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EXACT SOLUTIONS AND NUMERICAL SOLUTIONS MATHEMATICAL MODELS OF THE EFFECT OF CHEMOTHERAPY ON CANCER CURE

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Abstract
Cancer is one of the main causes of death in the world. According to the National Cancer Institute, there are many types of cancer treatment. Chemotherapy is a type of cancer treatment by administering drugs into the sufferer's body. The effect of chemotherapy on cancer cure can be modeled in a system of differential equations. In this research, we will discuss the formation of a mathematical model of the effect of chemotherapy on cancer healing along with determining the exact solution using differential equation analysis. Numerical solutions will also be sought using Euler's method. Based on the analysis carried out, it was concluded that the chemotherapy drug (doxorubicin) had a positive influence on cancer cells in the recovery of cancer patients.
Keywords: Chemotherapy, Cancer, Mathematical Model, Euler Method.

1. INTRODUCTION

Cancer or malignant tumors are one of the main causes of death throughout the world. According to the Global Cancer Observatory (GCO), an interactive web-based platform that provides global cancer statistics to inform cancer control and research. The high number of cancer cases and cancer deaths is closely related to cancer risk factors that should be preventable. For cancer detected early, there are better treatment options. Therefore, preventive efforts must be made to increase awareness of the symptoms and risks of cancer so that preventive measures and early detection can be determined quickly.

According to the National Cancer Institute, there are many types of treatment for treating cancer, including biomarker testing, chemotherapy, hormone therapy, hyperthermia, immunotherapy, photodynamic therapy, radiotherapy, stem cell transplantation, surgery and targeted therapy. Among all this, the author chose chemotherapy as a treatment for cancer which will be tested for its effect in treating cancer mathematically, namely by mathematical modeling.

According to Rainer Ansorge in the introduction to the book "Mathematical Models of Fluiddynamics (2002)", mathematical modeling is the process of replacing non-mathematical problems with mathematical problems. Next, the mathematical work of this model proceeds with theoretical and/or numerical steps, such as the transition from extra-mathematical phenomena to mathematical description, work on mathematical replacements, re-translation of results and model checking.

This is the author's background for researching mathematical models of the influence of the chemotherapy process in curing cancer. The research continued with determining the equilibrium point of the model and its stability. Apart from that, the exact solution of the model and the numerical solution using the Euler method were analyzed.

2. MATHEMATICAL MODEL OF THE EFFECT OF CHEMOTHERAPY ON CANCER

The mathematical models discussed in this research include:

1. Cancer cell population $T(t)$
2. Effector-immune cells $N(t)$
3. Population of circulating lymphocyte cells $C(t)$
4. Concentration of chemotherapy drugs $M(t)$

Of the four models above, all of them start from the following assumptions.

1. Cancer cells grow proportionally, where their growth rate is commensurate with their population and die after interacting with other cancer cells in the body.
2. There is an interaction between cancer cells and immune effector cells, which leads to the death of cancer cells and immune effector cells.
3. Effector-immune cells and lymphocyte cells originate from within the body and die at a death rate commensurate with the population.
4. Enzyme activity in the body causes immune effector cells to grow through a kinetic process.
5. Chemotherapy drugs come from outside the body and can kill cancer cells, immune effector cells and circulating lymphocyte cells.

Below we will show a diagram showing the relationship between cancer cells, immune effector cells, lymphocyte cells and chemotherapy drugs.

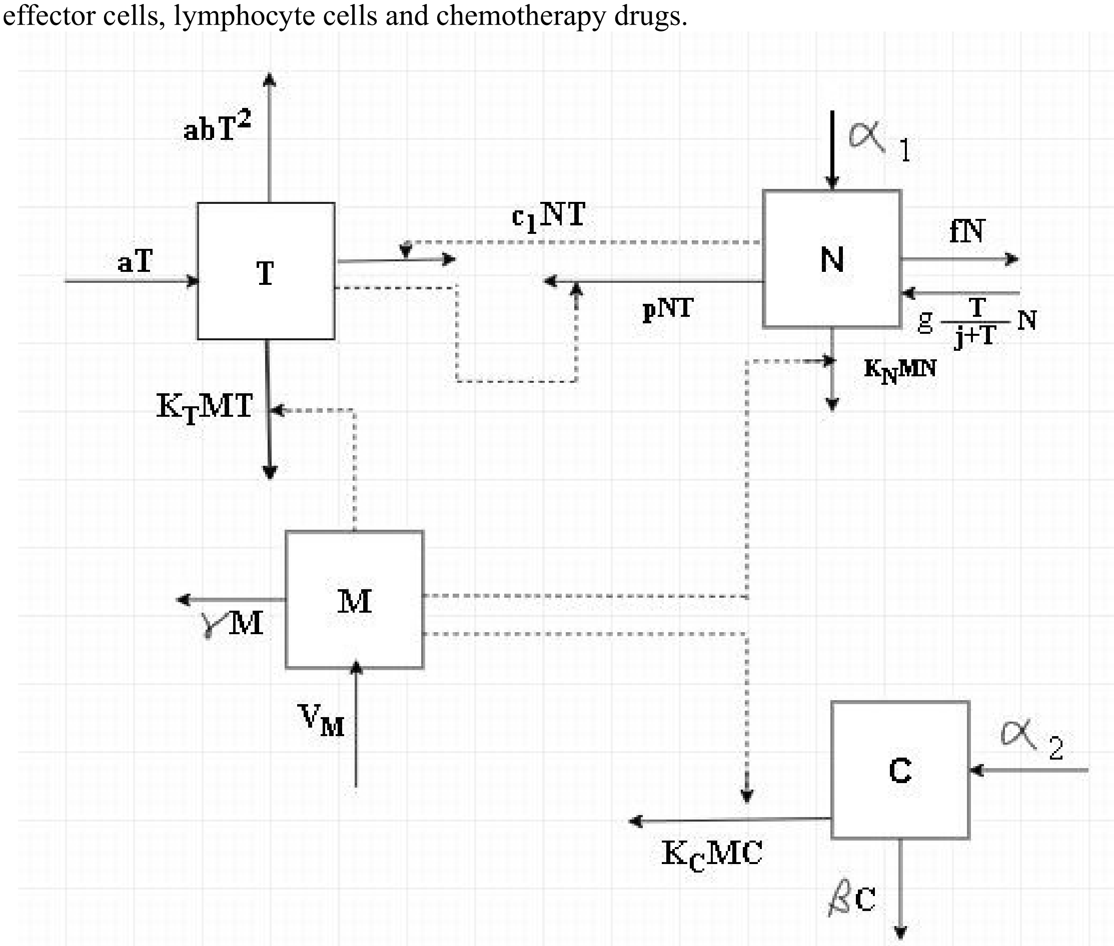

Figure 1. Cancer Chemotherapy Model Compartment Diagram

Information:

a		Cancer growth rate
$\frac{1}{b}$	:	Cancer cell capacity
d	:	Division of cancer cells killed by immune effector cells
f	:	Rate of death of immune-effector cells

g	:	Rate of recruitment of immune-effector cells by cancer cells
j	:	Stiffness coefficient of immune-effector cell recruitment curve
K_T	:	Killing of cancer cell fragments by chemotherapy drugs
K_N	:	The killing of immune-effector cell fragments by chemotherapy drugs
K_C	:	Killing of lymphocyte cell fragments by chemotherapy drugs
p	:	The rate of inactivation of effector cells by cancer cells
α_1	:	Constant source of effector cells
α_2	:	A constant source of circulating lymphocyte cells
β	:	Death rate of circulating lymphocyte cells
γ	:	The rate of reduction of chemotherapy drugs

From these assumptions and compartment diagrams, a system of nonlinear differential equations is formed

$$\dot{x} = F(x),\ x = \begin{bmatrix} T \\ N \\ C \\ M \end{bmatrix} \text{ and } F = \begin{bmatrix} F_1 \\ F_2 \\ F_3 \\ F_4 \end{bmatrix},$$

describes the growth, death, and interaction of chemotherapy with cancer cells, immune effector cells, and circulating lymphocyte cells, so that when written it becomes as follows.

$$\left.\begin{aligned} F_1 &= \frac{dT}{dt} = aT(1 - bT) - c_1NT - K_TMT \\ F_2 &= \frac{dN}{dt} = \alpha_1 - fN + g\frac{T}{j+T}N - pNT - K_NMN \\ F_3 &= \frac{dC}{dt} = \alpha_2 - \beta C - K_CMC \\ F_4 &= \frac{dM}{dt} = -\gamma M + V_M \end{aligned}\right\} \quad (1)$$

The system of Equation (1) has initial conditions as will be shown as follows.

$$T(0) = T_0, N(0) = N_0, C(0) = C_0, M(0) = M_0$$

with each initial condition being positive $(T_0 > 0, N_0 > 0, C_0 > 0, M_0 > 0)$. L.G. de Pillis et al in a journal entitled "Chemotherapy for tumors: An analysis of the dynamics and a study of quadratic and linear optimal controls (2006)" estimated the value of each parameter of Equation (1). These values will be shown in Table 1.

Table 1. Estimated Equation System Parameter Values

Parameter	Unit	Description	Estimated Value	Reference
a	per day	Cancer growth rate	4.31×10^{-3}	(L.G. de Pillis et al, 2006)
b	per cell	$1/b$ is the carrying capacity of cancer cells	1.02×10^{-14}	(L.G. de Pillis et al, 2006)
c_1	per cell per day	Rate of death of immune-effector cells	3.41×10^{-10}	(L.G. de Pillis et al, 2006)
K_T	per day	The rate of death of cancer cells due to the influence of chemotherapy drugs	8.00×10^{-1}	(Perry, 2001)

Parameter	Unit	Description	Estimated Value	Reference
α_1	per cell per day	Effector cell source constant	1.20×10^4	(Kuznetsov et al, 1994)
f	per day	Effector cell death rate	4.12×10^{-2}	(Kuznetsov et al, 1994)
g	per day	Maximal rate of effector cell recruitment by cancer cells	1.5×10^{-2}	(Kuznetsov et al, 1994) (Diefenbach et al, 2011)
j	cell ^{2}	Stiffness coefficient of effector cell recruitment curve	2.02×10^1	(L.G. de Pillis et al, 2006)
p	per cell per day	The rate of inactivation of effector cells by cancer cells	2.00×10^{-11}	(L.G. de Pillis et al, 2006)
K_N	per day	The rate of death of immune effector cells due to the influence of chemotherapy drugs	6.00×10^{-1}	(Perry, 2001)
α_2	per cell per day	Source constants of circulating lymphocyte cells	7.50×10^8	(L.G. de Pillis et al, 2006)
β	per day	Death rate of circulating lymphocyte cells	1.20×10^{-2}	(Hanser, 2001)
K_C	per day	The rate of death of circulating lymphocyte cells due to the influence of chemotherapy drugs	6.00×10^{-1}	(Perry, 2001)
γ	per hari	The rate of reduction of chemotherapy drugs	9.00×10^{-1}	(Calabresi, 1993)

3. DISCUSSION

3.1. Equilibrium Point

To find out the equilibrium point of the System of Equations (1), it is necessary to fulfill the following conditions.

$$\frac{dT}{dt} = \dot{T} = 0, \frac{dN}{dt} = \dot{N} = 0, \frac{dC}{dt} = \dot{C} = 0, \frac{dM}{dt} = \dot{M} = 0.$$

Thus, based on the calculation results, an equilibrium point is obtained

$$\left(\hat{T}, \hat{N}, \hat{C}, \hat{M}\right) = \left(0, \frac{\alpha_1\gamma}{f\gamma + K_N V_M}, \frac{\alpha_2\gamma}{\beta\gamma + K_C V_M}, \frac{V_M}{\gamma}\right).$$

3.2. Exact Solution

Below we will present an attempt to determine an exact solution to a system of linear equations from a mathematical model of the effect of chemotherapy on cancer. The exact solution to the system of equations is as follows. First, it is necessary first to find the general solution of the system of equations $\dot{y} = J(F(x))y$ namely as follows.

$$T = \hat{T} + C_4 T_* e^{St}$$

$$N = \hat{N} + C_1 N_* e^{-\gamma t} + C_3' e^{\left(\frac{-\gamma f - K_N V_M}{\gamma}\right)} + C_4' e^{St}$$

$$C = \hat{C} + C_1 C_* e^{-\gamma} + C_2{}' e^{\left(\frac{-\gamma\beta - K_C V_M}{\gamma}\right)t}$$
$$M = \widehat{M} + C_1{}' e^{-\gamma t}$$

with

$$T_* = \frac{\gamma^2 \alpha f + \gamma\alpha K_N V_M - \gamma^2 c_1 \alpha_1 + \gamma^2 f^2 + 2\gamma K_N V_M - \gamma f K_T V_M + (K_N)^2 (V_M)^2}{\gamma^2 \alpha_1 (p-1)}$$
$$S = \frac{\gamma^2 \alpha f + \gamma\alpha K_N V_M - \gamma^2 c_1 \alpha_1 - \gamma f K_T V_M - K_T K_N (V_M)^2}{\gamma^2 f + \gamma K_N V_M}$$
$$N_* = \frac{\gamma^2 \alpha_1 K_N}{(\gamma f + K_N V_M)(\gamma(\gamma - f) - K_N V_M)}$$
$$C_* = \frac{\gamma^2 \alpha_2 K_C}{(\gamma\beta + K_C V_M)(\gamma(\gamma - \beta) - K_C V_M)}$$

where $(\hat{T}, \widehat{N}, \hat{C}, \widehat{M})$ equilibrium point.
Because the initial conditions are known

$$T(0) = T_0, N(0) = N_0, C(0) = C_0, M(0) = M_0 .$$

then a special solution can be determined, namely equation

$$T(t) = T_0^{\left(\frac{\gamma^2 \alpha f + \gamma\alpha K_N - \gamma^2 C_1 \alpha_1 - \gamma f K_T V_M - K_T K_N (V_M)^2}{\gamma^2 f + \gamma K_N V_M}\right)}$$
$$N(t) = \frac{\alpha_1 \gamma}{\gamma f + K_N V_M} + \left(M_0 - \frac{V_M}{\gamma}\right)\left(\frac{\gamma^2 \alpha_1 K_N}{(\gamma f + K_N V_M)(\gamma(\gamma - f) - K_N V_M)}\right) e^{-\gamma t} + N_{**} e^{\left(\frac{-\gamma f - K_N V_M}{\gamma}\right)t} + N_{***} e^{St}$$
$$C(t) = \frac{\alpha_2 \gamma}{\gamma\beta + K_C V_M} + \left(M_0 - \frac{V_M}{\gamma}\right)\left(\frac{\gamma^2 \alpha_2 K_C}{(\gamma\beta + K_C V_M)(\gamma(\gamma - \beta) - K_C V_M)}\right) e^{-\gamma t} + \left(C_0 - \frac{\alpha_2 \gamma}{\gamma\beta + K_C V_M} - \frac{\gamma^2 \alpha_2 K_C M_0}{V_M (\gamma\beta + K_C V_M)(\gamma(\gamma - \beta) - K_C V_M)}\right) e^{\left(\frac{-\gamma\beta - K_C V_M}{\gamma}\right)t}$$
$$M(t) = \frac{V_M}{\gamma} + \left(M_0 \frac{\gamma}{V_M}\left(\frac{\alpha_1 K_N}{(\gamma f + K_N V_M)(\gamma(\gamma - f) - K_N V_M)}\right)\right) e^{-\gamma t}$$

with

$$N_{**} = N_0 - \frac{\alpha_1 \gamma}{\gamma f + K_N V_M} - \left(M_0 - \frac{V_M}{\gamma}\right)\left(\frac{\gamma^2 \alpha_1 K_N}{(\gamma f + K_N V_M)(\gamma(\gamma - f) - K_N V_M)}\right) - \frac{T_0 \gamma^2 \alpha_1 (p-1)}{\gamma^2 \alpha f + \gamma\alpha K_N V_M - \gamma^2 c_1 \alpha_1 + \gamma^2 f^2 + 2\gamma K_N V_M - \gamma f K_T V_M + (K_N)^2 (V_M)^2}$$
$$N_{***} = \frac{T_0 \gamma^2 \alpha_1 (p-1)}{\gamma^2 \alpha f + \gamma\alpha K_N V_M - \gamma^2 c_1 \alpha_1 + \gamma^2 f^2 + 2\gamma K_N V_M - \gamma f K_T V_M + (K_N)^2 (V_M)^2}$$

3.3. System Solution Via Euler's Method

By applying Euler's method to the System of Equations (1), it can be written as follows.

$$\begin{aligned}
T_{i+1} &= T_i + h\left(aT_i(1 - bT_i) - c_i N_i T_i - K_{T_i} M_i T_i\right) \\
N_{i+1} &= N_i + h\left(\alpha_i - fN_i + g\tfrac{T_i}{j + T_i} N_i - pN_i T_i - K_{N_i} M_i N_i\right) \\
C_{i+1} &= C_i + h\left(\alpha_2 - \beta C_i - K_{C_i} M_i C_i\right) \\
M_{i+1} &= M + h\left(-\gamma M_i + V_{M_i}\right)
\end{aligned} \qquad (2)$$

where $T(0) = T_0, N(0) = N_0, C(0) = C_0, M(0) = M_0$, $n = 30$ minute, $h = 60$ minute, and $i = 0,1,2,3,4,5$. To solve the problem in the System of Equations (2) using the Euler method, we need initial values. If given initial values as shown in Table 2.

Table 2. Parameter and Initial Condition Value

No	Parameter	Initial Condition Value
1	a	4.31×10^{-3}
2	b	1.02×10^{-14}
3	c_1	3.41×10^{-10}
4	K_T	8.00×10^{-1}
5	α_1	1.20×10^{4}
6	f	4.12×10^{-2}
7	g	1.5×10^{-2}
8	j	2.02×10^{1}
9	p	2.00×10^{-11}
10	K_N	6.00×10^{-1}
11	α_2	7.50×10^{8}
12	β	1.20×10^{-2}
13	K_C	6.00×10^{-1}
14	γ	9.00×10^{-1}
15	V_M	0
16	$T(t_0)$	9.8039×10^{13}
17	$N(t_0)$	6.1199
18	$C(t_0)$	6.25×10^{10}
19	$M(t_0)$	0

By entering the values from the table above into the System of Equations (2), it can be obtained
Iteration 2 (I = 1)

$$T_1 = 9.80390036 \times 10^{13}$$
$$N_1 = 6.4305831$$
$$C_1 = 6.25 \times 10^{10}$$
$$M_1 = 0$$

We do the same thing for iterations 3 – 8 and the results are written in Table 3.

Table 3. Numerical Solutions Using Euler's Method

I	t	T	N	C	M
0	0	9.8039×10^{13}	6.1199	6.25×10^{10}	0
1	5	$9.80390036 \times 10^{13}$	6.4305831	6.25×10^{10}	3660
2	10	$-1.43519298 \times 10^{18}$	–73647.01022	-6.861875×10^{14}	–12510
3	15	$-7.22712832 \times 10^{22}$	$-1.05725312 \times 10^{13}$	$-2.57532619 \times10^{19}$	44085
4	20	$-1.13665658 \times 10^{30}$	$-1.51596399 \times10^{21}$	3.40597345×10^{24}	–153997.5

I	t	T	N	C	M
5	25	$-2.8692986 \times 10^{44}$	$-1.72313045 \times 10^{41}$	1.5735374×10^{30}	539291.25
6	30	$-3.05103523 \times 10^{149}$	$2.75668209 \times 10^{122}$	$-2.54578338 \times 10^{36}$	1887219.375
7	35	$-2.04617084 \times 10^{283}$	$8.41073415 \times 10^{261}$	$1.44133528 \times 10^{43}$	–6604967.815

Table 3 shows the rate of cancer T cells, immune effector cells N, circulating C lymphocytes and chemotherapy drug concentrations (Doxurubicin) for 35 days. In the first 5 days, when the drug was given with a concentration of 3660 and a dose of 60, the value of cancer cells increased, namely 3600000. However, in the next 5 days, the value of cancer cells decreased continuously for up to 35 days.

The value of effector-immune cells increased when the drug was given with a concentration of 3660 and a dose of 60, namely 0.3106831. However, in the following 20 days, the value of immune effector cells continued to decrease, to a value of . Then, effector-immune cells experienced a significant increase in the next 10 days.

Not much different from the rate of change in effector-immune cells, circulating lymphocyte cells also experience phases of ups and downs. From day 6 to day 15, circulating lymphocyte cells decreased in value. Circulating lymphocyte cells experienced an increase in value on day 16 to day 25. The value of circulating lymphocyte cells increased again when the chemotherapy drug concentration was 1887219.375.

Chemotherapy drug concentrations do not increase consistently. Fluctuations are also experienced by chemotherapy drug concentrations. Since the drug was administered into the body, the drug concentration values were respectively 3660, -12510, 44085, -153997.5, 539291.25. Furthermore, the drug concentration value increases temporarily. On days 31 to 35, the chemotherapy drug concentration values decreased again.

This is the rate of change of the four models carried out within a period of 35 days. The four models experience changes in value from each iteration. So, it can be said that chemotherapy treatment has a positive influence on cancer.

4. CONCLUSION

The conclusion is

1. The mathematical model of the effect of chemotherapy on cancer describes the rate of change in the cancer cell population, immune effector cells, circulating lymphocyte cells and the concentration of the chemotherapy drug (Doxurubicin).
2. The equilibrium point of the mathematical model of the effect of chemotherapy on cancer is $\left(\hat{T},\hat{N},\hat{C},\hat{M}\right)=\left(0,\frac{\alpha_1\gamma}{f\gamma+K_N V_M},\frac{\alpha_2\gamma}{\beta\gamma+K_C V_M},\frac{V_M}{\gamma}\right)$.
3. The exact solution to the mathematical model of the effect of chemotherapy on cancer is in subsection 3.2.
4. Numerical solution of the mathematical model of the effect of chemotherapy on cancer using the Euler method approach, namely in Table 3. The value of cancer cells, which was initially positive, changes to a value that indicates cancer cells will be passive or die. With these changes, it can be said that the chemotherapy drugs used have an effect on the recovery of cancer patients.

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