International Journal of Difference Equations (IJDE).
ISSN 0973-6069, Volume 17, Number 1, (2022). 19-32

http://www.ripublication.com/ijde.htm

Mathematical Model of the Journey of Breast Cancer Patients Affected by Chemotherapy Response

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Abstract

Chemotherapy is the most wellknown and effective cancer treatment for many types of cancer. Tumor response after chemotherapy was evaluated using the criteria for response evaluation for solid tumors (RECIST). These responses are represented in a system of differential equations based on changes in cancer stage. The discussion includes model construction, search for equilibrium point, analysis of existence and stability, and a numerical simulation. The dynamic analysis carried out in this study resulted in a point of equilibrium.

The equilibrium point obtained is called endemic, this condition exists and will be stable if the basic reproduction number is more than one. However, if the basic reproduction number is less than one, then the endemic condition will not be achieved. This study can be used as an early prediction of the course of cancer in a population with cancer in a hospital, where the patient is treated with chemotherapy.

Keywords: Chemotherapy, Breast Cancer, Cancer Response, Stages, Mathematical Model.

AMS Subject Classification: 92-10, 99A00

1. INTRODUCTION

Breast Cancer (*Breast Cancer*) is a malignant tumor that attacks the breast tissue. Breast cancer causes cells and tissue to change shape to become abnormal and multiply uncontrollably. Breast cancer is one type of carcinoma with a high prevalence. It can occur in men and women, where the prevalence is higher in women. Data *World Health Organization* (WHO) in 2018, out of approximately 8.6 million women diagnosed with cancer, as many as 2,088,849 or 11.6% of the total number of world cancer cases from developing countries. This number is only different from 5,027 lung cancer cases, which occupies the first position. Based on this number, 626,679 of them are cases of death, majority of which were from sub-Saharan African countries [1, 2, 3, 4].

The main types of cancer treatment include surgery, radiotherapy, chemotherapy, hormone therapy, immunotherapy, and gene therapy, either in isolation or a combination of two or more [5]. Chemotherapy is a breast cancer treatment that uses cancer-killing drugs given intravenously (injected into a vein) or by mouth [6]. Chemotherapy is given in cycles, with each treatment period followed by a recovery period. Treatment usually lasts for several months. Although chemotherapy has a positive impact on curing cancer, it also has side effects detrimental to health. Chemotherapy side effects arise because chemotherapy drugs destroy cancer cells and attack healthy cells. However, chemotherapy is the most well-known and effective cancer treatment for many types of cancer [7].

Chemotherapy is usually given to patients with early-stage breast cancer. Chemotherapy reduces recurrence and mortality rates and improves survival rates in patients with early-stage breast cancer [9]. Tumor response after chemotherapy was evaluated using the criteria for response evaluation for solid tumors (RECIST), namely complete response, partial response, incomplete response/stable disease, and

progressive disease [8]. Cancer stage also affects cancer response after chemotherapy. Women with small tumor size (early-stage breast cancers) have excellent survival, with a high probability of experiencing a complete response after chemotherapy [10].

Patients with a complete response diagnosis are not necessarily free from cancer forever. Breast cancer survivors remain at high risk of a second breast cancer for many years after initial diagnosis [11, 12]. Breast cancer survivors are at increased future risk of developing locoregional recurrences and contralateral breast cancers (CBCs) [12, 13, 14]. Progressive disease is also experienced by many patients after chemotherapy, some studies related to progressive disease are: [15, 16, 17]. Some chemotherapy patients do not experience significant changes, so the cancer does not appear to be reduced (Stable disease) [18, 19, 20]

Research on biological and health phenomena can be done with mathematics. The role of mathematics in biology and health is to form a mathematical model of a disease. The existence of a mathematical model can be used as a prediction of the best and worst possibilities of disease. Mathematical predictions of the development of a disease can be made using dynamic analysis. Mathematical modeling of breast cancer has been developed over the years, both at the enzyme and cellular level, such as [22, 23, 24]. In recent years, research on mathematical models of breast cancer related to cancer treatment has been carried out by several researchers, including: [21, 25, 26, 27].

There are no existing studies that discuss the mathematical model of chemotherapy at the cancer population level. Based on these considerations, this study discusses the phenomenon of the journey of breast cancer patients, which is influenced by the response to chemotherapy and the second recurrence. The grouping of patients is based on the stage of cancer detected first. Cancer can increase and decrease to another stage as the tumor progresses and the treatment is given. The discussion includes model construction, search for equilibrium point, analysis of existence and stability, and a numerical simulation.

2. MATERIALS AND METHODS

The model is constructed with four compartments describing the subpopulations of the cancer patients studied: patients at stages 0 and 1, dormancy, stage 2 and 3, and stage 4. Each subpopulation is represented by the variables A, B, C and D. Dormancy is the period of (inactive) cancer cells that can last for several years. During the period of dormancy, cancer cells reshape their genetic makeup and get ready for the next stage of development. The compartment diagram is shown in Figure (1). The compartment

diagram Figure (1) assumes that stage 0 and 1 cancer patients can recover, but stage 2 and 3, and 4 patients are less likely to recover, so $0 < \mu_{DA} \leq \frac{\epsilon}{2} \leq \mu_{CA} \leq \epsilon < 1$.

People affected by cancer are assumed to occur when the person comes for the first visit to the hospital. At that time, the patient data begins to be taken. Patients were classified into subpopulations of stages 0 and 1, stages 2 and 3, or stage 4. The assumption used in this study is that the patient's stage is always checked so that that stage changes can be known at any time. Over time, patients will experience changes in the severity of cancer so that each subpopulation will experience changes in the number of individuals. The rate of change of each subpopulation is described in The Model Construction.

3. MODEL CONSTRUCTION

3.1 The rate of change of subpopulation A (stages 0 and 1)

The number of individuals was relatively smaller than the other subpopulations. Therefore, the Stage 0 and 1 cancer patients were placed in one subpopulation (A). Most cancer patients who have undergone treatment already have advanced-stage cancer. Individuals who came for treatment for the first time diagnosed with stage 0 and 1 cancer were included in subpopulation A with a rate of θ_1. While still in stage 1 or 2, cancer patients can recover from cancer at a rate of h. In the event of death, patients with stage 1 or 2 are assumed to have natural death at a rate of d_1. Patients can also move from stages 0 and 1 to dormancy, or vice versa at the rate of μ_{BA} and μ_{AB}, respectively. Stage changes of cancer stage can occur over time from stages 0 and 1 to stages 2 and 3, and vice versa with the rates μ_{AC} and μ_{CA}, respectively. Patients from stage 4 can also experience recovery although the probability is minimal, so there is a rate of change from stage 4 back to stages 0 and 1, namely μ_{DA}. Thus, a model for the rate of change of stage 0 and 1 subpopulations per unit time can be made, namely:

$$\frac{dA}{dt} = \theta_1 - hA - d_1A - \mu_{AB}A + \mu_{BA}B + \mu_{CA}C - \mu_{AC}C + \mu_{DA}D \quad (3.1)$$

3.2 The rate of change of subpopulation B (Dormancy)

As previously explained, dormancy is a period of (inactive) cancer cells that can last for several years. The subpopulations that can be in this phase are assumed to be subpopulations from stages 0 and 1, so there is a rate A to B, namely μ_{AB}. Patients who are in the dormancy phase if they die are assumed to experience natural death

with a rate of d_1. After experiencing a dormancy period, cancer cells will reactivate so that there is a phase shift from dormancy to stage 0 and 1, stage 2 and 3, or stage 4 with each rate μ_{BA}, μ_{BC} , and μ_{BD}. Thus, a model of the rate of change of dormancy subpopulations per unit time can be made, namely :

$$\frac{dB}{dt} = \mu_{AB}A - \mu_{BA}B - \mu_{BC}B - \mu_{BD}B - d_1B \tag{3.2}$$

3.3 The rate of change of subpopulation C (stages 2 and 3)

Individuals who came for treatment for the first time diagnosed with stage 2 and 3 cancer were included in subpopulation C with a rate of θ_2. Subpopulation C can increase with changes from stage 0 and 1 by μ_{AC} and from dormancy by μ_{BC}. Subpopulation C can also move to subpopulation A as the patient's condition improves at a rate of μ_{CA}. Subpopulation C can move to subpopulation D as the patient's condition worsens at a rate of μ_{CD}. Patients in stage 2 and 3 subpopulations can die from cancer at a rate of d_2. Thus, it is possible to model the rate of change of stage 2 and 3 subpopulations per unit time, namely:

$$\frac{dC}{dt} = \theta_2 + \mu_{AC}A - \mu_{CA}C - d_2C + \mu_{BC} - \mu_{CD}C \tag{3.3}$$

3.4 The Rate of change of subpopulation D (Stage 4)

Individuals who came for treatment for the first time diagnosed with stage 2 and 3 cancer were included in subpopulation C with a rate of θ_2. Subpopulation D can grow by moving from stages 2 and 3 by μ_{CD} and from a dormancy period of μ_{BD}. On the other hand, the stage 4 subpopulation may also be reduced by d_2 cancer deaths and d_3 neutropenia deaths. Patients in subpopulation D can also recover, although the probability is minimal, namely a change from stage 4 to stage 0 and 1 with a rate of μ_{DA}. Thus, it is possible to model the rate of change of the stage 4 subpopulation per unit time, namely:

$$\frac{dD}{dt} = \theta_3 + \mu_{CD}C + \mu_{BD}B - \mu_{DA}D - d_3D - d_2D$$

Based on the rate of change of stages 0 and 1, dormancy, stage 2 and 3 subpopulations,

and stage 4 subpopulations, a system of differential equations is formed.

$$\begin{aligned}
\frac{dA}{dt} &= \theta_1 - hA - d_1A - \mu_{AB}A + \mu_{BA}B + \mu_{CA}C - \mu_{AC}C + \mu_{DA}D \\
\frac{dB}{dt} &= \mu_{AB}A - \mu_{BA}B - \mu_{BC}B - \mu_{BD}B - d_1B \\
\frac{dC}{dt} &= \theta_2 + \mu_{AC}A - \mu_{CA}C - d_2C + \mu_{BC}B - \mu_{CD}C \\
\frac{dD}{dt} &= \theta_3 + \mu_{CD}C + \mu_{BD}B - \mu_{DA}D - d_3D - d_2D
\end{aligned} \tag{3.4}$$

with the compartment model shown in Figure 1. The parameters used in the system of equations are as follows in Table 1.

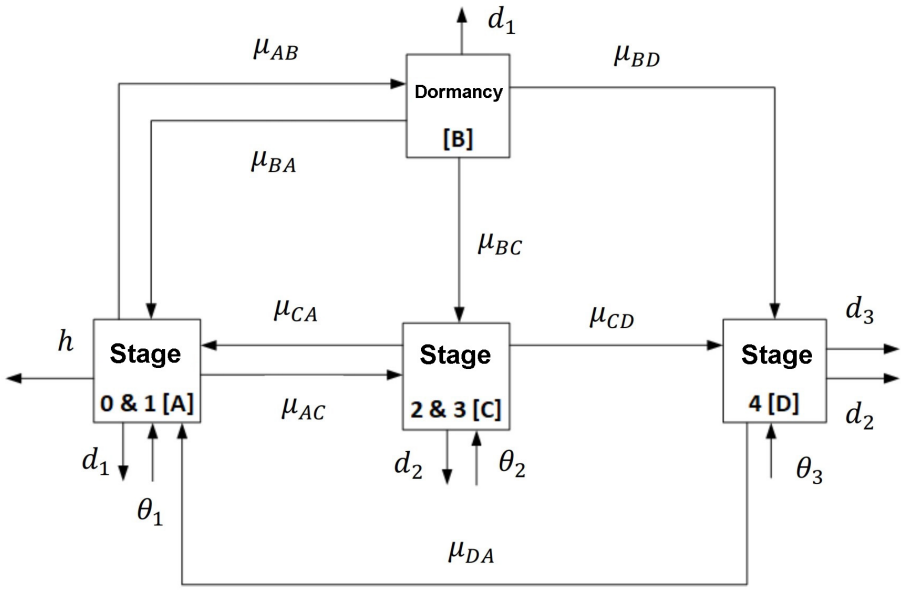

Figure 1: Compartment Diagram

Table 1: Parameters

Parameters	Description
μ_{ij}	Rate i to j
h	Recovery rate
d_1	Natural death rate
d_2	Cancer death rate
d_3	Death rate from other diseases
$\theta_{1,2,3}$	Number of people with cancer

4. DYNAMICAL ANALYSIS

4.1 Equilibrium Point

The equilibrium point obtained from the system of equations (3.4) is equal to zero.

$$\begin{aligned} \theta_1 - hA - d_1A - \mu_{AB}A + \mu_{BA}B + \mu_{CA}C - \mu_{AC}C + \mu_{DA}D &= 0 \\ \mu_{AB}A - \mu_{BA}B - \mu_{BC}B - \mu_{BD}B - d_1B &= 0 \\ \theta_2 + \mu_{AC}A - \mu_{CA}C - d_2C + \mu_{BC}B - \mu_{CD}C &= 0 \\ \theta_3 + \mu_{CD}C + \mu_{BD}B - \mu_{DA}D - d_3D - d_2D &= 0 \end{aligned} \tag{4.5}$$

By using elimination and substitution in the four equations, we get one point of equilibrium, namely $P^* = (A^*, B^*, C^*, D^*)$ with a value of A^* is translated into equation (4.6), B^* is translated into equation (4.7), C^* is translated into equation (4.8), and D^* is translated into equation (4.9). The equilibrium point $P^* = (A^*, B^*, C^*, D^*)$ is an endemic equilibrium point, because in that condition all subpopulations have a number of individuals.

$$A^* = \frac{(\mu_{BA} + \mu_{BC} + \mu_{BD} + d_1)\, B^*}{\mu_{AB}} \tag{4.6}$$

$$B^* = \frac{A}{B} \tag{4.7}$$

$$C^* = \frac{C}{(\mu_{CA} + d_2 + \mu_{CD})\, \mu_{AB}} \tag{4.8}$$

$$D^* = \frac{D}{(\mu_{DA} + d_3 + d_2)\, (\mu_{CA} + d_2 + \mu_{CD})\, \mu_{AB}} \tag{4.9}$$

with

$$\begin{aligned} A =& (\mu_{DA} + d_3 + d_2)\, (\mu_{CA} + d_2 + \mu_{CD})\, \mu_{AB}\theta_1 + (\mu_{DA} + d_3 + d_2)\, (\mu_{CA} - \mu_{AC})\, \mu_{AB}\theta_2 + \\ & (\mu_{CA} + d_2 + \mu_{CD})\, \mu_{DA}\mu_{AB}\theta_3 + \mu_{DA}\mu_{CD}\mu_{AB}\theta_2 \\ B =& (\mu_{DA} + d_3 + d_2)\, (\mu_{CA} + d_2 + \mu_{CD})\, (h + d_1 + \mu_{AB})\, (\mu_{BA} + \mu_{BC} + \mu_{BD} + d_1) - \\ & (\mu_{DA} + d_3 + d_2)\, (\mu_{CA} + d_2 + \mu_{CD})\, \mu_{AB}\mu_{BA} - (\mu_{DA} + d_3 + d_2)\, (\mu_{CA} - \mu_{AC}) \\ & (\mu_{AC}\, (\mu_{BA} + \mu_{BC} + \mu_{BD} + d_1)) - (\mu_{DA} + d_3 + d_2)\, (\mu_{CA} - \mu_{AC})\, \mu_{AB}\mu_{BC} - \\ & \mu_{CD}\mu_{AC}\mu_{DA}\, (\mu_{BA} + \mu_{BC} + \mu_{BD} + d_1) + \mu_{CD}\mu_{AB}\mu_{BC}\mu_{DA} + \\ & (\mu_{CA} + d_2 + \mu_{CD})\, \mu_{AB}\mu_{BD}\mu_{DA} \end{aligned}$$

$$C = \mu_{AB}\theta_2 + (\mu_{AC}(\mu_{BA} + \mu_{BC} + \mu_{BD} + d_1))B^* + (\mu_{AB}\mu_{BC})B^*$$
$$D = (\mu_{CA} + d_2 + \mu_{CD})\mu_{AB}\theta_3 + \mu_{CD}\mu_{AB}\theta_2 + (\mu_{CD}\mu_{AC}(\mu_{BA} + \mu_{BC} + \mu_{BD} + d_1))B^* + (\mu_{CD}\mu_{AB}\mu_{BC} + (\mu_{CA} + d_2 + \mu_{CD})\mu_{AB}\mu_{BD})B^*$$

4.2 Existence and Stability Analysis

If observed from the equilibrium point, the values of A^*, C^*, and D^* are all positive, and contain the value of B^* in them. While the value of B^* itself is not necessarily positive. Therefore, the equilibrium point exists if the value $B^* > 0$. So the existence of the equilibrium point P^* can be obtained with the condition

$$\mu_{AC} < \frac{D}{\theta_2(\mu_{DA} + d_3 + d_2)} \tag{4.10}$$

with

$$\begin{aligned} D =& d_2(d_2\theta_1 + d_3\theta_1 + \mu_{DA}\theta_1 + \mu_{DA}\theta_3) + \mu_{CA} \\ & (d_2\theta_1 + d_2\theta_2 + d_3\theta_1 + d_3\theta_2 + \mu_{DA}\theta_1 + \mu_{DA}\theta_2 + \mu_{DA}) \\ & + \mu_{CD}(d_2\theta_1 + d_3\theta_1 + \mu_{DA}\theta_1 + \mu_{DA}\theta_2 + \mu_{DA}\theta_3) \end{aligned}$$

Based on the equation (4.10) we get the basic reproduction number $\mathcal{R}_0$.

$$\mathcal{R}_0 = \frac{D}{\mu_{AC}\theta_2(\mu_{DA} + d_3 + d_2)} \tag{4.11}$$

Remark 4.1. If $\mathcal{R}_0 > 1$ then there is a stable endemic equilibrium point. This means that in this condition there is only a population that has breast cancer.

Remark 4.2. If $\mathcal{R}_0 < 1$ then the endemic equilibrium point does not exist so that its stability cannot be seen.

5. NUMERICAL SIMULATION

The simulation was carried out using MATLAB with the RK4 method. Numerical simulation is displayed with two conditions, namely when Basic Reproductive Number $\mathcal{R}_0 > 1$ and $\mathcal{R}_0 < 1$. The simulation results are shown in the following pictures (Figure 2-4).

1. Basic Reproductive Number is greater than one, $\mathcal{R}_0 > 1$.

Table 2: Parameter Values

Parameter	Values	Parameter	Values
μ_{AB}	0,2	d_2	0,1
μ_{BA}	0,4	d_3	0,1
μ_{CA}	0,7	θ_1	1
μ_{AC}	0,9	θ_2	6
μ_{CD}	0,4	θ_3	4
μ_{BC}	0,4	h	0,05
μ_{BD}	0,4	d_1	0,1
μ_{DA}	0,01		

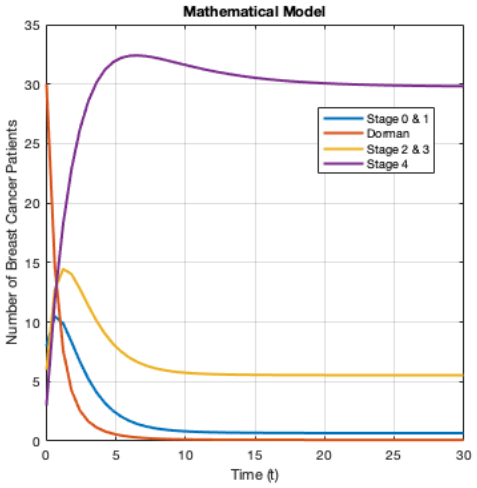

Figure 2: Population change based on time when $\mathcal{R}_0 > 1$

The simulation is carried out using $(A_0, B_0, C_0, D_0) = (8, 30, 6, 3)$ (the initial conditions) and the parameter values are as follows in Table (2). Based on the values in the Table (2) we get the Basic Reproductive Number $\mathcal{R}_0 = 1.045$. The simulation results are displayed on a population change graph as shown in Figure (2). From the figure it can be seen that with the initial population condition $(A_0, B_0, C_0, D_0) = (8, 30, 6, 3)$, the population has increased and decreased over time. 0 to 27 as shown in the graph. After reaching time 27, the population stabilizes at the endemic equilibrium point $(A^*, B^*, C^*, D^*) = (0.6636.0.1021, 5.5318, 29.7788)$. The phase portrait shown in Figure (3), it can be seen that the solution goes to an endemic equilibrium point. The simulation results are in accordance with the dynamic analysis that if $\mathcal{R}_0 > 1$, then the endemic equilibrium point exists and is stable.

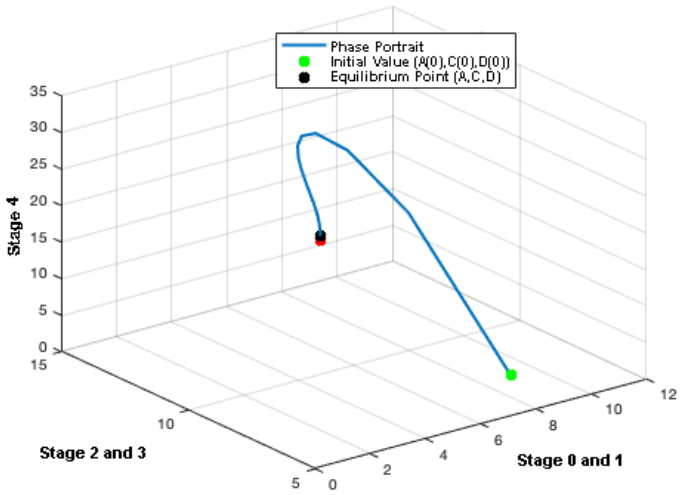

Figure 3: Phase Portrait when $\mathcal{R}_0 > 1$

2. Basic Reproductive Number is less than one, $\mathcal{R}_0 < 1$.
   The simulation is carried out using the parameter values and initial conditions in the table (2) by changing $\mu_{AC} = 1.5$ to get the Basic Reproductive Number $\mathcal{R}_0 = 0.627$. The simulation results are displayed on a population change graph as shown in Figure (4). From the figure it can be seen that with the initial population condition $(A_0, B_0, C_0, D_0) = (8, 30, 6, 3)$, the population increased and decreased to Finally, there is a negative value in the population of stages 0 and 1 and is dormancy. Because the population cannot be negative, it is proven that if $\mathcal{R}_0 < 1$, then there is no equilibrium point.

6. CONCLUSIONS

Mathematical modeling in this study was used to predict the development of breast cancer after chemotherapy over time. The cancer response after chemotherapy can be in the form of a complete response, meaning that the cancer is no longer visible, but this is considered a dormancy cancer condition. In dormancy conditions, cancer cells can grow back, even to a more severe stage. Cancer response can also be more malignant, so that the cancer increases after chemotherapy, this condition is called progressive disease. Sometimes, the cancer response after chemotherapy does not appear to have changed, this condition can be in the form of partial response or stable disease. These responses are represented in a system of differential equations based on changes in

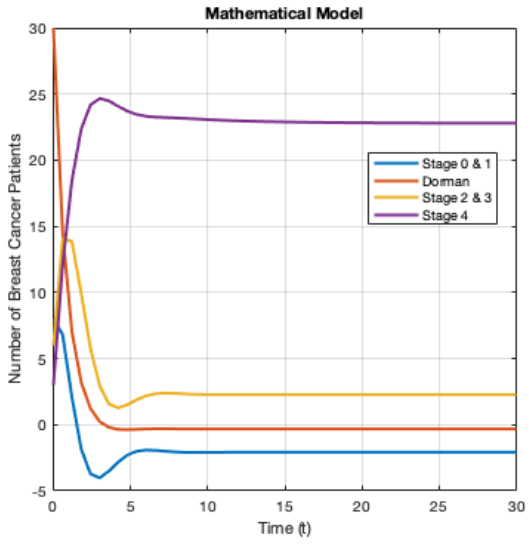

Figure 4: Population change based on time when $\mathcal{R}_0 < 1$

cancer stage.

This study can be used as an early prediction of the course of cancer in a population with cancer in a hospital, where the patient is treated with chemotherapy. The dynamic analysis carried out in this study resulted in a point of equilibrium. This happens because the system is formed without any interaction, only the movement of the population from one status to another. The equilibrium point obtained is called endemic, this condition exists and will be stable if the basic reproduction number is more than one. If the basic reproduction number is less than one, then the endemic condition will not be achieved and further analysis is needed regarding the population dynamics that occur.

Acknowledgement

The authors thank the Deputy for Research and Strengthening Development of the Ministry of Research and Technology Indonesia (the National Research and Innovation Agency) which has provided research funding through Penelitian Disertasi Doktor (PDD) with contract agreement numbers 6/E1/KP.PTNBH/2021 and 2264/UN1/DITLIT/DIT-LIT/PT/2021. The authors also thank the Department of Mathematics, Faculty of Mathematics and Natural Sciences, Universitas Gadjah Mada for the support in research facilities.

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