Bioautomation, 2008, 11, Suppl., 49-56 ISSN 1312 – 451X

**Preprints of the 21st Int. Symposium Bioprocess Systems**
**Sofia, Bulgaria, November 4-5, 2008**

# Identification of the Parameters of the Tumor Therapy Process at Viral Hepatitis B

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**Summary:** A generalized mathematical model of the tumor therapy process is considered as a nonlinear system of ordinary differential equations. Parameter identification of the model is carried out using experimental data of patients with viral hepatitis B. As a result of the identification procedure numerical values of the model coefficients are obtained. It is shown that the experimental clinical data are maximal near to the theoretical curves obtained by numerical simulations of the model.

***Key words:*** dynamics of immunological systems, mathematical modeling, identification of the parameters, numerical simulations.

## 1. INTRODUCTION

Development of the clinical and experimental immunology has gradually led to understanding of the leader weed immune protective mechanisms in the pathogenesis of infectious diseases, and together with perfection of computer facilities to creation of mathematical models [1-4]. The part of models mentioned above have a enough simple and convenient form for analytical research that enables to study the general dynamical laws of s immune protection of an organism. Many year extensive efforts have been dedicated to mathematical modeling of cancer development. A variety of mathematical approaches contributes to modeling of cancer progression from different standpoints and takes stock of various factors affecting tumor growth [5-7]. In principle, the most traditional method of research of the nonlinear multiple-parameter problem is imitating modeling One of most often solved within the limits of this approach problems is restoration of parameters according to supervision (standard identification of parameters).

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Data in a considered field of knowledge as a rule are characterized by incompleteness and discrepancy that complicates the analysis of models and interpretation of received results. Incompleteness of data creates a problem of validity estimations of mode parameters. Here we address a complex process that involves both virus-cell interaction and tumor growth, namely to the interaction of the so-called oncolytic viruses with tumors. Oncolytic viruses are viruses that specifically infect and kill cancer cells but not normal cells. Many types of oncolytic viruses have been studied as candidate therapeutic agents including adenoviruses, herpesviruses, reoviruses, paramyxoviruses, retroviruses, and [8, 9]. However, the simplest mathematical models describing a growing tumor infected with an oncolytic virus fail to incorporate all possible outcomes; in particular, these models do not allow tumor elimination [11-13]. Here, we present a conceptual model of tumor cells-virus interaction, which, depending on system parameter values, exhibits various behaviors including deterministic elimination of the cancer cells [10].

## 2. A GENERALIZED MATHEMATICAL MODEL OF THE TUMOR THERAPY PROCESS

Several mathematical models that describe the evolution of tumors under viral injection were recently developed [14-17]. For instance, in [7, 10] a mathematical model describing the interaction between two types of tumor cells (the cells that are infected by the virus and the cells that are not infected, but are susceptible to the virus so far as they have a cancer phenotype) and the immune system is proposed. Next, in [21] the authors neglect the effects of the immune system and investigate only the direct killing of tumor cells by an oncolytic virus. In this way the model suggested in [21] has the following general form

$$\frac{dX}{dt} = F_1(X,Y)X - G(X,Y)Y \tag{2.1}$$

$$\frac{dY}{dt} = F_2(X,Y)Y + G(X,Y)Y \tag{2.2}$$

where $X(t)$ and $Y(t)$ are the sizes of uninfected and infected cell populations, respectively; $F_i(X, Y)$, $i$ = 1, 2, are the per capita birth

rates of uninfected and infected cells; and $G(X, Y)$ is a function that describes the force of infection, i.e., the number of cells newly infected by the virus released by an infected cell per time unit. Here we must note that there is not separate equation for the free virions, i.e. it is assumed that virion abundance is proportional to infected cell abundance. The last one can be justified if the free virus dynamics is faster than infected cell turnover [2]. In this way the model assumes that upon division of infected cells, the virus is passed on to both daughter cells. This circumstance is certain when the viruses integrate into the tumor cell genome, but it should also be appropriate for non-integrating viruses. It is in view of the fact that the active virion production should result in a very high probability if the virus is transmitted to both daughter cells. For the system (2.1-2.2) the functions used in [21, 10] are

$$F_1(X,Y) = R_1(1-\frac{X+Y}{K}) - D$$

$$F_2(X,Y) = R_2(1-\frac{X+Y}{K}) - A \qquad (2.3)$$

$$G(X,Y) = BX$$

where $R_1$, $R_2$, $D$, $A$, $B$, $K$ are positive parameters. The assumptions made in [10] could be express in the following manner: The tumor growh has a logistic fashion (i.e. there is possibility about different rates for growth of the uninfected and infected tumor cells); The incidence of the infection is proportional to the product $XY$. The second assumption is based on chemical kinetics, i.e on the mass action law. The main result by the analysis of model (2.1-2.2), presented in [21], could be expressed to determination of the conditions required for maximum reduction of the tumor load. It has been suggested that "because a deterministic model is used, the tumor can not completely extinct but can be reduced to very low levels"; Elimination of the tumor might occur through stochastic effects which are not involved in the models, presented in [7, 10]. In contrast, in [21] it is shown that a straightforward modification of the model (2.1-2.2) can lead to dynamical regimes that describe deterministic elimination of the tumor cells. This means that a plausible change at the system modeling by consideration of two

competing populations of cells (infected by a virus and no infected), can result in a remarkable change in the model dynamics.

## 3. PARAMETER IDENTIFICATION OF THE TUMOR THERAPY PROCESS AT VIRAL HEPATITIS B

In this section identification of the parameters of the model (2.1-2.2) will be done. The main task of the identification procedure has been formulated as it follows: Based on given experimental data about the real process, to find the coefficients (constants) of the system (2.1-2.2) in a manner such, that in a certain optimum sense the mathematical model to become as close to the real process as possible. The mathematical model (2.1-2.2) describes the changes of the following kinetic variables: $X(t)$ (the size of uninfected cell population) and $Y(t)$ (the size of infected cell population) as a result of penetrating of the virus in a healthy organism. The size of uninfected cells is connected in direct proportion to the antibodies concentration, and the size of the infected cells is connected in direct proportion to the antigen concentration. For the identification procedure we use clinical data of patients with a cyclic form of viral hepatitis B presented in [18]. The experimental data for different patients are theoretically framed, as a result of that the smooth experimental curves are obtained for the each kinetic variables using the fuzzy sets apparatus [19]. For our convenience the data have been provided in non-dimensional form. Thus the non-dimensional smooth clinical values of each kinetic variable for 15 intervals of time (15 intervals of 2 day) are presented in Table 2 with index *"E"*. Their theoretical analogues are derived by solving the system of ordinary differential equations (2.1)-(2.2) using the RKGS program of the SSP package (Table 2 with index *"T"*). The initial values of the parameters $R_1$, $R_2$, $D$, $A$, $B$, $K$ are taken from [7, 10, 20] and are complied with the specifics of the disease (Table 1, column 1). The proximity of the model to the real process is established by using of the mean quadratic criterion, which in our case is expressed by the following functional:

$$J = \sum [(X_i^E - X_i^T)^2 + (Y_i^E - Y_i^T)^2] \qquad (3.1)$$

where $F_i^E = \{X_i^E, Y_i^E\}$ are the non-dimensional clinical values of the kinetic variables of for $i$-moments of the time ($i = 1 \div 15$)

(Table 2, index *"E"*) and $F_i^T = \{X_i^T , Y_i^T\}$ are the respective theoretical values of the same kinetic variables received by solving of the system (2.1-2.2).

Table 1. Numerical values of the parameters of the model (2.1-2.2)

| № | Initial value | Final value |
|---|---|---|
| $R_1$ | 0,5 | 0.483 |
| $R_2$ | 0.5 | 0.532 |
| $D$ | 0.3 | 0,365 |
| $A$ | 0.3 | 0.277 |
| $B$ | 0.1 | 0.092 |
| $K$ | 0.1 | 0.139 |

In this aspect our purpose reduces to establishment of such values of the parameters of the model (2.1)-(2.2), for which the functional $J$ would reach its minimum. The minimum is approached by applying of the ARSTI (Adaptive Method for Random Search with Translation of Intervals) method [20], which is designated for search of local and global extremities of parametric functions. The optimized values of the parameters $R_1$, $R_2$, $D$, $A$, $B$, $K$, received by using the method cited above, are demonstrated in Table 1 (column 2).

Table 2. Experimental and theoretical data for dynamics of uninfected and infected cell populations

| $i$[*day*] | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 |
|---|---|---|---|---|---|---|---|---|
| $Y_i^E$ | 1.00 | 0.95 | 0.80 | 0.75 | 0.70 | 0.60 | 0.50 | 0.40 |
| $Y_i^T$ | 1.00 | 0.96 | 0.82 | 0.74 | 0.68 | 0.57 | 0.49 | 0.38 |
| $X_i^E$ | 0.00 | 0.05 | 0.10 | 0.15 | 0.20 | 0.25 | 0.35 | 0.45 |
| $X_i^T$ | 0.00 | 0.04 | 0.12 | 0.16 | 0.22 | 0.27 | 0.37 | 0.48 |
| $i$[*day*] | 18 | 20 | 22 | 24 | 26 | 28 | 30 | |
| $Y_i^E$ | 0.30 | 0.15 | 0.05 | 0.03 | 0.02 | 0.01 | 0.01 | |
| $Y_i^T$ | 0.29 | 0.13 | 0.04 | 0.02 | 0.01 | 0.00 | 0.00 | |
| $X_i^E$ | 0.55 | 0.65 | 0.75 | 0.90 | 0.95 | 0.98 | 0.99 | |
| $X_i^T$ | 0.57 | 0.67 | 0.76 | 0.92 | 0.96 | 0.99 | 1.00 | |

In Table 2 the numerical values of the kinetic variables obtained by solving of the system (2.1-2.2), for which the functional (3.1) has

minimum are presented by index "*T*" for period of 30 days. From consideration of the same table it is visible that the deviations between experimental data and the results obtained theoretically, are small enough to be negligible (less than 10%). This proves that the model applied is sufficiently adequate to the real process.

## 4. CONCLUSION

The main merit of this study reduces to parameter identification of a dynamical model of the tumor therapy process at a hepatitis B infection. For the purpose one of the most perfect optimization methods (ARSTI) is applied, for the first time. The use of the method allowed us to derive the numerical values of the parameters (constants) of the model (2.1)-(2.2), which render it as close to the real process as possible. Under the parameter values derived hereof, numerical simulations of the system (2.1)-(2.2) are made for period of 30 days. The comparison between theoretical and experimental curves shows that the difference between the results obtained theoretically, and the clinical data is very minimal (10%).

## ACKNOWLEDGMENT

*The second author thanks ESF, OP "Human Resources Development", grant № BG051PO001/07/3.3-02 -55/17.06.2008 for its financial support.*

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