Stability analysis of endemic equilibrium points on cancer cells mathematical model

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Abstract. The purposes of this study are to find out an endemic equilibrium point and to analyze it. The pattern of the spread of cancer cells can be modeled in the form of differential equation systems. The research obtained asymptotically stable endemic equilibrium point. Based on simulation results, the greater the rate of cancer growth, the faster the cancer spreads and is present in the cell.

1. Introduction
Cancer is a non-communicable disease between individuals [1]. The malignancy of cancer depends on how many cells spread and produce abnormally. It is estimated that 1 of 6 deaths is caused by cancer [2]. For men, the most common cancer sequences are lung, prostate, colorectal, stomach and liver cancer. As for women, those are breast, colorectal, lung, cervical and thyroid cancer. Discussion of cancer in both medical and mathematical terms continues. From the medical side, research on cancer is directed at how cells are activated until they become cancer cells [3], how normal cells become cancer cells, and how to prevent them from being cancer cells.

There are various cancer treatments, including surgery and treatments with modern technology. From the mathematical side, the discussion about cancer and the contribution of mathematics in the analysis of this disease is to form a model. Mathematical models on cancer are widely discussed, including how mathematical models with radiation treatment [4], immunotherapy treatment [5], and chemotherapy treatment [6].

The initial research that corresponds with this study is Lestari et al. [7]. However, the discussion only reached the point of disease-free equilibrium. Therefore, this research continues to endemic equilibrium points. The formation of a mathematical model is discussed in section 2, while section 3 discusses the equilibrium point of disease free and its analysis, followed by section 4 on endemic equilibrium point, then in section 5 numerical simulations. At the end of the article is a conclusion.
2. Assumptions and Mathematical Model

The discussed population in this article is cells in the body, namely effector cells, tumor cells and cells that are given chemotherapy drugs. The number of effector cells in time \( t \) is denoted with \( E(t) \), and the number of tumor cells in time \( t \) is denoted with \( T(t) \). This article discusses chemotherapy treatment, and chemotherapy drugs injected into the body in the time \( t \) is notated with \( M(t) \).

For the model formation, several things are assumed such as the growth rate of tumor cells logically, the natural death rate that only occurs in effector cells, the population discussed that is not a constant population. According to the literature study [8]–[11], Table 1 as follow is given to find out the parameter values.

| Parameter | Definition | Baseline (Unit) | Unit |
|-----------|------------|-----------------|------|
| \( p \)   | degree of recruitment of maximum immune-effector cells in relation with cancer cells | 0.015 | (1/day) |
| \( r \)   | rate of tumor growth | \( 4.31 \times 10^{-3} \) | (1/day) |
| \( b \)   | capacity of the tumor cell | \( 10^{-9} \) | (1/cells) |
| \( a \)   | parameter of cancer cleanup | \( 3.41 \times 10^{-10} \) | (1/cells) |
| \( g \)   | half-saturation for cancer cleanup | \( 10^5 \) | (cells) |
| \( s \)   | growth rate of normal/effector cells | \( 1.2 \times 10^4 \) | (cells/day) |
| \( m \)   | degree of inactivation of effector cells by tumor cells | \( 2 \times 10^{11} \) | (1/cells.day) |
| \( \mu \) | rate of natural demise of effector cells | \( 4.12 \times 10^{-2} \) | (1/day) |
| \( \gamma \) | rate of decrease in concentration of chemotherapy drug | 0.9 | (1/day) |
| \( h \)   | steepness coefficient of the recruitment curve of effector-immune cells | 2.02 \times 10^{-6} \) | Cells |

Based on the assumptions and parameters shown in Table 1, the mathematical model formed by Lestari et. al [7] is like in the Ordinary Differential Equation System (1).

\[
\frac{dE}{dt} = s + p \frac{ET}{h+T} - mET - \mu E - K_E M E \\
\frac{dT}{dt} = rT(1 - bT) - a \frac{ET}{T+g} - K_T M T \\
\frac{dM}{dt} = -\gamma M + V_M(t) \tag{1}
\]
The first equation states the rate of change in effector cells with increasing time due to growth rate and because effector cells defeat tumor cells. The negative sign in the first equation is because the number of effector cells is reduced by natural death, the effects of chemotherapy and death from fighting tumor cells.

The second equation states the rate of change in tumor cells with time. The number of tumor cells increases along with the rate of logistic growth. The reduction in tumor cells follows the Michaelis Menten equation because of the effect of chemotherapy drug doses. The third equation states the rate of change of chemotherapy drugs with time, which increases because of the drug dose injected into the body and decreases due to decreased concentration. Through System (1) the equilibrium point is determined and then behavior is analyzed around the equilibrium point.

3. Stability Analysis of Disease Free Equilibrium Point

Equilibrium points on the system (1) are obtained if \( \frac{dE}{dt} = 0, \frac{dT}{dt} = 0, \frac{dM}{dt} = 0 \). It would discuss on the Lemma 1.

**Lemma 1**

(i) If \( E = T = 0 \), the system (1) has an equilibrium point \( P_0 \left( 0, 0, \frac{V_M}{\gamma} \right) \).

(ii) If \( E = 0 \), the system (1) has an equilibrium point \( P_1 \left( \frac{r - K_f \frac{M}{\gamma}}{rb}, \frac{V_M}{\gamma} \right) \).

(iii) If \( T = 0 \), the system (1) has an equilibrium point \( P_2 \left( \frac{s \gamma}{\mu \gamma + K_f V_M}, 0, \frac{V_M}{\gamma} \right) \).

The Jacobian matrix of System (1) is obtained by linearization of System (1). Jacobian matrix of System (1) is

\[
J = \begin{bmatrix}
\frac{pT}{h + T} - mT - \mu - K_f M & \frac{pE(h + T) - pET}{(h + T)^2} - mE & -K_f E \\
-\frac{aT}{T + g} & r(1 - bT) - brT - \frac{aE(T + g) - aET}{(T + g)^2} - K_f M & -K_f T \\
0 & 0 & -\gamma
\end{bmatrix}
\]

(2)

and the behavior of solution of System (1) around equilibrium point using Jacobian (2) is discussed in Lemma 2.
Lemma 2

(i) If \( V_M > \frac{r\gamma}{K_y} \), then equilibrium point \( P_0 \left( 0, 0, \frac{V_M}{\gamma} \right) \) is local asymptotically stable.

(ii) If \( p > \left( m\hat{T} + \mu + K_E \frac{V_M}{\gamma} \right) \left( \frac{h + \hat{T}}{\hat{T}} \right) \) and \( V_M < r \left( 1 - 2b\hat{T} \right) \frac{\gamma}{K_y} \), then equilibrium point \( P_0 \left( 0, \hat{T}, \frac{V_M}{\gamma} \right) \), dengan \( \hat{T} = \frac{r - K_y \frac{V_M}{\gamma}}{rb} \), is local asymptotically stable.

(iii) If \( \alpha > \left( r - K_t \frac{V_M}{\gamma} \right) \frac{g}{E} \), then equilibrium point \( P_2 \left( \hat{E}, 0, \frac{V_M}{\gamma} \right) \), where \( \hat{E} = \frac{s\gamma}{\mu\gamma + K_E V_M} \), is local asymptotically stable.

Full proofs of Lemma 1 and 2 are in Lestari et. al [7].

4. Endemic Equilibrium Point

This section discusses how endemic equilibrium points are obtained. If \( \frac{dM}{dt} = 0 \) then from the third equation from System (1) \( M = \frac{V_M}{\gamma} \). If \( M = \frac{V_M}{\gamma} \), \( T \neq 0 \) and \( E \neq 0 \) is substituted to the second equation of System (1), and if \( \frac{dT}{dt} = 0 \), then what is obtained is

\[
T(1 - bT) - a\frac{ET}{T+g} - K_TMT = 0
\]

or

\[
E^* = \frac{rT(1 - bT) - K_TMT}{T} = \frac{\alpha T + g}{aT} = \left( \frac{rT(1 - bT) - K_TMT}{aT} \right)(T + g) \quad (3)
\]

If \( M = \frac{V_M}{\gamma} \), \( T \neq 0 \) and \( E \neq 0 \) is substituted to the first equation of System (1), and if \( \frac{dE}{dt} = 0 \), then we obtain

\[
s + \frac{E^*T}{h + T} - mE^*T - \mu E^* - K_EME^* = 0
\]

or

\[
s + \frac{\left[ rT(1 - bT) - K_TMT \right] T}{aT} - m \cdot \frac{\left[ rT(1 - bT) - K_TMT \right] (T + g)}{aT} - \mu \cdot \frac{\left[ rT(1 - bT) - K_TMT \right] (T + g)}{aT} - K_EM \cdot \frac{\left[ rT(1 - bT) - K_TMT \right] (T + g)}{aT} = 0
\]

(4)

The above equation in the \( T \) variable obtains \( T^* \) solution so that the endemic equilibrium point of the model is \( (E, T, M) = \left( E^*, T^*, \frac{V_M}{\gamma} \right) \) where \( E^* \) and \( T^* \) like the above equation.
5. **Endemic Equilibrium Point Stability Analysis with Numerical Simulation**

Simulation for the changed parameter was conducted in Table 2 as follows

| Parameter | Definition | Baseline | Simulasi 1 | Simulasi 2 | Reference |
|-----------|------------|----------|------------|------------|-----------|
| $p$       | The maximum recruitment rate of effector-immune cells from cancer cells | 0.015 | 0.15 | 0.015 | [12], [13] |
| $r$       | Tumor growth rate | 0.18 | 0.431 | 0.47 | [14] |
| $b$       | Tumor cell capacity | $10^{-9}$ | $10^{-9}$ | $10^{-9}$ | [10] |
| $a$       | Cancer cleanup parameters | 1 | $3.41 \times 10^{-10}$ | $3.41 \times 10^{-10}$ | [10] |
| $g$       | Half-saturation for cancer cleanup | $10^5$ | $10^5$ | $10^5$ | [10] |
| $m$       | Degree of inactivation of effector cells by tumor cells | $2 \times 10^{-11}$ | $2 \times 10^{-11}$ | $2 \times 10^{-11}$ | [10] |
| $\gamma$  | Rate of decrease in concentration of chemotherapy drug | 0.9 | 0.9 | 0.9 | [15] |
| $h$       | Steepness coefficient of the recruitment curve of effector-immune cells | 2.02x10 | 2.02x10 | 2.02x10 | [10] |

According to Table 2, an asymptotic stable tumor free equilibrium point is obtained. It means that in the long term there is no more tumor disease as shown in Figure 1.

![Figure 1. Solution graph of System (1)](image)

**5.1. Simulation 1**

If parameter values as shown in Table 2 and $K_E = 0.06$, $K_T = 0.08$, $V_M = 0.5$ then the endemic equilibrium point $(E_T, M)$ which $E = 1.133820133 \times 10^{14}$, $T = 19.95017683$, $M = 0.5555555556$ is obtained.
If these values are substituted into the Jacobian matrix (2), the following eigenvalues are obtained:

\[
\begin{bmatrix}
0.0003854727938 + 0.12039630451 \\
-0.9000000000 \\
0.0003854727938 - 0.12039630451
\end{bmatrix}
\]

Because there is a positive Jacobian matrix eigenvalue, the endemic equilibrium point of the tumor is unstable.

5.2. Simulation 2

If parameter values as shown in Table 2 and \( K_E = 0.6; \ K_T = 0.8; \ V_M = 0.5 \) then the endemic equilibrium point \( (E, T, M) \) which \( E = 33275.94994; \ T = 5.43735224610^7; \ M = 0.5555555556 \) is obtained. It means a number of efector cells is about 33276 cells, a number of Tumor cells is about 54373522 cells, a number of concretion drug is about 0.56.

If these values are substituted into the Jacobian matrix (2), the following eigenvalues are obtained:

\[
\begin{bmatrix}
-0.0255555570 \\
-0.3606208095 \\
-0.8999999998
\end{bmatrix}
\]

Because the Jacobian matrix eigenvalues are all negative, the endemic equilibrium point of the tumor is local asymptotically stable. This means that the tumor remains. Figures 2 and 3 are the simulations 1 and 2.

It can be seen from Figure 2, the tumor cell decreases along the greater time. Figure 3, because the endemic equilibrium point is asymptotically stable, the tumor cells are still present. The number of tumor cells continues to increase. This is what needs to be watched out for.
6. Conclusion
In this study, through Model (1) the endemic equilibrium point is determined. We obtain an endemic equilibrium point, \( (E^*, T^*, M) = \left( E^*, T^*, \frac{V_M}{\gamma} \right) \), which is asymptotically stable. Based on the results of numerical simulations it can be concluded that the greater the tumor growth rate parameter value, the faster the tumor spreads and is present in cells.

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