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DYNAMICS OF THE TUMOR—IMMUNE SYSTEM COMPETITION—THE EFFECT OF TIME DELAY

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The model analyzed in this paper is based on the model set forth by V.A. Kuznetsov and M.A. Taylor, which describes a competition between the tumor and immune cells. Kuznetsov and Taylor assumed that tumor-immune interactions can be described by a Michaelis-Menten function. In the present paper a simplified version of the Kuznetsov-Taylor model (where immune reactions are described by a bilinear term) is studied. On the other hand, the effect of time delay is taken into account in order to achieve a better compatibility with reality.

Keywords: mathematical model, tumor growth, differential equation, time delay

1. Introduction

1.1. Biological background

When an unknown tissue, an organism or tumor cells appear in a body, the immune system tries to identify them and, if it succeeds, it tries to eliminate them. The immune system response consists of two different interacting responses—the cellular response and the humoral response. The cellular response is carried by T lymphocytes. The humoral response is related to the other class of cells, called B lymphocytes. A dynamics of the antitumor immune response *in vivo* is complicated and not well understood.

The immune response begins when tumor cells are recognized as being nonself. Then tumor cells are caught by macrophages which can be found in all tissues in the body and circulate round in the blood stream. Macrophages absorb tumor cells, eat them and release series of cytokines which activate T helper cells (i.e., a subpopulation of T lymphocytes) that coordinate the counterattack. T helper cells can also be directly stimulated to interact with antigens. These helper cells cannot kill tumor cells, but they send urgent biochemical signals to a special type of T lymphocytes called natural killers (NKs). T cells begin to multiply and release other cytokines that further stimulate more T cells, B cells and NK cells. As the number of B cells increases, T helper cells send a signal to start the process of the production of antibodies. Antibodies circulate in the blood and are attached to tumor cells, which implies that they are more quickly engulfed by macrophages or killed by natural killer cells. Like all T cells, NK cells are trained to recognize one specific type of an infected cell or a cancer cell. NK cells are lethal. They constitute a critical line of the defense.

1.2. Kuznetsov and Taylor's Model

The idea of the model presented in this paper comes from the paper of Kuznetsov and Taylor (1994). Other similar models of tumor-immune interactions can be found in the literature (e.g., (Foryś, 2002; Mayer *et al.*, 1995; Kirschner and Panetta, 1998; Waniewski and Zhivkov, 2002)). In this section Kuznetsov and Taylor's model and results from (Kuznetsov and Taylor, 1994) are presented. We recall Kuznetsov and Taylor's findings and restore their numerical results in order to compare them with those obtained by us and described in the next sections.

The model proposed in (Kuznetsov and Taylor, 1994) describes the response of effector cells (ECs) to the growth of tumor cells (TCs). This model differs from others because it takes into account the penetration of TCs by ECs, which simultaneously causes the inactivation of ECs. It is assumed that interactions between ECs and TCs *in vitro* can be described by the kinetic scheme shown in Fig. 1, where E, T, C, E^* and T^* are the local concentrations of ECs, TCs, EC-TC complexes, inactivated ECs, and "lethally hit" TCs, respectively, k_1 and k_{-1} denote the rates of bindings of ECs to TCs and the detachment of ECs from TCs without damaging them, k_2 is the rate at which EC-TC interactions program TCs for lysis, and k_3 is the rate at which EC-TC interactions inactivate ECs.

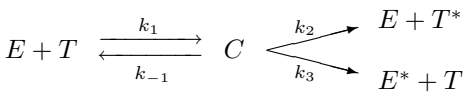

Fig. 1. Kinetic scheme describing interactions between ECs and TCs.

Kuznetsov and Taylor's model is as follows:

$$\begin{aligned}
\frac{\mathrm{d}E}{\mathrm{d}t} &= s + F(C,T) - d_1 E - k_1 ET + (k_{-1} + k_2)C,\\
\frac{\mathrm{d}T}{\mathrm{d}t} &= aT(1 - bT) - k_1 ET + (k_{-1} + k_3)C,\\
\frac{\mathrm{d}C}{\mathrm{d}t} &= k_1 ET - (k_{-1} + k_2 + k_3)C,\\
\frac{\mathrm{d}E^*}{\mathrm{d}t} &= k_3 C - d_2 E^*,\\
\frac{\mathrm{d}T^*}{\mathrm{d}t} &= k_2 C - d_3 T^*,
\end{aligned} \tag{1}$$

where s is the normal (i.e., not increased by the presence of the tumor) rate of the flow of adult ECs into the tumor site, $F(C,T)$ describes the accumulation of ECs in the tumor site, d_1, d_2, and d_3 are the coefficients of the processes of destruction and migration for E, E^* and T^*, respectively, a is the coefficient of the maximal growth of tumor, and b is the environment capacity.

In (Kuznetsov and Taylor, 1994) it is claimed that experimental observations motivate the approximation $\mathrm{d}C/\mathrm{d}t \approx 0$. Therefore, it is assumed that $C \approx KET$, where $K = k_1/(k_2 + k_3 + k_{-1})$, and the model can be reduced to two equations which describe the behavior of ECs and TCs only. Moreover, in (Kuznetsov and Taylor, 1994) it is suggested that the function F should be in the following form:

$$F(C,T) = F(E,T) = \frac{pET}{r+T},$$

where p and r are positive constants.

The dimensionless form of the model studied in (Kuznetsov and Taylor, 1994) is as follows:

$$\begin{aligned}
\frac{\mathrm{d}x}{\mathrm{d}t} &= \sigma + \frac{\rho xy}{\eta + y} - \mu xy - \delta x,\\
\frac{\mathrm{d}y}{\mathrm{d}t} &= \alpha y(1 - \beta y) - xy,
\end{aligned} \tag{2}$$

where x denotes the dimensionless density of ECs, y stands for the dimensionless density of the population of TCs,

$$\sigma = \frac{s}{nE_0T_0}, \quad \rho = \frac{fK}{Kk_2T_0}, \quad \eta = \frac{g}{T_0},$$

$$\mu = \frac{k_2}{k_3}, \quad \delta = \frac{d_1}{Kk_2T_0}, \quad \alpha = \frac{a}{Kk_2T_0}, \quad \beta = bT_0.$$

For better understanding of the model behavior, in Fig. 2 the regions of different types of qualitative behavior of solutions to Eqn. (2) are shown in the (σ, δ)-plane. Equation (2) was proposed to describe two different stages of the tumor: the dormant tumor and the sneaking-through mechanism. Tumor dormancy means that the level of the tumor cells does not change. Sneaking through refers to a situation in which for some initial level of TCs, when the initial level of ECs is sufficiently small, the state of tumor dormancy is achieved in the organism, but if the initial level of ECs is higher, then this initially high level of ECs decreases due to the small and constant level of TCs and, when the level of ECs is sufficiently small, the tumor cells start to proliferate and they break through the immune defense and successfully generate the tumor (Kuznetsov and Taylor, 1994). The typical phase portraits for Regions 1–5 are shown in Fig. 3. These portraits were obtained here as a result of numerical simulations. The steady state on the x-axis means the total recovery (Fig. 3(a)). The steady state with a low level of ECs and a medium level of TCs corresponds to the dormant tumor (Figs. 3(b) and (c)), whereas in Region 5 (Figs. 3(e) and (f)) we observe the sneaking-through mechanism.

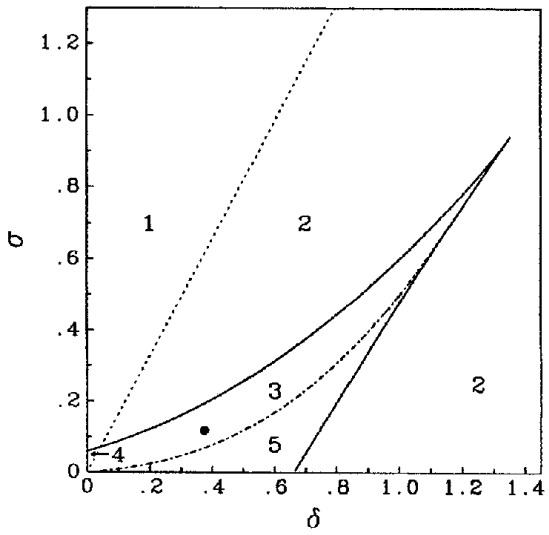

Fig. 2. Regions of qualitatively different types of behavior of Eqn. (2) (parameters σ and δ change while other parameters remain constant).

2. Simplified Model

In the present paper we focus on the model with a time delay. At the beginning, we study the behavior of a sim-

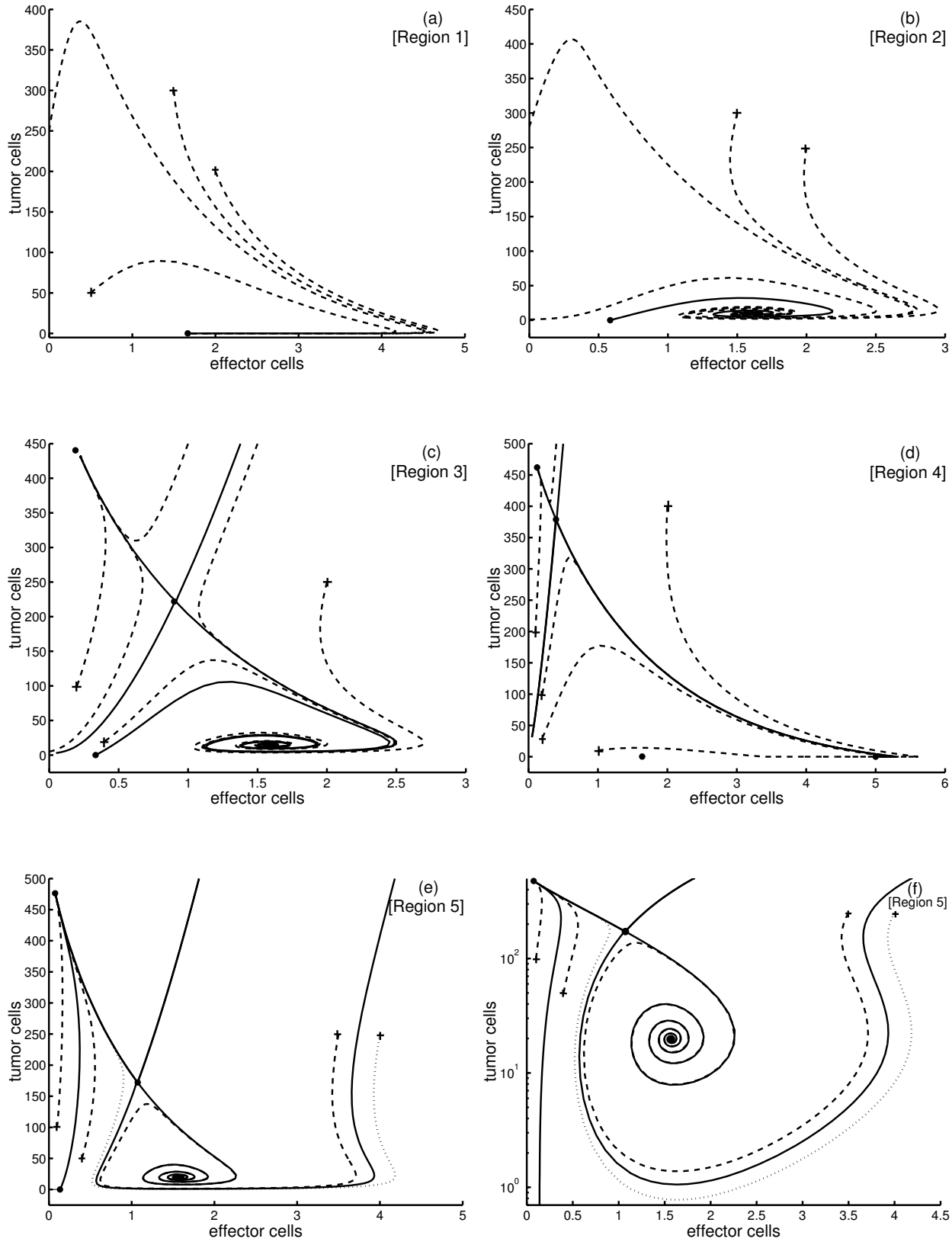

Fig. 3. Phase portraits corresponding to Eqn. (2), for Regions 1–5 and (δ, σ): (0.1908,0.318), (0.545,0.318), (0.545, 0.182), (0.009,0.045) and (0.545,0.073), respectively, $\alpha = 1.636,\ \beta = 0.002,\ \rho = 1.131,\ \eta = 20.19, \mu = 0.00311$.

plified model (based on Eqn. (2)), then we include time delay in it.

We change the model proposed in (Kuznetsov and Taylor, 1994) by replacing the Michaelis-Menten form of the function F with a Lotka-Volterra form (i.e., the function F becomes bilinear and has the form $F(E,T) = \theta ET$). Therefore, the model takes the form

$$\begin{aligned} \frac{\mathrm{d}E}{\mathrm{d}t} &= s + \alpha_1 ET - dE, \\ \frac{\mathrm{d}t}{\mathrm{d}t} &= aT(1-bT) - nET, \end{aligned} \tag{3}$$

where $\alpha_1 = \theta - m$, and the parameters a, b, s have the same meaning as in Eqn. (1); $n = K/k_2$, $m = K/k_3$, $d = d_1$. All coefficients except α_1 are positive.

The sign of α_1 depends on the relation between θ and m. If the stimulation coefficient of the immune system exceeds the neutralization coefficient of ECs in the process of the formation of EC-TC complexes, then $\alpha_1 > 0$.

We use the dimensionless form of the model:

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= \sigma + \omega xy - \delta x, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \alpha y(1-\beta y) - xy, \end{aligned} \tag{4}$$

where x, y, α, β, δ and σ have the same meaning as in Eqn. (2) and $\omega = \alpha_1/n$.

This form of the model allows us to compare the behavior of solutions to Eqns. (2) and (4).

Now we shall study the basic properties of Eqn. (4).

Lemma 1. *For every nonnegative initial condition (x_0, y_0), a nonnegative unique solution $(x(t), y(t))$ to Eqn. (4) exists for every $t > 0$.*

Proof. Since the right-hand side of Eqn. (4) is a polynomial, there exists a unique local solution to Eqn. (4) for any initial data. It is easy to see that for all $t > 0$

$$y(t) = y_0 e^{\int_0^t (\alpha(1-\beta y(s)) - x(s))\,\mathrm{d}s}$$

and

$$x(t) \geq x_0 e^{\int_0^t (\omega y(s) - \delta)\,\mathrm{d}s}.$$

Thus, if $x_0, y_0 \geq 0$, then $x(t)$ and $y(t)$ remain nonnegative for every $t > 0$.

Since $x(t)$ and $y(t)$ are nonnegative, we have

$$\dot{y} \leq \alpha y(1-\beta y)$$

and then

$$y(t) \leq \max\Big(y_0, \frac{1}{\beta}\Big) = y_{\max}.$$

Using $y_{\max}$, we can estimate the first equation:

$$\dot{x} \leq \sigma + x\gamma$$

and then

$$x(t) \leq x_o e^{\gamma t} + \sigma e^{\gamma t} \int_0^t e^{-\gamma s}\,\mathrm{d}s,$$

where

$$\gamma = \begin{cases} \omega y_{\max} - \delta & \text{if } \omega \geq 0, \\ -\delta & \text{if } \omega < 0. \end{cases}$$

This implies that for any finite time moment, $x(t)$ and $y(t)$ are bounded, and this is a sufficient condition for the existence of solutions for every $t > 0$. ■

Now, we study the asymptotical behavior of the model. There exist up to three steady states. The steady state $P_0 = (\sigma/\delta, 0)$ always exists. Other steady states are described by the system of equations:

$$\begin{cases} 0 = \alpha\beta\omega y^2 - \alpha(\beta\delta + \omega)y + \alpha\delta - \sigma, \\ x = -\alpha\beta y + \alpha. \end{cases} \tag{5}$$

If $\Delta = \alpha^2(\beta\delta - \omega)^2 + 4\alpha\beta\sigma\omega > 0$, then additionally there are two solutions $P_1 = (x_1, y_1)$ and $P_2 = (x_2, y_2)$ to this system, where

$$x_1 = \frac{-\alpha(\beta\delta - \omega) - \sqrt{\Delta}}{2\omega}, \quad y_1 = \frac{\alpha(\beta\delta + \omega) + \sqrt{\Delta}}{2\alpha\beta\omega},$$

$$x_2 = \frac{-\alpha(\beta\delta - \omega) + \sqrt{\Delta}}{2\omega}, \quad y_2 = \frac{\alpha(\beta\delta + \omega) - \sqrt{\Delta}}{2\alpha\beta\omega}.$$

The characteristic polynomial for Eqn. (4) and the point P_0 is

$$W(\lambda) = \Big(\alpha - \frac{\sigma}{\delta} - \lambda\Big)(-\delta - \lambda)$$

and, therefore, the following lemma is true:

Lemma 2. *If $\alpha > \sigma/\delta$, then the point P_0 is unstable. If $\alpha < \sigma/\delta$, then the point P_0 is stable.*

For the points P_1 and P_2 we can prove the following result:

Lemma 3. *If the point P_1 exists and has nonnegative coordinates, then it is unstable.*

Proof. To examine the stability of Eqn. (4) at the point P_1, we linearize Eqn. (4) around (0,0) and then we have to find the sign of the trace of the Jacobi matrix

$$J = \begin{bmatrix} \omega y_1 - \delta & \omega x_1 \\ -y_1 & \alpha - 2\alpha\beta y_1 - x_1 \end{bmatrix}.$$

If $\mathrm{tr}(J) > 0$, then the point P_1 is unstable. We have

$$\mathrm{tr}J = \frac{\omega^2 - \omega(\alpha\beta + \beta\delta) - \alpha\beta^2\delta}{2\beta\omega} + \frac{\omega - \alpha\beta}{2\alpha\beta\omega}\sqrt{\alpha^2(\beta\delta+\omega)^2 - 4\alpha\beta\omega(\alpha\delta-\sigma)}. \quad (6)$$

The inequality $\mathrm{tr}(J) > 0$ is true if the following condition is fulfilled:

$$\alpha\big(\omega^2 - \omega(\alpha\beta + \beta\delta) - \alpha\beta^2\delta\big) > (-\omega + \alpha\beta)\sqrt{\alpha^2(\beta\delta + \omega)^2 - 4\alpha\beta\omega(\alpha\delta - \sigma)}.$$

The point P_1 exists and has nonnegative coordinates when $\alpha\delta < \sigma$ and $\omega < -\beta\delta$. Then it is easy to verify that $\omega^2 - \omega\beta(\alpha + \delta) - \alpha\beta^2\delta > 0$ and both sides of the inequality are positive. Squaring and simplifying yield

$$-\sigma\omega^2 - \omega(\alpha^2\beta\delta - 2\alpha\beta\sigma) + \alpha^2\beta^2\delta^2 + \alpha^3\beta^2\delta - \alpha^2\beta^2\sigma < 0. \quad (7)$$

It is easy to verify that for $\omega < -\beta\delta$ and $\alpha\delta < \sigma$ this inequality is true. If the point P_1 exists and has nonnegative coordinates, then $\mathrm{tr}(J) > 0$ and the point P_1 is unstable. ■

Analogously, it is possible to prove the following lemma:

Lemma 4. *If the point P_2 exists and has nonnegative coordinates, then it is stable.*

Now we will examine the existence of closed orbits in the system. To this end, the Dulac-Bendixon criterion (see, e.g., (Perko, 1991)) is applied.

Lemma 5. *There is no nonnegative periodic solution to Eqn. (4).*

Proof. Define the auxiliary function which appears in the Dulac-Bendixon criterion as $M(x, y) = 1/xy$. Then

$$\begin{aligned}\mathrm{div}\, MF &= \frac{\mathrm{d}}{\mathrm{d}x}\Big(M\frac{\mathrm{d}x}{\mathrm{d}t}\Big) + \frac{\mathrm{d}}{\mathrm{d}y}\Big(M\frac{\mathrm{d}y}{\mathrm{d}t}\Big)\\ &= \frac{\mathrm{d}}{\mathrm{d}x}\Big[\frac{1}{xy}(\sigma + \omega xy - \delta x)\Big]\\ &\quad + \frac{\mathrm{d}}{\mathrm{d}y}\Big[\frac{1}{xy}(\alpha y(1 - \beta y) - xy)\Big]\\ &= -\Big(\frac{\sigma}{x^2y} + \frac{\alpha\beta}{x}\Big) < 0.\end{aligned}$$

The Dulac-Bendixon criterion implies that there is no closed orbits in the region $\{(x, y) : x \geq 0, y \geq 0\}$. ■

Table 1. Stationary points with nonnegative coordinates and their stability.

Region	Conditions	P_0	P_1	P_2
1	$\omega > 0, \quad \alpha\delta < \sigma$	stable	—	—
2	$\omega > 0, \quad \alpha\delta > \sigma$	unstable	—	stable
3	$\omega < 0, \quad \alpha\delta > \sigma,$ $\alpha(\beta\delta - \omega)^2 + 4\beta\omega\sigma > 0$	unstable	—	stable
4	$\omega < 0, \quad \alpha\delta < \sigma,$ $\omega + \beta\delta < 0,$ $\alpha(\beta\delta - \omega)^2 + 4\beta\omega\sigma > 0$	stable	unstable	stable
5	$\omega < 0,$ $\alpha(\beta\delta - \omega)^2 + 4\beta\omega\sigma < 0$	stable	—	—

In Table 1 we present all possible cases of stability and instability for the points $P_0,\ P_1,\ P_2$. In turn, in Fig. 4 we present all types of possible asymptotical behavior of Eqn. (4) for nonnegative x and y. The steady state on the x-axis means a total recovery (Fig. 4(a)). The steady state with a low level of ECs and a medium level of TCs (Figs. 4(b), (c) and (d)) corresponds to the state of the dormant tumor. Unfortunately, in the model (4) the sneaking-through mechanism is not described.

Summing up, the dynamics of Eqn. (4) are simpler than the dynamic of Eqn. (2). However, usually the solutions to both models are similar (see Figs. 7 and 8(a), (b)). In Eqn. (4) it is possible to describe the dormant tumor. The sneaking-through mechanism is not described, but the tumor escape under immunoregulation appears.

3. Model with Time Delay

In Eqn. (4) the parameter ω describes the immune response to the appearance of the tumor cells. The immune system needs some time to develop a suitable response after the recognition of non-self cells and therefore, we introduce time delay into the model.

Now, the model takes the form

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= \sigma + \omega x(t-\tau)y(t-\tau) - \delta x,\\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \alpha y(1 - \beta y) - xy,\end{aligned} \quad (8)$$

where the parameters $\alpha,\ \beta,\ \delta,\ \sigma$ and ω have the meaning introduced previously and τ is constant time delay. Time delays in connection with the tumor growth also appear in (Bodnar and Foryś, 2000a; 2000b; Byrne, 1997; Foryś and Kolev, 2002; Foryś and Marciniak-Czochra, 2002). We study Eqn. (8) with nonnegative continuous initial functions x_0 and y_0 defined on $[-\tau, 0]$.

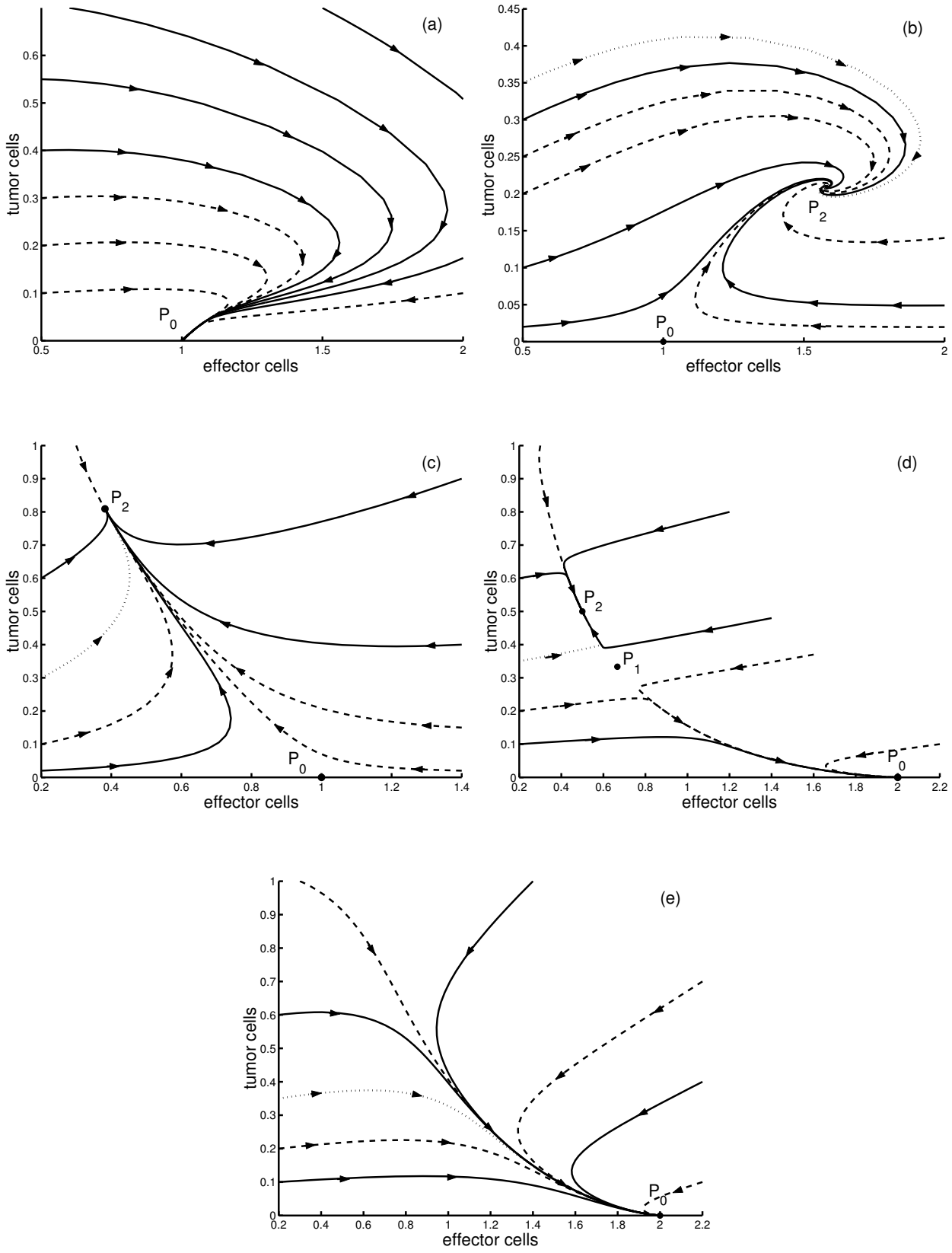

Fig. 4. Phase portraits of Eqn. (4), for Regions 1–5, respectively.

Lemma 6. *A unique solution to Eqn. (8) exists for every* $t > 0$.

Proof. Since the right-hand side of Eqn. (8) is a Lipschitz continuous function, then, locally, there exists a unique solution to Eqn. (8) for any continuous initial function (x_0, y_0) (see (Hale, 1997)). We will show that this solution exists for every $t > 0$.

Let $t \in [0, \tau]$. We know $x(t-\tau)$ and, $y(t-\tau)$ and, therefore, we can solve the first equation using the formula

$$x(t) = x_0(0)e^{-\delta t} + e^{-\delta t}\int_0^t e^{\delta s}\big(\sigma + \omega x_0(t-\tau)y_0(t-\tau)\big)\mathrm{d}s.$$

Knowing $x(t)$, we can estimate the second equation:

$$\dot{y}(t) \le \alpha y(t)\big(1 - \beta y(t)\big) + x_{\max}y(t),$$

where $x_{\max}$ is the maximal value of x on $[0, \tau]$. Hence

$$\dot{y}(t) \le (\alpha + x_{\max})y(t)\Big(1 - \frac{\alpha\beta}{\alpha x_{\max}}y(t)\Big)$$

and therefore

$$y(t) \le \max\Big(y_0(0), \frac{\alpha + x_{\max}}{\alpha\beta}\Big).$$

This implies that $y(t)$ and its derivative are bounded on the interval $[0, \tau]$. Hence the solution to Eqn. (8) exists on the whole interval $[0, \tau]$. Using the step method, we can obtain similar estimates on every interval $[k\tau, (k+1)\tau]$, $k \in \mathbb{N}$, which guarantee the existence of solutions for every $t > 0$. ■

The following lemmas result immediately from (Bodnar, 2000):

Lemma 7. *If* $\omega \ge 0$*, then the solutions to Eqn. (8) are nonnegative for any nonnegative initial condition.*

Lemma 8. *If* $\omega < 0$*, then there exist nonnegative initial conditions such that* $x(t)$ *becomes negative in a finite time interval.*

The application range of this model is restricted to the cases when both the variables are nonnegative, i.e., if $t_{\min} \min\{t_0 > 0 : \exists \epsilon > 0\ \forall t \in [t_0, t_0 + \epsilon]\ \ x(t) < 0\}$, then for $t > t_{\min}$ we take $x(t) = 0$.

Steady states in Eqns. (4) and (8) are the same. In the case of Eqn. (8), in order to prove the stability or the instability of the steady states, we can use the following Mikhailov criterion (Kuang, 1993):

Criterion 1. *(*Mikhailov*) Let* N *and* M *be polynomials,* $\deg M < \deg N = n$ *(where* deg *denotes the degree of a polynomial), and assume that the quasi-polynomial* $D(p) = N(p) + M(p)e^{-p\tau}$ *has no roots on the imaginary axis. Then all the roots of the quasi-polynomial D have negative real parts if and only if the argument of the vector* $D(i\psi)$ *increases by* $n\pi/2$ *as* ψ *increases from* 0 *to* $+\infty$.

Lemma 9. *The steady state* P_0 *of Eqn. (8) is locally asymptotically stable if*

$$\alpha < \frac{\sigma}{\delta} \quad \textit{and} \quad \tau < \frac{\pi}{2\delta}.$$

The steady state P_0 *of Eqn. (8) is unstable if*

$$\alpha > \frac{\sigma}{\delta} \quad \textit{or} \quad \Big(\alpha < \frac{\sigma}{\delta} \quad \textit{and} \quad \tau > \frac{\pi}{2\delta}\Big).$$

Proof. Consider Eqn. (8) and the steady state $P_0 = (\sigma/\delta, 0)$. Let us introduce new variables $\widetilde{x}(t) = x(t) - \sigma/\delta$ and $\widetilde{y}(t) = y(t)$. After rewriting Eqn. (8), we linearize it around $(0, 0)$ (see, e.g., (Hale, 1997)) and obtain the following system:

$$\begin{aligned}\frac{\mathrm{d}\widetilde{x}}{\mathrm{d}t} &= \omega\frac{\sigma}{\delta}\widetilde{y}(t-\tau) - \delta\widetilde{x}(t-\tau),\\ \frac{\mathrm{d}\widetilde{y}}{\mathrm{d}t} &= \alpha\widetilde{y} - \widetilde{y}\frac{\sigma}{\delta},\end{aligned} \tag{9}$$

which leads to the characteristic quasi-polynomial $W(\lambda) = (\lambda + \sigma/\delta - \alpha)(\lambda + \delta e^{-\lambda\tau})$.

The form of the quasi-polynomial W implies that the necessary condition for the asymptotic stability of P_0 is $\alpha < \sigma/\delta$. To find a sufficient condition for the asymptotic stability of the point P_0, we have to know whether all roots of the quasi-polynomial $D(\lambda) = \lambda + \delta e^{-\lambda\tau}$ have negative real parts. To this end, we use the Mikhailov criterion. The first assumption of the criterion (i.e., $\deg M < \deg N$) is fulfilled. Let ψ be a real number. Then

$$\begin{aligned}D(i\psi) &= i\psi + \delta e^{-i\psi\tau}\\ &= i\psi + \delta\big(\cos(\psi\tau) - i\sin(\psi\tau)\big)\\ &= \delta\cos(\psi\tau) + i\big(\psi - \delta\sin(\psi\tau)\big),\end{aligned}$$

and therefore $\Re(D(i\psi)) = \delta\cos(\psi\tau)$, $\Im(D(i\psi)) = \psi - \delta\sin(\psi\tau)$.

Let φ be the argument of $D(i\psi)$. It is easy to see that

$$\sin\varphi = \frac{\psi - \delta\sin\psi\tau}{\sqrt{(\psi - \delta\sin\psi\tau)^2 + \delta^2\cos^2\psi\tau}} \longrightarrow 1 \quad \text{as} \quad \psi \to +\infty,$$

$$\cos\varphi = \frac{\delta\cos\psi\tau}{\sqrt{(\psi-\delta\sin\psi\tau)^2+\delta^2\cos^2\psi\tau}} \longrightarrow 0$$

$$\text{as} \quad \psi \to +\infty.$$

Hence $\varphi(\psi) \to \pi/2 + 2k\pi,\ k \in \mathbb{Z},$ as $\psi \to +\infty$.

We have $\varphi(0) = 0$. To obtain stability, we need $\Delta\varphi = \pi/2$, where $\Delta\varphi$ is the change in the argument $D(i\psi)$ as ψ increases from 0 to $+\infty$.

We have $\Re(D(i\psi)) = 0$ for $\psi\tau = \pi/2 + 2k\pi$ or $\psi\tau = 3\pi/2 + 2k\pi$ $(k \in \mathbb{N})$:

- if $\psi\tau = \pi/2 + 2k\pi$, then $\Im(D(i\psi)) = \psi - \delta$;
- if $\psi\tau = 3\pi/2 + 2k\pi$, then $\Im(D(i\psi)) = \psi + \delta$.

The first value of ψ for which $\Re(D(i\psi)) = 0$ is $\psi = \pi/2\tau$. For this ψ we get $\Im(D(i\psi)) = \pi/2\tau - \delta$. If $\pi/2\tau > \delta$ then for all values of ψ, if $\Re(D(i\psi)) = 0$ then $\Im(D(i\psi)) > 0$, and the point P_0 is stable.
If $\pi/2\tau < \delta$ then

- $\Im(D(i\psi)) < 0$ for $\psi = \pi/2\tau$,
- $\Im(D(i\psi)) > 0$ (for $\psi = 3\pi/2\tau$, the next value of ψ for which $\Re(D(i\psi)) = 0$),
- either $\Im(D(i\psi)) < 0$ for the third value of ψ for which $\Re(D(i\psi)) = 0$, or for all ψ if $\Re(D(i\psi)) = 0$ then $\Im(D(i\psi)) > 0$.

Therefore, if $\pi/2\tau < \delta$, then the point P_0 is unstable.

Consequently, if $\alpha < \delta/\sigma$ and $\pi > 2\delta\tau$, then the point P_0 is locally asymptotically stable. If $\alpha > \sigma/\delta$ or if $\alpha < \sigma/\delta$ and $\pi < 2\delta\tau$, then the point P_0 is unstable. ■

The analysis of stability for the remaining steady states is much more complicated.

We consider the case of $\omega > 0$ and $\alpha > \sigma/\delta$. Then two steady states exist: P_0 and P_2. Lemma 9 implies that the point P_0 is unstable. Calculating the characteristic quasi-polynomial for the point P_2, we obtain

$$D(\lambda) = P(\lambda) + Q(\lambda)e^{-\lambda\tau}, \tag{10}$$

where $P(\lambda) = \lambda^2 + \lambda(\delta + C) + C\delta$, $Q(\lambda) = A - \lambda B$, and $A = \alpha\omega y_2(1 - 2\beta y_2) > 0$, $B = \omega y_2 > 0$, $C = 2\alpha\beta y_2 - \alpha + y_2$ (here x_2 and y_2 are the coordinates of the point P_2).

The point P_2 is stable for $\tau = 0$. If it loses stability, then there exists $\tau_0 > 0$ such that the corresponding eigenvalue is purely imaginary. Therefore, there exist τ_0 and s_0 such that

$$P(is_0) + Q(is_0)e^{-s_0\tau_0} = 0$$

(i.e., $|P(is_0)| = |Q(is_0)|$). We consider the auxiliary function $\Phi(s_0) = |P(is_0)|^2 - |Q(is_0)|^2$. The necessary condition for the change in stability is $\Phi(s_0) = 0$.

If $\delta^2C^2 - A^2 > 0$ and $\delta^2 + C^2 - B^2 > 0$, then $\Phi(s_0)$ has no root and the point P_2 is stable.

Let λ be a root of the characteristic quasi-polynomial (10), $\lambda = f + hi$, $f = f(\lambda), h = h(\lambda)$. If the steady state P_2 is stable for $\tau = 0$, then the existence of $\tau_0 > 0$ for which $\lambda = is_0$ and $\mathrm{d}f(s_0, \tau_0)/\mathrm{d}\tau > 0$ constitutes a sufficient condition for a change in the stability of the point P_2 (Hale, 1997). A numerical analysis shows that a switching in the stability occurs, e.g., for the following values of the parameters: $\alpha = 1.636$, $\beta = 0.002$, $\sigma = 0.1181$, $\delta = 0.3747$ (these parameter values come from medical experiments (Kuznetsov and Taylor, 1994)) and $0.00184 < \omega < 0.01185$. A computer analysis of the Mikhailov hodograph demonstrates the switching in the stability (Figs. 5 and 6).

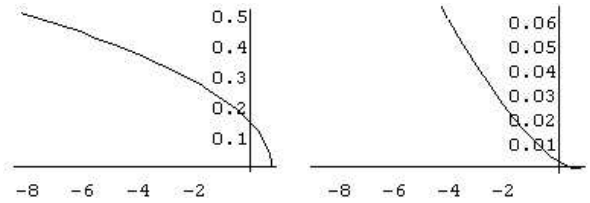

Fig. 5. Example of the Mikhailov hodograph in the case of stability ($\tau = 0$ and $\tau = 0.23$).

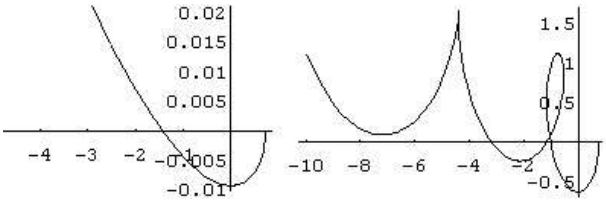

Fig. 6. Example of the Mikhailov hodograph in the case of instability ($\tau = 0.25$ and $\tau = 5$).

The behavior of the solutions to Eqn. (8) is more complex than that for Eqn. (4). Oscillations appear in the solutions to Eqn. (8), which are observed for neither (2) nor (4). To compare solutions to Eqn. (8) with solutions to Eqns. (2) and (4), in numerical simulations we used the same values of parameters α, β, σ and δ for all equations (we refer to them as common parameters). In addition to that, in Eqn. (2) we could freely select ρ, η and μ, in much the same way as ω in Eqn. (4) and ω and τ in Eqn. (8). In most sets of common parameters we tried, we found values of the other parameters such that solutions to all systems behave in a similar manner. In Figs. 7 and 8 we present examples of the behavior of solutions to Eqns. (2), (4) and (8) for the same values of common parameters and the same initial conditions.

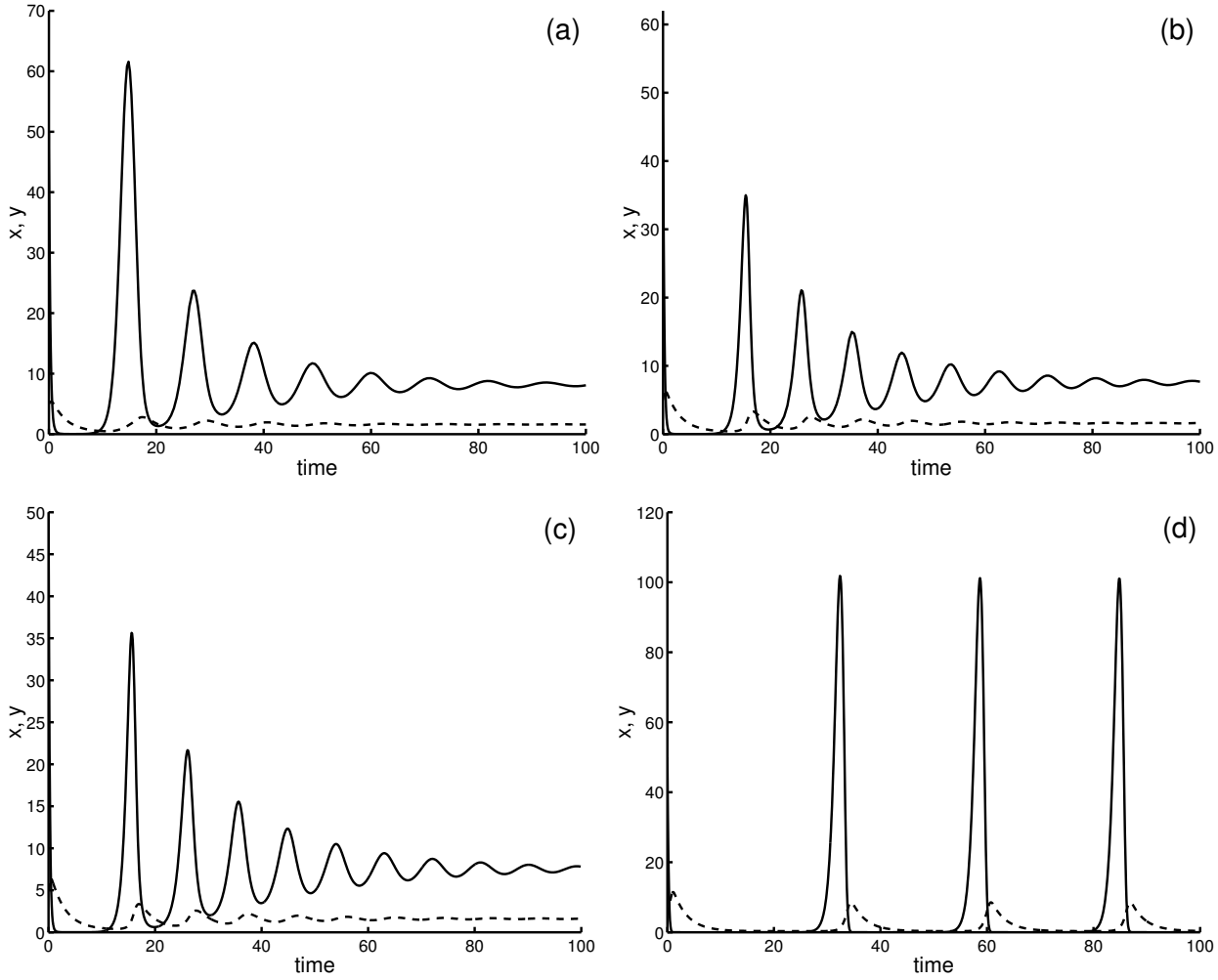

Fig. 7. Solutions to Eqns. (2) and (4) ((a) and (b), respectively) and (8) ((c) and (d)) for the following parameter values: $\alpha = 1.636,\ \beta = 0.002,\ \sigma = 0.1181,\ \delta = 0.3743,\ \omega = 0.04,\ n = 20.19,\ m = 0.00311, p = 1.131,\ \tau = 0.01$ (c) and $\tau = 0.8$ (d); the x variable is denoted by the solid line and the y variable corresponds to the dashed line.

The state of the dormant tumor is reflected in Figs. 7(a)–(c), and a breakdown in the immune response by the tumor cells is shown in Figs. 8(a)–(d). When we introduce higher values of time delay (for the same values of the other parameters as for Fig. 7(c)), we may obtain the state of a "returning" tumor (Kirschner and Panetta, 1998), which is shown in Fig. 7(d). Sometimes, when we change the initial values of ECs (while the initial values of TCs and the parameter values remain the same), the behavior of the solutions changes. For a smaller initial level of ECs the state of a dormant tumor is achieved, whereas for a higher level of ECs, a breakdown in the immune response takes place. This is the sneaking-through mechanism (Figs. 9(a) and (b)). Such behavior is not observed for solutions to Eqns. (4) and (8) (Figs. 9(c)–(h)) because when we increase the initial level of ECs, we obtain either the same situation as for a smaller initial level of ECs, or the level of TCs drops to zero (because then the immune system is sufficiently strong).

4. Conclusions

We have compared three different models: the model proposed by Kuznetsov and Taylor (Eqn. 2), a simplified version of this model (Eqn. (4), we refer to it as a simplified model), and a simplified version of the Kuznetsov-Taylor model with time delay (Eqn. (8), we refer to it as a simplified model with time delay).

We present conclusions concerning the stability of the steady state while assuming that a steady state exists and has nonnegative coordinates.

Kuznetsov and Taylor's model was proposed to describe two different stages of the tumor: the dormant tumor and the sneaking-through mechanism. There exist up to four steady states in this model. These steady states can describe various stages of the tumor growth: a total recovery, a dormant tumor and an escape under immunoregulation. The steady state describing the total recovery al-

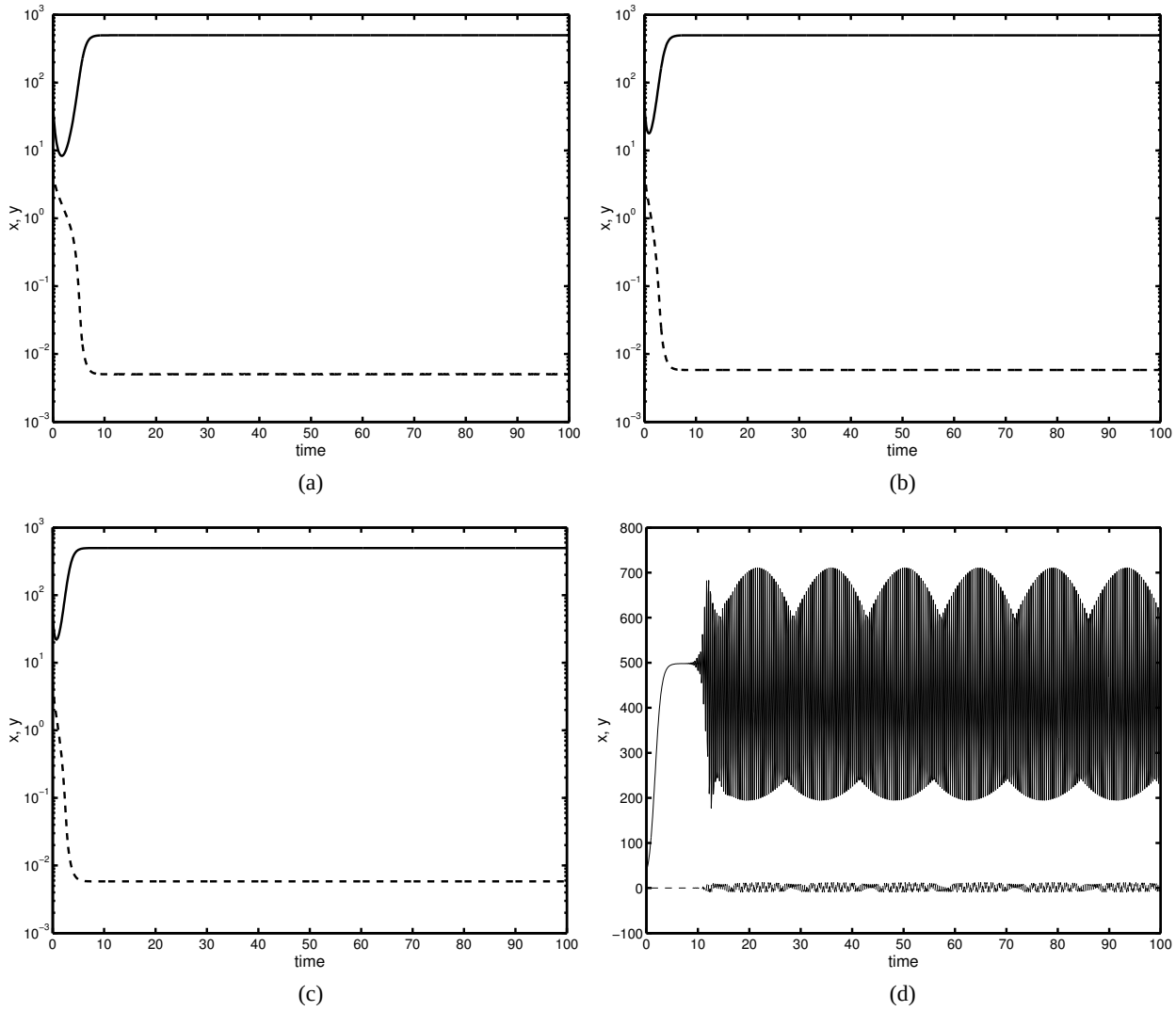

Fig. 8. Solutions to Eqns. (2) and (4) ((a) and (b), respectively) and (8) ((c) and (d)) for the following parameter values: $\alpha = 1.636,\ \beta = 0.002,\ \sigma = 0.1181,\ \delta = 0.3743,\ \omega = -0.04,\ n = 50,\ m = 0.05,\ p = 2,\ \tau = 0.01$ (c) and $\tau = 0.1$ (d); the x variable is denoted by the solid line and the y variable corresponds to the dashed line.

ways exists and may change its stability. The steady state referring to the dormant tumor and the steady state describing the tumor's escape under immunoregulation are always stable. Additionally, there may be another steady state which is unstable.

After a modification and a transformation into the simplified model, the dynamics of the solutions become less complicated. In this model the sneaking-through mechanism is not described, yet still the state of the dormant tumor appears. There are up to three steady states in the simplified model. In this model one steady state can describe, depending on the parameter values, either the dormant tumor or the tumor's escape under immunoregulation.

When time delay is additionally introduced into the simplified model, a state of the "returning" tumor can be observed. Steady states are the same as in the simplified model, but the stability or unstability of these states are more difficult to prove. The stability of the steady states can be different than in the model without time delay, e.g., for some values of time delay, the point P_0 may be unstable, although in the simplified model for the same parameter values (without time delay) it is stable.

Therefore, it seems to us that only Kuznetsov and Taylor's model describes the sneaking-through mechanism, but the simplified model with time delay is also interesting because it allows us to get oscillating solutions, which are also observed in reality (Kirschner and Panetta, 1998).

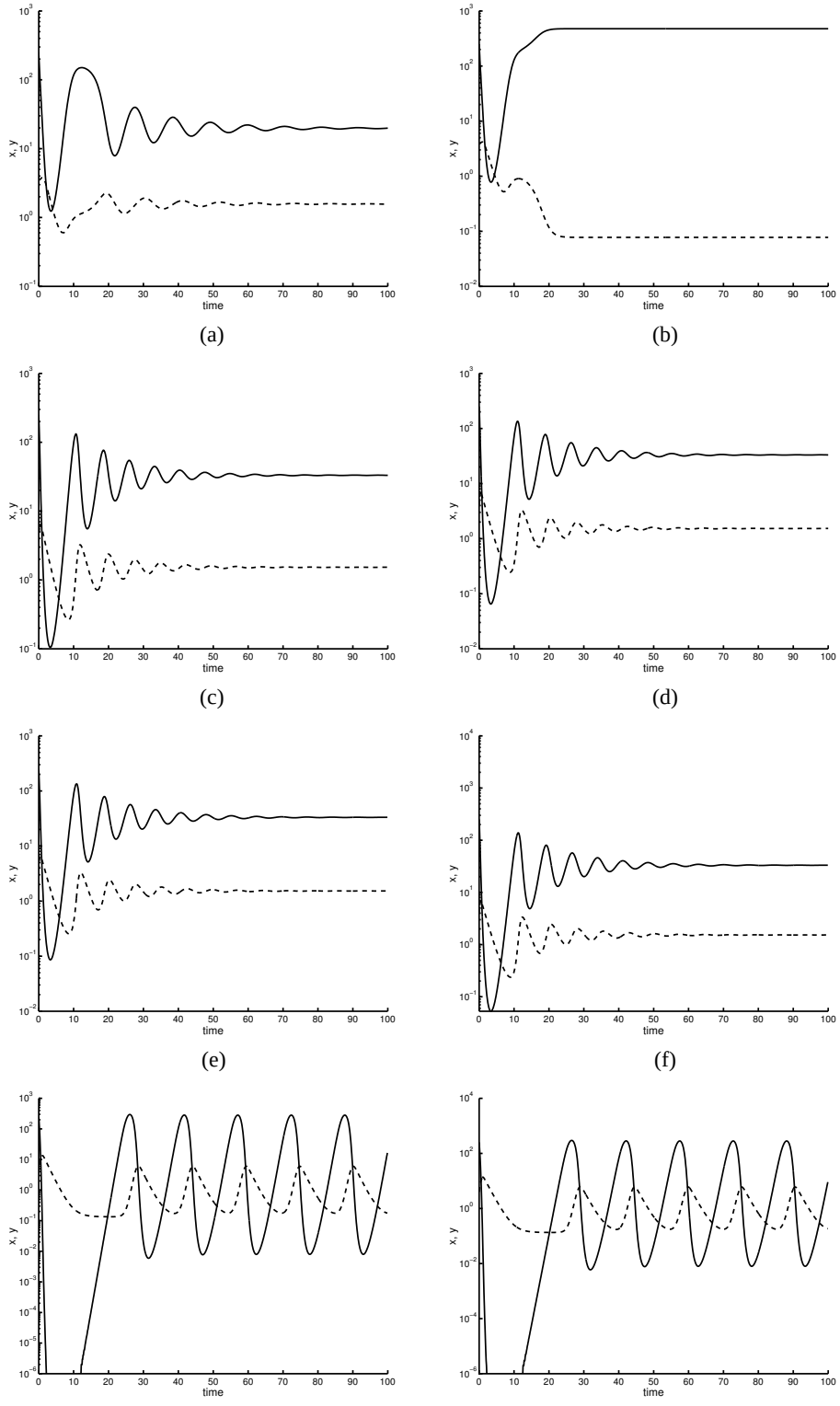

Fig. 9. Solutions to Eqns. (2) ((a) and (b)), (4) ((c) and (d)) and (8) ((e) to (h)) for the following parameter values: $\alpha = 1.636,\ \beta = 0.002,\ \sigma = 0.073,\ \delta = 0.545,\ \omega = 0.015,\ n = 20.19,\ m = 0.00311,\ p = 1.131,$ $\tau = 0.01$ ((e) and (f)) and $\tau = 0.8$ ((g) and (h)); $y(0) = 250$, $x(0) = 3.6$ ((a), (c), (e) and (g)) and $x(0) = 4$ ((b), (d), (f) and (h)); the x variable is denoted by the solid lines and the y corresponds to the dashed lines.

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References

Bodnar M. (2000): *The nonnegativity of solutions of delay differential equations*. — Appl. Math. Lett., Vol. 13, No. 6, pp. 91–95.

Bodnar M. and Foryś U. (2000a): *Behaviour of solutions to Marchuk's model depending on a time delay.* — Int. J. Appl. Math. Comput. Sci., Vol. 10, No. 1, pp. 97–112.

Bodnar M. and Foryś U. (2000b): *Periodic dynamics in the model of immune system.* — Appl. Math., Vol. 27, No. 1, pp. 113–126.

Byrne H.M. (1997): *The effect of time delay on the dynamics of avascular tumour growth*. — Math. Biosci., Vol. 144, No. 2, pp. 83–117.

Foryś U. (2002): *Marchuk's model of immune system dynamics with application to tumour growth*. — J. Theor. Med., Vol. 4, No. 1, pp. 85–93.

Foryś U. and Kolev M. (2002): *Time delays in proliferation and apoptosis for solid avascular tumour.* — Prep. Institute of Applied Mathematics and Mechanics, No. RW 02–10 (110), Warsaw University.

Foryś U. and Marciniak-Czochra A. (2002): *Delay logistic equation with diffusion*. — Proc. 8-th Nat. Conf. *Application of Mathematics in Biology and Medicine*, Lajs, pp. 37–42.

Hale J.K. (1997): *Theory of functional differential equations* — New York: Springer.

Kirschner D. and Panetta J.C. (1998): *Modeling immunotherapy of the tumor—immune interaction* — J. Math. Biol., Vol. 37, No. 3, pp. 235–252.

Kuang Y. (1993): *Delay Differerntial Equations with Applications in Population Dynamics* — London: Academic Press.

Kuznetsov V.A. and Taylor M.A. (1994): *Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis*. — Bull. Math. Biol., Vol. 56, No. 2, pp. 295–321.

Mayer H., Zänker K.S. and der Heiden U. (1995) *A basic mathematical model of the immune response*. — Chaos, Vol. 5, No. 1, pp. 155–161.

Perko L. (1991): *Differential Equations and Dynamical Systems* — New York: Springer.

Waniewski J. and Zhivkov P. (2002): *A simple mathematical model for tumour-immune system interactions*. — Proc. 8-th Nat. Conf. *Application of Mathematics in Biology and Medicine*, LAjs, pp. 149–154.