Applied Mathematical Sciences, Vol. 2, 2008, no. 6, 293 - 304

Attractiveness of a Positive Steady State in a Population Tumor Growth Model with Quiescence

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Abstract

We are interested in the asymptotic behavior of solutions of a dynamic population tumor cells model, having a trivial and a possible nontrivial stationary equilibrium points, first proposed by Gyllenberg and Webb in (1989) [6]. The dynamics of the equilibrium points are studied in terms of local and asymptotic stability. We show that under an appropriate conditions on the parameters of the model, the trivial equilibrium point is unstable and the nontrivial one attracts any nontrivial solution.

Keywords: Tumor growth model, Lyapunov function, omega limit set. PDE, mean value theorem

1 Introduction

Many mathematical models describing the behavior of cell populations have been developed over the last half century, including models differentiated by size [2], [12]. Variations of these models have been subject to rigorous mathematical analysis, especially in terms of the existence and stability of the steady size distribution that they may exhibit under certain conditions (see [3], [10], [11]). A survey of cell size models have been considered in [1].

In this paper, we are interested by a non linear quiescence model structured by cell size first proposed by Gyllenberg and Webb [6] (1989) which employs

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quiescence as a mechanism to explain characteristic sigmoid growth curves. In a series of paper ([5], [6], [7], [8]), the authors develop and analyze the model. They consider two situations: the unstructured quiescent model and the structured one. Under an appropriate hypothesis and using essentially the Poincaré-Bendixon theorem, they show that all nontrivial solution of the unstructured model goes to the nontrivial equilibrium as t goes to infinity. The asymptotic behavior of the model has been treated by A. Grabosh in 1994 [4] by functional analytic methods and in 1996, Ulm [13] proposes a generalization of the model and presents some simplifications of A. Grabosh approach, using a perturbation argument. Recently, R. Yafia [15] has introduced a delay in the proliferating term of the unstructured model and expecting the local stability with respect to the delay.

Our goal in this paper is to study the asymptotic stability of the structured model. Under an appropriate conditions on the parameter of the model (quit similar as in the unstructured case), we show that the nontrivial equilibrium attracts any nontrivial solution.

Section 2 is a brief review of gradient like-systems. Section 3 deals with the main results for the unstructured model. By using a Lyapunov function, and under an appropriate conditions on the parameters of the model, we show that the positive stationary equilibrium attracts any nontrivial solution of the model. In section 4 and 5, the structured model is considered. Under an appropriate hypotheses, we show that the trivial stationary equilibrium is unstable and as in the unstructured model, the nontrivial one attracts any nontrivial solution at infinity.

2 Gradient-like system [9]

Let $F : X \to I\!R$, a continuous function on a Banach space. The flow φ on X is called gradient-like with respect to F if, for all $t > 0$,

$$\varphi(x,t) \neq x \quad \text{imply} \quad F(\varphi(x,t)) < F(x).$$

Thus F is strictly decreasing on nonconstant solutions; in particular φ cannot have any periodic or homoclinic orbits.

Proposition 1 *Let φ be gradient-like flow in $I\!R^n$ with respect to F, with isolated critical points.*

i) If $\varphi(x, I\!R^+)$ (resp.$\varphi(x, I\!R^-)$) is nonconstant and bounded positive (resp. negative) orbit, then the omega limit set $\omega(x)$ (resp. alpha limit set $\alpha(x)$) is a single equilibrium point.

ii) If $F(x) \to +\infty$ *(resp.* $F(x) \to -\infty$*) as* $\|x\| \to +\infty$*, then* $\varphi(x, I\!R^+)$ *(resp.* $\varphi(x, I\!R^-)$*) is bounded.*

Proof. i) We indicate the proof for positive orbits. For every $x \in I\!R^n$, the map $t \to F(\varphi(x,t))$ is nonincreasing and $\varphi(x, I\!R^+)$ is bounded. So, $\lim\limits_{t\to+\infty} F(\varphi(x,t)) = l$ exist and thus for every $y \in \omega(x)$, with $y = \lim\limits_{n\to+\infty} \varphi(x, t_n)$,

$$F(y) = F\left(\lim_{n\to+\infty} \varphi(x,t_n)\right) = \lim_{n\to+\infty} F(\varphi(x,t_n)) = l.$$

Also, for all $t > 0$,

$$F(\varphi(y,t)) = \lim_{n\to+\infty} F(\varphi(x, t+t_n)) = l.$$

therefore $\varphi(y,t) = y$ and y is a critical point.

As $\omega(x)$ is connect and the equilibrium points are isolated, $\omega(x)$ is a single point.

ii) If $F(x) \to +\infty$ as $\|x\| \to +\infty$ and $\varphi(x, I\!R^+)$ is not bounded, then there exist $(t_n)_n \subset I\!R^+$ going to $+\infty$ such that $\lim\limits_{n\to+\infty} \varphi(x,t_n) = +\infty$ and $\lim\limits_{n\to+\infty} F(\varphi(x,t_n)) = +\infty$.

As $t_n \geq 0$, $F(\varphi(x,t_n)) \leq F(\varphi(x,0))$, a contradiction. ■

Note that the only bounded solutions in the gradient-like system are the critical points and orbits connecting the critical points.

3 The unstructured model

The unstructured model is given by the following system of ordinary differential equations:

$$\begin{cases} P' = \{\beta - \mu_P - r_P(N)\} P + r_Q(N) Q \\ Q' = r_P(N) P - \{r_Q(N) + \mu_Q\} Q \end{cases} \tag{1}$$

$P(t)$ (resp. $Q(t)$) is the number of proliferating (resp. quiescent) cells at time t. $N := P + Q$ is the total number of cells in the tumor (or the size of the tumor) at time t; $\beta > 0$ is the division rate, $\mu_P \geq 0, \mu_Q \geq 0$ are the mortality rates of proliferating and quiescent cells respectively, $r_P(N)$ is the (nonlinear) transition rate from the proliferating class to the quiescent class and $r_Q(N)$ is the (nonlinear) transition rate from the quiescent class to the proliferating class. $r_P(N)$ and $r_Q(N)$ are assumed to be nondecreasing and nonincreasing respectively and Lipschitz continuous on bounded sets of N in $I\!R^+$.

Let's show that (1) is a gradient-like system.

3.1 A Lyapunov function

System (1) leads,

$$\begin{cases} N' = P' + Q' = bP - \mu_Q Q \\ N = P + Q \end{cases}$$

with $b = \beta - \mu_P$. So,

$$\begin{cases} P = \frac{N' + \mu_Q N}{b + \mu_Q} \\ Q = \frac{-N' + bN}{b + \mu_Q} \end{cases}, \quad \begin{cases} P' = \frac{N'' + \mu_Q N'}{b + \mu_Q} \\ Q' = \frac{-N'' + bN'}{b + \mu_Q} \end{cases}$$

Thus,

$$N'' = \left[b - \mu_Q - r_P(N) - r_Q(N)\right] N' + \left[b\left(\mu_Q + r_Q(N)\right) - \mu_Q r_P(N)\right] N$$

By the variable change: $u = N$, $v = N'$, we get

$$\begin{cases} u' = v \\ v' = \left[b - \mu_Q - r_P(u) - r_Q(u)\right] v + \left[b\left(\mu_Q + r_Q(u)\right) - \mu_Q r_P(u)\right] u \end{cases} \tag{2}$$

Proposition 2 *Assume,* (H_1) $\quad b - \mu_Q - r_P(u) - r_Q(u) < 0$, *for all* $u \geq 0$.
then system (2) is gradient-like with respect to the function

$$F(u, v) = \frac{1}{2} v^2 - \mu_Q b \frac{u^2}{2} + \mu_Q \rho_P(u) - b \rho_Q(u)$$

where $\rho_P(u) = \int_0^u s r_P(s)\, ds$ *and* $\rho_Q(u) = \int_0^u s r_Q(s)\, ds$.

Proof. On solutions of (2) one has,

$$\frac{d}{dt} F(u, v)(t) = \left[b - \mu_Q - r_P(u(t)) - r_Q(u(t))\right] v(t)^2 .$$

Then hypothesis (H_1) imply that $\frac{d}{dt} F(u, v)(t) < 0$, $\forall t \geq 0$. ■.

3.2 Stationary solutions and stability

From (2), the stationary solutions equation reads,

$$\begin{cases} v = 0 \\ \left[b\left(\mu_Q + r_Q(u)\right) - \mu_Q r_P(u)\right] u = 0 \end{cases}$$

The nontrivial equilibrium satisfies the equation

$$b\left(\mu_Q + r_Q(u)\right) - \mu_Q r_P(u) = 0$$

Proposition 3 *[8] Assume,* (H_2) *i)* $\mu_Q > 0$, *ii)* $\mu_Q r_P(0) < b(\mu_Q + r_Q(0))$ *and* (H_3) $l_P := \lim\limits_{N\to\infty} r_P(N) < \infty$, $l_Q := \lim\limits_{N\to\infty} r_Q(N) \geq 0$ *and* $b\left(1 + \frac{l_Q}{\mu_Q}\right) < l_P$

Then, system (1) has two stationary points: $(0,0)$ *and* $\left(\bar{N}, 0\right)$*; where* $\bar{N}$ *is the unique solution of the following equation*

$$b\mu_Q - \mu_Q r_P\left(\bar{N}\right) + b r_Q\left(\bar{N}\right) = 0.$$

Proof. In view of (H_2) and (H_3), the function $f(s) := \mu_Q r_P(s) - b r_Q(s)$ is nondecreasing and satisfy: $f(0) < b\mu_Q < f(+\infty)$. Then, there exist one root $\bar{N} \in]0,\infty[$ such that, $f\left(\bar{N}\right) = b\mu_Q$. Thus, $\left(\bar{N}, 0\right)$ is the second equilibrium of system (2). ■

Let the hypotheses:

(NH_1) $b - \mu_Q - r_P(u) - r_Q(u) > 0$, for all $u \geq 0$,

(NH_2) i) $\mu_Q > 0$, ii) $\mu_Q r_P(0) > b(\mu_Q + r_Q(0))$.

From the characteristic equation of the linearized system of (2) at the trivial steady state $(0,0)$ one can deduce the following,

Theorem 4 *under the hypotheses* (H_1) *and* (NH_2), $(0,0)$ *is asymptotically stable and under* (H_2) *and* (NH_1), *it is unstable.*

About the asymptotic stability, we have,

Theorem 5 *[8] Assume* (H_1), (H_2) *and* (H_3). *Then* $\left(\bar{N}, 0\right)$ *attract any positive solution of system (2) at infinity* $+\infty$.

Proof. As system (2) is gradient-like, the ω-limit set of any bounded positive orbit belongs to the set of equilibrium: $\left\{(0,0), \left(\bar{N}, 0\right)\right\}$. As, $\lim\limits_{\|(u,v)\|\to+\infty} F(u,v) = +\infty$, all solution of (2) is bounded at $+\infty$.

In fact, as $\rho_P(u) \sim \frac{1}{2}u^2 l_P$ and $\rho_Q(u) \sim \frac{1}{2}u^2 l_Q$ at $+\infty$,

$$F(u,v) \sim \frac{1}{2}v^2 - \frac{1}{2}u^2\left\{\mu_Q b - \mu_Q l_P + b l_Q\right\} \text{ at } +\infty$$

So, in view of the hypothesis (H_3) of proposition 3, $F(u,v) \to +\infty$, $\|(u,v)\| \to +\infty$.

Suppose that a solution $(u(t), v(t))$ of (2) goes to $(0,0)$ as $t \to +\infty$, with $u(t) \geq 0$ and $v(t) \geq 0$. Recall that the matrix of the linearized system of (2) around $(0,0)$ has two eigenvalue $\lambda_1 < 0 < \lambda_2$, with

$$\begin{aligned} \lambda_1 &= \frac{1}{2}\{-(\mu_Q + r_P(0) + r_Q(0) - b) \\ &\quad - \left((\mu_Q + r_P(0) + r_Q(0) - b)^2 + 4(\mu_Q(b - r_P(0)) + b r_p(0))\right)^{\frac{1}{2}}\right\}. \end{aligned}$$

So, as $t \to \infty$, $(u(t), v(t))$ becomes tangent to the eigenspace $(-2r_p(0), \delta)\mathbb{R}$ associated to the eigenvalue λ_1, with

$$\begin{aligned} \delta &= -(\mu_Q + r_P(0) + r_Q(0) - b) \\ &\quad - \left((\mu_Q + r_P(0) + r_Q(0) - b)^2 + 4(\mu_Q(b - r_Q(0)) + br_P(0)) \right)^{\frac{1}{2}} \Big\}. \end{aligned}$$

Then, $v(t)/u(t) \to -\delta/2r_p(0)$, with $v(t)/u(t) \geq 0$ and $-\delta/2r_p(0) < 0$, which lead to a contradiction. ■

4 The structured model

The structured model is given by the following system of partial differential equations,

$$\left\{ \begin{array}{l} \frac{\partial}{\partial t} p(t,x) + \frac{\partial}{\partial x}[g(x)p(t,x)] = 2\{2 - r(x, N(t))\} b(2x) p(t,2x) - b(x) p(t,x) \\ -\mu_p(x) p(t,x) + \rho(x, N(t)) q(t,x), \quad t > 0, \frac{x_0}{2} \leq x < x_1, \\ \frac{\partial}{\partial t} q(t,x) = 2r(x, N(t)) b(2x) p(t,2x) - \mu_q(x) q(t,x) - \rho(x, N(t)) q(t,x), \\ \qquad t > 0, \frac{x_0}{2} \leq x < \frac{x_1}{2} \end{array} \right. \tag{3}$$

with, $p\left(t, \frac{x_0}{2}\right) = 0$, $t > 0$,

$p(0,x) = \varphi(x)$, $\frac{x_0}{2} \leq x < x_1$ and $q(0,x) = \psi(x)$, $\frac{x_0}{2} \leq x < \frac{x_1}{2}$

where $p(t,x)$ and $q(t,x)$ are the densities with respect to cell size x of the proliferating and quiescent classes, respectively at time t. The minimum division size is x_0 and the maximum division size is x_1. It is assumed that $\frac{x_1}{2} < x_0$.

$P(t) = \int_{\frac{x_0}{2}}^{x_1} p(t,x)\,dx$ is the total population of the proliferating class at time t,

$Q(t) = \int_{\frac{x_0}{2}}^{\frac{x_1}{2}} q(t,x)\,dx$ is the total population of the quiescent class at time t,

$N(t) = P(t) + Q(t)$ is the size of the tumor at time t,

$g(x)$ is the growth rate of individual cells of size x. It is assumed that $g(x) > 0$ on $\left[\frac{x_0}{2}, x_1\right)$,

$r(x,N)$ and $\rho(x,N)$ describe the interaction between the two classes. One takes $0 \leq r(x,N) \leq 2$, $0 \leq \rho(x,N)$, $r(x,N)$ is increasing in N, $\rho(x,N)$ is decreasing in N.

$b(x)$ is the per capita fission rate. One takes $b(x)$ to be positive on (x_0, x_1) and 0 outside this interval.

$\mu_p(x) \geq 0$ and $\mu_q(x) \geq 0$ are the size dependent per capita mortality rates of the proliferating and quiescent class respectively.

4.1 Stationary solutions

From (3), the stationary solutions equation reads:

$$\left\{\begin{array}{l} \frac{d}{dx}\left[g\left(x\right)p\left(x\right)\right] = 2\left\{2 - r\left(x,N\right)\right\}b\left(2x\right)p\left(2x\right) - b\left(x\right)p\left(x\right) \\ -\mu_p\left(x\right)p\left(x\right) + \rho\left(x,N\right)q\left(x\right), \text{ for } \quad \frac{x_0}{2} \leq x < x_1 \\ 0 = 2r\left(x,N\right)b\left(2x\right)p\left(2x\right) - \mu_q\left(x\right)q\left(x\right) - \rho\left(x,N\right)q\left(x\right), \\ \qquad \text{for } \ \frac{x_0}{2} \leq x < \frac{x_1}{2} \end{array}\right. \tag{4}$$

As q is not defined outside $\left(\frac{x_0}{2},\frac{x_1}{2}\right)$ we will take $\rho\left(x,N\right)=0$, for $x > \frac{x_1}{2}$ and system (4) becomes,

for $\frac{x_1}{2} \leq x < x_1$,

$$\frac{d}{dx}\left[g\left(x\right)p\left(x\right)\right] = -\left\{b\left(x\right) + \mu_p\left(x\right)\right\}p\left(x\right), \tag{5}$$

and for $\frac{x_0}{2} \leq x \leq \frac{x_1}{2}$,

$$\left\{\begin{array}{l} \frac{d}{dx}\left[g\left(x\right)p\left(x\right)\right] = 2\left\{2 - r\left(x,N\right)\right\}b\left(2x\right)p\left(2x\right) - \left\{b\left(x\right) + \mu_p\left(x\right)\right\}p\left(x\right) + \rho\left(x,N\right)q\left(x\right), \\ 0 = 2r\left(x,N\right)b\left(2x\right)p\left(2x\right) - \left\{\mu_q\left(x\right) + \rho\left(x,N\right)\right\}q\left(x\right) \end{array}\right. \tag{6}$$

The goal is to found a non trivial equilibrium solutions (P,Q) of the model, where $P = \int_{\frac{x_0}{2}}^{x_1} p\left(x\right)dx$, $Q = \int_{\frac{x_0}{2}}^{\frac{x_1}{2}} q\left(x\right)dx$ and (p,q) satisfy (4). We' l deduce the existence from the so called the characteristic equation associated to (3),

$$\Delta\left(\lambda,N\right) := \int_{x_0}^{x_1}\left[2 - \frac{\mu_q\left(\frac{x}{2}\right) + \lambda}{\mu_q\left(\frac{x}{2}\right) + \rho\left(\frac{x}{2},N\right) + \lambda}r\left(\frac{x}{2},N\right)\right]\frac{b\left(x\right)}{g\left(x\right)}W_\lambda\left(\frac{x}{2},x\right)dx \tag{7}$$

with, $W_\lambda\left(x,y\right) = \exp - \int_x^y \frac{\mu_p(s)+b(s)+\lambda}{g(s)}ds$ (obtained by substituting a solution $\left(\exp\left(\lambda t\right)p\left(x\right), \exp\left(\lambda t\right)q\left(x\right)\right)$ in (3), see [14]).

In fact, resolution of systems (5), (6), with the condition $p\left(\frac{x_1}{2}\right) \neq 0$ leads to the following equation:

$$\Delta\left(0,N\right) = 1 \tag{8}$$

Proposition 6 *[8] Assume that* (H_2') *i)* $\mu_q > 0$ *in* $\left(\frac{x_0}{2},\frac{x_1}{2}\right)$, $g > 0$ *in* $\left(\frac{x_0}{2},x_1\right)$, *ii)* $\Delta\left(0,0\right) > 1$ *and,* (H_3') $r\left(x,+\infty\right), \ \rho\left(x,+\infty\right)$ *exist and* $\Delta\left(0,\infty\right) < 1$.

Then, there exist a unique non trivial equilibrium solution (P^*,Q^*) *of (3) such that* $N^* := P^* + Q^*$ *is the unique solution of equation (8).*

Proof. The function $N \to \Delta\left(\lambda,N\right)$ is continuous nonincreasing and in view of (H_1'), satisfies,

$$\Delta\left(0,\infty\right) < 1 < \Delta\left(0,0\right).$$

So, there exist one root $N^* \in (0, \infty)$, solution of equation (8). Thus, N^* is the second equilibrium of system (3). ■

Our objective now is to show that the stationary solution (P^*, Q^*) attracts any positive solution (P, Q), with $P = \int_{\frac{x_0}{2}}^{x_1} p(t,x)\,dx$ and $Q = \int_{\frac{x_0}{2}}^{\frac{x_1}{2}} q(t,x)\,dx$ and (p, q) satisfy (3).

4.2 Formulation in terms of ordinary differential equations

Proposition 7 *Assume,* (H_0) $g(x_1) = 0$.

Then, for every solution (p, q) *of equation (3), there exist* $\zeta_i^1 = \zeta_i^1(p) \in (x_0, x_1)$ *and* $\zeta_i^2 = \zeta_i^2(q) \in \left(\frac{x_0}{2}, \frac{x_1}{2}\right)$, $i = 1, 2$ *such that*

$$\begin{cases} P'(t) = [b_1 - r_2(N)\, b_2 - \mu_{p1}]\, P(t) + \rho_1(N)\, Q(t) \\ Q'(t) = r_2(N)\, b_2 P(t) - [\mu_{q2} + \rho_1(N)]\, Q(t) \end{cases} \tag{9}$$

where P *and* Q *are as above,* $N = P + Q$, $b_i = b(\zeta_i^1)$, $r_2(N) = r\left(\frac{\zeta_2^1}{2}, N\right)$, $\mu_{p1} = \mu_p(\zeta_1^1)$, $\rho_1(N) = \rho(\zeta_1^2, N)$ *and* $\mu_{q2} = \mu_q(\zeta_2^2)$

Proof. By integrating the first and the second equation of (3) between x_0, x_1 and $\frac{x_0}{2}$, $\frac{x_1}{2}$ respectively and using the mean value theorem and assumption (H_0) of proposition 7, we get system (9) for $t > 0$. ■

4.3 Stability

To expect asymptotic stability for system (3), consider the general situation of system (9) where we take a system depending on parameters: $c_i^1 \in (x_0, x_1)$ and $c_i^2 \in \left(\frac{x_0}{2}, \frac{x_1}{2}\right)$, $i = 1, 2$,

$$\begin{cases} P'(t) = [b_1 - r_2(N)\, b_2 - \mu_{p1}]\, P(t) + \rho_1(N)\, Q(t) \\ Q'(t) = r_2(N)\, b_2 P(t) - [\mu_{q2} + \rho_1(N)]\, Q(t) \end{cases} \tag{10}$$

with $N = P + Q$, $b_i = b(c_i^1)$, $r_2(N) = r\left(\frac{c_2^1}{2}, N\right)$, $\mu_{p1} = \mu_p(c_1^1)$, $\rho_1(N) = \rho(c_1^2, N)$ and $\mu_{q2} = \mu_q(c_2^2)$.

Note that system (10) is a family of systems depending on parameters, which are like to the initial one (1), and (9) can be obtained from (10) by a particular values of the parameters.

We summarize the main result as in section 3 in,

Theorem 8 *Assume the following hypothesis:* (H) *for every* $x, y \in (x_0, x_1)$ *and* $z, t \in \left(\frac{x_0}{2}, \frac{x_1}{2}\right)$,

i) $\mu_q(t) > 0$,

ii) $b(x) - \mu_P(x) - \mu_Q(t) - r\left(\frac{y}{2}, u\right) b(y) - \rho(z, u) < 0,$ *for all* $u \geq 0.$

iii) $b(y)\mu_Q(t) r\left(\frac{y}{2}, 0\right) < (b(x) - \mu_P(x))(\mu_Q(t) + \rho(z, 0))$ *and*

iv) $l_P(y) := \lim\limits_{u \to \infty} r(y, u) < \infty$, $l_Q(z) := \lim\limits_{u \to \infty} \rho(z, u) \geq 0$ *and* $(b(x) - \mu_P(x))(\mu_Q(t) + l_Q(z)) < b(y)\mu_Q(t) l_P\left(\frac{y}{2}\right)$,

then system (10) has two stationary points: $(0, 0)$ *and* $\left(\bar{P}, \bar{Q}\right)$*; where* $\bar{N} := \bar{N}(x, y, z, t) = \bar{P} + \bar{Q}$ *is the unique solution of the following equation*

$$b(y)\mu_Q(t) r\left(\frac{y}{2}, \bar{N}\right) = (b(x) - \mu_P(t))\left(\mu_Q(t) + \rho\left(z, \bar{N}\right)\right)$$

furthermore, $\left(\bar{P}, \bar{Q}\right)$ *attracts any solution of (10).*

Corollary 9 *Assume the hypothesis* (H) *and* (H_0).

Then system (9) has two stationary points: $(0, 0)$ *and* (P^*, Q^*)*; where* $N^* := P^* + Q^*$ *is the unique solution of equation (8) (given by proposition 6). Furthermore* $(0, 0)$ *is unstable and* (P^*, Q^*) *attracts any solution of system (3) at infinity.*

Proof. The characteristic equation corresponding to the linearized equation of system (3) around a critical point (p_0, q_0) is

$$\Delta(\lambda, N_0) = 1$$

with $N_0 = P_0 + Q_0$, $P_0 = \int_{\frac{x_0}{2}}^{x_1} p_0(x)\,dx$, $Q_0 = \int_{\frac{x_0}{2}}^{\frac{x_1}{2}} q_0(x)\,dx$.

For $N_0 = 0$, one has $\Delta(0, 0) > 1$ and from equation (7) we get $\lim\limits_{\lambda \to \infty} \Delta(\lambda, 0) = 0$. So, there exist $\lambda > 0$ such that $\Delta(\lambda, 0) = 1$ and the stationary equilibrium $(0, 0)$ is unstable.

For the attractiveness of (P^*, Q^*), section 3 can be applied and we only have to show that $N^* = \bar{N}$. By a straightforward calculation, we verify that the hypothesis iii) and iv) in (H) imply the hypothesis (H_2') and (H_3') respectively.

In fact, iv) in (H) imply,

$$\left[2 - \frac{\mu_Q(t) l_P\left(\frac{y}{2}\right)}{\mu_Q(t) + l_Q(z)}\right] \frac{b(y)}{g(y)} < \frac{2b(y) - b(x) + \mu_P(x)}{g(y)}$$

For $y = x$, $t = z = \frac{x}{2}$ and by multiplying the two members of inequality by $W\left(\frac{x}{2}, x\right)$ and integrating between x_0 and x_1 we obtain,

$$\Delta(0,\infty) < \int_{x_0}^{x_1} \frac{b(x)+\mu_P(x)}{g(x)} W\left(\frac{x}{2}, x\right) dx$$

where, W denote W_0 (corresponding to $\lambda = 0$ in (7)).

For $x_0 \leq x < x_1$, $W\left(\frac{x}{2}, x\right) \leq W(x_0, x)$ and, in view of hypothesis (H_0), $\int_x^{x_1} \frac{ds}{g(s)} = +\infty$ and $\int_{x_0}^{x_1} \frac{b(x)+\mu_P(x)}{g(x)} W(x_0, x)\, dx = 1$.

Now, from the monotonicity of $r\left(\frac{x}{2}, .\right)$ and $\rho\left(\frac{x}{2}, .\right)$, and the hypothesis (H_0), we can see that $\Delta(0,0) > 1$. In fact, the function $\left[2 - \frac{\mu_q\left(\frac{x}{2}\right)}{\mu_q\left(\frac{x}{2}\right)+\rho\left(\frac{x}{2},0\right)} r\left(\frac{x}{2}, 0\right)\right]$ is nonnegative and from the mean value theorem, there exists $c \in (x_0, x_1)$ such that

$$\Delta(0,0) = \left[2 - \frac{\mu_q\left(\frac{c}{2}\right)}{\mu_q\left(\frac{c}{2}\right) + \rho\left(\frac{c}{2}, 0\right)} r\left(\frac{c}{2}, 0\right)\right] b(c)\, W\left(\frac{c}{2}, c\right) \int_{x_0}^{x_1} \frac{dx}{g(x)}.$$

■

5 Conclusion

In [8], existence of the positive equilibrium for the unstructured model with it's attractiveness is assured by the following conditions: i) $\mu_Q > 0$, ii) $\mu_Q r_P(0) < b(\mu_Q + r_Q(0))$ and iii) $b\left(1 + \frac{l_Q}{\mu_Q}\right) < l_P$, with $l_P := \lim_{N\to\infty} r_P(N) < \infty$, $l_Q := \lim_{N\to\infty} r_Q(N) \geq 0$

In this paper an analogous comportment of the positive equilibrium as well as the unstability of the trivial one for the structured model are obtained under the following similar conditions: for every $x, y \in (x_0, x_1)$ and $z, t \in \left(\frac{x_0}{2}, \frac{x_1}{2}\right)$,

i) $\mu_q(t) > 0$,

ii) $b(x) - \mu_P(x) - \mu_Q(t) - r\left(\frac{y}{2}, u\right) b(y) - \rho(z, u) < 0$, for all $u \geq 0$.

iii) $b(y)\, \mu_Q(t)\, r\left(\frac{y}{2}, 0\right) < (b(x) - \mu_P(x))\, (\mu_Q(t) + \rho(z, 0))$ and

iv) $(b(x) - \mu_P(x))\, (\mu_Q(t) + l_Q(z)) < b(y)\, \mu_Q(t)\, l_P\left(\frac{y}{2}\right)$, with $l_P(y) := \lim_{u\to\infty} r(y, u) < \infty$, $l_Q(z) := \lim_{u\to\infty} \rho(z, u) \geq 0$,

with the supplementary hypothesis that the growth rate of individual cells of size x is zero at the maximal size x_1,

Therefore, for any non trivial solution (p, q), with nonnegative initial conditions of system (3), $\left(\int_{\frac{x_0}{2}}^{x_1} p(t, x)\, dx\ , \int_{\frac{x_0}{2}}^{\frac{x_1}{2}} q(t, x)\, dx\right)$ goes to the positive equilibrium (P^*, Q^*) when t goes to the infinity and the growth of the tumor is stopped.

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Received: June 30, 2007