CAUCHY –Jurnal Matematika Murni dan Aplikasi
Volume 5(4) (2019), Pages 186-194
p-ISSN: 2086-0382; e-ISSN: 2477-3344

Stability of Cancerous Chemotherapy Model with Obesity Effect

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ABSTRACT

In this paper we present stability of cancerous chemotherapy model with obesity effect. This is a four-population model that includes immune cells, cancer cells, normal cells, and fat cells. The analytical result shows that there are four equilibrium points in case the drugs given and fat cells were not equal to zero, i.e., dead equilibrium, total cancer invasion equilibrium, cancer-free equilibrium, and coexistence equilibrium. Some numerical simulation also presented to illustrate the results.

Keywords: cancer; obesity; chemotherapy

INTRODUCTION

In the last few years, many studies have shown a relationship between obesity and cancers such as [1], [2], [5], [6], [7], [8]. Not only research in the medical field, but also the relationship between cancer and obesity also studied mathematically. In 2015, Ku-Carrillo, Delgadillo, and Chen-Charpentier construct mathematics model for the effect of the obesity on cancer growth and on the immune system response [3]. And the next year, they do research on the effect of the obesity on optimal control schedules of chemotherapy on a cancerous tumor [4]. This paper orginized as follows. In Section 2, we describe methods that we used to do the research. In Section 3, we find the equilibrium points and its stability, and numerical simulations. Finally, conclusions are presented in Section 4.

METHODS

This research was conducted by doing few steps as folows. We use the model that originally discussed by Ku-Carrillo

$$
\begin{aligned}
\frac{dI}{dt} &= s + \frac{\rho IT}{\alpha + \mu F + T} - c_1 IT - d_1 I - a_1\left(1-e^{-u}\right)I \\
\frac{dT}{dt} &= r_1 T\left(1-b_1 T\right) - c_2 IT - c_3 TN + c_5 TF - a_2\left(1-e^{-u}\right)T \\
\frac{dN}{dt} &= r_2 N\left(1-b_2 N\right) - c_4 TN - a_3\left(1-e^{-u}\right)N \\
\frac{dF}{dt} &= r_3 F\left(1-b_3 F\right) - c_6 TF - a_4\left(1-e^{-u}\right)F \\
\frac{du}{dt} &= v - d_2 u
\end{aligned}
\tag{1}
$$

Submitted: December 07, 2017 Reviewed: March 14, 2018 Accepted: May 31, 2019
DOI: http://dx.doi.org/10.18860/ca.v5i4.4558

where I denotes the number of immune cells, T denotes the tumor cells, N denotes the normal cells, F denotes the fat cells which is stored in adipocytes. The constants r_i, b_i, c_i, a_i denote cells growth rate, inverse of the population carrying capacity, competition coefficients, and the kill effectiveness of the drug on population respectively. The function $v(t)$ models the application protocol of chemotherapy. Parameters s, ρ, α, μ, u denote basal response, the immune response stimulated by the cancer cells, the immune response caused by tumor respectively.

We refer to system (1) that will be analyzed then. We will determined of the equilibrium points by solving the nullcline equations of system (1). And then observe the local stability of the equilibrium points by using eigen values of the Jacobian matrix of each equilibrium points.

RESULTS AND DISCUSSION

3.1. *Mathematical Model of Cancer Growth with Obesity Effect on The Immune System Response*

In this paper the model that we investigate is originally discussed by Ku-Carrillo [4], that is

$$\begin{aligned}
\frac{dI}{dt} &= s + \frac{\rho IT}{\alpha + \mu F + T} - c_1 IT - d_1 I - a_1\left(1 - e^{-u}\right)I \\
\frac{dT}{dt} &= r_1 T\left(1 - b_1 T\right) - c_2 IT - c_3 TN + c_5 TF - a_2\left(1 - e^{-u}\right)T \\
\frac{dN}{dt} &= r_2 N\left(1 - b_2 N\right) - c_4 TN - a_3\left(1 - e^{-u}\right)N \\
\frac{dF}{dt} &= r_3 F\left(1 - b_3 F\right) - c_6 TF - a_4\left(1 - e^{-u}\right)F
\end{aligned} \qquad (2)$$

In this system we ignore the last equation from the original ones because of the aimed of the research is to find the stability of equilibrium points by which the drug dose is not equal to zero. Where in the origin drug dose system is given by control procedure.

3.2. *Equilibrium Points and Existence*

Equilibrium point of system (2) was hold by solving the following system

$$\begin{aligned}
& s + \frac{\rho IT}{\alpha + \mu F + T} - c_1 IT - d_1 I - a_1\left(1 - e^{-u}\right)I = 0 \\
& r_1 T\left(1 - b_1 T\right) - c_2 IT - c_3 TN + c_5 TF - a_2\left(1 - e^{-u}\right)T = 0 \\
& r_2 N\left(1 - b_2 N\right) - c_4 TN - a_3\left(1 - e^{-u}\right)N = 0 \\
& r_3 F\left(1 - b_3 F\right) - c_6 TF - a_4\left(1 - e^{-u}\right)F = 0
\end{aligned}$$

System (2) has eight equilibrium which is can be separated to two groups, i.e., four equilibrium under the zero fat condition and four equilibrium under the certain amount of fat condition. Our discussion is focused on the second condition. The second condition is impossible because there is always amount of fat in human body.

The equilibrium points are the dead point:

$$E_0 = \left(\frac{s}{a_1\left(1 - e^{-u}\right) + d_1}, 0, 0, \frac{1}{b_3} - \frac{a_4\left(1 - e^{-u}\right)}{b_3 r_3}\right),$$

the total cancer invansion point:

$$E_1 = \left(-\frac{s}{\dfrac{\rho T_1^*}{\alpha + \mu\left(\dfrac{1}{b_3} - \dfrac{a_4\left(1-e^{-u}\right)+c_6 T_1^*}{b_3 r_3}\right) + T_1^*} - c_1 T_1^* - d_1 - a_1\left(1-e^{-u}\right)}, T_1^*, 0, \frac{1}{b_3} - \frac{a_4\left(1-e^{-u}\right)+c_6 T_1^*}{b_3 r_3} \right),$$

where

$$p = -\frac{b}{3a}$$

$$q = p^3 + \frac{bc - 3ad}{6a^2} \quad a = c_1 x_1 x_2$$

$$r = \frac{c}{3a}$$

$$b = -\left(x_6 - x_7\right) x_1 x_2 + c_1 x_2 x_4$$

$$c = s c_2 x_2 + x_1 x_5 + x_4 x_6 - x_2 x_4 x_7$$

$$d = s c_2 \left(\alpha + \mu x_3\right) - x_4 x_5$$

$$x = 1 - e^{-u}$$

$$x_1 = b_1 r_1 + \frac{c_5 c_6}{b_3 r_3}$$

$$x_2 = 1 - \mu \frac{c_6}{b_3 r_3}$$

$$x_3 = \frac{r_3 + a_4 x}{b_3 r_3}$$

$$x_4 = r_1 + \frac{c_3 r_3 - a_4 c_5 x}{b_3 r_3} - a_2 x$$

$$x_5 = \left(d_1 + a_1 x\right)\left(\alpha + \mu x_3\right)$$

$$x_6 = \rho - \alpha c_1 - \mu c_1 x_3$$

$$x_7 = d_1 + a_1 x$$

The cancer-free equilibrium point:

$$E_2 = \left(\frac{s}{a_1\left(1-e^{-u}\right) + d_1}, 0, \frac{1}{b_2} - \frac{a_3\left(1-e^{-u}\right)}{b_2 r_2}, \frac{1}{b_3} - \frac{a_4\left(1-e^{-u}\right)}{b_3 r_3} \right),$$

and the coexist equilibrium point $E_3 = \left(I_3^*, T_3^*, N_3^*, F_3^*\right)$, where

$$I_3^* = -\frac{s}{\dfrac{\rho T_3^*}{\alpha + \mu\left(\dfrac{1}{b_3} - \dfrac{a_4\left(1-e^{-u}\right)+c_6 T_3^*}{b_3 r_3}\right)+T_3^*} - c_1 T_3^* - d_1 - a_1\left(1-e^{-u}\right)}$$

$$T_3^* = \sqrt[3]{q+\sqrt{q^2+\left(r-p^2\right)^3}} + \sqrt[3]{q-\sqrt{q^2+\left(r-p^2\right)^3}} + p$$

$$N_3^* = \frac{1}{b_2} - \frac{a_3\left(1-e^{-u}\right)+c_4 T_3^*}{b_2 r_2},$$

$$F_3^* = \frac{1}{b_3} - \frac{a_4\left(1-e^{-u}\right)+c_6 T_3^*}{b_3 r_3}.$$

$$p = -\frac{b}{3a}$$

$$q = p^3 + \frac{bc-3ad}{6a^2}$$

$$r = \frac{c}{3a}$$

$$a = x_5 x_8$$

$$b = x_6 x_8 - x_4 x_5$$

$$c = sc_2 c_6 x_3 - sc_2 - x_4 x_6 - x_8$$

$$d = x_4 x_7 - \alpha s c_2 - sc_2 x_1 x_3$$

$$x = 1 - e^{-u}$$

$$x_1 = r_3 - a_4 x$$

$$x_2 = d_1 + a_1 x$$

$$x_3 = \frac{\mu}{b_3 r_3}$$

$$x_4 = \frac{c_3}{b_2 r_2}\left(r_2 - a_3 x\right) + \frac{c_5 x_1}{b_3 r_3} + r_1 - a_2 x$$

$$x_5 = -c_1\left(1 + x_3\right)$$

$$x_6 = \rho - \alpha c_1 - x_2 - c_1 x_1 x_3 + c_6 x_2 x_3$$

$$x_7 = x_1 x_2 x_3 + \alpha x_2 + c_6$$

$$x_8 = b_1 r_1 + \frac{c_3 c_4}{b_2 r_2} + \frac{c_5 c_6}{b_3 r_3}$$

3.3. *Stability of Equilibrium Points*

The local stability of equilibrium points of system (1) is investigate by linearizing system (1) around the points. Jacobian matrix is obtained from this process which is its eigen values can be used to determine the stability of each points.

The Jacobian matrix of system (2) is

$$J = \begin{bmatrix} \dfrac{\rho T}{\alpha+\mu F+T} - c_1 T - d_1 - a_1(1-e^{-u}) & \dfrac{\rho I}{\alpha+\mu F+T} - \dfrac{\rho I T}{\left(\alpha+\mu F+T\right)^n} - c_1 I & 0 & \dfrac{\mu\rho I T}{\left(\alpha+\mu F+T\right)^2} \\ -c_2 T & r_1\left(1-b_1 T\right) - b_1 r_1 T - c_2 I - c_3 N + c_5 F - a_2\left(1-e^{-u}\right) & -c_3 T & c_5 T \\ 0 & -c_4 N & r_2\left(1-b_2 N\right) - b_2 r_2 N - c_4 T - a_3\left(1-e^{-u}\right) & 0 \\ 0 & -c_6 F & 0 & r_3\left(1-b_3 F\right) - b_3 r_3 F - c_6 T - a_4\left(1-e^{-u}\right) \end{bmatrix}$$

The eigen value of $J(E_0)$ are $\lambda_1 = a_4\left(1-e^{-u}\right)-r_3$, $\lambda_2 = -a_3\left(1-e^{-u}\right)+r_2$, $\lambda_3 = -a_1\left(1-e^{-u}\right)-d_1$, and

$$\lambda_4 = -\frac{\left(a_1a_2b_3r_3 + a_1a_4c_5\right)\left(1-e^{-u}\right)^2 - \left(a_1b_3r_1r_3 - a_2b_3d_1r_3 + a_1c_5r_3 - a_4c_5d_1\right)\left(1-e^{-u}\right) + b_3c_2r_3s - b_3d_1r_1r_3 - c_5d_1r_3}{\left(a_1\left(1-e^{-u}\right)+d_1\right)b_3r_3}.$$

Thus E_0 is stable when $a_4\left(1-e^{-u}\right) < r_3$, $a_3\left(1-e^{-u}\right) > r_2$, and

$$\left(a_1a_2b_3r_3 + a_1a_4c_5\right)\left(1-e^{-u}\right)^2 - \left(a_1b_3r_1r_3 - a_2b_3d_1r_3 + a_1c_5r_3 - a_4c_5d_1\right)\left(1-e^{-u}\right) + b_3c_2r_3s - b_3d_1r_1r_3 - c_5d_1r_3 > 0.$$

At E_2, the eigen values of Jacobian matrix are $\lambda_1 = a_4\left(1-e^{-u}\right)-r_3$, $\lambda_2 = a_3\left(1-e^{-u}\right)-r_2$, $\lambda_3 = -a_1\left(1-e^{-u}\right)-d_1$, and

$$\lambda_4 = -\frac{\left(-a_1a_3b_3c_3r_3 + a_1a_4b_2c_5r_2 + a_1a_2b_2b_3r_2r_3\right)\left(1-e^{-u}\right)^2}{\left(a_1\left(1-e^{-u}\right)+d_1\right)b_2r_2b_3r_3}$$

$$+\frac{\left(a_1b_2b_3r_1r_2r_3 - a_1b_3c_3r_2r_3 + a_3b_3c_3d_1r_3 + a_1b_2c_5r_2r_3 - a_4b_2c_5d_1r_2 - a_2b_2b_3d_1r_2r_3\right)\left(1-e^{-u}\right)}{\left(a_1\left(1-e^{-u}\right)+d_1\right)b_2r_2b_3r_3}$$

$$+\frac{b_2b_3d_1r_1r_2r_3 - sc_2b_2b_3r_2r_3 - b_3c_3d_1r_2r_3 + b_2c_5d_1r_2r_3}{\left(a_1\left(1-e^{-u}\right)+d_1\right)b_2r_2b_3r_3}.$$

The first three eigen values are the same with $J(E_0)$ eigen values. And this point is stable under the conditions $\lambda_i < 0$ for i = 1, 2, 3, 4.

The Jacobian of the total cancer invasion equilibrium and the coexist equilibrium points are produce very long and complex term eigen values, so here we just do some numerical analysis to proof its stability.

3.4. *Numerical Simulations*

To illustrate the analytical result, we do some numerical simulations by using the parameters in table 1.

Table 1 Parameters values

Parameter	Value			
	Simulation I	Simulation II	Simulation III	Simulation IV
s	0.33	0.125	0.125	0.2
ρ	0.25	0.75	0.25	0.5
α	0.3	0.7	0.3	0.005
μ	0.013	0.03	0.015	0.8
c_1	1	0.001	0.5	0.85
d_1	0.2	0.04	0.3	0.005
a_1	0.2	0.1	0.4	0.025
r_1	0.45	0.45	0.5	0.1
b_1	1	0.2	0.2	0.1
c_2	0.5	0.201	0.6	0.025
c_3	1	0.24	0.5	0.02
c_5	0.13	0.13	0.5	1
a_2	0.5	0.2	0.8	0.6
r_2	0.04	0.04	0.5	0.1

b_2	1	0.9	0.2	0.1
c_4	1	0.3	0.5	0.025
a_3	0.1	0.02	0.4	0.05
r_3	1	0.07	0.5	0.1
b_3	1	1.5	0.2	0.1
c_6	1	0.72	0.4	0.025
a_4	0.5	0.1	0.1	0.05
u	1	1	1	1

Numerical simulation is performed by taking parameter values on the table. This simulation is aimed to show the stability of the dead equilibrium point, the total cancer invasion equilibrium, the cancer-free equilibrium, and the coexistence equilibrium. For each equilibrium point we use initial value $I(0) = 0$, $T(0) = 0.01$, $N(0) = 1$, $F(0) = 0.8$.

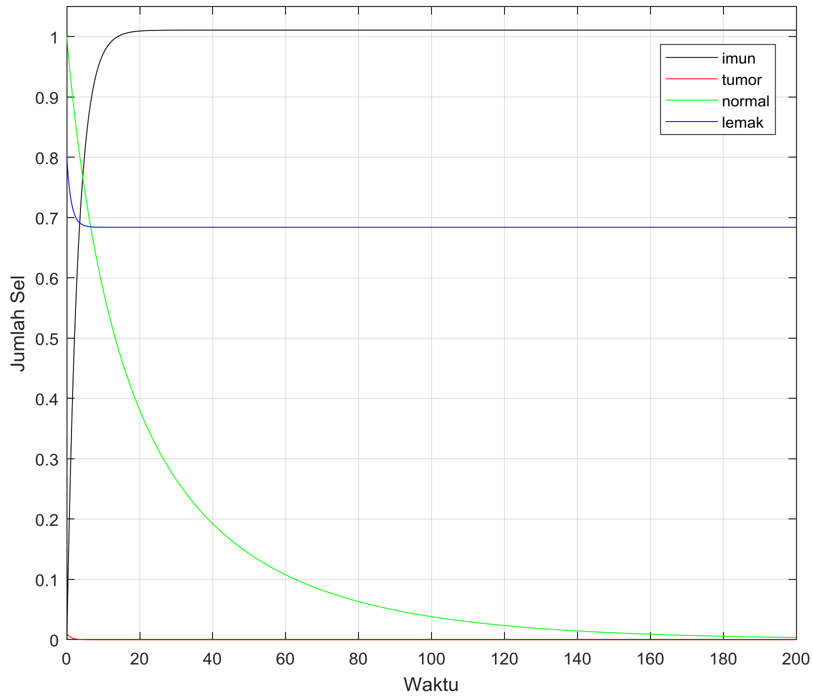

Figure 1 Number of total cells every time of the dead equilibrium point

The first simulation is aimed to show the stability of the dead equilibrium. By using simulation I parameters we get the eigen values are $\lambda_1 = -0.6839$, $\lambda_2 = -0.0232$, $\lambda_3 = -0.3264$, and $\lambda_4 = -0.2826$. and the dead equilibrium point is $E_0 = (1.0110, 0, 0, 0.6839)$. From figure 1 we observe that the dead equilibrium point reach after day 200.

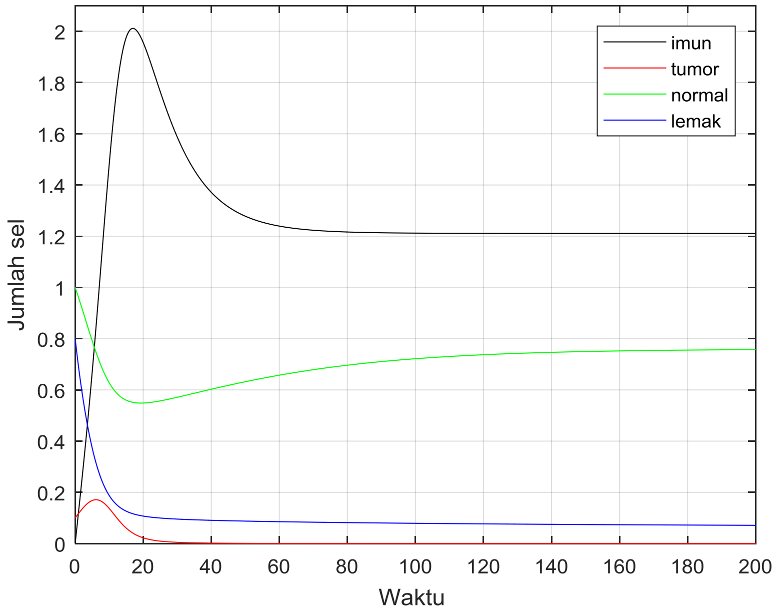

Figure 2 Number of total cells every time of the cancer-free equilibrium point

The second simulation produce $\lambda_1 = -0.0068, \lambda_2 = -0.0274, \lambda_3 = -0.1032$, dan $\lambda_4 = -0.0938$ and cancer-free equilibrium $E_1 = (1.2111, 0, 07599, 0.0646)$. The result of second simulation is presented in figure 2.

The result of next simulation are $\lambda_1 = -0.9038$, $\lambda_2 = -0.0470 + 0.2695i$, $\lambda_3 = -0.0470 - 0.2695i$, $\lambda_4 = -0.2508$ with the total cancer invasion equilibrium point is $E_3 = (0.1454, 0.9958, 0, 0.3845)$. It is shown in figure 3 that the complex eigen value conduce oscillation part of the number of total cells in the first time the drug is given. But along the given drug, the total cells number converge to equilibrium point.

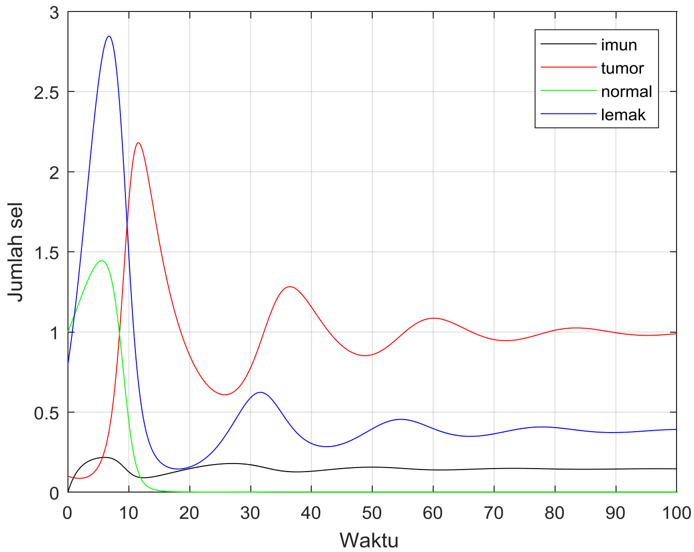

Figure 3 Number of total cells every time of the total cancer invansion equilibrium point

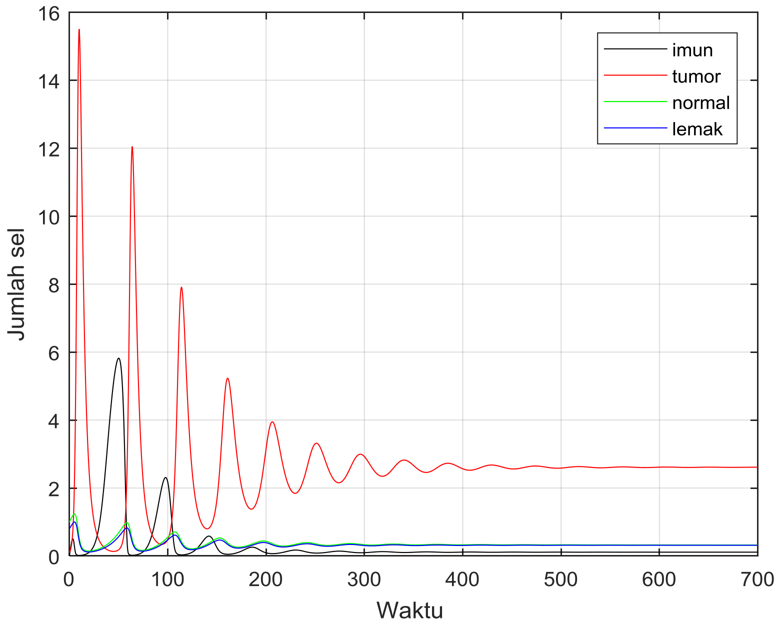

Figure 4 Number of total cells every time of the coexist equilibrium point

The last simulation is conducted to explore the last equilibrium points behaviour. From the figure 4 we can find that although in the end the drug no longer has an effect on the cells number, but the number of cancer cells is more than the number of normal cells, for parameter that is used in this simulation. But it is possible with different parameter values will be produced different result.

CONCLUSION

We have shown that cancerous chemotherapy model with obesity effect has four equilibriums, in case fat cells not equal to zero, namely the dead equilibrium point (E_0), the cancer-free equilibrium point (E_1), the total cancer invansion point (E_2), and the coexist equilibrium point (E_3). All of them are stable under some condition.

ACKNOWLEDGMENTS

This work was supported by Faculty of Mathematics and Natural Science, Brawijaya University: Indonesia: Contract Number: 24/UN10.F09.01/PN/2017 dated August 31, 2017.

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