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BANG-BANG CONTROLS FOR ANTI-ANGIOGENESIS UNDER LOGISTIC GROWTH OF THE TUMOR

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Abstract: The scheduling of angiogenic inhibitors is analyzed as an optimal control problem for a mathematical model for tumor anti-angiogenesis proposed by Ergun et al [3] with a logistic growth function modeling tumor growth. It is shown that optimal controls are bang-bang with at most two switchings.

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1. Introduction

Tumor anti-angiogenesis is a cancer treatment approach that targets the vasculature of a growing tumor. Anti-angiogenic treatments bring in external inhibitors to disrupt this process and thus indirectly effect the tumor which, deprived of necessary nutrition, regresses. These inhibitors, like endostatin, are very expensive biological agents. Since there also always is a need to keep side effects under control, the question how to administer an a priori given amount of inhibitors in an optimal way arises naturally and this leads to optimal control problems.

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In the literature there exist several mathematical models [3, 2] that summarize the essential aspects of tumor anti-angiogenesis as low dimensional dynamical systems described by ordinary differential equations. Many of these are based on the biologically validated model by Hahnfeldt, Panigrahy, Folkman and Hlatky, [4]. In this paper we analyze the modification proposed by Ergun, Camphausen and Wein [3] with a logistic model on the growth of the tumor volume. In [3] a Gompertzian growth function was used instead and we showed in [5] that optimal controls contained a segment along which the control is given by a time-varying singular feedback control. Such controls are not practically realizable with current state of medical technologies. In this paper we show that if the model on the growth of the cancer volume is changed from Gompertzian to a logistic one, then optimal controls in fact are bang-bang (changing between full dose and no dose) with at most two switchings.

2. Mathematical Model [3]

As in the underlying model by Hahnfeldt et al [4], in this modification by Ergun et al the state variables are the primary tumor volume, p, and the carrying capacity of the vasculature, q. A classical logistic growth model with varying capacity defined by q is taken for the tumor volume, i.e.,

$$\dot{p} = \xi p \left(1 - \left(\frac{p}{q}\right)\right), \quad p(0) = p_0 \tag{1}$$

with ξ a tumor growth parameter and the dynamics for the carrying capacity q is given in the form

$$\dot{q} = bq^{\frac{2}{3}} - \mu q - dq^{\frac{4}{3}} - Guq, \quad q(0) = q_0. \tag{2}$$

In these equations the terms with the coefficients b and d are endogeneous stimulation and inhibition terms (mnemonically labeled for 'birth' and 'death') and the powers of the exponent $\frac{2}{3}$ arises since angiogenic inhibitors are being released through the tumor surface scaling down the volume to the surface area. The terms μq and Guq describe, respectively, loss to the endothelial cells through natural causes (death etc.), and 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. We then consider the optimal control problem to maximize the tumor reduction achievable with a given amount of inhibitors, $\int_0^T u(t)dt \leq A$. For the analysis of the resulting optimal control problem it is more convenient to add a third state variable y that tracks

the amount of inhibitors used, i.e.,

$$\dot{y} = u, \quad y(0) = 0, \quad y(T) \leq A, \tag{3}$$

and thus arrive at the following problem formulation:

(OC) For a free terminal time T, minimize $J(u) = p(T)$ over all Lebesgue measurable functions $u : [0, T] \to [0, a]$ subject to the dynamics (1), (2) and (3).

3. Analysis of Optimal Controls

First-order necessary conditions for optimality given by the *Pontryagin Maximum Principle* (e.g., [1]). With $\lambda = (\lambda_1, \lambda_2, \lambda_3)$ define the Hamiltonian $H = H(\lambda, p, q, u)$ as

$$H = \lambda_1 \xi p \left(1 - \left(\frac{p}{q}\right)\right) + \lambda_2 \left(bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - Guq - \mu q\right) + \lambda_3 u. \tag{4}$$

Then, if u_* is an optimal control defined over the interval $[0, T]$ with corresponding trajectory (p_*, q_*, y_*), there exist a constant $\lambda_0 \geq 0$ and an adjoint vector $\lambda : [0, T] \to (\mathbb{R}^3)^*$ such that:

(a) $(\lambda_0, \lambda(t)) \neq (0, 0)$ for all $t \in [0, T]$,

(b) λ_3 is constant, and λ_1 and λ_2 satisfy the adjoint equations

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial p}, \qquad \dot{\lambda}_2 = -\frac{\partial H}{\partial q} \tag{5}$$

with transversality conditions $\lambda_1(T) = \lambda_0$ and $\lambda_2(T) = 0$.

(c) for almost every time $t \in [0, T]$ the optimal control $u_*(t)$ minimizes the Hamiltonian along $(\lambda(t), p_*(t), q_*(t))$ over the control set $[0, a]$ with minimum value given by 0.

The following statements summarize some properties of optimal controls that were proven in [6]: Along an optimal trajectory (p_*, q_*, y_*), all available inhibitors are exhausted, $y_*(T) = A$, and at the final time we have $p_*(T) = q_*(T)$. All extremals for problem (OC) are normal, $\lambda_0 = 1$, and the multipliers λ_1, λ_2 and λ_3 are positive on $[0, T)$.

The minimum condition on the Hamiltonian H is equivalent to minimizing the linear function $(\lambda_3 - \lambda_2(t)Gq_*(t))\, v$ over $v \in [0, a]$. Thus, if we define the so-called *switching function* Φ as

$$\Phi(t) = \lambda_3 - \lambda_2(t)Gq_*(t), \tag{6}$$

then optimal controls satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0\,, \\ a & \text{if } \Phi(t) < 0\,. \end{cases} \tag{7}$$

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 canonical 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. We therefore need to analyze the switching function and its derivatives. If we express the dynamics in vector form as $\dot{z} = f(z) + ug(z)$ with $z = (p, x, y)^T$ and

$$f(z) = \left(\xi p\left(1 - \left(\frac{p}{q}\right)\right), bq^{\frac{2}{3}} - \mu q - dq^{\frac{4}{3}} - Guq, u\right)^T, \tag{8}$$

$$g(z) = (0, -Gq, 1)^T, \tag{9}$$

then the derivatives of the switching function can be calculated using the following well-known fact: 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 for control u and a solution λ to the corresponding adjoint equations is given by

$$\dot{\Psi}(t) = \langle \lambda(t), [f + ug, h]z(t)\rangle\,, \tag{10}$$

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 $[f, h](z) = Dh(z)f(z) - Df(z)h(z)$ where Df denotes the matrix of the partial derivatives of f.

For the given system the Lie brackets take the form

$$[f, g](z) = \left(\xi Gq\left(\frac{p}{q}\right)^2, -\frac{1}{3}G\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right), 0\right)^T, \tag{11}$$

$$[g, [f, g]](z) = \left(\xi G^2 q\left(\frac{p}{q}\right)^2, -\frac{1}{9}G^2\left(bq^{\frac{2}{3}} - dq^{\frac{4}{3}}\right), 0\right)^T. \tag{12}$$

Thus

$$\langle \lambda(t), [g, [f, g]](z(t))\rangle = G^2\left[\lambda_1 \xi q\left(\frac{p}{q}\right)^2 + \frac{\lambda_2}{9}\left(-bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right)\right].$$

Using the fact that $\lambda_1 \xi q\left(\frac{p}{q}\right)^2 = \frac{\lambda_2}{3}\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right)$ along a singular arc since

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

$$\langle \lambda(t), [g,[f,g]](z(t)) \rangle = \frac{2}{9} G^2 \lambda_2 \left[b q^{\frac{2}{3}} + 2 d q^{\frac{4}{3}} \right]. \tag{13}$$

Since λ_2 is positive the Legendre-Clebsch condition [1] is violated and in this case singular controls are locally maximizing.

We thus can concentrate on bang-bang controls and their switchings. We first analyze the regions of the state-space where **0a**-respectively **a0**-switchings are possible. It follows from (7) that the derivative of the switching function must be non-positive at a switching time τ if the switching is from 0 to a (**0a**) and non-negative if the switching is from a to 0 (**a0**). Since $H \equiv 0$ we have at any switching time both $\langle \lambda(\tau), g(z(\tau)) \rangle = 0$ and $\langle \lambda(\tau), f(x(\tau)) \rangle = 0$. Extend the vector fields f and g to a basis of $\mathbb{R}^3$ by adding the constant field $h(z) = (0,0,1)^T$ and write $[f,g](z)$ as a linear combination of $f(z)$, $g(z)$ and h in the form

$$[f,g](z) = \alpha(z) f(z) + \beta(z) g(z) + \gamma(z) h\,, \tag{14}$$

where α, β and γ are analytic functions of z. We then obtain that

$$\dot{\Phi}(\tau) = \langle \lambda(\tau), [f,g] z(\tau) \rangle = \gamma(z(\tau)) \lambda_3. \tag{15}$$

Since λ_3 is positive $\dot{\Phi}(\tau)$ and $\gamma(z(\tau))$ have the same sign. Further analysis of this function γ (see [7] for more details) leads to the following theorem that describes the structure of optimal bang-bang controls in the biologically relevant region R given by $R = \{(p,q) : p_a \le p \le \bar{p}, q_a \le q \le \bar{q}\}$ where q_a and $\bar{q}$ are the equilibria of the q-dynamics for the constant controls $u = a$ and $u = 0$, respectively.

Theorem 1. *For initial conditions (p_0, q_0) in the biologically relevant region R optimal controls are bang-bang with at most two switchings of the type* **0a0**. *Switchings from $u = 0$ to $u = a$ can only occur in the region $\mathcal{R}_- = \{(p,q) \in R : p < q\}$ while switchings from $u = a$ to $u = 0$ must lie in $\mathcal{R}_+ = \{(p,q) \in R : p > q\}$.*

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