



# Analysis of a Kinetic Cellular Model for Tumor-Immune System Interaction

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**Abstract**—Starting at a kinetic level from the equations for the evolution of dominance in populations of interacting organisms, and taking proliferative and destructive encounters into account, a simple model describing the competition between tumor cells and immune system is studied in some detail. Under reasonable assumptions, a closed set of macroscopic balance equations for macroscopic observables is derived by a moment procedure, and analyzed in the frame of the theory of dynamical systems. It is shown that a transcritical bifurcation of equilibria generates a region in the phase space in which, according to the model, the immune system defeats the tumor and leads to its depletion. Numerical results are presented and briefly commented on. © 1999 Elsevier Science Ltd. All rights reserved.

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## 1. INTRODUCTION

It is widely recognized that the problem of evolution of dominance is crucial in population dynamics. The interested reader is referred to [1] and to the bibliography therein. In the same paper, a stochastic model governing such an evolution is provided, which describes binary individual interactions at a microscopic level, and follows from the Chapman-Kolmogoroff equation in the frame of the theory of Markov processes. The approach is essentially the same as for the derivation of the nonlinear Boltzmann equation of gas kinetic theory, and such a connection has been studied in detail in [2]. The dependent variable to be investigated is the dominance distribution function, whose first few state moments provide the macroscopic observables. As typical of kinetic theory, exact evolution equations at macroscopic level may be derived for the above physical quantities by taking moments of the microscopic nonlinear integrodifferential equation, but the resulting set of differential equations turns out not to be closed [3]. The kinetic approach of [1] has been applied in recent years to immunology problems, and in particular to the competition between tumors and immune system [4–6]. The motivation is that the stage of the early growth of a tumor belongs to the so-called free cells regime, in which the tumor cells are not yet condensed in a macroscopically observable spatial structure, and the interactions between tumor and immune system occur at a cellular level. This makes the kinetic approach particularly

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appropriate, not only for the better insight allowed by a deeper description, but also because the more common macroscopic description based on classical diffusion-convection equations in the framework of continuum mechanics [7], would fail in this case. On the other hand, this stage is particularly important since the competition between tumor cells and immune system can still lead to the depletion of the tumor. At the same time, spatial effects are of minor importance, to leading order, in the balance equations, which implies considerable simplifications in the analytical investigation. In the present paper, a four species model proposed already in the literature will be considered [4,6]. This requires a generalization of the original equations for dominance [1] to include the nonconservative effects of cell proliferation and destruction. Again, this is easily done in the same way as the extended kinetic equations can be obtained as generalizations of the standard Boltzmann equation in the frame of the scattering kernel formulation [8]. Now, for a numerical solution of the resulting integrodifferential system with quadratic nonlinearities, a suitable discretization technique is needed anyhow. In this way, the description of the evolution of the various cellular populations involves a finite number of key macroscopic parameters, deduced appropriately from the actual collision frequencies and probability distributions characterizing the microscopic interaction, which are instead functions of a continuous kinetic variable, and would be quite hard to determine in full detail by comparison with experiments. The various possible discretization procedures and strategies, in order to benefit also of the cellular character of the approach where they originate from, and the various biological rules to be taken into account, along with their consequences, have been thoroughly investigated in [9]. In this work, the discretization is achieved by integration over partial ranges with respect to the kinetic variable, and grouping together all individual cells with a value of state in the same range to form a single separated population. Under very reasonable assumptions on the microscopic interaction parameters, a closed set of autonomous ODEs is derived, representing a sort of macroscopic continuity equations in the sense of kinetic theory. The qualitative analysis of the evolution problem can then be performed in the well-established framework of the theory of dynamical systems [10]. A first important step in such an analysis is determination of fixed points, as stationary living conditions of the considered organism, and of their stability. Further essential steps are investigation of their basins of attraction, representing regions of the phase space where immune system wins the competition and leads to recovery, and determination of possible bifurcations for varying parameters. Extensive numerical simulations have been performed, in order to test and improve the analytical predictions, by using random selected values of the dimensionless parameters, aiming mainly at analyzing in depth the essential features of the model, rather than at focusing on the numerical ranges of major immunological interest. The external action of a treatment for improving and strengthening the immune system can also be simulated by the addition of a proper source term, even though that makes the set of ODEs nonautonomous.

The paper is organized as follows. The governing evolution equations at kinetic level and the well posedness of the relevant Cauchy problem are discussed in Section 2. Section 3 deals with the derivation of the tumor-immune system model and its discretization. Section 4 is devoted to dynamical system analysis of the resulting set of ODEs, and shows, in particular, occurrence of a transcritical bifurcation of equilibria with significant practical impact on the dynamics. In Section 5, numerical results are presented and commented on. In spite of its extreme simplicity, the proposed model seems to show sensible and meaningful predictive capability. If the strength of the immunological defense is above a given threshold (in the sense explained below), a sufficiently weak initial tumor is depleted. The larger the defense above the threshold, the stronger the tumor that can be defeated, but with a clear saturation effect which bounds the safety region that can be reached asymptotically. However, even outside the safety region, an external treatment to support the immune system can produce the same depletion effect, if it is timely and intensive enough. Of course, it would be interesting to compare the present results with experimental data.

## 2. EVOLUTION EQUATION

In a mixture of  $N$  different populations, each individual of a general species  $i$  is assumed to be characterized by an attribute, which may be called state in this new frame, and described by a real variable  $u \in [-1, 1]$ . We are interested in the distribution functions  $f_i(u, t)$ , where  $f_i(u, t) du$  is the expected number of individuals of the species  $i$  that at time  $t$  have a value of state in the interval  $(u, u + du)$ , and in their time evolution due to binary interactions with other individuals of the same or different species. Spatial gradients will not be considered for the reasons explained in the Introduction. Interaction rates in the balance equation for a given population can be split in a gain and a loss term due to encounters [1,6,8], which, in the absence of correlations [3], are in turn described in terms of collision frequencies and transition probabilities with reference to the above distribution functions alone. For obvious physical reasons, the  $f_i$  must be smooth nonnegative functions of their arguments, and the number densities are given by

$$n_i(t) = \int_{-1}^1 f_i(t, u) du, \quad i = 1, 2, \dots, N. \quad (2.1)$$

Encounters are allowed to be of conservative or nonconservative type. In the former case, the number of participating individuals of each species is conserved and only states are subject to change; in the latter, individuals may disappear or be generated in the interaction by some kind of destructive or proliferative mechanism, similar to absorption and ionization for electrons in kinetic theory. Balance equations are easily derived in a probabilistic setting upon introducing the phenomenological interaction parameters listed below, which have to satisfy obvious smoothness requirements from a mathematical point of view, but have to be determined on the basis of experiments. The approach is essentially the same as in the quoted references, only with a slightly modified meaning of parameters, to make them closer to the corresponding ones arising in kinetic theory [8].

By  $\eta_{ij}(u, v) = \eta_{ji}(v, u) \geq 0$ , we will denote the microscopic collision frequency for a conservative encounter between an  $i$ -individual with state  $u$  and  $j$ -individual with state  $v$ . In the same encounter,  $\psi_{ij}(u, v; w) \geq 0$  will represent the probability density that, after interaction, the  $i$ -individual ends up with state in the interval  $(w, w + dw)$ , with the obvious normalization

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

Similarly,  $d_{ij}(u, v)$  will be used for the microscopic collision frequency of an  $(i, u)$  individual with a  $(j, v)$  individual for an encounter which is not conservative for the species  $i$  and  $\mu_{ij}(u, v) \leq d_{ij}(u, v)$  will stand for the fraction of it relevant to proliferative interactions only. For the latter events, the number of  $i$ -individuals which end up in the state interval  $(w, w + dw)$  will be labeled by  $\varepsilon_{ij}(u, v; w) dw$  and the integral

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

gives the total number of  $i$ -individuals generated on the average in a proliferative encounter  $(i, u)$ - $(j, v)$ . Such a number is, in general, greater than unity.

At this point, evolution at this kinetic level is governed by the balance equations

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

where  $\gamma_i$  represents the rate of supply of a possible external source of individuals of the  $i$ -population at state  $u$ . This is a set of integrodifferential nonlinear equations which closely resembles *mutatis mutandis*, the Boltzmann equation for gas mixtures [3] in the scattering kernel formulation [8]. Continuity equations are obtained by integration with respect to  $u$ , but the result is not closed, in general, with respect to the number densities (the only macroscopic observables of interest here), since it reads as

$$\frac{dn_i}{dt}(t) = \sum_{j=1}^N \int_{-1}^1 \int_{-1}^1 [\mu_{ij}(u, v)m_{ij}(u, v) - d_{ij}(u, v)] f_i(u, t)f_j(v, t) du dv + \Gamma_i, \quad (2.5)$$

$$i = 1, \dots, N,$$

where  $\Gamma_i = \int_{-1}^1 \gamma_i(u) du$ . Of course, conservative encounters are not influential, and the positive or negative contribution for the  $i^{\text{th}}$  species of the general  $i$ - $j$  interaction depends on the sign of  $\mu_{ij}m_{ij} - d_{ij}$ . When all such parameters are constant, the collision term in (2.5) becomes a quadratic form in the densities  $n_i$ .

It might happen that one or more species in the mixture have a much larger density than the others, and their distribution function is consequently almost not affected by the process. As in [8], they may be considered as background species, whose host individuals have a distribution function which is essentially known *a priori*. That reduces the number of actual unknowns in (2.4), and at the same time introduces linear integral terms in the collision integrals on the right-hand side (those for which the index  $j$  is background), as it occurs in transport theory [11].

As regards the well posedness of the mathematical problem (2.4), endowed with suitable initial conditions  $f_i(u, 0)$ , the natural setting seems to be the space of summable functions, since all unknowns are nonnegative and their norm provides the number density. As physically clear, all nonnegative functions  $\eta, \mu, d, \psi, \varepsilon, \gamma$  will be assumed bounded on their domains. Among the several possible approaches (see also [6]), we propose here, following [12], one that is based on approximate solutions in the sense of [13]. Let  $E$  be the Banach space  $[L_1[-1, 1]]^N$  with norm

$$\|f\|_E = \sum_{i=1}^N \|f_i\|_{L_1} = \sum_{i=1}^N \int_{-1}^1 |f_i(u)| du, \quad (2.6)$$

and let  $E^+$  be the cone of nonnegative functions in it. By solution of the mathematical problem, we mean an application  $f : [0, T] \rightarrow E^+$ , differentiable there, satisfying the Cauchy problem (2.4) with the relevant initial conditions in  $E^+$ . The Cauchy problem may be written in abstract form as

$$\frac{df}{dt} = Af, \quad f(0) = f^0, \quad (2.7)$$

where  $A : E \rightarrow E$  is the affine integral operator defined by the right-hand sides of (2.4). Introducing the constant  $K = \sup[2\eta_{ij}(u, v) + d_{ij}(u, v) + \mu_{ij}(u, v)m_{ij}(u, v)]$ , the sup being taken with respect to  $i, j = 1, 2, \dots, N$  and  $u, v \in [-1, 1]$ , easy manipulations show that the following lemma holds: for  $f^0 \in E^+$ ,  $R > 0$ ,  $\forall f, g \in E^+$  such that  $\|f - f^0\|_E < R$  and  $\|g - f^0\|_E < R$ , there exists  $L = L(\|f^0\|_E)$  such that

$$\|Af - Ag\|_E \leq L\|f - g\|_E. \quad (2.8)$$

In particular,  $L = 2K(R + \|f^0\|_E)$ . Another lemma that can be easily verified by analogous manipulations is the following: for  $f^0 \in E^+$ ,  $R \geq 0$ ,  $\forall f \in E^+$  such that  $\|f - f^0\|_E \leq R$ , there results

$$\|Af\|_E \leq M, \quad M = K(R + \|f^0\|_E)^2 + \sum_{i=1}^N \Gamma_i. \quad (2.9)$$

Finally, the following third lemma holds. Let  $f^0 \in E^+$ ,  $R \geq 0$ ; then,  $\forall f \in E^+$  with  $\|f - f^0\|_E \leq R$ , we have

$$\lim_{h \rightarrow 0^+} \inf \frac{d(f + hAf, E^+)}{h} = 0, \quad (2.10)$$

where  $d(\varphi, E^+)$  denotes distance of  $\varphi \in E$  to the set  $E^+$ . For the proof, it is sufficient to show that  $\forall \varepsilon > 0$ ,  $\forall h > 0$ ,  $\exists g \in E^+$ ,  $\exists h_1 < h$  ( $h_1 > 0$ ) such that  $\|f + h_1Af - g\|_E < \varepsilon h_1$ . For that purpose, take

$$h_1 = \min \left\{ h, [K(R + \|f^0\|_E)]^{-1} \right\}$$

and

$$\begin{aligned} g_i(u) = & \gamma_i(u) + f_i(u) \left\{ 1 - h_1 \sum_{j=1}^N \int_{-1}^1 [\eta_{ij}(u, v) + d_{ij}(u, v)] f_j(v) dv \right\} \\ & + h_1 \sum_{j=1}^N \int_{-1}^1 \int_{-1}^1 \{ \eta_{ij}(v, w) [\psi_{ij}(v, w; u) + \varepsilon_1] \\ & + \mu_{ij}(v, w) [\varepsilon_{ij}(v, w; u) + \varepsilon_1] \} f_j(v) f_j(w) dv dw, \end{aligned} \quad (2.11)$$

with  $\varepsilon_1$  free parameter to be determined. Then, it is easy to check that  $g \in E^+$  and that the choice  $\varepsilon_1 = \varepsilon [K(R + \|f^0\|_E)^2]^{-1}$  does the job. Now, due to the three previous lemmas, local existence and uniqueness of solution in the sense defined above follows from a theorem of [13]. In addition, by the same theorem, for any  $R$  which is applicable, the maximal existence interval  $[0, T]$  is defined by  $T \leq T^*$ , where  $T^*$  is subject to the constraint

$$0 < T^* < R \left[ K(R + \|f^0\|_E)^2 + \sum_{i=1}^N \Gamma_i \right]^{-1}, \quad (2.12)$$

but otherwise arbitrary, and, in that interval, we have  $\|f - f^0\|_E \leq R$ . In any case, the right-hand side of (2.12) has a positive finite maximum for varying  $R$ , and the theorem remains local. As regards extension to global solvability, it is linked as usual to the dependence of the estimate (2.12) on the norm of the initial datum, in order to start new initial value problems again and again and to reach any assigned value of time. It is apparent that such a procedure works, for instance, in all conservative cases, i.e., when all  $d_{ij}$  (and then  $\mu_{ij}$ ) and  $\gamma_i$  vanish. We would have in fact  $\|f\|_E = \sum_{i=1}^N n_i$  for  $f \in E^+$  and  $n_i = \text{constant}$ ,  $\forall i$  due to (2.5), so that  $\|f\|_E$  is constant during the whole evolution and any time is reached by repeated applications of (2.12). On the other hand, it is also very easy to give an example in which the opposite occurs, and even the solution blows up in finite time. It is sufficient to take any model, for which, in the  $i^{\text{th}}$  equation,  $\mu_{ii}m_{ii} - d_{ii}$  is a positive constant and all other coefficients vanish, to get  $\frac{dn_i}{dt} = cn_i^2$  and then divergence for  $t \rightarrow 1/cn_i^0$ .

### 3. MODELLING THE TUMOR-IMMUNE SYSTEM COMPETITION

We specialize here the set (2.4) in order to describe the interaction between tumor cells and host organism according to a biological model first introduced in [14] and then further developed. The physical system is assumed to consist of four interacting populations, and the index  $i$ , increasing from 1 to  $N = 4$ , refers, respectively, to tumors cells, cells of the host environment, cells of the immune system, and interleukines. A discussion on the validity of these assumptions and on the role played by the interleukines in modifying the tumor-immune system interaction, and in contributing to the destruction of tumor cells, can be found in the literature. The value of state  $u$  of each cell is a measure of its capability of prevailing in a binary interaction, and we may call active all cells with state close to 1 or at least positive, and passive those cells with state close

to  $-1$  or at least negative. Following phenomenological and experimental observations [4–6], the following specializations will be adopted for collision frequencies and transition probabilities. The former will be also taken for simplicity to be constant on the state domain where they are different from zero, which corresponds to the Maxwell molecule assumption of gas kinetic theory [3,8].

A collision between a tumor cell and a cell of the immune system leads to destruction of the tumor and to conservative transition to a passive state for the other cell, if the immune system before collision is active. Otherwise, the same collision yields proliferation of tumor cells and conservation of the other cells, whose state decreases and remains negative.

An encounter between a cell of the immune system and an interleukine is conservative for both species, and increases the state of the immune system, in such a way that a passive cell always undergoes a transition to a positive state.

An interaction between a tumor cell and a cell of the host environment always ends up with tumor proliferation.

Host environment and interleukines may be regarded as background species in the sense explained in the previous section, and their distribution versus state is of no practical relevance. The host population is considered to be stationary, whereas a positive external source for interleukines may be present to simulate a therapeutical treatment to enhance, via the interleukines themselves, the immunological defense.

All other interaction channels are of minor importance for the evolution and may be disregarded in the balance equation.

The previous assumptions on the collision frequencies are expressed quantitatively by the formulae

$$\begin{aligned} d_{12}(v, w) &= \mu_{12}(u, w) = \bar{\mu}_{12}, \\ d_{13}(v, w) &= \bar{\mu}_{13}, \quad \mu_{13}(v, w) = \bar{\mu}_{13}U(-w), \\ \eta_{31}(v, w) &= \bar{\mu}_{13}, \quad \eta_{34}(v, w) = \bar{\eta}_{34}, \end{aligned} \quad (3.1)$$

where  $U$  is the unit step function, with all other  $d_{ij}$ ,  $\mu_{ij}$ , and  $\eta_{ij}$  equal to zero. The relevant probability distributions  $\varepsilon_{12}$ ,  $\varepsilon_{13}$ ,  $\psi_{31}$ , and  $\psi_{34}$  are subject to the constraints

$$\psi_{31}(v, w; u) = 0, \quad \forall u > 0, \quad \psi_{34}(v, w; u) = 0, \quad \forall u < 0. \quad (3.2)$$

Finally, all  $\gamma_i$  vanish except  $\gamma_4$ . Balance equations for this simplified, but still kinetic, model read as

$$\begin{aligned} \frac{\partial f_1}{\partial t}(u, t) &= \bar{\mu}_{12} \int_{-1}^1 \int_{-1}^1 \varepsilon_{12}(u, v; w) f_1(v, t) f_2(w, t) dv dw - \bar{\mu}_{12} n_2(t) f_1(u, t) \\ &\quad + \bar{\mu}_{13} \int_{-1}^1 \int_{-1}^0 \varepsilon_{13}(v, w; u) f_1(v, t) f_3(w, t) dv dw - \bar{\mu}_{13} n_3(t) f_1(u, t), \\ \frac{\partial f_2}{\partial t}(u, t) &= 0, \\ \frac{\partial f_3}{\partial t}(u, t) &= \bar{\mu}_{13} \left( \int_{-1}^1 \int_{-1}^1 \psi_{31}(v, w; u) f_3(v, t) f_1(w, t) dv dw - n_1(t) f_3(u, t) \right) \\ &\quad + \bar{\eta}_{34} \left( \int_{-1}^{-1} \int_{-1}^1 \psi_{34}(v, w; u) f_3(v, t) f_4(w, t) dv dw - n_4(t) f_3(u, t) \right), \\ \frac{\partial f_4}{\partial t}(u, t) &= \gamma_4(u). \end{aligned} \quad (3.3)$$

It is clear that there are only two actual participating species, since  $f_2$  and  $f_4$  are known functions, determined independently of the process, and in particular  $f_2$  is constant. It seems reasonable to assume that the average number of cells created in proliferative encounters is independent of the states of the colliding cells, which combined to the normalization condition (2.2),

enables us an easy integration to get the present version of the continuity equations (2.5), namely

$$\begin{aligned}\frac{\partial n_1}{\partial t} &= \bar{\mu}_{12} (m_{12} - 1) k_2 n_1(t) + \bar{\mu}_{13} m_{13} n_1(t) \int_{-1}^0 f_3(w, t) dw - \bar{\mu}_{31} n_1(t) n_3(t), \\ \frac{\partial n_3}{\partial t} &= 0, \\ \frac{\partial n_4}{\partial t} &= \Gamma_4,\end{aligned}\tag{3.4}$$

which do not constitute a closed set, due to the presence of a half-range integration, and where again, the last equation decouples to provide independently  $n_4$  versus time. But a closed set of macroscopic balance type is easily obtained here by grouping together active cells of the immune system to form a separate population, and the same for the passive immune cells, while keeping together tumor cells in a single population. Indeed, this is suggested by the interaction mechanisms of the considered model, which makes state a crucial attribute mainly for the immune system only, since completely different behaviors are expected from active and passive cells. Other discretization procedures in which other populations are also divided into active and passive parts are discussed in [9]. Setting

$$n_3^\pm(t) = \pm \int_0^{\pm 1} f_3(u, t, ) du\tag{3.5}$$

and bearing (3.2) in mind, integration over half ranges in (3.3) yields the closed set of ordinary differential equations with quadratic nonlinearities

$$\begin{aligned}\frac{dn_1}{dt} &= \bar{\mu}_{12} (m_{12} - 1) n_2 n_1(t) + \bar{\mu}_{13} (m_{13} - 1) n_1(t) n_3^-(t) - \bar{\mu}_{13} n_1(t) n_3^+(t), \\ \frac{dn_3^+}{dt} &= -\bar{\mu}_{13} n_1(t) n_3^+(t) + \bar{\eta}_{34} n_4(t) n_3^-(t), \\ \frac{dn_3^-}{dt} &= \bar{\mu}_{13} n_1(t) n_3^+(t) - \bar{\eta}_{34} n_4(t) n_3^-(t),\end{aligned}\tag{3.6}$$

where  $n_2$  is the known constant environment density, and  $n_4$  the known interleukine density. A further simplification is allowed by the already established conservation of the immune system as a whole (all possible interactions are conservative for it), since, if  $n_3$  denotes its constant known density, we may eliminate  $n_3^-$  as  $n_3 - n_3^+$  and get the set of only two equations

$$\begin{aligned}\frac{dn_1}{dt} &= [\bar{\mu}_{12} (m_{12} - 1) n_2 + \bar{\mu}_{13} (m_{13} - 1) n_3] n_1(t) - \bar{\mu}_{13} m_{13} n_1(t) n_3^+(t), \\ \frac{dn_3^+}{dt} &= \bar{\eta}_{34} n_3 n_4(t) - \bar{\eta}_{34} n_4(t) n_3^+(t) - \bar{\mu}_{13} n_1(t) n_3^+(t).\end{aligned}\tag{3.7}$$

These simple model equations seem to deserve attention, first for their great simplicity, then for providing directly the essential macroscopic quantities, and for requiring the knowledge of biological parameters which are within the reach of experiments. It still incorporates the basic features of the original kinetic model. It becomes autonomous when interleukines are a stationary population, namely for  $\Gamma_4 = 0$ , and in that case, the relevant dynamical system can be studied in some detail, as shown in the next section.

#### 4. STABILITY AND BIFURCATION ANALYSIS

The set (3.7) with  $n_4 = \text{constant}$  can be made dimensionless in several ways, but it seems convenient measuring densities in units of  $n_2$  (with  $x_1 = n_1/n_2$  and  $x_2 = n_3^+/n_2$ ) and time in units of the characteristic multiplication time of tumor in the absence of immune system  $[\bar{\mu}_{12}(m_{12}-1)n_2]^{-1}$  (dimensionless time will be denoted again by  $t$ ). As dimensionless parameters,

it proves convenient to single out the overall size of the immune system  $X$ , and the rate at which tumor cells and cells of the active immune system collide  $A$ , given by

$$X = \frac{n_3}{n_2}, \quad A = \bar{\mu}_{13} [\bar{\mu}_{12} (m_{12} - 1)]^{-1}. \quad (4.1)$$

The remaining coefficients are expressed by the further adimensionalized parameters

$$B = \bar{\mu}_{13} (m_{13} - 1) [\bar{\mu}_{12} (m_{12} - 1)]^{-1}, \quad C = \bar{\eta}_{34} n_4 [\bar{\mu}_{12} (m_{12} - 1) n_2]^{-1}, \quad (4.2)$$

which measure, respectively, tumor proliferation due to passive immune system and activation of cells of the immune system due to interleukines. The dimensionless form of (3.7) then reads as

$$\begin{aligned} \dot{x}_1 &= (1 + BX)x_1 - (A + B)x_1x_2, \\ \dot{x}_2 &= C(X - x_2) - Ax_1x_2, \end{aligned} \quad (4.3)$$

with phase space given by the strip  $[0, +\infty) \times [0, X]$ . All four parameters  $X$ ,  $A$ ,  $B$ , and  $C$  are positive. Fixed points are

$$(0, X) \quad \text{and} \quad \left( \frac{C}{A} \frac{AX - 1}{BX + 1}, \frac{BX + 1}{A + B} \right), \quad (4.4)$$

where the first is a border point, but represents the optimal working condition of the organism (no tumor, immune system fully active), whereas the second makes sense only when it belongs to the phase space, i.e., for  $A \geq 1/X$ . The two equilibria coincide when  $A = 1/X$ . Eigenvalues of the Jacobian matrix relevant to (4.3) at  $(0, X)$  are  $-C$  and  $1 - AX$ , which means that such a stationary solution is asymptotically stable (attractive node) for  $A > 1/X$ , and unstable (saddle) for  $A < 1/X$ . The other stationary solution, which is physical only for  $A > 1/X$ , coexists thus with a stable attracting point, and eigenvalues are determined by the characteristic polynomial

$$\lambda^2 + \frac{CX(A+B)}{BX+1}\lambda - C(AX-1), \quad (4.5)$$

which exhibits two real zeroes with opposite sign, so that the second equilibrium is unstable (saddle), when it exists. It would instead be an attractive node out of the phase space. Focusing our attention on the crucial parameter  $A$ , we see that  $A = 1/X$  is a bifurcation value [10]. The circumstance that a movable equilibrium coalesce and split with a fixed equilibrium when  $A$  increases past  $1/X$ , and exchanges stability with it, suggest that the bifurcation should be transcritical, namely topologically equivalent to that occurring for  $\dot{x} = \mu x - x^2$  at  $x = 0$ ,  $\mu = 0$ . Denoting by  $\underline{f}(x_1, x_2; A)$  the vector field defined by (4.3), by  $\underline{J}(x_1, x_2; A)$  the associated Jacobian matrix, it is easily verified that  $\underline{f}(0, X; A) = \underline{0}$ ,  $\forall A$  and that  $\underline{J}(0, X; 1/X)$  has a simple eigenvalue  $\lambda = 0$  (the other is  $-C$ ) with right eigenvector  $\underline{r} \equiv (C, -1)$  and left eigenvector  $\underline{l} \equiv (1, 0)$ . In addition, using the repeated index convention, we have

$$\begin{aligned} l_i \frac{\partial^2 f_i}{\partial A \partial x_j} \left( 0, X; \frac{1}{X} \right) r_j &= -CX \neq 0, \\ l_i \frac{\partial^2 f_i}{\partial x_j \partial x_k} \left( 0, X; \frac{1}{X} \right) r_j r_k &= 2C \left( B + \frac{1}{X} \right) \neq 0. \end{aligned} \quad (4.6)$$

The above facts prove, according to a standard theorem on dynamical system [10], that the bifurcation is actually transcritical.

The first equation alone in (4.3) is sufficient to reveal a sorry tale. From  $x_2 \leq X$ , we get

$$\dot{x}_1 \geq [B(X - x_2) + 1 - AX] x_1, \quad (4.7)$$



where the right-hand side is positive at any interior point of the phase space and on the lower border  $x_2 = 0$  for  $A \leq 1/X$ , and also on the upper border  $x_2 = X$  for  $A < 1/X$ . The phase space itself is positively invariant, with the vector field pointing inwards on the horizontal borders, and tangential on the vertical segment  $x_1 = 0$ , which represents, however, the ideal but not interesting situation that tumor cells never appear. Therefore, the qualitative analysis of phase trajectories obtained from the knowledge of the vector field rules out any possibility for the immune system to defeat the tumor, no matter how weak it appears initially, when  $A \leq 1/X$ : tumor cells density increases in time without any bound. The crucial safety threshold that the immunological defense must overcome is thus expressed by  $A > 1/X$ , that corresponds to

$$\bar{\mu}_{13}n_3 > \bar{\mu}_{12}(m_{12} - 1)n_2 \quad (4.8)$$

relating essentially the macroscopic collision frequency (inverse time) for tumor-immune system to the macroscopic collision frequency for tumor-host environment interactions, the latter corrected by the net cell production in proliferation encounters. It may be regarded as a condition on  $n_3$  once the other parameters are known.

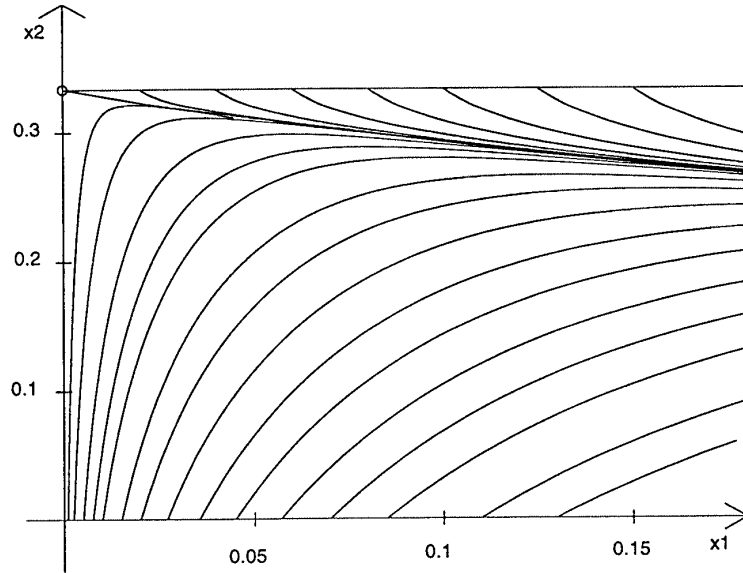
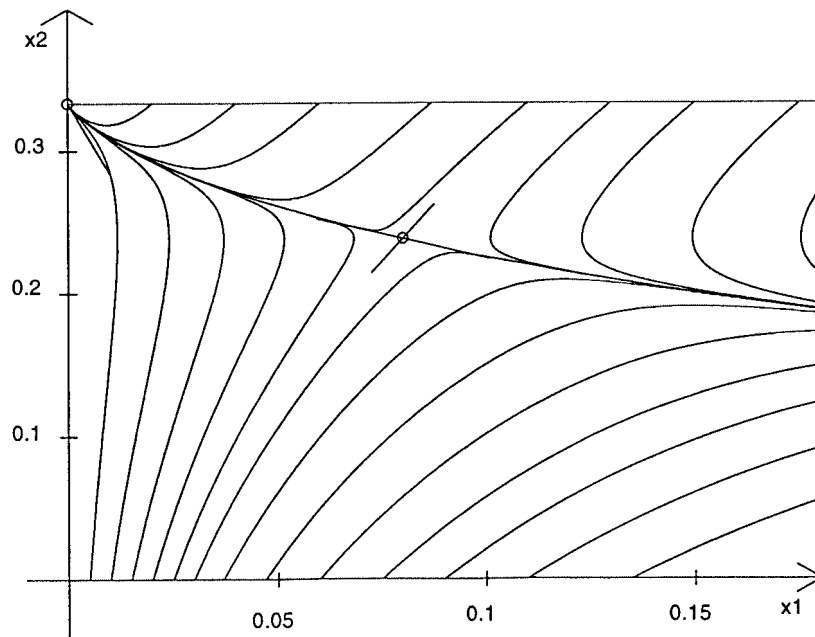
Let us examine then the option  $A > 1/X$ . The phase space remains, of course, positively invariant, and now the same happens to the rectangular domains  $0 \leq x_1 \leq a$ ,  $b \leq x_2 \leq X$ , provided  $a \leq C(AX - 1)/A(BX + 1)$  and  $b \geq (BX + 1)/(A + B)$ . The field is dissipative in the subset of the phase space defined by

$$Ax_1 + (A + B)x_2 > BX + 1 - C. \quad (4.9)$$

The trend of the vector field indicates that the stable manifold of the saddle point should separate the phase space in two different regions: the basin of attraction of the stable node on one side, and a region where all trajectories diverge to infinity when  $t \rightarrow +\infty$  on the other. Any initial point in the former region should be bound to converge asymptotically to the optimal equilibrium  $(0, X)$ , i.e., the immune system is capable of defeating the tumor if it is initially weak enough. In particular, the branch of the unstable manifold of the saddle on this safe side would join the saddle itself to the node, and constitute then a heteroclynic orbit. One would like to enlarge the previous basin of attraction as much as possible, and it is expected that such an effect can be obtained by pushing the saddle point deeper and deeper inside the phase space, i.e., as physically clear, by increasing  $A$  more and more. In this game, also the other parameters  $B$  and  $C$  would play an important role. It is obvious that increasing  $C$  (which amounts to strengthening the effects of interleukines) moves the saddle point to the right, as desired. The above predictions will be tested numerically in the next section.

## 5. NUMERICAL RESULTS AND COMMENTS

Extensive numerical experiments have been performed by using Matlab 4.2 software on a personal computer. A small sample of the results obtained is given below. With parameters  $B$ ,  $C$ , and  $X$  kept fixed at the reference values 2, 1, and  $1/3$ , we let the crucial parameter  $A$  vary with respect to its bifurcation value  $A = 3$ . Phase trajectories are given in full extent within the phase space  $[0, +\infty) \times [0, 1/3]$  and it is understood that they start from the initial condition  $(x_{01}, x_{02})$  at which the tumor is first detected. A typical phase portrait for  $A < 3$  is shown in Figure 1. It leaves no hope, tumor density always increases, and all trajectories eventually escape to infinity. The situation changes in Figure 2, relevant to  $A = 5$ . The stable fixed point  $(0, 1/3)$  is an attractor with a well-defined basin of attraction bounded by the borders of phase space, and by the stable manifold of the unstable fixed point  $(2/25, 5/21)$ . Such a manifold intersects the upper border at a point  $(\alpha, 1/3)$  with  $\alpha = 0.114$ , and lower border at a point  $(\beta, 0)$  with  $\beta = 0.027$ , and its points tend asymptotically to the saddle point  $(2/25, 5/21)$ , as  $t \rightarrow +\infty$ . For all initial points on the right-hand side of the previous manifold, the dynamics is

Figure 1. Phase portrait for  $A = 2$ .Figure 2. Phase portrait for  $A = 5$ .

hopeless and leads to tumor explosion, even though there might be an initial decreasing trend due to the action of the immune system which, however, is going to be defeated. Figure 3 is relevant to the same values of parameters, and shows explicitly the saddle point, the direction of its eigenvectors, and its stable and unstable manifolds, tangent to such directions [10]. The “safety” region, in which a tumor is destroyed by the immunological defense, is on the left of the stable manifold, and in such basin of attraction, the unstable manifold is the expected heteroclinic orbit joining the saddle to the attracting stable node  $(0, 1/3)$ . Changing the value of  $A$  above the threshold  $A = 3$  amounts to shifting the saddle point inside the phase space along the curve defined by (4.4), with limiting value  $(CX/(BX + 1), 0)$  as  $A \rightarrow +\infty$ , and to moving correspondingly the intersection abscissas  $\alpha$  and  $\beta$ . This is illustrated in Figure 4, where the trend in the phase space of the fixed point and of its eigenvectors when  $A$  increases is shown, and

Table 1.

A	$\alpha$	$\beta$
5	0.114	0.0274
10	0.261	0.076
50	0.458	0.061
10E2	0.493	0.179
10E3	0.529	0.198
10E4	0.532	0.199
10E5	0.532	0.2
10E6	0.532	0.2
10E7	0.532	0.2

Table 2.

$x_{01}$	$D^*$
0.2	0.482
0.3	1.236
0.4	2.093
0.5	3.012
0.6	3.973
0.7	4.965
0.8	5.978
1.0	8.06
2.0	18.9

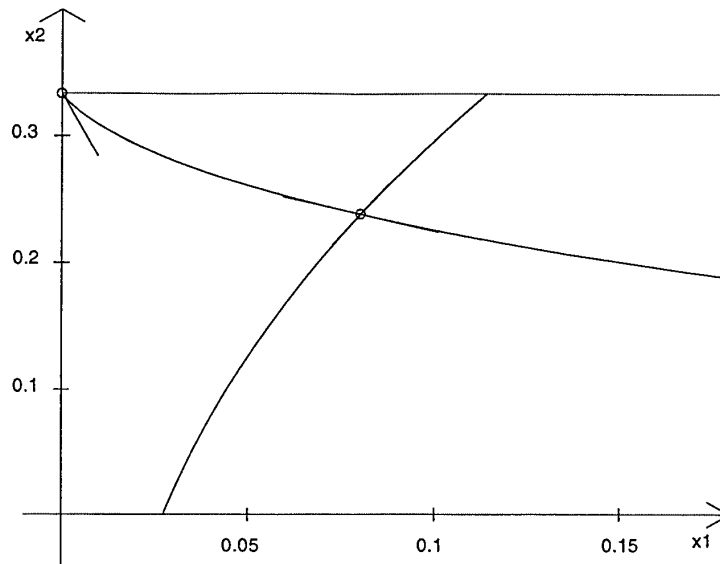


Figure 3. Stable and unstable manifold of the saddle point.

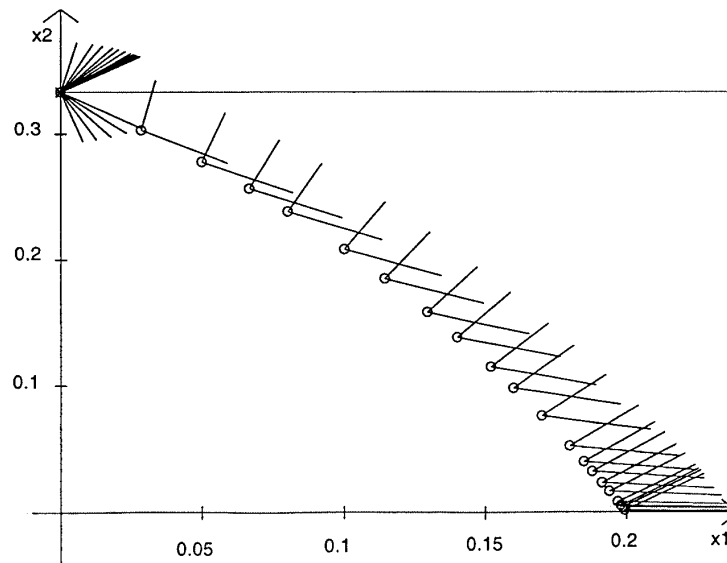
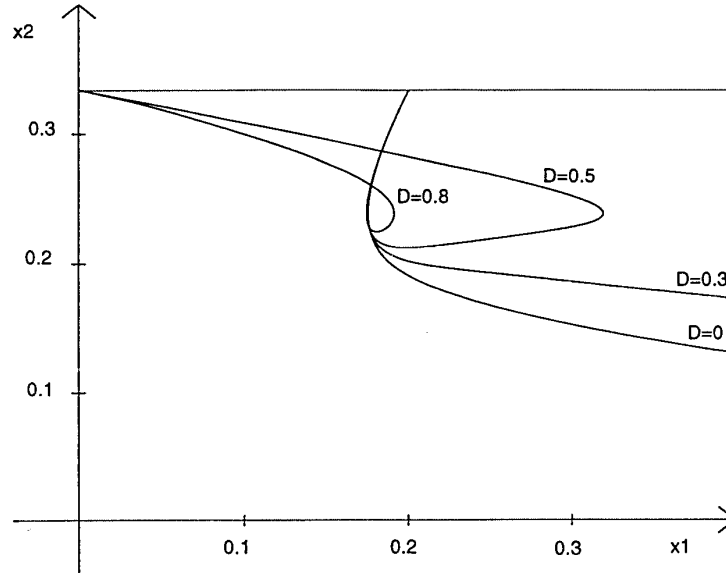


Figure 4. Trend of the fixed points in the phase space.

in Table 1, where  $\alpha$  and  $\beta$  are listed versus  $A$ . Both abscissas exhibit a monotonically increasing trend, but with an evident saturation, and with a finite limit for diverging  $A$  (this was easily predictable for  $\beta$ , whose asymptotic value is  $CX/(BX + 1)$ ). The practical effect is that the

Figure 5. Solutions for increasing value of  $D$ .

basin of attraction increases but remains bounded for increasing  $A$ , and there are then points with tumor strong enough to inhibit any recovery, no matter how large  $A$  is kept. Just in this respect, we have investigated numerically the possibility of establishing a recovery by an external treatment aimed at strengthening the interleukine population (this corresponds to a positive, rather than vanishing, interleukine source  $\Gamma_4$  in the dimensional balance equation). Taking for simplicity such a supply rate to be constant, the situation changes only in that  $n_4(t) = n_{04} + \Gamma_4 t$ , and then, upon defining

$$D = \bar{\eta}_{34} \Gamma_4 [\bar{\mu}_{12} (m_{12} - 1) n_2]^{-2}, \quad (5.1)$$

we end up with the slightly modified set of ODEs

$$\begin{aligned} \dot{x}_1 &= (1 + BX)x_1 - (A + B)x_1 x_2, \\ \dot{x}_2 &= (C_0 + Dt)(X - x_2) - Ax_1 x_2, \end{aligned} \quad (5.2)$$

which is not autonomous any more, and does not give rise to a dynamical system. Since the first equation is unchanged, the situation remains hopeless for  $A \leq 1/X$ . It is worth examining whether a positive  $D$  may lead to tumor depletion when  $A > 1/X$  and the initial point is outside the previous basin of attraction. An example of the solution is provided by Figure 5, relevant to  $A = 5$  and to the other fixed values of  $B$ ,  $C$ , and  $X$ . Time evolution is plotted for increasing values of  $D$  starting from an initial point  $(1/5, 1/3)$  where  $1/5 > \alpha = 0.114$ . For small values of  $D$ , the trajectory escapes to infinity, like for  $D = 0$ , with a similar trend. But when  $D$  overcomes a certain threshold  $D^*$ , the trajectory gets reversed after a while, and tends asymptotically to the point  $(0, X)$ , which remains a stationary solution in spite of time dependence in (5.2). The numerical value of  $D^*$  turns out to be 0.482. Notice the loop made by “safe” trajectories in this nonautonomous case. The possibility of getting this inversion, with eventual monotonic decrease and depletion of tumor, has been observed for all numerically tested initial points  $(x_{01}, X)$ . Of course, the threshold  $D^*$  is a function of parameters. For the numerical values of  $A$ ,  $B$ ,  $C$ , and  $X$  used in Figure 5, Table 2 shows  $D^*$  versus  $x_{01}$ , for  $x_{01} > \alpha$  with  $\alpha = 0.114$ . There seems to be no saturation effect, but  $D^*$  will, of course, sooner or later reach numerical values so high to exceed any practical applicability, also because it is unlikely that the treatment starts without any time delay.

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