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MATHEMATICAL MODELING OF THE DEVELOPMENT OF DORMANT TUMORS AND IMMUNE STIMULATION OF THEIR GROWTH

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UDC 519.6+612:017-006

A degeneration of a normal cell into a malignant cell is accompanied by development on the cell membrane of molecules specific for tumor cells — the tumor antigens. Such antigens stimulate the immune response in the body, and near the tumor cells cytotoxic T-lymphocytes (CTL), natural killers (NK), and macrophages appear, which bond to tumor cells and kill them.

Both in vitro and in clinical experiments, however, a strengthening of the immune system in immunotherapy has been observed to stimulate tumor growth [1, 2]. The mechanisms of this paradoxical effect are unclear, but its existence is a restraining factor to immunotherapy [1, 2].

Another paradox in tumor development is the so-called state of tumor dormancy. This is a phenomenon where a small clinically unidentifiable number of tumor cells may exist in a body for a long time (months or years) [3, 4].

Such a state develops after successful treatment of a tumor (in the phase of remission) which usually leaves in the body a few tumor cells (metastases and residual tumors). These cells eventually determine the outcome of the relationship of the tumor to the body. The neoplastic process, surgery, chemotherapy, and radiotherapy reduce the number of immunocomponent cells and their functions. This creates conditions for a long-term local dynamic equilibrium between the cell and the immune system.

Various disturbing factors (such as stress, trauma, or old age) may disrupt these dormant states of a tumor and allow the tumorous growth to resume [3, 4]. There is convincing experimental evidence that mechanisms of cell immunity play an important part in the resuscitation of dormant tumors [4].

These phenomena have not been studied sufficiently, and the mechanisms responsible for them are unknown [1-4]. In particular, there is a lack of experimental models of dormant tumors and immune stimulation of tumor growth in vitro.

Translated from Kibernetika, No. 4, pp. 96-102, July-August, 1987. Original article submitted August 1, 1984.

 0011-4235/87/2304-0556$12.50

Mathematical modeling may be a useful tool in this area. In the early mathematical simulations of antitumor immunity, some solutions were obtained that can be interpreted as dormant states of a tumor [5-11]. In [6] a model of T-cell immunity demonstrated that an increase in CTL may be conducive to growth, rather than obliteration, of a tumor. In [10-12] a simulation of the combined effect of CTL and NK (or NK-like cells) on tumors demonstrated the possibility of the development of a dormant state of a tumor and the stimulation of tumor growth when the activities of NK as well as of CTL are varied. Immunostimulation of tumor growth may occur in the framework of a model of tumor-NK interaction [13]. In [14] a mathematical modeling of the interaction of lymphocytes with tumor cells indicates that an increased concentration of the growth factor of lymphocytes IL-2 may promote a progressive development of a tumor.

The effect of immunostimulation of tumor growth is closely associated with observations of a two-phase nature of the interaction of T-lymphocytes with allogenic stem cells [15] and the effect of tumor "escape" [1, 16, 17]: When transplanted into experimental animals, small tumors ($1\text{-}10^2$ cells) and large tumors (over 10^5 cells) grow, while medium-sized tumors are rejected or grow slowly. A similar behavior of the tumor-immune system has been discovered and investigated in several mathematical models [10, 13, 16, 18-20].

An elementary mathematical model describing these effects has been suggested in [13].

Tumor cells are attacked not only by CTL, as was believed in the 1970s [17], but by other effector cells (EC) as well. On this basis, in [9, 10, 17] a concept of two-level antitumor resistance of the body was formulated which resolved some of the theoretical difficulties [17]. It was assumed that immune control is performed by two complementary subsystems: natural antitumor resistivity of the organism that is comprised on NK and macrophages, and a specific resistivity for which CTL are the EC. The former subsystem is characterized by a rapid recognition of the various tumors and their subsequent elimination, but the possibility of accumulation of EC near the tumor cells is limited. The specific subsystem is highly selective to tumor antigens, with a capacity of an intense immune response to tumor antigens, but a long time is required for EC to develop (from a few weeks to several months). In the framework of this concept, the behavior of a mathematical model has been studied for slowly growing (spontaneous) tumors [9, 12, 21] in which the delay in the appearance of CTL from the memory cells can be disregarded. This constraint is not included in our model.

Mathematical Model

Under the concept of two-level antitumor resistance of a body, we consider a mathematical model of the growth of a clone of immunogenic tumor cells. The model generalizes models proposed earlier [11-13, 21]. Based on the experimental data on paired interactions of NK and CTL with tumor cells and the principles of chemical kinetics [22], we can write the model as follows:

$$dT/dt_1 = T(c_1 - c_2C - c_3N), \tag{1}$$

$$dN/dt_1 = j_N - c_4N - c_5NT, \tag{2}$$

$$dS/dt_1 = c_6T/(1 + T/c_7) - c_8S, \tag{3}$$

$$dP/dt_1 = c_9CT/(c_{10} + S) - c_{11}P - c_{12}PT, \tag{4}$$

$$dC/dt_1 = c_{13}\theta(t_1 - \tau_1)P(t_1 - \tau_1) + j_C/(1 + S/c_{14}) - c_{15}CT - c_{16}C, \tag{5}$$

where T, N, S, P, and C are the current values of the local concentrations of free (not bonded with other cells) tumor cells, NK or NK-like cells, suppressors (T-lymphocytes and macrophages) or molecular factors of suppression induced by the tumor (proteases and gangliosides), CTL memory cells, and mature CTL; $\theta(t_1 - \tau_1)$ is the Heaviside function; $\theta = 1$ at $t_1 - \tau_1 \geqslant 0$, $\theta = 0$ at $t_1 - \tau_1 < 0$; j_N, j_C are the constants of the velocity of flows of NK and CTL from outside into the localization area of the tumor cells; c_1 is the growth rate of the tumor mass; c_2 and c_3 are constants characterizing the sensitivity of tumor cells to the destructive action of cytotoxic EC; c_4, c_8, c_{11}, c_{16} are the rates of natural death; c_6 and c_9 are the maximum cell accumulation rates; c_7 is the concentration of tumor cells at which the rate of generation of the suppressors is reduced by half; c_{10} and c_{14} are the concentrations of suppressors at which the accumulation rate of the precursor cells of CTL and mature CTLs is reduced by half; c_5, c_{12}, c_{15} are the rates of inactivation of immunocytes on contact with tumor cells; c_{13} is the rate of conversion of the memory cells into CTL; and τ_1 is the delay in the appearance of CTL that is comprised of the times of proliferation and differentiation

of the precursor cells and/or migration of CTL. In this model, CTL memory cells and suppressors induced by tumor antigens are included explicitly. In order to clarify the function of delays in the development of mature CTL from memory cells as they affect the formation of a dormant state of a tumor and its resuscitation, we will consider several simplified versions of the model.

For numerous spontaneous tumors the characteristic times of the doubling of their mass are relatively long compared with the characteristic times of development of the immune response of NK and suppressors [3, 17, 22]; the variables N and S in model (1)-(5) can therefore be viewed as fast variables. If we assume, in addition, that the memory cells change velocity compared with the tumor growth velocity is high, then upon attaining a quasistationary condition in the variables N, S, and P we will have, instead of (1)-(5),

$$dT/dt_1 = (c_1 - c_2C - c_3N)\,T, \tag{6}$$

$$dC/dt_1 = c_{13}\theta\,(t_1 - \tau_1)\,P\,(t_1 - \tau_1) + j_C/(1 + S/c_{14}) - c_{15}CT - c_{16}C, \tag{7}$$

$$N = j_N/(c_4 + c_5T), \tag{8}$$

$$S = (c_6T/c_8)/(1 + T/c_7), \tag{9}$$

$$P = c_9CT/(c_{10} + (c_6T/c_8)/(1 + T/c_7))/(c_{11} + c_{12}T). \tag{10}$$

If the data on the facilitated induction of suppressor cells and suppressor factors by tumors cells [23, 24] are considered, we can set $T \ll c_7$. There is experimental evidence to the effect that suppressors more often affect the generation of CTL [23, 24]. We can assume thus that $S \ll c_{14}$ (or $T \ll c_{14}c_8/c_6$). The analysis of the qualitative behavior of the model is then reduced to an examination of a system of the second order:

$$dT/dt_1 = (c_1 - c_2C - c_3j_N/(c_4 + c_5T))\,T, \tag{11}$$

$$dC/dt_1 = \frac{c_{13}c_9\theta\,(t_1 - \tau_1)\,C\,(t_1 - \tau_1)\,T\,(t_1 - \tau_1)}{\left(c_{10} + \frac{c_6}{c_8}T\,(t_1 - \tau_1)\right)(c_{11} + c_{12}T(t_1 - \tau_1))} + j_C - c_{15}CT - c_{16}C. \tag{12}$$

The other variables, according to (8)-(10) are dependent on T and are "driven" variables.

To simplify the analysis, let us make the variables t_1, T, and C dimensionless. We normalize time (accurate to within ln 2) by the tumor doubling period ($t_1 = t/c_1$) and set $C = (c_1/c_2)x$, $T = (c_{11}/c_{12})y$. Now, (11) and (12) are rewritten as

$$dx/dt = \frac{d\theta\,(t - \tau)\,x\,(t - \tau)\,y\,(t - \tau)}{(1 + y\,(t - \tau))\,(1 + \delta y\,(t - \tau))} + j - \beta xy + \gamma x, \tag{13}$$

$$dy/dt = y\,(1 - x - \mu/(1 + \nu y)), \tag{14}$$

where $\mu = c_3j_N/(c_1c_4)$, $\nu = c_5c_{11}/(c_4c_{12})$, $\tau = c_1\tau_1$, $j = j_C \cdot c_2/c_1^2$, $\alpha = c_{13}c_9/(c_1c_{10}c_{12})$, $\beta = c_{15}c_{11}/(c_1c_2)$, $\gamma = c_{16}/c_1$.

When $t < \tau$ in system (13)-(14), the term with the lag becomes equal to 0 and at $\mu < 1$, $\mu + j/\gamma > 1$ or at $\mu > 1$ the model has in the positive quadrant $\{x, y\}_+$ two stationary points: $A(x_1 = j/\gamma, y_1 = 0)$ is a stable node, and $B(x_2, y_2)$ is the saddle point. The coordinates of the point B are defined by the positive solution of the system

$$\begin{aligned} x_2 &= 1 - \mu/(1 + \nu y_2), \\ b_0y_2^2 + b_1y_2 + b_2 &= 0, \end{aligned} \tag{15}$$

where $b_0 = -\nu\beta$, $b_1 = -\beta\,(1 - \mu) + \nu\,(j - \gamma)$, $b_2 = \gamma\,(\mu - 1) + j$. If $\mu + j/\gamma < 1$, then in $\{x, y\}_+$ the only stationary point A is a saddle point.

Thus, for $t < \tau$ a stable stationary state with nonzero value of the variable y(t), i.e., the development of a dormant state of a tumor, is impossible. When $t > \tau$, stationary solutions of system (13)-(14) coincide with the stationary solutions at $\tau = 0$. This can readily be shown if the term with the lag argument is expanded as a Taylor series generalized for piecewise smooth functions [11] and the definition of stationary solutions for a system of differential equations is taken. A system for $\tau = 0$ and $\{x, y\}$ allows from one to four stationary solutions. The first stationary solution has the coordinates $A(x_1 = j/\gamma, y_1 = 0)$; the remaining three are defined by the positive solutions of the system

$$x_i = 1 - \mu/(1 + \nu y_i),$$

$$a_0 y_i^4 + a_1 y_i^3 + a_2 y_i^2 + a_3 y_i + a_4 = 0, \tag{16}$$

where $i = 2, 3, 4$, $a_0 = -\beta\nu\delta$, $a_1 = \delta\nu(j - \beta - \gamma) + \beta(\mu\delta - \delta - \nu)$, $a_2 = j(-\delta + \nu\delta + \nu) + (\mu - 1)(\beta\delta + \gamma\delta + \beta) + \nu(\alpha - \beta - \gamma\delta - \gamma)$, $a_3 = j(\delta + \nu + 1) + (\mu - 1)(\beta + \gamma + \gamma\delta - \alpha) - \gamma\nu$, $a_4 = j + \gamma(\mu - 1)$.

The number of stationary solutions $\{x, y\}_+$ is defined according to the Descartes theorem and the Sturm method. Only one of these solutions can be stable and interpreted as the dormancy of the tumor.

Applying Lyapunov's theorem of stability in first approximation to systems (13)-(14) and analyzing the distribution of the solutions with respect to the stationary solutions, we have proved the following theorems.

THEOREM 1. The sufficient condition of the asymptotic stability of a stationary solution ($x_1 = j/\gamma$, $y_1 = 0$) is the inequality

$$x_1 + \mu > 1. \tag{17}$$

THEOREM 2. If $x_1 + \mu > 1$, $x_1 < 1$ and $x(0) = x_1$, $0 < y(0) < y_{cr}$, where

$$y_{cr} = (\mu + x_1 - 1)/(\nu(1 - x_1)), \tag{18}$$

the solution $y(t)$ decreases on the interval in $t \in [0, \infty]$, where $y(t) \to 0$ at $t \to \infty$.

Returning to the initial notations, the biological interpretation of this theorem is that the growth of a tumor (y) from a single transformed cell or in the case where there are a few such cells is impossible if the growth rate of the tumor c_1 is smaller than the sum of products of "basal" concentrations of effector cells ($C_1^* = j_C/c_{16}$, $N_1^* = j_N/c_4$) multiplied by their corresponding coefficients of sensitivity of tumor cells to the damaging action of effector cells (c_2, c_3), i.e.,

$$C_1^* c_2 + N_1^* c_3 > c_1. \tag{19}$$

The growth of a tumor and its prolonged existence are impossible if the number of new tumor cells in a tissue volume considered is smaller than

$$T_{cr} = \frac{c_4(C_1^* c_2 - N_1^* c_3 - c_1)}{c_5(c_1 - C_1^* c_2)}. \tag{20}$$

Condition (19) guarantees the existence in a body of a so-called "immune barrier" [20, 25] that would not allow a prolonged existence of limited (obviously, small) tumors or metastases and, hence, dormant tumors.

From (12) and (19) it follows that such a barrier can exist even in the absence of CTL [when $C(t) = 0$], and its value T_{cr} is independent of the mechanisms of generation of CTL and the suppressor effect of a tumor upon CTL.

From an analysis of the experimental data in [21] it follows that the sensitivity of tumor cells to the damaging action of NK, CTL, and macrophages, if such sensitivity exists, is of the same order, while the "basal" concentrations of the specific CTL are usually by two or three orders of magnitude lower than NK or macrophages. As seen from (19), the main contribution to the immune barrier is made by cells comprised in the subsystem of natural antitumor resistance of the body.

If condition (19) is not fulfilled, then, as numerical calculations show (Fig. 1), an unlimited growth of the tumor (curves 1 and 2), its elimination (curve 3), or stabilization of the tumor in a dormant state (curves 4 and 5) may take place. The values of the model parameters were taken from [21]. As seen from Fig. 1, small tumors can grow and stabilize in a dormant state (and thus preserve the threat of a relapse), medium-size tumors will be rejected, while large tumors will continue to grow. These results can be interpreted as a version of the tumor escape effect [16].

Note that Theorems 1 and 2 can be generalized to extend to the case of an n-component system of immune surveillance.

Conditions of Asymptotic Stability of a Stationary Solution: The Existence of Tumor Dormancy

Consider the conditions of existence of tumor dormancy and the role of the delay τ in the development of CTL.

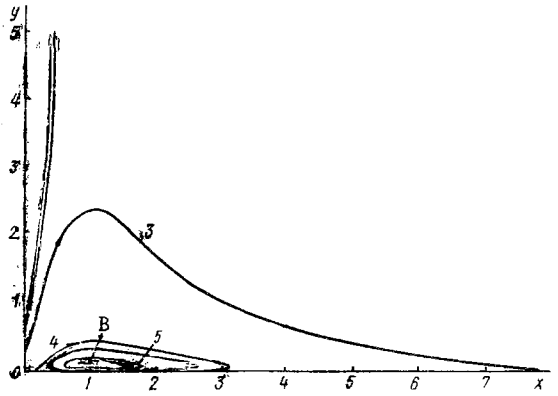

Fig. 1. Solution of system (13)-(14) at $j_C = j_N = 0$ (no external inflow of effector cells) $\alpha = 7$; $\beta = 1.125$; $\gamma = 0.5$; $\delta = 3.0$; $\tau = 0.3$. Wide line shows the stable limiting cycle with period 14.4. Arrows indicate the direction of the process in time.

Set in (13)-(14) $\delta = 0$. The characteristic quasipolynomial of system (13)-(14) for stationary solutions in that case appears as

$$(e_0 + e_1 z + e_2 z^2)\operatorname{ch} z + (d_0 + d_1 z + d_2 z^2)\operatorname{sh} z = 0, \tag{21}$$

where, for stationary solutions defined by (16)-(18),

$$z = \lambda\tau/2, \quad e_0 = -(j/x_i)\,\mu\nu y_i/(1+\nu y_i)^2 + y_i x_i\,[\alpha/(1+y_i)^2 - \beta], \quad e_1 = 2\,[(j/x_i) -$$
$$-\mu\nu y_i/(1+\nu y_i)^2]/\tau, \quad e_2 = 4/\tau^2, \quad d_0 = -(\alpha y_i/(1+y_i) + \beta y_i + \gamma)\,(\mu\nu y_i/(1+y_i)^2) - x_i y_i\,(\alpha/(1+y_i)^2 + \beta),$$
$$d_1 = 2\,[(\alpha y_i/(1+y_i) + \beta y_i + \gamma) - \mu\nu y_i/(1+\nu y_i)^2]/\tau, \quad d_2 = 4/\tau^2, \quad i = 2, 3, 4. \tag{22}$$

The subscript i marks the nontrivial stationary solutions of the system; λ is the characteristic root.

Let $B(x_2, y_2)$ be a positive stationary solution of system (3)-(14) (of the type of a topological node at $\tau = 0$) corresponding to tumor dormancy. The existence conditions of this solution have been defined in [12]. From an analysis of the signs of coefficients of (21) we see that for $B(x_2, y_2)$ the necessary and sufficient conditions of asymptotic stability are possible. The necessary and sufficient conditions of asymptotic stability of quasipolynomials of the type (21) with real coefficients have been obtained by Chebotarev and refined by Guretskii [26].

Introduce notations

$$\operatorname{tg} r_{1,2} = \pm\sqrt{(-D - (D^2 - 4AC)^{1/2})/2C},$$

where $A = e_0 e_1^2 e_2$, $C = d_0 d_1^2 d_2$, $D = e_1 e_2 d_1\,(e_0 + d_0) - (d_2 - e_2)^2 e_0^2$, E[z] is the integral part of the number z. Then for stationary solution $B(x_2, y_2)$, for the specific expressions of the coefficients of the quasipolynomial (22), the following theorem takes place.

THEOREM 3. The necessary and sufficient conditions of an asymptotic stability of a positive stationary solution $B(x_2, y_2)$ of system (3)-(14) are the conditions

$$e_0 > 0, \quad e_1 > 0, \quad e_1 + d_1 > 0,$$
$$E\left[-\frac{r_1}{\pi} + \frac{1}{\pi}\,\frac{(e_0 - d_0)\operatorname{tg} r_1}{e_1 + d_1 \operatorname{tg}^2 r_1}\right] = E\left[-\frac{r_2}{\pi} + \frac{1}{\pi}\,\frac{(e_0 - d_0)\operatorname{tg} r_0}{e_1 + d_1 \operatorname{tg}^2 r_2}\right]. \tag{23}$$

COROLLARY 1. A stationary solution $B(x_2, y_2)$ is asymptotically stable at $\tau = 0$, but it does not remain asymptotically stable if $\tau > \tau' = 2\sigma/d_1$, where σ is the coefficient at the linear term in the characteristic equation for the stationary solution $B(x_2, y_2)$ at $\tau = 0$.

In biological terms this means that the appearance or an increase of an existing delay in the generation of cytotoxic T-lymphocytes caused by various effects reduces the stability of a dormant tumor and when $\tau > \tau'$ resuscitates it.

Other stationary solutions of the system defined from (16)-(18) (which, at $\tau = 0$, are saddle points) are assymptotically unstable at $\tau \geq 0$.

COROLLARY 2. At $j = 0$ the stationary solution $B(x_2, y_2)$ is asymptotic unstable at $\tau \geq 0$; the stability or instability of all stationary solutions defined from (16)-(18) remains unchanged for any $\tau \geq 0$.

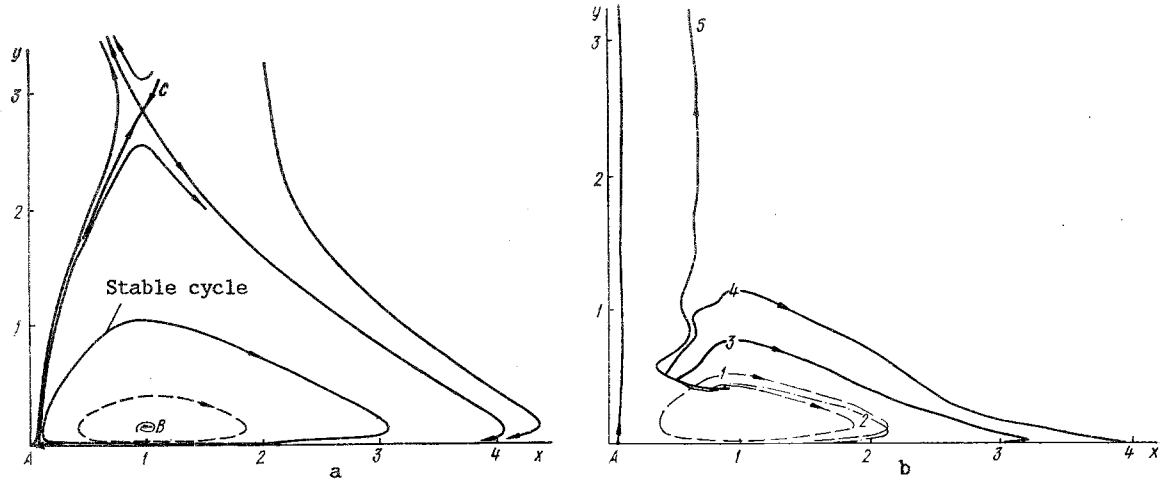

Fig. 2. Solutions of system (13)-(14) at $\tau = 0$ (a) and at $\tau > 0$ (b). 1) $\tau = 0.05$; 2) $\tau = 0.2$; 3) $\tau = 0.7$; 4) $\tau = 0.9$; 5) $\tau = 1.0$. Coefficients in the model: $\mu = 0.4$; $j = 0.02$; $\alpha = 5.0$; $\beta = 1.125$; $\gamma = 0.5$; $\nu = 129.6$; $\delta = 0$. B is the stable focus; C is the saddle point.

In other words, the absence of a steady flow of cytotoxic T-lymphocytes j into the tumor focus causes a resuscitation of a dormant tumor and the transition of the system either to a stationary oscillational regime or to an unsuppressible growth of the tumor ($x \to 0$, $y \to \infty$; $t \to \infty$).

Nonstationary Solutions and Their Interpretations

What is the subsequent course of development of a destabilized tumor as affected by the value of the parameter τ? Numerical experiments on a computer show that τ is an important parameter. Figure 2 represents the projections of solutions of system (13)-(14) onto planes in the positive quadrant $\{x, y\}_+$ for zero delay (a) and for various $\tau > 0$ (b). At $\tau = 0$, depending on the initial conditions, two types of tumor dormancy are possible: 1) the number of tumor cells is constant (a stable stationary point B), and 2) the number of cells in the tumor varies periodically within a certain range (a stable limiting cycle).

At $\tau = 0$ the model allows two nontrivial stable stationary solutions: a point $B(x_2, y_2)$ and a limiting cycle (Fig. 2a), i.e., two types of tumor dormancy.

Even a relatively small delay of the specific cell immune response much smaller than the tumor doubling period (curves 1 and 2, Fig. 2b) will destabilize a dormant tumor, and the development time of the process will be reduced. At small τ, recovery will be achieved ($y \to 0$) (curves 1-4), while with τ comparable to tumor doubling period (curve 5) a rapid unlimited growth of the tumor ($y \to \infty$) will result in the death of the individual.

Similar qualitative regularities have been discovered with the consideration of delays in models of humoral immunity [25, 27]. A destabilization and a growth of leukosic clone can be caused by an unbalanced demand for the generation of cells of various histogenesis (including the cells of the lymphoid series) to the level of regulation of stem cells [28]. The relationship of the asymptotic behavior of solutions in system (13)-(14) as a function of τ, however, may be much more complex. Figure 3 plots in the positive quadrant $\{x, y\}_+$ projections of solutions of system (13)-(14) that go out of the stationary point $B(x_2, y_2)$ (the state of a dormant tumor). The instances of moderate ($\mu = 2$) (Fig. 3a) and "heightened" ($\mu = 5$) (Fig. 3b) levels of the natural body resistance to a tumor are considered. As seen from the figures, an unlimited growth of a tumor may occur not only with large τ (curves 4 and 5, Fig. 3a; curve 5, Fig. 3b) but also at smaller τ (curve 1, Fig. 3a; curve 2, Fig. 3b). These values of τ are separated by a region with favorable outcome of the disease ($y \to 0$) (curves 2 and 3, Fig. 3a; curves 1, 3, and 4, Fig. 3b). In other words, a monotonic increase of τ starting from zero passes through an alternation of favorable ($y \to 0$) and unfavorable ($y \to \infty$) outcomes, until at a sufficiently large τ the resuscitation of a dormant tumor will result in the death of the organism. Hence, an immunization accelerating T-cell immune response (and thus reducing a delay in the development of CTL) may under certain circumstances stimulate unlimited growth of a tumor or its metastases. A comparison of Fig. 3a and 3b

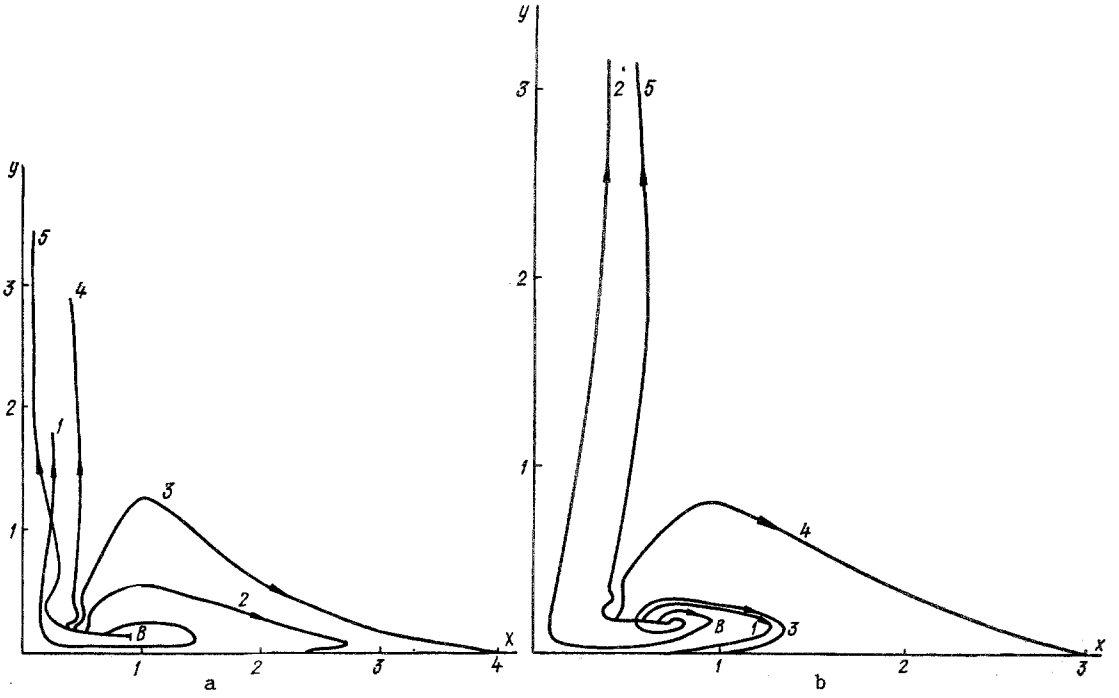

Fig. 3. Solution of system (13)-(14) for the various values of τ. $j = 0.0$; $\alpha = 5.0$; $\beta = 1.125$; $\gamma = 0.5$; $\nu = 129.6$; $\delta = 0$ (a). $\mu = 2.0$: 1) $\tau = 0.4$; 2) $\tau = 0.8$; 3) $\tau = 1.0$; 4) $\tau = 1.2$; 5) $\tau = 2.0$ (b). $\mu = 5.0$: 1) $\tau = 0.1$; 2) $\tau = 0.2$; 3) $\tau = 0.4$; 4) $\tau = 0.8$; 5) $\tau = 1.0$.

indicates, however, that at a "heightened" level of natural body resistance ($\mu = 5$) the same effects of immune stimulation appear as with a "moderate" level ($\mu = 2$), but they are seen at a smaller value of τ. For example, at $\tau = 1.0$ the solution $y(t)$ in Fig. 3a tends to zero (recovery), while in Fig. 3b with the same value of $\tau = 1.0$ $y(t) \to \infty$ (death).

The biological implications of these results can be formulated as follows:

1. An accelerated development of specific CTL or a rise of the level of natural antitumor resistance stimulates the tumor growth under certain conditions.
2. In order for the effect of immune stimulation of tumor growth to appear, a direct participation of suppressor cells induced by tumor antigens is not necessary, contrary to what is frequently assumed [1, 2, 29].
3. The biological causes of the immune stimulation of tumor growth may vary. Mathematically, they are due to specific nonlinearities in tumor growth and body response processes. Under the concept of a two-level antitumor resistance, the immune stimulation of dormant tumors is due to the existence of two populations of killer cells with different generation velocities and different initial concentrations in the body. Suppose, for example, that NK and/or macrophages, usually present in far larger amounts in a tissue than are cytotoxic T-lymphocytes, kill tumor cells slowly while the time required for damage to the tumor cell in the EC-target cell conjugate is comparable to or greater than the time of division of the target cell of the tumor. With a certain delay in the development of specific CTL from memory cells the CTL may come up in a period when most of the tumor cells will be "screened" by NK and/or macrophages. In that case, at a low immune response of CTL to tumor antigen [1] the population of tumor cells as a whole will grow. These interpretations could be tested experimentally.
4. For a successful fight against cancer cells, the host body sought to have mechanisms that maintains certain optimal interval relations between the activity of specific and nonspecific resistance subsystems. In particular, despite the different origins of CTL and NK, a certain conjugation should exist between the time of delay in the development of CTL and the cytotoxic activity of the NK, as follows from the data obtained. It can thus be assumed that maintaining certain interval proportions between relatively autonomous immunity subsystems is essential for an immune homeostasis.

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MATHEMATICAL MODEL OF LONG-TERM PREDICTION OF FLUCTUATIONS OF THE IMMUNOLOGICAL CHARACTERISTICS OF THE BLOOD AND A COMPUTER PROGRAM IMPLEMENTING IT

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UDC 61:578.087.1+612.017.1+612.014.4+523.7+577.49

The biological rhythms of processes in living organisms and correlations of these biorhythms with heliogeophysical rhythms have been studied intensely in the past few years by biologists and physicians. The lack of a mathematical approach for separating from background noise reliable parameters of hierarchies of rhythms in the dynamics of indicators has stood in the way of revealing steady patterns in fluctuations of man's immunological status [1, 2].

The present study pursues two goals;

- to construct a mathematical model for isolating a hierarchy of reliable rhythms with previously unknown periods and phases proceeding from a limited number of sample values in the dynamic series of immunological indicators; and
- to define the natural parameters of monthly heliorhythms and biorhythms of immunological indicators and evaluate their frequency and phase correlations so as to be able to use the patterns identified for long-term forecasting of variation trends of immunological indicators in the blood of healthy male subjects.

In a mathematical approach to these problems with standard procedures used to discover hidden periodicities, three constraints prevent the application of the familiar methods to studies of biological rhythms: 1) spectral methods require the availability of a large data file, while in a practical biological study only a limited number of measurements can be taken for each indicator; 2) with spectral methods, the true period and phase of the oscillations of the indicators studied are difficult to evaluate; this is contrary to the needs of biorhythmology, because frequency and phase carry information about the specifics of a living organism and time correlations of life-sustaining metabolic processes; and 3) because of the ongoing adjustment of the rhythms of various characteristics to changing external and internal factors affecting the functioning of a living organism, it becomes necessary to estimate the drift of periods about their mean values and to consider that a hierarchy of the rhythms of an indicator may contain periods that are not exact multiples of one another. Several mathematical techniques have been used to overcome these constraints of spectral analysis.

1. In order to reveal the hierarchies of the biorhythms of different frequencies within a limited data file obtained by sampling with a constant time interval, the familiar method of analysis of a periodogram of the initial series is combined [3] with a procedure estimating the probability that what is identified by analysis as a harmonic component is in fact "white noise." We consider a model

$$x_t = m_t + \varepsilon_t,$$

where x_t is the observed time series; m_t is a period function of the form

Translated from Kibernetika, No. 4, pp. 103-108, July-August, 1987. Original article submitted October 21, 1985.

 0011-4235/87/2304-0564$12.50