drug resistance, branching random walk,
infinite-dimensional systems, Laplace transforms

Andrzej ŚWIERNIAK[*], Marek KIMMEL[**],
Jarosław ŚMIEJA[*], Joanna RZESZOWSKA-WOLNY[***]

ARE INFINITE DIMENSIONAL MODELS APPLICABLE IN MODELLING AND ANALYSIS OF CANCER CHEMOTHERAPY?

Drug resistance and phase dependence have been regarded by many authors as the main obstacles against successful cancer chemotherapy. We propose a model which takes into account both these phenomena and give a tool to use phase specificity as an advantage rather than a fault and make it resistant of drug resistance. 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 mathematical description is given by an infinite dimensional state equation with a system matrix, the form of which enables decomposition of the model into two interacting subsystems. While the first one, of finite dimension, can have any form, the second one is infinite dimensional and tridiagonal.

1. INTRODUCTION

Models based on infinite number of state equations may be applied to a variety of systems. In our previous papers e.g. [1], [2] studies of infinite dimensional models may were shown to lead to compact results, convenient in further analysis, which would be impossible or very difficult to obtain in finite dimensional approximation.

In this paper phase-specific control of the drug-sensitive cancer population will be addressed. 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 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.

[*] Department of Automatic Control, Silesian University of Technology, Akademicka 16, 44-101 Gliwice, Poland
[**] Department of Automatic Control, Silesian University of Technology, Akademicka 16, 44-101 Gliwice, Poland and Department of Statistics, Rice University, Houston TX 77251, USA
[***] Department of Clinical and Experimental Biology, Institute of Oncology Branch Gliwice, 44-101 Gliwice, Poland

2. BRANCHING RANDOM WALK MODEL IN DRUG RESISTANCE MODELS

The original model and its properties were thoroughly discussed in [4], [5]. However, the basic underlying biological background remains the same also for the subject of this paper and therefore needs to be introduced in brief.

In this section certain model of cell population with evolving drug resistance caused by gene amplification or other mechanisms is presented. The model which follows the idea proposed in [2] is general enough to accommodate different interpretations.

We consider a population of neoplastic cells stratified into subpopulations of cells of different types, labelled by numbers $i = 0,1,2, \ldots$. 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 $i = 1,2, \ldots$. 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 countably 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 α 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, and we assume the simplest case, in which the resistant cells are insensitive to drug's action, and there are no differences between parameters of cells of different type, the model is described by the following system of ODE's

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

So far, only 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:

$$\begin{cases} \dot{N}_0(t) = [1-2u(t)]\lambda N_0(t) - \alpha N_0(t) + dN_1(t) \\ \dot{N}_1(t) = \lambda N_1(t) - (b+d)N_1(t) + dN_2(t) + \alpha N_0(t) \\ \quad \dots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) + dN_{i+1}(t) + bN_{i-1}(t),\ i \geq 2 \\ \quad \dots \end{cases} \tag{2}$$

However, using the same line of reasoning that has been applied to that case, it is also possible to analyse less simplified model. 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:

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

Moreover, multivariable control is allowed, meaning that either certain types of the resistant cells can be affected by chemotherapy or that different drugs are being used. One possible control problem is establishing constant control u 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:

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

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.

3. PHASE SPECIFIC CONTROL OF DRUG RESISTANT POPULATION

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 e.g. [6]. 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

$$\begin{cases} \dot{N}_0(t) = -\lambda_0 N_0(t) + [1-u(t)](2\lambda_1 - \alpha)N_1(t) + dN_2(t) \\ \dot{N}_1(t) = -\lambda_1 N_1(t) + \lambda_0 N_0(t) \\ \dot{N}_2(t) = \lambda_2 N_2(t) - (b+d)N_2(t) + \alpha N_1(t) + bN_3(t) \\ \qquad \cdots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) + dN_{i+1}(t) + bN_{i-1}(t), \quad i \geq 3 \\ \qquad \cdots \end{cases} \tag{5}$$

Similarly, multidrug therapy including blocking drugs as well as the killing agent could be analysed in the same way, as presented in the subsequent sections.

Thus the system belongs to the following class of state equation models:

$$\dot{N} = \left(\mathbf{A} + \sum_{i=0}^{m} u_i \mathbf{B}_i \right) N, \tag{6}$$

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

$$\mathbf{A} = \begin{bmatrix} \widetilde{\mathbf{A}}_1 & | & \mathbf{0}_1 \\ - & - & - \\ \mathbf{0}_2 & | & \widetilde{\mathbf{A}}_2 \\ & | & \end{bmatrix}, \qquad \mathbf{B} = \begin{bmatrix} \widetilde{\mathbf{B}}_i & | & \mathbf{0}_1 \\ - & - & - \\ & \mathbf{0}_3 & \end{bmatrix} \tag{7}$$

$$\widetilde{\mathbf{A}}_1 = \begin{bmatrix} a_{00} & a_{01} & \dots & a_{0,l-1} & 0 \\ a_{10} & a_{11} & \dots & a_{1,l-1} & 0 \\ \vdots & \vdots & \dots & \vdots & 0 \\ a_{l-1,0} & a_{l-1,1} & \dots & a_{l-1,l-1} & a_{l-1,l} \end{bmatrix}, \quad \widetilde{\mathbf{A}}_2 = \begin{bmatrix} c_1 & a_2 & a_3 & 0 & 0 & \dots \\ 0 & a_1 & a_2 & a_3 & 0 & 0 \dots \\ 0 & 0 & a_1 & a_2 & a_3 & 0 \dots \\ \vdots & \vdots & \ddots & \ddots & \ddots & \ddots \ddots \end{bmatrix}, \quad \widetilde{\mathbf{B}}_i = \begin{bmatrix} b^i_{0,0} & b^i_{0,1} & \dots & b^i_{0,l-1} \\ b^i_{1,0} & b^i_{1,1} & \dots & b^i_{1,l-1} \\ \vdots & \vdots & \dots & \vdots \\ b^i_{l-1,0} & b^i_{l-1,1} & \dots & b^i_{l-1,l-1} \end{bmatrix}$$

$u(t)$ – m-dimensional control vector $u = [u_0\, u_1\, u_2 \dots u_{m-1}]^{\mathrm{T}}$, $\mathbf{0}_1$, $\mathbf{0}_2$, $\mathbf{0}_3$– zero matrices of dimensions ∞ x l–1, l–2 x ∞ and ∞ x ∞, 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, full 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).

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

$$\begin{cases} \dot{N}_l(t) = a_2 N_l(t) + a_3 N_{l+1}(t) \\ \dot{N}_{l+1}(t) = a_1 N_l(t) + a_2 N_{l+1}(t) + a_3 N_{l+2}(t) \\ \dots \\ \dot{N}_i(t) = a_1 N_{i-1}(t) + a_2 N_i(t) + a_3 N_{i+1}(t) \\ \dots \end{cases} \tag{8}$$

Using methods similar to that shown in our previous works devoted to biomedical modelling 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:

$$N_l^k(s) = \frac{1}{a_3}\left(\frac{s - a_2 - \sqrt{(s-a_2)^2 - 4a_1a_3}}{2a_1} \right)^{k-l+1} \tag{9}$$

$$N_\Sigma^k(s) = \frac{1}{s - (a_1 + a_2 + a_3)}\left[1 - \left(\frac{s - a_2 - \sqrt{(s-a_2)^2 - 4a_1a_3}}{2a_1} \right)^{k-l+1} \right] \tag{10}$$

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). Now, let us assume that $k = l$. Then, after calculating inverse Laplace transform the following formulae are obtained:

$$N_l^l(t) = \frac{1}{a_3}\left(\sqrt{\frac{a_3}{a_1}} \right) \frac{I_1\left(2\sqrt{a_1a_3}\, t\right)}{t} \exp(a_2 t) \tag{11}$$

$$N_{\Sigma}^{l}(t)=\sum_{i\geq l}N_i(t)=\exp\left[(a_1+a_2+a_3)t\right]\cdot\left[1-\left(\sqrt{\frac{a_3}{a_1}}\right)\int_0^t\frac{I_1\left(2\sqrt{a_1a_3}\ \tau\right)}{\tau}\exp\left[-(a_1+a_3)\tau\right]d\tau\right] \qquad (12)$$

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

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

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

$$a_2 \leq -2\sqrt{a_1a_3} \qquad (13)$$

Now we can determine the following transfer function:

$$K_1(s)=\frac{N_l(s)}{N_{l-1}(s)}=\frac{c_1}{a_3}\frac{s-a_2-\sqrt{(s-a_2)^2-4a_1a_3}}{2a_1} \qquad (14)$$

Moreover

$$\sum_{i\geq l}N_i(t)=N_{\Sigma}^{l}(t)+N^{+}(t) \qquad (15)$$

where

$$N^{+}(t)=c_1\int_0^t N_{\Sigma}^{l}(t-\tau)N_{l-1}(\tau)d\tau \qquad (16)$$

and $N_{\Sigma}^{l}(t)$ is defined by (12).

Let us now introduce the following notation:

$$\hat{\mathbf{B}}_1=\begin{bmatrix}0\\ \vdots\\ 0\\ a_{l-1,l}\end{bmatrix},\ \mathbf{C}=[0,...,0,1]\text{ – l-dimensional vector} \qquad (17)$$

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

$$K_2(s)=\frac{X_{l-1}(s)}{X_l(s)}=\mathbf{C}(s\mathbf{I}-\tilde{\mathbf{A}}_1)^{-1}\hat{\mathbf{B}}_1\,. \qquad (18)$$

Taking into account linear form of such system, it is possible to present the model in the form of block diagram shown in Fig.1. This makes it possible to analyse dynamical properties of the closed-loop system.

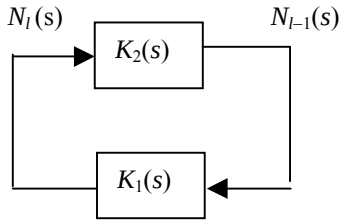

Fig. 1. Block diagram of the system without control

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

Then, the transfer function $K_2(s)$ representing the finite dimensional subsystem in the Fig. 1 takes the following form:

$$K_2(s) = \frac{X_{l-1}(s)}{X_l(s)} = \mathbf{C}[s\mathbf{I} - (\tilde{\mathbf{A}}_1 + \sum_{i=0}^{m} \tilde{\mathbf{B}}_i)]^{-1} \hat{\mathbf{B}}_1 . \qquad (19)$$

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

The system description in the form of infinite number of ODEs, although may be used in different approaches to optimisation problems that will be considered in next section, is not very convenient. Instead, a model transformation into integro-differential one may be proposed.

Let us denote

$\mathbf{C_k} = [c_j,]$, $c_k = 1$, $c_j = 0$ for $j \neq k$, i = 1,2, ... 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 non-zero initial condition can be incorporated into the final solution). Then, the last equation in the first subsystem, influenced directly by control, can be transformed into an integro-differential form:

$$\dot{N}_{l-1}(t) = \sum_{j=0}^{l-1} \sum_{i=0}^{m} b_{l-1,i}^{j} u_i(t) N_j(t) + \sum_{i=0}^{l-1} a_{l-1,i} N_i(t) + a_{l-1,l} \int_0^t k_1(t-\tau) N_{l-1}(\tau) d\tau , \qquad (20)$$

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

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

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's maximum principle. 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 (17. Therefore, it should be rewritten to emphasise this relation:

$$J = \sum_{i=0}^{l-1} N_i(T) + r_1 N_\Sigma^l(T) + \int_0^T \left[r_1 c_1 N_\Sigma^l(T-\tau) N_{l-1}(\tau) + r \sum_{k=0}^{m} u_k(\tau) \right] d\tau \qquad (21)$$

A number of formulations of necessary conditions for the optimisation problem for dynamical systems governed by integro-differential equations can be found in literature. 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. We have followed the line of reasoning presented in [1], it is possible to derive the necessary conditions for optimal control which allow us to find that 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, following the line of reasoning presented in [3].

4. CONCLUSION

In this paper we have shown applicability of infinite-dimensional models to analysis and design of cancer chemotherapy. Basing on model decomposition, it is possible to analyse analytically and numerically some of their dynamical properties. The transformation of system description into one integro-differential equation allows solving an optimal control problem which takes into account also a cumulative negative effect on critical normal tissues.

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The first three authors were supported by internal grant of SUT BW/Rau1/2004