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Optimal Control for a System Modelling Tumor Anti-Angiogenesis

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Abstract

The scheduling of angiogenic inhibitors to control a vascularized tumor is analyzed as an optimal control problem. For the underlying dynamics the model by Ergun, Camphausen and Wein [3], which is an approximation and simplification of the more complex model developed by Hahnfeldt et al. [4], is taken. Two formulations of the problem are considered. In the first model optimal controls minimize the tumor volume for a given amount of angiogenic inhibitors to be administered while the second formulation tries to achieve a balance between tumor reduction and total amount of angiogenic inhibitors given. For both models a full synthesis of optimal solutions is presented and the differences in the two solutions are discussed.
Keywords: *Optimal control, bang-bang and singular controls, cancer treatments, angiogenic inhibitors.*

1 Introduction

One aspect that severely limits the effectiveness of chemotherapy in cancer treatments is drug resistance. Different from normal cells, cancer cells are genetically highly unstable and thus quite diversified in their structure. As a consequence, some cancer cells are simply not affected by current drugs (intrinsic drug resistance) while others easily generate resistant mutations (acquired drug resistance). As a result, even if chemotherapy shows success initially, only all too often cancer comes back in a resistant form. Hence there is a strong interest in alternate treatments that would not be prone to drug resistance. Anti-angiogenesis, a treatment approach that has been pursued in the U.S. in laboratory experiments since the mid-nineties and is now in clinical trials, is a mechanism that offers such a hope for the treatment of tumor cancers.

A tumor, after it grows to just a few millimeters in diameter, no longer can rely on blood vessels of the host for its supply of nutrients and oxygen, but must develop its own system of capillaries. In this process, called *angiogenesis*, an important role is played by endothelial cells which provide the lining for the newly forming blood vessels of the tumor. Angiogenic inhibitors, like endostatin, target those cells preventing the tumor from developing its own blood vessel system and thus blocking its growth. The tumor, deprived of necessary nutrition, regresses. Since the treatment targets normal cells, no occurrence of drug resistance has been reported in lab studies. For this reason tumor anti-angiogenesis has been called a therapy "resistant to resistance" that provides a new hope in treatment of tumor type cancers [6].

Tumor angiogenesis and its inhibitors have been studied extensively since the mid nineties. Although the process in itself is spatial, and thus properly described by partial differential equations, also low-order approximations in terms of ordinary differential equations that are easier to analyze have been developed. One of the earliest mathematical models of this type that has been medically validated was formulated by Hahnfeldt et al. in [4]. In this model, the volume of primary tumor cells, p, and the volume of the vascular endothelial cells, e, are distinguished and their interactive growth is modelled in the dynamics. An analysis of dynamic properties of this model and some extensions has been given by d'Onofrio and Gandolfi in [2]. The model in [4] also was modified and mathematically simplified by Ergun, Camphausen and Wein [3]. In their model, based on an approximation of the spatial analysis in [4], the angiogenic inhibitor is taken proportional to the tumor radius, not the tumor surface (see [3] for details on the justification of their equations and the relations between the two models).

Introducing an objective that minimizes the primary tumor volume for a given total amount of an-

giogenic inhibitors, Ergun, Camphausen and Wein [3] analyzed the problem of optimal scheduling of anti-angiogenic therapy within an optimal control framework. However, their analysis still left several questions open and a complete solution to the problem was given by us in [5]. It is shown there that optimal controls are concatenations of at most five pieces of the form *0asa0* where *0* denotes an interval when no inhibitors are administered, a denotes an interval when inhibitors are given at a maximum dose a, and s denotes an interval where the optimal control is singular and takes values strictly between 0 and the maximum value a. (Depending on the specific initial condition, not all of these pieces need to be present.) Since the total amount of angiogenic inhibitors is taken as a constraint in this formulation, it is intuitively clear (and easily verified analytically) that optimal controls will use up the full amount. Consequently, even if there is only a small reduction in tumor size to be gained, if inhibitors are still available, they will be used regardless of cost and side effects. In this paper, we therefore consider the problem with a different objective which is designed to avoid such a situation, but balances the total amount of inhibitors given with the benefit to be gained in tumor reduction. Rather than specifying the total amount of inhibitors a priori, we incorporate it in the objective and then minimize a weighted average between the inhibitors given over the therapy interval and the tumor volume at the end of the therapy. Clearly, other kind of objectives can be considered as well, and they all may lead to both qualitatively and quantitatively different results. As we shall show here, this model still preserves the qualitative structure of solutions in the form *0asa0*, but it differs in its quantitative aspects.

We briefly review the underlying mathematical model and the results from [5] in section 2 and then consider the model with the new objective in section 3.

2 Anti-Angiogenic Therapy: Model I

In this model [3, 5] the spatial aspects of the underlying diffusion that stimulate and inhibit angiogenesis are incorporated into a non-spatial two-compartment model for cancer cells and vascular endothelial cells. Let p denote the volume of primary tumor cells and let e denote the volume of the vascular endothelial cells. It is assumed that the tumor growth is Gompertzian with a variable carrying capacity. This results in the following equation for the rate of change in the volume of primary tumor cells,

$$\dot{p} = -\xi p \ln(\frac{p}{e}), \tag{1}$$

with ξ denoting a tumor growth parameter. The equation modelling the rate of change in the volume of vascular endothelial cells is taken in the form

$$\dot{e} = be^{\frac{2}{3}} - de^{\frac{4}{3}} - Gue, \tag{2}$$

where b (birth) and d (death) are endothelial stimulation and inhibition parameters, respectively. (In comparison with [4], Ergun, Camphausen and Wein simplify this dynamics by formulating it entirely in e and they choose the exponent $\frac{2}{3}$ based on a good approximation of the functional form to actual data. Essentially, it is the interplay of the three-dimensional tumor volume with the endothelial cells which are active on the two-dimensional surface area which causes the exponents to be related by $\frac{2}{3}$ [4].) The variable u represents the control in the system and corresponds to the angiogenic dose rate; G is a constant that represents the anti-angiogenic killing parameter.

Ergun, Camphausen and Wein then consider the following optimal control problem: for a free terminal time T, minimize the value $p(T)$ subject to the dynamics (1) and (2) over all Lebesgue measurable functions $u : [0, T] \to [0, \infty)$ which satisfy a constraint of the form

$$\int_0^T u(t)dt \leq A. \tag{3}$$

For the case $d = 0$ it is shown in [3] that optimal controls generally follow a three part regimen starting with a large initial dose, then a phase of drug intensification where the system follows a specific trajectory (a so-called singular arc), and a terminal phase when the system leaves this singular arc. However, the details of the initial and final stage of the regimen are left open in the analysis [3, pg. 415]. In [5] we have modified the problem slightly by adding an upper bound on the maximum dose, $0 \leq u \leq a < \infty$. Since the dynamics is linear in the control with the control set a compact interval, it follows from the Maximum Principle [7] that the prime candidates for optimal controls are the constant controls $u = 0$ and $u = a$ given by the limits of the control set. We call these the *bang* controls. However, also special controls which take values in the interior of the control set, so-called *singular* controls, are possible (see section 3 below). For this problem such a control indeed exists and is optimal. The optimal solution then needs to be synthesized from these bang and singular controls. In short, in [5] we have shown that the most general structure of optimal controls is of the form **0asa0** denoting a concatenation of a trajectory with no anti-angiogenic therapy followed by a period of maximum rate therapy until a singular arc is reached. Along the singular arc a specific varying dose at less than maximum is given. This is followed at the end by possibly another period of maximum dose therapy before therapy is terminated. Anti-angiogenic treatment stops when equality holds in (3), i.e. when the allowable total amount of anti-angiogenic treatment is reached. However, due to after effects that still reduce the tumor size, there will always be a final interval with

$u = 0$, and the maximum tumor reduction is reached at time T when $p(T) = e(T)$.

As these results will be relevant for our second problem formulation, we briefly review them [5]. Note that equation (2) for the rate of change in the volume of vascular endothelial cells is not Lipschitz at $e = 0$ and indeed has multiple solutions. For a mathematical analysis it is preferable to eliminate the biologically irrelevant trivial solution $e \equiv 0$ and to work with a smooth dynamical system instead. We therefore change the variable from e to x defined by $e = x^3$. This results in the following equivalent optimal control problem:

(P1) For a free terminal time T, minimize

$$J_1(u) = p(T) \tag{4}$$

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

$$\dot{p} = -\xi p \ln(\frac{p}{x^3}), \qquad p(0) = p_0, \tag{5}$$

$$\dot{x} = \frac{1}{3}\left(b - dx^2 - Gux\right), \qquad x(0) = x_0, \tag{6}$$

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

and the terminal condition

$$y(T) = A. \tag{8}$$

It is clear that for any control u the strip $\{x \in \mathbb{R} : 0 < x < \sqrt{\frac{b}{d}}\}$ is positively invariant, i.e. if the initial condition x_0 lies in $(0, \sqrt{\frac{b}{d}})$, then the solution exists for all times $t \geq 0$ and lies in $(0, \sqrt{\frac{b}{d}})$, and that the state p remains positive. However, this region is too large as set of meaningful initial conditions and it allows for some degenerate optimal solutions which we simply prefer to exclude altogether. The system Σ_a corresponding to the control $u \equiv a$ has an asymptotically stable node at $(p_a, x_a) = (\bar{x}^3, \bar{x})$ where

$$\bar{x} = \frac{-Ga + \sqrt{G^2a^2 + 4bd}}{2d}, \tag{9}$$

and for $u \equiv 0$ the corresponding system Σ_0 has an asymptotically stable node at $(p_0, x_0) = (\frac{b}{d}\sqrt{\frac{b}{d}}, \sqrt{\frac{b}{d}})$ (see [5]). Initial conditions x_0 which lie below $\bar{x}$ given by (9) are not meaningful medically [3] and therefore we also restrict the initial data to lie in the set

$$D = \{(p, x) : \bar{x} \leq x \leq \sqrt{\frac{b}{d}}, p > 0\}. \tag{10}$$

Analyzing the phase portraits of the systems Σ_0 and Σ_a, it follows that this set also is positively invariant under any admissible control, i.e. if the initial condition (p_0, x_0) lies in D, then for any admissible control the solution $(p(t), x(t))$ exists for all times $t > 0$ and lies in D. The following results are proven in [5]:

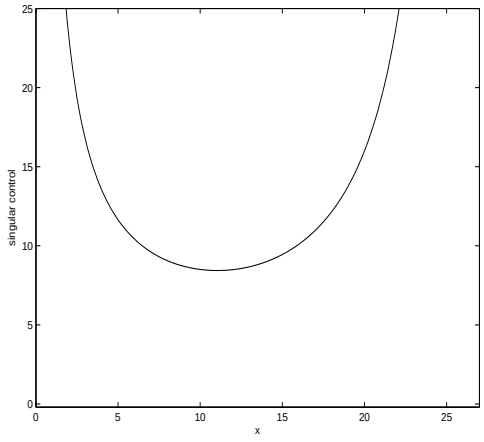

Figure 1: Singular control $u_{\sin}$

Proposition 2.1 *[5] For problem (P1) there exists a locally minimizing singular arc S defined in (p, x)-space by*

$$p = p(x) = x^3 \exp\left(3\frac{b - dx^2}{b + dx^2}\right) \tag{11}$$

for $x_\ell^* \leq x \leq x_u^*$. The corresponding singular control is given in feedback form as

$$u_{\sin}(x) = \psi(x) = \frac{1}{G}\left(\frac{b - dx^2}{x} + 3\xi\frac{b + dx^2}{b - dx^2}\right). \tag{12}$$

The function $u_{\sin}$ is strictly convex and the values x_ℓ^* and x_u^*, $x_\ell^* < x_u^*$, are the unique points where the singular control saturates at the upper control limit, i.e. the solutions to the equation $\psi(x) = a$ in $(0, \sqrt{\frac{b}{d}})$.

We illustrate the graph of $u_{\sin}$ in Fig. 1. This singular arc becomes the center piece for a synthesis of optimal controls. However, since the singular arc saturates we need to extend it using the trajectories for control $u \equiv a$. Let S_- denote the integral curve of Σ_a through the upper saturation point (p_u^*, x_u^*) of the singular arc for $t \leq 0$ until the value $x = \sqrt{\frac{b}{d}}$ is reached and let S_+ denote the integral curve of Σ_a through the lower saturation point (p_ℓ^*, x_ℓ^*) for $t \geq 0$. This trajectory reaches the equilibrium $(p_a, x_a) = (\bar{x}^3, \bar{x})$ asymptotically as $t \to \infty$. Then denote the curve which corresponds to a concatenation of S_- with the admissible singular arc S and then with S_+ by $\mathcal{S}$. Note that, over a finite interval, the curve $\mathcal{S}$ is an admissible trajectory for the problem $(P1)$ as long as the constraint $\int_0^t y(s)ds \leq A$ will not be violated. Once an optimal trajectory meets $\mathcal{S}$, it can be shown that it follows this curve until the full amount A of drug is exhausted. The curve $\mathcal{S}$ divides the region D into a connected region D_0 which lies above $\mathcal{S}$ and another region D_a which lies below $\mathcal{S}$. Combining the phase-portraits of the flows Σ_0 and Σ_a with our results on optimal controls we get the following characterizations of optimal controls:

Theorem 2.1 *[5] For an initial condition $(p_0, x_0) \in D_0$ the optimal control at the beginning takes the value $u \equiv 0$ on an interval $[0, \tau_1]$ and τ_1 is the unique time when the integral curve of Σ_0 starting at (p_0, x_0) intersects the curve $\mathcal{S}$. Then the optimal trajectory follows the curve $\mathcal{S}$ for an interval $(\tau_1, \tau_4]$ where τ_4 is the unique time when $y(\tau_4) = A$. Depending on the value of A and whether the initial portion of the trajectory intersects $\mathcal{S}$ at time τ_1 in the section S_-, S, or S_+, there exist times τ_2 and τ_3, $\tau_1 \leq \tau_2 < \tau_3 \leq \tau_4$, such that $u \equiv a$ on $(\tau_1, \tau_2]$ and $(\tau_3, \tau_4]$ and u is given by the singular control $u_{\sin}$ on $(\tau_2, \tau_3]$. (Not all pieces need to be present.) Then the optimal control still is $u \equiv 0$ on a final interval $(\tau_4, T]$ and the optimal terminal time T is the unique time when the terminal portion of the trajectory satisfies $p(T) = x^3(T) = e(T)$.*

Theorem 2.2 *[5] For an initial condition $(p_0, x_0) \in D_a$ the optimal control immediately takes the value $u \equiv a$ on some interval $[0, \tau_2]$. It will only switch if the singular arc S is reached before the overall amount of drug is exhausted i.e. $y(\tau_2) < A$. In this case, the optimal trajectory then follows $\mathcal{S}$ over an interval $(\tau_2, \tau_4]$ until $y(\tau_4) = A$ (possibly including an interval $(\tau_3, \tau_4]$ along S_+). The final portion is characterized as in Theorem 2.1. Degenerate subcases arise if $y(\tau) = A$ occurs on the initial portion before $\mathcal{S}$ is reached. In this case, depending on whether $p(\tau) > x^3(\tau)$ or $p(\tau) \leq x^3(\tau)$, either a terminal portion $[\tau, T]$ with $u \equiv 0$ and T described as above is added, or the trajectory simply terminates at $T = \tau$.*

Our analysis is independent of the specific parameter values in the dynamics and the qualitative structure of optimal solutions is robust. For our simulations below we use the following numerical values that are based on [4] and are taken from [3, Table 1]: $\xi = \frac{0.192}{\ln 10} = 0.084$ per day (adjusted for the natural logarithm), $b = 5.85$ mm per day, $d = 0.00873$ per mm per day, $G = 0.15$ per concentration (mg per kg) of dose. Examples of projections of optimal trajectories in (p, x)-space for these values are given in Fig. 2. The function $p = p(x)$ describing the singular curve is strictly increasing for $x \geq 0$ with a stationary point for $x = \sqrt{\frac{b}{d}}$, which for the data above is given by 25.8863. Using $a = 15$ we have $x_\ell^* = 2.9005$ and $x_u^* = 23.0704$, so that the admissible piece of the singular arc almost connects with the lower equilibrium $(p_a, x_a) = (\bar{x}^3, \bar{x})$. The admissible singular arc is shown as a curve with small circles indicating its initial and end points where saturation occurs at $u = a$. Integral curves for $u \equiv a$ entering the singular arc are shown as 'dash-dot' lines on the right hand side and integral curves for $u \equiv 0$ are shown as 'dash-dash' lines both on the left side entering the singular arc and on the bottom portion of the right side leaving the singular arc. We identify by a 'star' end points of optimal trajectories which occur on the curve $p = x^3 = e$.

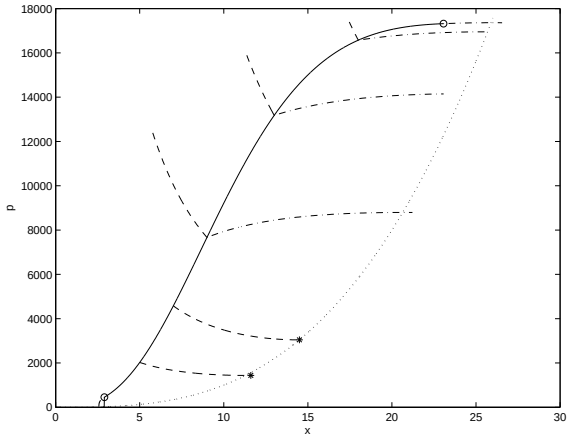

Figure 2: Synthesis of optimal controls for problem (P1)

3 Anti-Angiogenic Therapy: Model II

The objective chosen in problem (P1) does not penalize usage of angiogenic inhibitors and thus optimal solutions exhaust the available drugs regardless of incremental benefits. We now consider a modification of Model I where we do not restrict the total amount of anti-angiogenic treatment a priori, but rather try to balance this amount with a reduction in tumor size over time. Mathematically, we now formulate the problem as follows:

(P2) For a free terminal time T, minimize

$$J_2(u) = p(T) + k \int_0^T u(t)dt \tag{13}$$

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

$$\dot{p} = -\xi p \ln(\frac{p}{x^3}), \qquad p(0) = p_0, \tag{14}$$

$$\dot{x} = \frac{1}{3}\left(b - dx^2 - Gux\right), \qquad x(0) = x_0. \tag{15}$$

In the objective, as in model I, the term $\int_0^T u(t)dt$ represents the total amount of anti-angiogenic treatment administered. But this term can also be viewed as a measure of possible side effects or cost of the treatment. In this formulation we thus attempt to keep a balance between cost or side-effects and effectiveness of the treatment by adding this integral with a positive weight, $k > 0$, to the overall criterion to be minimized. This balance between tumor reduction and side-effects can be fine-tuned through the parameter k.

We first show that the qualitative structure of solutions does not change, i.e. optimal controls for problem (P2) still follow the regimen **0asa0**, but the conditions for termination of anti-angiogenic treatment will de different.

First-order necessary conditions for optimality of a control u are given by the *Pontryagin Maximum Principle* [7, 1]. It is easily seen that the problem is normal and thus these conditions can be formulated as follows: if u_* is an optimal control defined over the interval $[0,T]$ with corresponding trajectory (p_*, x_*), then there exists an absolutely continuous co-vector, $\lambda : [0,T] \to (\mathbb{R}^2)^*$, (which we write as row-vector) that satisfies the adjoint equations with transversality condition,

$$\dot{\lambda}_1 = \xi\lambda_1 \left(\ln\left(\frac{p_*(t)}{x_*^3(t)}\right) + 1 \right), \qquad \lambda_1(T) = 1, \quad (16)$$

$$\dot{\lambda}_2 = -3\xi\lambda_1 \frac{p_*(t)}{x_*(t)} + \frac{1}{3}\lambda_2(2dx_*(t) + Gu_*(t)), \quad (17)$$

$$\lambda_2(T) = 0,$$

such that along $(\lambda(t), p_*(t), x_*(t))$ the optimal control u_* minimizes the Hamiltonian H,

$$H = ku - \lambda_1\xi p \ln\left(\frac{p}{x^3}\right) + \frac{1}{3}\lambda_2\left(b - dx^2 - Gux\right), \quad (18)$$

over the control set $[0,a]$ with the minimum value given by 0.

We call a pair $((p,x),u)$ consisting of an admissible control u with corresponding trajectory (p,x) for which there exist a multiplier λ such that the conditions of the Maximum Principle are satisfied an *extremal* (pair) and the triple $((p,x),u,\lambda)$ is an extremal lift (to the cotangent bundle). The adjoint equations are the same as in [5] and thus it follows from those results that the multiplier λ_1 is positive on the closed interval $[0,T]$, while λ_2 is positive on $[0,T)$.

The minimization condition on the Hamiltonian H is equivalent to minimizing the linear function

$$\left(k - \frac{1}{3}\lambda_2(t)Gx_*(t)\right)v \quad (19)$$

over $v \in [0,a]$. Thus, if we define the so-called *switching function* Φ as

$$\Phi(t) = k - \frac{1}{3}\lambda_2(t)Gx_*(t), \quad (20)$$

then optimal controls satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ a & \text{if } \Phi(t) < 0 \end{cases}, \quad (21)$$

leading to the bang controls as prime candidates for optimality. A priori the control is not determined by the minimum condition 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 may determine the control. These are precisely the so-called *singular* controls already mentioned above. Optimal controls then need to be synthesized from these candidates through an analysis of the switching function. This analysis is identical to the computations done in [5] for problem $(P1)$. The reason is that the extra multiplier λ_3 associated with the constraint on y is constant and in essence the two problems (P1) and (P2) are compatible. Hence, with some minor modification in the actual computation of the singular curve, these results all carry over. Thus *the singular curve and its admissible portion are given as in Proposition 2.1.* The differences in the optimal solutions lie in how long controls stay on this singular arc. We now analyze this structure of optimal controls.

Lemma 3.1 *Optimal controls end with an interval $[\tau,T]$ where the optimal control is given by $u_*(T) \equiv 0$. The optimal final time T is the unique time when the corresponding trajectory satisfies the relation*

$$p_*(T) = x_*^3(T) = e_*(T). \quad (22)$$

Proof. These are simple consequences of the conditions of the Maximum Principle. Since $\Phi(T) = k > 0$, optimal controls u_* end with an interval $[\tau,T]$ where $u_*(T) \equiv 0$. Hence the transversality condition $H(T) = 0$, in conjunction with $\lambda_1(T) = 1$ and $\lambda_2(T) = 0$, implies that $p_*(T) = x_*^3(T) = e_*(T)$. $\square$.

While it is now no longer possible to determine the optimal time τ_* analytically, there is a straightforward way to compute it by introducing τ as a parameter and then minimize the resulting parameterized objective: Given an initial condition (p_0, x_0), let $\bar{\gamma} = (\bar{p}, \bar{x}) : [0,\infty) \to \mathbb{R}^2_+$ denote the trajectory of the system which follows the control strategy $0asa$. Specifically, depending on in which region D_0 or D_a of Theorems 2.1 or 2.2 the initial condition (p_0, x_0) lies, the corresponding control $\bar{u}$ starts with either $u = 0$ or $u = a$ and follows the corresponding trajectory until the curve $\mathcal{S}$ is reached at some time σ. Recall that the curve $\mathcal{S}$ is the concatenation of S_- with the admissible singular arc S and then with S_+ as defined earlier (recall that the curves S_- and S_+ are integral curves for $u = a$). Depending on the specific portion in which $\bar{\gamma}(\sigma)$ lies, the control then switches between $u = a$ and the singular control, and in the limit $t \to \infty$ reaches the lower equilibrium $(p_a, x_a) = (\bar{x}^3, \bar{x})$ defined in (9).

We now construct a 1-parameter family of extremal input-trajectory pairs $(\xi,\eta) = (\xi(\tau), \eta(\tau))$ by following this trajectory $\bar{\gamma}$ up to some time $\tau > \sigma$ and then at time τ switch to $u = 0$ ending the trajectory at time $T = T(\tau)$ as the curve $p = x^3 = e$ is reached. Denote the value of the corresponding objective by $I(\tau)$, i.e.

$$\begin{aligned} I(\tau) &= J_2(\eta(\tau)) \\ &= \xi(T(\tau)) + k\int_0^\tau \bar{u}(t)dt. \end{aligned} \quad (23)$$

Let I_1 and I_2 denote the first and second term respectively. It follows from the geometric properties of the curve $\mathcal{S}$ (see Fig. 1) that the endpoint $\xi(T(\tau))$ will have a lower value if the time τ is increased. Thus $I_1(\tau) = \xi(T(\tau))$ is strictly decreasing on $[\sigma,\infty)$.

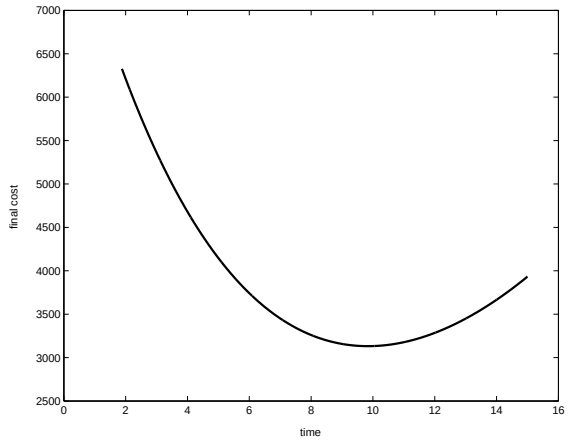

Figure 3: Graph of $I(\tau)$

Furthermore, the decrease in I_1 diminishes to zero as the singular arc approaches the lower equilibrium $(p_a, x_a) = (\bar{x}^3, \bar{x})$. The precise functional form is complicated since it depends on the initial value $\bar{\gamma}(\tau)$ for the integral curve for $u = 0$. The second term, however, is easily analyzed. We have $\dot{I}_2(\tau) = k\bar{u}(\tau) > 0$, so that I_2 is strictly increasing, and the second derivative is 0 if τ is such that $\bar{\gamma}(\tau)$ lies on S_+ and it is given by

$$\ddot{I}_2(\tau) = ku'_{sin}(\bar{x}(\tau))\dot{\bar{x}}(\tau) \tag{24}$$

if $\bar{\gamma}(\tau)$ lies on the singular arc. In this case we always have $\dot{\bar{x}}(\tau) < 0$ and since $u_{\sin}$ is strictly convex (see Fig. 1), it therefore follows that I_2 will be strictly concave on some initial interval $[\sigma, \rho)$ and then strictly convex on (ρ, ∞). (Note that $\bar{x}$ decreases as τ increases.) The time ρ is determined by the relation that the singular control $u_{\sin}$ has its minimum at $\bar{x}(\rho)$. For large enough τ, namely when $\bar{x}(\tau) \in S_+$, the second term increases linearly at a rate a and thus $I_2(\tau) \to \infty$ as $\tau \to \infty$. Hence the overall objective $I(\tau)$ has a minimum at some finite value τ_*.

This value τ_* is best computed numerically. We illustrate this in Figs. 3-5. The data for the parameters are the same as given earlier and the upper limit for the control is taken as $a = 15$. The initial condition is chosen as $(x_0, p_0) = (20, 12000) \in D_a$ corresponding to a value of $e = 8000$. Thus the control is initially $u = a$ until the trajectory meets the singular arc at $\sigma = 0.88$ and then follows the singular control. Fig. 3 gives the graph of the function $I(\tau)$ for the range $2 \le \tau \le 15$. The minimum is attained for $\tau = 9.84$. While the administration of the angiogenic inhibitors stops at this time, due to after effects the tumor volume still shrinks and reaches its minimum at the optimal final time $T = 13.20$. The corresponding optimal control u_* is given by

$$u_*(t) = \begin{cases} a & \text{for } 0 \le t \le 0.88 \\ u_{\sin} & \text{for } 0.88 < t \le 9.84 \\ 0 & \text{for } 9.84 \le t \le 13.20 \end{cases} . \tag{25}$$

Figs. 4 and 5 show the optimal control and its corresponding trajectory in (p, x)-space. Also the singular curve is indicated as a dotted curve in Fig. 5. Starting from the initial condition which is marked with a small circle, the trajectory corresponding to $u = a$, hits the singular curve at $t = 0.88$ and then descends along the singular arc until $\tau = 9.84$ when no more inhibitors are given. But the number of cancer cells still decreases until it reaches it minimum at time $T = 13.20$ marked with a star. Note that the trajectory is identical in structure with the solutions to problem (P1). The total amount of angiogenic inhibitors used up for this solution is 79.05. If in problem (P1) the limit A on the total amount of angiogenic inhibitors is larger, then the optimal solution for problem (P1) will continue longer on the singular arc until the condition $y(T) = A$ is reached.

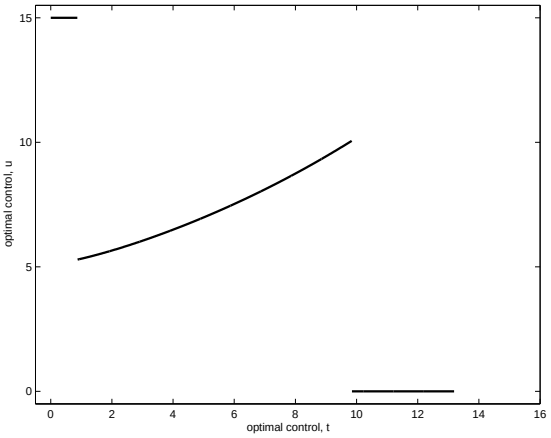

Figure 4: Optimal control

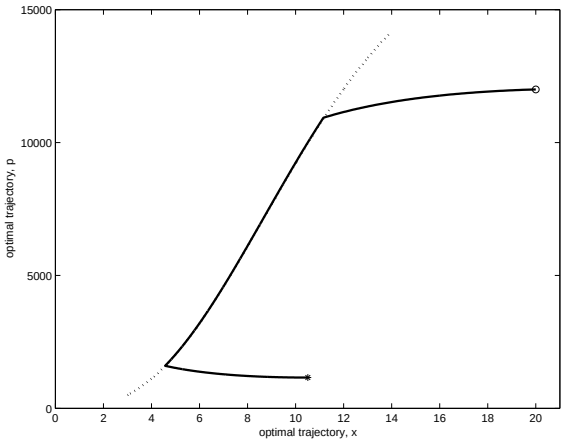

Figure 5: Corresponding optimal trajectory

4 Conclusion

We described the solutions for two related optimal control problems for tumor anti-angiogenesis. Central to both solutions is a curve $\mathcal{S}$ anchored by an

optimal singular arc. The solutions differ in how long it is optimal to follow this curve. If the total amount of angiogenic inhibitors is imposed as a constraint, problem (P1), then naturally all available drugs will be exhausted and therapy is ended as this limit is reached along $\mathcal{S}$. If the objective tries to achieve a balance between the amount of inhibitors given and their cost or side effects, problem (P2), there exists a unique time when the benefits in tumor reduction from giving additional inhibitors are offset by negative side effects or cost as measured by the integral of the control.

For the model considered, our results describe the theoretically optimal way of scheduling angiogenic inhibitors. While such an administration that follows an optimal singular arc is not practical, at least not yet, these results provide the milestone against which other more realistic therapy administrations should be measured.

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