ANTI - TUMOUR IMMUNITY AND TUMOUR ANTI - IMMUNITY IN A MATHEMATICAL MODEL OF TUMOUR IMMUNOTHERAPY

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ABSTRACT

A two-dimensional system of ordinary differential equations is used to characterise the basic types of phase portraits of the immune system - tumour interactions model, and to study the impact of anti - immune activity by tumour on the outcome of immunotherapy. The focus is on specific (acquired) immunity and different forms of immunotherapy as active therapy with in vivo stimulation of the immunity, and passive one with infusion of ex vivo produced specific immunity. The analysis is performed for two families of stimulation function, which describes the dynamics of the stimulation of the immune system by tumour antigens: 1) antigen dependent, and 2) antigen per one immunity unit dependent functions, with Michaelis - Menten and sigmoid functions in each family. We show that there are no limit cycles in the system, and that anti - immune activity by tumour changes all equilibrium points from global to local ones. In the latter case the immune system has no control over the growth of large tumours. Furthermore, if the immunity is weak, the immune system cannot eradicate even small tumours. The weak immunity and stimulation strength result in unrestricted tumour growth. The patterns of asymptotic behaviour of the system do not depend on the type of the stimulation function, but do depend on its parameters. Our results reflect the basic clinical and experimental knowledge about immunotherapy and its effectiveness, and yield new suggestions for an efficient immunotherapy.

Key words or phrases: ordinary differential; equations; stability analysis; phase portrait; tumour vaccine; immune response

INTRODUCTION

Tumour immunotherapy is a fast growing field of experimental and clinical studies aimed on stimulation of the immune system for destroying tumour cells and delaying tumour growth [15]. The natural immunity can prevent the growth of some tumours, but many other can escape immune surveillance by various means [12, 15]. Lymphocytes sensitive to tumour antigens are typically present in the body, but the full development of the immune response does not occur. Moreover, even if it occurs, the tumour cells can protect themselves from contacts with lymphocytes, or destroy them by providing apoptotic signals during the contact [15]. Therapeutic stimulation or creation of anti - tumour immunity may be achieved by many different ways, in accordance with various types of the immune response. Native, non - specific immunity may be stimulated by incubation of patient's natural killer lymphocytes with interleukin 2 to enhance their activity, and then their reinfusion into the patient [15]. Tumours have characteristic antigens, and the acquired, antigen specific immunity can be boosted as well. This can be achieved passively, as for example by ex vivo creation of antibodies against tumour antigen and their infusion into the body [15]. Another form of passive specific immunotherapy is the ex vivo growth of patient's tumour specific cytotoxic lymphocytes and their infusion back to the patient [15].

Active immunisation consists in an external stimulation of patient's immune system for its normal (or even enhanced) activity [15]. It may be preventive, as are most of vaccines against infectious parasites, or therapeutic, i.e. applied during the disease. The preventive vaccination against tumours is usually not possible because one cannot predict in general what tumour antigens will appear [15]. Nevertheless, some promising animal experiments with preventive tumour vaccine has already been performed [9]. In contrast, the therapeutic active vaccine against growing tumours may be prepared using the existing tumour cells as templates. Such procedure is possible with tumours but not with most infectious diseases (except rabies) because of relatively slow growth rate of tumours compared to that of infectious parasites [15].

A failure in efficient presentation of tumour antigens to T helper cells and T cytotoxic cells was found to be among the major reasons for the weakness of specific anti-tumour immune response. Promising new tumour vaccines are based on loading antigen presenting cells (mainly dendritic cells) with tumour specific antigens, and enabling the efficient presentation of tumour antigens to competent, antigen specific lymphocytes [15, 16].

The immune response directed against the antigen involves a few types of cells. B lymphocytes, which produce antibodies, and cytotoxic T lymphocytes are the effector cells that directly participate in the destruction of the antigen and the antigen bearing cells [13]. However, the efficient development of the immune response needs T helper lymphocytes that provide growth factors and other signals necessary for the multiplication and differentiation of lymphocytes [13]. T suppressor cells may also appear to terminate the immune response [13]. All these four lines of cells are present in the body in the form of small number of precursor cells, and only after the appearance of the antigen, the cells get activated and may start to multiply [13, 14]. Their number increases, and some of them may differentiate into effector cells and others into memory cells [13, 14].

The tumour vaccination may start the immune response at various stages of the tumour growth. The state of the immune system at the initial moment may also be manipulated because of possible passive immunisation that changes the number of antibodies or/and cytotoxic lymphocytes. Other cell types, antigen presenting cells, T helper cells, etc. can also, at least in principle, be prepared ex vivo and infused into the body. Thus, the question: "How the initial state of the system influences the final outcome of the therapy?" is of practical importance. In the mathematical model the initial position of the system in the phase space may be selected in different ways, and we are interested in the relationship between the asymptotic behaviour of the system and its initial state. Furthermore, the activity of the cells and intensity of the cell-cell interactions may be to some extent therapeutically changed by providing auxiliary cytokines and other (so called secondary) signals that change the kinetics of interactions. Again, in mathematical model, this opportunity to manipulate the interaction intensity yields a question about the relationships between the values of the model parameters and the asymptotic state of the system. The natural scatter of the immune characteristics among the patients also leads to the same problem. Therefore, the classic problem of mathematical modelling — the characterisation of asymptotic states of the system within the parameter space and on the phase space — has, in the case of modelling of tumour immunotherapy, its practical counterpart.

The immune response is a very complex phenomenon and its realistic description needs many variables to be taken into account. A model of the humoral immune response, a part of the immune response that involves only the growth of antibody producing B lymphocytes with the help of growth factor produced by T helper cells, was based on 12 variables and the respective ordinary differential equations [14]. Such models are studied using numerical simulations [14]. To gain some insight into the possible behaviour of the system simplified models are formulated. Although they cannot provide the detail description of the dynamics of the system, they may be applied for qualitative understanding of some relationships involved in the modelled phenomena [2, 10, 11, 14].

We investigate a simple model with only two variables: 1) the size of tumour, Y, and 2) the size of specific anti-tumour immunity, X. Our main goal is to characterise all possible outcomes of the interactions between the tumour and the immune system and to understand how the anti-immune activity of the tumour can influence the natural or therapeutically induced immune response. This anti-immune activity can involve a few different phenomena. Antibodies usually bind antigens and the antibody-antigen complexes are destroyed. In this way antibodies are removed from the pool of free antibodies [2, 10, 14]. Lymphocytes, in particular T cytotoxic lymphocytes, which form conjugates with tumour cells to kill them, can get apoptotic signals through Fas ligands expressed on the surface of some tumour cells and enter the process of self-destruction [15]. It is obvious that such tumour activity diminishes the chance of successful therapy. We evaluate what is the impact of this activity on the asymptotic states of the system in relation to the values of the model parameters. In particular, we provide global classification of the possible phase portraits of the system with and without anti-immune activity of the tumour. The obtained asymptotic behaviours of the system match all typically reported outcomes of clinical and experimental studies on immunotherapy (see Discussion).

All our results are obtained for two alternative families of the so called stimulation functions. Stimulation may be defined as the fraction of cells X stimulated by a signal S for some transformation. In our model X denotes immunocompetent cells, S denotes antigen, and the stimulated process is the multiplication of cells (i.e. the growth of the population X). In general, stimulation function F is a function of S and X. However, the stimulation functions were also applied for the description of many other processes, as for example the stimulation of lymphocytes by interleukins for proliferation or differentiation [14]. Two different functions $F(S,X)$ were previously applied for the description of the immune response [2, 10, 14]: 1) ratio dependent stimulation function $F_1(S,X) = \frac{(S/X)^\alpha}{k^\alpha + (S/X)^\alpha}$, and 2) signal dependent simulation function $F_2(S,X) = \frac{S^\alpha}{k^\alpha + S^\alpha}$. In both cases k denotes the sensitivity of population X to signal S (but it is a different parameter in each case, e.g. it has different physical units). If one defines $s = S/X$ in the first case, and $s = S$ in the second case, then in both cases one has the same function $F(s) = s^\alpha/(k^\alpha + s^\alpha)$. Parameter α describes the switching characteristic of the function, with Michaelis-Menten function for $\alpha = 1$ and S-shaped functions for $\alpha > 1$.

In the case of the ratio dependent function F_1 the stimulation depends on the amount of signal molecules per one cell. This means, that each cell must be stimulated by some critical number of signal molecules to enter the transformation, or, more precisely that the probability of the stimulation of one cell depends on the number of molecules in the vicinity of this cell. This function was proposed by Prikrylova and applied in modelling of the immune response for $\alpha = 2$ [14]. The second function assumes that the given amount of signal can stimulate the same fraction of X population independently of the size of X. It was applied in a few models [2, 10]. A similar distinction between ratio dependent and prey dependent functions (with $\alpha = 1$) was recently made in ecological modelling, and the ratio dependent function was found to have many interesting properties [5, 6, 7]. Our model, although it has some features of the predator-prey model, has a different mathematical structure than typical ecological models, and the mechanistic interpretation of the stimulation function is also different. We show, that in our model the asymptotic states of the system are the same for F_1 and F_2, but models with $\alpha > 1$ have a class of phase portraits that is absent in models with $\alpha = 1$. The case $\alpha = 1$ was already investigated in [18].

MODEL FORMULATION

The model describes the interactions between the immune system and tumour using two variables: X for the size of overall specific immunity against tumour, and Y for the size of tumour, or, to be precise, the amount of tumour antigen(s). In the absence of antigen or if the antigen is not effectively presented to the immune system, two processes has to be taken into account [14]: 1) the constant production at the rate w of precursor cells that are able to respond to the antigen, and 2) the natural death of these precursors at the rate uX. As the result of those two processes the constant level of the immunity is kept within the body; we call it the background or native immunity, and it will be shown to be crucial for the outcome of the therapy. The initial state of the immunity need not however to be the same as the background immunity. As mentioned in Introduction, passive forms of tumour vaccines may increase X over its background value at the start of the therapy or during it.

The appearance of antigen or its therapeutic presentation to the immune system initiates the fast increase in the size of immunity [13, 14]. The rate of growth is assumed to be proportional to the actual immunity X, and the coefficient of proportionality F is itself a function of the tumour, Y, and immunity, X, sizes. This coefficient of proportionality is called the stimulation function (see Introduction). Finally, the maximal possible (i.e. for $F = 1$) growth rate a of one unit of immunity is another crucial parameter for the asymptotic behaviour of the system.

The immunity can be destroyed by the tumour (see Introduction) and this process is described by the bilinear function XY (e.g. as for a chemical process of antigen-antibody interaction [2, 14], or tumour cell-cytotoxic lymphocyte conjugate formation [8]) with the rate constant b. If this kind of anti-immunity is absent, then $b = 0$.

The tumour growth is a complex process with different phases and different rates. Human tumours often grow irregularly with phases of fast increase separated by phases of dormancy [3]. In contrast, some experimental tumours grow exponentially until the death of the host [17]. The growth of other experimental tumours was shown to be well described by logistic or Gompertz functions [1]. We assume an exponential growth of tumour with the rate rY mainly for the mathematical simplicity reason that enables us with full characterisation of phase portraits of the system. The destruction of the tumour by the immunity agents is described by the bilinear function XY with the rate constant c.

The above assumptions yield the following system of ordinary differential equations:

$$\left\{ \begin{array}{lcl} \frac{dX}{d\tau} & = & w - uX + aF(X,Y)X - bXY \\ \frac{dY}{d\tau} & = & rY - cXY \end{array} \right. , \tag{1}$$

where w, u, a, r, $c > 0$, $b \geq 0$ are parameters (rate constants) that characterise the rate of immunity production, immunity decay, multiplication of immunity after the stimulation by antigen, tumour growth, tumour decay due to activity of the immune system, and decline of immunity due to interactions with the tumour, respectively, and τ denotes time. F is a function that describes the fraction of immunity activated by the antigen to proliferate (stimulation function). Two different forms of F, i.e. $F = F_1$ and $F = F_2$, are considered, where:

$$F_1(X,Y) = \frac{(Y/X)^\alpha}{k_1^\alpha + (Y/X)^\alpha}, \tag{2}$$

$$F_2(X,Y) = \frac{Y^\alpha}{k_2^\alpha + Y^\alpha}, \tag{3}$$

with k_1, $k_2 > 0$, and $\alpha \geq 1$.

We study Eqs. (1) in the phase space $\mathrm{R}^+ \times \mathrm{R}^+ \backslash (0,0)$, where the exclusion of $(0,0)$ point is related to the definition of a stimulation function F_1.

To formulate a non-dimensional version of the model we define at first $X_0 = r/c$, and then, without loosing the generality of consideration, an equivalence relationship between functions F_1 and F_2 by putting $k_1 = k$ and $k_2 = kX_0$. Using non-dimensional variables $x = X/X_0$, $y = Y/(kX_0)$, $t = r\tau$, and non-dimensional parameters $p = cw/r^2$, $d = u/r$, $q = a/r$, $g = bkX_0/r$, one gets the following non-dimensional version of the model:

$$\left\{ \begin{array}{lcl} \frac{dx}{dt} & = & p - dx + qf(x,y)x - gxy \\ \frac{dy}{dt} & = & y(1-x) \end{array} \right. , \tag{4}$$

with f in the form of

$$f_1(x,y) = \frac{(y/x)^\alpha}{1+(y/x)^\alpha}, \tag{5}$$

or

$$f_2(x,y) = \frac{y^\alpha}{1+y^\alpha}. \tag{6}$$

We use also another parametrisation of the model:

$$\left\{ \begin{array}{lcl} \frac{dx}{dt} & = & d\left[\omega - x + \rho F(x,y)x - \psi xy\right] \\ \frac{dy}{dt} & = & y(1-x) \end{array} \right. , \tag{7}$$

where $\omega = p/d$ is called the *native (background) immunity* (i.e., the level of immunity in the absence of antigen), $\rho = q/d$ is the *stimulation strength*, and $\psi = g/d$ is the *strength of anti-immune activity*. The parameter $\mu = \omega - 1 + \rho$ is called the *(overall) immune capacity*.

Now, the studied problems can be made precise: 1) What are possible asymptotic behaviours of the system with Eqs. (7) and how do they depend on the model parameters? 2) What is the role of tumour-based anti-immunity ($\psi = 0$ vs. $\psi > 0$)? 3) How does the choice of F and α influence the asymptotic behaviour of the system?

ASYMPTOTIC STATES

Our main goal is to study asymptotic properties of Eqs. (7). To do this one needs to know that the solutions exist for every $t > 0$. Hence, we formulate the following lemma (for the proof of this Lemma and Theorems presented in this Section see Appendix).

Lemma 1. *If x_0, $y_0 > 0$, then for every $t > 0$ there exists an unique positive solution to Eqs. (7).*

Knowing that the solution to Eqs. (7) exists for every $t > 0$, one can study its asymptotic behaviour. At the beginning we show that there are no limit cycles and periodic orbits to Eqs. (7).

Theorem 1. *There is no periodic solution to Eqs. (7).*

The next step is to find equilibrium states. The equations for the nullclines of the system are:

$$\omega - x + \rho f(x,y)x - \psi xy = 0, \tag{8}$$

for x - nullcline, and

$$\begin{array}{rcl} y & = & 0 \\ x & = & 1 \end{array}, \tag{9}$$

for y - nullclines. There exists an equilibrium point A for $y = 0$ with $x_A = \omega$, $y_A = 0$. The eigenvalues of the Jacobian are equal to $\lambda_1 = 1 - \omega$, $\lambda_2 = -d$. Thus, A is a saddle point for $\omega < 1$, and a stable node for $\omega > 1$. This result holds for both f_1 and f_2.

Other equilibrium points may be found for $x = 1$ and $y > 0$. In this case, they have to be solutions to Eq. (8) with $x = 1$ and $f(1, y) = f_1(1, y) = f_2(1, y) = y^\alpha/(1 + y^\alpha)$. Using this expression for $f(1, y)$ one gets:

$$\frac{(\omega - 1 - \psi y)(1 + y^\alpha) + \rho y^\alpha}{1 + y^\alpha} = 0, \tag{10}$$

which is equivalent to the equation $H(y) = 0$, with $H(y) = (\omega-1+\rho-\psi y)(1+y^\alpha)-\rho$.

At first we discuss the case of absent anti - immune activity by the tumour, $\psi = 0$.

Theorem 2. *Let $\psi = 0$. If $\omega < 1$, then there is one equilibrium point to Eqs. (7) with $y > 0$ and $x = 1$, and it is a globally stable node or focus. If $\omega > 1$, then there is no equilibrium point with $y > 0$ and $x = 1$.*

In the case $\psi > 0$ (i.e., with anti - immune response present), we show that beside the equilibrium point A with $x_A = \omega$, $y_A = 0$, Eqs. (7) may have up to three other equilibrium points.

Theorem 3. *Let $\psi > 0$. If $\omega < 1$, then there are no or two equilibrium points to Eqs. (7) with $y > 0$ and $x = 1$. If there are two equilibrium points B and C with $x = 1$ and $y > 0$ such that $y_B < y_C$, then $B(1, y_B)$ is a stable node or focus, and $C(1, y_C)$ is a saddle point. If $\omega > 1$, then there are one or three equilibrium points with $y > 0$ and $x = 1$. If there is one such equilibrium point B or there are three such equilibrium points B, C and D with $y_B < y_C < y_D$, then $B(1, y_B)$ is a saddle point, $C(1, y_C)$ is a stable node or focus, and $D(1, y_D)$ is a saddle point.*

DISCUSSION

In the analysis of the model described by Eqs. (7) six different types of phase portraits were found. In all six cases, if there is no tumour the immune system tends asymptotically to its background level ω. However, if the initial tumour size is higher than zero then one of the following pattern may happen (Figure 7): 1) asymptotic unrestricted growth (UG) of tumour independently of the initial size of tumour, 2) globally stable equilibrium (GS) with finite size of tumour, i.e. the stabilisation of tumour growth by the immune system independently of the initial size of tumour, 3) global eradication (GE) of tumour by the immune system independently of the initial size of tumour, i.e. globally stable equilibrium with no tumour, 4) local stabilisation (LS) of tumour growth at finite size, what means the stabilisation of tumour growth if the initial size of tumour is small and otherwise infinite tumour growth, i.e. locally stable equilibrium with finite size of tumour, 5) local eradication

(LE) of tumour, which is the same as LS but with zero size of tumour at the locally stable equilibrium, and 6) bi-stability (BS) with eradication of tumour if its initial size is small, stabilisation of tumour growth if its initial size is medium, and infinite growth of large tumours, i.e. two locally stable equilibria exist — one with zero tumour size and the other with finite tumour size — and there is an area of phase plane with trajectories of infinite tumour growth. The expressions "small", "medium", and "large" for tumour size in cases 4 - 6 are of course relative and must be defined separately for each set of the model parameters and the initial size of the immunity. In the cases of locally stable equilibrium states the region of the phase plane with infinite growth of tumour is separated from the attraction basins of the equilibrium states by the stable manifolds of the saddle point.

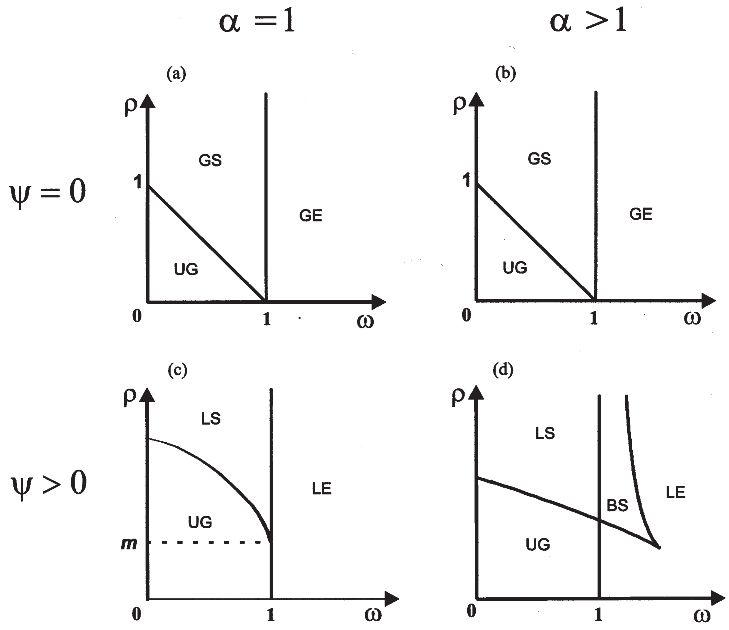

Fig. 1. Asymptotic pattern outcomes of the system (7) for $\alpha \geq 1$ and $\psi \geq 0$. Region UG: unrestricted tumour growth. Region GS: global stabilisation. Region GS: global eradication. Region LS: local stabilisation. Region LE: local eradication. Region BS: bi-stability.

The background immunity ω is an important parameter for the system. If $\omega < 1$ then the immune system is too weak to eradicate the tumour completely. At most, it can stabilise the tumour size (Figure 7). Note that the parameter ω can be defined as $\omega = \bar{X}/X_0$, where $\bar{X} = w/u$ is the immunity level without antigen, and $X_0 = r/c$ is the level of immunity which can stop (at least transiently, $dY/d\tau = 0$) the growth of tumour. Thus, to be able to eradicate the tumour the background level of immunity must be higher than the level of immunity that stops the tumour growth. The cases (rather rare) of complete remission of tumours after immunotherapy show that such strong immune systems exist. Unfortunately, the failure of the treatment is more often. Can the balance be shifted to the immune system by any therapeutic measures? The parameters u (natural decay rate constant of the immunity) and r (growth rate constant for tumour) are rather out of the scope of immunotherapy.

Nevertheless, the tumour growth rate r may be reduced by chemotherapy or combined immuno- and chemotherapy [17]. On the other hand, the parameter w (the natural inflow of fresh immune agents to the system) may be increased by persistent repeated infusions of ex-vivo grown lymphocytes and/or antibodies. Currently, only single infusions are applied, which, in mathematical language, change the state of the immune system but not the parameters that describe its kinetic characteristics. Single infusions of immune agents may move the system across the separatrices of different attractors, which also may be of benefit for the patient. Thus, $\bar{X} = w/u$ may be increased by increasing w. Furthermore, $X_0 = r/c$ may be decreased by increasing c that describes the anti - tumour activity of the immune system. Various means for that, as infusion of cytokines and other helper factors concomitantly with active in-vivo immunisation against the tumour, are under experimental or clinical examination [15]. Even the tumour cells themselves can be genetically engineered to provide secondary signals for lymphocytes [15]. One can hope that combination of various therapeutic measures can result in the characteristics favourable for the immune system.

Another important parameter is the stimulation strength, $\rho = a/d$, which is an intrinsic characteristic of the immune system. The finding that tumour antigen are not presented to lymphocytes, i.e. $a = 0$, yielded the method of artificial loading of antigen presenting cells (APC) with tumour antigen to get $a > 0$. However, if the immune system is weak, $\omega < 1$, then the stimulation strength should be high to stop the growth of tumour (Figure 7). The most common situation for aggressive tumours is perhaps weak immune system ($\omega < 1$) and weak (or non - existing) stimulation (small ρ). The anti - immune tumour activity ($\psi > 0$) increases of course the critical value of ρ, over which an effective immune response is possible (Figure 7).

In clinical cases and experimental studies of immunotherapy one observes: 1) failure of the therapy, what means an unrestricted tumour growth, 2) stabilisation, at least transient, of the tumour size, and 3) regression of tumour [15, 16]. The general clinical experience is that the earlier the anti - tumour therapy is started the better outcome is obtained. In the case of immunotherapy this observation is related to the tumour size and the ineffectiveness of this therapy against large tumours [15]. Therefore, immunotherapy is considered to be the treatment applied mainly after the decrease in the size of tumour by other therapies (surgery, chemotherapy, radiotherapy). Its main role is expected to be in the removal of metastases and the prevention of reoccurrence of the tumour. This observation may suggest that mathematical patterns of local eradication or stabilisation of tumour better describe the real behaviour of the system than the patterns based on globally stable equilibria. Our results show that the observed limitation of successful immunotherapy to small tumours may be related to anti - immune activity of the tumour: with non-zero anti - immunity ($\psi > 0$) the eradication or stabilisation of large tumours is not possible (Figure 7). Therefore, the models with anti - immunity may be considered as more realistic description of the typical behaviour of the system.

Persistent oscillations of the tumour size are not reported in medical literature. Consistently with this lack of medical and experimental data, our model does not describe any limit cycles in the system.

No difference in the asymptotic dynamics patterns of the system between models with two types of stimulation function, F_1 and F_2, was found. This fact comes basically from the common non-dimensional version of the model which follows the equivalence between the two types of stimulation function, which is described in Section 2. Thus, for any function F_1 one may find such value of parameter k_2 in function F_2 (with the same α as in F_1) that the positions of equilibrium points are the same for F_1 and F_2. The stability analysis showed also that the stability of those points is the same in both models. However, the detailed type of stability (focus vs. node) may depend on the choice between F_1 and F_2 [18].

There is a difference in the possible types of phase portraits between the stimulation functions with $\alpha > 1$ and those with $\alpha = 1$. If $\psi > 0$ and $\alpha > 1$ then, for some values of the parameters of the system, there are two locally stable equilibria of the system: one without the tumour, and the other with the stabilised tumour size (Figure 7).

APPENDIX

In this Section we present the proofs of lemma and theorems formulated in Section "Aymptotic states".

Lemma 1.

Proof. The second equation of Eqs. (7) is equivalent to the following integral one:

$$y(t) = y_0 \exp\left(\int_0^t (1 - x(s))ds\right).$$

Therefore, if $y_0 > 0$, then $y(t) > 0$ for every $t > 0$, for which the solution exists. Let us study the first variable $x(t)$. If it becomes negative, then there exists the point t_1, such that $x(t_1) = 0$ and $\frac{dx}{dt}(t_1) \leq 0$. Knowing that $y(t_1) > 0$, one obtains $\frac{dx}{dt}(t_1) = d\omega > 0$, which contradicts the definition of t_1. Hence, if the solution exists, then it is positive for positive initial data.

For every x_0, $y_0 > 0$, there exists a neighbourhood of the point (x_0, y_0), such that the right-hand side of Eqs. (7) is of class $\mathbf{C}^1$. This implies that the solution exists and it is unique. Now, we show that it exists for every $t > 0$. Assume that it exists only on finite interval $(0, t^*)$. It is easy to see that $y(t) \leq y_0 \exp(t^*)$. Moreover, $\frac{dx}{dt} \leq d(\omega + \rho x)$, which yields $x(t) \leq (x_0 + d\omega t^*) \exp(d\rho t^*)$. Therefore, both variables and their derivatives are bounded. This allows us to extend the solution through the point t^*. Hence, the solution exists for every $t > 0$. □

Theorem 1.

Proof. This may be proved using the Dulac criterion [4]. Namely, denoting the right-hand side of Eqs. (7) as:

$$\left\{ \begin{array}{lcl} U(x,y) & = & d\left((\omega - x) + \rho f(x,y)x - \psi xy\right) \\ V(x,y) & = & y(1-x) \end{array} \right., \tag{11}$$

and defining an auxiliary function $B(x,y) = 1/(xy)$, one gets that the divergence div of the vector field (BU, BV): $div = \frac{\partial(BU)}{\partial x} + \frac{\partial(BV)}{\partial y}$, is negative for all x, $y > 0$. This follows from the observation that BV is independent of y, and BU is a decreasing function of x for both f_1 and f_2 and for all x, $y > 0$. $\square$

Theorem 2.

Proof. For $\psi = 0$ the equation $H(y) = 0$ reduces to $\mu(1 + y^\alpha) = \rho$. Assuming $\mu = \omega - 1 + \rho \neq 0$, one gets:

$$y^\alpha = \frac{\rho}{\mu} - 1 = \frac{1-\omega}{\rho - (1-\omega)}. \tag{12}$$

This solution exists and is positive if $\omega < 1$ and $\rho > 1 - \omega$. Under these conditions, Eqs. (7) has the second equilibrium point B with the co-ordinates:

$$\begin{cases} x_B &= 1 \\ y_B &= \left(\frac{1-\omega}{\rho-(1-\omega)}\right)^{1/\alpha} \end{cases}. \tag{13}$$

The direct calculation of the Jacobian J to Eqs. (7) at the point B demonstrates that $\operatorname{tr} J < 0$ and $\det J > 0$, and this means that B is a stable focus or node. $\square$

Theorem 3.

Proof. To proof these statements about equilibrium points let us define the auxiliary function $h(y) = H(y)/\psi = [(\nu - y)(1 + y^\alpha) - \sigma]$, where $\nu = \mu/\psi = \sigma + \zeta(\omega - 1)$ with $\sigma = \rho/\psi$ and $\zeta = 1/\psi$, and consider the equation

$$h(y) = 0. \tag{14}$$

Note that $h(0) = \nu - \sigma = \zeta(\omega - 1)$, and $h(y) \to -\infty$ for $y \to +\infty$.

If $\nu > \sigma$ (i.e. $\omega > 1$), then $h(0) > 0$, and Eq. (14) has at least one solution. If $\nu < \sigma$ (i.e. $\omega < 1$), then $h(0) < 0$, and Eq. (14) may have no solutions. To find the number of solutions to Eq. (14), we examine the number of local extrema y_m of $h(y)$ and the sign of $h(y_m)$. These local extrema are defined by the solutions to $h'(y) = 0$. Calculating the derivative $h'(y) = [\alpha\nu - (\alpha + 1)y]y^{\alpha-1} - 1$ one can see that the equation $h'(y) = 0$ is equivalent, for $y > 0$, to the equation

$$G(y) = K(y), \tag{15}$$

where $G(y) = \alpha\nu - (\alpha + 1)y$ and $K(y) = y^{1-\alpha}$.

Case $\nu < 0$. For $\nu < 0$, we have $G(y) < 0$, whereas $K(y) > 0$, and therefore, Eq. (15) has no solutions.

In the following, we consider the case $\nu > 0$. It is obvious that K is convex and G is a linear function of y. Therefore, Eq. (15) may have at most two solutions, Figure 1.

Case $\nu > 0$ **and** $\alpha > 1$. For each $\alpha > 1$ there exists a critical value ν_α of ν, such that for $\nu < \nu_\alpha$ there is no solution to Eq. (15), for $\nu > \nu_\alpha$ there are two solutions to Eq. (15), and for $\nu = \nu_\alpha$ there is one solution to Eq. (15), Figure 1.

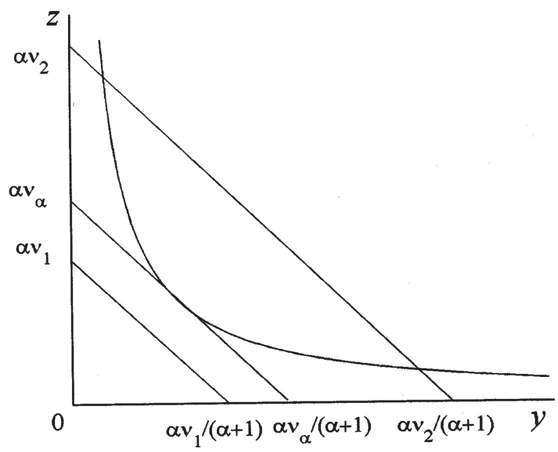

Fig. 2. Three possible arrangements of the curve $K(y)$ and the straight line $G(y)$ for $\alpha > 1$. For $\nu = \nu_1$ there is no solution to Eq. (15), for $\nu = \nu_2$ there are two solutions to Eq. (15), for $\nu = \nu_\alpha$ there is one solution to Eq. (15)

Exactly one solution exists if the tangent lines to G and K coincide for $\nu = \nu_\alpha$ at some $y > 0$. The equation of the tangent line to G at $y = \tilde{y}$ is $z = G(\tilde{y}) + G'(\tilde{y})(y - \tilde{y})$, where $G'(\tilde{y}) = -(\alpha + 1)$, and the equation of the tangent line to K at $y = \tilde{y}$ is $z = K(\tilde{y}) + K'(\tilde{y})(y - \tilde{y})$, where $K'(y) = -(\alpha - 1)y^{-\alpha}$. Using the equation $G'(\tilde{y}) = K'(\tilde{y})$ one gets that $\tilde{y} = [(\alpha + 1)/(\alpha - 1)]^{-1/\alpha}$, and from $G(\tilde{y}) = K(\tilde{y})$ that $\nu_\alpha = [\tilde{y}^{1-\alpha} + (\alpha + 1)\tilde{y}]/\alpha = [(\alpha + 1)/(\alpha - 1)]^{(\alpha-1)/\alpha} > 1$. Thus, $h(y)$ has no extremum for $\nu < \nu_\alpha$, and it has two local extrema for $\nu > \nu_\alpha$ (The investigation of $h''(y)$ shows that for $\nu \neq \nu_\alpha$ and y such that $h'(y) = 0$, $h''(y) \neq 0$). However, the existence of local extrema does not guarantee the existence of additional solutions to Eq. (14). To find such conditions we need to discuss the sign of $h(y_m)$ at the points of local extremum y_m.

If $\nu > \nu_\alpha$ and $\nu < \sigma$ (i.e. $\omega < 1$ and $h(0) < 0$), then the necessary and sufficient condition for the existence of two solutions to Eq. (14) is that $h(y_{\max}) > 0$ (Figure 2a). If $\nu > \nu_\alpha$ and $\nu > \sigma$ (i.e. $\omega > 1$ and $h(0) > 0$), then the necessary and sufficient condition for the existence of three solutions to Eq. (14) is that $h(y_{\max}) > 0$ and $h(y_{\min}) < 0$, where $y_{\max}$ and $y_{\min}$ are the positions of maximum and minimum of $h(y)$, respectively (Figure 2b).

Thus, we need to evaluate the sign of $h(y_m)$, where y_m is the position of an extremum of $h(y)$, and therefore, it must be a solution to the equation $h'(y_m) = 0$. This yields that $y_m^\alpha = y_m[\alpha\nu - (\alpha + 1)y_m]^{-1}$. Using this expression for y_m^α in the definition of h, one gets:

$$h(y_m) = \frac{\alpha y_m^2 + b y_m + c}{\alpha\nu - (\alpha + 1)y_m}, \tag{16}$$

where $b = -[2\alpha\nu - (\alpha + 1)\sigma]$ and $c = \alpha\nu(\nu - \sigma)$. Note that $y_m < y_0 = \alpha\nu/(\alpha + 1)$, where y_0 is the solution to the equation $G(y) = 0$, Figure 2. Therefore, the denominator in Eq. (16) is always positive. The sign of $h(y_m)$ changes at $y_{m,cr}$ such

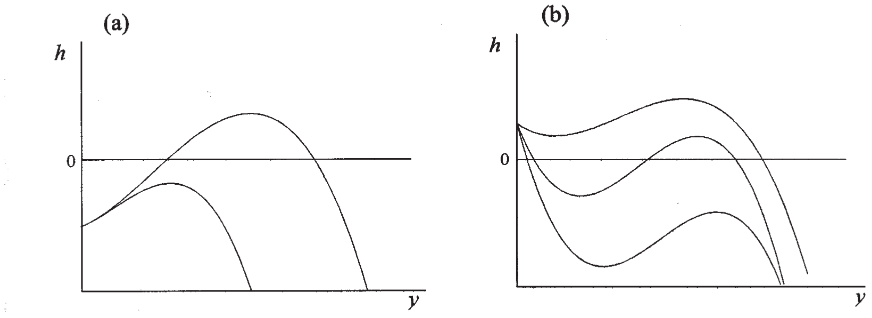

Fig. 3. Possible shapes of the function $h(y)$. a) If $\omega < 1$ then $h(y)$ has no or two positive roots. b) If $\omega > 1$ then $h(y)$ has one or three positive roots.

that $h(y_{m,cr}) = 0$, or, from Eq. (16), $\alpha y_{m,cr}^2 + b y_{m,cr} + c = 0$. This implies:

$$y_{m,cr} = \frac{-b \pm \sqrt{b^2 - 4\alpha c}}{2\alpha}. \tag{17}$$

For $\nu > \sigma$ we have $b < 0$ and $c > 0$. To get real values of $y_{m,cr}$, we need the condition $b^2 - 4\alpha c \geq 0$, which means that $\sigma \geq 4\alpha\nu/(\alpha+1)^2$. With this condition, both values of $y_{m,cr}$ are positive. For $\nu < \sigma$ we have $c < 0$, and there exists only one positive $y_{m,cr}$. The summary of all obtained conditions for numbers of equilibrium points is presented in Figure 3.

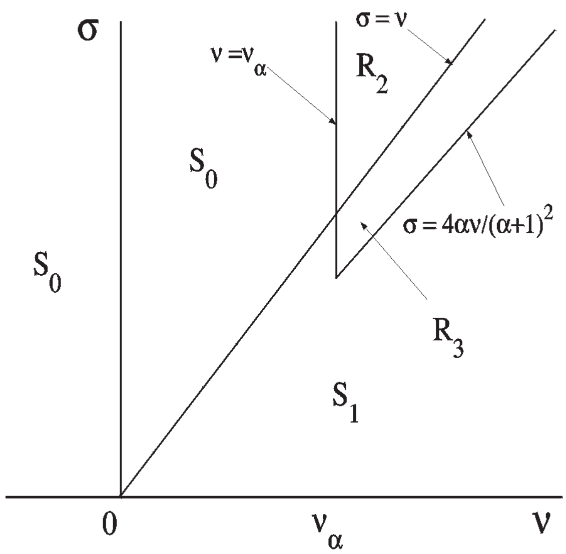

Fig. 4. The possible number of solutions to Eq. (14) in relation to parameters σ and ν. S_0 — no solution, S_1 — one solution, R_2 — no or two solutions, R_3 — one or three solutions.

To obtain a precise demarcation between the parameter regions with one or three equilibrium points (for $\nu > \sigma$), and between the regions with nil or two equilibrium points (for $\nu < \sigma$), one may proceed for any $\alpha > 1$ as follows:

1. calculate $y_{m,cr}$ as a function of ν from the $h'(y_{m,cr}) = 0$

2. draw the line $\sigma = f(\nu)$ using the equation $h(y_{m,cr}) = 0$.

The equation $h(y_{m,cr}) = 0$ means that the extremum is at the border between the regions with the numbers of quilibrium points differing by 2. In general, step 1 can be done only numerically, but for $\alpha = 2, 3, 4...$ there is also an analytical solution. The case of $\alpha = 2$ is presented below.

For $\alpha = 2$, the equation $h'(y_{m,cr}) = 0$ is equivalent to $3y_{m,cr}^2 - 2\nu y_{m,cr} + 1 = 0$, and $y_{m,cr} = \left(\nu \pm \sqrt{\nu^2 - 3}\right)/3$ under the condition $\nu \geq \nu_2 = \sqrt{3}$. From $h(y_{m,cr}) = 0$, one gets $\sigma = (\nu - y_{m,cr})(1 + y_{m,cr}^2)$ for each of two $y_{m,cr}$. The result is shown in Figure 4.

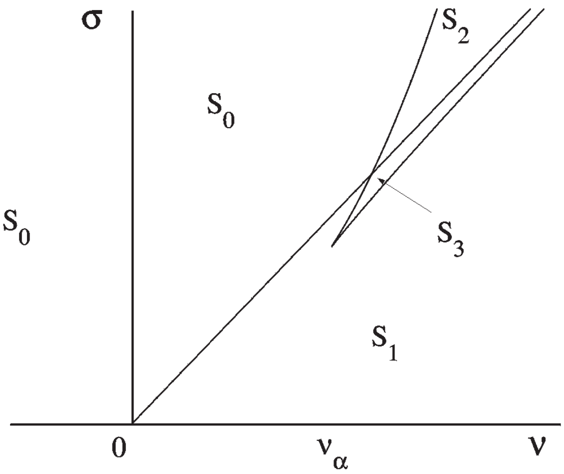

Fig. 5. The number of positive roots of $h(y_m)$, Eq.(14), for $\alpha = 2$ as a function of parameters σ and ν. S_0 — no solution, S_1 — one solution, S_2 — two solutions, S_3 — three solutions.

Case $\nu > 0$ and $\alpha = 1$. This case may be analyzed directly [18] or using similar arguments as for $\alpha > 1$. If $\psi > 1$, then, by direct calculation, one finds that for $\nu > 1$ the function $h(y)$ has only one maximum at $y_m = (\nu - 1)/2$, and $h(y_m) = (\nu + 1)^2/4 - \sigma$. Thus, $h(y_m) > 0$, if $\sigma < (\nu + 1)^2/4$. Therefore, Eqs. (7) may have not more than two equilibrium points with $y > 0$, see Figure 5.

Stability analysis. For $U(x, y) = d\psi(\zeta(\omega - x) + \sigma f(x, y) - xy)$ and $V(x, y) = y(1 - x)$ defined by Eqs. (8), $f = f_1$ and the equilibrium point $(1, y_c)$, the elements of the Jacobian are:

$$\begin{array}{lllll} a_{11} & = & \frac{\partial U}{\partial x}(1, y_c) & = & g\left(-\zeta + \sigma\frac{y_c^\alpha}{1+y_c^\alpha} - \sigma\frac{\alpha y_c^\alpha}{(1+y_c^\alpha)^2} - y_c\right), \\ a_{12} & = & \frac{\partial U}{\partial y}(1, y_c) & = & g\left(\alpha\sigma\frac{\alpha y_c^{\alpha-1}}{(1+y_c^\alpha)^2} - 1\right), \\ a_{21} & = & \frac{\partial V}{\partial x}(1, y_c) & = & -y_c, \\ a_{22} & = & \frac{\partial V}{\partial y}(1, y_c) & = & 0. \end{array} \tag{18}$$

From Eq. (10) one gets $(\omega\zeta - 1 - y_c)(1 + y_c^\alpha) + \sigma y^\alpha = 0$ and a_{11} is equal to:

$$a_{11} = g\left(\frac{H(y_c)}{1 + y_c^\alpha} - \omega\zeta - \frac{\alpha\sigma y_c^\alpha}{(1 + y_c^\alpha)^2}\right) = -g\left(\omega\zeta + \alpha\sigma\frac{y_c^\alpha}{(1 + y_c^\alpha)^2}\right),$$

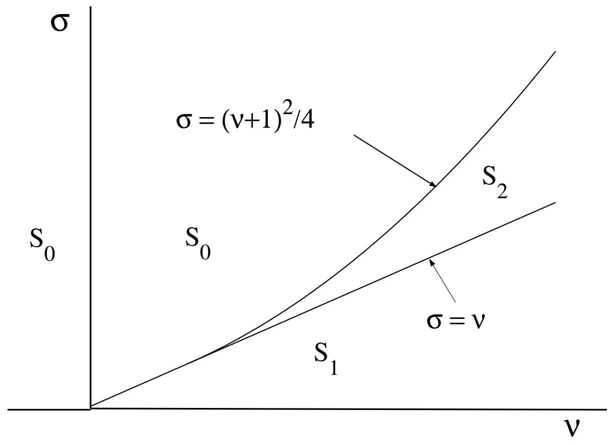

Fig. 6. The number of the positive roots of $h(y_m)$ for $\alpha = 1$ as a function of σ and ν. S_0 — no solution, S_1 — one solution, S_2 — two solutions.

because $H(y_c) = 0$. The trace of the Jacobian, $\beta = a_{11} + a_{22}$, is equal to:

$$\beta = -g\left(\zeta\omega + \sigma\frac{\alpha y_c^\alpha}{(1+y_c^\alpha)^2}\right). \tag{19}$$

Thus, $\beta < 0$ for any equilibrium point with $y_c > 0$. This means that any such point is stable or it is a saddle. To discriminate between these two cases one has to evaluate the sign of the determinant of the Jacobian $\gamma = a_{11}a_{22} - a_{12}a_{21} = y_c\frac{\partial U}{\partial y}(1, y_c)$. Therefore, the sign of γ is the same as the sign of $(\partial U/\partial y)(1, y_c)$.

The equilibrium points $(1, y_c)$ lie on the crossing of two nullclines: $x = 1$ and $U(x, y) = 0$. The equilibrium point $A(\omega, 0)$ is on the nullcline $U(x, y) = 0$, too. If $\omega > 1$ and there are three equilibrium points $B(1, y_{c_1})$, $C(1, y_{c_2})$ and $D(1, y_{c_3})$ with $0 < y_{c_1} < y_{c_2} < y_{c_3}$, then the nullcline $U(x, y) = 0$ must be a decreasing function of y at B, an increasing function of y at C, and again a decreasing function at D: $(\partial U/\partial y)(1, y_{c_1}) < 0$, $(\partial U/\partial y)(1, y_{c_2}) > 0$, and $(\partial U/\partial y)(1, y_{c_3}) < 0$, Figure 6a. If $\omega > 1$ and there is one equilibrium point $B(1, y_{c_1})$ with $0 < y_{c_1}$, then the nullcline $U(x, y) = 0$ must be a decreasing function of y at B: $(\partial U/\partial y)(1, y_{c_1}) < 0$, Figure 6a. In summary, $B(1, y_{c_1})$ is a saddle point, $C(1, y_{c_2})$ is a stable node or focus, and $D(1, y_{c_3})$ is a saddle point.

If $\omega > 1$ and there are two equilibrium points $B(1, y_{c_1})$ and $C(1, y_{c_2})$ with $0 < y_{c_1} < y_{c_2}$, then the nullcline $U(x, y) = 0$ must be an increasing function of y at B, and a decreasing function of y at C: $(\partial U/\partial y)(1, y_{c_1}) < 0$ and $(\partial U/\partial y)(1, y_{c_2}) > 0$, Figure 6b. Thus, $B(1, y_{c_1})$ is a stable node or focus, and $C(1, y_{c_2})$ is a saddle point. The discrimination between cases of stable node and stable focus needs the consideration of the discriminant of the Jacobian $\Delta = \beta^2 - 4\gamma$, which involves all four parameters g, ω, ζ, σ, and cannot be performed in the general case.

The case of $f = f_2$ can be analysed in the same way, with the only difference from the case $f = f_1$ in the expression for a_{11}:

$$a_{11} = \frac{\partial U}{\partial x}(1, y_c) = g\left(-\zeta + \sigma\frac{y_c^\alpha}{1+y_c^\alpha} - y_c\right).$$

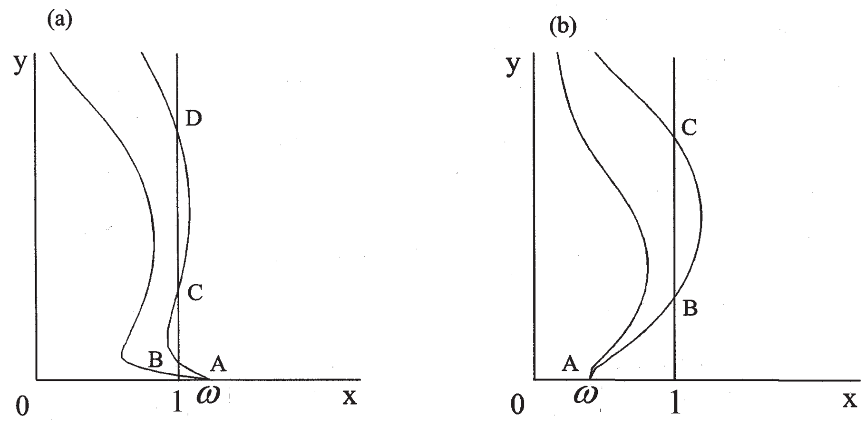

Fig. 7. Exemplary graphs of x and y nullclines given by the solution of $U(x, y)$=0, see Eqs. (8), and straight line $x = 1$. Note the signs of $\frac{\partial U}{\partial y}(1, y)$ for different stationary points A, B and C. a) $\omega > 1$, b) $\omega < 1$.

The stability analysis for the case $\alpha = 1$ may be done directly, or using the same method as for $\alpha > 1$. □

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