Thai Journal of Mathematics
Volume 15 (2017) Number 3 : 611–627
http://thaijmath.in.cmu.ac.th
ISSN 1686-0209

Stability Analysis for Mathematical Model of Outer Rim on Avascular Tumor Growth

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Abstract : In this paper we study the linear stability of the outer rim on an avascular tumor growth model through the nonlinear system of ordinary differential equations, focusing on the relationship between growth, mutated and dead rate parameters on the proliferating and quiescent layers. We show that the system may have one or two equilibrium points, depending on whether the growth rate is less than or greater than the mutation rate of the cell density. Also, the results may be indicative for cancer treatment by radiotherapy.

Keywords : mathematical modeling; stability; avascular tumor growth.
2010 Mathematics Subject Classification : 34D20; 93A30.

1 Introduction

Nowadays, cancer is a disease that many people need to be alerted about. It is one group of diseases related to abnormal cell growth, in which the stem cell begins to divide without stopping and spreads into the surrounding tissues and can eventually affect any part of the body [1]. The survival rate of cancer is different depending on the cancer type and the diagnosed period. Inefficient treatment comes from the fact that the stem cell has spread beyond the original

Thanks! This research was supported by Chiang Mai University.

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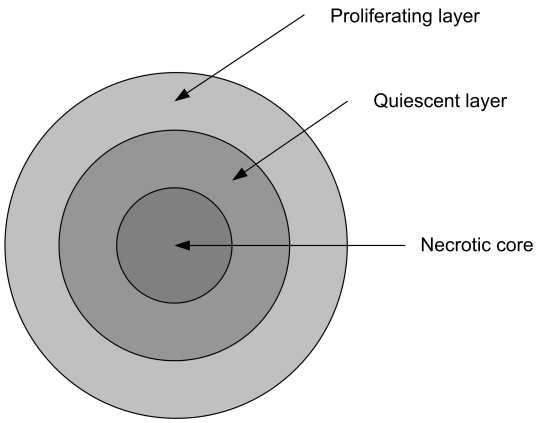

Figure 1: The structure of a multicellular tumor spheroid is divided into the proliferating layer, quiescent layer and necrotic core, respectively.

area, making diagnosis much more precarious; therefore, prevention of the cell invasion of cancer at an early stage of development is crucial.

Avascular tumor growth is abnormal cell distributions that have not passed through the blood vessels, and consequently, the understanding of its mechanics is not complicated. However, it is essential to obtain elementary surveillance before the tumor becomes cancerous because dead cells will create the necrotic core in the tumor and can be seen by X-rays. Moreover, radiation inhibition on the outer rim is also useful in preventing the overgrowth of tumors.

The first phase of tumor growth is hard to detect because of its small size. However, [2] studied the early growth by using the multicellular spheroid approach and under their experiments, they found that a seed cell is taken from a tumor cell line in place from a medium containing appropriate nutrients. Subsequently, the cells will divide indefinitely and spread out in a spheroidal shape. In obtaining nutrients, the cells cannot reach nutrients at the center of the spheroid. As a result, the tumor growth is divided into three layers following the cell nutrient consumptions, i.e. the proliferating layer, quiescent layer and necrotic core as shown in Figure 1. In the quiescent layer, the cells do not divide but remain alive. The cells can also be re-divided if the environment is suitable. That is important, since most cancer treatments, such as radiotherapy, focus on the cells that divide (see Figure 2). This is one example of therapeutic failures [3].

The mathematical modeling of an avascular tumor growth has a long history dating back to [4]. The previous models have fallen into two majority categories. The easiest method was developed by [5, 6], who used the ODE model for predicting variations in oxygen and other nutrient concentrations through spheres using experimental data to unknown quantities, such as diffusion rates. A more sophisticated model was developed by [7], who proposed a three-part cell division based on mitotic inhibitors. This model is useful to determine the position of inter-

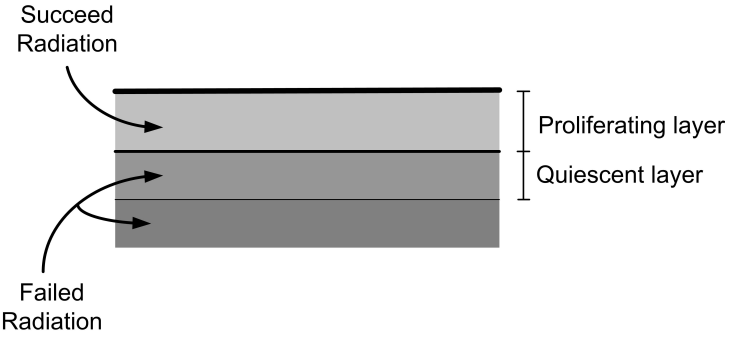

Figure 2: The outer rim of an avascular tumor and the succeed area of radiotherapy

faces between channels controlled by nutrient levels and inhibitors. Moreover, this method has been used extensively [8, 9, 10, 11, 12, 13]. In addition to these two modeling approaches, spatial structures are involved in the models. For example, a model that focuses on the evolution of cells irrespective of spatial structure, such as [14].

Recently, the role of cell death (apoptosis) in tumor growth has led to new mathematical models. Apoptosis was studied by [15, 16, 17, 18]. In some cases, the lack of dead cells causes neoplastic growth. Byrne and Chaplain [19] considered apoptosis and necrosis as mechanisms of different cell loss that analyze the effects of nutrients and inhibitors on the existence and stability of time- independent solutions for a multi-cell spheroid. Various other stability analyses of the avascular tumor growth have been studied by [12, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32].

Here, we provide the model of the outer rim on avascular tumor growth, which was formulated from the base on [33]. The model is formulated in terms of cell densities in the proliferating layer, quiescent layer, and the necrotic core with nonlinear diffusion term by using two variables, spatial coordinate (x) and time (t). In this research, we would like to precisely focus our work on the outer rim of the tumor growth because it affects the type of radiotherapy treatment performed. Thus, we will assume the cell densities are only in the proliferating and quiescent layers, called $p(t)$ and $q(t)$, respectively. Here, the spatial coordinate is ignored, which may affect the mixing of cell densities at the joints of the two layers. The behavior of cell densities in both layers is different according to some of the nutrients available. The cell's expansion rate is assumed to be restricted. The cell density is crowded until it does not consume enough of some of the nutrients. The tumor growth model set the nutrients as constant parameters and the meaning of the three parameters as α, β and γ, which correspond with the growth, mutated and death rate of cell densities in the proliferating and quiescent layers. A parameter α means the rate of cell division, which is in the proliferating

layer. The rate of cell parameter β is neither dividing nor preparing to divide of the cell. The death rate of cells is appearances up to parameter γ. We will study the relations among these three parameters by using mathematical theory to determine the behavior of the cell density in each layer and analyze the width of the proliferating and quiescent bands that match up with these parameters. The results will help us to make a decision about which process can prevent the cell extensions.

2 Mathematical Model

In this section, we consider a mathematical model for the outer rim of avascular tumor growth based on the model of [33]. Our model examines the cell densities of the proliferating layer $p(t) \geq 0$ and quiescent layer $q(t) \geq 0$, where t is time. As mentioned above, we assume that the tumor growth resembles a spheroid [2]. For mathematical simplicity, we are only interested in the thickness of the outer layer. This study facilitates analysis and will not have a significant effect except when the radius of the tumor is slight. We assume that the cell movement is not affected by other conditions. A reasonable mathematical model for the outer rim of avascular tumor growth is expressed in the nonlinear dynamical system

$$\begin{aligned} \dot{p} &= \alpha p(1-p-q) - \beta p \\ \dot{q} &= \beta p - \gamma q, \end{aligned} \tag{2.1}$$

where α, β and $\gamma > 0$ are the growth, mutated and death rate parameters. The first equation shows that cell populations have been rescaled so that a value of 1 corresponds to a completely close-packed population, while the cell density in the proliferating layer is lost in a standard linear decay to the quiescent layer. The rate of change in quiescent layer depends linearly on decay term from the proliferating layer, and it uses standard linear decay. From (2.1), we are able to analyze the local stability of the system according to Theorem 2.1.

Theorem 2.1. *Consider the system* (2.1)*, under the conditions of* $p(t)$, $q(t) \geq 0$, *for all* $t \geq 0$ *and* α, β,$\gamma > 0$. *Then:*

1. *If* $\alpha < \beta$, *then the system* (2.1) *has only one equilibrium point at the origin and locally stability is a stable node.*
2. *If* $\alpha > \beta$, *then the system* (2.1) *has two equilibrium points at the origin and the equilibrium point,*

$$(p^*, q^*) = \left(p^*, \frac{\beta}{\gamma} p^*\right), \quad p^* = \frac{1 - \frac{\beta}{\alpha}}{1 + \frac{\beta}{\gamma}}, \tag{2.2}$$

where their locally stabilities are saddle node and asymptotically stable, respectively.

Moreover, the system (2.1) *has a transcritical bifurcation point at* $\alpha = \beta$.

Proof. Examining the equilibria of the system (2.1), we take the two equilibrium points. One is the origin and another is (2.2).

It is clear that if $\alpha < \beta$, the equilibrium p^* is a negative value. Therefore, there is only one equilibrium point.

Next, we find the linearized system of (2.1) at the origin. By the Jacobian matrix, we get that

$$J(0,0) = \begin{pmatrix} \alpha - \beta & 0 \\ \beta & -\gamma \end{pmatrix},$$

the eigenvalues are $\alpha - \beta$ and $-\gamma$, implying a stable node when $\alpha < \beta$, and a saddle point when $\alpha > \beta$.

Next, let us reform into the linearization matrix at the equilibrium point (2.2), and we have

$$J(p^*, q^*) = A = \begin{pmatrix} \alpha\left(1 - 2p^* - \frac{\beta}{\gamma}p^*\right) - \beta & -\alpha p^* \\ \beta & -\gamma \end{pmatrix}. \tag{2.3}$$

Using the trace-determinant theorem and considering the case of $\alpha > \beta$. Thus, we get that

$$\mathrm{tr}A = -\gamma\left(\frac{\gamma + \alpha}{\gamma + \beta}\right) < 0, \quad \det A = \gamma(\alpha - \beta) > 0.$$

It follows that (2.2) is asymptotically stable.

Moreover, the system (2.1) can be reformulated into the normal form of the local transcritical bifurcation as such

$$\dot{p} = (\alpha - \beta)p - \alpha\left(1 + \frac{\beta}{\gamma}\right)p^2,$$

and this implies that the bifurcation point occurs at $\alpha = \beta$. □

The next theorem provides the specific stability at (2.2) from the relations between the parameters α, γ and β.

Theorem 2.2. *Consider the system* (2.1) *under the conditions of* $p(t)$, $q(t) \geq 0$, *for all* $t \geq 0$ *and* $\alpha > \beta > 0$, $\gamma > 0$. *Define a function* $f : \mathbb{R}^3_+ \to \mathbb{R}$ *by*

$$f(\alpha, \beta, \gamma) = \gamma\left(\frac{\alpha + \gamma}{\beta + \gamma}\right)^2 - 4(\alpha - \beta). \tag{2.4}$$

Then:

1. *An equilibrium point* (2.2) *is a stable node when*

$$f(\alpha, \beta, \gamma) > 0.$$

2. *An equilibrium point* (2.2) *is a stable focus when*

$$f(\alpha, \beta, \gamma) < 0,$$

Proof. Since

$$(\mathrm{tr}A)^2 - 4\det A = \gamma f(\alpha, \beta, \gamma),$$

and recall the trace-determinant theorem. □

The plotting of function (2.4) is shown in Figure 3.

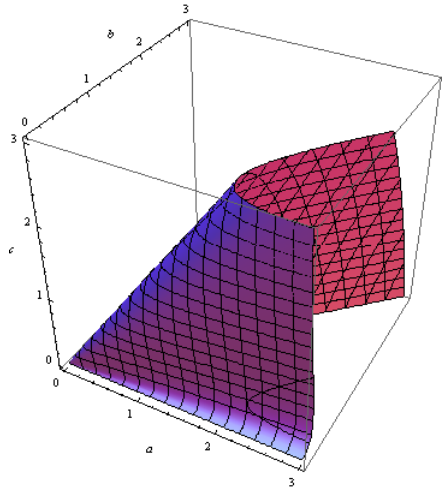

Figure 3: Plotting of function (2.4), with α (a-axis), β (b-axis) and γ (c-axis).

The next corollary shows about the other relations among the three parameters.

Corollary 2.3. *Consider the system* (2.1) *under the conditions of* $p(t)$, $q(t) \geq 0$, *for all* $t \geq 0$ *and* $\alpha > \beta > 0$, $\gamma > 0$. *Define a function* $f : \mathbb{R}^3_+ \to \mathbb{R}$ *by* (2.4). *Then:*

1. *An equilibrium point* (2.2) *is a stable node when* γ *tends to infinity or* α *is close to* β.
2. *An equilibrium point* (2.2) *is a stable focus when* γ *approaches to zero.*

Proof. First, we use Theorem 2.2 and the setting γ tends to infinity, so that (2.4) goes to infinity for all α, $\beta > 0$.

For α is close to β. We let α approaches to β, therefore

$$\lim_{\alpha \to \beta^+} f(\alpha, \beta, \gamma) = \gamma > 0,$$

the stable node at (2.2) will occur by Theorem 2.2.

In the next step, we start by setting γ approaches to zero and get that

$$\lim_{\gamma \to 0^+} f(\alpha, \beta, \gamma) = -4(\alpha - \beta) < 0.$$

Then, we conclude that (2.2) is a stable focus by using Theorem 2.2. □

Figure 4 provides the stable node region, when γ is fixed as 0.1, 2 and 4, respectively.

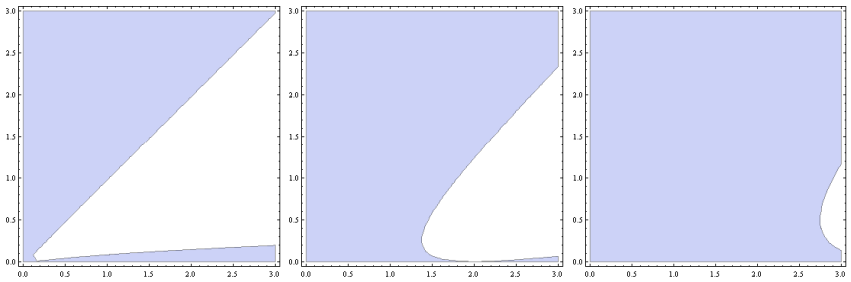

Figure 4: The region plot of function (2.4) is positive when γ is fixed at 0.1, 2 and 4. The parameters α and β are expressed as the horizontal-axis and vertical-axis, respectively.

Subsequently, we would like to know why the trajectory results have to stay in the closed boundary region.

Let us consider the relation between β and γ, which gives the meaning of a line slope (2.2) as shown in Figure 5, but it is not over the domain because of the closed-packed population,

$$T = \{(p, q) \in \mathbb{R}^2_+ \mid p + q < 1\} \tag{2.5}$$

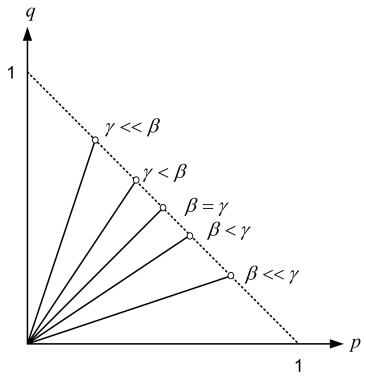

Figure 5: The graph for the family of equilibrium points comparing between β and γ.

The following proposition explains the bounded domain for testing the global stability of the system (2.1).

Proposition 2.4. *The region $T_0 = T \cup [0, 1]^2$ is positively invariant.*

Proof. Firstly, we will try to prove that all directional fields have to be inward in the region T_0 as shown in Figure 6.

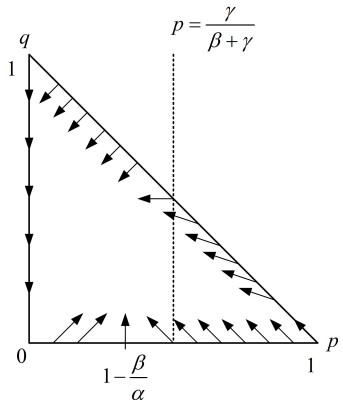

Figure 6: The region T_0 is invariant.

Secondly, we check that the direction of the vector field is along the boundary of T_0. The field is tangent to the boundary along $p = 0$ as well as at $(0, 1)$. Along the lower edge $q = 0$, we get

$$\dot{p} = \alpha p\left(1 - \frac{\beta}{\alpha} - p\right)$$
$$\dot{q} = \beta p > 0$$

So, we get $\dot{p} = 0$ at $p = 0$ and $p = \frac{\alpha-\beta}{\alpha} = 1 - \frac{\beta}{\alpha}$ and

- if $0 \leq p \leq 1 - \frac{\beta}{\alpha}$, it means that $\dot{p} > 0$
- if $1 - \frac{\beta}{\alpha} \leq p \leq 1$, it means that $\dot{p} < 0$

We would like to show that $\dot{p} < 0$, means its tangent is equal to a diagonal in the boundary T_0 at $(1, 0)$. Consider the following;

$$\left.\frac{dq}{dp}\right|_{(1,0)} = \left.\frac{\dot{q}}{\dot{p}}\right|_{(1,0)} = \left.\frac{\beta p - \gamma q}{\alpha p(1 - p - q) - \beta p}\right|_{(1,0)} = -1$$

Hence, the vector field points inward for $0 \leq p < 1$ and at $p = 1$ the vector field is tangent in the boundary of T_0. Along the hypotenuse, we get $p + q = 1$, that is

$$\dot{p} = -\beta p < 0$$
$$\dot{q} = (\beta + \gamma)\left(p - \frac{\gamma}{\beta + \gamma}\right)$$

So that $\dot{q} = 0$ at $p = \frac{\gamma}{\beta+\gamma} < 1$.

- if $0 < p < \frac{\gamma}{\beta+\gamma}$, it means that $\dot{q} < 0$.
- if $\frac{\gamma}{\beta+\gamma} < p < 1$, it means that $\dot{q} > 0$.

Next, we have to check that in case $\frac{\gamma}{\beta+\gamma} < p < 1$, the vector field should be inward or conclude that the tangent has to be greater than -1. Consider

$$\frac{dq}{dp} = -1 + \frac{\gamma}{\beta}\left(\frac{1}{p} - 1\right) \tag{2.6}$$

Then, let us consider the second term on the right hand side of (2.6), we have

$$0 < \frac{\gamma}{\beta}\left(\frac{1}{p} - 1\right) < 1$$

Then

$$-1 < \frac{dq}{dp} < 0$$

The proof is completed and for further understanding see Figure 6. □

3 Discussion

We summarize the characteristics of the tumor growth according to the growth rate (α), mutated rate (β) and dead rate (γ) parameters in two ways. First, we discuss the tumor rim growth over time. Secondly, we explain how the width of the tumor margin can be interpreted by considering the relations among the parameters.

We start by interpreting the results of the model from studying the relations of parameters with the stability analysis and give some recommendations on how to prevent each type of tumor growth as follows.

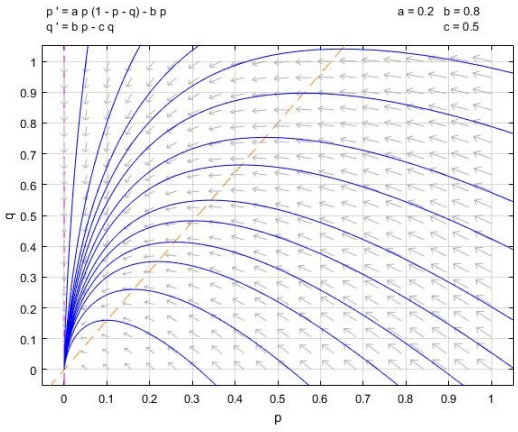

Figure 7: 2-D phase portrait of the cell densities p and q when $\alpha = 0.2$, $\beta = 0.8$ and $\gamma = 0.5$

Case I: The growth rate is less than the mutated rate ($\alpha < \beta$)

The stability of the system is shown in Figure 7 with a stable node at the origin. An example of the cell densities in both of the two layers approaches to zero as seen in Figure 8.

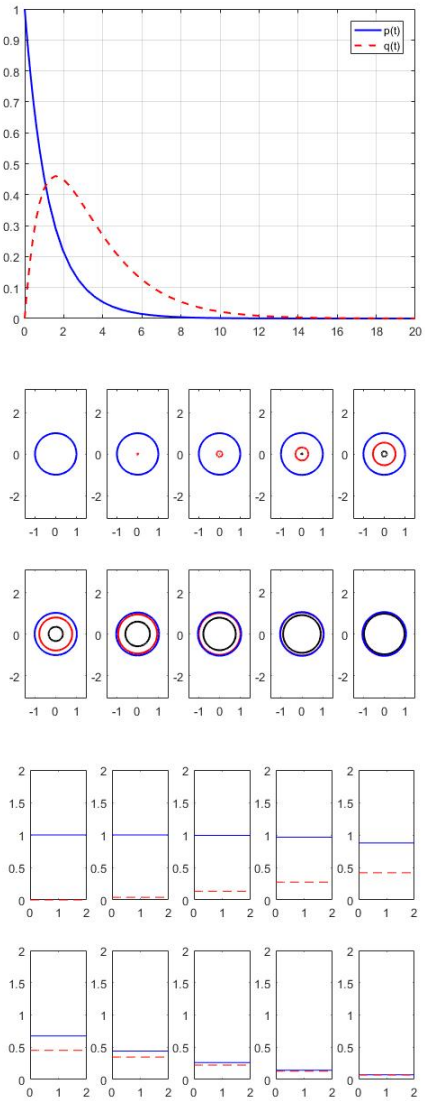

Figure 8: The cell densities over time and the snapshots of the tumor growth obtained from the results when $\alpha < \beta$

This figure setting is 20 time-steps and put the initial values at $p(0) = 1$ and $q(0) = 0$. It shows that the tumor growth is extended in the first phase.

After that it does not grow because the equilibrium point is stationary at the origin, and the outer rim of the tumor does not develop, like shown in Figure 8. The death cells appear after several cell cycles, and the percentage of death cells is a limited value. The cancer treatment recommendations are to prevent the stem cells from expanding into the bloodstream to avoid the metastasis or suppress the tumor by cutting it off.

Case II: The growth rate is greater than the mutated rate ($\alpha > \beta$)

From Theorem 2.2, the stability at (2.2) can be expressed in two possible ways up to (2.4). There are stable nodes and stable focus stabilities, as shown in Figure 9 and 10, respectively.

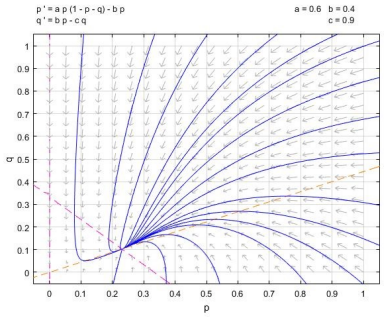

Figure 9: 2-D phase portrait of the cell densities p and q when $\alpha = 0.6$, $\beta = 0.4$ and $\gamma = 0.9$, with a stable node stability at an equilibrium point $(0.23, 0.1)$

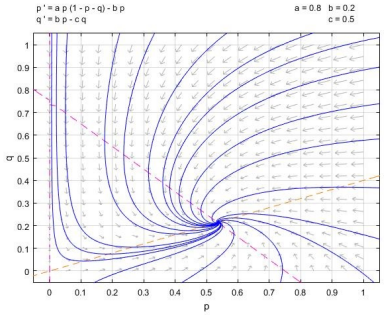

Figure 10: 2-D phase portrait of the cell densities p and q when $\alpha = 0.8$, $\beta = 0.2$ and $\gamma = 0.5$, with a stable focus stability at an equilibrium point $(0.54, 0.21)$

The description of tumor growth is quite complicated. In the initial analysis, it is possible to analyze the growth in the two major locations near the origin and (2.2). If the initial value of cell density p appears near zero, the rim of the tumor narrows to the point of almost disappearing, but it does not. After that, the cell densities will increase and approach to (2.2) because of the results from Theorem 2.1, a trajectory line is visible near the q-axis as seen in Figure 9 and 10. Nevertheless, this case does not appear because it is

not possible to initiate the cell density in the proliferating layer near zero in real situations. In the long run, no matter where the initial cell densities are, the cell densities enter to (2.2) in two ways, i.e., node and focus, depending on each condition in Theorem 2.2. Thus, the tumor growth is classified into two modes. Such example results are shown in Figure 11.

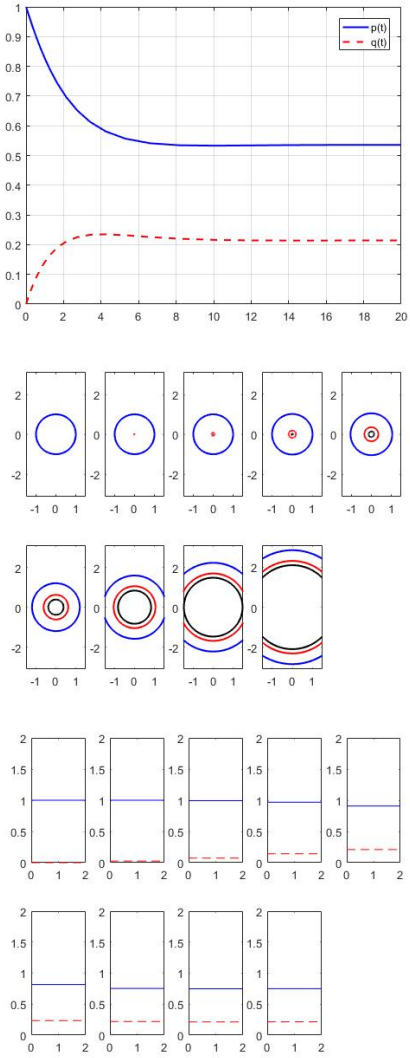

Figure 11: The cell densities over time and the snapshots of the tumor growth obtained from simulations at different times for the case of $\alpha > \beta$.

The tumor growth is particularly problematic at this point because the growth factor has the potential to expand the dangerous cells into the blood vessels (metastasis), and the cell densities p and q are the equilibrium points

for a long time. The cell density in the quiescent layer accumulates into the necrotic core, which is the source of the tumor growth. Here, the outer rim of the tumor can be predicted and it is useful to inhibit the growth by irradiation to the stratum where the cell is divided (proliferating layer). This study explains the behavior of the outer rim in two cases. First, the stable node at the equilibrium point means that the tumor enters the stationary band in a direct way. That is different with the stable focus stability, where the behavior of the outer rim increases and decreases in a periodic manner to the equilibrium point. Therefore, radiotherapy must maintain caution in predicting the width of the layer to avoid irradiation errors. Moreover, additional conditions have been studied in Corollary 2.3, which can be characterized in the medical field.

- The growth rate is close to the mutated rate, or the dead rate is much higher implies that the equilibrium point is a stable node.
- The dead rate is close to zero, and thus, predicates that the equilibrium point is a stable focus.

Case III: The growth rate is equal to the mutated rate ($\alpha = \beta$)

In this case, we cannot explain much about the behavior of the system in mathematical theory because it is a case of the transcritical bifurcation point. However, we can study the behavior by using the numerical method, as shown Figure 12. An example is shown in Figure 13.

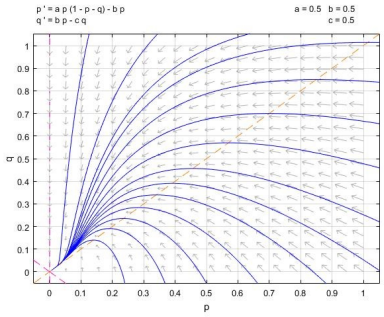

Figure 12: The 2-D phase portraits of the cell densities p and q when $\alpha = 0.5$, $\beta = 0.5$ and $\gamma = 0.5$

It indicates that the cell density at the margin of the tumor slowly enters to the equilibrium point at the origin. i.e., the tumor will slowly grow. Therefore, the medical cure guidelines may not have to hasten the treatment like that of the second case, but we cannot let tumors grow as well. The treatment may be performed in a non-aggressive way, such as by pharmacotherapy or pure tumor inhibition, which is safer than radiotherapy.

Another positive condition is the prediction of the width of the tumor rim, which is demonstrated by the relation between parameters β and γ. It is examined

from (2.2) and shown in Figure 5. It is useful for irradiation to hit the right target. Hence, the result is presented in the three cases:

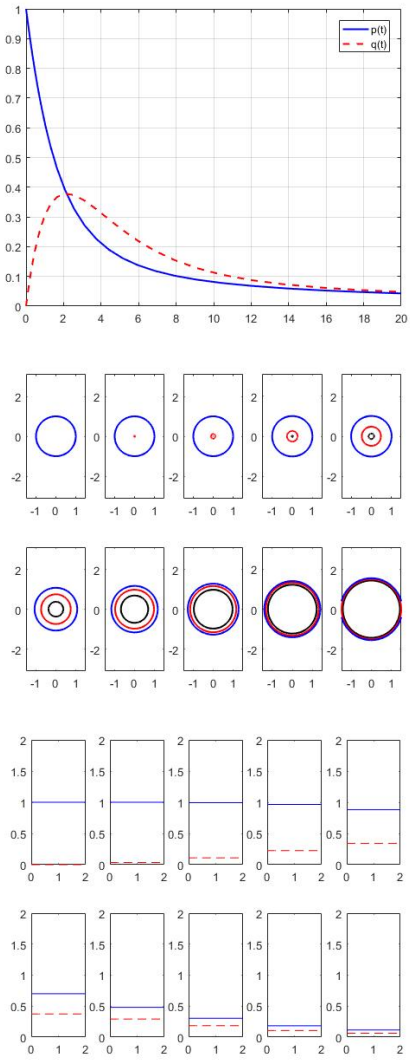

Figure 13: The cell densities over time and the snapshots of the tumor growth obtained from simulations at different times for the case of $\alpha = \beta$.

Case I: The mutated rate is less than the dead rate ($\beta < \gamma$)

The research shows that the thickness of the outer rim of the tumor (proliferating layer) is thicker than the layer where the cells are stationary. The opportunity to inhibit growth through radiation has a greater chance of success.

Case II: The mutated rate is equal to the dead rate ($\beta = \gamma$)

The cell densities of the tumor rim at the equilibrium point are symmetric in this case. It means that the widths are the same on both layers of the tumor edge.

Case III: The mutated rate is greater than the dead rate ($\beta > \gamma$)

The results designate that radiotherapy confronts an obstacle since the quiescent layer is thicker than the proliferating layer. This may lead to failed radiotherapy.

In this study, we used the mathematical model for predicting the tumor growth based on growth, mutated, and death rate parameters, with a focus on the stability of the nonlinear dynamical system. The result is a type of local stability at the equilibrium points. It is useful in applications such as selection of the appropriate treatment or tumor suppressor suitable for each type of tumor growth. Furthermore, if it is possible to obtain adequate and reliable observed data on the relevant parameters, it can be better developed for our models. However, these data are often the property of a pharmaceutical company that sponsors experiments for qualitative research. Nevertheless, our results can generate significant quantitative predictions for tumor growth which may be useful for tumor prognosis and individual therapies. Finally, we hope that our work will be helpful to improve the suitable results for cancer treatment in the future.

Acknowledgements : This research was supported by Chiang Mai University.

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(Received 9 August 2017)
(Accepted 10 September 2017)