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TIME DELAY IN NECROTIC CORE FORMATION

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Abstract. A simple model of avascular solid tumor dynamics is studied in the paper. The model is derived on the basis of reaction-diffusion dynamics and mass conservation law. We introduce time delay in a cell proliferation process. In the case studied in this paper, the model reduces to one ordinary functional-differential equation of the form that depends on the existence of necrotic core. We focus on the process of this necrotic core formation and the possible influence of delay on it. Basic mathematical properties of the model are studied. The existence, uniqueness and stability of steady state are discussed. Results of numerical simulations are presented.

1. **Introduction.** The process of tumor growth and its dynamics is one of the most intensively studied processes in recent years. Many papers devoted to it have appeared (cf. [2, 3, 6, 8, 11, 18] and references therein). This process can be divided into several different stages, starting from the very early stage of a solid tumor without a necrotic core inside (cf. [6]). In the present paper, we focus on the next stage, that is, the process of necrotic core formation. In this stage, there are three main cellular processes: proliferation, apoptosis, and necrosis. It should be noted that solid tumor growth leads to limited size, which is shown theoretically (compare [17, 19]) and experimentally ([1, 3, 9, 11, 20]) as well.

Following [8], we introduce time delay to the model studied in this paper. In [6], the model with delay in the proliferation process was analyzed in more detail, while in [11] the model of necrotic core formation without time delay was considered. On the other hand, the model studied in [6] does not include a process of necrotic core formation. The aim of this paper is to derive and analyze the model of necrotic core formation with the presence of time delay in the proliferation process, as proposed in [8]. We focus on passing from the model without necrotic core to the model with its presence, with delay in both cases. Our main interest is to study existence and stability of critical points depending on the delay parameter as well as the uniqueness of such a point, which was not considered in [8] or in [11].

The model we study is based on the idea of symmetric growth of avascular multicellular spheroids (MCS), which was described in [8]. It is assumed that the tumor growth depends on the nutrient (such as glucose or oxygen) concentration. However, the mean time of the nutrient diffusion is much shorter then the mean

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time of tumor doubling, which leads to a quasi-steady-state approximation. The following notation is used in this paper:

- $R(t)$ and $R_{\rm nec}(t)$ denote the external and necrotic radius of MCS,respectively, at time t.
- σ_∞ denotes the external concentration of nutrients, which is assumed to be constant; σ_N is the minimal nutrient concentration needed for proliferation; $\sigma = \sigma_\infty - \sigma_N$ and we assume $\sigma > 0$.
- Γ, a, and b are positive coefficients of proliferation, apoptosis, and necrosis, respectively.

In the derivation of the model in [8] and then in [6, 7, 11, 12] some scaling constant s appears. In this paper, we use $s = 1$ for simplicity, as in [6, 7, 12]. In [8], the curvature γ of MCS is also taken into account. To simplify calculations we study the model without it.

Following [8], we introduce time delay to the model, namely, in the proliferation process. A heuristic argument for introducing time delay is the duration of the mitosis process, which could be important. Time delays can also be introduced for other cellular processes (compare [7, 8, 12, 13]) or for the next stages of tumor growth, for example, for angiogenesis as in [4], where delays explain oscillations that appear in vascular tumor growth [14].

Finally, in the case of the presence of a necrotic part, the tumor evolution is governed by the following system of equations (see [8] for the detailed derivation)

$$\sigma = \frac{\Gamma}{6R}(R - R_{\rm nec})^2(R + 2R_{\rm nec})\,, \tag{1a}$$

$$\begin{aligned} R^2(t)\frac{dR}{dt} &= G(R(t-\tau), R_{\rm nec}(t-\tau)) - \frac{1}{3}(aR^3(t) - (b-a)R_{\rm nec}^3(t)) \\ &\stackrel{\rm def}{=} f_0(R(t), R(t-\tau))\,, \end{aligned} \tag{1b}$$

where

$$G(R, R_{\rm nec}) = \frac{\Gamma}{30}\left(R^5 - R_{\rm nec}^5\right) - \frac{\Gamma}{6}R^2R_{\rm nec}^2(R - R_{\rm nec}) + \frac{\sigma_N}{3}\left(R^3 - R_{\rm nec}^3\right)$$

and $R_{\rm nec}$ is described by the implicit function of R in equation (1a).

2. **Derivation and analysis of the model.** At the beginning of this section, we notice that equations (1) are well posed only if there exist solutions $R_{\rm nec}(t)$ and $R_{\rm nec}(t-\tau)$ to (1a) for $R = R(t)$ and $R = R(t-\tau)$, respectively, and $R_{\rm nec}(t) < R(t)$ and $R_{\rm nec}(t-\tau) < R(t-\tau)$. Now we derive a final model and study the existence and properties of solutions to it.

Equation (1a) defines the implicit function that describes the connection between R and $R_{\rm nec}$. Following the analysis presented in [11], we obtain that if R is small (i.e. $R \le \tilde{R} = \sqrt{\frac{6\sigma}{\Gamma}}$), then there is no positive solution to equation (1a) and then it is reasonable to assume that $R_{\rm nec} = 0$. On the other hand, if

$$R > \tilde{R} = \sqrt{\frac{6\sigma}{\Gamma}}\,, \tag{2}$$

then equation (1a) has exactly one positive solution.

We consider four cases.

If $R(t-\tau) > \tilde{R}$ and $R(t) > \tilde{R}$, then the tumor growth is described by equations (1).

If $R(t-\tau) > \tilde{R}$, but $R(t) \le \tilde{R}$, then we get

$$R^2(t)\frac{dR}{dt} = G(R(t-\tau), R_{\text{nec}}(t-\tau)) - \frac{1}{3}aR^3(t) \stackrel{\text{def}}{=} f_1(R(t), R(t-\tau))\,. \quad (3)$$

If $R(t-\tau) \le \tilde{R}$ we should exclude the parameter σ_N, which is connected with the necrosis process. Therefore, equation (1a) yields $\sigma_N = \sigma_\infty - \frac{\Gamma}{6}R^2(t-\tau)$. Then equation (1b) takes the form

$$R^2(t)\frac{dR}{dt} = \frac{1}{3}\left(-\frac{\Gamma}{15}R^5(t-\tau) + \sigma_\infty R^3(t-\tau) - aR^3(t)\right) \stackrel{\text{def}}{=} f_2(R(t), R(t-\tau)) \quad (4)$$

if $R(t) \le \tilde{R}$ and

$$\begin{aligned} R^2(t)\frac{dR}{dt} &= \frac{1}{3}\left(-\frac{\Gamma}{15}R^5(t-\tau) + \sigma_\infty R^3(t-\tau) - aR^3(t) + (a-b)R^3_{\text{nec}}(t)\right) \\ &\stackrel{\text{def}}{=} f_3(R(t), R(t-\tau)) \end{aligned} \quad (5)$$

if $R(t) > \tilde{R}$.

Combining equations (1b), (3), (4), and (5), we obtain the final model

$$R^2(t)\frac{dR}{dt} = \begin{cases} f_0(R(t), R(t-\tau)) & \text{if } R(t) > \tilde{R} \text{ and } R(t-\tau) > \tilde{R}\,; \\ f_1(R(t), R(t-\tau)) & \text{if } R(t) \le \tilde{R} \text{ and } R(t-\tau) > \tilde{R}\,; \\ f_2(R(t), R(t-\tau)) & \text{if } R(t) \le \tilde{R} \text{ and } R(t-\tau) \le \tilde{R}\,; \\ f_3(R(t), R(t-\tau)) & \text{if } R(t) > \tilde{R} \text{ and } R(t-\tau) \le \tilde{R} \end{cases} \quad (6)$$

with an initial condition $R(t) = R_0(t)$ for $t \in [-\tau, 0]$ and some positive continuous function R_0. The right-hand side of equation (6) is a continuous Lipschitz function of $R(t)$ and $R(t-\tau)$. This implies that the model is well posed and that its solutions exist and are unique (see [16]).

Notice that $\bar{R} = \sqrt{\frac{15}{\Gamma}(\sigma_\infty - a)}$ is the steady state for equation (4). We focus on the process of necrotic core formation, and hence, $R_0(t) < \tilde{R}$ for all $t \in [-\tau, 0]$; that is there is no necrotic part at the beginning. We have two cases:

1. If $\bar{R} < \tilde{R}$ or, equivalently, $3\sigma_\infty + 2\sigma_N < 5a$, then $\sigma_\infty < \frac{5a}{2} < 4a$. Consequently, Theorem 2.1 from [6] implies that the steady state $\bar{R}$ is stable independently of τ. Following the proof of Theorem 3.1 from [6], we prove that if the initial data satisfies $R_0(t) < \tilde{R}$, then the steady state $\bar{R}$ is globally stable. Hence, no necrotic core is formed in this case.
2. If $\bar{R} > \tilde{R}$, then following the proof of Theorem 3.1 from [6] we show that $R(t)$ reaches the level $\tilde{R}$ for some $t > 0$ and the necrotic core is formed.

For the necrotic core formation, the only interesting case is the second one. Hence, combining the inequality that defines the second case with the assumption $\sigma > 0$, one gets

$$5a < 3\sigma_\infty + 2\sigma_N < 5\sigma_\infty\,. \quad (7)$$

As in [11], the asymptotic behavior of $R_{\text{nec}}(R)$ can be approximated as follows:

$$R_{\text{nec}}(R) \sim R - \sqrt{\frac{2\sigma}{\Gamma}} - \frac{2\sigma}{3\Gamma}\frac{1}{R}\,, \quad \text{as} \quad R \to +\infty\,.$$

On the other hand, if $R_{\rm nec} \to 0$ (i.e. $R \to \tilde{R}$), the asymptotic is the following:

$$R_{\rm nec}(R) = \sqrt{\frac{4\sigma}{\Gamma} - \frac{4\sigma}{\Gamma R}\sqrt{\frac{6\sigma}{\Gamma}}}\,.$$

Using the formula for $R'_{\rm nec}(R)$ that was calculated in [11], we have

$$\frac{d}{dR}\left(R - R_{\rm nec}(R)\right) = 1 - \frac{R^2 + RR_{\rm nec} + R_{\rm nec}^2}{3RR_{\rm nec}} = -\frac{(R - R_{\rm nec})^2}{3RR_{\rm nec}} < 0\,.$$

This yields that the size of the proliferation ring decreases as the tumor radius increases and give the following estimate for $R_{\rm nec}$:

$$\sqrt{\frac{2\sigma}{\Gamma}} \leq R(t) - R_{\rm nec}(t) \leq \sqrt{\frac{6\sigma}{\Gamma}}\,. \tag{8}$$

The same analysis as in [11] shows that there exists at least one steady state $\bar{R}$. In the next section we focus on the problem of the uniqueness and stability of $\bar{R}$.

LEMMA 1 (nonnegativity). *For any nonnegative initial datum, the solution to* (6) *is nonnegative.*

Proof: Notice that if a solution to our model is negative, then there exists time t_0 such that $R(t_0) = 0$. If $R(t_0 - \tau) < \tilde{R}$, then the solution fulfills equation (4), and analysis presented in [6] yields that it cannot be negative. On the other hand, if $R(t_0 - \tau) > \tilde{R}$, then the inequality

$$G(R, R_{\rm nec}) = \frac{\Gamma}{30}\left(R - R_{\rm nec}\right)^3\left(R^2 + 3RR_{\rm nec} + R_{\rm nec}^2\right) + \frac{\sigma_N}{3}\left(R^3 - R_{\rm nec}^3\right) > 0$$

holds, and theorems from [5] yield that solutions to our model are nonnegative. ■

LEMMA 2 (global existence). *Let an initial datum $R_0(t) \geq 0$ for all $t \in [-\tau, 0]$. Then for any $t > 0$ the following inequality*

$$R(t) \leq \max\left\{\sup_{t\in[-\tau,0]} R_0(t), \left(\sigma_\infty - a + \sqrt{3}\right)\tilde{R}\right\} = R_{max} \tag{9}$$

holds and the solution is globally defined.

Proof: Assume that inequality. (9) does not hold for some time $t > 0$. Because of continuity of R, there exists time t_0 such that $R(t_0) = R_{\rm max}$, $R(t) \leq R_{\rm max}$ for any $t < t_0$, and $R'(t_0) \geq 0$. The estimates (8) yields

$$R^2\frac{dR}{dt} \leq R_{\rm max}^2\left(\left(\sigma_\infty - a + \sqrt{3}\right)\tilde{R} - R_{\rm max}\right) < 0\,,$$

which contradicts the assumption $R'(t_0) > 0$. The upper estimates together with nonnegativity of the solution yield that it is globally defined. ■

3. **Steady state.** It is obvious that a trivial steady state always exists. For its stability, we refer to [6]. In this section, we focus on the problem of uniqueness of the positive steady state for (6) in the case when a formation of a necrotic core is possible. To reduce the number of coefficients, we denote

$$\beta_1 = \frac{10\sigma_N}{\Gamma}\,, \qquad \beta_2 = \frac{10a}{\Gamma}\,, \qquad \beta = \beta_1 - \beta_2\,, \qquad \gamma = \frac{10b}{\Gamma}\,, \qquad \eta = \sqrt{\frac{6\sigma}{\Gamma}} = \tilde{R}\,.$$

Thus, we can rewrite the right-hand side of equation (1b) in the form

$$\frac{\Gamma}{30}F(x,y) = \frac{\Gamma}{30}\left((x-y)^3(x^2+3xy+y^2) + \beta(x-y)(x^2+xy+y^2) - \gamma y^3\right)\,, \quad (10)$$

and equation (1a) as

$$\eta^2 x = (x-y)^2(x+2y)\,. \quad (11)$$

First we state the following lemma

LEMMA 3. *Let $\gamma > 0$, $\eta > 0$, $\beta > 0$, $\eta > 0$, and*

$$\gamma < \left(\frac{12}{11}\left(6+\sqrt{3}\right) - 1\right)\beta \sim 7.43\beta\,. \quad (12)$$

Let $y(x)$ be a solution to (11) having the property $0 \le y(x) \le x$. Then there is a unique solution to equation $F(x, y(x)) = 0$ for $x \ge \eta$.

Proof: Denote a solution to $F(x, y_0) = 0$ by $y_0(x)$. Notice first, that function y_0 is well defined for $x > \eta$. Indeed, $F(x, 0) = x^3(x^2 + \beta) > 0$ for $x > \eta$ if $\eta^2 + \beta > 0$. On the other hand,

$$\frac{\partial F}{\partial y}(x,y) = -5y(x-y)^2(y+2x) - 3(\beta+\gamma)y^2 < 0\,.$$

and for any fixed x_0 $\lim_{y\to+\infty} F(x_0, y) = -\infty$.

Using an implicit-function theorem we obtain:

$$y'(x) = \frac{x^2+xy+y^2}{3xy}\,,$$
$$y_0'(x) = \frac{5x(x-y)^2(x+2y) + 3\beta x^2}{5y(x-y)^2(y+2x) + 3(\beta+\gamma)y^2}\,.$$

We would like to show that $y' - y_0'$ grows. This yields that $y - y_0$ has at most one extreme and this gives that there exists only one solution to $F(x, y(x)) = 0$, since the number of solution to $F(x, y(x)) = 0$ is odd. We subtract and then differentiate $y'(x) - y_0'(x)$ with respect to x. Since the denominator is positive, we consider only the nominator, which has the form

$$\begin{aligned}
\bar{V}(x,y) =& 25(x-y)^5(x+2y)(2x^4+2x^3y+9x^2y^2+4xy^3+y^4) && (13a)\\
&+30(x-y)^3\Big(\beta(x+y)(3x^4+x^3y+9x^2y^2+3xy^3+2y^4) && (13b)\\
&\qquad + \gamma y(x+2y)(x^3+5x^2y+2xy^2+y^3)\Big) && (13c)\\
&+9\beta^2 y(x-y)(x+2y)(2x+y)(3x^3-2xy+y^2) && (13d)\\
&+18\beta\gamma y(x-y)(x+2y)(3x^3-x^2y+y^3) && (13e)\\
&-9\gamma^2y^2(x-y)^2(x+2y)(x+y)\,. && (13f)
\end{aligned}$$

Notice that for $\beta > 0$ lines (13a)–(13c) are nonnegative. Hence, we consider the second part of $\bar{V}$, presented in lines (13d)–(13f). Subtracting a common part $9y(x-y)(x+2y)$, which is positive, we consider

$$V(x,y) = \beta^2(2x+y)(3x^3-2xy+y^2) + 2\beta\gamma(3x^3-x^2y+y^3) - \gamma^2 y(x-y)(x+y)\,.$$

We show that $V(x,y) > 0$, assuming that $\frac{\eta}{\sqrt{3}} \leq x-y \leq \eta$. Algebraic manipulations leads to

$$V(x,y) = (\beta+\gamma)(6\beta x^3 - (\beta+\gamma)x^2y + (\beta+\gamma)y^3)\,.$$

Substituting $\mu = \frac{\beta+\gamma}{6\beta}$, and using the assumption $\frac{\eta}{\sqrt{3}} \leq x-y \leq \eta$, we obtain

$$\frac{1}{6\beta(\beta+\gamma)}V(x,y) = x^3 - \mu x^2 y + \mu x y^2 \geq x^3 - \mu x^2(x-\frac{\eta}{\sqrt{3}} + \mu x(x-\eta)^2 = g(x)\,.$$

Therefore,

$$g(x) = x\left(x^2 - \frac{6-\sqrt{3}}{3}\mu\eta x + \mu\eta^2\right).$$

It can be readily calculated that the assumptions of Lemma 3 give $g(\eta) > 0$. Calculating the roots of $g(x)$, we obtain that the greatest root is the following:

$$x_1 = \frac{1}{2}\left(\mu\eta\left(\frac{6-\sqrt{3}}{3}\right) + \sqrt{\mu^2\eta^2\left(\frac{6-\sqrt{3}}{3}\right)^2 - 4\mu\eta^2}\right).$$

It can be easily calculated that $x_1 < \eta$, because of the assumptions of the lemma. Thus, $g(x) > 0$ for $x > \eta$, and the proof is completed. ■

Analogous calculations lead to the following estimate. There exists a unique positive steady state if the condition

$$27\gamma^4 < 14K\beta^2\,,\ \text{with } K = \frac{100}{9}\eta^4 + 15\eta^2\beta + 20\eta^2\gamma + 18\beta\gamma\,,$$

is fulfilled.

Using Lemma 3 we can readily prove the following theorem

THEOREM 4. *Let the assumptions of Lemma 3 be fulfilled and all coefficients be positive. Then there exists a unique positive steady state $\hat{R}$ of model* (6)*. Moreover $\hat{R} > \sqrt{\frac{6\sigma}{\Gamma}}$, and it is asymptotically stable independently of the magnitude of τ.*

Proof: First, notice that (7) is equivalent to (12). Hence, Lemma 3 yields that the steady state exists and is unique.

To study the stability of the steady state, we substitute $x(t) = R^3(t)$ and $y(t) = R^3_{\text{nec}}(t)$. Let

$$\zeta(x,y) = (\sqrt[3]{x} - \sqrt[3]{y})^3(\sqrt[3]{x^2} + 3\sqrt[3]{xy} + \sqrt[3]{y^2}) + \beta_1(x-y)\,.$$

Hence, equation (1b) takes the form

$$\dot{x} = \frac{\Gamma}{30}\zeta(x(t-\tau), y(t-\tau)) - (\beta_2(x(t)-y(t)) + \gamma y(t))\ .$$

Without loss of generality, we may assume that $\frac{\Gamma}{30} = 1$ (we can rescale time to eliminate this coefficient). Thus, we have

$$\dot{x} = \zeta(x(t-\tau), y(t-\tau)) - (\beta_2(x(t)-y(t)) + \gamma y(t))\ . \tag{14}$$

Calculating the characteristic quasi polynomial at the steady state $\bar{x}$ and denoting $\bar{y} = y(\bar{x})$, one obtains

$$W(\lambda) = \lambda - Ae^{-\lambda\tau} - B\,, \tag{15}$$

where

$$\begin{aligned} A =& \frac{5(\sqrt[3]{\bar{x}} - \sqrt[3]{\bar{y}})^3(\sqrt[3]{\bar{x}^2} + 4\sqrt[3]{\bar{x}\bar{y}} + \sqrt[3]{\bar{y}^2})}{9\bar{x}} \\ &+ \frac{\beta_1(\sqrt[3]{\bar{x}} - \sqrt[3]{\bar{y}})(3\sqrt[3]{\bar{x}^2} + 2\sqrt[3]{\bar{x}\bar{y}} + \sqrt[3]{\bar{y}^2})}{3\bar{x}}\,, \end{aligned} \tag{16}$$

$$B = -\frac{\beta_2(\sqrt[3]{\bar{x}} - \sqrt[3]{\bar{y}})(3\sqrt[3]{\bar{x}^2} + 2\sqrt[3]{\bar{x}\bar{y}} + \sqrt[3]{\bar{y}^2})}{3\bar{x}} - \frac{\gamma\sqrt[3]{\bar{y}}(\sqrt[3]{\bar{x}^2} + 4\sqrt[3]{\bar{x}\bar{y}} + \sqrt[3]{\bar{y}^2})}{3\bar{x}} \tag{17}$$

For $\tau = 0$, the uniqueness of the steady state and the condition $F(\eta, 0) > 0$ imply that the steady state is stable and $A + B < 0$. It is easy to see that $B - A < 0$ for every positive parameter that implies stability of $\hat{R}$ independently of τ, for details see [10]; compare also [15]. ■

4. **Numerical simulations and discussion.** In this section we present the results of numerical simulations. The aim of these simulations is to compare the behavior of solutions to the model presented in this paper with the models that do not consider the necrotic core formation as well as illustrate some possible behavior of the solution to model (6). We also study dependence of solutions on the model parameters, particularly on time delay. Theorem 4 implies that for a wide range of coefficients there should be no quantitative change in the behavior of the solutions. At the beginning, we use the following values of parameters:

$$\sigma_\infty = 12.0\,, \quad \sigma_N = 1.0\,, \quad \Gamma = 30.0\,, \quad a = 2.0\,, \quad b = 2.0\,, \quad \tau = 0.6\,. \tag{18}$$

In this case, the coefficients used in section 3 are the following

$$\beta = -\frac{1}{3}\,, \qquad \gamma = \frac{2}{3}\,, \qquad \eta = \sqrt{2.2} \sim 1.48\,.$$

The constant function $R_0(t) = R_0 = 0.5$ is taken as an initial one. The notation used in the figures is the following: the solid line (R_1) denotes the tumor radius in the model with necrotic core formation; the dashed line (R_{nec}) describes the radius of the necrotic core; and the dotted line (R_2) describes the radius of tumor without necrotic core formation. The stars denote points at which the tumor radius reaches the level $\bar{R}$; that is the level at which the necrotic core is forms (or disappears).

First, notice that periodic solutions which appear in the model without necrotic core formation are not present if we consider this process (see Figure 1). The coefficients used in the cases presented in Figure 1 do not fulfill the assumption of Theorem 4, since $\beta < 0$. The case where $\beta > 0$ but inequality (12) do not hold is presented in Figure 2. It turns out that for a wide range of coefficients the dependence of solutions on time delay is not relevant.

Figure 1 also show the dependence of the solution on parameters Γ and σ_N. If we put Γ small, then (as it could be expected) the tumor growth is slower at the beginning. However, the behavior of solutions for greater values of time t is similar to those with larger Γ. In fact, notice that changes of Γ do not change condition (12).

In Figure 3 and on the right-hand side of Figure 2, the solutions form "stairs". Notice, that solutions stabilize very fast at some level. When, after some time,

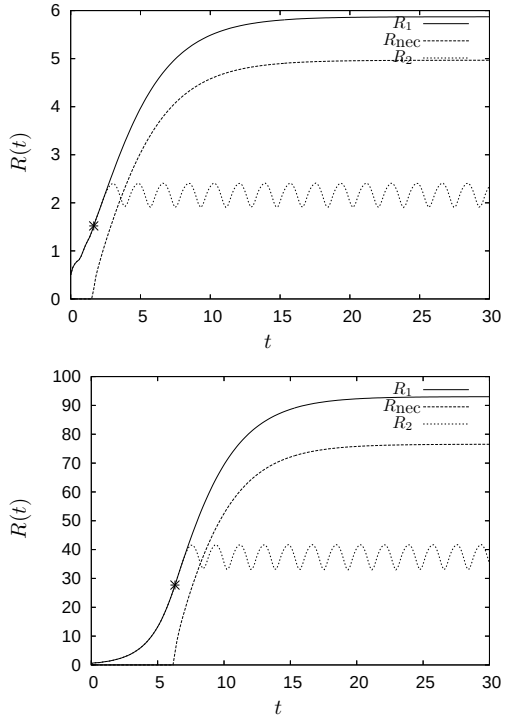

FIGURE 1. In the left-hand side graphs coefficients as stated in (18), while in the right-hand side $\sigma_N = 0$ and $\Gamma = 0.1$.

delayed functions reach the higher values the solution grows very rapidly to the new quasi-steady state. This behavior suggests that the convergence of solutions under the given assumptions, constant delayed function, this is when $R(t-\tau)$ is constant, is very fast. Notice that the time the solution needs to approximate to the steady state is greater for larger values of the delay parameter. These are the only observed influences of time delay.

We would like to point out that in the cases presented in Figure 3, solutions to the model without necrotic core formation become negative very fast (for t around 4 for the case presented in the left-hand side of figure 3 and for t around 12 for the case presented in the right-hand side).

The conclusion is that the process of necrotic core formation is very important. The behavior of solutions is more stable in this case. Theorem 4 yields that for a wide range of coefficients the steady state is asymptotically stable. On the other hand, computer simulations suggest that the assumptions of Theorem 4 can be weakened.

The analysis shows that if $\bar{R} < \tilde{R}$, then the steady state is globally stable. Simulations suggest that it remains stable when the necrotic core is formed.

Next, we study the dependence on the minimal nutrient concentration σ_N. Although the qualitative behavior is similar for all positive values of σ_N, the surprising numerical result is that the steady state is not a decreasing function of σ_N (see Figure 4). For $\sigma_N = 0$ the tumor radius stabilizes around 4.2; then, this level increases

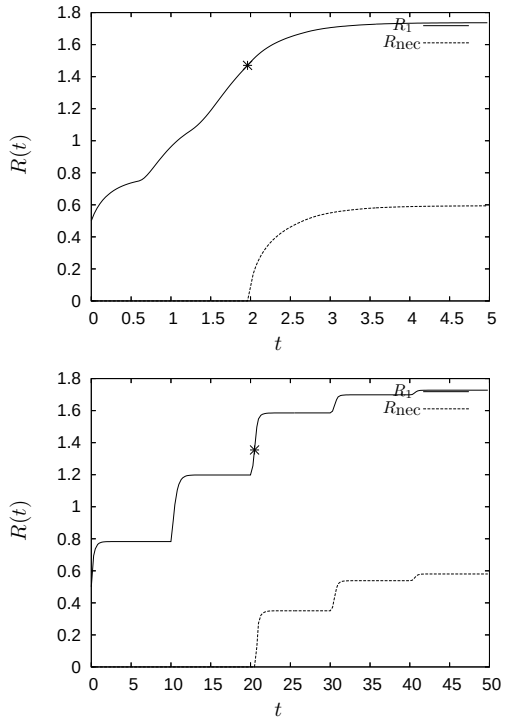

FIGURE 2. In the left-hand side graphs $b = 90$, in the right-hand side graph $b = 90$ and $\tau = 10$.

and the maximal value is achieved for σ_N between 6 and 7 and then the value of the steady state decreases.

On the other hand, the width of the proliferation ring decreases as σ_N increases (i.e., σ decreases), which could be expected.

Finally, we want to suggest that delay may be important. Figure 5 show that undumping oscillations may arise. However, to obtain it, negative values of parameter σ_N were used, which implies that the assumptions of Theorem 4 are not valid for this case. Hence, there is no way to consider it from the biological point of view.

For the values of coefficients used in the simulations, the qualitative behavior of the model (6) with different values of the delay parameter is similar to the model without delay presented in [11]. However, for large values of time delay, the influence of the delay is noticeable (see Figure 3) On the other hand, Figure 5 shows that delay could be important for some values of parameters. However, we have shown only that the steady state is locally stable for some range of parameters, the results of the simulations suggest that there might exist only one globally stable steady state for any nonnegative coefficients. The solutions to model (6) are more stable than the solutions to the model presented in [6], in which the process of necrotic core formation was not considered.

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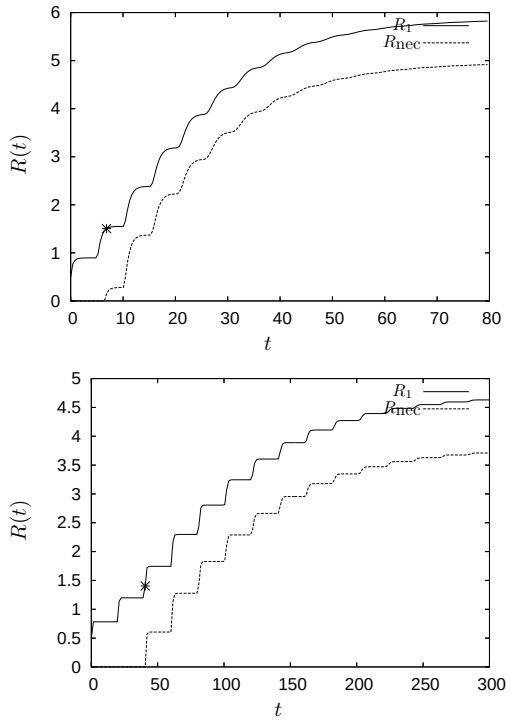

FIGURE 3. Comparison of solutions to the model with necrotic core formation depending on parameter τ. For the left-hand side $\tau = 5$, for the right-hand side and $\tau = 20$, and $a = 3.0$.

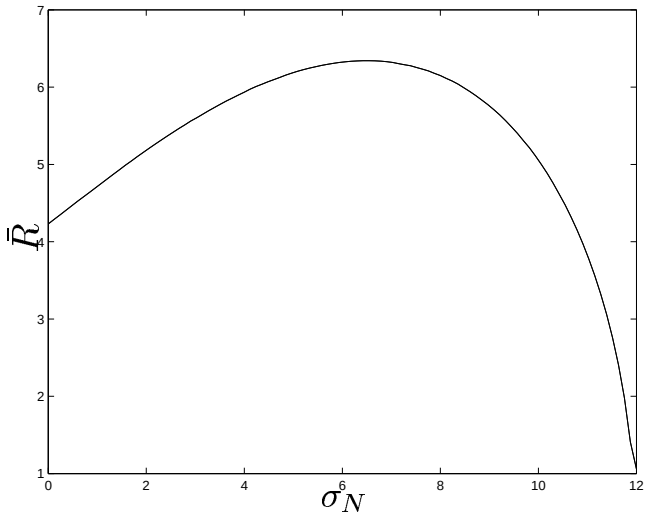

FIGURE 4. The dependence of the value of the steady state (shown on the vertical axis) on the minimal nutrient coefficient σ_N (shown on the horizontal axis).

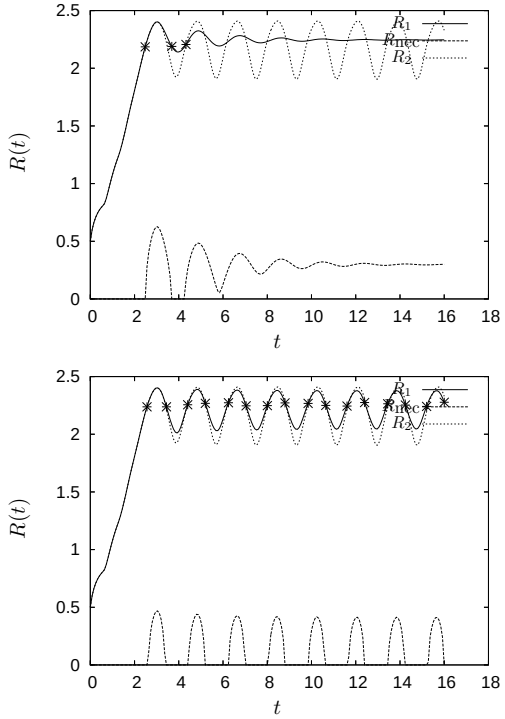

FIGURE 5. Comparison of solutions to the model with necrotic core formation depending on parameter σ_N. In the left-hand side $\sigma_N = -12$, in the right-hand side $\sigma_N = -14$.

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