Two Optimal Control Problems for a Model of Tumor Anti-Angiogenesis*

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Abstract

The scheduling of angiogenic inhibitors to control a vascularized tumor is analyzed as an optimal control problem for a mathematical model developed by Hahnfeldt et al. [14]. Two formulations of the problem are considered. In the first model the primary tumor volume is minimized for a given amount of angiogenic inhibitors to be administered while a balance between tumor reduction and the total amount of angiogenic inhibitors given is minimized in the second formulation. The optimal solutions to both problems are presented and compared.

Keywords: *Optimal control, bang-bang and singular controls, cancer treatments, angiogenic inhibitors.*

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1 Introduction

Tumor anti-angiogenesis is a cancer treatment approach targeted at the vasculature of a growing tumor. A primary solid tumor, after going through a state of avascular growth, at the size of about 2mm in diameter, starts the process of *angiogenesis* to recruit surrounding, mature, host blood vessels in order to develop its own blood vessel capillaries needed for supply of nutrients. The lining of these newly developing blood vessels consist of endothelial cells and the tumor produces vascular endothelial growth factor (VEGF) to stimulate their growth [18] as well as inhibitors to suppress it [12]. Anti-angiogenic treatments rely on these mechanisms by bringing in external angiogenic inhibitors (e.g., endostatin) targeting the endothelial cells and thus blocking their growth. This indirectly effects the tumor which, ideally, deprived of necessary nutrition, regresses. Since contrary to traditional chemotherapy this treatment targets normal, not cancer cells, it was observed that no resistance to the angiogenic inhibitors developed in experimental cancer [4]. For this reason tumor anti-angiogenesis has been called a therapy "resistant to resistance" that provides a new hope for the treatment of tumor type cancers [16]. As such it became an active area of research in the last ten years not only in medicine [10, 14, 15, 17], but also in other disciplines including mathematical biology, [1, 9, 11, 13, 26].

In mathematical modelling several models describing the dynamics of angiogenesis have been proposed. Some of these attempt to fully reflect the complexity of the biological processes, e.g., [2, 3], and allow for large scale simulations, but are not amenable to mathematical analysis since most theoretical techniques from such fields as dynamical systems or optimal control theory can only effectively be used in low dimensional systems. Hahnfeldt, Panigrahy, Folkman and Hlatky, [14], a group of researchers then at Harvard Medical School, in 1999 developed and biologically validated a two-dimensional model of ordinary differential equations for the interactions between the tumor volume, p, and the carrying capacity of the endothelial cells, q. The latter is defined as the maximum tumor volume sustainable by the vascular network. Henceforth we also refer to this as the endothelial support of the tumor for short. This model, and the underlying spatial analysis carried out in that research, has generated various modifications, for example by d'Onofrio and Gandolfi [9] at the European Institute of Oncology in Milan, or by Ergun, Camphausen and Wein [11] at the Cancer Research Institute at NIH and still is an area of active research [1, 8, 13, 20, 22, 27]. In this paper we consider two related formulations of tumor antiangiogenesis as optimal control problems for the original model by Hahnfeldt et al. [14].

In the first formulation, mathematically already analyzed in [23], the primary tumor volume is minimized with a given amount of angiogenic inhibitors to be administered as constraint. It has been shown in [23] that optimal controls are concatenations of at most five pieces of the form *0asa0* where *0* denotes an interval when no inhibitors are administered, a denotes an interval

when inhibitors are given at an a priori determined maximum dose a, and s represents an interval where the optimal control is singular and follows an explicitly computed time varying feedback control that takes values strictly between 0 and the maximum value a. (Depending on the specific initial condition, not all of these pieces need to be present.) Based on this characterization the numerical computation of optimal controls and trajectories is easily accomplished and a complete synthesis of optimal controls and trajectories for all initial conditions was given in [23]. In this formulation, since the total amount of angiogenic inhibitors is taken as a constraint, it is intuitively clear, and easily verified analytically, that optimal controls will use up the full amount. Consequently, even if there is only a small reduction in tumor size to be gained, if inhibitors are still available, they will be used regardless of cost or potential side effects. Given the fact that inhibitors are biological agents that need to be grown in a lab, and hence are very expensive, this may not be a cost effective strategy. Therefore, in this paper, we modify the above problem formulation to better balance the total amount of inhibitors given with the benefit to be gained in tumor reduction. Rather than specifying the total amount of inhibitors a priori, we incorporate this amount as a penalty term in the objective and then minimize a weighted average between the inhibitors given and the minimum tumor volume. Clearly, other kind of objectives can be considered as well, and they all may lead to both qualitatively and quantitatively different results. Our formulation naturally connects with the problem already solved in [23] and preserves the qualitative structure of solutions in the form *0asa0*, but it differs in its quantitative aspects. Also, a bifurcation analysis of the structure of optimal trajectories depending on the weight given to the angiogenic inhibitors in the objective is easily accomplished and will be illustrated with numerical results. Our results here complement those in [20, 21] obtained for a simplified version of the underlying model considered in this paper.

2 Anti-Angiogenic Therapy: Formulation I

We briefly review the underlying mathematical model that was developed and biologically validated by Hahnfeldt, Panigrahy, Folkman and Hlatky in [14]. State variables are the primary tumor volume, p, and the carrying capacity of the vasculature, q. Tumor growth is modelled as Gompertzian growth with a variable carrying capacity represented by q, that is

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

where ξ denotes a tumor growth parameter. The dynamics for the endothelial support is given in the form

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

where bp models the stimulation of endothelial cells by the tumor and the term $dp^{\frac{2}{3}}q$ models endogenous inhibition of the tumor (see [14]). The exponent $\frac{2}{3}$ arises since these inhibitors are being released through the tumor surface and the product $p^{\frac{2}{3}}q$ comes from the interactions of inhibitors with endothelial cells. The coefficients b and d are growth constants. 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. Generally μ is small and often this term is negligible compared to the other factors and thus in the literature sometimes μ is set to 0 in this equation. The following result from [9] guarantees the existence and positivity of solutions for all times and arbitrary controls u.

Proposition 1 [9] *For any non-negative locally bounded Lebesgue measurable function u and arbitrary positive initial conditions p_0 and q_0 the corresponding solution (p, q) exists for all times $t \geq 0$ and both p and q remain positive.* □

It is shown in [9] that the uncontrolled model ($u = 0$) has a unique globally asymptotically stable equilibrium point given by $\bar{p} = \bar{q} = \left(\frac{b-\mu}{d}\right)^{\frac{3}{2}}$ which for realistic values of the parameters naturally is biologically not viable. Adding a control term $u = a$, for large enough a, $Ga > b - \mu$, this globally asymptotically stable node ceases to exist and all trajectories for the corresponding system converge to the origin in infinite time. This, in principle, would be the desired situation since, at least theoretically, it allows eradication of the tumor using a constant dose $u = a$ for all time. But clearly this is not a feasible strategy due to limits on the total amount of inhibitors and potential side effects. The problem of how to administer a given amount of inhibitors to achieve the "best possible" effect thus arises naturally.

One possible formulation, considered first in [11] and then taken up by us in [22, 23, 24], is to solve the following optimal control problem: for a free terminal time T, minimize the value $p(T)$ subject to the dynamics (1) and (2) over all Lebesgue measurable functions $u : [0, T] \to [0, a]$ that satisfy a constraint on the total amount of anti-angiogenic inhibitors to be administered,

$$\int_0^T u(t)dt \leq A. \tag{3}$$

The upper limit a in the definition of the control set $U = [0, a]$ is a previously determined maximum dose at which inhibitors can be given. In this formulation the time T does not correspond to a therapy period, but instead the solution to this problem gives the maximum tumor reduction achievable with an overall amount A of inhibitors available and T is the time when this minimum tumor volume is being realized. Mathematically it is more convenient to

adjoin the constraint as third variable and define the problem in $\mathbb{R}^3$. Hence we consider the following optimal control problem:

(P1) For a free terminal time T, minimize the value $p(T)$ subject to the dynamics

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right), \qquad p(0) = p_0, \tag{4}$$

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}}\right) q - Guq, \qquad q(0) = q_0, \tag{5}$$

$$\dot{y} = u, \qquad y(0) = 0, \tag{6}$$

over all piecewise continuous functions $u : [0, T] \to [0, a]$ for which the corresponding trajectory satisfies $y(T) \leq A$.

For simulations in this paper we use the following parameter values that are taken from [14]: The variables p and q are volumes measured in mm^3; $\xi = \frac{0.192}{\ln 10} = 0.084$ *per day* (adjusted to the natural logarithm), $b = 5.85$ *per day*, $d = 0.00873$ *per* mm^2 *per day*, $G = 0.15$ *kg per mg of dose per day*, and for illustrative purposes we chose a small positive value for μ, $\mu = 0.02$ *per day*. Finally, we have chosen $a = 75$ and $A = 300$ for the limits on the control. These values are merely used for numerical illustrations; the mathematical results presented here are valid in general under the reasonable assumption that $Ga > b - \mu > 0$, i.e., that the parameters related to outside inhibition are able to overcome the net effect of "birth" minus "death" of the endothelial support.

We summarize and compare the general structure of optimal trajectories based on our earlier results and then proceed to a precise description of the optimal controls. However, in order to exclude discussions about the structure of optimal controls in regions where the model does not represent the underlying biological problem, we restrict our discussions to the biologically realistic domain

$$\mathcal{D} = \{(p, q) : 0 < p \leq \bar{p},\ 0 < q \leq \bar{q}\}. \tag{7}$$

Theorem 1 [23] *For any initial condition* $(p_0, q_0) \in \mathcal{D}$*, 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** *represents 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 a time-varying feedback control (that will be specified below), the so-called singular control. This control is only optimal while the system follows a particular curve* $\mathcal{S}$ *in the* (p, q)*-space, the optimal singular arc. However, depending on the initial condition* (p_0, q_0)*, not all of these intervals need to be present in a specific solution. For the biologically most relevant initial conditions typically optimal controls have the form* **bs0**

with **b** *stands for an interval along which the optimal control is given by either* **a** *or* **0** *depending on the initial condition.*

Despite their name, which is related to some classical control literature from the sixties (e.g., [7]), singular controls and the corresponding singular curves are to be expected in a synthesis of optimal controls for a problem of the type $(P1)$ for nonlinear models [5]. If singular controls exist they typically will be either locally maximizing or minimizing for the objective and higher order conditions for optimality, like the Legendre-Clebsch conditions [7, 5], allow to determine their optimality status. In fact, for the 3-dimensional optimal control problem $(P1)$ optimal singular trajectories can only lie on *one* specific curve in (p, q)-space, the singular curve $\mathcal{S}$. If singular controls are locally minimizing, as it is the case here, then this curve forms the anchor piece to the optimal synthesis. Thus for this model singular controls and the geometry of the singular curve S are an essential part of the design of the optimal protocols and in order to construct a full synthesis of solutions, the formulas for singular controls and corresponding singular trajectories need to be determined. The proposition below gives these formulas. All mathematical arguments leading to the full derivation of these formulas can be found in [23]

Proposition 2 [23] *The singular curve $\mathcal{S}$ lies in the sector $\{(p, q) : x_1^* q < p < x_2^* q\}$ where x_1^* and x_2^* are the unique zeroes of the equation*

$$\varphi(x) = \frac{b}{d} x(\ln x - 1) + \frac{\mu}{d} = 0 \tag{8}$$

and satisfy $0 \leq x_1^* < 1 < x_2^* \leq e$. In the variables (p, x) with $x = \frac{p}{q}$ the singular curve $\mathcal{S}$ can be parameterized in the form

$$p^2 + \varphi(x)^3 = 0 \qquad \text{for} \quad x_1^* < x < x_2^*. \tag{9}$$

The singular control keeps the system on the singular curve and is given as a feedback function of x in the form

$$u_{\sin}(x) = \frac{1}{G} \left[\left(\frac{1}{3}\xi + bx \right) \ln x + \frac{2}{3}\xi \left(1 - \frac{\mu}{bx} \right) \right]. \tag{10}$$

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

The two graphs given in Fig. 1 illustrate the proposition for the parameter values from [14] specified earlier. Fig. 1(a) shows the plot for the singular control defined by (10) also indicating the values x_ℓ^* and x_u^* where the control saturates at $u_{\sin}(x) = 0$ and $u_{\sin}(x) = a$. Fig. 1(b) shows

the graph of the singular curve $\mathcal{S}$ given by formula (9). Saturation of the singular control at x_ℓ^* and x_u^* restricts the admissible part of this petal-like curve to the portion lying between the lines $p = x_l^* q$ and $p = x_u^* q$. This portion is marked with a solid line in Fig. 1(b). The qualitative structures shown in Fig. 1 are generally valid for arbitrary parameter values both for the control and the singular curve. But naturally, with decreasing values for the upper control limit a the admissible portion shrinks until it disappears and the singular control no longer is admissible.

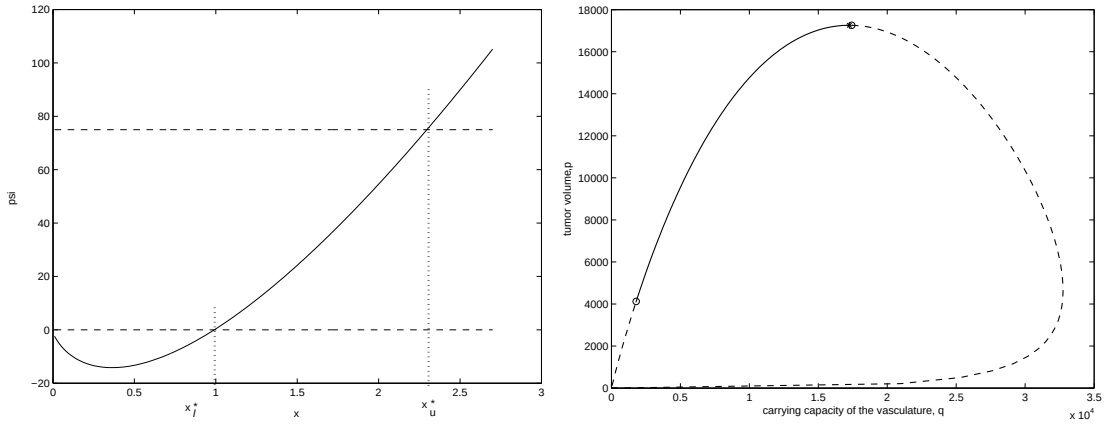

Figure 1: (a) singular control and (b) admissible singular arc

The admissible singular arc becomes the center piece of the synthesis of optimal solutions given in Fig. 2. The top gives a representation of the synthesis as a whole and the bottom portions give an example of one particular optimal trajectory and its corresponding optimal control. The important curves for the synthesis are the admissible portions of the singular curve (solid blue curve), portions of trajectories corresponding to the constant controls $u = 0$ (dashed-dot green curves) and $u = a$ (solid green curves), and the line $p = q$ (dotted black line) where the trajectories achieve the maximum tumor reduction. These diagrams represent the optimal trajectories as a whole and each of the different curves gives a different optimal trajectory depending on the actual initial condition. The thick lines in the graphs mark one specific such trajectory. For this case the initial value p_0 for the tumor volume and q_0 for the endothelial support are high and require to immediately start the treatment. The optimal trajectory therefore initially follows the curve corresponding to the control $u = a$. Note that, although inhibitors are given at full dose along this curve, this shows very little effect on the number of the cancer cells in a sense of decrease. Once the trajectory corresponding to the full dose hits the singular arc S, according to our analysis it is no longer optimal to give full dose and the optimal controls here switch to the singular control and the optimal trajectory follows the singular arc. Only at this point a significant tumor reduction commences. Ignoring some

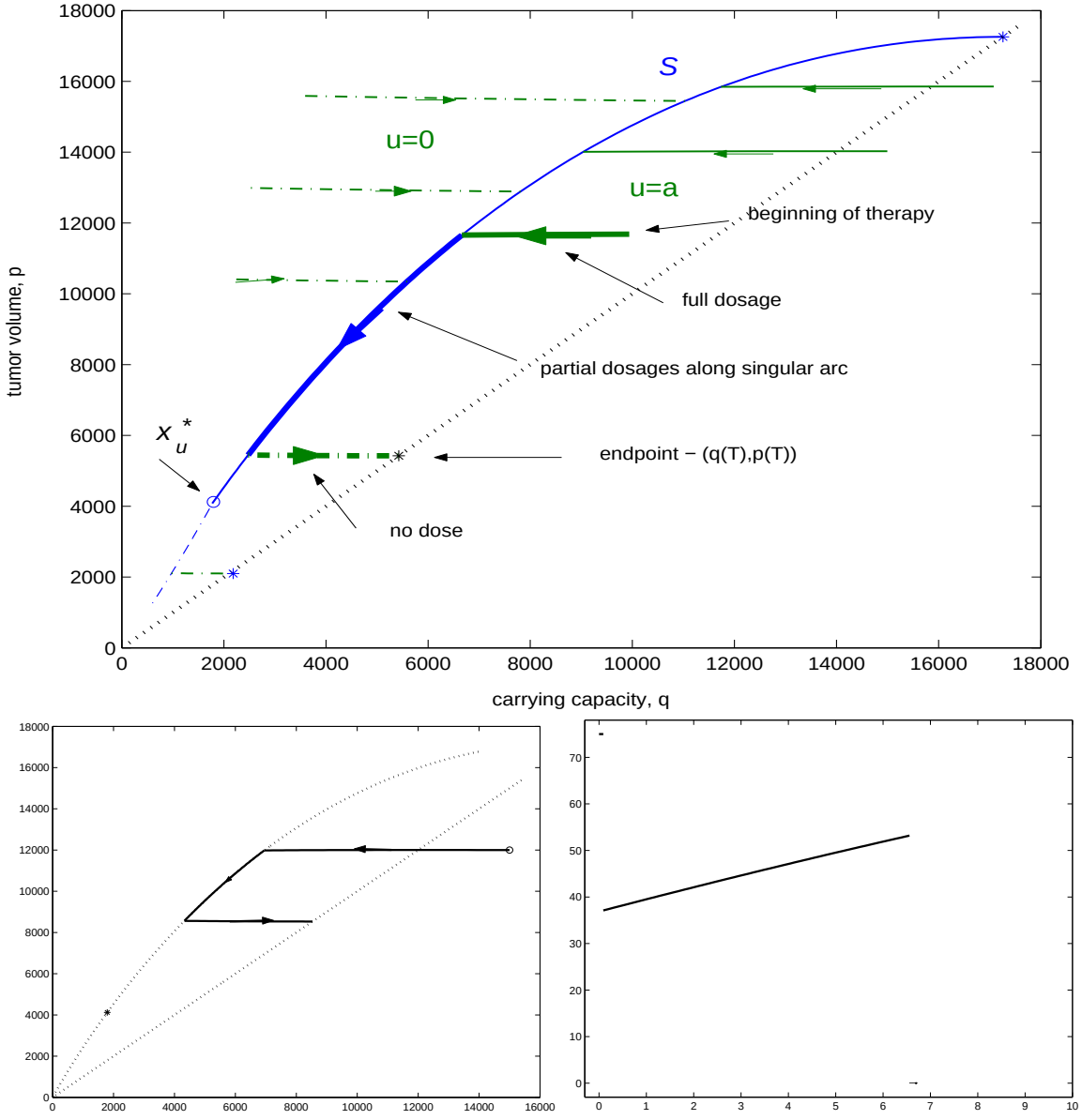

Figure 2: Synthesis of optimal trajectories (top) and an example of the optimal trajectory (bottom, left) and corresponding optimal control (bottom, right) for initial condition $(p_0, q_0) = (12,000; 15,000)$

special cases that are due to saturation of the singular control along this arc and are described in [23], the optimal control will now follow the singular arc until all inhibitors are exhausted according to the condition that $y(T) = A$. When the inhibitors have been exhausted, therapy is over and the optimal trajectory now follows a trajectory for the control $u = 0$. The reason for this lies in the fact that due to aftereffects in the dynamics the minimum tumor volume is only realized along this trajectory when it crosses the diagonal $p = q$. The corresponding time T then is the limit of the horizon considered in the problem formulation $(P1)$.

3 Anti-Angiogenic Therapy: Formulation II

The objective chosen in problem (P1) does not put a prize on the usage of angiogenic inhibitors and thus naturally optimal solutions exhaust the available inhibitors regardless of incremental benefits. We therefore now consider a modification of this model where we do not restrict the total amount of anti-angiogenic treatment a priori, but rather try to balance this amount with a reduction in tumor size over time.

(P2) For a free terminal time T, minimize

$$J_2(u) = p(T) + \kappa \int_0^T u(t)dt \tag{11}$$

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

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right), \qquad p(0) = p_0, \tag{12}$$

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}}\right) q - Guq, \qquad q(0) = q_0. \tag{13}$$

In the objective, as in model $(P1)$, the term $\int_0^T u(t)dt$ represents the total amount of anti-angiogenic treatment administered. This term can also be viewed as a measure for the cost of the treatment or related to side effects. In this formulation we thus attempt to keep a balance between cost or side-effects and effectiveness of the treatment by adding this integral with a positive weight, $\kappa > 0$, to the overall criterion to be minimized.

We first show that the qualitative structure of solutions does not change, i.e. optimal controls for problem $(P2)$ still follow the regimen **0asa0**. But the conditions for termination of anti-angiogenic treatment will de different. First-order necessary conditions for optimality of a control u are given by the *Pontryagin Maximum Principle* [28, 7]. It is easily seen that the problem is normal and thus these conditions can be formulated as follows: if u_* is an optimal control defined over the interval $[0, T]$ with corresponding trajectory (p_*, q_*), then there exists an absolutely

continuous co-vector, $\lambda : [0,T] \to (\mathbb{R}^2)^*$, (which we write as row-vector) that satisfies the adjoint equations with transversality condition,

$$\dot{\lambda}_1 = \xi\lambda_1 \left(\ln\left(\frac{p_*(t)}{q_*(t)}\right) + 1 \right) + \lambda_2 \left(\frac{2}{3} d \frac{q_*(t)}{p_*^{\frac{1}{3}}(t)} - b \right), \qquad \lambda_1(T) = 1, \tag{14}$$

$$\dot{\lambda}_2 = -\xi\lambda_1 \frac{p_*(t)}{q_*(t)} + \lambda_2 \left(\mu + d p_*^{\frac{2}{3}}(t) + Gu \right), \qquad \lambda_2(T) = 0, \tag{15}$$

such that along $(\lambda(t), p_*(t), q_*(t))$ the optimal control u_* minimizes the Hamiltonian H,

$$H = \kappa u - \lambda_1 \xi p \ln\left(\frac{p}{q}\right) + \lambda_2 \left(bp - \left(\mu + d p^{\frac{2}{3}} \right) q - Guq \right), \tag{16}$$

over the control set $[0,a]$ with the minimum value given by 0. We call a pair $((p,q),u)$ consisting of an admissible control u with corresponding trajectory (p,q) for which there exist a multiplier λ such that the conditions of the Maximum Principle are satisfied an *extremal* (pair) and the triple $((p,q),u,\lambda)$ is an extremal lift (to the cotangent bundle).

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

$$\Phi(t) = \kappa - \lambda_2(t) G q_*(t), \tag{17}$$

then optimal controls satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ a & \text{if } \Phi(t) < 0 \end{cases}. \tag{18}$$

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. These are precisely the so-called *singular* controls already mentioned above. Optimal controls then need to be synthesized from these candidates through an analysis of the switching function. Generally, if singular controls can be excluded from the potential candidates for optimality, like it is the case, for example, for some models for cancer chemotherapy (e.g., [19]), then it is reasonable to expect that optimal controls will be *bang-bang*, that is, switch between the extreme points $u = 0$ and $u = a$ of the control set. For this case optimization based sufficient conditions for local optimality exist (e.g., [25, 19]). However, for the problem considered here singular controls are optimal and so far besides constructions of local fields of extremals like in the calculus of variations no other local optimality conditions exist for this situation. In fact, the optimality of the synthesis for problem $(P1)$ was proven by verifying the conditions of a regular synthesis in the sense of Boltyansky [6] and for problem $(P2)$ we also draw on these constructions for our claims of optimality.

The analysis of the singular arc is somewhat different from the 3-dimensional system $(P1)$, but as we will show now leads to the same result. If the control u is singular on an open interval I, then $\Phi(t) \equiv 0$ and thus also the derivative of the switching function vanishes, i.e.,

$$\begin{aligned}
0 \equiv \dot{\Phi}(t) &= -\dot{\lambda}_2(t) G q_*(t) - \lambda_2(t) G \dot{q}_*(t) \\
&= \left[\xi \lambda_1(t) \frac{p_*(t)}{q_*(t)} - \lambda_2(t) \left(\mu + d p_*^{\frac{2}{3}}(t) + G u(t) \right) \right] G q_*(t) \\
&\quad - \lambda_2(t) G \left[b p_*(t) - \left(\mu + d p_*(t)^{\frac{2}{3}} \right) q_*(t) - G u q_*(t) \right] \\
&= \left[\xi \lambda_1(t) - b \lambda_2(t) \right] G p_*(t).
\end{aligned}$$

Since $p_*(t)$ is positive we therefore have that

$$\xi \lambda_1(t) - b \lambda_2(t) = 0. \tag{19}$$

Furthermore, the Hamiltonian vanishes identically and thus $\Phi(t) \equiv 0$ also implies that

$$\lambda_1(t) \xi p(t) \ln \left(\frac{p(t)}{q(t)} \right) - \lambda_2(t) \left(b p(t) - \left(\mu + d p(t)^{\frac{2}{3}} \right) q(t) \right) = 0$$

and therefore

$$\lambda_2(t) \left(b p(t) \left[\ln \left(\frac{p(t)}{q(t)} \right) - 1 \right] + \left(\mu + d p(t)^{\frac{2}{3}} \right) q(t) \right) = 0.$$

Also, from $\Phi(t) \equiv 0$ we get

$$\lambda_2(t) G q_*(t) = \kappa > 0$$

which implies $\lambda_2(t) > 0$ along a singular arc. Thus the singular arc is given by the locus of all points (p, q) that satisfy

$$\mu + d p^{\frac{2}{3}} \equiv -b \frac{p}{q} \left(\ln \left(\frac{p}{q} \right) - 1 \right). \tag{20}$$

In the variables p and $x = \frac{p}{q}$ this exactly is (9),

$$p^2 = - \left(\frac{b x \left(\ln x - 1 \right) + \mu}{d} \right)^3. \tag{21}$$

The explicit formula (10) can be verified by differentiating (19) once more, and then solving for the control that explicitly appears in this derivative. However, the relation (21) will need to be used to simplify to the specified form. For an alternate and more elegant derivation in terms of Lie brackets we refer the reader to [23].

This short computation is included to highlight for one case how the calculations and subsequent analysis are strongly related and in many instances identical with the computations done in [23] for problem $(P1)$. The reason is that the extra multiplier λ_3 in formulation $(P1)$

associated with the constraint on y is constant and in essence the two problems $(P1)$ and $(P2)$ become compatible if we set $\lambda_3 = \kappa$. Hence the computations and subsequent analysis all carry over to problem formulation $(P2)$. In particular, *the singular curve and its admissible portion are given as in Proposition 2* and *the concatenation structure of optimal controls is identical for both problems*. But there are quantitative differences in how long the optimal solutions stay on this singular arc.

In formulation $(P1)$ optimal controls typically follow the singular arc until all inhibitors have been exhausted. There are some exceptions if the singular control saturates at its upper value a that are described in [23], but in this paper we only consider the most typical situation. Because of after effects in the dynamics, optimal controls end with a segment with $u = 0$ until the maximum tumor reduction is achieved at time T when the trajectory crosses the diagonal, $p(T) = q(T)$. For problem $(P2)$ optimal trajectories leave the singular arc at some optimal time τ_* determined by the balance of tumor reduction and increase in the objective. While it is not possible to determine the optimal time τ_* analytically, it is not difficult to compute it numerically by introducing a 1-dimensional parameter τ that measures for how long the trajectory follows the optimal protocol for problem $(P1)$. As before, it then ends with a segment for $u = 0$ until the diagonal $p = q$ is reached. We thus simply need to minimize the resulting parameterized objective.

We now formalize this procedure. For simplicity of presentation we restrict to one specific concatenation structure. The necessary modifications for the other cases will be clear. We consider initial conditions (p_0, q_0) for which the optimal control u_* for formulation $(P1)$ has the most typical form **as0**. That is, the control starts with an initial segment when inhibitors are given at maximum dose a until the corresponding trajectory reaches the singular arc at time σ_1, then the control becomes singular and the trajectory follows the singular arc until all inhibitors become exhausted at time σ_2, and the optimal control ends with a segment where no inhibitors are given until the diagonal $p = q$ is reached at time $\bar{T}$,

$$u_*(t) = \begin{cases} a & \text{for } 0 \le t \le \sigma_1 \\ u_{\sin} & \text{for } \sigma_1 < t \le \sigma_2 \\ 0 & \text{for } \sigma_2 < t \le \bar{T} \end{cases} . \tag{22}$$

Given such an initial condition (p_0, q_0), let $\bar{\gamma} = (\bar{p}, \bar{q}) : [0, \bar{T}] \to \mathbb{R}^2_+$ denote the corresponding $(P1)$-optimal trajectory. The $(P2)$-value of this $(P1)$-optimal strategy is given by $J_2(u_*) = \bar{p}(\bar{T}) + \kappa A$. Assuming that the tumor reduction achieved is smaller than the penalty on the inhibitors, $p_0 - \bar{p}(\bar{T}) < \kappa A$, it follows that u_* is no longer optimal for problem $(P2)$, simply since the trivial strategy of doing nothing already gives a better value for the objective. (We can always guarantee that $p_0 - \bar{p}(\bar{T}) < \kappa A$ by choosing A large enough, but the concatenation

sequence may then change to $asa0$ if the singular control saturates.) We thus construct a 1-parameter family of extremal input-trajectory pairs $(p_\tau(\cdot), q_\tau(\cdot))$ by following the $(P1)$-optimal trajectory $\bar{\gamma}$ up to some time τ, $0 \le \tau \le \sigma_2$, and then at time τ switch to $u = 0$ ending the trajectory at time $T = T(\tau)$ as the curve $p = q$ is reached,

$$u_\tau(t) = \begin{cases} u_*(t) & \text{for } 0 \le t \le \tau \\ 0 & \text{for } \tau < t \le T(\tau) \end{cases}, \tag{23}$$

and we denote the value of the corresponding objective by $I(\tau)$, i.e.

$$I(\tau) = p_\tau(T(\tau)) + \kappa \int_0^\tau u_*(t)dt.$$

Since the qualitative structure of $(P2)$-optimal controls is the same as for problem $(P1)$, it follows that the $(P2)$-optimal trajectory is a member of this family. For $\tau = 0$ formally the trajectory of doing nothing is included and we simply get the initial tumor volume as value, $I(0) = p_0$. For $\tau = \sigma_2$ we obtain the $(P1)$-optimal trajectory, $I(\sigma_2) = \bar{p}(\bar{T}) + \kappa A$. It is easily seen that the function $I : [0, \sigma_2] \to \mathbb{R}$, $\tau \mapsto I(\tau)$, is continuous and thus has a minimum over the compact interval $[0, \sigma_2]$. If the minimum occurs at $\tau_* < \sigma_2$, then the corresponding parameter defines the $(P2)$-optimal solution. If $\tau_* = \sigma_2$, then it becomes necessary to consider problem $(P1)$ with a higher total limit A on the inhibitors as will be explained below.

We illustrate the procedure with numerical results for the initial condition $(p_0, q_0) = (15,000; 15,000)$. Based on the synthesis of optimal solutions constructed in [23] the corresponding optimal control and trajectory are easily computed and we have $\sigma_1 = 0.04$, $\sigma_2 = 8.91$ and $\bar{T} = 9.09$ so that the $(P1)$-optimal control u_* is given by

$$u_*(t) = \begin{cases} a & \text{for } 0 \le t \le 0.04 \\ u_{\sin} & \text{for } 0.04 < t \le 8.91 \\ 0 & \text{for } 8.91 < t \le 9.09 \end{cases}. \tag{24}$$

The control and corresponding trajectory are shown in Fig. 3.

Fig. 4 shows the graphs of the objective I for various values of the weight κ in the penalty term. Since the $(P1)$-optimal control starts with $u = a$ for this initial condition the penalty term is dominant for large values of κ and in these cases the function I will be increasing as shown for the case $\kappa = 21.5$ in Fig. 4(a). This simply means that for this problem formulation and such a high weight, it would be "optimal" in the sense of minimizing the objective to do nothing, i.e., the best parameter value is given by the left end point $\tau = 0$. This will be correct for all $\kappa > \kappa_1^*$ where the coefficient κ_1^* is defined as the smallest value for which the optimal solution is still attained at the parameter $\tau_1^* = 0$. As κ decreases below κ_1^* the structure of the $(P2)$-optimal control becomes **a0** and does not yet include a piece on the singular arc. Since

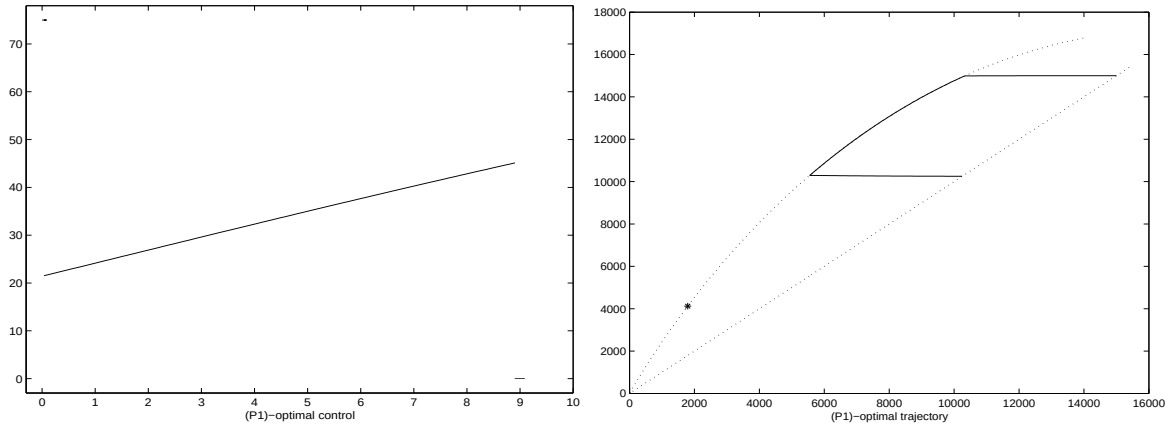

Figure 3: $(P1)$-optimal control (left) and corresponding optimal trajectory (right)

the dynamics for $u = a$ is very fast - the $(P1)$-optimal control is at full dose only for time 0.04 - this structure is only optimal over a tiny interval (κ_1^*, κ_2^*) in κ, (κ_1^*, κ_2^*) contained in $(20.75, 21)$ for this initial condition. The coefficient κ_2^* is determined by the condition that the associated optimal parameter τ_2^* is given by the time σ_1 when the $(P1)$-optimal control becomes singular, $\tau_2^* = \sigma_1 = 0.04$. Thus in this case the $(P2)$-optimal trajectory follows the $u = a$ trajectory until it hits the singular arc $\mathcal{S}$ and then immediately bounces off with control $u = 0$. As κ decreases below κ_2^* the minimum is achieved for a parameter $\tau > \tau_2^*$ and thus the structure of the $(P2)$-optimal control now is **as0** as for problem $(P1)$, but the optimal control follows the singular arc only until time τ. For example, the graph of I for $\kappa = 20$ is shown in Fig. 4(b) and the minimum of I is attained for $\tau = 1.37$; the $(P2)$-optimal control is given by

$$u(t) = \begin{cases} a & \text{for } 0 \le t \le 0.04 \\ u_{\sin} & \text{for } 0.04 < t \le 1.37 \\ 0 & \text{for } 1.37 < t \le T(1.37) \end{cases} . \tag{25}$$

including a small portion of the singular arc. This control and its corresponding trajectory are shown in Fig. 5. As κ decreases further the parameter value for which the minimum is attained moves to the right and the interval along which the $(P2)$-optimal control is singular becomes longer. For example, for $\kappa = 15$ the control is now singular until time $\tau = 5.56$ as shown in Fig. 6.

Eventually, as κ decreases further for some value κ_3^* the parameter value τ where the function I attains its minimum becomes equal to the time $\tau_3^* = \sigma_2 = 8.91$ when the singular control has used up exactly the amount A given as constraint in problem $(P1)$. In this case the $(P1)$ and

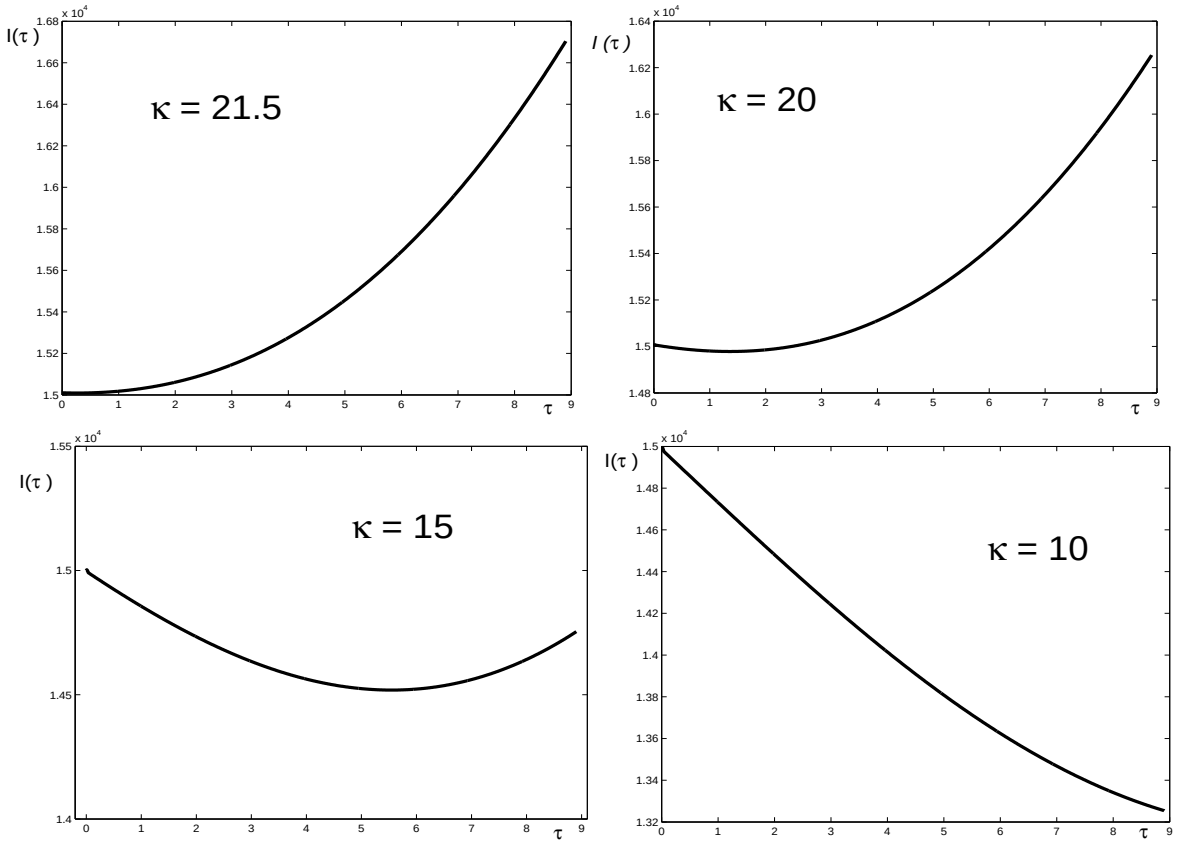

Figure 4: Graphs of the function I for $\kappa = 21.5$ (top left, a), $\kappa = 20$ (top right, b), $\kappa = 15$ (bottom left, c), $\kappa = 10$ (bottom right, d)

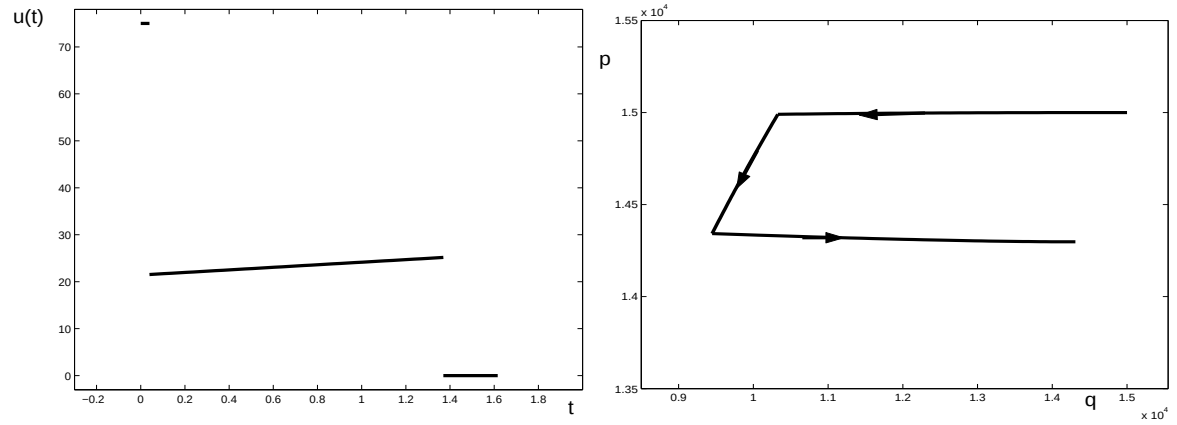

Figure 5: ($P2$)-optimal control (left, a) and corresponding trajectory (right, b) for $\kappa = 20$.

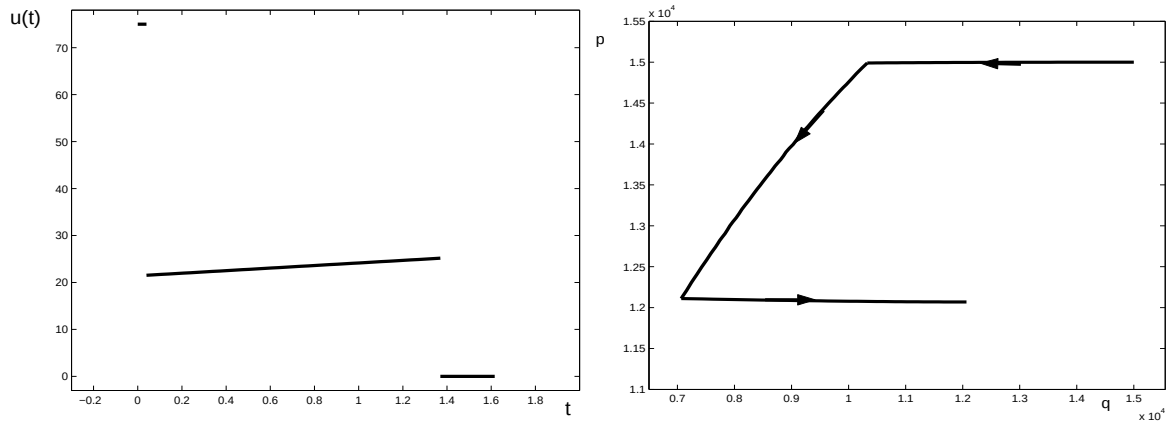

Figure 6: $(P2)$-optimal control (left, a) and corresponding trajectory (right, b) for $\kappa = 15$.

$(P2)$-optimal controls are identical. For $\kappa < \kappa_3^*$ the function I is strictly decreasing on the interval $[0, \sigma]$ as shown in Fig. 4(d) for $\kappa = 10$. In this case the $(P2)$-optimal control uses more inhibitors than were allowed in model formulation $(P1)$ and it therefore becomes necessary to recompute the optimal $(P1)$-solution with a higher overall amount of inhibitors. For example, here for $\kappa = 10$, if we take $A = 600$, then the upper limit σ_2 increases to $\sigma_2 = 14.68$ and now the minimum is attained for $\tau = 11.17$ inside the interval $[0, \sigma_2]$, see Fig. 7. Also, for these values the singular control still does not saturate and thus the structure $as0$ is retained for the $(P2)$-optimal solution.

4 Conclusion

We described the solutions for two related optimal control problems for tumor anti-angiogenesis. Central to both solutions is an optimal singular arc $\mathcal{S}$, but the solutions differ in how long it is optimal to follow this curve. If the total amount of angiogenic inhibitors is imposed as a constraint, problem $(P1)$, then naturally all available drugs will be exhausted and therapy is ended as this limit is reached along $\mathcal{S}$. If the objective tries to achieve a balance between the amount of inhibitors given and their cost or side effects, problem $(P2)$, there exists a unique time when the benefits in tumor reduction from giving additional inhibitors are offset by negative side effects or cost as measured by the integral of the control. Based on the knowledge of the synthesis of $(P1)$-optimal controls and trajectories constructed in [23] the $(P2)$-optimal controls and trajectories can then easily be computed through a 1-dimensional numerical minimization procedure.

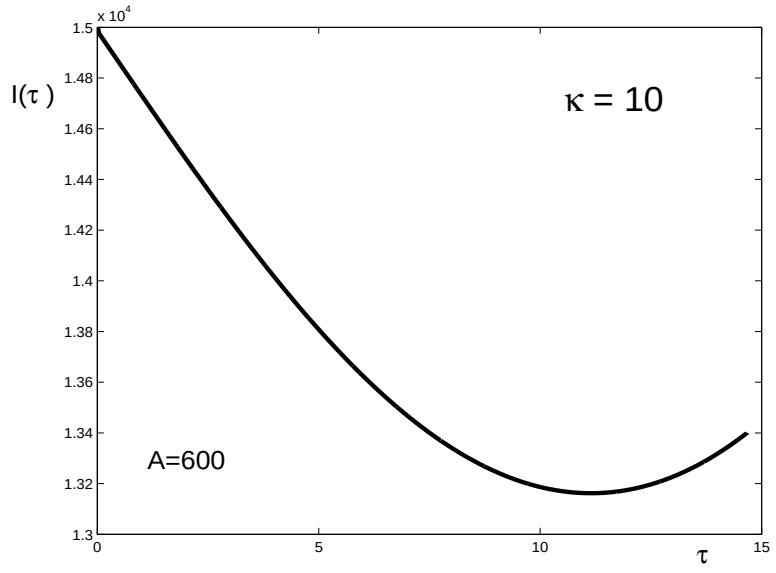

Figure 7: Graph of the function I for $\kappa = 10$ with $A = 600$

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