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OPTIMAL MULTIDRUG TREATMENT IN THE PRESENCE OF DRUG RESISTANCE STEMMING FROM GENE AMPLIFICATION

The paper is concerned with development of optimal treatment protocols that take into account both action of several drugs and the evolution of drug resistance. It is a result of analysis of evolution of drug resistance in cancer population but presented methodology can be applied in any case involving drug resistance stemming from gene amplification. First, a biological background is given. In subsequent sections of the paper, the developed technique is presented and some early analytical results, which form a basis for more precise modeling, are shown. Afterwards, the model description is transformed into a vector integro-differential equation, which makes it possible to define necessary conditions of optimal solution to the minimization problem arising from the search for the optimal treatment. Finally, some remarks on the model applicability are presented.

1. INTRODUCTION

We present a system of models of cancer chemotherapy based on a stochastic approach to evolution of cancer cells.

Despite a long history of mathematical modeling of cancer chemotherapy its practical application to development of chemotherapy protocols has been arguably negligible (with minor exceptions). However, one cannot underestimate its importance in the development of ideas of chemotherapy scheduling, multidrug protocols, and recruitment.

Two issues addressed below have not been studied in one model so far, due to their mathematical complexity, and no successful approach to take into account both of them is known to authors of this paper. These issues are: the dynamics of emergence of resistance of cancer cells to chemotherapy stemming from gene amplification and multidrug chemotherapy protocols.

Asymptotic analysis of the models results in some understanding of their dynamics and reveals their unique features. This is the first step towards appropriate mathematical modeling of the dynamics of drug resistance and/or metastasis, as well as optimal treatment protocols.

A factor that can have a strong influence on the evolution of drug resistance of cancer cells is gene amplification. This process includes an increase in the number of copies of a gene coding for a protein that supports either removal or metabolization of the drug. The more copies of the gene present, the more resistant the cell, in the sense that it can survive under higher concentrations of

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the drug. Increase of drug resistance by gene amplification has been observed in numerous experiments with *in vivo* and cultured cell populations (see e.g. [4] and [10]). In addition, it has been established that, at least in some experimental systems, tumor cells may increase the number of copies of an oncogene in response to unfavorable environment [3].

Mathematical modeling of gene amplification has provided good fits to experimental data [1, 2, 3, 4]. For example, models with gene amplification predict the observed pattern of gradual loss of resistance in cancer cells placed in a non-toxic medium. The multistage stepwise model of gene amplification or, more generally, of transformations of cancer cells, leads to new mathematical problems and results in novel dynamic properties of the systems involved. These problems were first studied mathematically in [3] for the time-discrete models and in [4] for the time-continuous models. In this paper, we stress the same aspect of drug resistance as Harnevo and Agur [2]. Therefore, we consider models based on amplification of the resistance gene up to a very large number of copies. Our approach is to study basic mathematical properties of the models, in hope they will be of help in understanding the control problem.

The motivation behind it is that most of existing forms of therapy consist in using several drugs, instead of a single one. Then, modeling should take into account increasing drug resistance to each of the used chemotherapeutic agents.

2. PROBLEM FORMULATION

Let us consider the case of simultaneously using two types of drugs. The methodology presented below makes it possible to address also more complex protocols, however, for the sake of clarity, only two drugs are taken into account in the considerations.

Let us assume the simplest case, in which the resistance of the cells means that they are insensitive to drug's action, and there are no differences between parameters of cells of different type. 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 first and second agent, respectively, and type $i \geq 3$ that is resistant to both drugs. The second hypothesis for the model proposed at the beginning of this section has to be modified in the following way:

A cell of type $i = 0$ may mutate in a short time interval $(t, t+dt)$ into a type 1 cell with probability $\alpha_{01}\, dt + o(dt)$, into a type 2 cell with probability $\alpha_{02}\, dt + o(dt)$ or into a type 3 cell with probability $\alpha_{03}\, dt + o(dt)$.

Each cell of type $i = 1$ or $i = 2$ may mutate in a short time interval $(t, t+dt)$ into a type 3 cell with probability $\alpha_{13}\, dt + o(dt)$ and $\alpha_{23}\, dt + o(dt)$ respectively, or into a type 0 cell with probability $d_{10}\, dt + o(dt)$ and $d_{20}\, dt + o(dt)$, respectively

A cell of type $i = 3$ may mutate in a short time interval $(t, t+dt)$ into a type 0, 1 or 2 cell with probability $d_{30}\, dt + o(dt)$, $d_{31}\, dt + o(dt)$ and $d_{32}\, dt + o(dt)$, respectively, or into a type 4 cell with probability $b\, dt + o(dt)$.

A cell of type $i \geq 4$ may mutate in a short time interval $(t, t+dt)$ into a type $i+1$ cell with probability $b\, dt + o(dt)$ and into type $i-1$ cell with probability $d\, dt + o(dt)$., where $\alpha_{i\varphi}$ is several orders of magnitude smaller than b and d.

The chemotherapeutic agent affects cells of different types differently. It is assumed that its action results in fraction u_i of ineffective divisions in cells of type i (hence $0 \leq u_i \leq 1$).

If we denote by $N_i(t)$ the expected number of cells of type i at time t, we obtain the following infinite system of differential equations:

$$\begin{cases} \dot{N}_0(t) = \left[1 - \beta_0 u_0(t) - \beta_1 u_1(t)\right]\lambda N_0(t) \\ \qquad - \left(\alpha_{01} + \alpha_{02} + \alpha_{03}\right)N_0(t) + \\ \qquad d_{10}N_1(t) + d_{20}N_2(t) + d_{30}N_3(t) \\ \\ \dot{N}_1(t) = \left[1 - 2u_0(t)\right]\lambda N_1(t) - (\alpha_{13} + d_{10})N_1(t) + \\ \qquad + d_{31}N_3(t) + \alpha_{01}N_0(t) \\ \dot{N}_2(t) = \left[1 - 2u_1(t)\right]\lambda N_2(t) - (\alpha_{23} + d_{20})N_2(t) + \\ \qquad + d_{32}N_3(t) + \alpha_{02}N_0(t) \\ \dot{N}_3(t) = \lambda N_3(t) - (b + d_{30} + d_{31} + d_{32})N_3(t) + \\ \qquad + dN_4(t) + \alpha_{03}N_0(t) + \alpha_{13}N_1(t) + \alpha_{23}N_2(t) \\ \qquad \cdots \\ \dot{N}_i(t) = \lambda N_i(t) - (b + d)N_i(t) + \\ \qquad + dN_{i+1}(t) + bN_{i-1}(t), \quad i \geq 4 \\ \qquad \cdots \end{cases} \tag{1}$$

$$0 \leq u_i(t) \leq 1 \tag{2}$$

where β_1, β_2 are efficiency factors and $\beta_1+\beta_2=2$.

Several control problems arising in all these cases may be addressed basing on the model. One of them is establishing constant control values u_i (in that case it leads to determination of feedback parameters) that stabilizes the infinite dimensional system. In biological terms, it refers to calculating constant doses of chemotherapeutic agents that suppress 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 solve the optimal control, which minimizes the performance index:

$$J = r_0 \sum_{i=0}^{i=3} N_i(T) + r_1 \sum_{i=4}^{\infty} N_i(T) + r \int_0^T \left[u_1(\tau) + u_2(\tau)\right] d\tau \tag{3}$$

The idea on which such optimization is based is to minimize the resistant cancer subpopulation at the end of therapy with simultaneous minimization of negative cumulative effect of the drugs represented by the integral component.

3. DECOMPOSITION OF THE MODEL

The proposed methodology consists in decomposing the model into two parts as shown on Fig.1. The first one, is bilinear and only that one is directly affected by the drug. The second subsystem is infinite dimensional, but linear, with tridiagonal system matrix, and does not include terms containing control variables $u(t)$.

Applying the same line of reasoning as in our works devoted to modeling of a single drug chemotherapy [5], [8], [9], relations describing dynamical behaviour of the infinite dimensional subsystem from Fig. 1 can be derived.

Let us first assume that there is no influx of new cells to the second subsystem and the initial condition is given by $N_i(0) = \delta_{i4}$ (Kronecker delta), i.e. $N_4(0) = 1$, $N_i(0) = 0$ for $i \neq 4$. Although this assumption would be very hard to justify biologically, it is needed only for some mathematical discussion and after that it will not be needed. Therefore, it does not introduce any additional constraints to applicability of the model

Then, the following relations hold true:

$$N_4(s) = \frac{s+b+d-\lambda-\sqrt{(s+b+d-\lambda)^2-4bd}}{2bd} \tag{4}$$

$$N_\Sigma(s) = \frac{1}{s+\lambda}\cdot\left[1-\frac{s+b+d-\lambda-\sqrt{(s+b+d-\lambda)^2-4bd}}{2b}\right] \tag{5}$$

where $N_4(s)$ and $N_\Sigma(s)$ are Laplace transforms of $N_4(t)$ and $\sum_{i\geq 4} N_i(t)$, respectively. These formulae describe behavior of the second subsystem, when treated as an autonomous model. After calculating inverse Laplace transform the following results are obtained:

$$\begin{aligned}
\dot{N}_0(t) &= \left[1-\beta_0 u_0(t)-\beta_1 u_1(t)\right]\lambda N_0(t) - (\alpha_{01}+\alpha_{02}+\alpha_{03})N_0(t) + \\
&\quad + d_{10}N_1(t) + d_{20}N_2(t) + d_{30}N_3(t) \\
\dot{N}_1(t) &= \left[1-2u_0(t)\right]\lambda N_1(t) - (\alpha_{13}+d_{10})N_1(t) + d_{31}N_3(t) + \alpha_{01}N_0(t) \\
\dot{N}_2(t) &= \left[1-2u_1(t)\right]\lambda N_2(t) - (\alpha_{23}+d_{20})N_2(t) + d_{32}N_3(t) + \alpha_{02}N_0(t) \\
\dot{N}_3(t) &= \lambda N_3(t) - (b+d_{30}+d_{31}+d_{32})N_3(t) + dN_4(t) + \alpha_{03}N_0(t) + \alpha_{13}N_1(t) + \alpha_{23}N_2(t)
\end{aligned}$$

$$\begin{aligned}
\dot{N}_4(t) &= \lambda N_4(t) - (b+d)N_4(t) + dN_5(t) + bN_3(t) \\
&\vdots \\
\dot{N}_i(t) &= \lambda N_i(t) - (b+d)N_i(t) + dN_{i+1}(t) + bN_{i-1}(t), \quad i \geq 4 \\
&\vdots
\end{aligned}$$

Fig.1. System decomposition

$$N_4(t) = \sqrt{\frac{1}{bd}}\,\frac{I_1\left(2\sqrt{bd}\ t\right)}{t}\,e^{(-b-d+\lambda)t} \tag{6}$$

$$N_\Sigma(t) = \sum_{i\geq 4} N_i(t) = e^{\lambda t}\cdot\left[1-\left(\sqrt{\frac{d}{b}}\right)\int_0^t \frac{I_1\left(2\sqrt{bd}\ \tau\right)}{\tau}e^{-(b+d)\tau}d\tau\right] \tag{7}$$

where $I_1(t)$ – modified Bessel function of the 1st order.

Using an asymptotic expansion of (7) it has been found [7] that the solution starting from $N_4(0) = 1$, $N_i(0) = 0$, $i > 4$ decays exponentially to zero, as $t \to \infty$:

$$d > b, \tag{8}$$

$$\sqrt{d} - \sqrt{b} > \sqrt{\lambda}\,. \tag{9}$$

If λ is considered the only parameter affected by control, this means that unless somehow accessed by cytostatics, the resistant subpopulation may maintain itself even in the subcritical case.

4. ANALYSIS OF THE COMPLETE MODEL

Using standard control theory techniques it can be easily proved that the following relation holds true:

$$K_1(s) = \frac{N_4(s)}{N_3(s)} = \frac{s+b+d-\lambda-\sqrt{(s+b+d-\lambda)^2-4bd}}{2d} \tag{10}$$

The inverse Laplace transform of this function, needed in further analysis, is given by

$$k_1(t) = \frac{1}{\sqrt{bd}}\,\frac{I_1\left(2\sqrt{bd}\,t\right)}{t}\,\mathrm{e}^{-(b+d)t} \tag{11}$$

Moreover,

$$\sum_{i\geq 4} N_i(t) = N_\Sigma(t) + N^+(t) \tag{12}$$

where $N_\Sigma(t)$ is defined by (7) and

$$N^+(t) = d\int_0^t N_\Sigma(t-\tau)N_3(\tau)d\tau \tag{13}$$

Let us now assume the initial conditions $N_i(0) = 0$ for $i \geq 1$. The assumption is justified since at the beginning of chemotherapy all cancer cells belong to the sensitive subpopulation. Moreover, the same method can also be applied to other cases as well if only finite number of non-zero initial conditions is assumed. Then, the model can be transformed into the following set of equations

$$\begin{cases} \dot{N}_0(t) = \left[1-\beta_0 u_0(t)-\beta_1 u_1(t)\right]\lambda\, N_0(t) \\ \qquad -(\alpha_{01}+\alpha_{02}+\alpha_{03})N_0(t)+ \\ \qquad d_{10}N_1(t)+d_{20}N_2(t)+d_{30}N_3(t) \\ \dot{N}_1(t) = \left[1-2u_0(t)\right]\lambda\, N_1(t)-(\alpha_{13}+d_{10})N_1(t)+ \\ \qquad +d_{31}N_3(t)+\alpha_{01}N_0(t) \\ \dot{N}_2(t) = \left[1-2u_1(t)\right]\lambda\, N_2(t)-(\alpha_{23}+d_{20})N_2(t)+ \\ \qquad +d_{32}N_3(t)+\alpha_{02}N_0(t) \\ \dot{N}_3(t) = \lambda\, N_3(t)-(b+d_{30}+d_{31}+d_{32})N_3(t)+ \\ \qquad +\alpha_{03}N_0(t)+\alpha_{13}N_1(t)+\alpha_{23}N_2(t)+ \\ \qquad +d\int_0^t k_1(t-\tau)N_3(\tau)d\tau \end{cases} \tag{14}$$

The necessary conditions for optimal control are given by

$$u^{opt} = \arg\min_u \Big[\left(r-\lambda_0\beta_0 N_0(t)p_1(t)-2\lambda_1 N_1(t)p_2(t)\right)u_0(t)+ \\ +\left(r-\lambda_0\beta_1 N_0(t)p_1(t)-2\lambda_2 N_2(t)p_3(t)\right)u_1(t) \Big] \tag{15}$$

$$\dot{p}_1(t) = -p_1(t)\Big[\left(1-\beta_0 u_0(t)-\beta_1 u_1(t)\right)\lambda_0-(\alpha_{01}+\alpha_{02}+\alpha_{03})\Big]- \\ p_2(t)\left[\alpha_{01}+p_3(t)\alpha_{02}+p_4(t)\alpha_{03}\right] \tag{16}$$

$$\dot{p}_2(t) = -p_2(t)\left[\left(1-2u_0(t)\right)\lambda_1-\alpha_{13}-d_{10}\right]-p_1(t)d_{10}-p_4(t)\alpha_{13} \tag{17}$$

$$\dot{p}_3(t) = -p_3(t)\left[\left(1-2u_1(t)\right)\lambda_2-\alpha_{23}-d_{20}\right]-p_1(t)d_{20}-p_4(t)\alpha_{23} \tag{18}$$

$$\dot{p}_4(t) = -p_4(t)\left[\lambda_3-b-d_{30}-d_{31}-d_{32}\right]-dr_1 p_0(t)N_\Sigma(T-t) \\ -p_1(t)d_{30}-p_2(t)d_{31}-p_3(t)d_{32}-db\int_t^T k_1(t-\tau)p_4(\tau)d\tau \tag{19}$$

$$p_i(T) = 1,\ i = 1,2,3,4. \tag{20}$$

Taking into account the constraints (2), it can be easily noticed that, in order to satisfy (15), the optimal control must be bang-bang one. Hence, the problem is now reduced to finding optimal number of switches and optimal switching times.

5. CONCLUSIONS

This paper is concerned with an infinite dimensional bilinear model of dynamical systems representing evolution of resistance to two different drugs in chemotherapy. Basing on model decomposition, it is possible to analyze analytically some of the dynamical properties of the model. The transformation of system description into one integro-differential equation allows solving an optimal control problem with the performance index defined in l^1 space of summable sequences.

Until now, the treatment protocols have been designed mainly on the basis of experimental results and general knowledge about drug activity. However, there exists no general mathematical approach, which would help to explain obtained results or design treatment in chemotherapy. Results of this work may be used to show desired form of optimal treatment protocol and give certain hints to its development. It can be also utilized in qualitative analysis of chosen protocol. Moreover, presented method can be also used in other biomedical applications, where there arises a problem of drug resistance caused by gene amplification.

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