

A MODEL FOR THE GROWTH OF TUMORS: STATIONARY SOLUTIONS

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Abstract. We prove the existence of stationary solutions for a nonlinear problem modelling the growth of a nonnecrotic spheroid tumor in absence of inhibitor agents. We assume that the rate of consumption of nutrients by the cells is greater than the rate of transference of nutrients from the vasculature and that this balance is an increasing function of the nutrient concentration. The proliferation rate considered depends on the nutrient concentration and is given by either an increasing function or one that assumes only a negative minimum value. Some bounds for the stabilizing radius also are presented.

Keywords. Nonlinear free boundary problem, stationary solutions, growth of tumors, nonnecrotic tumors.

1. Introduction

In recent years a great number of mathematical models has been proposed in order to describe the growth of tumors. Most of them are free boundary value problems consisting of one or more reaction-diffusion equations and an equation derived from conservation of mass for tumor cells. The model we consider here is a nonlinear version of that one initially proposed by Greenspan (1972,1976), and recently studied by Byrne-Chaplain (1995) and Friedman-Reitich (1999), to describe the growth of a nonnecrotic tumor. In this paper we treat the existence of stationary solutions for this model.

In Section 2.1 we establish results of existence, uniqueness and localization of stationary solutions. The proliferation rate S , which depends only on the nutrient concentration σ , is supposed to be either an increasing function or one that assumes only a negative minimum value. In turn, the absorption rate $f(\sigma)$ is assumed to be a nondecreasing function, what is a natural assumption. These conditions are more general than that ones handled in some recent articles, see (Byrne-Chaplain, 1996; Cui-Friedman, 2001; Friedman-Reitich, 1999). In these articles, both the absorption and proliferation rates are linear functions.

The technique used to prove the existence of stationary solutions (sub- and supersolutions combined with finding zeroes of a function) is easy to handle in a computational approach to the problem. Our conclusions are also more general than the existence results described in the literature, where only linear functions are considered. Estimates on the radius of the stabilizing solutions are given. Since these estimates are quite general, we think that this article is an important step in the evaluation of the model considered.

A natural question posed by our results is the stability of the stationary solutions. We intend to treat this question in a future work.

2. Description of results

2.1 The nonnecrotic model

In the model, the tumor is basically regarded as a spherical mass of live cells, which receive nourishment not only by diffusion but also by its own vasculature (see Byrne et al., 1995). We consider here only the phase in which the tumor is nonnecrotic. This means that the concentration of nutrients remains above a critical, experimentally obtained value $\sigma_{nec} \geq 0$, which maintains the cells proliferation. Below this value, the formation of a necrotic core originates the necrotic phase of the tumor.

One of the equations of the model is a reaction-diffusion equation for the nutrient concentration $\sigma(r, t)$:

$$\epsilon \frac{\partial \sigma}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \sigma}{\partial r} \right) - f(\sigma), \quad 0 < r < R(t), \quad t > 0. \quad (1)$$

The boundary $R(t)$ of the tumor is unknown. The diffusion coefficient $\epsilon \ll 1$ is the ratio between the time scales of the nutrient diffusion and tumor growth. The reaction term $f(\sigma)$ is the balance between the rate of consumption of nutrients by the cells and the rate of transference of nutrients from the vasculature (Byrne-Chaplain, 1995; Friedman-Reitich, 1999). We assume that the function $f(\sigma)$, referred here as **absorption rate**, vanishes only at $\sigma = \sigma_0 \geq 0$. We suppose that the absorption rate is increasing for $\sigma \in (\sigma_0, \bar{\sigma}]$, where $\bar{\sigma}$ stands for the external nutrient concentration, which is considered to be constant. Therefore, if $\sigma > \sigma_0$, the consumption rate is greater than the transference rate and the balance between these rates decreases when the concentration of nutrients is decreasing.

The initial conditions for the unknowns $R(t)$ and $\sigma(r, t)$ are, respectively,

$$R(0) = R_0 \quad \text{and} \quad \sigma(r, 0) = \sigma_0(r), \quad 0 < r < R_0, \quad (2)$$

and the boundary conditions for σ are

$$\frac{\partial \sigma}{\partial r}(0, t) = 0 \quad \text{and} \quad \sigma(R(t), t) \equiv \bar{\sigma}, \quad t > 0. \quad (3)$$

(The condition on σ_r produces smooth solutions at the origin.) For compatibility, the initial data must satisfy $\sigma'_0(0) = 0$ and $\sigma_0(R_0) = \bar{\sigma}$.

The **second equation** of the model

$$R^2 \frac{dR}{dt} = \int_0^R S(\sigma(r, t)) r^2 dr \quad (4)$$

describes the evolution of the tumor radius $R(t)$ and is obtained (Greenspan, 1972) by applying mass conservation to the tumor, assuming that its rate of growth depends on the number of proliferating cells, which is measured by the **proliferation rate** $S(\sigma)$. This function is a balance between the birth (mitosis) and death (apoptosis) rates of cells. We assume that S is continuous and either monotonic on the interval $[\sigma_0, \bar{\sigma}]$ or that it assumes only one local extrema on this interval. However, supposing that the number of cells is growing when the nutrient concentration is $\bar{\sigma}$, it follows that $S(\bar{\sigma}) > 0$. And assuming that S increases in a neighborhood of $\bar{\sigma}$, our analysis is done when $S(\sigma)$ is either increasing on $[\sigma_0, \bar{\sigma}]$ or decreasing on $[\sigma_0, \Lambda]$ and increasing on $[\Lambda, \bar{\sigma}]$, Λ denoting the local minimum of S .

Similar models are consider in Adam (1996 - see also the references therein).

A **stationary solution** is an equilibrium configuration in which the radius of the tumor stabilizes. It is obtained as a pair $(\sigma_R(r), R)$ such that both the concentration of nutrients $\sigma_R(r)$ and the *stabilizing radius* R do not depend on the time t .

So, the stationary solutions for the system (1)-(4) are the solutions of the problem:

$$\begin{cases} (r^2 \sigma'_R)' = r^2 f(\sigma_R), & 0 < r < R, \\ \sigma'_R(0) = 0; & \sigma_R(R) = \bar{\sigma}; \\ \int_0^R S(\sigma_R(r)) r^2 dr = 0. \end{cases}$$

Putting $\lambda := R^2$, the change of variables $\sigma_\lambda(r) = \sigma_R(rR)$ transforms this system into the boundary value problem (BVP)

$$\begin{cases} (r^2 \sigma'_\lambda)' = \lambda r^2 f(\sigma_\lambda), & 0 < r < 1, \\ \sigma'_\lambda(0) = 0; & \sigma_\lambda(1) = \bar{\sigma}, \end{cases} \quad (5)$$

and the integral equation

$$\int_0^1 S(\sigma_\lambda(r)) r^2 dr = 0. \quad (6)$$

Therefore, a stationary solution for the system (1)-(4) is equivalent to a pair $(\sigma_\lambda, \lambda)$ satisfying (5)-(6).

In the next subsection we apply the method of sub- and supersolutions to obtain a family of solutions $\{\sigma_\lambda\}_{\lambda \geq 0}$ of (5). In Subsection 2.1.2 we solve the integral equation (6) and give an estimate for the stabilizing radius. Since the proofs of the results in this paper are technical, they will not be presented here.

Of course, our approach in this paper is more general than the method employed in Byrne-Chaplain (1995) or Friedman-Reitich (1999) to find stationary solutions. In that papers, both the absorption rate f and the proliferation rate S depend linearly on σ and thus gives rise to an explicit algebraic equation: finding a stationary solution is equivalent to solve this equation for $\sqrt{\lambda}$.

Remark 1 Since σ_{nec} is a experimentally obtained value, the relation between σ_0 and σ_{nec} is unclear: it may be, for example, $\sigma_0 < \sigma_{nec} < \bar{\sigma}$. Let the pair $(\sigma_{\lambda_*}, \lambda_*)$ denote a solution of the problem (5)-(6). Since we first solve equation (5) and then consider λ as a parameter in order to find a solution of equation (6), the stationary solution for the nonnecrotic model makes sense only when $\sigma_{\lambda_*}(r)$ is above σ_{nec} . This condition is fulfilled if $\sigma_{nec} \leq \sigma_0 < \bar{\sigma}$: as we shall see, $\sigma_\lambda(r) > \sigma_0$ for all $\lambda \geq 0$.

2.1.1 Solutions of the BVP

In this subsection we summarize the main properties of the solutions of the BVP (5).

Definition 2 A function $u_\lambda \in C^0([0, 1])$ is a **subsolution** of (5) if satisfies:

$$\begin{cases} (r^2 u'_\lambda)' \geq \lambda r^2 f(u_\lambda), & r \in [0, 1] \\ u'_\lambda(0) = 0, & u_\lambda(1) \leq \bar{\sigma}. \end{cases}$$

A function $v_\lambda \in C^0([0, 1])$ is a **supersolution** of (5) if satisfies:

$$\begin{cases} (r^2 v'_\lambda)' \leq \lambda r^2 f(v_\lambda), & r \in [0, 1] \\ v'_\lambda(0) = 0, & v_\lambda(1) \geq \bar{\sigma}. \end{cases}$$

Theorem 3 (Method of Sub- and Supersolutions) Let us suppose that, in problem (5), f is a lipschitzian function with constant k . Let u_λ and v_λ be, respectively, sub- and supersolution of that problem Then problem (5) has at least one solution σ_λ such that $u_\lambda \leq \sigma_\lambda \leq v_\lambda$.

The proof of theorem 3 is technical and can be found, e.g., in Figueiredo (1982).

Remark 4 The method of sub- and supersolutions is valid if $f \in C([\sigma_0, \bar{\sigma}])$ and if there exists a constant k such that $f(\sigma) - k\sigma$ is decreasing (a condition that is fulfilled when f is Lipschitz continuous). Its numerical implementation is simple (see also section 2.2): the method produces solutions of Eq. (5) given as limits of the iterative sequence $\{\sigma_n\}_{n=1}^{\infty}$, where

$$\begin{aligned} (r^2 \sigma'_{n+1})' - k\lambda r^2 \sigma_{n+1} &= \lambda r^2 (f(\sigma_n) - k\sigma_n) \\ \sigma'_{n+1}(0) &= 0; \quad \sigma_{n+1}(1) = \bar{\sigma}, \end{aligned}$$

for both $\sigma_1(r) \equiv \sigma_0$ and $\sigma_1(r) = \bar{\sigma}$.

Taking into account the uniqueness of solutions that we state below, both sequences have the same limit.

Our first result is:

Theorem 5 *If $f(\sigma) \in C^1([\sigma_0, \bar{\sigma}])$ is increasing and vanishes only at $\sigma = \sigma_0$, then, for each $\lambda \geq 0$, there exists a unique solution $\sigma_\lambda \in C^2([0, 1])$ of the BVP (5) satisfying*

$$\sigma_0 < \sigma_\lambda(r) \leq \bar{\sigma} \text{ for all } r \in [0, 1]. \quad (7)$$

The properties of u_λ (monotonicity w.r.t. r and λ , convexity and convergence to σ_0) are illustrated in the following figure:

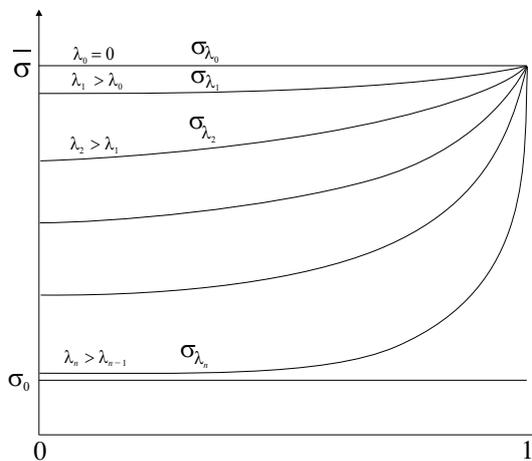


Figure 1: For each $\lambda \geq 0$, the functions σ_λ are convex and increasing. The sequence $\{\sigma_{\lambda_n}\}$ converges uniformly to σ_0 in compact subsets of $[0, 1)$ when $\lambda_n \rightarrow \infty$.

The proof of theorem 5 is technical and rests on a form of the maximum principle. The convexity of the solutions u_λ will make it possible to handle non-monotonous proliferation rates.

2.1.2 Stationary solutions

Let the pair $(\sigma_{\lambda_*}, \lambda_*)$ denote a solution of the problem (5)-(6). Then λ_* is obtained as a zero of the equation $I(\lambda) = 0$, where the continuous function $I : [0, \infty) \rightarrow \mathbb{R}$ is defined by

$$I(\lambda) = \int_0^1 S(\sigma_\lambda(r)) r^2 dr \quad (8)$$

and σ_λ is given by theorem 5.

In this case, the pair (σ_*, R_*) is a stationary solution for the system (1)-(4), where $R_* = \sqrt{\lambda_*}$ is the stabilizing radius and $\sigma_*(r) = \sigma_{\lambda_*}(r/R_*)$ for all $r \in [0, R_*]$.

Theorem 6 *If the continuous function $S(\sigma)$ satisfies the condition*

$$S(\sigma_0)S(\bar{\sigma}) < 0 \quad (9)$$

then there exists at least one positive value λ_ such $I(\lambda_*) = 0$. Moreover, if $S(\sigma)$ is also monotonic, then λ_* is unique.*

Proof. Since

$$I(0) = \int_0^1 S(\bar{\sigma}) r^2 dr = \frac{S(\bar{\sigma})}{3}$$

and

$$\lim_{\lambda \rightarrow \infty} I(\lambda) = \int_0^1 S \left(\lim_{\lambda \rightarrow \infty} \sigma_\lambda(r) \right) r^2 dr = \frac{S(\sigma_0)}{3},$$

the existence is consequence of the continuity of the function $I(\lambda)$. The uniqueness follows from the monotonicity of $I(\lambda)$. \square

We now handle more general cases. The proof of the next result is based on a geometrical construction that strongly depends on the convexity of σ_λ .

Theorem 7 *Suppose that, for some $\alpha \in (\sigma_0, \bar{\sigma})$, S is nondecreasing on $[\alpha, \bar{\sigma}]$ and*

$$\int_\alpha^{\bar{\sigma}} S(\sigma)(\sigma - \alpha)^2 d\sigma = 0. \quad (10)$$

Then there exists $\lambda_ > 0$ such that $I(\lambda_*) = 0$. Moreover,*

$$3 \frac{(\bar{\sigma} - \alpha)}{f(\bar{\sigma})} \leq \lambda_* \leq 6 \frac{(\bar{\sigma} - \alpha)}{f(\alpha)}. \quad (11)$$

Remark 8 Theorem 7 is also valid if $S \in C([\sigma_0, \bar{\sigma}])$ attains a minimum value at $\sigma = \Lambda \in (\sigma_0, \bar{\sigma})$, being decreasing if $\sigma \in [\sigma_0, \Lambda]$ and increasing if $\sigma \in [\Lambda, \bar{\sigma}]$. Under this situation, if $S(\sigma_0) \leq 0 < S(\bar{\sigma})$, we change (10) by

$$\int_\Lambda^{\bar{\sigma}} S(\sigma)(\sigma - \Lambda)^2 d\sigma \leq 0.$$

The technique applied in the last proof may also be used to obtain bounds for λ_* , even when S does not satisfy (10). As an example we cite

Proposition 9 *Suppose that the continuous function $S(\sigma)$ is increasing and satisfies $S(\sigma_0) < 0 < S(\bar{\sigma})$. Then*

$$\lambda_* \geq \max \left\{ \frac{3(\bar{\sigma} - \alpha)}{f(\bar{\sigma})}, \frac{6(\bar{\sigma} - \beta)}{f(\bar{\sigma})} \right\}, \quad (12)$$

where

$$\alpha = \min \left\{ \xi \in [\sigma_0, \bar{\sigma}] : \int_\xi^{\bar{\sigma}} S(\sigma)(\sigma - \xi)^2 d\sigma \geq 0 \right\}$$

and

$$\beta = \min \left\{ \eta \in [\sigma_0, \bar{\sigma}] : \int_\eta^{\bar{\sigma}} S(\sigma) \sqrt{\sigma - \eta} d\sigma \geq 0 \right\}.$$

Now we state the existence of solutions for (5)-(6) when neither (9) nor (10) are satisfied. From now on we assume that the proliferation rate $S \in C([\sigma_0, \bar{\sigma}])$ attains a minimum value at $\sigma = \Lambda \in (\sigma_0, \bar{\sigma})$, being decreasing if $\sigma \in [\sigma_0, \Lambda]$ and increasing if $\sigma \in [\Lambda, \bar{\sigma}]$. The proof of the result below is obtained by refining the technique used to demonstrate theorem 7.

Theorem 10 *Let S be as above. In addition, suppose that $S(\sigma_0) = 0 < S(\bar{\sigma})$ and*

$$\int_{\sigma_0}^{\bar{\sigma}} S(\sigma) d\sigma \leq 0.$$

Then there exists at least one λ_ such that $I(\lambda_*) = 0$. Moreover,*

$$\lambda_* \geq 6 \frac{(\bar{\sigma} - \Lambda)}{f(\bar{\sigma})}. \quad (13)$$

Remark 11 In the last Theorem, we can change S for a function that increases from σ_0 to a maximum value Λ and then decreases from Λ to $\bar{\sigma}$. However, the form of S stated in the Theorem appears to be more natural under the model considered. See section 2.3.

2.2 Numerical implementation

The analytical techniques used to solve problem (5)-(6) induces naturally a numerical method to deal with the problem. The numerical procedure described below was first intended to test this method and to compare our outputs with results given in other papers. Since the numerical outputs are coherent with the theoretical results obtained by us and other authors (for linear rates), we have in mind a rigorous analysis of our method.

To compare our results with those obtained by other authors, we consider

$$f(\sigma) = (\sigma - 0.3)(\sigma + 0.5), \quad S(\sigma) = 4\sigma \left(\frac{\sigma}{\bar{\sigma}} - 1 \right)$$

and

$$I(\lambda) = \int_0^1 S(\sigma_\lambda(r)) r^2 dr.$$

The values of $\bar{\sigma}$ are calculated from the given values of α by the equation

$$\bar{\sigma} = \frac{2(\alpha^2 + 3\alpha + 6)}{5(\alpha + 3)}, \quad \frac{\bar{\sigma}}{2} \leq \alpha \leq 1,$$

which is equivalent to Eq. (19).

In the figures below the graphs of $S(\sigma)$ and $I(\lambda)$ are shown, for $\alpha = 0.6, 0.7, 0.8$ and 0.9 . The interval $[\lambda_1, \lambda_2]$ is displayed, where

$$\lambda_1 = \frac{3(\bar{\sigma} - \alpha)}{f(\bar{\sigma})} = \frac{3(1 - \alpha)}{1.05}$$

e

$$\lambda_2 = \frac{6(\bar{\sigma} - \alpha)}{f(\alpha)} = \frac{6(1 - \alpha)}{(\alpha - 0.3)(\alpha + 0.5)}.$$

The zero λ_* of $I(\lambda)$ is to be found in this interval, according to theorem 7, what is confirmed by our numerical results.

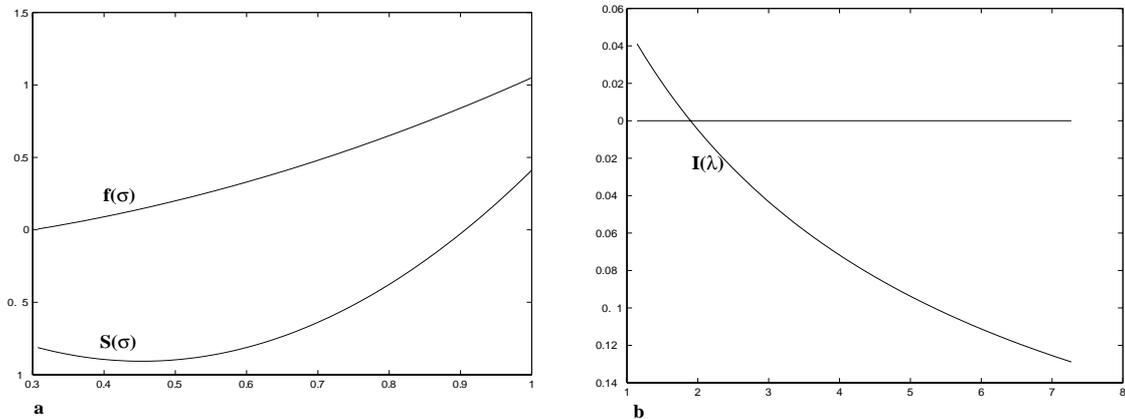


Figure 2: In Fig. (2) we have $\bar{\sigma}$ correspondent to $\alpha = 0.6$. The right-hand side (a) displays the graphs of $f(\sigma)$ and $S(\sigma)$. The left-hand side (b) displays $I(\lambda)$; the interval considered is $\lambda_1 \approx 1.1428$, $\lambda_2 \approx 7.2727$, and $\lambda_* \approx 1.8967$.

To approximate the functions $\sigma_* = \sigma_{\lambda_*}$ we used an iterative method based on super- and subsolutions (see remark 4), where two numerical sequences are generated, one departing from the subsolution and the other from the supersolution. Both sequences converge to the solution, which is unique (see theorem 5). One function of these sequences was chosen to represent the solution, when the difference between the functions of each sequence was less the 10^{-3} and also the difference between elements of both sequences. In each iteration, centered finite difference was used in a uniform 100 points grid. A maximum of 9 iterations was necessary, in the “critical case” correspondent to the least possible value for α . We point out, however, that we have no error analysis for the iterative method.

The simplest method was chosen to evaluate $I(\lambda)$: trapezoidal rule in a 100 points uniform grid. To find the zero λ_* of $I(\lambda)$, the bisection method with approximation of the order of 10^{-3} was used.

To compare our results with those obtained in other papers, we have considered the linear case

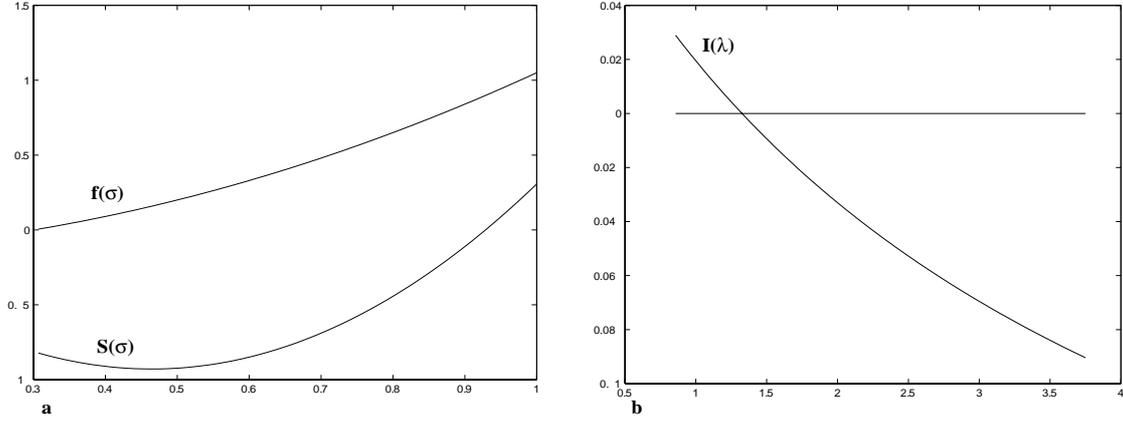


Figure 3: Here we have $\tilde{\sigma}$ correspondent to $\alpha = 0.7$. The right-hand side (a) displays the graphs of $f(\sigma)$ and $S(\sigma)$. The left-hand side (b) displays $I(\lambda)$; the interval considered is $\lambda_1 \approx 0.8571$, $\lambda_2 \approx 3.75$, and $\lambda_* \approx 1.3257$.

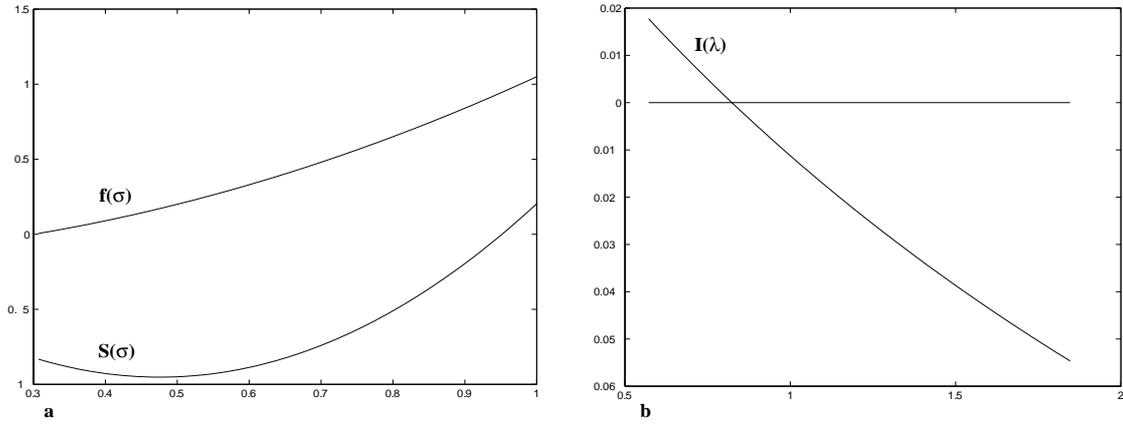


Figure 4: In Fig. (4) we have $\tilde{\sigma}$ correspondent to $\alpha = 0.8$. The right-hand side (a) displays the graphs of $f(\sigma)$ and $S(\sigma)$. The left-hand side (b) displays $I(\lambda)$; the interval considered is $\lambda_1 \approx 0.5714$, $\lambda_2 \approx 1.8462$, and $\lambda_* \approx 0.8232$.

$$f(\sigma) = \sigma \quad \text{and} \quad S(\sigma) = \sigma - \tilde{\sigma},$$

with $\sigma_0 = 0$, $\bar{\sigma} = 1$ and $0 \leq \tilde{\sigma} < 1$. It holds

$$\alpha = 4\tilde{\sigma}^{-3}, \quad \lambda_1 = 12(1 - \tilde{\sigma}) \quad \text{and} \quad \lambda_2 = \frac{24(1 - \tilde{\sigma})}{4\tilde{\sigma} - 3}, \quad \text{for } 0.75 < \tilde{\sigma} < 1.$$

Theorem 7 guarantees that

$$2.64 \leq \lambda_* \leq 44, \quad \text{if } \tilde{\sigma} = 0.78$$

and

$$0.48 \leq \lambda_* \leq 1.1429, \quad \text{if } \tilde{\sigma} = 0.96.$$

Using the numerical approach described above, we find

$$\lambda_* \approx 4.7697, \quad \text{if } \tilde{\sigma} = 0.78 \tag{14}$$

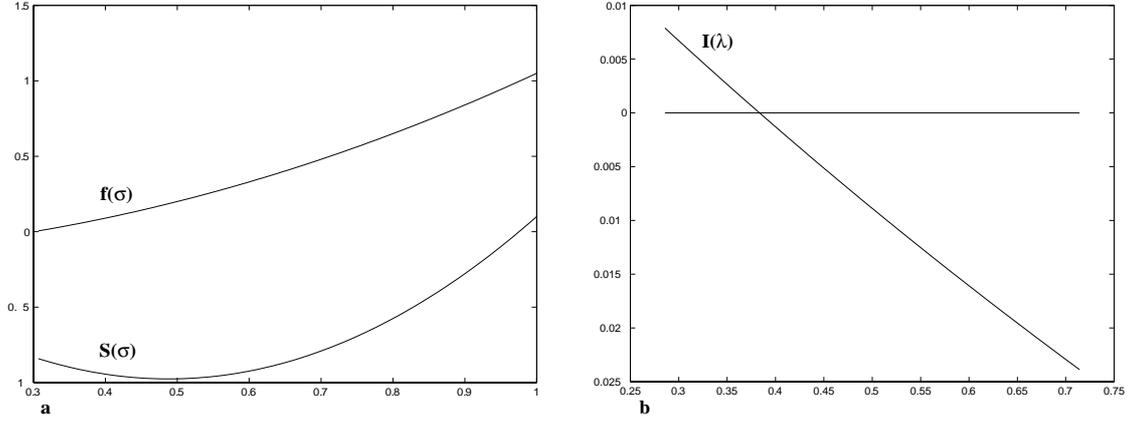


Figure 5: Here we have $\tilde{\sigma}$ correspondent to $\alpha = 0.9$. The right-hand side (a) displays the graphs of $f(\sigma)$ and $S(\sigma)$. The left-hand side (b) displays $I(\lambda)$; the interval considered is $\lambda_1 \approx 0.2857$, $\lambda_2 \approx 0.7143$, and $\lambda_* \approx 0.3832$.

and

$$\lambda_* \approx 0.6363, \quad \text{if } \tilde{\sigma} = 0.96. \quad (15)$$

However, as mentioned before, $\eta = \sqrt{\lambda_*}$ is obtained as a solution of an algebraic equation, namely

$$\tanh(\eta) = \frac{\eta}{1 + \Lambda\eta^2}, \quad (16)$$

where $\Lambda = \tilde{\sigma}/3 \in (0, 1/3)$. The approximate solutions of Eq. (16) are

$$\lambda_* = \eta^2 \approx 4.7681 \quad \text{if } \tilde{\sigma} = 0.78$$

and

$$\lambda_* = \eta^2 \approx 0.6362 \quad \text{if } \tilde{\sigma} = 0.96,$$

which are very close to our results, given by Eqs. (14) and (15).

Friedman-Reitich (1999) observed that the constant $\Lambda_{\text{crit}} = 0.2727\dots$ satisfies

$$\eta(\Lambda) < \frac{1}{\sqrt{\Lambda}}, \quad \text{if } \Lambda_{\text{crit}} < \Lambda < 1/3, \quad (17)$$

where $\eta(\Lambda)$ denotes the solution of Eq. (16) for $\Lambda \in (0, 1/3)$. The estimate we have obtained is

$$\eta(\Lambda) \leq 2\sqrt{\frac{3(1-3\Lambda)}{4\Lambda-1}}, \quad \text{if } 0.25 < \Lambda < \frac{1}{3}.$$

Our estimate is not only valid in a larger interval than that described in Eq. (17) but also better when Λ is very close to $1/3$. For example, when $\Lambda = 0.32$, we have

$$2\sqrt{\frac{3(1-3\Lambda)}{4\Lambda-1}} \approx 1.3093 < \frac{1}{\sqrt{\Lambda}} \approx 1.76781.$$

2.3 Comments

The logistic form $S(\sigma) = a\sigma(1 - \sigma/\tilde{\sigma})$ is considered in Byrne-Chaplain (1995), where $\tilde{\sigma}$ is a constant, the terms $a\sigma$ and $a\sigma^2/\tilde{\sigma}$ meaning the birth and death rates, respectively.

In this case, if $\sigma \in (0, \tilde{\sigma})$, it holds $S(\sigma) > 0$ and, if $\sigma > \tilde{\sigma}$, $S(\sigma) < 0$. Therefore,

$$0 \leq \sigma_0 < \tilde{\sigma} < \bar{\sigma} \quad (18)$$

is a necessary condition for the existence of stationary solutions, since $\sigma_\lambda(r) \in (\sigma_0, \bar{\sigma}]$ for all $\lambda \geq 0$ and $r \in [0, 1]$. So, it was impossible to find a stationary solution as a limit of evolutionary solutions in the numerical experiment presented in that paper, where $f(\sigma) = 2\sigma - 1.2$ and $\sigma_0 = \tilde{\sigma} = 0.6$.

If $\sigma_0 > 0$ in (18), there exists a stationary solution, since (9) is fulfilled. If $\sigma_0 = 0$ in (18) (which corresponds to an avascular tumor in Byrne-Chaplain (1995)), then the existence of λ_* may be proved as in Theorem 10, if $\int_{\sigma_0}^{\bar{\sigma}} S(\sigma) d\sigma > 0$ (see Remark 11).

However, (18) does not appear to be natural: it implies that $S(\bar{\sigma}) < 0$, that is, the proliferation rate is negative when the concentration of nutrients is maximal, and $S(\sigma)$ grows when this concentration decreases, until it reaches the maximum value $S(\tilde{\sigma}/2)$.

On the other hand, if we suppose a proliferation rate of the form

$$S(\sigma) = a\sigma \left(\frac{\sigma}{\tilde{\sigma}} - 1 \right),$$

then (18) is still a necessary condition for the existence of a stationary solution. Remark 8 then implies the existence of at least one stationary solution if

$$0 < \sigma_0 < \tilde{\sigma} < \bar{\sigma} \quad \text{and} \quad \int_{\tilde{\sigma}/2}^{\bar{\sigma}} \sigma \left(\frac{\sigma}{\tilde{\sigma}} - 1 \right) \left(\sigma - \frac{\tilde{\sigma}}{2} \right)^2 d\sigma \leq 0$$

or

$$\sigma_0 = 0 < \tilde{\sigma} < \bar{\sigma} \quad \text{and} \quad \int_{\sigma_0}^{\bar{\sigma}} \sigma \left(\frac{\sigma}{\tilde{\sigma}} - 1 \right) d\sigma \leq 0.$$

In the first case, we obtain the estimates

$$3 \frac{(\bar{\sigma} - \alpha)}{f(\bar{\sigma})} < \lambda_* < 6 \frac{(\bar{\sigma} - \alpha)}{f(\alpha)}$$

where $\alpha \in [\tilde{\sigma}/2, \bar{\sigma}]$ is such that

$$\int_{\alpha}^{\bar{\sigma}} \sigma \left(\frac{\sigma}{\tilde{\sigma}} - 1 \right) (\sigma - \alpha)^2 d\sigma = 0. \quad (19)$$

In the second case, we obtain the lower bound

$$\lambda_* > 6 \frac{(\bar{\sigma} - \tilde{\sigma}/2)}{f(\bar{\sigma})}.$$

2.4 Conclusion

The first theoretical results for the nonnecrotical model treated here were obtained by Friedman-Reitich (1999). Since both the absorption and proliferation rates considered there are linear functions, an explicit stationary solution is available. (We stress that Friedman-Reitich is mainly devoted to the stability of the stationary solution).

However, since the linearity of the absorption and proliferation rates is an approximation of the actual data, it is natural to consider more general rates. Of course, neither an explicit stationary solution nor an standard approach to the problem (5)-(6) is now at hand. Our approach suggests, as a byproduct, a numerical treatment for the problem and gives bounds for the stabilizing radius $R_* = \sqrt{\lambda_*}$. Comparing with the stabilizing radius for linear absorption and proliferations rates, our bounds did well.

With respect to the evolutionary problem (1) – (4), we have already some results concerning the stability of the stationary solution for small values of ϵ (a condition satisfied in actual conditions): if the solution $\sigma(r, t)$ stabilizes, it converges monotonically to the stationary solution σ_{λ_*} presented in this paper. Since the stabilizing radius R^* can be numerically computed when the absorption and proliferations rates are known, this would imply, for example, that if a tumor has radius $R_0 = R(t_0) < R_*$ for some time $t = t_0$ and $R_1 = R(t_1) > R_*$ for $t = t_1 > t_0$, then either no stationary solution will be achieved or the tumor will pass to the necrotic phase.

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