A Synthesis of Optimal Controls for a Model of Tumor Growth under Angiogenic Inhibitors[1]

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***Abstract*— A mathematical model for the scheduling of angiogenic inhibitors to control a vascularized tumor is considered as an optimal control problem. A complete synthesis of optimal solutions is given.**

I. Introduction

In all cancer treatments which have cells of abnormal growth as the target, an important factor seriously limiting the success of these therapies is acquired drug resistance. Various biological phenomena like gene amplification or just simple mutation often create new cancer cells which no longer show a response to drugs being used. At the same time, it is interesting to notice that similar phenomena do not take place for the healthy proliferating cells. For example, regretfully bone marrow does not develop drug resistance to the killing agent [6]. A natural thought therefore is to try to turn this fact to our advantage and search for a cancer therapy which would primarily target healthy cells and cancerous ones only indirectly. Anti-tumor angiogenesis is such a mechanism. A growing tumor, after it reaches just a few millimeters in size, no longer can rely on blood vessels of the host, but it needs to develop its own system for blood supply. 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. (These treatments still only are in an experimental stage.) For this reason anti-tumor angiogenesis has been called a therapy resistant to resistance which provides a new hope in treatment of tumor type cancers [6].

Although tumor angiogenesis and its inhibitors seem to have been seriously researched medically only since the mid nineties, mathematical models to describe these phenomena are already being developed by the biomedical community. In this paper, we follow a path initiated by Hahnfeld et al. in [5] where a model for tumor growth under the action of angiogenic stimulation and inhibition was developed and medically validated. It was modified and formulated within an optimal control framework by Ergun, Camphausen and Wein in [4]. Introducing an objective, they analyzed the problem of optimal scheduling of anti-angiogenic therapy and radiotherapy as monotherapies and in combination. However, their analysis, even for the case of anti-angiogenic therapy as monotherapy, left several questions open. Although singular controls were computed, it was not clear how they combine with constant controls in a full synthesis of optimal controls. In this paper we continue the analysis from [4] and present such a full synthesis of optimal controls for the model.

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II. Mathematical Model for Dynamic Anti-Angiogenic Monotherapy [4]

We consider the problem formulation from [4] that is based on the previously developed and validated model in [5]. In this model the spatial aspects of the underlying diffusion that stimulate and inhibit angiogenesis are incorporated into a non-spatial 2-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 resulting in the following equation for the rate of change in the volume of primary tumor cells:

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

where ξ denotes 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. 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. (In [5] the following numerical values are given for these parameters[1]: $\xi = \frac{0.192}{\ln 10} = 0.084$ per day, $b = 5.85$ mm per day, $d = 0.00873$ per mm per day, $G = 0.15$

[1]Only the value of ξ needs to be adjusted to the natural logarithm.

kg per mg of dose). This model represents a simplification of the spatial analysis in [5] in the sense that the angiogenic inhibitor is taken proportional to the tumor radius, not the tumor surface (see [4] for details on the justification of the equations and the relations between the two models).

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

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

on the total amount of anti-angiogenic treatment administered. For the case $d = 0$ it is shown in [4] 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 an optimal 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 [4, pg. 415].

In this paper, for the model when the dose rate u is bounded, $0 \leq u \leq a$, we augment the analysis in [4] to give a complete characterization of optimal controls in form of a synthesis. As will be seen, the most general structure of optimal controls is of the form "$\mathbf{0asa0}''$ 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. While there will always be a final interval where $u = 0$, this only holds since the terminal time T is free in the problem. In general, anti-angiogenic treatment stops exactly when equality holds in (3), i.e. when the allowable total amount of anti-angiogenic treatment is reached. If this occurs along the singular arc, then optimal controls directly switch to $u = 0$ as postulated in [4]. But it is possible that the singular arc saturates before this happens (i.e. the dose rate needed to maintain the singular arc exceeds the postulated upper bound a) and in this case an extra interval with maximum rate therapy is inserted. Without this upper bound on u (as the problem was considered in [4]) the initial and terminal phases of therapy become much guess work and therefore the authors were "unable to characterize the final, nonsingular portion of the solution". Also, in our analysis here we do not assume that $d = 0$.

Equation (2) for the rate of change in the volume of vascular endothelial cells is not Lipschitz and indeed has multiple solutions at $e = 0$. For a mathematical analysis it is preferable to eliminate the for the problem biologically irrelevant trivial solution $e \equiv 0$ and to work with a smooth dynamical system instead. We therefore change variable from e to x defined by $e = x^3$. This results in the following dynamical system:

$$\dot{x} = \frac{1}{3}\left(b - dx^2 - Gux\right). \tag{4}$$

Hence we consider the following equivalent optimal control problem:

(P) minimize $p(T)$ over all Lebesgue measurable functions $u : [0, T] \to [0, a]$ subject to

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

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

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

and terminal condition $y(T) \leq A$ with the terminal time T free.

We briefly summarize some elementary properties of the controlled dynamical system Σ given by (5) and (6): It is clear from (6) that the strip $\{x \in \mathbb{R} : 0 < x < \sqrt{\frac{b}{d}}\}$ is positive invariant for any control u. Also the state p remains positive. (For $z = \ln p$ we have $\dot{z} = -\xi z + f(t)$ for some continuously differentiable function f and therefore z cannot blow up.) Hence all trajectories lie in the region $R = \{(p, x) : p > 0, 0 < x < \sqrt{\frac{b}{d}}\}$. However, this region still is too large as set of meaningful initial conditions and will allow for some degenerate optimal solutions which we simply prefer to exclude altogether. It is easily seen that 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

$$\bar{x} = \frac{-Ga + \sqrt{G^2a^2 + 4bd}}{2d}, \tag{8}$$

and for $u \equiv 0$ the corresponding system Σ_0 has an asymptotically stable node at $(p_0, x_0) = (\frac{b}{d}\sqrt{\frac{b}{d}}, \sqrt{\frac{b}{d}})$. Fig. 1 gives the phase-portrait of the uncontrolled system Σ_0 for the numerical values specified earlier [5].

Initial conditions x_0 which lie below $\bar{x}$ given by (8) are not meaningful medically [4] and therefore we also restrict the initial data to lie in the set

$$D = \{(p, x) : \bar{x} \leq x \leq \sqrt{\frac{b}{d}}, p > 0\}. \tag{9}$$

It is easily seen from the phase portraits of the systems Σ_0 and Σ_a that this set is positively invariant under any admissible control.

III. Analysis of the Mathematical Model

First-order necessary conditions for optimality of a control u are given by the *Pontryagin Maximum Principle* [8], [2]. If u_* is an optimal control defined over the interval $[0, T]$ with corresponding trajectory (p_*, x_*, y_*), then there exist a constant $\lambda_0 \geq 0$ and an absolutely continuous co-vector, $\lambda : [0, T] \to (\mathbb{R}^3)^*$, (which we write as row-vector) such that $(\lambda_0, \lambda(t)) \neq (0, 0)$ for all $t \in [0, T]$, satisfying the adjoint

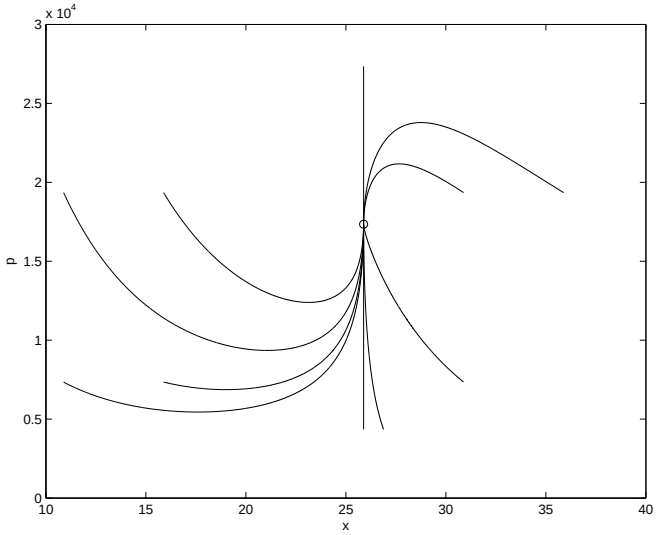

Fig. 1. Phaseportrait for Σ for $u = 0$

equations with transversality condition,

$$\dot{\lambda}_1 = \xi\lambda_1 \left(\ln\left(\frac{p_*(t)}{x_*^3(t)}\right) + 1 \right), \qquad \lambda_1(T) = \lambda_0, \tag{10}$$

$$\dot{\lambda}_2 = -3\xi\lambda_1 \frac{p_*(t)}{x_*(t)} + \frac{1}{3}\lambda_2(2dx_*(t) + Gu_*(t)), \lambda_2(T) = 0, \tag{11}$$

$$\dot{\lambda}_3 = 0, \qquad \lambda_3(T) = \begin{cases} 0 & \text{if } y(T) < A \\ \text{free} & \text{if } y(T) = A \end{cases}, \tag{12}$$

such the optimal control u_* minimizes the Hamiltonian H,

$$H = -\lambda_1 \xi p \ln\left(\frac{p}{x^3}\right) + \frac{1}{3}\lambda_2\left(b - dx^2 - Gux\right) + \lambda_3 u, \tag{13}$$

along $(\lambda_0, \lambda(t), p_*(t), x_*(t), y_*(t))$ over the control set $[0, a]$ and the minimum value is given by 0.

We call a pair $((p, x, y), u)$ consisting of an admissible control u with corresponding trajectory (p, x, y) for which there exist multipliers (λ_0, λ) such that the conditions of the Maximum Principle are satisfied an *extremal* (pair) and the triple $((p, x, y), u, (\lambda_0, \lambda))$ is an extremal lift (to the cotangent bundle). Extremals with $\lambda_0 = 0$ are called abnormal while those with a positive multiplier λ_0 are called normal. Here all extremals are normal and we henceforth normalize $\lambda_0 = 1$. We summarize this statement and other basic properties in the Lemmas below.

Lemma 3.1: All extremals for problem (P) are normal.

Proof. If $\lambda_0 = 0$, then by (10) and (11) both λ_1 and λ_2 vanish identically. Thus by the nontriviality of the multiplier λ_3 can never vanish in $[0, T]$. But then by $H \equiv 0$ we must have $u \equiv 0$ and thus $y(T) < A$ implying $\lambda_3(T) = 0$. Contradiction. □

Lemma 3.2: The multiplier λ_1 is positive on $[0, T]$, λ_2 is positive on $[0, T)$ and λ_3 is constant.

Proof. Since $\lambda_1(T) = 1$, the first statement is immediate from (10). The second one follows from the fact that whenever $\lambda_2(\tau) = 0$, then we have $\dot{\lambda}_2(\tau) = -3\xi\lambda_1(\tau)\frac{p_*(\tau)}{x_*(\tau)} < 0$. Since $\lambda_2(T) = 0$ this implies that λ_2 is positive for $t < T$. □

Lemma 3.3: If u_* is an optimal control, then $y(T) = A$.

Proof. Suppose $y(T) < A$. Then $\lambda_3 \equiv 0$ and it follows from $H(T) = 0$ that $p(T) = x^3(T)$. Extend the control by adding another interval $[T, T + \Delta]$ where $u \equiv a$ and $\Delta > 0$ is chosen so that $y(T + \Delta) = A$. It follows from the phase portrait of the system Σ_a for the control $u = a$ that the p-value decreases along this final piece and thus $p(T + \Delta) < p(T)$ contradicting the minimality of $p(T)$. □

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

$$\left(\lambda_3(t) - \frac{1}{3}\lambda_2(t)Gx_*(t)\right) v \tag{14}$$

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

$$\Phi(t) = \lambda_3(t) - \frac{1}{3}\lambda_2(t)Gx_*(t), \tag{15}$$

then optimal controls satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ a & \text{if } \Phi(t) < 0 \end{cases}. \tag{16}$$

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. Controls of this kind are called *singular* 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. For example, if $\Phi(\tau) = 0$, but $\dot{\Phi}(\tau) \neq 0$, then the control has a switch at time τ. In order to analyze the structure of the optimal controls we therefore need to analyze the switching function and its derivatives.

These computations simplify significantly within the framework of geometric optimal control theory and we therefore now write the state as $z = (p, x, y)^T$ and express the dynamics in the form

$$\dot{z} = f(z) + ug(z) \tag{17}$$

where

$$f(z) = \begin{pmatrix} -\xi p \ln\left(\frac{p}{x^3}\right) \\ \frac{1}{3}\left(b - dx^2\right) \\ 0 \end{pmatrix} \quad \text{and} \quad g(z) = \begin{pmatrix} 0 \\ -\frac{1}{3}Gx \\ 1 \end{pmatrix}. \tag{18}$$

Then the derivatives of the switching function can easily be computed using the following well-known result that can be verified by a direct calculation.

Proposition 3.1: Let h be a continuously differentiable vector field and define $\Psi(t) = \langle \lambda(t), h(z(t)) \rangle$. Then the derivative of Ψ along a solution to the system equation (17) for control u and a solution λ to the corresponding adjoint equations (10)-(12) is given by

$$\dot{\Psi}(t) = \langle \lambda(t), [f + ug, h] z(t) \rangle, \tag{19}$$

where $[f,h]$ denotes the Lie bracket of the vector fields f and h. ■

Recall that the Lie bracket is computed in local coordinates as

$$[f,h](z) = Dh(z)f(z) - Df(z)h(z) \tag{20}$$

where Df denotes the matrix of the partial derivatives of f.

We therefore have for

$$\Phi(t) = \langle \lambda(t), g(z(t)) \rangle \tag{21}$$

that

$$\dot{\Phi}(t) = \langle \lambda(t), [f,g]z(t) \rangle \tag{22}$$

$$\ddot{\Phi}(t) = \langle \lambda(t), [f+ug,[f,g]]z(t) \rangle \tag{23}$$

Direct computations give that

$$[f,g](z) = \begin{pmatrix} \xi G p \\ -\frac{1}{9} G\left(b + dx^2\right) \\ 0 \end{pmatrix}, \tag{24}$$

$$[f,[f,g]](z) = \begin{pmatrix} \xi^2 G p + \frac{1}{3}\xi G p \frac{b+dx^2}{x} \\ -\frac{4}{27} G b d x \\ 0 \end{pmatrix}, \tag{25}$$

and

$$[g,[f,g]](z) = \begin{pmatrix} 0 \\ -\frac{1}{27} G^2\left(b - dx^2\right) \\ 0 \end{pmatrix}. \tag{26}$$

Proposition 3.2: If u_* is an optimal control, then u_* can take on the value 0 only along an initial interval $[0,\tau_1]$ and a final interval $[\tau_4,T]$.

Proof. Suppose there exists an interval $[\alpha,\beta] \subset (0,T)$ such that $\Phi(\alpha) = \Phi(\beta) = 0$ and Φ is positive on (α,β). Then there exists a time $\tau \in (\alpha,\beta)$ where Φ attains its maximum and with all functions evaluated at τ we have

$$\begin{aligned} 0 = \dot{\Phi}(\tau) &= \langle \lambda, [f,g](z) \rangle \\ &= \lambda_1 \xi G p - \frac{1}{9}\lambda_2 G\left(b + dx^2\right). \end{aligned} \tag{27}$$

But

$$\begin{aligned} \ddot{\Phi}(\tau) &= \langle \lambda, [f,[f,g]](z) \rangle \\ &= \lambda_1 \xi G p \left(\xi + \frac{b+dx^2}{3x}\right) - \frac{4}{27}\lambda_2 G b d x \\ &= \frac{1}{9}\lambda_2 G\left(b+dx^2\right)\left(\xi + \frac{b+dx^2}{3x}\right) - \frac{4}{27}\lambda_2 G b d x \\ &= \frac{1}{9}\lambda_2 G\left(\xi\left(b+dx^2\right) + \frac{\left(b-dx^2\right)^2}{3x}\right) > 0. \end{aligned}$$

Thus Φ has a local minimum at τ. Contradiction. Hence the switching function is strictly increasing or decreasing along the control $u \equiv 0$ and thus 0-arcs can only lie at the ends of the interval $[0,T]$. □

While it follows from the synthesis given below that there can exist optimal trajectories which end with an interval where $u \equiv a$, this only happens in certain degenerate (and medically unrealistic) scenarios if the upper limit A on the total amount of anti-angiogenic treatment administered is too small. The typical scenario is indeed that optimal trajectories end with a 0-arc defined over an interval $[\tau_4,T]$. It then follows from the condition $H(T) = 0$ that

$$p(T) = x^3(T). \tag{28}$$

This condition determines the terminal time T in the problem.

The middle section of optimal controls is determined by an *optimal singular arc*. If u_* is singular on an open interval I, then

$$\Phi(t) = \langle \lambda(t), g(z(t)) \rangle \equiv 0 \tag{29}$$

on I and differentiating Φ twice yields

$$\dot{\Phi}(t) = \langle \lambda(t), [f,g]z(t) \rangle \equiv 0 \tag{30}$$

and

$$\ddot{\Phi}(t) = \langle \lambda(t), [f+ug,[f,g]]z(t) \rangle \equiv 0. \tag{31}$$

Here we have that

$$\langle \lambda(t), [g,[f,g]]z(t) \rangle \equiv -\frac{1}{27}\lambda_2(t) G^2\left(b - dx(t)^2\right) \tag{32}$$

and this quantity is negative by Lemma 3.2 and the invariance properties of x. Thus the singular control is of order 1 and satisfies the strengthened Legendre-Clebsch condition for minimality [7] (and hence is locally minimizing). The singular control can therefore formally be computed as

$$u_{\sin}(t) = -\frac{\langle \lambda(t), [f,[f,g]]z(t) \rangle}{\langle \lambda(t), [g,[f,g]]z(t) \rangle}. \tag{33}$$

For our system the vector fields g, $[f,g]$ and $[g,[f,g]]$ are everywhere linearly independent and thus $[f,[f,g]]$ can be expressed as a linear combination in this basis. A direct computation verifies that

$$[f,[f,g]] = \left(\xi + \frac{1}{3}\frac{b+dx^2}{x}\right)[f,g] - \psi(x)[g,[f,g]] \tag{34}$$

where

$$\psi(x) = \frac{1}{G}\left(\frac{b-dx^2}{x} + 3\xi\frac{b+dx^2}{b-dx^2}\right). \tag{35}$$

Since $\langle \lambda(t), [f,g](z(t)) \rangle \equiv 0$ on I, it therefore follows that the singular control is given as a smooth feedback control (that only depends on x) by

$$u_{\sin}(t) = \psi(x(t)). \tag{36}$$

However, this control is only admissible if the value lies in the interval $[0,a]$. It is easy to see that the function ψ is strictly convex ($\psi''(x) > 0$) and positive on $(0,\sqrt{\frac{b}{d}})$ with poles at $x = 0$ and $x = \sqrt{\frac{b}{d}}$. Hence, for large enough a there exist exactly two values x_ℓ^* and x_u^*, $0 < x_\ell^* < x_u^* <$

$\sqrt{\frac{b}{d}}$, such that the singular control is admissible for $x \in [x_\ell^*, x_u^*]$, saturates with values $u_* = a$ at x_ℓ^* and x_u^*, and is inadmissible for $x \notin [x_\ell^*, x_u^*]$. If a is too small, the singular arc is inadmissible or shrinks to a point. (In this case the synthesis of optimal controls has the form "$0a0$" and we do not discuss it further.)

However, for a trajectory to be an extremal, the singular arc also needs to satisfy the extra requirement that $H \equiv 0$, or, equivalently

$$\langle \lambda(t), f(z(t)) \rangle \equiv 0. \tag{37}$$

Since $\lambda(t) \neq 0$ (e.g. Lemma 3.2) the three conditions (37), (29) and (30) are consistent if and only if the determinant for the corresponding linear system in λ_1, λ_2 and λ_3 vanishes. This is equivalent to the linear dependence of the vector fields f, g and $[f, g]$, i.e.

$$0 = \begin{vmatrix} -\xi p \ln\left(\frac{p}{x^3}\right) & 0 & \xi G p \\ \frac{1}{3}(b - dx^2) & -\frac{1}{3}Gx & -\frac{1}{9}G(b + dx^2) \\ 0 & 1 & 0 \end{vmatrix}$$

$$= -\frac{1}{3}\xi G p \begin{vmatrix} -\ln\left(\frac{p}{x^3}\right) & 1 \\ b - dx^2 & -\frac{1}{3}(b + dx^2) \end{vmatrix}$$

$$= -\frac{1}{3}\xi G p \left(\frac{1}{3}(b + dx^2) \ln\left(\frac{p}{x^3}\right) - b + dx^2 \right),$$

or, equivalently,

$$\ln\left(\frac{p}{x^3}\right) = 3\frac{b - dx^2}{b + dx^2}. \tag{38}$$

Summarizing, we have

Proposition 3.3: There exists a locally minimizing singular arc S defined in (p, x)-space by

$$p = p(x) = x^3 \exp\left(3\frac{b - dx^2}{b + dx^2}\right) \tag{39}$$

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

$$u_{\sin}(x) = \psi(x) = \frac{1}{G}\left(\frac{b - dx^2}{x} + 3\xi\frac{b + dx^2}{b - dx^2}\right) \tag{40}$$

and the values x_ℓ^* and x_u^* are the unique solutions to the equation $\psi(x) = a$ in $(0, \sqrt{\frac{b}{d}})$. ■

Fig. 2 gives the graph of the singular curve defined by (39) for the numerical values in [5], $b = 5.85$, $d = 0.00873$, $\xi = 0.084$, $G = 0.15$, and it also identifies the admissible arc for $a = 15$. In this case $x_\ell^* = 2.9005$ and $x_u^* = 23.0704$, so that the admissible piece of the singular arc almost starts at the origin. The function $p = p(x)$ 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.

Proposition 3.4: Except for the lower saturation point x_ℓ^*, concatenations of the type $\mathbf{sa}$ are not optimal: for $x > x_\ell^*$,

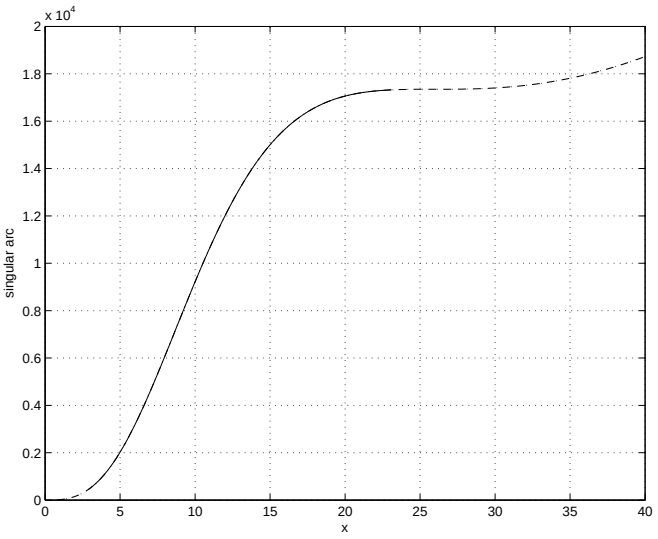

Fig. 2. Singular curve and admissible arc

optimal controls leave the singular arc with the constant control $u = 0$. ■

Essentially this follows from the local optimality of the singular arc which makes it superior to small bang-bang segments of the type $\mathbf{a0}$ that would return the system back to the singular arc. Mathematically, a computation akin to the one given in the proof of Prop. 3.2 can be invoked to verify that there cannot be any $a0$ switches in the x-range where the singular control is admissible and this can be used to prove the proposition above. However, due to space limitations this argument is omitted.

IV. Synthesis of Optimal Controls

Based on these results a complete synthesis of optimal controls can now be developed. 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 $\mathcal{S}$ corresponds to an admissible trajectory for the problem (P) as long as the constraint $y \leq A$ will not be violated. 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 4.1: For an initial condition $(p_0, x_0) \in D_0$ the optimal control initially 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

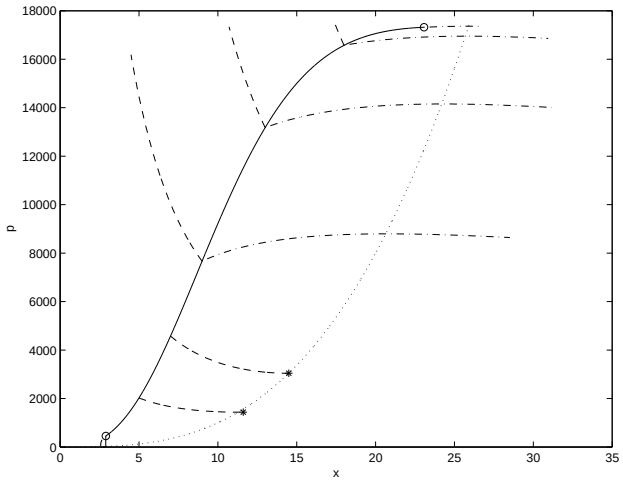

Fig. 3. Synthesis in (p, x)-space

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 $p(T) = x^3(T)$.

Theorem 4.2: 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 4.1. 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 $T = \tau$.

Some examples of projections of optimal trajectories in (p, x)-space are given in Fig. 3. The admissible singular arc is shown as a curve with 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 $p = x^3 = e$.

The actual synthesis defined by the specifications in Theorems 4.1 and 4.2, however, is constructed in (p, x, y)-space and is memoryless. The optimality of the controls in the field directly follows from existing results about *regular synthesis*, such as Boltyansky's [1], or the more general results of of Piccoli and Sussmann [9]. The verification that all required conditions are met is routine.

V. Conclusion

In this paper we gave a complete synthesis of optimal controls for an optimal control problem formulated in [4] for the control of tumor growth under angiogenic inhibitors. We have kept the formulation as it was in [4], but several extensions of the problem formulation readily can be analyzed with similar methods. For example, the choice of a free terminal time T generates the somewhat unrealistic scenario of 'stopping' treatment at the most opportune time when in reality in absence of treatment the value of p will then be increasing again approaching the equilibrium (p_0, x_0) in steady-state. On the other hand, this formulation gives the minimum size tumor, respectively maximum shrinkage possible and this is a quantity of medical interest. But clearly it follows from the synthesis and the structure of the phase portrait Σ_0 that any such shrinkage is temporary and and will need to reinforced with other treatment intervals as time progresses.

References

[1] V.G. Boltyansky, *Sufficient conditions for optimality and the justification of the dynamic programming method*, SIAM J. on Control, **4**, (1966), pp. 326-361

[2] A.E. Bryson and Y.C. Ho, *Applied Optimal Control*, Hemisphere Publishing, 1975

[3] M. Eisen, *Mathematical Models in Cell Biology and Cancer Chemotherapy*, Lecture Notes in Biomathematics, Vol. 30, Springer Verlag, (1979)

[4] A. Ergun, K. Camphausen and L.M. Wein, Optimal scheduling of radiotherapy and angiogenic inhibitors, *Bull. of Math. Biology*, **65**, (2003), pp. 407-424

[5] P. Hahnfeldt, D. Panigrahy, J. Folkman and L. Hlatky, Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy, *Cancer Research*, **59**, (1999), pp. 4770-4775

[6] R.S. Kerbel, A cancer therapy resistant to resistance, *Nature*, **390**, (1997), pp. 335-336

[7] A. Krener, The high-order maximal principle and its application to singular controls, *SIAM J. Control and Optimization*, **15**, (1977), pp. 256-293

[8] L.S. Pontryagin, V.G. Boltyanskii, R.V. Gamkrelidze and E.F. Mishchenko, *The Mathematical Theory of Optimal Processes*, MacMillan, New York, (1964)

[9] B. Piccoli and H.J. Sussmann, Regular synthesis and sufficiency conditions for optimality, *SIAM J. Control Optimization*, **39**, (2000), pp. 359-410