# Scheduling of Angiogenic Inhibitors for Gompertzian and Logistic Tumor Growth Models

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**Abstract**

For tumor anti-angiogenesis the problem of scheduling a given amount of angiogenic inhibitors in order to maximize the tumor reduction achievable is considered as an optimal control problem. For a dynamical model for the evolution of the carrying capacity of the vasculature formulated in [12] optimal controls are computed for both a Gompertzian and logistic model for the tumor growth. While optimal controls for a Gompertzian model typically contain a segment along which the control is singular, optimal controls are bang-bang with at most two switchings for a logistic model.

## 1 Introduction

An important factor seriously limiting the success of cancer chemotherapy is drug resistance, both intrinsic and acquired. Various biological phenomena including a great genetic diversity of cancer cells and fast mutations coupled with gene amplifications that create new cancer cells that no longer show a response to the drugs being used often lead to a failure of chemotherapy over longer time horizons. At the same time, it is interesting to notice that similar phenomena do not seem to take place for the genetically much more stable healthy proliferating cells. For example, regretfully bone marrow does not develop drug resistance to the killing agent. A natural thought therefore is to try to turn this fact into an advantage and search for a cancer therapy which would primarily target healthy cells and cancerous ones only indirectly. Tumor anti-angiogenesis is such a mechanism. A growing tumor, once it reaches just a few millimeters in size, no longer can rely on surrounding cells of the host for its supply of oxygen and nutrients, but needs to develop its own system of blood vessels and capillaries. In this process called angiogenesis an important role is played by endothelial cells which provide the lining for the newly forming blood vessels. Angiogenic inhibitors like endostatin target those cells preventing the tumor from developing its

own blood vessel system and thus indirectly block its growth. Ideally, the tumor, deprived of necessary nutrition, regresses. Since this treatment targets normal cells, no occurrence of drug resistance has been reported in experimental studies [5, 19]. For this reason tumor anti-angiogenesis has been called a therapy "resistant to resistance" that provides a new hope in treatment of tumor type cancers [19].

Although inhibitors of tumor angiogenesis seem to have been seriously researched medically only since the mid nineties [11, 21], a number of mathematical models to describe these phenomena have already been developed by the biomedical community. They include large scale models more suitable for simulations (e.g., [1, 2]), but also low-dimensional models in which quantities have been aggregated and which are suitable for mathematical analysis. In this paper we follow this path initiated by Hahnfeldt et al. in [18] where a model for tumor growth under the action of angiogenic stimulation and inhibition was developed and biologically validated. The principal variables in this model are the primary tumor volume $p$ and the carrying capacity of the vasculature $q$. The latter is defined as the maximum tumor volume sustainable by the vasculature. Since then this model has undergone various modifications. Ergun, Camphausen and Wein [12] and d'Onofrio and Gandolfi [10] modify the dynamics for the carrying capacity and d'Onofrio and Gandolfi [10], Swierniak et al. [34] and Forys et al. [17] also consider different models for the tumor growth.

Ergun et al. in [12] were the first to consider the problem of scheduling angiogenic inhibitors in an optimal control framework. Applications of optimal control to mathematical models arising in biomedical problems have a long history with the early focus on models in connection with cancer chemotherapy and these efforts have continued to the present day (e.g., [29, 35, 13]). Recently there has been a strong resurgence of this methodology in the analysis of newer models. This especially holds for novel treatment approaches to cancer like anti-angiogenesis discussed here or models describing the immune response to viruses like HIV [20] or to cancer and resulting immunotherapies (e.g., [7, 8, 9]), a second approach currently intensively pursued in cancer research. Introducing an objective Ergun et al. analyzed the problem of optimal scheduling of anti-angiogenic therapy and radiotherapy as mono-therapies and in combination. However, even for the case of anti-angiogenic therapy as mono-therapy, their analysis left several questions open, particularly related to the occurrence of singular controls as a part of the solution. These questions were answered in [22] where we presented a full synthesis of optimal controls, but without complete proofs. Following these results, we also analyzed the original model by Hahnfeldt as optimal control problem in [24] and, although the models have a substantially different dynamics for the carrying capacity $q$, their syntheses of optimal solutions are qualitatively equivalent. For both models optimal controls are concatenations of at most five pieces of the structure "**0asa0**". Here **0** stands for an interval where $u = 0$, i.e., a time period when no dose is administered, **a** denotes an interval with $u = a$, i.e., therapy is proceeding at full dose of the inhibitors, and **s** denotes a segment when the optimal control is singular corresponding to treatment with time-varying partial doses. Typically in optimal control problems singular controls are the most challenging ones to analyze since their formulas along with the corresponding singular arcs have to be determined explicitly. Clearly, in the implementation as optimal protocols, singular controls present a serious challenge and obstacle because of their time varying feedback type formulas. Nevertheless, if optimal controls are singular, then these solutions provide the benchmark to which simpler and medically implementable suboptimal strategies need to be compared with [25, 28].

In this paper the effect the dynamical model for tumor growth has on the structure of optimal solutions is analyzed for the model proposed by Ergun, Camphausen and Wein [12] in two cases: (a) for the original formulation of the dynamics using a Gompertzian growth function for the cancer cells and (b) when instead the growth of cancer cells is assumed to be logistic. Both versions of the model are augmented by including the presence of a natural death term in the dynamics for the carrying capacity

that was not considered before. It is shown that this change in the dynamics for the tumor growth does effect the qualitative structure of the solutions significantly. In the model with the Gompertzian growth the singular control plays an essential role in the synthesis whereas for the case when cancer cells follow logistic growth singular controls are maximizing rather than minimizing the objective. The consequences for the overall structure of the synthesis are analyzed and in the case of logistic growth optimal controls are bang-bang with at most two switchings of the type **0a0**.

# 2 A Mathematical Model for Tumor Anti-Angiogenic Therapy [12]

In this paper we consider a mathematical model for tumor anti-angiogenesis that was formulated by Ergun, Camphausen and Wein in [12] and is a modification of a previously developed and biologically validated model by Hahnfeldt et al. from [18]. In both models 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. The latter is the tumor volume sustainable by the vascular network that supplies the tumor with nutrients. It largely depends on the volume of endothelial cells and thus for short we also call it the endothelial support of the tumor. Different from the papers [12] and [18] in which tumor growth was modelled by a Gompertzian growth function, in this paper we consider a rather general model on the growth of the primary tumor in the form

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

where $\xi$ denotes a tumor growth parameter and $F$ is a function defined in terms of the scalar variable $x = \frac{p}{q}$. The quotient $\frac{1}{x} = \frac{q}{p}$ is related to what also is called the endothelial density in the literature. We *assume* that

**(F)** the function $F : (0, \infty) \to \mathbb{R}$, $x \mapsto F(x)$, is twice continuously differentiable, strictly decreasing, and satisfies $F(1) = 0$.

In view of the definition of the variables, these are natural assumptions to make: Since $q$ is the carrying capacity, for $p = q$ the endothelial support and tumor volume are balanced and thus $p$ should not change whereas the tumor volume should shrink for inadequate endothelial support ($p > q$) and increase if support is available ($p < q$). It is reasonable to assume that these processes are more pronounced the smaller the quotient $x$ is. Standard examples of growth functions that have these properties are given by classical Gompertzian growth, $F(x) = -\ln x$, classical logistic growth, $F(x) = 1 - x$, or generalized logistic growth, $F(x) = 1 - x^\alpha$, for some positive coefficient $\alpha$. These are the growth functions we shall consider in this paper. The dynamics proposed in [12] for the equation modelling the change in the carrying capacity or endothelial support is given by

$$\dot{q} = bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - Guq - \mu q, \tag{2}$$

where $b$ (birth) and $d$ (death), respectively, are endogeneous stimulation and inhibition parameters for the endothelial support. The term $\mu q$ represents natural death terms and $Guq$ stands for additional exogenous inhibition. Thus the variable $u$ represents the control in the system and corresponds to the angiogenic dose rate and $G$ is a constant that represents the anti-angiogenic killing parameter.

The endogenous inhibition and stimulation terms, $I(q) = dq^{\frac{4}{3}}$ and $S(q) = bq^{\frac{2}{3}}$, are a modification of the corresponding terms, $I(p,q) = dp^{\frac{2}{3}}q$ and $S(p) = bp$, chosen in [18] that result in a significant mathematical simplification of the $q$-dynamics since they eliminate the tumor volume $p$ from this equation. While this may look suspect, there are good reasons for this change. The argument made for this modification by Ergun, Camphausen and Wein in [12] is the differential-algebraic nature of the original model with a $q$-dynamics that reaches its steady-state extremely fast. With the modification proposed this no longer is the case and overall there is a better balance in the substitution of stimulation and inhibition. Since $p$ and $q$ tend to move together in steady state, and this is what the model intends to capture, there is some justification to replace $p$ with $q$ in the $q$-dynamics and arrive at an equation of the form

$$\dot{q} = bq^{\gamma} - bq^{\gamma+\frac{2}{3}}$$

for the endogeneous inhibition and stimulation terms. A choice of $\gamma = 1$ in this sense would be consistent with the spatial analysis carried out in [18] while the choice $\gamma = \frac{2}{3}$ made by Ergun, Camphausen and Wein is consistent with the inhibition term being proportional to the tumor radius, not its surface area. (The tumor is modelled as a small sphere in [18]). Another consequence of this choice is that now even for a constant angiogenic dose rate $u = a$ the tumor volume $p$ does not shrink to 0 as this is the case for the model by Hahnfeldt et al. [10], but there still exists a globally asymptotically stable equilibrium at

$$p_a = \left( \frac{-(Ga+\mu) + \sqrt{(Ga+\mu)^2 + 4bd}}{2d} \right)^3 = q_a, \tag{3}$$

which for realistic parameter values is very small reflecting the fact that even without endothelial support (which in principle the tumor now is being denied through the constant application of inhibitors) the tumor grows to a small size. Finally, one of the strongest argument in support of this modification is that, as we shall show, for the optimal control problem of administering a given amount of angiogenic inhibitors in order to maximize the tumor reduction achievable, the structure of optimal solutions is qualitatively identical to the one for the original model by Hahnfeldt et al. Thus, while clearly simplifying the dynamics, this modification does retain all essential qualitative features of the original model.

The optimal control problem considered here was initially formulated in [12] for a Gompertzian growth function $F$, $F(x) = -\ln x$, and we then expanded on its solution (for $\mu = 0$) in [22] while giving the full synthesis of optimal solutions and its proof only here. Mathematically the problem can be formulated as to minimize the value $p(T)$ for a free terminal time $T$ subject to the dynamics (1) and (2) over all Lebesgue measurable functions $u : [0,T] \to [0,a]$ which satisfy a constraint of the form

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

on the total amount of anti-angiogenic inhibitors administered. The number $a$ has been introduced in [22] as an upper limit on the dosage of the inhibitors, i.e., $0 \leq u \leq a$. This change makes the control set compact which leads to a mathematically better posed problem for which a complete solution can be given. Also, mathematically it is more convenient to incorporate the constraint (4) into the dynamics by introducing a new variable $y$ which will keep track of the amount of the drug used. Hence we consider the following equivalent optimal control problem:

**(OC)** for a free terminal time $T$, minimize $p(T)$ over all Lebesgue measurable functions $u : [0,T] \to [0,a]$

subject to

$$\dot{p} = \xi p F\left(\frac{p}{q}\right), \qquad p(0) = p_0, \tag{5}$$

$$\dot{q} = bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \mu q - Guq, \qquad q(0) = q_0, \tag{6}$$

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

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

In [22] an outline of the solution was given for a Gompertzian growth function $F$ and the case $\mu = 0$. There the system was analyzed with state variables $(p, x, y)$ where $x^3 = q$ which eliminates the fractional powers. On the other hand, this substitution makes the comparison of the solutions with other models, like the original model by Hahnfeldt at al. [18] analyzed in [24] or the modification by d'Onofrio [10] analyzed in [26] more difficult. Here we therefore retain the modelling in the variables $p$ and $q$ and throughout we keep a nonzero death term $\mu$. We present the complete solution of the problem and compare the optimal when the dynamics for the cancer growth changes from a Gompertzian to a logistic growth function.

## 2.1 Biologically relevant region

Not all states $(p, q)$ are of biological interest and in order to avoid irrelevant discussions about the structure of optimal controls outside of this region we will restrict the domain of the state space. Note that equilibria must lie on the diagonal $p = q$ and a simple calculation shows that for $u \equiv a$ there exists a unique globally asymptotically stable node at $p_a = q_a$. In particular, for the uncontrolled system, i.e., for $u = 0$, we have

$$\bar{p} = \bar{q} = \left(\frac{-\mu + \sqrt{\mu^2 + 4db}}{2d}\right)^3.$$

Fig. 1 shows the phase portraits of the controlled ($u = a$) and uncontrolled system ($u = 0$) for the case of a Gompertzian growth function. We shall always plot $p$ on the vertical and $q$ on the horizontal axis since this better visualizes tumor reductions and in all our simulations we use the following parameter values that are taken from [18]: $\xi = \frac{0.192}{\ln 10} = 0.084$ per day (this value is adjusted to the natural logarithm.), $b = 5.85$ mm per day, $d = 0.00873$ per mm per day, $G = 0.15$ kg per mg of dose and we have taken $a = 15$. In this case the equilibria are at $\bar{p} = 15,191\ mm^3$ and $p_a = 17\ mm^3$. Also, for illustrative purposes we selected $\mu = 0.02$.

Fig. 2 gives the phase portraits for the case of a classical logistic growth function, $F(x) = 1 - x$, for the uncontrolled system (left) and the fully controlled system (right). Comparing with the corresponding phase portraits for a Gompertzian growth function, we see that the qualitative behavior of the dynamical system does not change.

We will use the above numerical values throughout the paper for our simulations, but our analysis does not depend on these values. We only require that

$$Ga > b - \mu > 0. \tag{8}$$

This condition simply states that outside inhibition is able to overcome the net effect of the birth minus the natural death of the endothelial support. Otherwise it is not possible to reduce the endothelial support and no reduction in the tumor volume is possible.

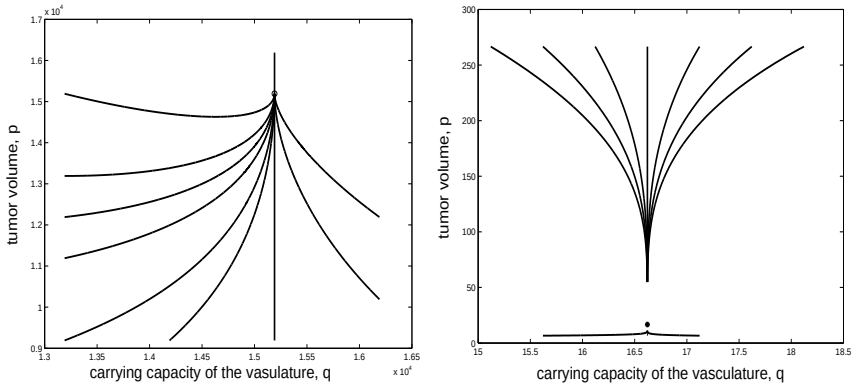


Figure 1: Phaseportrait of the uncontrolled ($u \equiv 0$, left) and the controlled ($u \equiv a = 15$, right) system for Gompertzian growth

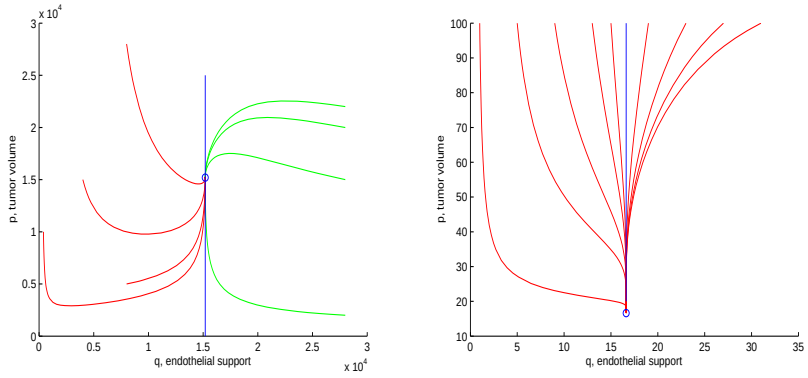


Figure 2: Phase portraits of the uncontrolled ($u \equiv 0$, left) and the controlled ($u \equiv a = 15$, right) system for logistic growth

The biologically relevant region cannot extend beyond the values of the equilibria and thus we restrict our analysis to the compact set $R$ given by

$$R = \{(p,q) : p_a \leq p \leq \bar{p},\ q_a \leq q \leq \bar{q}\}. \tag{9}$$

Initial conditions that lie outside the set $R$ are not meaningful biologically since the endothelial support is either far too small or far too large.

**Proposition 1** *The compact set $R = \{(p,q) : p_a \leq p \leq \bar{p},\ q_a \leq q \leq \bar{q}\}$ is positively invariant for the flow of the control system, i.e., if $(p_0, q_0) \in R$ , 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 $R$, $(p(t), q(t)) \in R$.*

**Proof.** We need to show that controlled trajectories cannot leave the set $R$ and thus analyze the dynamics on the boundary $\partial R$ for all possible control values. Special cases arise since the boundary segments $R_{p\bar{q}} = \{(p,q) : p_a \leq p \leq \bar{p},\ q = \bar{q}\}$ and $R_{pq_a} = \{(p,q) : p_a \leq p \leq \bar{p},\ q = q_a\}$ are positively invariant under the constant controls $u = 0$ and $u = a$, respectively. Clearly this prevents trajectories from escaping from $R$ through these lines for those controls. Aside from these two special cases we now verify that for any admissible control the dynamics points inside $R$ at any point in the boundary of $R$. This implies that the trajectory starting at any $(p_0, q_0) \in R$ will stay in $R$ for all times $t \geq 0$.

It follows from the general properties of the growth function $F$ that we have $\dot{p} > 0$ for points with $p < q$ and $\dot{p} < 0$ for points with $p > q$. Furthermore, for a constant $q = \bar{q}$ and $u > 0$ we have that $\dot{q} = -Guq < 0$ and so the $q$-dynamics points to the left while for $q = q_a$ and $u < a$ we have

$$\dot{q} = bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - Guq - \mu q > bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - Gaq - \mu q = 0$$

and thus the $q$-dynamics points to the right. Combining these inequalities it follows that, except for the two positively invariant segments mentioned above, trajectories enter $R$ from points in the boundary of $R$. For example, at the corner point $(p_0, q_a)$ we have for any control $u$ that $\dot{p} < 0$ and $\dot{q} > 0$. This completes the proof. □

However, the set $R$ still may contain initial conditions that give rise to degenerate cases. These arise if the available amount of inhibitors simply is too small to achieve a reduction in the tumor volume and we also would like to exclude them from our analysis. We denote by $\mathcal{R}_0$ the diagonal of the region $R$, i.e., $\mathcal{R}_0 = \{(p,q) \in R : p = q\}$. The diagonal divides $R$ into two subregions $\mathcal{R}_+ = \{(p,q) \in R : p > q\}$ and $\mathcal{R}_- = \{(p,q) \in R : p < q\}$. Both the trajectories for the constant controls $u = 0$ and $u = a$ cross the diagonal portion $\mathcal{R}_0$ transversally: for $u = 0$ trajectories cross from $\mathcal{R}_+$ into $\mathcal{R}_-$, while they cross in opposite direction from $\mathcal{R}_-$ into $\mathcal{R}_+$ for $u = a$. Also, trajectories for $u = 0$ approach the stable equilibrium $(p_0, q_0)$ from within the region $\mathcal{R}_-$ while trajectories for $u = a$ converge to $(p_a, q_a)$ in the region $\mathcal{R}_+$. It follows from the dynamics for $p$, (5), that the $p$-value of trajectories is always decreasing in $\mathcal{R}_+$ and always increasing in $\mathcal{R}_-$. As a result, for some initial conditions $(p_0, q_0) \in \mathcal{R}_-$, it is possible that the (mathematically) optimal time $T$ is $T = 0$. This situation arises when the amount of available inhibitors simply is not sufficient to reach a point in the region $R$ that would have a lower $p$-value than $p_0$. In such a case it is not possible to decrease the tumor volume with the available amount of inhibitors. It is only possible to slow down the tumor's growth. Indeed, it is correct that the best way of doing this is to give the full dose $u = a$ until all inhibitors run out - this follows from the structure of optimal controls to be shown later - but this is not the mathematically "optimal" solution for our problem. This one is simply to do nothing and take $T = 0$. Since this introduces a number of degeneracies into the analysis, we make the following definition:

**Definition 1** *We say an initial condition* $(p_0, q_0)$ *is* well-posed *if the optimal time* $T$ *is positive and call* $(p_0, q_0)$ ill-posed *if* $T = 0$. *In this case it is not possible to reach a point* $(p, q)$ *with* $p < p_0$.

It is clear that all initial conditions with $(p_0, q_0) \in \mathcal{R}_+ \cup \mathcal{R}_0$ are well-posed (since $p$ decreases in $\mathcal{R}_+$ and trajectories with $u = a$ enter $\mathcal{R}_+$ from $\mathcal{R}_0$) and it is easily decided whether an initial condition $(p_0, q_0) \in \mathcal{R}_-$ is ill-posed. For our analysis of optimal controls, however, we *only consider well-posed initial conditions.*

## 2.2 General properties of extremals for Problem (OC)

We briefly summarize the first-order necessary conditions for optimality given by the *Pontryagin Maximum Principle* [**?**] and some of its consequences for the case of a general growth function $F$. For a row-vector $\lambda = (\lambda_1, \lambda_2, \lambda_3) \in (\mathbb{R}^3)^*$, define the Hamiltonian $H = H(\lambda, p, q, u)$ as

$$H = \lambda_1 \xi p F\left(\frac{p}{q}\right) + \lambda_2 \left(b q^{\frac{2}{3}} - d q^{\frac{4}{3}} - G u q - \mu q\right) + \lambda_3 u. \tag{10}$$

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 absolutely continuous co-vector, $\lambda : [0, T] \to (\mathbb{R}^3)^*$, such that the following conditions hold:

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

**(b)** $\lambda_3$ is constant, and $\lambda_1$ and $\lambda_2$ satisfy the adjoint equations

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial p} = -\lambda_1 \xi \left(F\left(\frac{p}{q}\right) + \frac{p}{q} F'\left(\frac{p}{q}\right)\right) \tag{11}$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial q} = \lambda_1 \xi \left(\frac{p}{q}\right)^2 F'\left(\frac{p}{q}\right) + \lambda_2 \left(-\frac{2}{3} b (q_*(t))^{-\frac{1}{3}} + \frac{4}{3} d (q_*(t))^{\frac{1}{3}} + G u_*(t) + \mu\right) \tag{12}$$

with transversality conditions

$$\lambda_1(T) = \lambda_0, \quad \lambda_2(T) = 0, \quad \text{and} \quad \lambda_3(T) = \begin{cases} 0 & \text{if } y(T) < A \\ \text{free} & \text{if } y(T) = A \end{cases} \tag{13}$$

**(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.

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 $(\lambda_0, \lambda)$ 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). Extremals with $\lambda_0 = 0$ are called abnormal while those with a positive multiplier $\lambda_0$ are called normal.

The next two lemmas summarize some general properties of optimal controls and extremals for problem $[OC]$ for well-posed initial conditions that were proven in [27]

**Lemma 1** [27] *Along an optimal trajectory* $(p_*, q_*, y_*)$*, all available inhibitors are exhausted,* $y_*(T) = A$*, and at the final time* $p_*(T) = q_*(T)$. ■

**Lemma 2** [27]*All extremals for problem* $[OC]$ *are normal. The multiplier* $\lambda_3$ *is constant and non-negative.* ■

Without loss of generality we thus normalize $\lambda_0 = 1$. The general results about the signs of multipliers of [27] can be strengthened for the $q$-dynamics considered here:

**Lemma 3** *The multiplier $\lambda_1$ is positive on $[0,T]$ and $\lambda_2$ is positive on $[0,T)$.*

**Proof.** In this case the adjoint equation (11) for $\lambda_1$ is a homogeneous linear ODE. Since $\lambda_1(T) = 1$, the first statement is immediate. The second one follows from the fact that whenever $\lambda_2(\tau) = 0$, then we have

$$\dot{\lambda}_2(\tau) = \xi\lambda_1(\tau)\left(\frac{p_*(\tau)}{q_*(\tau)}\right)^2 F'\left(\frac{p_*(\tau)}{q_*(\tau)}\right)$$

which is negative since by assumption $F$ is strictly decreasing. Since $\lambda_2(T) = 0$ this implies that $\lambda_2$ is positive for $t < T$. □

**Corollary 1** *If $\lambda_3 = 0$, then the corresponding optimal control is constant over the interval $[0,T]$ and given by the control $u \equiv a$.*

**Proof.** In this case the function multiplying the control $u$ in the Hamiltonian is given by $-\lambda_2 Gq$ and is negative over $[0,T)$. Thus the minimizing control is given by $u \equiv a$. □

Except for one extremely degenerate case (the initial condition is such that with giving the full dose we reach the diagonal exactly when all inhibitors have been exhausted) we can, as we henceforth do, without loss of generality therefore assume that $\lambda_3$ is positive.

**Lemma 4** *Extremal trajectories only cross the diagonal from $\mathcal{R}_- = \{(p,q) \in \mathcal{R} : p < q\}$ into $\mathcal{R}_+ = \{(p,q) \in \mathcal{R} : p > q\}$ using the control $u = a$, but do not cross from $\mathcal{R}_+$ into $\mathcal{R}_-$. In the latter the case the optimal final time $T$ is reached as the trajectory reaches the diagonal.*

**Proof.** Suppose an optimal controlled trajectory is on the diagonal at time $\tau$, $p(\tau) = q(\tau)$. In this case it follows from (10) and condition (c) that

$$\lambda_2(\tau)\left(bq(\tau)^{\frac{2}{3}} - dq(\tau)^{\frac{4}{3}} - Gu(\tau)q(\tau) - \mu q(\tau)\right) + \lambda_3(\tau)u(\tau) = 0.$$

Along $u = a$ trajectories transversally cross from $\mathcal{R}_-$ into $\mathcal{R}_+$ and nothing needs to be shown. If $u(\tau) < a$, then the minimization property of the optimal control implies that

$$\left(\lambda_3(\tau) - \lambda_2(\tau)Gq(\tau)\right)u(\tau) = 0$$

and thus

$$\lambda_2(\tau)\left(bq(\tau)^{\frac{2}{3}} - dq(\tau)^{\frac{4}{3}} - \mu q(\tau)\right) = 0.$$

In the biologically relevant region the term $bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \mu q$ is positive and thus we must have $\lambda_2(\tau) = 0$ which implies $\tau = T$. □

## 2.3 The switching function and singular controls

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

$$\left(\lambda_3 - \lambda_2(t)Gq_*(t)\right)v$$

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

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

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. 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, for example, see [3, 30, 33]. 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 $\tau$. In order to analyze the structure of the optimal controls we therefore need to analyze the switching function and its derivatives.

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

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

where

$$f(z) = \begin{pmatrix} \xi p F\left(\frac{p}{q}\right) \\ bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \mu q \\ 0 \end{pmatrix} \quad \text{and} \quad g(z) = \begin{pmatrix} 0 \\ -Gq \\ 1 \end{pmatrix} . \tag{17}$$

The adjoint equation then simply becomes

$$\dot{\lambda}(t) = -\lambda(t) \left(Df(z(t)) + u_*(t) Dg(z(t))\right) \tag{18}$$

where $Df$ and $Dg$ denote the matrices of the partial derivatives of the vector fields which are evaluated along $z(t)$. The switching function in this notation becomes

$$\Phi(t) = \langle \lambda(t), g(z(t)) \rangle . \tag{19}$$

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 2** *Let $h$ be a continuously differentiable vector field and define*

$$\Psi(t) = \langle \lambda(t), h(z(t)) \rangle .$$

*Then the derivative of $\Psi$ along a solution to the system equation (16) for control $u$ and a solution $\lambda$ to the corresponding adjoint equations is given by*

$$\dot{\Psi}(t) = \langle \lambda(t), [f + ug, h] z(t) \rangle , \tag{20}$$

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

Recall that the Lie bracket is computed in local coordinates as

$$[f, h](z) = Dh(z) f(z) - Df(z) h(z) \tag{21}$$

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

We therefore have that

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

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

It is a necessary condition for minimality of the singular control, the so-called Legendre-Clebsch condition [3], that

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

and, if this quantity is negative, the so-called strengthened Legendre-Clebsch condition, we can formally solve for the singular control as

$$u_{\sin}(t) = -\frac{\langle \lambda(t), [f,[f,g]]z(t) \rangle}{\langle \lambda(t), [g,[f,g]]z(t) \rangle}. \tag{25}$$

However, further simplifications, depend on the vector fields $f$ and $g$ and we now need to pursue the analysis separately depending on the type of growth function $F$.

# 3 Synthesis of Optimal Controls for a Gompertzian Growth Function $F(x) = -\ln(x)$

## 3.1 Singular Controls and Trajectories

In this case direct computations give that

$$[f,g](z) = \begin{pmatrix} \xi G p \\ -\frac{1}{3} G \left( b q^{\frac{2}{3}} + d q^{\frac{4}{3}} \right) \\ 0 \end{pmatrix}, \tag{26}$$

$$[f,[f,g]](z) = \begin{pmatrix} \xi G p \left( \xi + \frac{1}{3} \left( b q^{-\frac{1}{3}} + d q^{\frac{1}{3}} \right) \right) \\ -\frac{4}{9} G b d q - \frac{1}{9} G \mu \left( b q^{\frac{2}{3}} - d q^{\frac{4}{3}} \right) \\ 0 \end{pmatrix}, \tag{27}$$

and

$$[g,[f,g]](z) = \begin{pmatrix} 0 \\ -\frac{1}{9} G^2 \left( b q^{\frac{2}{3}} - d q^{\frac{4}{3}} \right) \\ 0 \end{pmatrix}. \tag{28}$$

Hence

$$\langle \lambda(t), [g,[f,g]]z(t) \rangle \equiv -\frac{1}{9} \lambda_2(t) G^2 \left( b q(t)^{\frac{2}{3}} - d q(t)^{\frac{4}{3}} \right). \tag{29}$$

For $q < \bar{q}$ we have that $bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \mu q > 0$ and since also $\lambda_2(t) > 0$ by Lemma 3, it follows that

$$\langle \lambda(t), [g,[f,g]]z(t)\rangle < -\frac{1}{9}\lambda_2(t)G^2\mu q < 0.$$

Thus the strengthened Legendre-Clebsch condition for minimality of a singular control is satisfied and the singular control can be computed as

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

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

$$[f,[f,g]](z) = \left(\xi + \frac{1}{3}\frac{b+dq^{\frac{2}{3}}}{q^{\frac{1}{3}}}\right)[f,g](z) - \psi(z)[g,[f,g]](z) \tag{30}$$

where

$$\psi(z) = \frac{1}{G}\left(\frac{b-dq^{\frac{2}{3}}}{q^{\frac{1}{3}}} + 3\xi\frac{b+dq^{\frac{2}{3}}}{b-dq^{\frac{2}{3}}} - \mu\right). \tag{31}$$

If now $u_*$ is singular over an open interval $I$, then $\langle \lambda(t), [f,g](z(t))\rangle \equiv 0$ on $I$, and it therefore follows that

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

If we define

$$\Psi(x) = \frac{1}{G}\left(\frac{b-dx^2}{x} + 3\xi\frac{b+dx^2}{b-dx^2} - \mu\right), \tag{32}$$

then the singular control is thus given by

$$u_{\sin}(t) = \Psi\left(q^{\frac{1}{3}}(t)\right), \tag{33}$$

a smooth feedback control that only depends on $q^{\frac{1}{3}}$.

For this control to be admissible its value needs to lie in the interval $[0,a]$. The function $\Psi$ is strictly convex ($\Psi''(x) > 0$) with poles at $x = 0$ and $x = \sqrt{\frac{b}{d}}$. Hence, for large enough $a$ there exist exactly two values $q_\ell^*$ and $q_u^*$, $0 < q_\ell^* < q_u^* < \sqrt{\left(\frac{b}{d}\right)^3}$, such that the singular control is admissible for $q \in [q_\ell^*, q_u^*]$, saturates with value $u_* = a$ at $q_\ell^*$ and $q_u^*$, and is inadmissible for $q \notin [q_\ell^*, q_u^*]$. Fig. 3 gives the graph of the singular control defined by (31) in a feedback form with the horizontal axis representing the variable $q$. For the numerical values from [18] introduced earlier and $a = 15$ we have $q_\ell^* = 23.69$ and $q_u^* = 12,319$ which determines the admissible portion of the singular arc. For comparison, the equilibrium value is $\bar{q} = 15,191$.

This singular control, however, is only optimal on one specific arc that we now determine. For, the optimal trajectory needs to satisfy the condition of the Maximum Principle that $H \equiv 0$. Thus, if the control is singular on an open interval, i.e.,

$$\langle \lambda(t), g(z(t))\rangle \equiv 0, \tag{34}$$

then on $I$ we also must have that

$$\langle \lambda(t), f(z(t))\rangle \equiv 0. \tag{35}$$

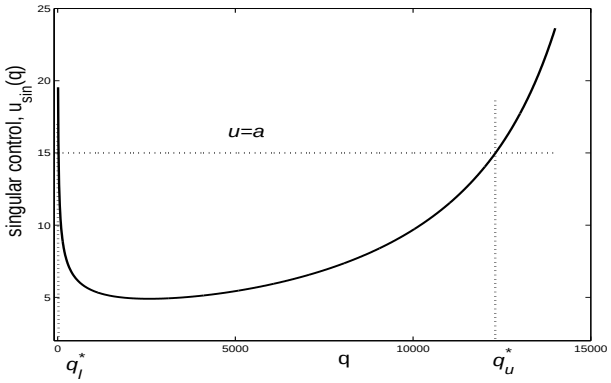


Figure 3: Singular control and its admissible part for Gompertzian growth

In addition the fact that $\dot{\Phi}(t) \equiv 0$ on $I$ also gives that

$$\langle \lambda(t), [f,g](z(t)) \rangle \equiv 0. \tag{36}$$

By Lemma 3 $\lambda(t) \neq 0$ and thus the three conditions (35), (34) and (36) are consistent if and only if the determinant for the corresponding linear system in $\lambda_1$, $\lambda_2$ and $\lambda_3$ vanishes. This is equivalent to the linear dependence of the vector fields $f$, $g$ and $[f,g]$, i.e.,

$$0 = \begin{vmatrix} -\xi p \ln\left(\frac{p}{q}\right) & 0 & \xi G p \\ bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \mu q & -Gq & -\frac{1}{3}G\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right) \\ 0 & 1 & 0 \end{vmatrix}$$

$$= -\xi G p \begin{vmatrix} -\ln\left(\frac{p}{q}\right) & 1 \\ bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \mu q & -\frac{1}{3}\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right) \end{vmatrix}$$

$$= -\xi G p \left[\frac{1}{3}\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right) \ln\left(\frac{p}{q}\right) - \left(bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \mu q\right)\right],$$

or, equivalently,

$$\ln\left(\frac{p}{q}\right) = 3\frac{b - dq^{\frac{2}{3}} - \mu q^{\frac{1}{3}}}{b + dq^{\frac{2}{3}}}. \tag{37}$$

Summarizing, we have

**Proposition 3** *There exists a locally minimizing singular arc $S$ defined in $(p,q)$-space by*

$$p_{\sin} = p_{\sin}(q) = q \exp\left(3\frac{b - dq^{\frac{2}{3}} - \mu q^{\frac{1}{3}}}{b + dq^{\frac{2}{3}}}\right) \tag{38}$$

*for $q_\ell^* \le q \le q_u^*$. The corresponding singular control is given in feedback form as*

$$u_{\sin}(q) = \psi(q) = \frac{1}{G}\left(\frac{b - dq^{\frac{2}{3}}}{q^{\frac{1}{3}}} + 3\xi\frac{b + dq^{\frac{2}{3}}}{b - dq^{\frac{2}{3}}} - \mu\right) \tag{39}$$

*and the values $q_\ell^*$ and $q_u^*$ are the unique solutions to the equation $\psi(q) = a$ in $(0, \sqrt{\left(\frac{b}{d}\right)^3})$.* ■

Fig. 4 gives the graph of the singular curve defined by (38) corresponding to the singular control given in Fig. 3.

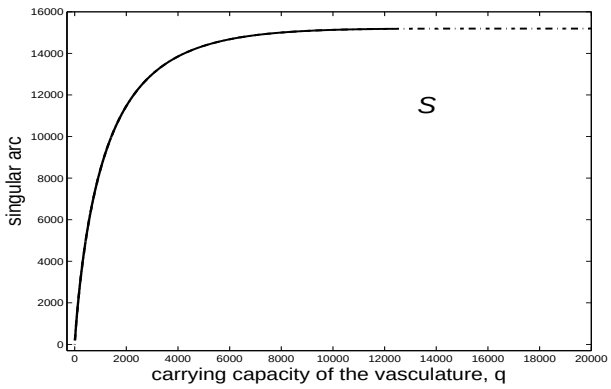


Figure 4: Singular arc and its admissible part for Gompertzian growth

## 3.2 Optimal concatenations of controls

Once singular controls satisfy the strengthened Legendre-Clebsch condition singular arcs become a viable candidate for optimality and possible concatenation sequences with bang arcs need to be analyzed. An important first result that severely limits these concatenations for this problem is proven in the following Proposition:

**Proposition 4** *If $u_*$ is an optimal control, then $u_*$ can take on the value 0 only along an initial interval $[0, \tau]$ or a final interval $[\tau, T]$.*

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

$$\begin{aligned} 0 = \dot{\Phi}(\tau) &= \langle \lambda(\tau), [f, g](z(\tau)) \rangle \\ &= \lambda_1 \xi G p - \frac{1}{3}\lambda_2 G\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right). \end{aligned}$$

Using this identity in the formula for the second derivative at time $\tau$ we get that

$$\begin{aligned}
\ddot{\Phi}(\tau) &= \langle \lambda(\tau), [f,[f,g]](z(\tau))\rangle \\
&= \lambda_1(\xi^2 Gp + \frac{1}{3}b\xi Gpq^{-\frac{1}{3}} + \frac{1}{3}d\xi Gpq^{\frac{1}{3}}) - \frac{1}{9}\lambda_2(4Gbdq + Gb\mu q^{\frac{2}{3}} - Gd\mu q^{\frac{4}{3}}) \\
&= \frac{1}{3}\lambda_2 G\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right)\left(\xi + \frac{1}{3}(bq^{-\frac{1}{3}} + dq^{\frac{1}{3}})\right) - \frac{4}{9}\lambda_2 Gbdq - \frac{1}{9}\lambda_2 G\mu q(bq^{-\frac{1}{3}} - dq^{\frac{1}{3}}) \\
&= \frac{1}{9}\lambda_2 G\left(3\xi\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right) + \frac{\left(bq^{\frac{2}{3}} - dq^{\frac{4}{3}}\right)^2}{q} - \mu(bq^{\frac{2}{3}} - dq^{\frac{4}{3}})\right) = \\
&= \frac{1}{9}\lambda_2 G\left(3\xi\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right) + (bq^{\frac{2}{3}} - dq^{\frac{4}{3}})\frac{bq^{\frac{2}{3}} - \mu q - dq^{\frac{4}{3}}}{q}\right).
\end{aligned}$$

The trajectory lies in the region $q < \bar{q}$ and there the expression $bq^{\frac{2}{3}} - \mu q - dq^{\frac{4}{3}}$ is positive. Hence $\ddot{\Phi}(\tau) > 0$ and so $\Phi$ has a local minimum at $\tau$. Contradiction. Hence the switching function is strictly increasing or decreasing along the control $u \equiv 0$ and thus 0-arcs can only lie at the ends of the interval $[0, T]$. □

**Proposition 5** *If $u_*$ is an optimal control, then there exists at most one interval $I$ where the control is singular.*

**Proof.** Since the singular control is of order 1, at every singular junction there is a switch to either $u = 0$ or $u = a$. If there is more than one singular segment, then by the previous lemma there must exist a concatenation sequence of the form **sas**. However, the vector field corresponding to the control $u = a$ is everywhere transversal to the singular arc pointing into the region where $p > p_{\text{sin}}(q)$. This prevents a return to the singular arc along the control $u = a$. □

We thus have proven the following result:

**Theorem 1** *Given a well-posed initial condition $(p_0, q_0)$, optimal controls are at most concatenations of the form* **0asa0** *where* **0** *denotes an interval along which the optimal control is given by the constant control $u = 0$, that is no inhibitors are given,* **a** *denotes an interval along which the optimal control is given by the constant control $u = a$ at full dose, and* **s** *denotes an interval along which the optimal control follows the time-varying singular feedback control (39). This control is only optimal while the system follows the optimal singular arc $\mathcal{S}$ defined by (38) in the $(p, q)$-space.* ■

Depending on the initial condition, however, not all of the intervals in **0asa0** need to be present in a specific solution. In fact, for the biologically most relevant situation typically optimal controls have the form **bs0** where **b** stands for an interval along which the optimal control is given by either $u = a$ or $u = 0$ depending on the initial condition. But concatenations that end with **sa0** arise if the singular control saturates before all inhibitors have been exhausted. Indeed, in this case it is not optimal to remain on the singular arc until the saturation point, but optimal trajectories leave the singular arc prior to this point with the control $u = a$.

**Proposition 6** *If $u_*$ is an optimal control that is singular on the interval $[\sigma, \tau]$ and saturates at $\tau$ with the value $u_*(\tau) = a$, then $y(\tau) = A$. In other words, the only way that an optimal control would reach the saturation point is that if this is the time when all inhibitors run out. It is not optimal for the control $u = a$ to concatenate with the singular control at saturation points.*

While this result may be somewhat unexpected, this is indeed the typical behavior at saturation in low dimensions (see, for example, [32] or [4]).

**Proof.** Consider a trajectory that follows the singular arc and at the saturation time $\tau$ continues with the control $u = a$. In general, using (30) we have that

$$\begin{aligned}\ddot{\Phi}(t) &= \langle \lambda(t), [f + ug, [f, g]](z(t))\rangle \\ &= \left(\xi + \frac{1}{3}\frac{b + dq(t)^{\frac{2}{3}}}{q(t)^{\frac{1}{3}}}\right)\dot{\Phi}(t) + (u(t) - \psi(p(t), q(t)))\,\langle \lambda(t), [g, [f, g]](z(t))\rangle\,.\end{aligned}$$

Along the singular arc $\dot{\Phi}(t) = 0$ and since $\psi(p(\tau), q(\tau)) = a$ at the saturation point, we also have $\ddot{\Phi}(\tau) = 0$ for the control $u = a$. Hence, along $u = a$ we get from the right that

$$\begin{aligned}\Phi^{(3)}(\tau+) &= -\left(\frac{d}{dt}_{|t=\tau}\psi(p(t), q(t))\right)\langle \lambda(t), [g, [f, g]](z(t))\rangle \\ &= \left(\frac{d}{dt}_{|t=\tau}\psi(p(t), q(t))\right)\frac{1}{9}\lambda_2(\tau)G^2\left(bq(\tau)^{\frac{2}{3}} - dq(\tau)^{\frac{4}{3}}\right).\end{aligned}$$

By Lemma 3 $\lambda_2(\tau) > 0$ and also $bq(\tau)^{\frac{2}{3}} - dq(\tau)^{\frac{4}{3}} > \mu q(\tau) > 0$. In order to calculate the derivative of $\psi$ recall that $\psi(p(t), q(t)) = \Psi(x(t))$ with $x = q(\tau)^{\frac{1}{3}}$ and $\Psi$ defined in (32). We thus have

$$\frac{d}{dt}_{|t=\tau}\psi(p(t), q(t)) = \Psi'(q(\tau)^{\frac{1}{3}})\frac{\dot{q}(\tau)}{3q(\tau)^{\frac{2}{3}}}.$$

In the set $R$ along the control $u = a$ we have that

$$\dot{q}(\tau) = bq(\tau)^{\frac{2}{3}} - dq(\tau)^{\frac{4}{3}} - Gaq(\tau) - \mu q(\tau) < 0$$

and, since the saturation is at the lower value $q^*_\ell$, it follows from the convexity of the function $\Psi$ that $\Psi'(q(\tau)^{\frac{1}{3}}) < 0$. Hence

$$\Phi^{(3)}(\tau+) > 0$$

and $\Phi$ is positive for $t > \tau$, $t$ near $\tau$, contradicting the minimization property for $u = a$.

Similarly, if a trajectory for $u = a$ connects with the singular arc at time $\sigma$ at the higher saturation value $q^*_u$, then the same calculation is valid with the one change that now $\Psi'(q(\tau)^{\frac{1}{3}}) > 0$ which implies $\Phi^{(3)}(\sigma-) < 0$. Hence in this case the switching function is positive prior to time $\sigma$ which again would imply that the optimal control is $u = 0$. □

### 3.3 Optimal Synthesis

Based on these results a complete synthesis of optimal controls can now be developed. A synthesis provides a full "road map" of how optimal protocols look like depending on the initial condition in the problem, both qualitatively and quantitatively. For our problem we know that the singular control given by (31) is locally optimal as long as it takes a value between 0 and $a$. Consequently then the admissible part of the corresponding singular trajectory given by (38) between $q^*_\ell$ and $q^*_u$ will become an essential part of the synthesis of optimal controls. Once the maximally possible optimal concatenation sequence is known to be **0asa0**, it is not difficult to compute the optimal control for a particular initial condition $(p_0, q_0)$. For initial points above the singular arc ($p_0 > u_{\sin}(q_0)$) initially the optimal control is given by $u = 0$ until the singular arc is reached and similarly for initial points below the singular arc ($p_0 < u_{\sin}(q_0)$) the optimal control is given by $u = a$ until the singular arc is reached. At this time the optimal control

switches to the singular control and follows the singular arc. Depending on the amount of inhibitors available the control either remains singular until all inhibitors have been exhausted or, if saturation were to occur, leaves the singular with the control $u = a$. Numerically this leads to a 1-dimensional optimization problem with the time along the singular arc as parameter. The time along the second arc with $u = a$ is determined by the fact that inhibitors run out and the time along the last $u = 0$ arc is determined so that the system reaches the diagonal $p = q$ when the maximum tumor reduction is realized. A rather detailed description of this construction is given in the paper [24] for the model by Hahnfeldt et al. [18] and we shall not repeat it here since given the same optimal concatenation structure the argument is identical.

Some examples of projections of optimal trajectories into the $(p, q)$-space are given in Fig. 5. The admissible singular arc is shown as a solid blue curve which becomes dotted after the saturation points. Trajectories corresponding to $u \equiv a$ are marked as solid green curves whereas trajectories corresponding to $u \equiv 0$ are also in green, but marked as dashed curves. The dotted black line on the graph is the diagonal, $p = q$. We highlighted with bold one specific, characteristic example of the synthesis. Because of the value of the initial conditions at the beginning of the therapy (marked on the graph) the optimal control initially is given by the full dose $u = a$ and there is no initial segment with $u = 0$. This typically is the case for initial conditions $(p_0, q_0)$ that lie below the singular arc, $p < p_{\sin}(q)$. Note the relatively small shrinkage of the tumor volume $p$ compared with the changes in the endothelial support $q$ along this initial segment. 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 until all inhibitors become exhausted. Now there is a significant shrinkage of the tumor volume along the singular arc. The last part of the optimal trajectory is a thick dashed green curve representing the trajectory for $u = 0$, no dose. There still is a sizable shrinkage of the tumor along this trajectory due to after effects since the inhibitors are being exhausted in the region $p > q$ and thus, regardless of the control the tumor volume still shrinks until the trajectory reaches the diagonal $p = q$ at the final time $T$.

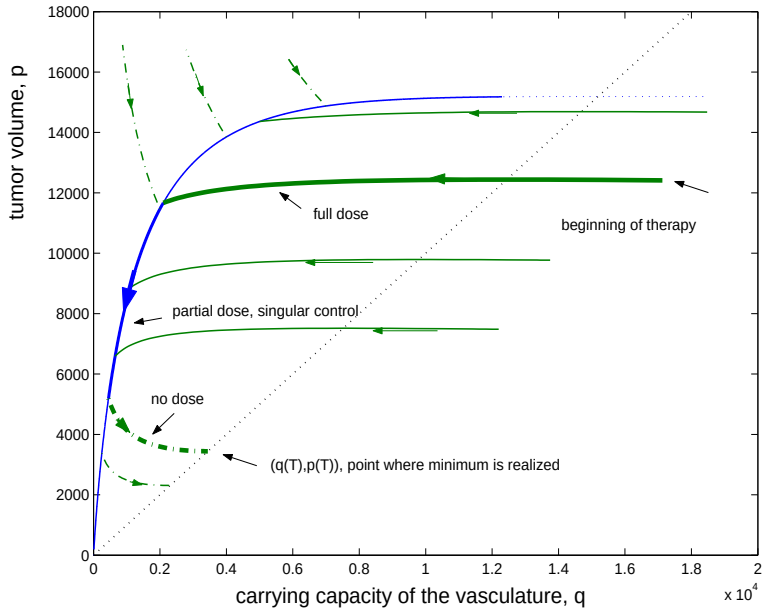


Figure 5: Synthesis of optimal trajectories. Vertical axis represents variable $p$, horizontal variable $q$.

This structure is the most typical synthesis of the type **as0**, but, as mentioned above, other concatenation sequences are possible near saturation or, for example, if the initial condition already lies on the admissible part of the singular arc in which case the optimal control naturally starts with **s**. Also, if the initial condition lies above the singular arc, i.e., in case of a very large tumor volume $p$ and relatively small endothelial support $q$, optimal trajectories start with $u = 0$ until they hit the singular arc and then continue as before. Thus in this case the optimal synthesis will be **0s0** or **0sa0** with no $u = a$ portion present if inhibitors run out before saturation of the singular control occurs. This is biologically fully justified because a large tumor with inadequate endothelial support will originally shrink by itself, so it is better to wait with administration of the inhibitors. On the other hand, if the overall amount of inhibitors is so large that the lower saturation point on the singular arc would be reached with inhibitors remaining, then by Proposition 6 it is actually not optimal to wait until this point is reached, but optimal trajectories need to leave the singular arc earlier when they switch to the control $u = a$ until all inhibitors are being used up. Numerically these times are not difficult to compute and they occur when the trajectories are close to the actual saturation points. The behavior of the optimal solutions around the saturation point on the singular arc is actually a complex mathematical problem and its analysis for a general system can be found in [32] or in [4] for an application from the chemical industry. These arguments equally apply to the model considered here and the model by Hahnfeldt et al. in [18] considered in [24].

Figure 6 gives an example of the optimal control (a) and its corresponding trajectory (b) for the initial condition $p_0 = 12,000, q_0 = 15,000$. Graph (a) illustrates the time duration of each of the doses with a significant part (middle) of the singular control (partial doses) and relatively short durations of the full dose period. Note also that the optimal singular control administers the inhibitors first at lower levels and then the dosage intensifies along the singular arc, an observation already made by Ergun et al. in [12]. The corresponding trajectory follows the pattern **as0** typical for this range of initial conditions.

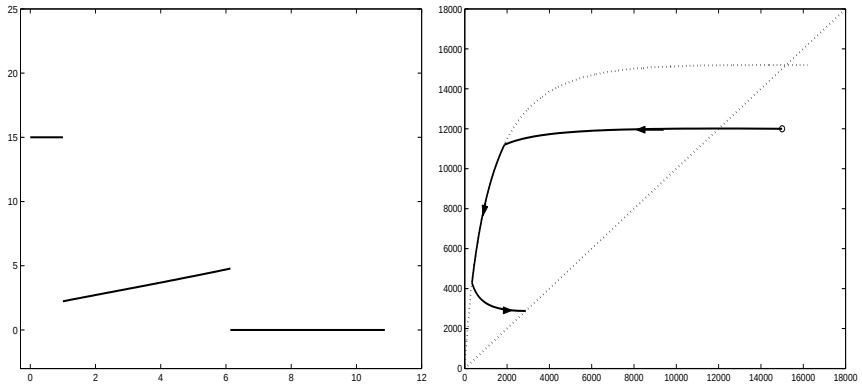


Figure 6: Optimal control (left) and corresponding trajectory (right) for initial conditions $p_0 = 12,000$ and $q_0 = 15,000$

# 4 Optimal Controls with Logistic Growth Models

We now replace the Gompertzian growth model on the tumor volume with a generalized logistic model. As before, $p$ denotes the volume of the primary tumor and $q$ the carrying capacity of the vasculature or

endothelial support, but now the dynamics of the system takes the form

$$\dot{p} = \xi p\left(1 - \left(\frac{p}{q}\right)^{\alpha}\right), \qquad p(0) = p_0 \tag{40}$$

$$\dot{q} = bq^{\frac{2}{3}} - \mu q - dq^{\frac{4}{3}} - Guq, \qquad q(0) = q_0 \tag{41}$$

for some positive exponent $\alpha$. Otherwise the parameters are as before and we again consider the optimal control problem $(OC)$ in the variables $(p, q, y)$. The equilibrium structure and biologically relevant region are left unchanged by this change in the growth function and so are the basic properties of extremals. But now there are significant changes in the optimality of singular controls. As before the switching function $\Phi(t)$ is given by $\Phi(t) = \lambda_3 - \lambda_2(t)Gq(t)$.

## 4.1 Analysis of singular controls

As before we express the dynamics in vector form as

$$\dot{z} = f(z) + ug(z) \tag{42}$$

with $z = (p, x, y)^T$ where now

$$f(z) = \begin{pmatrix} \xi p\left(1 - \left(\frac{p}{q}\right)^{\alpha}\right) \\ bq^{\frac{2}{3}} - \mu q - dq^{\frac{4}{3}} - Guq \\ u \end{pmatrix} \tag{43}$$

and $g$ is unchanged from (17). Here the Lie brackets take the form

$$[f, g](z) = \begin{pmatrix} \xi G\alpha q\left(\frac{p}{q}\right)^{\alpha+1} \\ -\frac{1}{3}G\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right) \\ 0 \end{pmatrix} \tag{44}$$

and

$$[g, [f, g]](z) = \begin{pmatrix} \xi G^2\alpha^2 q\left(\frac{p}{q}\right)^{\alpha+1} \\ -\frac{1}{9}G^2\left(bq^{\frac{2}{3}} - dq^{\frac{4}{3}}\right) \\ 0 \end{pmatrix} \tag{45}$$

Thus

$$\langle \lambda(t), [g, [f, g]](z(t))\rangle = G^2\left[\lambda_1\xi\alpha^2 q\left(\frac{p}{q}\right)^{\alpha+1} + \frac{\lambda_2}{9}\left(-bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right)\right].$$

Along a singular arc, since $\dot{\Phi}(t) = \langle \lambda(t), [f, g](z(t))\rangle = 0$, we therefore have that

$$\lambda_1\xi\alpha q\left(\frac{p}{q}\right)^{\alpha+1} = \frac{\lambda_2}{3}\left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}}\right),$$

and it follows that

$$\begin{aligned}\langle \lambda(t), [g,[f,g]](z(t))\rangle &= G^2\left[\alpha\frac{\lambda_2}{3}\left(bq^{\frac{2}{3}}+dq^{\frac{4}{3}}\right)+\frac{\lambda_2}{9}\left(-bq^{\frac{2}{3}}+dq^{\frac{4}{3}}\right)\right]\\ &= \frac{1}{3}G^2\lambda_2\left[bq^{\frac{2}{3}}(\alpha-\frac{1}{3})+dq^{\frac{4}{3}}(\alpha+\frac{1}{3})\right]. \end{aligned} \tag{46}$$

Since $\lambda_2$ is positive by Lemma 3, the expression in (46) is positive for $\alpha \geq \frac{1}{3}$ and thus the Legendre-Clebsch condition is violated. In fact, in this case singular controls are locally maximizing. For $\alpha < \frac{1}{3}$ this is still the case for singular arcs that lie in the region above the level

$$\hat{q}(\alpha) = \left(\frac{b(1-3\alpha)}{d(1+3\alpha)}\right)^{\frac{3}{2}} \tag{47}$$

and only if the singular arc lies below this level it satisfies the strengthened Legendre-Clebsch condition and becomes locally optimal. For example, for the values given earlier and $\alpha = \frac{1}{6}$ this value is given by $\hat{q}(\alpha) = 3338.3$ and generally only for smaller values singular arcs become possible candidates for optimality while optimal controls will be bang-bang at higher levels.

## 4.2 Analysis of bang-bang controls for classical logistic growth

We now consider the case of classical logistic growth, $\alpha = 1$, and show that optimal controls are bang-bang with at most two switchings of the form **0a0**. We first analyze the regions of the state-space where **0a**- respectively **a0**-switchings are possible. Since optimal controls satisfy

$$u^\star(t) = \begin{cases} 0 & \text{for } \Phi(t) > 0 \\ a & \text{for } \Phi(t) < 0 \end{cases},$$

the derivative of the switching function must be non-positive at a switching time $\tau$ if the switching is from 0 to $a$ (**0a**) and non-negative if the switching is from $a$ to 0 (**a0**). as before, at any switching time we have both

$$\Phi(\tau) = \langle \lambda(\tau), g(z(\tau))\rangle = 0$$

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

$$h(z) = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}$$

and write $[f,g](z)$ as a linear combination of $f(z)$, $g(z)$ and $h$ in the form

$$[f,g](z) = \alpha(z)f(z) + \beta(z)g(z) + \gamma(z)h \tag{48}$$

where $\alpha$, $\beta$ and $\gamma$ are analytic functions of $z$. We then obtain that

$$\begin{aligned}\dot{\Phi}(\tau) &= \langle \lambda(\tau), [f,g]z(\tau)\rangle \\ &= \alpha(z(\tau))\langle \lambda(\tau), f(z(\tau))\rangle + \beta(z(\tau))\langle \lambda(\tau), g(z(\tau))\rangle + \gamma(z(\tau))\langle \lambda(\tau), h(z(\tau))\rangle \\ &= \gamma(z(\tau))\lambda_3.\end{aligned}$$

By Lemma 3 $\lambda_3$ is positive and thus,

$$\operatorname{sgn}\dot{\Phi}(\tau) = \operatorname{sgn}\gamma(z(\tau)). \tag{49}$$

A direct computation verifies that the functions $\alpha$, $\beta$ and $\gamma$ are given by

$$\alpha(z) = G\frac{p}{q-p}, \qquad \beta(z) = -\gamma(z)$$

and

$$\gamma(z) = -\frac{1}{3}\left(bq^{-\frac{1}{3}} + dq^{\frac{1}{3}}\right) - \frac{\left(bq^{\frac{2}{3}} - \mu q - dq^{\frac{4}{3}}\right)}{q} \cdot \frac{\frac{p}{q}}{\left(1-\frac{p}{q}\right)}.$$

In the biologically relevant region $R$ the quantity $bq^{\frac{2}{3}} - \mu q - dq^{\frac{4}{3}}$ is positive for $q < \bar{q}$ and it vanishes for $q = \bar{q}$. Therefore in the region $\mathcal{R}_-$, that is for $p < q$, the function $\gamma$ is always negative and thus only switchings from $u = 0$ to $u = a$ are optimal in $\mathcal{R}_-$.

In the region $\mathcal{R}_+$, that is for $p > q$, the function $\gamma$ is positive if and only if

$$p\left(2b - 3\mu q^{\frac{1}{3}} - 4dq^{\frac{2}{3}}\right) + \left(bq + dq^{\frac{5}{3}}\right) > 0. \tag{50}$$

The polynomial $P(x) = 4dx^2 + 3\mu x - 2b$ has a unique positive zero at

$$\hat{x} = \frac{-3\mu + \sqrt{9\mu^2 + 32bd}}{8d}.$$

Note that $\hat{x} < \bar{x} = \bar{q}^{\frac{1}{3}}$ where $\bar{q}$ is the equilibrium point for the control $u = 0$. For $q \le \hat{q} = \hat{x}^{\frac{1}{3}}$ the inequality (50) is thus always satisfied and $\gamma$ is positive in $\mathcal{R}_+ \cap \{q \le \hat{q}\}$.. For $q \le \hat{q}$, (50) is equivalent to

$$p < q\frac{b + dq^{\frac{2}{3}}}{4dq^{\frac{2}{3}} + 3\mu q^{\frac{1}{3}} - 2b} = q\frac{b + dq^{\frac{2}{3}}}{P\left(q^{\frac{1}{3}}\right)}. \tag{51}$$

Define a function $Q = Q(x)$ by

$$Q(x) = x^3\frac{b + dx^2}{4dx^2 + 3\mu x - 2b} = \frac{x^3\left(b + dx^2\right)}{P(x)}, \tag{52}$$

so that $Q$ is negative for $0 < x < \hat{x}$ and positive for $x > \hat{x}$. The derivative of $Q$ is given by

$$Q'(x) = \frac{6x^2(b + 2dx^2)}{(4dx^2 + 3\mu x - 2b)^2} \cdot (dx^2 + \mu x - b) \tag{53}$$

and has a unique positive zero at the equilibrium value $x = \bar{x}$. Hence the rational function $Q$ attains its minimum over the interval $(\hat{x}, \infty)$ at $\bar{x}$ and the minimum value is given by

$$\begin{aligned} Q(\bar{x}) &= \bar{x}^3\frac{\left(b + d\bar{x}^2\right)}{4d\bar{x}^2 + 3\mu\bar{x} - 2b} = \bar{x}^3\frac{b + (b - \mu\bar{x})}{4\left(b - \mu\bar{x}\right) + 3\mu\bar{x} - 2b} \\ &= \bar{x}^3\frac{2b - \mu\bar{x}}{2b - \mu\bar{x}} = \bar{x}^3 = \bar{q} \end{aligned}$$

(see Fig. 7). Hence the inequality (51) is satisfied for all $(p, q) \in \mathcal{R}_+$ and thus only switchings from $u = a$ to $u = 0$ are optimal in $\mathcal{R}_+$.

Summarizing we therefore have shown the following result:

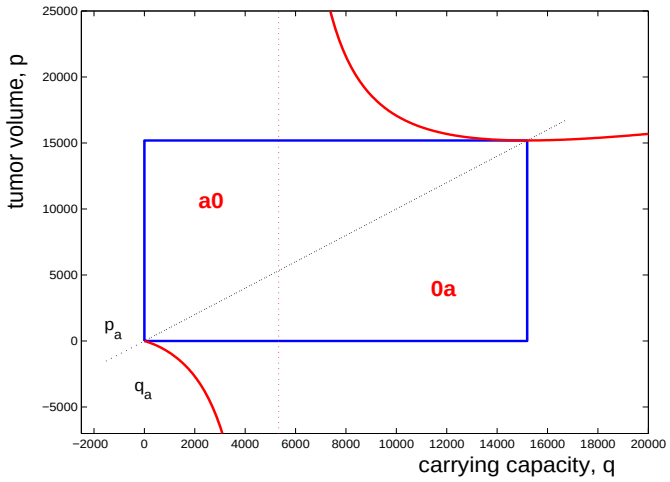


Figure 7: Optimal bang-bang switchings for the model with classical logistic tumor growth

**Theorem 2** *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 $\mathcal{R}_-$ while switchings from $u = a$ to $u = 0$ must lie in $\mathcal{R}_+$.*

**Proof.** It follows from Lemma 4 that trajectories can cross the diagonal only once from $\mathcal{R}_-$ into $\mathcal{R}_+$ along the control $u = a$. Thus overall controls can at most be of the type **0a0** and must then end on the diagonal $\mathcal{R}_0$. □

# 5 Conclusion

Using tools of geometric optimal control theory we analyzed two mathematical models for tumor anti-angiogenesis as optimal control problems with the objective of maximizing the tumor reduction achievable with a given amount of inhibitors and determined the optimal protocols and corresponding trajectories. The two types of dynamics considered differed in how the growth of the primary tumor was modelled. For the original model by Ergun et al. [12] with a Gompertzian growth model on the primary tumor volume, optimal controls consist of concatenations of singular (varying partial doses) and bang-bang pieces (full dose or no dose). Formulas for the optimal singular controls and corresponding trajectories were derived and incorporated into a full synthesis of optimal solutions. When the dynamics of cancer cells follows a logistic growth model we showed that singular controls typically are not optimal and for the case of classical logistic growth we further specified the structure of optimal controls as bang-bang with at most two switchings. These results show that that a change in the model for tumor growth effects the structure of optimal solutions not only quantitatively, but may also lead to significant qualitative changes. Hence the choice of the growth functions should be carefully justified in the modelling based on the specifics of the underlying biology.

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