambda_2$  and this effects the terminal portion of optimal trajectories.

As before, let

$$J_{\theta,u}(t) = \theta p(t) + (1 - \theta)q(t) \quad (25)$$

and for the moment assume that the optimal control ends with  $u = 0$ . In this case the necessary condition  $H = 0$  implies that

$$\begin{aligned} \frac{dJ_{\theta,u}}{dt}(T) &= -\theta\xi p \ln\left(\frac{p}{q}\right) \\ &+ (1 - \theta) \left( bp - \left( \mu + dp^{\frac{2}{3}} \right) q \right) = 0 \end{aligned}$$

and thus the optimal time  $T_\theta$  is determined by the fact that the corresponding trajectory reaches the curve  $\mathcal{T}_\theta$  given in the variables  $p$  and  $x = \frac{p}{q}$  by

$$\mu + dp^{\frac{2}{3}} = bx - \frac{\theta}{1 - \theta} \xi x \ln x. \quad (26)$$

Note that this curve is identical with the singular arc  $\mathcal{S}$  for

$$\theta_* = \frac{b}{b + \xi} \quad (27)$$

(see (22)). Fig. 6 shows the geometry of the curves  $\mathcal{T}_\theta$  for various values of  $\theta$  and the parameter values specified earlier.

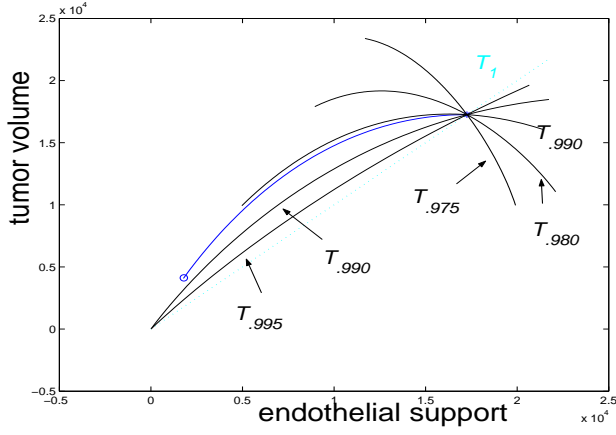


Figure 6: Terminal curves  $T_\theta$

For  $\theta > \theta_*$  the curve  $T_\theta$  lies in the region between the singular curve  $\mathcal{S}$  and the diagonal  $p = q$  and in this case the optimal synthesis is virtually identical to the one for the case  $\theta = 1$ . Optimal trajectories end with a piece along the control  $u = 0$  and the minimum of the objective is realized when this trajectory reaches the curve  $T_\theta$ . Note that the curve  $T_1$  precisely is the diagonal  $p = q$ , the terminal curve for the case  $\theta = 1$ .

A special case arises for  $\theta = \theta_*$ . In this case the terminal curve  $T_{\theta_*}$  agrees with the singular arc and the terminal time is given by the time when inhibitors run out along the singular arc. (Recall that we are assuming that no saturation occurs prior to this time.) Hence optimal controls are of the type **bs**. For the numerical values given earlier this value is  $\theta_* = 0.9858$ , very close to 1.

For  $\theta < \theta_*$  the concatenation sequence of optimal trajectories changes at the end. In this case the curve  $T_\theta$  lies above the singular curve  $\mathcal{S}$  in Fig. 6 (that is, in the region where  $\mu + dp^{\frac{2}{3}} > bx(1 - \ln x)$ ) and this curve no longer is reachable from the singular arc by means of the constant control  $u = 0$ . Hence the condition  $H = 0$  of the Maximum principle together with the requirement that all inhibitors need to be exhausted, now forces optimal controls to leave the singular arc before this happens. All the other arguments in [29] regarding the concatenation structure of optimal trajectories remain valid. It is still possible that optimal controls are concatenations of the type **bsa0**, but in this sequence the last leg for  $u = 0$  is only present if the second trajectory for  $u = a$  is able to steer the system above the terminal curve  $T_\theta$ . In this case a last piece for  $u = 0$  is added when all inhibitors run out to again come down to the curve  $T_\theta$ . More typically, now the optimal time  $T_\theta$  simply is the time when all inhibitors become exhausted along the  $u = a$  trajectory. When this happens before the curve  $T_\theta$  is

reached, then it is no longer optimal to add another leg for  $u = 0$  and the minimum is realized at the time when all inhibitors are exhausted, that is, the optimal concatenation sequence is of the form **bsa**. This holds for all our numerical illustrations below.

Knowing the concatenation sequence of optimal controls a priori (based on our theoretical analysis) allows to set up a straightforward numerical 1-dimensional minimization procedure by using the time  $\tau$  when the system leaves the singular arc as a parameter and minimizing over the corresponding value of the objective. The diagrams below give the numerical solutions for the initial conditions

$$(p_0, q_0) = (12,000 \text{ mm}^3; 15,000 \text{ mm}^3),$$

the same one as used above for  $\theta = 1$ , and for the parameter values  $\theta = 0.95, 0.85$  and  $0.75$ . The time it takes for the optimal trajectory to reach the singular arc is the same for each computation and is given by  $t_1 = 0.0905$  (days). Then  $\tau$  denotes the time spent along the singular arc starting with 0 and this is the parameter in the one-dimensional minimization. Thus with  $\hat{\tau}$  denoting the optimal parameter value, the overall time when the trajectory leaves the singular arc is given by  $t_{sin}^* = t_1 + \hat{\tau}$ .

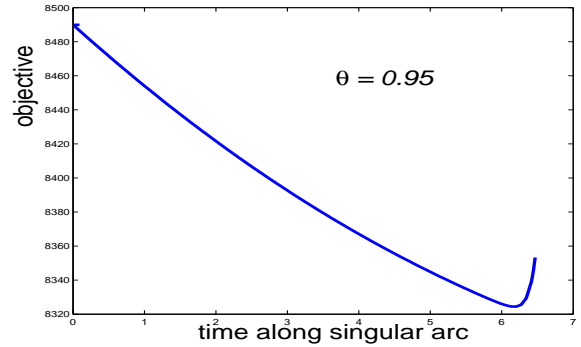


Figure 7: Objective  $J_{0.95}(\tau)$

Fig. 7 gives the graph of the objective as a function of the minimization parameter  $\tau$  for  $\theta = 0.95$ . In this case the optimal parameter is given by  $\hat{\tau}_{0.95} = 6.1775$  and thus the optimal time to leave the singular arc is  $t_{0.95}^* = 6.2680$ ; the overall optimal time  $T_{0.95}$  is  $T_{0.95} = 6.4794$  and the minimum value of the objective is given by  $J_{0.95} = 8324.4$ . The corresponding controls and trajectories are shown in Fig. 10.

As the value of  $\theta$  is decreased, the optimal time  $\tau$  to leave the singular arc becomes shorter and the time along the last  $u = a$  leg increases. For  $\theta = 0.85$  we have  $\hat{\tau}_{0.85} = 6.0375$  and the optimal time to leave the singular arc is given by  $t_{0.85}^* = 6.1280$ ; the minimum value is  $J_{0.85} = 7805.9$ . For  $\theta = 0.75$  these values are



given by  $\hat{\tau}_{0.75} = 5.9775$ ,  $t_{0.75}^* = 6.0680$  and  $J_{0.85} = 7286.1$ . Figs. 8 and 9 show the objective for the values  $\theta = 0.85$  and  $\theta = 0.75$ .

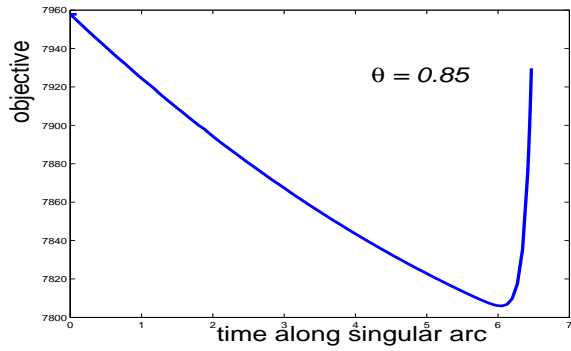


Figure 8: Objective  $J_{0.85}(\tau)$

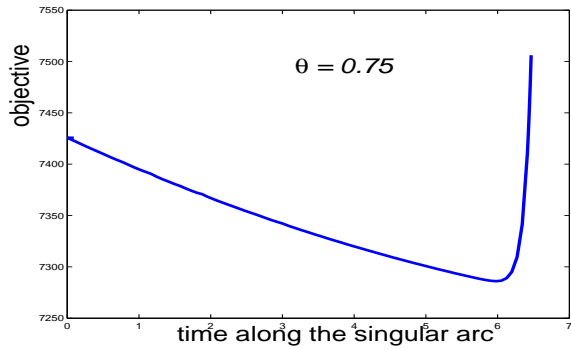


Figure 9: Objective  $J_{0.75}(\tau)$

The changes in the optimal times are very small and the corresponding optimal controls and trajectories which are given in Figs. 10 - 12 are very close to each other. As these diagrams show, the significant change in the structure of optimal controls and their corresponding trajectories occurs as the parameter  $\theta$  in the objective crosses the bifurcation value  $\theta_*$ , but as  $\theta$  is decreased further the changes are quantitatively small and do not lead to substantial changes in the optimal protocols.

## 6 Conclusion

In this paper we showed how the structure of optimal solutions changes for a problem for tumor anti-angiogenesis when the level of endothelial support is included in the objective at the terminal time. While optimal controls always end with a segment along the control  $u = 0$  if  $\theta > \theta_*$  when a high weight is assigned to the tumor volume, for  $\theta < \theta_*$  optimal controls end with a segment along the full dose control

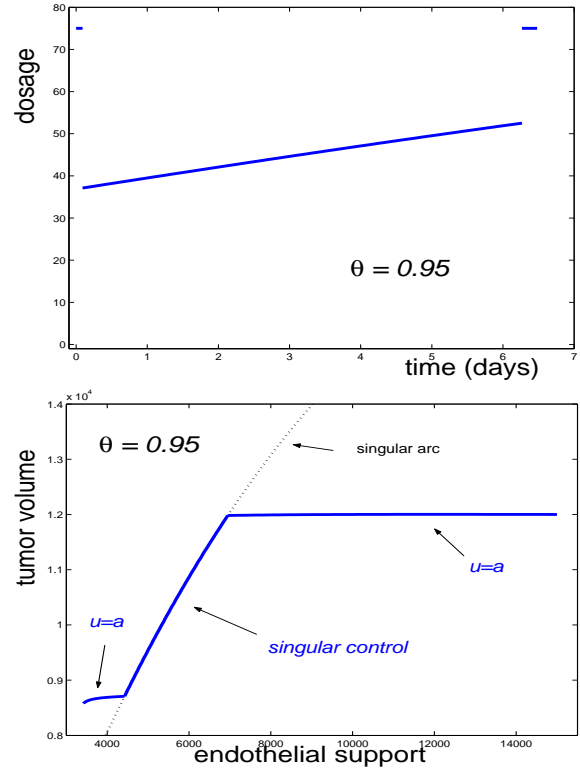


Figure 10: Optimal control and corresponding trajectory for  $\theta = 0.95$

$u = a$  as all inhibitors are exhausted. Modulo the bifurcation in the optimal controls and trajectories for the parameter value  $\theta_*$  the structure of the synthesis is fully robust and stable under variations of other parameters in the system.

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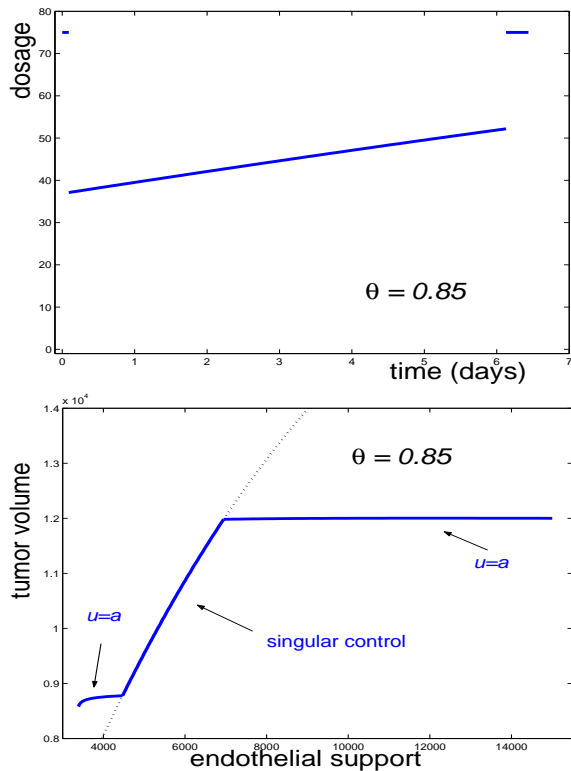


Figure 11: Optimal control and corresponding trajectory for  $\theta = 0.85$

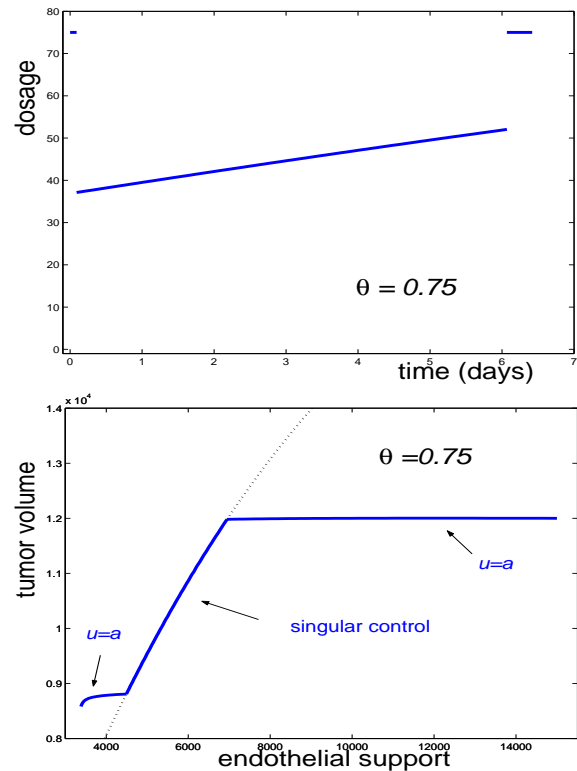


Figure 12: Optimal control and corresponding trajectory for  $\theta = 0.75$

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