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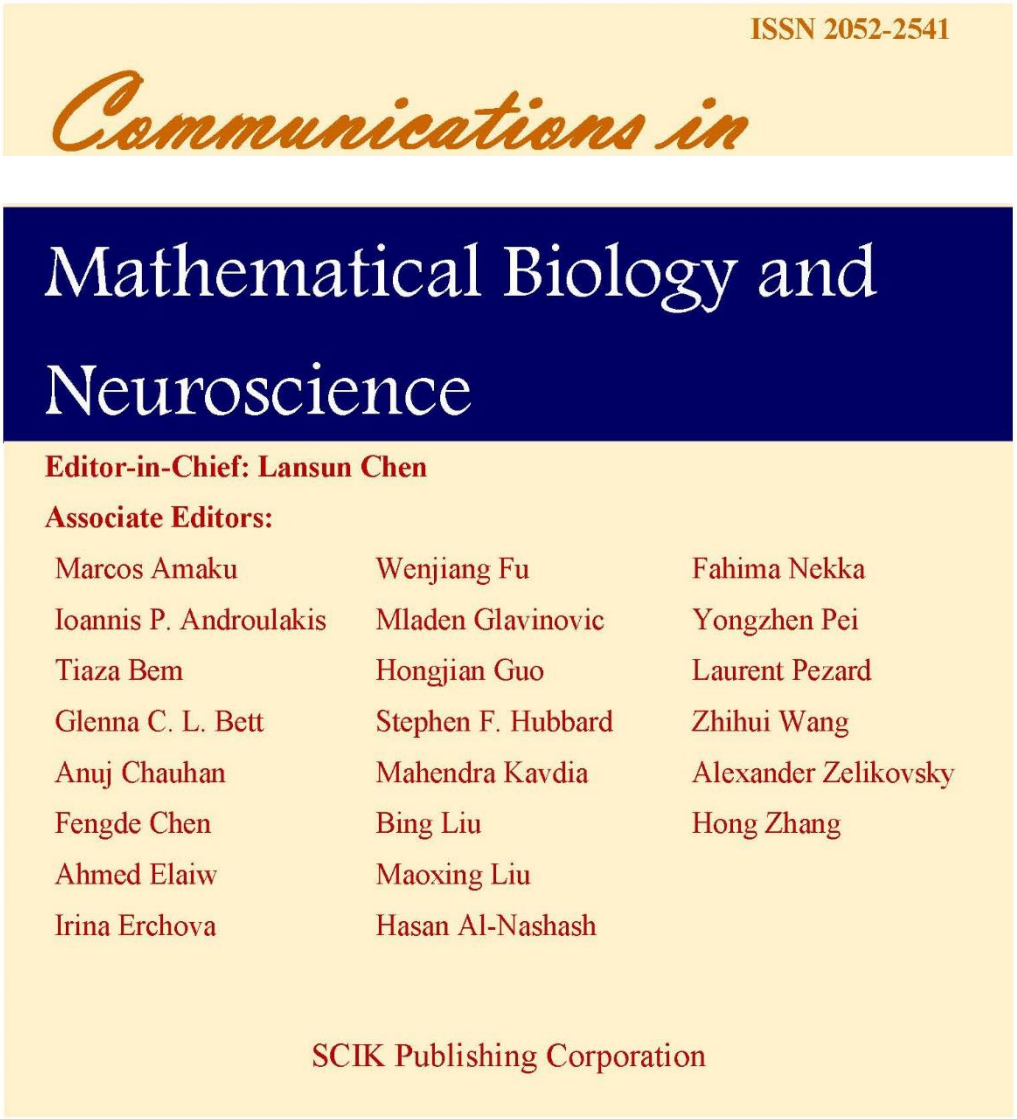

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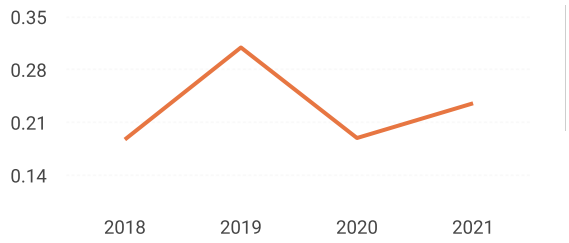

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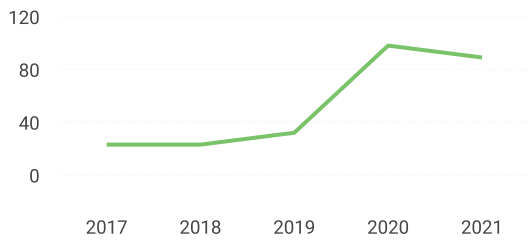

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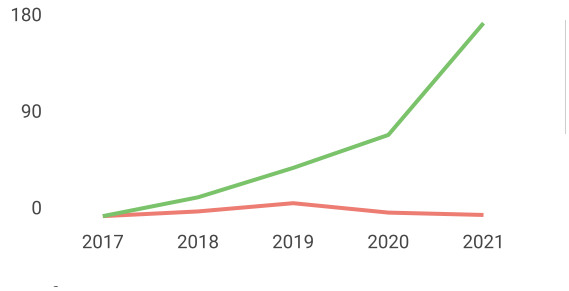

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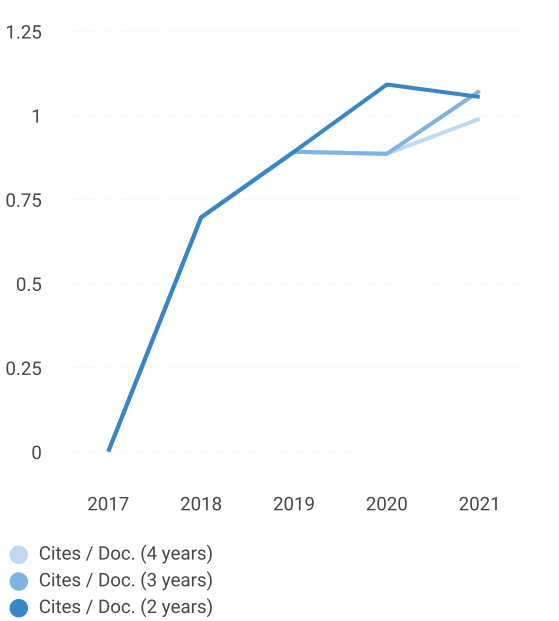

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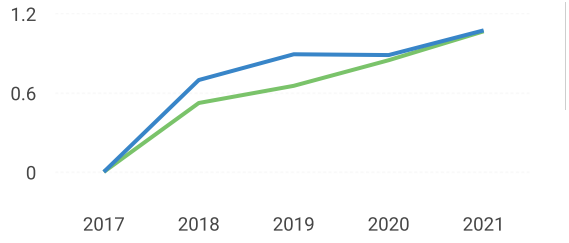

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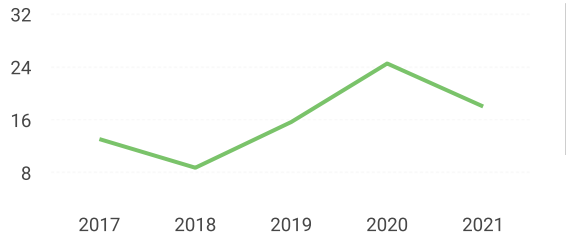

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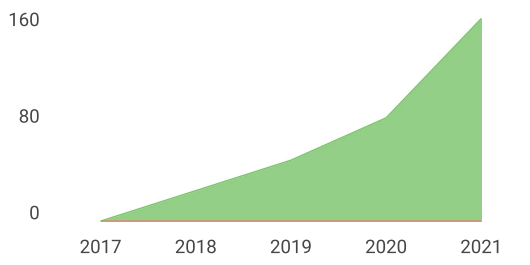

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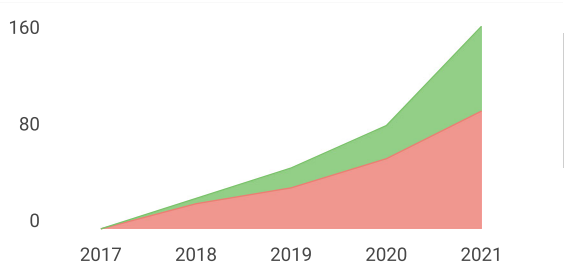

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PARAMETER ESTIMATION AND ANALYSIS ON *SIS-SEIS* TYPES MODEL OF TUBERCULOSIS TRANSMISSION IN EAST JAVA INDONESIA

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Abstract: In this work, the parameter estimation of the *SIS-SEIS* types of Tuberculosis (TB) model is considered based on the data of TB-infected cases in East Java Province, Indonesia. We utilize the combination of the performance index approach in the optimal control theory and genetic algorithm to estimate the TB model parameters. Two basic reproduction numbers were also determined as well. The sensitivity analysis is performed to establish the most significant parameters on the TB model transmission dynamics. Based on the parameter estimation results of the *SIS-SEIS* types TB models, the basic reproduction numbers for both models are greater than one which means that, TB disease will persist in the province. Furthermore, the simulation of the TB model is carried out using the parameter estimation results which confirms that the spread of TB is ongoing in East Java Indonesia, and is yet to reach its endemicity.

Keywords: tuberculosis; model; parameter estimation; optimal control theory; genetic algorithm.

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1. INTRODUCTION

Tuberculosis (TB) is a disease caused by Mycobacterium tuberculosis in the form of bacilli or rods. Mycobacterium tuberculosis usually only affects the lungs (pulmonary TB), but it is possible that the bacteria also affect other parts of the body such as the brain, spine, and central nervous system (extrapulmonary TB). TB disease can be transmitted directly by an infected human to healthy human through the air when a person infected with TB coughs, spits, sneezes, or talks [1]. According to WHO, in the late 1800s, the main cause of death was induced by TB occurred in several countries in Europe such as the Netherlands and Russia. In 2000, global TB cases were 10 million people infected with TB. TB sufferers are mostly male and more adults than children. In 2017, as many as 10 million people contracted TB, among TB sufferers 1.6 million people died and 0.3 million people contracted HIV. In 2017, the TB cases in Indonesia is reported about 425,089 and 442,172 new TB cases with recurring diseases which put Indonesia in the third position in the world from the original fifth region in the world infected TB countries [1].

Mathematical modeling is needed to determine, understand, and control the spread of a disease in a population, including TB disease. Castillo-Chavez and Song analyzed a mathematical model of TB spread which focuses on TB control strategies with treatment and vaccination [2]. The model of TB spread taking into account the latent period and active infection by age-dependent have been studied in Xu et al. paper [3]. The TB model by incorporate the cases of the treatment in homes and hospitals can be found in Yıldız & Karaoğlu article [4]. The compartment model of the TB infection with imperfect vaccines is presented in Egonmwan & Okuonghae work [5]. Ahmadin and Fatmawati developed the mathematical modeling of drug resistance in TB transmission by incorporate the optimal control [6]. Recently, the optimal control strategies of the TB model based on the discrete age-structured were explored by Fatmawati et al. [7].

Several researchers have carried out the implementation of the TB model on the real cases in the population. Zhang et al. have estimated parameters of the TB model with attention to hospital care using the Chi-Square test method based on data from China [8]. Kim et al. [9] applied the TB data in the Philippines to estimate the parameters of the TB model through the SEIL (Susceptible

- High-Risk Latent - Infected - Low-Risk Latent) type using the least-squares method. Ullah et al. [10] investigated the dynamic of TB infection using the TB confirmed notified cases in the city of Khyber Pakhtunkhwa, Pakistan. Khan et al. [11] developed a mathematical model with the standard incidence rate of the TB transmission and applied the least-squares method to estimate the model based on data in the city of Khyber Pakhtunkhwa, Pakistan.

The implementation of the real problem of the spread of TB in Indonesia is not widely discussed. Damayanti et al. [12] explored the identification of the nonlinear dynamics of the TB transmission and estimated the parameters model using the genetic algorithm multilayer perceptron-based data on TB patients in East Java, Indonesia. Fatmawati et al. [13] presented the mathematical model of TB transmission in Indonesia and parameterized the model via the least-squares method based on the cumulative TB case data per 100,000 population in Indonesia from 2008 to 2017.

In this study, we consider the parameter estimation of the TB model on Susceptible - Infectious – Susceptible (SIS) and Susceptible - Exposed - Infectious – Susceptible (SEIS) types TB model using the performance index approach in the optimal control theory with the optimization approach. The estimation parameters using the maximum Pontryagin principle by utilizing the existing performance index in the optimal control theory have been proposed by Götz et al. [14] and applied the approach for dengue cases in Semarang city, Indonesia. In this study, we used the genetic algorithm method to minimize the performance index of the TB infected on the model and then observed TB data in East Java Indonesia.

2. THE SIS TYPE MODEL OF TB TRANSMISSION

In this section, we discuss the *SIS* type of the mathematical model of TB transmission. The total human population (N) is divided into two populations, namely the susceptible (S) and the infected (I) human population. We assume that the rate of recruitment of the susceptible population is proportional to the total number of the populations. The human birth rate is assumed the same as the natural human death rate and the infected population can return to being susceptible due to the

temporary immunity. The explanation of the variables and parameters used in the SIS type for TB is given by Table 1 and Table 2, respectively.

Table 1. The definition of the variables on the SIS TB model

Variable	Explanation
$S(t)$	The susceptible population at time t
$I(t)$	The TB infected at time t
$N(t)$	The total population at time t

Table 2 The definition of the parameters on SIS TB model

Parameter	Explanation	Unit
μ	The natural death rate	$\frac{People}{time}$
β	The transmission rate	$\frac{People}{time}$
γ	The recovered rate	$\frac{People}{time}$

Biologically, the variables used in the model represent the population at a certain time t, so that all variables are non-negative. In addition, in order to have biological meaningful region, all parameters are also assumed to be positive. Based on these assumptions, the *SIS* type model of the TB transmission can be represented as follows.

(1) $\frac{dS}{dt} = \mu N - \frac{\beta SI}{N} - \mu S + \gamma I,$

(2) $\frac{dI}{dt} = \frac{\beta SI}{N} - \mu I - \gamma I,$

where $N = S + I$ and the initial condition of the model are non-negative, $S(0) = S_0 > 0$, $I(0) = I_0 \geq 0$.

3. THE SEIS MODEL OF THE TB TRANSMISSION

This section discusses the *SEIS* (Susceptible - Exposed - Infectious - Susceptible) type on the dynamical model of the TB transmission. The total human population (N) is divided into three populations, namely the susceptible (S), the exposed (E), and the infected (I) human populations.

The following are the assumptions used in the $SEIS$ mathematical model for the spread of TB. The exposed population consists of individuals infected by TB disease, but without an infectious status. We assume that the recruitment rate of the susceptible population is proportional to the total number of the populations. The human birth rate is the same as the natural human death rate. The TB infected population can return to being susceptible because of temporary immunity. The description of the variables and parameters for the $SEIS$ type for TB is depicted in Table 3 and Table 4, respectively.

Table 3 The description of the variables on the $SEIS$ TB model.

Variable	Description
$S(t)$	The susceptible population at time t
$E(t)$	The exposed TB disease at time t
$I(t)$	The TB infected at time t
$N(t)$	The total population at time t

Table 4 The description of the parameters on the $SEIS$ TB model.

Parameter	Description	Unit
μ	The natural death rate	$\frac{People}{time}$
β	The rate of transmission	$\frac{People}{time}$
γ	The rate of recovered	$\frac{People}{time}$
α	The progression rate from E to I	$\frac{People}{Year}$

Similarly, all parameters are assumed to be positive. The model equation describing the *SIS* type transmission model for TB dynamics is therefore given by

$$\frac{dS}{dt} = \mu N - \frac{\beta SI}{N} - \mu S + \gamma I, \tag{3}$$

$$\frac{dE}{dt} = \frac{\beta SI}{N} - (\mu + \alpha)E, \tag{4}$$

(5) $\frac{dI}{dt} = \alpha E - (\mu + \gamma)I,$

where $N = S + E + I$. The initial conditions are $S(0) = S_0 > 0, E(0) = E_0 \geq 0$, and $I(0) = I_0 \geq 0$.

4. PARAMETER ESTIMATION

Here, the optimal parameter values are sought from the mathematical models of *SIS* and *SEIS* for the TB transmission. The estimation is carried out using genetic algorithms with the aim of minimizing the performance index in the optimal control theory with the parameters contained in the model being constant and the parameter values ranging from 0 to 1.

The performance index of the SIS and $SEIS$ types of the TB model are thus defined

(6) $$\min J_s = \frac{1}{2}\int_0^{t_f}\left(I(t) - I_{\sim}^{data}(t)\right)^2 + \beta^2 + \gamma^2\, dt$$

(7) $$\min J_e = \frac{1}{2}\int_0^{t_f}\left(I(t) - I_{\sim}^{data}(t)\right)^2 + \beta^2 + \gamma^2 + \alpha^2\, dt$$

respectively, with $t_f = 1$ (t_f being a final time). To obtain the optimal parameter values, it is necessary to minimize the values of J_s and J_e which are at the same time to obtain the difference between the I estimate of the TB model and the $I_{\sim}^{data}$. Here, $I_{\sim}^{data}$ represent the confirm of TB infected data. We use the TB infected cases reported from the year 2002 to 2017 in East Java, Indonesia. In this study, the parameter of natural death rate (μ) is obtained from the demographic conditions of the East Java province population. The parameter μ is calculated as the inverse of the life expectancy of the East Java Province in year 2017. According to [15], the life expectancy of the East Java in year 2017 is 70.80 years. Hence, the value of μ is calculated to be $\mu = \frac{1}{70.80}$.

The steps to perform parameter estimation are as follows:

i. Enter the number of population
ii. Input the crossover rate value
iii. Input mutation rate value

iv. Determine the number of iterations

v. Generating random population data

vi. Entering real data and parameter initiation

vii. Specifies the upper and lower limits with values between 0 to 1

viii. Calculating the fitness value by performing the Runge-Kutta process of order 4 by minimizing the value of the performance index

ix. Calculating relative fitness to determine prospective bloodstocks to determine bloodstocks that will carry out the crossover process

x. Carry out the crossover process and calculate fitness to enter the mutation process

xi. Then calculate the best fitness to determine the next iteration process

xii. The iteration will stop after reaching the number of iterations specified at the beginning and calculating the MMRE (Mean Magnitude Relative Error) to carry out the process of fitting the estimated data with real data.

The estimation results of the SIS and $SEIS$ types of the TB model can be seen in the Table 5 and Table 6, respectively. Furthermore, a comparison simulation between solution of the SIS and $SEIS$ types for the TB model and the real data from East Java Province is depicted in Figure 1 and Figure 2, respectively.

Table 5 Parameter values of the SIS type model.

Parameter	Parameter Value	Unit	Source
β	0.9546	$\frac{People}{Year}$	Estimation Results
γ	0.8782	$\frac{People}{Year}$	Estimation Results
μ	$\frac{1}{70.80}$	$\frac{People}{Year}$	[15]

Table 6 Parameter values of the $SEIS$ type model.

Parameter	Parameter Value	Unit	Source
β	0.1211	$\frac{People}{Year}$	Estimation Results
γ	0.0124	$\frac{People}{Year}$	Estimation Results
α	0.9024	$\frac{People}{Year}$	Estimation Results
μ	$\frac{1}{70.80}$	$\frac{People}{Year}$	[15]

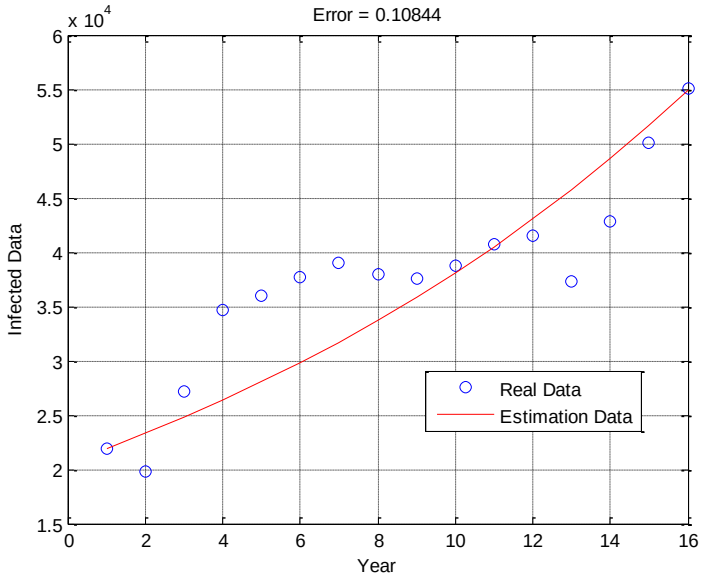

Figure 1. Fitted curve between the TB data and SIS-type model

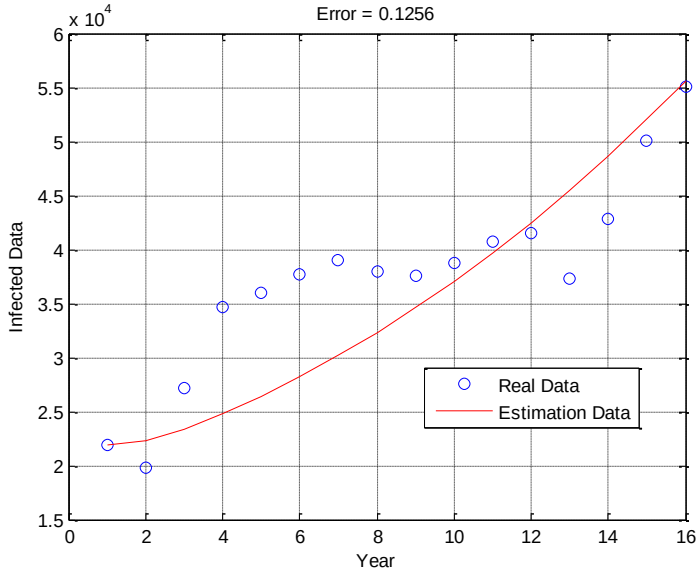

Figure 2. Fitted curve between the TB data and $SEIS$-type model

Figure 1 and Figure 2 show that the real TB data and the estimated data on TB patients in East Java Province are a good fit. It is increasing every year, per the real-life scenario of TB infection dynamics presently in East Java Province of Indonesia.

5. SENSITIVITY ANALYSIS OF THE PARAMETER

To determine the sensitivity analysis of the model parameters, we begin by calculating the basic reproduction number of the SIS and $SEIS$ type model using NGM (Next-Generation Matrix). The basic reproduction number is the expected number of secondary cases per primary case in a susceptible population [16]. The model SIS have a disease-free equilibrium (DFE) $E_0 = (N, 0)$, while the DFE of *SEIS* model is given by $E^0 = (N, 0,0)$. By using NGM approach, the basic reproduction numbers R_{0s} and R_{0e} of the SIS, and $SEIS$ model, respectively as follows:

$$R_{0s} = \frac{\beta}{\mu+\gamma} \text{ and } R_{0e} = \frac{\beta\alpha}{(\mu+\alpha)(\mu+\gamma)}.$$

Based on the results of parameter estimation are presented in Tables 5 and 6, the value of the basic reproduction numbers for the SIS and $SEIS$ models are R_{0s}= 1.0698 and R_{0e} = 4.4953, respectively. Hence, the basic reproduction number for both models are greater than one, which means that the spread of TB disease in East Java will continue to exist in the population. Therefore,

it is necessary to carry out various kinds of interventions by the government and public awareness in order to control TB disease in East Java province, Indonesia.

Next, the sensitivity analysis was performed on the basic reproduction numbers (R_{0s} and R_{0e}) to determine the most influential parameters in the spread of TB. The sensitivity analysis is calculated using the following formulation as stated in [17]

$$e_m = \left(\frac{\partial R_0}{\partial m}\right) \times \frac{m}{R_0} \tag{8}$$

where m depicts the related parameter, e_m represents the sensitivity index of each parameter, and R_0 describes the basic reproduction number. The sensitivity indices of R_{0s} and R_{0e} associated with the parameters can be computed in a similar way as in (8). Based on the parameter values in Table 5 and 6, the sensitivity indices of our model parameters are set in Table 7 and Table 8, respectively.

Table 7 Sensitivity index of the parameter for SIS type model.

Parameter	Sensitivity Index (R_{0s})
β	1
μ	-0.01583
γ	-0.98417

Table 8 Sensitivity index of the parameter for $SEIS$ type model.

Parameter	Sensitivity Index (R_{0e})
β	1
α	0.01541
μ	-0.54791
γ	-0.46749

It can be seen observed in Tables 7 and 8, that the transmission rate due to the interaction between the human population susceptible to TB and the human population infected with TB (β) is the most influential parameter and the rate of transmission because there is temporary immunity

(γ) occupies the second position after the parameter β.

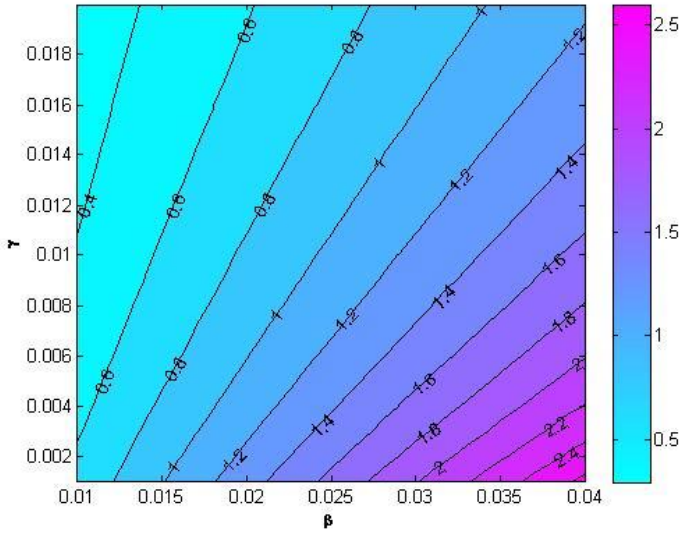

Figure 3. The behavior of R_{0s} to the parameters β and γ for the SIS type model.

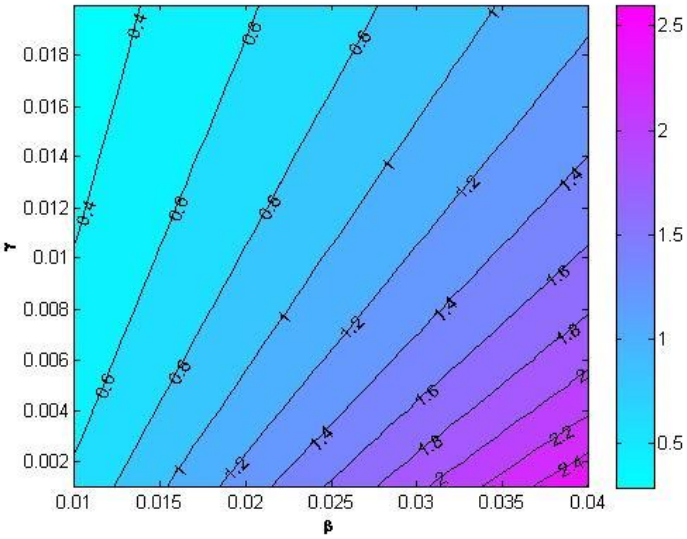

Figure 4. The behavior of R_{0e} to the parameters β and γ for the $SEIS$ type model.

Based on contour plot in Figure 3 and Figure 4, it is found that the basic reproduction numbers $(R_{0s}$ and $R_{0e})$ will increase in proportion to the results of the sensitivity analysis in Table 7 and Table 8, respectively. The parameter β has a positive relation and will decrease in proportion to the parameter γ which has a negative relation.

5. NUMERICAL SIMULATION

In this section, we examine the numerical simulation of the TB spread using the SIS and $SEIS$ types of models. We employ the parameters displayed in Tables 5 and 6, respectively. According to the Indonesia Bureau of Statistics, the population of East Java province in the 2002 census is estimated as 35,301,796 [18]. We take the total initial population as $N(0) = 35{,}301{,}796$. The initial infected as supplied in the TB data is $I(0) = 21918$. Hence, the initial values of the SIS type model are $\big(S(0), I(0)\big) =$ (35279878; 21918). For the $SEIS$ type model, we assume that the initial of exposed population $E(0) = 40000$. Further, the initial conditions of $SEIS$ type model is given by $\big(S(0), E(0), I(0)\big)$ =(35239878; 40000; 21918). The dynamical behavior of the SIS and $SEIS$ type models are displayed in Figures 5 and 6, respectively. Figures 5 and 6, shows that the number of infectious humans tends to decrease as the parameter β decreases. However, when the value of the parameter β increases, the number of infectious human populations will also increase.

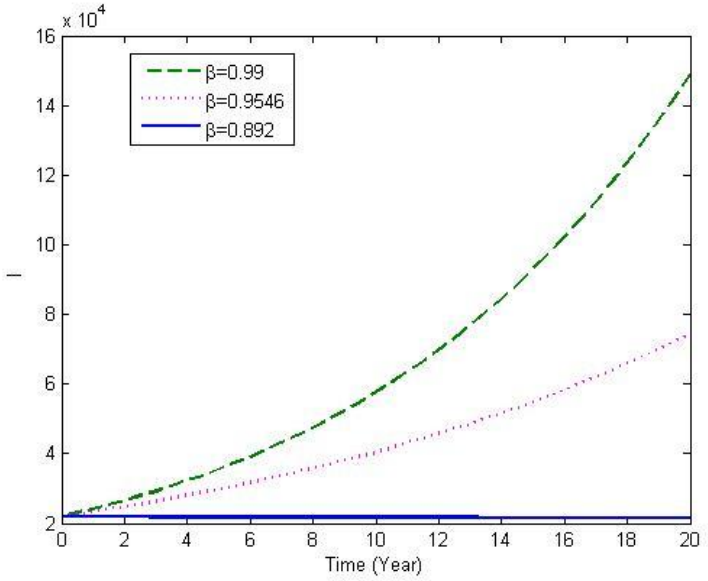

Figure 5. Dynamic of infected population for different values of β using SIS type model.

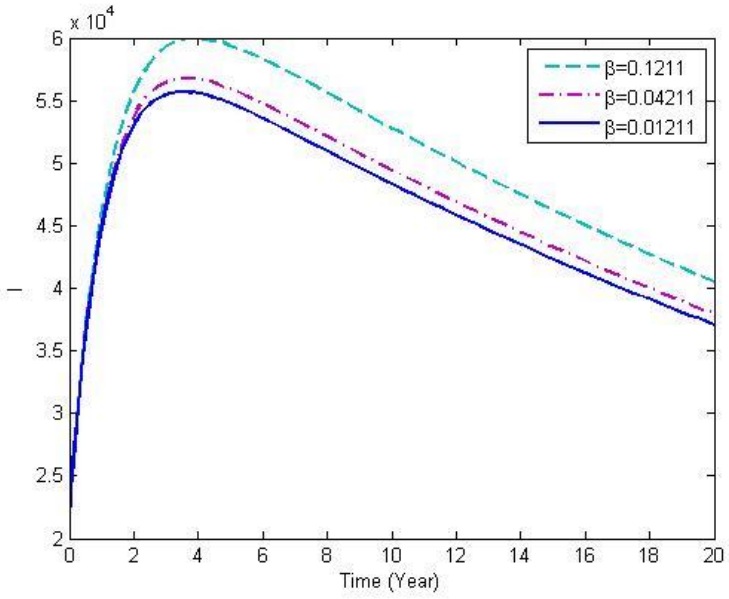

Figure 6. Dynamic of infected population for different values of β using $SEIS$ type model.

7. CONCLUSION

This study presented the parameter estimation using the performance index approach in the optimal control theory and genetic algorithm of SIS and $SEIS$ types on the dynamic of TB transmission. We used the TB data from the year 2002 to 2017 in East Java, Indonesia. Furthermore, from the parameter estimation results for the two TB models, the values of the basic reproduction numbers are greater than unity, which means that there is an endemic condition for the spread of TB in East Java Province. The sensitivity analyzes of the basic reproduction numbers were performed and sensitivity indices of various model parameters were obtained. The result of the sensitivity model shows that the most sensitive parameter is the transmission rate β. Hence, to control and reduce TB infection, it is prominent to minimize contact with TB-infected individuals by decreasing the value of β.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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