MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **2**, Number **3**, August **2005**

http://www.mbejournal.org/

pp. **657–670**

ANALYSIS AND OPTIMIZATION OF DRUG RESISTANT AND PHASE-SPECIFIC CANCER CHEMOTHERAPY MODELS

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Abstract. This paper presents analysis and biomedical implications of a certain class of bilinear systems that can be applied in modeling of cancer chemotherapy. It combines models that so far have been studied separately, taking into account both the phenomenon of gene amplification and drug specificity in chemotherapy in their different aspects. The methodology of analysis of such models, based on system decomposition, is discussed. The mathematical description is given by an infinite dimensional state equation with a system matrix, the form of which allows decomposing the model into two interacting subsystems. While the first one, of a finite dimension, can have any form, the second one is infinite-dimensional and tridiagonal. Then the optimal control problem is defined in l^1 space. To derive necessary conditions for optimal control, the model description is transformed into an integrodifferential one.

1. **Introduction.** Our previous works (e.g., [15, 21]) dealt with models with a tridiagonal system matrix. They led to the development of a methodology for investigating such systems and formed a basis for further generalization. This work pushes the research a step further, studying properties of a model in which significantly less simplification has been made and less additional assumptions are required. Moreover, it combines models that so far have been studied separately, taking into account both the phenomenon of gene amplification and multidrug chemotherapy in their different aspects.

Two examples are discussed in this paper, each of them addressing different aspects of cancer cell modeling.

As the first one, a model taking into account partial sensitivity of the resistant subpopulation will be introduced. In this case, it is assumed that the resistant subpopulation consists of two parts–one sensitive to the drug (but, contrary to previous works, may contain cells of different drug sensitivity), and another, completely drug resistant.

In the second example, phase-specific control of the drug-sensitive cancer population will be addressed. Actually, each drug affects cells in specific phases, 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

2000 *Mathematics Subject Classification.* 92D25, 93C23, 92C50.

Key words and phrases. biomedical modeling, infinite dimensional systems, multivariable control.

considered with no 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 modeling much closer to its clinical application. Despite a long history of research and rich literature devoted to problems of modeling and control of infinite dimensional systems, almost all efficient methods developed to deal with them present approaches suitable for partial differential equations (PDE) models, and optimisation solutions are often limited to linear–quadratic (LQ) problems. More general solutions, involving abstract differential equations [6], 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 [9, 12] that are analysed in this paper, they may also describe, for example, resistor–capacitor ladders, which are approximations of long transmission lines [23]; microsatellite repeats evolution [22] which plays an important role in genetic disorders [14]; telomere shortening [1, 11] responsible for cell aging and death; or some queuing systems [10]. Usually, additional assumptions are made, resulting in system matrices of tridiagonal form. Moreover, analysis of such models is often limited to their finite-dimensional approximation. However, in that case, some dynamical properties may be neglected. Moreover, as shown in our previous papers (e.g., [18, 20]), 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 approximation.

2. **Problem statement.** The original model and its properties have been thoroughly discussed (see, e.g., [20, 21]). However, the basic underlying biological background remains the same for the subject of this paper and therefore needs to be introduced in brief.

In this section, a model of cell population with evolving drug resistance caused by gene amplification or other mechanisms is presented. The model, based on the results of [2, 8, 9], is general enough to accommodate different interpretations.

We consider a population of neoplastic cells stratified into subpopulations of cells of different types, labeled 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 or cytotoxic agent. Through a mutation the sensitive cell of type 0 can acquire a copy of gene that makes it resistant to the agent. Likewise, the resistant cells can change the number of gene copies in the process of cell division. 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 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 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 $1/\lambda_i$ 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 α is several orders of magnitude smaller than any of b_is or d_is.

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

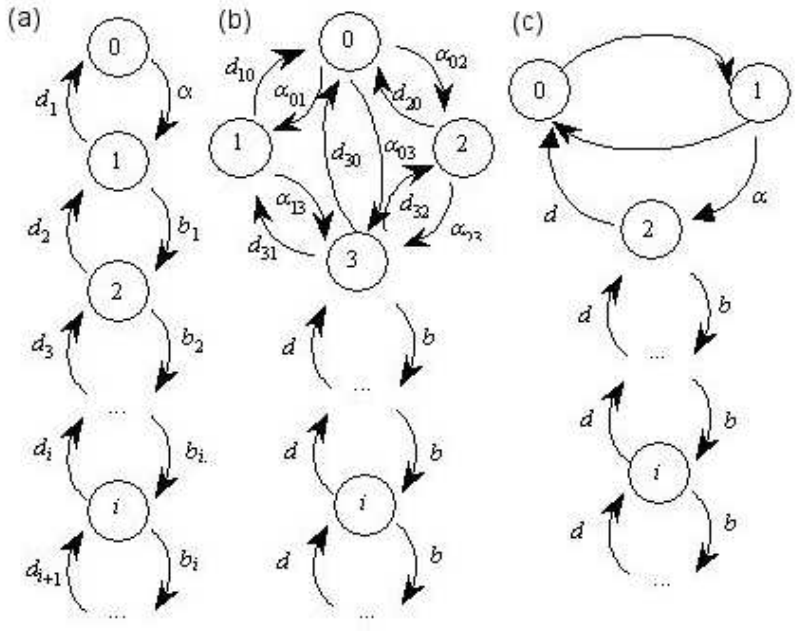

FIGURE 1. Flows between subpopulations for the model, taking into account (a) the original assumptions or the partial sensitivity of the resistant subpopulation; (b) two-drug chemotherapy; (c) phase-specific chemotherapy. In all cases, numbers denote cell types.

The graph representing the possible flows between subpopulations is presented in the Figure 1a. 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 ordinary differential equations (ODEs)

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

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

$$\begin{cases} \dot{N}_0(t) = & [1-2u(t)]\lambda N_0(t) - \alpha N_0(t) + d N_1(t), \\ \dot{N}_1(t) = & \lambda N_1(t) - (b+d)N_1(t) + d N_2(t) + \alpha N_0(t), \\ \cdots, & \\ \dot{N}_i(t) = & \lambda N_i(t) - (b+d)N_i(t) + d N_{i+1}(t) + b N_{i-1}(t), \\ \cdots, & \qquad i \geq 2. \end{cases} \tag{2}$$

However, using the same line of reasoning that has been applied to that case, it is also possible to analyze a less simplified model. If it is assumed that the parameters can vary for an arbitrarily chosen finite number of cell subpopulations and are the same only for the infinite-dimensional tail of the system, the following model can be investigated:

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

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

Several control problems arising in all these cases may be addressed by the model presented in the paper. One of those problems is establishing constant control u (in that case it leads to the determination of feedback parameters) that stabilizes the infinite-dimensional system. In biological terms, it refers to calculation of a constant dose rate of a chemotherapeutic agent that suppresses the growth of the resistant subpopulation. However, the constant treatment protocol, which guarantees decay of the cancer population after sufficiently long time, is unrealistic. Most of all, it does not take into account the cumulative negative effect of the drug on normal tissues. To make the solution more realistic, it is justifiable to find the optimal control, which minimizes the performance index,

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

where $r_1, r \geq 0$ are weighing factors, m is the number of drugs being used, and T represents the time horizon for chemotherapy.

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

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

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

where $0 \leq \mu_i \leq 1$ are "efficiency factors" that determine the effectiveness of the drug in relation to a particular type of cell. Given the general assumptions about the model, presented at the beginning of this section, these factors satisfy the following relations:

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

$$0 \leq u \leq u_{max} \leq 1. \tag{7}$$

4. **Phase-specific control of the drug-sensitive cancer population.** The cell cycle is composed of a sequence of phases that each cell undergoes from its birth to its division. Actually, each drug affects cells that are in a particular phase and it makes sense to combine these drugs so that their cumulative effect on the cancer population will be the greatest. So far, phase-specific chemotherapy has been considered only in the finite-dimensional case, with no regard to problems stemming from increasing drug resistance [17, 18]. Combining the infinite-dimensional model of drug resistance with the phase-specific model of chemotherapy should move mathematical modeling 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 $i = 0$, in the phase $G_1 + S$, and $i = 1$, 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:

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

where α is the intensity of the primary mutational event as in model (1).

The graph illustrating possible transfers between different subpopulations is presented in Figure 1c.

Similarly, multidrug therapy that includes blocking drugs [4, 19] as well as the killing agent (or multiple killing agents) could be analysed in the same way. One of the simplest possible scenarios in which there are two drugs and the cells can be sensitive to both of them, resistant to one, or resistant to both drugs (the infinite-dimensional tail has the same interpretation as in the model given by (2)) is presented in Figure 1b. The mathematical form of such a model is not discussed in detail, since a more general case can be addressed in which there are many different compartments, representing various drug actions and various forms of drug resistance. The mathematical framework for that modeling is presented in the subsequent sections.

5. **Properties of the models.** The system is described by the following state equation:

$$\dot{\mathbf{N}} = \left(\mathbf{A} + \sum_{i=0}^{m} u_i \mathbf{B_i} \right) \mathbf{N}. \tag{9}$$

where $\mathbf{N} = [N_0\ N_1\ N_2\ \ldots\ N_i\ \ldots]'$ is an infinite-dimensional state vector ($'$ denotes transposition); $\mathbf{A}$ and $\mathbf{B}$ are the system and control matrices, respectively, of the form

$$\mathbf{A} = \begin{bmatrix} \tilde{\mathbf{A}}_1 & & | & \mathbf{0}_1 \\ - & - & - & - \\ \mathbf{0}_2 & | & \tilde{\mathbf{A}}_2 & \end{bmatrix}, \tag{10}$$

$$\mathbf{B_i} = \begin{bmatrix} \tilde{\mathbf{B}}_i & | & \mathbf{0}_1 \\ - & - & - \\ & \mathbf{0}_3 & \end{bmatrix}, \tag{11}$$

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

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

$$\tilde{\mathbf{B}}_\mathbf{i} = \begin{bmatrix} b^i_{0,0} & b^i_{0,1} & \dots & b^i_{0,l-1} \\ b^i_{1,0} & b^i_{1,1} & \dots & b^i_{1,l-1} \\ \vdots & \vdots & \dots & \vdots \\ b^i_{l-1,0} & b^i_{l-1,1} & \dots & b^i_{l-1,l-1} \end{bmatrix};$$

$\mathbf{u}(t)$ is the m-dimensional control vector $\mathbf{u} = [u_0 u_1 u_2 \dots u_{m-1}]'$, $\mathbf{0_1}, \mathbf{0_2}, \mathbf{0_3}$- zero matrices of dimensions $l \times \infty$, $\infty \times l-1$, and $\infty \times \infty$, respectively; and $l > m$.

It is important to note that the model parameters satisfy the following relations: $a_3 > a_1 > 0$ and $a_2 < 0$. However, a 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 performance index to be minimised is given by (4). The specific structure of system and control matrices may be used to decompose the system for its analysis as well as optimal control synthesis.

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

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

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

Using methods similar to those demonstrated in our previous work devoted to biomedical modeling [16, 21], it is possible to show that for initial condition $N_i(0) = \delta_{ik}$ (Kronecker delta)–that is $N_k(0) = 1, N_i(0) = 0$ for $i \neq k$–the following relations hold true:

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

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

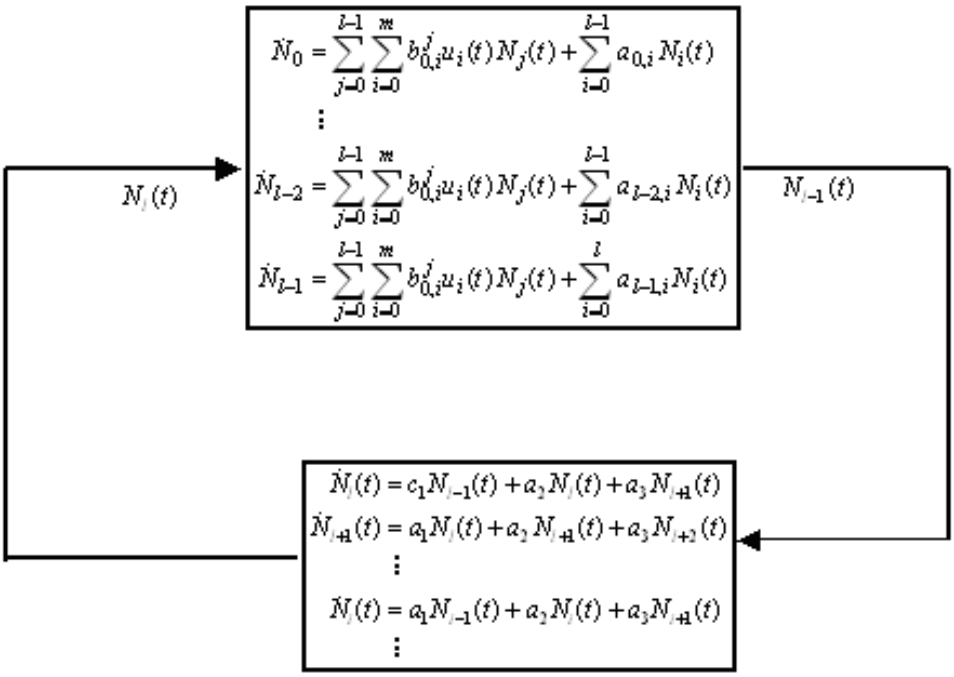

FIGURE 2. Decomposition of the system model.

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

$$N_l^l(t) = \frac{1}{a_3}\left(\sqrt{\frac{a_3}{a_1}}\right)\frac{I_1\left(2\sqrt{a_1 a_3}t\right)}{t}\exp(a_2 t) \tag{15}$$

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

where $I_1(t)$ is a 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 applicability of the model. Because of the infinite-dimensional tail's linearity any finite non-zero initial condition can be incorporated into the final solution.

Using an asymptotic expansion of (16) it has been found [12] that, assuming $a_3 \geq a_1$, a stability condition for the autonomous system is given by

$$a_2 \leq -2\sqrt{a_1 a_3}. \tag{17}$$

To understand the implications of those conditions, let us rewrite them using biological parameter notation. Then, they can be presented as $d \geq b$ and $\sqrt{d}-\sqrt{b} \geq \sqrt{\lambda}$. The first, assumed inequality is confirmed by experimental data, and it means that the amplification ratio should not be greater than the deamplification ratio. Surprisingly, this is not sufficient to the stability of the autonomous system (it does not lead to the extinction of the resistant subpopulation when there is no influx of cells from the sensitive compartment). The additional condition implies that the difference in those rates must be large enough to prevent amplification before cells divide (parameter λ corresponds to the cell lifespan).

Relation (13) can be used to determine the following transfer function in the model (9):

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

Moreover,

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

where

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

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

Let us now introduce the following notation:

$$\hat{\mathbf{B}}_1 = \begin{bmatrix} 0 \\ \vdots \\ 0 \\ a_{l-1,l} \end{bmatrix}, \quad \mathbf{C} = [0, \ldots, 0, 1], \quad \dim \mathbf{C} = l. \tag{21}$$

Then, applying standard control theory techniques [23], the following relation holds true for $u(t) = 0$:

$$\mathbf{K}_2(s) = \frac{N_{l-1}(s)}{N_l(s)} = \mathbf{C}(s\mathbf{I} - \tilde{\mathbf{A}}_1)^{-1}\hat{\mathbf{B}}_1. \tag{22}$$

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

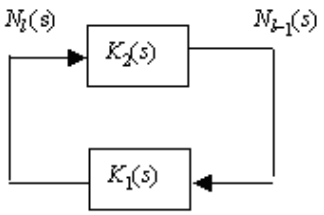

FIGURE 3. Block diagram of the system without control.

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

$$\mathbf{K}_2(s) = \frac{N_{l-1}(s)}{N_l(s)} = \mathbf{C}\left[s\mathbf{I} - \left(\tilde{\mathbf{A}}_1 + \sum_{i=0}^{m}\tilde{\mathbf{B}}_i\right)\right]^{-1}\hat{\mathbf{B}}_1 \tag{23}$$

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

7. **Optimization problem.** The system description (9) in the form of an infinite number of ODEs, is not very convenient, although it may be used in different approaches to optimization problems that will be considered in this section. Instead, a model transformation into an integrodifferential one is proposed.

Let us denote

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

and $\mathbf{C_k} = [c_j], c_k = 1, c_j = 0$ for $j \neq k$, $i = 1, 2, \ldots, l-1$.

Let us also assume the initial conditions $N_i(0) = 0$ for $i > l-1$ (once again it should be stressed that any finite nonzero initial condition can be incorporated into the final solution). Then, the last equation in the first subsystem, influenced directly by control, as presented in Figure 2, can be transformed into an integrodifferential form:

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

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:

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

where $\mathbf{h}(..), \tilde{\mathbf{f}}(...)$ are the respective l–dimensional vector functions

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

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

After transforming the system description, it is possible to address effectively the arising optimal control problem.

Let the system be governed by equation (9), which afterwards is transformed into the form (26). The control is bounded:

$$0 \leq u_i(t) \leq u_{imax} \leq 1, \quad i = 0, 1, \ldots, m, \tag{29}$$

where $u_i(t) = u_{imax}$ represents the maximum allowable dose of the drug i and $u_i(t) = 0$ represents no application of the drug i. 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 by applying an appropriate version of Pontryagin's maximum principle [13].

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)–(20). Therefore, it should be rewritten to emphasize this relation:

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

A number of formulations of necessary conditions for the optimization problem for dynamical systems governed by integro-differential equations can be found in the literature (see, e.g., [3, 5, 7]). However, they usually are either too general to be efficiently applied in such a particular problem or have overly strong constraints–for example, smoothness of the control function. Nevertheless, following the line of reasoning presented in [3], it is possible to derive the necessary conditions for optimal control:

$$\mathbf{u}^{opt}(t) = \arg\min_{\mathbf{u}} \left[r \sum_{k=0}^{m} u_k(t) + \mathbf{p}'(t)\mathbf{h}(\mathbf{u}, \tilde{\mathbf{N}}) + a_{l-1,l} \int_t^{'} p_{l-1}(\tau) k_1(t-\tau) N_{l-1}(\tau) d\tau \right], \quad (31)$$

$$\dot{\mathbf{p}}'(t) = -\left[\mathbf{q}'(t) + \mathbf{p}'(t)\mathbf{h}_{\tilde{N}}(\mathbf{u}, \tilde{\mathbf{N}}) + \int_t^{'} \mathbf{p}'(\tau) \tilde{\mathbf{f}}_{\tilde{N}}(t-\tau) d\tau \right], \quad (32)$$

$$\mathbf{q}(t) = \left[\begin{array}{cccc} 0 & \dots & 0 & r_1 c_1 N_\Sigma^l(T-t) \end{array} \right]', \quad (33)$$

$$p_i(T) = 1, \quad i = 0, 1, \dots, l-1, \quad (34)$$

where $\mathbf{p}(t)$ is an adjoint vector.

Taking into account constraint (7) and the bilinear form of (27), it can be proved that to satisfy (31), the optimal control must be of bang-bang type. Then, to find the optimal number of switches and switching times, a gradient method can be developed, following the line of reasoning presented in [15].

8. **Conclusions.** This paper is concerned with an infinite-dimensional bilinear model of dynamical systems. Basing on model decomposition, it is possible to analyze some of their dynamical properties. Transforming the system description into one integrodifferential equation makes it possible to solve an optimal control problem with the performance index defined in l^1 space of summable sequences.

Possible applications of the model presented in this paper include modeling of emergence of drug resistance in cancer cells and analyzing possible chemotherapy protocols. Until now, the treatment protocols have been designed mainly on the basis of experimental results and general knowledge about drug activity. However, no general mathematical approach exists that would help to explain obtained results or design treatment in chemotherapy.

It should be stressed that the control **u** in the model represents the effect of the drug action and not the time course of the drug treatment (in particular, the drug concentration). Therefore, further research is crucial to establish the relation between those variables, taking into account both the pharmacokinetics of different agents used in chemotherapy and the spatial distribution of drug concentration in growing cancer tissue.

In our opinion, this model can be used as a basis for other research concerning the development of drug resistance and the evolution of populations of cancer cells. So far the population evolution is more suited to such cancers as leukemia. However, combining it with models of the spatial growth of solid tumors seems to be very promising, and in fact it is a subject of our future research. Another possible extension of this work, though apparently much more difficult and distant in the future, is relating drug effects given by control **u** to actual drug administration.

Acknowledgments. This work was supported partially by an internal grant of the SUT, no. BK/Rau1/2005, and partially by a collaborative Polish American grant financed jointly by the National Science Foundation and Polish Academy of Sciences in 2003 and 2004 and by the European FP6 network, no. MRTN-CT-2004-503661.

REFERENCES

[1] O. Arino, M. Kimmel and G.F. Webb, Mathematical modeling of the loss of telomere sequences, J. Theor. Biol. 177 (1995) 45–57.

[2] D.E. Axelrod, K.A. Baggerly and M. Kimmel, Gene amplification by unequal chromatid exchange: Probabilistic modeling and analysis of drug resistance data, J. Theor. Biol. 168 (1994) 151-159.

[3] R.B. Bate, The optimal control of systems with Transport Lag, Advances in Control Systems, 7 (1969) 165–224.

[4] B.W. Brown and J.R. Thompson, A rationale for synchrony strategies in chemotherapy, in Epidemiology, SIAM Publ., Philadelphia, 31–48, 1975.

[5] M.A. Connor, Optimal control of systems represented by differential-integral equations, IEEE Trans. on Automatic Control, AC-17 (1972) 164–166.

[6] R.F. Curtain and H.J. Zwart, An introduction to infinite-dimensional linear systems theory, Springer–Verlag, New York, 1995.

[7] R. Gabasov and F.M. Kirilowa, Qualitative theory of optimal processes, Nauka, Moscow, 1971.

[8] L.E. Harnevo and Z. Agur, Use of mathematical models for understanding the dynamics of gene amplification, Mutat Res 292 (1993) 17–24.

[9] M. Kimmel and D.E. Axelrod, Mathematical models of gene amplification with applications to cellular drug resistance and tumorigenicity, Genetics 125 (1990) 633–644.

[10] L. Kleinrock, Queuing Systems, vol.1, Theory, Wiley, New York, 1975.

[11] P. Olofsson and M. Kimmel, Stochastic models of telomere shortening, Math Biosci 158 (1999) 75–92.

[12] A. Polanski, M. Kimmel and A. Swierniak, Qualitative analysis of the infinite-dimensional model of evolution of drug resistance, in Advances in Mathematical Population Dynamics—Molecules, Cells and Man, World Scientific, 595–612, (1997).

[13] L.S. Pontryagin, V.G. Boltyanski, R.V. Gamkrelidze and E.F. Mischenko, Mathematical theory of optimal processes, Wiley, New York, (1962).

[14] C. Ramel, Mini- and microsatellites, Environ. Health Persp. 105 (1997) 781–789.

[15] J. Smieja, Z. Duda and A. Swierniak, Optimal Control for the Model of Drug Resistance Resulting from Gene Amplification, 14th World Congress of IFAC, preprint L (1999) 71–75.

[16] J. Smieja, A. Swierniak and Z. Duda, Gradient Method for Finding Optimal Scheduling in Infinite Dimensional Models of Chemotherapy, J. Theor. Med. 3 (2000) 25–36.

[17] G.W. Swan, Role of optimal control theory in cancer chemotherapy, Math Biosci 101 (1990) 237–284.

[18] A. Swierniak, M. Kimmel, A. Polanski and J. Smieja, Asymptotic Properties of Infinite Dimensional Model of Drug Resistance Evolution, Proc. ECC'97, Brussels, CD-ROM, Summary in vol.1, (1997), TU-A-C-4.
[19] A. Swierniak, A. Polanski, Z. Duda and M. Kimmel, Phase-Specific Chemotherapy of Cancer: Optimisation of Scheduling and Rationale for Periodic Protocols, Biocybernetics and Biomed. Eng. 16 (1997) 13–43.
[20] A. Swierniak, M. Kimmel and A. Polanski Infinite dimensional model of evolution of drug resistance of cancer cells, J. Math. Syst. Estim. Cont. 8 (1998) 1–17.
[21] A. Swierniak, A. Polanski, M. Kimmel, A. Bobrowski and J. Smieja, Qualitative analysis of controlled drug resistance model - inverse Laplace and semigroup approach, Control and Cybernetics 28 (1999) 61–74.
[22] A. Swierniak, A. Polanski, J. Smieja, M. Kimmel and J. Rzeszowska-Wolny, Control theoretic approach to random branching walk models arising in molecular biology, Proc. ACC Conf. (2002) 3449–3453.
[23] L.A. Zadeh and C.A. Desoer, Linear System Theory. The State Space Approach, McGraw-Hill, New York, 1963.

Received on January 1, 2005. Revised on August 8, 2005.

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