Int. J. Appl. Math. Comput. Sci., 2003, Vol. 13, No. 3, 297–305

DIFFERENT MODELS OF CHEMOTHERAPY TAKING INTO ACCOUNT DRUG RESISTANCE STEMMING FROM GENE AMPLIFICATION

JAROSŁAW ŚMIEJA*, ANDRZEJ ŚWIERNIAK*

* Department of Automatic Control
Silesian University of Technology
ul. Akademicka 16, 44–100 Gliwice, Poland
e-mail: {jsmieja, aswierniak}@ia.polsl.gliwice.pl

This paper presents an analysis of some class of bilinear systems that can be applied to biomedical modelling. It combines models that have been studied separately so far, taking into account both the phenomenon of gene amplification and multidrug chemotherapy in their different aspects. The mathematical description is given by an infinite dimensional state equation with a system matrix whose form allows decomposing the model into two interacting subsystems. While the first one, of a finite dimension, can have any form, the other is infinite dimensional and tridiagonal. A methodology of the analysis of such models, based on system decomposition, is presented. An optimal control problem is defined in the l^1 space. In order to derive necessary conditions for optimal control, the model description is transformed into an integro-differential form. Finally, biomedical implications of the obtained results are discussed.

Keywords: biomedical modelling, infinite dimensional systems, multivariable control

1. Introduction

Despite the long history of research and the rich literature devoted to modelling and control problems of infinite dimensional systems, almost all efficient methods developed to deal with them present approaches suitable for PDE models, and optimisation techniques are often limited to LQ problems. More general solutions, involving abstract differential equations (Curtain and Zwart, 1995), lead, in turn, to theoretical results whose applicability is arguable.

Models based on an infinite number of state equations may be applied to a variety of systems. Besides the models of drug resistance evolution caused by gene amplification (Kimmel and Axelrod, 1990; Polański *et al.*, 1997) analysed in this paper, they may also describe, e.g., RC ladders, which are approximations of long transmission lines (Zadeh and Desoer, 1963), microsatellite repeats evolution (Świerniak *et al.*, 2002), which plays an important role in genetic disorders (Ramel, 1997), telomere shortening (Arino *et al.*, 1995; Olofsson and Kimmel, 1999) responsible for cell aging and death, or some queuing systems (Kleinrock, 1976). Usually, additional assumptions are made, resulting in tridiagonal system matrices. Moreover, the analysis of such models is often limited to their finite-dimensional approximations. However, in that case, some dynamical properties may be neglected. Moreover, as shown in our previous papers (Świerniak *et al.*, 1997a; 1998), studies of infinite dimensional models may lead to compact results, convenient in further analysis, which would be impossible or very difficult to obtain in a finite dimensional approximation.

Our previous works (e.g., Świerniak *et al.*, 1999; Śmieja *et al.*, 1999) dealt with models with tridiagonal system matrices. They led to the development of a methodology for investigating such systems and formed a basis for further generalisation. This work pushes the research a step further, studying the properties of a model, in which significantly fewer simplifications have been made and fewer additional assumptions are required. Moreover, it combines models that have been studied separately so far, taking into account the phenomenon of both gene amplification and multidrug chemotherapy in their different aspects.

Three different examples are discussed in this paper, each of them addressing different aspects of cancer cell modelling. As the first one, a model taking into account the partial sensitivity of the resistant subpopulation will be introduced. In this case, it is assumed that the resistant subpopulation consists of two parts: the one which is sensitive to the drug (but, unlike in previous works, may contain cells of a different drug sensitivity), and the other, which is completely drug-resistant.

Subsequently, an attempt to model multidrug protocols will be presented. The motivation behind it is that

most of the existing forms of therapy consist in using several drugs instead of a single one. Then, modelling should take into account increasing drug resistance to each chemotherapeutic agent used.

Finally, the phase-specific control of the drug-sensitive cancer population will be addressed. Actually, each drug affects cells being in particular phases and it makes sense to combine these drugs so that their cumulative effect on the cancer population is the greatest. So far, phase-specific chemotherapy has been considered without any regard to problems stemming from increasing drug resistance. Combining the infinite dimensional model of drug resistance with the phase-specific model of chemotherapy should bring mathematical modelling much closer to its clinical application.

2. Original Mathematical Model

The original model and its properties were thoroughly discussed, e.g., in (Świerniak *et al.*, 1998; 1999). However, the underlying biological background remains the same also for the subject of this paper and therefore it needs to be briefly introduced.

In this section some model of a cell population with evolving drug resistance caused by gene amplification or other mechanisms is presented. Based on some results of (Kimmel and Axelrod, 1990; Axelrod *et al.*, 1994; Harnevo and Agur, 1993), the model is general enough to allow various interpretations.

We consider a population of neoplastic cells stratified into subpopulations of cells of different types, labelled with the numbers $i = 0, 1, 2, \ldots$. If the biological process considered is gene amplification, then the cells of different types are identified with different numbers of copies of the drug resistance gene and varying levels of resistance. Cells of Type 0, with no copies of the gene, are sensitive to the cytostatic agent. Due to the mutational event, a sensitive cell of Type 0 can acquire a copy of the gene that makes it resistant to the agent. Likewise, the division of resistant cells can result in a change in the number of gene copies. The resistant subpopulation consists of cells of Types i for $1, 2, \ldots$. The probability of the mutational event in a sensitive cell is several orders smaller than the probability of the change in the 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 in 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 $1/\lambda_l$ for cells of Type i.
2. A cell of Type i for $i \geq 1$ may mutate in a short time interval $(t, t + \mathrm{d}t)$ into a Type $i + 1$ cell with probability $b_i\,\mathrm{d}t + o(\mathrm{d}t)$ and into a Type $i - 1$ cell with probability $d_i\,\mathrm{d}t + o(\mathrm{d}t)$. A cell of Type $i = 0$ may mutate in a short time interval $(t, t + \mathrm{d}t)$ into a Type 1 cell with probability $\alpha\,\mathrm{d}t + o(\mathrm{d}t)$, where α is several orders of magnitude smaller than any of b_i's and d_i's.
3. The drug action results in a fraction u_i of ineffective divisions in the 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.

A graph representing the possible flows between subpopulations is presented in Fig. 1(a).

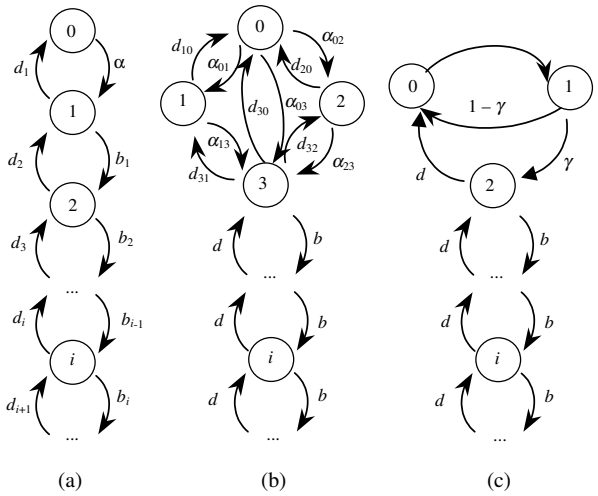

Fig. 1. Flows between subpopulations for the model taking into account (a) the original assumptions or partial sensitivity of the resistant subpopulation, (b) two-drug chemotherapy, and (c) phase-specific chemotherapy; in all the cases the numbers denote cell types.

If we denote by $N_i(t)$ the expected number of cells of Type i at time t, and we assume the simplest case, in which the resistant cells are insensitive to the drug's action, and there are no differences between the parameters of cells of different types, the model is described by the following system of ODE's:

$$\begin{cases} \dot{N}_0(t) = \big[1 - 2u_0(t)\big]\lambda_0 N_0(t) - \alpha N_0(t) + d_1 N_1(t), \\ \dot{N}_1(t) = \big[1 - 2u_1(t)\big]\lambda_1 N_1(t) - (b_1 + d_1)N_1(t), \\ \qquad\qquad +d_2 N_2(t) + \alpha N_0(t), \\ \qquad\quad \vdots \\ \dot{N}_i(t) = \big[1 - 2u_i(t)\big]\lambda_i N_i(t) - (b_i + d_i)N_i(t) \\ \qquad\qquad +d_{i+1} N_{i+1}(t) + b_{i-1} N_{i-1}(t) \ \text{ for } \ i \geq 2. \end{cases} \tag{1}$$

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

$$\begin{cases} \dot{N}_0(t) = \big[1-2u(t)\big]\lambda N_0(t) - \alpha N_0(t) + \mathrm{d}N_1(t), \\ \dot{N}_1(t) = \lambda N_1(t) - (b+d)N_1(t) + dN_2(t) \\ \qquad +\alpha N_0(t), \\ \qquad \vdots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) + dN_{i+1}(t) \\ \qquad +bN_{i-1}(t) \ \text{ for } \ i \geq 2. \end{cases} \tag{2}$$

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

$$\begin{cases} \dot{N}_0(t) = \big[1-2u_0(t)\big]\lambda_0 N_0(t) - \alpha N_0(t) \\ \qquad +d_1 N_1(t), \\ \dot{N}_1(t) = \big[1-2u_1(t)\big]\lambda_1 N_1(t) - (b_1+d_1)N_1(t) \\ \qquad +d_2 N_2(t) + \alpha N_0(t), \\ \qquad \vdots \\ \dot{N}_{l-1}(t) = \big[1-2u_{l-1}(t)\big]\lambda_{l-1} N_{l-1}(t) \\ \qquad -(b_{l-1}+d_{l-1})N_{l-1}(t) + d_l N_l(t) \\ \qquad +b_{l-2}N_{l-2}(t), \\ \qquad \vdots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) + dN_{i+1}(t) \\ \qquad +bN_{i-1}(t) \ \text{ for } \ i \geq l. \end{cases} \tag{3}$$

Moreover, multivariable control is allowed, meaning that either some types of the resistant cells can be affected by chemotherapy or different drugs are being used. A justification of its usefulness is presented in the following sections.

Several control problems arising in all these cases can be addressed based on the model. One of them is establishing constant control u (in that case it leads to the determination of feedback parameters) that stabilises the infinite dimensional system. In biological terms, it refers to calculating a constant dose of the chemotherapeutic agent that suppresses the growth of the resistant subpopulation. However, the constant treatment protocol, which guarantees the decay of the cancer population after a sufficiently long time, is not realistic. First 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 sensible to find the optimal control which minimises the performance index

$$J = \sum_{i=0}^{l-1} N_i(T) + r_1 \sum_{i=l}^{\infty} N_i(T) + r \sum_{k=0}^{m} \int_0^T u_k(\tau)\,\mathrm{d}\tau, \tag{4}$$

where r_1 and r are non-negative weighting factors.

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

3. Model Taking into Account the Partial Sensitivity of the Resistant Subpopulation

In this case, it is assumed that the resistant subpopulation consists of two parts: the one, which is partially sensitive to the drug, and the other, which is completely drug-resistant. Then the following set of equations is obtained:

$$\begin{cases} \dot{N}_0(t) = \big[1-2u(t)\big]\lambda_0 N_0(t) - \alpha N_0(t) + d_1 N_1(t), \\ \dot{N}_1(t) = \big[1-2\mu_1 u(t)\big]\lambda_1 N_1(t) - (b_1+d_1)N_1(t) \\ \qquad +d_2 N_2(t) + \alpha\, N_0(t), \\ \qquad \vdots \\ \dot{N}_{l-1}(t) = \big[1-2\mu_{l-1}u(t)\big]\lambda_{l-1} N_{l-1}(t) \\ \qquad -(b_{l-1}+d_{l-1})N_{l-1}(t) + d_l N_l(t) \\ \qquad +b_{l-2}N_{l-2}(t), \\ \qquad \vdots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) + dN_{i+1}(t) \\ \qquad +bN_{i-1}(t) \ \text{ for } \ i \geq l, \end{cases} \tag{5}$$

where the μ_i's satysfying $0 \leq \mu_i \leq 1$ are "efficiency factors", determining the effectiveness of the drug in relation to a particular type of cell. Due to the general assumptions about the model, which were presented at the beginning of this section, these factors satisfy the following relations:

$$0 \leq \mu_i \leq \mu_{i-1} \leq 1, \quad i = 1, 2, \ldots, l-1. \tag{6}$$

4. Multidrug Protocols

Most of the existing forms of therapies consist in using several drugs instead of a single one. Coldman and Goldie (1986) suggested that a such chemotherapy might reduce the drug resistance effects. Then the modelling should take into account the increasing drug resistance to each of the chemotherapeutic agents used. There is no known mathematical approach to analysing such a problem.

Let us consider the case of a simultaneous use of two types of drugs. Assume the simplest case, in which the

resistance of the cells means that they are insensitive to the drugs' actions, and there are no differences between the parameters of cells of different types. Then we could distinguish four different subpopulations of cells: Type 0, which is sensitive to both drugs, Type 1 and Type 2, sensitive only to the first and the second agent, respectively, and Type $i \geq 3$, resistant to both drugs. The second hypothesis for the original model has to be modified in the following way:

- A cell of Type 0 may mutate in a short time interval $(t, t+\mathrm{d}t)$ into a Type 1 cell with probabilities $\alpha_{13}\,\mathrm{d}t + o(\mathrm{d}t)$ or into a Type 2 cell with probability $\alpha_{02}\,\mathrm{d}t + o(\mathrm{d}t)$ or into a Type 3 cell with probability $\alpha_{03}\,\mathrm{d}t + o(\mathrm{d}t)$.
- Each cell of Type 1 or Type 2 may mutate in a short time interval $(t, t+\mathrm{d}t)$ into a Type 3 cell with probabilities $\alpha_{13}\,\mathrm{d}t + o(\mathrm{d}t)$ and $\alpha_{23}\,\mathrm{d}t + o(\mathrm{d}t)$, respectively, or into a Type 0 cell with probabilities $d_{10}\,\mathrm{d}t + o(\mathrm{d}t)$ and $d_{20}\,\mathrm{d}t + o(\mathrm{d}t)$, respectively.
- A cell of Type 3 may mutate in a short time interval $(t, t+\mathrm{d}t)$ into a Type 0, Type 1 or a Type 2 cell with probabilities $d_{30}\,\mathrm{d}t + o(\mathrm{d}t)$, $d_{31}\,\mathrm{d}t + o(\mathrm{d}t)$ and $d_{32}\,\mathrm{d}t + o(\mathrm{d}t)$, respectively, or into a Type 4 cell with probability $b\,\mathrm{d}t + o(\mathrm{d}t)$.
- A cell of Type i, $i \geq 4$, may mutate in a short time interval $(t, t+\mathrm{d}t)$ into a Type $i+1$ cell with probability $b\,\mathrm{d}t + o(\mathrm{d}t)$ and into Type $i-1$ cell with probability $d\,\mathrm{d}t + o(\mathrm{d}t)$, where $\alpha_{l\varphi}$ is several orders of magnitude smaller than b and d.

A graph illustrating the possible transfers between different subpopulations is presented in Fig. 1(b). The following set of equations is obtained:

$$\begin{cases} \dot{N}_0(t) = \big[1-\beta_0 u_0(t) - \beta_1 u_1(t)\big]\lambda N_0(t) \\ \qquad -(\alpha_{01}+\alpha_{02}+\alpha_{02})N_0(t) + d_{10}N_1(t) \\ \qquad +d_{20}N_2(t), \\ \dot{N}_1(t) = \big[1-2u_0(t)\big]\lambda N_1(t) - (\alpha_{13}+d_{10})N_1(t) \\ \qquad +d_{31}N_3(t) + \alpha_{01}N_0(t), \\ \dot{N}_2(t) = \big[1-2u_1(t)\big]\lambda N_2(t) \\ \qquad -(\alpha_{23}+d_{20})N_2(t) + d_{32}N_3(t) \\ \qquad +\alpha_{02}N_0(t), \\ \dot{N}_3(t) = \lambda N_3(t) - (b+d_{30}+d_{31}+d_{32})N_3(t) \\ \qquad +dN_4(t) + \alpha_{13}N_1(t) + \alpha_{23}N_2(t), \\ \qquad \vdots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) + dN_{i+1}(t) \\ \qquad +bN_{i-1}(t) \ \text{ for } \ i \geq 4, \end{cases} \tag{7}$$

where β_1 and β_2 are efficiency factors, and $\beta_0+\beta_1 \leq 2$.

Although in the mathematical model given above it is assumed that the mechanism for resistance is independent for each drug, the methodology developed makes it possible to analyse also the case when different drugs affect the same gene simultaneously. In that case, the model (7) should be combined with (5). In fact, this combination is possible in the general model introduced in Section 6.

5. Phase-Specific Control of the Drug-Sensitive Cancer Population

The cell cycle is composed of a sequence of phases undergone by each cell from its birth to division. Actually, each drug affects the cell being in a particular phase and it makes sense to combine these drugs so that their cumulative effect on the cancer population is 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 (Świerniak *et al.*, 1997a; Swan, 1990). Combining the infinite dimensional model of drug resistance with the phase-specific model of chemotherapy should bring mathematical modelling much closer to its clinical application.

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

$$\begin{cases} \dot{N}_0(t) = -\lambda_0 N_0(t) + 2(1-\gamma)[1-u(t)]\lambda_1 N_1(t) \\ \qquad +dN_2(t), \\ \dot{N}_1(t) = -\lambda_1 N_1(t) + \lambda_0 N_0(t), \\ \dot{N}_2(t) = \lambda_2 N_2(t) - (b+d)N_1(t) \\ \qquad +2\gamma\big[1-u(t)\big]\lambda_1 N_1(t) + bN_3(t), \\ \qquad \vdots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) + dN_{i+1}(t) \\ \qquad +bN_{i-1}(t) \ \text{ for } \ i \geq 3, \end{cases} \tag{8}$$

where γ is the probability of the primary mutational event. A graph illustrating possible transfers between different subpopulations is presented in Fig. 1(c). Similarly, a multidrug therapy including blocking drugs (Świerniak *et al.*, 1997b; Brown and Thompson, 1975) as well as the killing agent could be analysed in the same way, as presented in the subsequent sections.

6. General Mathematical Model

The system is described by the following state equation:

$$\dot{N} = \left(\boldsymbol{A} + \sum_{i=0}^{m} u_i \boldsymbol{B}_i \right) N, \tag{9}$$

where $N = [N_0 \ N_1 \ N_2 \ \dots \ N_i \ \dots]^T$ is an infinite dimensional state vector,

$$\boldsymbol{A} = \begin{bmatrix} \tilde{\boldsymbol{A}}_1 & \vdots & \boldsymbol{0}_1 \\ \cdots & \cdots & \cdots \\ \boldsymbol{0}_2 & \vdots & \tilde{\boldsymbol{A}}_2 \end{bmatrix}, \tag{10}$$

$$\boldsymbol{B} = \begin{bmatrix} \tilde{\boldsymbol{B}}_i & \vdots & \boldsymbol{0}_1 \\ \cdots & \cdots & \cdots \\ & \boldsymbol{0}_3 & \end{bmatrix}, \tag{11}$$

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

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

$$\tilde{\boldsymbol{B}}_i = \begin{bmatrix} b^i_{0,0} & b^i_{0,1} & \cdots & b^i_{0,l-1} \\ b^i_{1,0} & b^i_{1,1} & \cdots & b^i_{1,l-1} \\ \vdots & \vdots & \cdots & \vdots \\ b^i_{l-1,0} & b^i_{l-1,1} & \cdots & b^i_{l-1,l-1} \end{bmatrix},$$

$u(t)$ stands for the m-dimensional control vector $u = [u_0 \ u_1 \ u_2 \ \dots \ u_{m-1}]^T$, $\boldsymbol{0}_1, \boldsymbol{0}_2$ and $\boldsymbol{0}_3$ are zero matrices of dimensions $l \times \infty$, $\infty \times (l+1)$ and $\infty \times \infty$, respectively, $l > m$.

It is important to note that the model parameters satisfy the relations $a_3 > a_1 > 0$ and $a_2 < 0$. However, a full problem analysis can be made in other possible cases (e.g., when no additional conditions are to be satisfied by the parameters a_1 and a_3) using exactly the same line of reasoning. The performance index to be minimised is given by (4).

7. Model Decomposition

To make an analysis of the model, it is convenient to present it in the form of a block diagram shown in Fig. 2, effectively decomposing the model into two parts. The first one, of the finite dimension, does not require that parameters meet any particular assumptions. The second subsystem is infinite dimensional, with a tridiagonal system matrix, and does not include terms containing control variables $u_i(t)$.

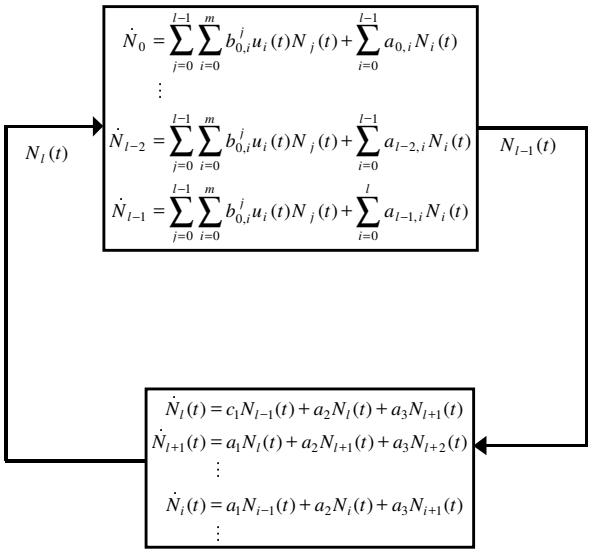

Fig. 2. Decomposition of the system model.

7.1. Infinite Dimensional Subsystem

First, consider the infinite dimensional tail without the influence of cells N_{l-1}:

$$\begin{cases} \dot{N}_l(t) = a_2 N_l(t) + a_3 N_{l+1}(t), \\ \dot{N}_{l+1}(t) = a_1 N_l(t) + a_2 N_{l+1}(t) + a_3 N_{l+2}(t), \\ \qquad \vdots \\ \dot{N}_i(t) = a_1 N_{i-1}(t) + a_2 N_i(t) + a_3 N_{i+1}(t), \\ \qquad \vdots \end{cases} \tag{12}$$

Using methods similar to that outlined in our previous works devoted to biomedical modelling (Świerniak *et al.*, 1999; Śmieja *et al.*, 2000), it is possible to show that for the initial condition $N_i(0) = \delta_{ik}$ (the Kronecker delta), i.e., $N_k(0) = 1$, $N_i(0) = 0$ for $i \neq k$, the following relations hold true:

$$N^k_l(s) = \frac{1}{a_3} \left(\frac{s - a_2 - \sqrt{(s-a_2)^2 - 4a_1 a_3}}{2a_1} \right)^{k-l+1}, \tag{13}$$

$$N_{\Sigma}^{k}(s) = \frac{1}{s-(a_1+a_2+a_3)} \times \left[1-\left(\frac{s-a_2-\sqrt{(s-a_2)^2-4a_1a_3}}{2a_1}\right)^{k-l+1}\right], \quad (14)$$

where $N_l^k(s)$ and $N_{\Sigma}^k(s)$ constitute the Laplace transforms of $N_l^k(t)$ and $\sum_{i\geq 1} N_i^k(t) = N_{\Sigma}^k(t)$, respectively (the superscript k is introduced to emphasize the index of the state variable with a non-zero initial condition). Now, assume that $k = l$. Then, after calculating the inverse Laplace transform, the following formulae are obtained:

$$N_l^l(t) = \frac{1}{a_3}\left(\sqrt{\frac{a_3}{a_1}}\right)\frac{I_1\left(2\sqrt{a_1a_3}t\right)}{t}\exp(a_2t), \quad (15)$$

$$N_{\Sigma}^l(t) = \sum_{i\geq l} N_i(t) = \exp\left[(a_1+a_2+a_3)t\right] \times \left[1-\left(\sqrt{\frac{a_3}{a_1}}\right)\int_0^t \frac{I_1(2\sqrt{a_1a_2}\tau)}{\tau} \times \exp\left[-(a_1+a_3)\tau\right]\mathrm{d}\tau\right], \quad (16)$$

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

It should be emphasised that the assumption about the initial condition does not introduce any additional constraints to the model applicability. Due to the linearity of the infinite dimensional tail, any finite non-zero initial condition can be incorporated into the final solution.

Using an asymptotic expansion of (16) and assuming $a_3 \geq a_1$, it was found (Polański *et al.*, 1997) that the stability condition for the autonomous system is

$$a_2 \leq -2\sqrt{a_1a_3}. \quad (17)$$

7.2. Analysis of the Complete Model without Control

The relation (6) can be used to determine the following transfer function in the model (9):

$$K_1(s) = \frac{N_l(s)}{N_{l-1}(s)} = \frac{c_1}{a_3}\frac{s-a_2-\sqrt{(s-a_2)^2-4a_1a_3}}{2a_1}. \quad (18)$$

Moreover,

$$\sum_{i\geq l} N_i(t) = N_{\Sigma}^l(t) + N^+(t), \quad (19)$$

where

$$N^+(t) = c_1\int_0^t N_{\Sigma}^l(t-\tau\,)N_{l-1}(\tau)\,\mathrm{d}\tau \quad (20)$$

and $N_{\Sigma}^l(t)$ is defined by (16).

Let us now introduce the following notation:

$$\hat{\boldsymbol{B}}_1 = \begin{bmatrix} 0 \\ \vdots \\ 0 \\ a_{l-1,l} \end{bmatrix}, \quad \boldsymbol{C} = \underbrace{[0,\ldots,0,1]}_{l \text{ components}}. \quad (21)$$

Then, applying the standard control theory techniques (Zadeh and Desoer, 1963), the following relation holds true for $u(t) = 0$:

$$K_2(s) = \frac{X_{l-1}(s)}{X_l(s)} = \boldsymbol{C}(s\boldsymbol{I}-\tilde{\boldsymbol{A}}_1)^{-1}\hat{\boldsymbol{B}}_1. \quad (22)$$

Taking into account the linear form of this system, it is possible to present the model in the form of a block diagram, shown in Fig. 3. This makes it possible to analyse the dynamical properties of the closed-loop system.

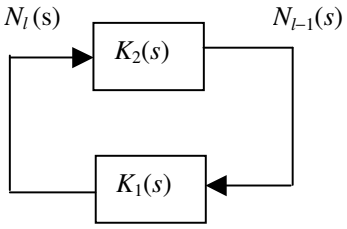

Fig. 3. Block diagram of the system without control.

7.3. Case of a Constant Control Vector

Let us now consider the problem of stabilizing the system (9) by constant control. Then the transfer function $K_2(s)$ representing the finite dimensional subsystem in Fig. 3 takes the following form:

$$K_2(s) = \frac{X_{l-1}(s)}{X_l(s)} = \boldsymbol{C}\left[s\boldsymbol{I}-\left(\tilde{\boldsymbol{A}}_1+\sum_{i=0}^{m}\tilde{\boldsymbol{B}}_i\right)\right]^{-1}\hat{\boldsymbol{B}}_1. \quad (23)$$

Again, the standard control theory techniques, including the Nyquist criterion (Zadeh and Desoer, 1963), can be applied to find stability conditions for such a system.

8. Integro-Differential Model

The system description (9) in the form of an infinite number of ODEs is not very convenient, although it can be used in different approaches to optimisation problems that

will be considered in the next section. Instead, a model transformation into an integro-differential one is proposed in this section.

Set

$$\tilde{x} = \begin{bmatrix} N_0 \\ \vdots \\ N_{l-1} \end{bmatrix} \tag{24}$$

and $\boldsymbol{C}_k = [c_j]$, $c_k = 1$, $c_j = 0$ for $j \neq k$, $i = 1, 2, \ldots, l-1$. Let us also assume that $N_i(0) = 0$ for $i > l-1$ (once again it should be stressed that any finite non-zero initial condition can be incorporated into the final solution). Then the last equation in the first subsystem, influenced directly by control, as presented in Fig. 2, can be transformed into the integro-differential form

$$\dot{N}_{l-1}(t) = \sum_{j=0}^{l-1}\sum_{i=0}^{m} b^j_{l-1,i} u_i(t) N_j(t) + \sum_{i=0}^{l-1} a_{l-1,i} N_i(t) + a_{l-1,l} \int_0^t k_1(t-\tau) N_{l-1}(\tau)\,\mathrm{d}\tau, \tag{25}$$

where $k_1(t)$ is the inverse Laplace transform of $K_1(s)$ given by (18).

Similarly, other equations can also be rewritten in the same way, leading to the transformation of the model (9) into the following form:

$$\dot{\tilde{x}} = h(u, \tilde{x}) + \int_0^t \tilde{f}(\tilde{x}, t, \tau)\,\mathrm{d}\tau, \quad \tilde{x}(0) = \tilde{x}_0, \tag{26}$$

where $h(\cdot,\cdot)$ are $\tilde{f}(\cdot,\cdot,\cdot)$ are the respective l-dimensional vector functions:

$$h_k(u, \tilde{x}) = \sum_{j=0}^{l-1}\sum_{i=0}^{m} b^j_{k,i} u_i(t) N_j(t) + \sum_{i=0}^{l-1} a_{k,i} N_i, \tag{27}$$

$$\tilde{f}_k(\tilde{x}, t, \tau) = \begin{cases} 0 & \text{for } k < l-1, \\ a_{l-1,l} k_1(t-\tau) N_{l-1}(t) & \text{for } k = l-1. \end{cases} \tag{28}$$

9. Necessary Conditions for Optimal Control

After the transformation of the system description presented in the previous section, it is possible to effectively address the resulting optimal control problem.

Let the system be governed by Eqn. (9), which is then transformed into the form (26). The control is bounded, i.e.,

$$0 \leq u_k(t) \leq 1, \tag{29}$$

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 (4). Due to the particular form of both the performance index and the equation governing the model, it is possible to find the solution to the problem applying the appropriate version of Pontryagin's maximum principle (Pontryagin *et al.*, 1962).

It is important to notice that, although the performance index (4) seems to consist of two components (a sum and an integral), the sum actually involves another integral, which stems from (19) and (20). Therefore, it should be rewritten to emphasise this relation:

$$J = \sum_{i=0}^{l-1} N_i(T) + r_1 N^l_\Sigma(T) + \int_0^T \left[r_1 c_1 N^l_\Sigma(T-\tau) N_{l-1}(\tau) + r \sum_{k=0}^{m} u_k(\tau) \right] \mathrm{d}\tau. \tag{30}$$

A number of formulations of necessary conditions for the optimisation problem for dynamical systems governed by integro-differential equations can be found in the literature, e.g., (Bate, 1969; Connor, 1972; Gabasov and Kirilowa, 1971). However, they are usually too general to be efficiently applied to such a particular problem or they have too strong constraints (e.g., regarding the smoothness of the control function). Nevertheless, following the line of reasoning presented by Bate (1969), it is possible to derive the necessary conditions for optimal control:

$$u^{\mathrm{opt}}(t) = \arg\min_u \left[r \sum_{k=0}^{m} u_k(t) + p^T(t) h(u, \tilde{x}) + a_{l-1,l} \int_t^T p_{l-1}(\tau) k_1(t-\tau) N_{l-1}(\tau)\,\mathrm{d}\tau \right], \tag{31}$$

$$\dot{p}^T(t) = -\left[q^T(t) + p^T(t) h_{\tilde{x}}(u, \tilde{x}) + \int_t^T p^T(\tau) \tilde{f}_{\tilde{x}}(t-\tau)\mathrm{d}\tau \right], \tag{32}$$

$$q(t) = \begin{bmatrix} 0 & \ldots & 0 & r_1 c_1 N^l_\Sigma(T-t) \end{bmatrix}^T,$$

$$p_i(T) = 1, \quad i = 0, 1, \ldots, l-1, \tag{33}$$

$p(t)$ being the adjoint vector.

Taking into account the constraint (29) and the bilinear form of (27), it can be proved that, in order to satisfy (31), optimal control must be of the bang-bang type. Then, to find an optimal number of switches and switching times, a gradient method can be developed, following the line of reasoning presented in (Śmieja *et al.*, 1999).

10. Conclusions

This paper is concerned with an infinite dimensional bilinear model of dynamical systems. Based on model de-

composition, it is possible to analyse analytically some of their dynamical properties. The transformation of system description into one integro-differential equation allows solving an optimal control problem with the performance index defined in the l^1 space of summable sequences.

One of the possible model applications is the modelling of drug resistance emergence in cancer cells and the analysis of possible chemotherapy protocols. Until now, treatment protocols have been designed mainly on the basis of experimental results and the general knowledge about the drug activity. However, no general mathematical approach exists which would help to explain the obtained results or to design a treatment in chemotherapy. The results of this work can be used to reveal the desired form of an optimal treatment protocol and to give some hints as to its development. It can be also employed in a qualitative analysis of the chosen protocol, taking into account both the increasing resistance to chemoterapeutic agents and allowing multidrug and phase-specific treatments.

The main application of the obtained results is in the field of biomedical modelling, from which the form of the performance index in the analysed problem stems. Nevertheless, taking into account the broad class of systems described by the presented model, it should easily be adapted for usage in other areas.

Acknowledgement

This work was partially supported by the grant of the State Committee for Scientific Research (KBN) in Poland No. 4T11F 01824.

References

Arino O., Kimmel M. and Webb G.F. (1995): *Mathematical modelling of the loss of telomere sequences*. — J. Theor. Biol., Vol. 177, No. 1, pp. 45–57.

Axelrod D.E., Baggerly K.A. and Kimmel M. (1994): *Gene amplification by unequal chromatid exchange: Probabilistic modelling and analysis of drug resistance data*. — J. Theor. Biol., Vol. 168, No. 2, pp. 151–159.

Bate R.R. (1969): *The optimal control of systems with transport lag*, In: Advances in Control and Dynamic Systems (C.T. Leondes, Ed.). — Academic Press, Vol. 7, pp. 165–224.

Brown B.W. and Thompson J.R. (1975): *A rationale for synchrony strategies in chemotherapy*, In: Epidemiology (D. Ludwig and K.L. Cooke, Eds.). — Philadelphia: SIAM Publ., pp. 31–48.

Coldman A.J. and Goldie J.H. (1986): *A stochastic model for the origin and treatment of tumors containing drug-resistant cells*. — Bull. Math. Biol., Vol. 48, No. 3–4, pp. 279–292.

Connor M.A. (1972): *Optimal control of systems represented by differential-integral equations*. — IEEE Trans. Automat. Contr., Vol. AC-17, No. 1, pp. 164–166.

Curtain R.F. and Zwart H.J. (1995): *An Introduction to Infinite-Dimensional Linear Systems Theory*. — New York: Springer.

Gabasov R. and Kirilowa F.M. (1971): *Qualitative theory of optimal processes*. — Moscow: Nauka, (in Russian).

Harnevo L.E. and Agur Z. (1993): *Use of mathematical models for understanding the dynamics of gene amplification*. — Mutat. Res., Vol. 292, No. 1, pp. 17–24.

Kimmel M. and Axelrod D.E. (1990): *Mathematical models of gene amplification with applications to cellular drug resistance and tumorigenicity*. — Genetics, Vol. 125, No. 3, pp. 633–644.

Kleinrock L. (1976): *Queuing Systems. Vol. 1: Theory*. — New York: Wiley.

Olofsson P. and Kimmel M. (1999): *Stochastic models of telomere shortening*. — Math. Biosci., Vol. 158, No. 1, pp. 75–92.

Polański A., Kimmel M. and Świerniak A. (1997): *Qualitative analysis of the infinite-dimensional model of evolution of drug resistance*, In: Advances in Mathematical Population Dynamics—Molecules, Cells and Man (O. Arino, D. Axelrod and M. Kimmel, Eds.). — Singapore: World Scientific, pp. 595–612.

Pontryagin L.S., Boltyanski V.G., Gamkrelidze R.V. and Mischenko E.F. (1962): *Mathematical Theory of Optimal Processes*. — New York: Wiley.

Ramel C. (1997): *Mini- and microsatellites*. — Environmental Health Perspectives, Vol. 105, Suppl. 104, pp. 781–789.

Śmieja J., Duda Z. and Świerniak A. (1999): *Optimal control for the model of drug resistance resulting from gene amplification*. — Prep. 14th IFAC World Congress, Beijing, China, Vol. L, pp. 71–75.

Śmieja J., Świerniak A. and Duda Z. (2000): *Gradient method for finding optimal scheduling in infinite dimensional models of chemotherapy*. — J. Theor. Med., Vol. 3, No. 1, pp. 25–36.

Swan G.W. (1990): *Role of optimal control theory in cancer chemotherapy*. — Math. Biosci., Vol. 101, No. 2, pp. 237–284.

Świerniak A., Śmieja J., Rzeszowska-Wolny J. and Kimmel M. (2001): *Random branching walk models arising in molecular biology—control theoretic approach*. — Proc. IASTED MIC Conf., Innsbruck, Austria, Vol. II, pp. 584–589.

Świerniak A., Kimmel M., Polański A. and Śmieja J. (1997a): *Asymptotic properties of infinite dimensional model of drug resistance evolution*. — Proc. ECC'97, Brussels, TU-A-C-4, CD-ROM.

Świerniak A., Polański A., Duda Z. and Kimmel M. (1997b): *Phase-specific chemotherapy of cancer: Optimisation of scheduling and rationale for periodic protocols*. — Biocybern. Biomed. Eng., Vol. 16, No. 1–2, pp. 13–43.

Świerniak A., Kimmel M. and Polański A. (1998): *Infinite dimensional model of evolution of drug resistance of cancer cells*. — J. Math. Syst. Estim. Contr., Vol. 8, No. 1, pp. 1–17.

Świerniak A., Polański A., Kimmel M., Bobrowski A. and Śmieja J. (1999): *Qualitative analysis of controlled drug resistance model—inverse Laplace and semigroup approach*. — Contr. Cybern., Vol. 28, No. 1, pp. 61–74.

Świerniak A., Polański A., Śmieja J., Kimmel M. and Rzeszowska-Wolny J. (2002): *Control theoretic approach to random branching walk models arising in molecular biology*. — Proc. ACC Conf., Anchorage, pp. 3449–3453.

Zadeh L.A. and Desoer C.A. (1963): *Linear System Theory. The State Space Approach*. — New York: McGraw-Hill.