

# Direct and indirect control of cancer populations

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**Abstract.** This paper presents a brief survey of our research in which we have used control theoretic methods in modelling and control of cancer populations. We focus our attention on two classes of problems: optimization of anticancer chemotherapy taking into account both phase specificity and drug resistance, and modelling, and optimization of antiangiogenic therapy. In the case of chemotherapy the control action is directly aimed against the cancer cells while in the case of antiangiogenic therapy it is directed against normal cells building blood vessels and only indirectly it controls cancer growth. We discuss models (both finite and infinite dimensional) which are used to find conditions for tumour eradication and to optimize chemotherapy protocols treating cell cycle as an object of control. In the case of antiangiogenic therapy we follow the line of reasoning presented by Hahnfeldt et al. who proposed to use classical models of self-limiting tumour growth with variable carrying capacity defined by the dynamics of the vascular network induced by the tumour in the process of angiogenesis. In this case antiangiogenic protocols are understood as control strategies and their optimization leads to new recommendations for anticancer therapy.

**Key words:** biomedical models, optimal control, nonlinear control systems, anticancer therapy.

## 1. Introduction

Two major obstacles in successful chemotherapy are phase dependence of cytotoxic drugs and drug resistance. Cell-cycle-phase specificity is important since it makes sense to apply anticancer drugs when cells gather in sensitive phases of the cell cycle. It can be approached by considering dissection of the cell cycle into an increasing number of disjoint compartments, with drug action limited to only some of them. In many papers we have provided a classification of several models of this kind and analyzed a problem of protocol optimization basing on them. Mathematical problems encountered include singularity and non-uniqueness of solutions and give rationale for periodic protocols (e.g. [1–4]). The emergence of resistance to chemotherapy has been first considered in a point mutation model of Coldman and Goldie (e.g. [5]) and then in the framework of gene amplification by Agur and Harnevo (e.g. [6]). The main idea is that there exist spontaneous or induced mutations of cancer cells towards drug resistance and the scheduling of treatment should anticipate them. The point mutation model can be translated into simple recommendations which have been even tested in clinical trials. The gene amplification model was extensively simulated and also resulted in recommendations for optimized therapy.

Although mathematical modelling of cancer dynamics and anticancer therapy has had more than four decades of history, regarding practical results it has been, with minor exceptions, a failure. The reasons for that failure are not always clearly perceived. They stem from the direction of both biomedicine and mathematics: important biological processes are ignored and crucial parameters are not known, but also the mathematical intricacy of the models is not appreciated. Because of recent progress in methods of monitoring cancer cell

populations, new insights and more precise measurements became possible. This, together with a progress in mathematical tools has renewed hopes for improving chemotherapy protocols. Moreover a new philosophy in molecular biology and biotechnology called system biology builds a bridge between many biologists and even clinicians from one side and mathematicians and engineers from the other.

In our research we have developed a model of chemotherapy based on a stochastic approach to evolution of cancer cells (e.g. [7–9]). Our works dealt with models with tridiagonal system matrix. They led to development of a methodology for investigating such systems and formed a basis for further generalisation. More recently (e.g. [10–12]) the research has been pushed a step further, studying properties of a model, in which significantly less simplification has been made and less additional assumptions are required. Moreover, it has combined models that so far have been studied separately, taking into account both the phenomenon of gene amplification and multidrug chemotherapy, in their different aspects.

As far as phase-specificity of chemotherapy is concerned it was usually considered without any regard to problems stemming from increasing drug resistance. Combining infinite dimensional model of drug resistance with the phase-specific model of chemotherapy should move mathematical modelling much closer to its clinical application. Despite long history of research and rich literature devoted to problems of modelling and control of infinite dimensional systems, almost all efficient methods developed to deal with them present approaches suitable for PDE models and optimisation solutions are often limited to LQ problems (see e.g. [13]). As shown in our papers, studies of infinite dimensional models may lead to compact results, convenient in further analysis, which would be impossible or very difficult to obtain in finite dimensional

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approximation. On the other hand the optimality conditions for such systems are usually much weaker than those for finite dimensional systems and their mathematical analysis is far from being rigorous. Thus we decided to compare the results for such systems with the ones for finite dimensional models which have been preliminary studied by us and our co-workers (e.g. [14]). Optimization of the chemotherapy in the presence of evolving drug resistance may be viewed as the progress in overcoming this phenomenon.

The important factor which should be taken into account is that while drug resistance is acquired by cancer cells the normal tissues retain sensitive 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 [15] a therapy resistant to drug resistance. We use a class of models proposed by Hahnfeldt in [16] to find conditions for tumour eradication in asymptotic sense and to optimize protocols of antiangiogenic therapy. In contrast to the control problems arising in phase-specific and drug resistant chemotherapy, modeling antiangiogenic therapy leads to indirect control problems in the sense that the control action is directed against normal tissues and only indirectly enables formation of dynamics of cancer populations.

## 2. Modeling drug resistance and phase-specificity

The model, based on results of [6, 17–18] is general enough to accommodate different interpretations (see e.g. [9]). The original model of drug resistance evolution and its properties were thoroughly discussed in e.g. [7, 8]. Briefly, we consider a population of neoplastic cells stratified into subpopulations of cells of different types, labelled by numbers  $i = 0, 1, 2, \dots$ . If the biological process considered is gene amplification, then cells of different types are identified with different numbers of copies of the drug resistance gene and differing levels of resistance. Cells of type 0, with no copies of the gene, are sensitive to the cytostatic agent. Due to the mutational event the sensitive cell of type 0 can acquire a copy of gene that makes it resistant to the agent. Likewise, the division of resistant cells can result in the change of the number of gene copies. The resistant subpopulation consists of cells of types  $i = 1, 2, \dots$ . The probability of mutational event in a sensitive cell is of several orders smaller than the probability of the change in number of gene copies in a resistant cell. Since we do not limit the number of gene copies per cell, the number of different cell types is denumerably infinite.

Cell division and the change of the number of gene copies are stochastic processes with the following hypotheses:

1. The lifespans of all cells are independent exponentially distributed random variables with means  $1/\lambda_i$  for cells of type  $i$ .
2. A cell of type  $i \geq 1$  may mutate in a short time interval  $(t, t + dt)$  into a type  $i + 1$  cell with probability  $b_i dt + o(dt)$  and into type  $i - 1$  cell with probability  $d_i dt + o(dt)$ . A cell

of type  $i = 0$  may mutate in a short time interval  $(t, t + dt)$  into a type 1 cell with probability  $\alpha dt + o(dt)$ , where  $\alpha$  is several orders of magnitude smaller than any of  $b_i$  and  $d_i$ .

3. The drug action results in fraction  $u_i$  of ineffective divisions in cells of type  $i$  (hence  $0 \leq u_i \leq 1$ ).
4. The process is initiated at time  $t = 0$  by a finite population of cells of different types.

If we denote  $N_i(t)$  the expected number of cells of type  $i$  at time  $t$ , the model is described by the following system of ODE's:

$$\left\{ \begin{array}{l} \dot{N}_0(t) = [1 - 2u_0(t)] \lambda_0 N_0(t) - \alpha N_0(t) + d_1 N_1(t) \\ \dot{N}_1(t) = [1 - 2u_1(t)] \lambda_1 N_1(t) - (b_1 + d_1) N_1(t) \\ \quad + d_2 N_2(t) + \alpha N_0(t) \\ \dots \\ \dot{N}_i(t) = [1 - 2u_i(t)] \lambda_i N_i(t) - (b_i + d_i) N_i(t) \\ \quad + d_{i+1} N_{i+1}(t) + b_{i-1} N_{i-1}(t), \\ \dots \end{array} \right. \quad (1)$$

Mainly the simplest case has been investigated, in which the resistant cells are completely insensitive to drug's action and there are no differences between parameters of cells of different type:

$$\left\{ \begin{array}{l} \dot{N}_0(t) = [1 - 2u(t)] \lambda N_0(t) - \alpha N_0(t) + d N_1(t) \\ \dot{N}_1(t) = \lambda N_1(t) - (b + d) N_1(t) + d N_2(t) + \alpha N_0(t) \\ \dots \\ \dot{N}_i(t) = \lambda N_i(t) - (b + d) N_i(t) + d N_{i+1}(t) + b N_{i-1}(t), \\ \quad i \geq 2 \\ \dots \end{array} \right. \quad (2)$$

However, using the same line of reasoning that has been applied to that case, it is also possible to analyse less simplified model [12]. If it is assumed that the parameters can vary for arbitrarily chosen finite number of cells and are the same only for the infinite dimensional tail of the system, the following model can be investigated:

$$\left\{ \begin{array}{l} \dot{N}_0(t) = [1 - 2u_0(t)] \lambda_0 N_0(t) - \alpha N_0(t) + d_1 N_1(t) \\ \dot{N}_1(t) = [1 - 2u_1(t)] \lambda_1 N_1(t) - (b_1 + d_1) N_1(t) \\ \quad + d_2 N_2(t) + \alpha N_0(t) \\ \dots \\ \dot{N}_{l-1}(t) = [1 - 2u_{l-1}(t)] \lambda_{l-1} N_{l-1}(t) \\ \quad - (b_{l-1} + d_{l-1}) N_{l-1}(t) + d_l N_l(t) + b_{l-2} N_{l-2}(t) \\ \dots \\ \dot{N}_i(t) = \lambda N_i(t) - (b + d) N_i(t) + d N_{i+1}(t) + b N_{i-1}(t), \\ \quad i \geq l \\ \dots \end{array} \right. \quad (3)$$

Moreover, multivariable control is allowed, meaning that either certain types of the resistant cells can be affected by chemotherapy in different way or the different drugs are being used.

Now we are prepared to include phase specificity of the drug in our model. The cell cycle is composed of a sequence of phases undergone by each cell from its birth to division. Actually, each drug affects cell being in particular phase and it makes sense to combine these drugs so that their cumulative effect on the cancer population would be the greatest. So far, phase-specific chemotherapy has been considered only in the finite-dimensional case, without any regard to problems stemming from increasing drug resistance [1–4, 19]. Combining infinite dimensional model of drug resistance with the phase-specific model of chemotherapy should move mathematical modelling much closer to its clinical application.

Once again, some modification of the assumptions underlying mathematical model presented at the beginning of this section should be introduced. The sensitive subpopulation consists of two types of cells: type  $i = 0$ , being in the phase  $G_1 + S$  and  $i = 1$ , being in the phase  $G_2M$ . The phase-specific drug affects only cells of type  $i = 1$ . Then the following set of equations can represent the system dynamics

$$\begin{cases} \dot{N}_0(t) = -\lambda_0 N_0(t) + [1 - u(t)](2\lambda_1 - \alpha)N_1(t) + dN_2(t) \\ \dot{N}_1(t) = -\lambda_1 N_1(t) + \lambda_0 N_0(t) \\ \dot{N}_2(t) = \lambda_2 N_2(t) - (b + d)N_2(t) + \alpha N_1(t) + bN_3(t) \\ \dots \\ \dot{N}_i(t) = \lambda N_i(t) - (b + d)N_i(t) + dN_{i+1}(t) + bN_{i-1}(t), \\ \dots \end{cases} \quad i \geq 3 \quad (4)$$

Similarly, multidrug therapy including blocking drugs [19, 20] (used to synchronise cancer cell cohorts) as well as the killing agent could be analysed in the same way, as presented in the subsequent sections.

### 3. Infinite dimensional bilinear models

All the models discussed above have the following state equation form:

$$\dot{N} = \left( \mathbf{A} + \sum_{i=0}^m u_i \tilde{\mathbf{B}}_i \right) N, \quad (5)$$

where  $N = [N_0 \ N_1 \ N_2 \ \dots \ N_i \ \dots]^T$  is an infinite dimensional state vector,  $\mathbf{A}$  – the system matrix of the following form:

$$\mathbf{A} = \begin{bmatrix} - & \tilde{\mathbf{A}}_1 & | & \mathbf{0}_1 & - \\ \mathbf{0}_2 & | & - & \tilde{\mathbf{A}}_2 & - \end{bmatrix}, \quad (6)$$

$$\tilde{\mathbf{A}}_1 = \begin{bmatrix} a_{00} & a_{01} & \dots & a_{0,l-1} & 0 \\ a_{10} & a_{11} & \dots & a_{1,l-1} & 0 \\ \vdots & \vdots & \dots & \vdots & 0 \\ a_{l-1,0} & a_{l-1,1} & \dots & a_{l-1,l-1} & a_{l-1,l} \end{bmatrix},$$

$$\tilde{\mathbf{A}}_2 = \begin{bmatrix} c_1 & a_2 & a_3 & 0 & 0 & \dots \\ 0 & a_1 & a_2 & a_3 & 0 & 0 & \dots \\ 0 & 0 & a_1 & a_2 & a_3 & 0 & \dots \\ \vdots & \vdots & \ddots & \ddots & \ddots & \ddots & \ddots \end{bmatrix},$$

$$\tilde{\mathbf{B}}_i = \begin{bmatrix} b_{0,0}^i & b_{0,1}^i & \dots & b_{0,l-1}^i \\ b_{1,0}^i & b_{1,1}^i & \dots & b_{1,l-1}^i \\ \vdots & \vdots & \dots & \vdots \\ b_{l-1,0}^i & b_{l-1,1}^i & \dots & b_{l-1,l-1}^i \end{bmatrix},$$

$u(t)$  –  $m + 1$ -dimensional control vector  $u = [u_0 \ u_1 \ u_2 \ \dots \ u_m]^T$ ,  $\mathbf{0}_1$ ,  $\mathbf{0}_2$ , – zero matrices of dimensions  $\infty \times l - 1$ ,  $l - 2 \times \infty$  respectively,  $l > m$ .

It is important to note that model parameters satisfy the following relations:  $a_3 > a_1 > 0$ , and  $a_2 < 0$ . However, complete problem analysis can be done in other possible cases (e.g. when no additional conditions are to be satisfied by parameters  $a_1$ ,  $a_3$ ), using exactly the same line of reasoning. The specific structure of system and control matrices may be used to decompose the system both for its analysis as well as optimal control synthesis. To make analysis of the model possible it is convenient to present it in the form of a block diagram shown in Fig.1, effectively decomposing the model into two parts. The first one, of finite dimension, does not require parameters to meet any particular assumptions. The second subsystem is infinite dimensional, with tridiagonal system matrix, and does not include terms containing control variables  $u_i(t)$ . It may be interpreted as decomposition of the cancer cells population into two compartments: the one, finite dimensional which contains cells completely or at least partially sensitive to the drug, and the second one, infinite dimensional which contains drug resistant cells which directly could not be controlled by variables representing the effect of the drug. The positive feedback in the scheme represents reversibility of gene amplification process that should be interpreted as possible two sided communication between both compartments. Since only stepwise mutation is assumed thus the  $(l-1)$ -th type of cells is the output of the first compartment and the  $l$ -th one is its input.

First, let us consider the infinite dimensional tail without the influx of cells  $N_{l-1}$ :

$$\begin{cases} \dot{N}_l(t) = a_2 N_l(t) + a_3 N_{l+1}(t) \\ \dot{N}_{l+1}(t) = a_1 N_l(t) + a_2 N_{l+1}(t) + a_3 N_{l+2}(t) \\ \dots \\ \dot{N}_i(t) = a_1 N_{i-1}(t) + a_2 N_i(t) + a_3 N_{i+1}(t), \\ \dots \end{cases} \quad i \geq l + 2 \quad (7)$$

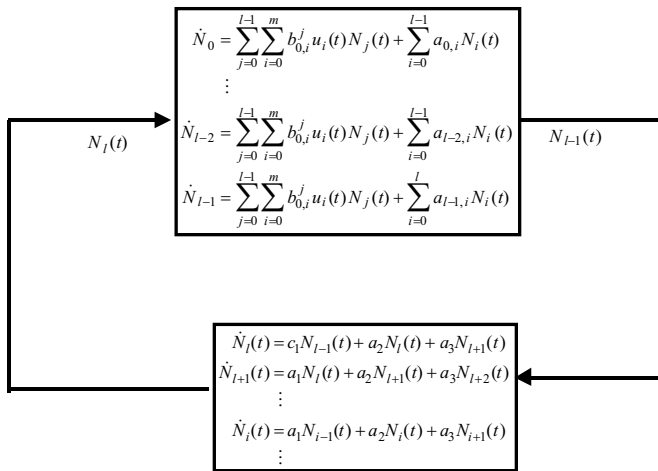


Fig. 1. The model as a system with positive feedback

Using methods similar to that shown in our previous works e.g. [4, 7–9], [21] it is possible to show that for initial condition  $N_i(0) = \delta_{ik}$  (Kronecker delta), i.e.  $N_k(0) = 1$ ,  $N_i(0) = 0$  for  $i \neq k$ , following relations hold true:

$$N_l^k(s) = \frac{1}{a_3} \left( \frac{s - a_2 - \sqrt{(s - a_2)^2 - 4a_1a_3}}{2a_1} \right)^{k-l+1}, \quad (8)$$

$$N_{\Sigma}^k(s) = \frac{1}{s - (a_1 + a_2 + a_3)} \left[ 1 - \left( \frac{s - a_2 - \sqrt{(s - a_2)^2 - 4a_1a_3}}{2a_1} \right)^{k-l+1} \right], \quad (9)$$

where  $N_l^k(s)$ ,  $N_{\Sigma}^k(s)$  – Laplace transforms of  $N_l^k(t)$  and  $\sum_{i \geq 1} N_i^k(t) = N_{\Sigma}^k(t)$ , respectively (superscript  $k$  is introduced to underscore the index of the state variable with non-zero initial condition). The interesting finding is that similar transfer functions could be found in some control systems with distributed delay [22–23]. Now, let us assume that  $k = l$ . Then, after calculating inverse Laplace transform the following formulae are obtained:

$$N_l^l(t) = \frac{1}{a_3} \left( \sqrt{\frac{a_3}{a_1}} \right) \frac{I_1(2\sqrt{a_1a_3}t)}{t} \exp(a_2t), \quad (10)$$

$$N_{\Sigma}^l(t) = \sum_{i \geq l} N_i(t) = \exp[(a_1 + a_2 + a_3)t] \left[ 1 - \left( \sqrt{\frac{a_3}{a_1}} \right) \int_0^t \frac{I_1(2\sqrt{a_1a_3}\tau)}{\tau} \exp[-(a_1 + a_3)\tau] d\tau \right], \quad (11)$$

where  $I_1(t)$  – modified Bessel function of the first order.

Using an asymptotic expansion of (11) it has been found [11] that, assuming  $a_3 \geq a_1$ , a stability condition for the autonomous system is given by

$$a_2 \leq -2\sqrt{a_1a_3}. \quad (12)$$

Relation (8) can be used to determine the following transfer function in the model

$$K_1(s) = \frac{N_l(s)}{N_{l-1}(s)} = \frac{c_1}{a_3} \frac{s - a_2 - \sqrt{(s - a_2)^2 - 4a_1a_3}}{2a_1}. \quad (13)$$

Moreover

$$\sum_{i \geq l} N_i(t) = N_{\Sigma}^l(t) + N^+(t), \quad (14)$$

where

$$N^+(t) = c_1 \int_0^t N_{\Sigma}^l(t - \tau) N_{l-1}(\tau) d\tau, \quad (15)$$

and  $N_{\Sigma}^l(t)$  is defined by (11).

Let us now introduce the following notation:

$$\hat{\mathbf{B}}_1 = \begin{bmatrix} 0 \\ \vdots \\ 0 \\ a_{l-1,l} \end{bmatrix}, \quad \mathbf{C} = [0, \dots, 0, 1] - l\text{-dimensional vector}. \quad (16)$$

Then, applying standard control theory techniques, the following relation holds true for  $u(t) = 0$

$$K_2(s) = \frac{N_{l-1}(s)}{N_l(s)} = \mathbf{C}(s\mathbf{I} - \tilde{\mathbf{A}}_1)^{-1} \hat{\mathbf{B}}_1, \quad (17)$$

where  $\mathbf{I}$  is a unit matrix. Taking into account linear form of such system, it is possible to present the model in the form of block diagram shown in Fig. 2. This makes it possible to analyse dynamical properties of the closed-loop system.

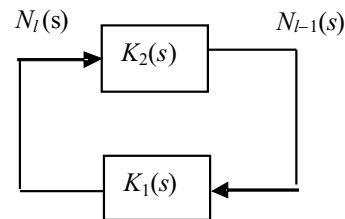


Fig. 2. Block diagram of the system without control

Let us now consider the problem of stabilisation of the system (5) by a constant control.

Then, the transfer function  $K_2(s)$  representing the finite dimensional subsystem in the Fig. 2 takes the following form:

$$K_2(s) = \frac{N_{l-1}(s)}{N_l(s)} = \mathbf{C} \left[ s\mathbf{I} - \left( \tilde{\mathbf{A}}_1 + \sum_{i=0}^m \tilde{\mathbf{B}}_i \right) \right]^{-1} \hat{\mathbf{B}}_1. \quad (18)$$

Again, standard control theory techniques, including the Nyquist criterion [23] can be applied to find stability conditions for such system.

Several control problems may be addressed basing on the model. One of them is establishing constant control  $u$  (in that case it leads to determination of feedback parameters) that stabilises the infinite dimensional system. In biological terms, it

refers to calculating constant dose of chemotherapeutic agent that suppresses growth of the resistant subpopulation. However, the constant treatment protocol, which guarantees decay of the cancer population after sufficiently long time, is not realistic. Most of all, it does not take into account the cumulated negative effect of the drug upon normal tissues. To make the solution more realistic, it is justifiable to find the optimal control, which minimises the performance index:

$$J = \sum_{i=0}^{l-1} N_i(T) + r_1 \sum_{i=l}^{\infty} N_i(T) + r \sum_{k=0}^m \int_0^T u_k(\tau) d\tau \quad (19)$$

where  $r_1, r \geq 0$  are weighing factors.

The idea on which such optimisation is based is to minimise the resistant cancer subpopulation at the end of therapy with simultaneous minimisation of negative cumulative effect of the drug represented by the integral component.

To formulate and solve control optimization problem related to anticancer therapy a model transformation of the infinite system of ODE's into integro-differential form is proposed.

Let us denote

$$\tilde{x} = \begin{bmatrix} N_0 \\ \vdots \\ N_{l-1} \end{bmatrix}. \quad (20)$$

Let us also assume the initial conditions  $N_i(0) = 0$  for  $i > l - 1$ . Then, the equation describing dynamics of the subpopulation of type  $l - 1$ , influenced directly by control, as presented on Fig. 2, can be transformed into an integro-differential form:

$$\begin{aligned} \dot{N}_{l-1}(t) = & \sum_{j=0}^{l-1} \sum_{i=0}^m b_{l-1,i}^j u_i(t) N_j(t) + \sum_{i=0}^{l-1} a_{l-1,i} N_i(t) \\ & + a_{l-1,l} \int_0^t k_1(t-\tau) N_{l-1}(\tau) d\tau, \end{aligned} \quad (21)$$

where  $k_1(t)$  is the inverse Laplace transform of  $K_1(s)$ , given by (13).

Similarly, other equations can also be rewritten in the same way leading to the transformation of the model (4) into the following form:

$$\begin{aligned} \dot{\tilde{x}} &= h(u, \tilde{x}) + \int_0^t \tilde{f}(\tilde{x}, t, \tau) d\tau, \\ \tilde{x}(0) &= \tilde{x}_0, \end{aligned} \quad (22)$$

where  $h(\dots), \tilde{f}(\dots)$  – respective  $l$ -dimensional vector functions

$$h_k(u, \tilde{x}) = \sum_{j=0}^{l-1} \sum_{i=0}^m b_{k,i}^j u_i(t) N_j(t) + \sum_{i=0}^{l-1} a_{k,i} N_i, \quad (23)$$

$$\tilde{f}_k(\tilde{x}, t, \tau) = \begin{cases} 0 & \text{for } k < l - 1 \\ a_{l-1,l} k_1(t-\tau) N_{l-1}(t) & \text{for } k = l - 1 \end{cases}. \quad (24)$$

After transformation of the system, it is possible to address effectively the arising optimal control problem.

Let the system be governed by the equation (4), which, afterwards, is transformed into the form (21). The control is bounded:

$$0 \leq u_k(t) \leq 1, \quad (25)$$

where  $u_k(t) = 1$  represents the maximum allowable dose of the drug  $k$  and  $u_k(t) = 0$  represents no application of the drug  $k$ .

The goal is to minimise the performance index given by (19).

Due to particular form of both performance index and the equation governing the model it is possible to find the solution to the problem, applying an appropriate version of Pontryagin maximum principle [24, 25].

It is important to notice that, although the performance index (19) seems to consist of two components - a sum and an integral, the sum actually involves another integral, which stems from (15)–(16). Therefore, it is convenient to rewrite it in the following form:

$$\begin{aligned} J = & \sum_{i=0}^{l-1} N_i(T) + r_1 N_{\Sigma}^l(T) \\ & + \int_0^T \left[ r_1 c_1 N_{\Sigma}^l(T-\tau) N_{l-1}(\tau) + r \sum_{k=0}^m u_k(\tau) \right] d\tau. \end{aligned} \quad (26)$$

A number of formulations of necessary conditions for the optimisation problem for dynamical systems governed by integro-differential equations can be found in literature, e.g. [13, 26, 27]. However, they usually either are too general to be efficiently applied in such particular problem or have too strong constraints for example smoothness of the control function. Nevertheless, following the line of reasoning presented by [26] it is possible to derive the necessary conditions for optimal control:

$$\begin{aligned} u^{opt}(t) = & \arg \min_u \left[ r \sum_{k=0}^m u_k(t) + p^T(t) h(u, \tilde{x}) \right. \\ & \left. + a_{l-1,l} \int_t^T p_{l-1}(\tau) k_1(t-\tau) N_{l-1}(\tau) d\tau \right], \end{aligned} \quad (27)$$

$$\dot{p}^T(t) = - \left[ q^T(t) + p^T(t) h_{\tilde{x}}(u, \tilde{x}) + \int_t^T p^T(\tau) \tilde{f}_{\tilde{x}}(t-\tau) d\tau \right], \quad (28)$$

$$\begin{aligned} q(t) &= \left[ 0 \quad \dots \quad 0 \quad r_1 c_1 N_{\Sigma}^l(T-t) \right]^T, \\ p_i(T) &= 1, \quad i = 0, 1, \dots, l-1, \end{aligned} \quad (29)$$

$p(t)$  – adjoint vector.

Taking into account constraint (25) and bilinear form of (26), it can be proved that, in order to satisfy (27), the optimal control must be of bang-bang type. Then, to find optimal number of switches and switching times, a gradient method can be developed, similarly as presented in [21]. The possibility of singular arcs could not be excluded.



#### 4. Finite dimensional models

For comparison with finite dimensional problems let consider the simple case [14] when only two levels of drug resistance are distinguished, i.e. overall the model has three compartments consisting of drug sensitive, partially resistant and resistant cells. We denote the average numbers of cells in these compartments by  $S, P$  and  $R$ , respectively, and denote the inverse of the average transit times through these compartments by  $a, b$  and  $c$ . In the model only transitions between sensitive and partially resistant cells and between partially resistant and fully resistant cells are allowed. If a sensitive cell undergoes cell division, the mother cell dies and one of the daughters will remain sensitive. The other daughter with probability  $q$ ,  $0 < q < 1$ , changes into a partially resistant cell. However, for cancer cells it is possible that a resistant cell may mutate back into a sensitive cell by loosing extra gene copies. Therefore, if a partially resistant cell divides, again the mother dies and one of the daughters remains partially resistant, but the second daughter with probability  $s$ ,  $0 < s < 1$ , undergoes gene amplification and becomes resistant or with probability  $r$ ,  $0 \leq r < 1 - s$ , undergoes gene deamplification and becomes sensitive. The case  $r = 0$  when this is excluded is called stable gene amplification while unstable gene amplification refers to the phenomenon  $r > 0$ . Finally, when a resistant cell undergoes cell division, one of the daughters may change back to partially resistant. This probability is the same as for partially resistant cells. We now consider a cytostatic killing agent. Similarly as before let  $u$  denote the drug dose,  $0 \leq u \leq 1$ , with  $u = 0$  corresponding to no drug being used and  $u = 1$  corresponding to a full dose. It is assumed that the drug kills a fixed proportion  $u$  of the outflow of the sensitive cells at time  $t$ ,  $aS(t)$ , and therefore only the remaining fraction  $(1 - u) aS(t)$  of cells undergoes cell division. Of these new cells then  $(2 - q) (1 - u)aS(t)$  remain sensitive, while a fraction  $q(1 - u)aS(t)$  mutates to partially resistant cells. The effectiveness of the drug on partially resistant cells is weaker, but not void yet, so we add a coefficient  $\beta$ ,  $0 < \beta < 1$  to represent it. Thus only a portion of the out-flowing cells from the partially sensitive compartment proportional to  $\beta u$  is killed by the drug and surviving portion  $(1 - \beta u)bP$  undergoes cell division with one of the daughter cells possibly mutating. Thus, overall the controlled dynamics can be described by the following equations:

$$\dot{S} = -aS + (1 - u)(2 - q)aS + (1 - \beta u)rbP, \quad (30)$$

$$\dot{P} = -bP + (1 - \beta u)(2 - r - s)bP + (1 - u)qaS + rcR, \quad (31)$$

$$\dot{R} = -cR + (2 - r)cR + (1 - \beta u)sbP. \quad (32)$$

Here the first terms on the right hand sides account for the deaths of the mother cells, the second terms describe the return flows into the compartments and the remaining terms give the cross-over flows in the presence of a drug. Note that the effects of the drug show up at all return and cross-over flows except for resistant compartment. We expand the model above to include phase specificity in the sensitive and partially resistant compartments. The most commonly used killing

agents are  $G_2/M$  phase specific. Therefore within the sensitive and partially sensitive compartments we combine the second growth phase  $G_2$  and mitosis  $M$  into a second sub-compartment and group the remaining phases ( $G_0, G_1$  and  $S$ ) into a first sub-compartment. We denote the average numbers of cancer cells in these compartments by  $S_1, S_2, P_1$  and  $P_2$ , respectively, and denote the corresponding inverse transit times of cells through these compartments by  $a_1, a_2, b_1$  and  $b_2$ . Cells are killed in the second sub-compartments, i.e. all cells leave, but only the surviving ones reenter the cell cycle. The dynamics of the resistant compartment is not changed. A model which includes a  $G_2/M$  phase specific killing drug, partial and complete resistance of cancer cells to this drug while allowing for reverse of unstable gene amplification can therefore be described by

$$\begin{aligned} \dot{S}_1 &= -a_1S_1 + (1 - u)(2 - q)a_2S_2 + (1 - \beta u)rb_2P_2, \\ \dot{S}_2 &= -a_2S_2 + a_1S_1, \end{aligned} \quad (33)$$

$$\begin{aligned} \dot{P}_1 &= -b_1P_1 + (1 - \beta u)(2 - r - s)b_2P_2 \\ &\quad + (1 - u)qa_2S_2 + rcR, \end{aligned} \quad (34)$$

$$\dot{P}_2 = -b_2P_2 + b_1P_1,$$

$$\dot{R} = -cR + (2 - r)cR + (1 - \beta u)sb_2P_2. \quad (35)$$

Both models are single-input bilinear systems. If, similarly as it is done in previous section more compartments are added to further differentiate the levels of drug resistance, or if blocking and/or recruiting agents (without additional killing effects) are modeled as well, then multi-input bilinear systems of the form (5) arise the only difference being the final dimension of the state variable  $N$ . The performance index which enables to formulate the optimization problem has the form similar to (19) with respective changes regarding the number of the state variables. An obvious state space constraint for these models is that the number of cells remains positive. A simple sufficient condition for this to hold is that all the matrices  $A + \sum_{i=m}^i u_i B_i$ ,  $u \in U$ , have negative diagonal entries, but non-negative off-diagonal entries (i.e. are so-called Metzler matrices.) In cell-cycle specific compartmental models for cancer chemotherapy which do not consider drug resistance this condition is always satisfied since there are only outflows from the  $i$ -th compartment. The importance of this condition however, is more related to the fact that it also implies negative invariance of the positive octant under the adjoint flow which describes the evolution of the multipliers in the Maximum Principle. For the models described above, the system matrices no longer are Metzler matrices. However, it is not difficult to see that states remain positive for all the models introduced above. On the other hand, in the analysis of optimal controls it would be of importance to also have a good invariance properties of the adjoint flow and these need to be investigated. In [3] necessary conditions for optimality for a general dynamics which satisfies the above mentioned condition have been analyzed. Since the dynamics and objective are linear in the control variables, the prime candidates for

optimality are concatenations of bang-bang and singular controls. The optimality of possible singular controls needs to be investigated on a case-by-case basis and it is intended to perform such an analysis, possibly investigating whether there exist common features in these models described above which would allow to give a broader criterion. Preliminary computations show that the optimality of singular controls depends on the relative portion of resistant cells, but further analysis is needed. Aside from singular controls, bang-bang controls are the natural candidates and typically there will be many trajectories corresponding to bang-bang controls which satisfy the first order necessary conditions for optimality, but are not optimal. In [3] sharp necessary and sufficient conditions for optimality of bang-bang controls for a general  $n$ -compartment model are developed and may be applied for considered models.

## 5. Angiogenesis and antiangiogenic therapy

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 [28] 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 nutrient supplies 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 called tumor angiogenesis 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. 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 [15] 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 [29].
- 2) The discovery of vascular endothelial growth factor and its receptor tyrosine kinases on activated endothelial cells [30].
- 3) The discovery of angiopoietins and their tyrosine kinase receptors [31].
- 4) The discovery of endogenous inhibitors of angiogenesis [32].
- 5) The discovery of additional molecular markers in newly formed blood vessels [33].
- 6) The development of quantitative assays for angiogenesis [34].
- 7) Recognition of the prognostic significance of tumor angiogenesis [35].
- 8) Lack of acquired resistance to direct acting antiangiogenic drugs [29].
- 9) The discovery of the impact of angiogenesis on liquid hematologic malignancies [31].
- 10) The discovery of the accidental antiangiogenic effects of various conventional or new anticancer drugs and other agents, see e.g. [36].

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. [34, 30]) 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. [16] 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. This type of model or more precisely its modification proposed in [37] has been used in our study [38]. In [37] it has been proved that using sufficiently high doses of antiangiogenic drugs we are able to annihilate completely the vascular network of the tumour and indirectly eradicate the tumor itself. It can be reached, not only using a constant dose of the drug, but also by periodic therapy more reasonable from clinical point of view. We present the resume of these results. Since the results have an asymptotic character it means that the process of eradication is theoretically infinite and the same the patient once treated by the antiangiogenic therapy should remain under such control to the end of his life. To overcome this difficulty we propose to optimize the therapy in finite horizon. The optimization problem for yet another modification of Hahnfeldt model was solved in [39] by Ergun and coworkers. Their model has a drawback that there exists only one cross-coupling between the two compartments which

results, for example, in trivial stability conditions. The rigorous treatment of this model has been recently presented in [40].

The idealized scheme of cell cycle kinetics represented by previously considered compartmental models is confounded in solid tumors by the existence of a geometric gradient of availability of oxygen and nutrients. This causes a stratification in viability of cells: usually cycling cells are near the surface or near blood vessels, further layers are occupied by dormant cells, while the deepest regions form a necrotic core. This may lead to self-limiting growth phenomena, which may be described by nonlinear models including Pearl-Verhulst (logistic) or Gompertz-type equations. In the Gompertz-type equation we introduce a varying coefficient  $a(t)$ :

$$\dot{N} = a(t)N, N(0) = N_0, \quad (36)$$

$$\dot{a} = -\beta a, a(0) = \alpha \Rightarrow$$

$$N = N_0 e^{\alpha/\beta(1-e^{-\beta t})} \quad (37)$$

The growth is bounded by:

$$N_\infty = N_0 e^{\alpha/\beta}, \quad (38)$$

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

$$\dot{N}/N = -\beta \ln N/N_\infty \approx 1/PDT, \quad (39)$$

where by  $PDT$  we understand potential doubling time of the considered population.

Hahnfeldt [16] 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:

$$N_\infty = K, \quad \dot{N}/N = -\beta \ln N/K. \quad (40)$$

Although equation (40) looks similarly to equation (39) but now the carrying capacity is not constant 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:

$$\dot{N}/N = \beta(1 - N/K). \quad (41)$$

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

$$PDT_k = f(MF, SF, IF). \quad (42)$$

In [16] it has been assumed that the inverse of  $PDT$  is the sum of these three factors i.e.

$$1/PDT_k = MF + SF + IF. \quad (43)$$

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  $K^b N^c$  slower than the endogenous inhibition of previously generated vasculature represented by  $IF$  (e.g. through endothelial cell death or disaggregation). 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. Parameters  $b$  and  $c$  satisfy the following formula:

$$b + c = 2/3. \quad (44)$$

The reason is that analyzing a diffusion-consumption equation for the concentration of stimulator or inhibitor inside and outside the tumor, Hahnfeldt *et al* concluded that inhibitor will impact on 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 proportional 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 [16] has therefore the following form:

$$\dot{K}/K = \gamma N/K - (\lambda N^{2/3} + \mu). \quad (45)$$

$\gamma, \lambda, \mu$  being constant parameters representing the effect of stimulation, inhibition and natural mortality, respectively. The modification of this model proposed in [37] which also satisfies Hahnfeldt's suggestions given by (48) 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:

$$\dot{N}/N = -\beta \ln N/K. \quad (46)$$

$$\dot{K}/K = \gamma - (\lambda N^{2/3} + \mu). \quad (47)$$

Combinations of tumor growth models (46), (41) with vascular network models (45), (47) result in four nonlinear models of tumor angiogenesis. The interesting finding is that all these systems have the same nontrivial equilibrium point  $(N^*, K^*)$ :

$$\dot{N}/N = \dot{K}/K = 0 \Rightarrow N^* = K^* = ((\gamma - \mu)/\lambda)^{3/2}. \quad (48)$$

The model is strongly nonlinear but by logarithmic change of variable and some scaling transformation we are able to simplify them and find their asymptotic properties using standard Lyapunov type analysis of stability [41] (local and global) – see e.g. [37], [38] for analysis of three of these models.

Using the following transformation:

$$\begin{aligned} x &= \ln N/N^*, \quad y = \ln K/K^*, \quad x^* = y^* = 0, \\ \tau &= \beta t, \quad \vartheta = (\gamma - \mu)/\beta, \quad x' = dx/d\tau, \quad y' = dy/d\tau, \end{aligned} \quad (49)$$

we are led for example:

for model (46), (47) to the following quasi-linear system:

$$x' = y - x, \quad y' = \vartheta(1 - e^{2/3x}), \quad (50)$$



or:

$$\begin{aligned} z &= y - x, \\ x' &= z, \\ z' &= -z - \vartheta(e^{2/3x} - 1) \end{aligned} \tag{51}$$

and for model (41), (45) to slightly more complicated system:

$$\begin{aligned} z &= 1 - e^{x-y}, \\ x' &= z, \\ z' &= (z - 1)(z(1 + \gamma/\beta) + \vartheta(e^{2/3x} - 1)). \end{aligned} \tag{52}$$

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 (47) it leads to the following equation:

$$\dot{K}/K = \gamma - (\lambda N^{2/3} + \mu + \eta u(t)), \tag{53}$$

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

$$N^* = K^* = ((\gamma - \mu - \eta U)/\lambda)^{3/2}, \tag{54}$$

which according to the conditions of stability given in [37] leads to the conclusion that:

$$\eta U \approx \gamma - \mu \Rightarrow K^* \rightarrow 0. \tag{55}$$

The form of condition (55) 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 [37] it has been proved that the same effect could be reached for periodic therapy with mean value satisfying condition (55) or greater. The similar analysis for other models lead to the same conclusions. The exception is the original Hahnfeldt model for which (55) is only necessary but not sufficient condition for tumor eradication under periodic protocol. Yet another simplified model was proposed by Ergun et al [39]. In this case the growth of the vascular network is independent of the tumor size.

$$\dot{K}/K = \gamma K^{-1/3} - \lambda K^{1/3}. \tag{56}$$

Or in the case when therapy is included:

$$\dot{K}/K = \gamma K^{-1/3} - \eta u - \lambda K^{1/3}. \tag{57}$$

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 population growth (Gompertz or logistic type) and thus we are led to two additional models. Although during simulation all the models lead to similar

transients for tumor growth and vascular network 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. Constant or periodic therapies which ensure tumor eradication discussed previously have an important drawback. They should be applied in long therapy horizon. Shortage in the antiangiogenic drugs, their costs, and side effects although lower than in chemotherapy but not completely recognized cause that the 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 [39] and [40] the optimal control problem for the Ergun's model and a free terminal time is solved under the constraint on a bound on the total amount of inhibitors. The authors found that optimal strategy consists of bang-bang and singular intervals – in [39] the problem is only stated and partly solved while in [40] a full synthesis of solutions is presented. In [38] we have proposed to optimize the protocol in the fixed finite time of therapy with the primary goal which is to find the control maximizing  $TCP$  (treatment cure probability) for the model (46), (47) that leads to the following equivalent form of an optimal control problem:

$$\begin{aligned} J &= N(T_k), \int_0^{T_k} u(t)dt \leq \Xi \\ 0 &\leq u(t) \leq U_m, \end{aligned} \tag{58}$$

with known constraining constant parameters:  $U_m, \Xi$ . 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 constraint on the control. Of course in this case the weighting factor  $r$  is unknown and should be treated as a value of an associated Lagrange multiplier. Thus the two formulations are equivalent only if the weight is chosen in such a way that it corresponds to the value of the Lagrange multiplier which solves the primary optimization problem. Moreover we may use the transformed variables  $x$  and  $y$  (or  $x$  and  $z$ ) to formulate the modified performance criterion in the form:

$$\begin{aligned} I &= gx(T_f) + hy(T_f) + r \int_0^{T_f} u(\tau)d\tau, \\ 0 &\leq u \leq 1, T_f = T_k\beta, \end{aligned} \tag{59}$$

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:

$$x' = y - x, y' = \vartheta(1 - e^{2/3x}) + \nu u, \nu = -\eta/\beta. \tag{60}$$

The weight coefficients  $h, g, r$  may change in broad ranges depending on the type of therapy used and the strength of the integral constraint. The additional term related to the volume of vascular network may be regarded as yet another constraint

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 [24] for Hamiltonian and adjoint variables  $p, q$  defined as:

$$H = ru + \nu qu + p(y - x) + q\vartheta(1 - e^{2/3x}), \quad (61)$$

$$p' = p + 2/3q\vartheta e^{2/3x}, \quad (62)$$

$$p(T_f) = g, \quad q' = -p, \quad q(T_f) = h.$$

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

$$q = -r/\nu, \quad u = \begin{cases} 1 \\ 0 \end{cases} \Leftarrow \min H. \quad (63)$$

Rewriting the adjoint equation in the form of scalar second order ODE we have:

$$\begin{aligned} q'' - q' + 2/3q\vartheta e^{2/3x} &= 0, \\ q(T_f) &= h, \quad q'(T_f) = -g. \end{aligned} \quad (64)$$

The important finding is that singular arcs 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 (in [42] the authors proved that the obtained optimal bang-bang control has at most two switchings). On the other hand Ledzewicz and Schattler solved [43] the optimal control problem for the standard Hahnfeldt model following the line of reasoning used before for the Ergun's model in [40] and once more proved that in the optimal strategy some parts are singular. It should be mentioned that the analysis in this case is much more elaborate

We are able to prove that reasonable reformulation of optimization problem (see [44]) for five from the six models leads to pure bang-bang optimal strategies. The only exception is the Hahnfeldt original model with the Gompertz type growth of the tumor where optimal solution typically contains a singular control as a middle part of the control strategy [43].

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

$$\begin{aligned} z &= \ln KN^\vartheta, \\ \theta &= \gamma/\beta, \\ x &= \ln N, \\ \varepsilon &= \lambda/\beta. \end{aligned} \quad (65)$$

It leads to the following state equations:

$$\begin{aligned} x' &= 1 - e^{(\theta+1)x-z} \\ z' &= \vartheta - \varepsilon e^{2/3x} + \nu u. \end{aligned} \quad (66)$$

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 adjoint variables  $p$  and  $q$  are given by the following equations:

$$\begin{aligned} p' &= p(\theta + 1)e^{(\theta+1)x-z} + (2/3)q\varepsilon e^{2/3x} \quad p(T_f) = g, \\ q' &= -pe^{(\theta+1)x-z} \quad q(T_f) = 0. \end{aligned} \quad (67)$$

Thus the necessary conditions of optimality have the form: (formally identical to (63)):

$$\begin{aligned} q &= -r/\nu > 0, \\ u &= \begin{cases} 1 \\ 0 \end{cases} \Leftarrow \min H. \end{aligned} \quad (68)$$

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  $g = 0$  than because 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:

$$\dot{y} = \gamma e^{-1/3y} - \lambda e^{1/3y} - \eta u. \quad (69)$$

The Hamiltonian and the adjoint variable are given by:

$$\begin{aligned} H &= p(\gamma e^{-1/3y} - \lambda e^{1/3y}) + (r - \eta p)u \\ \dot{p} &= \frac{1}{3}p(\gamma e^{-1/3y} + \lambda e^{1/3y}), \quad p(T_k) = h \end{aligned} \quad (70)$$

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

$$\begin{aligned} p &= r/\eta > 0, \\ u &= \begin{cases} 1 \\ 0 \end{cases} \Leftarrow \min H \end{aligned} \quad (71)$$

and singular controls cannot be optimal for the same reasons as in the two previously analyzed problems. Of course it should be noted that such formulation of the optimal control problem is different than the one presented in [39, 40] and the results presented in this section do not contradict the results in [40].

## 6. Conclusions and final remarks

In this study we have shown how using quite simple models we can analyze and design therapy protocols for chemotherapy benefiting from phase dependence and overcoming drug resistance and for antiangiogenic therapy. This latter type of therapy is still in experimental and clinical trials. The results are promising however still the knowledge of the processes behind the evolution of cancer vascular network, the equilibrium between stimulatory and inhibitory factors, different form of antiangiogenic therapy and its side effects is far from being complete. We hope that our results may help in the progress in

this field. Our results must be treated as introduction of more rigorous mathematical treatment of models of antiangiogenic therapy from one side and translation of its results into more specific recommendation for therapy protocols or at least planning of clinical experiments. The results could be extended onto the problem of combined anticancer therapy for example antiangiogenic and radiation as proposed in [39, 45] although the complexity of the model discussed in [39] leads to difficulties in its rigorous treatment. We hope that this approach may be also applied for analysis and design of combined antiangiogenic and chemotherapy. Such combination seems to be even more reasonable since it may be free from the major disadvantages of the standard chemotherapy discussed in the paper. On the other hand it leads to much more complicated models as it has been discussed above. There exist a number of possible variants of the proposed approach the solution of which is almost on the same level of mathematical complexity. We may solve the optimal control problem with the performance index (58) and state variables before log transformation. We may also decide to solve suboptimal control problems for specified types of therapy protocols for example periodic ones. In this case we are led to the problem of parametric optimization instead of functional one with two parameters (frequency and pulses duration) to be chosen. Moreover we may incorporate some models of pharmacokinetics by introducing linear or nonlinear additional first order compartments. In this case the analysis will be however much more complicated one (but not the only) reason being the higher order of system dynamics.

All possible applications of mathematical models of chemotherapy and antiangiogenic therapy are contingent on our ability to estimate their parameters. There has been a progress in that direction, particularly concerning precise estimation of drug action in culture and estimation of cell cycle parameters of evolving resistant cell clones [10]. New possibilities in cell cycle parameters estimation both in vitro and in vivo are now established by DNA microarray technology. By processing the data on expression of thousands of genes in different time samples one can identify the dynamics behavior of the analyzed cell populations. There have been a number of bioinformatical and biomathematical tools developed to cope with such analysis. Among them many belong to techniques frequently used by control engineers. The very good examples are algorithms based on singular value decomposition or support vector machines (e.g. [46]). More generally DNA microarrays experiments are performed to help study issues in biology and clinical practice, regarding cellular mechanisms, the functions of genes and proteins, the structure of gene networks and pathways, relating the risk of being affected by diseases to gene expression profiles, etc. Gene expression profiling has been successfully used in many medical research programs concerning monitoring cellular process, measuring the response of cells or tissues to therapeutic agents, classification or detection of disease symptoms and many other problems. Two tasks related to the classification of expression profile data are class prediction and pattern discovery. Class prediction uses information about expression profiles and the

known classification of the data sets to construct classifiers applicable to future data. In our research projects we constructed a number of such classifiers based on SVM technique which allow not only to predict classes of tissues basing on their expression profiles but to select the best set of genes for such prediction (e.g. [47]). On the other hand SVD based techniques used for unsupervised classification enabled us to discover patterns in the profiles i.e. to confirm that the information implied in the design of experiments is also encoded in the gene expression profiles collected and to explore the data from the angle of existence of unknown relations and mechanisms.

**Acknowledgements.** The author was partly supported by internal SUT grant BK209/RAu1/2008.

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