Dynamics of a mathematical model of cancer cells with chemotherapy

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Abstract. As commonly known, cancer is one of the fatal diseases to which considerable attention needs to be paid. The purpose of the research concerned here was to form a mathematical model of the spread of cancer with chemotherapy and to know the dynamics of its solution. As for the stages in achieving the purpose, they were forming a mathematical model, determining the point of equilibrium, determining the basic reproduction number, analyzing the stability around the equilibrium point, and conducting numerical simulation with the parameters given. The pattern of how cancer cells spread could be modeled in the form of a mathematical equation according to the system of differential equation. From the system formed, an equilibrium solution and an analysis of the behavioral dynamics of the cell spread with treatment in the form of chemotherapy were attained. Simulation with graphs indicates that the growth rate of cancer cells influences the population of the said cells. The greater the growth rate of cancer cells, the greater the population of those cells. Besides, it is also obtained that the increasing dosage of the drug given with the limits allowed, the lower of those cancer cells.

1. Introduction
Cancer is a general term for a large group of diseases that could affect every part of the body. Other terms used are malignant tumor and neoplasm. One of the symptoms of cancer is the fast growth of abnormal cells which grow beyond normal limits and then could invade a body part and spread from organ to organ. The process is called metastasis. Metastasis is the main cause of death due to cancer. Cancer occurs when cell growth in the body happens overly fast and unrestrictedly. It could also occur when cells lose the ability to decay [1].

According to data from Globocan in WHO [1], it is estimated that there were 14.1 million new cases of cancer, 8.2 million cancer-caused deaths, and 32.6 million people suffering from cancer (within the period of 5 years since diagnosis) in 2012 all over the world. Up to 57% of the 14.1 million new cancer cases, 65% of the 8.2 million deaths due to cancer, and 48% of the 32.6 million people suffering from cancer within that 5-year period since diagnosis have been evenly distributed in less-developed regions. It indicates that cancer is still a disease considerably causing people’s suffering in various countries.
The interaction between the cells that are called effector cells and those that are tumor cells in gene therapy has been mathematically modeled by Tsygvinsev, et al [2]. In their research, They have applied a simple mathematical model to investigate the growth dynamics of effector cells and tumor cells in treatments using gene therapy, with the purpose of predicting the optimum approach combination leading to tumor cleanup. The mathematical model for gene therapy has been formed with the predator-prey model as basis.

The predator-prey model is basically applied on cancer cases because in such cases immune cells develop quickly and unrestrictedly while tumor cells keep preying on immune cells so that a predator-prey pattern occurs at the level of the disease known as cancer. In the research concerned here, the role of immune cells (as effector cells) is as predator and that of tumor cells is as prey so that the model used consisted of two classes, namely, Class $E$ to represent the population of effector cells (in this case as predator) and Class $T$ to represent the population of tumor cells (in this case as prey).

The previous researches about mathematical models model can be seen on the paper written by Waziri AS, et.al. [3], C.C. Chavez and B.J. Sony. [4], and J.P. Aparico and C.C. Chavez. [5]. Furthermore, about stability analysis of avian influenza and AIDS epidemic models have been researched by M. Derouich and A. Boutayeb [6], Cai Liming Xue Chi Li, et.al. [7], and C.N. Wahyuda and D. Lestari [8].

A piece of research by Moore and Natasha K. [9] concerning the development of naive T cells, effector cells, and tumor/cancer cells in the spread of cells causing cancer of the blood (or leukemia) was followed up with another piece of research by Nanda,S., Moore, and Lenhart [10] concerning the optimum control of cancer cells by using therapy. This research was developed from previous research that focus on a logistic growth model for tumor cells. Besides, the population of effector cells is influenced by the Michaelis-Menten growth of their response of toward tumor cells. And the decrease in the population of tumor cells was because of the parameter of tumor cleanup by effector cells amounting to $\alpha$ in magnitude, with the interaction between effector cells was portrayed through the Michaelis-Menten kinetic form. The research concerned here dealt with the dynamics of a mathematical model of the spread of cancer cells with chemotherapy. The effect of chemotherapy was portrayed in terms of the rate of drug concentration. In the last discussion describes the simulation of that mathematical model.

### 2. Research Method

This research conducted by literature method from some journals and references books. The steps are they were forming a mathematical model, determining the point of equilibrium, determining the basic reproduction number, analyzing the stability around the equilibrium point, and conducting numerical simulation with the parameters given.

### Assumptions and Mathematical Model

The following is a list of the assumptions required for getting the mathematical model:

1. The growth of tumor cells follows the growth of logistics.
2. Natural death happens to the effector cells.
3. The population is not constant.
4. The dosage of the drug in the chemotherapy serves as variable

According to the literature study [2,11,12,13,14,15] define the parameter values which are mostly based on previous research. The parameters are as given in table 1.

| Table 1. 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) |
From the assumptions and definitions presented, the model form could be described as follows:

1. Population of Effector Cells
   a. The population of effector cells would increase because of their constant growth rate of $s$ in magnitude in accordance with the equation as follows
   \[
   \frac{dE}{dt} = s
   \] (1)
   b. The population of effector cells would decrease because of their rate of natural demise of $\mu$ in magnitude in accordance with the equation as follows
   \[
   \frac{dE}{dt} = -\mu E
   \] (2)
   c. The increase in the population of effector cells is influenced by the Michaelis-Menten growth of their response toward tumor cells with a rate of $p$ in magnitude in accordance with the equation as follows
   \[
   \frac{dE}{dt} = p \frac{ET}{h + T}
   \] (3)
   d. The decrease of effector cells due to their interaction with tumor cells with a rate of $m$ in magnitude and with the chemotherapy drug causing the demise of effector cells with a rate of $K_E$ in magnitude were in accordance with the equation as follows
   \[
   \frac{dE}{dt} = -mET - K_E ME
   \] (4)

   From equation (1) through to equation (4), a model of the rate of the population of effector cells over time was found to be in accordance with the following equation:
   \[
   \frac{dE}{dt} = s - \mu E + p \frac{ET}{h + T} - mET - K_E ME
   \] (5)

2. Population of Tumor Cells
   a. The population of tumor cells would increase with the assumption that the growth rate of the population of tumor cells followed the growth rate of the logistics with a growth rate of $r$ in magnitude in accordance with the following equation:
\[ \frac{dT}{dt} = rT(1 - bT) \quad (6) \]

b. The decrease in the population of tumor cells was because of the parameter of tumor cleanup by effector cells amounting to \( a \) in magnitude, with the interaction between effector cells was portrayed through the Michaelis-Menten kinetic form in accordance with the following equation:

\[ \frac{dT}{dt} = -a \frac{ET}{T + g} \quad (7) \]

c. The decrease in the population of tumor cells was also due to the influence of the interaction between tumor cells and the chemotherapy drug causing the demise of tumor cells with a rate of \( K_T \) in magnitude in accordance with the following equation:

\[ \frac{dT}{dt} = -K_T MT \quad (8) \]

From Equation (6) through to Equation (8), a model of the population of tumor cells over time was found to be in accordance with the following equation:

\[ \frac{dT}{dt} = rT(1 - bT) - a \frac{ET}{T + g} - K_T MT \quad (9) \]

3. **Change in the Concentration of Chemotherapy Drug Over Time**

The amount of the concentration of chemotherapy drug would increase because of the occurrence of a drug from outside the body being administered up to \( V_M(t) \) in magnitude. The amount of the concentration of chemotherapy drug would undergo a decrease in proportion to that with the decrease being \( \gamma \) in magnitude. Therefore, the rate of change in the amount of the concentration of chemotherapy drug over time could be shown to be in accordance with the following equation:

\[ \frac{dM}{dt} = -\gamma M + V_M(t) \quad (10) \]

The mathematical model for cancer with chemotherapy as follows:

\[ \frac{dE}{dt} = s + p \frac{ET}{r + T} - mET - \mu E - K_E ME \]
\[ \frac{dT}{dt} = rT(1 - bT) - a \frac{ET}{T + g} - K_T MT \]
\[ \frac{dM}{dt} = -\gamma M + V_M(t) \quad (11) \]

3. **Equilibrium Points**

Equilibrium points on the system (11) obtained when \( \frac{dE}{dt} = 0, \frac{dT}{dt} = 0, \frac{dM}{dt} = 0 \). It would discuss on the following lemma.

Lemma 1

(i) If \( E = T = 0 \), the system (11) has an equilibrium point \( P_0 \left( 0, 0, \frac{V_M}{\gamma} \right) \).
(ii) If $E = 0$, the system (11) has an equilibrium point $P_1 \left( \frac{r - K_T}{r b}, 0, \frac{r b}{r b}, \frac{V_m}{\gamma} \right)$.

(iii) If $T = 0$, the system (11) has an equilibrium point $P_2 \left( \frac{s \gamma}{\mu r + K_E V_m}, 0, \frac{V_m}{\gamma} \right)$.

Proof:

(i) If $E = T = 0$, then Equation (11) and $\frac{dM}{dt} = 0$ yield $-\gamma M + V_m = 0$ or $M = \frac{V_m}{\gamma}$. In other word, obtained $0, 0, \frac{V_m}{\gamma}$.

(ii) If $\frac{dM}{dt} = 0$, then from equation (11) yield $M = \frac{V_m}{\gamma}$. By substituting $E = 0$, and $\frac{dT}{dt} = 0$ to equation (11), and $M = \frac{V_m}{\gamma}$, we have

$$rT(1 - bT) - K_T \frac{V_m}{\gamma} T = 0$$

or

$$T \left( r(1 - bT) - K_T \frac{V_m}{\gamma} \right) = 0$$

Such that $T = 0$ or $r(1 - bT) - K_T \frac{V_m}{\gamma} = 0 \Leftrightarrow T = \frac{r - K_T \frac{V_m}{\gamma}}{r b}$. In other word, we have

$$P_1 \left( \frac{r - K_T}{r b}, 0, \frac{r b}{r b}, \frac{V_m}{\gamma} \right)$$.

For $T = 0$ will be obtained as part (i).

(iii) For $\frac{dM}{dt} = 0$, so equation (11) yields $M = \frac{V_m}{\gamma}$. By taking $T = 0$, and $\frac{dE}{dt} = 0$ in equation (5),

then substitute $M = \frac{V_m}{\gamma}$, we have

$$s - \mu E - K_E \frac{V_m}{\gamma} E = 0$$

or $E = \frac{s \gamma}{\mu + K_E \frac{V_m}{\gamma}}$. Therefore we obtain $P_2 \left( \frac{s \gamma}{\mu r + K_E V_m}, 0, \frac{V_m}{\gamma} \right)$.

4. Stability Analysis

The Jacobian matrix of System (11) is obtained by linearization of System (11).

Lemma 2
(i) If $V_M > \frac{r_y}{K_T}$, then equilibrium point $P_0 \left(0, 0, \frac{V_M}{\gamma} \right)$ is local asymptotically stable.

(ii) If $p > \left( m\hat{T} + \mu + K_E \frac{V_M}{\gamma} \right) \left( \frac{h + \hat{T}}{T} \right)$ and $V_M < r \left(1 - 2b\hat{T} \right) \frac{\gamma}{K_T}$, then equilibrium point $P_1 \left(0, \hat{T}, \frac{V_M}{\gamma} \right)$, dengan $\hat{T} = \frac{r - K_T \frac{V_M}{\gamma}}{rb}$, is local asymptotically stable.

(iii) If $a > \left(r - K_T \frac{V_M}{\gamma} \right) \frac{g}{\hat{E}}$, 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.

Proof:

(i) It can be produced eigen values of $J(P_0)$ are $\lambda_1 = -\mu - K_E \frac{V_M}{\gamma}$, $\lambda_2 = r - K_T \frac{V_M}{\gamma}$, $\lambda_3 = -\gamma$. Clearly, $\lambda_1, \lambda_2, \lambda_3 < 0$. Because of $V_M > \frac{r_y}{K_T}$, then $\lambda_2 < 0$. So, $P_0 \left(0, 0, \frac{V_M}{\gamma} \right)$ is local asymptotically stable.

(ii) Eigen values of $J(P_1)$ are $\lambda_1 = \frac{p\hat{T}}{h + \hat{T}} - m\hat{T} - \mu - K_E \frac{V_M}{\gamma}$, $\lambda_2 = r \left(1 - b\hat{T} \right) - br\hat{T} - K_T \frac{V_M}{\gamma}$, $\lambda_3 = -\gamma$. Clearly, $\lambda_3 < 0$.

Because of $p > \left( m\hat{T} + \mu + K_E \frac{V_M}{\gamma} \right) \left( \frac{h + \hat{T}}{T} \right)$ and $V_M < r \left(1 - 2b\hat{T} \right) \frac{\gamma}{K_T}$, then $\lambda_1, \lambda_2 < 0$. So, $P_1 \left(0, \hat{T}, \frac{V_M}{\gamma} \right)$ is local asymptotically stable.

(iii) From $J(P_2)$ yields eigen values are $\lambda_1 = -\mu - K_E \frac{V_M}{\gamma}$, $\lambda_2 = r - \frac{a\hat{E}}{g} - K_T \frac{V_M}{\gamma}$, $\lambda_3 = -\gamma$.

Automatically, $\lambda_1, \lambda_2, \lambda_3 < 0$. Because of $a > \left(r - K_T \frac{V_M}{\gamma} \right) \frac{g}{\hat{E}}$, then $\lambda_2 < 0$. In the other word, we have $P_2 \left(\hat{E}, 0, \frac{V_M}{\gamma} \right)$, where $\hat{E} = \frac{s\gamma}{\mu\gamma + K_E V_M}$, is local asymptotically stable.

5. Numerical Simulation

The simulation in this research is illustrated in three graphs with the value of the basic parameters and some parameter values that are changed. The parameters that are changed in value are the rate of cancer cell growth and the rate of concentration of the chemotherapy drugs $V_M(t)$. Simulation 1 with parameter values in table 1, simulation 2 based on assumption with a value of $r = 0.47$ (cancer growth rate) and the concentration rate of drug concentration are assumed to be constant at $V = 0.5$ [16]. Meanwhile, simulation
3 uses the same parameter value as simulation 2 with a value of \( V = 0.6 \). The results of the three simulations are shown in graphs 1a, 1b and 1c using initial value \( E(0) = 30000 \) cells, \( T(0) = 40000 \) cells, and \( M(0) = 0 \).

![Graph 1a](image1a.png)

![Graph 1b](image1b.png)

![Graph 1c](image1c.png)

![Graph 2](image2.png)

Based on figure 1a, it can be seen initially a number of cancer cell is 40000 cells. The graph shows with a cancer growth rate \( r = 4.31 \times 10^{-3} \) and \( V = 0.5 \), the number of cancer cells decreases near to zero. In the value of this parameter a cancer free equilibrium point is obtained \((E, T, M) = (1.1125 \times 10^5, 0, 0.111)\).

Meanwhile, figure 1b describes with a cancer growth rate \( r = 0.47 \) and \( V = 0.5 \), we obtain a cancer free equilibrium point \((E, T, M) = (32.0398 \times 10^3, 0, 0.556)\) and an endemic equilibrium point \((E, T, M) = (33.2759 \times 10^3, 5.4375 \times 10^7, 0.556)\).

Figure 1c, illustrated population of cancer cells decrease over time. It caused by chemotherapy treatment. If the concentration of drug given more with the limits allowed, so the cancer cells will decrease. With a cancer growth rate \( r = 0.47 \) and \( V = 0.6 \), a cancer free equilibrium point is obtained \((E, T, M) = \)
It can be seen a dosage of drug given increasing over time in figure 2. After around 5 days will be constant that is 0.556. In this case, a cancer cells will be increased. It means a cancer still persist.

6. Conclusion

In this research obtained the epidemic model of cancer with chemotherapy in the form of a system of non linear differential equations with three sub-populations. Mathematically, we get equilibrium points are the cancer free equilibrium point and the cancer equilibrium point. Stability Analysis of equilibrium points produces a local asymptotically stable with certain conditions that must be satisfied. A cancer-free equilibrium point is a local asymptotically stable means that for a certain period of time the cancer will disappear. Meanwhile, the cancer equilibrium point is a local asymptotically stable means that for a certain period of time cancer is still persist. Based on the simulation, the greater the growth rate of cancer with other parameter values is constant, the higher the cancer cells. Besides, it is also obtained that the increasing dosage of the drug given with the limits allowed, the lower of those cancer cells.

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