# Behavior of tumors under nonstationary theraphy

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We present a model for the interaction dynamics of lymphocytes-tumor cells population. This model reproduces all known states for the tumor. Futherly, we develop it taking into account periodical immunotheraphy treatment with cytokines alone. A detailed analysis for the evolution of tumor cells as a function of frecuency and theraphy burden applied for the periodical treatment is carried out. Certain threshold values for the frecuency and applied doses are derived from this analysis. So it seems possible to control and reduce the growth of the tumor. Also, constant values for cytokines doses seems to be a succesful treatment.

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## I. INTRODUCTION

Cancer is one of the leading research areas, since this desease is a main cause of death. Surgery and chemotherapy are unsuccessful in many cases. Today the principal efforts are addressed to search new treatment strategies e.g. in immunotherapy (see Refs. [1,2] and references therein). In this case we refer to the use of cytokynes to stimulate the immune system. This is a protein hormone produced by activated lymphocytes which mediate both natural and specific immunity. The use of cytokines alone to boost the immune system represent one of the methods more commonly used in immunotherapy. The temporal evolution for this treatment comprises different steps: by supplying a starting dose of cytokines the rate of lymphocytes begins to increase due to the immunological reaction [1] reaching a maximum value; afterwards the lymphocytes begin to decay because of the decrease of cytokines concentration inside the body until it reaches normal values. In the following we shall call this time the activation period of the immune system. This proccess repeats again between any two succesive dose suplies. We consider these injections separated in time by the dosage period. Otherwise, it would provoke an overdose or failure in the treatment for shorter and longer time, respectively.
This work is devoted to understand the temporal tumor behavior when a periodical immunotherapy treatment is provided. Besides, we want to explore the set of parameter values to reproduce with our model the same features presented in [2](like short tem oscillation in tumor size and long term tumor relapse).
For this reason we reformulate the predator-prey model including new terms in the model which give account of tumor agressiveness, the diffusion of lymphocytes and the effect caused by cytokines on the tumor (Section 2). We analyse the model from the mathematical and biological points of view (Sections 3 and 4). We study in detail tumor evolution for different treatment regimes (Section 5) and, in the last section, we discuss our results and suggest some options for improving the model.

## II. THE MODEL

An extensive review of all models of tumor-immune system dynamics [2–12] as far as we know was done. We agree with the idea that such dynamics is determined by a competence of interacting species resembling the predator-prey model. The main difference between our model and the clasical deterministic model (e.g. Bell 1973) [4] is the inclusion of new terms taking into account, (1) the death of lymphocytes due to the increase of malignant cells population, (2) the flux of lymphocytes towards the place of local interaction and (3) the effect produced by the application of cytokine doses.
Let $X$ and $Y$ denote respectively the number of malignant and lymphocyte cells. The rate of malignant cells $\left(\frac{dX}{dt}\right)$ is given by:

$$\frac{dX}{dt} = aX - bXY \tag{1}$$

We assume a growth rate proportional to $X$ and a decrease rate proportional to the frecuency of interaction with lymphocytes. Coefficients are $a$ and $b$, respectively, where $a$ is tissue dependent.

On the other hand, the growth rate of lymphocytes $\left(\frac{dY}{dt}\right)$ is described by:

$$\frac{dY}{dt} = dXY - fY - kX + u \tag{2}$$

It is proportional to the interaction with malignant cells and also to the flux per unit time of lymphocytes to the place of interaction. These effects are represented by the first and fourth terms in the right-hand side of equation

2. This last term characterizes the difussion process of lymphocytes that takes place in the surroundings of the tumor assuming a constant lymphocytes flux [7]. On the other hand, the decrease rate depends on two factors: natural death and growth of malignant cells related to the effective area of tumor interacting directly with the lymphocytes. These are given by the second and third terms of this same equation where $f$ and $k$ are their respective coefficients of proportionality.

In order to introduce the effects produced by the treatment with cytokines in the proccess of activation of the immune system, we add a periodical function that mimics the periodical dosage. As a first approximation, we propose the function $F\cos^2\omega t$, where $\omega$ is the frecuency of the periodical behavior for cytokines inside the body. The modified Eq 2 will be given by the expression

$$\frac{dY}{dt} = dXY - fY - kX + u + F\cos^2\omega t \tag{3}$$

Taking into account Eq.1, we get the following system of differential equations.

$$\frac{dX}{dt} = aX - bXY \tag{4}$$

$$\frac{dY}{dt} = dXY - fY + Q \tag{5}$$

$$Q = -KX + u + Fcos^2(\omega t) \tag{6}$$

where $Q$ is a function that picking up all the news contributions respecting the standard predator-prey model. with $X(0) = X_0$ and $Y(0) = Y_0$ as initial conditions.

From the analysis for $Q = 0$ the system of Eq.4, Eq.5and Eq.6 reduces to the predator-prey model, which has as equilibrium points a saddle point at the phase portrait origin and a center in the first quadrant of the phase diagram [13]. This center reflects the oscillating behavior of the competence between both predator and prey, which is characterized by an oscillation frecuency (number of cycles per unit time around the center of the phase diagram). Taking the reverse of this frecuency as a characteristic time $t_0 = \frac{1}{\sqrt{af}}$ and rescaling the equations of the system of Eq.4, Eq.5and Eq.6 by means of the following scaling parameters:

$$t = t_0\tau$$
$$X = X'x$$
$$Y = Y'y$$

the system given by the Eq.4, Eq.5and Eq.6 become:

$$\frac{X'}{t_0}\dot{x} = axX' - bxyX'Y' \tag{7}$$

$$\frac{Y'}{t_0}\dot{y} = (dxX' - f)yY' + Q \tag{8}$$

$$Q = F\cos^2(\omega\, t_0\tau) + u - K\, X'x \tag{9}$$

sustituting the scaling parameters by the following values:

$$t_0 = \frac{1}{\sqrt{af}}$$
$$X' = \frac{\sqrt{af}}{d}$$
$$Y' = \frac{\sqrt{af}}{b}$$

we get the following rescaled equations

$$\frac{dx}{d\tau} = \alpha\, x - xy \tag{10}$$

$$\frac{dy}{d\tau} = xy - \frac{1}{\alpha}\, y - kx + \sigma + V\cos^2(\beta\,\tau) \tag{11}$$

with $x(0) = x_0$ and $y(0) = y_0$ as initial conditions.

where $V = \frac{Fb}{af}$, $k = \frac{K}{bd}\sqrt{af}$,
$\alpha = \sqrt{\frac{a}{f}}$, $\sigma = \frac{ub}{af}$ and $\beta = \frac{\omega}{\sqrt{af}}$
Analysing in detail the prior expressions we can interpret these parameters as follows:

From $V$ it is deduced that its value depends on the net value for doses ($F$) and on the action of the immune system on malignant cells ($b$). Hence it would represent an effective value of all doses employed in the activation of lymphocytes, namely, those necesary for activating the lymphocytes that take action directly against the tumor cells.
On the one hand, $k$ is directly proportional to $K$ which accounts for the negative effects exerted on the population of lymphocytes due to the size of the tumor and it is inversely proportional to the recognition ($d$) and attack ($b$) frequencies of the immune systen to malignant cells. So, we infer that the inverse value of this parameter ($1/k$) gives, "in some sense", the control exerted by the immune system over the aggressiveness of the tumor due to its size.
From the similarity of the expressions for $\sigma$ and $V$, taking into account the remarks done for $V$ we interpret that $\sigma$ which depends on the action of the immune system on malignant cells ($b$) represent of all lymphocytes flux $u$ those effective value involved in the attack on tumor cells. Finally, $\alpha$ and $\beta$ are directly related to the proliferation of malignant cells and the frecuency of treatment, respectively.

## III. DYNAMICS AND STABILITY ANALYSIS WITHOUT TREATMENT

The system of Eq.10 and Eq.11 corresponding to $V = 0$( no treatment) is an autonomous system given by the following equations:

$$\frac{dx}{d\tau} = \alpha\, x - xy \tag{12}$$

$$\frac{dy}{d\tau} = xy - \frac{1}{\alpha}\, y - kx + \sigma \tag{13}$$

with $x(0) = x_0$ and $y(0) = y_0$ as initial conditions.
Susbstituting the Eq.12 in the Eq.13 we get the differential equation

$$\frac{d^2x}{d\tau^2} + (\frac{1}{\alpha} - x - \frac{1}{x}\frac{dx}{d\tau})\frac{dx}{d\tau} = (k-\alpha)x^2 + \sigma x \qquad (14)$$

with $x(0) = x_0$, $\dot{x}(0) = v_0$ as initial conditions.

This equation is similar to that describing the motion of a particle in a force field [12], whose potential is:

$$U(x) = -\frac{1}{3}(k-\alpha)x^3 - \frac{1}{2}\sigma x^2 \qquad (15)$$

This potential has two extremes given by

$$x_1 = 0 \qquad \text{and} \qquad x_2 = \tfrac{\sigma-1}{k-\alpha}$$

These extreme points depend on $\alpha$, $k$ and $\sigma$ as:

$$\sigma > 1 \rightarrow \begin{cases} x_1 = 0 & \text{minimum} \\ \frac{k}{\alpha} > 1, \quad x_2 > 0 & \text{maximum} \\ \frac{k}{\alpha} < 1, \quad x_2 < 0 & \text{maximum} \end{cases}$$

and for

$$\sigma < 1 \rightarrow \begin{cases} x_1 = 0 & \text{maximum} \\ \frac{k}{\alpha} > 1, \quad x_2 > 0 & \text{minimum} \\ \frac{k}{\alpha} < 1, \quad x_2 < 0 & \text{minimum} \end{cases}$$

We only consider motion for $x > 0$, the suitable potential fields describing the motion of the particle are depicted in Fig. 1a and Fig. 1b. In Fig. 1a , the maximum represents an unstable point for the particle motion, contrary in Fig. 1b the particle oscillates around the minimum.
The analysis of fixed points in the phase space for Eq.12 and Eq.13 shows two steady-states. A fixed point is $L_0 = (0, \alpha\sigma)$ with associated eigenvalues

$$\lambda_\pm = \frac{\alpha^2(1-\sigma) - 1}{2\alpha} \pm \left| \frac{\alpha^2(1-\sigma) + 1}{2\alpha} \right| \qquad (16)$$

For $\sigma < 1$, $L_0$ is a saddle point while for $\sigma > 1$ is a stable node.
The other fixed point is $L_1 = \left(\frac{1-\sigma}{\alpha-k}, \alpha\right)$ with associated eigenvalues given by:

$$\lambda_\pm = \frac{k - \alpha\sigma}{2\alpha(\alpha-k)} \pm \sqrt{\left[\frac{k - \alpha\ \sigma}{2\alpha(\alpha-k)}\right]^2 - (1-\sigma)} \qquad (17)$$

The real part of this eigenvalue is zero for $\frac{k}{\alpha} = \sigma$ with $v_0 < 1$.
When condition $(\alpha-k)^2 - \frac{k}{\alpha} > -1$ is fulfilled, we get two values for $\sigma_c$ solutions of

$$\alpha^2\sigma_c^2 - 2\alpha[k - 2\alpha(\alpha-k)^2]\sigma_c + k^2 - 4\alpha^2(\alpha-k)^2 = 0$$

given by

$$\sigma_c = \frac{k}{\alpha} - 2\alpha^2\left(1 - \frac{k}{\alpha}\right)^2 \pm 2\alpha|1 - \frac{k}{\alpha}|\sqrt{\alpha^2\left(1 - \frac{k}{\alpha}\right)^2 - \frac{k}{\alpha} + 1} \qquad (18)$$

defining the region of complex eigenvalues and focus-like behavior.

The analysis of these eigenvalues provides a rich dynamics. For the case $\frac{k}{\alpha} < 1$ we have different situations. The states and its stability for the second fixed point are depicted schematically in Fig. 2.
If $\sigma < \frac{k}{\alpha}$ ($Re\lambda_\pm > 0$), we have an unstable focus or node depending on the parameter value $\sigma_c$ relative to those given by Eq.18.
On the contrary, stable behavior (focus or node) appears when $\frac{k}{\alpha} < \sigma < 1$ ($Re\lambda_\pm < 0$).
Now, if $1 < \sigma$ the fixed point corresponds to a negative population of malignant cells, with no physical meaning.
For the case $\frac{k}{\alpha} > 1$ and $\sigma < 1 < \frac{k}{\alpha}$ ($Re\lambda_\pm < 0$) the critical point moves to the second quadrant of the phase diagram, being discarded as before.
For values of $\sigma$ in the ranges $1 < \sigma < \frac{k}{\alpha}$ and $1 < \frac{k}{\alpha} < \sigma$ we get a saddle point ($\lambda_+ > 0$ and $\lambda_- < 0$), whose separatrix splits the phase portrait into stable and unstable zones as can be seen in Fig.5. In all the cases the dynamics in the phase diagram is represented by a homeomorfism [14] between two fixed points.

## IV. BIOLOGICAL SIGNIFICANCE

So far, we have presented a detailed analitical study of the linear stability of our model when $V$ is set equal to zero. The interpretation of this preliminary results will give us the esential features of the system.
Let us start with the case $\frac{k}{\alpha} < 1$.
For $\sigma < \frac{k}{\alpha}$ the system evolves towards a state of uncontrolable tumor growth(see Fig. 3a) This case can be interpreted as a *recurrence* like behavior [15,16] very similar to q-switching oscillations observed in physical phenomena as, for example, in lasers. On the contrary, when $\frac{k}{\alpha} < \sigma < 1$, our system evolves towards a controlable mass of malignant cells in a damped oscillating way (Fig. 3b). This state is considered by some authors as a dormant state [7–9,15,16].
However in both cases, there exist populations of malignant cells that grow towards a state in which immunological activity has been suppressed. In the first case this happens for any initial conditions, while in the second it only happens for an initially weak inmunological response (Fig. 4a and 4b). Let us now analyse the reverse condition $\frac{k}{\alpha} > 1$.
In this case there are two possible ranges for $\sigma$:

$$1 < \tfrac{k}{\alpha} < \sigma \text{ and } 1 < \sigma < \tfrac{k}{\alpha}$$

In both situations we are in the presence of a saddle point which means that for populations of cancer cells be-

low the horizontal separatrix the dynamics is irreversible: this curve represents the critical amount of malignant cells for a fixed population of lymphocytes.
This situation is similar to the case analised before for a weak immnune system as an initial condition: the population of malignant cells grows towards a value such that the immunological response is reduced to zero (Fig. 5). This would represent a state where illness is not the cause of death but leaves the body unprotected against other diseases.
However for malignant cells above the horizontal separatrix it is possible to observe regression of tumor as has been reported in clinical experiments(see Ref. [15] and references therein)

## V. STABILITY ANALYSIS WITH TREATMENT AND BIOLOGICAL IMPLICATIONS

The system represented by Eq.10 and Eq.11 with $V \neq 0$ (cytokines doses amplitude) can be analised as an autonomous system [17]. The procedure consists in substituting the oscillating function $\cos\beta t$ of the driven term $F\cos^2\beta t$ in the Eq.11 by a new variable $u$, which is a solution of the second order differential equation of a linear oscillator

$$\frac{d^2u}{dt^2} + \beta^2 u = 0 \tag{19}$$

(where $u(0) = 1$, $\dot{u}(0) = 0$) which can be written as two linear coupled differential equations

$$\frac{dz}{d\tau} = -\beta^2 u \tag{20}$$

$$\frac{du}{d\tau} = z \tag{21}$$

(with $u(0) = 1$, $z(0) = 0$)
Then Eq.10 and Eq.11 become:

$$\frac{dx}{d\tau} = \alpha\, x - \ xy \tag{22}$$

$$\frac{dy}{d\tau} = \ xy - \frac{1}{\alpha}\, y - \ kx + \sigma + Vu^2 \tag{23}$$

$$\frac{dz}{d\tau} = -\beta^2 u \tag{24}$$

$$\frac{du}{d\tau} = z \tag{25}$$

with $x(0) = x_0$, $y(0) = y_0$, $u(0) = 1$, $z(0) = 0$ as initial conditions.
This system presents the critical points $L_0^* = (0, \alpha\sigma, 0, 0)$ and $L_1^* = \left(\frac{1-\sigma}{\alpha-k}, \alpha, 0, 0\right)$ whose projection in the $y$-$x$ plane coincides with those critical points of the unperturbed system (Eq.12 and Eq.13) with the same eigenvalues given by the Eq.16 and Eq.17 plus the new conjugate pair $\lambda_\pm = \pm\, i\beta$.
In this case we are in presence of a center manifold where solutions can be expanding or contracting, i.e., the asymptotic stability analysis carried out before loses its validity, needing more complex developments.
In order to avoid such complexity and gain a better comprehension, we may consider this system like a couple of one linear (Eq.19) and one nonlinear (Eq.14) oscillators, allowing us a more intuitive interpretation of the different regimes. Thus the changes from recurrent to dormant states of tumor cells in the periodical dosage regime can be interpreted as a lock of the unstable oscillations of the nonlinear oscillator imposed by the linear one. We can understand the complex behavior of coupled oscillators by representing its dynamics as a function of control parameters $V$ and $\beta$ [17,18]. In order to depict it we plot, in the parameter space ($V$vs$\beta$), those points for which tumor growth is uncontrolable.
In the case $\frac{k}{\alpha} < 1$ for $\sigma < \frac{k}{\alpha}$, for effective value of doses and frecuencies higher than certain threshold, the system can revert from uncontrolable growth to a treatment controled population. Namely, for every set of parameter values $\alpha$,$k$ and $\sigma$, there are threshold values for $\beta$ and $V$ which split the parameter space (see Fig 6) into two zones corresponding to uncontrolable and controlable growth of malignant cells. The Fig 6 was generated for a fixed set of initial conditions. Although the behavior of the parameter space for different initial conditions is qualitatively the same, the threshold values show strongh dependence of the initial conditions.
From this result and taking into account the meaning of the parameters $\beta$ and $V$, we can infer that treatment is specific for each patient and kind of tumor since threshold doses values depend on the immunological response of each individual, on the malignant cells population at the begining of the treatment and also on the rate of proliferation of the tissue. Besides, the existence of threshold values reflects the fact that reaching controlable populations of malignant cells is only possible by mantaining a minimal dose above certain threshold given by the continuous line depicted in Fig 6, which can be well fitted by a hiperbolic function.
For effective doses and frecuencies below these threshold values, the system behaves qualitatively the same as without treatment. However, contrary to this statement it is also found that for low frecuencies the growth of malignant cells can be controlled in spite of being below the threshold values (see, for details, Fig 6).
There exists a "paradoxical" phenomenon observed in experiment and the clinic, consisting in the fact that the enhacement of the inmune system with immunotherapy stimulates tumor growth [19], which could be explained, "in some way", by this result, i.e., why, for fixed doses burden , the growth becomes uncontrolable at given frecuencies above those localized in the region of controlable growth of malignant cells (Fig. 6). Such values would represent an optimal treatment as it reduces doses burden and treatment frecuency.
Also, for higher frecuencies with small $V$, growth of can-

cer cells can be controlled as shown in Fig 6. The observance of these optimal values would be important because of the negative effects produced when cytokines concentration reaches above a critical concentration [20,21]..
Now, increasing the amplitud of the effective dose value for a fixed frecuency above the threshold, a malignant cells population reduction is obtained, in spite of an uncontrolable growth being observed for some higher doses burden (see Fig 6).
On the other hand, setting $V$ to some value and varying the frecuency from zero to higher values, different behaviors are reproduced. At zero treatment frecuency, tumor cells population is controlable with the lowest values of doses burden (Fig. 6). However, for frecuencies different from zero, we find zones of recurrent and dormant growth of tumor cells. The population of cancer cells controled under treatment presents an oscillating behavior (see Fig. 7) [2].
For values of the parameters satisfying $\frac{k}{\alpha} < \sigma < 1$ (that we interpret as a dormant state), malignant cells population can be reduced by increasing effective doses. On the other hand, varying the frecuency for fixed effective doses values, an oscillating behavior for the population of malignant cells is obtained, as in the previous case.
In all these cases, regrowth of malignant cells takes place after treatment interruption [9]. This can be easily understood if we take into account that the population of malignant cells with zero value ($x = 0$) represents, in the mechanical analogue (Eq.14), an unstable point (a potential maximum, as that shown in Fig. 1b). This means that any variation will lead the system towards a minimal potential position. Therefore for a residual population slightly greater than zero, a regrowth of tumor cells will take place after the treatment.
Analysing the behavior when $\frac{k}{\alpha} > 1$ we arrive at the following results. The range of values with physical sense for $\sigma$, i.e. $1 < \frac{k}{\alpha} < \sigma$ and $1 < \sigma < \frac{k}{\alpha}$ allows only two critical points: a stable node and a saddle point. In this case dynamics in the phase portrait is the same as that without treatment. There are no possible changes in the dynamics, so treatment is useless.
Hence, for $\frac{k}{\alpha} > 1$, only initial conditions determine the final outcome of tumor evolution, irrespective of the applied treatment.

## VI. CONCLUSIONS

In this work we intend to give a new focus to the dynamics of tumor growth in a periodical regime of immunotherapy. We explain such dynamics considering this system as two coupled oscillators, namely, the competence between the immune system and malignant cells analized as a nonlinear oscillator coupled with a linear one that simulates the treatment.
This simple model allowed us to describe all possible states in wich a tumour can be found. It also presented some of the features found in tumor dynamics, outlined by some authors, such as the existence of short term oscillations of tumor size as well as the long term tumor relapse. On the other hand, this model gives the dependence of tumor growth on some parameter values related to the treatment: the frecuency and amount of applied doses. We conclude from this study that the evolution of tumor submitted to immunotherapy has a strong dependence on these parameter values.
In some cases, growth of malignant cells can be reverted with inmunotherapy treatment. Corresponding threshold values are obtained for treatment frequency and dose above which growth is stopped and malignant cells population reduced.
Also, for those inmunological parameters for which a stable population of malignant cells exists, the size of the dormant tumor can be reduced by increasing dose burden.
It was shown, as well, that for certain relation among the parameter values, tumor presents a recurrent behavior with or without treatment.
In all these cases, when a reduction of the tumor is possible, best results are obtained for low constant values of the dose. Nevertheless in all cases previously analyzed, after the interruption of the treatment, tumor regrowth is observed.
This would confirm the fact that treatment with immunotherapy using cytokines alone is not succesful enough in the treatment against cancer [2]. Therefore another kind of therapy would be required.
As a way to improve the model, we propose the introduction of other terms taking into account effects produced by stochastic perturbations due to enviromental conditions [6,7,11]. Some authors atribuit to these perturbations the main cause of possible jumps from stable to unstable behavior in tumor growth dynamics. This will be considered in a future work.


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FIG. 1. Potential barriers in which the particle moves. (a) $\alpha = 1$, $k = 1.5$ and $\sigma = 3$. (b) $\alpha = 2$, $k = 0.2$ and $\sigma = 0.25$ ..

FIG. 2. States and its stability for the second fixed point as a function of parameters $\alpha$, $k$, $\sigma$.

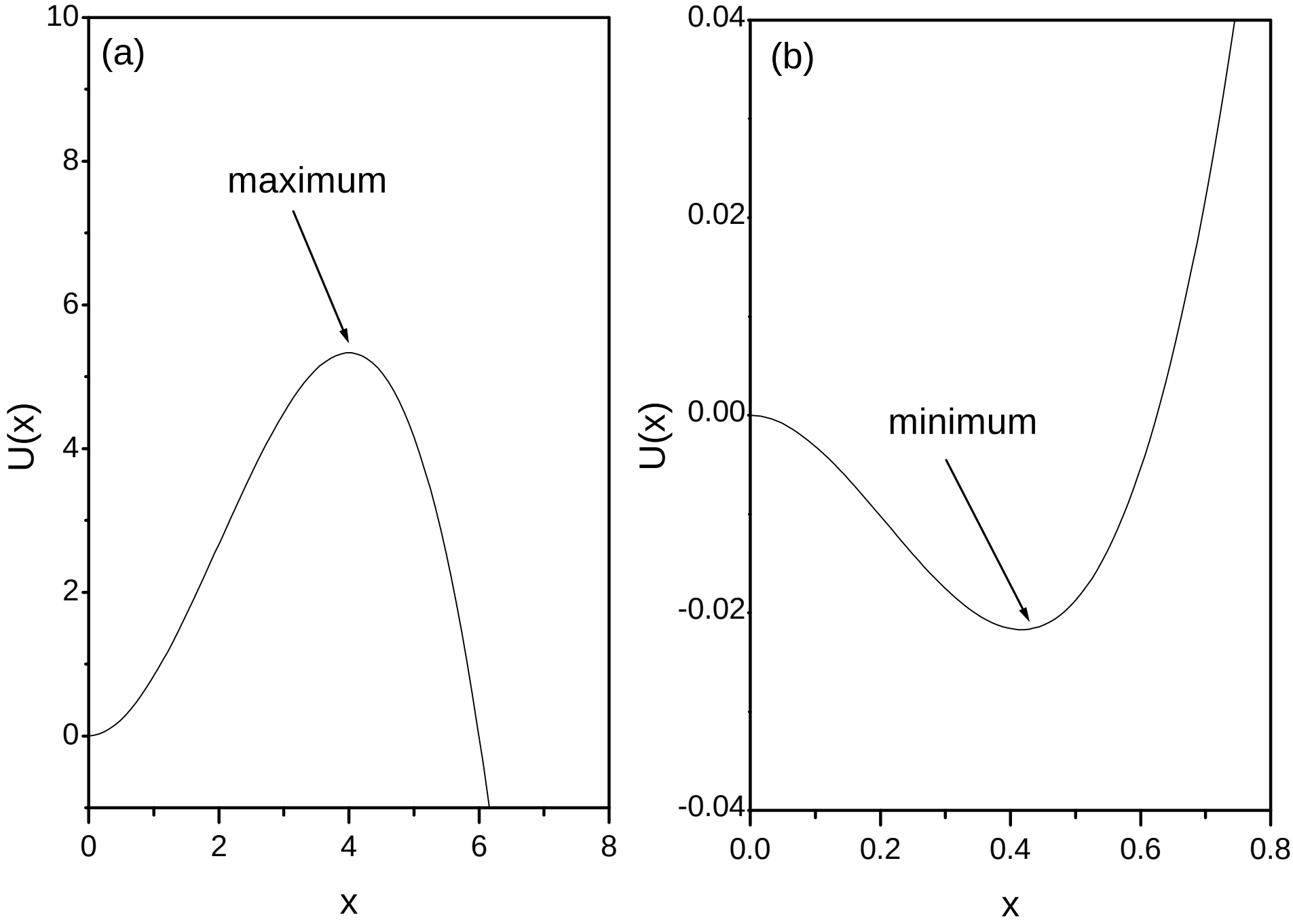
FIG. 3. Evolution of malignant cells on time without treatment. (a) $\alpha = 2$, $k = 0.2$ and $\sigma = 0.05$ with $x_0 = 2.1$ and $y_0 = 2.7$. (b) $\alpha = 2$, $k = 0.2$ and $\sigma = 0.25$ with $x_0 = 5.3$ and $y_0 = 6.7$.

FIG. 4. Phase portraits (lymphocytes population versus malignant cells). (a) $\alpha = 2$, $k = 0.2$ and $\sigma = 0.09$. (b) $\alpha = 2$, $k = 0.2$ and $\sigma = 0.25$.

FIG. 5. Saddle point in the phase portrait for values of parameters $\alpha = 1$, $k = 1.5$, $\sigma = 3$.

FIG. 6. Growth behavior of malignant cells with treatment for $\alpha = 2$, $k = 0.2$ and $\sigma = 0.05$ with $x_0 = 5.3$ and $y_0 = 6.7$ depicted in the parameter space ($V$, $\beta$). Uncontrolable growth (gray points). Controlable growth (white points). Black solid line (hiperbolic function $V = 0.10478 + 0.00044/(0.05343 + \beta)^{2.7313}$).

FIG. 7. Limit cycles for $V = 0.25$ and different values of parameter $\beta$ in the phase portrait.



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