Far East Journal of Mathematical Sciences (FJMS)

http://www.pphmj.com
http://dx.doi.org/10.17654/MS103101535
Volume 103, Number 10, 2018, Pages 1535-1546 **ISSN: 0972-0871**

GLOBAL STABILITY OF THE DISEASE FREE EQUILIBRIUM IN A CERVICAL CANCER MODEL: A CHANCE TO RECOVER

Lina Aryati[1], Tri Sri Noor-Asih[2], Fajar Adi-Kusumo[1] and Mardiah Suci Hardianti[3]

[1]Department of Mathematics
Faculty of Mathematics and Natural Sciences
Universitas Gadjah Mada
Indonesia

[2]Department of Mathematics
Faculty of Mathematics and Natural Sciences
Semarang State University
Indonesia

[3]Faculty of Medicine
Universitas Gadjah Mada
Indonesia

Abstract

We consider a cervical cancer model with a treatment focusing on the precancerous cells. As one of the objectives of treatment is dealings with recovery, in this paper, we give the sufficient conditions for the disease free equilibrium to be globally asymptotically stable. These conditions hopefully could guide us in the effort of healing. We also give numerical simulation to illustrate the dynamic of recovery process.

Received: November 10, 2017; Revised: January 19, 2018; Accepted: February 3, 2018
2010 Mathematics Subject Classification: 37N25, 62P10.
Keywords and phrases: cervical cancer, disease free equilibrium, global stability.

1. Introduction

It is known that cervical cancer is one of the malignant diseases which is caused by Human Papilloma Virus (HPV). It is the fourth most common cause of cancer-related deaths in women [9] and getting worse if there is a co-infection by HIV [7, 8].

The usual treatment be given to the patient is chemotherapy. The standard chemo drugs often works against the cancer cells, but it can also affect other cells in the body that divide quickly, which can sometimes lead to serious side effects [10]. This problem makes the medical researchers tried to see other possibilities treatment, such as targeted therapy. Many targeted drugs go after the cancer cells' inner working the programming that makes them different from normal, healthy cells, while leaving most healthy cells alone [10]. On other hand, the precancerous changes caused by HPV can be detected by Pap tests and treated [3]. If left untreated, it may take 10 years or more for precancerous condition of cervix to turn into cervical cancer, but sometimes this happen in less time [6]. Furthermore, in [4], we learned that the therapy should be focused to the precancerous cells. This research is intended to the possibility in recovering from cervical cancer with a specific treatment on the precancerous cells and it is the continuation of our research in [4, 5]. Therefore, in Section 2, we concentrate on global stability of the disease free equilibrium (DFE) of the model, then give numerical simulation to illustrate the analytical behavior in Section 3, and finally conclude with some remarks.

2. Mathematical Model and the DFE Stability Analysis

We consider our nondimensional model in [4, 5] with giving a treatment which is to be focused to the precancerous cells. We assume the treatment will reduce the precancerous cell population linearly with rate β and give side effect to the cancer cell population, decays by term $m\frac{PC}{1+P^2}$. Therefore, we concern with the following model:

$$\dot{S} = rS(1-(S+I)) - \alpha SV,$$

$$\dot{I} = \alpha SV - aI - \delta I,$$

$$\dot{V} = nI - \gamma V,$$

$$\dot{P} = \delta\rho I + bP - \theta\frac{P^2}{1+P^2} - \beta P,$$

$$\dot{C} = \theta\frac{P^2}{1+P^2} - kC - m\frac{PC}{1+P^2}. \tag{1}$$

Note that if $\beta = m = 0,$ system (1) will be reduced to our model in [4, 5]. In this model, we have five compartments: susceptible (normal) cells (S), infected cells (I), free virus (V), precancerous cells (P), and cancer cells (C). The parameters r and α are successively the intrinsic growth rate and the infection rate. The infected cell population grows or decays linearly with rate a and has possibility become a precancerous form with rate δ. New virions are produced at a rate proportional to the death rate of infected cells, which is n, and decay linearly at rate γ. The parameter θ is the maximal progression rate from precancerous to cancerous. The precancerous cell population grows or decays at rate b and the transition from precancerous to cancerous form is governed by a saturating term $\theta P^2/(1+P^2)$. Cancer cells, once formed, will have a growth rate $-k$.

Let $N = S + I + V + P + C.$ If $b < 0$ and $a + \delta(1-\rho) - n > 0,$ then from (1) we have

$$\dot{N} \le (r+1) - \mu N,$$

where $\mu = \min\{1, a + \delta(1-\rho) - n, \gamma, \beta - b, k\}$. The set

$$\Omega = \left\{(S, I, V, P, C) | 0 \le V, 0 \le S, I, P, C \le 1, S + I + V + P + C \le \frac{r+1}{\mu}\right\}$$

is then a feasible region of the model. It can be proved that the set Ω is positively invariant.

The following theorem shows that the DFE $(1, 0, 0, 0, 0)$ is locally asymptotically stable.

Theorem 2.1. *Given the basic reproduction number* $R_0 = \frac{\alpha n}{\gamma(a+\delta)}$. *If* $b < 0$ *and* $R_0 < 1$, *then the DFE* $(1, 0, 0, 0, 0)$ *is locally asymptotically stable*.

Proof. It is easy to derive that the Jacobian matrix at the DFE $(1, 0, 0, 0, 0)$ is

$$J(DFE) = \begin{pmatrix} -r & -r & -\alpha & 0 & 0 \\ 0 & -(a+\delta) & \alpha & 0 & 0 \\ 0 & n & -\gamma & 0 & 0 \\ 0 & \delta\rho & 0 & b-\beta & 0 \\ 0 & 0 & 0 & 0 & -k \end{pmatrix}.$$

If $b < 0$ and $R_0 < 1$, then we have $b - \beta < 0$ and $\gamma(a+\delta) - \alpha n > 0$, respectively. Since all other parameters are positive, the eigenvalues of $J(DFE)$ are all negative. □

From the above theorem, we know that its sufficient conditions for the DFE to be locally asymptotically stable remind the same with those in [4], but later, the numerical simulation will show that the treatment will accelerate the recovery process.

Next, we will deal with global stability of the DFE. We consider the domain $D = \left\{(S, I, V, P, C) \in \Omega \mid P \le \frac{m}{\theta} C\right\}$. We use the next generation method given by Brauer and Castillo-Chavez in [1] to prove the following theorem.

Theorem 2.2. *Given* $R_0 = \frac{\alpha n}{\gamma(a+\delta)}$. *If* $R_0 < 1$, *then the DFE* $(1, 0, 0, 0, 0)$ *is globally asymptotically stable in D*.

Proof. Take $X = (I, V, P, C)$ and $Y = S$. System (1) then can be written as

$$Y' = g(X, Y), \tag{2}$$

$$X' = \mathcal{F}_i(X, Y) - \mathcal{V}_i(X, Y), \quad i = 1, 2, 3, 4, \tag{3}$$

where $\mathcal{F}_i$ and $\mathcal{V}_i$ are, respectively, the components of column vector

$$\mathcal{F} = \begin{pmatrix} \alpha SV \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} aI + \delta I \\ \gamma V - nI \\ \theta \dfrac{P^2}{1+P^2} + \beta P - \delta\rho I - bP \\ kC + m\dfrac{PC}{1+P^2} - \theta\dfrac{P^2}{1+P^2} \end{pmatrix}.$$

We straightforward have, for $i = 1, 2, 3, 4$, $\mathcal{F}_i(0, Y) = 0$ and $\mathcal{V}_i(0, Y) = 0$, for every $Y \geq 0$. The functions $\mathcal{F}_i(X, Y) \geq 0$, for every $X, Y \geq 0$. For $i = 1, 2, 3, 4$, if $X_i = 0$, then $\mathcal{V}_i(X, Y) = 0$. Since $y' = g(0, Y) = ry(1 - y)$, its DFE $(0, 1)$ is locally asymptotically stable. Furthermore, we find that

$$\sum_{i=1}^{4} \mathcal{V}_i(X, Y) = (a + \delta(1 - \rho) - n)I + \gamma V + \beta P - bP + kC + m\frac{PC}{1+P^2},$$

which is nonnegative, since it is provided that $b < 0$ and $a + \delta(1 - \rho) - n > 0$. The matrix

$$F = \left(\frac{\partial \mathcal{F}_i}{\partial X_j}\right)_{(0, 1)} = \begin{pmatrix} 0 & \alpha & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

is nonnegative. Next, we have

$$V = \left(\frac{\partial \mathcal{V}_i}{\partial X_j}\right)_{(0,\,1)} = \begin{pmatrix} a+\delta & 0 & 0 & 0 \\ -n & \gamma & 0 & 0 \\ -\delta\rho & 0 & \beta - b & 0 \\ 0 & 0 & 0 & k \end{pmatrix}.$$

By choosing $s = a + \delta + \gamma + \beta - b + k,$ the matrix V can be written as $V = sI_{4\times 4} - B,$ with

$$B = \begin{pmatrix} \gamma + \beta - b + k & 0 & 0 & 0 \\ n & a + \delta + \beta - b + k & 0 & 0 \\ \delta\rho & 0 & a + \delta + \gamma + k & 0 \\ 0 & 0 & 0 & a + \delta + \gamma + \beta - b \end{pmatrix}.$$

Since $b < 0,$ and all other parameters are positive, we get $B \geq 0,$ and therefore V has Z-sign pattern. It can be calculated that

$$V^{-1} = \begin{pmatrix} \frac{1}{a+\delta} & 0 & 0 & 0 \\ \frac{n}{\gamma(a+\delta)} & \frac{1}{\gamma} & 0 & 0 \\ \frac{\delta\rho}{(\beta-b)(a+\delta)} & 0 & \frac{1}{\beta-b} & 0 \\ 0 & 0 & 0 & \frac{1}{k} \end{pmatrix},$$

which is also nonnegative for $b < 0.$ Hence, V is a non-singular M-matrix. If $R_0 = \frac{\alpha n}{\gamma(a+\delta)} < 1,$ then from

$$FV^{-1} = \begin{pmatrix} \frac{\alpha n}{\gamma(a+\delta)} & \frac{\alpha}{\gamma} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

we know that $\rho(FV^{-1}) = \dfrac{\alpha n}{\gamma(a+\delta)} = R_0 < 1$. Furthermore, we can rewrite the system (3) as

$$\begin{pmatrix} \dot{I} \\ \dot{V} \\ \dot{P} \\ \dot{C} \end{pmatrix} = (F - V)\begin{pmatrix} I \\ V \\ P \\ C \end{pmatrix} - f(X, Y), \tag{4}$$

where

$$f(X, Y) = \begin{pmatrix} \alpha V(1-S) \\ 0 \\ \theta \dfrac{P^2}{1+P^2} \\ \dfrac{P}{1+P^2}(-\theta P + mC) \end{pmatrix}.$$

Therefore, in the domain D, the function $f(X, Y) \geq 0$, and the proof is complete. □

Remark. Suppose $A = V - F$. Then (4) can be written as

$$\dot{X} = -AX + f(X, Y).$$

Given initial value $X(0)$, then we have solution

$$X(t) = e^{-At}X(0) - \int_0^t e^{-(t-s)A} f(X(s), Y(s))ds.$$

It can be proved that A is an M-matrix

$$-A = \hat{B} - sI,$$

with $\hat{B} \geq 0$. This implies that

$$e^{-tA} = e^{t\hat{B}}e^{-stI} = e^{t\hat{B}}e^{-st}I = e^{t\hat{B}}e^{-st} \geq 0.$$

Note that $f(X, Y) \geq 0$ in D, hence we get

$$0 \leq X(t) \leq e^{-tA} X(0).$$

It means that the solution is nonnegative and tends to zero as t tends to infinity.

3. Numerical Simulation

In the following, we give numerical simulation to illustrate the analytical results. We take parameter values:

$$r = 0.2,\ \alpha = 0.5,\ a = 100,\ \delta = 0.01,\ n = 98,\ \gamma = 50,$$

$$\rho = 1.4,\ \theta = 1.5,\ k = 0.02,\ b = -0.00001,\ \beta = 0.9,\ m = 0.9,$$

except in the case without treatment, of course, we take $\beta = m = 0$. The basic reproduction number is $R_0 = 0.0098$.

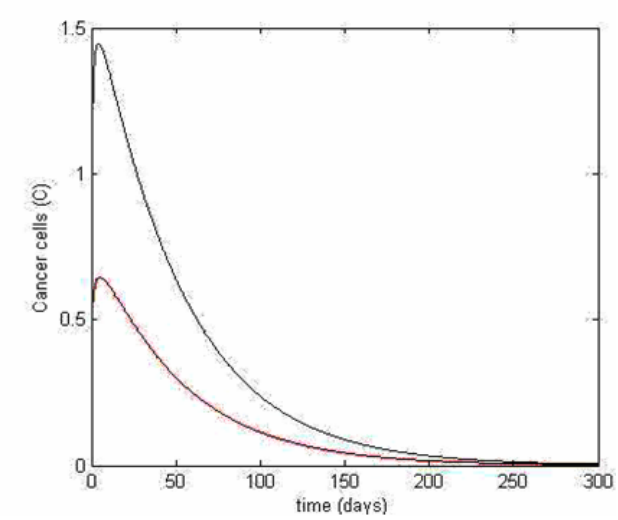

Figure 1. Trajectory of the cancer cells without treatment with initial value $(S, I, V, P, C) = (0, 1, 100, 0.7, 1)$ (black) and $(S, I, V, P, C) = (0, 1, 100, 0.3, 0.5)$ (red).

Figure 1 shows the nontreatment case, that is, for $m = \beta = 0$, as the initial condition sufficiently large, then the spread of cancer is quite quickly. The cancer cell population increases significantly which indicates a possibility of metastasis. This result is reasonable, because without any treatment, as state in [4], the DFE is only locally asymptotically stable. This problem will not happen under treatment, the metastasis can be avoided as shown in Figure 2. Figures 2 and 3 also give illustrations that giving treatment will decrease the precancerous cells as well as the cancer cells faster that those without treatment. Patients with treatment will recover faster that those without treatment.

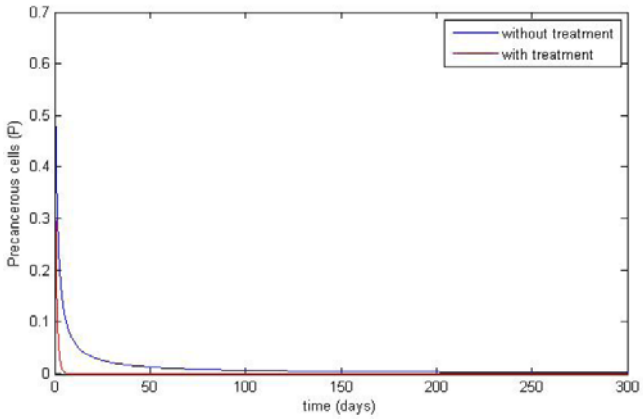

Figure 2. Trajectory of the precancerous cells with initial value $(S, I, V, P, C) = (0, 1, 100, 0.7, 1)$.

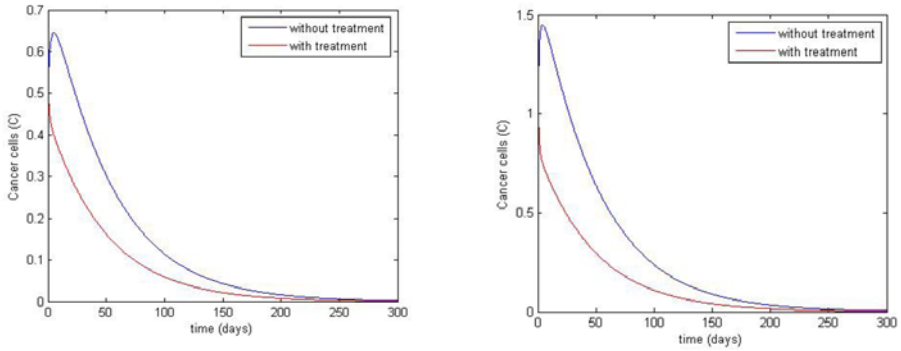

Figure 3. Trajectory of the cancer cells with initial value $(S, I, V, P, C) = (0, 1, 100, 0.3, 0.5)$ (left) and $(S, I, V, P, C) = (0, 1, 100, 0.7, 1)$ (right).

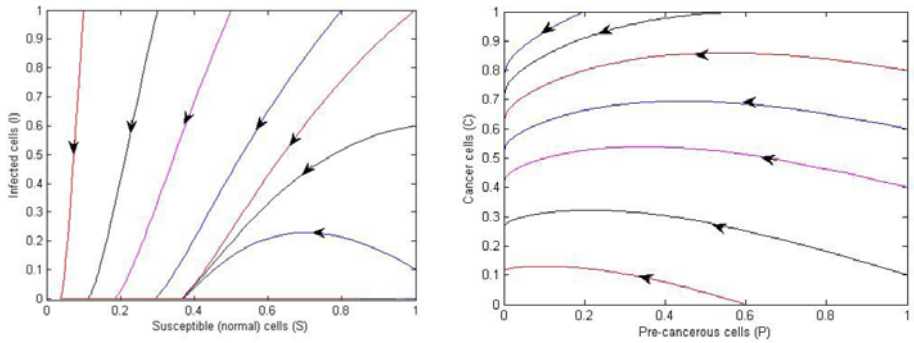

Figure 4. Phase Portrait S vs I (left) and P vs C (right).

Figure 4 shows numerically that the DFE is globally asymptotically stable, the treatment can eradicate the infected, precancerous, and cancer cells. Patient recovers from cervical cancer.

4. Concluding Remarks

During the past several years, the role of targeted and biologic therapy has been evaluated in cervical cancer [2]. Although many targeted drugs go after the cancer cells' inner workings, but there are less common but more serious side effects including problem with bleeding, blood clots, wound healing [10]. This research hopefully could give an idea that focusing

treatment on the precancerous cells will give more chance for patients to recover. Our results agree with those for hepatocellular carcinoma given by Zheng et al. in [11]. They have introduced an effective precancerous cell-targeted therapy base on animal model and stated that anti-precancerous cell drug development should be a major target during cancer elimination. However, the implementation in the medical sense still needs times. It will become a reality that development of drugs that target to the precancerous cells of cervix will help patients to recover. For a future work we will do bifurcation analysis and sensitivity parameter of our model.

Acknowledgments

The authors would like to thank the Directorate Research and Community Services, Directorate General of Higher Education, the Ministry of Research, Technology, and Higher Education, Republic of Indonesia, for financial support through the Research Grant “Penelitian Terapan Unggulan Perguruan Tinggi (PTUPT)” Universitas Gadjah Mada, No: 001/SP2H/LT/DRPM/V/2017. The authors also would like to express their gratitude to the anonymous reviewers for useful comments and suggestions.

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