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Bifurcation Analysis and Nonlinear Decay of a Tumor in the Presence of an Immune Response

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The decay of a planar compact surface that is reduced through its boundary is considered. The interest of this problem lies in the fact that it can represent the destruction of a solid tumor by a population of immune cells. The theory of curves is utilized to derive the rate at which the area of the set decreases. Firstly, the process is represented as a discrete dynamical system. A recurrence equation describing the shrinkage of the area at any step is deduced. Then, a continuum limit is attained to derive an ordinary differential equation that governs the decay of the set. The solutions to the differential equation and its implications are discussed, and numerical simulations are carried out to test the accuracy of the decay law. Finally, the dynamics of a tumor-immune aggregate is inspected using this law and the theory of bifurcations. As the ratio of immune destruction to tumor growth increases, a saddle-node bifurcation stabilizes the tumor-free fixed point.

Keywords: Bifurcation analysis; nonlinear systems; mathematical modeling; cancer dynamics; geometry of curves.

1. Introduction

Competition models are widely used to study the growth dynamics of cancer cell populations [Panetta & Adam, 1995; Gatenby & Gawlinsky, 1996; Pinho *et al.*, 2002; de Pillis & Radunskaya, 2003; Itik & Banks, 2010]. Cancer cells interact with other cells and substances in their tissue microenvironment, leading to complex and unpredictable behavior. In particular, Lotka–Volterra models have been used to study the cellular immune response to tumor growth [Bellomo & Preziosi, 2000; Kuznetsov *et al.*, 1994; de Pillis *et al.*, 2005; López *et al.*, 2014]. Using these models, a variant of the Michaelis–Menten kinetics has been proposed to describe the rate at which a tumor is destroyed by a population of cytotoxic immune cells [López *et al.*, 2017, 2016].

In this context, it has been recently suggested that the rate at which the area of a two-dimensional tumor is reduced by a population of cytotoxic lymphocytes obeys a linear function of time [López *et al.*, 2016]. The problem is posed in two dimensions for simplicity and the parabolic decay of the area holds when there is no tumor infiltration, the immune cells lyse at a constant rate and surround the tumor completely. If the tumor is spherical and the radius decreases linearly with time at speed c, the nonlinear differential equation governing the decay is

$$T'(t) = -dT^{1/2}(t), \tag{1}$$

where $T(t)$ is the size of the tumor cell population at time t and $d = 2\pi^{1/2}c\sigma^{1/2}$, σ being the surface density of cells, which was missing in previous works [López *et al.*, 2016].

However, when the shape of the tumor deviates from a disk, this equation constitutes a reasonable approximation, but it is inexact after all. Using mathematical arguments, a new alternative equation is here proposed to describe the decay of the area $A(t)$ of an arbitrary planar convex and compact set

$$A'(t) = -cL_0 + 2\pi c^2 t, \tag{2}$$

where L_0 is the length of the boundary of the initial set.

In the present work we rigorously demonstrate this equation. To this end, we describe the process as follows. We consider that at each time step n, the tumor can be represented by a simply connected and compact set, whose boundary corresponds to a closed curve C_n (see Fig. 1). Moreover, we assume that the set is convex. Otherwise, the topology of this set might change during its evolution, becoming disconnected. Using a parametric representation, these curves can be written as $\mathbf{x}_n(\lambda)$, with $\lambda \in [0, 2\pi)$ and $n \in \mathbb{N}$. If the surface is reduced from the outside and in the normal direction to its boundary, we can relate the boundaries at the nth and at $(n+1)$th steps, by

$$\mathbf{x}_{n+1}(\lambda) = \mathbf{x}_n(\lambda) + \Delta R\mathbf{p}_n(\lambda), \tag{3}$$

where $\mathbf{p}_n(\lambda)$ is the normal unit vector at the point $\mathbf{x}_n(\lambda)$ of the nth boundary curve C_n. As shown in Fig. 1, the value ΔR represents the thickness of the erased layer. Note that the plus sign assumes that the planar set is convex, as previously stated. Thus, we regard the progressive shrinkage of the set as a sequence of curves $(C_0, C_1, \ldots)$. These curves are related via Eq. (3), and the sequence converges to the empty set, which can be regarded as the attractor of the dynamical system. The following notation is adopted from the literature [Kreyszig, 1991] to carry out the analysis. The modulus of a vector $\mathbf{y}$ is represented as $|\mathbf{y}|$. The derivative of any vector $\mathbf{y}$ defined on the curve with respect to the arclength s is represented as $\dot{\mathbf{y}}$, while the derivative with respect to the parameter λ is denoted as $\mathbf{y}'$. The tangent,

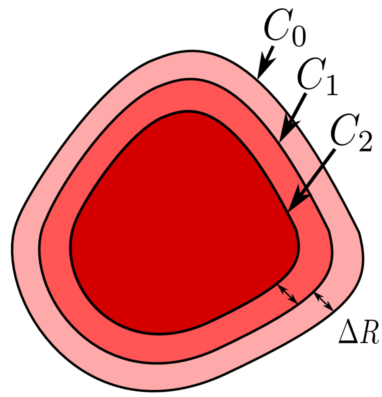

Fig. 1. *The shrinkage of a planar surface.* An initial planar convex set whose boundary C_0 is iteratively reduced in the direction given by its unit normal vector by an amount ΔR.

normal and binormal vectors are written as $\mathbf{t}(\lambda)$, $\mathbf{p}(\lambda)$ and $\mathbf{b}(\lambda)$, respectively.

Finally, the nonlinear decay law that we derived in the previous sections is used to study the dynamics of a tumor-immune aggregate, as a function of the tumor growth rate, its carrying in the absence of immune response and the rate of tumor destruction by the immune cytotoxic cells. A bifurcation analysis reveals how the malignant tumor attractor decreases as the immune response strengthens, until a threshold value is reached, by which it suddenly disappears.

2. Preliminary Results

In the present section we demonstrate two propositions, which are used later on, to derive the continuous equations.

Lemma 1. *Let $\mathbf{x}_0(\lambda)$ be a parametric representation of class $r \geq 2$ of an initial closed curve $C_0 \subset \mathbb{R}^2$, which evolves according to the recurrence relation defined by Eq. (3). Then, if the condition $k_n(\lambda)\Delta R \leq 1$ holds for all n and λ, the recurrence functions for the vectors $\mathbf{t}_n(\lambda)$, $\mathbf{p}_n(\lambda)$ and $\mathbf{b}_n(\lambda)$ are all equal to the identity map. The curvature $k_n(\lambda)$ and the speed $|\mathbf{x}_n'(\lambda)|$ are determined from the original set through the recurrence relations $k_{n+1}(\lambda) = k_n(\lambda)/(1 - k_n(\lambda)\Delta R)$ and $|\mathbf{x}_{n+1}'(\lambda)| = |\mathbf{x}_n'(\lambda)| \cdot (1 - k_n(\lambda)\Delta R)$.*

Proof. Differentiating Eq. (3) with respect to λ and using the Frenet–Serret formula $\dot{\mathbf{p}}_n(\lambda) = -k_n(\lambda)\mathbf{t}_n(\lambda)$ yields

$$\mathbf{x}_{n+1}'(\lambda) = \mathbf{x}_n'(\lambda) \cdot (1 - k_n(\lambda)\Delta R).$$

Taking the modulus on both sides of this last equation, and bearing in mind the condition $k_n(\lambda)\Delta R \leq 1$, allows to write $|\mathbf{x}'_{n+1}(\lambda)| = |\mathbf{x}'_n(\lambda)| \cdot (1 - k_n(\lambda)\Delta R)$. Recalling the definition of the tangent vector $\mathbf{x}'_n(\lambda) = |\mathbf{x}'_n(\lambda)|\mathbf{t}_n(\lambda)$, we obtain $\mathbf{t}_{n+1}(\lambda) = \mathbf{t}_n(\lambda)$. Differentiating this equation with respect to λ and using the Frenet–Serret formula $\dot{\mathbf{t}}_n(\lambda) = k_n(\lambda)\mathbf{p}_n(\lambda)$, we obtain the equality $\mathbf{p}_{n+1}(\lambda)k_{n+1}(\lambda)|\mathbf{x}'_{n+1}(\lambda)| = \mathbf{p}_n(\lambda)k_n(\lambda)|\mathbf{x}'_n(\lambda)|$. Since by definition we have $|\mathbf{p}_n(\lambda)| = 1$, the equation $k_{n+1}(\lambda) = k_n(\lambda)/(1 - k_n(\lambda)\Delta R)$ holds. Therefore, the equation $\mathbf{p}_{n+1}(\lambda) = \mathbf{p}_n(\lambda)$ holds as well. ■

Lemma 2. *Let $\mathbf{x}_0(\lambda)$ be a parametric representation of class $r \geq 2$ of an initial closed curve $C_0 \subset \mathbb{R}^2$, which evolves according to the recurrence relation defined by Eq. (3). If the conditions $k_n(\lambda)\Delta R \leq 1$ and $\sigma_n(\lambda)\Delta R \leq 1$ hold for all n and λ, the area A_n enclosed by the curve C_n can be iterated by means of the equation*

$$A_{n+1} = A_n - \frac{\Delta R}{2}\oint (k_n(\lambda) + \sigma_n(\lambda))|\mathbf{x}_n(\lambda) \times \mathbf{x}'_n(\lambda)|d\lambda + \frac{(\Delta R)^2}{2}\oint k_n(\lambda)\sigma_n(\lambda)|\mathbf{x}_n(\lambda) \times \mathbf{x}'_n(\lambda)|d\lambda, \tag{4}$$

where $\sigma_n(\lambda) = 1/r_n(\lambda)$, with $r_n(\lambda) = -\mathbf{x}_n(\lambda) \cdot \mathbf{p}_n(\lambda)$.

Proof. An allowable parametrization $\mathbf{y}_n(r, \lambda)$ of the planar surface S_n delimited by C_n is $\mathbf{y}_n(r, \lambda) = r\mathbf{x}_n(\lambda)$, with $r \in [0, 1]$. The element of area dA_n can be computed from the metric g_n as $\sqrt{\det g_n}drd\lambda$. In the present case we have $\sqrt{\det g_n} = r|\mathbf{x}_n(\lambda) \times \mathbf{x}'_n(\lambda)|$. Consequently, the area at the $(n+1)$th step is

$$A_{n+1} = \frac{1}{2}\oint |\mathbf{x}_{n+1}(\lambda) \times \mathbf{x}'_{n+1}(\lambda)|d\lambda. \tag{5}$$

Equation (3) and $\mathbf{x}'_{n+1}(\lambda) = \mathbf{x}'_n(\lambda) \cdot (1 - k_n(\lambda)\Delta R)$ permit to write

$$A_{n+1} = \frac{1}{2}\oint (1 - k_n(\lambda)\Delta R)|\mathbf{x}_n(\lambda) \times \mathbf{x}'_n(\lambda) + \Delta R\mathbf{p}_n(\lambda) \times \mathbf{x}'_n(\lambda)|d\lambda. \tag{6}$$

Since $\mathbf{p}_n(\lambda) \times \mathbf{x}'_n(\lambda) = -(\mathbf{x}_n(\lambda) \times \mathbf{x}'_n(\lambda)) \cdot \sigma_n(\lambda)$ and we are considering the restriction $\sigma_n(\lambda)\Delta R \leq 1$, we have

$$A_{n+1} = \frac{1}{2}\oint (1 - k_n(\lambda)\Delta R)(1 - \sigma_n(\lambda)\Delta R) \times |\mathbf{x}_n(\lambda) \times \mathbf{x}'_n(\lambda)|d\lambda. \tag{7}$$

The expansion of this equation in powers of ΔR completes the proof. ■

3. Proof of the Main Theorem

Before demonstrating the core proposition of this work, we first derive three continuous formulae describing the time evolution of the position vector, the curvature and the speed related to the boundary curves. The idea is to associate a continuous time variable t to the discrete step n. Then, the following iteration $n + 1$ can be related to $t + dt$, as long as we consider that $\Delta R \to dR$, with $dR = cdt$. Clearly stated, we assume that the distance from the boundary along the normal direction decreases linearly with time at speed c. Therefore, a continuous equation expressing the time evolution of the curvature can be written as $k(t + dt, \lambda) = k(t, \lambda)/(1 - k(t, \lambda)dR)$. A Taylor series expansion of this relation on the variable dR about the origin leads to $k(t + dt, \lambda) = k(t, \lambda) + k^2(t, \lambda)cdt$, where the terms $O(dt^2)$ have been disregarded. Thus we have the differential equation $dk = k^2cdt$, whose solution is $k(t, \lambda) = k_0(\lambda)/(1 - k_0(\lambda)ct)$, with $k_0(\lambda) = k(0, \lambda)$. To simplify notation, we now define $v(t, \lambda) \equiv |\mathbf{x}'(t, \lambda)|$. This function obeys the difference equation $v(t + dt, \lambda) = v(t, \lambda) - k(t, \lambda) v(t, \lambda)cdt$, which is tantamount to the differential equation $dv = -kvcdt$. The solution to this equation is $v(t, \lambda) = v_0(\lambda)(1 - k_0(\lambda)ct)$. Finally, since $\mathbf{p}(t, \lambda)$ does not change over time, we can write Eq. (3) as $\mathbf{x}(t, \lambda) = \mathbf{x}_0(\lambda) + ct\mathbf{p}_0(\lambda)$. This, in turn, allows us to write $r(t, \lambda) = r_0(\lambda) - ct$. We now proceed to introduce our main result.

Theorem 1. *The area A of a convex and compact planar set S_0, whose boundary is of class $r \geq 2$ and shrinks continuously in the normal direction at a constant rate c, decreases following a parabolic function of time*

$$A(t) = A_0 - cL_0t + \pi c^2t^2, \tag{8}$$

where A_0 is the area of the original set S_0 and L_0 is the length of its boundary ∂S_0.

Proof. Disregarding the terms $O(dt^2)$, Eq. (4) can be written in the form

$$A(t+dt) - A(t) = -dt\frac{c}{2}\oint(k(t,\lambda) + \sigma(t,\lambda))|\mathbf{x}(t,\lambda)\times\mathbf{x}'(t,\lambda)|d\lambda, \tag{9}$$

with $\sigma(t,\lambda) = 1/r(t,\lambda)$. Therefore, the following differential equation governs the decay of the area

$$A'(t) = -\frac{c}{2}\oint(1 + k(t,\lambda)r(t,\lambda))v(t,\lambda)d\lambda. \tag{10}$$

This equation can be expanded and rewritten as

$$A'(t) = -\frac{c}{2}\left(L(t) + \oint k(t,\lambda)r(t,\lambda)v(t,\lambda)d\lambda\right), \tag{11}$$

where $L(t)$ is the length of the boundary of the shrinking set at time t. We now recall that

$$L(t) = \oint v(t,\lambda)d\lambda = L_0 - ct\oint k_0(\lambda)v_0(\lambda)d\lambda, \tag{12}$$

by virtue of the equation $v(t,\lambda) = v_0(\lambda)(1 - k_0(\lambda)ct)$. Substituting Eq. (12) in Eq. (11) and expressing the equations $k(t,\lambda)$, $v(t,\lambda)$ and $r(t,\lambda)$ in terms of the initial conditions yields

$$A'(t) = -\frac{c}{2}\left(L_0 + \oint k_0(\lambda)r_0(\lambda)v_0(\lambda)d\lambda - 2ct\oint k_0(\lambda)v_0(\lambda)d\lambda\right). \tag{13}$$

The second integral appearing on the right-hand side of Eq. (13) equals 2π by the Gauss–Bonnet theorem. We now solve the remaining integral

$$\oint k_0(\lambda)r_0(\lambda)v_0(\lambda)d\lambda = \oint k_0(s)r_0(s)ds = -\oint \ddot{\mathbf{x}}_0\cdot\mathbf{x}_0 ds, \tag{14}$$

where s is the length of arc of C_0. This integral can be solved by parts and it is immediate to show that its value is L_0, recalling that

$$\ddot{\mathbf{x}}_0\cdot\mathbf{x}_0 = \frac{1}{2}\frac{d^2}{ds^2}(\mathbf{x}_0^2) - 1. \tag{15}$$

Thus we finally obtain the differential equation

$$A'(t) = -cL_0 + 2\pi c^2 t, \tag{16}$$

which has the simple solution $A(t) = A_0 - cL_0t + \pi c^2t^2$. ■

4. Numerical Simulation

We test the formula governing the reduction of the area of an initial set, by considering the case of an ellipse. To simulate the shrinkage of this planar surface, we devise the following elementary algorithm, which can be considered as a simplification of the complex cellular automata presented in previous works that study tumor lysis [López *et al.*, 2017]. A planar grid of cells is represented, where those cells that belong to the initial set are assigned a value of one, while the remaining cells are set to a value of zero. Then, at each step, the updating rule proceeds by setting to a value of zero all those cells which have a value of one and are at a distance from the boundary smaller than or equal to a fixed value. The shrinkage of the set is represented in Fig. 2. The algorithm continues until the set has been eradicated. By counting cells, the size of the set at each step is computed and represented graphically. Finally, the graph given by Eq. (8) is represented together for comparison. The results are shown in Fig. 3. As can be seen, such equation faithfully describes the shrinkage of the set.

According to Eq. (8), the time τ it takes to reduce completely the set is

$$\tau = \frac{L_0}{2\pi c}\left(1 - \sqrt{1 - \frac{4\pi A_0}{L_0^2}}\right). \tag{17}$$

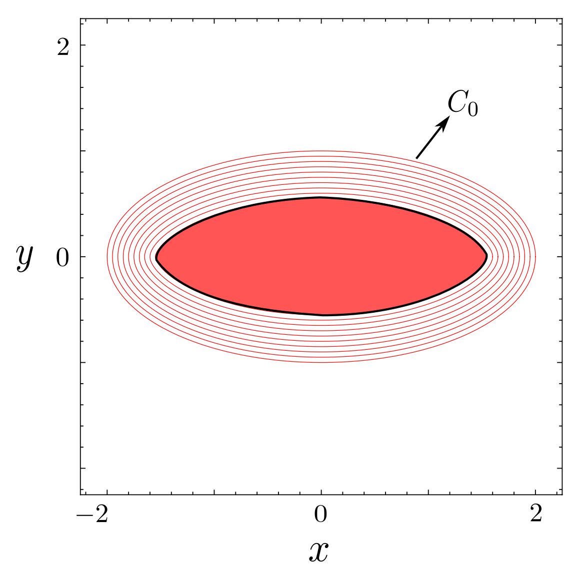

Fig. 2. *The shrinkage of an ellipse.* A simulation of the shrinkage of an initial planar convex set C_0 with the shape of an ellipse. The semi-minor and semi-major axes of the initial ellipse take a value of one and two, respectively. A sequence of sets are generated as the original set is progressively erased by a fixed distance of value $\Delta R = 0.05$ in its normal direction.

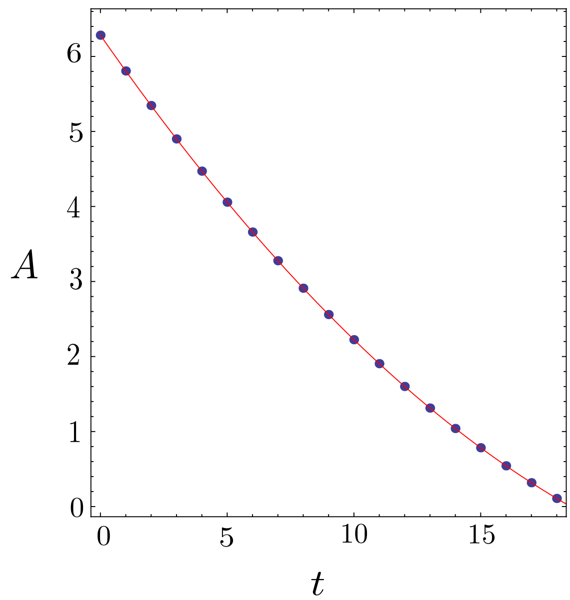

Fig. 3. *The decay of the area of an ellipse.* The results obtained with the algorithm (dots) together with the curve that represents the decay of the area as given by the equation $A(t) = A_0 - cL_0 t + \pi c^2 t^2$. The values $A_0 = 2\pi$, $c = 0.05$ and $L_0 = 4E(\sqrt{3}/2)$ have been used, where E is the complete elliptic integral of the second kind.

Since the isoperimetric inequality [Osserman, 1978] imposes $4\pi A_0 \le L_0^2$, where the saturation is attained for a disk, it takes less spherical sets less time to disappear. Concerning the lysis of a tumor, as long as there is no lymphocyte infiltration, this means that those tumors with a less spherical morphology are easier to eradicate by the immune system. This occurs because their boundary of contact, relative to their size, is larger [López *et al.*, 2017].

It is worth to establish how Eq. (16) differs from Eq. (1). Beginning with Eq. (8), it is immediate to demonstrate that the differential equation governing the decay of a disk is precisely $A'(t) = -2\pi^{1/2} c A^{1/2}(t)$, as shown in Eq. (1). However, when the shape differs from a disk, a form factor

$$\delta(t) = \sqrt{\frac{L^2(t)}{4\pi A(t)}} \tag{18}$$

is deserved. The inverse of $\delta(t)$ has been called the sphericity [Wadell, 1935]. Therefore, a more general differential equation that can be derived from Eq. (8) is $A'(t) = -2\pi^{1/2} c\delta(t) A^{1/2}(t)$. When the sphericity of the tumor barely changes with time, we can make use of Eq. (1) and derive from the first principles the value of the constant appearing in such equation as $d = 2\pi^{1/2} c\sigma^{1/2}\delta_0$.

5. Bifurcation Analysis of the Dynamics of a Tumor-Immune Aggregate

Finally, we conclude our study of the process of lysis of a tumor according to Eq. (1), taking into account its growth, which we assume to be described by a sigmoid function [de Pillis & Radunskaya, 2003]. In particular, for simplicity, we assume a logistic growth with constant rate r and carrying capacity K. Therefore, the differential equation that governs the dynamics of the tumor is

$$T'(t) = rT(t)\left(1 - \frac{T(t)}{K}\right) - dT^{1/2}(t). \tag{19}$$

The previous equation can be nondimensionalized by defining the new time coordinate $\tau = rt$ and the relative tumor size as $x = T/K$. Renaming the time variable to its standard, yields

$$x'(t) = x(t)(1 - x(t)) - \mu x^{1/2}(t), \tag{20}$$

where the parameter $\mu = d/(rK^{1/2})$ has been defined. Therefore, the dynamics of the tumor-immune aggregate depends, not only on the ratio between the rate at which the tumor is destroyed and the rate at which it grows, but also on its carrying capacity in the absence of lysis. In Fig. 4 we represent a bifurcation diagram, showing how the fate of the tumor depends on the parameter μ. In

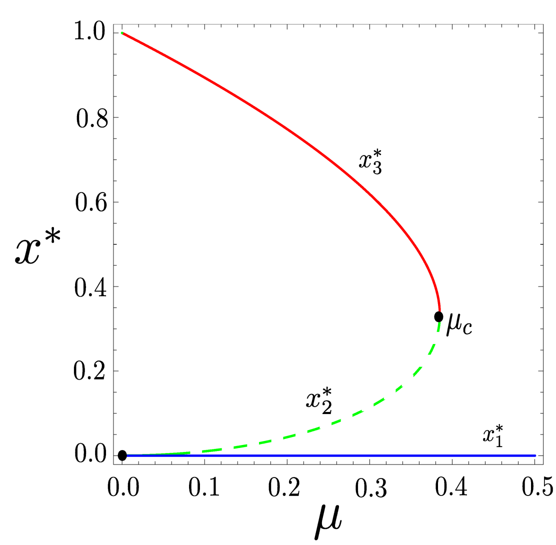

Fig. 4. *Bifurcation diagram.* As the parameter μ is increased, two bifurcations take place. The first occurs at $\mu = 0$. A new fixed point is born in the vicinity of $x = 0$. In the interval $[0, \mu_c]$ two stable fixed points, x_1^* and x_3^*, coexist separated by the unstable fixed point x_2^*. Finally, two fixed points disappear through a saddle-node bifurcation, leaving x_1^* as a global attractor.

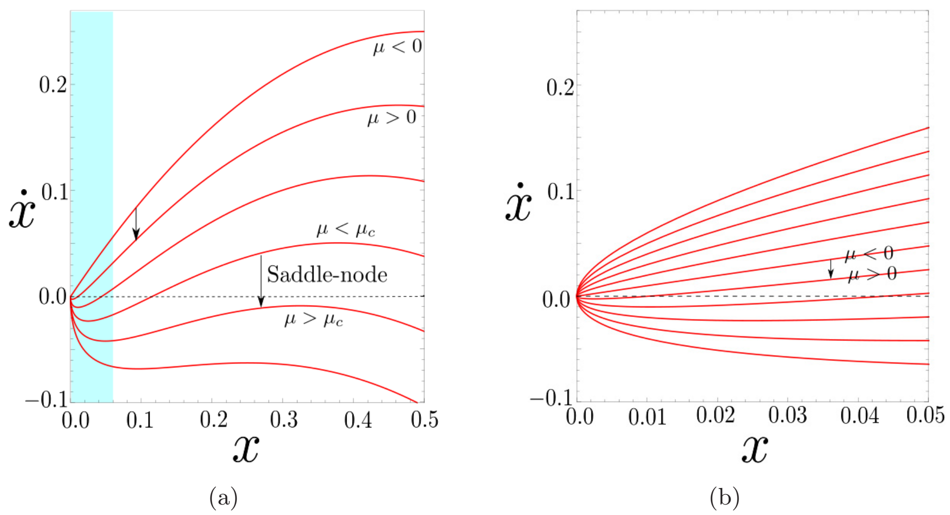

Fig. 5. *The function* $f(x) = x(1-x) - \mu x^{1/2}$ *for various* μ. (a) As we can see, two bifurcations occur as we increase μ from negative values to positive ones. The second bifurcation is a saddle-node bifurcation, while the first one is unknown to us. (b) A blow up of the blue region appearing in the previous figure. At $\mu = 0$ the sign of the slope and the curvature of the function $f(x)$ close to $x = 0$ change, allowing the appearence of a new fixed point and a switch of the stability of $x = 0$ from unstable to stable. We recall that $f'(x)$ becomes unbounded at $x = 0$, except for $\mu = 0$.

the absence of an immune response ($\mu = 0$), we simply have a logistic growth, where $x = 0$ is an unstable fixed point and $x = 1$ corresponds to a stable attractor. However, precisely at $\mu = 0$ a bifurcation occurs, and the unstable fixed point $x = 0$ gives birth to a second fixed point, becoming stable. This new fixed point arises through a change in the curvature of the function $f(x) = x(1-x) - \mu x^{1/2}$, as it is shown in Fig. 5. In the interval $\mu \in [0, \mu_c]$, where $\mu_c = 2/(3\sqrt{3})$, the tumor can exist below its original carrying capacity or it can be destroyed by the immune system, depending on its size at the time that the immune response is triggered. Finally, at $\mu = \mu_c$ a saddle-node bifurcation occurs and only the fixed point $x = 0$ remains. Therefore, when the immune response becomes strong enough, relative to the growth rate of the tumor, it can be effectively destroyed.

6. Conclusions

In summary, the shrinkage of a set from its boundary follows a power law decay. When the size of the set is fixed, those sets with higher boundary to interior ratio decay faster. This conclusion has some relevance in the context of immunotherapy, where cytotoxic T cells are tamed to destroy a tumor mass. It allows to estimate the speed at which the tumor is destroyed, as long as there is no severe immune cell infiltration. As it has been reasoned in previous works [López *et al.*, 2016], if the infiltration is severe, an exponential decay represents a better approximation. Finally, the ultimate fate of a growing tumor in the presence of an immune response, depends on the relative rate of lysis and growth μ. As we have shown, our bifurcation analysis suggests the existence of a threshold value of this parameter above which the complete destruction of the tumor is guaranteed, independently of its size at the beginning of the immune response. Nevertheless, even if we are below this threshold and the immune system is not capable of completely eradicating the tumor, its carrying capacity can be considerably reduced by a more active immune system (higher c), or by an increase of the tumor surface of contact (higher δ_0).

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