Analysis of Local Stability and Bifurcation in Cervical Cancer and Immune Cells Interaction

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Abstract. The dynamics of cervical cancer cells and immune cell interaction are modeled into a three-dimensional nonlinear differential equation system. It is a representation of the interaction model between one prey and two predators, with cervical cancer cells as prey and two types of immune cells as predators. The nature between these predators is a supportive relationship. Based on the mathematical model is obtained that there are six steady states in which three of them exist and the others do not exist for biological cases. Based on the analysis of stability near these steady states there has a bifurcation point about the steady states. By modifying some parameters value, there is a possibility to heal the cervical cancer sufferers.

1. Introduction

Cervical cancer is a malignant disease with mortality (death) of 275,128 people and estimated morbidity (illness) of 529,828 people each worldwide. In Indonesia, cervical cancer is the second-largest type of cancer in which the number of cases about 32,469 people in 2018 [1]. WHO reports about 99.7% of cervical cancer cases caused by Human papillomavirus (HPV).

The formation of cervical cancer cells begins at the multiplier of Human papillomavirus (HPV) that enters the tissues of the human cervix. Cervical cancer cells fail when it is absorbed by identifiers immune cells (macrophages). While the resting T cells then activate attack immune cells through a substance produced by the identifying immune cells.

HPV is considered as non-self (antigen) by the macrophage. Macrophage recognizes, destroys, and swallows phagocytes against the antigens it faces. Macrophages exist in the blood membranes, capillary lymphatic in the bone marrow, spleen, lymph nodes, and liver. In addition to shifting around, macrophages are also the first immune cells to look for places of infection, transmit information about recognized antigens to T-helper cells and then replicate themselves into multiple attack cells with the help of cytokine compounds. The attacker's immune cells attack any antigen or cell containing antigens (cervical cancer cells). This process will be finished if all substances considered antigens can be eliminated from the human body.

A summary of the relation between the three cells can be explained in Figure 1. To get more analysis of the relationship between the three variables, we did local stability and bifurcation analysis to find the critical parameters that can make changes in the behaviour of the system near the steady states.
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The model developed in this study refers to [4]. This paper describes the interaction between healthy cells, tumor cells, and immune cells. The results show that there is a bifurcation in the model depending on the interval of the parameter value specified. This research specifically discusses a more specific cervical cancer and contributes to determining other steady states and its stability. In addition, the bifurcation analysis will be done analytically.

Another paper referred to as Bifurcation Analysis of the Cervical Cancer Cells, Effector Cells, and IL-2 Compound Interaction Model with Immunotherapy published in the Journal of far East Journal of Mathematic Sciences specifically examined bifurcation analysis of cervical cancer models with the help of immune therapy. In the study [8] there was one infection-free equilibrium point and six equilibrium points of HPV infection whose stability was not obtained analytically using the Jacobian matrix because it contained the roots of a sixth-rank polynomial that could not be explicitly determined in value. Bifurcation analysis is used to determine the local stability of the equilibrium points. The difference between this study and the study [8] is in the variables used, where [8] model the interaction between cervical cancer cells, immune cells, and IL-2 cells. Model analysis [8] was referenced in this study for equilibrium points as well as local stability and bifurcation.

Another reference study, Modelling Immunotherapy of the Tumor Immune Interaction was developed by [9] published in the Journal of Mathematical Biology. In his research, bifurcation analysis of tumor cell interaction models with effector cells, and IL-2 numerically using XPPAUT 3.0 software. According to [9], antigenicity plays an important role in the healing of tumors. The dynamics of tumor-immune without immunotherapy depend on the antigenicity of tumor cells.

2. Discussion

2.1. Mathematical Models
Mathematical models that describe the interaction among three variables, i.e., identifying immune cells, natural killer cells, and infected cells follow these assumptions:
1. The first predator on the model is the immune cell identifier (Macrophage).
2. Macrophage absorbs tumor cells, eat them, and release cytokines that activate the attacker's immune cells (Natural Killer Cells).
3. Resting T-Cells can be directly stimulated to produce natural killer cells.
4. Conversion resting cells into attacking cells cause a reduction in the number of resting cells undergoing their natural growth and the addition of the number of attack cells.
5. Cancer cells are reduced at a rate proportional to cancer cell density and follow the Mass Action Law.
6. After converting into an effector cell, then the predator cell cannot return to the resting cell. So the active cell will die with a constant chance per unit of time.
7. During the resting phase, the prey and predators have an infinite food supply, experience mitosis, and tumor cells benefit from the proliferation of normal cells.

The model is arranged in the following system

\[
\begin{align*}
\frac{dx}{dt} &= 1 + x(a_1 - x) - y \\
\frac{dy}{dt} &= y(a_2 y - a_3) \\
\frac{dz}{dt} &= z(a_4 (1 - z) - a_5 y - a_6)
\end{align*}
\]

(1) (2) (3)

Where \(x(t), y(t), \text{ and } z(t)\) are density of cervical cancer, attacker immune cell, and identifier immune cell.

2.2. Steady States

According to [12], steady states of the model is obtained by solving

\[
\frac{dx}{dt} = 0
\]

(4)

with \(x \in D, D \subseteq E \subseteq R^n\). There are two cases by solving \(\frac{dy}{dt} = 0\), i.e. \(y = 0\) or \(z = \frac{a_1}{a_2}\).

After substituting \(y = 0\) to System (4), we found four steady states. The result below are obtained

1. Steady states \(E_1 = (x_1, y_1, z_1)\) with \(x_1 = \frac{1}{2} \left(1 + \sqrt{1 + \frac{4}{a_1}}\right), y_1 = 0, \text{ and } z_1 = 0\)
2. Steady states \(E_2 = (x_2, y_2, z_2)\) with \(x_2 = \frac{1}{2} \left(1 - \sqrt{1 + \frac{4}{a_1}}\right), y_2 = 0, \text{ and } z_2 = 0\)
3. Steady states \(E_3 = (x_3, y_3, z_3)\) with \(x_3 = \frac{1}{2} \left(1 + \sqrt{1 + \frac{4}{a_1}}\right), y_3 = 0, \text{ and } z_3 = 1 - \frac{a_6}{a_4}\)
4. Steady states \(E_4 = (x_4, y_4, z_4)\) with \(x_4 = \frac{1}{2} \left(1 - \sqrt{1 + \frac{4}{a_1}}\right), y_4 = 0, \text{ and } z_4 = 1 - \frac{a_6}{a_4}\)

Afterwards, by doing substitution \(z = \frac{a_1}{a_2}\) into System (4), it gives \(E_5\) and \(E_6\) respectively
1. Steady states $E_5 = (x_5, y_5, z_5)$ with \[ x_5 = \frac{-\delta + \sqrt{\delta^2 + 4a_1}}{2a_1}, \quad y_5 = \frac{a_4}{a_5} \left( 1 - \frac{a_3}{a_2} - \frac{a_6}{a_4} \right), \]
and $z_5 = \frac{a_3}{a_2}$.

2. Steady states $E_6 = (x_6, y_6, z_6)$ with \[ x_6 = \frac{-\delta - \sqrt{\delta^2 + 4a_1}}{2a_1}, \quad y_6 = \frac{a_4}{a_5} \left( 1 - \frac{a_3}{a_2} - \frac{a_6}{a_4} \right), \]
and $z_6 = \frac{a_3}{a_2}$. Where $\delta = \frac{a_4}{a_5} \left( 1 - \frac{a_3}{a_2} - \frac{a_6}{a_4} \right) - a_1$.

Thus, there are six steady states in the model of interaction of cervical cancer cells and the immune cells where all of those points are the HPV infection. As for infection free cases, the condition is not satisfied by models due to contradictions with Equation (1).

The existence at the six steady states is explained through the following Theorem.

**Theorem 1:** Let $E_i$ is the steady states on System (1)-(3). The existence of each steady states is given as follows:

i. $E_1$ is biologically existed

ii. $E_3$ is biologically existed with condition $a_6 \leq a_4$

iii. $E_5$ is biologically existed with condition $a_6 \leq \frac{1 - a_4 (a_3 - a_2)}{a_2}$

iv. $E_2, E_4$, and $E_6$ does not biologically existed.

**Proof:**

Remarks the value of $x_i, y_i,$ and $z_i$ on steady states $E_i$ i.e. $x_i = \frac{1}{2} \left( 1 + \sqrt{1 + \frac{4}{a_1}} \right), \quad y_i = 0,$ and $z_i = 0$ which are real, positif, or equal to zero. Since all variables are non negative real number, then $E_i$ is biologically existed.

Remarks the value of $x_2, y_2,$ and $z_2$ on steady states $E_2$ i.e. $x_2 = \frac{1}{2} \left( 1 - \sqrt{1 + \frac{4}{a_1}} \right), \quad y_2 = 0,$ and $z_2 = 0,$ $y_2$ and $z_2$ have a real value and nonnegative. Furthermore $x_2 \geq 0$ is analyzed as follow
The result make a contradiction to biology cases that ensures all variables must have a real positive number. Hence $E_3$ is not biologically existed. Analogue for $E_4$ and $E_6$. Furthermore, the investigation must be done by analyzing $E_3$ and $E_5$ are also biologically existed with condition $a_6 \leq a_4$ and

$$a_6 \leq \frac{1-a_4(a_3-a_2)}{a_2}.$$

It’s easy to check for $E_3$. For $E_5$, see $x_5$ and $y_5$ on $E_5$

$$x_5 \geq 0$$
$$\Leftrightarrow -\delta + \sqrt{\delta^2 + 4a_1} \geq 0$$
$$\Leftrightarrow \sqrt{\delta^2 + 4a_1} \geq \delta$$
$$\Leftrightarrow 4a_1 \geq 0$$
$$\Leftrightarrow a_1 \geq 0$$

There is no contradiction

$$y_5 \geq 0$$
$$\Leftrightarrow 1 - \frac{a_4}{a_2} - \frac{a_6}{a_4} \geq 0$$
$$\Leftrightarrow a_2(a_6 - a_4) \leq 1 - a_4a_4$$
$$\Leftrightarrow a_6 \leq \frac{1-a_4(a_3-a_2)}{a_2} \tag{5}$$

Therefore, $E_5$ is biologically existed if satisfy Equation (5).

2.3. Local Stability Analysis

Local stability analysis near the steady states is performed by doing linearization using the Jacobian Matrices [13]. The Jacobian Matrices ($J$) is defined by

$$J = \begin{bmatrix}
\frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_3} \\
\frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \frac{\partial f_2}{\partial x_3} \\
\frac{\partial f_3}{\partial x_1} & \frac{\partial f_3}{\partial x_2} & \frac{\partial f_3}{\partial x_3}
\end{bmatrix}$$
with \( f_1 = 1 + x\left(a_1 (1 - x) - \right), f_2 = y\left(a_2 z - a_3 \right), \) and \( f_3 = z\left(a_4 (1 - z) - a_5 y - a_6 \right). \)

2.3.1. Local Stability Analysis Near \( E_1 \). It is given by Theorems 2.

Theorems 2. Given \( E_1 \) is one of the steady states of System (1)-(3) with \( E_1 = (x_1, y_1, z_1) \),

\[
x_1 = \frac{1}{2} \left( 1 + \sqrt{1 + \frac{4}{a_1}} \right), \quad y_1 = 0, \quad \text{and} \quad z_1 = 0.
\]

If one of the following conditions is met:

i. \( a_4 < a_6 \) then \( E_1 \) is asymptotically stable
ii. \( a_4 > a_6 \) then \( E_1 \) is not stable
iii. \( a_4 = a_6 \) then \( E_1 \) is defined as non hyperbolic steady states.

2.3.2. Local Stability Analysis Near \( E_3 \). It is given by Theorems 3.

Theorems 3. Given \( E_3 \) is one of the steady states of System (1)-(3) with \( E_3 = (x_3, y_3, z_3) \),

\[
x_3 = \frac{1}{2} \left( 1 + \sqrt{1 + \frac{4}{a_3}} \right), \quad y_3 = 0, \quad \text{and} \quad z_3 = 1 - \frac{a_6}{a_4}.
\]

If satisfied:

i. \( a_3 > a_2 \left( 1 - \frac{a_6}{a_4} \right) \) then \( E_3 \) is asymptotically stable
ii. \( a_3 < a_2 \left( 1 - \frac{a_6}{a_4} \right) \) then \( E_3 \) is not stable
iii. \( a_3 = a_2 \left( 1 - \frac{a_6}{a_4} \right) \) then \( E_3 \) is defined as non hyperbolic steady states.

2.3.3. Local Stability Analysis Near \( E_5 \). Local stability analysis near \( E_5 \) is given by Theorems 4.

Theorems 4. Given \( E_5 \) is steady states of System (1)-(3) with \( E_5 = (x_5, y_5, z_5) \) as follows

\[
x_5 = \frac{-\delta + \sqrt{\delta^2 + 4\gamma}}{2a_1}, \quad y_5 = \frac{a_1}{a_5} \left( 1 - \frac{a_3}{a_2} - \frac{a_5}{a_4} \right), \quad z_5 = \frac{a_3}{a_5}, \quad \text{and} \quad \gamma > 0 \text{ with}
\]

\[
\gamma = \left( \frac{a_4}{a_5} \right)^2 - 2a_2 a_6 a_5^2 - 2a_2 a_3 a_5^2 + 2a_2 a_3 a_5^2 + 2a_2 a_3 a_5^2 + 2a_2 a_3 a_5^2 + 2a_2 a_3 a_5^2
\]

Let

\[
\phi = \sqrt{-4a_3^2 a_5 a_6 + 4a_3^2 a_5 a_6 + 4a_3^2 a_5 a_6 + (a_3 a_4)^2}, \quad \delta = \frac{a_4}{a_5} \left( 1 - \frac{a_3}{a_2} - \frac{a_5}{a_4} \right), \quad \text{and}
\]

\[
\theta = \frac{-a_4 a_5^2 + 4a_3^2 a_5 (1 - a_5)}{4a_5^2}.
\]

If

i. \( \phi > 0 \) and \( a_4 > \frac{\phi}{a_5} \) then \( E_5 \) is asymptotical stable with different real eigen.

ii. \( \phi > 0 \) and \( a_4 < \frac{\phi}{a_5} \) then \( E_5 \) is not stable.
iii. $\phi > 0$ and $a_4 = \frac{\phi}{a_3}$ then $E_5$ is defined as nonhyperbolic steady states

iv. $\phi = 0$ then $E_5$ is asymptotical stable with mutual real eigen

v. $\phi < 0$ and $a_6 < \theta$ then $E_5$ is asymptotical stable with complex conjugate eigen

3. Bifurcation Analysis

Based on the analysis of the problem that has been created, the critical points are obtained at there points, i.e. on $E_1$, the critical point is $\mu_1 : a_6 < a_4$. Bifurcation that occur on this points are:

i. $\mu_1 < 0 : E_1$ is asymptotical stable steady states

ii. $\mu_1 > 0 : E_1$ is not stable steady states.

While on $E_3$, the critical points is $\mu_2 : a_3 - a_2\left(1 - \frac{a_6}{a_4}\right)$. Bifurcation that occur are $E_3$ asymptotical stable if $\mu_3 > 0$ and $E_3$ id not stable steady states. On $E_5$, we found parameters $\phi, \mu_3$, and $\mu_4$. Bifurcation that occur i.e. $E_5$ is asymptotical stable (node stable) if $\phi > 0$ and $\mu_5 > 0$. $E_5$ is not stable if $\phi > 0$ and $\mu_5 < 0$, $E_6$ become non hyperbolic steady state if $\phi > 0$ and $\mu_5 = 0$.

While $\phi = 0$ then $E_5$ is asymptotical stable, and $E_4$ is asymptotical stable (spiral stable) if fulfill $\phi < 0$ and $\mu_4 < 0$, with $\phi = \sqrt{-4a_2^2a_4a_6 + 4a_2^2a_3a_6 + 4a_3a_2^2a_4 + (a_3a_4)^2}$, $\mu_3 = a_4 - \frac{\phi}{a_3}$, and $\mu_4 = a_6 - \theta$.

4. Conclusion

Mathematical model on cervical cancer and immune cells have three infection steady states. Healthy conditions can be obtained by changing the parameter values associated with the bifurcation value at each steady state. If parameter $a_6 > a_4$ then $E_1$ is not stable that means the condition of healing is satisfied. For $a_3 < a_2\left(1 - \frac{a_6}{a_4}\right)$ then $E_3$ is not stable that means the condition of healing is satisfied.

For the last cases, it relies on several parameters namely $\phi, \mu_3$, and $\mu_4$. Healthy conditions are obtained if $\phi > 0$ and $\mu_5 < 0$ are fulfill. In further research, we will analyse the relationship between bifurcation regions of each steady states.

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