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Annals of Mathematical Modeling, 2 (2), 2022, 67-75

Mathematical analysis of SLIPR infectious model without vaccination: A case study of measles outbreaks

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Abstract: A five-compartment epidemiological model is analyzed to illustrate the dynamics of infectious diseases. In this model, the population is compartmented into susceptible, latent, infected, post-infection, and recovered. The model is a system of ordinary differential equations, where the stability is analyzed using Routh's stability criterion. Two equilibrium points; disease-free and endemic equilibrium are stable but depends on the basic reproduction number. Derivation of the basic reproduction number is given using the next-generation method. This study ended by providing a case study of measles outbreaks before the effective implementation of the vaccine. The analysis of data fitting is done by using the Simulated Annealing minimization routine and the error value is 0.0406.

Keywords: epidemiological model; basic reproduction number; stability analysis; data fitting; simulated annealing

INTRODUCTION

There are a variety of models to study the spread of pathogenic disease. One of the basic approaches to simulate the disease outbreak is by using a compartmental model. In this model, multiple compartments that allow individuals to jump between compartment is considered. The famous model in studying infectious disease is the SIR model. The model consists of three compartments, namely the susceptible, infected, and recovered individuals. The susceptible individuals are people that have never in contact with that particular infectious disease. When contact happens, they will become infected individuals and able to infect others. The recovered individuals are people who have recovered from the disease. This SIR model was introduced by Kermack and McKendrick and has played a major role in mathematical epidemiology (Brauer, 2005).

In this paper, we add another two compartments, which are the class of latent and post-infection. The latent state is a latent period of an infectious disease. Latent means the presence of a pathogen in the body without causing diseases and it as the period between a susceptible individual to become an infected individual (Eisenberg, Brookhart, Rice, Brown,& Colford Jr, 2002). The assumption of the latent class is the susceptible individuals do not immediately become infected individuals after close contact with infected individuals. While the post-infection state is a condition where the infected individuals are no longer can cause infection but may have several sicknesses due to the infection before fully recovered (Oswald et al., 2007). The model formulation is explained in the following section.

Suppose a population density model contains a five-compartmental state, namely susceptible ($\bar{S}$), latent ($\bar{L}$), infected ($\bar{I}$), post-infection ($\bar{P}$), and recovered ($\bar{R}$) individuals. The total population density is given as $\bar{N}$(t) = $\bar{S}$(t) + $\bar{L}$(t) + $\bar{I}$(t) + $\bar{P}$(t) + $\bar{R}$(t). The $\bar{S}\bar{L}\bar{I}\bar{P}\bar{R}$ model is formulated as follows:

$$\left.\begin{aligned}
\frac{d\bar{S}}{dt} &= \mu\bar{N} - \beta(\bar{I})\bar{S} - \mu\bar{S} + \psi\bar{R},\\
\frac{d\bar{L}}{dt} &= \beta(\bar{I})\bar{S} - \mu\bar{L} - \eta\bar{L},\\
\frac{d\bar{I}}{dt} &= \eta\bar{L} - (\mu+\delta)\bar{I} - \sigma\bar{I} - \mathrm{P}\bar{I},\\
\frac{d\bar{P}}{dt} &= \sigma\bar{I} - \mu\bar{P} - \rho\bar{P},\\
\frac{d\bar{R}}{dt} &= \rho\bar{P} + \mathrm{P}\bar{I} - \mu\bar{R} - \psi\bar{R},
\end{aligned}\right\} \qquad (1)$$

where μ is the population growth rate, $\beta(I)$ is the force of infection with respect to infected individuals, ψ is the immunity decay rate and be susceptible individuals, η is the rate of the latent individuals leave to infected state, δ is the disease mortality rate, σ is the infected individuals leave to post-infection state, ϑ is the recovery rate of infected individuals into the recovered state, and ρ is the rate of post-infection individuals leave into recovered individuals. In our case study on the measles outbreak, parameter ψ will vanish due to permanent immunity formed in the human body after measles illness (Buchanan & Bonthius, 2012).

In this paper, we use the function of the force of infection as $\beta(I) = \alpha\gamma\bar{I}/\bar{N}$, where α is the contact rate, γ is the chance of pathogen transmissibility. Model (1) can be simply transformed into terms of the population proportion. To do that, we rescale model (1) by

$$S = \frac{\bar{S}}{\bar{N}}, L = \frac{\bar{L}}{\bar{N}}, I = \frac{\bar{I}}{\bar{N}}, P = \frac{\bar{P}}{\bar{N}}, R = \frac{\bar{R}}{\bar{N}}.$$

Then, the population proportion of model (1) can be written as:

$$\left.\begin{aligned}
\frac{dS}{dt} &= \mu - \alpha\gamma IS - \mu S + \psi R,\\
\frac{dL}{dt} &= \alpha\gamma IS - \mu L - \eta L,\\
\frac{dI}{dt} &= \eta L - \theta I,\\
\frac{dP}{dt} &= \sigma I - \mu P - \rho P,\\
\frac{dR}{dt} &= \rho P + \mathrm{P}I - \mu R - \psi R,
\end{aligned}\right\} \qquad (2)$$

where $\theta = \mu + \delta + \sigma + \vartheta$. Due to the purpose of monitoring the human population, the models satisfy the condition of the positivity of states at time $t \geq 0$ with non-negative parameters. Measles outbreaks: an overview

Measles, caused by the measles virus is a viral respiratory infection that attacks the immune system and very contagious to any person that does not have immunity (Leung, Hon, Leong,& Sergi, 2018). It spread through person-to-person transmission mode. Measles can affect all ages but it can easily affect the children who are below 10 years old. Measles fever may only happen once in a lifetime. When someone recovered from this illness, natural immunity will form in their body (Buchanan & Bonthius, 2012). Someone who had been affected within 1 or 2 days did not show any symptoms until 4 days later, rashes appear. For children and babies, it is the first and worst fever that possibly can lead to blindness, deafness, or impaired vision. The symptoms of measles are high body temperature, skin rash, coughing, and sore throat, muscle aches, watery eyes, and sensitive eyes to light. Measles viruses keep active in the air or on objects and surfaces in a close area for up to 2 hours (Filia et al., 2015).

Measles illness is largely preventable by measles-mumps-rubella (MMR) vaccines. Vaccines are a great tool that can eliminate the disease from the map. As shown in Figure 1, a dramatically decreasing number of measles incidence can be observed since the effective vaccination program. In Malaysia, the measles vaccine is introduced in 1982 (Chen & Lam, 1985), but only in 1987 onwards, the vaccine covers more than half of the susceptible population.

Children will get two doses of MMR vaccine when they are 9 months old and another dose when they are 12 months old (Kusnin, 2017). Once someone already encounters measles at an early age, they do not have to take the vaccine but if they are unsure, it is advisable to take the vaccine. Some cases arise nowadays are due to anti-vax individuals that refuse to take a vaccine for their children (Helps, Leask, Barclay,& Carter, 2019).When people are not vaccinated, infectious diseases that have become uncommon quickly reappear. If we stop vaccination, diseases will return even though with better hygiene, sanitation, and safe water. Vaccine misinformation is a major threat to global health that could reverse decades of progress made in tackling preventable diseases.

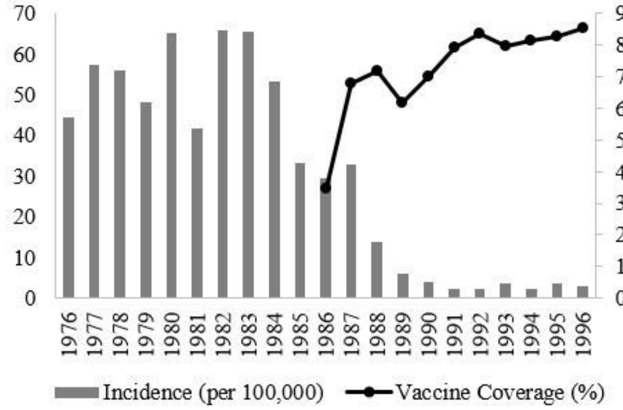

Figure 1: A selected case study: Measles infectious data in Malaysia(Kusnin, 2017).

In this work, we analyzed a general model of infectious disease that contains five-compartmental states. The work is separated in two ways. First is by analyzing the stability of the model and its basic reproduction number. The second is involving a case study of the model dynamics towards measles incidence before the vaccination strategy cover more than half of the susceptible population (1976 – 1986). Even though measles infection is no longer a global threat nowadays, we are interested to investigate the population dynamics of the model (1) compared to the actual data.

In the following, we briefly explained the mathematical methods used in this paper. Then, we discussed the mathematical analysis of the model using any appropriate value of parameters. A case study is done by using the incidence data of measles illness before the vaccination program effectively covers half the susceptible individuals. An infectious model with a vaccination strategy will be considered by the authors in another work. Lastly, the concluding section summarizes this study.

METHODOLOGY

This paper discussed the dynamics of model (2) with three aspects of methodologies, which is the next-generation method, Routh's stability criterion, and Simulated Annealing minimization routine.

Next-generation method

The next-generation matrix is a method that commonly use to deal with complicated compartmental epidemic models(Diekmann, Heesterbeek,& Roberts, 2010). It is used to derive the basic reproduction number, R_0 for an infectious disease model. R_0 is the fundamental threshold of any infectious disease model, either the disease will eventually eliminate or consistently persist throughout the population.

The essential step in the next-generation method is the identification of states for the gains and losses terms. Gains terms are from the relevant states for which an infection event increases, while losses terms are from the relevant states for which the current or future infector disappears or loss from these states. Then, the diseases free equilibrium point is determined for evaluating matrix **F** and **V**. The disease-free equilibrium point is quite easy to obtained and usually by intuition with reasonable assumption. Matrix **F** is constructed by the gains terms of each state that differentiated with respect to each state, while matrix **V** is by the losses terms that differentiated with respect to each state. Then, both matrices are evaluated at the disease-free equilibrium and compute $\mathbf{F}\cdot\mathbf{V}^{-1}$. R_0 is determined by the spectral radius or the dominant eigenvalue of $\mathbf{F}\cdot\mathbf{V}^{-1}$ (Diekmann, Heesterbeek,& Roberts, 2010).

Routh's stability criterion

By following other comprehensive texts (Anagnost & Desoer, 1991; Thowsen, 1981), suppose a generic characteristic polynomial in the form of:

$$a_0\lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2}+\ldots+a_{n-1}\lambda^1 + a_n, \quad (3)$$

where $a_0 \neq 0$ and $a_n > 0$. The Routh array is constructed in order to employ Routh's stability criterion (Sivanandam & Deepa, 2007). Routh array is defined as follows:

$$\begin{array}{c|ccccc}
\lambda^{n} & a_0 & a_2 & a_4 & a_6 & \cdots \\
\lambda^{n-1} & a_1 & a_3 & a_5 & a_7 & \cdots \\
\lambda^{n-2} & b_1 & b_2 & b_3 & b_4 & \cdots \\
\lambda^{n-3} & c_1 & c_2 & c_3 & c_4 & \cdots \\
\lambda^{n-4} & d_1 & d_2 & d_3 & d_4 & \cdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \\
\lambda^{0} & & & & &
\end{array}$$

The coefficient of b_i, c_i, d_i, and the rest is calculated in this following manners:

$$\begin{array}{lll}
b_1 = \dfrac{a_1a_2 - a_0a_3}{a_1}, & c_1 = \dfrac{b_1a_3 - a_1b_2}{b_1}, & d_1 = \dfrac{c_1b_2 - b_1c_2}{c_1}, \\
b_2 = \dfrac{a_1a_4 - a_0a_5}{a_1}, & c_2 = \dfrac{b_1a_5 - a_1b_3}{b_1}, & d_2 = \dfrac{c_1b_3 - b_1c_3}{c_1}, \\
b_3 = \dfrac{a_1a_6 - a_0a_7}{a_1}, & c_3 = \dfrac{b_1a_7 - a_1b_4}{b_1}, & \vdots \\
\vdots & \vdots &
\end{array}$$

and goes on until the n^{th} row of the array complete, where the cross multiplication is from the previous two rows. These coefficients need to be generated until all subsequent coefficients are zero. Therefore, the first column in the Routh array is observed to determine the stability of the system.

The stability criteria are described in the following condition: (i) if all elements are positive, the system is stable (all the roots lie on the left half of the λ-plane); (ii) if there are negative elements of sign changes from positive to negative or otherwise, the system is unstable (there are roots lie on the right-half of the λ-plane). Note that the number of roots on the right-half of the λ-plane is equal to the number of sign changes in the Routh array. There are some special cases in computing the Routh array which is row zeros element and zero first-column elements.

Simulated annealing optimization routine

Simulated annealing as a global optimization was first introduced in the early 1980s by Kirkpatrick, Gelatt,& Vecchi (1983). The simulated annealing algorithm mimics the annealing process: a process by which a solid in a heat bath melts when the temperature of the heat bath is increased to a maximum value. At high temperatures, all particles in the liquid-phase move randomly in high energy. The temperature of the heat bath is then decreased slowly until the particles arrange themselves in the low energy state of the solid. Simulated annealing is a powerful technique in minimizing or maximization an objective function, which has been applied in many different disciplines, for example in model data fitting by minimizing the error between model simulation and actual data.

The simulated annealing algorithm accepts all points that lower the objective function and it also accepts all points that make the objective function go up with probability ω. The probability of accepting downhill or uphill moves is given by:

$$\omega = \begin{cases} 1 & \text{if} \quad \Delta\Phi < 0, \\ exp(\frac{-\Delta\Phi}{\Theta}) & \text{if} \quad \Delta\Phi > 0, \end{cases} \tag{4}$$

where $\Delta\Phi$ is the increase in objective function Θ. In this way, the algorithm does not stuck in local minima, which is a major advantage of simulated annealing over other methods(Busetti, 2003). We use the *simulannealbnd* routine in the procedure of data fitting.

RESULTS AND DISCUSSION

Stability analysis and R_0

An infectious model deals with two important points, namely the disease-free equilibrium (ε_0) and the endemic equilibrium (ε_1). Finding the equilibria is essential to understand long-term behaviour without the need to analytically solve the model (May, 1976). At equilibrium, the derivatives of model (2) are set equal to zero:

$$\left.\begin{aligned} &\mu - \alpha\gamma IS - \mu S + \psi R = 0, \\ &\alpha\gamma IS - \mu L - \eta L = 0, \\ &\eta L - \theta I = 0, \\ &\sigma I - \mu P - \rho P = 0, \\ &\rho P + \mathrm{P} I - \mu R - \psi R = 0. \end{aligned}\right\} \tag{5}$$

Equilibrium needs to satisfies the condition of Eq. (5). Note that the equilibrium ε_0 exists in a condition of infected individuals to eventually terminated (I = 0) and the entire population consists of only susceptible individuals (Bawa, Abdulrahman, Jimoh,& Adabara, 2013). Thus, $\varepsilon_0 = (1, 0, 0, 0, 0)$. While analyzing $\varepsilon_1 = (S_1, L_1, I_1, P_1, R_1)$ is a little bit tricky.

In an endemic situation, the disease is permanently existing in the population ($I_1 \neq 0$). According to Jones (2007), the critical proportion of susceptible individuals to occur an epidemic is expressed as $S_1 = R_0^{-1}$, where R_0 is the basic reproduction number. Therefore, the next-generation matrix is employed to compute R_0. Note that the relevant states are L and I. The terms involve in gains and losses to L is $\alpha\gamma IS$ and $(\mu L + \eta L)$, respectively, while the terms involve in gains and losses to I is 0 and $(-\eta L + \theta I)$, respectively. Then, the matrix **F** and **V** are computed at ε_0 and expressed as follows:

$$\mathbf{F} = \begin{bmatrix} 0 & \alpha\gamma \\ 0 & 0 \end{bmatrix}, \mathbf{V} = \begin{bmatrix} \mu + \eta & 0 \\ -\eta & \theta \end{bmatrix} \tag{6}$$

Then, R_0 is determined by evaluating the spectral radius of $\mathbf{F}\cdot\mathbf{V}^{-1}$ or the dominant eigenvalue that satisfies the determinant of $\mathbf{F}\cdot\mathbf{V}^{-1}$. Thus, the R_0 is expressed as:

$$R_0 = \frac{\alpha\gamma\eta}{(\eta + \mu)\theta}. \tag{7}$$

For $\varepsilon_1 = (S_1, L_1, I_1, P_1, R_1)$, there exist a unique equilibrium with $S_1 = [\theta(\eta+\mu)/\alpha\gamma\eta]$. It is necessary for ε_1 to exist such that $0 < S_1 = R_0^{-1} < 1$, or equivalently, $R_0 > 1$. On contrary, $R_0 < 1$ is sufficient for ε_0 to exist. In a nutshell, R_0 is a threshold parameter that determines the coexistence on the type of equilibria. Jacobian matrix is then evaluated at ε_0 to examine the local stability as ε_0 is of the interest in eliminating the epidemic. The Jacobian matrix at ε_0 is written as:

$$J(\varepsilon_0) = \begin{bmatrix} -\mu & 0 & -\alpha\gamma & 0 & \psi \\ 0 & -\mu-\eta & \alpha\gamma & 0 & 0 \\ 0 & \eta & -\theta & 0 & 0 \\ 0 & 0 & \sigma & -\mu-\rho & 0 \\ 0 & 0 & \mathrm{P} & \rho & -\mu-\psi \end{bmatrix} \tag{8}$$

After some algebraic manipulation, the characteristic polynomial with eigenvalue λ is expressed as follows:

$$\begin{gathered}(-\lambda - \mu)\cdot(-\alpha\gamma\eta + \eta\theta + \eta\lambda + \theta\lambda + \lambda^2 + \theta\mu + \lambda\mu)\cdot \\ (-\lambda - \mu - \rho)\cdot(-\lambda - \mu - \psi) = 0. \end{gathered} \tag{9}$$

From the characteristic polynomial, the eigenvalues may be negative, positive, zero, or any combinations of these alternatives. Therefore, the equilibrium could be stable, unstable, or saddle which is depending on the values of parameters. Analysis continued with numerical experimentation with a set of parameters value.

To examine ε_0 for further interpretation, the characteristic polynomial Equation (9) is analyzed using the Routh stability criterion. On the purpose of the existence of ε_0, the parameter settings with guaranteed $R_0 < 1$ are as follows

$$\left.\begin{aligned} &\mu = 0.035, \alpha = 0.014, \gamma = 0.9, \psi = 0.084, \rho = 0.0063, \\ &\eta = 0.049, \delta = 0.0001, \sigma = 0.0035, \mathrm{P} = 0.0042, \\ &S(0) = 0.5, L(0) = 0.1, I(0) = 0.3, P(0) = 0.025, R(0) = 0.075. \end{aligned}\right\} \quad (10)$$

By substituting the value of parameter into Eq. (9), yield:

$$\lambda^5 + 3.221 \times 10^{-1}\lambda^4 + 3.8267 \times 10^{-2}\lambda^3 + 2.0882 \times 10^{-3}\lambda^2$$
$$+5.3153 \times 10^{-5}\lambda + 5.1223 \times 10^{-7} = 0,$$

Then, using the Routh's stability criterion in Section 2.2 to analyze Equation above. The constructed Routh array is as follows:

λ^5	1	3.8267×10^{-2}	5.3153×10^{-5}
λ^4	3.221×10^{-1}	2.0882×10^{-3}	5.1223×10^{-7}
λ^3	3.1784×10^{-2}	5.1563×10^{-5}	
λ^2	1.5656×10^{-2}	5.1223×10^{-7}	
λ^1	4.1164×10^{-5}		
λ^0	5.1223×10^{-7}		

From the Routh array, there are no sign changes in the first column. According to the Routh stability criterion, the system is stable at ε_0.

Next, model simulation using the aid of *ode45* Matlab built-in function is carried out by using parameter value in (10).

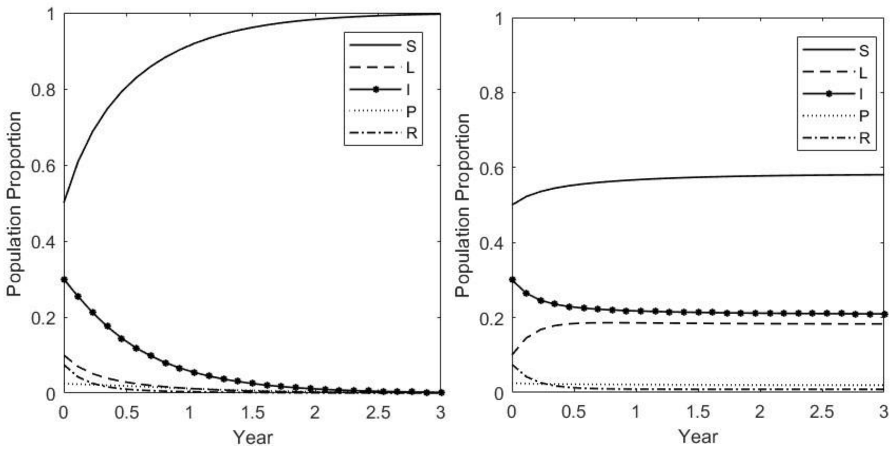

Figure 3: Simulation for α = 0.014 week^{-1} (left) and α = 0.14 week^{-1} (right).

For $R_0 = 0.1717 < 1$, the model simulation is provided in Figure 3 (left). As shown in Figure 3 (left), model (2) reach ε_0 as t increases. Suppose parameter α is increased to 0.14 week^{-1}, R_0 become 1.7173 which is greater than 1. As shown in Figure 3(right), the system tends to ε_1 for $R_0 > 1$ in 3 years. As $t \to \infty$, $\varepsilon_1 = (0.5823, 0.1824, 0.2089, 0.0194, 0.0084)$ where $S_1 = 0.5823 = 1/R_0$.

Data fitting of measles outbreaks: a case study

To do data fitting, an additional ODE is introduced to collect the infected data of measles per time. Suppose $\bar{I}_{cum}(\mathrm{t})$ as the number of cumulative measles infectious individuals at time t, then the ODE is defined as follows:

$$\frac{d\bar{I}_{\mathrm{cum}}}{dt} = \eta\bar{L}. \quad (11)$$

Thus, the number of cumulative infected individuals keeps increase over time. Due to the large number of $\bar{I}_{cum}$, a rescale number of $\log_{10}(1+\bar{I}_{cum})$ is introduced. Hence, the objective function to minimize the error between model and actual data is expressed as follows:

$$\mathrm{Error} = \sum_{i=0}^{n}\left[log_{10}\left(1+\bar{I}_{\mathrm{cum}}(i)\right) - log_{10}\left(1+\bar{I}_{\mathrm{cum,data}}(i)\right)\right]^2. \quad (12)$$

This error function is minimized by using the Simulated Annealing minimization routine. The result is summarized in Table 3.

Some of the parameters are obtained from a known source. The total population in 1976 is approximately 12.46×10^6 with a growth rate of 2.52% (Worldometers, 2019). Measles infection affects children only, thus we consider $S(0) = 2 \times 10^6$, and the parameter μ is set to 0.0252 year^{-1}. Parameter ψ is vanished due to a measles body immune will naturally be produced after recovered (Buchanan and Bonthius, 2012). The rest of the parameters are estimated within the parameter interval. These estimated values give $R_0 = 1.2889$, hence model (2) is stable at ε_1. However, when the vaccination program has effectively covered for more than half the susceptible population in 1987, the measles cases has decreased significantly. The result of our case study is presented in Figure 5, where both simulated and actual data are expressed in logarithmic scale.

As shown in Figure 4, the model has successfully fit with the actual measurement of measles outbreaks with an error value of 0.0406. This is the best value obtained by the Simulated Annealing minimization routine. With these results, the mathematical analysis of this work concluded here.

Table 3: The estimated parameter of the data fitting procedure.

Interval		Source	Value
Initial Condition	$S(0)$	Fixed	2×10^6
	$L(0)$ in $[4.5, 5] \times 10^3$	Estimated	4.7131×10^3
	$I(0)$	Data	$I(1976)$
	$P(0)$ in $[1, 1.5] \times 10^3$	Estimated	1.2858×10^3
	$R(0)$	Fixed	0
Parameter	μ	Fixed	0.0252 year^{-1}
	α in [0.1, 1]	Estimated	0.9976 year^{-1}
	γ in [0, 1]	Estimated	0.9972
	ψ	Fixed	0
	η in [0.1, 1]	Estimated	0.9925 year^{-1}
	δ in [0.1, 1]	Estimated	0.1414 year^{-1}
	σ in [0.1, 1]	Estimated	0.2106 year^{-1}
	ϑ in [0.1, 1]	Estimated	0.3755 year^{-1}
	ρ in [0.1, 1]	Estimated	0.9709 year^{-1}

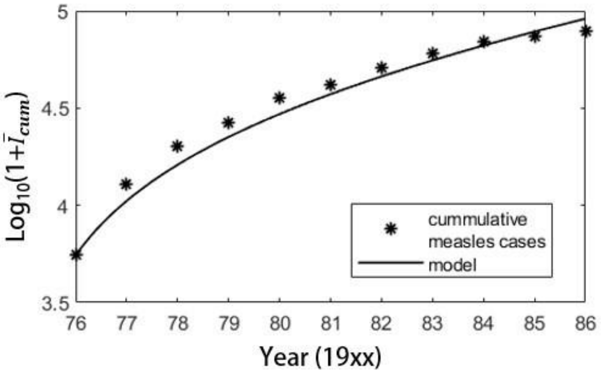

Figure 4: Data fitting using the scaled value of cumulative measles cases.

CONCLUSION

The traditional SIR model is analyzed by adding two compartments, namely latent and post-infection state. From this study, the connection of R_0 as a threshold is analyzed, where $R_0 < 1$ means the diseases will be extinct in the population implies the model is stable at ε_0 but unstable at ε_1. Whereas, a vice-versa case occurs in condition $R_0 > 1$. In the case study of measles outbreaks, the model able to match the incidence data with a reasonable error value. For future research, the recommendation that can take into account is by studying the vaccination case infectious model with more detailed data. Overall, the exercise discussed in this work could provide a framework to develop a generic model for predicting the incidence of other contagious pathogenic diseases, such as severe acute respiratory syndrome, Ebola, tuberculosis, influenza, Covid-19, and other emerging infectious diseases.

ACKNOWLEDGEMENT

This work was supported by Ministry of Education Malaysia and Universiti Teknologi Malaysia. The second author would like to thank Universiti Malaysia Terengganu for the research facilities.

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