STRANGE ATTRACTORS IN IMMUNOLOGY OF TUMOR GROWTH.

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The time delayed cytotoxic T-lymphocyte response on the tumor growth has been developed on the basis of discrete approximation (2-dimensional map). The growth kinetic has been described by logistic law with growth rate being the bifurcation parameter. Increase in the growth rate results in instability of the tumor state and causes period-doubling bifurcations in the immune+ tumor system. For larger values of tumor growth rate a strange attractor has been observed. The model proposed is able to describe the metastable-state production when time series data of the immune state and the number of tumor cells are irregular and unpredictable. This metastatic disease may be caused not by exterior (medical) factors, but interior density dependent ones.

**I. INTRODUCTION**

An immune system as an evolution formed one has a very high degree of complexity and demonstrates the combination of chaotic and deterministic properties. Different host defense cells are able to suppress the growth tumor cells or destroy them. However, in some experimental and clinical cases it has been observed that stimulation of an immune system by immunotherapy results in stimulation of a tumor cell growth but not suppression. Dormancy, regression, recurrence are possible stages of tumor growth [1] which represent static state, reduction and expansion of the tumor respectively. By dormancy we mean that a tumor, though being variable, does not grow, i.e. the volume...
or cell number does not change with time. It is frequently presumed that tu-
мор cells do not grow because immune effector cells kill tumor cells at a rate
equal to that at which they are generated. Regression requires that the tumor
shrinks, and recurrence means that the dormant tumor is now forced into a
new growth phase. In some clinical experiments a tumor volume follows an ir-
regular cycle, whereas at other cases it fluctuates drastically [2]. The discovery
that fluctuating in time patterns in immunological systems may be described
by deterministic chaos has revived the tumor growth study. A tumor also
is able to generate new clones resistant to cytolytic mechanisms, or is able
to express the receptor to growth factor, or penetrate into another tissues.
So, a tumor is a rather complicated system that can change its properties.
Order and chaos in immunology of a tumor growth can be linked by hierarchi-
cal organization. Chaotic systems are entirely deterministic without random
inputs in spite of showing nonperiodic and noise-like motion. Furthermore,
they exhibit sensitive dependence on initial conditions, i.e. nearby trajecto-
ries separate exponentially. Chaos in biological systems was identified and
modeled in several kinds of situations, including ecology, tumor growth, and
neural systems. The nonlinear character of biological populations and their
fractal properties are now recognized as properties of nature. In this context,
biophysical investigation of nonlinear systems is able to explain paradoxical
phenomena in oncology and predict possible scenarios of a disease evolution
and treatment.

In this paper, we have both investigated the immune response on the
tumor growth on the base of 2-dimensional maps and demonstrated the
possibility of metastable states of an immune+tumor system. 2-dimensional
discrete maps are very useful for modeling realistic systems when there is no
enough empirical data to make a reasonable approximation and/or data is
very noisy. Population biologists often model dynamical population systems
using discrete-time model, which yields a prediction of a population at the
next cycle based on the population at the previous cycle.

After visualization and bifurcation analysis of the model it will be shown
that for a biological reasonable region of parameters the immune response
delay leads to a metastable state which in mathematical description represent
the strange attractor in the immunology of tumor growth. We have been dealt
with first order difference equation systems with discretely changing variables.

II. DESCRIPTION OF THE IMMUNOLOGICAL MODEL.

We define the immune competence as the elimination capacity of an im-
mune system with respect to tumor cells. The tumor, which cells are immuno-
genetic and attacked by cytotoxic effector cells, can trigger processes in the
immune system leading to competence against tumor cells. Activated nonspe-
cific precursor immune cells generate specific effector cells, e.g. natural killers
or cytotoxic T-lymphocyte (CTL) playing a dominant role. Applying the Eu-
ler’s method to the continuous-time system [1] yields the discrete-time model.
There is time delay $\Delta \tau$ between the moment of stimulation of nonspecific
precursor immune cells and generation of specific effector cells. Furthermore,
for the fast growing tumor cell division time can be about few days. The im-
mune+tumor system is composed of two distinct populations, $x$ and $y$. Now
we approximate $x_n$ and $y_n$ as constants in the time interval from $t_n = n\Delta \tau$
to $t_{n+1} = (n + 1)\Delta \tau$. In numerous studies it was found that the growth of
tumor cell population is exponential for small quantities of tumor cells, but
growth is slower at large population size. The interaction between effector
cell concentration $x_n$ and tumor cell concentration $y_n$ can be described by the
difference equations:

$$x_{n+1} = x_n + \left( \frac{c x_n y_n}{\phi + y_n} - \beta x_n y_n - \gamma x_n + j \right) \Delta \tau = F(x_n, y_n),$$

(1)
\[ y_{n+1} = y_n + (\alpha y_n - \theta y_n^2 - ax_n y_n) \Delta \tau = G(x_n, y_n), \]

here \( \alpha \) is the logistic growth rate of tumor population, \( \beta \) and \( a \) are the rate of effector and tumor cells inactivation respectively, \( \theta \) is the parameter of competition for resources (glucose, oxygen, etc.), \( c \) is the rate at which cytotoxic effector cells accumulates in the region of tumor cells, and \( \Delta \tau \) takes into account times necessary for tumor cell division and molecule production, proliferation, differentiation of immune cells, transport, etc.

Analytically the system (1) in concentration scales has 1 to 4 non-trivial steady states. One of them is the excluding point \( A \) with coordinates \( x_A = j/\gamma, y_a = 0 \). The point \( C \) separates the basins of attraction for \( B \) and \( D \) attractors, so that

\[ x^* = F(x^*, y^*), \]
\[ y^* = G(x^*, y^*). \]  

(2)

The stability properties at the fixed points we investigate by evaluation of the eigenvalues of the community matrix

\[
\Gamma = \begin{pmatrix}
\frac{\partial F_x}{\partial G_x} & \frac{\partial F_y}{\partial G_x} \\
\frac{\partial F_x}{\partial G_y} & \frac{\partial F_y}{\partial G_y}
\end{pmatrix} = \begin{pmatrix}
1 - \gamma - \beta y^* + cy^*/(\phi + y^*) & -\beta x^* - cx^* y^*/(\phi + y^*)^2 \\
-ay^* & 1 + \alpha - ax^* - 2\theta y^*
\end{pmatrix}
\]

(3)

In addition, we would note that equilibrium points (constant stable solutions) of continues-time systems [1] correspond to fixed points of a discrete-time model. For the point \( A \) the associated eigenvalue equation, \( |\Gamma(A) - \lambda I| = 0 \), has two solutions, \( \lambda_1 = 1 - \gamma \) and \( \lambda_2 = 1 + \alpha - aj/\gamma \). The attractor \( A \) will be stable if both \( |\lambda_{1,2}| < 1 \) (normal wound healing). The stability of \( A \) steady state depends upon relative values of the parameters \( \alpha, j, \) and \( \gamma \). For example, the increase in the logistic rate \( \alpha \) or \( \gamma \) lead to instability of the \( A \) steady state, and transcritical bifurcation involving \( A \) and \( B \) steady states takes place. The stable steady state \( B(x_b, y_b) \) (tumor dormancy) is characterized by a relatively low tumor cells amount. The stable steady state \( D(x_d, y_d) \)
is characterized by a relatively high tumor and low effector-cell amounts and corresponds to an uncontrolled tumor growth. The steady state \( C(x_c, y_c) \) separates the basins of attraction for the \( B \) and \( D \) attractors (Fig.1). The coordinates of steady states \( B, C, \) and \( D \) can be obtained by finding the positive roots of the equation:

\[
a_3y^3 + a_2y^2 + a_1y + a_0 = 0
\]  

and

\[
x = (\alpha - \theta y)/a,
\]

where

\[
a_0 = \varphi(a_j - \alpha \gamma), a_1 = \alpha(c - \beta \varphi - \gamma) + a_j + \varphi \theta, a_2 = \theta(\gamma + \beta \varphi - c) - \alpha \theta, a_3 = \beta \theta, \Delta \tau = 1
\]

The corresponding eigenvalues for steady states \( B, C, \) and \( D \) are given by \( |\lambda_{1,2}| = 1 \), characteristic bifurcations occur. It should be noted, that \( |\lambda_{1,2}| \gg 1 \) for point \( C \) everywhere. In this situation two outcomes can be realized depending on initial conditions:

i) tumor dormancy - there is a high effector cell level and tumor presence is reduced but not eliminated (the stable steady state \( B \))

ii) uncontrolled tumor growth and immunological paralysis (the system approaches the stable steady state \( D \)).

A phase portrait of the system is presented at the Fig. 1 for the parameters estimated in [1] for BCL lymphoma in the spleen of chimeric mice:

\[
\alpha = 1.3, \ a = 0.1, \ c = 0.1, \ \beta = 3 \cdot 10^{-4}, \ \gamma = 4 \cdot 10^{-2}, \ \theta = 20, \ \theta = 2 \cdot 10^{-3}, \ \text{and} \ j = 10^{-2}.
\]

This portrait for small parameter \( \alpha \) is similar to ones for differential equations without time delay [1]. It should be noted, that a tumor has a
lot of possibilities to overcome limitations of growth. Tumor cells change their genetics, penetrate into other organs, become insensitive for attack of effector cells, etc. This changing we associate with an increase in $\alpha$, $\beta$ and decrease in $a$ and $c$. We can see that $\alpha$ is the bifurcation parameter in controlling the stability of solutions, so there are different stationary periodic and chaotic attractors depending on the parameters values. For $\alpha < 1.0$ the point $A$ is stable, and for $\alpha < 2.0$ the points $B$ and $D$ are stable whereas the point $A$ is unstable. As it is well known for the logistic map, the instability of $B$ and $D$ appears for $\alpha > 2.2$, in which a bifurcation takes place. Chaotic dynamics occurs after a period-doubling-bifurcation scenario shown in the Fig. 2. A dynamical system is called chaotic if at least one Lyapunov exponent is positive and chaotic strange attractor covers a region with fractal dimension. Using 100,000 time steps for parameter $\alpha = 2.7$ (Fig.3) we got Lyapunov exponents: $\Lambda_1 = 0.35$, $\Lambda_2 = -0.388$, and dimension $D_L = 1.92$. It should be noted that the range of chaotic dynamics depends on other relevant parameters.

### III. CONCLUSIONS.

A quantitative discrete model has been proposed to describe the interaction of effector cells and cells of a growing tumor. The model adequately describes the kinetics of tumor growth and regression over a wide interval of tumor growth rate. Hypothesizing that cytotoxic effector cells are responsible for the antitumor reactivity, we have been found that the model can account for many phenomena observed in vivo. According to our model the dynamics of the tumor-growth the slow Malthusian growth rate is the most predictable. In this case, results of our discrete model, which can be estimated as a pseudo-Euler’s method, is similar to that of continuous-time models [1,2]. For a malignant and potentially lethal tumor when the time of
number-doubling of tumor cells \( T = \ln 2/\alpha \leq \Delta \tau \) the metastatic disease has been realized. In this case the numbers of effector and tumor cells fluctuates drastically and the immunity+tumor system is unpredictable. Besides that, any chaotic system posses a property called sensitive dependence on initial conditions, and this property precludes long-term predictions. Nevertheless, attempts to predict the future in chaotic time series in clinical experiments in vivo can provide useful information about system generating time series and scenario for immunotherapy and may eventually be used as an alternative procedure for identifying some parameters which measurement impossible in vivo. Special routines, known as nonlinear forecasting programs, may be developed for such predictions on the basis of the proposed discrete models (2-dimensional maps).We believe such a system could help in understanding self-organization properties of immune systems and real temporal series in immunology of tumor growth. The model may also be applicable to other immunology processes, where the target of effector cells may be any biological material such as bacteria, viruses, tumor cells, etc.

**A. Literature**

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