OPTIMAL CONTROLS OF A GENERALIZED MATHEMATICAL MODEL FOR TUMOR ANTI-ANGIOGENESIS

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ABSTRACT
We describe optimal protocols for a more general mathematical model for tumor anti-angiogenesis for the problem of minimizing the tumor volume with an a priori given amount of vessel disruptive agents. Based on the biological results of [1, 2, 3], we will consider a modified model. We get the optimal control solution with singular arc for the new model.

Keywords: *Optimal controls, Tumor anti-angiogenesis, Angiogenic inhibitors, Singular arc.*

1. INTRODUCTION

A growing tumor needs a steady supply of oxygen and nutrients for cell duplication. Initially during avascular growth, it is provided through the surrounding environment. At the tumor becomes larger, these mechanisms become inadequate and tumor cells enter the dormant stage of the cell cycle. As a consequence, vascular endothelial growth factors (VEGF) are released that stimulate the formulation of new blood vessels and capillaries in order to supply the tumor with needed nutrients. This process is called tumor angiogenesis. The anti-angiogenesis is a treatment approach for cancer that aims at depriving the tumor of this vasculature. Ideally, without an adequate support network, the tumor shrinks.

Tumor anti-angiogenesis is an indirect cancer treatment approach with aim to limit the tumor's growth, possibly even shrink the tumor, by depriving it of the vasculature it needs for a steady supply with nutrients. It had already been proposed by J. Folkman in the seventies [4], but was only enabled with the discovery mechanisms of the tumor in the nineties [5, 6]. The treatment targets the endothelial cells that form the lining of the newly developing blood vessels and capillaries. These are healthy, genetically stable cell lines and consequently no clonal resistance to angiogenic inhibitors has been observed in experimental cancer [7]. Since developing drug resistance all too often is the limiting factor in conventional chemotherapy treatments, tumor anti-angiogenesis has been called a new hope for the treatment of tumor [8]. Although these high hopes have not been realized in practice, these still is strong interest and active research on tumor anti-angiogenesis as a method that normalizes the vasculature [9, 10]. Thus it is not efficient as a stand-alone or monotherapy treatment, but it needs to be combined with other mechanisms like chemotherapy [2] that kill cancer cell.

In the paper, we formulate a class of mathematical models for tumor anti-angiogenesis as optimal control problems. Specifically we consider the problem of how to schedule an a priori given amount of anti-angiogenic (e.g., vessel disruptive) agents in order to minimize the tumor volume. For similar formulations with a modified objective where the tumor volume is minimized over a fixed therapy horizon, see the work of Swierniak et al. [11, 12]. The principal state variables are the primary tumor volume, p, and the carrying capacity of the vasculature, q. The latter is a measure for the tumor volume sustainable by the vascular network. The tumor volume p changes according to same growth function dependent on the variable carrying capacity q and the q-dynamics consists of a balance of stimulatory and inhibitory effects. Hahnfeldt et al. carry out an asymptotic analysis of the underlying consumption-diffusion model that leads to the form for these terms proposed in [1]. Here, we will consider a more generalized model. We show that optimal controlled trajectories for all these models are characterized by the fact that there exists a unique "path" in(p,q)-space along which the optimal tumor reductions are realized. Optimal controls steer the system to this path as quickly as possible (using maximum dosages) and then follow the optimal path determined by a so-called singular arc (using specific partial dosages) until all inhibitors run out.

2. MATHEMATICAL MODELING

The model we consider are minimally parameterized and population based. We formulate a mathematical model for combination of tumor anti-angiogenesis with chemotherapy that is based on a model by Ergun, Camphausen and Wein in [2]. This model itself is a modification of a biologically validated model by Hahnfeldt at el. form [1] in which 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. Intuitively, the latter defines the ideal tumor volume sustainable by the vascular network. It is related to the volume of endothelial cells and for this reason we also call it the endothelial support of the tumor for short.

Tumor growth is modeled by a Gompertzion growth function,

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

where ξ denotes a tumor growth parameter. The dynamics proposed in [13] for its basic structure can be written in the form

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

where *I* and *S*, respectively, denote endogenous inhibition and stimulation terms and the term μq that has been separated describes the net balance between endothelial cell proliferation and loss to the endothelial cell through natural causes (death etc.). These effects are small when compared with the stimulation and inhibition exerted by the tumor and μ typically is a small constant that is set to 0 in many models. It is included here, but with the understanding that its value is small in absolute value. The components that define the dynamics are the functional forms for the endogenous inhibition and stimulation terms. Hahnfeldt et al. [1] carry out a spatial analysis of the underlying consumption-diffusion model that leads to the following two principal conclusions for the relations between endogenous inhibition and stimulation:

1. The inhibitor will impact endothelial cells in a way that grows like volume of cancer cell to the power $\frac{2}{3}$. More generally, we shall consider replacing the exponent $\frac{2}{3}$ with δ $(0 < \delta < 1)$.

2. The inhibitor term tends to grow at a rate of $q^m p^n$ faster than the stimulater term where $m + n = \frac{2}{3}$.

Based on the first conclusion in [1], the inhibitor term is taken with form

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

Here, we will consider more generally form of inhibition term

$$I(p,q) = dp^{\alpha} q^{\beta}, \quad (0 \le \alpha \le 1, 0 \le \beta \le 1) \tag{4}$$

with d a constant. But there exists freedom in the choice of *m* and n and this has become a source for other models considered in the literature. In [1], the natural assumption is made to take the stimulation term proportional to tumor volume,

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

with b a constant, which represents as the birth rate. This corresponds to the choice $m = \alpha - 1$ and $n = \beta$ ($\frac{I}{S} = \frac{d}{b} p^{\alpha-1} q^{\beta}$). But based on [1] other choice are possible and, for example, if we take $m = \alpha$ and $n = \beta - 1$, then the we get equally simple form

$$S(p,q) = bq \tag{6}$$

when the stimulation is proportional to the carrying capacity. The second choice generates a considerably simpler q-dynamics for the model in which q factors. Since p and q are expected to be closely related in steady-state, one expects similar behavior for these models. In [14] d'Onofrio and Gandolfi fully analyze both dynamics with special attention to the effects of periodic treatment regimes.

A third model that more strongly makes the steady state assumption of relation p with q was formulated by Ergun, Camphansen and Wein in [2]. In this paper the following forms are used for inhibition and stimulation

$$I(q) = dq^{\frac{\alpha}{2}+\beta}, \qquad S(q) = bq^{\frac{3\alpha+6\beta}{4}} \tag{7}$$

This choice eliminates any p-dependence from the dynamics for the endothelial support. The authors' motivation for this approximation lies in a different balance for the substitution of stimulation and inhibition that slows down the q-dynamics. The main advantage of replacing p with q lies in a significant mathematical simplification. On the other hand, this step eliminates a direct link between tumor volume p and endothelial support q and thus the overall consequences of this modeling change might appear drastic.

In this paper, we consider a formulation that does not replace p with q. This leads to the following inhibition and

stimulation terms

$$I(p,q)=dp^{\alpha}q^{\beta}, \qquad S(p)=bp^{\theta} \tag{8}$$

with θ a parameter. If we choose $\theta=1$, $\alpha=\frac{2}{3}$ and $\beta=1$, then it corresponds to the term chosen in [1]; while if we choose $\theta=\frac{2}{3}$, $\alpha=\frac{2}{3}$ and $\beta=1$, it will be consistent with the modification made in [2]. Note that if $\theta=1$, we have $\frac{I}{S}=\frac{d}{b}p^{\alpha-1}q^{\beta}$ and $m+n=\alpha-1+\beta$. Otherwise $m+n\neq\frac{2}{3}$ violating the second modeling premise in [1]. Thus these models can be seen as one between the models of [1] and [2]. We summarize and label the q-dynamics of all eight models in Table 1.

Model	inhibition $I(p,q)$	stimulation $S(p,q)$	Reference
H_1	$dp^{\frac{2}{3}}q$	bp	[1]
$\widetilde{H}_1$	$dp^{\alpha}q^{\beta}$	bp	
H_0	$dp^{\frac{2}{3}}q$	bq	[1]
$\widetilde{H}_0$	$dp^{\alpha}q^{\beta}$	bq	
I_θ	$dp^{\frac{1}{3}}q$	bp^{θ}	[3]
$\widetilde{I}_\theta$	$dp^{\alpha}q^{\beta}$	bp^{θ}	
E	$dq^{\frac{4}{3}}$	$bq^{\frac{2}{3}}$	[2]
$\widetilde{E}$	$dq^{\frac{\alpha}{2}+\beta}$	$bq^{\frac{3\alpha+6\beta}{4}}$	

Table 1: Models for inhibition and stimulation.

3. SINGULAR CONTROL AND SINGULAR ARC FOR MODELS ($\widetilde{I}_\theta$).

Let $z=(p,q,y)^T$, then the system will be rewritten as

$$z'=f(z)+ug(z), \tag{9}$$

where

$$f(z)=\begin{Bmatrix} -\xi p\ln(\frac{p}{q}) \\ bp^{\theta}-dp^{\alpha}q^{\beta}-\mu q \\ 0 \end{Bmatrix}, \tag{10}$$

and

$$g(z)=\begin{Bmatrix} 0 \\ -\gamma q \\ 1 \end{Bmatrix}. \tag{11}$$

In this notation, the switching function becomes the inner product of the multiplier $\lambda = (\lambda_1, \lambda_2, \lambda_3)$ and the vector field g along the solution $z(t)$, $\Phi(t) = \langle \lambda(t), g(z(t)) \rangle$. More generally, the derivative of a function

$$\Psi(t) = \langle \lambda(t), h(z(t)) \rangle \tag{12}$$

where h is any continuously differentiable vector field, can easily be computed directly and is given by

$$\Psi'(t) = \langle \lambda(t), [f + ug, h](z(t)) \rangle \tag{13}$$

with $[f,h]$ denoting the Lie bracket of the vector f and h given by

$$[f,h](z) = Dh(z)f(z) - Df(z)h(z) \tag{14}$$

and Df denote the matrix of the partial derivatives of f. We therefore have that

$$\Phi'(t) = \langle \lambda(t), [f,g](z(t)) \rangle, \tag{15}$$

$$\Phi''(t) = \langle \lambda(t), [f + ug, g](z(t)) \rangle, \tag{16}$$

and for the model $\widehat{I_\theta}$ direct calculations verify that these brackets are given by

$$[f,g](z) = \begin{Bmatrix} \xi\gamma p \\ -b\gamma p^{\theta} + dp^{\alpha} q^{\beta} (1-\beta) \\ 0 \end{Bmatrix}, \tag{17}$$

$$[g,[f,g]](z) = \begin{Bmatrix} 0 \\ -b\gamma^2 p^{\theta} - \gamma d p^{\alpha} q^{\beta} (1-\beta)^2 \\ 0 \end{Bmatrix}, \tag{18}$$

and

$$[f,[f,g]](z) = \gamma p^{\theta} \begin{Bmatrix} \omega_1 \\ \omega_2 \\ \omega_3 \end{Bmatrix}. \tag{19}$$

Here we denote

$$\omega_1 = \xi^2 p^{1-\theta} + \frac{\xi b p}{q} - \frac{d\xi p^{\alpha+1-\theta} q^{\beta-1}(1-\beta)}{\gamma},$$

$$\omega_2 = \theta\xi b(\ln\frac{p}{q} - 1) - \frac{\xi\alpha d p^{\alpha-\theta} q^{\beta}[(1-\beta)\ln(\frac{p}{q}) - \gamma]}{\gamma} + \frac{bd\beta p^{\alpha} q^{\beta-1}(1-\beta-\gamma)}{\gamma} + \frac{\mu d p^{\alpha-\theta} q^{\beta}(1-\beta)^2}{\gamma} - \mu b$$

and

$$\omega_3 = 0.$$

It is a necessary condition for minimality of the singular control, the Legendre-Cledsch condition [15], that

$$\langle \lambda(t), [g,[f,g]](z(t)) \rangle \le 0. \tag{20}$$

If this quantify is negative, i.e., if the strengthened Legendre-Cledsch conditions holds, then we can formally solve the equation $\Phi''(t) \equiv 0$ (see [4]) for the *singular control* as

$$u_{\sin}(t) = -\frac{\langle \lambda(t), [f,[f,g]](z(t)) \rangle}{\langle \lambda(t), [g,[f,g]](z(t)) \rangle}. \tag{21}$$

For this model we have that

$$\langle \lambda(t),[g,[f,g]](z(t))\rangle \equiv (-b\gamma^2 p^\theta - \gamma d p^\alpha q^\beta (1-\beta)^2)\lambda_2(t). \tag{22}$$

The switching function $\Phi(t) = \lambda_3 - \lambda_2(t)\gamma q_*(t)$ vanishes along a singular arc. It follows that λ_3 cannot vanish. Otherwise λ_2 must vanish as well, and then by (16) in [3], λ_1 will also vanishes identically along the singular arc. Since λ_1 and λ_2 are solutions to a homogeneous linear differential equation this contradicts $\lambda_1(T=1)$. It then can be shown as in [16] that λ_3 actually must be positive. Hence λ_2 is positive along a singular arc. Thus *the strengthened Legendre-Cledsch condition is satisfied and singular controls will be locally optimal.*

The vector fields g, $[f,g]$ and $[g,[f,g]]$ are linearly independent everywhere and therefore we can express the vector field $[f,[f,g]]$ as a linear combination of this basis, say

$$[f,[f,g]](z) = a_1(z)g(z) + a_2(z)[f,g](z) + a_3(z)[g,[f,g]](z). \tag{23}$$

Hence

$$\langle \lambda(t),[f,[f,g]](z(t))\rangle = a_1(z)\langle \lambda(t),g(z)\rangle + a_2(z)\langle \lambda(t),[f,g](z)\rangle + a_3(z)\langle \lambda(t),[g,[f,g]](z)\rangle.$$

But λ vanishes against g and $[f,g]$ along the singular arc,

$$\langle \lambda(t),g(z(t))\rangle = \langle \lambda(t),[f,g](z)\rangle = 0,$$

and thus the singular control is simply given as

$$u_{sin}(z(t)) = -a_3(z(t)). \tag{24}$$

The coefficients a_i are easily computed. Since the third component of $[f,[f,g]]$ vanishes, we have $a_1(z) \equiv 0$, and comparing the first coordinates we see that $a_2(z) = q + b\dfrac{p^\theta}{q} - \dfrac{dp^\alpha q^{\beta-1}(1-\beta)}{\gamma}$. At last, we get

$$\begin{aligned} a_3(z) \;=\; & \frac{\xi b\gamma p^\theta[\theta(\ln\frac{p}{q}-1)+1] - \xi d p^\alpha q^\beta[\alpha[(1-\beta)\ln\frac{p}{q}-\gamma]+(1-\beta)]}{-b\gamma^2 p^\theta - \gamma b p^\alpha q^\beta (1-\beta)^2} \\ & + \frac{b d p^{\alpha+\theta} q^{\beta-1}[1-\beta-\gamma-2(1-\beta)] + \frac{b^2 p^{2\theta}\gamma}{q} + \mu d p^\alpha q^\beta (1-\beta)^2 - \mu b\gamma p^\theta}{-b\gamma^2 p^\theta - \gamma b p^\alpha q^\beta (1-\beta)^2}, \end{aligned}$$

giving the singular control as a feedback function of p and q.

The corresponding *singular arc* is determined by the requirement that λ also vanishes against f along the singular arc. This holds because the Hamiltonian H must be identically zero. Since λ is non-zero (recall that $\lambda_1(T)=1$)£¬the vector fields f, g and $[f,g]$ must be linearly dependent along the singular arc :

$$0 = \det(f,g,[f,g]) = \begin{vmatrix} -\xi p\ln(\frac{p}{q}) & 0 & \xi\gamma p \\ bp^\theta - dp^\alpha q^\beta - \mu q & -\gamma q & -b\gamma p^\theta + dp^\alpha q^\beta(1-\beta) \\ 0 & 1 & 0 \end{vmatrix}$$

$$= -\gamma\xi p \begin{vmatrix} -\ln\frac{p}{q} & 1 \\ bp^\theta - dp^\alpha q^\beta - \mu q & -bp^\theta + \frac{dp^\alpha q^\beta(1-\beta)}{\gamma} \end{vmatrix}$$

$$= -\gamma\xi p[bp^\theta(\ln\frac{p}{q}-1) + dp^\alpha q^\beta(1-\frac{1-\beta}{\gamma}) + \mu q].$$

Writing $x = \frac{p}{q}$, we thus have the following result :

Theorem 3.1 *For model* $(\tilde{I}_\theta)$ *there exists locally optimal singular arc defined as the zero set of the equation*

$$bx(1-\ln(x)) = dp^{\alpha+1-\theta}q^{\beta-1}(1-\frac{1-\beta}{\gamma}) + \mu p^{1-\theta}. \tag{25}$$

The singular control that makes this curve invariant is given by the feedback control

$$\begin{aligned} u_{\sin}(z) \;=\; & \frac{\xi b\gamma p^{\theta}[\theta(\ln\frac{p}{q}-1)+1] - \xi d p^{\alpha}q^{\beta}[\alpha[(1-\beta)\ln\frac{p}{q}-\gamma]+(1-\beta)]}{b\gamma^2 p^{\theta} + \gamma b p^{\alpha}q^{\beta}(1-\beta)^2} \\ & + \frac{bdp^{\alpha+\theta}q^{\beta-1}[1-\beta-\gamma-2(1-\beta)] + \frac{b^2 p^{2\theta}\gamma}{q} + \mu d p^{\alpha}q^{\beta}(1-\beta)^2 - \mu b\gamma p^{\theta}}{b\gamma^2 p^{\theta} + \gamma b p^{\alpha}q^{\beta}(1-\beta)^2} \end{aligned} \tag{26}$$

Proof. The proof is easily followed by the above discussion.

For the modifications of the model $(\tilde{H}_1)$ from the original model (H_1) form [1], this relation is given by

$$\mathrm{bx}(1-\ln \mathrm{x}) = \mathrm{dp}^{\alpha}\mathrm{q}^{\beta-1}(1-\frac{1-\beta}{\gamma}) + \mu \tag{27}$$

This equation corresponds to a choice $\theta = 1$ and the only difference lies in the exponent at the d -term which is $\frac{2}{3}$ if inhibition is taken proportional to the surface area, and $\frac{1}{3}$ if it is taken proportional to the tumor radius.

Based on these computation, it is now not difficult to construct a synthesis of optimal controlled trajectories. Essentially, this follows the steps of the construction given in [16] and it provides the same structure for the generalized systems $(\tilde{I}_\theta)$, $(\frac{2}{3} \le \theta \le 1)$, as for model $(\tilde{H}_1)$. Comparing the structure with the optimal syntheses for the model $(\tilde{H}_1)$ and $(\tilde{E})$, the same features are easily recognized. While the actual geometric shape of the singular arc more closely resembles the one for the model $(\tilde{H}_1)$, the trajectories corresponding to the control $\mathrm{u} = 0$ much closer follow trajectories similar to those for the model $(\tilde{E})$.

4. CONCLUSION

Assuming a Gompertzian growth model, for a wide class of mathematical models for tumor anti-angiogenesis, including models that make significant differences in their modeling assumptions, there exists a unique path in (p,q)-space along which optimal tumor reductions are achieved. This path is given by a so-called singular arc whose precise analytical structure can be determined explicitly, but of course depends on the functions entering the dynamics of the models. There solutions are fully robust with respect to parameter variations. In our simulations above we have used parameter values from [1] that were biologically validated, but the underlying theoretical results do not need to make any assumptions about these numerical values and are generally valid.

Naturally, the feedback control that defines the optimal dosages along the singular arc is not a feasible treatment strategy. However, for both the models (H_1) and (E) there exist excellent, and themselves fully robust suboptimal approximations to the optimal controls given by piecewise constant controls [17]. In fact, these approximations also are highly insensitive towards the initial value q_0 of the carrying capacity and only show strong dependence on the initial tumor volume p_0. Given the fact that q_0 is an idealistic quantity that cannot be measured accurately, this feature of the optimal protocols would seen to be of practical importance.

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