Global stability of solutions to a free boundary problem of ductal carcinoma in situ*

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Abstract

In the paper we present some remarks on the global stability of steady state solutions to a free boundary model studied by Y.Xu [see Y.Xu, A free boundary problem model of ductal carcinoma in situ, discrete and continuous dynamical systems-series B, 4 (2004) 337–348] and also prove some new results of global stability of steady state solutions to the model.

Key words and phrases. Mathematical model, Ductal carcinoma in Situ, Free boundary problem, Global stability

1 Introduction

The process of tumor growth and its dynamics is one of the most intensively studied processes in the recent years. There have appeared many papers devoted to develop mathematical models to describe the process, cf. [1, 4–7, 13, 14, 21–27] and references therein. Most of those models are based on the reaction diffusion equations and mass conservation law. Analysis of such mathematical models has drawn great interest, and many results have been established, cf. [3, 8–11, 15–17, 19, 28, 29] and references therein.

Ductal carcinoma in situ (DCIS) refers to a specific diagnosis of cancer that is isolated within the breast duct, and has not spread to other parts of the breast. There are two categories of DCIS: non-comedo and comedo. Noncomedo type CDIS tends to be less aggressive. The most common non-comedo types of DCIS are: (1) Solid DCIS: cancer cells completely fill the affected breast ducts. (2) Cribiform DCIS: cancer cells do not completely fill the affected breast ducts; there are gaps between the cells. (3) Papillary DCIS: the cancer cells arrange themselves in a fern-like pattern within the affected breast ducts. (More information may be found in <http://imagingis.com> or [30]).

* This work is partially supported by NSF of China (11301474, 11171295), Foundation for Distinguished Young Teacher in Higher Education of Guangdong, China (Yq2013163).
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In a talk Mary Edgerton described two special patterns found in DCIS vividly: one lining up like baby trees and one spreading out evenly with gaps.

In [30], the author modifies a model proposed by Byrne and Chaplain [5], (also see Friedman and Reitich [18]), for the growth of a tumour consisting of live cells (nonnecrotic tumour) to describe the homogeneous growth inside a cylinder, a model mimicking the growth of a ductal carcinoma. The one dimensional model is in the form of a free boundary problem as follows.

$$c \frac{\partial \sigma}{\partial t} = \frac{\partial^2 \sigma}{\partial z^2} - \lambda \sigma, \text{ in } B(t), \quad t > 0, \quad (1.1)$$

$$\frac{\partial \sigma}{\partial z}(0, t) = 0, \quad \sigma(R(t), t) = \sigma_1, \quad (1.2)$$

$$\sigma(z, 0) = \sigma_0(z), \text{ in } B(0), \quad (1.3)$$

$$\frac{\partial s}{\partial t} = \mu \int_0^{s(t)} (\sigma - \tilde{\sigma}) dz, \quad t > 0, \quad (1.4)$$

$$s(0) = z_0, \quad (1.5)$$

where $B(t) = \{z | 0 < z < s(t)\}$, $s(t)$ which represents the growing boundary of the tumour is unknown function; λ, μ are positive constants. $\lambda \sigma$ in (1.1) is the consumption rate of nutrient in a unit volume; σ_1 denotes the external concentration of nutrients, which is assumed to be constant. $c = T_{diffusion}/T_{growth}$ is the ratio of the nutrient diffusion time scale to the tumour growth time scale. Typically $c \ll 1$. (cf. [9, 18] and [30].) The two terms on the righthand side of (1.4) are explained as follows: The first term $\mu \int_0^{s(t)} \sigma dz$ is the total volume increase in a unit time interval induced by cell proliferation, the proliferation rate is $\mu \sigma$; The second term $\mu \int_0^{s(t)} \tilde{\sigma} dz$ is the total volume decrease in a unit time interval caused by natural death, and the natural death rate is $\mu \tilde{\sigma}$. For details of the model, please see [30].

Global stability of steady state solutions to problem (1.1)-(1.5) were obtained in [30]. We realized that there are some mistakes in [30], which were reflected in theorem 2.2 formulated in [30], so they were needed to be corrected. In presented paper we consider the global stability of solutions to one dimensional model studied in [30].

2 The limiting case when $c = 0$

First, we consider the limiting case when $c = 0$, i.e., we consider the following problem

$$\frac{\partial^2 \sigma}{\partial z^2} = \lambda \sigma, \text{ in } B(t), \quad t > 0, \quad (2.1)$$

$$\frac{\partial \sigma}{\partial z}(0, t) = 0, \quad \sigma(s(t), t) = \sigma_1, \quad (2.2)$$

$$\sigma(z, 0) = \sigma_0(z), \text{ in } B(0), \quad (2.3)$$

$$\frac{\partial s}{\partial t} = \mu \int_0^{s(t)} (\sigma - \tilde{\sigma}) dz, \quad t > 0, \quad (2.4)$$

$$s(0) = z_0. \quad (2.5)$$

The solution to (2.1), (2.2) is

$$\sigma(z, t) = \frac{\sigma_1 \cosh(\sqrt{\lambda} z)}{\cosh \sqrt{\lambda} s(t)}. \quad (2.6)$$

Substituting (2.6) to (2.4), and setting $\sqrt{\lambda} s(t) = \eta(t)$, one can get

$$\eta'(t) = \mu \sigma_1 \tanh \eta - \mu \tilde{\sigma} \eta =: \mu f(\eta). \quad (2.7)$$

The specific value of μ will not affect the results of the model. We shall take $\mu = 1$ for simplicity in the following of the paper.

Lemma 2.1 *Consider the following problem*

$$x'(t) = f(x(t)), \quad t > 0, \quad (2.8)$$

$$x(0) = x_0 > 0. \quad (2.9)$$

Assume that f is defined and continuously differentiable on $(0, \infty)$ and $f(0) = 0$.

(i) If $f'(x) > 0$ for $0 < x < a$, $f'(x) < 0$ for all $x > a$, where a is a positive constant. Then exists a unique positive constant $x_s > a$ such that $f(x_s) = 0$, and the following assertion holds:

$$\lim_{t \rightarrow \infty} x(t) = x_s.$$

(ii) If $f'(x) < 0$ for all $x > 0$, then

$$\lim_{t \rightarrow \infty} x(t) = 0.$$

Proof. It is obvious there exists a unique solution to the problem (2.8), (2.9). In the following we prove the asymptotic behavior of this solution. For (i), we claim that if $x_0 < x_s$, then $x(t) < x_s$ for all $t > 0$. If not, there exists a point t_0 such that

$$x(t_0) = x_s, \quad x'(t_0) > 0, \quad x(t) < x_s \quad \text{for } t < t_0. \quad (2.10)$$

On the other hand,

$$x'(t_0) = f(x(t_0)) = f(x_s) = 0,$$

which is in contradiction with (2.10). Thus the claim is true. Then $x(t)$ is monotone increasing and has a upper bound, so $x(t)$ has a limit as $t \rightarrow \infty$. This limit must be equal to x_s .

If $x_0 > x_s$, the proof is similar. This completes the proof of (i).

(ii) is obvious, we omit the proof here.

By simple computation, one can get

$$f'(\eta) = \sigma_1 \left[1 - \frac{\tilde{\sigma}}{\sigma_1} - \tanh^2 \eta \right] \quad (2.11)$$

By the fact the function $\tanh \eta$ is monotone increasing for all $\eta > 0$ and $\tanh 0 = 0$, one can get: If $\tilde{\sigma} < \sigma_1$, there exists a unique positive constant $\eta_1 > 0$ such that $f'(\eta) > 0$ for $0 < \eta < \eta_1$, $f'(\eta) < 0$ for $\eta > \eta_1$; If $\tilde{\sigma} > \sigma_1$, $f'(\eta) < 0$ for $\eta > 0$.

Therefore, if $\tilde{\sigma} < \sigma_1$, there exists a unique positive constant $\eta_s > \eta_1 > 0$ such that $f(\eta_s) = 0$ and $f(\eta) > 0$ for $0 < \eta < \eta_s$, $f(\eta) < 0$ for $\eta > \eta_s$. Moreover, $f'(\eta_s) < 0$; if $\tilde{\sigma} > \sigma_1$, $f'(\eta) < 0$ for $\eta > 0$. Then by Lemma 2.1, we have

Theorem 2.2 *The problem (2.1)-(2.5) has a unique solution $(\sigma(z, t), s(t))$. For any positive initial value z_0 , if $\sigma_1 > \tilde{\sigma}$, $s(t)$ tends to z_s , where z_s is the unique positive constant solution to the equation $f(\sqrt{\lambda}z) = 0$; if $\sigma_1 < \tilde{\sigma}$, $s(t)$ tends to 0.*

3 Global stability of steady state solutions to problem (1.1)-(1.5)

The existence and uniqueness of solutions to problem (1.1)-(1.5) has been proved by Xu [30]. The global stability of steady state solutions to problem (1.1)-(1.5) was also studied in [30]. It is important to realize that there are some mistakes in [30], which need to be corrected (see remark in this section).

In this section we shall mainly study global stability of steady state solutions to problem (1.1)-(1.5) under the following assumption (A):

(A) $0 \leq \sigma_0(z) \leq \sigma_1$ for $0 \leq z \leq z_0$, and $\sigma_0(z)$ is a continuous function.

Lemma A (see Theorem 2.1 in [30]) *Under the assumption of (A), the free boundary problem (1.1)-(1.5) has a unique solution $(\sigma(z, t), s(t))$ and*

$$0 < \sigma \leq \sigma_1, \quad 0 < z \leq s(t), \quad t \geq 0, \quad (3.1)$$

$$-\tilde{\sigma}s(t) \leq s'(t) \leq (\sigma_1 - \tilde{\sigma})s(t), \quad t \geq 0, \quad (3.2)$$

$$s(0)e^{-\tilde{\sigma}t} \leq s(t) \leq s(0)e^{(\sigma_1 - \tilde{\sigma})t}, \quad t \geq 0. \quad (3.3)$$

By (3.3), one can easily get

Theorem 3.1 *Under the assumption of (A), the problem (1.1)-(1.5) has a unique solution $(\sigma(z, t), s(t))$. For any positive initial value z_0 and $c > 0$, if $\sigma_1 < \tilde{\sigma}$, $s(t)$ tends to 0.*

From [30], we known that the free boundary problem (1.1)-(1.5) has a unique stationary

solution

$$(\sigma_s(z), z_s) = \left(\frac{\sigma_1 \cosh(\sqrt{\lambda}z)}{\cosh \sqrt{\lambda}z_s}, z_s \right)$$

if $\sigma_1 > \tilde{\sigma}$, where z_s is the unique positive constant solution to the equation $f(\sqrt{\lambda}z) = 0$. Our main results of this section is the following theorem.

Theorem 3.2 *Under the assumption of (A), the problem (1.1)-(1.5) has a unique solution $(\sigma(z, t), s(t))$. If $\sigma_1 > \tilde{\sigma}$, then for any $\varepsilon > 0$, there exists positive constants c_0, γ and C such that if $\varepsilon < z_0 < \frac{1}{\varepsilon}$ and $0 < c \leq c_0$,*

$$|s(t) - z_s| \leq Ce^{-\gamma t}, \quad |s'(t)| \leq Ce^{-\gamma t}, \quad |\sigma(z, t) - \sigma_s(z)| \leq Ce^{-\gamma t}$$

for all $0 \leq z \leq s(t), t \geq 0$.

Remark. The global stability of steady state solutions to problem (1.1)-(1.5) was studied in [30] (see Theorem 2.2 in [30]), but there is a mistake in the proof of that Theorem. In the proof of Theorem 2.2 in [30], the author use the equation

$$s''(t) = \mu(\sigma(s(t), t) - \tilde{\sigma})s'(t) = \mu(\sigma_1 - \tilde{\sigma})s'(t).$$

Actually it should be replaced by

$$s''(t) = \mu(\sigma(s(t), t) - \tilde{\sigma})s'(t) + \mu \int_0^{s(t)} \frac{\partial \sigma}{\partial t}(z, t) dz = \mu(\sigma_1 - \tilde{\sigma})s'(t) + \mu \int_0^{s(t)} \frac{\partial \sigma}{\partial t}(z, t) dz$$

since the function σ depends on z and t , namely, $\sigma = \sigma(z, t)$.

In order to prove Theorem 3.2, we first prove the following three Lemmas (Lemma 3.3–Lemma 3.5).

Let $v(z, t) = \frac{\sigma_1 \cosh(\sqrt{\lambda}z)}{\cosh \sqrt{\lambda}s(t)}$. Then v satisfies the following equations (3.4) and (3.5).

$$\frac{\partial^2 v}{\partial z^2} = \lambda v, \quad \text{in } B(t), \quad t > 0, \quad (3.4)$$

$$\frac{\partial v}{\partial z}(0, t) = 0, \quad v(s(t), t) = \sigma_1. \quad (3.5)$$

Lemma 3.3 Let $(\sigma(z, t), s(t))$ is the solution to (1.1)-(1.5). Assume that for some $0 < T \leq \infty$ and $\varepsilon > 0$

$$|s'(t)| \leq L \leq L_0, \quad \varepsilon \leq s(t) \leq \frac{1}{\varepsilon}. \quad (3.6)$$

Assume further that $0 \leq z \leq z_0$,

$$|\sigma(z, 0) - v(z, 0)| \leq M \leq M_0. \quad (3.7)$$

Then there exist positive constant C independent of c, T, L, M and z_0 but depend of ε such that

$$|\sigma(z, t) - v(z, t)| \leq C(Lc + Me^{-\frac{\lambda t}{c}}) \quad (3.8)$$

for arbitrary $0 \leq z \leq s(t), 0 \leq t < T$.

Proof. By direct computation, we have

$$\frac{\partial v}{\partial t} = \frac{-\sqrt{\lambda}\sigma_1 \cosh(\sqrt{\lambda}z)s'(t) \sinh(\sqrt{\lambda}s(t))}{(\cosh \sqrt{\lambda}s(t))^2}$$

Hypothesis (3.6) implies that

$$|\frac{\partial v}{\partial t}| \leq CL,$$

for $0 < z < s(t), t \geq 0$, where C depends only on σ_1, λ and ε . Let $\sigma_{\pm}(z, t) = v \pm \frac{CLc}{\lambda} \pm Me^{-\frac{\lambda t}{c}}$. Then

$$c \frac{\partial \sigma_+}{\partial t} - \frac{\partial^2 \sigma_+}{\partial^2 z} + \lambda \sigma_+ \geq -CLc + CLc = 0$$

By (3.5), we have

$$\frac{\partial \sigma_+}{\partial z}(0, t) = 0, \quad \sigma_+(s(t), t) > \sigma_1, \quad \text{for } t > 0, \quad \sigma_+(z, 0) \geq \sigma_0(z) \quad \text{for } 0 \leq z \leq z(0).$$

Then by comparison principle we obtain

$$\sigma_+(r, t) \geq \sigma(r, t) \quad \text{for } 0 \leq r \leq R(t), \quad 0 \leq t < T.$$

Similarly arguments can prove that

$$\sigma_-(r, t) \leq \sigma(r, t) \quad \text{for } 0 \leq r \leq R(t), \quad 0 \leq t < T.$$

Hence (3.8) holds. This completes the proof.

Lemma 3.4 *Let $(\sigma(z, t), s(t))$ is the solution to (1.1)-(1.5). If $\sigma_1 > \tilde{\sigma}$, assume for some $\varepsilon > 0$, $\varepsilon \leq s(0) = z_0 \leq \frac{1}{\varepsilon}$. Then there exists a positive constant c_0 independent of $c, s(t)$ for $t \geq 0$ such that*

$$\frac{1}{2} \min(z_s, \varepsilon) < s(t) < 2 \max(z_s, \frac{1}{\varepsilon}) \quad (3.9)$$

for arbitrary $t \geq 0$ and $0 < c \leq c_0$.

Proof. Assume that (3.9) is not valid for some t . It follows that there exists $T > 0$ such that for $0 \leq t < T$,

$$\frac{1}{2} \min(z_s, \varepsilon) < s(t) < 2 \max(z_s, \frac{1}{\varepsilon})$$

and either $s(T) = 2 \max(z_s, \frac{1}{\varepsilon})$ or $s(T) = \frac{1}{2} \min(z_s, \varepsilon)$.

If $s(T) = 2 \max(z_s, \frac{1}{\varepsilon})$, then

$$s'(T) \geq 0. \quad (3.10)$$

By (3.1) and the fact that for $0 \leq t < T$, $\frac{1}{2} \min(z_s, \varepsilon) < s(t) < 2 \max(z_s, \frac{1}{\varepsilon})$, we have $|s'(t)| \leq L_0$, L_0 is a positive constant independent of c and T . Obviously $|\sigma(z, 0) - v(z, 0)| \leq \sigma_1$. By Lemma 3.3, it follows

$$|\sigma(z, t) - v(z, t)| \leq C(Lc + Me^{-\frac{\lambda t}{c}}) \quad (3.11)$$

for arbitrary $0 \leq z \leq s(t)$, $0 \leq t < T$ and $0 < c \leq c_0$. Then we have for $t > 0$

$$\begin{aligned} s'(t) &= \int_0^{s(t)} (\sigma(z, t) - \tilde{\sigma}) dz \\ &\leq \int_0^{s(t)} (v(z, t) - \tilde{\sigma}) dz + C(Lc + Me^{-\frac{\lambda t}{c}})s(t) \end{aligned}$$

It follows that

$$s'(T) \leq f(\sqrt{\lambda}s(T)) + C(Lc + Me^{-\frac{\lambda T}{c}})s(T).$$

Noticing $s(T) > z_s$ we have $f(\sqrt{\lambda}s(T)) < 0$, then if c_0 is sufficiently small and $0 < c \leq c_0$ it follows that $s'(T) < 0$ which contracts to the fact $s'(T) \geq 0$.

If $s(T) = \frac{1}{2} \min(\varepsilon, R_s)$ similar arguments can prove the desired assertion. This completes the proof.

Lemma 3.5 *Let $(\sigma(z, t), s(t))$ is the solution to (1.1)-(1.5). Assume further that for all $t > 0$,*

$$C_* \leq s(t) \leq C^*, \quad (3.12)$$

where C_ and C^* are two constants independent of c . Let α_0 be a given positive number. If $\sigma_1 > \tilde{\sigma}$, Then there exist positive constants c_0, θ, T_0 and C independent of c such that the following assertions holds: If $0 < c \leq c_0$, for any $\alpha \in (0, \alpha_0]$, if the inequalities*

$$|s(t) - z_s| \leq \alpha, |s'(t)| \leq \alpha, |\sigma(z, t) - \sigma_s(z)| \leq \alpha. \quad (3.13)$$

hold for all $0 \leq z \leq s(t), t \geq 0$ and $|s'(t)| \leq \alpha$ holds for all $0 \leq z \leq s(t), t \geq 0$, then also the inequalities

$$|s(t) - z_s| \leq C\alpha(c + e^{-\theta t}), |s'(t)| \leq C\alpha(c + e^{-\theta t}), |\sigma(z, t) - \sigma_s(z)| \leq C\alpha(c + e^{-\theta t}) \quad (3.14)$$

hold for all $0 \leq z \leq s(t), t \geq T_0$.

Proof. By the mean value theorem and the inequalities (3.13), one can get

$$|v(z, t) - \sigma_s(z)| = \left| \frac{\sigma_1 \cosh(\sqrt{\lambda}z)}{\cosh \sqrt{\lambda}s(t)} - \frac{\sigma_1 \cosh(\sqrt{\lambda}z)}{\cosh \sqrt{\lambda}z_s} \right| \leq C|s(t) - z_s| \leq c\alpha \quad (3.15)$$

for $0 \leq z \leq s(t)$, $t \geq 0$. Here and hereafter we use the same notation C to denote various different positive constants independent of c and α . Then

$$|\sigma(z, t) - v(z, t)| \leq |\sigma(z, t) - \sigma_s(z)| + |v(z, t) - \sigma_s(z)| \leq C\alpha.$$

In particular $|\sigma_0(z) - v(z, 0)| \leq C\alpha$ for $0 \leq z \leq z_0$. Since also $|s'(t)| \leq \alpha$ for all $t \geq 0$, by Lemma 3.3, we infer that there exists positive constant c_0 independent of c and α such that

$$|\sigma(z, t) - v(z, t)| \leq C\alpha(c + e^{-\frac{\lambda t}{c}}) \quad (3.16)$$

for all $0 \leq z \leq s(t)$, $t \geq 0$ and $0 < c \leq c_0$. Since

$$\int_0^{s(t)} (v(z, t) - \tilde{\sigma}) dz = f(\sqrt{\lambda}s(t))$$

by (3.16) one can get

$$|s'(t) - f(\sqrt{\lambda}s(t))| = \left| \int_0^{s(t)} (\sigma(z, t) - v(z, t)) dz \right| \leq C\alpha(c + e^{-\frac{\lambda t}{c}})s(t).$$

It follows for $t > 1$,

$$f(\sqrt{\lambda}s(t)) - C\alpha cs(t) \leq s'(t) \leq f(\sqrt{\lambda}s(t)) + C\alpha cs(t) \quad (3.17)$$

Using similar argument as section 2, one can easily prove that for any $0 < \alpha \leq \alpha_0$ and $0 < c \leq c_0$, the equations $f(\sqrt{\lambda}s) + C\alpha cs = 0$ has respectively unique solutions $z_s^\pm$ and any solutions of differential equations $s'(t) = f(\sqrt{\lambda}s(t)) + C\alpha cs(t)$ which respectively denoted by $s^\pm(t)$ converge respectively to $z_s^\pm$ as $t \rightarrow \infty$. Using these facts and (3.17) we can deduce as in [9, 10, 18] that there exists $\theta > 0$ and $T_0 > 0$ independent of c and α such that for any $0 < c \leq c_0$, $0 < \alpha \leq \alpha_0$ and $t \geq T_0$ there hold

$$|s(t) - z_s| \leq C\alpha(c + e^{-\theta t}), |s'(t)| \leq C\alpha(c + e^{-\theta t}),$$

which in turn implies (by (3.15)) that $|v(z, t) - \sigma_s(r)| \leq C\alpha(c + e^{-\theta t})$ for all $0 \leq z \leq s(t)$, $t \geq T_0$. By (3.16), one can get $|\sigma(z, t) - \sigma_s(z)| \leq C\alpha(c + e^{-\theta t})$ for all $0 \leq z \leq s(t)$, $t \geq T_0$. This completes proof of Lemma 3.5.

Proof of Theorem 3.2 By Lemma 3.4 we know that there exists $c_0 > 0$ such that if $0 < c \leq c_0$ then

$$\frac{1}{2} \min(z_s, \varepsilon) < s(t) < 2 \max(z_s, \frac{1}{\varepsilon})$$

for $t \geq 0$. Thus (3.12) holds for all $t \geq 0$. Besides, it follows that $|s(t) - z_s| \leq \frac{2}{\varepsilon} + 3z_s =: \alpha_1$ for $t \geq 0$ and by (1.4), we have $|s'(t)| \leq \sigma_1(\frac{2}{\varepsilon} + 3z_s) =: \alpha_2$ for $t \geq 0$. Since clearly $|\sigma(z, t) - \sigma_s(z)| \leq 2\sigma_1$ for $0 \leq z \leq s(t)$, $t \geq 0$, we see that (3.13) holds for $\alpha = \max\{\alpha_1, \alpha_2, 2\sigma_1\}$. Let C and θ be as in (3.14) and take c_0 smaller, T_0 larger (if necessary) such that $c_0 + e^{-\theta T_0} \leq \frac{1}{2}$. Then by successively applying Lemma 3.5 over the time intervals $[nT_0, \infty)$ ($n = 1, 2, 3, \dots$) as in [9, 10, 18] one can get desired assertions.

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