Application of Optimal Control to a System Describing Tumor Anti-Angiogenesis

Urszula Ledzewicz and Heinz Schättler

***Abstract*— We describe the structure of optimal trajectories for a mathematical model for minimizing the tumor volume under anti-angiogenic treatment. The model under consideration was developed by Hahnfeldt, Panigrahy, Folkman and Hlatky in [6] and has an optimal singular arc that determines the form of optimal protocols. The most typical scenario of optimal controls is given by first giving full dose treatment until the system reaches the singular arc, then follow the singular arc until all available inhibitors have been exhausted with a final uncontrolled segment along which the tumor volume attains its minimum.**

***Keywords*— optimal control, mathematical models for cancer treatments, anti-angiogenic therapy**

I. Introduction

The main reason for the practical failure of most cancer chemotherapy treatments lies in both intrinsic and acquired drug resistance of the highly heterogeneous cancer cell population. In recent years two new approaches that aim at circumventing this problem have been investigated in experimental stages - immunotherapy and anti-angiogenic treatments. While immunotherapy tries to trick the body's immune system to take action against the cancerous growth, tumor anti-angiogenesis aims at depriving a tumor from developing the necessary blood cells and capillaries that it needs for further growth. Angiogenic inhibitors, like endostatin, target normal cells, the so-called endothelial cells, and so far no occurrence of drug resistance has been reported in lab studies.

In this paper we analyze a mathematical model for tumor anti-angiogensis that was formulated by Hahnfeldt, Panigrahy, Folkman and Hlatky in [6] as an optimal control problem. This is a clinically validated, medical model on which several later modifications and simplifications are based [3], [4]. These modifications were undertaken to make the underlying mathematical model easier and more tractable for analysis. For example, for the same optimal control problem considered in this paper, it is easily seen that optimal controls for the modification considered by d'Onofrio and Gandolfi in [3] are bang-bang with one switching [12] and a solution of the same optimal control problem for the model by Ergun, Camphausen and Wein is given in [4], [8]. While these models are variations on the specific dynamics proposed in [6], in the papers by Agur, Arakelyan, Daugulis and Ginosar [1] and Forys, Kheifetz and Kogan [5] more generally dynamical properties of models for angiogenesis are investigated under minimal growth assumptions on the functions describing the dynamics.

In this paper, however, we only consider the specific model originally formulated in [6]. This model is more difficult to analyze mathematically and here we formulate the results for this model, but proofs will only be given elsewhere [10]. Qualitatively optimal controls for the model by Hahnfeldt et al. are the same as in the simplified model by Ergun, Camphausen and Wein [4] and are concatenations of bang controls (constant controls that either give a full or no dose of inhibitors) and optimal singular controls (specific smooth controls that administer the inhibitors using a time varying schedule at less than a maximum rate). The most general structure of optimal controls possible 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. If this singular arc saturates before all available inhibitors have been exhausted, then another period of maximum dose therapy is inserted until all inhibitors have been used up and the the minimum of the tumor volume is reached along a final uncontrolled arc. However, the most typical and most relevant medical scenario consists of optimal controls of the form "$\mathbf{as0}$".

II. Medical Background and Mathematical Model [6]

A growing tumor, after it reaches just a few millimeters in size, no longer can rely on blood vessels of the host for its supply of nutrients, but it needs to develop its own

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system for blood supply. In this process, called angiogenesis, there is a bi-directional reciprocal signaling between endothelial cells, which provide the lining for the newly forming blood vessels of the tumor, and tumor cell growth. Endothelial cells produce growth factors that stimulate the proliferation of the tumor cell population and the major targets of pharmacologic therapies are vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). Overall, angiogenesis can be viewed as a complex balance of tightly regulated stimulatory and inhibitory mechanisms balanced by microenvironmental factors.

In the model developed by Hahnfeldt, Panigrahy, Folkman and Hlatky in [6] these effects are summarized in a two-dimensional dynamical system with primary tumor cells, p, and vascular endothelial cells, q, as variables. A growth function describes the size of the tumor dependent on the volume of endothelial cells and in this model is chosen as Gompertzian with a variable carrying capacity defined by q. Thus the rate of change in the volume of primary tumor cells is modelled as

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

where ξ denotes a tumor growth parameter. Endothelial cells produce growth factors that stimulate the proliferation of the tumor cell population, but also have receptors which make them sensitive to inhibitors of inducers of angiogenesis like, for example, endostatin. The overall dynamics is a balance between stimulation and inhibition and its basic structure is of the form

$$\dot{q} = -\mu q + S(p,q) - I(p,q) - Guq \tag{2}$$

where μq describes loss to the endothelial cells through natural causes (death etc.), I and S denote inhibition and stimulation terms, respectively, and Guq represents the loss of endothelial cells due to additional outside inhibition. The variable u represents 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 μ is small and often this term is negligible compared to the other factors and thus in the literature often μ is set to 0 in this equation.

In [6] a spatial analysis of the underlying consumption-diffusion model was carried out that led to the following two conclusions:

- The inhibitor will impact endothelial cells in a way that grows like volume of cancer cells to the power $\frac{2}{3}$.

Essentially, the exponent $\frac{2}{3}$ arises through the interplay between the surface of the tumor through which the inhibitor needs to be released with the volume of endothelial cells. Thus in [6] the inhibitor term is taken in the form

$$I(p,q) = dp^{\frac{2}{3}}q \tag{3}$$

with d a constant, the death rate. The second implication of the analysis in [6] is that:

- The inhibitor term will tend to grow at a rate of $q^{\alpha}p^{\beta}$ faster than the stimulator term with $\alpha + \beta = \frac{2}{3}$.

In [6] the authors select $\alpha = 1$ and $\beta = -\frac{1}{3}$ resulting in a stimulation term of the form

$$S(p,q) = bp \tag{4}$$

with b a constant, the birth rate. However, the authors indicate that other choices are possible and, for example, choosing $\alpha = 0$ and $\beta = \frac{2}{3}$ results in the equally simple form

$$S(p,q) = bq \tag{5}$$

chosen in [3]. In that paper the dynamics for both models is analyzed and it is shown for the uncontrolled system that there exists a unique globally asymptotically stable equilibrium (which, however, is not medically acceptable). Adding a control term, this equilibrium can be shifted to lower values, or, depending on the parameter values, even eliminated altogether. In the latter case all trajectories converge to the origin in infinite time. This, in principle, would be the desired situation.

The problem then becomes how to administer a given amount of inhibitors to achieve the "best possible" effect. In this paper we use the dynamics of the original model from [6] and formulate it as the following optimal control problem:

[OC] For a free terminal time T minimize the value $p(T)$ subject to the dynamics

$$\dot{p} = -\xi p \ln(\frac{p}{q}), \qquad p(0) = p_0, \tag{6}$$

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

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

over all measurable functions $u : [0,T] \to [0,a]$ for which $y(T) \leq A$.

Note that we adjoin the constraint as third variable. The following result about the dynamical behavior of the system is proven in [3]:

Proposition 2.1: For any admissible control and positive initial conditions the solution (p,q) exists for all times $t \geq 0$ and both p and q remain positive. □

In our numerical computations later on we use the following parameter values which are taken from [6]: $\xi = \frac{0.192}{\ln 10} = 0.084$ per day, $b = 5.85$ mm per day, $d = 0.00873$ per mm per day, $G = 0.15$ kg per mg of dose (the value of ξ has been adjusted for the natural logarithm) and for

illustrative purposes we chose a small positive value for $\mu = 0.02$. But we want to emphasize that *our mathematical analysis and conclusions are independent of the specific parameter values* and lead to robust implications about the structure of optimal controls for this model.

III. The Maximum Principle and some General Properties of Optimal Solutions

First-order necessary conditions for optimality of a control u are given by the *Pontryagin Maximum Principle* [11], [2]: If u_* is an optimal control defined over the interval $[0, T]$ with corresponding trajectory (p_*, q_*, y_*), then there exist a constant $\lambda_0 \geq 0$ and an absolutely continuous covector, $\lambda : [0, T] \to (\mathbb{R}^3)^*$, (which we write as row-vector) such that $(\lambda_0, \lambda(t)) \neq (0, 0)$ for all $t \in [0, T]$, satisfying the adjoint equations with transversality condition,

$$\dot{\lambda}_1 = \xi\lambda_1 \left(\ln\left(\frac{p_*(t)}{q_*(t)}\right) + 1 \right) + \lambda_2 \left(\frac{2}{3} d q_*(t) p_*^{-\frac{1}{3}}(t) - b \right), \quad \lambda_1(T) = \lambda_0, \tag{9}$$

$$\dot{\lambda}_2 = -\xi\lambda_1 \frac{p_*(t)}{q_*(t)} + \lambda_2 \left(\mu + d p_*^{\frac{2}{3}}(t) + Gu \right), \quad \lambda_2(T) = 0, \tag{10}$$

$$\dot{\lambda}_3 = 0, \qquad \lambda_3(T) = \begin{cases} 0 & \text{if } y(T) < A \\ \text{free} & \text{if } y(T) = A \end{cases}, \tag{11}$$

for which the optimal control u_* minimizes the Hamiltonian H,

$$H = -\lambda_1 \xi p \ln\left(\frac{p}{q}\right) + \lambda_2 \left(bp - (\mu + d p^{\frac{2}{3}}) q - Guq \right) + \lambda_3 u, \tag{12}$$

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

We call a pair $((p, q, y), u)$ consisting of an admissible control u with corresponding trajectory (p, q, 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 $((p, q, y), u, (\lambda_0, \lambda))$ is an extremal lift (to the cotangent bundle).

The following properties of extremal trajectories and optimal controls follow from the conditions of the Maximum Principle using standard arguments:

1) *Extremals are normal*, i.e. $\lambda_0 > 0$, and henceforth we normalize $\lambda_0 = 1$.
2) The multipliers λ_1 and λ_2 cannot vanish simultaneously; λ_2 has isolated zeroes.
3) Except for degenerate cases (when it is optimal to choose $T = 0$ since no reduction of the overall number of cancer cells is possible because of the initial condition), if u_* is an optimal control with corresponding trajectory (p_*, q_*, y_*), then at the final time $p_*(T) = q_*(T)$ and $y_*(T) = A$, i.e. *all the inhibitors are used up*.
4) The multiplier λ_3 is non-negative. Besides the degenerate case mentioned under 3), $\lambda_3 = 0$ is only possible in the trivial case of a constant control $u_* \equiv a$ with trajectory ending at $p_*(T) = q_*(T)$. Henceforth we thus assume that $\lambda_3 > 0$.

IV. The Switching Function

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

$$(\lambda_3(t) - \lambda_2(t) G q_*(t))\, v \tag{13}$$

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

$$\Phi(t) = \lambda_3(t) - \lambda_2(t) G q_*(t), \tag{14}$$

then optimal controls satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ a & \text{if } \Phi(t) < 0 \end{cases}. \tag{15}$$

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 can be expressed concisely within the framework of geometric optimal control theory and we therefore now write the state as $z = (p, q, y)^T$ and express the dynamics in the form

$$\dot{z} = f(z) + u g(z) \tag{16}$$

where

$$f(z) = \begin{pmatrix} -\xi p \ln\left(\frac{p}{q}\right) \\ bp - \left(\mu + d p^{\frac{2}{3}}\right) q \\ 0 \end{pmatrix} \text{and } g(z) = \begin{pmatrix} 0 \\ -Gq \\ 1 \end{pmatrix}. \tag{17}$$

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 4.1: Let h be a continuously differentiable vector field and define

$$\Psi(t) = \langle \lambda(t), h(z(t)) \rangle. \tag{18}$$

Then the derivative of Ψ along a solution to the system equation (16) for control u and a solution λ to the corresponding adjoint equations (9)-(11) 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. In local coordinates the Lie bracket is expressed as $[f, h](z) = Dh(z)f(z) - Df(z)h(z)$ where Df and Dh denote the matrices of the partial derivatives of f and h, respectively. □

Thus, for

$$\Phi(t) = \langle \lambda(t), g(z(t)) \rangle \tag{20}$$

we have that

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

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

V. The Singular Curve

If u_* is singular on an open interval I, then both the switching function and all its derivatives vanish on I. If $\langle \lambda(t), [g, [f, g]] z(t) \rangle$ does not vanish on I, we can formally solve the equation $\ddot{\Phi}(t) = 0$ for the singular control as

$$u_{\sin}(t) = -\frac{\langle \lambda(t), [f, [f, g]] z(t) \rangle}{\langle \lambda(t), [g, [f, g]] z(t) \rangle}. \tag{23}$$

In this case the singular control is said to be of order 1 and it is a necessary condition for minimality, the so-called Legendre-Clebsch condition [7], that

$$\langle \lambda(t), [g, [f, g]] z(t) \rangle < 0. \tag{24}$$

Elementary computations verify that the Lie brackets are given by

$$[f, g](z) = Gp \begin{pmatrix} \xi \\ -b \\ 0 \end{pmatrix}, \tag{25}$$

and

$$[g, [f, g]](z) = -bG^2 p \begin{pmatrix} 0 \\ 1 \\ 0 \end{pmatrix}. \tag{26}$$

The vector fields g, $[f, g]$ and $[g, [f, g]]$ are everywhere linearly independent and $[f, [f, g]]$ can be expressed as a linear combination of this basis. A direct computation verifies that

$$[f, [f, g]] = \left(\xi + b\frac{p}{q} \right) [f, g] - \psi [g, [f, g]] \tag{27}$$

with $\psi = \psi(p, q)$ given by

$$\psi = \frac{1}{G} \left(\xi \ln \left(\frac{p}{q} \right) + b\frac{p}{q} + \frac{2}{3} \xi \frac{d}{b} \frac{q}{p^{\frac{1}{3}}} - \mu - dp^{\frac{2}{3}} \right). \tag{28}$$

Along a singular arc we have that

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

and thus

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

Since $\lambda_3 > 0$ it follows from that $\Phi(t) \equiv 0$ that λ_2 is positive along a singular arc and thus

$$\langle \lambda(t), [g, [f, g]](z(t)) \rangle = -\lambda_2(t) bG^2 p(t) < 0, \tag{30}$$

i.e. the strengthened Legendre-Clebsch condition is satisfied. Hence singular controls are of order 1 and locally optimal. The corresponding singular control is given by

$$u_{\sin}(t) = -\frac{\langle \lambda(t), [f, [f, g]] z(t) \rangle}{\langle \lambda(t), [g, [f, g]] z(t) \rangle} = \psi(p(t), q(t)). \tag{31}$$

But the singular control is only admissible if the value lies in the interval $[0, a]$.

Before addressing this issue, we first compute the singular curve. In order to be an extremal, the singular arc also needs to satisfy the extra requirement that $H \equiv 0$, or, equivalently that

$$\langle \lambda(t), f(z(t)) \rangle \equiv 0. \tag{32}$$

Hence along a singular arc $\lambda(t)$ vanishes against the vector fields f, g and $[f, g]$. Since $\lambda(t) \neq 0$, these vector fields must be linearly dependent, i.e.

$$0 = \begin{vmatrix} -\xi p \ln \left(\frac{p}{q} \right) & 0 & \xi \\ bp - \left(\mu + dp^{\frac{2}{3}} \right) q & -Gq & -b \\ 0 & 1 & 0 \end{vmatrix}. \tag{33}$$

Equivalently,

$$\ln \left(\frac{p}{q} \right) = 1 - \frac{\mu + dp^{\frac{2}{3}}}{b} \frac{q}{p}. \tag{34}$$

Summarizing, we have

Proposition 5.1: There exists a locally minimizing singular curve $\mathcal{S}$ defined in (p, q)-space by the relation (34) and the corresponding singular control, if admissible, is given by the function ψ defined in (28). □

The geometry of the singular curve becomes clear if we make a blow-up in the variables of the form

$$p = xq, \quad x > 0 \tag{35}$$

In the variables x and p the singular curve takes the form

$$p^2 + \varphi(x)^3 = 0 \tag{36}$$

with

$$\varphi(x) = \frac{bx(\ln x - 1) + \mu}{d}. \tag{37}$$

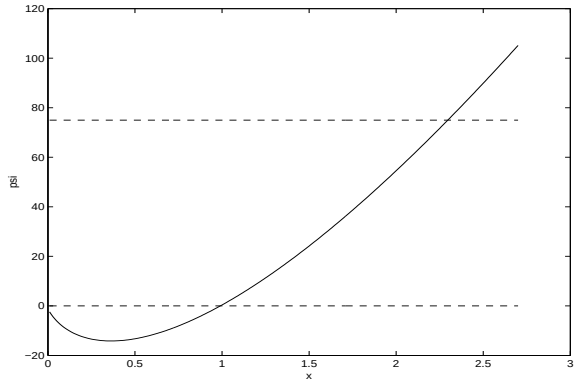

Fig. 1. Singular control ψ for $a = 75$

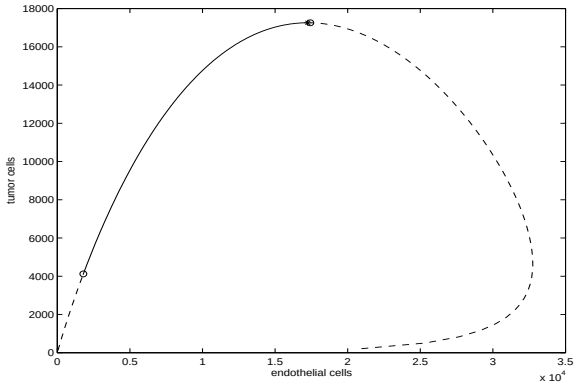

Fig. 2. Singular curve $\mathcal{S}$

This function is strictly convex with a minimum at $x = 1$ with minimum value $\frac{\mu-b}{d}$. In particular, if $\mu \geq b$, then this equation has no positive solutions and thus no admissible singular arc exists. The case $\mu < b$ is the medically relevant one. In this case it can be shown that there exist unique values x_1^* and x_2^*, $0 < x_1^* < x_2^* < \infty$, so that $\varphi(x) < 0$ for $x \in (x_1^*, x_2^*)$ and for every such x, there is a unique $p > 0$ so that (36) is satisfied. Along the singular arc the singular control can be expressed solely in the variable x: we have

$$\psi = \frac{1}{G}\left(\xi \ln x + bx + \frac{2}{3}\xi\frac{d}{b}\frac{1}{x}p^{\frac{2}{3}} - \mu - dp^{\frac{2}{3}}\right). \quad (38)$$

and substituting $p^{\frac{2}{3}} = -\varphi(x)$ yields a function of x only,

$$\psi = \frac{1}{G}\left[\left(\frac{1}{3}\xi + bx\right)\ln x + \frac{2}{3}\xi\left(1 - \frac{\mu}{bx}\right)\right]. \quad (39)$$

Proposition 5.2: For $\mu < b$ there exists exactly one connected arc on the singular curve $\mathcal{S}$ along which the control is admissible, i.e. satisfies the bounds $0 \leq \psi \leq a$. This arc is defined over an interval $[x_\ell^*, x_u^*]$, $x_1^* < x_\ell^* < x_u^* < x_2^*$, and x_ℓ^* and x_u^* are the unique solutions to the equations $\psi(x_\ell^*) = 0$ and $\psi(x_u^*) = a$. □

Fig. 1 gives the graph of the values of the singular control as a function of x for the parameter values given earlier and $a = 75$. The corresponding petal like singular curve $\mathcal{S}$ is shown in Fig. 2 as a dashed line with the admissible portion marked as a solid curve. The qualitative structures shown in Figs. 1 and 2 are generally valid with the admissible portion shrinking for smaller values a.

VI. Structure of Optimal Controls

We now describe the structure of optimal controls. While our statements about invariance properties of the flows are generally easy to verify, we refer the reader to [10] for the (sometimes lengthy) proofs of some of the statements about the structures of optimal controls and trajectories. This section only gives an outline of the argument.

The uncontrolled system ($u = 0$) has a unique globally asymptotically stable equilibrium point at $(\bar{p}, \bar{q})$ given by $\bar{p} = \bar{q} = \left(\frac{b-\mu}{d}\right)^{\frac{3}{2}}$ [3]. This value naturally is far too high to be acceptable and the medically relevant region is $p < p_*$. In order to exclude irrelevant discussions about the structure of the synthesis in regions where to begin with the model does not represent the underlying medical problem, we therefore restrict our discussions to the following domain:

$$\mathcal{D} = \{(p, q) : 0 < p \leq \bar{p},\ 0 < q \leq \bar{q}\}. \quad (40)$$

It is not difficult to see that this region is positively invariant for the flow of the control system, i.e. if $(p_0, q_0) \in \mathcal{D}$, then for any admissible control u defined over the interval $[0, \infty)$ the solution $(p(\cdot), q(\cdot))$ to the corresponding dynamics with initial condition $(p(0), q(0)) = (p_0, q_0)$ exists for all times $t \geq 0$ and lies in $\mathcal{D}$. We also restrict our discussions in this paper to the case when

$$(\mathbf{A}) \qquad \mathbf{Ga} > \mathbf{b} - \mu > \mathbf{0}. \quad (41)$$

Under this assumption the system for the constant control $u = a$ does not have an equilibrium point and for $u = a$ every trajectory converges towards the origin for $t \to \infty$. Thus in principle eradication of the tumor is possible, but not with a limited amount A of inhibitors. Let $\mathcal{D}_+ = \{(p, q) \in \mathcal{D} : p > q\}$, $\mathcal{D}_0 = \{(p, q) \in \mathcal{D} : p = q\}$ and $\mathcal{D}_- = \{(p, q) \in \mathcal{D} : p < q\}$. Both the flows Γ_0 for the constant control $u = 0$ and Γ_a for the constant control $u = a$ cross the diagonal portion $\mathcal{D}_0$ transversally: Γ_0 flows from $\mathcal{D}_+$ into $\mathcal{D}_-$, while Γ_a crosses in opposite direction from $\mathcal{D}_-$ into $\mathcal{D}_+$ (see Figs. 3 and 4). Trajectories for $u = 0$ approach the stable equilibrium $(\bar{p}, \bar{q})$ from within the region $\mathcal{D}_-$, while trajectories for $u = a$ converge to the origin as $t \to \infty$ in the region $\mathcal{D}_+$.

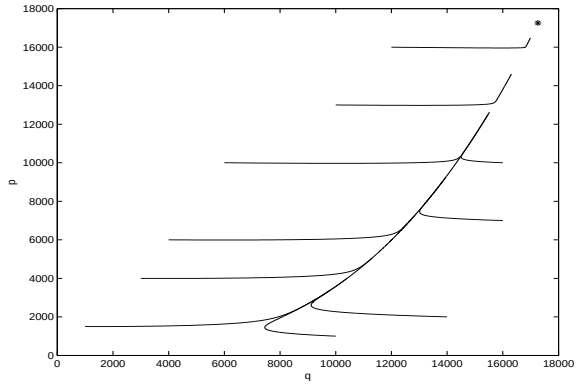

Fig. 3. Phase portrait for $u = 0$

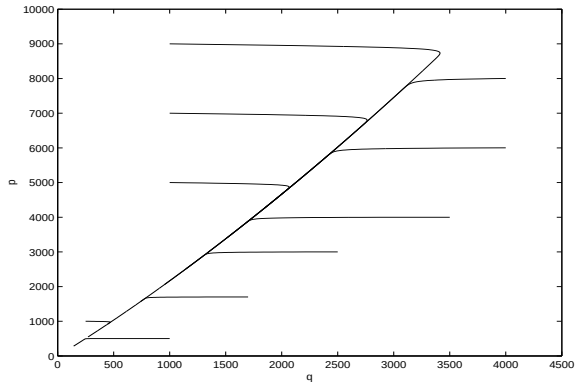

Fig. 4. Phase portrait for $u = a = 75$

Note that the p-value of trajectories is always decreasing in $\mathcal{D}_+$ and always increasing in $\mathcal{D}_-$. As a result, for initial conditions (p_0, q_0, y_0) with $(p_0, q_0) \in \mathcal{D}_-$ degenerate cases are included in the domain when it is best to choose the optimal time T as $T = 0$. This situation arises when the amount of available inhibitors simply is not sufficient to reach a point in the region $\mathcal{D}_+$ that would have a lower p-value than p_0. But this is clearly an indication that this initial condition is not realistic medically and henceforth for this discussion we also ignore these degenerate cases.

Let $\mathcal{L}$ denote the sub-region of $\mathcal{D}$ consisting of all points (p, q) that lie within the loop formed by the singular curve $\mathcal{S}$. Then the first important step towards constructing a synthesis of optimal trajectories is to show that there are no switchings from $u = 0$ to $u = a$ at points $(p_0, q_0) \in \mathcal{L}$ and that there are no switchings from $u = a$ to $u = 0$ at points (p_0, q_0) outside the closure of $\mathcal{L}$. This is done by setting up an appropriate variation and explicitly computing its effect using Lie-algebraic computations [10]. Based on this result, it then follows from the general results in section III that optimal trajectories cannot cross over from $\mathcal{D}_+$ into $\mathcal{D}_-$, but that they terminate on the diagonal $\mathcal{D}_0$. Furthermore, except for the possible degenerate cases mentioned above, initially the optimal control is always given by $u \equiv a$ on $\mathcal{L}$. Overall in this case the optimal control will be of one of the following structures: (i) $\mathbf{as0}$ if the initial trajectory for $u = a$ intersects the admissible singular arc and then inhibitors become exhausted while the trajectory follows the singular arc, (ii) $\mathbf{asa0}$ if the initial trajectory for $u = a$ intersects the admissible singular arc and saturation occurs before inhibitors run out, or (iii) simply $\mathbf{a0}$ if the initial trajectory does not meet the admissible portion of the singular arc.

For initial conditions in $\mathcal{D}_+$ that lie outside $\mathcal{L}$, initially the control can be either $u = 0$ or $u = a$. However, if an optimal trajectory has an arc corresponding to the constant control $u \equiv 0$ over some interval (α, β) that lies in $\mathcal{D}_+ \cup \mathcal{D}_0$, then it is not possible that the trajectory has switchings at both the initial point $(p_*(\alpha), q_*(\alpha))$ and at the final point $(p_*(\beta), q_*(\beta))$: if there is a switching at $(p_*(\alpha), q_*(\alpha)) \in \mathcal{D}_+$, then β must be the final time T and the trajectory ends at time β on $\mathcal{D}_0$, if there is a switching at $(p_*(\beta), q_*(\beta)) \in \mathcal{D}_+$, then $\alpha = 0$ must be the initial time [10]. Hence optimal controls are at most of the type $\mathbf{0sa0}$. Since trajectories cannot leave $\mathcal{D}_+$, arcs for $u = 0$ can only be at the end and switchings from $u = 0$ to $u = a$ are not optimal in this region. Typically optimal controls start with a segment for $u = 0$ until the singular arc is reached, then follow the singular arc (and possibly its extension by the $u = a$ trajectory through the saturation point) until all inhibitors have been administered and as above end with a segment for $u = 0$. But note that this structure also includes trajectories corresponding to the control sequence $\mathbf{0a0}$ avoiding the singular arc all together. However, for these there are strict limitations on the geometry of switchings: the $\mathbf{0a}$ concatenation must lie outside the loop $\mathcal{L}$ and the $\mathbf{a0}$ concatenation must lie inside $\mathcal{L}$. Here the synthesis near the saturation point still needs to be worked out fully.

Finally, if the initial condition lies in $\mathcal{D}_-$, but outside $\mathcal{L}$, then in principle concatenations of the full form $\mathbf{0asa0}$ are possible. However, these initial conditions are not really realistic for the model and some of these initial conditions are ill-posed in the sense that again the best strategy is to choose $T = 0$. Since these are of no interest for the underlying medical problem, we do not go into a further analysis of the synthesis of optimal trajectories here. Summarizing, we have

Theorem 6.1: Let $(p_0, q_0, 0)$ be an initial point with $(p_0, q_0) \in \mathcal{D}$. Optimal controls are at most concatenations of the form $\mathbf{0asa0}$ with $\mathbf{0}$ denoting an arc along the constant control $u = 0$, $\mathbf{a}$ denoting an arc along the constant control $u = a$, and $\mathbf{s}$ denoting an arc along the

singular curve $\mathcal{S}$. □

The structure of some optimal trajectories projected into (q, p)-space is illustrated in Fig. 5. We highlight one specific optimal trajectory of the type **as0** starting at $(q(0), p(0)) \in \mathcal{D}_-$ and ending at $(q(T), p(T)) \in \mathcal{D}_0$.

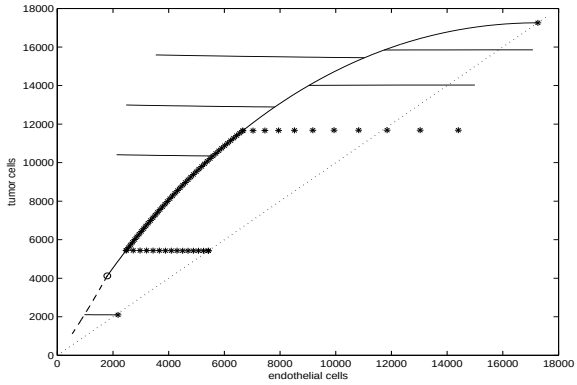

Fig. 5. Synthesis of optimal trajectories

VII. Conclusion

In the paper a synthesis of optimal controls for the model of anti-angiogenic treatment by Hahnfeldt et al. from [6] is presented. The presence of an optimal singular arc leads to a more difficult mathematical analysis. It turns out that the qualitative structure of solutions is identical with the one for the simplified model by Ergun, Camphausen and Wein [4] obtained in our earlier work [8]. The analysis of quantitative differences in the optimal controls for the models will be done elsewhere.

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