Simple biophysical model of tumor evasion from immune system control

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The competitive nonlinear interplay between a tumor and the host's immune system is not only very complex but is also time-changing. A fundamental aspect of this issue is the ability of the tumor to slowly carry out processes that gradually allow it to become less harmed and less susceptible to recognition by the immune system effectors. Here we propose a simple epigenetic escape mechanism that adaptively depends on the interactions per time unit between cells of the two systems. From a biological point of view, our model is based on the concept that a tumor cell that has survived an encounter with a cytotoxic T-lymphocyte (CTL) has an information gain that it transmits to the other cells of the neoplasm. The consequence of this information increase is a decrease in both the probabilities of being killed and of being recognized by a CTL. We show that the mathematical model of this mechanism is formally equal to an evolutionary imitation game dynamics. Numerical simulations of transitory phases complement the theoretical analysis. Implications of the interplay between the above mechanisms and the delivery of immunotherapies are also illustrated.

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I. INTRODUCTION

Tumor cells are characterized by a vast number of genetic and epigenetic events leading to the appearance of specific antigens (e.g., mutated proteins, under- and/or overexpressed normal proteins, and many others), triggering reactions by the both the innate and the adaptive immune system (IS) [1,2]. These observations have provided a theoretical basis to the old empirical hypothesis of immune surveillance, i.e., that the IS may act to eliminate tumors [3]. Despite the accumulation of much indirect experimental and epidemiologic evidence in favor of this hypothesis [4], as yet no consensus has been reached regarding it. However, we believe that this evidence at least clearly shows that the IS is often a potent inhibitor of tumor growth.

Of course, the competitive interaction between tumor cells and the IS involves a considerable number of events and molecules, and as such is extremely complex. Thus the time course of the interplay between tumor cells and the IS is strongly nonlinear.

However, besides nonlinearity, another important point to stress is that the structure of the above-mentioned interactions is also characterized by a series of adaptive phenomena. As is well known, the IS is not in all cases able to eliminate a neoplasm, which may escape from IS control. In other cases, a dynamic equilibrium may also be established, such that the tumor may survive in a dormant steady state, which is undetectable by diagnostic equipment [5]. This was largely inferred from clinical data, but recently Koebel *et al.* [6] were able to experimentally show, through an *ad hoc* mouse model, that adaptive immunity can maintain occult cancer in an equilibrium state.

It is quite intuitive that this equilibrium can be disrupted by sudden events. Indeed, if disease-related impairments of innate and adaptive immune systems occur or immunosuppressive treatments preceding organ transplants, then tumors start redeveloping [4,7]. This has been shown both by means of mouse models and epidemiologic studies [4,7].

However, there is a major class of causes of disruption of the equilibrium that is not related to immunosuppression. Indeed, over a long period of time [4], the neoplasm may develop multiple strategies to circumvent the action of the IS [2,4], which may allow it to recommence growing into clinically apparent tumors [6], which theoretically can reach their carrying capacity [5]. From an ecological point of view, we might say that the tumor has adapted itself to survive in a hostile environment in which the antitumor immune response is activated [4,5]. For example, the tumor may develop mechanisms to spread by reducing its immunogenicity [2,4]. In other words, the immunogenic phenotype of the tumor is ââsculptedââ by the interaction with the IS of the host. For this reason, the theory of interaction between a tumor and the IS has been called immunoediting theory in [4].

In the interaction between the tumor and the immune system, the adaptation on the part of the prey and the consequential temporal variation of parameters are aimed at maximizing the final size reached by the tumor, whereas the aim of the initial phase of the adaptive process of IS is the opposite, i.e., minimizing the size of the tumor through fully effective immune control.

As far as the mathematical description of tumor and immune system interaction is concerned, many works have appeared using an approach based on specific differential-equations models with constant [8–11] or stochastically varying [12,13] parameters and, more recently, based on a family of models [5,14]. The basic idea of [8,9] as well as of [5,14] is simple: tumor cells and the effector cells of IS are seen as two competing populations. Tumor cells are mainly the prey of the

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immune effectors, whose proliferation and local recruitment is stimulated, in turn, by the presence of the tumor. However, malignant cells also induce a loss of effectors, and there is an influx of effectors whose intensity may depend on the size of the tumor [14].

Another very interesting way of studying immuno-oncological dynamics is the approach by Bellomo and co-workers [15,16], where cellular interactions are represented by generalized kinetic (Boltzmann) models of nonlinear statistical mechanics. This approach allows tumor dynamics to be studied in far greater detail than do classical models.

In [5] the immunoediting phenomenon was empirically included in the theoretical framework of [14] simply by allowing the presence of slowly time-varying generic parameters in the metamodels (time scales significantly longer than those typical of the tumor-IS interaction). In other words, the behavioral strategies interrelated with phenotype changes were described by means of meta-modelling similar to the Lotka-Volterra models with adaptively changing interaction strength [17–19], particularly with slowly varying parameters [18], and in [20] all the phases were considered by means of nonmonotonically varying parameters.

Recently, in the framework of his above-mentioned kinetic approach, Bellomo proposed a generic model for the "learning" of immune effectors and for the "hiding" of tumor cells based on the concept of mutual change of the levels of activities [16].

Here we propose a different and specific dynamic approach for the description of tumor evasion, based on the concept that a tumor cell that has survived an encounter with a cytotoxic T-lymphocyte (CTL) has an information gain that it transmits to the other cells of the neoplasm. The consequence of this information increase is a decrease in the probabilities of being killed and of being recognized by a CTL.

This hypothesis, although new, is in line with the general schema of tumor escape from the immune response. Indeed, as stressed by Stewart and Abrams [7], tumor cells may escape from immune control through two general paradigms: (a) mechanisms that involve the secretion of soluble factors; (b) mechanisms that are dependent on the contact between the tumor cells and the effectors and that are aimed at reducing antigen recognition/adhesion and apoptotic resistance. In current experimental knowledge the above-mentioned factors are primarily aimed—apart from, in many cases, their mitogenic action—at inducing the emergence of immunosuppressive networks [21]. We propose here that soluble factors might be used in the intercellular communication of the information acquired in the contact with the immune effectors. This could, for example, be related to the experimental findings by Kurnick *et al.* [22], who showed that melanoma cells produce soluble factors that diminish Melanoma-A/MART-1 Ag expression with the concomitant loss of recognition by the specific CTLs.

II. MODELS OF TUMOR-CTL INTERPLAY

In this section we briefly summarize the definition and main properties of the well-known model by Kuznetsov *et al.* [9,10] describing the growth of an immunogenic tumor and its interplay with cytotoxic T-lymphocytes:

$$\begin{aligned} x' &= rx\left(1-\frac{x}{K}\right) - kxy + k_{-1}C + k_2(1-p)C, \\ y' &= \frac{fC}{a+x} - \mu_0 y - kxy + k_{-1}C + k_2 pC + \sigma, \\ C' &= kxy - \delta C - k_{-1}C - k_2 C, \end{aligned} \tag{1}$$

where

(1) $x(t)$ is the tumor size at the time t and $y(t)$ is the size of CTL compartment at time t, $C(t)$ is the size of TC-CTL complexes.

(2) The rate of binding between tumor cells and immune effectors is kxy.

(3) The complexes have a loss rate δ and have a total rate of unbinding $k_{-1}+k_2$, where k_{-1} is the rate at which neither the tumor cell nor the effector are damaged, and k_2 is the rate at which either the tumor cell or the effector are lethally damaged.

(4) The probability that, at the end of the short lifespan of a complex, the tumor cell is killed is p. As a consequence the probability that the tumor cell survives (and the effector is lethally damaged or inactivated) is $(1-p)$. As a consequence, the influx of surviving tumor cells is $(1-p)k_2C$ and the influx of surviving effectors is k_2pC.

(5) In the absence of an immune reaction the tumor follows a logistic law: $x' = rx(1-\frac{x}{K})$.

(6) The recruitment rate of CTLs is given by $fC/(a+x)$, their baseline death rate is μ_0, and σ is their external inflow.

Since the lifespan of the complexes is very short, in [9] it is supposed that complexes are at quasiequilibrium so that

$$(\delta + k_{-1} + k_2)C \approx kxy,$$

thus leading to the following bidimensional system:

$$\begin{aligned} x' &= rx\left(1-\frac{x}{K}\right) - k\frac{k_2}{\delta+k_{-1}+k_2}pxy \\ y' &= \frac{\beta x}{a+x}y - \left[\mu_0 + k\frac{k_2}{\delta+k_{-1}+k_2}(1-p)x\right]y + \sigma. \end{aligned} \tag{2}$$

In [9,10] and, for a class of models extending (2), in [14] it was shown that the above models, whose dynamics are characterized by a vast repertoire of nonlinear behaviors, can summarize well the complex interactions between tumors and CTLs.

III. THE IMMUNOEVASIVE PROCESSES

In previous works [5,20] one of the authors (d'Onofrio) stressed that one of the critical points of models of tumor-immune system interplay is that the number of tumor cells killed per time unit [k_2pC in the model (1)] as well as the number of tumor-stimulated effectors born and/or recruited per time unit [$fC/(a+x)$ in the model (1)] are static in the sense that these functions do not directly depend on time. Initially focusing on the interpretation of the biological natural history of tumors, a rough "kinematic" approach was employed by qualitatively introducing some time-varying parameters, which were explicitly given. In [5], for example, in order to model immunoediting, in the family of bidimensional models [14] some time-decreasing parameters were introduced

(namely, exponential functions of time) and both simulations and a bifurcation analysis were performed. It was thus shown that the re-explosion of a tumor may be read as a catastrophic transition from a locally stable dormant state to a globally attractive macroscopic steady state near the full carrying capacity in the absence of immune reactions.

Here we are interested in offering an explicit and biophysically grounded model of the processes of long-term evasion from immune control. Our main hypothesis is that at each encounter between a tumor cell and a CTL, if the tumor cell survives, the information that the tumor cell now has regarding immune control is increased, thus decreasing the probability p:

$$p(t+dt) = p(t) - \eta(p) \times \{dt[k_{-1} + k_2(1-p)]C\} \times p,$$

where $\eta(p) \geqslant 0$, so that

$$p' = -\eta(p)[k_{-1} + k_2(1-p)]Cp. \tag{3}$$

It is important to stress here that we implicitly assumed that the information acquired by each surviving cell after its successful detachment from a CTL is then transmitted to the other cells via intercellular communication, which is a rapid process. Of course, the same mechanism might also act upon encounter with effectors, for example, of the innate IS.

Note that with $p(t)$ being a probability, Eq. (3) must be such that if $p(0) \in [0,1]$ then $p(t) \in [0,1]$ for all times $-\infty < t < +\infty$. This is trivially verified for $t \geqslant 0$, whereas in order that it may be true also for $t < 0$, it has to be the case that

$$\eta(1) = 0. \tag{4}$$

Thus we set

$$\eta(p) = \eta_0(p)(1-p), \tag{5}$$

where $\eta_0(p) \geqslant 0$ is bounded, for example: $\eta_0(p) = const.$ Thus Eq. (3) reads

$$p' = -\eta_0(p)[k_{-1} + k_2(1-p)]C(1-p)p. \tag{6}$$

In the hypothesis that the dynamics of the complexes C is very fast $(k_{-1} + k_2) \gg 1$, and that, as a consequence, they may considered at quasiequilibrium, i.e., $C \approx kxy/(\delta + k_{-1} + k_2)$, Eq. (6) becomes

$$p' = -\eta_0(p)[\delta + k_{-1} + k_2(1-p)]\frac{k}{k_{-1}+k_2}xy(1-p)p. \tag{7}$$

Note that in a macroscopic tumor where the process of immunoevasion is not yet appreciable, it has to be the case that $p(0) \approx 1$. Since the adaptive rate of the tumor at each encounter must, per force, be small, it follows that for a long time-interval it is $p' \approx 0$, which matches well the fact that immune evasion is a phenomenon with long time scales.

Note that the total number of complexes that do not lead to the death of the involved tumor cell, i.e., the number of nonlethal encounters for tumor cells, is given by

$$N'(t) = \{k_{-1} + k_2[1 - p(t)]\}C(t). \tag{8}$$

Thus by using both (6) and (8), one straightforwardly obtains that

$$\frac{d}{dN}p = -\eta_0(p)p(1-p). \tag{9}$$

In the case of constant η_0, Eq. (9) yields

$$p(N) = \frac{p(0)}{p(0) + [1-p(0)]\exp(\eta_0 N)}, \tag{10}$$

which is simply the mathematical counterpart of the intuitive fact that the probability q is a decreasing function of the total number of nonlethal complex-forming encounters N.

Remark. Equation (6) *is formally the model of an evolutionary imitation game* [23], *which in this case is asymmetric since the positive payoff is* 0 *and the negative payoff is proportional to the encounter rate* kxy.

Note now that the parameter k encodes two distinct phenomena: the baseline rate k^0 at which a tumor cell meets an immune cell and also the probability z that an immune cell may recognize the tumor cell, so that k should be modelled as a time-varying function as follows:

$$k(t) = k^0 z(t).$$

The probability z may also be subject to evolutionary changes. Thus, similarly to (3) we may write

$$z' = -\gamma_0(z)[k_{-1} + k_2(1-p)]C(1-z)z. \tag{11}$$

Quite interestingly, the use of a quasiequilibrium approximation sheds some further insight into the dynamics of z:

$$z' = -\gamma_0(z)[\delta + k_{-1} + k_2(1-p)]\frac{k^0}{k_{-1}+k_2}xy(1-z)z^2. \tag{12}$$

Finally, here we briefly link the release of immunosuppressive factors by tumor cells with our hypothesis on the onset of immunoediting. Namely, we assume that tumor cells that were not lethally hit acquire and transmit information allowing an increased production of an immunosuppressive factor inducing the apoptosis of the CTLs. At variance with the previous case, the modeling of these immunoediting phenomena preliminarily requires the inclusion of new terms in the equation for $y(t)$ of the static model [10]. Indeed, we suppose that tumor cells produce a factor W, which is taken up by CTLs, and which is toxic to them. The production rate of this factor is $\beta(t)$, and it is adaptively changed by the tumor cells so that

$$W' = \beta(t)x - qyW - dW,$$

where q is the uptake rate by CTLs and d is the degradation rate of the chemical. Assuming, finally, that the chemokine W degrades sufficiently rapidly, we may set $W \approx [\beta(t)/d]x/(1+\epsilon y)$, where $\epsilon = q/d$. By assuming that the additional CTL death rate induced by the factor W is proportional to its uptake rate $\gamma^* qyW$, it follows that CTL dynamics is given by

$$y' = \frac{fC}{a+x} - \mu_0 y - kxy + k_{-1}C + k_2 pC + \sigma - b(t)b_M\frac{x}{1+\epsilon y}y, \tag{13}$$

where $b_M = (\gamma^* \epsilon)\beta_M$, β_M being the maximum production rate of W, and $0 \leqslant b(t) \leqslant 1$. Thus proceeding as in the previous section yields the following equation:

$$b' = \xi_0(b)[k_{-1} + k_2(1-p)]C(1-b)b, \qquad (14)$$

where the term $(1-b)$ follows from the saturation in the production of the immunotoxic factor.

IV. SIMULATIONS

In the previous section we did not analyze the asymptotic behavior of the model since it is trivial in the sense that $\lim_{t\to+\infty} p(t) = 0^+$ and $\lim_{t\to+\infty} z(t) \to 0$. Indeed, what matters in this and other biological contexts is to assess the typical transitory behaviors during a simulated realistic lifespan of the host organism.

We first simulated models (1)–(6) by using for the parameters the numerical values that were estimated in [10] for the model (1) with constant p, which refers to chimeric mice with murine B cell lymphoma, an experimental tumor that is often in quiescence. For the sake of notation simplicity we adimensionalized the values of x, y, and c by using as a unit 10^6 cells (note that in [10] the steady-state value for the tumor size to adimensionalize x, y, and z). As a consequence, the values of the parameters are [10]

$$r = 0.18day^{-1}, K = 500,\ k \in (0.1,0.4)day^{-1}$$
$$f = 29.88day^{-1},\ a = 20.19$$
$$\mu_0 = 0.0412day^{-1},\ \sigma = 0.0136day^{-1}$$
$$k_{-1} = 24.0day^{-1},\ k_2 = 7.2day^{-1},\ \delta = 0day^{-1}.$$

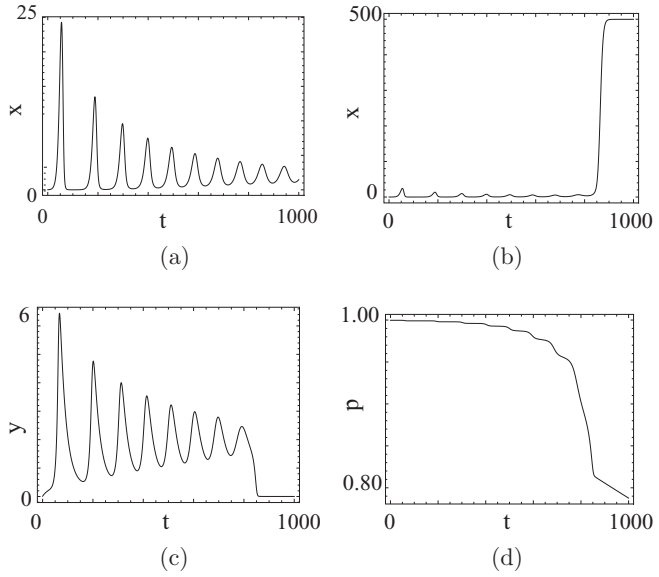

FIG. 1. Panel (a): Baseline behavior of tumor size $x(t)$ in the absence of dynamical changes in p and $z(t)$ in the case of $k = 0.4day^{-1}$, $\gamma_0 = \eta_0 = 0$ $z(t) = 1$, and $p = 0.9997$. Panels (b–d): Effects of dynamical changes in $p(t)$ in the case $\eta = 4.5 \times 10^{-3}$. Panel (b): Behavior of $x(t)$, immunoevasion onsets at $t \approx 850$. Panel (c): Behavior of the CTLs. Panel (d): Time changes of $p(t)$. Other parameters as in [10]. Time is measured in days.

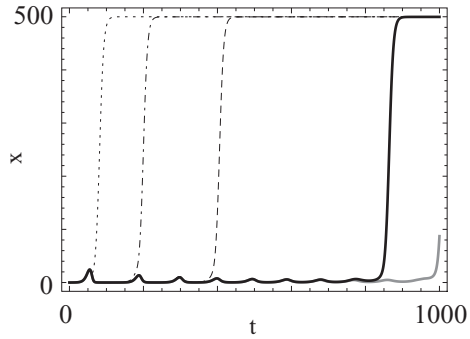

FIG. 2. Effect on $x(t)$ of varying η_0 in the case of $k = 0.4day^{-1}$, $\gamma_0 = 0$ $z(t) = 1$, and $p(0) = 0.9997$. Solid gray line $\eta_0 = 0.86 \times 4.5 \times 10^{-3}$; solid black line: $\eta_0 = 4.5 \times 10^{-3}$; dashed line: $\eta_0 = 2 \times 4.5 \times 10^{-3}$; dot-dashed line: $\eta_0 = 4 \times 4.5 \times 10^{-3}$; dotted line: $\eta_0 = 8 \times 4.5 \times 10^{-3}$. Other parameters as in [10]. Time is measured in days.

In [10] the estimated constant value for p in model (1) was $p = 0.9997$, which we use in our simulations as the initial value for p.

Since the lifespan for chimeric mice is approximately 3 years, we simulated the model up to $t = 1000$ days. In Fig. 1 we set $k = 0.4day^{-1}$. In the baseline case of constant p (first panel), i.e., $\eta_0 = 0$, the tumor size (as well as the immune effectors) exhibits damped oscillations around a small value, indicating tumor dormancy. However, (second panel) for $\eta_0 = 4.5 \times 10^{-3}$ there is the onset of a sudden immunoevasion at $t \approx 850$ days. The corresponding behavior for the effectors is shown in the third panel. The final panel shows the dynamics of $p(t)$. Note that at the onset of immunoevasion $p \approx 0.82$, which is very far from zero. With reference to the parametric values used in Fig. 1, Fig. 2 shows how the onset of the immunoevasion depends on η_0, and one may see that for $4.5 \times 10^{-3} < \eta < 3.6 \times 10^{-2}$ the onset starts at times that are adequately long, whereas for $\eta_0 < 0.86 \times 4.5 \times 10^{-3}$ the onset of immunoevasion is at nonrealistic times greater than 1000 days.

In Fig. 3 we set $k = 0.25day^{-1}$. Unlike the previous simulation, in the baseline case of constant p (first panel), i.e., $\eta = 0$, the tumor size (as well as the immune effectors) exhibits sustained oscillations spacing from relatively small tumor sizes up to quite large sizes. However, (second panel) for $\eta = 1.1 \times 10^{-3}$ there is the onset of a sudden immunoevasion at $t \approx 850$ days. The corresponding behaviors for the phase planes are shown, respectively, in the third and fourth panels.

Here, to focus on the role of $z(t)$, we report some baseline simulations where we set constant $p(t) = 0.997$ (i.e., we assumed $\eta = 0$), $\gamma_0 = const > 0$, and $z(0) = 0.9999$. Including the dynamics of $z(t)$ revealed that the system is more robust with respect to this time-varying parameter than with respect to $p(t)$. Indeed, the immunoevasion onsets only for small values of $z(t)$. Moreover, the dynamics of $z(t)$ was slower than those of $p(t)$ obtained in the other set of simulations; thus the ranges of (constant) γ_0 required to onset immunoevasion were quite larger than those of η_0 used in Figs. 1 and 3. For example, to reproduce a behavior similar to that reported in Fig. 1, we had to set $\gamma_0 = 0.013$. In Fig. 4 we report the simulations done for the case $k^0 = 0.25$ [as in Fig. 1, where,

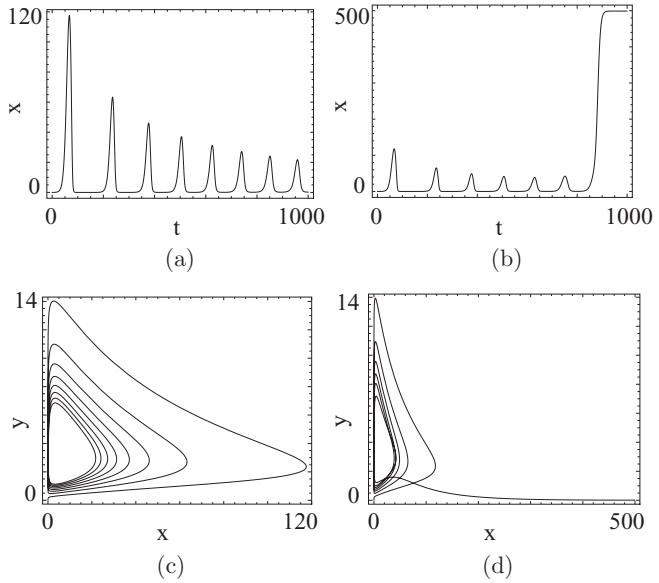

FIG. 3. Panels (a) and (c): Behavior of, respectively, tumor size $x(t)$ and of the phase plane $[x(t), y(t)]$ in the absence of dynamical changes in p and z, in the case of $k = 0.25 day^{-1}$, $z(t) = 1$, $\gamma_0 = 0$, and $p = 0.9997$. Panels (b) and (d): Effects of dynamical changes in $p(t)$ in the case $\eta = 1.1 \times 10^{-3}$. Panel (b): Behavior of $x(t)$, immunoevasion onsets at $t \approx 850$. Panel (d): Corresponding phase-plane plot. Other parameters as in [10]. Time is measured in days.

we recall, $z(t) = 1$]. Immunoevasion is triggered at $t \approx 850$ for $\gamma_0 \approx 0.0030$, when $z(850) \approx 0.2$. With reference to the parametric values used in Fig. 4, Fig. 5 shows how the onset of the immunoevasion depends on γ_0, suggesting that γ_0 should range in $3.47 \times 10^{-3} < \gamma_0 < 1.56 \times 10^{-2}$. Note that here the

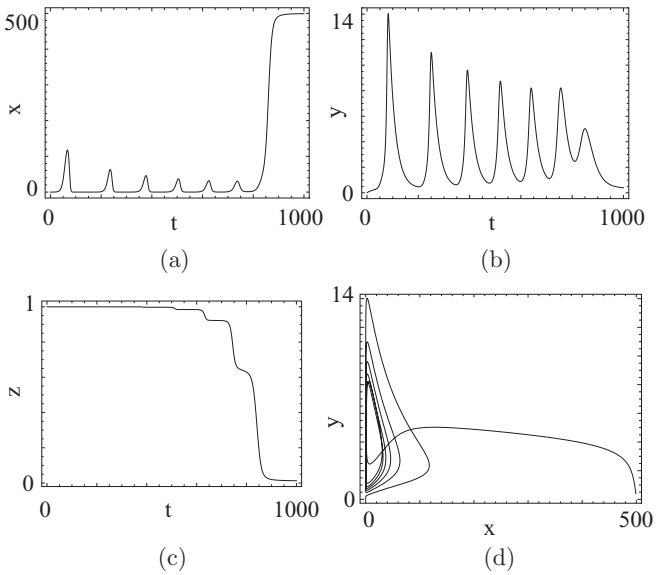

FIG. 4. Behavior of tumor-CTLs in the presence of dynamical changes in $z(t)$ with constant $\gamma_0(z) = 0.0039$, $k = 0.25 day^{-1}$, $z(0) = 0.9999$, $\eta_0 = 0$, and $p = 0.9997$. Panel (a): Behavior of $x(t)$, immunoevasion onsets at $t \approx 800$. Panel (b): Behavior of the CTLs. Panel (c): Time changes of $p(t)$. Panel (d): (x, y) phase plane plot. Other parameters as in [10]. Time is measured in days.

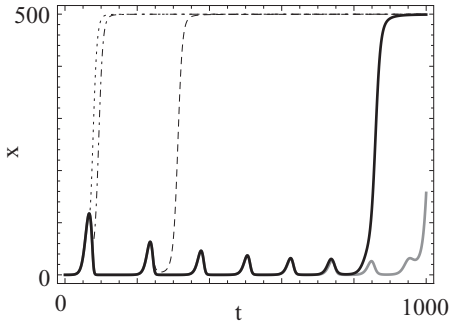

FIG. 5. Effect on $x(t)$ of varying γ_0 in the case of $k = 0.25 day^{-1}$, $\eta_0 = 0$, $z(t) = 0.9999$, and $p(0) = 0.9997$. Solid gray line: $\gamma_0 = 0.89 \times 3.9 \times 10^{-3}$; solid line: $\gamma_0 = 3.9 \times 10^{-3}$; dashed line: $\gamma_0 = 2 \times 3.9 \times 10^{-3}$; dot-dashed line: $\gamma_0 = 4 \times 3.9 \times 10^{-3}$; dotted line: $\gamma_0 = 8 \times 3.9 \times 10^{-3}$. Other parameters as in [10].

onset depends on γ_0 by means of a sharp saturation, reached at approximatively $\gamma_0 \approx 3.9 \times 10^{-3}$.

Regarding the strategy of evasion through the production of factors that are toxic to CTLs, we performed some numerical simulations that had a behavior that is qualitatively similar to those we reported above (see Fig. 6).

Finally we illustrate the negative effect of the proposed immunoevasion mechanisms on the outcome of an immunotherapy, also in the case of a highly idealized and efficient therapy (see Fig. 7). Here we consider an aggressive tumor characterized by a smaller influx of CTLs. Namely, we set $\sigma = 0.00136 day^{-1}$, i.e., one tenth of the value we used in the other simulations. The other parameters were not changed. In the absence of immunoevasion, the tumor rapidly grows, reaching in 80 days about 80% of its theoretical carrying capacity, so that the animal dies. In the presence of immunoevasion with $\eta = 0.0005$, the full carrying capacity is reached at $t = 90 day$. In both cases we simulated a highly idealized adoptive cellular immunotherapy, whose effect is modelled by increasing by twentyfold the rate σ up to the value $\sigma = 0.0272 day^{-1}$. The therapy starts at $t = 14 day$ and is uninterrupted, which is, of course, an idealized scenario. Both in the presence and absence of immunoevasion, the therapy is

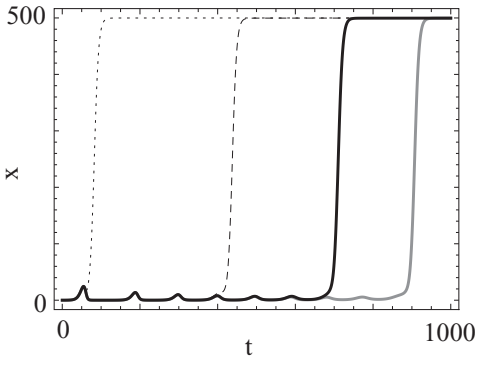

FIG. 6. Evasion through the production of factors toxic for CTLs, in the case of constant $p(t)$ and $k(t)$. Effect on $x(t)$ of varying ξ_0 in the case of $\epsilon = 0.01$, $b_M = k = 0.4\, day^{-1}$ and $p(0) = 0.9997$. Solid gray line: $\xi_0 = 4 \times 10^{-3}$; solid line: $\xi_0 = 5 \times 10^{-3}$; dashed line: $\xi_0 = 7.5 \times 10^{-3}$; dotted line: $\gamma_0 = 3.5 \times 10^{-2}$. Other parameters as in [10].

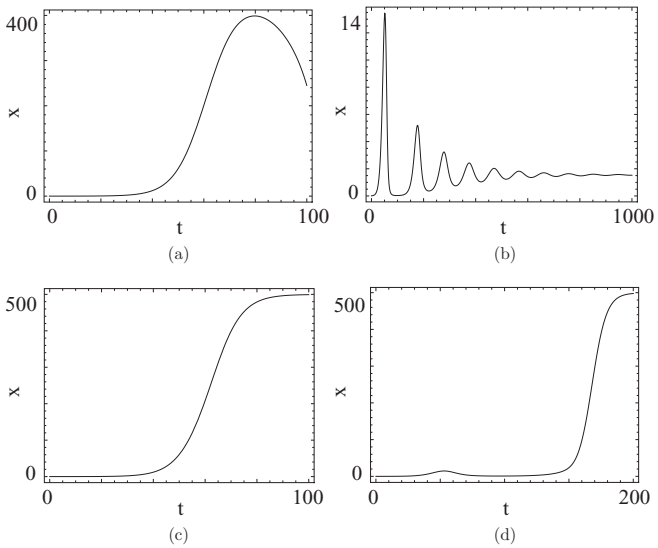

FIG. 7. Behavior of tumor-CTLs under an ideal adoptive cellular immunotherapy in the absence and in presence of dynamical changes of $p(t)$. Baseline influx rate of CTLs: $\sigma = 0.00136 day^{-1}$, $k = 0.25 day^{-1}$, $p(0) = 0.9997$. Panel (a): tumor growth in absence of therapy and constant $p(t) = 0.9997$. Panel (b): controlled growth of $x(t)$ in presence of therapy such that for $t \geqslant 14 day$ it is $\sigma = 0.0272 day^{-1}$, but constant $p(t)$. Panel (c): tumor growth in absence of therapy and with time-varying $p(t)$ with $\eta = 0.0005$. Panel (d): growth of $x(t)$ in presence of therapy such that for $t \geqslant 14 day$ it is $\sigma = 0.0272 day^{-1}$, but time-varying $p(t)$ with $\eta = 0.0005$. Other parameters as in [10]. Time is measured in days.

initially very effective and in the case $\eta = 0$ the tumor remains perfectly controlled at a small size. Conversely, although the therapy is intensive and uninterrupted, in the case $\eta = 0.0005$ a relapse is observed at $t \approx 150 day$.

V. CONCLUDING REMARKS

In this work we have developed a model of immunoevasion of tumors that is based on adaptive phenomena, which are of importance in the biophysical study of interacting populations [19,24]. Although our model is very simple and to some extent oversimplified (as are many other well-known models [9–11]), and although it uniquely focuses on the interplay of tumor cells with cytotoxic T lymphocytes, it is nevertheless able to qualitatively reproduce the phenomenon of immunoevasion. Its main characteristics are that it is an epigenetic model and that it is based on the adaptive ability of tumor cells.

However, we stress here that we only focused on two contributions to the immunoevasive process, i.e., (i) the ability of tumor cells to mitigate the probability p of being killed by the immune effectors and (ii) the probability z that a tumor cell is recognized by a CTL. Moreover, noticing that in the reduced model (2) the total loss rate of effectors can be written as $\mu(x) = \mu_0 + w(1-p)x$, where $w = kk_2/(\delta + k_{-1} + k_2)$, it follows that the decrease of p indirectly increases the loss rate of effectors. We note that one should take into account that also the recruitment and proliferation of immune effectors is evolutionarily modulated, and it decreases. This phenomenon may be modelled in a similar way to the evolutionary decrease of the killing rate here studied. However, we were interested in proposing a model whereby all the state variables have a well-defined biophysical meaning, and where all the involved biological processes are clearly identified.

As far as the differences of the relative impact of z and p are concerned, we would note here that our simulations on murine B lymphoma suggest that: (i) the onset of immunoevasion is extremely dependent on $p(t)$: small changes in p can switch the tumor state from a small equilibrium under control to a large equilibrium; (ii) immunoevasion is not very sensitive even to large changes in z and it is triggered when $z(t)$ reaches small values (e.g., $z \approx 0.2$); and (iii) the dynamics of $z(t)$ is slower than that of $p(t)$ in the case where setting $\gamma_0 = \eta$. Thus, we may speculate that in some cases (for example, for the murine B lymphoma we simulated) the prevalent reason underlying immunoevasion is the reduction of the probability of killing a tumor cell, not the reduction of probability of recognizing a tumor cell by a CTL.

In this work we dealt with the interplay between tumors and specific immunity. We chose this approach because of the experimental evidence on the relevance of CTLs in determining dormancy or evasion of many major tumors such as melanomas, ovarian carcinomas, and colorectal carcinomas [25], where the presence of infiltrating lymphocite is a useful prognostic marker. Moreover, we built up our model on the tumor-CTLs model of [10], where parameters were fitted to experimental animal data. However, embedding the proposed evolutionary mechanism in a more complex setting, where a more detailed description of both adaptive and innate immunity is included, should lead to results that are qualitatively similar to those illustrated here.

As far as the temporal details of our model are concerned, we note that in the proposed model we have many time scales: (i) the average lifespan of immune effectors; (ii) the growth of the tumor (the main process); and (iii) the escape adaptive process, which is comparable with the lifespan of the host organism. Moreover, there is another time scale: that of the propagation of intercellular communication. However, we stress here that since this time scale is extremely small in comparison with all the other three scales, we neglected it. One might encode it in the equation as a lumped or distributed delay but without gain of physical information.

However, it is important to stress that our model is only a rough deterministic approximation of the real stochastic evolutionary scenario leading to immunoevasion. For the sake of simplicity, let us use the modeling framework proposed by [26], where phenotypes are modelled through a finite number of parameters. Thus, we may say that our model assumes that the tumor immuno-phenotype has an average given by the vector $f(t) = [p(t), k(t)]$, and a variance that is very small. This is a consequence of our hypothesis that a very efficient and rapid (with respect to the tumor growth) intercellular communication exists between tumor cells. We are currently working toward a more appropriate framework where we have also added details on spatial dynamics. In the limit where the complex's tumor cell-CTL is at quasi-steady state, we showed that the dynamics of p are ruled by an equation that, from a mathematical point of view, is an imitation evolutionary game.

Although it is unclear to us which, and if any, underlying biological process is linked to the imitation schema, the asymmetry of the payoffs, where only the payoff corresponding to

a utility in case of decrease of p, is clear: the neoplasm has no interest in increasing the probability of being killed by an immune effector. Interestingly, one of the anonymous referees proposed to interpret the proposed model as an evolutionary game between the tumor and the cytotoxic T cells.

It is known in the literature [27] that adaptive phenomena may be linked to evolutionary game theory. However, Sato *et al.* observed in [28] that adaptive agents may have no knowledge of the game. This is not surprising in the context of games played by cellular populations, because the implementation of a strategy, in this case, is simply dictated by the genome and by mutations and epigenetic changes, as clearly stressed by Tomlinson and Bodmer [29].

Tomlinson and Bodmer were also the first to introduce game theoretic methods in oncology [29]. Quite interestingly, their models are also based on intercellular communications, although considering scenarios and signals that are different from those studied here. In fact, their models are based on abstract games between "signal producer" tumor cells and "signal nonproducer" tumor cells. Other examples of applications of game theory in modeling tumor biology are given in Ref. [30]. In this work we were essentially interested in the basic facts of immune response to tumors. However, a number of antitumor immunotherapies have been proposed and also theoretically investigated (see Refs. [11,14,31,32] and references therein). We believe that both the experimental results concerning immunoevasion of tumors and the theoretical findings we proposed here might have some relevance to clinical applications. Indeed, our numerical simulations confirm, also in very idealized immunotherapeutic settings, the clinical intuition summarized by M. Rescigno *et al.* [32] as follows: "immunoediting... can impair not only host-generated immunosurveillance, but also attempts to harness the immune response for therapeutic purposes, namely immunotherapies." More generally, we share the opinion of Zitvogel *et al.* [25], who stressed that recent progresses in immuno-oncology have not influenced the way anticancer therapies are conceived and applied in clinics.

Finally, we should make one important observation: our model, although based on a biological and biophysical background, is speculative and requires experimental validation. In the literature, to the best of our knowledge, immunoediting is illustrated only by means of qualitative clinical or molecular experimental findings. Indeed, a complete quantitative study of the adaptive evasion from tumor dormancy allowing, for example, the plotting of tumor growth curves would be remarkably resource-consuming. Thus we hope that this theoretical work may trigger experimental investigations of this kind, which would allow validation of our model.

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