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Prey-predator models in the analysis of tumor - immune system interaction (**)

Dedicated to the memory of Giulio Di Cola

1 - Introduction

In recent years it has been shown that many immunology problems can be studied in the frame of the evolution of dominance in interacting populations [**1**]. This applies, in particular, to the competition between tumors and immune system [**2**]-[**5**]. In this context, the dominance character is represented by the state of activity of cells, that means the ability to carry out the typical functions of the species, which corresponds to the capacity of growth for tumor cells, and of defence for the immune system. On the other hand, the study of dominance is a very useful model at a mesoscopic level, which leads to equations of the same kind as in the kinetic theory of gases, as it was shown in [**6**].

In the simple model presented in [**5**], which, starting from a kinetic level, yields a closed system of macroscopic balance equations, destruction and proliferation terms are assumed, as typical in the kinetic frame, bilinear with respect to the densities of interacting species.

The present paper aims at taking into account the saturation effect that realistically occurs to immune system, when it is surrounded by a large number of tumor cells, in defeating the tumor. To this end, we consider two different models, proposed, respectively, by C. S. Holling [**7**] and by V.S. Ivlev [**8**] in the field of bio-

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mathematics, which change the type of nonlinearity of the evolution equations obtained in our study.

The paper is organized as follows. After recalling the model of ref. [**5**], with the assumptions and the notations showed therein (Sect. **2**), modifications are carried out which lead to equations taking into account saturation effects (Sect. 3). The latter involve a positive parameter describing the asymptotic limit of the immune system capability to destroy the tumor. The smaller such a parameter is, the stronger saturation effects become. In Sect. 4 the mathematical problem derived from the Holling model is studied, whereas the Ivlev model is examined in Sect. 5. Numerical comparisons between the results from these models and the previous ones are presented in Sect. 6. It can be seen that, as expected, the possibilities of recovery are better in the situation of ref. [**5**] than in the modified models. Moreover, the Ivlev model is more favourable than the Holling one, with the same value of the above-mentioned asymptotic parameter, and in both cases recovery is enhanced when such a value increases.

A similar deduction holds as regards a possible external treatment to support the immune system. Numerical experiments show that the intensity of an external source, which makes the treatment effective, depends on the initial conditions, and is more favourable to recovery in the model of ref. [**5**] than in the Ivlev model, which, in turn, is more favourable than the Holling one. Finally, it clearly appears how, in the last two models, the intensity ot the external treatment to recover decreases when the asymptotic parameter value increases, that is when saturation effects are smaller.

2 - A recall on a mathematical model for the problem

As stated in the introduction, the problem of the analysis of tumor - immune system interactions can be reduced, from the mathematical point of view, to the problem of the evolution of dominance in N different populations. Corresponding to each interacting species, we consider a distribution function $f_i(u, t)$, where the real variable $u \in [-1, 1]$ indicates the state («dominance») of the i-th population, relevant to the problem under examination. Functions $f_i(u, t)$ are nonnegative in their arguments, and the quantity

$$n_i(t) = \int_{-1}^{1} f_i(u, t)\, du \tag{2.1}$$

represents the number density of the i-th species. Now index i takes the values from 1 to 4, and, more precisely, $i = 1$ will refer to tumor cells, $i = 2$ to cells of the

host background, $i = 3$ to cells of the immune system, $i = 4$ to interleukines. The latter are particular proteins secreted by the immune system, whose task is to activate lymphocytes, which are responsible for immunity reaction.

Let us recall the considerations related in ref. [**5**], leading to the problem we are going to deal with in this paper. We consider binary interactions («collisions») among the different species; the variable u measures the capability of particles («cells») to prevail in a binary collision (we call them «active cells» when $u > 0$, and «passive cells» when $u < 0$). Collisions may be of conservative type, when the number of participating individuals is conserved, and of nonconservative type, when such a number increases or decreases during an encounter.

By $\eta_{ij}(u, v) = \eta_{ji}(v, u) \geq 0$ we denote the microscopic collision frequency for conservative collisions between an (i, u) individual (i.e. an i individual with u state) and a (j, v) individual. Moreover $\psi_{ij}(u, v; w) \geq 0$ is the probability density that, in the above-mentioned encounter, the i individual takes a state in the interval $(w, w + dw)$. The normalization condition

$$\int_{-1}^{1} \psi_{ij}(u, v; w)\, dw = 1 \quad \forall u, v \in [-1, 1] \quad \forall i, j = 1, 2, \ldots, N \tag{2.2}$$

must be satisfied.

Similarly, by $d_{ij}(u, v) \geq 0$ we denote the collision frequency for nonconservative encounters between an (i, u) individual and a (j, v) individual, and by $\mu_{ij}(u, v) \leq d_{ij}(u, v)$ the fraction of it relating to proliferative interactions only. For the latter, by $\varepsilon_{ij}(u, v; w)$ we denote the number of i individuals ending in a state in the interval $(w, w + dw)$ after collision, so that

$$m_{ij}(u, v) = \int_{-1}^{1} \varepsilon_{ij}(u, v; w)\, dw \geq 1 \tag{2.3}$$

denotes the total number of individuals generated in a proliferative encounter $(i, u) - (j, v)$. Finally $\gamma_i(u)$ is the possible external source of i individuals with u state.

Balance equations for N species then take the form

$$\begin{aligned} \frac{\partial f_i(u, t)}{\partial t} &= \sum_{j=1}^{N} \int_{-1}^{1} \int_{-1}^{1} [\eta_{ij}(v, w)\, \psi_{ij}(v, w; u) + \mu_{ij}(v, w)\, \varepsilon_{ij}(v, w; u)]\, f_i(v, t)\, f_j(w, t)\, dv\, dw \\ &- f_i(u, t) \sum_{j=1}^{N} \int_{-1}^{1} [\eta_{ij}(u, v) + d_{ij}(u, v)]\, f_j(v, t)\, dv + \gamma_i(u), \quad i = 1, 2, \ldots, N\,. \end{aligned} \tag{2.4}$$

Set [5] shows clear analogies with the so-called extended Boltzmann equations for a gas mixture, in the «scattering kernel» formulation [11].

Integrating with respect to u and taking (2.1)-(2.4) into account, we obtain, setting

$$\Gamma_i = \int_{-1}^{1} \gamma_i(u)\, du, \quad i = 1, \ldots, N \tag{2.5}$$

the equation set

$$\frac{dn_i(t)}{dt} = \sum_{j=1}^{N} \int_{-1}^{1} \int_{-1}^{1} [\mu_{ij}(u, v)\, m_{ij}(u, v) - d_{ij}(u, v)]\, f_i(u, t)\, f_j(v, t)\, du\, dv + \Gamma_i, \tag{2.6}$$
$$i = 1, \ldots, N,$$

which is not generally closed with respect to the functions $n_i(t)$.

The question of well posedness for the mathematical problem (2.5), under suitable initial conditions $f_i(u, 0)$, has been dealt with and discussed in ref. [5]. Now we will instead re-examine set (2.6) and recall the assumptions for the immunological problem we are drawing our attention on.

(a) The host medium and interleukines can be regarded as background species: they take part in collisions, but their distribution does not change. Besides, the host population distribution («2-cells») is steady, whereas a positive external source for interleukines («4-cells») may be present.

(b) A collision between a tumor cell («1-cell») and an immune system cell («3-cell») results in the following situation: if the 3-cell is active ($u > 0$), after collision the 1-cell is destroyed and the 3-cell becomes passive; if the 3-cell is passive, new 1-cells are created (that is the tumor proliferates) and the 3-cell state decreases further.

(c) A collision between a 3-cell and a 4-cell is conservative for both species, and increases the 3-cell state, so that a passive cell always becomes active.

(d) A collision between a 1-cell and a 2-cell always produces new 1-cells (the tumor proliferates).

Moreover collision frequencies are assumed as constant. Then we have

$$\begin{aligned}
&d_{12}(v, w) = \mu_{12}(v, w) = \bar{\mu}_{12} \\
&d_{13}(v, w) = \bar{\mu}_{13} \qquad \mu_{13}(v, w) = \bar{\mu}_{13}\, U(-w) \\
&\eta_{31}(v, w) = \bar{\mu}_{13} \qquad \eta_{34}(v, w) = \bar{\eta}_{34} \\
&\psi_{31}(v, w; u) = 0 \quad \forall u > 0, \qquad \psi_{34}(v, w; u) = 0 \quad \forall u < 0
\end{aligned} \tag{2.7}$$

where U stands for the unit step function, $\bar{\mu}_{12}, \bar{\mu}_{13}, \bar{\eta}_{34}$ are positive constants, $d_{ij} = \mu_{ij} = \eta_{ij} = 0$ for all the other pairs of indices, and γ_i is assumed to vanish for $i = 1, 2, 3$.

Then set (2.4) takes the form

$$\frac{\partial f_1(u,t)}{\partial t} = \bar{\mu}_{12} \int_{-1}^{1} \int_{-1}^{1} \varepsilon_{12}(u, v; w)\, f_1(v,t)\, f_2(w,t)\, dv\, dw - \bar{\mu}_{12} n_2(t)\, f_1(u,t)$$

$$+ \bar{\mu}_{13} \int_{-1}^{1} \int_{-1}^{0} \varepsilon_{13}(v, w; u)\, f_1(v,t)\, f_3(w,t)\, dv\, dw - \bar{\mu}_{13} n_3(t)\, f_1(u,t),$$

$$\frac{\partial f_2(u,t)}{\partial t} = 0, \tag{2.8}$$

$$\frac{\partial f_3(u,t)}{\partial t} = \bar{\mu}_{13} \left[\int_{-1}^{1} \int_{-1}^{1} \psi_{31}(v, w; u)\, f_3(v,t)\, f_1(w,t)\, dv\, dw - n_1(t)\, f_3(u,t) \right]$$

$$+ \bar{\eta}_{34} \left[\int_{-1}^{1} \int_{-1}^{1} \psi_{34}(v, w; u)\, f_3(v,t)\, f_4(w,t)\, dv\, dw - n_4(t)\, f_3(u,t) \right],$$

$$\frac{\partial f_4(u,t)}{\partial t} = \gamma_4(u).$$

The distribution functions f_2 and f_4 are therefore determined independently of the process, and in particular f_2 is constant. Then $n_2 = k_2$ (constant), whereas $n_4(t) = \Gamma_4 t + k_4$ (k_4 constant). From (2.8) we obtain, integrating with respect to u and taking (2.2) into account,

$$\frac{dn_1(t)}{dt} = \bar{\mu}_{12}(m_{12} - 1)\, k_2\, n_1(t) + \bar{\mu}_{13} m_{13}\, n_1(t) \int_{-1}^{0} f_3(w,t)\, dw - \bar{\mu}_{31}\, n_1(t)\, n_3(t)$$

$$\frac{dn_3(t)}{dt} = 0. \tag{2.9}$$

From the second equation of (2.9) we find out, in agreement with the model, that the total number of 3-cells is conserved ($n_3 = k_3 = \text{constant}$). But the first equation is not self-consistent, owing to the integral on the negative half-range only.

But a closed set can easily be obtained introducing

$$n_3^{\pm} = \pm \int_0^{\pm 1} f_3(u, t)\, du \tag{2.10}$$

that is, considering the 3-cell active population and the passive one as distinct, and integrating the third equation in (2.8) on suitable half-ranges.

By simple calculations, we get to

$$\begin{aligned} \frac{dn_1(t)}{dt} &= \overline{\mu}_{12}(m_{12}-1)\, k_2\, n_1(t) + \overline{\mu}_{13}(m_{13}-1)\, n_1(t)\, n_3^-(t) - \overline{\mu}_{13}\, n_1(t)\, n_3^+(t) \\ \frac{dn_3^+(t)}{dt} &= -\overline{\mu}_{13}\, n_1(t)\, n_3^+(t) + \overline{\eta}_{34}\, n_4(t)\, n_3^-(t) \\ \frac{dn_3^-(t)}{dt} &= \overline{\mu}_{13}\, n_1(t)\, n_3^+(t) - \overline{\eta}_{34}\, n_4(t)\, n_3^-(t). \end{aligned} \tag{2.11}$$

As $n_3^-(t) = k_3 - n_3^+(t)$, we are led to the set of only two equations

$$\begin{aligned} \frac{dn_1(t)}{dt} &= [\overline{\mu}_{12}(m_{12}-1)\, k_2 + \overline{\mu}_{13}(m_{13}-1)\, k_3]\, n_1(t) - \overline{\mu}_{13}\, m_{13}\, n_1(t)\, n_3^+(t), \\ \frac{dn_3^+(t)}{dt} &= \overline{\eta}_{34}\, k_3\, n_4(t) - \overline{\eta}_{34}\, n_4(t)\, n_3^+(t) - \overline{\mu}_{13}\, n_1(t)\, n_3^+(t). \end{aligned} \tag{2.12}$$

Sets (2.11) and (2.12) are first order ODE systems, generally non-autonomous, becoming autonomous, and then resulting in dynamical systems, when $\Gamma_4 = 0$, i.e. when interleukines are a steady population ($n_4 = k_4 = \text{constant}$). In the next section, we will examine sets (2.11) or (2.12), when $\Gamma_4 = 0$, looking for possible and significant modifications.

3 - Modified problems following Holling and Ivlev models

Let us take set (2.11) into consideration, examining the meaning of the last term of the r.h.s. in the first equation. It represents a decrease in the number of tumor cells due to the presence of active immune system cells. The fact that this term, after fixing n_3^+, is proportional to n_1, corresponds to the assumption that immune system active cells are able to destroy a quantity of tumor cells which is proportional to the number density of the latter.

With reference to typical problems in biomathematics, such as the prey-predator problem, the above-mentioned assumption would correspond to the situation of the Lotka-Volterra model (see, for example, ref. [7] and the bibliography

quoted therein). The presence of such a term denotes, in particular, a situation where a predator's attacks increase indefinitely when the prey increases. In literature some models have been proposed, taking more realistically into account the «saturation» effect on predators. The analogy between such a saturation effect and the limitation of the capability of immune system active cells to destroy the tumor, when surrounded by a large number of tumor cells, seems clear.

Following a model proposed by C.S. Holling on the basis of artificial experimental situations [**7**], we may replace in (2.11) the term $\overline{\mu}_{13}\, n_1(t)\, n_3^{+}(t)$ with the term

$$\overline{\mu}_{13}\, \frac{\beta n_1(t)}{\beta + n_1(t)}\, n_3^{+}(t)\,, \tag{3.1}$$

where β is a positive constant, having the same physical dimensions as n_1. It can easily be seen that the ratio $\beta n_1/(\beta + n_1)$ is always less than n_1, it behaves as $n_1 + O(n_1^2)$ when $n_1 \to 0$, and tends to the finite value β when $n_1 \to \infty$. Moreover, when β varies, the ratio tends to n_1 if $\beta \to \infty$, which reproduces the Lotka-Volterra term.

A qualitatively analogous model, proposed by V.S. Ivlev [**8**] and substantially coincident with the one proposed by K.E.F. Watt [**9**], on an experimental basis, always referring to the prey-predator problem (see also [**10**]), leads us to replace the term $\overline{\mu}_{13}\, n_1(t)\, n_3^{+}(t)$ by

$$\overline{\mu}_{13}\beta\left(1 - e^{-\frac{n_1(t)}{\beta}}\right) n_3^{+}(t) \tag{3.2}$$

($\beta > 0$ constant, having the same meaning as in (3.1)). It can be seen immediately that, also in that case, the term replacing n_1 relating to (2.11) is less than n_1, it behaves as $n_1 + O(n_1^2)$ when $n_1 \to 0$, it tends to the finite value β when $n_1 \to \infty$, and tends to n_1 when $\beta \to \infty$.

Sets (2.11) and (2.12), with the above modifications, read, respectively, as

$$\frac{dn_1(t)}{dt} = \overline{\mu}_{12}(m_{12}-1)\, k_2 n_1(t) + \overline{\mu}_{13}(m_{13}-1)\, n_1(t)\, n_3^{-}(t) - \overline{\mu}_{13} n_3^{+}(t)\, \frac{\beta n_1(t)}{\beta + n_1(t)}$$

$$\frac{dn_3^{+}(t)}{dt} = -\,\overline{\mu}_{13}\, n_3^{+}(t)\, \frac{\beta n_1(t)}{\beta + n_1(t)} + \overline{\eta}_{34}\, n_4(t)\, n_3^{-}(t) \tag{3.3}$$

$$\frac{dn_3^{-}(t)}{dt} = \overline{\mu}_{13}\, n_3^{+}(t)\, \frac{\beta n_1(t)}{\beta + n_1(t)} - \overline{\eta}_{34}\, n_4(t)\, n_3^{-}(t)\,,$$

and

$$\frac{dn_1(t)}{dt} = [\bar{\mu}_{12}(m_{12}-1)\,k_2 + \bar{\mu}_{13}(m_{13}-1)\,k_3]\,n_1(t)$$

$$-\bar{\mu}_{13}\,n_3^{+}(t)\,\frac{(m_{13}-1)\,\beta + (m_{13}-1+\beta)\,n_1(t)}{\beta + n_1(t)} \tag{3.4}$$

$$\frac{dn_3^{+}(t)}{dt} = -\bar{\mu}_{13}\,n_3^{+}(t)\,\frac{\beta n_1(t)}{\beta + n_1(t)} + \bar{\eta}_{34}\,n_4(t)[k_3 - n_3^{+}(t)]$$

in the case of the problem modified after the Holling model (we will call «Holling model» for short), and as

$$\frac{dn_1(t)}{dt} = \bar{\mu}_{12}(m_{12}-1)\,k_2\,n_1(t) + \bar{\mu}_{13}(m_{13}-1)\,n_1(t)\,n_3^{-}(t) - \bar{\mu}_{13}n_3^{+}(t)\,\beta\left(1-e^{-\frac{n_1(t)}{\beta}}\right)$$

$$\frac{dn_3^{+}(t)}{dt} = -\bar{\mu}_{13}\,n_3^{+}(t)\,\beta\left(1-e^{-\frac{n_1(t)}{\beta}}\right) + \bar{\eta}_{34}\,n_4(t)\,n_3^{-}(t) \tag{3.5}$$

$$\frac{dn_3^{-}(t)}{dt} = \bar{\mu}_{13}\,n_3^{+}(t)\,\beta\left(1-e^{-\frac{n_1(t)}{\beta}}\right) - \bar{\eta}_{34}\,n_4(t)\,n_3^{-}(t)$$

and

$$\frac{dn_1(t)}{dt} = [\bar{\mu}_{12}(m_{12}-1)\,k_2 + \bar{\mu}_{13}(m_{13}-1)\,k_3]\,n_1(t)$$

$$-\bar{\mu}_{13}\,n_3^{+}(t)\left[(m_{13}-1)\,n_1(t) + \beta\left(1-e^{-\frac{n_1(t)}{\beta}}\right)\right] \tag{3.6}$$

$$\frac{dn_3^{+}(t)}{dt} = -\bar{\mu}_{13}\,n_3^{+}(t)\,\beta\left(1-e^{-\frac{n_1(t)}{\beta}}\right) + \bar{\eta}_{34}\,n_4(t)[k_3 - n_3^{+}(t)]$$

in the case of the problem modified after the Ivlev model (we will call «Ivlev model», likewise).

In the following sections we will study the two models.

4 - Analysis of the Holling model

In this section we will study the dynamical system we obtain from (3.4) in the case $\Gamma_4 = 0$ ($n_4 = k_4 =$ constant), following the guidelines of ref. [5], and discuss in particular its fixed points and their stability.

Let us use adimensional variables, setting

$$x_1 = \frac{n_1}{k_2}\,, \qquad x_2 = \frac{n_3^{+}}{k_2} \tag{4.1}$$

and introducing a dimensionless time

$$\tau = \overline{\mu}_{12}(m_{12} - 1)\, k_2 t \tag{4.2}$$

which will be denoted again by t.

Let us also introduce the dimensionless positive parameters

$$A = \frac{\overline{\mu}_{13}}{\overline{\mu}_{12}}\,, \qquad B = \frac{\overline{\mu}_{13}(m_{13} - 1)}{\overline{\mu}_{12}(m_{12} - 1)}\,, \qquad X = \frac{k_3}{k_2} < 1\,.$$
$$C = \frac{\overline{\eta}_{34} k_4}{\overline{\mu}_{12}(m_{12} - 1)\, k_2}\,, \qquad h = \frac{\beta}{k_2}\,. \tag{4.3}$$

Set (3.4) then takes the form

$$\begin{aligned} \dot{x}_1 &= (1 + BX)\, x_1 - \left(B + \frac{Ah}{h + x_1}\right) x_1 x_2 \\ \dot{x}_2 &= C(X - x_2) - \frac{Ah}{h + x_1}\, x_1 x_2 . \end{aligned} \tag{4.4}$$

The set obtained from (2.12) with the adimensionalization of variables is

$$\begin{aligned} \dot{x}_1 &= (1 + BX)\, x_1 - (A + B)\, x_1 x_2 \\ \dot{x}_2 &= C(X - x_2) - A x_1 x_2 . \end{aligned} \tag{4.5}$$

The phase space of (4.4) is given by the strip $[0, +\infty) \times [0, X]$, and the search for fixed points supplies the solutions

$$P_1 \equiv (0, X) \qquad P_2 \equiv \left(\frac{Ch(AX - 1)}{Ah(1 + BX) + C}\,,\ \frac{h(1 + BX) + CX}{h(A + B) + C} \right). \tag{4.6}$$

Point P_1 exists whatever the value of parameters is, and represents the optimal

condition where no tumor cells are present and all immune system cells are active. Point P_2 belongs to the phase space only when $A \geq 1/X$, and coincides with P_1 when $A = 1/X$. As regards to stability analysis, it appears to be similar to, though quite more complicated than, the one performed in ref. [**5**] for set (4.5). Thus the conclusions we can draw are analogous.

So we obtain that the point $(0, X)$ is unstable (saddle point) when $A < 1/X$, asymptotically stable (attractive node) when $A > 1/X$, whereas when $A = 1/X$ it presents a transcritical bifurcation [**12**]. Instead P_2 exists only when $A > 1/X$, and it is always unstable (saddle point). Let us remember that the second fixed point for (4.5), also existing when $A > 1/X$, is

$$\overline{P_2} \equiv \left(\frac{C(AX-1)}{A(BX+1)}, \frac{BX+1}{A+B} \right). \tag{4.7}$$

A comparison between coordinates of P_2 and $\overline{P_2}$ shows that it is always

$$\begin{aligned} x_1^{P_2} &< x_1^{\overline{P_2}} \\ x_2^{P_2} &> x_2^{\overline{P_2}}. \end{aligned} \tag{4.8}$$

It can also be seen that, when $h \to 0$, point P_2 tends to P_1, whereas when $h \to \infty$, $P_2 \to \overline{P_2}$. The latter consideration was fully to be expected, since when $h \to \infty$ set (4.4) tends to set (4.5). On the other hand, if $h = 0$, then the immune system does not fight the tumor, and we have the solution

$$\begin{aligned} x_1(t) &= x_1(0)\, e^{\,t + \frac{B}{C}[X - x_2(0)](1 - e^{-Ct})} \\ x_2(t) &= X - [X - x_2(0)]\, e^{-Ct} \end{aligned} \tag{4.9}$$

which clearly shows how, if $x_1(0) \neq 0$ (that is if tumor cells initially exist), the tumor tends to explode, notwithstanding the presence of an active immune system.

For each $h > 0$, the phase space is positively invariant, and the same occurs to the rectangular domains $0 \leq x_1 \leq a$, $b \leq x_2 \leq X$, with $a \leq \dfrac{Ch(AX-1)}{Ah(1+BX)}$, $b \geq \dfrac{h(1+BX)+CX}{h(A+B)+C}$.

The vector field defined by (4.4) is dissipative in the part of the phase space over the (cubic) curve Γ whose equation is

$$x_2 = \frac{(x_1 + h)\{(BX + 1 - C)\, h - [Ah - (BX + 1 - C)]\, x_1\}}{Ah^2 + B(x_1 + h)^2}. \tag{4.10}$$

If $\Delta = BX + 1 - C > 0$ and $h > \Delta/A$, such a curve crosses the phase space along an arc γ intersecting x_1 and x_2 axis, respectively, in the points

$$Q_1 \equiv \left(\frac{h\Delta}{Ah - \Delta}, 0 \right) \quad \text{and} \quad Q_2 \equiv \left(0, \frac{\Delta}{A + B} \right) \tag{4.11}$$

(the other intersection with x_1 axis is always outside the phase space).

Let us remember that, for set (4.5), the analogous dissipative area is bounded by the straight line $\bar{\Gamma}$ whose equation is $x_2 = (\Delta - Ax_1)/(A + B)$, which, when $\Delta > 0$, has the same intersection Q_2 with the x_2 axis and, for $x_1 > 0$, is always situated under curve Γ, which tends to $\bar{\Gamma}$ when $h \to \infty$. We argue that the dissipative area for set (4.4) is more limited than for set (4.5). We can also see that it tends to vanish for $h \to 0$ (When $\Delta < 0$, that is when the number of interleukines is large, the dissipative area contains the whole phase space, both for (4.4) and (4.5)).

Examining the trend of the vector field of (4.4) for $A > 1/X$ would denote that the stable manifold of the saddle point should separate the phase space into two different regions: the first is the basin of attraction of the stable node $(0, X)$, so that each point initially therein converges onto the node itself asymptotically; in the second region, on the other hand, each trajectory diverges to infinity when $t \to \infty$. It is also evident that the first of these regions should be «the safety area», where the immune system would be able to defeat the tumor, whereas the second one corresponds to a situation of unlimited increase of the tumor cells. The situation to be reached in order to increase the possibility of recovery is represented by widening the first area and reducing the second one.

Numerical evidence confirming some of the situations discussed in the present section and showing comparisons with the model in ref. [**5**] and that of Ivlev will be presented in Sect. **6**.

5 - Analysis of the Ivlev model

As shown in Sect. **3**, the Ivlev model leads to sets (3.5) and (3.6). Introducing adimensionalizations (4.1), (4.2), (4.3) again, set (3.6) takes the form

$$\begin{aligned} \dot{x}_1 &= (1 + BX)\, x_1 - \left[Bx_1 + Ah\left(1 - e^{-\frac{x_1}{h}}\right) \right] x_2 \\ \dot{x}_2 &= C(X - x_2) - Ah\left(1 - e^{-\frac{x_1}{h}}\right) x_2 . \end{aligned} \tag{5.1}$$

In this case the phase space is also constituted by the strip $[0, +\infty] \times [0, X]$, and we still have point $(0, X)$ as a fixed point. To look for other possible fixed

points, we should solve, as regards x_1 coordinate, the trascendental equation

$$F(x_1) \equiv \left[C + Ah(1 + BX)\left(1 - e^{-\frac{x_1}{h}}\right)\right] x_1 - ACHX\left(1 - e^{-\frac{x_1}{h}}\right) = 0 , \tag{5.2}$$

which has the solution $x_1 = 0$ and which, taking into account that $\lim_{x_1 \to +\infty} F(x_1) = +\infty$, has further positive solutions if $F'(0) < 0$. But we have $F'(0) = C(1 - AX)$, and, moreover, we can easily verify that $F''(0) > 0$, $F''(x_1) = 0$ for one and only one positive value $\overline{x_1}$ of x_1 and $F''(x_1) < 0$ for all $x_1 > \overline{x_1}$. Thus for $x_1 > 0$ we have one and only one solution when $A > 1/X$, no solution when $A < 1/X$, whereas if $A = 1/X$ the root $x_1 = 0$ is double. On the other hand, since we have, corresponding to fixed points,

$$x_2 = \frac{CX}{C + Ah\left(1 - e^{-\frac{x_1}{h}}\right)} < X , \tag{5.3}$$

we actually obtain a second fixed point P_2^* belonging to the phase space when $A > 1/X$.

As regards the study of fixed points and of the behaviour of trajectories, we can make the same considerations as the ones we made for the Holling model. Concerning the search for the region where the vector field defined by (5.1) is dissipative, we can see that it is situated in the part of the phase space over the curve Γ^*, whose equation is

$$x_2 = \frac{\Delta - Ah\left(1 - e^{-\frac{x_1}{h}}\right)}{Ae^{-\frac{x_1}{h}} + B} . \tag{5.4}$$

When $\Delta > 0$ and $h > \Delta/A$, Γ^* intersects the phase space along a curve γ^* which has points $Q_1^* \equiv \left(h \log \frac{Ah}{Ah - \Delta}, 0\right)$ and $Q_2^* \equiv \left(0, \frac{\Delta}{A + B}\right) \equiv Q_2$ in common with axes x_1 and x_2, respectively.

It can be observed that, for $x_1 > 0$, curve Γ^* lies between $\overline{\Gamma}$ and Γ, so that it can be said that the dissipative area, with the same parameter values, is halfway between the larger one of set (4.5) and the more restricted one of set (4.4).

Finally the trend of the vector field for this model are similar to those for the Holling model, as will be also confirmed numerically.

6 - Numerical results and comments

Various numerical experiments have been performed, using Software MATLAB 4.2 Numerical Library on a personal computer, for both the Holling model

(HOL) and the Ivlev model (IVL), comparing the results between the two models, and between them and the model of ref. [**5**] (INS). The analogy of the results of the three models from the qualitative point of view seems evident, as it was easy to guess on account of last sections.

Let us now examine the most typical and meaningful cases. We start fixing the values of B, C, X to 2, 1 and 1/3, respectively: then we have the (transcritical) bifurcation point when $A = 3$. Therefore the phase space is given by $[0, +\infty) \times [0, 1/3]$. In fig. 1 the phase portrait is represented corresponding to $A = 2.5$, for INS, for HOL when $h = 0.05$ and when $h = 100$, and for IVL with the same values of h.

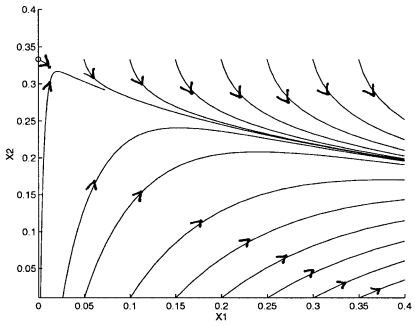
The conclusion is the same in all the above situations: all trajectories diverge to infinity, meaning that, whatever the initial point within the phase space, the tumor cell number increases indefinitely, leaving no hope for recovery.

In the case $A = 5$ (then with $A > 1/X$), point $(0, 1/3)$ is an attractor for all models, with a basin of attraction bounded by the border of the phase space and by the stable manifold of the unstable fixed point. The latter is $(2/25, 5/21)$ for INS, $\left(\frac{2h}{25h+3}, \frac{5h+3}{3(7h+1)} \right)$ for HOL. Then, whatever h is, $x_1^{HOL} < x_1^{INS}$, $x_2^{HOL} > x_2^{INS}$, as shown in Sect. **4**, with increasing and decreasing values of x_1^{HOL} and x_2^{HOL}, respectively, while h increases, and tending to x_1^{INS} and x_2^{INS} when $h \to \infty$. Moreover, numerical calculations show that $x_1^{HOL} < x_1^{IVL} < x_1^{HOL}$ and $x_2^{HOL} > x_2^{IVL} > x_2^{INS}$ for each fixed value of h. In all cases, however, such a stable manifold bounds the «safety area», meaning that the tumor always explodes if the initial point is on the right of such a line, whereas the immune system is able to destroy the tumor when such a point is situated on the left, that is in the attraction basin of the stable fixed point.

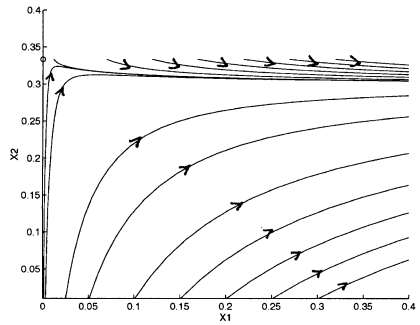
Phase portraits corresponding to various models, all for the value $A = 5$, are represented in fig. 2. From them we can argue that passing from INS to IVL and to HOL the safety area gets narrower, and enlarges in the last two models when h increases, tending towards the situation of INS when h is large enough. It appears that the stable manifold of the unstable fixed point joins this point to the stable one, constituting a heteroclynic orbit.

It is interesting to note, examining the variation of the unstable fixed point when parameter A varies, that the described curve is the same for all the three models, and precisely it is an arc of the hyperbola whose equations is

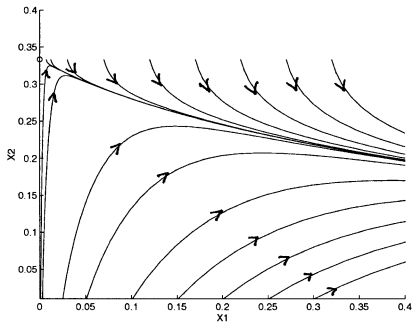
$$x_2 = \frac{CX - (BX + 1)x_1}{C - Bx_1} . \tag{6.1}$$



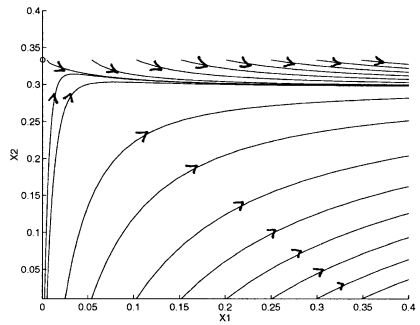
INS $A = 2.5$



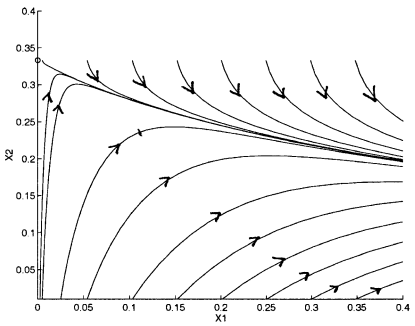
HOL $A = 2.5, \quad h = 0.05$



HOL $A = 2.5, \quad h = 100$



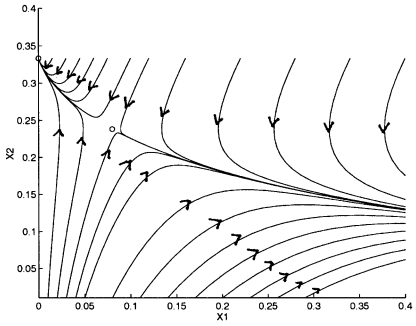
IVL $A = 2.5, \quad h = 0.05$



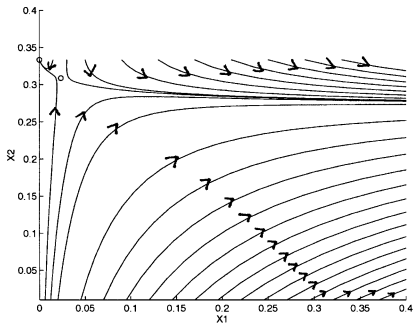
IVL $A = 2.5, \quad h = 100$

Figure 1 - Phase portraits for $A < 1/X$ ($B = 2$, $C = 1$, $X = 1/3$).

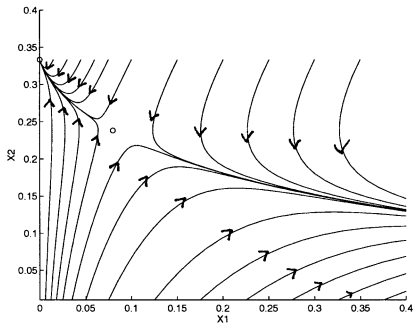
This can be obtained analytically for INS and HOL. In the case of IVL, we can verify that the solution (different from $(0, X)$) of the equations obtained equating to zero the righ-hand-sides of (5.1) satisfies (6.1). So we have the same unstable fixed points for all the three models, but they are obtained for different values of



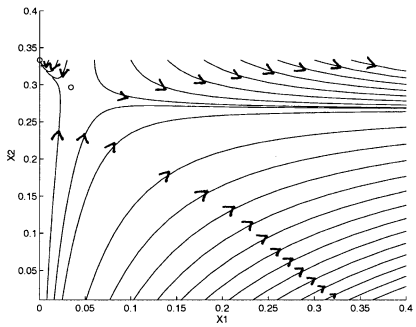
INS $A = 5$



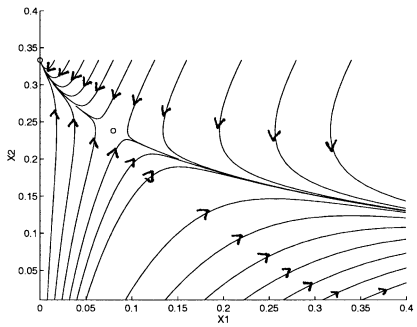
HOL $A = 5, \quad h = 0.05$



HOL $A = 5, \quad h = 100$



IVL $A = 5, \quad h = 0.05$



IVL $A = 5, \quad h = 100$

Figure 2 - Phase portraits for $A > 1/X$ ($B = 2$, $C = 1$, $X = 1/3$).

A. More precisely, fixing the value of the other parameter and of h, we find that $A^{INS} < A^{IVL} < A^{HOL}$ corresponding to the same point. For example, we obtain point $(2/25, 5/21)$, corresponding to $A^{INS} = 5$ in the above examined case, for $A^{HOL} = 5.4$ and $A^{IVL} = 5.203$, when $h = 1$.

TABLE I.

	INS	model	HOL	$h=0.05$	IVL	$h=0.05$	HOL	$h=100$	IVL	$h=100$
A	α	β	α	β	α	β	α	β	α	β
5	0.114	0.0275	0.0257	0.0062	0.039	0.0095	0.1138	0.0275	0.114	0.0275
10	0.261	0.0761	0.0791	0.0225	0.1015	0.0309	0.2607	0.0760	0.2608	0.0761
50	0.4587	0.1617	0.2754	0.0938	0.3018	0.1060	0.4585	0.1616	0.4586	0.1617
100	0.4938	0.1793	0.3624	0.1283	0.3825	0.1382	0.4937	0.1792	0.4938	0.1793
10^3	0.5291	0.1978	0.5085	0.1893	0.5122	0.1912	0.5291	0.1978	0.5291	0.1978
10^4	0.5329	0.1998	0.5307	0.1989	0.5311	0.1991	0.5329	0.1998	0.5329	0.1998
10^5	0.5333	0.2000	0.5330	0.1998	0.5331	0.1999	0.5332	0.2000	0.5333	0.2000
10^6	0.5333	0.2000	0.5333	0.2000	0.5333	0.2000	0.5333	0.2000	0.5333	0.2000
10^7	0.5333	0.2000	0.5333	0.2000	0.5333	0.2000	0.5333	0.2000	0.5333	0.2000

As regards the α and β intersection value of the stable manifold (which limits the safety area) with the straight lines $x_2 = X$ and $x_2 = 0$ respectively, table I shows the trend in the three models, which denotes how in any case they vary monotonically on A increasing and tend to the same finite value asymptotically when $A \to \infty$. We argue that the safety area is always limited and that, in any case, if the initial value x_{10} of x_1 exceeds a certain value there is no hope for recovery, no matter how large is the value of A.

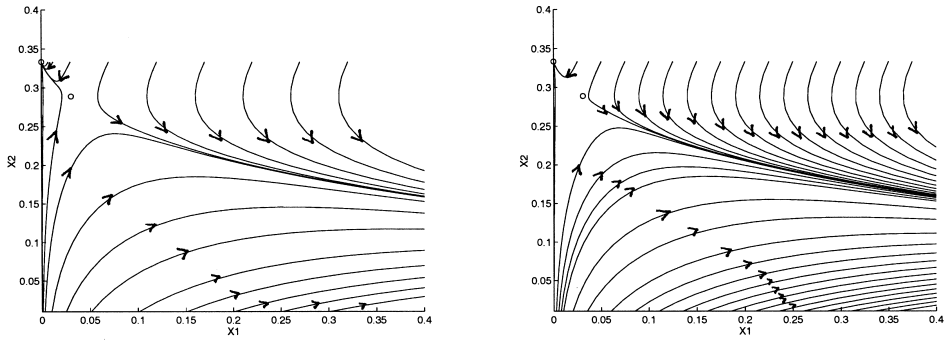
We can then examine what occurs, once the other parameters are fixed, when either B or C varies. Bearing in mind that B measures the tendency of tumor cells to proliferate, whereas C measures the immune system cell activation by interleukines, we can expect a narrowing of the safety area as B increases, and a widening as C increases. The graphs in fig. 3 confirm the above expectation.

To conclude, let us shortly refer to the case where an external treatment is applied, for example an external source (which we will consider, for simplicity's sake, as a constant) for interleukines. Then we assume $\Gamma_4 \neq 0$ in (2.11), so that $n_4(t) = \Gamma_4 t + k_4$. Setting

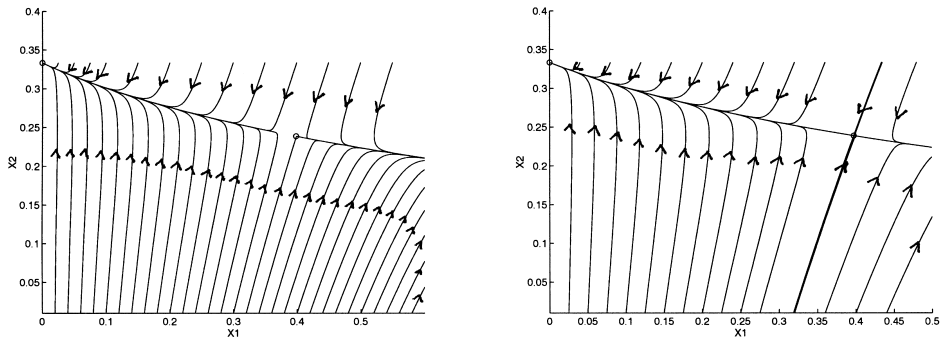
$$D = \frac{\overline{\eta}_{34}\,\Gamma_4}{[\overline{\mu}_{12}(m_{12}-1)\,k_2]^2}\,, \tag{6.2}$$

sets (4.4) and (5.1) take the forms

$$\begin{aligned} \dot{x}_1 &= (1+BX)\,x_1 - \left(B + \frac{Ah}{h+x_1}\right) x_1 x_2 \\ \dot{x}_2 &= (C+Dt)(X-x_2) - \frac{Ah}{h+x_1}\,x_1 x_2 \end{aligned} \tag{6.3}$$



HOL $B = 10, C = 1, h = 100$ IVL $B = 10, C = 1, h = 100$



HOL $B = 2, C = 100, h = 100$ IVL $B = 2, C = 100, h = 100$

Figure 3 - Phase portraits when either B or C is increased ($A = 5$, $X = 1/3$).

and

$$\begin{aligned} \dot{x}_1 &= (1 + BX)\, x_1 - \left[Bx_1 + Ah\left(1 - e^{-\frac{x_1}{h}}\right)\right] x_2 \\ \dot{x}_2 &= (C + Dt)(X - x_2) - Ah\left(1 - e^{-\frac{x_1}{h}}\right) x_2 \end{aligned} \tag{6.4}$$

respectively. They are no longer autonomous and do not result in dynamical systems.

The first equations in (6.3) and (6.4) do not vary with respect to (4.4) and (5.1). Then, when $A < 1/X$, the situation remains hopeless, whatever the initial conditions might be. Instead, if $A > 1/X$, it is interesting to examine the possibility for phase trajectories to enter the $(0, X)$ fixed point attraction basin, even though starting from points which, for $D = 0$, would be out of the safety area. Fixing $X = 1/3$, $A = 5$, $B = 2$, $C = 1$ again and considering $(1/5, 1/3)$ (outside the safety area when $D = 0$) as a starting point, we find, for HOL, the threshold values

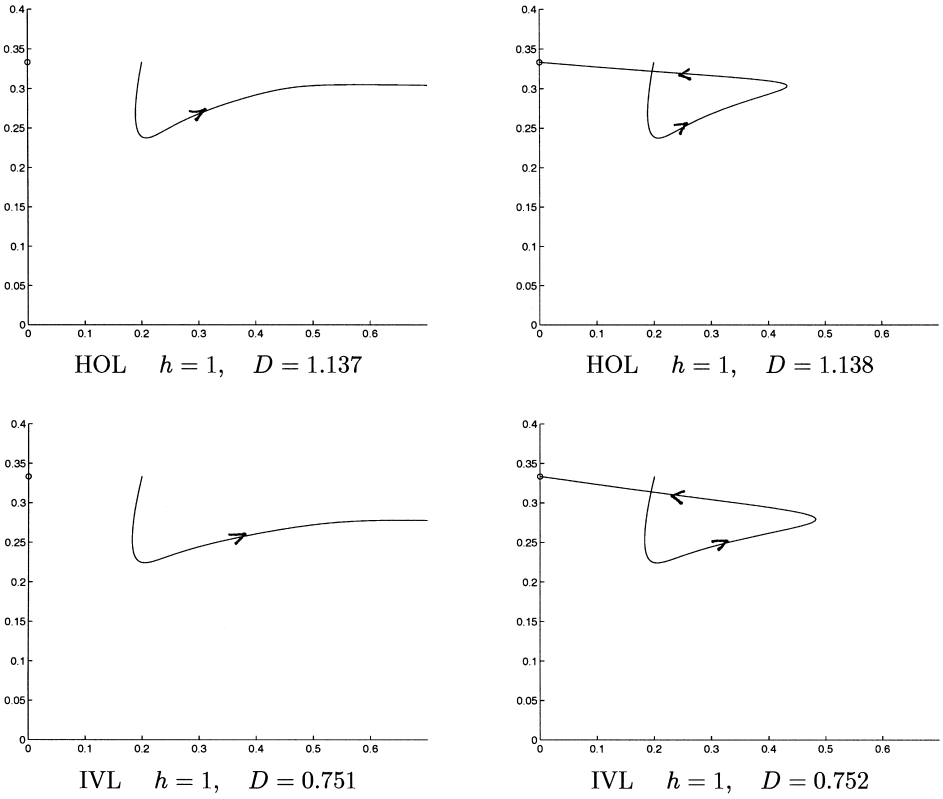


Figure 4 - Phase trajectories for values of D close to the threshold ($A = 5$, $B = 2$, $C = 1$, $X = 1/3$, $x_{10} = 1/5$, $x_{02} = 1/3$).

$D^* = 1.138$ for $h = 1$, $D^* = 0.525$ for $h = 10$ and $D^* = 0.486$ for $h = 100$. Then for $D < D^*$ trajectories diverge to infinity, whereas for $D > D^*$, after a while, they reverse and tend looping to the $(0, X)$ point.

In IVL and for the same value of parameters we find $D^* = 0.752$, $D^* = 0.503$ and $D^* = 0.484$, respectively. Note that, in the case of INS, $D^* = 0.482$ was found. In fig. 4 phase trajectories relevant to values close to the threshold, for both HOL and IVL, are shown.

These examples show how the D^* value increases as h decreases, how it is higher in HOL than in IVL (with the same value of h), and how D^* values tends to converge on each other and, when h is large enough, with the value of INS. The latter, in turn, is always lower than the one in other models, for fixed parameters values.

For small h values (e.g. $h = 0.1$) D values causing tumor regression were not found.

Moreover, on increasing initial value abscissa, the D^* value appears to grow larger and larger, in all cases.

TABLE II.

	INS	HOL $h=1$	IVL $h=1$	HOL $h=10$	IVL $h=10$	HOL $h=100$	IVL $h=100$
x_{10}	D^*	D^*	D^*	D^*	D^*	D^*	D^*
0.2	0.482	1.138	0.752	0.525	0.503	0.486	0.484
0.3	1.236	3.604	2.097	1.356	1.294	1.247	1.240
0.4	2.093	8.881	4.108	2.334	2.211	2.115	2.104
0.5	3.012	22.719	7.088	3.425	3.213	3.050	3.031
0.6	3.973	90.837	11.629	4.612	4.283	4.031	4.002
0.7	4.965		18.950	5.887	5.410	5.046	5.005
0.8	5.978		31.911	7.248	6.589	6.089	6.033
1.0	8.06		137.574	10.228	9.090	8.238	8.146
2.0	18.9			31.266	24.380	19.772	19.347

Table II shows the above-discussed situations, in the various models. Empty boxes mean that we were not able to find corresponding values by our numerical experiments. It seems that there is no saturation effects with respect to increasing x_{01}, but it is clear that, in practice, D cannot exceed certain values. Therefore, when initially the tumor is in an advanced stage, no external intervention will lead to recovery.

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Abstract

The problem of the competition between tumor cells and immune system, discussed in a previous paper in terms of Lotka-Volterra type interactions, is examined starting from equations for the evolution of dominance in populations of interacting organisms. The saturation effects in the capability of the immune system to destroy the tumor are taken into account, on the basis of two different models proposed in the literature («Holling model» and «Ivlev model»). In both cases, we deal with a closed set of macroscopic equations, which is examined in the frame of the theory of dynamical systems. Situations leading to depletion of the tumor are studied, comparing the results of the different models, also on the basis of numerical experiments.

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