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The effects of drugs in chemotherapy as optimal control of tumor growth dynamical model

Abstract. Cancer is the disease caused by disordered hormone so that it causes the lumps grow abnormally on body tissue and it is known as malignant tumor. About 16.65 percents, the mortality in the world is caused by cancer while in Indonesia, cancer contributes the third largest death. This research will explain about stability and optimal control of tumor growth dynamical model by drugs in chemotheraphy. In tumor growth dynamical model, there are normal cells, tumor cells and immune cells. From mathematical model of tumor growth, there are some equilibrium points which will be analyzed their stability using eigen value. In this research, from mathematical model of tumor growth, it will be added control such as drugs in chemotherapy. The method used for solving optimal control problem and resulting numerical solutions is Forward Backward Sweep Method. Based on simulation results, drugs in chemotherapy give effects in normal cell, tumor cell and immune cell.

1. Introduction

Cancer is the disease caused by disordered hormone so that it causes the lumps grow abnormally on body tissue and it is known as malignant tumor. About 16.65 percents, the mortality in the world is caused by cancer. In Indonesia, cancer contributes the third largest death. Unhealthy diet and life, smoke are dominant factors causing the cancer. Cancer occurs when normal cells become cancer cells through mutation process or abnormal growth. Some treatments for reducing cancer have been applied such as chemotherapy and traditional drugs.

There are many diseases which have been constructed to mathematical model such as influenza [6],[7], bird flu [9], dengue fever [11]. In mathematical model of disease spread, generally there are susceptible population, infected population, and recovered population [4],[5]. From three populations, they can be determined reproduction number based on available parameters for determining the stability. Beside that, predator prey model has also been developed for the stability in the natural selection [10].

This research will explain about stability and optimal control of tumor growth dynamical model by drugs in chemotheraphy. In tumor growth dynamical model, there are normal cells, tumor cells and immune cells [8]. From mathematical model of tumor growth, there are some equilibrium points which will be analyzed their stability using eigen value. In this research, from mathematical model of tumor growth, it will be added control such as drugs in chemotherapy for reducing amount of tumor cell. However in pratical, this process also affects normal cell and immune cell, so that normal cell and immune cell are also reduced. The usage of drugs in chemotherapy should be proportional. Less drugs cause tumor cells stay grow, and over drugs cause expensive cost and bad for the body tissue.

The method used for solving optimal control problem and resulting numerical solutions is Forward Backward Sweep Method. This method uses state variables with initial condition and adjoint variables with final condition in its computation [2]. Based on simulation results, drugs in chemotherapy give effects in normal cell, tumor cell and immune cell.

2. Mathematical model of tumor growth

In mathematical model of tumor growth, there are three populations included in system such as normal cell, tumor cell, and immune cell. This model used predator-prey model concept.

2.1. *Mathematical Model*

Mathematical model of tumor growth is as follows [8] :

$$\dot{N} = r_2 N(1 - b_2 N) - c_4 N \tag{1}$$

$$\dot{T} = r_1 T(1 - b_1 T) - \frac{\rho IT}{\alpha + T_0} - c_2 IT + c_3 N \tag{2}$$

$$\dot{I} = s + d_2 \left(\frac{\rho IT}{\alpha + T_0} \right) - c_1 IT - d_1 I \tag{3}$$

Note that the denominator $\alpha + T_0$ is assumed constant. The other parameters are :

$N(t)$: the population of normal cell
$T(t)$: the population of tumor cell
$I(t)$: the population of immune cell

r_1 : instrinsic rate of tumor cell growth
r_2 : instrinsic rate of normal cell growth
b_1 : carrying capacity of the tumor cell population
b_2 : carrying capacity of the normal cell population
ρ : search rate of tumor cell by the immune cell
d_2 : conversion factors
d_1 : natural death rate of immune cell
α : half saturation constant
s : the growth rate of immune cell (constant)

c_1 : coefficient of inactive immune cell due to interaction with tumor cell
c_2 : coefficient of dead tumor cell due to interaction with immune cell
c_3 : the rate of increasing tumor cell due to normal cell mutation to tumor cell
c_4 : the rate of decreasing normal cell due to normal cell mutation to tumor cell

From the model, without the existance of immune cells, the tumor cells grow based on logistic function and without existance of tumor cells, the immune cells grow constantly.

2.2. *Existance of solution*

The solutions of this problem can be said exist if $N(t) \geq 0, T(t) \geq 0, I(t) \geq 0$. The equilibrium points also should satisfy these conditions [1].

2.3. *Equilibrium Point*

The equilibrium points can be determined by $\dot{N} = 0, \dot{T} = 0, \dot{I} = 0$ in equation (4), equation (5) and equation (6).

$$r_2 N(1 - b_2 N) - c_4 N = 0 \tag{4}$$

$$r_1 T(1 - b_1 T) - \frac{\rho IT}{\alpha + T_0} - c_2 IT + c_3 N = 0 \tag{5}$$

$$s + d_2\left(\frac{\rho IT}{\alpha + T_0}\right) - c_1 IT - d_1 I = 0 \tag{6}$$

From equation (4), equation (5) and equation (6), we obtain three equilibrium points :

1. Equilibrium point 1 : $N_{e1} = 0, T_{e1} = 0, I_{e1} = \frac{s}{d_1}$
2. Equilibrium point 2 : $N_{e2} = 0, T_{e2} = \frac{1}{b_1} - \frac{\rho I_{e2}^+}{(\alpha + T_0) r_1 b_1} - \frac{c_2 I_{e2}^+}{r_1 b_1}, I_{e2} = I_{e2}^+$ with I_{e2}^+ is the positive solution of :

$$s + \left(\frac{1}{b_1} - \frac{\rho I_{e2}^+}{(\alpha + T_0) r_1 b_1} - \frac{c_2 I_{e2}^+}{r_1 b_1}\right)\left(d_2\left(\frac{\rho I_{e2}^+}{\alpha + T_0}\right) - c_1 I_{e2}^+\right) - d_1 I_{e2}^+ = 0$$

3. Equilibrium point 3 : $N_{e3} = \frac{1}{b_2} - \frac{c_4}{b_2 r_2}, T_{e3} = T_{e3}^+, I_{e1} = \frac{-r_1 T_{e3}^+ (1 - b_1 T_{e3}^+) - c_3\left(\frac{1}{b_2} - \frac{c_4}{r_2 b_2}\right)}{\frac{-\rho T_{e3}^+}{\alpha + T_0} - c_2 T_{e3}^+}$ with T_{e3}^+ is the positive solution of :

$$s + \left(\frac{-r_1 T_{e3}^+ (1 - b_1 T_{e3}^+) - c_3\left(\frac{1}{b_2} - \frac{c_4}{r_2 b_2}\right)}{\frac{-\rho T_{e3}^+}{\alpha + T_0} - c_2 T_{e3}^+}\right)\left(d_2\left(\frac{\rho T_{e3}^+}{\alpha + T_0}\right) - c_1 T_{e3}^+ - d_1\right) = 0$$

From each equilibrium point, it will be analyzed the its stability using eigen value method from jacobian matrix.

2.4. Stability Analysis

From differential equation system in equation (1), equation (2) and equation (3), they will be constructed Jacobian matrix in equation (7). Suppose :

$$f_1 = r_2 N(1 - b_2 N) - c_4 N$$

$$f_2 = r_1 T(1 - b_1 T) - \frac{\rho IT}{\alpha + T_0} - c_2 IT + c_3 N$$

$$f_3 = s + d_2\left(\frac{\rho IT}{\alpha + T_0}\right) - c_1 IT - d_1 I$$

Then Jacobian matrix is :

$$Jac = \begin{bmatrix} \frac{\partial f_1}{\partial N} & \frac{\partial f_1}{\partial T} & \frac{\partial f_1}{\partial I} \\ \frac{\partial f_2}{\partial N} & \frac{\partial f_2}{\partial T} & \frac{\partial f_2}{\partial I} \\ \frac{\partial f_3}{\partial N} & \frac{\partial f_3}{\partial T} & \frac{\partial f_3}{\partial I} \end{bmatrix} = \begin{bmatrix} r_2 - 2r_2b_2N - c_4 & 0 & 0 \\ c_3 & r_1 - 2r_1b_1T - \frac{\rho I}{\alpha + T_0} - c_2 I & -\frac{\rho T}{\alpha + T_0} - c_2 T \\ 0 & \frac{d_2 \rho I}{\alpha + T_0} - c_1 I & \frac{d_2 \rho T}{\alpha + T_0} - c_1 T - d_1 \end{bmatrix} \tag{7}$$

For analyzing the stability, we determine the eigen value from equilibrium point on jacobian matrix using $\det(\lambda I - Jac) = 0$. The system is stable if all real of eigen value are $\lambda_1 < 0, \lambda_2 < 0, \lambda_3 < 0$ (negative).

3. Optimal control of tumor growth by drugs

In optimal control of tumor growth, there are drugs in chemotherapy process as control u applied to tumor cell to reduce amount of tumor cell. However in pratical, this process also affects normal cell and immune cell, so that normal cell and immune cell are also reduced. The effectiveness range of u is [0,1]. Therefore the mathematical model from equation (2), (3) and (4) become mathematical model in equation (8), (9) and (10) respectively.

$$\dot{N} = r_2 N(1 - b_2 N) - c_4 N - a_1 u N \tag{8}$$

$$\dot{T} = r_1 T(1 - b_1 T) - \frac{\rho I T}{\alpha + T_0} - c_2 I T + c_3 N - a_2 u T \tag{9}$$

$$\dot{I} = s + d_2 \left(\frac{\rho I T}{\alpha + T_0} \right) - c_1 I T - d_1 I - a_3 u I \tag{10}$$

with a_1, a_2, a_3 is the rate of reducing normal cell, tumor cell, and immune cell due to drugs in chemoterapy.

For the model, the objective function which is minimized is :

$$J = \int_0^T A_1 T + A_2 u^2 dt \tag{11}$$

With weights are $A_1 > 0, A_2 > 0$ related to amount of tumor cell and cost of drugs in chemoterapy respectively. From the model, amount of tumor cell and the cost of drugs in chemoterapy will be minimized. The goal is to find optimal control u^*.

3.1. Pontryagin's Maximum Principle

If u is an optimal control corresponding state system, there exist adjoint variables $(\lambda_N \quad \lambda_T \quad \lambda_I)$ which satisfy the following [5] :

$$\dot{\lambda}_N = -\frac{\partial H}{\partial N} = -\lambda_N (r_2 - 2r_2 b_2 N - c_4 - a_1 u) - \lambda_T c_3 \tag{12}$$

$$\dot{\lambda}_T = -\frac{\partial H}{\partial T} = -A_1 - \lambda_T \left(r_1 - 2r_1 b_1 T - \frac{\rho I}{\alpha + T_0} - c_2 I - a_2 u \right) - \lambda_I \left(d_2 \left(\frac{\rho I}{\alpha + T_0} \right) - c_1 I \right) \tag{13}$$

$$\dot{\lambda}_I = -\frac{\partial H}{\partial T} = -\lambda_T\left(-\frac{\rho T}{\alpha + T_0} - c_2 T\right) - \lambda_I\left(d_2\left(\frac{\rho T}{\alpha + T_0}\right) - c_1 T - d_1 - a_3 u\right) \tag{14}$$

$$\lambda_N(T) = 0, \lambda_T(T) = 0, \lambda_I(T) = 0 \tag{15}$$

Where the Hamiltonian is :

$$H = A_1 T + A_2 u^2 + \begin{pmatrix} \lambda_N & \lambda_T & \lambda_I \end{pmatrix} \begin{pmatrix} r_2 N(1 - b_2 N) - c_4 N - a_1 u N \\ r_1 T(1 - b_1 T) - \frac{\rho I T}{\alpha + T_0} - c_2 I T + c_3 N - a_2 u T \\ s + d_2\left(\frac{\rho I T}{\alpha + T_0}\right) - c_1 I T + d_1 I - a_3 u I \end{pmatrix} \tag{16}$$

Furthermore, we can find optimal control u^*

$$\frac{\partial H}{\partial u} = 0 \tag{17}$$

$$\frac{\partial H}{\partial u} = 2A_2 u + \lambda_N(-a_1 N) + \lambda_T(-a_2 T) + \lambda_I(-a_3 I) = 0 \tag{18}$$

$$u = \min\left(1, \max\left(0, \frac{\lambda_N a_1 N + \lambda_T a_2 T + \lambda_I a_3 I}{2A_2}\right)\right) \tag{19}$$

3.2. *Forward Backward Sweep Method*

Forward backward sweep method applied on optimal control of tumor growth can be designed as follows [3]:

Suppose state variables and adjoint variables are :

$$f_1 = rN(1 - b_2 N) - c_4 N - a_1 u N$$

$$f_2 = rT(1 - b_1 T) - \frac{\rho I T}{\alpha + T_0} - c_2 I T + c_3 N - a_2 u T$$

$$f_3 = s + d_2\left(\frac{\rho I T}{\alpha + T_0}\right) - c_1 I T - d_1 I - a_3 u I$$

$$g_1 = -\lambda_N(r_2 - 2r_2 b_2 N - c_4 - a_1 u) - \lambda_T c_3$$

$$g_2 = -A_1 - \lambda_T\left(r_1 - 2r_1 b_1 T - \frac{\rho I}{\alpha + T_0} - c_2 I - a_2 u\right) - \lambda_I\left(d_2\left(\frac{\rho I}{\alpha + T_0}\right) - c_1 I\right)$$

$$g_3 = -\lambda_T\left(-\frac{\rho T}{\alpha + T_0} - c_2 T\right) - \lambda_I\left(d_2\left(\frac{\rho T}{\alpha + T_0}\right) - c_1 T - d_1 - a_3 u\right)$$

The forward backward sweep method algorithm is as follows :

while(process has not converged yet)

$u_{old} = u$

1. Compute solution of state variables forward with initial condition N_0, T_0, I_0 are given using Runge Kutta fourth order.

$$k_{1j} = f_j\left(N_i, T_i, I_i, u_i\right), j = 1,2,3$$

$$k_{2j} = f_j\left(N_i + \frac{h}{2}k_{11}, T_i + \frac{h}{2}k_{12}, I_i + \frac{h}{2}k_{13}, \frac{u_i + u_{i+1}}{2}\right), j = 1,2,3$$

$$k_{3j} = f_j\left(N_i + \frac{h}{2}k_{21}, T_i + \frac{h}{2}k_{22}, I_i + \frac{h}{2}k_{23}, \frac{u_i + u_{i+1}}{2}\right), j = 1,2,3$$

$$k_{4j} = f_j\left(N_i + hk_{31}, T_i + hk_{32}, I_i + hk_{33}, u_{i+1}\right), j = 1,2,3$$

$$N_{i+1} = N_i + \frac{h}{6}\left(k_{11} + 2k_{21} + 2k_{31} + k_{41}\right)$$

$$T_{i+1} = T_i + \frac{h}{6}\left(k_{12} + 2k_{22} + 2k_{32} + k_{42}\right)$$

$$I_{i+1} = I_i + \frac{h}{6}\left(k_{13} + 2k_{23} + 2k_{33} + k_{43}\right)$$

2. Compute solution of adjoint variables backward with final condition $\lambda_{N(T)}, \lambda_{T(T)}, \lambda_{I(T)}$ are given using Runge Kutta fourth order.

$$l_{1j} = g_j\left(\lambda_{N(i)}, \lambda_{T(i)}, \lambda_{I(i)}, N_i, T_i, I_i, u_i\right), j = 1,2,3$$

$$l_{2j} = g_j\left(\lambda_{N(i)} - \frac{h}{2}l_{11}, \lambda_{T(i)} - \frac{h}{2}l_{12}, \lambda_{I(i)} - \frac{h}{2}l_{13}, \frac{N_i + N_{i-1}}{2}, \frac{T_i + T_{i-1}}{2}, \frac{I_i + I_{i-1}}{2}, \frac{u_i + u_{i-1}}{2}\right), j = 1,2,3$$

$$l_{3j} = g_j\left(\lambda_{N(i)} - \frac{h}{2}l_{21}, \lambda_{T(i)} - \frac{h}{2}l_{22}, \lambda_{I(i)} - \frac{h}{2}l_{23}, \frac{N_i + N_{i-1}}{2}, \frac{T_i + T_{i-1}}{2}, \frac{I_i + I_{i-1}}{2}, \frac{u_i + u_{i-1}}{2}\right), j = 1,2,3$$

$$l_{4j} = g_j\left(\lambda_{N(i)} - hl_{31}, \lambda_{T(i)} - hl_{32}, \lambda_{I(i)} - hl_{33}, N_{i-1}, T_{i-1}, I_{i-1}, u_{i-1}\right), j = 1,2,3$$

$$\lambda_{N(i-1)} = \lambda_{N(i)} - \frac{h}{6}\left(l_{11} + 2l_{21} + 2l_{31} + l_{41}\right)$$

$$\lambda_{T(i-1)} = \lambda_{T(i)} - \frac{h}{6}\left(l_{12} + 2l_{22} + 2l_{32} + l_{42}\right)$$

$$\lambda_{I(i-1)} = \lambda_{I(i)} - \frac{h}{6}\left(l_{13} + 2l_{23} + 2l_{33} + l_{43}\right)$$

3. Compute optimal control u^* using equation (19)
4. Update optimal control

$$u \leftarrow \frac{u + u_{old}}{2} \tag{20}$$

End

5. Compute performance index as objective function

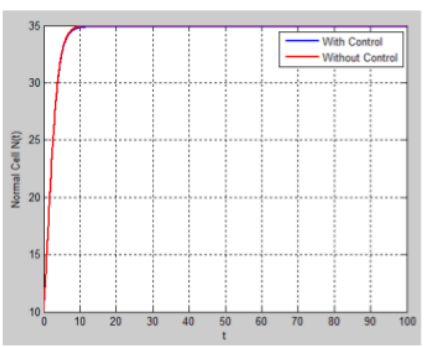
$$J(u) = \sum_{k=0}^{T-1}\left(A_1 T(k)^2 + A_2 u(k)^2\right) \tag{21}$$

4. Results

Parameters used in optimal control of tumor growth simulation and initial condition used are are as follows :

The population of normal cell $N(0)$	10
The population of tumor cell $T(0)$	5
The population of immune cell $I(0)$	10
Instrinsic rate of tumor cell growth r_1	1
Instrinsic rate of normal cell growth r_2	1
Carrying capacity of the tumor cell population b_1	1/2
Carrying capacity of the normal cell population b_2	1/50
Search rate of tumor cell by the immune cell ρ	0.01
Conversion factors d_2	0.5
Natural death rate of immune cell d_1	0.2
Half saturation constant α	0.3
The growth rate of immune cell (constant) s	5
Coefficient of inactive immune cell due to interaction with tumor cell c_1	0.2
Coefficient of dead tumor cell due to interaction with immune cell c_2	0.6
The rate of increasing tumor cell due to normal cell mutation to tumor cell c_3	0.3
The rate of decreasing normal cell due to normal cell mutation to tumor cell c_4	0.3
Weight related to amount of tumor cell A_1	1
Weight related to the cost of drugs in chemotherapy A_2	5

Figure 1(a)-(c) shows numerical solution of normal cell, tumor cell, and immune cell with and without drugs in chemotherapy as control respectively. From the graph, the effect of drugs in chemoterapy can reduce amount of tumor cell. In normal cell, the effects of drugs in chemotherapy are almost zero, so that the graphs look similar. However, the immune cell with control is higher than immune cell without control.



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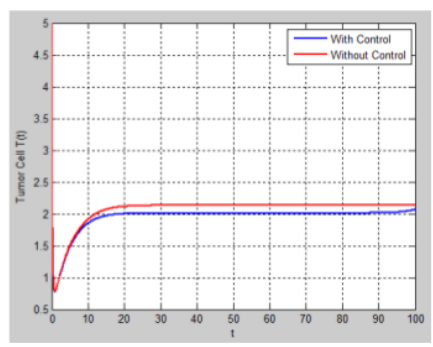

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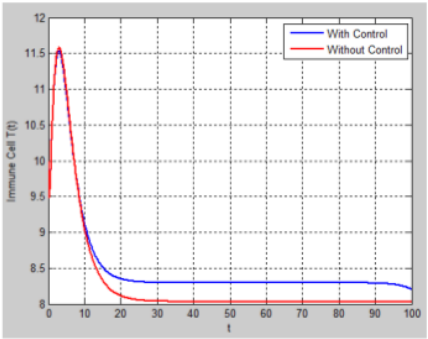

(c)

Figure 1. Numerical solutions of tumor growth. (a) Normal cell (b) Tumor cell. (c) Immune cell.

Figure 2 shows control function of dtugs in chemotherapy. The control function has the interval of effectiveness between 0 to 1 with 0 represents control functions are fail and 1 represents control functions are success.

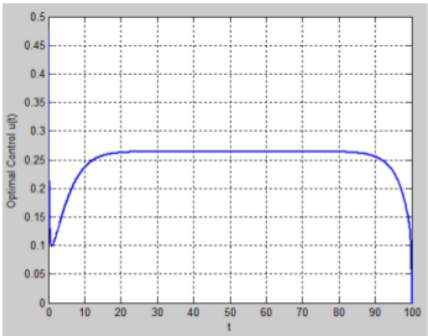

Figure 2. Optimal control of drugs in chemotherapy

5. Conclusions

In tumor growth dynamical model, there are normal cells, tumor cells and immune cells. From mathematical model of tumor growth, there are some equilibrium points which will be analyzed their stability using eigen value. In this research, from mathematical model of tumor growth, it will be added control i.e. drugs in chemotherapy. The method used for solving optimal control problem and resulting numerical solutions is Forward Backward Sweep Method. Based on simulation results, drugs in chemotherapy give effects in normal cell, tumor cell and immune cell. The development of this research is optimizing weights of performance index so that performance index is more optimal.

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MATEMATIKA DAN PENDIDIKAN MATEMATIKA (SENATIK) 2020
PROGRAM STUDI PENDIDIKAN MATEMATIKA FPMIPATI
UNIVERSITAS PGRI SEMARANG

No. : 224/Pan.SENATIK/P.Mat/IX/2020 Semarang, 11 September 2020
Lamp. : -
Hal : *Letter of Acceptance* (LOA)

Kepada
Yth. Dinita Rahmalia
Pemakalah Seminar Nasional Matematika dan Pendidikan Matematika (SENATIK) V Universitas PGRI Semarang
di Tempat

Dengan hormat,

Berdasarkan hasil review *full paper* yang telah dilakukan oleh tim reviewer dan editor, maka panitia Seminar Nasional Matematika dan Pendidikan Matematika (SENATIK) 2020 memutuskan artikel dengan

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Nama Penulis : A Muhith, D Rahmalia and T Herlambang

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Demikian surat keterangan ini dibuat untuk dapat dipergunakan sebagaimana mestinya. Kami mengucapkan terimakasih atas perhatian dan partisipasinya dalam Seminar Nasional Matematika dan Pendidikan Matematika (SENATIK) V Tahun 2020.

Mengetahui,
Ketua Program Studi
Pendidikan Matematika

Dr. Lilik Ariyanto, M.Pd.
NPP. 088602194

Semarang, 11 September 2020
Ketua Pelaksana

SENATIK
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