EARLY STAGE OF TUMOR-IMMUNE COMPETITION WITH TIME DEPENDENT PARAMETER AND EXTERNAL SOURCE

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The qualitative analysis, existence of equilibria and asymptotic behavior of the competition between tumor and immune cells are studied under the assumption of the time dependence of the parameters and the existence of a source (representing the therapeutical action). In particular, the time-dependent parameters are taken into account, by assuming that they are represented by a decaying sigmoid-like function. The background model of time-dependence parameters belongs to the hiding-learning dynamics [12, 13, 14] *of kinetic models* [2, 3, 4, 5, 6, 7, 8, 9, 15, 34]

Keywords: Dynamical systems, population models, asymptotic analysis, nonlinearity.

1. Introduction

In recent years, the competition between tumor cells and immune-system cells has been mathematically modeled by some dynamical systems [2, 3, 10, 12, 13, 18, 20, 21, 22, 23, 24, 27, 28, 29, 30, 40, 32, 33, 34, 35, 37, 38, 40, 41] typical of the competition of populations [1, 16, 17, 30]. Based on the classical Lotka-Volterra competition model, some nonlinear dynamical systems have been proposed, which identifies the evolution of the number of cells belonging to different interacting populations, tumor cells and immune-system cells and take into account the different scales: molecular, cellular and macroscopic.

At the microscopic level, depending on the basic assumptions, there are many different models such us the exponential [41], logistic, Gompertz [41, 39], Hart-Schochat-Agur [11], von Bertanlaffy [39], Stepanova [37], etc.. (see also references in [21, 22, 23, 24]).

In the following we will consider the dynamical system, proposed by d'Onofrio [22, 23, 24], which is mainly based on the following assumptions that

: i) there exists a tumor free equilibrium,

: ii) the number of tumor cells may tend asymptotically either to infinity or to a finite positive value,

: iii) there exist an equilibrium state compatible with a finite small value of the tumor cells,

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: iv) for any time t, negative values of the variables do not exist,
: v) the influx of lymphocytes is a function of the tumor cells.

However, all these models are autonomous systems which avoid an explicit time dependence. Therefore we propose a generalization which takes into account some delay in the immune system reaction and the non-stationarity of the competition. This can be realized either by using some delay models (see e.g. [17, 28, 29, 40]) or by assuming the time dependence of the parameters [38]. This time dependence is due to the nonstationary behavior of the interaction model [38], but can be further interpreted, at the microscopic scale, by the evolution of the dynamical system due to the hiding-learning process of cells [9, 10, 29, 36, 39] which has been studied by Cattani-Ciancio in the kinetic models of hybrid systems [12, 14]. In fact, during their interactions, the cells exchange also information and, after processing the information, they choose a suitable strategy, such as hiding, competing, etc., which can be modified in time (due to the learning process). These features, which are typical of biological units, belong to the cells activity (which is usually neglected in classical competition models).

In general, the mathematical definition of the cells activity is a complex task which implies at least three different approaches: microscopic, macroscopic, hybrid. Active particles show the existence of a biological function, or better a mathematical function of a biological parameter which can be shortly summarized as the activity. The main problem is the mathematical definition of this function, however it is possible to indirectly characterize it by the some axioms:

(1) Active particles belong to the same population of cells if their activity is characterized by the same biological function.
(2) If all particles of a single population express the biological function in the same way then we have the microscopic approach, in other words the biological function (as a function of the activity) is constant [2, 5, 6, 8, **?**, 19, 25, 26, 11].
(3) The biological function is characterized by the parameters in the dynamical system.
(4) Activity, as nonstationary process, implies the time-dependence of the parameters in the dynamical system
(5) The time dependence of the parameters in the microscopic model can be explained by the kinetic models at the macroscopic scale [12, 14]

If the biological function is statistically distributed on the population then we have the macroscopic model of the kinetic theory [2, 3, 4, 7, 8, 9, 12, 13, 14, 15, 34]. In the hybrid model, instead, the biological function is constant (with respect to activity) but at least one coefficient of the modelling equations is time dependent thus showing an interaction statistically distributed [12, 13, 14]. Thus, in the simplest case, it seems to be reasonable to take into account of the cells activity by assuming the time dependence of at least one parameter of the dynamical system. This functional dependence can be seen and justified in the more general framework of the kinetic equations model, where the two scales microscopic-macroscopic join together. Indeed only at the macroscopic level the cells distribution function is time dependent. Thus, in order to enable the competition to take into account the hiding-learning strategy of cells, as a part of the cells activity, the basic structure of the dynamical system has to change time to time and therefore a more realistic competition model should be a nonautonomous system.

A further generalization is to take into account also the effects of a therapy [20, 21, 22, 38], however in this paper is proposed a function with some high frequency oscillations which play as pseudo-random noise on the therapy.

The qualitative-asymptotic analysis is done, for the general case, by showing the conditions to be fulfilled by the parameters to keep the solution bounded. We have analyzed the asymptotic behaviour of the non autonomous system, when a time dependent coefficients representing the hiding-learning dynamics (due to a microscopic-stochastic interaction) is introduced. This time dependence of one parameter might explain some time delay in the reaction of biological system. The time evolution of the parameters will be characterized with respect to a discretization of the time interval into three typical ranges: initial, corresponding to the approaching learning behavior, transition with fast learning and the final asymptotic stage. In the early stage of the competition, as well as in the early stage of transition, the linearized equation will be studied in details.

2. **A nonlinear model for the immune competition of complex systems**

Let us consider a system of two interacting and competing populations. Each population is constituted by a large number of individuals called *active particles*, their microscopic state is called (biological) *activity*. This activity enable the particle to organize a suitable response with respect to any information process. In absence of prior information, the activity reduces either to a minimal loss of energy or to a random process.

In active particle competitions the simplest model of binary interaction is based on proliferation destructive competition. That is when, one of the populations get aware of the presence of the other competing population it starts to proliferate and/or to destroy the competing cells. However, in this process an important step is the ability of cells to hide them selves and to learn about the activity of the competing population [12, 13, 14].

In details, consider the relatively simpler case, when all particles are the same in each population. Then the state of the system is identified by the sizes:

$$n_i = n_i(t)\,, \quad [0,T] \to \mathbb{R}_+\,, \tag{1}$$

for $i = 1, 2$, with particles homogeneously distributed in space. The modeling of the immune competition can be approached, at the super-macroscopic level, by a system of ordinary differential equations describing the evolution of the number of cells belonging to the two competing populations. Specifically we consider the following model proposed by D'Onofrio [21]-[22]-[24]

$$\begin{cases} \dfrac{dn_1}{dt} &= c_1 n_1 F(n_1) - c_2 \alpha(t) \phi(n_1) n_1 n_2, \\ \dfrac{dn_2}{dt} &= -c_3 \psi(n_1) n_2 + c_4 \beta(t) q(n_1) + \Omega(t)\ . \end{cases} \tag{2}$$

specifically n_1 is the numerical density of tumor cells, n_2 the numerical density of lymphocyte population, under conditions $n_1 \geq 0$ and $n_2 \geq 0$, while $F(n_1), \phi(n_1), \psi(n_1)$ and $q(n_1)$ are deterministic functions of n_1.

This model, might be considered as the generalization of the Lotka-Volterra model

$$\begin{cases} \dfrac{dn_1}{dt} &= An_1 - Bc_2 n_1 n_2, \\ \dfrac{dn_2}{dt} &= (Cn_1 - D)n_2 \ . \end{cases} \tag{3}$$

where A, B, C, D are constans.
The model (3) is obtained from (2) by choosing

$$c_1 F(n_1) = A \ , \ c_2\alpha(t)\phi(n_1) = B \ , \ -c_3\psi(n_1) = (Cn_1 - D), \ c_4\beta(t)q(n_1) = 0 \ , \ \Omega(t) = 0 \ .$$

According to d'Onofrio [21, 22], system (2) is appropriate for the description of tumor-immune cells competition, because:

i) There not exist negative solutions of the numerical densities n_1 , n_2, for non small t, since they are physically unacceptable, so that

$$n_1(t) \geq 0 \quad , \quad n_2(t) \geq 0 \qquad \forall t \ .$$

ii) The function $\psi(n_1)$ describes the stimulatory effect of the tumor cells on the immune cells. We can assume that this function is positive (at least initially)

$$\psi(0) > 0 \ ,$$

and might be negative only in a finite interval. It is reasonable to assume

$$|\psi'(0)| \leq 1 \ ,$$

so that, at least initially, the death rate of lymphocytes is not greater than in the linear model.

iii) Tumor growth rate $F(n_1)$ is a positive function which summarizes the carrying capacity (or malignancy) such that

$$F(0) > 0 \ , \quad \frac{\mathrm{d}}{\mathrm{d}n_1} F(n_1) \leq 0 \ , \quad \lim_{n_1 \to 0} n_1 F(n_1) = 0 \ ,$$

with the additional assumption that initially it is $F'(0) = 0$, where primes denote derivation with respect to n.

iv) The loss of tumor cells, which depends on the competition with lymphocytes, is represented by the function $\phi(n_1)$ characterized by

$$\phi(n_1) > 0 \ , \quad \frac{\mathrm{d}}{\mathrm{d}n_1} \phi(n_1) \leq 0 \ , \quad \lim_{n_1 \to \infty} n_1 \phi(n_1) = \ell < \infty \ .$$

In other words, if the tumor growth tends to infinity the loss of tumor cells would tend to a constant rate. It can be also assumed that

$$\phi'(0) = 0 \ .$$

v) Regarding the influx of immune cells $q(n_1)$ we take

$$q(0) = 1 \quad , \quad |q'(0)| \leq 1 \ ,$$

so that, at least initially, the influx of effector cells is not greater than in the linear model.

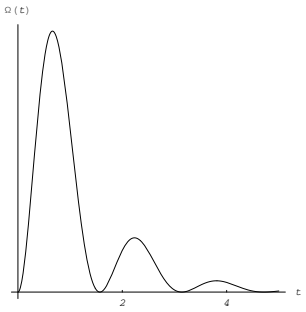

FIGURE 1. The source term $e^{-t}\sin^2(2t)$.

vi) The source term $\Omega(t)$ models the time dependent effects of a therapy on the immune system. This function can be considered as a positive rapidly decay function, localized nearby the initial time, i.e.

$$\Omega(t) > 0 \ , \quad \lim_{t\to\infty} \Omega(t) = 0 \ , \quad \exists \max_{t<\varepsilon} \Omega(t) \ .$$

According to the experimental results should be also assumed that $\Omega(t)$ is an oscillating function, like e.g. (Fig. 1)

$$\boxed{\Omega(t) = e^{-t}\sin^2(mt) \quad , \quad m \in \mathbb{N}} \ . \tag{4}$$

By assuming

$$x = n_1 \ , \ y = \frac{n_2}{c_4} \ , \ c_3 = 1$$

and

$$a = c_1 \ , \ b = 1 \ , \ \mu = c_2 c_4 \tag{5}$$

we get the non dimensional model [22, 23, 24]

$$\boxed{\begin{cases} \dfrac{dx}{dt} &= axF(x) - \mu\alpha(t)\phi(x)xy \ , \\ \\ \dfrac{dy}{dt} &= -y\psi(x) + \beta(t)q(x) + \Omega(t) \ . \end{cases}} \tag{6}$$

2.1. Hiding-learning parameters

We suppose that the learning-hiding actions express themselves via the two parameters $\alpha(t)$, $\beta(t)$ that we shall call the learning-hiding parameters. They are qualitatively similar: since they encode both the initial phase of learning by the immune system and the following phase of immunoevasion, we suppose that it exists a $\widehat{t}_p$ such that:

$$0 < t < \widehat{t}_p \Rightarrow p'(t) > 0 \ , p = \alpha, \beta$$

and

$$t > \widehat{t}_p \Rightarrow p'(t) < 0 \ , p = \alpha, \beta \ .$$

Moreover, assuming as initial time the time of the onset of tumor, it is important to remark that the process of increase of the parameters is far faster than the process of decrease, since they mirror similar phenomena having two very different time scales:

- The learning of immune system of the presence of tumor cells, which is a fast process;
- The learning of tumor cells in evading from the immune control which is very slow

In turn, the initial phase of immuno-learning may be decomposed in a first phase of - relatively - slow increase of parameters, followed by a rapid increase.
Summarizing, the generic learning parameters are characterized by three characteristic times: τ_1, τ_2, which characterize the learning phase, and τ_3 of the hiding phase that are such that:

$$\tau_1 > \tau_2$$

and

$$\tau_1 << \tau_3$$

We propose as a function replying this qualitative behavior the following:

$$p(t) = \left[P_1 + P_2 \operatorname{erf}\left(\frac{t-\tau_1}{\tau_2}\right)\right] \exp\left(-\frac{t}{\tau_3}\right) \tag{7}$$

being P_1 , P_2 some positive constant ($P_2 \geq 0$) values and

$$p(0) = \left[P_1 + P_2 \operatorname{erf}\left(\frac{-\tau_1}{\tau_2}\right)\right] \quad , \quad \lim_{t\to\infty} p(t) = 0 \ .$$

In other words, initially the immune system shows some (time) delay before recognizing the tumor cells but in long range the immune is always able to fully recognize the cancer growth.

It is assumed that

$$p(t) \geq 0, \ \forall t \geq 0$$

so that

$$p(0) = P_1 - P_2 \operatorname{erf}\frac{\tau_1}{\tau_2} \geq 0$$

and

$$P_1 \geq P_2 \operatorname{erf}\frac{\tau_1}{\tau_2} \ .$$

When

$$P_1 = P_2 \operatorname{erf}\frac{\tau_1}{\tau_2} \ ,$$

the initial value of $p(t)$ is zero, which means that the hiding-learning process starts from the absence of knowledge-information.

Therefore we can assume, without lost of generality,

$$P_1 = 2P_2 \operatorname{erf}\frac{\tau_1}{\tau_2}, \ P_2 = 1, \ \tau_1 = 2\tau_2, \ \tau_3 = 10\tau_1$$

so that (7) becomes (Fig. 2)

$$\boxed{p(t) = \left[2 \operatorname{erf} 2 + \operatorname{erf}\left(\frac{t-2\tau_2}{\tau_2}\right)\right] \exp\left(-\frac{t}{20\tau_2}\right) \ .} \tag{8}$$

It can be seen from (8) and Fig. 2 that the peak p_* of (8), reached at the time t_*, is independent on τ_2, and it is given by

$$\frac{40}{\sqrt{\pi}} \exp\left[-\frac{(t-\tau_2)^2}{\tau_2^2}\right] - 2 \operatorname{erf} 2 - \operatorname{erf}\left(\frac{t}{\tau_2} - 2\right) = 0 \ .$$

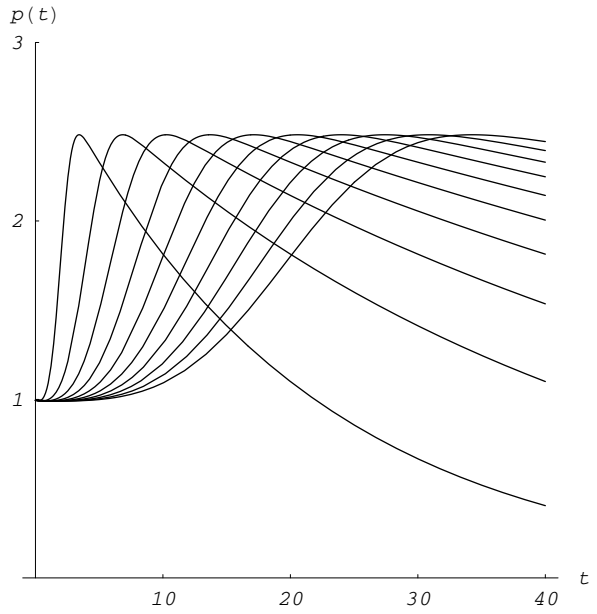

FIGURE 2. Hiding learning function of Eq. (8) for different values of τ_2.

Lower values of τ_2 correspond to a function reaching a maximum in a shorter time, thus corresponding to a faster process of hiding-learning. Thus we can distinguish between two classes of learning processes: the fast one corresponding to a small value of τ_2 (let say $\tau_2 = 1$) represented by the function

$$\boxed{p(t) = [2\,\mathrm{erf}\,2 + \mathrm{erf}\,(t-2)]\exp\left(-\frac{t}{20}\right)} \tag{9}$$

corresponding to a quick process of learning and the weak process represented by a big value of τ_2 (let say $\tau_2 = 10$):

$$\boxed{p(t) = \left[2\,\mathrm{erf}\,2 + \mathrm{erf}\left(\frac{t-20}{10}\right)\right]\exp\left(-\frac{t}{200}\right)\ .} \tag{10}$$

In any case we can roughly distinguish three time intervals corresponding to three different biological activities:

$$\begin{aligned} &I_0 : t_0 = 0 \le t \le t_1 && \text{approach} \\ &I_t : t_1 \le t \le t_* && \text{transition : hiding} - \text{learning game} \\ &I_\infty : t_* \le t && \text{full awariness} \end{aligned} \tag{11}$$

We can assume, more precisely for the fast process (Fig. 3), that

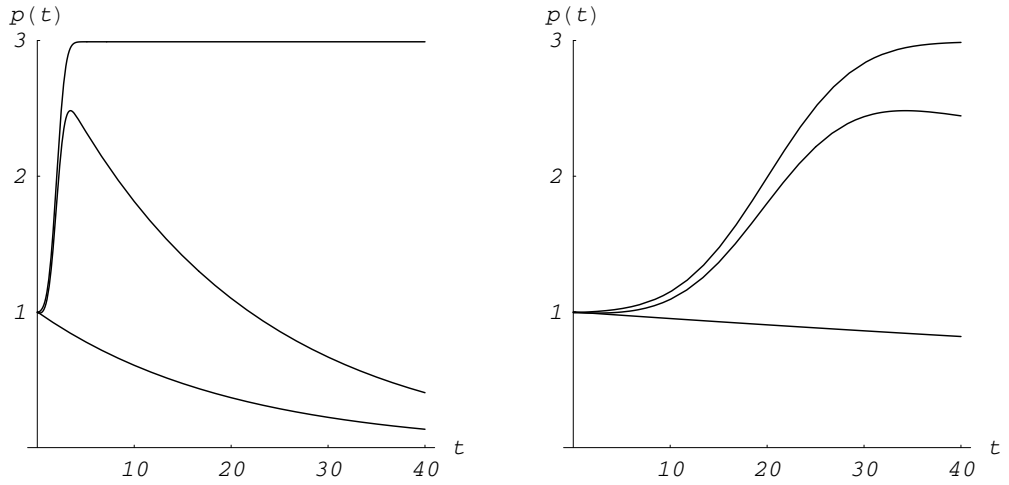

FIGURE 3. Fast (left) and weak hiding learning process: the function (8) and its components: $2\,\mathrm{erf}\,2+\ \mathrm{erf}\left(\dfrac{t-2\tau_2}{\tau_2}\right)$ and $\exp\left(-\dfrac{t}{20\tau_2}\right)$.

$$\begin{cases} p(t)\cong p(0)=p_0 & \text{in } I_0 \\ p(t)\cong 2\,\mathrm{erf}\,2+\ \mathrm{erf}\left(\dfrac{t-2\tau_2}{\tau_2}\right) & \text{in } I_t \\ p(t)\cong p_*\exp\left(-\dfrac{t-t_*}{20\tau_2}\right) & \text{in } I_\infty\ . \end{cases} \tag{12}$$

In the following we will discuss only the fast process (9) where $\tau_2=1$. In this case I_0 is a very short interval and we can linearize the system (2).

Comments. Indeed in the hiding-learning process one should take into account also some small oscillations (as shown in [12]) or random noise so that (7) should be modified as (see Fig. 4)

$$p(t)=\left\{\left[P_1+P_2\,\mathrm{erf}\left(\frac{t-\tau_1}{\tau_2}\right)\right]+\epsilon\sin\frac{\pi t}{2\epsilon}\right\}\exp\left(-\frac{t}{\tau_3}\right) \tag{13}$$

In other words, a more reasonable interpretation of the hiding-learning dynamics should reflect the small amplitude oscillation in the learning assessment due to some uncertainty and improvements. In both case (7),(13) we assume that the learning process is an increasing function with an absolute peak.

Separable system. The parameter μ in (6): $0\le\mu\le 1$, plays an important role for modelling the cells competition. When $\mu=0$, tumor cells grows according to the law

$$\int_{x_0}^{x(t)}\frac{dx}{axF(x)}=t\ ,$$

which represents the evolution of tumor cells in absence of competition with the immune system. This could be either the initial evolution of the tumor cells when they are not yet recognized by the immune system, or the final stage of the evolution

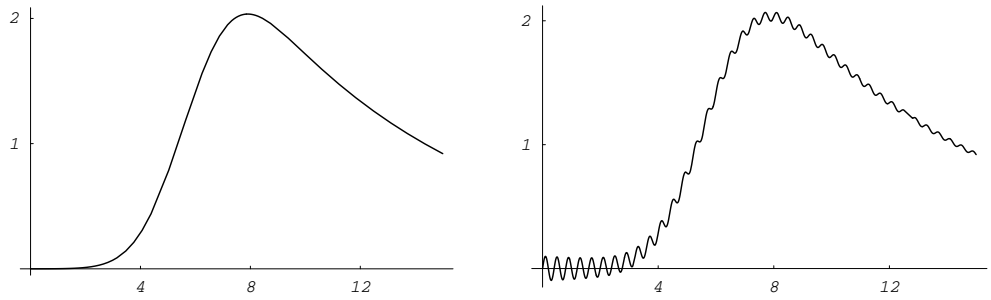

FIGURE 4. Hiding learning process explained by the time dependent parameters smooth as (7) (on the left) and with periodic small amplitude oscillations (on the right) as represented by Eq. (13).

when the immune system is unable to compete with tumor cells. Once $x(t)$ is computed by the previous equation we can solve Eq. $(6)_2$ which is a linear differential equation with variable coefficients

$$\frac{dy}{dt} + \psi[x(t)]y = \beta(t)q[x(t)] + \Omega(t) \ .$$

Let us take $\mu = 1$ and study only a one-parameter model: either $\alpha(t)$ or $\beta(t)$ constant, so that

$$\boxed{\begin{cases} \dfrac{dx}{dt} &= axF(x) - \alpha(t)\phi(x)xy \ , \\ \dfrac{dy}{dt} &= -y\psi(x) + q(x) + \Omega(t) \ , \end{cases}} \tag{14}$$

and

$$\boxed{\begin{cases} \dfrac{dx}{dt} &= axF(x) - \phi(x)xy \ , \\ \dfrac{dy}{dt} &= -y\psi(x) + \beta(t)q(x) + \Omega(t) \ . \end{cases}} \tag{15}$$

In a special case, when

$$a < 0$$

it is possible to show that the solution are bounded, and to compute the range of the unknown functions.

Let us show for (14):

Theorem 2.1. *When $a < 0$ it is*

$$\boxed{\begin{cases} 0 \le x(t) \le x_0 \ , \\ \dfrac{q(x_{\min}) + \min\limits_{t\ge 0}[\Omega(t)]}{\psi(x_{\max})} \le y(t) \le y_0 \ . \end{cases}} \tag{16}$$

Proof: Due to the preliminary assumptions about the positivity of the second term in the r.h.s., it is

$$\frac{dx}{dt} = axF(x) - \alpha(t)\phi(x)xy < axF(x)$$

or

$$\frac{dx}{dt} < axF_M$$

with

$$F_M \equiv \max_{0\le x\le x_{\max}} F(x)$$

so that

$$x(t) \le x_0 e^{aF_M t} \ .$$

There follows that, when $a < 0$

$$x(t) \le x_{\max} = x(0) = x_0 \ ,$$

and

$$x(t) \ge x_{\min} = \lim_{x\to\infty} x_0 e^{aF_M t} = 0 \ ,$$

so that

$$0 \le x(t) \le x_0 \ .$$

In this case from the second equation of (14) we have

$$\frac{dy}{dt} = -y\psi(x) + q(x) + \Omega(t) \ge -y\psi(x_{\max}) + q(x_{\min}) + \min_{t\ge 0}[\Omega(t)] \ ,$$

$$\frac{dy}{dt} \ge -y\psi(x_{\max}) + q(x_{\min}) + \min_{t\ge 0}[\Omega(t)] \ ,$$

so that

$$y(t) \ge \frac{q(x_{\min}) + \min_{t\ge 0}[\Omega(t)]}{\psi(x_{\max})} + \left[y_0 - \frac{q(x_{\min}) + \min_{t\ge 0}[\Omega(t)]}{\psi(x_{\max})} \right] e^{-\psi(x_{\max})t}$$

being

$$y_0 \equiv y(0) \ .$$

Since

$$\lim_{t\to\infty} \frac{q(x_{\min}) + \min_{t\ge 0}[\Omega(t)]}{\psi(x_{\max})} + \left[y_0 - \frac{q(x_{\min}) + \min_{t\ge 0}[\Omega(t)]}{\psi(x_{\max})} \right] e^{-\psi(x_{\max})t}$$

$$= \frac{q(x_{\min}) + \min_{t\ge 0}[\Omega(t)]}{\psi(x_{\max})} \ ,$$

there follows for $y(t)$ the limits:

$$\frac{q(x_{\min}) + \min_{t\ge 0}[\Omega(t)]}{\psi(x_{\max})} \le y(t) \le y_0 \ .$$

■

Analogously, for (15), it can be shown that

Theorem 2.2. *When $a < 0$ it is*

$$\boxed{\begin{cases} 0 \leq x(t) \leq x_0 \ , \\ \\ \dfrac{\min\limits_{t\geq 0}[\beta(t)]q(x_{\min}) + \min\limits_{t\geq 0}[\Omega(t)]}{\psi(x_{\max})} \leq y(t) \leq y_0 \ . \end{cases}}$$

In particular, by choosing (4),

$$\min_{t\geq 0}[\Omega(t)] = 0 \ , \tag{17}$$

and the conditions (16) become

$$\begin{cases} 0 \leq x(t) \leq x_0 \ , \\ \\ \dfrac{q(x_{\min})}{\psi(x_{\max})} \leq y(t) \leq y_0 \ . \end{cases}$$

and analogously, for system (15),

$$\begin{cases} 0 \leq x(t) \leq x_0 \ , \\ \\ \dfrac{\min\limits_{t\geq 0}[\beta(t)]q(x_{\min})}{\psi(x_{\max})} \leq y(t) \leq y_0 \ . \end{cases}$$

These results deserve some comments: when $a < 0$, the evolution in cells competitions is such that

- independently on $\alpha(t)$, $\beta(t)$ both populations $x(t)$, $y(t)$ are bounded, even in presence of a bounded therapy $\Omega(t)$;
- when (17) holds, the range of the populations doesn't depend on $\alpha(t)$ and it depends, (only for system (15)) on $\beta(t)$.

The case $a \geq 0$, for which it is not possible to give a simple estimate of the evolving populations, will be considered in the following section, by assuming $a = 1$.

3. Qualitative analysis of system (14) in I_0

In this section we will discuss the system (14) for a fast process in the initial stage of the competition, so that according to (12) it is

$$\boxed{\begin{cases} \dfrac{dx}{dt} &= xF(x) - \alpha_0\phi(x)xy \ , \\ \\ \dfrac{dy}{dt} &= -y\psi(x) + q(x) + \Omega(t) \end{cases}} \quad , 0 \leq t \leq t_1 \cong 0 \tag{18}$$

with $\Omega(t)$ given by (4).

3.1. **Critical points of the homogeneous system**

Let us first discuss the equilibrium points for the homogeneous system:

$$\begin{cases} x\left(F(x)-\alpha_0\phi(x)y\right) &= 0\ , \\ \\ -y\psi(x)+q(x) &= 0\ , \end{cases} \tag{19}$$

We have $P_0 \equiv (x_0, y_0)$ and eventually $\overline{P} \equiv (\overline{x}, \overline{y})$ with

$$x_0 = 0\ , \quad y_0 = \frac{1}{\psi(0)}\ ,$$

$$F(\overline{x})\psi(\overline{x}) - \alpha_0 b\phi(\overline{x})q(\overline{x}) = 0\ , \quad \overline{y} = \frac{q(\overline{x})}{\psi(\overline{x})}\ .$$

The jacobian is

$$\begin{pmatrix} F(x)+xF'(x)-\alpha_0\phi'(x)xy-\alpha_0\phi(x)y & -\alpha_0\phi(x)x \\ -y\psi'(x)+q'(x) & -\psi(x) \end{pmatrix}$$

which, taking into account (i)÷(v), in P_0 is

$$\begin{pmatrix} F(0)-\alpha_0\dfrac{\phi(0)}{\psi(0)} & 0 \\ -\dfrac{\psi'(0)}{\psi(0)}+q'(0) & -\psi(0) \end{pmatrix}.$$

The eigenvalues in P_0 are

$$\lambda_1 = -\psi(0)\ , \quad \lambda_2 = F(0) - \alpha_0\frac{\phi(0)}{\psi(0)}\ .$$

Since $\psi(0) > 0$, we have that

(1) P_0 is a stable node if $F(0) < \alpha_0\dfrac{\phi(0)}{\psi(0)}$,

(2) P_0 is an unstable saddle point if $F(0) > \alpha_0\dfrac{\phi(0)}{\psi(0)}$,

(3) P_0 is a node (type II) point (stable or unstable) if $\lambda_1 = \lambda_2$ i.e. $F(0) = \alpha_0\dfrac{\phi(0)}{\psi(0)} - \psi(0)$, with, according to the hypotheses, $\alpha_0\dfrac{\phi(0)}{\psi(0)} > \psi(0)$, i.e. $\psi(0)^2 < \alpha_0\phi(0)$.

The linearization in P_0 gives the system

$$\begin{cases} \dfrac{dx}{dt} &= \left[F(0)-\alpha_0\dfrac{\phi(0)}{\psi(0)}\right]x\ , \\ \\ \dfrac{dy}{dt} &= \left[-\dfrac{\psi'(0)}{\psi(0)}+q'(0)\right]x-\psi(0)y\ , \end{cases}$$

so that, by taking into account (4), the nonautonoumous system in I_0 is

$$\begin{cases} \dfrac{dx}{dt} &= \left[F(0) - \alpha_0 \dfrac{\phi(0)}{\psi(0)}\right] x \ , \\ \dfrac{dy}{dt} &= \left[-\dfrac{\psi'(0)}{\psi(0)} + q'(0)\right] x - \psi(0) y + e^{-t} \sin^2(mt) \ , \end{cases}$$

which is solved by

$$\begin{cases} x(t) &= x_0 e^{At} \\ \\ y(t) &= \dfrac{1}{2} e^{-Ct} \Big[2(y_0 - D) + \dfrac{2Bx_0(e^{(A+C)t} - 1)}{A + C} \Big] \\ &+ \dfrac{D}{em^2} \Big[(C-1)^2 \sin^2(mt) - m(C-1)\sin(2mt) + 2m^2 \Big] \ , \end{cases}$$

with

$$A \equiv F(0) - \alpha_0 \frac{\phi(0)}{\psi(0)} \ , \ B \equiv -\frac{\psi'(0)}{\psi(0)} + q'(0) \ , \ C \equiv \psi(0) \ , \ D \equiv \frac{2m^2}{(C-1)^3 + 4m^2(C+1)}$$

In order to have some bounded solutions, we get the following constraint on the initial values and α_0:

$$A \leq 0 \Longrightarrow \alpha_0 \geq \frac{\psi(0)}{\phi(0)} F(0)$$

After the initial stage of the competition, the transition starts, however $\alpha(t)$ should be considered no longer constant, thus at the beginning of the transition we can still consider a linearized system where $\alpha(t)$ is given by $(12)_2$

$$\begin{cases} \dfrac{dx}{dt} &= \left[F(0) - [2\,\mathrm{erf}\,2 + \mathrm{erf}\,(t-2)] \dfrac{\phi(0)}{\psi(0)}\right] x \ , \\ \dfrac{dy}{dt} &= \left[-\dfrac{\psi'(0)}{\psi(0)} + q'(0)\right] x - \psi(0) y + e^{-t} \sin^2(mt) \ . \end{cases}$$

Also in this case, where the functions $F(x)$, $\Phi(x)$, $\Psi(x)$, $q(x)$ are still unspecified, we can easily find the solution. It is

$$x(t) = x_0 \exp\left\{ -\frac{1}{\psi(0)} \left[\frac{\phi(0)}{\sqrt{\pi}} e^{-(t-2)^2} - F(0)\psi(0)t + 2(\,\mathrm{erf}\,2)\phi(0)t \right.\right. \\ \left.\left. + \phi(0)(t-2)\,\mathrm{erf}\,(t-2) \right] \right\} \ .$$

With this value, the equation can also be solved for $y(t)$ and we can see that both solutions are still bounded, as predicted by the above theorems.

Conclusions

A nonlinear and non autonomous dynamical system is proposed for the qualitative analysis of the competition between tumor and immune cells under the assumption the existences of a therapeutical action which is chosen as a positive rapidly decay function, localized nearby the initial time. A qualitative analysis of the parameters of hiding-learning process is studied and the proprieties of the critical points are discussed.

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