# On the Structure of Optimal Controls for a Mathematical Model of Tumor Anti-Angiogenic Therapy with Linear Pharmacokinetics

Urszula Ledzewicz
Dept. of Math. and Statistics
Southern Illinois University Edwardsville
Edwardsville, Illinois, 62026-1653
uledzew@siue.edu

Heinz Schättler
Dept. of Electrical and Systems Engr.
Washington University
St. Louis, Missouri, 63130-4899
hms@wustl.edu

Andrew Berman
Dept. of Electrical and Systems Engr.
Washington University
St. Louis, Missouri, 63130-4899
amb1022@ese.wustl.edu

***Abstract*— A mathematical model for tumor anti-angiogenesis that was formulated and biologically validated by Hahnfeldt et al. [13] is considered as an optimal control problem. In earlier research, the optimal scheduling of anti-angiogenic agents has been analyzed under the simplifying assumption that dosage and concentration were identified. In this case, there exists an optimal singular arc of order $1$ that forms the centerpiece of a synthesis of optimal controlled trajectories. Here we consider the same model with standard pharmacokinetic equations added that define the concentration as the state of a first-order linear system driven by the dosage. The singular arc and its optimality status are preserved under this modelling extension and an explicit feedback formula that defines the optimal singular control in the simplified model now becomes the singular concentration for the extended system. Optimal controls track this concentration of inhibitors along the singular arc. However, the order of the singular arc increases from $1$ to $2$ and the overall concatenation structure in the synthesis of optimal trajectories changes. Now optimal transitions to and from the singular arc can only occur through chattering arcs.**

## I. Introduction

Tumor anti-angiogenesis is a relatively new treatment approach for cancer that aims at preventing a growing tumor from developing the network of blood vessels and capillaries that it needs for its supply of nutrients and oxygen. After going through an initial state of avascular growth, at the small size of about $1-2\ mm$ in diameter, a tumor initiates the process of *angiogenesis*, that is, the recruitment of surrounding host blood vessels to facilitate its supply of nutrients. Remarkably, through a complex bi-directional signaling mechanism, the tumor both stimulates and *inhibits* the growth of endothelial cells that form the lining of these newly developing capillaries. Anti-angiogenic treatments - proposed already in the early seventies by J. Folkman [12], but only enabled by the discovery of the inhibitory mechanisms of the tumor in the nineties [3] - bring in external anti-angiogenic agents to disrupt the growth of endothelial cells. This indirect treatment approach does not kill cancer cells, but rather than targeting the fast duplicating and continuously mutating tumor cells, it targets the genetically far more stable endothelial cells. As a consequence, no clonal resistance to the angiogenic inhibitors has been observed in experimental cancer. All too often, developing drug resistance is the limiting factor in conventional chemotherapy treatments. Hence anti-angiogenesis has been called a new hope for the treatment of tumors [14]. Naturally, as such, in the last ten years, it has been an active area of research not only in medicine, but also in related disciplines including mathematical biology.

Mathematical models for tumor angiogenesis can broadly be divided into two groups: those that try to accurately reflect the biological processes, e.g., [1], [2], and those that aggregate variables into low-dimensional dynamical systems, e.g., [9], [10], [13]. While the former allow for realistic, large-scale simulations, the latter enable a theoretical mathematical analysis. A distinctive place among the second group is taken up by the model proposed by Hahnfeldt, Panigrahy, Folkman and Hlatky in [13], a group of researchers then at Harvard Medical School. Modelling the tumor as a sphere and analyzing the underlying consumption-diffusion process theoretically, in this research a two-dimensional model of ordinary differential equations for the interactions between the primary tumor volume, $p$, and the carrying capacity of the vasculature, $q$, was developed and biologically validated. The carrying capacity is the maximum tumor volume sustainable by the vascular network that supports the tumor with nutrients. Since it largely depends on the volume of endothelial cells, we also call $q$ the endothelial support of the tumor for short. An analysis of the dynamics of this model and some of its modifications and extensions has been carried out by d'Onofrio and Gandolfi in [9].

In all medical applications, the question of how to schedule medication in time arises. The two main reasons for this are that side effects need to be kept tolerable (for example, this is the most important criterion in chemotherapy applications) and that resources are limited. The second reason is the main limitation for anti-angiogenic treatments, where most inhibitors are biological agents that need to be grown in a lab environment and thus are not readily available and also are very expensive. Hence the problem of how to schedule medication in an optimal way arises naturally. Applications of optimal control to mathematical models arising in biomedical problems have had a long history with the early focus on models in cancer chemotherapy, but there has been a strong resurgence of this methodology in the analysis of newer models. This especially holds for novel treatment approaches

This material is based upon research supported by the National Science Foundation under collaborative research grants DMS 0707404/0707410.

to cancer like tumor anti-angiogenesis, the topic of this paper (e.g., [17], [19], [25], [24]). Optimal control approaches also have been applied to models describing the immune response to viruses (e.g., HIV, [15]) or to cancer and its resulting immunotherapies (e.g., [6], [7], [8]), a second approach currently intensively pursued in medical research. For tumor anti-angiogenesis, the limitation of vessel disruptive and other inhibitory agents makes it natural to seek a solution that maximizes the tumor reduction achievable with an a priori specified amount of medication. This is the formulation that was suggested by Ergun, Camphausen and Wein in their paper [10] where a modification of the model by Hahnfeldt et al. was proposed and investigated. Using methods of geometric optimal control, Ledzewicz and Schättler gave a complete solution to this optimal control problem both for the original model by Hahnfeldt et al. [19] and also its modification by Ergun et al. [17].

Naturally, in view of the tremendous complexity of cancer and its response to treatment, for the analysis of mathematical models it is a good strategy to start with simplified versions and later incorporate increasingly more complex and medically more realistic features into the model. In this sense, a commonly made simplification in the literature, (and this also was done in our analysis of the models for tumor anti-angiogenesis mentioned above,) is to identify the drug dosage with its concentration and its effects. In reality, these clearly are different phenomena and their relations are studied under the names of *pharmacokinetics (PK)* and *pharmacodynamics (PD)*. Pharmacokinetic equations model the drug's concentration in the body plasma and pharmacodynamics models the effectiveness of the drugs. In short, *PK/PD* stands for the description of the full process, also known as *drug delivery* in the medical literature. The important question that thus arises is whether, and if so, how the structure of optimal solutions changes as these new features are included in the modelling (see also, [18]).

In this paper, we consider the model by Hahnfeldt et al. with a standard linear system describing pharmacokinetics added. Without PK, a singular arc largely determines the structure of optimal controlled trajectories [19]. We will show here that the optimality status of this singular arc and its analytic form as a function of $p$ and $q$ are preserved when a *linear* PK model is added. Furthermore, what was the singular control in the reduced order model now becomes the singular concentration. Thus, these explicit computations directly carry over and essential features of the simplified model are preserved. At the same time, however, under this modelling extension the order of the singular arc increases from 1 without PK to 2 in the model with linear PK. This has significant implications on the optimal concatenations of trajectories since it no longer is optimal to directly switch from a full dose to the singular regimen. This transition can only be accomplished by means of chattering controls [4], [26]. Thus, while essential features are preserved verbatim under this modelling extension, the structure of the optimal synthesis does change. However, based on the earlier results, it is possible to construct simple suboptimal protocols by tracking the singular arc. From a practical point of view, optimal controls that contain chattering arcs are not realizable anyway and our constructions provide satisfactory control schemes.

## II. An Optimal Control Problem for a Mathematical Model for Anti-Angiogenic Therapy

We briefly review the mathematical model for tumor anti-angiogenesis that was formulated and biologically validated by Hahnfeldt et al. [13] and then recall the structure of optimal solutions for the problem of maximizing the tumor reduction achievable with an a priori given amount of inhibitors [19].

### A. Model formulation [13]

The spatial aspects of the underlying consumption-diffusion processes that stimulate and inhibit angiogenesis are incorporated into a non-spatial 2-compartment model with the primary tumor volume, $p$, and its carrying capacity, $q$, as variables. Tumor growth is modelled by a Gompertzian growth function of the form

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

where $\xi$ denotes a growth parameter. The dynamics for the carrying capacity consists of a balance between stimulatory and inhibitory effects and is given by

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

The term $bp$ represents stimulation of the vasculature by the tumor and is taken proportional to the tumor volume. The three terms with negative signs represent different types of inhibition. Loss of vascular support through natural causes (death of endothelial cells etc.) is modelled as $\mu q$. Generally $\mu$ is small and often this term is negligible compared to the other factors. Thus, in the literature sometimes $\mu$ is set to 0 in this equation. The second term $dp^{\frac{2}{3}}q$ represents endogenous inhibition due to the fact that the tumor also produces inhibitors that impact its vascular support. These inhibitors are released through the tumor surface (hence the scaling of the tumor volume $p$ to its surface area $p^{\frac{2}{3}}$) and interact with the endothelial cells that form the lining of the newly developing capillaries. The last term $\gamma uq$ models loss of vascular support due to giving outside anti-angiogenic agents and the variable $u$ represents the control in the system. It corresponds to the angiogenic dose rate with $\gamma$ a constant that represents the anti-angiogenic killing parameter.

We consider the optimal control problem as it was initially proposed in [10]: for a free terminal time $T$ minimize the tumor volume,

$$J(u) = p(T), \tag{3}$$

subject to the dynamics (1) and (2) over all Lebesgue measurable functions $u : [0, T] \to [0, a]$ that satisfy a

constraint on the total amount of anti-angiogenic inhibitors administered,

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

Mathematically it is more convenient to incorporate the constraint (4) into the dynamics by introducing a new variable $y$ that keeps track of the amount of the drug used, i.e., we add the trivial dynamics

$$\dot{y} = u, \tag{5}$$

with the boundary conditions $y(0) = 0$ and $y(T) \leq A$.

### *B. Singular control and corresponding singular arc*

Necessary conditions for optimality are given by the *Pontryagin Maximum Principle* (e.g., [4], [5]). Essentially, its conditions state the existence of a nontrivial multiplier $\lambda$, an absolutely continuous co-vector, $\lambda : [0, T] \to (\mathbb{R}^3)^*$, that satisfies a time-varying, linear differential equation along an optimal controlled trajectory $(p_*, q_*, y_*)$, so that the optimal control $u_*$ minimizes the Hamiltonian $H$,

$$H = -\lambda_1 \xi p \ln\left(\frac{p}{q}\right) + \lambda_2 \left(bp - \left(\mu + dp^{\frac{2}{3}} + \gamma u\right) q\right) + \lambda_3 u \tag{6}$$

along $(\lambda(t), p_*(t), q_*(t))$ over the control set $[0, a]$ with minimum value given by 0. This minimum condition is equivalent to minimizing the linear function $(\lambda_3 - \lambda_2(t)\gamma q_*(t))\, v$ over $v \in [0, a]$. The multiplier $\lambda_3$ associated with the variable $y$ is constant. Thus, if one defines the so-called *switching function* $\Phi$ as

$$\Phi(t) = \lambda_3 - \lambda_2(t)\gamma q_*(t), \tag{7}$$

then optimal controls satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ a & \text{if } \Phi(t) < 0 \end{cases}. \tag{8}$$

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 $u = 0$ and $u = a$ as *bang* controls. These two classes are the canonical candidates for optimal controls and there exists a wealth of literature, both classical and modern, analyzing their optimality status. For some recent references, see [4], [11], [22], [23]. For the model considered here, singular controls are indeed optimal and we recall these earlier results [19].

*Proposition 2.1:* There exists a locally minimizing singular arc $\mathcal{S}$ in $(p, q)$-space which, using a blow-up of the form $x = \frac{p}{q}$, can be parameterized in the form

$$\mathcal{S}: \qquad dp^{\frac{2}{3}} = bx(1 - \ln x) - \mu \tag{9}$$

with $x \in (x_1^*, x_2^*)$ where $x_1^*$ and $x_2^*$ are the unique zeroes of the equation $bx(1 - \ln x) - \mu = 0$. These zeroes satisfy $0 < x_1^* < 1 < x_2^* < e$. The singular control keeps the singular curve invariant and is given as a feedback function of $p$ and $q$ as

$$u_{\sin}(t) = \frac{1}{\gamma}\left(\xi \ln\left(\frac{p(t)}{q(t)}\right) + b\frac{p(t)}{q(t)} + \frac{2}{3}\xi\frac{d}{b}\frac{q(t)}{p^{\frac{1}{3}}(t)} - \left(\mu + dp^{\frac{2}{3}}(t)\right)\right). \tag{10}$$

Using the relation (9), the singular control can equivalently be expressed as a function of $x$ alone in the form

$$u_{\sin}(t) = \frac{1}{\gamma}\left[\left(\frac{1}{3}\xi + bx(t)\right)\ln x(t) + \frac{2}{3}\xi\left(1 - \frac{\mu}{bx(t)}\right)\right]. \tag{11}$$

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

This structure is fully robust and only requires that $\gamma a > b - \mu > 0$, natural conditions for the problem. Fig. 1 gives the graph of the singular curve defined by (9) with the admissible portion marked as solid curve. For the parameter values for this illustration we used the following data from [13]: $\xi = \frac{0.192}{\ln 10} = 0.084$ per day (this value is adjusted to the natural logarithm.), $b = 5.85$ mm per day, $d = 0.00873$ per mm per day, $\gamma = 0.15$ kg per mg of dose. For the upper limit $a$ on the dosage we selected $a = 75$ and for illustrative purposes we also set $\mu = 0.02$.

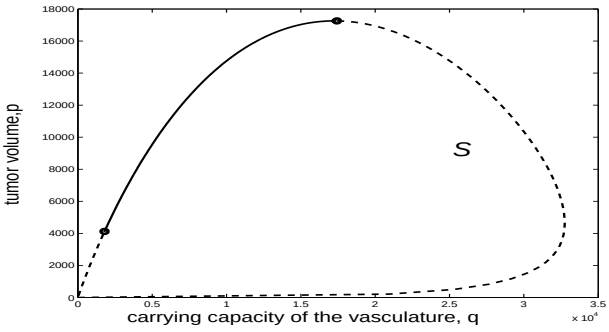


Fig. 1. Singular arc and its admissible part

### *C. Synthesis of optimal controls and trajectories*

Optimal controls then need to be synthesized from singular and bang controls 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 $\tau$. In [19] we carried out this analysis and, excluding certain ill-posed initial conditions $(p_0, q_0)$ for which it is not possible to lower the tumor volume below $p_0$, we proved the following result:

*Theorem 2.1:* [19] Optimal controls are at most concatenations of the form $\mathbf{0asa0}$ where $\mathbf{0}$ denotes an interval along which the optimal control is constant given by $u \equiv 0$, that is no inhibitors are given, $\mathbf{a}$ denotes an interval along which the optimal control is given at full dose, $u \equiv a$, and $\mathbf{s}$ denotes

an interval along which the optimal control follows the time-varying singular feedback control (10). This control is only optimal while the system follows the optimal singular arc $\mathcal{S}$ defined by (9). ■

A synthesis then provides a full "road map" for how optimal protocols look like depending on the initial condition in the problem, both qualitatively and quantitatively. Once it is known that the maximally possible optimal concatenation sequence is of the form **0asa0**, it is not difficult to compute the optimal control for a particular initial condition $(p_0, q_0)$. Figs. 2 and 3 show a characteristic example of an optimal control and its corresponding trajectory for the initial conditions $p_0 = 12,000$ and $q_0 = 15,000$. The trajectory is plotted with $p$ along the vertical axis and $q$ along the horizontal axis. This choice of variables better visualizes tumor reduction. In this case the optimal control initially is given by the full dose $u = a$. This typically is the case for initial conditions $(p_0, q_0)$ that lie below the singular arc. Once the trajectory corresponding to $u = a$ hits the singular arc, it is not optimal any more to give a full dose and the optimal control becomes singular following the singular arc. In the absence of saturation, the optimal control remains singular until all inhibitors become exhausted. Contrary to the initial full dose segment, now there is a significant shrinkage of the tumor volume along the singular arc. In this case the inhibitors become exhausted in the region $p > q$ and therefore the tumor volume will still be shrinking until the system crosses the diagonal $p = q$ at time $T$ when the minimum tumor volume is being realized. Thus, the last part of the optimal trajectory consists of a curve representing a no dose trajectory, $u = 0$. In the overall synthesis this structure, **as0**, is the most typical one. But other concatenation sequences are possible near saturation or, for example, if the initial condition already lies on the admissible part of the singular arc.

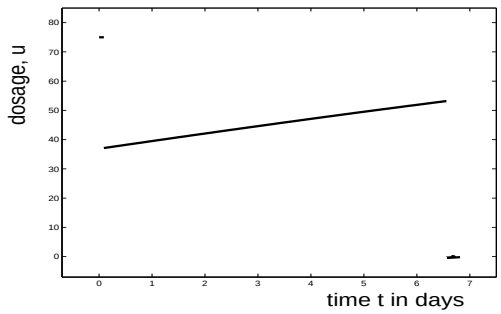


Fig. 2. Optimal control for initial conditions $p_0 = 12,000$ and $q_0 = 15,000$

## III. The Extended Model with PK

In the model formulation considered above - and this is a common first approximation in many biomedical systems - the concentration $c$ of the drug is identified with its dosage $u$ and effects $e$ are assumed instantaneous. Clearly, this is not the case, and bringing $PK$ into the model more realistically represents the dynamics of the treatment. We thus now consider an extended version of the optimal control problem formulated above where the concentration $c$ and its dosage $u$ are linked by a first order linear ODE with constant coefficients,

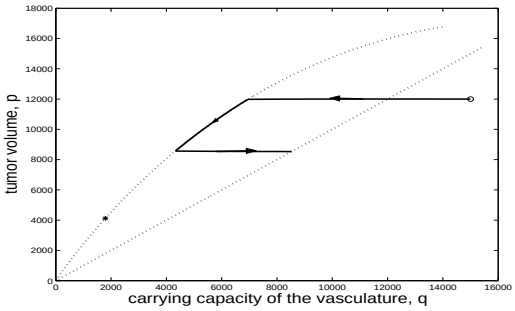


Fig. 3. Optimal trajectory for initial conditions $p_0 = 12,000$ and $q_0 = 15,000$

$$\dot{c} = -kc + hu, \qquad c(0) = 0. \tag{12}$$

The model itself is one of exponential growth and decay and is the standard and most commonly used model for $PK$. The maximum concentration is determined by the parameters as $c_{\max} = \frac{ha}{k}$ and the clearance rate $k$ is related to the half-life of the inhibitor as $\frac{\ln 2}{k}$. Thus, overall, the model now becomes:

(LPK) for a free terminal time $T$, minimize

$$J(u) = p(T) \tag{13}$$

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

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right), \qquad p(0) = p_0 \tag{14}$$

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}} + \gamma c\right) q, \quad q(0) = q_0 \tag{15}$$

$$\dot{c} = -kc + hu, \qquad c(0) = 0 \tag{16}$$

$$\dot{y} = u, \qquad y(0) = 0 \tag{17}$$

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

### A. Singular controls for the model with $PK$

The dynamical equations form a single input, control-affine system of the form

$$\dot{z} = F(z) + uG \tag{18}$$

with 4-dimensional state vector $z = (p, q, c, y)^T$, drift $F = F(z)$, and a constant control vector field $G$, $G = (0, 0, h, 1)^T$. The extended Hamiltonian takes the form

$$H = -\lambda_1 \xi p \ln\left(\frac{p}{q}\right) + \lambda_2 \left(bp - \left(\mu + dp^{\frac{2}{3}} + \gamma c\right) q\right) + \lambda_3(-kc + hu) + \lambda_4 u \tag{19}$$

with switching function

$$\Psi(t) = \lambda_3(t)h + \lambda_4. \tag{20}$$

If the control $u$ is singular on an open interval $I$, then all its derivatives must vanish identically. If we denote the multiplier by

$$\Lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4), \tag{21}$$

then a direct computation readily verifies (for example, see [19]) that for any smooth vector field $K = K(z)$ the derivative of the function

$$\Xi(t) = \langle \Lambda(t), K(z(t)) \rangle \tag{22}$$

along a solution to the system equation (18) for control $u$ and a solution $\Lambda$ to the corresponding adjoint equation,

$$\dot{\Lambda}(t) = -\Lambda(t)\left(DF(z(t)) + u(t)DG(z(t))\right), \tag{23}$$

is given by

$$\dot{\Xi}(t) = \langle \Lambda(t), [F + uG, K](z(t)) \rangle, \tag{24}$$

where $[F, K]$ denotes the Lie bracket of the vector fields $F$ and $K$. In local coordinates the Lie bracket is expressed as

$$[F, K](z) = DK(z)F(z) - DF(z)K(z)$$

with $DF$ and $DK$ denoting the matrices of the partial derivatives of $F$ and $K$, respectively.

Since the vector field $F$ does not depend on the variable $y$, and since the control vector field $G$ is constant, we get that

$$[F, G](z(t)) = -h\frac{\partial F}{\partial c}(z(T)) \tag{25}$$

and

$$[G, [F, G]](z(t)) = h^2\frac{\partial^2 F}{\partial c^2}(z(T)) \equiv 0. \tag{26}$$

It is this relation that makes the singular arc of higher order. For now, and using the notation $ad_F(K) = [F, K]$ for iterated Lie brackets, for the switching function $\Psi$ we have that

$$\dot{\Psi}(t) = \langle \Lambda(t), [F, G](z(t)) \rangle \equiv 0, \tag{27}$$

$$\ddot{\Psi}(t) = \left\langle \Lambda(t), ad_F^2(G)(z(t)) \right\rangle \equiv 0, \tag{28}$$

$$\dddot{\Psi}(t) = \left\langle \Lambda(t), ad_F^3(G)(z(t)) \right\rangle \equiv 0, \tag{29}$$

and the control is only determined by the fourth derivative,

$$\Psi^{(4)}(t) = \left\langle \Lambda(t), [F + uG, ad_F^3(G)](z(t)) \right\rangle \equiv 0. \tag{30}$$

An analysis of the conditions of the Maximum principle for this problem shows that the multiplier $\Lambda$ cannot vanish and that the multipliers $\lambda_2(t)$ and $\lambda_4$ are positive along a singular arc. The latter implies that the Kelley condition [26] for optimality of an order 2 singular control is satisfied,

$$\begin{aligned}\frac{\partial}{\partial u}\left(\frac{d^4}{dt^4}\Psi(t)\right) &= \left\langle \Lambda(t), [G, ad_F^3(G)](z(t)) \right\rangle \\ &= \lambda_2(t)h\gamma^2 bp(t) > 0.\end{aligned} \tag{31}$$

We now indicate how the relevant computations for the singular arc and singular control carry over from the previously considered model to the extended system with PK. Since the vector fields $F$ and $G$ do not depend on the variable $y$, (except for $G$ itself, the $y$-coordinate of all other brackets is zero,) $G$ is independent of any other vector field. Since $\Lambda(t)$ is nonzero and vanishes against the vector fields $F$, $ad_F(G)$ and $ad_F^2(G)$, these vector fields must be linearly dependent on the *singular set*:

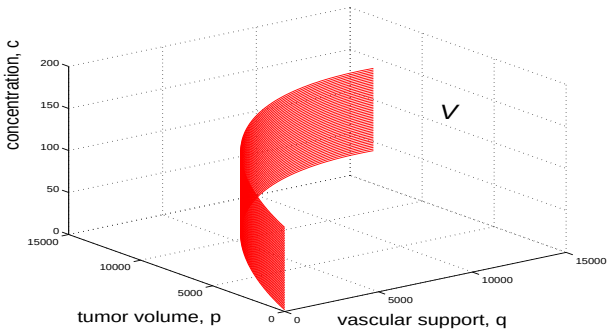


Fig. 4. Vertical singular surface in $(p, q, c)$-space

$$0 = \begin{vmatrix} -\ln\left(\frac{p}{q}\right) & 0 & -\gamma \\ bp - \left(\mu + dp^{\frac{2}{3}} + \gamma c\right)q & \gamma q & \gamma(bp + kq) \\ -c & 1 & k \end{vmatrix} \tag{32}$$

A direct computation verifies that this reduces to the relation (9) defining the singular curve for the model without $PK$. Now, however, this relation, which does not depend on the concentration $c$, only defines a vertical surface in $(p, q, c)$-space (see Fig. 4). But $\Lambda(t)$ also vanishes against the vector field $ad_F^3(G)$ and the linear dependence of the vector fields $ad_F(G)$, $ad_F^2(G)$ and $ad_F^2(G)$ determines the concentration. Taking advantage of linear dependencies in these vector fields, this relation simplifies to

$$0 = \begin{vmatrix} 0 & -1 & -\xi - b\frac{p}{q} \\ q & bp & \alpha(p, q, c) \\ 1 & 0 & 0 \end{vmatrix} \tag{33}$$

where

$$\begin{aligned}\alpha(p, q, c) = \xi bp\left(1 - \ln\left(\frac{p}{q}\right)\right) - \frac{2}{3}\xi dp^{\frac{2}{3}}q \\ + bp\left(\mu + dp^{\frac{2}{3}} + \gamma c\right).\end{aligned} \tag{34}$$

Solving for $c$, we get the formula (10). Thus the same relation that defines the optimal singular control for the model without PK, now defines the corresponding *singular concentration* (see Fig. 5).

Equivalently, this singular concentration $c_{\sin}(t)$ could also have been calculated by taking the derivative of (9) along the trajectory and substituting $\dot{p}$ and $\dot{q}$ from the state equations. Differentiating once more, an explicit expression for the *singular dosage (control)* can be obtained from

$$\gamma\dot{c}(t) = \left[b\left(1 + \ln x(t)\right) + \frac{1}{3}\frac{\xi}{x(t)}\left(1 + \frac{2\mu}{bx(t)}\right)\right]\dot{x}(t) \tag{35}$$

with

$$\dot{x} = x\left(\gamma c - (\xi + bx)\ln x\right). \tag{36}$$

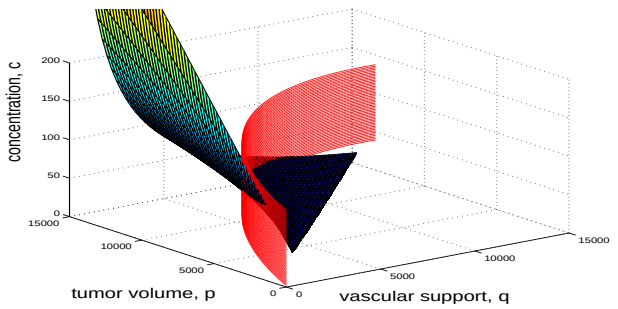


Fig. 5. Singular arc in $(p, q, c)$-space

Overall, we thus have the following result:

*Theorem 3.1:* The singular arc $\mathcal{S}$ of the model without $PK$ defined by (9) is preserved verbatim as a vertical 3-dimensional surface $\mathcal{V}$ in $(p, q, c)$-space. Equation (10) now defines the optimal concentration $c_{\sin}$ and the graph of this function intersects $\mathcal{V}$ in a unique curve, the new singular arc. The corresponding singular dosage is obtained through implicit differentiation along this singular arc. □

These facts are no coincidence, but are consequences of general properties of the Lie bracket configurations when the control in a control-affine system is replaced by the state of a first-order *linear* system. These general properties will be presented elsewhere [21].

### B. Synthesis of controls

While the singular arc is preserved with all its quantitative formulas, its order increases to 2 and it is well-known that an optimal singular arc of order 2 cannot be concatenated with the constant controls $u = 0$ or $u = a$, but that such a connection has to come by means of a chattering arc (e.g., [4], [26]). Clearly, such a control is not practicable. Hence, and similar to the model without PK, one has to look for realizable simple protocols [16], [20]. Given the knowledge of the optimal synthesis for the model without $PK$, it seems reasonable to postulate that a good suboptimal control $\tilde{u}$ produces as concentration $c_{\sin}(t)$. Of course, because of the inertia of the $PK$ dynamics and the constraints on $u$, the actual concentration cannot follow the discontinuous optimal control of the original model. This leads us to consider suboptimal controls that actuate $c(t)$ to track $c_{\sin}(t)$ "closely". These controls need to start with a full dose segment where $\tilde{u}(t) = a$ along some interval $[0, t'_a)$ and the treatment ends with $\tilde{u}(t) = 0$ on a final interval $[t'_s, T]$. In between, we track the originally optimal singular control, now the singular concentration. As complexities occur in the optimal transitions from the bang controls to the singular control, the easiest approximations simply concatenate by using one additional switching. A full investigation of both optimal and suboptimal protocols still needs to be undertaken.

## REFERENCES


[1] A. Anderson and M. Chaplain, Continuous and discrete mathematical models of tumor-induced angiogenesis, *Bull. Math. Biol.*, **60**, 1998, pp. 857-899

[2] L. Arakelyan, V. Vainstain and Z. Agur, A computer algorithm describing the process of vessel formation and maturation, and its use for predicting the effects of anti-angiogenic and anti-maturation therapy on vascular tumour growth, *Angiogenesis*, **5**, (2003), 203ff

[3] T. Boehm, J. Folkman, T. Browder, and M.S. O'Reilly, Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance, *Nature*, **390**, (1997), pp. 404-407

[4] B. Bonnard and M. Chyba, Singular Trajectories and their role in Control Theory, Mathématiques & Applications, vol. 40, Springer Verlag, Paris, 2003

[5] A. Bressan and B. Piccoli, *Introduction to the Mathematical Theory of Control*, American Institute of Mathematical Sciences, 2007

[6] F. Castiglione and B. Piccoli, Optimal control in a model of dendritic cell transfection cancer immunotherapy, *Bulletin of Mathematical Biology*, **68**, (2006), pp. 255-274

[7] L.G. de Pillis and A. Radunskaya, A mathematical tumor model with immune resistance and drug therapy: an optimal control approach, *J. of Theoretical Medicine*, **3**, (2001), pp. 79-100

[8] A. d'Onofrio, A general framework for modeling tumor-immune system competition and immunotherapy: mathematical analysis and biomedical inferences, *Physica D*, **208**, 2005, pp. 220-235

[9] A. d'Onofrio and A. Gandolfi, Tumour eradication by antiangiogenic therapy: analysis and extensions of the model by Hahnfeldt et al., *Math. Biosci.*, **191**, 2004, pp. 159-184

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

[11] U. Felgenhauer, On stability of bang-bang type controls, *SIAM J. Control Optim.*, **41**, No. (6), (2003), 1843-1867

[12] J. Folkman, Antiangiogenesis: new concept for therapy of solid tumors, *Ann. Surg.*, **175**, (1972), pp. 409-416

[13] 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

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

[15] D. Kirschner, S. Lenhart, and S. Serbin, Optimal control of chemotherapy of HIV, *J. Math. Biol.*, **35**, (1997), pp. 775-792

[16] U. Ledzewicz, J. Marriott, H. Maurer and H. Schättler, *The scheduling of angiogenic inhibitors minimizing tumor volume J. of Medical Informatics and Technologies*, **12**, (2008), pp. 23-28

[17] U. Ledzewicz, J. Munden and H. Schättler, Scheduling of Angiogenic Inhibitors for Gompertzian and Logistic Tumor Growth Models, *Discrete and Continuous Dynamical Systems, Series B*, to appear

[18] U. Ledzewicz and H. Schättler, The influence of PK/PD on the structure of optimal control in cancer chemotherapy models, *Mathematical Biosciences and Engineering (MBE)*, **2**, no. 3, (2005), pp. 561-578

[19] U. Ledzewicz and H. Schättler, Anti-Angiogenic therapy in cancer treatment as an optimal control problem, *SIAM J. Contr. Optim.*, **46**, 2007, pp. 1052-1079

[20] U. Ledzewicz and H. Schättler, Optimal and suboptimal protocols for a class of mathematical models of tumor anti-angiogenesis, *J. of Theoretical Biology*, **252**, (2008), pg. 295-312

[21] U. Ledzewicz and H. Schättler, Singular controls and chattering arcs in optimal control problems arising in biomedicine, *Control and Cybernetics*, to appear

[22] H. Maurer, C. Büskens, J.-H. Kim and Y. Kaja, Optimization techniques for the verification of second-order sufficient conditions for bang-bang controls, *Optimal Control, Applications and Methods*, **26**, (2005), pp. 129-156

[23] G. Stefani, On sufficient optimality conditions for singular extremals, Proceedings of the *42nd IEEE Conference on Decision and Control (CDC)*, Maui, Hi, USA, December 2003, pp. 2746-2749

[24] A. Swierniak, Direct and indirect control of cancer populations, *Bulletin of the Polish Academy of Sciences, Technical Sciences*, **56** no. 4, (2008), pp. 367-378

[25] A. Swierniak, G. Gala, A. Gandolfi and A. d'Onofrio, Optimization of angiogenic therapy as optimal control problem, Proceedings of the 4th IASTED Conference on Biomechanics, Acta Press, (Ed. M. Doblare), (2006), pp. 56-60

[26] M.I. Zelikin and V.F. Borisov, *Theory of Chattering Control with Applications to Astronautics, Robotics, Economics and Engineering*, Birkhäuser, 1994