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ANALYSING THE EFFECT OF TRASTUZUMAB TREATMENT ON BREAST CANCER STAGES AND CARDIAC FUNCTION: A MATHEMATICAL MODELING AND NUMERICAL SIMULATION

MARYEM EL KARCHANI[1,*], NADIA IDRISSI FATMI[1], KARIMA MOUDEN[2]

[1]LIPIM, ENSAK, Sultan Moulay Slimane University of Beni Mellal, Morocco

[2]Radiation, Oncologist, Régional Center of Oncology, Beni Mellal, Morocco

Abstract. Breast cancer is the second most common cause of death among women worldwide. Trastuzumab is the first humanised monoclonal antibody against HER2-positive metastatic breast cancer. However, the most serious side effect of trastuzumab is cardiotoxicity, which has become a limiting factor in the drug's safe use. In this study, we investigated the effect of trastuzumab treatment on breast cancer stages and cardiac function. Therefore, we constructed a mathematical model based on breast cancer patients. The model was created using a differential equation system, and equilibrium point and stability analysis were employed to study the associated temporal dynamics. The stability of the equilibrium point was analysed using the Routh-Hurwitz criteria, which identified an asymptotically stable equilibrium point. To valudate these findings, numerical simulations were performed, which demonstrated that the equilibrium point is always stable regardless of the initial conditions. Finally, our results suggest that the five sub-populations of patients will reach a stable state upon reaching the equilibrium point.

Keywords: breast cancer; cardiotoxicity; cancer stage; trastuzumab; mathematical model; numerical simulation.
2020 AMS Subject Classification: 92-10, 34A30.

*Corresponding author
E-mail address: elkarchani.maryem@gmail.com
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1. INTRODUCTION

Breast cancer is the most common malignant disease and among the most frequent causes of cancer mortality in females worldwide [1]. Breast cancer has the highest occurrence rate when compared to other types of cancer. It occurs when breast tissue and cells grow uncontrollably, resulting in an abnormal breast shape. Breast cancer is the world's second most common type of cancer, after lung cancer, and it can affect any woman. According to The World Health Organization (WHO) [2], there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the worlds most prevalent cancer. World health experts are still unsure what causes breast cancer. Only a few risk factors that influence a woman's likelihood of developing breast cancer can be identified by medical professionals. Some cancer risk factors, such as age and race, cannot be changed, whereas others, particularly those related to environment and behavior, such as smoking, alcohol consumption, and dietary habits, can change over time.

The stages of cancer determine the severity of the disease. Doctors use the TNM system (Tumor, Node, Metastasis) to describe the stage of cancer. This system employs three criteria to determine the cancer stage: tumor size, spread to lymph nodes, and spread to other organs (metastasis). If breast cancer is detected at an early stage, the healing process is relatively simple. However, the chances of recovery decrease as the cancer advances to higher stages.There are various treatment techniques available for cancer prevention, including surgery, gene therapy, bisphosphonates, immunotherapy, targeted therapy drugs, hormone therapy, bone marrow transplants and stem cell therapy, radiotherapy, and complementary and alternative therapies. The chances of successful treatment for breast cancer are higher when it is detected and diagnosed early, as is the case with most types of cancer.

There are several types of breast cancer, and any of them can metastasise. About 15% to 20% of breast tumors have higher levels of a protein known as HER2. These cancers are called HER2-positive breast cancers [3] and it's the type we are discussing in this paper. Cancers that are characterised as 'HER-2 positive' can be effectively treated using targeted biological therapies, like trastuzumab. These biological therapies are very effective but also very expensive,

because they are antibodies rather than chemicals. When targeted biological therapies are given, they are combined with chemotherapy to make them effective at killing cancer cells[2].

Trastuzumab is a monoclonal antibody used to treat HER2-positive breast cancer. However, one of the major side effects of trastuzumab treatment is cardiotoxicity, which can lead to heart failure. Mathematical modeling has been used to understand the mechanisms underlying trastuzumab-induced cardiotoxicity and to optimise treatment strategies to minimise cardiotoxicity. Over time, modeling breast cancer has become an invaluable tool for understanding the dynamic behavior of tumor growth during the treatment process. The role of mathematical modeling in combination therapy for tumors was explored by Onofrio et al. [4]. Studies conducted by Kermack and McKendrick [6, 5], as well as other investigations [7, 8], have demonstrated the usefulness of mathematical modeling of biological phenomena in solving epidemiological problems. Most mathematical models of cancer are based on differential equations. Ordinary differential equations with two or three cell populations containing tumor cells and effector cells have been used to investigate essential patterns of tumor growth and decay [9, 10]. Several mathematical models have been proposed to study the effects of trastuzumab on breast cancer cells and the development of cardiotoxicity. For example, Jarrett et al. [11], develop an integrated, mathematical-experimental approach for understanding the interactions between the immune system and the effects of trastuzumab on breast cancer that overexpresses the human epidermal growth factor receptor 2 (HER2+). Kitani et al. [12] aimed to develop a human-induced pluripotent stem cell (hiPSC) model of trastuzumab-induced cardiac dysfunction in breast cancer patients. The researchers compared hiPSCs derived from patients with breast cancer who had received trastuzumab treatment to hiPSCs derived from healthy individuals. The hiPSCs were then differentiated into cardiomyocytes and tested for response to trastuzumab treatment. Maadi and Wang [13] aimed to investigate the mechanism underlying the inhibitory effects of trastuzumab on the growth of HER2-positive breast cancer cells. The researchers used several HER2-positive breast cancer cell lines and treated them with trastuzumab to evaluate the effects on cell proliferation, cell cycle progression, and apoptosis. They also performed gene expression analysis to identify potential signaling pathways involved in the response to

trastuzumab. Therefore, based on the studies that we have discussed so far, none of them appear to have focused on a mathematical model of breast cancer at the patient population level. for that, this study explores a mathematical model that examines the stages of breast cancer and the potential side effects on the heart in patients receiving trastuzumab treatment.

Therefore, this work is organised as follows: In the first section, we construct a mathematical model of breast cancer with side effects on the heart in trastuzumab patients. The five compartments are modeled by creating a system of differential equations. We utilise this differential equation system to construct the model and analyse the associated temporal dynamics by studying the equilibrium point and its stability. To analyse the stability of the equilibrium point, we use the Routh-Hurwitz criteria, which allows us to identify an asymptotically stable equilibrium point. We then confirm these results through numerical simulations, which demonstrate that the equilibrium point is always stable regardless of the initial conditions, without any additional conditions. Ultimately, our findings suggest that the five sub-populations of patients will reach a stable state upon reaching the equilibrium point.

2. Formulation of the Model

Motivated by the empirical observation that compartmental epidemiological models have played a significant role in advancing our understanding of epidemic transmission mechanisms and the various preventive strategies used against it, we propose a deterministic mathematical model that utilises ordinary differential equations.

We assumed that no patients were healthy upon their first arrival at the hospital. Upon their first medical record, patients were classified into sub-populations of stage I, stage II, stage III, or stage IV. During their treatment process at the hospital, all patients were presumed to receive Trastuzumab treatment. Some patients experienced recovery, while others experienced worsening conditions of the disease during Trastuzumab treatment, and some experienced cardiotoxic effects during the treatment process.

The model consists of five compartments that represent sub-populations of breast cancer patients. Each sub-population is denoted by variables A, B, C, D, and E. Subpopulation A represents patients with stage I and II cancer. Subpopulation B represents patients with stage III cancer. Subpopulation C represents patients with stage IV cancer. Subpopulation D represents

patients with a disease-free condition after Trastuzumab treatment. Subpopulation E represents cancer patients who experience cardiotoxicity. The compartment diagram is illustrated in Figure (1).

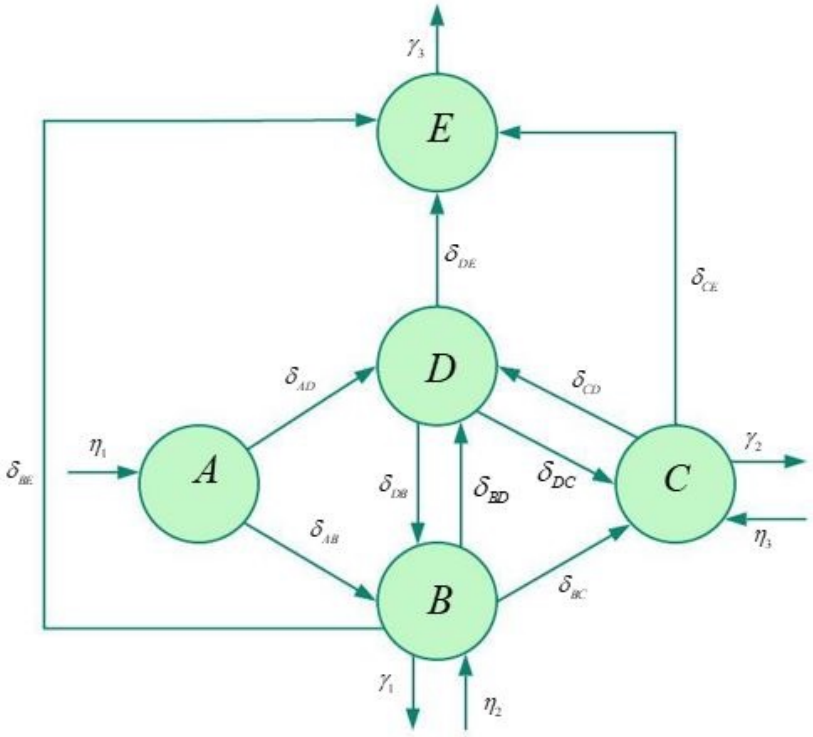

FIGURE 1. Compartment Diagram

Patients affected by breast cancer are assumed to occur when the patient comes for the first time to the hospital.

The patients whose tumor size exceeds 2cm but not more than 5cm are diagnosed with stage I and II cancer, which are referred to as early breast cancer. Invasive breast cancer occurs when cancer cells within the milk duct or lobules break out into nearby tissue. Early breast cancer is invasive breast cancer that is contained within the breast and may or may not have spread to the lymph nodes in the breast or armpit. Some cancer cells may have spread outside the breast and armpit area but cannot be detected. Because the number of patients diagnosed with stage I and II cancer is smaller than the other stages, they are placed in a sub-population denoted as A. The majority of cancer patients who have already been treated have advanced cancer. Therefore, patients diagnosed with stage I and II cancer are included in sub-population A with a rate of

ν_1. Patients in this sub-population who undergo Trastuzumab treatment have two possibilities: they may either recover (become disease-free) with a rate of δ_{AD} or worsen with a rate of δ_{AB}.

Patients diagnosed with stage III cancer upon their first visit to the hospital are included in sub-population B with rate ν_2. At this stage, the axillary lymph node is typically enlarged (greater than 5 cm), and the cancer becomes inflammatory. In sub-population B, patients may transition from sub-population A (stages I and II) with rate δ_{AB} or from the disease-free sub-population D with rate δ_{DB}. This sub-population receives more intense Trastuzumab treatment than sub-population A, with patients either dying from cancer with rate γ_1, transitioning to the recovery sub-population D with rate δ_{BD}, or worsening with rate δ_{BC}. Additionally, sub-population B is more prone to experiencing cardiotoxicity due to the intensive Trastuzumab treatment, with a rate of δ_{BE}.

Patients who are treated for the first time can also enter into sub-population C because the cancer has metastasised or spread to distant parts of the body, typically the bones, lungs, or liver. This is an advanced stage of cancer, called metastatic breast cancer or Stage IV breast cancer. During this stage, targeted treatment is unlikely to cure cancer, so the rate towards recovery is low with rate δ_{CD}. This sub-population can grow by moving from stage III with a rate δ_{BC} and from disease-free with a rate δ_{DC}. On the other hand, this sub-population may also be reduced with a cancer death rate of γ_2. It is assumed that the rate of cardiotoxicity δ_{CE} is high because patients are receiving very intensive Trastuzumab treatment. This sub-population can also experience cancer death with a rate of γ_2.

Subpopulation D (disease-free) increased from the first tree sub-population A, B and C and lose recovery with the rates δ_{DB}, δ_{DC} and δ_{DC} respectively.

The patients in sub-population E comes from B, C and D and taste cardiac death with a rate γ_3.

Then the dynamics of breast cancer with Trastuzumab treatement treatment with the above assumptions is given by the following system of $EDOs$:

$$\begin{cases} \dfrac{dA}{dt} = \eta_1 - \delta_{AB}A - \delta_{AD}A, \\ \dfrac{dB}{dt} = \eta_2 + \delta_{AB}A + \delta_{DB}D - \delta_{BC}B - \delta_{BD}B - \delta_{BE}B - \gamma_1 B, \\ \dfrac{dC}{dt} = \eta_3 + \delta_{BC}B + \delta_{DC}D - \delta_{CD}C - \delta_{CE}C - \gamma_2 C, \\ \dfrac{dD}{dt} = \delta_{AD}A + \delta_{BD}B + \delta_{CD}C - \delta_{DB}D - \delta_{DC}D - \delta_{DE}D, \\ \dfrac{dE}{dt} = \delta_{BE}B + \delta_{CE}C + \delta_{DE}D - \gamma_3 E, \end{cases} \tag{1}$$

with appropriate initial condition for vector

$$A(0) > 0,\ B(0) > 0,\ C(0) > 0,\ D(0) > 0$$

3. Dynamical Analysis

In this section we study the existence and stability of the equilibrium point who is also represents the critical point of the system (1).

3.1. Equilibrium Point. To find the equilibrium point of the system (1), we set all the fractional derivative of (1) to zero and obtain the equilibrium point given by $P_e^* = (A^*, B^*, C^*, D^*, E^*)$. The equilibrium point exist and it is

$$A^* = \frac{\eta_1}{k_1}, \qquad B^* = \frac{\alpha}{k_1\lambda}, \qquad C^* = \frac{\beta}{k_1\lambda}, \qquad D^* = \frac{\xi}{k_1\lambda}, \qquad E^* = \frac{\nu}{k_1\lambda\gamma_3},$$

where,

$$k_1 = \delta_{AD} + \delta_{AB}, \qquad k_2 = \delta_{BD} + \delta_{BC} + \delta_{BE} + \gamma_1, \qquad k_3 = \delta_{CD} + \delta_{CE} + \gamma_2,$$

$$k_4 = \delta_{DB} + \delta_{DC} + \delta_{DE}, \qquad \text{and} \qquad k_5 = \gamma_3$$

$$\begin{aligned} \alpha =& \left(k_3\delta_{BD} + (\delta_{DE} + \delta_{DC})\gamma_2 + (\delta_{DE} + \delta_{DC})\delta_{CE} + \delta_{DE}\delta_{CD}\right)\eta_2\delta_{AB} + \left(k_3\eta_1 + \delta_{CD}\eta_3\right)\delta_{DB} \\ &+ \eta_1\left(\delta_{DE} + \delta_{DC}\right)\gamma_2 + \left(\delta_{DE} + \delta_{DC}\right)\delta_{CE} + \delta_{DE}\delta_{CD}\right)\delta_{AB} + \delta_{AD}\left(\left(k_3\delta_{DB} + (\delta_{DE} + \delta_{DC})\gamma_2\right.\right. \\ &\left.\left. + (\delta_{DE} + \delta_{DC})\delta_{CE} + \delta_{DE}\delta_{CD}\right)\eta_2 + \left(k_3\eta_1 + \delta_{CD}\eta_3\right)\delta_{DB}\right), \\ \beta =& \left(k_2\delta_{DC} + (\delta_{DB} + \delta_{DE})\delta_{BC} + (\gamma_1 + \delta_{BD} + \delta_{BE})\delta_{DE} + \delta_{DB}(\gamma_1 + \delta_{BE})\right)k_1\eta_3 \\ &+ \left(\left((\eta_1 + \eta_2)\delta_{BC} + (\gamma_1 + \delta_{BD} + \delta_{BE})\eta_1 + \delta_{BD}\eta_2\right)\delta_{DC} + (\eta_2\delta_{DE} + \delta_{DB}(\eta_1 + \eta_2))\delta_{BC}\right)\delta_{AD} \\ &+ \left((\delta_{BC} + \delta_{BD})\delta_{DC} + (\delta_{DB} + \delta_{DE})\delta_{BC}\right)(\eta_1 + \eta_2)\delta_{AB}, \end{aligned}$$

$$\begin{aligned}
\xi =& ((k_2\eta_1+(\eta_1+\eta_3)\delta_{BD}+\delta_{BC}\eta_2+\eta_3(\gamma_1+\delta_{BC}+\delta_{BE})\delta_{CD}\ +((k_2\eta_1+\delta_{BD}\eta_2)(\gamma_2+\delta_{CE})))\delta_{AD}\\
&+\delta_{AB}((\delta_{BC}+\delta_{BD})\eta_1\ +(\eta_2+\eta_3)\delta_{BD}+\delta_{BC}\eta_2+\eta_3(\gamma_1+\delta_{BC}+\delta_{BE})\delta_{CD}+\delta_{BD}(\eta_1+\eta_2)(\gamma_2+\delta_{CE})),\\
v =& ((\eta_1+\eta_2+\eta_3)\delta_{BE}+(\gamma_1+\delta_{BC}+\delta_{BD})\eta_1+(\delta_{BC}+\delta_{BD})\eta_2\ +\eta_3(\gamma_1+\delta_{BC}+\delta_{BD}))\delta_{DE}\delta_{AD}\delta_{CE}\\
&+(\delta_{DB}+\delta_{DC})(\eta_1+\eta_2+\eta_3)\delta_{BE}+((\delta_{DB}+\delta_{DC})\delta_{BC}+\delta_{DC}(\gamma_1+\delta_{BD})\eta_1\\
&+((\delta_{BD}+\delta_{DC})\delta_{BC}+\delta_{BD}\delta_{DC})\eta_2+((\delta_{DB}+\delta_{DC})\delta_{BC}+\gamma_1\delta_{DB}\ +\delta_{DC}(\gamma_1+\delta_{BD}))\eta_3\delta_{AD}\delta_{CE}\\
&+(((\eta_1+\eta_2+\eta_3)\delta_{BE}\ +(\delta_{BC}+\delta_{BD})\eta_1+(\delta_{BC}+\delta_{BD})\eta_2+\eta_3(\gamma_1+\delta_{BC}\ +\delta_{BD}))\delta_{DE})\delta_{AB}\delta_{CE}\\
&+((\delta_{DB}+\delta_{DC})(\eta_1+\eta_2+\eta_3)\delta_{BE}\ +(\delta_{DB}+\delta_{DC})\delta_{BC}+\delta_{BD}\delta_{DC})\eta_1)\delta_{AB}\delta_{CE}\\
&+(((\delta_{DB}+\delta_{DC})\delta_{BC}+\delta_{BD}\delta_{DC})\eta_2\ +((\delta_{DB}+\delta_{DC})\delta_{BC}+\gamma_1\delta_{DB}+\delta_{DC}(\gamma_1+\delta_{BD}))\eta_3)\delta_{AB}\delta_{CE}\\
&+\delta_{DE}\delta_{AD}(((\gamma_2+\delta_{CD})\eta_1+(\gamma_2+\delta_{CD})\eta_2+\eta_3\delta_{CD})\delta_{BE}\ +(\gamma_2+\delta_{CD})(\gamma_1+\delta_{BC}+\delta_{BD}))\eta_1\\
&+(((\delta_{BC}+\delta_{BD})\delta_{DC}+\gamma_2\delta_{BD})\eta_2\ +\eta_3\delta_{CD}(\gamma_1+\delta_{BC}+\delta_{BD}))\delta_{DE}\delta_{AD}+\delta_{BE}((\gamma_2+\delta_{CD})\delta_{DB}\eta_1\\
&+(\delta_{DB}\delta_{CD}+\gamma_2(\delta_{DB}+\delta_{DC}))\eta_2+\eta_3\delta_{CD}\delta_{DB})\delta_{AD}+\delta_{AB}\delta_{DE}(((\gamma_2+\delta_{CD})\eta_1+(\gamma_2+\delta_{CD})\eta_2\\
&+\eta_3\delta_{CD})\delta_{BE}((\delta_{BC}+\delta_{BD})\delta_{CD}+\gamma_2\delta_{BD})\eta_1)+\delta_{AB}\delta_{DE}(((\delta_{BC}+\delta_{BD})\delta_{CD}+\gamma_2\delta_{BD})\eta_2\\
\lambda =& k_1k_2\delta_{DE}+((\delta_{DB}+\delta_{DC})\gamma_1+(\delta_{DB}+\delta_{DC})\delta_{BE}+\delta_{BC}\delta_{DB}\ +(\delta_{BC}+\delta_{BD})\delta_{DC})\gamma_2+((\delta_{DB}+\delta_{DC})\gamma_1\\
&+(\delta_{DB}+\delta_{DC})\delta_{BE}+\delta_{BC}\delta_{DB}+(\delta_{BC}+\delta_{BD})\delta_{DC})\delta_{CE}+\delta_{CD}\delta_{DB}(\gamma_1+\delta_{BE})
\end{aligned}$$

These equilibrium points are important in analysing this breast cancer model with Trastuzumab treatement and can predict sufficient condition for the spread of the infection. The results of this investigation are as follows:

Theorem 3.1. *There exist an equilibrium of the system (1) of the breast cancer without any condition.*

3.2. Stability. To determine the stability of the equilibium point, the equation is first given in matrix form

$$\mathscr{K} = \mathscr{F}\mathscr{G} + \mathscr{H}$$

with:

$$\mathscr{K} = \begin{bmatrix} \dot{A} \\ \dot{B} \\ \dot{C} \\ \dot{D} \\ \dot{E} \end{bmatrix}; \mathscr{F} = \begin{bmatrix} -k_1 & 0 & 0 & 0 & 0 \\ \delta_{AB} & -k_2 & 0 & \delta_{DB} & 0 \\ 0 & \delta_{BC} & -k_3 & \delta_{DC} & 0 \\ \delta_{AD} & \delta_{BD} & \delta_{CD} & -k_4 & 0 \\ 0 & \delta_{BE} & \delta_{CE} & \delta_{DE} & -k_5 \end{bmatrix}; \mathscr{G} = \begin{bmatrix} A \\ B \\ C \\ D \\ E \end{bmatrix} \text{ and } \mathscr{H} = \begin{bmatrix} \eta_1 \\ \eta_2 \\ \eta_3 \\ 0 \\ 0 \end{bmatrix}$$

We will use the Rough-Hurwitz criterion [22] to determine the stability of the system. The characteristic equation is calculated using $\det(\mathscr{F} - \lambda I)$. We have:

$$P(\lambda) = \det(\mathscr{F} - \lambda I) = \begin{vmatrix} -k_1 - \lambda & 0 & 0 & 0 & 0 \\ \delta_{AB} & -k_2 - \lambda & 0 & \delta_{DB} & 0 \\ 0 & \delta_{BC} & -k_3 - \lambda & \delta_{DC} & 0 \\ \delta_{AD} & \delta_{BD} & \delta_{CD} & -k_4 - \lambda & 0 \\ 0 & \delta_{BE} & \delta_{CE} & \delta_{DE} & -k_5 - \lambda \end{vmatrix}$$

We get,

$$P(\lambda) = -(\lambda + k_1)(\lambda + k_5)\left(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3\right) \tag{2}$$

We can clearly see that this (2) has five eigenvalues $-k_1$, $-k_5$ and the rest of (three) eigenvalues are the roots of the following equations given below:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \tag{3}$$

where the coefficients are:

$$a_1 = k_2 + k_3 + k_4;$$

$$a_2 = k_2k_3 + k_2k_4 + k_3k_4 - \delta_{BD}\delta_{DB} - \delta_{CD}\delta_{DC}$$

$$a_3 = k_2k_3k_4 - k_2\delta_{CD}\delta_{DC} - \delta_{CD}\delta_{DB}\delta_{BC} - k_3\delta_{BD}\delta_{DB}$$

To study their nature, we Establish a Routh table for this equation, we have:

$$\begin{array}{c|ccc} \lambda^3 & 1 & a_2 & 0 \\ \lambda^2 & a_1 & a_3 & 0 \\ \lambda^1 & b_1 & 0 & \\ \lambda^0 & a_3 & & \end{array}$$

where

$$b_1 = \frac{\begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix}}{a_1}$$

Therefore, From the Routh Array, the sign of the first column are all positive, meaning that all real eigenvalues are negative [22].

Further, it is easy to show that $a_1 > 0$, $b_1 = a_1a_2 - a_3 > 0$ and $a_3 > 0$. Thus, it follows from the Routh-Hurwitz criteria that the system (1) is locally asymptotically stable.

4. Numerical Simulation and Discussions

In this section, a number of simulations are performed to examine the results of the analysis of our proposed breast cancer model with the adverse effect of trastuzumab treatment on the population of patients. We performed them using the parameter values in Table 1. The simulation is carried out using the initial values: $(A_0, B_0, C_0, D_0, E_0) = (14, 30, 20, 10, 10)$ Based on these parameters values, we obtained the following equilibruim point $P_e^* = (A^*, B^*, C^*, D^*, E^*) = (4.2, 14.46, 19.78, 8.96, 32.54)$. The numerical simulation result are shown in FIGURE 2.

Table 1. Parameters values.

Parameter	Values
η_1	5
η_2	20
η_3	11
γ_1	0.5
γ_2	0.8
γ_3	0.4
δ_{AB}	0.56
δ_{AD}	0.63
δ_{BC}	0.62
δ_{BD}	0.35
δ_{BE}	0.30
δ_{CD}	0.1
δ_{CE}	0.30
δ_{DB}	0.36
δ_{DC}	0.42
δ_{DE}	0.30

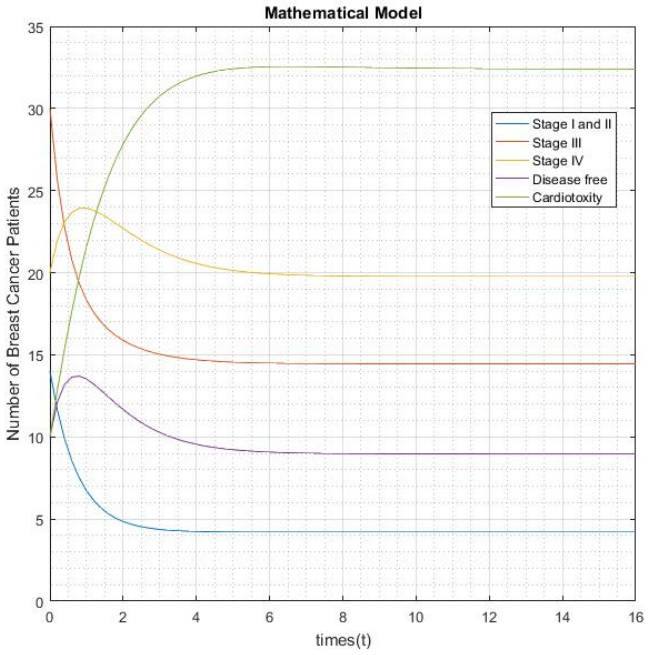

FIGURE 2. Simulation result with initial condition $(A_0, B_0, C_0, D_0, E_0) = (14, 30, 20, 10, 10)$

FIGURE 2 illustrates the equilibrium conditions beginning with the 7th period. Stage I and II sub-populations from the initial condition of 14 patients were reduced to 4 patients with equilibrium conditions. Similarly, the stage III sub-population from the initial condition of 30 patients fell to 14 under equilibrium conditions. Conditions are relatively constant in disease-free and stage IV sub-populations, where there is no significant change in the population from the initial condition to equilibrium. The sub-population with stage IV increased from 20 to 19 and the disease-free sub-population from 10 to 8. The cardiotoxic sub-population saw a significant increase from 10 patients initially to 32 patients in equilibrium. The result of this simulation is considered as the initial simulation.

For the second and third simulations, we will try to lower the relapse rate and cardiotoxity rate.

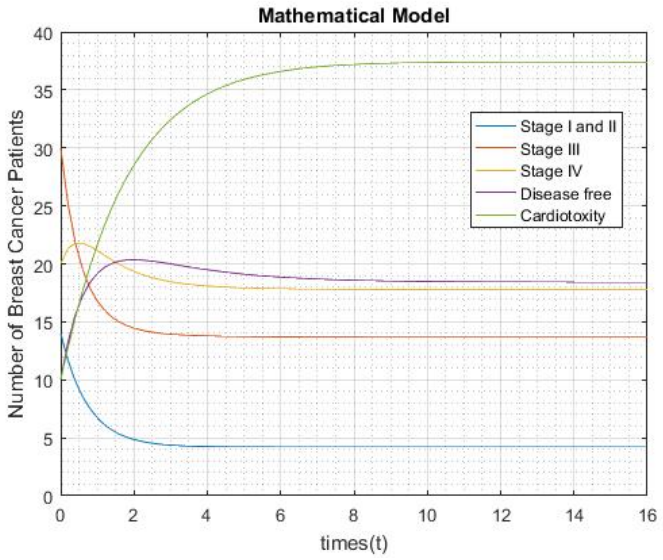

FIGURE 3. Simulation result of the model with $\delta_{DB} = 0.1$ and $\delta_{DC} = 0.1$

FIGURE 3 illustrate the simulation results by reducing the ralapse rate δ_{DB} and δ_{DC} to 0.1 both. The results show a slight increase in the disease-free sub-population to 18 patients. While the number of recovered individuals grew, the proportion of the population affected by cardiotoxicity also significantly increased. The situation for other sub-populations is largely the same as it was in the first simulation.

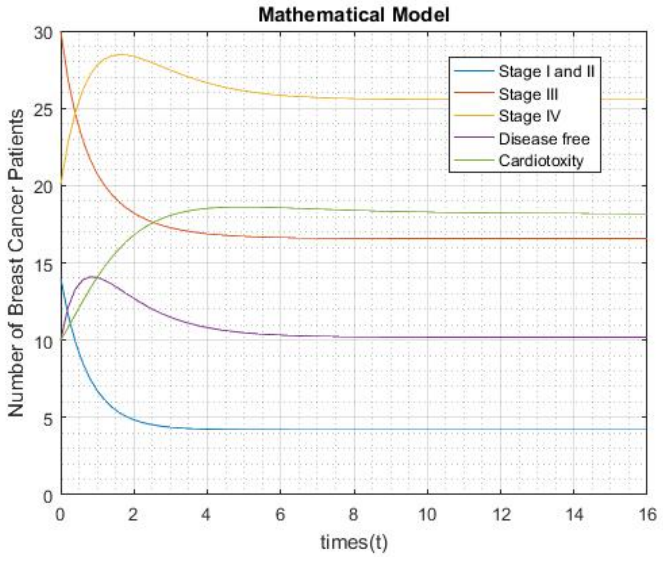

FIGURE 4. Simulation result of the model with $\delta_{BE} = 0.1$ and $\delta_{CE} = 0.1$

FIGURE 4 illustrate the simulation results by reducing the ralapse rate δ_{BE} and δ_{CE} to 0.1 both. We observed that the disease-free sub-population increased slightly to 10 patients. Additionally, a positive outcome was observed in the subset of patients affected by cardiotoxicity, as the number of patients in this group decreased to 18 at equilibrium. For the sub-population in stage III, there was a slight increase when compared to the initial simulation. For other sub-populations, the results remained similar to the initial simulation.

5. CONCLUSION

In this work, we constructed a mathematical model for breast cancer with the adverse effect of trastuzumab treatment on the population of patients to the heart of a patient. The model consists of tree sub-populations of breast cancer patients by stage, a disease-free sub-population and a cardiotoxic sub-population and sixteen parameters. A dynamic analysis is conducted to determine the dynamics of the number of patients in each sub-population at time t. The result of the dynamic analysis is a stable equilibrium point. Numerical simulations are conducted to examine the behavior of solutions. Based on the simulation results, we can conclude that if all parameters are considered constant, the status of the sub-population will be stable at a given time, with any initial conditions. This shows that the equilibrium point of the system proved to be stable without any conditions. An increase in cardiotoxic sub-populations was obtained as an unexpected result when the relapse rate was reduced. Reducing the cardiotoxicity rates led to significantly improved results, with a substantial increase in the number of disease-free sub-populations and a dramatic decrease in the number of cardiotoxic sub-populations. These simulation results provide a practical solution for minimizing the number of cardiotoxic patients and increasing the number of patients recovering from or having a complete response after trastuzumab. The solution is to decrease the rate of cardiotoxicity in stages III and IV of the sub-populations.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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