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MODELLING TUMOUR-IMMUNITY INTERACTIONS WITH DIFFERENT STIMULATION FUNCTIONS

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Tumour immunotherapy is aimed at the stimulation of the otherwise inactive immune system to remove, or at least to restrict, the growth of the original tumour and its metastases. The tumour-immune system interactions involve the stimulation of the immune response by tumour antigens, but also the tumour induced death of lymphocytes. A system of two non-linear ordinary differential equations was used to describe the dynamic process of interaction between the immune system and the tumour. Three different types of stimulation functions were considered: (a) Lotka-Volterra interactions, (b) switching functions dependent on the tumour size in the Michaelis-Menten form, and (c) Michaelis-Menten switching functions dependent on the ratio of the tumour size to the immune capacity. The linear analysis of equilibrium points yielded several different types of asymptotic behaviour of the system: unrestricted tumour growth, elimination of tumour or stabilization of the tumour size if the initial tumour size is relatively small, otherwise unrestricted tumour growth, global stabilization of the tumour size, and global elimination of the tumour. Models with switching functions dependent on the tumour size and the tumour to the immune capacity ratio exhibited qualitatively similar asymptotic behaviour.

Keywords: ordinary differential equations, critical points, stability analysis, immunotherapy

1. Introduction

The specific immune response is a clonal response to specific antigens via cytotoxic and humoral reactions (William, 1984). It involves antigen presenting cells (APC), B and T lymphocytes, antibodies and interleukins. A specific immune response starts by intensive proliferation of lymphocytes, and only after some time it is accompanied by the production of antibodies, interleukins and the cytotoxic activity of T cells. The presented simple models describe the processes of stimulating a specific response by tumour antigens.

Various functions were proposed for the description of the stimulation process of the immune system (Bell, 1973; de Pillis and Radunskaya, 2001; Mayer *et al.*, 1995; Prikrylova *et al.*, 1992; Romanovski *et al.*, 1975). It is natural to assume that the number of cells that can be stimulated to proliferate is proportional to the level of immunity X. However, the number of stimulated cells depends also on the level of antigen Y. The simplest assumption may be that the rate of immunity growth after the stimulation is proportional to the level of the antigen, i.e., the stimulation function is bilinear—proportional to YX (a Lotka-Voltera type of interaction). However, as the cells multiply with a stable (genetically determined) rate, there must be some limitation on the population growth rate. A frequently used assumption was that the stimulation function levels off with the increased antigen level in a Michaelis-Menten way: $Y/(K+Y)$, $K>0$, i.e., it is proportional to $YX/(K+Y)$ (Bell, 1973; de Pillis and Radunskaya, 2001; Mayer *et al.*, 1995; Prikrylova *et al.*, 1992; Romanovski *et al.*, 1975). Another approach takes into account the fact that each cell must be stimulated separately, and the probability of the stimulation depends in a switching-like way on the amount of antigen per cell, i.e. on the ratio of the amount of antigen to the immunity level Y/X : $(Y/X)^\alpha/(K+(Y/X)^\alpha)$, $\alpha \geq 1$, i.e. the stimulation function is proportional to $(Y/X)^\alpha X/(K+(Y/X)^\alpha)$ (Prikrylova *et al.*, 1992). Models with the Michaelis-Menten and ratio dependent limitations on the population growth rate were also discussed in mathematical ecology for predator-prey systems

(Ginzburg and Akcakaya, 1992). In this paper we compare the models of tumour-immunity interactions based on three different stimulation functions: (a) the Lotka-Volterra type, (b) with the Michaelis-Menten type of the growth limitation with an increased level of antigen, and (c) with the limitation dependent on the ratio (Y/X) put on immunity growth with $\alpha = 1$.

Tumours may destroy immune cells that approach them by providing apoptotic signals (Moingeon, 2001; Rosenberg, 2001). They may also decrease the efficiency of the immune response by other means. We study the role of such an anti-immune response of the tumour by introducing a term proportional to $-XY$ in the equation for immunity. The models with and without this term are then compared.

Still another problem in long-term interactions between tumours and immunity is the supply of new precursors of the immune cells after the initiation of the response. The production of new immunocompetent cells is known to diminish as the age advances (Kuby, 1998). How important can such a supply be for immunity? In our models we assume a constant rate of the supply, but we also discuss some versions of the model without it.

2. Model Description

The rate of change in immunity X is supposed to be influenced by four factors: (a) a constant production rate, (b) the first order death process, (c) a nonlinear stimulation function, and (d) a bilinear rate of the anti-immune tumour activity. The temporal change in the tumour size Y is determined by the difference between its reproduction rate, which is assumed to be linear, and the rate of tumour elimination by the immune response, assumed to be a bilinear function (a Lotka-Volterra type of interaction). Thus, the model equations are

$$\frac{\mathrm{d}X}{\mathrm{d}t} = w - uX + a\overline{F_i}(X,Y) - hYX, \tag{1}$$

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = rY - bYX, \tag{2}$$

with non-negative constants $w,\ u,\ a,\ h,\ r$ and b. The stimulation rate of the immune system by tumour antigens is described by one of the functions $\overline{F_i}(X,Y),\ i = 1,2,3$, which are

$$\overline{F}_1(X,Y) = YX,$$

$$\overline{F}_2(X,Y) = \frac{Y}{K+Y}X,$$

$$\overline{F_3}(X,Y) = \begin{cases} \dfrac{Y/X}{K+Y/X}X & \text{if} \quad (X,Y) \neq (0,0), \\ 0 & \text{if} \quad (X,Y) = (0,0). \end{cases} \tag{3}$$

$\overline{F}_1(X,Y) = XY$ is of the Lotka-Voltera type. $\overline{F}_2$ and $\overline{F}_3$ take into account a limited rate of the multiplication of immune cells after the stimulation. Equations (1)–(3) can be formulated in the following non-dimensional form:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = p - dx + qF_i(x,y) - fxy, \tag{4}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = y(1-x), \tag{5}$$

where for $F_1(x,y) = xy$ we have

$$x = \frac{b}{r}X, \quad y = \frac{b}{r}Y, \quad \tau = rt, \quad p = \frac{bw}{r^2},$$

$$d = \frac{u}{r}, \quad q = \frac{a}{b}, \quad f = \frac{h}{b}.$$

In turn, for

$$F_2(x,y) = \frac{xy}{m+y}$$

we get

$$x = \frac{b}{r}X, \qquad y = \frac{b}{r}Y, \qquad \tau = rt, \qquad p = \frac{bw}{r^2},$$
$$d = \frac{u}{r}, \qquad q = \frac{a}{r}, \qquad f = \frac{h}{b}, \qquad m = K\frac{b}{r}.$$

Finally, for

$$F_3(x,y) = \frac{xy}{x+y}$$

we get

$$x = \frac{b}{r}X, \quad y = \frac{b}{Kr}Y, \quad \tau = rt, \quad p = \frac{bw}{r^2},$$

$$d = \frac{u}{r}, \quad q = \frac{a}{r}, \quad f = \frac{h}{b}K.$$

The asymptotic behaviour of the system depends on four lumped parameters: (a) $\omega = p/d$, which describes the level of x without stimulation (i.e., the equilibrium level of the immune system in the absence of a tumour), and can be called "background immunity", (b) $\rho = q/f$, which describes the relative strength of the stimulation over the destruction of the immunity by a tumour, and can be called the "activation strength", (c) $\sigma = q/d$, which describes the relative strength of the stimulation over the natural decay of the immunity, and is used if $f = 0$, and (d) $\zeta = d/f$, which describes the relative strength of the two processes that tend to decrease the immunity. The mathematical analysis of the system is carried out only for $x \geq 0$ and $y \geq 0$, because of the biological interpretation of these variables.

3. Asymptotic System Behaviour

We show that all possible asymptotic outcomes of the assumed interactions between a tumour and the immune system found in our study can be classified using five patterns (cf. Fig. 1):

I. unrestricted tumour growth,

II. stabilization of the tumour size (a stable focus or a node, $y > 0$) if the initial tumour size is relatively small, and otherwise unrestricted tumour growth,

III. elimination of the tumour (a stable node, $y = 0$) if the initial tumour size is relatively small, otherwise unrestricted tumour growth,

IV. stabilization of the tumour size (a globally stable focus or a node, $y > 0$), and

V. elimination of the tumour (a globally stable node, $y = 0$).

In Patterns I, IV and V the asymptotic behaviour of the system does not depend on its initial state, whereas in Patterns II and III tumours of relatively small sizes are stabilized and eliminated, respectively, but relatively large tumours cannot be controlled by the immune system. Thus, the outcome of the tumour-immune system interactions in Patterns II and III is sensitive to the phase of tumour growth at which the interaction starts. Examples of all the five asymptotic patterns are shown in Fig. 1. Some of them appear for all the three stimulation functions (F_1, F_2 and F_3), as, e.g., Pattern I (in Fig. 1 it is shown only for F_1). In contrast, Pattern II does not appear for the stimulation function F_1, see the discussion below.

Stimulation function $F_1(x,y)$. Two y nullclines are described by the equations $y = 0$ and $x = 1$, respectively, and the x nullcline is characterized by the equation $p - dx + (q - f)xy = 0$. For all the values of model parameters there exists a critical point A with coordinates $(\omega, 0)$.

General case (all system parameters are positive). Another critical point B with coordinates $(1, \zeta(\omega - 1)/(1 - \rho))$ may exist, but only for some parameter values, see below. The linear analysis of the stability of critical points implies that the eigenvalues of the linearized system at point A are $\lambda_1 = 1 - \omega$, and $\lambda_2 = -d$, and at point B they are equal to $\lambda_{1,2} = d(-\omega \pm \sqrt{\omega^2 + 4(\omega - 1)/d})/2$. Combining the information about the position and stability characteristics of the critical points, we get the following asymptotic patterns for the system (cf. Fig. 2(a)):

Pattern I. If $\omega < 1$ and $\rho < 1$, then there is only one critical point $A = (\omega, 0)$, which is a saddle point, and the system does not have any other critical point, see Fig. 1, Panel I.

Pattern III. If $\omega > 1$ and $\rho < 1$, then there are two critical points. The critical point $A = (\omega, 0)$ is a locally stable node, and the critical point B is a saddle point. The elimination of the tumour $(y = 0)$ is observed if the initial tumour size is relatively small.

Pattern IV. If $\omega < 1$ and $\rho > 1$, then there are two steady states. The critical point $A = (\omega, 0)$ is a saddle point, and the critical point B is a globally stable focus if $\omega < 2(\sqrt{1 + d} - 1)/d$, or a globally stable node if $2(\sqrt{1 + d} - 1)/d < \omega < 1$. In this case the stabilization of the tumour size is observed regardless of the initial state of the system.

Pattern V. If $\omega > 1$ and $\rho > 1$, then there is only one steady state $A = (\omega, 0)$, which is a globally stable node. Therefore, the complete eradication of the tumour by the immune system occurs independently of the initial state of the system.

Case $f = 0$, i.e., the anti-immune activity of the tumour is absent. The asymptotic patterns of the system are described using two lumped parameters $\omega = p/d$ and $\sigma = q/d$, the latter takes the role of "stimulation strength". The critical point $(\omega, 0)$ has eigenvalues $\lambda_1 = 1 - \omega$, and $\lambda_2 = -d$. Another critical point $(1, (1 - \omega)/\sigma)$ exists if $\omega < 1$. Thus two asymptotic patterns may exist, cf. Fig. 2(b).

Pattern IV. If $\omega < 1$ (Region IV, Fig. 2(b)), there are two critical points. The steady state $(\omega, 0)$ is a saddle point. The critical point with eigenvalues $\lambda_{1,2} = d(-\omega \pm \sqrt{\omega^2 + 4(\omega - 1)/d})/2$ is a globally stable focus if $p < 2(\sqrt{1 + d} - 1)$, or a node if $p > 2(\sqrt{1 + d} - 1)$.

Pattern V. If $\omega > 1$ (Region IV, Fig. 2(b)), then there is only one critical point $(\omega, 0)$, which is a globally stable node.

The case of $p = 0$, i.e., production of the agents of the immune system is absent. If $\rho > 1$, then the system has steady states $(0, 0)$ and $(1, \zeta/(\rho - 1))$, and the eigenvalues are $\lambda_1 = 1$, $\lambda_2 = -d$ and $\lambda_{1,2} = \pm i\sqrt{d}$, respectively. Thus the steady states are a saddle point and a neutral centre, respectively. In this case our model is a classical Lotka-Voltera system. If $\rho < 1$, there is one steady state $(0, 0)$, which is a saddle point.

Stimulation function $F_2(x,y)$. Two y nullclines are described by the equations $y = 0$ and $x = 1$, respectively, and the x nullcline is characterized by the equation $(pm - dmx + y(p - dx + qx - fmx) - fxy^2)/(m + y) = 0$. There always exists a critical point $(\omega, 0)$.

General case (all system parameters are positive). Two other critical points (or one of them, see below) exist with coordinates $(1, y_i)$, $i = 1, 2$, where $y_{1,2} = (a_m \mp \sqrt{\Delta_m})/2$, $a_m = \rho - m + \zeta(\omega - 1)$, $\Delta_m = (\rho - m + \zeta(\omega - 1))^2 + 4m\zeta(\omega - 1)$, provided that

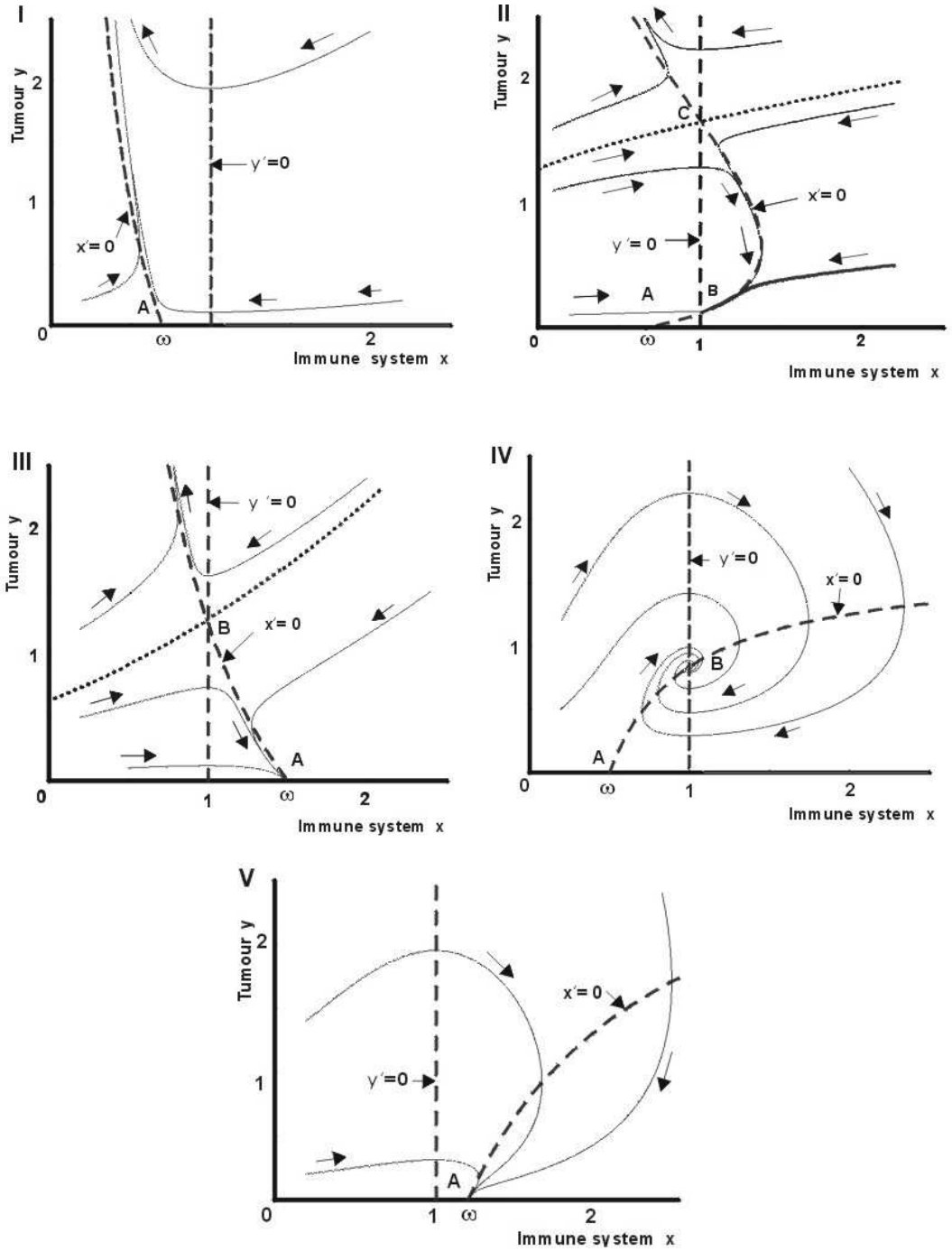
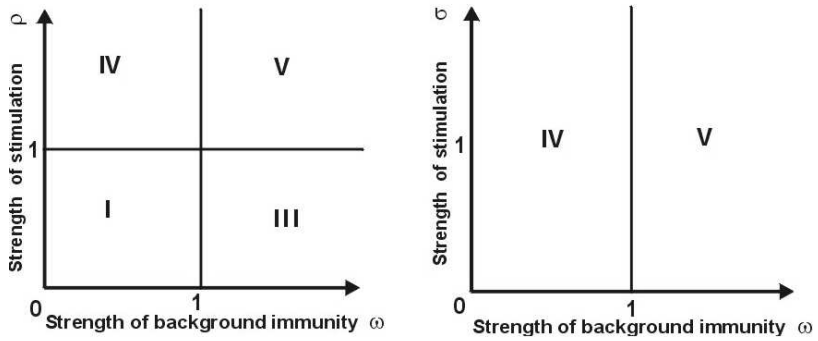


Fig. 1. Five different kinds of asymptotic behaviour of the system for different stimulation functions and model parameters. I: unrestricted tumour growth: $F_1(x,y),\ q=1,\ f=1.4,\ d=1,\ p=0.7$; the steady state $A=(\omega,0)$ is a saddle point. II: stabilization of the tumour size (a stable focus or a node, $y>0$) if the initial tumour size is relatively small, and otherwise unrestricted tumour growth: $F_2(x,y),\ q=15,\ f=5,\ d=2,\ p=3,\ m=1$; the steady state B is a locally stable node and the steady states A and C are saddle points. III: elimination of the tumour (a stable node, $y=0$) if the initial tumour size is relatively small, otherwise unrestricted tumour growth: $F_1(x,y),\ q=1,\ f=1.4,\ d=1,\ p=1.5$; the steady state $A=(\omega,0)$ is a locally stable node, and the steady state B is a saddle point. IV: stabilization of the tumour: $F_1(x,y),\ q=2,\ f=1.4,\ d=1,\ p=0.5$; the steady state B is a globally stable focus and the steady state $A=(\omega,0)$ is a saddle point. V: elimination of the tumour: $F_1(x,y),\ q=2,\ f=1.4,\ d=1,\ p=1.2$; the steady state $A=(\omega,0)$ is a globally stable node. The continuous lines correspond to system trajectories, the dashed lines denote system nullclines, and the dotted lines signify the separatrices of saddle points. Note that the x axis is also a y nullcline.



(a) (b)

Fig. 2. Types of asymptotic behaviour for different regions of the parameter space (ρ, ω) or (σ, ω) for the stimulation function $F_1(x, y)$: (a) the general case ($f > 0$), I: unrestricted tumour growth, III: elimination of the tumour (a stable node, $y = 0$) if the initial tumour size is relatively small, otherwise unrestricted tumour growth, IV: stabilization of the tumour size (a globally stable focus or a node, $y > 0$), V: elimination of the tumour (a globally stable node, $y = 0$), (b) the case of $f = 0$, IV: stabilization of the tumour size (a globally stable focus or a node, $y > 0$), V: elimination of the tumour (a globally stable node, $y = 0$).

$a_m \mp \sqrt{\Delta_m} > 0$. To describe this condition, we consider it on the plane (ω, ρ), where $\omega, \rho > 0$, with ζ as a parameter. Thus the inequality may be discussed for the regions of the plane delimited by the following three lines (Fig. 3): (a) the straight line $\rho = m - \zeta(\omega - 1)$, (b) the straight line $\omega = 1$, and (c) the parabola $\Delta_m = 0$. The parabola crosses the two straight lines at the point $(1, m)$, and the axis ρ at $\rho_1 = \zeta + m + 2\sqrt{m\zeta}$ and $\rho_2 = \zeta + m - 2\sqrt{m\zeta}$.

The eigenvalues of the linearized system for the point $(\omega, 0)$ are $\lambda_1 = 1 - \omega$ and $\lambda_2 = -d$, and for the points $(1, y_{1,2})$ we have $\lambda_{1,2} = (\beta_m \pm \sqrt{\beta_m^2 - 4\gamma_m}/2$, where $\beta_m = -d + q\, y_{1,2}^2/(m + y_{1,2})^2 - f y_{1,2}$ and $\gamma_m = y_{1,2}(qm/(m + y_{1,2})^2 - f)$. The stability analysis of the point $(\omega, 0)$ shows that it is a saddle point if $\omega < 1$ and a stable node if $\omega > 1$.

If the system parameters are in the region U_4, (cf. Fig. 3) then the system has one more steady state $(1, y_1)$. For this point we have

$$\gamma_m = \frac{-y_1 f}{2(1 + y_1)^2} \left(2m\sqrt{\Delta_m} + \left(a_m + \sqrt{\Delta_m} \right) \sqrt{\Delta_m} \right) < 0 \tag{6}$$

because $a_m + \sqrt{\Delta_m} > 0$, and therefore it is a saddle point.

If the system parameters are in the region U_3 (cf. Fig. 3), then the system has two equilibrium points $(1, y_{1,2})$ with $y_{1,2} > 0$. The point $(1, y_1)$ is a saddle point, cf. (6). For $(1, y_2)$ we have

$$\beta_m = -f\omega\zeta < 0, \tag{7}$$

$$\gamma_m = \frac{f y_2}{2(1 + y_2)^2} \left(\left(a_m - \sqrt{\Delta_m} \right) \sqrt{\Delta_m} + 2m\sqrt{\Delta_m} \right) > 0 \tag{8}$$

because $a_m - \sqrt{\Delta_m} > 0$, and therefore it is a stable node or a focus.

Combining the information about the position and the stability characteristics of the critical points, we get the following asymptotic patterns for the system (Fig. 4(a), see also Fig. 1, II and III, for the definitions of points A, B and C):

Pattern I. If $\omega < 1$, $(\rho - m + \zeta(\omega - 1))^2 + 4m\zeta(\omega - 1) < 0$ and $\rho - m + \zeta(\omega - 1) < 0$ (regions U_1 and U_2, Fig. 3), then the steady state $(\omega, 0)$ is a saddle point, and the system does not have any other critical points.

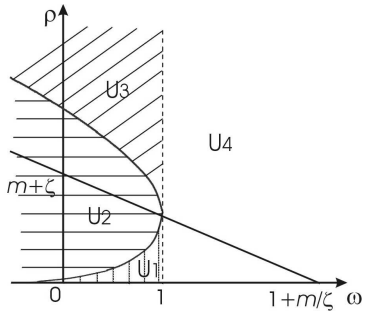


Fig. 3. Identification of the regions in the parameter space (ρ, ω) for different asymptotic patterns for the stimulation function $F_2(x, y) = xy/(m + y)$. The parabola $\Delta_m = (\rho - m + \zeta(\omega - 1))^2 + 4\zeta m(\omega - 1) = 0$ and the straight line $a_m = \rho - m + \zeta(\omega - 1) = 0$ (shown as functions $\rho = f(\omega)$ for $\zeta = \text{const}$), and the straight line $\omega = 1$. These three lines cross at the point $(1, m)$. Region U_1 ($\Delta_m > 0$, $a_m < 0$, and $\omega < 1$) and region U_2 ($\Delta_m < 0$): no critical points with $y > 0$. Region U_3 ($\Delta_m > 0$, $a_m > 0$, $\omega < 1$): two critical points with $y > 0$. Region U_4 ($\omega > 1$): one critical point with $y > 0$.

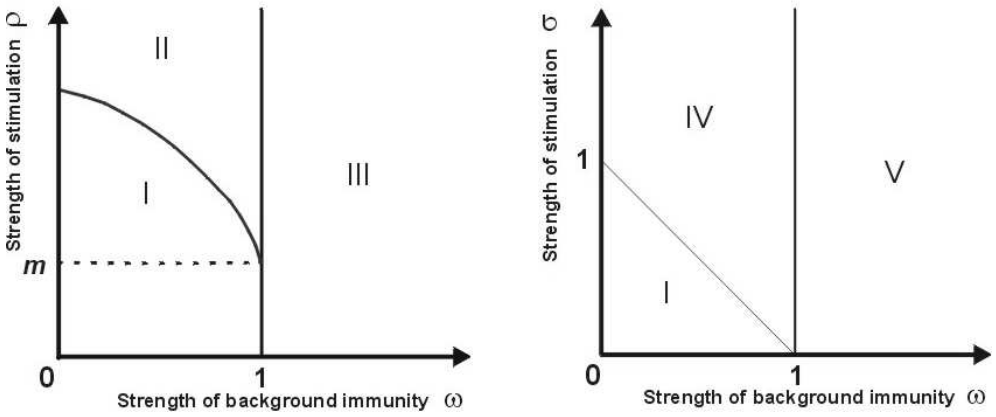


Fig. 4. Types of asymptotic behaviour for different regions of the parameter space and the stimulation function $F_2(x,y) = xy/(m+y)$: (a) the case of $f > 0$, I: unrestricted tumour growth, II: stabilization of the tumour size (a stable focus or a node, $y > 0$) if the initial tumour size is relatively small, and otherwise unrestricted tumour growth, III: elimination of the tumour (a stable node, $y = 0$) if the initial tumour size is relatively small, otherwise unrestricted tumour growth, (b) the case of $f = 0$, I: unrestricted tumour growth, IV: stabilization of the tumour size (a globally stable focus or a node, $y > 0$), V: elimination of the tumour (a globally stable node, $y = 0$).

Pattern II. If $\omega < 1$, $(\rho - m + \zeta(\omega - 1))^2 + 4m\zeta(\omega - 1) > 0$ and $\rho - m + \zeta(\omega - 1) > 0$ (region U_3, Fig. 3), then three critical points exist: the saddle point $A = (\omega, 0)$, the saddle point $C = (1, y_1)$, and the locally stable node or focus $B = (1, y_2)$.

Pattern III. If $\omega > 1$ (region U_4, Fig. 3) then two critical points exist: the locally stable node $(\omega, 0)$, and the saddle point $B = (1, y_1)$.

The case of $f = 0$, i.e., when the anti-immune activity of the tumour is absent. The asymptotic patterns of the system are as follows. The coordinates of the critical points are $(\omega, 0)$ and those of the second point B are $(1, \overline{y})$, where $\overline{y} = m(1-\omega)/(\omega - 1 + \sigma)$, and $\sigma = q/d$ takes the role of "stimulation strength". The critical point B exists if $1 - \sigma < \omega < 1$. The eigenvalues for the first equilibrium point are as in the general case. For point B the eigenvalues are $\lambda_{1,2} = (\beta_m \pm \sqrt{\beta_m^2 - 4\gamma_m})/2$, where $\beta_m = -p < 0$ and $\gamma_m = d(1-\omega)(\omega - 1 + \sigma)/\sigma > 0$. Therefore the critical point $(1, \overline{y})$ is a stable focus or a stable node. Thus the following three patterns may occur (cf. Fig. 4(b)):

Pattern I. If $\omega < 1 - \sigma$ then the system does not have any stable solution and $(\omega, 0)$ is a saddle point.

Pattern IV. If $1 - \sigma < \omega < 1$ then there are two critical points: the saddle point $(\omega, 0)$, and the globally stable focus or the node $(1, \overline{y})$.

Pattern V. If $\omega > 1$, then there is only one globally stable node $(\omega, 0)$.

Case $p = 0$, i.e., the production of the agents of the immune system is absent. For some parameter values there may exist two critical points with coordinates $(1, y_i)$, $i = 1, 2$, where $y_{1,2} = (a_{p,m} \mp \sqrt{\Delta_{p,m}})/2$, and $a_{p,m} = \rho - \zeta - m$, $\Delta_{p,m} = a_{p,m}^2 - 4\zeta m$. Combining the information about the position, the stability characteristics of the critical points and the results for the general case (cf. (6), (7) and (8) for $\omega = 0$), we get the following asymptotic patterns for the system (cf. Fig. 5):

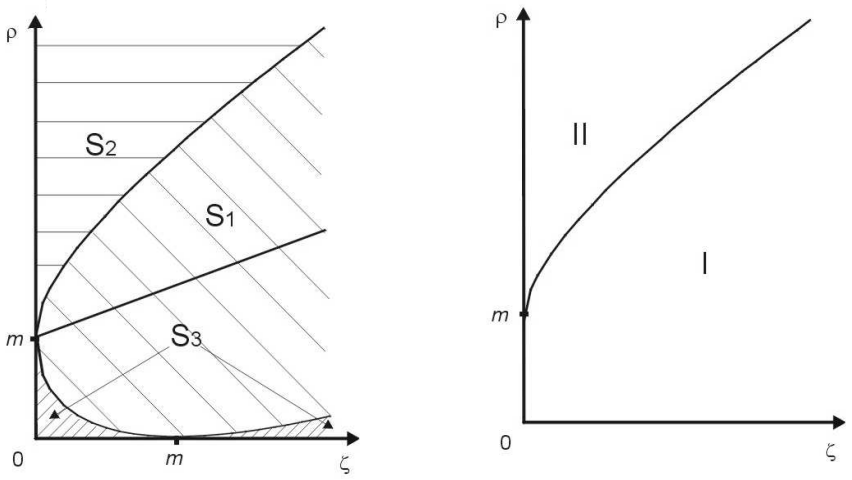
Pattern I. If $a_{p,m}^2 - 4\zeta m < 0$ or $a_{p,m}^2 - 4\zeta m > 0$ and $a_{p,m} < 0$, then the system does not have any critical point.

Non-generic pattern. If $a_{p,m}^2 - 4\zeta m > 0$ and $a_{p,m} > 0$, then two critical points exist: the saddle point $(1, y_1)$ and the neural centre $(1, y_2)$.

Stimulation function $F_3(x,y)$. Two y nullclines are described by the equations $y = 0$ and $x = 1$, respectively, and the x nullcline is characterized by the equation $(fxy^2 - y(p - fx^2 + qx - dx) - px + dx^2)/(x + y) = 0$. There always exists a critical point with coordinates $(\omega, 0)$.

General case (all system parameters are positive). Two other critical points (or only one of them, see below) exist with coordinates $(1, y_i)$, $i = 1, 2$, where $y_{1,2} = (a \mp \sqrt{\Delta})/2$ with $a = \rho - 1 + \zeta(\omega - 1)$ and $\Delta = a^2 + 4\zeta(\omega - 1)$, provided that $a \mp \sqrt{\Delta} > 0$. Note that a and Δ are specific cases of a_m and Δ_m, which were discussed for $F_2(x,y)$, for $m = 1$. Therefore the analysis of different regions in the parameter space (ω, ρ) performed for $F_2(x,y)$ is also valid for $F_3(x,y)$, see Fig. 3 and assume $m = 1$.

The eigenvalues of the linearized system for point $(\omega, 0)$ are $\lambda_1 = 1 - \omega$ and $\lambda_2 = -d$, and therefore it



(a) (b)

Fig. 5. Types of asymptotic behaviour in different regions of the parameter space (ζ, ρ) for $p = 0$ for the stimulation function $F_2(x, y) = xy/(m + y)$: (a) identification of different patterns of the critical points: the parabola $\Delta_{p,m} = (\rho - \zeta - m)^2 - 4m\zeta = 0$ and the straight line $a_{p,m} = \rho - \zeta - m = 0$ (both of them are shown as functions $\rho = f(\zeta)$). These two lines cross at the point $(0, m)$; region S_2 ($\Delta_{p,m} > 0$ and $a_{p,m} > 0$): two critical points with $y > 0$; regions S_1 ($\Delta_{p,m} < 0$) and S_3 ($a_{p,m} < 0$): no critical point with $y > 0$, (b) types of asymptotic behaviour in different regions of the parameter space, I: unrestricted tumour growth, II: oscillations of the tumour size (a center, $y > 0$) if the initial tumour size is relatively small, and otherwise unrestricted tumour growth; the regions are separated by the parabola $\Delta_p = (\rho - \zeta - m)^2 - 4m\zeta = 0$.

is a saddle point if $\omega < 1$ and a stable node if $\omega > 1$. The eigenvalues for points $(1, y_{1,2})$ are $\lambda_{1,2} = (\beta \pm \sqrt{\beta^2 - 4\gamma})/2$, where $\beta = -d + qy_{1,2}^2/(1+y_{1,2})^2 - fy_{1,2}$ and $\gamma = y_{1,2}(q/(1 + y_{1,2})^2 - f)$. Note that γ is a particular case of γ_m, which was discussed for $F_2(x, y)$, for $m = 1$, and all results for γ_1 are also valid for γ. If the system parameters are in the region U_4 (Fig. 3), then the system has a steady state $(1, y_1)$ with $y_1 > 0$. For this point $\gamma < 0$, cf. Eqn. (6), and therefore this critical point is a saddle point. If the system parameters are in the region U_3 (Fig. 3), then the system has two equilibrium points $(1, y_{1,2})$ with $y_{1,2} > 0$. The point $(1, y_1)$ is a saddle point, cf. (6) for $m = 1$. For $(1, y_2)$ we have

$$\beta = \frac{-f}{(1 + y_2)^2}\left(\zeta + \zeta(\omega + 1)y_2 + (1 + \zeta\omega)y_2^2\right) < 0 \quad (9)$$

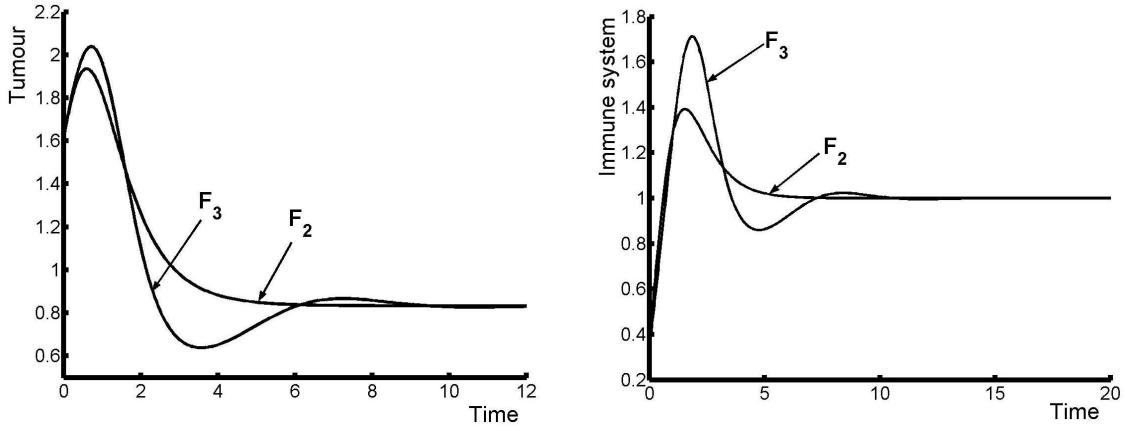
and $\gamma > 0$, cf. (8) for $m = 1$. Therefore the critical point $(1, y_2)$ is a stable node or a focus.

The case of $f = 0$, i.e., the anti-immune activity of the tumour is absent. The coordinates of the critical points are $(\omega, 0)$ and $(1, \overline{y})$ for $\overline{y} = (1-\omega)/(\omega-1+\sigma)$, cf. the case of $f = 0$ for $F_2(x, y)$. The eigenvalues for the first equilibrium point are as in the general case, and for the second point they are equal to $\lambda_{1,2} = (\beta \pm \sqrt{\beta^2 - 4\gamma})/2$, where $\beta = -d + q\overline{y}^2/(1 + \overline{y})^2 = d((1 - \omega)^2/\sigma - 1)$ and $\gamma = \overline{y}q/(1 + \overline{y})^2$. Note that $\gamma > 0$, and furthermore $\beta < 0$, because $1 - \omega < \sigma$ and $1 - \omega < 1$. Thus the signs of β and γ are the same as for $F_2(x, y)$, the case of $f = 0$, and the same three asymptotic patterns occur (cf. Fig. 4(b)).

The case of $p = 0$, i.e., the production of the agents of the immune system is absent. For some parameter values two critical points exist with coordinates $(1, y_i)$, $i = 1, 2$, where $y_{1,2} = (a_p \pm \sqrt{\Delta_p})/2$, $a_p = \rho - \zeta - 1$ and $\Delta_p = a_p^2 - 4\zeta$, $a_p \mp \sqrt{\Delta_p} > 0$. Note that a_p and Δ_p are specific cases of $a_{p,m}$ and $\Delta_{p,m}$, respectively, which were discussed for $F_2(x, y)$, for $m = 1$. Therefore the analysis of different regions in the parameter space (ω, ρ) performed for $F_2(x, y)$ is also valid for $F_3(x, y)$. Thus the same two critical points as for $F_2(x, y)$, $m = 1$ and $p = 0$ occur (cf. Fig. 5). However, there is a locally stable focus or node instead of the center in the former case.

4. Discussion

Several different asymptotic outcomes of interactions between exponentially growing tumours and the immune system were found to be predicted by the simple system of equations (1) and (2). The asymptotic patterns of interactions depend on the model parameters, the choice of the stimulation function, and also on the tumour size at the moment of the initiation of the interactions. This feature is important in view of immunotherapy that may be applied to stimulate the immune system when the tumour is already large.



(a) (b)

Fig. 6. Evolution of the tumour and the immune system in time for $q = 4$, $f = 0$, $d = 3$ and $p = 1$. Pattern II corresponds to the global stabilization of the tumour size. The approach to the equilibrium is of the node type for F_2, but of the focus type for F_3.

The general form of our model combines predator-prey and competitive $(f > 0)$ interactions. In such conditions, the elimination of the tumour by the immune system is possible only if the immune system is strong $(\omega > 1)$, the strength of stimulation is high $(\rho > 1)$, and there is no limitation on the growth rate of the immune system with an increase in the tumour size ($F = F_1$, Pattern V). The limitation on the growth of the immune system ($F = F_2$ or $F = F_3$) results in the inability to eliminate the tumour if it is too large, whereas sufficiently small tumours can be eliminated (Pattern III). A weak immune system $(\omega < 1)$ and a low strength of stimulation (small ρ) always result in unrestricted asymptotic growth of the tumour (Pattern I). A weak $(\omega < 1)$ but strongly stimulated (large ρ) immune system may stabilize small tumours if $F = F_2$ or $F = F_3$ (Pattern II), or any tumours if $F = F_1$ (Pattern IV).

The patterns with the outcome dependent on the size of the tumour (Patterns II and III) occur only if the tumour reveals any antimmune activity. Without such an activity $(f = 0)$ only global asymptotic behaviour (Patterns I, IV, and V) was found. This observation is valid for all three stimulation functions used in our model.

Another important factor, i.e., the supply of fresh precursors of the immune system $(p > 0)$ considerably increases the chances for effective treatment. If $p = 0$, the tumour may be at best stabilized at a finite size if its initial size is small (Pattern II) for $F = F_2$ and $F = F_3$, or globally stabilized if $F = F_1$, but it cannot be eliminated. This result can be interpreted in such a way that only a normal immune system with an inflow of fresh precursors which are therapeutically stimulated to start its normal activity can eliminate the tumour if some additional conditions are fulfilled.

Generally, our results match clinical and experimental findings: immunotherapy, and tumour vaccines in particular, may result in a complete or partial remission of the tumour, the stabilization of its growth, or it may fail (Chen and Wu, 1998; Fong and Engleman, 2000; Moingeon, 2001; Rosenberg, 2001). The smaller/younger the tumour, the more successful the therapy (Chen and Wu, 1998; Fong and Engleman, 2000; Moingeon, 2001; Rosenberg, 2001). It was suggested that immunotherapy should be applied not directly to large tumours, but rather after other forms of therapy, such as surgery, chemotherapy or radiotherapy, which reduce the tumour size, but sometimes are not able to remove it completely (Chen and Wu, 1998). These general findings from clinical studies reflect our analysis, but typically it is not possible to identify the factors which are involved into a successful outcome or a failure to respond to the therapy. Our results point out the strength of the background immunity, i.e., the immune capacity which is stimulated to be active by the therapy, the strength of the stimulation of the immunity growth by the tumour itself, the supply of fresh precursors of the immunity, and the tumour size at the moment of the initiation of the therapy.

No difference in the possible asymptotic behaviour was found between the models with the stimulation function being a switching function of the tumour size (F_2) and that of the ratio of the tumour to the immunity sizes (F_3). Furthermore, the division of the parameter space (ω, ρ, ζ) into regions with different asymptotic patterns for F_3 was the same as for F_2 with $m = 1$. However, this does not mean that there is no difference in the dynamic behaviour of the systems with F_2 and F_3. In fact, the non-dimensional forms of the equations were obtained by different transformations, and therefore the models with the same primary parameters w, u, a, h, b

and r but different stimulation functions (F_2 or F_3) may behave differently. Another difference may appear in Pattern II (local stabilization of the tumour size). This pattern combines two kinds of asymptotic behaviour: an oscillatory or a uniform approach to the equilibrium. The separation of these two sub-patterns may happen in models with different stimulation functions and the same parameters, as can be seen from computer simulations for F_2 and F_3 (cf. Fig. 6). Therefore, it is in principle possible to differentiate between the dynamics with F_2 and those with F_3 from observations.

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