Mathematical Model of Tumor Cell Growth Based on Age Structure

Atmini Dhoruri, Eminugroho Ratna Sari, and Dwi Lestari

***Abstract*—The purposes of this study are to formulate a mathematical model of tumor based on age structure and to simulate the model. We propose four classes: tumor cell, CTL cell, helper T-cell, and chemotherapy drug. For the initial research, we focused for tumor cell class which formed as age structure. Simulation of the model can be interpreted as behavior of solutions.**

***Index Terms*—Model, tumor, age structure.**

I. Introduction

Cells in the body naturally consist of normal cells and immune cells. Immune cells will be activated if there are foreign objects into the body. One of them is tumor cells. They can be attacked by immune cells. However, if the immune cells are not enough to defeat the tumor cells, the tumor cells can develop into cancer cells because they continue to divide indefinitely. WHO [1] has a long-term strategy to prevent cancer, i.e avoid tobacco use, always maintain the height of our body by healthy diet, regularly exercises, reduce alcohol, having safe sex, get vaccinated to avoid human papilloma virus (HPV) and hepatitis B, get regular medical check-up, reduce exposure to ultraviolet radiation. Mathematical model in medical problem was carried out by Kendrick [2]. This model was in system of ordinary differential equations in the form of S-I-R. It then modified becomes S-I-S, S-E-I-R, S-V-I-R, and so on. In the other hand, mathematical model of age structured with individual transmission has discussed by [3] in the form system of partial differential equations.

Cancer is one of the diseases the drugs of which are still being developed. Nowadays, to inhibit the growth of cancer cells, several therapies are carried out, such as surgery, biochemotherapy, gene therapy, radiation, hormone therapy, and chemotherapy [4]. Chemotherapy is performed by administering drugs. This action can kill cancer cells, but it can also kill normal cells as the side effect. Moreover, the most visible effects of a chemotherapy patient are hair loss, nausea, and thrush.

Research on the mathematical model of tumor cell growth has been carried out, starting from the ordinary differential equations system without any treatment which is then developed in therapy [5]. Furthermore, the model by Sari *et al* [6] which discussing the ordinary differential equations model without discussing cell age. Model of dynamic of tumor also has been discussed by Lestari *et al*. [7]. In contrast to existing research, this article discusses the mathematical model of tumor cell growth in the form of partial differential equations because it discusses the independent variables of time and age. Cell cycle is commonly represented as four stages: the S (synthesis) phase, the M (mitotic) phase, while the M and S phases are separated by two gap stages, the G1 phase and G2 phase [8]. Age cell is defined as the time elapsed from its last division (in M phase) and deal with this measurable quantity instead of the cell cycle phase [9]. Tumor cell division is important to analyze because when a tumor cell divides uncontrollably, it results in more malignant cancer.

The following Fig. 1 is a flow chart of this research.

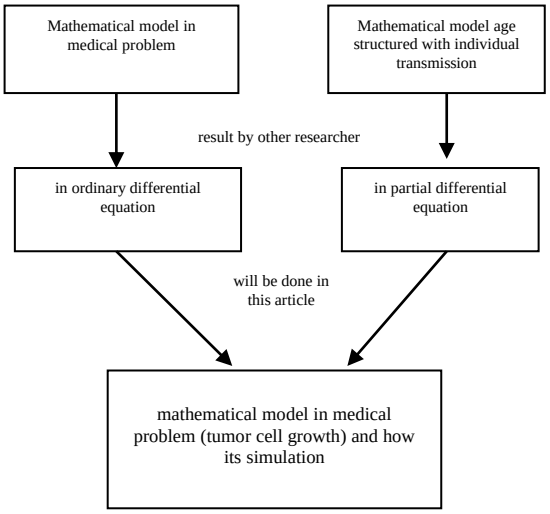

Fig. 1. State of the art of this article

Section II discusses basic theory used. Section III discussed the formulation of the model. Section IV discusses numerical simulations of models. Finally, Section V discusses conclusions and future work.

II. Basic Theory

A system of differential equations is a combination of two or more differential equations. Given vector $\mathrm{x} \in \mathbb{R}^n$ where $\mathrm{x} = \left(x_1, x_2, x_3, ..., x_n\right)^T$ and $x_1, x_2, x_3, ..., x_n \in \mathbb{R}$. If $\dot{x} = \frac{dx}{dt}$ as a notation for derivative x with respect to t, then $\dot{\mathrm{x}} = \left(\frac{dx_1}{dt}, \frac{dx_2}{dt}, \frac{dx_3}{dt}, ..., \frac{dx_n}{dt}\right)^T$ such that

Manuscript received September, 2019; revised December 3, 2019. This work was supported in part by LPPM UNY, Indonesia.

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DOI: 10.7763/IJMO.2020.V10.747

$$\begin{bmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \\ \frac{dx_3}{dt} \\ \vdots \\ \frac{dx_n}{dt} \end{bmatrix} = \begin{bmatrix} f_1(x_1, x_2, x_3, ..., x_n) \\ f_2(x_1, x_2, x_3, ..., x_n) \\ f_3(x_1, x_2, x_3, ..., x_n) \\ \vdots \\ f_n(x_1, x_2, x_3, ..., x_n) \end{bmatrix} \quad (1)$$

If in Equation (1) explicitly contains the *t* variable then the system is called a non-autonomous system, and if it does not explicitly contain the variable *t*, then it is called the autonomous system [10]. An autonomous system can be expressed in terms of

$$\dot{x} = f(x), \quad \forall x \in \mathbb{R}^n.$$

System of ordinary differential equation linear orde 1 where $x_1, x_2, x_3, ..., x_n$ as dependent variable and *t* as independent variable is denoted by

$$\begin{aligned} \frac{dx_1}{dt} &= a_{11}x_1 + a_{12}x_2 + a_{13}x_3 + \cdots + a_{1n}x_n + H_1(t) \\ \frac{dx_2}{dt} &= a_{21}x_1 + a_{22}x_2 + a_{23}x_3 + \cdots + a_{2n}x_n + H_2(t) \\ \frac{dx_3}{dt} &= a_{31}x_1 + a_{32}x_2 + a_{33}x_3 + \cdots + a_{3n}x_n + H_3(t) \\ &\vdots \\ \frac{dx_n}{dt} &= a_{n1}x_1 + a_{n2}x_2 + a_{n3}x_3 + \cdots + a_{nn}x_n + H_n(t). \end{aligned} \quad (2)$$

If *H* in (2) is equal with zero, then it is called homogeny system of differential equation. If *H* in (2) is not zero, then it is called non-homogeny.

Furthermore, if System (2) is expressed in matrix, then we have

$$\dot{x} = Ax + H(t)$$

where *A* is a matrix *n x n* which is a coefficient matrix of independent variables $x \in \mathbb{R}^n$, $a_{ij} \in \mathbb{R}$, $i = 1, 2, 3, ..., n,$ and $j = 1, 2, 3, ..., n$. We also have $H(t)$ is a matrix *n x n* as a function of *t*. It can be written as follow

$$\frac{dy}{dt} = \begin{bmatrix} a_{11} & a_{12} & \cdots & a_{1n} \\ a_{21} & a_{22} & \cdots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & a_{n3} & a_{nn} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{bmatrix} + \begin{bmatrix} H_1(t) \\ H_2(t) \\ \vdots \\ H_n(t) \end{bmatrix}.$$

From this theory then developed into partial differential equation.

III. Mathematical Model

This research is a continuation of previous research. In previous studies the model was still a system of ordinary differential equations because the independent variable was only time (*t*). Besides, the model discussed was a development of the one by Sharma [11]. In this study, what is discussed is that the independent variable depends not only on time (*t*) but also age (*a*). Thus, the model takes the form of a system of partial differential equations. Fig. 2 below is diagram transfer of our model.

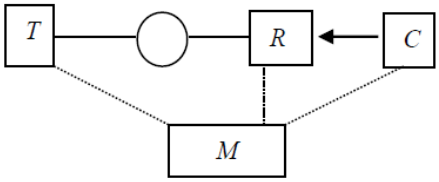

Fig. 2. Diagram transfer of tumor growth based on age structure.

Naturally, cells in the body produce T helper cells that activate CTL cells if there are tumor cells. However, there is a condition where tumor cells duplicate in such a way that they cannot be resisted by the body's immune system. Therefore we need medicine. There are several therapies to control this tumor cell, including biochemotherapy, immunotherapy, gene therapy [12] or chemotherapy. This study used chemotherapy to control the population of tumor cells.

On the other hand, the cell will be in a certain gap until it finally divides. This is called cell age [13]. As initial research, in this study we developed an independent variable age in tumor cells only to see in more detail how the tumor cell population at a certain age and a certain time continues to divide.

The population was divided into four classes, i.e. tumor cells, CTL cells, T helper cells, and chemotherapy drugs. The population of tumor cell (*T*) at time *t* and age *a* was denoted by $T(a,t)$. The population of CTL cell at time *t* was denoted by $C(t)$. The population of helper T cell was denoted by $R(t)$, and the population of chemotherapy drug was denoted by M. Drug is only dependent by time t. Mathematical model of this research can be described as follows

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$$\frac{\partial T}{\partial a} + \frac{\partial T}{\partial t} = x_1 T(1 - y_1 T) - z_1 MT - \alpha_1 T \quad (3a)$$

$$\frac{dC}{dt} = \beta CR - \mu C - z_2 MC - \alpha_2 C \quad (3b)$$

$$\frac{dR}{dt} = x_2 R(1 - y_2 R) - \beta CR - z_3 MR \quad (3c)$$

$$\frac{dM}{dt} = a - \gamma M. \quad (3d)$$

Equation (3a) shows the rate of change in tumor cell population with time *t* and age *a*. The first term shows logistic growth for tumor cells [11]. The second term is the interaction between tumor cells and chemotherapy drugs as much as z_1 . The parameter α_1 in the third term in (3a) is the rate of interaction between the tumor cell and CTL cell. In

this case the tumor cell has decreased indicated by a negative sign.

For (3b), the first term represents the rate at which CTL cells are activated by T helper cells, and the second term expresses the natural rate of death of CTL cells. Meanwhile, the effect of the drug is not only for tumor cells, but also for all cells shown by the third term (3b) and (3c). The fourth term in (3b) shows the interaction of CTL cells with tumor cells, but CTL cells "lose" so that they decrease.

Equation (3c) is the rate of change in T helper cell population over time t. The growth rate follows the logistic equation. Equation (3d) states the rate of chemotherapy drugs. Note that (3d) is only depends on M, so that it can be solved easily, which is then substituted into Equation (3a) - (3c). The solution of (3.d) is, $M(t) = K_0 e^{-\gamma t} + \frac{a}{\gamma}$, where $K_0 = \frac{-e^{\gamma K_1}}{\gamma}$. Thus, the model becomes

$$\frac{\partial T}{\partial a} + \frac{\partial T}{\partial t} = x_1 T(1 - y_1 T) - z_1\left(K_0 e^{-\gamma t} + \frac{a}{\gamma}\right)T - \alpha_1 T \quad (4a)$$

$$\frac{dC}{dt} = \beta CR - \mu C - z_2\left(K_0 e^{-\gamma t} + \frac{a}{\gamma}\right)C - \alpha_2 C \quad (4b)$$

$$\frac{dR}{dt} = x_2 R(1 - y_2 R) - \beta CR - z_3\left(K_0 e^{-\gamma t} + \frac{a}{\gamma}\right)R \quad (4c)$$

System (4) will be simulated in the next section.

IV. Simulation

Using the value as shown in Table I below, System (4) can be simulated.

TABLE I: Parameter Value

Parameter	Estimated value	Reference
x_2	0.0245 (1/time)	[11]
y_1	1×10^{-9} (1/cells)	[14]
y_2	1×10^{-10} (1/cells)	[11]
z_1	0.08 (1/time)	[11]
z_2	2×10^{-11} (1/time)	[11]
z_3	1×10^{-5} (1/time)	[11]
α_1	1.101×10^{-7} (1/cells/time)	[11]
α_2	3.422×10^{-10} (1/cells/time)	[11]
β	6.2×10^{-9} (1/cells/time)	[11]
μ	0.0412 (1/time)	[11]

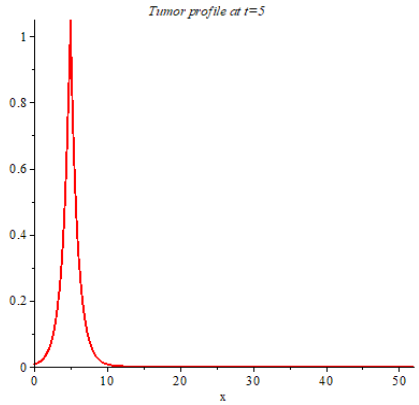

Fig. 4. Graphic Solution for tumor population at t = 5.

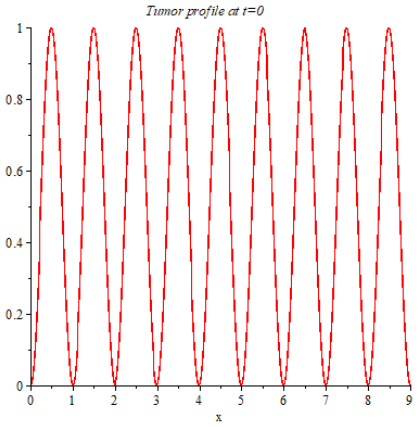

Fig. 5. Graphic Solution at t = 0.

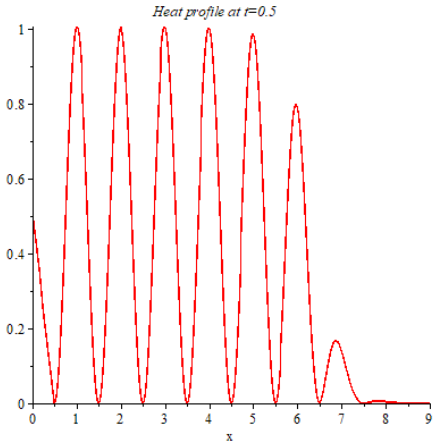

Fig. 6. Graphic Solution at t = 0.5.

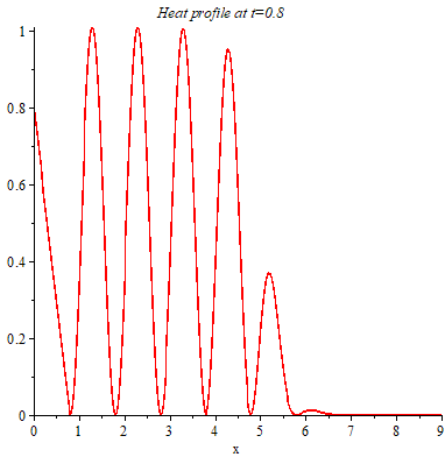

Fig. 7. Graphic Solution at t = 0.8.

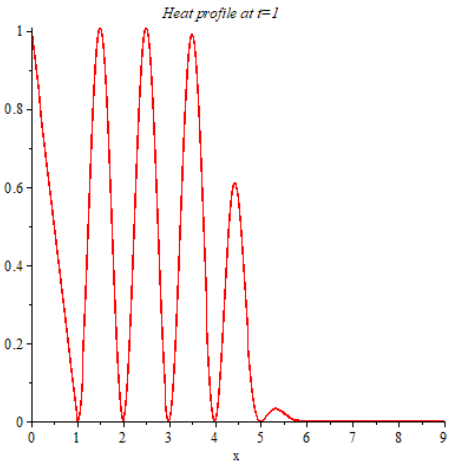

Fig. 8. Graphic Solution at t = 1.

Fig. 3 to show the behavior of tumor cell population at $t = 0$, it can be seen that the population decreases directly. If $t = 5$ (Fig. 4) which is higher than before, it can be seen that for the beginning the population increases and for the age (x- axis) 5, it become decreases.

Fig. 5-8 tells us the more time is given, the faster (depends on age) the solution will decrease. It shows us that the solution is periodic. There are several possibilities why the solution becomes periodic, such as the nonlinear model due to the movement of each cell to another class, for example from helper T cell class to CTL cells. In addition, it is because of periodical paramaters.

V. Conclusion

Mathematical model of interaction between tumor cells and normal cells (CTL cells and helper T cells) has been proposed. Analysis of the model is only using simulations. For further research may discuss equilibrium point and analytical solutions. Beside, all variables as age structure may be discussed.

Conflict of Interest

Authors declare no conflict of interest

Author Contributions

All authors have contributed in determining idea and formulating the mathematical model; all authors had approved the final version.

Acknowledgment

We would like to thank LPPM UNY for the PUPT grant, so this article was completed

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