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# Mathematical Model Analysis of Breast Cancer Stages with Side Effects on Heart in Chemotherapy Patients

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**Abstract.** Breast cancer is the second largest cause of death for women in the world. Cancer treatment is used to kill cancer cells, remove cancer cells through surgery, or prevent cancer from getting the signal needed for cell division. Cancer treatment does not necessarily have a good effect on patients. Breast cancer treatment with chemotherapy can effect heart health. Side effects of chemotherapy on the heart is called cardiotoxicity. Therefore, we have constructed a mathematical model from the breast cancer patient population in the hospital. A population is divided into five sub-populations. They are stage 1 and 2 ($A$), stage 3 ($B$), stage 4 ($C$), disease-free ($D$), and cardiotoxic ($E$). The model is constructed by using a differential equation system. The equilibrium point and stability analysis are used to study the dynamics associated with time. Analysis of equilibrium point stability using Routh Hurwitz criteria. Based on the analysis obtained an asymptotic stable equilibrium point. We verified the results of analysis with numerical simulations. Numerical simulations have a result that an equilibrium point is always stable without conditions using a variety of initial conditions. It is evident that the five sub-populations of patients will be stable when they reach the equilibrium point.

**Keywords:** Breast Cancer, Mathematical Model, Cardiotoxicity, Cancer Stage, Differential Equation System.



## INTRODUCTION

Breast Cancer is a malignant tumor that attacks breast tissue. Breast Cancer is the cancer with the highest incidence based on data from The Global Burden of Disease Cancer Collaboration [1]. Breast cancer causes cells and breast tissue to change shape to abnormal and grow out of control. Every woman in the world has a risk of developing breast cancer. The World Health Organization (WHO) in 2004 stated that breast cancer was the second-largest cancer after lung cancer. A survey was conducted by WHO states that 8-9 percent of women in the world solve breast cancer.

World health experts are still not sure what causes breast cancer. The medical world can only link several risk factors that have an impact on the possibility of a woman experiencing breast cancer. Some cancer risk factors cannot be changed, such as age and race. Some others can change over time, especially those related to environment and behavior, such as smoking, drinking alcohol, and dietary arrangements.

The cancer stages determine the severity of cancer. The method used by doctors to describe the stage of cancer is the TNM system (Tumor, Node, Metastasis). This system uses three criteria to determine the stage of cancer, namely tumor size, spread to lymph nodes and spread to other organs (metastasis). The process of healing breast cancer is easy to do if the cancer is detected since an early stage. The higher of the stage, the less chance of recovery

There are various types of cancer treatments; they are surgery, radiotherapy, hormone therapy, targeted therapy, and chemotherapy. This cancer treatment is used to kill cancer cells, remove cancer cells, or prevent cancer cells from getting signals for cell division. Chemotherapy is the most commonly performed cancer treatment. Chemotherapy is

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carried out using a cancer-killing drug (chemotherapy regimen) that is given intravenously (injected into a vein) or by mouth.

Chemotherapy does not only have a good effect on the patient's recovery but also hurts health. Treatment of breast cancer with chemotherapy can cause adverse side effects on the heart, called cardiotoxicity. Cardiotoxicity of chemotherapy has infected patients ranging from children to adults since thirty-five years ago [2]. Chemotherapy regimens that often cause cardiotoxic are anthracycline and trastuzumab. Complications from oncological treatment of anthracyclines and trastuzumab have dramatic clinical effects that can cause heart failure [3]. Prevention of cardiotoxicity due to chemotherapy remains a challenge for cardiologists and cancer experts until now.

Mathematical modeling can be used to model a disease dynamics. The journey of mathematical modeling of cancer was explained by [4] from 1954 [5] to 2004 [6] in his article. Mathematical modeling of cancer continues to grow until now. Dixit et al. [7] discussed the mathematical model of chemotherapy for cancer treatment. The model consists of specific tumor and energy cells in Adriamycin (chemotherapy drugs), while the energy of tumor cells depends on various tumor cells. Schättler et al. [8] made a mathematical model with minimal parameters for low-dose chemotherapy. They were taking into account angiogenic signals between tumors and vasculature as well as tumor inhibitory effects from tumor-immune system interactions. Jordão and Tavares [9] constructed a deterministic mathematical model are derived from biochemical models within a human cell in two distinct cases, for comparison: healthy cells and cancerous cell. Mahlbacher et al. [10] use mathematical modeling for the experimental investigation that is suggested to measure and predict interactions between Tumor and Immune.

Some studies specifically discussing breast cancer mathematical models are as follows. A mathematical model of breast cancer development local treatment and recurrence by Enderling et al. [11]. The breast cancer model uses the growth rates of clonal expansion of intermediate cells and mutation rates as parameters and builds two-six stage models to fit the agespecific incidence of breast cancers in the surveillance, epidemiology, and results (SEER) registry by Zhang, X. et al. [12]. Model of cancer treatment with radiotherapy and chemotherapy by Liu and Yang [13]. The breast cancer model focuses on its heterogeneity and the role of mathematical modeling and simulation in teasing apart the underlying biophysical processes by Simmons, A. et al. [14]. In previous studies no one has discussed the mathematical model of breast cancer at the patient population level.

In contrast, in the previous research, this study discusses mathematical models at the population level of people with cancer. We construct the Mathematical Model Analysis of Breast Cancer Stages with Side Effects on Heart in Chemotherapy Patients. The model consists of sub-populations of stage 1 and 2 (A), stage 3 (B), stage 4 (C), disease-free (D), and cardiotoxic (E). The five sub-populations are modeled by forming a system of differential equations. Equilibrium point analysis and stability used to determine the dynamics of the five populations with time. Numerical simulations enhance the results of dynamic analysis. Numerical simulation were use to visualize the results of the dynamic analysis obtained.



## RESULTS

The first discussion is about how to build mathematical models of population dynamics in cases of breast cancer cardiotoxicity. The second is on dynamic analysis, which calculates equilibrium points and determines the stability of equilibrium points. The third discussion is a numerical simulation, which is the result of simulation using numerical methods. The last is a discussion, which discusses the conclusions from the results of dynamic analysis and simulation, as well as appropriate medical actions based on the model.

### Model Construction

This study took the case of breast cancer patients in the "TULIP" Installation of RSUP dr. Sardjito Yogyakarta. The person affected by cancer is assumed to occur when the person comes first to the hospital. It is assumed that there were no healthy patients when they first arrived at the hospital. At the time of the first medical record, the patients are classified into sub-populations of stage 1 and 2, stage 3, or stage 4. In the process of treatment at the Hospital, all cancer patients are assumed to receive chemotherapy treatment. Patients will experience changes in the severity of the cancer over time, so that each sub-population will experience changes in the number of individuals. There are patients whose disease is getting worse, there are patients who experience recovery (disease-free), and there are patients who experience cardiotoxic during the chemotherapy process. Changes in population dynamics from these sub-populations are depicted in a diagram called the compartment diagram.

The model was constructed from five compartments representing sub-populations of breast cancer patients. Each sub-population is represented by variables A, B, C, D, and E. sub-population A represents patients with Ductal Carcinoma In Situ cancer, stage 1, 2A, and 2B. sub-population B represents stage 3A and 3B cancer patients. sub-population C expresses stage 4 cancer patients. sub-population D represents cancer patients with disease-free conditions after chemotherapy. In disease-free conditions, cancer is no longer seen by observation. sub-population E expresses cancer patients who have cardiotoxicity. The compartment diagram is shown in FIGURE 1. Rate of change from each sub-population is expressed in a system of differential equations as in equation (1). Note the set defined by $\Omega = \{(A, B, C, D, E)|A > 0, B > 0, C > 0, D > 0, E > 0\}$. That is, all solutions satisfy $(A(t), B(t), C(t), D(t), E(t)) \in \Omega$ for all $t$, if $(A(0), B(0), C(0), D(0), E(0)) \in \Omega$. All parameters described in TABLE 1 are assumed to have positive values.

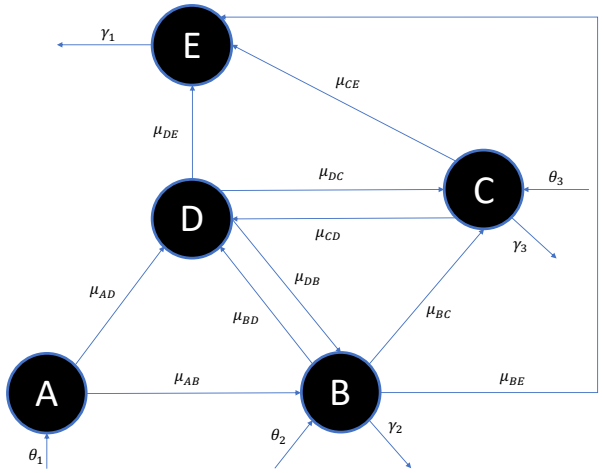



FIGURE 1: Compartment Diagram

$$
\begin{aligned}
\frac{dA}{dt} &= \theta_1 - \mu_{AD}A - \mu_{AB}A \\
\frac{dB}{dt} &= \theta_2 + \mu_{AB}A + \mu_{DB}D - \mu_{BD}B - \mu_{BC}B - \mu_{BE}B - \gamma_2 B \\
\frac{dC}{dt} &= \theta_3 + \mu_{BC}B + \mu_{DC}D - \mu_{CD}C - \mu_{CE}C - \gamma_3 C \\
\frac{dD}{dt} &= \mu_{AD}A + \mu_{BD}B + \mu_{CD}C - \mu_{DB}D - \mu_{DC}D - \mu_{DE}D \\
\frac{dE}{dt} &= \mu_{DE}D + \mu_{CE}C + \mu_{BE}B - \gamma_1 E
\end{aligned} \tag{1}
$$

Stage 1 and 2 cancer patients were placed in one sub-population A because the number of individuals both in the Hospital was relatively smaller than the other sub-populations. This is because most cancer patients who have undergone treatment have developed advanced cancer. Patients who first received treatment were diagnosed with stage 1 and 2 cancers included in the sub-population A with rate $\theta_1$. Patients with sub-population A who have been chemotherapy have two possibilities, namely recovery (disease-free) with rate $\mu_{AD}$ or worse with rate $\mu_{AB}$.

The patients who were first treated at the Hospital were mostly suffering from stage 3 cancer, so they were grouped in sub-population B with rate $\theta_2$. Patients in sub-population B were able to die from cancer with rate $\gamma_2$. Patients who are in this sub-population, after they experience chemotherapy can become a disease-free with rate $\mu_{BD}$ and can also become worse with rate $\mu_{BC}$. sub-population B with more intensive chemotherapy than sub-population A can cause patients to experience cardiotoxicity with rate $\mu_{BE}$.

Patients who are treated for the first time can also enter into sub-population C because cancer has undergone metastasis or stage 4. During this condition, it is unlikely that chemotherapy treatment can cure cancer, so the rate towards a disease-free with rate $\mu_{CD}$ is assumed to be the least compared to $\mu_{AD}$ and $\mu_{BD}$. Conversely, the rate $\mu_{CE}$

towards cardiotoxic is assumed to be of great value because the patient is experiencing very intensive chemotherapy. This sub-population also experienced cancer deaths with rate $\gamma_3$.

Disease-free in sub-population D can be increased from patients with sub-populations A, B, and C. The condition of this disease-free can last forever or only briefly. If it only lasts for a while, then patients in the sub-population D can return to be sub-populations of B and C with their respective rates are $\mu_{DB}$ and $\mu_{DC}$. An extended period of sub-population D can also directly experience cardiotoxicity with rate $\mu_{DE}$. Patients who experience cardiotoxicity or who are in the sub-population E can experience cardiac death with rate $\gamma_1$.

TABLE 1: Parameter Description

| Parameter | Description |
|---|---|
| $\theta_1$ | Number of new patients diagnosed to suffer in stage 1 and 2 cancer |
| $\theta_2$ | Number of new patients diagnosed to suffer in stage 3 cancer |
| $\theta_3$ | Number of new patients diagnosed to suffer in stage 4 cancer |
| $\mu_{AB}$ | Increased rate from stage 1 or 2 to stage 3 (progressive disease) |
| $\mu_{AD}$ | Rate of stage 1 or 2 patients who experience a complete response |
| $\mu_{BD}$ | Rate of stage 3 patients who experience a complete response |
| $\mu_{BC}$ | Increased rate from stage 3 to stage 4 (progressive disease) |
| $\mu_{BE}$ | Rate of stage 3 cancer chemotherapy patients who experience cardiotoxic |
| $\mu_{CD}$ | Rate of stage 4 patients who experience complate response |
| $\mu_{CE}$ | Rate of stage 4 cancer chemotherapy patients who experience cardiotoxic |
| $\mu_{DB}$ | Rate of disease-free patients who relapse back to stage 3 |
| $\mu_{DC}$ | Rate of disease-free patients who relapse back to stage 4 |
| $\mu_{DE}$ | Rate of disease-free patients who experience cardiotoxic |
| $\gamma_1$ | Death rate of cardiotoxic patients |
| $\gamma_2$ | Death rate of stage 3 cancer patients |
| $\gamma_3$ | Death rate of stage 4 cancer patients |

## Dynamical Analysis

Dynamic analysis performed on systems of equations (1) include calculation of equilibrium points and stability analysis. Investigation of equilibrium and stability points was used to determine the dynamics of the five populations over time. In analyzing the stability of equilibrium points using the Routh Hurwitz criterion. The Routh Hurwitz criterion determines conditions for left half plane (LHP) polynomial roods and cannot be directly used to investigate the stability of discrete-time systems. For characteristic equation

$$a_n\lambda^n + a_{n-1}\lambda^{n-1} + \cdots + a_1\lambda + a_0 = 0 \tag{2}$$

The Routh Array $\begin{bmatrix} \lambda^n & a_n & a_{n-1} & \cdots \\ \lambda^{n-1} & a_{n-1} & a_{n-3} & \cdots \\ \lambda^{n-2} & b_1 & b_2 & \cdots \\ \vdots & \vdots & \vdots & \ddots \\ \lambda^0 & 0 & 0 & 0 \end{bmatrix}$ where $b_1 = \frac{-\det\begin{pmatrix} a_n & a_{n-2} \\ a_{n-1} & a_{n-3} \end{pmatrix}}{a_{n-1}}, b_2 = \frac{-\det\begin{pmatrix} a_n & a_{n-4} \\ a_{n-1} & a_{n-5} \end{pmatrix}}{a_{n-1}}$. The system is stable (all $Re(p_k) < 0 \leftrightarrow$ all poles lie on LHP) iff the element of the first column of the Routh Array have same sign. The number of sign change is the number of poles that lies on the RHP [15].

### *Equilibrium Point*

From the system of equations (1) we get an equilibrium point, which is $\mathcal{E}^* = (A^*, B^*, C^*, D^*, E^*)$, with $A^*$, $B^*$, $C^*$, $D^*$, and $E^*$ values are given in equations (3). The values of $\alpha, \beta, \sigma, \nu, \rho$, and $k_1, k_2, k_3, k_4, k_5$ are given afterwards. Based on the equilibrium point, all sub-populations are positive, so it can be concluded that the equilibrium point exists without conditions.

$$A^* = \frac{\theta_1}{k_1}, B^* = \frac{\alpha}{k_1\rho}, C^* = \frac{\beta}{k_1\rho}, D^* = \frac{\sigma}{k_1\rho}, E^* = \frac{\nu}{k_1\rho\gamma_1} \tag{3}$$

$$
\begin{aligned}
\alpha &= (k_3\mu_{DB} + (\mu_{DE} + \mu_{DC})\gamma_3 + (\mu_{DE} + \mu_{DC})\mu_{CE} + \mu_{DE}\mu_{CD})\theta_2\mu_{AB} \\
&\quad + (k_3\theta_1 + \mu_{CD}\theta_3)\mu_{DB} + \theta_1((\mu_{DE} + \mu_{DC})\gamma_3 + (\mu_{DE} + \mu_{DC})\mu_{CE} + \mu_{DE}\mu_{CD})\mu_{AB} \\
&\quad + \mu_{AD}((k_3\mu_{DB} + (\mu_{DE} + \mu_{DC})\gamma_3 + (\mu_{DE} + \mu_{DC})\mu_{CE} + \mu_{DE}\mu_{CD})\theta_2 + (k_3\theta_1 + \mu_{CD}\theta_3)\mu_{DB}) \\
\beta &= (k_2\mu_{DC} + (\mu_{DB} + \mu_{DE})\mu_{BC} + (\gamma_2 + \mu_{BD} + \mu_{BE})\mu_{DE} + \mu_{DB}(\gamma_2 + \mu_{BE}))k_1\theta_3 \\
&\quad + (((\theta_1 + \theta_2)\mu_{BC} + (\gamma_2 + \mu_{BD} + \mu_{BE})\theta_1 + \mu_{BD}\theta_2)\mu_{DC} + (\theta_2\mu_{DE} + \mu_{DB}(\theta_1 + \theta_2))\mu_{BC})\mu_{AD} \\
&\quad + ((\mu_{BC} + \mu_{BD})\mu_{DC} + (\mu_{DB} + \mu_{DE})\mu_{BC})(\theta_1 + \theta_2)\mu_{AB} \\
\sigma &= ((k_2\theta_1 + (\theta_2 + \theta_3)\mu_{BD} + \mu_{BC}\theta_2 + \theta_3(\gamma_2 + \mu_{BC} + \mu_{BE}))\mu_{CD} + (k_2\theta_1 + \mu_{BD}\theta_2)(\gamma_3 + \mu_{CE}))\mu_{AD} \\
&\quad + \mu_{AB}(((\mu_{BC} + \mu_{BD})\theta_1 + (\theta_2 + \theta_3)\mu_{BD} + \mu_{BC}\theta_2 + \theta_3(\gamma_2 + \mu_{BC} + \mu_{BE}))\mu_{CD} + \mu_{BD}(\theta_1 + \theta_2)(\gamma_3 + \mu_{CE})) \\
\nu &= ((\theta_1 + \theta_2 + \theta_3)\mu_{BE} + (\gamma_2 + \mu_{BC} + \mu_{BD})\theta_1 + (\mu_{BC} + \mu_{BD})\theta_2 + \theta_3(\gamma_2 + \mu_{BC} + \mu_{BD}))\mu_{DE}\mu_{AD}\mu_{CE} \\
&\quad + (\mu_{DB} + \mu_{DC})(\theta_1 + \theta_2 + \theta_3)\mu_{BE} + ((\mu_{DB} + \mu_{DC})\mu_{BC} + \mu_{DC}(\gamma_2 + \mu_{BD}))\theta_1 \\
&\quad + ((\mu_{DB} + \mu_{DC})\mu_{BC} + \mu_{BD}\mu_{DC})\theta_2 + ((\mu_{DB} + \mu_{DC})\mu_{BC} + \gamma_2\mu_{DB} + \mu_{DC}(\gamma_2 + \mu_{BD}))\theta_3\mu_{AD}\mu_{CE} \\
&\quad + (((\theta_1 + \theta_2 + \theta_3)\mu_{BE} + (\mu_{BC} + \mu_{BD})\theta_1 + (\mu_{BC} + \mu_{BD})\theta_2 + \theta_3(\gamma_2 + \mu_{BC} + \mu_{BD}))\mu_{DE})\mu_{AB}\mu_{CE} \\
&\quad + ((\mu_{DB} + \mu_{DC})(\theta_1 + \theta_2 + \theta_3)\mu_{BE} + ((\mu_{DB} + \mu_{DC})\mu_{BC} + \mu_{BD}\mu_{DC})\theta_1)\mu_{AB}\mu_{CE} \\
&\quad + (((\mu_{DB} + \mu_{DC})\mu_{BC} + \mu_{BD}\mu_{DC})\theta_2 + ((\mu_{DB} + \mu_{DC})\mu_{BC} + \gamma_2\mu_{DB} + \mu_{DC}(\gamma_2 + \mu_{BD}))\theta_3)\mu_{AB}\mu_{CE} \\
&\quad + \mu_{DE}\mu_{AD}(((\gamma_3 + \mu_{CD})\theta_1 + (\gamma_3 + \mu_{CD})\theta_2 + \theta_3\mu_{CD})\mu_{BE} + (\gamma_3 + \mu_{CD})(\gamma_2 + \mu_{BC} + \mu_{BD}))\theta_1 \\
&\quad + (((\mu_{BC} + \mu_{BD})\mu_{CD} + \gamma_3\mu_{BD})\theta_2 + \theta_3\mu_{CD}(\gamma_2 + \mu_{BC} + \mu_{BD}))\mu_{DE}\mu_{AD} \\
&\quad + \mu_{BE}((\gamma_3 + \mu_{CD})\mu_{DB}\theta_1 + (\mu_{DB}\mu_{CD} + \gamma_3(\mu_{DB} + \mu_{DC}))\theta_2 + \theta_3\mu_{CD}\mu_{DB})\mu_{AD} \\
&\quad + \mu_{AB}\mu_{DE}(((\gamma_3 + \mu_{CD})\theta_1 + (\gamma_3 + \mu_{CD})\theta_2 + \theta_3\mu_{CD})\mu_{BE}((\mu_{BC} + \mu_{BD})\mu_{CD} + \gamma_3\mu_{BD})\theta_1) \\
&\quad + \mu_{AB}\mu_{DE}(((\mu_{BC} + \mu_{BD})\mu_{CD} + \gamma_3\mu_{BD})\theta_2 + \theta_3\mu_{CD}(\gamma_2 + \mu_{BC} + \mu_{BD})) \\
&\quad + \mu_{BE}\mu_{AB}((\mu_{DB}\mu_{CD} + \gamma_3(\mu_{DB} + \mu_{DC}))\theta_1 + (\mu_{DB}\mu_{CD} + \gamma_3(\mu_{DB} + \mu_{DC}))\theta_2 + \theta_3\mu_{CD}\mu_{DB}) \\
\rho &= k_3k_2\mu_{DE} + ((\mu_{DB} + \mu_{DC})\gamma_2 + (\mu_{DB} + \mu_{DC})\mu_{BE} + \mu_{BC}\mu_{DB} + (\mu_{BC} + \mu_{BD})\mu_{DC})\gamma_3 \\
&\quad + ((\mu_{DB} + \mu_{DC})\gamma_2 + (\mu_{DB} + \mu_{DC})\mu_{BE} + \mu_{BC}\mu_{DB} + (\mu_{BC} + \mu_{BD})\mu_{DC})\mu_{CE} + \mu_{CD}\mu_{DB}(\gamma_2 + \mu_{BE})
\end{aligned}
$$

and $k_1 = \mu_{AD} + \mu_{AB}, k_2 = \mu_{BD} + \mu_{BC} + \mu_{BE} + \gamma_2, k_3 = \mu_{CD} + \mu_{CE} + \gamma_3, k_4 = \mu_{DB} + \mu_{DC} + \mu_{DE}, k_5 = \gamma_1$.

*Stability*

Next, we look for stability from the equilibrium point. To determine the stability of the equilibrium point, the equation is first made in the form of a matrix

$$
\begin{aligned}
\mathcal{F} &= K\mathcal{G} + \Theta \\
\begin{bmatrix} \dot{A} \\ \dot{B} \\ \dot{C} \\ \dot{D} \\ \dot{E} \end{bmatrix} &= \begin{bmatrix} -k_1 & 0 & 0 & 0 & 0 \\ \mu_{AB} & -k_2 & 0 & \mu_{DB} & 0 \\ 0 & \mu_{BC} & -k_3 & \mu_{DC} & 0 \\ \mu_{AD} & \mu_{BD} & \mu_{CD} & -k_4 & 0 \\ 0 & \mu_{BE} & \mu_{CE} & \mu_{DE} & -k_5 \end{bmatrix} \begin{bmatrix} A \\ B \\ C \\ D \\ E \end{bmatrix} + \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \\ 0 \\ 0 \end{bmatrix}
\end{aligned} \tag{4}
$$

Equation $K$ is a coefficient matrix. The characteristic equation is calculated using the formula

$$
|K - \lambda I| = \begin{vmatrix} -k_1 - \lambda & 0 & 0 & 0 & 0 \\ \mu_{AB} & -k_2 - \lambda & 0 & \mu_{DB} & 0 \\ 0 & \mu_{BC} & -k_3 - \lambda & \mu_{DC} & 0 \\ \mu_{AD} & \mu_{BD} & \mu_{CD} & -k_4 - \lambda & 0 \\ 0 & \mu_{BE} & \mu_{CE} & \mu_{DE} & -k_5 - \lambda \end{vmatrix} \tag{5}
$$

The Routh Hurwitz criterion are used to determine the stability of the equilibrium point based on the characteristic

equations that have been obtained. Based on the Routh Hurwitz criterion obtained the Routh Table as follows

$$\begin{bmatrix} \lambda^5 & 1 & + & + \\ \lambda^4 & + & + & + \\ \lambda^3 & + & + & 0 \\ \lambda^2 & + & + & 0 \\ \lambda & + & 0 & 0 \\ 1 & + & 0 & 0 \end{bmatrix} \tag{6}$$

The "+" symbol explains that the elements of the Routh Array are positive. It can be seen from the Routh Array that all elements are positive and zero, meaning that all real eigenvalues are negative. So that it can be concluded that the equilibrium point in this system is asymptotically stable.

## Numerical Simulation

In this section, we verified the results of analysis with numerical simulations. Numerical simulations are carried out using parameter values $\theta_1 = 5, \theta_2 = 20, \theta_3 = 11, \mu_{AD} = 0.63, \mu_{AB} = 0.56, \mu_{BD} = 0.35, \mu_{BC} = 0.62, \mu_{BE} = 0.30, \mu_{DC} = 0.42, \mu_{DB} = 0.36, \mu_{DE} = 0.30, \mu_{CD} = 0.10, \mu_{CE} = 0.30, \gamma_1 = 0.4, \gamma_2 = 0.5$, and $\gamma_3 = 0.8$. Based on these parameter values, an equilibrium point $\mathcal{E}^*$ is obtained, where $A^* = 4.2, B^* = 14,45, C^* = 19.77, D^* = 8.96, E^* = 32.39$. The numerical simulation results are shown in FIGURE 2.

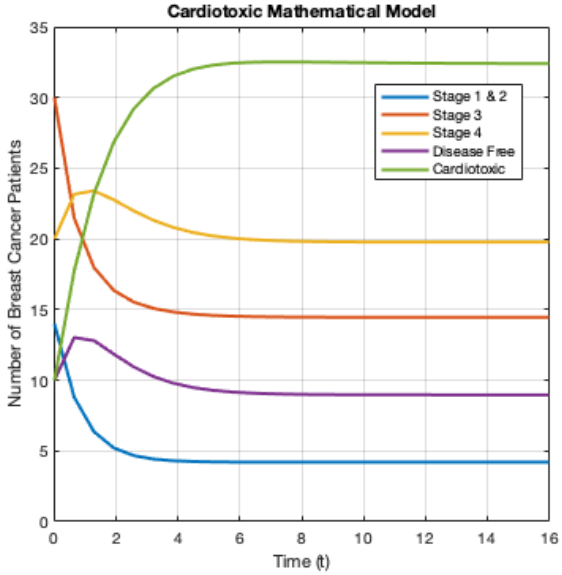
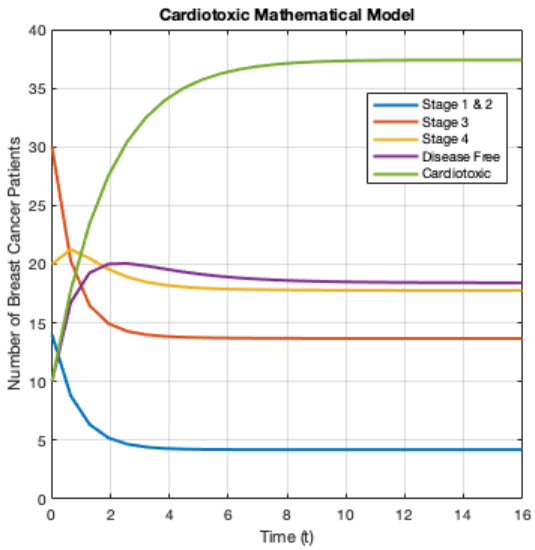


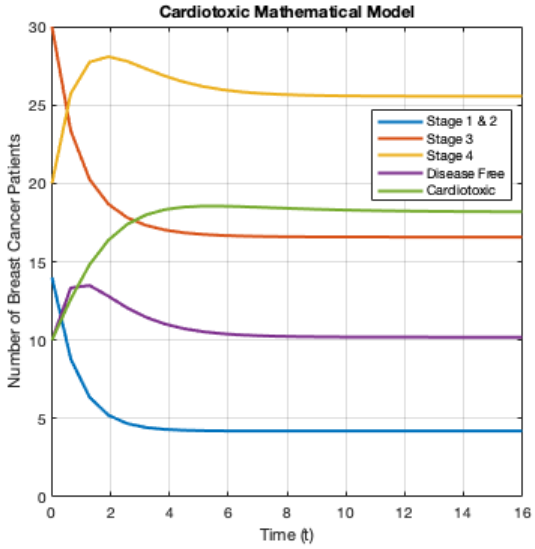

FIGURE 2: Simulation result with initial condition $A(0) = 14, B(0) = 30, C(0) = 20, D(0) = 10, E(0) = 10$

FIGURE 2 shows the equilibrium conditions occur from 7th time period. The stage 1 and 2 sub-populations from the initial condition with 14 patients dropped to 4 patients in equilibrium conditions. Likewise, the stage 3 sub-population from the initial condition of 30 patients fell to 14 in equilibrium conditions. Relatively constant conditions occur in the Disease-Free and Stage 4 sub-populations, both of which do not show a significant change in population from the initial condition to equilibrium. The stage 4 sub-population from 20 to 19 and the disease-free sub-population from 10 to 8. Unlike the case with the cardiotoxic sub-population, this population experienced a significant increase from the initial number of 10 patients drastically increasing to 32 patients in equilibrium conditions. The results of this simulation are stated as initial simulation. The second and third simulations are performed by reducing the relapse rate and cardiotoxic rate.

FIGURE 3a shows the simulation results by reducing the relapse rate, ie, $\mu_{DB}$ and $\mu_{DC}$ to 0, 1 for both. Simulation results show that the disease-free sub-population increased to 19 patients at equilibrium. Although it managed to add




(a) Simulation results by reducing parameter values $\mu_{CE}$ and $\mu_{BE}$




(b) Simulation results by reducing parameter values $\mu_{DC}$ and $\mu_{DB}$

FIGURE 3: Simulation result with reduce the relapse rate and cardiotoxic rate

people who recovered, cardiotoxic sub-population also experienced a significant increase. Cardiotoxic sub-population reached 37 patients in a stable condition. Other sub-populations are relatively the same as initial simulation. FIGURE 3b is carried out by reducing the value of the cardiotoxic rate, ie, $\mu_{CE}$ and $\mu_{BE}$ to 0.1 for both. FIGURE 3b shows that the disease-free sub-population increased slightly to 10 patients. Another positive thing was also seen from the cardiotoxic sub-population, which decreased the population to 18 patients at the time of equilibrium. For stage 3 sub-population, it increased slightly compared to the initial simulation. For other sub-populations, it is relatively the same as the initial simulation.

## DISCUSSION

In this study, a mathematical model was constructed with five variables and sixteen parameters. Mathematical models made according to medical phenomena about the chemo cardiotoxicity of breast cancer patients. The model consists of three sub-populations of breast cancer patients by stage, one disease-free sub-population, and one cardiotoxic sub-population. A dynamical analysis is carried out to determine the dynamics of the number of individual sufferers in each sub-population at any time. The results of the dynamical analysis is a stable equilibrium point. Numerical simulations are made to verify the behavior of solutions around the equilibrium point.

Based on the results of simulations, it can be concluded that if all parameters are assumed to be constant, the state of the population will be stable at a particular time with any initial conditions. This shows that the equilibrium point of the system proved to be stable without conditions. By reducing the relapse rate, an unexpected result is obtained, which is an increase in cardiotoxic sub-populations. Better results are obtained when reducing cardiotoxic rates. Under these conditions, the number of disease-free sub-populations increases, and the number of cardiotoxic sub-populations was decreases dramatically.

From the three simulation results, a practical solution is obtained in minimizing the number of cardiotoxic sufferers and increasing the number of patients recovering or experiencing a complete response after chemotherapy. The solution is to reduce the cardiotoxic rate of stage 3 and stage 4 sub-populations. In further research, we modified the system by considering psychological factors from cancer patients. The patients who undergo chemotherapy treatment interact with each other, so that it has an impact on the patient's psychological factors.

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