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CONTROL PROBLEMS IN ANTIANGIOGENIC THERAPY – COMPARISON OF SIX MODELS

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Abstract: Six models of antiangiogenic therapy are compared and analyzed from control theoretic point of view. All of them consist of a model of tumor growth bounded by the capacity of a vascular network developed by the tumor in the process of angiogenesis and different model of dynamics of this network and they are based on the idea proposed by Hahnfeldt et al. Moreover we analyse optimal control problems resulted from their use to treatment protocols design.. *Copyright © 2002 IFAC*

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1. INTRODUCTION

Angiogenesis is a complex process which leads to the formation of new vessels and it is stimulated and controlled by molecular factors called activators (stimulators) and inhibitors (blockers) of angiogenesis. During progression of tumor these factors are released by tumor itself to develop its own vascular network which enables its growth and in the next stage determines possibility of cancer metastasis. Since this network is necessary for tumor development in late sixties of the last century a new anticancer therapy was proposed target of which was not directly the cancer cells but the new born vasculature. This therapy is known as antiangiogenic therapy and the idea is to reduce the tumor volume reducing its vasculature. It has been first time hypothesized by Folkman (1971, 1972) more than thirty years ago. The main Folkman's suggestions are as follows:

a) primary solid tumors go through a prolonged state of avascular growth (almost quiescent) in which maximum attainable size is 1-2 mm in diameter, and the necessary oxygen and nutrients are supplied by passive diffusion,

b) these microscopic tumors can switch on angiogenesis by recruiting surrounding mature host blood vessels to start sprouting new blood vessel capillaries which grow and infiltrate the tumor mass thus setting the potential for metastatic spread,

c) the angiogenic switch is triggered by elaboration by tumor cells of a growth factor (*TAF*),

d) blocking tumor angiogenesis factor or simply destroying newly formed immature blood vessels may be used to affect tumor growth.

The most important obstacle against successful chemotherapy is drug resistance acquired by cancer cells while the normal tissues retain sensitivity to the drugs.

This negative feature of chemotherapy may be used as an advantage in the antiangiogenic therapy which is directed towards special part of normal tissues and only indirectly destroys tumor cells and it is why it has been called by Kerbel (1997) a therapy resistant to drug resistance. Therapy directed against tumor

vasculature does not exploit tumor cell sensitivity, relying instead on tumor suppression consequent to inhibition of associated vasculature. For more than ten years Folkman's ideas were not followed by experimental or clinical investigations but now tumor angiogenesis belongs to the most inspiring areas of cancer research in oncology. Kerbel (2000) presents 10 significant reasons for the explosive growth in tumor angiogenesis research and development of antiangiogenic drugs:

1) The discovery of basic fibroblast growth factor as the first pro-angiogenic molecule(Folkman and Klagsburn, 1987).
2) The discovery of vascular endothelial growth factor and its receptor tyrosine kinases on activated endothelial cells (Klagsburn and Soker, 1993).
3) The discovery of angiopoietins and their tyrosine kinase receptors (Davis and Yancopoulos, 1999).
4) The discovery of endogenous inhibitors of angiogenesis (Folkman, 1995).
5) The discovery of additional molecular markers in newly formed blood vessels (Bischoff, 1995).
6) The development of quantitative assays for angiogenesis (Folkman and Haudebschild, 1980).
7) Recognition of the prognostic significance of tumor angiogenesis(Weidner, 1995).
8) Lack of acquired resistance to direct acting antiangiogenic drugs (Kerbel, 2000).
9) The discovery of the impact of angiogenesis on liquid hematologic malignancies(D'Amato, *et al*, 1994).
10) The discovery of the accidental antiangiogenic effects of various conventional or new anticancer drugs (Denekamp, 1993).

The complexity of the process of vascularization as well as the way in which inhibitors, stimulators and antiangiogenic drugs act results in the complex models (see e.g.Mantzaris and Webb, 2004)) applicable for simulation of the process but less useful in synthesis or even analysis of therapy protocols. The exception is a class of models proposed by Hahnfeldt *et al* (1999) who suggested that the tumor growth with incorporated vascularization mechanism can be described by Gompertz type or logistic type equation with variable carrying capacity which defines the dynamics of the vascular network.. Roughly speaking the main idea of this class of models is to incorporate the spatial aspects of the diffusion of factors that stimulate and inhibit angiogenesis into a non-spatial two-compartmental model for cancer cells and vascular endothelial cells. The models considered here belong to this class.

2. MODELS OF CANCER GROWTH INCLUDING VASCULARIZATION AND ANTIANGIOGENIC THERAPY

The simplest model of population kinetics for cancer tissues is given by Malthusian growth which assumes exponential relationship between a size of the population and time. The dynamics is described by the equation:

$$\dot{N} = aN, N(0) = N_0 \tag{1}$$

resulting in the following form of the solution:

$$N = N_0 e^{at}, a = \ln 2 / PDT \tag{2}$$

with N denoting the size of the population and a Malthusian parameter defined by the inverse of the potential doubling time (*PDT*). The unlimited growth in this model can be avoided if we introduce a varying coefficient $a(t)$ as in the Gompertz model:

$$\begin{aligned} &\dot{N} = a(t)N, N(0) = N_0, \\ &\dot{a} = -\beta a, a(0) = \alpha \Rightarrow \end{aligned} \tag{3}$$

$$N = N_0 e^{\alpha/\beta(1-e^{-\beta t})} \tag{4}$$

The growth is bounded by:

$$N_\infty = N_0 e^{\alpha/\beta} \tag{5}$$

Which is called the carrying capacity in population dynamics. The same solution is obtained when we use the non-linear Gompertz equation in the form:

$$\dot{N} / N = -\beta \ln N / N_\infty \approx 1 / PDT \tag{6}$$

Hahnfeldt *et al* (1999) proposed to treat the carrying capacity which constraints the tumor growth as a varying tumor volume sustainable by the vessels and roughly proportional to the vessel volume:

$$N_\infty = K, \ \dot{N} / N = -\beta \ln N / K \tag{7}$$

Although the equations (6) and (7) appear similar, the carrying capacity is not constant in (7) but varies with changes of the volume of the vessels.

Similar behavior may be obtained if the Gompertz type growth is substituted by a logistic one (called also Pearl-Verhulst growth). Then we have:

$$\dot{N} / N = \beta(1 - N / K) \tag{8}$$

The dynamics of the growth of the volume K represented by its *PDT* depends on the stimulators of angiogenesis (*SF*), inhibitory factors secreted by tumor cells (*IF*) and natural mortality of the endothelial cells (*MF*):

$$PDT_k = f(MF, SF, IF) \tag{9}$$

In (Hahnfeldt, *et al,* 1999) it has been assumed that the inverse of PDT is the sum of these three factors i.e.

$$1/PDT_k = MF + SF + IF \qquad (10)$$

The spontaneous loss of functional vasculature represented by *MF* (*e.g.* through natural mortality of the endothelial cells) is supposed to be negative constant, the stimulatory capacity of the tumor upon inducible vasculature represented by *SF* (*e.g*. through angiogenic factors like vascular endothelial factor) is found to grow at rate K^bN^c slower than the endogenous inhibition of previously generated vasculature represented by *IF* (*e.g*. through endothelial cell death or disaggregation) where:

$$b + c \sim 2/3 \qquad (11)$$

It results from the assertion that tumor driven inhibitors from all sites act more systematically whereas tumor-derived stimulators act more locally to the individual secreting tumor site. On the other hand analyzing a diffusion-consumption equation for the concentration of stimulator or inhibitor inside and outside the tumor, Hahnfeld *et al* concluded that the inhibitor will influence target endothelial cells in the tumor in a way that grows ultimately as the area of the active surface between the tumor and the vascular network which in turn is propotional to the square of the tumor diameter. It leads to the conclusion that *IF* is proportional to the tumor volume in power 2/3 since volume is proportional to the cube of the diameter. The expression for *K* suggested in (Hahnfeldt, *et al,* 1999) has therefore the following form:

$$\dot{K}/K = \gamma N/K - (\lambda N^{2/3} + \mu) \qquad (12)$$

γ, λ, μ being constant parameters representing the effect of stimulation, inhibition and natural mortality, respectively. The modification of this model proposed in (D'Onofrio and Gandolfi, 1999) which also satisfies Hahnfeldt's suggestions given by (11) assumes that the effect of *SF* and *MF* on the inverse of PDT_K is constant while the *IF* is proportional to the active surface of the area of tumor being in contact with the vascular network and the same to the square of the tumor radius:

$$\dot{K}/K = \gamma - (\lambda N^{2/3} + \mu) \qquad (13)$$

Combinations of tumor growth models (7), (8) with vascular network models (12), (13) result in four nonlinear models of tumor angiogenesis. The interesting finding is that all these systems have the same nontrivial equilibrium point (*N**,*K**):

$$\dot{N}/N = \dot{K}/K = 0 \Rightarrow N^* = K^* = ((\gamma - \mu)/\lambda)^{3/2} \qquad (14)$$

The model is strongly nonlinear but by logarithmic change of variable and some scaling transformation we are able to simplify them and find their asymptoptic properties using standard Lyapunov type analysis of stability (local and global) – see e.g. (D'Onofrio and Gandolfi, 1999, Swierniak, *et al,* 2006) for analysis of three of these models.
More precisely by transformation:

$$\begin{aligned} &x = \ln N/N^*, y = \ln K/K^* \\ &x^* = y^* = 0, \tau = \beta t \\ &\vartheta = (\gamma - \mu)/\beta \\ &x' = dx/d\tau, y' = dy/d\tau \end{aligned} \qquad (15)$$

we are led:

- for model (7), (13) to the following quasi-linear system:

$$\begin{aligned} x' &= y - x, \\ y' &= \vartheta(e^{2/3x} - 1) \end{aligned} \qquad (16)$$

or to:

$$\begin{aligned} z &= y - x, \\ x' &= z, \\ z' &= -z - \vartheta(e^{2/3x} - 1) \end{aligned} \qquad (17)$$

- and for model (8), (12) to the slightly more complicated system:

$$\begin{aligned} z &= 1 - e^{x-y}, \\ x' &= z, \\ z' &= (z-1)(z(1+\gamma/\beta) + \vartheta(e^{2/3x} - 1)) \end{aligned} \qquad (18)$$

For other combinations of tumor and vascular network growth equations the resulting transformed models have similar form.

Application of antiangiogenic therapy can be incorporated to the model by a factor increasing multiplicatively the mortal loss rate of the vessels. For example in the case of the model (13) it leads to the following equation:

$$\dot{K}/K = \gamma - (\lambda N^{2/3} + \mu + \eta u(t)), \qquad (19)$$

where $u(t)$ denotes the dose of the agent scaled to its effect on vascular network and η is a constant parameter. For the constant dose *U*, the equilibrium points take the form:

$$N^* = K^* = ((\gamma - \mu - \eta U)/\lambda)^{3/2} \qquad (20)$$

which according to the conditions of stability given in (D'Onofrio and Gandolfi, 1999) leads to the conclusion that for:

$$\eta U \approx \gamma - \mu \Rightarrow K^* \to 0 \qquad (21)$$

The form of condition (21) results from the suggestion that even if the dose is not exactly equal to the value found from the equilibrium condition the convergence to 0 takes place. In other words the vascular network and in turn the tumor can be eradicated. This conclusion is crucial for the philosophy of the entire analysis. It is enough to ensure that population of endothelial cells responsible for the angiogenesis behaves in the required way because the size of tumor population in some sense tracks the same transients. In (D'Onofrio and Gandolfi, 1999) it has been proved that the same effect might be reached for periodic therapy with mean value satisfying condition (21) or greater. Nevertheless this condition is only necessary and not sufficient since for model (8), (12) eradication of the tumor depends on the shape of pulses in the periodic protocol. For the other models this condition is both necessary and sufficient. Yet another simplified model was proposed by Ergun *et al* (2003). In this case the growth of the vascular network is independent on the tumor size.

$$\dot{K} / K = \gamma K^{-1/3} - \lambda K^{1/3} \tag{22}$$

Or in the case when therapy is included:

$$\dot{K} / K = \gamma K^{-1/3} - \eta u - \lambda K^{1/3} \tag{23}$$

Since this equation is independent of the model of tumor growth the stability analysis in this case is much simpler than before. Nevertheless to have a complete model of the tumor growth in the vascular stage we should add one of the two proposed previously models of growth (Gompertz or logistic type) and thus we are led to two additional models. Although during simulation all the models lead to the similar evolution if uncontrolled their behaviour in the presence of control modeling different therapeutic protocols may differ significantly. Moreover clinical interpretation of the modelling results is also sensitive to the choice of the model.

3.OPTIMIZATION OF THERAPY IN FINITE HORIZON

Constant or periodic therapies which ensure tumor eradication discussed previously have an important drawback. They should be applied for long therapy horizon. Shortage in the antiangiogenic drugs, their costs, and side effects cause that the parameters of treatment protocols and cumulated dose of the drugs should be bounded. The reasonable solution is to formulate optimal control problem for the system given by the proposed model and the control objective which adequately represents the primary goal of the therapy. In (Ergun, *et al,*2003) and (Ledzewicz and Schattler) the optimal control problem for the Ergun's model and a free terminal time is solved. The authors found that optimal strategy consists of bang-bang (i.e. with the control switching between maximal and minimal values) and singular intervals (with intermediate values of the control variable). In (Swierniak, *et al,* 2006) we have proposed, for model (8), (13), to optimize the protocol in the fixed finite time of therapy with the primary goal of finding the control that maximizes *TCP* (tumor cure probability). This approach leads to the following equivalent form of an optimal control problem:

$$\begin{aligned} &J = N(T_k), \\ &\int_0^{T_k} u(t)dt \le \Xi \\ &0 \le u(t) \le U_m \end{aligned} \tag{24}$$

with known constraining constant parameters: U_m, Ξ.

Due to isoperimetric form of the problem it could be transformed into the problem with the integral part of the performance index instead of the integral constrain on the control. Moreover we may use the transformed variables x and y (or x and z) to formulate the modified performance criterion in the form:

$$\begin{aligned} &I = gx(T_f) + hy(T_f) + r\int_0^{T_f} u(\tau)d\tau, \\ &0 \le u \le 1, \\ &T_f = T_k\beta \end{aligned} \tag{25}$$

where state variables are defined by the equations depending on the model which is chosen from the six models mentioned. For the d'Onofrio-Gandolfi model with Gompertz type model for the cancer growth we have:

$$\begin{aligned} &x' = y - x, \\ &y' = \vartheta(e^{2/3x} - 1) + \nu u \\ &\nu = -\eta / \beta \end{aligned} \tag{26}$$

The weight coefficients *h, g, r* may change in broad ranges depending on the type of therapy used and the strength of the integral constrain. The additional term related to the volume of vascular network may be regarded as yet another constrain imposed on the possible dynamics of the system. On the other hand by the choice of the weighting coefficients we obtain a new possibility of analysis of the mutual dependence between the tumor growth and the volume of the vascular network. Thus it is reasonable to provide an extensive analysis of their effect on the solution of the optimal control problem. Necessary conditions of optimality can be found using Pontryagin maximum principle (Pontryagin, *et al*, 1964) for Hamiltonian and adjoint variables *p, q* defined as

$$H = ru + \nu qu + p(y - x) + q\vartheta(1 - e^{2/3x}) \quad (27)$$

$$\begin{aligned} p' &= p + (2/3)q\vartheta e^{2/3x} & p(T_f) &= g, \\ q' &= -p & q(T_f) &= h \end{aligned} \quad (28)$$

It leads to the following switching function and bang-bang control law:

$$\begin{aligned} q &= -r/\nu > 0 \\ u &= \begin{cases} 1 \\ 0 \end{cases} \Leftarrow \min H \end{aligned} \quad (29)$$

In other words we should apply only maximal admissible dose of the drug or use no drug depending on the value of the co-state variable.
Rewriting the adjoint equation in the form of scalar second order ODE we have:

$$\begin{aligned} &q'' - q' + (2/3)q\vartheta e^{2/3x} = 0 \\ &q'(T_f) = -g \qquad\qquad q(T_f) = h \end{aligned} \quad (30)$$

The solution differs from those obtained in (Ergun, *et al,* 2003) and (Ledzewicz and Schattler, 2005). The important finding is that singular arcs (e.g. Krener, 1977) are not feasible since there are no finite intervals of constant solutions to the adjoint equation. This leads to the conclusion that intermediate doses of the drug are not optimal and that the optimal protocol contains only switches between maximal dose and no drug intervals. It allows to find recurrently the solution of the TPBVP composed of the state and co-state equations with bang-bang control found from the switching condition by using for example shooting algorithm. The same result is obtained by us in (Swierniak, *et al,* 2006) for combined radio- and antiangiogenic therapy. Ledzewicz and Schattler (2005) solved the optimal control problem for standard Hahnfeldt model in the similar way as for Ergun's model and once more suggested that in the optimal strategy some parts are singular.

We are able to prove that reasonable reformulation of optimization problem for five from the six models enables avoidance of singular arcs and leads to pure bang-bang solutions. The only exception is the Hahnfeldt original model with the Gompertz type growth of the tumor where optimal solution may contain a singular control as a middle part of the control strategy.

For example in the case of the Hahnfeldt model with logistic type growth of the tumor we may define:

$$\begin{aligned} z &= \ln KN^{\theta}, \\ \theta &= \gamma/\beta, \\ x &= \ln N, \\ \varepsilon &= \lambda/\beta \end{aligned} \quad (31)$$

It leads to the following state equations:

$$\begin{aligned} x' &= 1 - e^{(\theta+1)x - z} \\ z' &= \vartheta - \varepsilon e^{2/3x} + \nu u \end{aligned} \quad (32)$$

For simplicity we may assume $h = 0$ in the performance index. Thus the Hamiltonian has the following form:

$$H = ru + \nu qu + p(1 - e^{(\theta+1)x - z}) + q(\vartheta - \varepsilon e^{2/3x})$$

And co state variables are given by the following equations:

$$\begin{aligned} p' &= p(\theta+1)e^{(\theta+1)x - z} + (2/3)q\varepsilon e^{2/3x} \\ q' &= -pe^{(\theta+1)x - z} \\ p(T_f) &= g, \\ q(T_f) &= 0 \end{aligned} \quad (33)$$

Thus the necessary conditions of optimality have the form (formally identical to (29)):

$$\begin{aligned} q &= -r/\nu > 0 \\ u &= \begin{cases} 1 \\ 0 \end{cases} \Leftarrow \min H \end{aligned} \quad (34)$$

Once more the singular arcs are not feasible since there are no finite intervals of constant solutions to the adjoint equation. For the d'Onofrio-Gandolfi model with the logistic type tumor growth the analysis is similar.

For the Ergun model the problem is even simpler. If we choose $g = 0$ then since the equation defining y is independent of x we are led to the first order optimization problem which has no singular solutions.

The problem is defined by the state equation:

$$\dot{y} = \gamma e^{-1/3y} - \lambda e^{1/3y} - \eta u \quad (35)$$

And the Hamiltonian and the adjoint variable is given by:

$$\begin{aligned} H &= p(\gamma e^{-1/3y} - \lambda e^{1/3y}) + (r - \eta p)u \\ \dot{p} &= \frac{1}{3} p(\gamma e^{-1/3y} + \lambda e^{1/3y}), p(T_k) = h \end{aligned} \quad (36)$$

It leads to the following form of the bang –bang candidate for optimality:

$$p = r/\eta > 0$$
$$u = \begin{cases} 1 \\ 0 \end{cases} \Leftarrow \min H \qquad (37)$$

and singular controls cannot be optimal for the same reasons as in the two previously analyzed problems.

4.CONCLUSION

In this study we have compared different modifications of Hahnfeldt model of vascular tumor growth and their application to rationales of antiangiogenic therapy. We consider advantages and drawbacks of six such models in context of their possible application and difficulties of mathematical analysis. We also discuss results of some other authors and discuss possible approaches to optimization problems arising from therapy protocols design. All considerations are however based on the assumption that the complex phenomena leading to vessel collapse and regression could be described by such simplified models. It should be interesting to check how robust are they by testing them on the much more complex models recently published (e.g. Bartha and Rieger, 2006).

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