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The Effect of Pharmacokinetics on Optimal Protocols for a Mathematical Model of Tumor Anti-Angiogenic Therapy

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***Abstract*— A mathematical model for the scheduling of angiogenic inhibitors that includes a pharmacokinetic equation is considered as an optimal control problem. When dosage and concentration of the inhibitor are identified, there exists an optimal singular arc of order 1 that forms the core of a synthesis of optimal controls. Under the standard pharmacokinetic linear model for the concentration this singular arc is preserved and still optimal, but its order increases to 2. This prevents concatenations of the singular arc with the constant bang controls and now the transitions to and from the singular arc are through chattering arcs. Optimal controls have the property that the associated concentration of inhibitors tracks the optimal singular arc for the reduced model without pharmacokinetic equations.**

I. Introduction

Anti-angiogenesis is a novel indirect treatment approach to tumor type cancers that aims at preventing a growing tumor from developing the network of blood vessels and capillaries that it needs for its supply of nutrients and oxygen to enable further tumor growth. Anti-angiogenic treatment was already proposed in the early seventies by J. Folkman [12], but only enabled by the discovery of the inhibitory mechanisms of the tumor in the nineties [7], [15]. It brings in external angiogenic agents to disrupt the growth of endothelial cells which form the lining of newly developing blood vessels and the tumor, deprived of necessary nutrition, ideally regresses. This indirect treatment approach does not kill the cancer cells, but rather than targeting the fast duplicating and continuously mutating tumor cells, it targets the genetically far more stable endothelial cells. As a consequence, no clonal resistance to angiogenic inhibitors has been observed in experimental cancer [2]. Since developing drug resistance all too often is the limiting factor in conventional chemotherapy treatments, tumor anti-angiogenesis has been called a new hope for the treatment of tumors [14].

Several mathematical models that describe the dynamics of angiogenesis have been proposed. Some of these aim at fully reflecting the complexity of the biological processes and allow for large-scale simulations (e.g., [1]), others aggregate variables into low-dimensional dynamical systems [13], [11], [9] and thus are amenable to mathematical analysis. Of these one of the most prominent models was developed by Folkman and his collaborators Hahnfeldt, Panigrahy, and Hlatky, then at Harvard Medical School. In [13] a two dimensional model of ordinary differential equations for the interactions between the tumor volume, p, and the carrying capacity of the vasculature, q, was developed and biologically validated. The latter is defined as the maximum tumor volume sustainable by the vascular network that supports the tumor with nutrients. It is closely related to the volume of endothelial cells and for short we also refer to it as the endothelial support of the tumor. Two main modifications of the original model have been formulated since then, one by Ergun, Camphausen and Wein from the National Cancer Institute in the U.S. [11], the other by d'Onofrio (at the European Institute of Oncology in Milan) and Gandolfi (at National Research Council in Rome) in [9].

Naturally, in all medical applications resources are limited (and very expensive in the case of anti-angiogenic treatments) and side-effects need to be kept tolerable. Thus the problem of how to apply given amounts of agents in an optimal way arises. Applications of optimal control to mathematical models arising in biomedical problems have had a long history with much of the focus on models in cancer chemotherapy (e.g., [18], [25], [26]). 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 (e.g., [19], [22], [27], [28]) and immunotherapies (e.g., [6], [8]). Also, models describing the immune response to viruses have been of strong interest (e.g., HIV [16]). In [11] the question how to schedule an a priori given amount of angiogenic inhibitors in such a way as to realize the maximum tumor reduction possible was posed as an optimal control problem by Ergun et al. and initially analyzed. Complete solutions to both the original model of [13] as well as its modifications from [9] and [11] were given by us in [19], [22], [23].

In view of the tremendous complexities of cancer treatments, for the analysis of mathematical models it is a good strategy to start with simplified models and then incorporate increasingly more complex and medically more realistic features into the model. In this sense, a commonly made simplification in the literature, and so far this also was made in the analysis of the models for tumor anti-angiogenesis

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mentioned above, is to identify the drug dosage with its concentration and even more, with its effects. In reality these clearly are different phenomena and their relations are studied under the names of *pharmacokinetics (PK)* and *pharmacodynamics (PD)*. Pharmacokinetic equations model the drug's concentration in the body plasma and pharmacodynamics models the effectiveness of the drugs. In short, *PK/PD* stands for the description of the full process, also known as *drug delivery* in the medical literature.

In this paper, for the model by Ergun, Camphausen and Wein [11], we extend our research to include the commonly used linear pharmacokinetic model in our analysis. It turns out that such an addition has significant implications if optimal singular arcs exist in the model. In fact, it can be shown that for a dynamics given by a control-affine system the optimality status of singular arcs does not change [24]. For example, for models for cancer chemotherapy singular controls are not optimal and thus the addition of linear PK has little effect on optimal protocols [20], [21]. For the model considered here, however, singular controls are optimal and a corresponding singular arc is the center piece to a synthesis of optimal controls. This curve is preserved and still optimal once PK is added to the model. But we shall show that the order of the singular arc increases by one making the synthesis of optimal controls a challenging problem. Still, as we shall show, all essential features of the simplified model are preserved and the optimal concentrations of inhibitors follow the identical singular arc. This allows for the construction of suboptimal controls by tracking this arc. From a practical point of view, optimal controls that contain chattering arcs are not realizable anyway and thus our constructions provide satisfactory control schemes.

II. A Mathematical Model for Tumor Anti-Angiogenic Therapy

In this paper we consider the mathematical model for tumor anti-angiogenesis that was formulated by Ergun, Camphausen and Wein in [11]. Based on the model by Hahnfeldt et al. [13], the spatial aspects of the underlying consumption-diffusion processes that stimulate and inhibit angiogenesis are incorporated into a non-spatial 2-compartment model with the primary tumor volume p and its carrying capacity q as variables. Tumor growth is modelled by a Gompertzian growth function of the form

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

where ξ denotes a tumor growth parameter. The dynamics proposed in [11] for the equation modelling the change in the endothelial support is given by

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

where b (birth) and d (death), respectively, denote endogenous stimulation and inhibition parameters for the endothelial support. The multiples of $\frac{2}{3}$ in the q-exponents arise through the scaling of tumor volume to the surface area through which inhibitors need to be released. This specific form was chosen in [11] since it achieves a better balance in the substitution of stimulation and inhibition compared with the differential-algebraic nature of the original model where the q-dynamics reaches its steady-state extremely fast. The last term Guq represents exogenous inhibition and thus the variable u that corresponds to the angiogenic dose rate is the control in the system and the constant G represents an anti-angiogenic killing parameter.

We consider the optimal control problem initially formulated in [11]: for a free terminal time T, minimize the tumor volume $J(u) = p(T)$ subject to the dynamics (1) and (2) over all Lebesgue measurable functions $u : [0, T] \to [0, a]$ which satisfy a constraint on the total amount of anti-angiogenic inhibitors administered,

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

Mathematically it is more convenient to eliminate the fractional powers with a change of coordinates, $x = q^{\frac{1}{3}}$, and to incorporate the constraint (3) into the dynamics by introducing a new variable y which keeps 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

$$\dot{p} = -\xi p \ln\left(\frac{p}{x^3}\right), \qquad p(0) = p_0, \tag{4}$$

$$\dot{x} = \frac{1}{3}(b - dx^2 - Gux), \qquad x(0) = x_0, \tag{5}$$

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

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

Necessary conditions for optimality are given by the *Pontryagin Maximum Principle* (e.g., [3], [4], [5]). Defining the Hamiltonian $H = H(\lambda, p, q, u)$ as

$$H = -\lambda_1 \xi p \ln\left(\frac{p}{x^3}\right) + \frac{\lambda_2}{3}\left(b - dx^2 - Gux\right) + \lambda_3 u, \tag{7}$$

these conditions imply that there exists a multiplier $\lambda = (\lambda_1, \lambda_2, \lambda_3) \in (\mathbb{R}^3)^*$, (which we write as a row-vector) that satisfies the adjoint equation

$$\dot{\lambda}(t) = -\frac{\partial H}{\partial x}(\lambda(t), p_*(t), x_*(t), u_*(t)) \tag{8}$$

so that the optimal control u_* minimizes the Hamiltonian along $(\lambda(t), p_*(t), x_*(t))$ over the control set $[0, a]$ with minimum value given by 0. This minimum condition is equivalent to minimizing the linear function $(\lambda_3 - \frac{1}{3}\lambda_2(t)Gx_*(t))v$ over the control set $[0, a]$. Thus, if we define the so-called *switching function* Φ as

$$\Phi(t) = \lambda_3 - \frac{1}{3}\lambda_2(t)Gx_*(t), \tag{9}$$

then optimal controls satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ a & \text{if } \Phi(t) < 0 \end{cases}. \tag{10}$$

A priori the control is not determined by the minimum condition at times when $\Phi(t) = 0$. However, if $\Phi(t) \equiv 0$ on an open interval, then also all derivatives of $\Phi(t)$ must vanish and this may determine the control. Controls of this kind are called *singular* while we refer to the constant controls $u = 0$ and $u = a$ as *bang* controls. For the model considered here, singular controls are indeed optimal and we recall these results from earlier publications [17], [19].

Proposition 2.1: There exists a locally minimizing singular arc S defined in (p, x)-space by

$$p_{\sin} = p_{\sin}(x) = x^3 \exp\left(3\frac{b - dx^2}{b + dx^2}\right) \tag{11}$$

over an interval $x_\ell^* \le x \le x_u^*$ and the corresponding singular control is given in feedback form as

$$u_{\sin}(x) = \psi(x) = \frac{1}{G}\left(\frac{b - dx^2}{x} + 3\xi\frac{b + dx^2}{b - dx^2}\right). \tag{12}$$

The values x_ℓ^* and x_u^* are the unique solutions to the equation $\psi(x) = a$ in $(0, \sqrt{\frac{b}{d}})$. ■

This structure is robust and does not depend on the parameter values chosen. (For the underlying problem, the coefficient b is larger then d by orders of magnitude, $b > d$.) Optimal controls then need to be synthesized from singular and bang controls through an analysis of the switching function. In the papers [17], [19] we carried out this analysis and, excluding certain degenerate initial conditions (p_0, q_0), $q_0 = x_0^3$, we proved the following result:

Theorem 2.1: Optimal controls are at most concatenations of the form $\mathbf{0asa0}$ where $\mathbf{0}$ denotes an interval along which the optimal control is given by the constant control $u = 0$, that is no inhibitors are given, $\mathbf{a}$ denotes an interval along which the optimal control is given by the constant control $u = a$ at full dose, and $\mathbf{s}$ denotes an interval along which the optimal control follows the time-varying singular feedback control (12). This control is only optimal while the system follows the optimal singular arc $\mathcal{S}$ defined by (11) in the (p, x)-space. ■

A synthesis then provides a full "road map" of how optimal protocols look like depending on the initial condition in the problem, both qualitatively and quantitatively. Once it is known that the maximally possible optimal concatenation sequence is of the form $\mathbf{0asa0}$, it is not difficult to compute the optimal control for a particular initial condition (p_0, q_0). Figure 1 gives a characteristic example of the optimal control (top) and its corresponding trajectory (bottom) for the initial conditions $p_0 = 12,000$ and $q_0 = 15,000$. For our numerical illustration we have used the following biologically validated data from [13] that are based on experiments with Lewis lung carcinoma implanted in white mice: $\xi = \frac{0.192}{\ln 10} = 0.084$ 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 for illustrative purposes we selected $a = 15$. The trajectory in Fig. 1 is plotted with p along the vertical axis and the original variable q along the horizontal axis. This choice of variables makes the visualization of tumor reduction easier and allows for an easier interpretation. For these initial conditions the optimal control starts as full dose $u = a$ and there is no initial segment with $u = 0$. Once the trajectory corresponding to $u = a$ hits the singular arc, it is no longer optimal to give a full dose. At this time the optimal control becomes singular following the singular arc until all inhibitors become exhausted at some time τ. Contrary to the initial full dose segment, there now is a significant shrinkage of the tumor volume along the singular arc. Since $p(\tau) > q(\tau)$, it follows that the tumor volume will still be shrinking for times $t > \tau$ until the diagonal is reached at time T, $p(T) = q(T)$. The minimum tumor volume is thus realized at this time T along a trajectory for $u = 0$. This structure is the most typical synthesis of the type $\mathbf{as0}$, but other concatenation sequences are also possible.

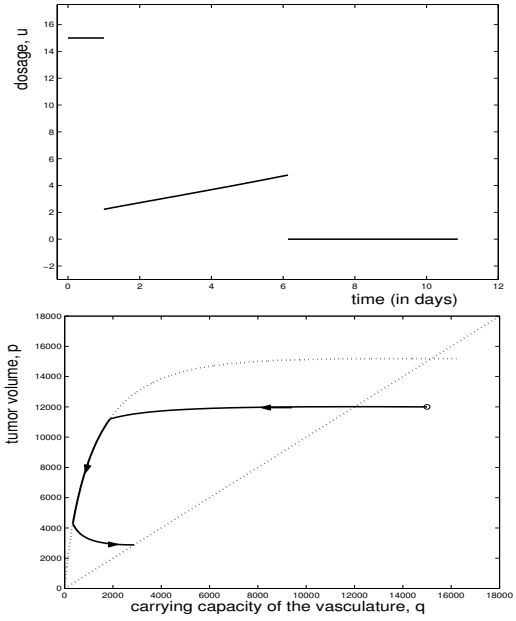

Fig. 1. Optimal control (top) and corresponding trajectory (bottom) for initial conditions $p_0 = 12,000$ and $q_0 = 15,000$

III. Concatenations with Singular Controls of Orders 1 and 2

The model considered above is a single-input control-affine system of the form

$$\dot{z} = f(z) + ug(z) \tag{13}$$

with $z = (p, x, y)^T$ and the switching function Φ can succinctly be expressed as the inner product

$$\Phi(t) = \langle \lambda(t), g(z(t)) \rangle . \tag{14}$$

Along a singular control all derivatives of the switching function must vanish and these conditions often allow the computation of singular controls and the analysis of their optimality status. Given any function

$$\Psi(t) = \langle \lambda(t), h(z(t)) \rangle , \tag{15}$$

where h is a continuously differentiable vector field, a direct calculation verifies that its derivative along a solution to the

system equation (13) for control u and a solution λ to the corresponding adjoint equations is given by

$$\dot{\Psi}(t) = \langle \lambda(t), [f + ug, h](z(t)) \rangle \tag{16}$$

where $[f, h]$ is the Lie bracket of the vector fields f and h given by $[f, h](z) = Dh(z)f(z) - Df(z)h(z)$ with Df and Dg denoting the matrices of the partial derivatives of the vector fields, all evaluated along $z(t)$. We also use the notation $ad_f(g) = [f, g]$, especially when higher order brackets will be involved.

Thus the first two derivatives of the switching function are given by

$$\dot{\Phi}(t) = \langle \lambda(t), [f, g](z(t)) \rangle \tag{17}$$

$$\ddot{\Phi}(t) = \langle \lambda(t), [f + ug, [f, g]](z(t)) \rangle . \tag{18}$$

For problem (OC) the strengthened Legendre-Clebsch condition [3] is satisfied, that is

$$\langle \lambda(t), [g, [f, g]](z(t)) \rangle < 0 \tag{19}$$

and thus the singular control can be expressed as

$$u_{\sin}(t) = -\frac{\langle \lambda(t), [f, [f, g]](z(t)) \rangle}{\langle \lambda(t), [g, [f, g]](z(t)) \rangle}. \tag{20}$$

Singular controls of this type are said to be of *order* 1 [5]. An important implication of the strengthened Legendre-Clebsch condition is that *order* 1 *singular controls that take values in the interior of the control set can be concatenated with the bang controls* $u = a$ *and* $u = 0$ *at any point along the singular arc*. For example, if the control is $u = 0$, then, since $\ddot{\Phi}(t) = 0$ along the singular control, the strengthened Legendre-Clebsch condition implies that $\ddot{\Phi}(\tau_{\pm}) > 0$ consistent with the minimum condition of the maximum principle, both for entry and exit from the singular arc.

If, however, the Lie bracket $[g, [f, g]]$ vanishes identically, then we have instead

$$\dddot{\Phi}(t) = \langle \lambda(t), [f, [f, g]](z(t)) \rangle \equiv 0, \tag{21}$$

$$\ddddot{\Phi}(t) = \left\langle \lambda(t), ad_f^3(g)(z(t)) \right\rangle \equiv 0, \tag{22}$$

and now the control u only appears for the first time in the fourth derivative of Φ,

$$\begin{aligned} \Phi^{(4)}(t) = &\left\langle \lambda(t), ad_f^4(g)(z(t)) \right\rangle \\ &+ u(t) \left\langle \lambda(t), [g, ad_f^3(g)](z(t)) \right\rangle . \end{aligned} \tag{23}$$

It now is a necessary condition for optimality that

$$\left\langle \lambda(t), [g, ad_f^3(g)](z(t)) \right\rangle \geq 0 \tag{24}$$

and if this quantity is positive, the singular control is said to be of *order 2*. However, in this case the signs of the derivative of the switching function violate the maximum principle if the singular control would be concatenated with the bang controls. For example, suppose for some $\varepsilon > 0$ the control is singular over the interval $(\tau - \varepsilon, \tau)$ and is given by $u = 0$ over the interval $(\tau, \tau + \varepsilon)$. Because of the change of sign we now have that

$$\Phi^{(4)}(\tau+) = \left\langle \lambda(\tau), ad_f^4(g)(z(t)) \right\rangle < 0 \tag{25}$$

and thus the switching function has a local maximum for $t = \tau$, i.e., is negative over the interval $(\tau, \tau + \varepsilon)$. But then the minimization property of the Hamiltonian implies that the control must be $u = a$. The analogous contradiction arises for other types of concatenations. Thus *an optimal singular control of order* 2 *that takes values in the interior of the control set cannot be concatenated with a bang control*. In fact, an optimal control needs to switch infinitely often between the controls $u = 0$ and $u = a$ on any interval $(\tau, \tau + \varepsilon)$ if a singular junction occurs at time τ. Corresponding trajectories are called *chattering arcs*.

IV. The Extended Model with PK

In many biomedical models it is assumed as a first approximation, as it was done here, that the concentration c of the drug is equal to its dosage u and effects e are instantaneous. Clearly, this is not the case and bringing PK and PD into the model will more realistically represent the dynamics of the treatment. We thus now consider an extended version of problem (OC) where a linear model for pharmacokinetics has been added; that is, the dosage u and concentration c of the inhibitors are no longer identified, but are linked by a first order linear ODE with constant coefficients,

$$\dot{c} = -kc + hu, \qquad c(0) = 0. \tag{26}$$

The model itself thus is one of exponential growth/decay and is commonly used as model for PK. The maximum concentration is given by $c_{\max} = \frac{ha}{k}$ and the clearance rate k is related to the half-life of the inhibitor as $\frac{\ln 2}{k}$. We also add a simple model for PD assuming the effect is proportional to the concentration of the inhibitors, $e = sc$ with $0 < s \leq 1$. Thus overall the model now becomes

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

$$\dot{p} = -\xi p \ln\left(\frac{p}{x^3}\right), \qquad p(0) = p_0 \tag{27}$$

$$\dot{x} = \frac{1}{3}(b - dx^2 - Gscx), \qquad x(0) = x_0 \tag{28}$$

$$\dot{c} = -kc + hu, \qquad c(0) = 0 \tag{29}$$

$$\dot{y} = u, \qquad y(0) = 0 \tag{30}$$

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

The system still is single input and control-affine of the form (13), but with 4-dimensional vector $z = (p, x, c, y)^T$ and adjusted drift and control vector fields f and g. The Hamiltonian now takes the form

$$\begin{aligned} H = &-\lambda_1 \xi p \ln\left(\frac{p}{x^3}\right) + \frac{1}{3}\lambda_2(b - dx^2 - Gscx) \\ &+ \lambda_3(-kc + hu) + \lambda_4 u \end{aligned} \tag{31}$$

and the switching function $\Phi(t)$ is given by

$$\Phi(t) = \lambda_3(t)h + \lambda_4. \tag{32}$$

As before, the maximum principle identifies bang and singular controls as canonical candidates for optimality, but now we have $[g, [f, g]] = 0$. Explicit computations verify that

the singular control is of order 2 and that the strengthened Legendre-Clebsch condition for minimality is satisfied,

$$\frac{\partial}{\partial u}\left(\frac{d^4}{dt^4}\Phi(t)\right) = \frac{1}{27}G^2s^2h^2\lambda_2(t)(b-dx(t)^2) > 0. \quad (33)$$

This result relies on the fact that $\lambda_2(t) > 0$ on the interval $[0, T)$.

In fact, the singular curve from problem (OC) is preserved: along a singular arc the multiplier λ vanishes against the vector fields f, g, $[f, g]$ and $[f, [f, g]]$. Since λ is nonzero, these four vector must be linearly dependent. (Although not obvious, it follows from general calculations that the vector field $ad_f^3(g)$ also lies in the span of these brackets [24].) But g is independent of the other vectors and thus

$$0 = \begin{vmatrix} -\xi p \ln\left(\frac{p}{x^3}\right) & 0 & -\xi pGsh \\ \frac{1}{3}(b-dx^2-Gscx) & \frac{1}{3}Gsxh & \frac{1}{9}Gsh(b+dx^2+3xk) \\ -kc & kh & k^2h \end{vmatrix}$$
$$= \frac{1}{9}\xi pkGsh^2\left\{(b+dx^2)\ln\left(\frac{p}{x^3}\right) - 3(b-dx^2)\right\}$$

which implies

$$\ln\left(\frac{p}{x^3}\right) = 3\frac{b-dx^2}{b+dx^2}. \quad (34)$$

Hence relation (11) for the singular arc is still valid for the model with PK.

The optimal singular concentration $c^*_{\sin}(t)$ can then be calculated by taking the derivative of (34) along the trajectory and substituting $\dot{p}$ and $\dot{x}$ from the state equations. Using the identity (34), after a somewhat lengthy calculation we obtain the *optimal singular concentration/effect* as

$$e^*_{\sin} = sc^*_{\sin} = \frac{1}{G}\left(\frac{b-dx^2}{x} + 3\xi\frac{b+dx^2}{b-dx^2}\right), \quad (35)$$

identical with (12) for the singular arc of problem (OC). But now this equation is for the effect/concentration, not for the optimal singular dosage. Differentiating one more time, an explicit, albeit lengthy formula for the singular control can be derived to obtain the following result:

Proposition 4.1: There exists a locally minimizing singular arc $\mathcal{S}$ defined in (p, x)-space by

$$p = p(x) = x^3\exp\left(3\frac{b-dx^2}{b+dx^2}\right) \quad (36)$$

which is admissible over an interval $x \in [x^*_l, x^*_u]$. The corresponding singular effect and concentration are given as a function of x by

$$e^*_{\sin}(x) = sc^*_{\sin}(x) = \frac{1}{G}\left(\frac{b-dx^2}{x} + 3\xi\frac{b+dx^2}{b-dx^2}\right), \quad (37)$$

and writing $\theta(x) = \frac{b+dx^2}{b-dx^2}$, the singular control can be expressed in feedback form as

$$u^*_{\sin}(x) = u^*_{\sin}(\theta(x), c^*_{\sin}(x))$$
$$= \frac{1}{h}\left[\frac{3\xi^2\theta}{Gs}(1-2\theta^2) + c^*_{\sin}(\xi\theta^2+k)\right]. \quad (38)$$

□

The singular arc $\mathcal{S}$ is the same as in the model without PK and what was the formula for the singular control when dosage, concentration and effect were identified, now becomes the optimal singular effect/concentration. *This clearly shows the usefulness of the simplified model as a first approximation.* However, since singular controls now are of order 2, no concatenations with bang controls are optimal and these connections are made through chattering arcs. Clearly such a control scheme is not realistic and it makes sense to consider sub-optimal, but simple and realizable protocols.

If we consider the serially connected system represented by Fig. 2 and take $e = sc$ as the input to the subsystem II, it follows from the above analysis that, ideally, the optimal drug effect e^* should have the same structure and expression as the optimal control does for the system without PK and PD, mostly in the form of "**as0**" as in the example given above.

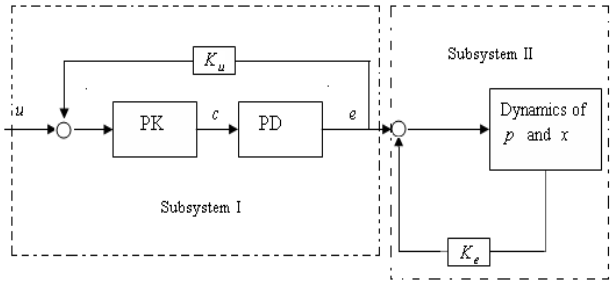

Fig. 2. Serially connected system with PK/PD

Given the knowledge of the optimal synthesis of the singular drug effect from the model without PK, it appears reasonable to conclude that the new optimal control $u^*(t)$ is one that produces as concentration the optimal $e^*(t)$ for the model without PK. But because of the inertia of the PK dynamics and the constraints on u, the real output $e(t)$ cannot follow the discontinuous $e^*(t)$ as represented in Fig. 3. This leads us to consider suboptimal controls u_{sub} under the PK and PD dynamics that actuate $e(t)$ to track $e^*(t)$ "closely". Clearly, these controls need to start with a full dose segment where $u^*(t) = 15$ along some interval $[0, t'_a)$ and the treatment ends with $u^*(t) = 0$ on a final interval $[t'_s, T]$. In between we track the originally optimal singular control, now the singular concentration/effect. As we have seen, complexities occur in the optimal transition (or concatenation) from the bang control to the singular control since the second order optimal singular control $u^*_{\sin}$ cannot be concatenated with either $u = 0$ or $u = a$, but chatters. Thus here we consider some direct suboptimal approximations. For example, we insert an additional segment for $u = 0$ in order to speed up the transition to the singular arc. The graphs of this control u^*_{sub} and its corresponding effect e^*_{sub} in time are shown in Fig. 4 and Fig. 5 represents an example of such a trajectory corresponding to an "**a0s0**"-structured suboptimal control.

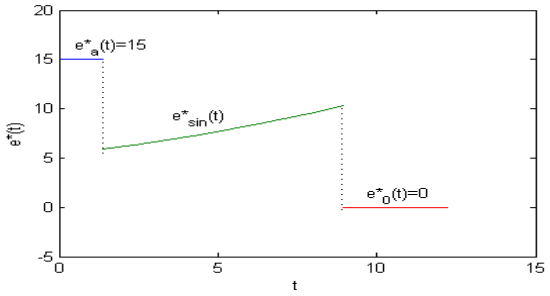

Fig. 3. Optimal control (dosage/concentration/effect) for the model without PK/PD

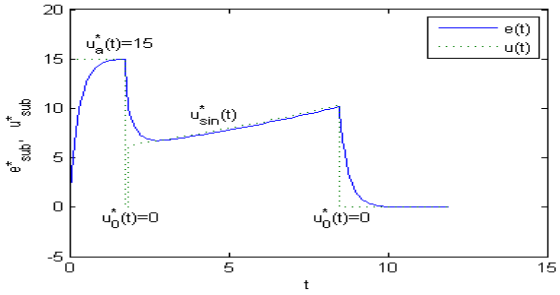

Fig. 4. Suboptimal approximation of the concentration/effect for the model with PK

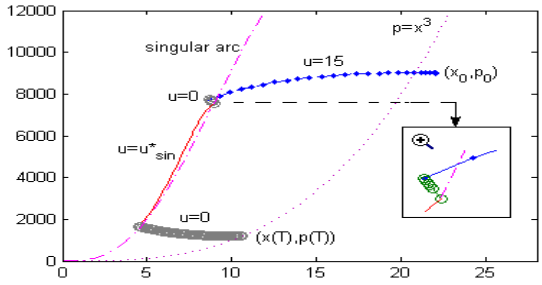

Fig. 5. Suboptimal (p, x)-trajectory for the model with PK

V. Conclusion

In this paper we have analyzed a mathematical model for tumor anti-angiogenesis as an optimal control problem. We have shown that while the addition of a pharmacokinetic model for the concentration of the inhibitors does change the structure of optimal solutions, nevertheless the most important features including an optimal singular arc are preserved. Thus in this case the simplified model does retain significant information about the solutions of the more realistic model.

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