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Kinetic models for cytokine-mediated tumor-immune system interaction (**)

dedicated to the memory of Giulio Di Cola

1 - Introduction

Mesoscopic approaches in population dynamics are becoming more and more popular since the pioneering work of Jäger and Segel [1]. The distribution of an attribute among a population is studied versus time by a probabilistic model yielding a set of nonlinear integro-differential equations. Validity and technical details of the procedure are much the same as for the Boltzmann equation of rarefied gas dynamics [2]. Such a model has been later extended to describe the competition between tumor and immune system, which requires consideration of additional destructive and proliferative encounters [3]. In this immunological frame, the attribute to be dealt with is the activity of each cell, to be understood as its capability in performing the task which is typical of its species. The resulting space homogeneous problem turns out to be particularly appropriate in the early stage of tumor growth, in which tumor cells are not yet condensed in a spatial structure, and interactions occur at a cellular level. This is an important stage since most easily tumor may be depleted by the action of the immune system. Validation of the

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mesoscopic model requires comparison with experiments at a macroscopic level, involving observable quantities which are suitable moments, with respect to the activity variable $u \in [-1, 1]$, of the unknown distribution functions f_i. Several papers have been published along this research line, dealing with various aspects of the problem, including well posedness in the proper mathematical setting: we mention, without pretending to be exhaustive, Refs. [4]-[8] and the bibliography quoted there.

In particular, in recent works [9]-[10], the presence of cytokine signals, possibly enhancing the immune defense system, has been taken into account. We will focus on that problem too, and refer the interested readers to the latter papers for all biological details. It suffices to recall here that recepting particular signals can modify the usual behavior of a cell, and, specifically, cytokine signals may increase the activity of the immune system, strengthening their capability of defeating tumor, and affecting the result of the overall competition without destroying or generating any cell. Also, it should be mentioned that this model introduces new important features with respect to previous work. More precisely, the immune system is allowed itself to undergo proliferation, with its growth controlled by the host environment, and an external source (from the bone marrow) is introduced for it.

Our equations, consistently inspired by the model above, are presented and discussed in the following two sections, for different specializations of parameters and probability densities characterizing the interactions. Analytical manipulations are carried out as far as possible, and in some cases reduction to a finite dimensional dynamical system can be achieved. A sample of the extensive numerical simulations that we have performed is finally presented in section 4, aimed at showing the main possible evolution trends and occurrence of bifurcations for varying parameters. Numerical values are selected randomly in order to investigate the different trends associated to different domains in the parameters space, and are not related to actual experimental data. Along with bifurcations relevant to transition from tumor explosion to tumor depletion, observed peculiar features of the model include existence of stable stationary solutions with non zero tumor population, and oscillating relaxations to equilibrium.

2 - The kinetic model of evolution

Following [9], consider two populations of cells (index 1 for tumor, index 2 for immune system) interacting between themselves and with a third background species constituting the host environment. Cells are endowed with an internal sta-

te, described by the real variable u, and active (passive) cells are characterized by a positive (negative) value of u. In particular, positive values of u correspond for tumor cells to aggressivity, whereas negative values to dormant states; for immune cells positive values of u correspond to defense capability, whereas negative values to inhibition and even cooperation with tumor. The distribution functions obey the set of integro-differential equations

$$\frac{\partial f_i}{\partial t} = \sum_{j=1}^{3} \int_{-1}^{1} \int_{-1}^{1} [\eta_{ij}(v, w)\, \psi_{ij}(v, w; u) + p_{ij}(v, w)\, \varphi_{ij}(v, w; u)]$$

$$\cdot f_i(v, t)\, f_j(w, t)\, dv\, dw - f_i(u, t) \sum_{j=1}^{3} \int_{-1}^{1} [\eta_{ij}(u, w) + d_{ij}(u, w)]\, f_j(w, t)\, dw \tag{2.1}$$

$$+ S_i(u, t)$$

for $i = 1, 2$, where f_3 is known (and, for simplicity, time independent), and S_i denotes the rate of generation by external sources. The quantities $\eta_{ij}(v, w) = \eta_{ji}(w, v)$ and $d_{ij}(v, w) = d_{ji}(w, v)$ represent the collision frequencies between species i and j, for conservative (changing only the state) and non-conservative (proliferative plus destructive) encounters, respectively, with $p_{ij}(v, w) \leqslant d_{ij}(v, w)$ standing for the collision frequency of those non-conservative interactions leading to proliferation of species i. Correspondingly, $\psi_{ij}(v, w; u)$ and $\varphi_{ij}(v, w; u)$ denote the expected density at u of i cells emerging in a conservative or proliferative interaction when the colliding partners were a (i, j) pair at activities v and w. They are normalized as

$$\int_{-1}^{1} \psi_{ij}(v, w; u)\, du = 1\,, \qquad \int_{-1}^{1} \varphi_{ij}(v, w; u)\, du = n_{ij}(v, w)\,, \tag{2.2}$$

where $n_{ij} > 1$ is the average number of i cells emerging from the considered (i, j) collision. Macroscopic observables are moments of the distribution functions. In particular, we will need the zero-th and first order partial and total moments

$$N_i^{\pm}(t) = \pm \int_{0}^{\pm 1} f_i(u, t)\, du\,, \qquad E_i^{\pm}(t) = \int_{0}^{\pm 1} u f_i(u, t)\, du$$

$$N_i^{\pm}(t) \geqslant 0\,, \qquad E_i^{\pm}(t) \geqslant 0 \tag{2.3}$$

$$N_i(t) = N_i^{+}(t) + N_i^{-}(t), \quad E_i(t) = E_i^{+}(t) - E_i^{-}(t), \quad N_i \geqslant 0\,,$$

expressing partial and total population densities or activity densities for each species, with $E_i^{\pm} \leqslant N_i^{\pm}$ (upper or lower sign).

According to the model proposed in [**9**], and taking into account all the several immunological requirements expounded there, collision frequencies and probability distributions will be specialized as follows. The only non vanishing collision frequencies are taken to be $\eta_{12} = \eta_{21} = \text{constant}$, $d_{12} = d_{21} = \text{constant}$, $d_{13} = \text{constant}$, and $d_{23}(v, w) = \delta_{23} wH(w)$, with the corresponding proliferative collision frequencies given respectively by

$$
\begin{aligned}
& p_{12}(v, w) = d_{12}[1 - H(v)\, H(w)], \quad p_{21}(v, w) = d_{12}, \\
& n_{12}(v, w) = 1 - \frac{\gamma_{12}}{d_{12}} vwH(v), \qquad n_{21}(v, w) = 1 + \frac{\gamma_{21}}{d_{12}} H(w),
\end{aligned} \tag{2.4}
$$

for $(1,2)$ encounters, by

$$
p_{13}(v, w) = d_{13}, \qquad n_{13}(v, w) = 1 + \frac{\gamma_{13}}{d_{13}} vwH(v)\, H(w), \tag{2.5}
$$

for $(1,3)$ interactions, and finally by $p_{23}(v, w) = 0$ for encounters between immune system and host environment.

In this way, proliferation and destruction of both tumor and immune cells are consistently modeled from an immunological point of view. The only conservative encounters in the process occur then between tumor and immune system. All other conservative interactions are negligible in the phase space balance. The symbols γ_{12}, γ_{21}, γ_{13} and δ_{23}, together with η_{12}, d_{12} and d_{13}, are positive constants, and the Heaviside functions H account for those selective immunological effects which take place only for certain values of the state variable. Moreover, along with

$$
\varphi_{ij}(v, w; u) = n_{ij}(v, w)\, \delta(u - v) \qquad (i, j) = (1, 2), (2, 1), (1, 3), \tag{2.6}
$$

where δ is the Dirac delta function (the clonal expansion considered in [**9**]), we shall analyze the further option

$$
\varphi_{ij}(v, w; u) = \frac{1}{2} n_{ij}(v, w) \qquad (i, j) = (1, 2), (2, 1), (1, 3), \tag{2.7}
$$

which corresponds to equipartition in activity of cells born by proliferation.

Furthermore we shall assume

$$
\psi_{ij}(v, w; u) = \delta[u - m_{ij}(v, w)] \qquad (i, j) = (1, 2), (2, 1), \tag{2.8}
$$

namely zero-variance distributions with mean values

$$m_{12}(v, w) = \begin{cases} v & \text{for } v \leqslant 0\,,\ w > 0 \\ v - \beta_{12}^{+} wv & \text{for } v > 0\,,\ w > 0 \\ v - \beta_{12}^{-} w(1 - v) & \text{for } w \leqslant 0 \end{cases} \tag{2.9}$$

and

$$m_{21}(v, w) = \begin{cases} v - \beta_{21} w(1 + v) & \text{for } w > 0 \\ v & \text{for } w \leqslant 0\,, \end{cases} \tag{2.10}$$

where all β coefficients range in the interval [0,1]. The latter coefficients describe the variation of activity in a cell of either tumor or immune system as a result of the conservative encounter, and model thus the effects of cytokines. Again, the physical facts underlying (2.9) and (2.10) are reported on in detail in [**9**]. Finally, sources read as

$$S_1(u, t) = 0\,, \qquad S_2(u, t) = \gamma_2 H(u)\,, \tag{2.11}$$

with γ_2 positive constant.

Local existence and uniqueness of solution of the initial value problem associated to (2.1) has been widely discussed in previous work (see also the review [**11**]), and is guaranteed in the positive cone of the summable functions under fairly weak smoothness conditions that are certainly in order here, so that this issue will not be considered further.

3 - The set of integro-differential equations

Under option (2.7), the kinetic equations take the explicit form

$$\begin{aligned} &\frac{\partial f_1}{\partial t} + f_1(u, t)[(\eta_{12} + d_{12})\, N_2(t) + d_{13} N_3] \\ &\quad = \eta_{12} \int_{-1}^{1} \int_{-1}^{1} \delta[u - m_{12}(v, w)]\, f_1(v, t)\, f_2(w, t)\, dv\, dw \\ &\quad + \frac{1}{2} d_{12}[N_1(t)\, N_2(t) - N_1^{+}(t)\, N_2^{+}(t)] \\ &\quad + \frac{1}{2} \gamma_{12} E_1^{+}(t)\, E_2^{-}(t) + \frac{1}{2} d_{13} N_1(t)\, N_3 + \frac{1}{2} \gamma_{13} E_1^{+}(t)\, E_3^{+}\,, \end{aligned}$$

$$\frac{\partial f_2}{\partial t} + f_2(u, t)[(\eta_{12} + d_{12})\, N_1(t) + \delta_{23} E_3^+]$$

$$= \eta_{12} \int_{-1}^{1} \int_{-1}^{1} \delta[u - m_{21}(v, w)]\, f_2(v, t)\, f_1(w, t)\, dv\, dw$$

$$+ \frac{1}{2} d_{12} N_2(t)\, N_1(t) + \frac{1}{2} \gamma_{21} N_2(t)\, N_1^+(t) + \gamma_2 H(u), \tag{3.1}$$

where N_3 and E_3^+ are given constant. A part from the integral term, the right hand sides and the square brackets on the left hand sides are completely determined in terms of the eight moments $N_i^\pm$ and $E_i^\pm$ (actually, only of six out of them). Indeed, it is easily realized that, in the absence of conservative encounters ($\eta_{12} = 0$), the set (3.1) can be formally solved for the f_i as a pair of uncoupled linear first order ordinary differential equations in term of the moments, whose knowledge would then determine explicitly in closed form also the distribution functions. On the other hand these moments are the most meaningful quantities for practical applications, and therefore their determination is then a crucial point by itself. To this end, it is remarkable that a closed set of exact moment equations can be deduced from (3.1) by suitable integrations, not only, as it is clear, in the case $\eta_{12} = 0$, but also for $\eta_{12} \neq 0$, provided $\beta_{\bar{1}2} = \beta_{21} = 0$, since then the zero-th and first order moments of the integral terms can be cast in closed forms involving only the moments (2.3). Integrating over either $u \in (0, 1)$ or $u \in (-1, 0)$ after multiplication by either 1 or u, and performing the simple u-integrations involving the delta function, leads in fact, after some algebra, to

$$\dot{N}_1^+(t) = -d_{12}(N_2^+(t) + N_2^-(t))\, N_1^+(t) - d_{13} N_3 N_1^+(t) + \frac{1}{2} d_{12}(N_1^-(t)\, N_2^-(t)$$

$$+ N_1^+(t)\, N_2^-(t) + N_1^-(t)\, N_2^+(t)) + \frac{1}{2} \gamma_{12} E_1^+(t)\, E_2^-(t) + \frac{1}{2} d_{13} N_3 (N_1^+(t)$$

$$+ N_1^-(t)) + \frac{1}{2} \gamma_{13} E_3^+\, E_1^+(t),$$

$$\dot{N}_1^-(t) = -d_{12}(N_2^+(t) + N_2^-(t))\, N_1^-(t) - d_{13} N_3 N_1^-(t) + \frac{1}{2} d_{12}(N_1^-(t)\, N_2^-(t)$$

$$+ N_1^+(t)\, N_2^-(t) + N_1^-(t)\, N_2^+(t)) + \frac{1}{2} \gamma_{12} E_1^+(t)\, E_2^-(t) + \frac{1}{2} d_{13} N_3 (N_1^+(t)$$

$$+N_1^-(t)) + \frac{1}{2}\gamma_{13}E_3^+ E_1^+(t),$$

$$\dot{N}_2^+(t) = -d_{12}(N_1^+(t)+N_1^-(t))\,N_2^+(t) - \delta_{23}E_3^+ N_2^+(t) + \frac{1}{2}d_{12}(N_1^+(t)+N_1^-(t))$$

$$\cdot(N_2^+(t)+N_2^-(t)) + \frac{1}{2}\gamma_{21}N_1^+(t)(N_2^+(t)+N_2^-(t)) + \gamma_2,$$

$$\dot{N}_2^-(t) = -d_{12}(N_1^+(t)+N_1^-(t))\,N_2^-(t) - \delta_{23}E_3^+ N_2^-(t) + \frac{1}{2}d_{12}(N_1^+(t)+N_1^-(t))$$

$$\cdot(N_2^+(t)+N_2^-(t)) + \frac{1}{2}\gamma_{21}N_1^+(t)(N_2^+(t)+N_2^-(t))$$

$$\dot{E}_1^+(t) = -d_{12}(N_2^+(t)+N_2^-(t))\,E_1^+(t) - d_{13}N_3E_1^+(t) + \frac{1}{4}d_{12}(N_1^-(t)\,N_2^-(t)$$

$$+N_1^+(t)\,N_2^-(t)+N_1^-(t)\,N_2^+(t)) + \frac{1}{4}\gamma_{12}E_1^+(t)\,E_2^-(t) + \frac{1}{4}d_{13}N_3(N_1^+(t)$$

$$+N_1^-(t)) + \frac{1}{4}\gamma_{13}E_3^+ E_1^+(t) - \eta_{12}\beta_{12}^+E_1^+(t)\,E_2^+(t),$$

$$\dot{E}_1^-(t) = -d_{12}(N_2^+(t)+N_2^-(t))\,E_1^-(t) - d_{13}N_3E_1^-(t) + \frac{1}{4}d_{12}(N_1^-(t)\,N_2^-(t)$$

$$+N_1^+(t)\,N_2^-(t)+N_1^-(t)\,N_2^+(t)) + \frac{1}{4}\gamma_{12}E_1^+(t)\,E_2^-(t) + \frac{1}{4}d_{13}N_3(N_1^+(t)$$

$$+N_1^-(t)) + \frac{1}{4}\gamma_{13}E_3^+ E_1^+(t),$$

$$\dot{E}_2^+(t) = -d_{12}(N_1^+(t)+N_1^-(t))\,E_2^+(t) - \delta_{23}E_3^+ E_2^+(t) + \frac{1}{4}d_{12}(N_1^+(t)+N_1^-(t))$$

$$\cdot(N_2^+(t)+N_2^-(t)) + \frac{1}{4}\gamma_{21}N_1^+(t)(N_2^+(t)+N_2^-(t)) + \frac{1}{2}\gamma_2,$$

$$\dot{E}_2^-(t) = -d_{12}(N_1^+(t)+N_1^-(t))\,E_2^-(t) - \delta_{23}E_3^+ E_2^-(t) + \frac{1}{4}d_{12}(N_1^+(t)+N_1^-(t))$$

(3.2) $$\cdot(N_2^+(t)+N_2^-(t)) + \frac{1}{4}\gamma_{21}N_1^+(t)(N_2^+(t)+N_2^-(t)).$$

We are left thus with a 7-dimensional dynamical system, generated by the seven coupled nonlinear differential equations involving N_1^+, N_1^-, N_2^+, N_2^-, E_1^+, E_2^+ and E_2^-. The eighth moment E_1^- decouples and may be evaluated «*a posteriori*». The same would be in order for E_2^+ when $\eta_{12} = 0$, reducing the dimensionality to six. Notice that the conservative interaction affects only the equation for E_1^+. More precisely, cytokines have a damping effect on the average state of the active part of the tumor population, through the positive factor β_{12}^+.

Previous manipulations are wiped out in the case of general β_{12}^-, $\beta_{21} > 0$. The double integral involving the delta function can be handled for instance as indicated in [**9**] in terms of single integrals on level lines, but can not lead to a closed set of moment equations. The same is true, even for $\eta_{12} = 0$, when resorting to the other option (2.6), in which case the relevant kinetic equations read as

$$\frac{\partial f_1}{\partial t} = \eta_{12} \int_{-1}^{1} \int_{-1}^{1} \delta[u - m_{12}(v,w)]\, f_1(v,t)\, f_2(w,t)\, dv\, dw - \eta_{12} N_2(t)\, f_1(u,t)$$

$$- d_{12} H(u)\, N_2^+(t)\, f_1(u,t) + \gamma_{12} u H(u)\, E_2^-(t)\, f_1(u,t) + \gamma_{13} u H(u)\, E_3^+\, f_1(u,t), \tag{3.3}$$

$$\frac{\partial f_2}{\partial t} = \eta_{12} \int_{-1}^{1} \int_{-1}^{1} \delta[u - m_{21}(v,w)]\, f_2(v,t)\, f_1(w,t)\, dv\, dw - \eta_{12} N_1(t)\, f_2(u,t)$$

$$+ \gamma_{21} N_1^+(t)\, f_2(u,\ t) - \delta_{23} E_3^+\, f_2(u,\ t) + \gamma_2 H(u).$$

Further analytical investigation, especially of the dynamical system (3.2), is left as future work. Numerical treatment of (3.1), (3.2), and (3.3) is the subject of the next Section. A result however can be easily achieved by inspection, namely the existence of a stationary solution $f_1(u) = 0$, $f_2(u) = \gamma_2 H(u)/(\delta_{23} E_3^+)$, the same for both models. This is the ideal working point for the considered organism, where tumor is absent and immune system has reached its equilibrium, with all cells active, under the action of the external source and the control by the host environment.

4 - Some numerical examples

In order to illustrate several typical dynamical behaviors that have been found in extensive computations, we present below a sample of figures, necessarily restricted, but still qualitatively significant. Calculations have been performed on a workstation by using MATLAB 4.2 Numerical Library. For the integro-differential equations (3.1) and (3.3) the double integrals have been evaluated following the re-

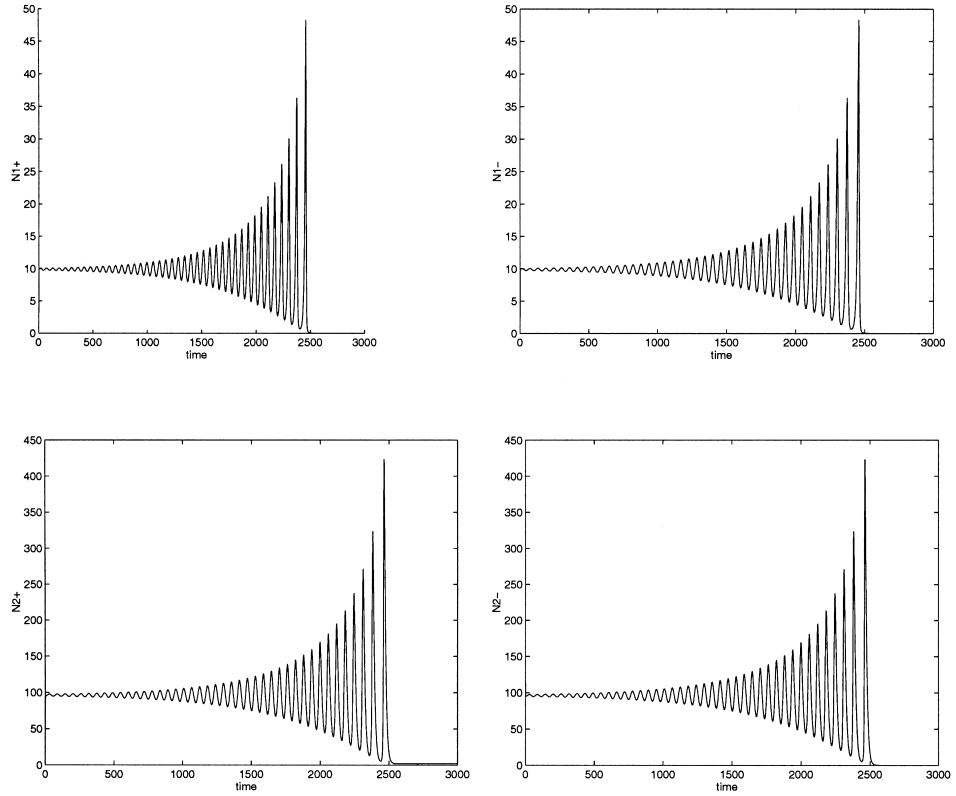

Fig. 1 - Time evolution of partial densities towards the fixed point (0,0,2,0,0,0).

cipes introduced in [9], which reduce them to one-dimensional line integrals, treated by the composite trapezoidal rule.

In all figures shown here initial conditions have been chosen of the type

$$\begin{cases} f_1(u, 0) = 1 + 0.2 \sin(\pi u) \\ f_2(u, 0) = k(1 - 0.3 \sin(\pi u)) \end{cases} \tag{4.1}$$

with varying k.

Fig. 1 is relevant to the option (2.7) with $\eta_{12} = 0$, which means no conservative interactions, so that all macroscopic quantities of interest follow from the solution of a set of six first order ordinary differential equations, deduced from (3.2). The immunological parameters take the numerical values $d_{12} = d_{13} = \delta_{23} = 0.2$, $\gamma_{12} = 0.79$, $\gamma_{21} = 0.01$, $\gamma_{13} = 1$, $\gamma_2 = 0.2$, $N_3 = 2$, and $E_3^+ = 1/2$, with $k = 100$ in (4.1). The analytically determined equilibrium corresponds to the point $(0, 0, 2, 0, 0, 0)$

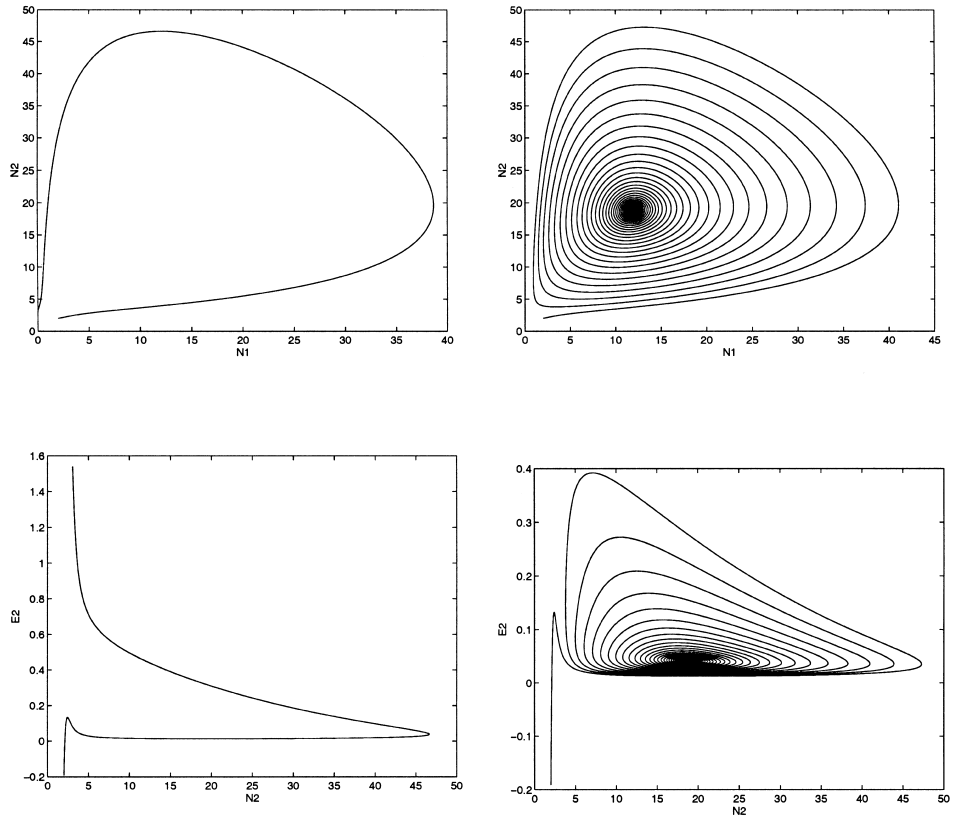

Fig. 2 - Phase diagrams for $\delta_{23} = 0.13$ (left column) and $\delta_{23} = 0.14$ (right column).

in the six-dimensional phase space. We do observe convergence to that fixed point, but after strong oscillations of increasing amplitude, that would suggest initially divergence to infinity of the phase trajectory. The time behavior of the partial densities $N_i^{\pm}$ is plotted in the figure; the same trend is in order for the activity densities $E_i^{\pm}$.

The previous fixed point is not necessarily unique for the considered problem, as shown in Fig. 2, where we use δ_{23} as varying parameter. Now $\gamma_{12} = 0.7$, $k = 1$, whereas all other parameters are kept as before. For $\delta_{23} = 0.13$ the «analytical» equilibrium $(0, 0, 40/13, 0, 0, 0)$ actually attracts our initial point, with a regular monotonic asymptotic behavior. It is sufficient to increase δ_{23} to 0.14 and a bifurcation occurs: the same initial point gets out of that basin of attraction and is captured instead by a different equilibrium point, into which the phase trajectory eventually spirals (damped oscillations) after an initial transient. This is described in the figu-

re by the (N_1, N_2) and (N_2, E_2) projections of the six dimensional phase diagram: the left and right columns refer to $\delta_{23} = 0.13$ and $\delta_{23} = 0.14$ respectively. Numerical experiments indicate that both fixed points are stable, and attract suitable regions of the phase space. The coordinates of the second one can be found numerically, and there results $N_1 > 0$, so that it represents a stationary state in which the organism coexists with non-vanishing tumor density. Eigenvalues of the Jacobian matrix there have negative real part, with at least a non-real pair.

There is of course a much worse bifurcation when the initial point gets out of the basin of attraction of a fixed point and tumor grows in time without any bound. If we set $k = 1$, let γ_{12} vary, and keep the other parameters as for Fig. 1, such a bifurcation occurs at about $\gamma_{12} = 0.79$, in the sense that the solution converges to the ideal fixed point $(0, 0, 2, 0, 0, 0)$ for $\gamma_{12} < 0.79$, whereas the phase trajectory escapes to infinity for $\gamma_{12} > 0.79$. Contrary to previous models [8], the immune system grows together with the tumor in case of divergence, often even faster, as already found in [9]. It is worth investigating if and how the situation can be restored by the effects of the conservative interactions, which are mediated by cytokines. For this purpose, we start from a diverging situation with fixed $\gamma_{12} > 0.79$, and, with $\eta_{12} = 0.3$, $\beta_{12}^{-} = \beta_{21} = 0$, we determine the solution for β_{12}^{+} increasing from 0 to 1. In this computation the phase space to be considered becomes seven-dimensional, since also the moment E_2^{+} enters the set of coupled ordinary differential equations. It is clear that the solution diverges for small values of β_{12}^{+}, but one can observe that a threshold appears, above which the phase trajectory is captured again by the fixed point, now given by $(0, 0, 2, 0, 0, 1, 0)$. If we plot these bifurcation values of β_{12}^{+} versus the parameter γ_{12} we get the following table

γ_{12}	0.81	0.85	0.89	0.93	0.97	1.01	1.05	1.09
β_{12}^{+}	0.04	0.17	0.31	0.44	0.57	0.71	0.84	0.97

Of course, bearing the meaning of the two parameters in mind, the larger the tumor proliferation parameter γ_{12}, the higher the threshold for cytokine effectiveness β_{12}^{+} which is needed in order to save the organism. However this positive feature gets saturated after a while, and not all situations can be restored: for $\gamma_{12} > 1.09$ tumor and immune system grow indefinitely even in the presence of the strongest cytokine action.

A bifurcation corresponding to transition from tumor divergence to tumor depletion is analyzed also in Figs. 3 and 4, still relevant to the option (2.7), but with all immunological parameters different from zero, so that the full set of integro-diffe-

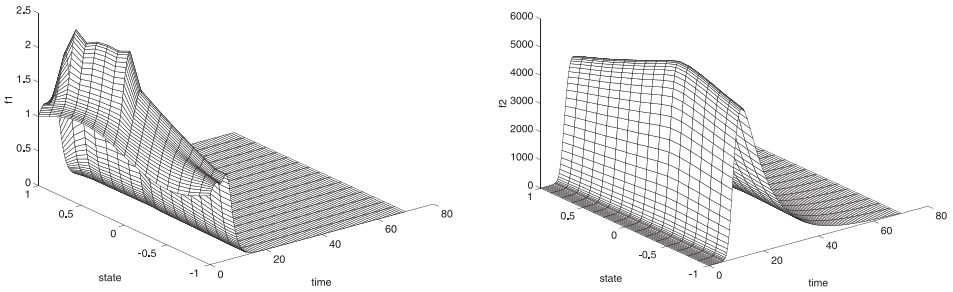

Fig. 3 - Tumor and immune system evolution for model (2.7) when $\beta_{21} = 0.65$.

rential equations (3.1) has actually to be solved (infinite dimensional problem). For the numerical solution of this system we have implemented time and space discretization schemes proposed in [**9**]. Here we have taken $\gamma_{21} = 0.79$, $\eta_{12} = 0.3$, and $\beta^{+}_{12} = \beta^{-}_{12} = 0.9$, with $k = 0$ in (4.1). The latter option allows to analyze initial absence of immune system, which is not qualitatively different from other initial conditions in this model, due to presence of an external source and of proliferation. All other parameters are the same as for Fig. 1, and β_{21} is used as control parameter. Fig. 3 shows the distribution functions f_1 and f_2 versus state u and time t for $\beta_{21} = 0.65$, in which case, after an initial growth, tumor is defeated and the organism relaxes to the optimal working state, represented by the equilibrium $f_1 = 0$, $f_2 = 2H(u)$. It is sufficient to increase β_{21} to 0.66 and the evolution changes dramatically to the one described in Fig. 4, where at a given point the organism seems to have overcome the crisis and to be recovering like before, but then another violent increase starts, which leads to divergence.

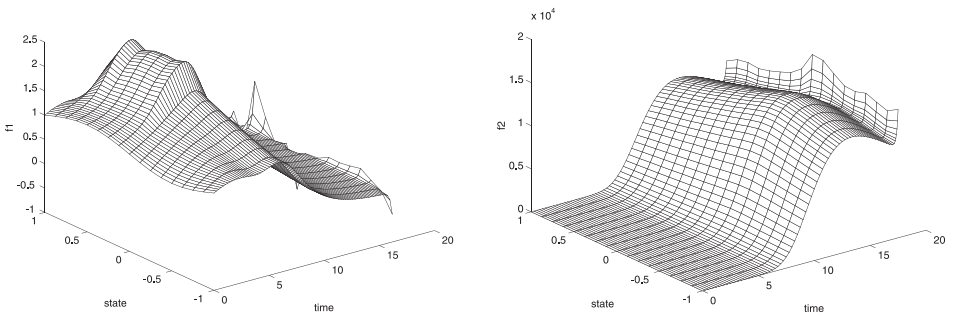

Fig. 4 - Tumor and immune system evolution for model (2.7) when $\beta_{21} = 0.66$.

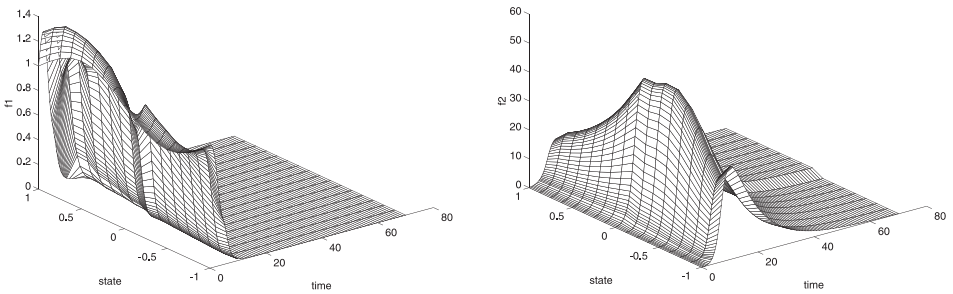

Fig. 5 - Tumor and immune system evolution for model (2.6) when $\beta_{21} = 0.54$.

Finally, Figs. 5 and 6 are relevant to the option (2.6), with exactly the same input parameters and initial conditions as for Figs. 3 and 4, and show the corresponding bifurcation taking place with respect to the parameter β_{21}. The ideal equilibrium is again the same, and it is reached asymptotically for any $\beta_{21} \leqslant 0.54$, whereas divergence is observed whenever $\beta_{21} \geqslant 0.55$. The distribution functions are plotted in Figs. 5 and 6 just when the two equal signs are in order, respectively.

We may observe that the model (2.7) turns out to be *more* healing-oriented than (2.6), since β_{21} is a measure of the *loss* of activity for the immune system, as clear from (2.10). For this particular case, the bifurcation leading to recovery occurs in the interval $(0.65, 0.66)$ for the former model, whereas one has to decrease further β_{21} down to the interval $(0.54, 0.55)$ in order to get the same effect with the latter.

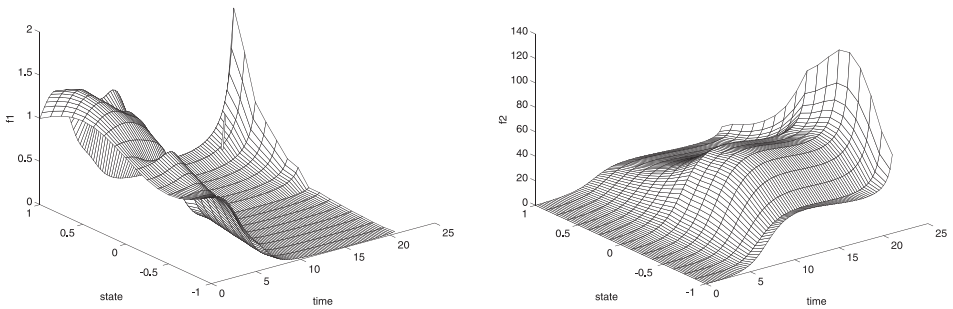

Fig. 6 - tumor and immune system evolution for model (2.6) when $\beta_{21} = 0.55$.

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Abstract

We consider the set of nonlinear integro-differential equations governing the competition between tumor cells and immune system at a kinetic level. According to a recently proposed model, effects of cytokines on the evolution problem are analyzed by both analytical and numerical techniques. The model allows several different dynamical trends and bifurcation phenomena for varying immunological parameters. A sample of illustrative results are presented and briefly discussed.

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