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A model for tumor catastrophe in the presence of immunocompetent cells

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Abstract

We present a model of the tumor-immune system interaction by means of a set of four coupled differential equations representing the tumor, effectors cells, inhibitory factors released by tumor and antitumor cytokines respectively. We discuss the stability of the system by usual methods (linearization and Routh-Hurwitz criterion). We find that there exist regions on a space of parameters associated to the tumor progression and regression. The structure of these regions provides an elegant description of tumor behavior, including the explanation of some current paradoxes and also of the so minted immune response dilemma. A fold catastrophe in our space of solutions appears to be the cause of such paradoxical behavior. Some recent reports seem to support our results.

Key words: Bifurcation curve; effectors cells; immune response; stable solution; stem cells.

Un modelo de catástrofe tumoral en presencia de células inmunocompetentes

Resumen

Se presenta un modelo de la interacción tumor-sistema inmune por medio de un conjunto de cuatro ecuaciones diferenciales que representan respectivamente al tumor, células efectoras factores inhibitorios producidos por el tumor, y citokinas antitumorales. Se discute la estabilidad de los puntos de equilibrio del sistema por los medios usuales (linearización y criterio de Routh-Hurwitz). Se encuentra que existen regiones en un espacio de parámetros asociadas a la progresión y regresión tumoral. La estructura de esas regiones provee una descripción elegante del comportamiento del tumor y explica algunas de las paradojas conocidas, así como del llamado dilema de la respuesta inmune. Una catástrofe de plegamiento resulta ser la causa de tales paradojas. Algunos resultados recientes parecen respaldar nuestros resultados.

Palabras clave: Células efectoras; células precursoras; respuesta inmune; solución estable; curva de bifurcación.

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I. Introduction

Cancer and oncorelated illness are the second most common cause of death in modern societies. Once declared, prognosis of cancers is often pessimistic, and their evolution is nearly irreversible. Cancerous cells of any type share, among others, two main characteristics: unrestricted growth and high invasiveness of healthy tissues. Tumor cells are not only source of antigens, but they also are antigens, as they express modified surface markers or over expression of others. Already at the beginning of the XX century Paul Erhlich advanced the hypothesis of immune surveillance: the immune system checks tumors, which otherwise would annihilate healthy organisms**.** This hypothesis is adverted by investigators, which argue that tumors currently progress: a fact known as immune response dilemma. Literature describes also several paradoxes related to existence of thresholds, tumor progression and regression. There exists a wealth of ODE-based models describing tumor-immune system behavior**,** so we limit ourselves in the following just to cite some pioneering works, as Hiernaux & Lefever (1), Stepanova (2), Kusnetzov *et al.* (3). A survey of models can be found in the text by Preziosi (4). Hiernaux and Lefever use in their model just an ODE because they consider that the effectors population is a fixed parameter. They describe dormancy, but they do not arrive to an explanation of their own experimental data (growth of mastocytoma cells *in vivo*). Stepanova uses fundamentally a system of two ODE, both stimulation and depression of the immune system caused by tumor are taken in consideration. Her model is compatible with the three clinically observed outcomes of cancer: regression, dormancy and progression. Kusnetzov and associated use a Michaelian term for describing some aspects of the tumor-effectors interaction. Their work is a very thorough one, and they success in parameter estimation and explanations of several types of tumor evolution. Most of current issued models share the use of two ordinary coupled differential equations, so isoclines tracing and global analysis via Poincaré-Bendixon theorem (bidimentional techniques) is possible for them. Catastrophe seems to be the hallmark of population competition (5), not just of cancer-immune system interaction. Some authors (6) describe the possible existence of a threshold in tumor mutagenicity that triggers off a catastrophe toward low speeds of tumor growth.

In this paper we make in section II a synopsis of known results on the interaction tumor-immune system. After, in section III we present our model and in section IV we discuss the stability of its equilibrium points. Tumor persistence is related to the existence of a stable, not null equilibrium point. Section V is devoted to the existence of bifurcations, associated to some combinations of system's parameters. Both rates of effectors creation and decay seem to be very important as they describe not only catastrophic behavior for the tumor, but also its possibility of deletion by strengthening the immune system. We show in section VI the results of some numerical integrations. Dormancy, this is, persistence of a tumor in a not-progressing state is dealt with in section VII. We discuss our results and present our conclusions in section VIII. Some mathematical details have been gathered in the appendix.

II. Synopsis of the biological facts

The immune system constitutes the main organism defense against non self substances, known as antigens. Tumors are a powerful source of such antigens as they can pour into their surrounding**s** diverse metabolites or mutation modified cytokines. Moreover, tumor cells can express on their surface diverse markers and antibody receptors expressed or not by normal cells (MAGE, CAGE, and CT, cancer testis antigens, among others) (7) which could be tar-

gets for organism effectors cells. A frequently invoked argument supporting the role of immune system in the prevention of cancer is that tumors are more common in people possessing an immune system subject to some type of impairment (age, autoimmunity, viral infection or therapeutic suppression could be causes of such immune depletion).

The diverse components of the immune system can elicit their own immune response against tumors. Some cancers are susceptible of humoral mediated lysis (by complements, as B-lymphoma cells, or by an antibody mediated response). It is known that tumor activated macrophages (TAM) and lymphocytes can migrate to sites of tumor infection, forming infiltrates inside them. Macrophages exert their action probably by means of lytic enzymes, activated oxygen intermediates, or cytokines (TNF-alpha). T-lymphocytes (T-helper and CTL) can segregate soluble factors that act on tumors. There is citolytic activity exercised by lymphocytes recognizing antigens-MIC complexes, or by effectors cells that do not recognize these complexes, as natural killer cells (8, 9, 10).

The facts just enumerated are challenged by a shocking reality: tumors currently progress. Moreover, there is a long list of paradoxes as thresholds, oscillations, and dormancy, apparently related to the interaction tumor-immune system (1, 11, 12). So, it has been suggested that for the majority of the tumors the immune response may be relatively late and ineffective. Among the causes of the just cited immune failure it is worthy mention the absence of recognizing tumor cells as not-self cells, absence of lethal hit by effectors cells, inadequate stimulation of effectors cells by T-helper cells, and interleukin and super antigen-induced effectors apoptosis (13, 14).

There exists good news, on the other hand. Effectors function and survival can be enhanced by stimulation by helper cells (15), for some leukemias stem cells transplants and T-cell depleted stem cell transplants (16, 17); and donor lymphocyte infusions (18) can produce patients recovery. Bone marrow transplants and donor lymphocyte transfusions but also, nonmyeloablative peripheral blood stem cells transplants have successfully been used in treatment of chronic myeloid leukemias (19). Non myeloablative allogeneic transplants have been used in treatment of metastatic renal cells carcinomas (20, 21, 22). Some less encouraging reports also exist. Some authors mention the feasibility of that approach just for a minority of patients (23), or the absence of favorable outcomes in some chronic leukemias (24) but there have occurred improvements to the nonmyeloablative techniques and currently efforts are made for extending them to investigation of others refractory-treatment genitourinary tumors (25, 26, 27). So it seems important developing models that could explain some of the facts and broaden the scope of some of the therapies just mentioned.

III. The model

We assume the existence of four entities in our model which densities are described as follows: tumor ρ, effectors cells E, cytokine density C, and down regulators proteins or lipids produced by tumor cells, Z. All densities are supposed positive and lesser than one, in particular $\rho = 1$ means complete saturation of the cavity or tissue containing the tumor. We propose the following system of coupled differential equations for our model (we use the symbol τ for the temporal variable):

$$\frac{d\rho}{d\tau} = d_1\rho(1-\rho) - d_2\rho E - d_3\rho C \qquad [1]$$

Tumor cells growth in absence of any other interaction is governed by a logistic equation. They are destroyed by the attack of effectors cells E, and this annihilatory action is described by the dynamical coeffi-

cient d_2. Tumor cells are also attacked by cytokines C produced by effectors cells, d_3 is the associated dynamical coefficient. Here effectors cells mean indistinctly natural killer cells, macrophages, or CTL cells. It is clear that just CTL cells are capable of producing cytokines.

$$\frac{dE}{d\tau} = b_1 - b_2 E - b_3 \rho E - b_4 EZ \qquad [2]$$

Effectors cells are produced in hematopoietic organs, with rate b_1, they have a lifetime $\tau_1 = (b_2)^{-1}$, and they are destroyed by the tumor in their mutually annihilatory interaction, b_3 is the dynamical coefficient that rules this interaction. Effectors action is blocked by tumor produced proteins, this down regulation does not imply necessarily death of effectors cells, but just an inhibition of their active antitumor behavior, and it could be caused by blocking of specific receptor effectors sites, by impairment of their lityc activity or indirectly by diminution of the number of antigen presenting cells

$$\frac{dZ}{d\tau} = c_1 \rho - c_2 Z \qquad [3]$$

Inhibitory proteins are produced by tumor cells proportionally to its density, being the adjustment coefficient. These proteins could inhibit the negative feedback circuit established by SOCS (suppressors of cytokine signaling). SOCS1 has been reported as a potential tumor suppressor (28). Others possible mechanisms of immune suppression are related to FASL (FAS ligand), vesicles liberated among others tumors, by melanomas, and the action of APL (altered peptide ligands) (29). We could consider in addition to the inhibitory behaviors above mentioned, the screening of tumor antigens by antibodies not cytopathic. Inhibitory proteins have a half lifetime $\tau_2 = (c_2)^{-1}$.

$$\frac{dC}{d\tau} = \lambda E - \omega C \qquad [4]$$

Antitumor cytokines (or lytic compounds) are produced by effectors cells (this is the case for CTL cells, which kill some cancer cells by means of perforins, (30)), also macrophages could contribute to this pool by means of complements. Cytokines have a lifetime $\tau_3 = (\omega)^{-1}$, as they degrade or they abandon tumor neighborhood by dilution and/or diffusion.

We make now the assumption that $\omega >> b_2$, this is, *C* and E cells are in equilibrium during the time evolution of any E cell. In such case we can substitute *C* for its equilibrium value, $C \to \overline{C} = (\lambda E/\omega)$. Upon this consideration equation 1) can be written as:

$$\frac{d\rho}{d\tau} = a_1 \rho(1-\rho) - a_2 \rho E \qquad [5]$$

with $a_1 = d_1$; $a_2 = \left(d_2 + \frac{\lambda}{\omega} d_3\right)$.

Now, we make some normalizations:

$$t = a_1 \tau;\ \varepsilon = \frac{a_2}{b_3} E;\ z = \frac{c_2}{c_1} Z;$$

$$\alpha = \frac{a_2 b_1}{a_1 b_3};\ \gamma = \frac{b_2}{a_1};\ \zeta = \frac{c_2}{a_1}$$

$$\nu_1 = \frac{b_3}{a_1};\ \nu_2 = \frac{b_4 c_1}{a_1 c_2},$$

therefore our fundamental system is:

$$\frac{d\rho}{dt} = \rho(1-\rho) - \nu_1 \rho\varepsilon, \text{ (tumor)} \qquad [6]$$

$$\frac{d\varepsilon}{dt} = \alpha - \gamma\varepsilon - \nu_1 \rho\varepsilon - \nu_2 \varepsilon z, \text{ (effectors cells)} \qquad [7]$$

$$\frac{dz}{dt} = \zeta(\rho - z), \text{ (toxin)} \qquad [8]$$

IV. Steady states and their stability

Let us consider the steady states of our model's equilibrium points. We look for non negative solutions $(\bar{\rho}, \bar{\varepsilon}, \bar{z})$ of the algebraic system obtained equating to zero the second members of these equations. We immediately obtain as a solution:

$$\rho_0 = 0;\ \varepsilon_0 = \frac{\alpha}{\gamma};\ z_0 = 0 \qquad [9]$$

which we call the trivial equilibrium point, because its tumor density is null. Note that the equilibrium value of effectors cells imposes the restriction $\frac{\alpha}{\gamma} < 1$. Next, we consider the case $\rho > 0$. It is useful defining a space of parameters (β, ξ) as follows:

$$\beta = \frac{\nu_1 \alpha}{\nu_1 + \nu_2},\ \xi = \frac{\gamma}{\nu_1 + \nu_2}$$

We limit our discussion to the xx region, that is, to the first quadrant of the (β, ξ) space. We obtain for this equilibrium point:

$$\bar{\rho}_{\pm} = \frac{\nu_1 + \nu_2 - \gamma \pm \sqrt{(\gamma + \nu_1 + \nu_2)^2 - 4\beta(\nu_1 + \nu_2)}}{2(\nu_1 + \nu_2)}$$

$$= \frac{1}{2}\left(1 - \xi \pm \sqrt{(1+\xi)^2 - 4\beta}\right) \qquad [10]$$

$$\bar{\varepsilon} = \frac{1 - \bar{\rho}}{\nu_1} \qquad [11]$$

$$\bar{z} = \bar{\rho} \qquad [12]$$

The number of possible roots ρ solution to equation [10] determines three regions in our (β, ξ) space (Figure 1):

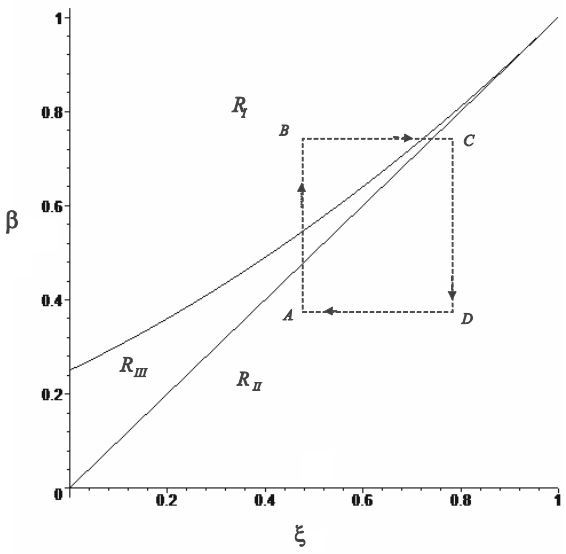


Figure 1. Existence and stability of the tumor equilibrium density in the space of parameters β and ξ. In R_I, $\beta > \left(\frac{\xi+1}{2}\right)^2$, or $\beta > \xi, \xi > 1$, there exists just ρ_0, the null population and therefore tumor recedes in this zone; in R_{III}, $\beta < \xi$, there exist both the roots ρ_0, unstable, and ρ_+. As ρ_+ is stable whenever it exists, tumor has the advantage here. In, R_{III}, $\xi < \beta < \left(\frac{\xi+1}{2}\right)^2$, $\xi < 1$, there exist the three roots ρ_0, the null population, ρ_+ stable and ρ_-, unstable. Tumor can progress or recede in this region, depending on the current values of $\rho(t)$ and $\varepsilon(t)$. The dotted square added shows the desired biological goal for a system, an evolution *A* to *B*, this is from $R_{II} \rightarrow R_{III} \rightarrow R_I$. More probably, a real system evolves as $A \rightarrow B \rightarrow C \rightarrow D \rightarrow A$.

In R_I, $\beta > \left(\frac{\xi+1}{2}\right)^2$, $\beta > \xi$, $\xi > 1$, there exists just ρ_0.

In R_{II}, $\beta < \xi$, there exist both the roots ρ_0 and ρ_+.

In R_{III}, $\xi < \beta < \left(\frac{\xi+1}{2}\right)^2$, $\xi < 1$, there exist the three roots ρ_0, ρ_- and ρ_+.

Note that $\beta_T \equiv \left(\frac{\xi+1}{2}\right)^2$ acts as a threshold for the tumor's existence, because there is no tumor if $\beta > \beta_T$. We now compute the derivatives $\frac{\partial \rho_\pm}{\partial \beta} = \mp \frac{1}{\sqrt{(1+\xi)^2 - 4\beta}}$, and $\frac{\partial \rho_\pm}{\partial \xi} = -\frac{1}{2} \pm \frac{(1+\xi)}{2\sqrt{(1+\xi)^2 - 4\beta}}$, both derivatives are defined just in the $\beta < \beta_T$ region. Then ρ_* is a monotonous decreasing function of β and ξ, but ρ_- grows always with β. Note, additionally, that β growth drives the tumor into the R_I region (only exits ρ_0), but ξ growth drives the system into the R_{II} region (there exist ρ_0, and ρ_+). We show in the appendix that ρ_0 is unstable if $\frac{\beta}{\xi} < 1$, ρ_+ is always stable, and ρ_- is always unstable. An interpretation to this fact can be reached by noting that $\frac{\beta}{\xi} = \frac{\nu_1 \alpha}{\gamma} = \frac{(\nu_1 \rho \varepsilon)}{\rho}\left(\frac{\alpha}{\gamma \varepsilon}\right)$. Now $\frac{1}{\rho}\nu_1 \rho \varepsilon \approx \frac{1}{\rho}\frac{d\rho}{dt}$, the time fraction of tumor cells destroyed by effectors cells, and $\frac{1}{\varepsilon}\left(\frac{\alpha}{\gamma}\right) \approx$ fraction of effectors cells created in a lifetime of these cells. Then $\frac{\beta}{\xi}$ is the rate of tumor cells destroyed, in equilibrium, by the immune system. So, if one effector cell destroys in equilibrium less than one tumor cell during its lifetime, the concentrations of tumor (or effectors) cells have no influence on system evolution, the only exception occurs in the R_{III} zone. Some particular cases follow. If $\nu_2 \to 0$, this is, if we neglect the existence of anti-effector proteins, then our equation (6) becomes desacoupled from the system, but it is possible to redefine the (β, ξ) space so that equation [10] remains valid, and tumor behavior in the new R_I, R_{II} and R_{III} remains unchanged. If $\nu_2 \to \infty$, this is, if the strength of the anti-effector protein is high, then $\beta \cong \xi \cong 0$, $\rho \to 1$, and the tumor saturates every disposable tissue or space. If $\nu_1 \to 0$, there is not antitumor activity, $\rho \to 1$, this is, the tumor flows toward its saturation value.

V. Catastrophic behavior

We shall use in this section some results obtained in the section IV. The equilibrium population $\bar{\rho}$ satisfies the equation $\bar{\rho}^2 + \bar{\rho}(\xi - 1) + \beta - \xi = 0$, which solutions are given by $\bar{\rho}_\pm = \frac{1}{2}\left(1 - \xi \pm \sqrt{(1+\xi)^2 - 4\beta}\right)$. Note that 1) both $\bar{\rho}_\pm$ do not exist in R_I region ($\beta > \left(\frac{\xi+1}{2}\right)^2$, or $\beta > \xi$, $\xi > 1$, and 2) ρ_- disappears in R_{II} region ($\beta < \xi$). So there occurs a catastrophe type fold in our space of parameters. The catastrophic region in the (β, ξ) space is bounded by the curves $\beta = \left(\frac{\xi+1}{2}\right)^2$ (ρ_*, stable, and ρ_-, unstable appear here, in addition to ρ_0, stable), and $\beta = \xi$ (ρ_-, unstable vanish here leaving ρ_0, now unstable, and ρ_+, stable; note the change in ρ_0 stability at $\beta = \xi$). In sake of the clearness we display in Figures 2-a and 2-b plots of $\bar{\rho} = \bar{\rho}(\beta, \xi)$. Figure 2-b is obtained making a 90 degrees azimuthal rotation of Figure 2-a. Remember that $\rho_0 = 0$ is also an equilibrium surface. Note that both in R_I and R_{II} there exists just a stable value for $\bar{\rho}$: ρ_0 in R_I and ρ_+ *in* R_{II}. Note that ρ_0 turns its stability in R_{II}, becoming now unstable, and that a catastrophe occurs in R_{III} zone. Alternatively, we can speak about the existence of a fold type bifurcation occurring at the curve $\beta = \left(\frac{\xi+1}{2}\right)^2$, $\rho = \frac{1-\xi}{2}$ (Roots ρ_+ and ρ_- both appears first time at this curve). The ρ_- surface acts as a repulsor, and the ρ_+ surface as an attractor. As we traverse the curve of bifurcation any small disturbance on the system can drive tumor concentra-

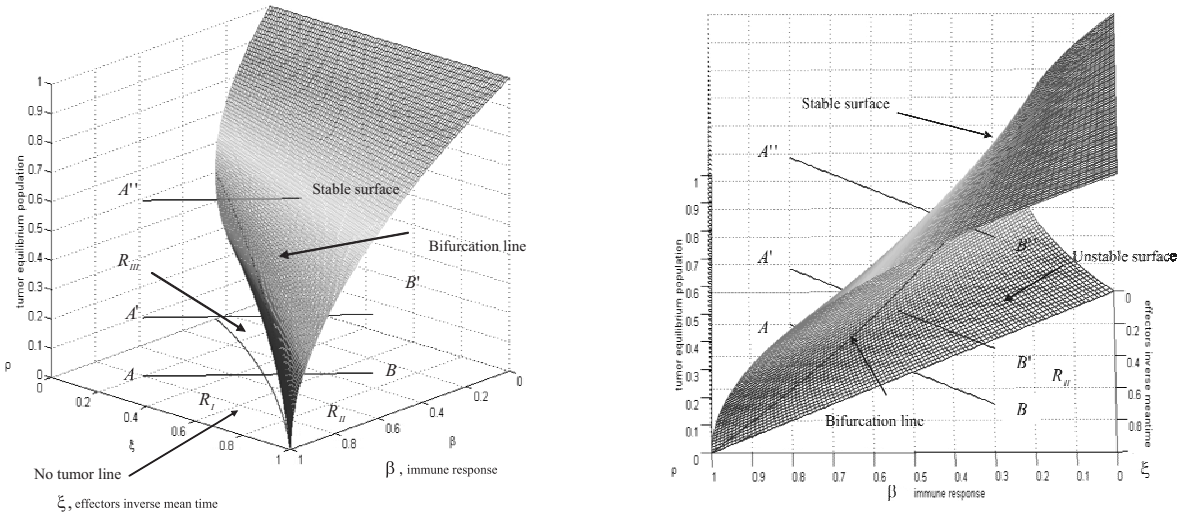


Figure 2. a) Plot of ρ, tumor density as function of β and ξ parameters, $\rho(\beta,\xi)$. We have indicated the regions R_I (There exists just the root $\rho_0 = 0$, stable), R_{III} (There exist the stable roots ρ_0, ρ_+, and the unstable one, ρ_-), and R_{II} (There exist ρ_0, unstable, and ρ_+, stable). Stable and unstable surfaced are also pointed out. Bifurcation curve is given by $\beta = \left(\frac{\xi+1}{2}\right)^2$, $\rho = \frac{1}{2}(1-\xi)$, and its projection on the plane $\rho = 0$ delimits the frontier of R_I and R_{III} zones. We show also three possible trajectories in the space of parameters with identical values of β and ξ, although ρ is different in each one of them. Bifurcation curve acts as a threshold because an insertion of ρ over or under this curve determines an opposite temporal evolution of our system. b) Another display of $\rho(\beta,\xi)$ with a 90 degrees azimuthal shift with respect to figure 5-a. Note that $A''B''$ trajectory cuts the ρ surface in the stable region over the bifurcation curve and tumor persists. $A'B'$ trajectory cuts the unstable side of the ρ surface, and tumor is rejected toward $\rho_0 = 0$. Both trajectories evolve through identical values of β and ξ parameters as given by AB trajectory.

tion up or down the repulsor ρ_- (therefore tumor may change its evolution from ρ_0 toward ρ_+ and vice versa, they both are stable here). We have traced three trajectories, AB, $A'B'$ and $A''B''$. System evolution is different at each one of them, although we move trough the same values of β and ξ. β parameter is related to creation rate of effectors cells and their activity, and ξ parameter to their time of permanence in blood stream. System catastrophic behavior is caused by the pulling of these two opposite tendencies, respectively described by β and ξ, but the current value of ρ is also important for it determines if the system get at the equilibrium surface up or down the bifurcation curve. The plane $\beta = \xi$ marks the disappearing of ρ_- ($\rho_- = 0$, $\rho_+ = 1-\xi$ there). Once we reach this plane (R_{II} region) the system has again well defined flux. Note, finally, that if $\beta \approx 1$, $\xi \approx 1$, ρ_+, although stable has minute values.

VI. Numerical results

We show now the results of some numerical integrations of our system. Figure 3 is a (tumor) vs. ε(effectors cells) plot in R_{II} re-

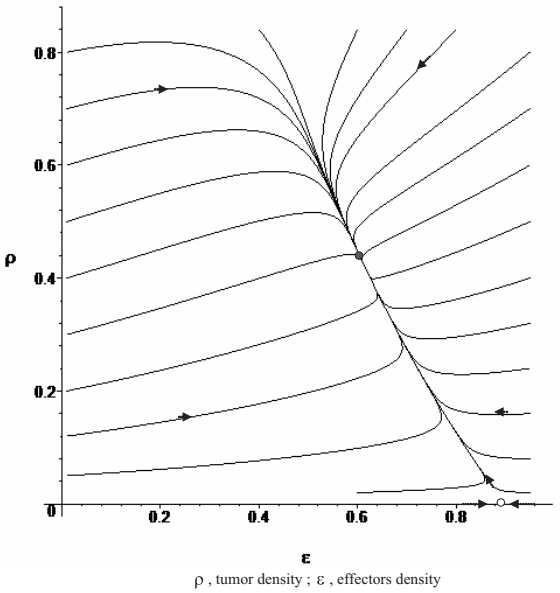


Figure 3. Tumor density, ρ vs. effectors density, ε diagram in R_{II} zone, ($\beta < \xi$). Values of parameters were: $\alpha = 0.9; \gamma = 1; \nu_1 = 0.95;$ $\nu_2 = 0.15;\ \zeta = 2,\ \beta = 0.7727,\ \xi = 0.9090$). All the curves, irrespective of the initial concentrations $\rho(0)$, $\varepsilon(0)$, z(0), migrate toward the stable point and tumor persists, although the presence in the upper half of the figure, of an appreciable density of cytotoxic cells. A higher value of initial effectors cells concentration just lessens the rate of tumour growth without affecting its final value. Stable equilibrium value is given by $\overline{\rho} = \overline{z} \cong 0.42, \overline{\varepsilon} = \dfrac{1-\overline{\rho}}{\nu_2} \cong 0.61$. Note the position of the unstable equilibrium point. An heterocyclic trajectory is also suggested. Tumor has the advantage here, and although the presence in some cases of an appreciable density of cytotoxic cells, cancer persists. This fact has been called "immune paradox", but it is just the consequence of that our system possesses of a non null equilibrium point. Some arrows point out the sense of the fluxes.

gion. We took $\beta = 0.7727 < \xi = 0.9090$ and $\zeta = 2$. The system evolves straightforwardly toward its equilibrium value, irrespective of the tumor initial concentration. Effectors initial concentration the higher, tumor growth toward its equilibrium value the slower. So, the effect of cytotoxic cells is just delaying the final, doomed outcome of tumor persistence. This fact is known as "immune paradox", but it is just the consequence of that our system has a non null, stable, equilibrium point. Figure 4 is also a ρ vs. ε plot, but in R_I zone. As high as could seem some tumor initial concentrations, we are in the safe immune region, and the system evolves toward the null equilibrium point. Curiously, if tumor concentration is low, it can transiently grow before receding. In Figure 5 we show a ρ vs. ε plot, with $\xi = 0.113,\ \beta = 0.3025,\ \xi < \beta < \left(\dfrac{\xi+1}{2}\right)^2$, ($R_{III}$). In this zone, there exist a repulsor, ρ_-, and two attractors, ρ_+ and ρ_0. There exist separatrices (these are curves that do not allow any solution cross them), some of them are easily noticed, and tumor evolution depends on initial conditions, as initial values $\rho(0)$, $\varepsilon(0)$ determine a point on a limited region from the plane here shown. Note, moreover, that we could change the system evolution by imposing a sudden (and artificial) variation on $\rho(t_0)$, and/or $\varepsilon(t_0)$ at certain time t_0, this is, by forcing the jumping of some separatrix.

VII. Dormancy

We assume that a viable, not progressing tumor of moderate size can pour into its surroundings diverse proteins and factors driving to the host disease, so we consider dormancy as tumor persistency on a not progressing condition and *low* concentration. A dormant tumor can escape from this condition, evolving to a progressing one, for instance after some change in the β and ξ parameters. Note, that if $\beta \cong \xi \cong 1$, then, from equation (10) $\rho_+ \cong \rho_- \cong 0$, and there exists a null or minute stable value for ρ, this

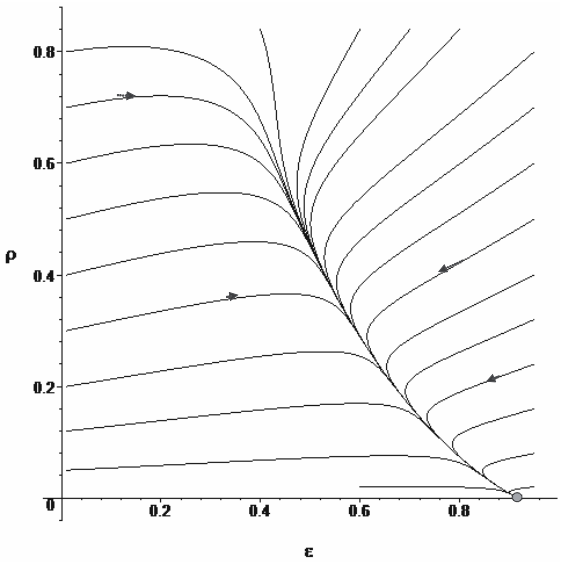


Figure 4. Tumor, ρ vs. effectors, ε diagram in R_I region. We took $\alpha = 1.1; \gamma = 1.2; \nu_1 = 1.4;$ $\nu_2 = 0.6;\ \zeta = 2,$ and $z(0) = \rho(0)$ $(\beta = 0.77 > \xi = 0.6)$. The equilibrium (null) punt is stable, and effectors concentration swings up before settle down at their equilibrium value (displayed as a solid circle). Tumor concentration shows also some transient maximum caused by the minute initial effectors concentration, but the immune system has the advantage here, as parameters belongs to R_I region and only the null equilibrium tumor density can exist. As usual in this type of diagrams, diverse segments are traversed with unequal velocity.

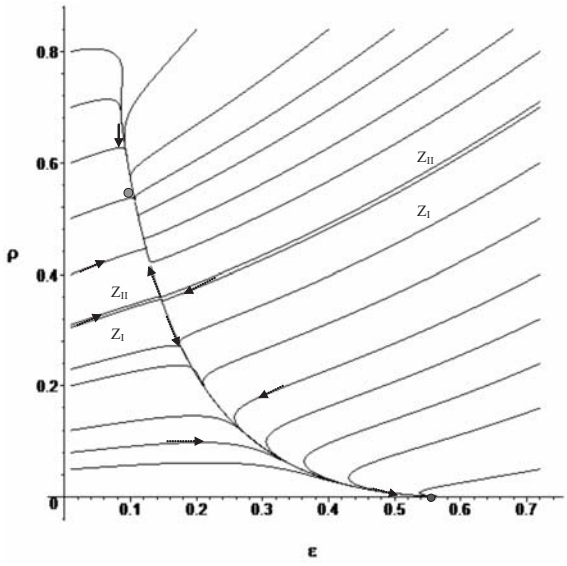
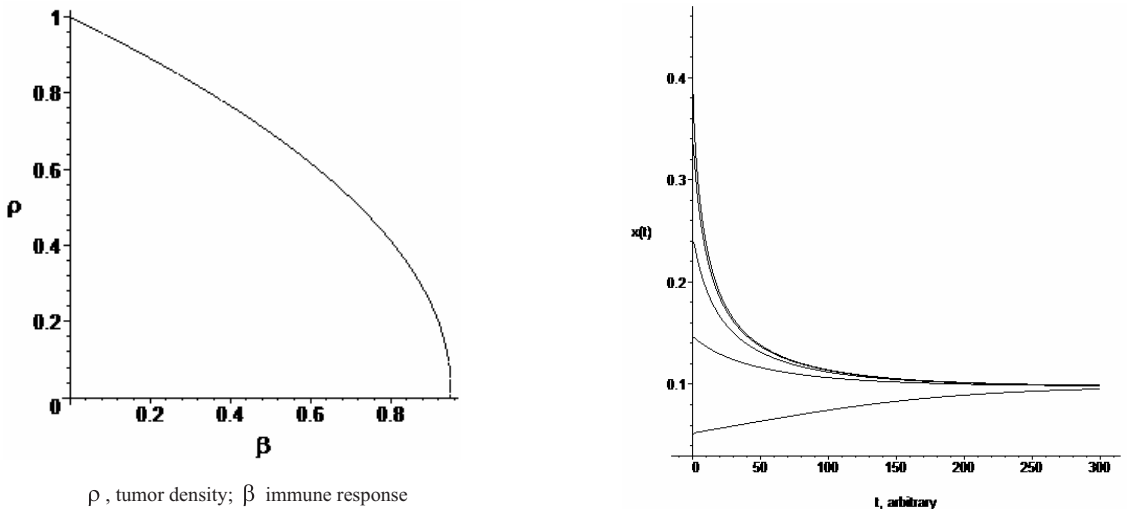


Figure 5. Tumor, ρ vs. effectors, ε graph in R_{III} region. We took $\alpha = 0.55;\ \gamma = 0.95;$ $\nu_1 = 4.40; \nu_2 = 3.60; \zeta = 2,$ and we settled $z(0)=0.1$. Then $\beta = 0.3025;\ \xi = 0.1187;$ $\xi < \beta < \left(\frac{\beta+1}{2}\right)^2$. Note the position of the stables (dark circles) and also of the unstable, saddle point (at the confluence of the separatrices). The immune safe zone, Z_I (no tumor at equilibrium) is located under the separatrices, and the risky one, Z_{II} (tumor persistence), above them. Now the current values of $\rho(t)$ and $\varepsilon(t)$ are important because arbitrary external perturbations can cause that the system runs thought the separatrices from Z_I to Z_{II} and vice versa.

is, tumor density can stay arbitrarily small for any time. This is shown in the Figure 6. In 6-a) we display a ρ_+ vs. β graph with $\xi = 0.95$, constant. Observe that for $\beta \to 1$, $\rho_+ \approx 0$ this is, tumor equilibrium density is minute and so remains irrespective of initial values of ε and z. A similar curve with identical interpretation is given in (1). 6-b) shows temporal evolution of tumor density up to 30000 steps of computation. The asymptotical limit $\rho \to 0.1$ is easily noticeable. Some curves which initial value is high were plotted just for verifying that dormant behavior is related to both high values of β and ξ parameters but not to some particular initialization of our system. High initial value of the effectors does not change systems flow but just the initial concavity of curves, being



ρ , tumor density; β immune response

Figure 6. Dormancy. a) Graph of $\rho^2 + \rho(\beta - \xi) + \xi - 1 = 0$, with $\xi = 0.95$, constant , and $0 \leq \beta \leq 1$. Note that for $\beta \cong 1$, $\rho \cong 0$, there exists a non progressing (equilibrium), minute tumor. b) Numerical integration of our system after 30.000 steps of integration. We took $\nu_1 = \nu_2 = 1.053$, $\alpha = 1.89$, $\gamma = \zeta = 2$, that is, $\beta = 0.945 < \xi = 0.95$. We also took $z(0) = 0.2$, and $\varepsilon(0) = 0.22$ fixed. System flows toward the value $\rho = 0.1$, irrespective of tumor initial density. Note that this is just a particular case of time evolution in R_{II} (Compare with figure 3).

convexes if $\varepsilon(0)$ is high (not visible on this scale). So, dormancy is an essential character of our model and it seems to be related to high creation rate of effectors cells, but short activated lifetime of them. A change in β (a diminution, for instance) can drive tumor into R_{II} region, the zone of tumor progression.

VIII. Discussion and Conclusions

We stress that our system states that ρ_+ is stable always that it exits but the stability of the null value ρ_0 (healthy state) depends on the value of the $\frac{\beta}{\xi}$ ratio. We suggest that dependence of tumor evolution on this ratio but neither on the current values of ρ nor ε could solve the so called "immune response dilemma", immune attack seem having no apparent effect on tumor evolution, as tumor fate (persistence or annihilation) does not depend on effectors or tumor concentrations, but on the ratio of their respective growth rates, as given by the $\frac{\beta}{\xi}$ quotient.

We stress that the existence of a non null, stable tumor means illness progression. The existence of the R_I, R_{II} and R_{III} regions could bring some insight on tumor temporal evolution. As in R_{II}, there exists just the null equilibrium point, we propose this region represents the normal, "healthy" population. In R_{II} there exists tumor irrespective of minute of big initial concentrations, or the applying of any perturbation (surgery, chemotherapy, and so forth). We propose, this region represents the "non healthy" population. The so-called "tumor dormancy", persistence of non progressing minute tumors, could be explained by realizing that if both $\beta \cong \xi \cong 1$, but in R_{II} zone, equilibrium values for the tumor are minute, see the Figures 2-a and 6-a. Thresholds existence could be related to the insertion of the system, $\rho = \rho(\beta, \xi)$, above or under bifurcation curve. Oscillations, that is, alternative cy-

cles of tumor progression-regression could be caused by variations of the β and ξ parameters, if in R_{III}, by instance, if these parameters make some cycle as A´→B´→B´´→ A´´→ A´, see the Figure 2-b. Similar individuals with different response after going trough identical treatment could be caused by the trespassing (or not) of some separatrix from Z_I to Z_{II}, see the Figure 5. We stated that system evolution depends on the $\frac{\beta}{\xi} = \frac{\nu_1 \alpha}{\gamma}$ ratio. Then, for obtaining a strong (healthy) response, it is necessary (I) to make grow ν_1 (more effective lethal hit on tumor, this also implies that effectors cells must always recognize tumor cells), (II) to make grow α, this implies more efficient creation of effectors cells. (III) Alternatively γ could diminish, this fact means effectors should remain active long time. All these requirements are fulfilled by the nonmyeloablative pioneer therapy (19, 20, 21, 22, 25, 26, 27). This technique comprises repetitive effectors cells transplants (I, III) and some immunosuppression for allowing bone marrow and stem cells grafting (II). Reports on cures and/or elongated patients survival appears to be related to enhanced immune response, for instance to the appearance of GVHD (graft vs. host disease). The mentioned therapy is a risky one however, and there exist reports on GVHD related deaths (21, 23, 24). Notwhistanding, we expect that current research will find ways of overcoming tumor related illness.

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Appendix

The Jacobian matrix associated to (8-10) system is:

$$J(\rho,\varepsilon,z)=\begin{Bmatrix}1-2\rho-\nu_1\varepsilon & -\nu_1\rho & 0\\ -\nu_1\varepsilon & -\gamma-\nu_1\rho-\nu_2 z & -\nu_2\varepsilon\\ s & 0 & -s\end{Bmatrix} \tag{A-1}$$

At the trivial critical point, the matrix $J\left(0,\frac{\beta}{\gamma}0\right)$ has eigenvalues $\lambda_1=-s$; $\lambda_2=-\gamma$; $\lambda_3=1-\frac{\nu_1\alpha}{\gamma}$. Because $s>0$ y $\gamma>0$, we see that the stability of this point depends just on the sign of λ_3 (stable if $\beta>\xi$), this is, on R_I and R_{III} regions, and unstable in R_{II}. Because for the others critical points we have that $z=\rho.\varepsilon=\frac{1-\rho}{\nu_1}$, we can express the Matrix of Jacobi as:

$$J(\rho,\varepsilon,z)=\begin{Bmatrix}-\rho & -\nu_1\rho & 0\\ -\nu_1\varepsilon & -\gamma-(\nu_1+\nu_2)\rho & -\nu_2\varepsilon\\ s & 0 & -s\end{Bmatrix} \tag{A-2}$$

and after some tedious algebra, we obtain the following characteristic polynomial for this matrix:

$$\begin{aligned}P_1(\lambda)&=\lambda^3+\lambda^2\left[\gamma+s+\rho(1+\nu_1+\nu_2)\right]\\&+\lambda\left\{\rho s+(\rho+s)\left[\gamma+(\nu_1+\nu_2)\rho\right]-\nu_1\rho(1-\rho)\right\}\\&+\rho s\left[\gamma+\rho(\nu_1+\nu_2)-(1-\rho)(\nu_1+\nu_2)\right]\end{aligned} \tag{A-3},$$

this is, an polynomial of the type $P(\lambda)=\lambda^3+a_1\lambda^2+a_2\lambda+\alpha_3$, with

$$a_1=\gamma+s+\rho(1+\nu_1+\nu_2)$$

$$a_2=\rho s+(\rho+s)\left[\gamma+(\nu_1+\nu_2)\rho\right]-\nu_1\rho(1-\rho)$$

$$a_3 = s\rho\left[\gamma + (\nu_1 + \nu_2)\rho - (1-\rho)(\nu_1 + \nu_2)\right]$$

In order to determine the stability of these non trivial critical points we use the Routh-Hurwitz criterion, namely:

$$a_1 > 0;\ a_1 a_2 - a_3;\ a_3 > 0$$

is a necessary and sufficient condition for the stability of the critical points given by equation [5].

Clearly $a_1 > 0$. If we replace the value of $\rho \pm$ into a_3, we obtain:

$$a_3(\pm) = \pm s\rho\sqrt{(\gamma + \nu_1 + \nu_2)^2 - 4\beta\nu_1(\nu_1 + \nu_2)} \quad \text{(A-4)}$$

Hence we conclude that the point $(\rho_-, \bar{\varepsilon}, \bar{z})$ is unstable. It remains to establish the stability of $(\rho_+, \bar{\varepsilon}, \bar{z})$. After some computations we obtain that the inequality $a_1 a_2 - a_3 > 0$ can be written as a second degree polynomial in ζ, this is:

$$P_3(\lambda) = a_1 a_2 - a_3 = A\zeta^2 + (A^2 + B)\zeta + AC$$

$$A = \gamma + (1 + \nu_1 + \nu_2) > 0$$

$$B = \rho\left|\begin{matrix}\rho(2\nu_1 + \nu_2) + \gamma \\ -\nu_1\sqrt{(\gamma + \nu_1 + \nu_2)^2 - 4\beta\nu_1(\nu_1 + \nu_2)}\end{matrix}\right|$$

$$C = \rho\left[\rho(2\nu_1 + \nu_2) - \gamma - \nu_1\right]$$

For concluding that P_2 is positive, we only have to check that the coefficients B and C are positive. This is done by simple but tedious algebra. A useful step in this task is realizing that $B = C - \rho\left|\sqrt{(\gamma + \nu_1 + \nu_2)^2 - 4\beta\nu_1(\nu_1 + \nu_2)}\right|$. So we obtain that the point $(\rho_+, \bar{\varepsilon}, \bar{z})$ is stable.