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MATHEMATICAL MODELLING OF INFECTIOUS DISEASE MODELS

MASTER DEGREE THESIS

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THESIS ACCEPTANCE AND APPROVAL

This thesis entitled "MATHEMATICAL MODELLING OF INFECTIOUS DISEASE MODELS" submitted by WALI HASSAN MOHAMMED in partial fulfillment of the requirements for the degree of Master in Mathematics Department, Siirt University by,

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THESIS NOTIFICATION

I hereby declare that this thesis is my unique authorial work, which I have worked out by my own. Every information bases, references and literature used or excerpted through explanation of this work are correctly cited and listed in complete reference to the owing cause.

Wali Hassan Mohammed

SİİRT-2017

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LIST OF SYMBOLS

Symbols		**Explanation**
S	:	Susceptible
V	:	Vaccinated
E_1	:	Latent undetectable
E_2	:	Latent detectable
I	:	Infectious
J	:	Isolated
D	:	Individuals
R	:	Recovered
N	:	total population

ÖZET

YÜKSEK LİSANS

BULAŞICI HASTALIK MODELLERİNİN MATEMATİKSEL MODELLENMESİ

Wali Hassan MOHAMMED

Siirt Üniversitesi Fen Bilimleri Enstitüsü
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ÖZET

Bu tezi sekiz bölüme ayırdık. Bu tezin ilk bölümü matematiksel modelleme ve modelleme süreci hakkında bir sunum verir. İkinci bölümü kimyasal kinetik ve kütleler etki yasasının genel denklemini sunar. Duyarlılık analizinin tekniği ve değişkenlerin ölçeği sırasıyla üçüncü ve dördüncü bölümde açıkça ifade edildi. Daha sonra beşinci bölümde bu çalışmada sayısal simülasyonlar için kullanılan yazılım araçlarını verdik. Bundan sonra altıncı bölümde SI, SIS ve SIR gibi bulaşıcı hastalık modellerini altıncı bölümde tanımladık. Yedinci bölümde yerel duyarlılık analizi ve nüfusların sayısı üzerine bazı sayısal simülasyonlarla birlikte Ebola virüsü hastalığı için matematiksel modellemeyi verdik. Son olarak sekizinci bölümde sonuçlar ve tavsiyeler verildi.

Anahtar Kelimeler: Matematiksel modelleme, Kimyasal kinetik, bulaşıcı hastalık modelleri, sayısal simülasyonlar, duyarlılık analizi.

ABSTRACT

MS. THESIS

MATHEMATICAL MODELLING OF INFECTIOUS DISEASE MODELS

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The Graduate School of Natural and Applied Science of Siirt University

The Degree of Master of Science

In Mathematics

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We divided this thesis into the eight sections.

The first section of this thesis gives an introduction regarding to mathematical modeling and modeling process.

The second section presents a general equation of chemical kinetics and mass action law. The technique of sensitivity analysis and scaling of variables are introduced clearly in the third and fourth section, respectively.

Then, in section five we give the software tools that used for computational simulations in this study.

After that, we define some infectious dieses models such as Susceptible-infected (SI), Susceptible-infected- Susceptible (SIS) and Susceptible-recovered (SIR) model in section six.

In section seven, we give the mathematical modeling for the Ebola virus disease (EVD) with some computational simulations based on the number of populations and local sensitivity analysis.

Finally, conclusions and recommendations are given in section eight.

Keywords: Mathematical Modeling, Chemical Kinetics, Infectious disease models, Computational Simulations, Sensitivity analysis.

1. INTRODUCTION

A mathematical model is a mathematical object established on a real situation and produced in the hope that its mathematical behavior resembles the real behavior. Mathematical modeling is the scientific art of creating, analyzing, validating and construing mathematical models. Otherwise stated, mathematical modeling is a branch of applied mathematics that dealing with describing and/or predicting real-world system behavior. There are some examples of real-world systems an object moving in a gravitational field; stock market fluctuations; predator-prey interactions; cell signaling pathways (Lawson, et al., 2008). To define a mathematical model, we should define three different things: variables, parameters and functional forms.

1.1. Modeling Process

There are a variety of steps that can be used to convert an idea into a theoretical model and then into a quantitative model (Lawson, et al., 2008). It is clear that a theoretical model presents our idea in a model diagram that involving arrows and boxes. Mathematical equations are also used to define the rate of each process. In Figure 1.1, it can be seen that a series of steps are required to define modeling process.

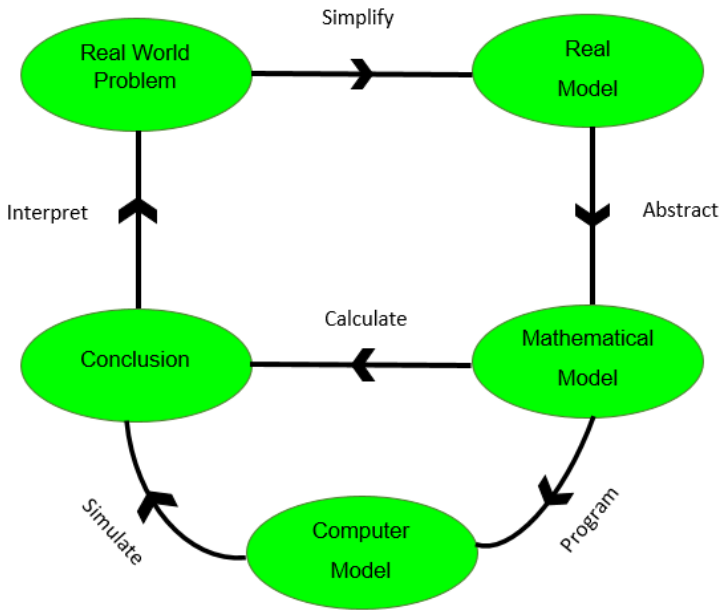


Figure 1.1. Mathematical modeling steps.

1.2. Conceptual Model

There is an epidemic model which is called SIR. A theoretical model diagram is given as follows (Lawson, et al., 2008):

$$S \xrightarrow{Transmission(\beta)} I \xrightarrow{Recovery(\alpha)} R. \tag{1}$$

The model state variables can be given in below:

(i) Susceptible (S): A group of people whose susceptible to the disease.

(ii) Infectious (I): A group of people is called infectious that able to spread the parasite to others people.

(iii) Recovered (R): A group of people is called recovered when they have immune or have died from the disease. We have two rate constants for this model, they are denoted by α and β, where α is recover rate constant and β is an infective rate constant. We can use the idea of mass action law to represent the model (1) as a system of nonlinear differential equations:

$$\begin{cases} \dfrac{dS}{dt} = -\beta S, & S(0) = S_0, \\ \dfrac{\mathrm{dI}}{\mathrm{dt}} = \beta S - \alpha \mathrm{I}, & I(0) = I_0, \\ \dfrac{\mathrm{dR}}{\mathrm{dt}} = \alpha \mathrm{I}, & \mathrm{R}(0) = 0. \end{cases} \tag{2}$$

1.3. Mathematical Modeling Types

1.3.1. Deterministic and Stochastic Models

There are some differences between deterministic and stochastic models. Firstly, there is no parameters in deterministic models that characterized by probability distribution functions, whereas we have some parameters in stochastic models. Secondly, deterministic models may produce the same result for fixed starting values, while we have many different results for stochastic models (Lawson, et al., 2008).

1.3.2. Continuous and Discrete Models

They are two common types of mathematical modelling. They are sometimes called differential equations and difference equations. (Lawson, et al., 2008).

1.3.3. Qualitative and Quantitative Models

Some models are called qualitative model when we have detailing about the model or we have numerical predictions, whereas others are called quantitative models when we have general descriptions (Lawson, et al., 2008).

1.4. Basic ideas and definitions

The main focal point here will be on the dynamics of populations. We introduce some basic definitions that can help us to understand further about ecological population.

Definition 1.4.1

A population is the collection of individuals for particular species. They have same sharing, they are sometimes living in the same area. (Murray, 2001).

Definition 1.4.2

The number of individuals is called population size in a given population, say $N(t)$. (Murray, 2001).

Definition 1.4.3

Population density is the number of individuals per unit area, say $u(r,t)$. The main aim of mathematical modeling is to show the properties of the functions $N(t)$ and/or $u(r,t)$. (Murray, 2001).

Definition 1.4.4

An area is called habitat that is surrounded by a special animal or plant species. It is sometimes an environment that organisms live there. There are two extreme circumstances. The first one is continuous habitat, and the other one is fragmented (disjointed) habitat. (Murray, 2001).

2. CHEMICAL KINETICS AND MASS ACTION LAW

2.1. Basic Ideas and Definitions

Definition 2.1.1

Law of Mass Action was discovered in chemistry in 19th century. It was progressed into a universal toolbox for modeling of processes. Biological processes can be presented in terms of mathematical modeling using the chemical kinetic methods . (Khoshnaw, 2015).

Definition 2.1.2

The population is classified into n components (or classes, or states, or types) of systems $A_1, A_2, \ldots, A_n$. In chemistry, A_i for $i = 1,2,\ldots,n$ are substances. (Khoshnaw, 2015).

Definition 2.1.3

In ecological modeling, components may be different species, populations, and subpopulations. (Khoshnaw, 2015).

Definition 2.1.4

N_i is the amount of substance A_i in the system, $N_i \geq 0$. N is the vector with coordinates, N_i for i=1,2,…, n. (Khoshnaw, 2015).

Definition2.1.5

In chemistry, another set of variables is occasionally used: concentrations $C_i = \frac{N_i}{V}$, where V is the volume of the system. We sometimes use the concentrations as $C_i = N_i$. (Khoshnaw, 2015).

2.2. Elementary Reactions

The elementary reaction is given by the stoichiometric equation:

$$\alpha_{p1}A_1 + \alpha_{p2}A_2 + \cdots + \alpha_{pn}A_n \rightarrow \beta_{p1}A_1 + \beta_{p2}A_2 + \cdots + \beta_{pn}A_n, \qquad (3)$$

where the stoichiometric coefficients $\alpha_{pi} \geq 0$ and $\beta_{pi} \geq 0$ are non-negative integers and ρ is the number of reactions. (Khoshnaw, 2015).

2.3. Stoichiometric Vector

For each reaction, the stoichiometric vector γ is explained from the stoichiometric coefficients (Khoshnaw, 2015).

$$\alpha_{pi} \geq 0 \text{ and } \beta_{pi} \geq 0, \qquad (4)$$

With coordinates

$$\gamma_p = \beta_{pi} - \alpha_{pi}. \tag{5}$$

2.4. Reaction Rate and Mass Action Law

Consider an irreversible reaction:

$$\alpha_{p1}A_1 + \alpha_{p2}A_2 + \cdots + \alpha_{pn}A_n \xrightarrow{k_p} \beta_{p1}A_1 + \beta_{p2}A_2 + \cdots + \beta_{pn}A_n. \tag{6}$$

and let $C_i = [A_i]$, for $i = 1,2,\ldots,n$ are concentration species. Then, we can use mass action law to define the reaction rate v_p which is explained in below:

$$v_p = k_p \prod_{i=1}^{n} C_i^{\alpha_{pi}}. \tag{7}$$

where k_p is the reaction rate constant (kinetic reaction constant). (Khoshnaw, 2015).

2.5. Kinetic Equation

If the elementary reactions are given with their stoichiometric equations and reaction rate constants then the kinetic equations (differential equations) for the concentration vector are

$$\frac{dc}{dt} = \sum_p \gamma_p v_p. \tag{8}$$

where p is the number of reactions, γ_p is stoichiometric vector and v_p is reaction rate, C is the concentration vector. (Khoshnaw, 2015).

Example 2.5.1

Consider a set of chemical reaction as below:

$$\xrightarrow{\alpha} R,\ F + R \xrightarrow{\beta} 2F,\ F \xrightarrow{\gamma}.$$

Let $c_1 = [R],\ c_2 = [F]$.

We have three stoichiometric vectors

$$\gamma_1 = \begin{pmatrix} 1 \\ 0 \end{pmatrix}, \qquad \gamma_2 = \begin{pmatrix} -1 \\ 1 \end{pmatrix} \text{ and } \gamma_3 = \begin{pmatrix} 0 \\ -1 \end{pmatrix}.$$

We have also three reaction rates

$$v_1 = \alpha, \qquad v_2 = \beta c_1 c_2, \qquad v_3 = \gamma c_2.$$

Then the kinetic equations are obtained as:

$$\frac{dc}{dt} = \sum_{p=1}^{3} \gamma_p v_p = \gamma_1 v_1 + \gamma_2 v_2 + \gamma_3 v_3,$$

$$\frac{dc}{dt} = \begin{pmatrix} c_1 \\ c_2 \end{pmatrix} = \begin{pmatrix} 1 \\ 0 \end{pmatrix} \alpha + \begin{pmatrix} -1 \\ 1 \end{pmatrix} \beta c_1 c_2 + \begin{pmatrix} 0 \\ -1 \end{pmatrix} \gamma c_2.$$

Thus, the system of differential equations takes the form

$$\frac{dc_1}{dt} = \alpha - \beta c_1 c_2,$$

$$\frac{dc_2}{dt} = \beta c_1 c_2 - \gamma c_2.$$

3. SENSITIVITY ANALYSIS

3.1. Historical Background

The idea of sensitivity analysis is one of the important methods that has been used for analyzing mathematical models in chemical kinetics and systems biology. (Rabitz, 1981) was the first person who introduced the notation of this method for such models. After that he also proposed the global and local techniques of sensitivity analysis. There are also many authors who developed the technique of sensitivity analysis in applied mathematics for example, finding parametric dependencies of ODE systems (Kramer et al., 1984), calculating the concentration, rate, and feature sensitivity analysis of chemical reactions (Turanyi, 1990), identifying of non-important species using rate sensitivity and of non-important reactions using principle component analysis (PCA) of the rate sensitivity matrix (Tomlin et al., 1992).

The method of sensitivity analysis can be used in some applications for models in systems biology. For example, using the method for parameter controlling of the NF-kB pathway signaling (Ihekwaba et al., 2004). In MAPK and PI3K signal pathways, the idea of time-dependent sensitivity analysis has been used in (Hu et al., 2006). The reader can easily find further studies about the applications of sensitivity analysis in (WH et al.,(2008), Perumal et al., (2011), Charzy´nska et al., (2012), Sumner et al., (2012), Azam et al., (2013), Rabitz et al., (1983) and Zi, (2011)).

Many software tools can be used for calculating local sensitivity for systems biology. For example, SimBiology Toolbox for Matlab (Korsunsky, et al., 2014). SensSB (Rodriguez-Fernandez et al., 2010), BioSens, COPASI (Hoops et al., 2006), Systems Biology Toolbox 2 (Schmidt et al., 2006), Tinker Cell (Chandran et al., 2009), SBML-SAT (Zi et al., 2008.) and Virtual (Slepchenko et al., 2003). While, there are some other software tools that can be applied to calculate global sensitivity in systems biology, for example SBML-SAT, SensSB and Systems Biology Toolbox 2.

In this study, we use local sensitivity analysis method as a technique to determine which variable is sensitive to a specific parameter in biochemical reactions.

3.2. Mathematical formulation

we consider a system of ODEs

$$\frac{dc_i}{dt} = \mathrm{W_i(c(t), \kappa)}, \quad \mathrm{i} = 1,2,\ldots,\mathrm{m}. \tag{10}$$

A vector of parameters k hare is a model input, whereas a vector of concentrations C is a model output. It is clear that the changes in state variables $c_i\,\{\, i = 1,2,\ldots,m\}$ with respect to parameters $K_p\,\{\; p = 1,2,\ldots,n\,\}$, are local sensitivity (Rabitz et al., (1983), Turanyi, (1990), WH et al., (2008) and Zi, (2011)). In a mathematical way, the first order derivatives are the time-dependent sensitivities of c_i with respect to each parameter value. This is given as bellows:

$$S_{ip} = \frac{\partial c_i}{\partial k_p} = \lim_{\Delta k_p \to 0} \frac{c_i\big(k_p + \Delta k_p\big) - c_i\big(k_p\big)}{\Delta k_p}. \tag{11}$$

For calculating the derivative Eq.(11), we have two methods. The first one is the finite difference approximation

$$S_{ip} = \frac{\partial c_i}{\partial k_p} \approx \frac{c_i(k_p + \Delta k_p) - c_i(k_p)}{\Delta k_p}. \tag{12}$$

The second method to calculate Eq. (11) is the direct sensitivity analysis. This technique is sometimes called "forward sensitivity analysis". By using this method, we can solve ordinary differential equations for the sensitivity coefficients.

$$\frac{\partial S_{ip}}{\partial t} = \frac{\partial}{\partial t}\left(\frac{\partial\, c_i}{\partial k_p}\right) = \frac{\partial}{\partial k_p}\left(\frac{\partial\, c_i}{\partial t}\right) = \frac{\partial}{\partial k_p}\left(\mathrm{W_i(c(t), \kappa)}\right). \tag{13}$$

We can also simplify Eq. (13) further by using the chain rule of differentiation,

$$\frac{\partial S_{ip}}{\partial t} = \frac{\partial W_i}{\partial k_p} + \sum_{j=1}^{m} \frac{\partial W_i}{\partial\, c_j} \times \frac{\partial c_j}{\partial k_p} = \frac{\partial W_i}{\partial k_p} + \sum_{j=1}^{m} \frac{\partial W_i}{\partial\, c_j} \times S_{jp}. \tag{14}$$

Then, Jacobian matrix form for Eq. (14) is given in below

$$\dot{S} = W_{kp} + J\,S, \qquad p = 1,2,\ldots,n. \tag{15}$$

Where the matrices S, W_{kp} and J are explained by

$$S = \begin{pmatrix} \frac{\partial c_1}{\partial k_\rho} \\ \frac{\partial c_2}{\partial k_\rho} \\ \vdots \\ \frac{\partial c_m}{\partial k_\rho} \end{pmatrix}, \qquad W_{k\rho} = \begin{pmatrix} \frac{\partial w_1}{\partial k_\rho} \\ \frac{\partial w_2}{\partial k_\rho} \\ \vdots \\ \frac{\partial w_m}{\partial k_\rho} \end{pmatrix}, \qquad J = \begin{pmatrix} \frac{\partial w_1}{\partial c_1} & \frac{\partial w_1}{\partial c_2} & \cdots & \frac{\partial w_1}{\partial c_m} \\ \frac{\partial w_2}{\partial c_1} & \frac{\partial w_2}{\partial c_2} & \cdots & \frac{\partial w_2}{\partial c_m} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial w_m}{\partial c_1} & \frac{\partial w_m}{\partial c_2} & \cdots & \frac{\partial w_m}{\partial c_m} \end{pmatrix}.$$

We can use the input parameter k_p and the initial condition of the output variables c_i for determining the initial conditions of Eq. (15). (Khoshnaw, et al., 2017).

Example 3.3.1

To calculate local sensitivity for a biochemical reaction model, we give a linear chain of chemical reactions as follows,

$$\overset{k_1}{\rightarrow} A_1 \overset{k_2}{\rightarrow} A_2 \overset{k_3}{\rightarrow} A_3\,, \tag{16}$$

where A_1, A_2 and A_3 are chemical components and $k_1\,, k_2$ and k_3 are chemical constants. Generally speaking, we have three sorts of reactions:

Production from source: $\phi \xrightarrow{k_i^+} A_i$, degradation: $A_i \xrightarrow{k_i^-} \phi$, conversion: $A_i \xrightarrow{k_{ji}} A_j$.

A system of ODEs here are given as:

$$\begin{cases} \dfrac{dc_1}{dt} = k_1 - k_2 c_1 = w_1(c_1, c_2, c_3, t), & c_1(0) = 0, \\ \dfrac{dc_2}{dt} = k_2 c_1 - k_3 c_2 = w_2(c_1, c_2, c_3, t), & c_2(0) = 0, \\ \dfrac{dc_3}{dt} = k_3 c_2 = w_3(c_1, c_2, c_3, t), & c_3(0) = 0. \end{cases} \tag{17}$$

where $c_1 = [A_1]$, $c_2 = [A_2]$, $c_3 = [A_3]$. We can solve Eq. (17) analytically. This is given

$$\begin{pmatrix} c_1(t) \\ c_2(t) \\ c_3(t) \end{pmatrix} = \begin{pmatrix} -\dfrac{k_1}{k_2} \\ \dfrac{k_1}{k_2 - k_3} \\ \dfrac{k_1 k_3}{k_2(k_3 - k_2)} \end{pmatrix} e^{-k_2 t} + \begin{pmatrix} 0 \\ \dfrac{k_1 k_2}{k_3(k_2 - k_3)} \\ \dfrac{k_1(2k_3 - k_2)}{k_3(k_3 - k_2)} \end{pmatrix} e^{-k_3 t} + \begin{pmatrix} w_1 \\ w_2 \\ w_3 \end{pmatrix}, \tag{18}$$

where

$$w_1 = -\frac{k_1}{k_2}, \quad w_2 = \frac{k_1}{k_3}, \quad w_3 = \frac{k_1(k_2 k_3(k_3 - k_2)t + k_2^2 - k_3^2)}{k_2 k_3(k_3 - k_2)}.$$

On the basis of the equation of local sensitivity, Eq.(15),

$$w_{k_1} = \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix}, w_{k_2} = \begin{pmatrix} -c_1 \\ c_1 \\ 0 \end{pmatrix}, w_{k_3} = \begin{pmatrix} 0 \\ -c_2 \\ c_2 \end{pmatrix},$$

and

$$J = \begin{pmatrix} \dfrac{\partial w_1}{\partial c_1} & \dfrac{\partial w_1}{\partial c_2} & \dfrac{\partial w_1}{\partial c_3} \\ \dfrac{\partial w_2}{\partial c_1} & \dfrac{\partial w_2}{\partial c_2} & \dfrac{\partial w_2}{\partial c_3} \\ \dfrac{\partial w_3}{\partial c_1} & \dfrac{\partial w_3}{\partial c_2} & \dfrac{\partial w_3}{\partial c_3} \end{pmatrix} = \begin{pmatrix} -k_2 & 0 & 0 \\ k_2 & -k_3 & 0 \\ 0 & k_3 & 0 \end{pmatrix},$$

As a result, we have the local sensitivity of c_1, c_2 and c_3 with respect to k_1, k_2 and k_3 as follows:

$$\begin{pmatrix}\dot{S}_{11}\\ \dot{S}_{21}\\ \dot{S}_{31}\end{pmatrix}=\begin{pmatrix}1\\ 0\\ 0\end{pmatrix}+\begin{pmatrix}-k_2 & 0 & 0\\ k_2 & -k_3 & 0\\ 0 & k_3 & 0\end{pmatrix}\begin{pmatrix}S_{11}\\ S_{21}\\ S_{31}\end{pmatrix},\qquad \begin{pmatrix}S_{11}(0)\\ S_{21}(0)\\ S_{31}(0)\end{pmatrix}=\begin{pmatrix}0\\ 0\\ 0\end{pmatrix}, \tag{19}$$

$$\begin{pmatrix}\dot{S}_{12}\\ \dot{S}_{22}\\ \dot{S}_{32}\end{pmatrix}=\begin{pmatrix}-c_1\\ c_1\\ 0\end{pmatrix}+\begin{pmatrix}-k_2 & 0 & 0\\ k_2 & -k_3 & 0\\ 0 & k_3 & 0\end{pmatrix}\begin{pmatrix}S_{12}\\ S_{22}\\ S_{32}\end{pmatrix},\qquad \begin{pmatrix}S_{12}(0)\\ S_{22}(0)\\ S_{32}(0)\end{pmatrix}=\begin{pmatrix}0\\ 0\\ 0\end{pmatrix}, \tag{20}$$

$$\begin{pmatrix}\dot{S}_{13}\\ \dot{S}_{23}\\ \dot{S}_{33}\end{pmatrix}=\begin{pmatrix}0\\ -c_2\\ c_2\end{pmatrix}+\begin{pmatrix}-k_2 & 0 & 0\\ k_2 & -k_3 & 0\\ 0 & k_3 & 0\end{pmatrix}\begin{pmatrix}S_{13}\\ S_{23}\\ S_{33}\end{pmatrix},\qquad \begin{pmatrix}S_{13}(0)\\ S_{23}(0)\\ S_{33}(0)\end{pmatrix}=\begin{pmatrix}0\\ 0\\ 0\end{pmatrix}. \tag{21}$$

We can solve the systems (19)-(21) analytically for identifying local sensitivity. In this study, we use SimBiology Toolbox for Matlab to calculate the local sensitivity analysis for high dimensional models. The reader can see different techniques of sensitivity analysis with details. (Rabitz et al., (1983), Zi, (2011) and Khoshnaw, (2015)).

4. SCALING OF VARIABLES

Scaling of variables is an important technique in systems biology for minimizing number of parametrs. Applying this technique is sometimes difficult because there would be more than one way for scaling of variables.

4.1. Simple Enzymatic Reaction

Briggs and Haldane introduced the simple model of enzymatic reactions (Sontag, 2014), and (Khoshnaw, 2013). The model reactions are given as:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \overset{k_2}{\rightarrow} E + P, \tag{22}$$

where E is enzyme, S is substrate, ES is enzyme-substrate complex and P is product. Model paramers are k_1, k_{-1} and k_2. We denote the model concentrations by

$$e = [E], \qquad s = [S], \qquad p = [P], \qquad c = [ES].$$

Using mass action law for Eq. (22), we can define a system of ordinary differential equations:

$$\begin{cases} \dfrac{de}{dt} = -k_1 es + k_{-1} c + k_2 c, \\ \dfrac{ds}{dt} = -k_1 es + k_{-1} c, \\ \dfrac{dc}{dt} = k_1 es - (k_{-1} + k_2) c, \\ \dfrac{dp}{dt} = k_2 c. \end{cases} \tag{23}$$

With the initial concentrations

$$e(0) = e_0, \;\; s(0) = s_0, \;\; c(0) = p(0) = 0. \tag{24}$$

There are two independent chemical conservation laws for system (23),

$$e + c = e_0, \quad s + p + c = s_0. \tag{25}$$

Subsituting Eq. (25) into Eq. (23) the system (23) becomes

$$\begin{cases} \dfrac{ds}{dt} = -k_1 (e_0 - c) S, \\ \dfrac{ds}{dt} = k_1 (e_0 - c) S - (k_{-1} + k_2) C. \end{cases} \tag{26}$$

Briggs and Haldane noticed that the total concentration of the enzymes is much smaller that the total concentration of substrstes ($i.e.\ e_0 \ll s_0$), (Gorban et al., 2011). A simple scaling is used in this model (Kumar, 2011) and (Murray, 2002). We intoduce the following new variables:

$$\tau = k_1 e_0 t,\ \ u(\tau) = \frac{s(t)}{s_0}, \text{and}\ \ v(\tau) = \frac{c(t)}{e_0}. \tag{27}$$

Then, the system of ODEs (26) can be given in different form:

$$\frac{du}{d\tau} = -u(1-v) + \alpha v, \qquad u(0) = 1, \tag{28}$$

$$\epsilon \frac{dv}{d\tau} = u(1-v) - \beta v, \qquad v(0) = 0, \tag{29}$$

where

$$\epsilon = \frac{e_0}{s_0},\ \ \alpha = \frac{k_{-1}}{s_0 k_1}, \qquad \text{and} \qquad \beta = \frac{k_{-1} + k_2}{s_0 k_1}.$$

The Eq. (28) is called slow subsystem, while the Eq. (29) is called fast subsystem (Khoshnaw, 2013).

5. SOFTWARE TOOLS

Software tools are an important challenge in systems biology to describe the dynamics of biochemical reaction networks. We have a variety of software tools that can be used for visualizing, modeling process and simulating. We use two software development tools in this study to find some numerical approximate solutions and identify critical model parameters.

5.1. Systems Biology Toolbox (SBToolbox)

This software tool is used for calculating numerical simulations and identifying steady state solutions for biochemical reaction networks (Schmidt et al., 2006).

5.2. SimBiology Toolbox

The computational toolbox has a great role in modeling process, especially for high dimensional models. This can be used for identifying critical model parameters and calculating local sensitivity (Schmidt et al., 2006).

6. SOME INFECTIOUS DISEASE MODELS

6.1. Susceptible-Infected Model (SI Model)

One of the simplest model of infectious disease is called SI model. In this model people are is categorized as either susceptible S or infective I, where susceptible people are healthy and infective people are unhealthy. (Abramson, (2011), Hethcote, (2000) and Ingalls, (2012)). The chemical reaction of the model assumes reaction:

$$S + I \xrightarrow{\beta} 2I. \tag{30}$$

where S is the susceptible people and I is the infective people. Both are variables of the model. β is the reaction rate constant (infective rate constant).

6.1.1. Mathematical Formulation

We use mass action law to define the mathematical equations for this model. Then, the kinetic equations take the following form:

$$\begin{cases} \dfrac{dS}{dt} = -\beta SI, \\ \dfrac{dI}{dt} = \beta SI. \end{cases} \tag{31}$$

With initial model populations $S(0) = S_0$ and $I(0) = I_0$. Adding differential equations in (31), we obtain

$$\frac{dS}{dt} + \frac{dI}{dt} = 0.$$

Consequently, we have the following relation

$$S + I = N, \tag{32}$$

where N is a total constant population.

The equation (32) is known as conservation law for SI model. By substituting Eq. (32) into Eq. (31), the differential equations can be given below as a single equation:

$$\frac{dS}{dt} = -\beta S(N - S). \tag{33}$$

The differential Eq. (33) can be solved analytically. The model has been solved as follows:

$$S(t) = \frac{N}{1 + \dfrac{N - S_0}{S_0} e^{\beta N t}},$$

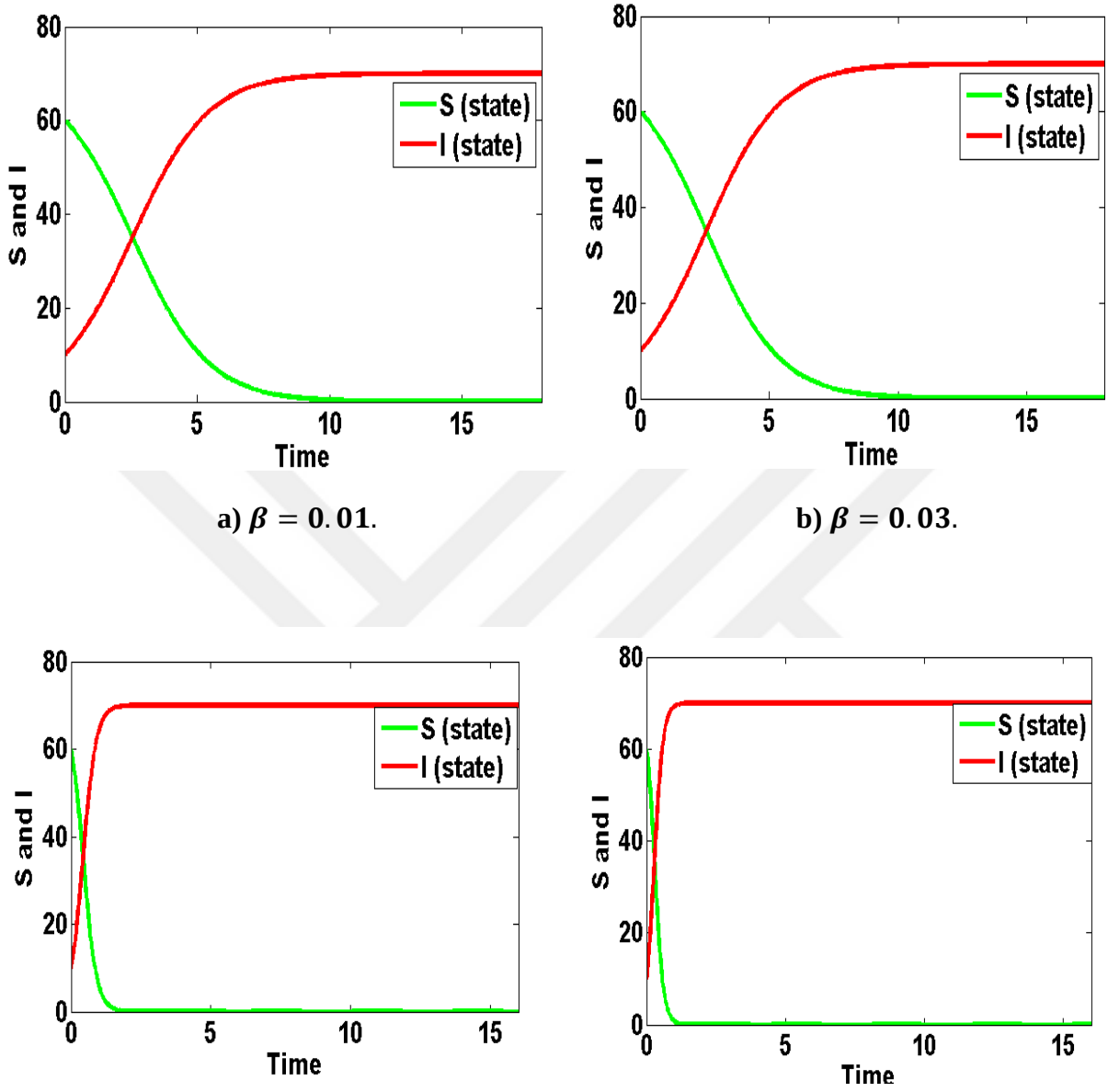
and then the solution of I(t) can be found from the conservation law

$$I(t) = \frac{N}{1 + \frac{N - S_0}{S_0} e^{-\beta N t}},$$

Interestingly, we can conclude that $S(t) \to 0$ and $I(t) \to N$ as $t \to \infty$.

6.1.2. Results and discussions

We use Matlab codes for numerical simulations in order to have some approximate solutions for the original model (30) for different parameters. Interestingly, the population of susceptible people becomes zero and the population of infective people becomes the entire population when there is not vaccination of the model.



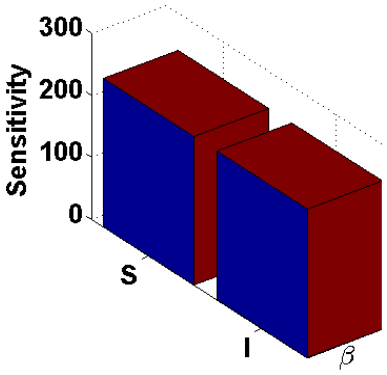
a) $\beta = 0.01$.

b) $\beta = 0.03$.

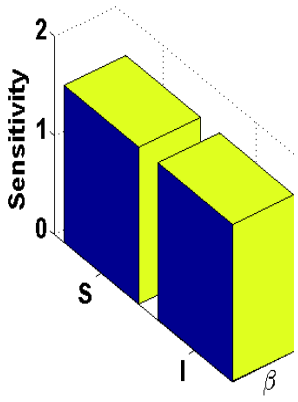
c) $\beta = 0.06$.

d) $\beta = 0.09$.

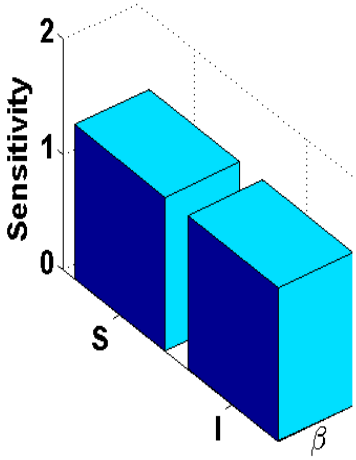
Figure 6.1. Dynamics and numerical simulations of the SI model with initial conditions $S(0) = 60$ and $I(0) = 10$.



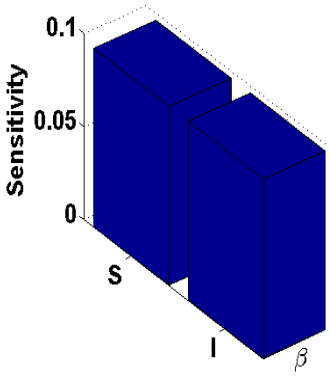
a) $\boldsymbol{\beta = 0.1}$.



b) $\boldsymbol{\beta = 1.23}$.



c) $\boldsymbol{\beta = 1.34}$.



d) $\boldsymbol{\beta = 5}$.

Figure 6.2. The local sensitivity of all variables with respect to parameter $\boldsymbol{\beta}$ using the SimBiology Toolbox for Matlab of the SI model with initial conditions $\boldsymbol{S(0) = 60}$ and $\boldsymbol{I(0) = 10}$.

6.2. Susceptible-Infected-Susceptible Model (SIS Model)

The SI model can be further developed to the SIS model, where an infective can recover and become susceptible again. The chemical reactions of the model can be given;

$$\begin{cases} S + I \xrightarrow{\beta} 2I, \\ I \xrightarrow{\gamma} 2I. \end{cases} \tag{34}$$

where S is susceptible people and I is infective people. Both are variables of the model. β and γ are the reaction constants (model parameters). (Khoshnaw (2015), Abramson (2011), Ingalls (2012), Baker (2011) and Briggs et al., (1925)).

6.2.1 Mathematical Formulation

We can find the stoichiometric vectors and reaction rates for the reactions (34). Applying the idea of mass action law to define the mathematical equations for this model, then the kinetic equations take the following form;

$$\begin{cases} \dfrac{dS}{dt} = -\beta SI + \gamma I, \\ \dfrac{dI}{dt} = \beta SI - \gamma I. \end{cases} \tag{35}$$

We have initial conditions of the model $S(0) = S_0$ and $I(0) = I_0$.

Adding differential equations (35), we obtain

$$\frac{dS}{dt} + \frac{dI}{dt} = 0.$$

Then, the above equation takes the following form,

$$S + I = N, \tag{36}$$

where N is a total constant population.

The Eq. (36) is known as conservation law for the model. This is very useful in minimizing the model dimension (minimizing the number of variables) in systems biology. By substituting Eq. (36) into Eq. (35), the differential equations can be expressed as a single equation as follows:

$$\frac{dI}{dt} = \beta I(N - I) - \gamma I. \tag{37}$$

After rearranging the Eq. (37), the equation becomes

$$\frac{dI}{dt} = \gamma(R_0 - 1)I\left(1 - \frac{1}{N\left(1 - \frac{1}{R_0}\right)}\right), \tag{38}$$

where $R_0 = \frac{\beta N}{\gamma}$. The Eq. (38) is a logistic equation with grow rate $\gamma(R_0 - 1)$ and carrying capacity $N\left(1 - \frac{1}{R_0}\right)$. The above Eq. (38) can be solved analytically. The solution takes the form

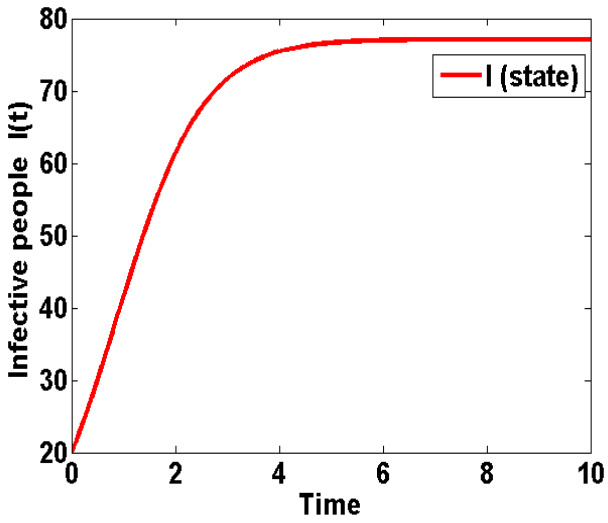
$$I(t) = \frac{I_0 N\left(1 - \frac{1}{R_0}\right)}{N\left(1 - \frac{1}{R_0}\right)e^{-\gamma(R_0-1)t} + I_0(1 - e^{-\gamma(R_0-1)t})}. \quad (39)$$

More interestingly, if the growth rate is negative that is $R_0 < 1$, then the disease will disappear and it will become endemic if the growth rate is positive that is $R_0 > 1$, for an endemic disease with $R_0 > 1$, the number of infected people approaches the carrying capacity:

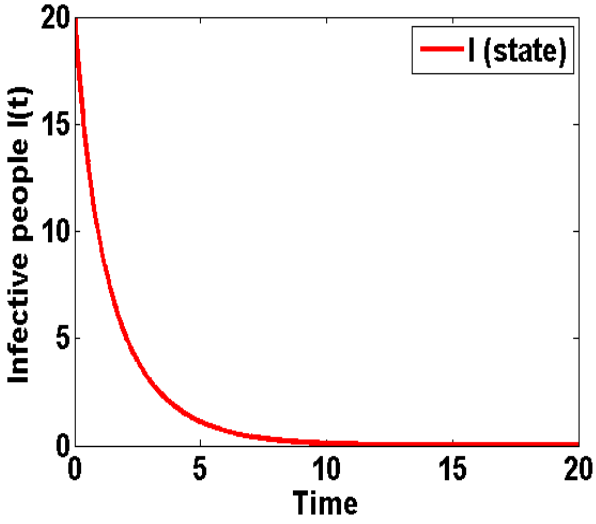
$$I \to \left(1 - \frac{1}{R_0}\right) \text{ as } t \to \infty.$$

6.2.2. Results and Discussions

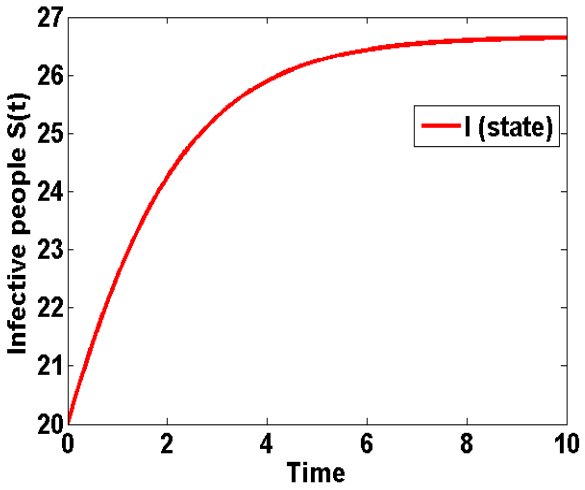
We simulate the reduced model (38) in numerical simulations in order to have some approximate solutions for different values of parameters. Interestingly, the population of infective becomes zero when the growth rate is negative, $\gamma(R_0 - 1) < 0$, that is $R_0 < 1$. While, the population of infective becomes the whole population when the growth rate is positive $(R_0 - 1) > 0$, that is $R_0 > 1$.



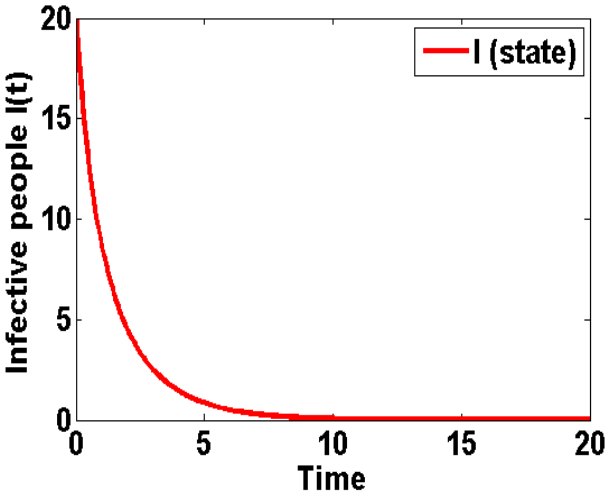
a) $N = 90, \gamma = 0.2, R_0 = 7.$



b) $N = 90, \gamma = 2.3, R_0 = 0.8.$

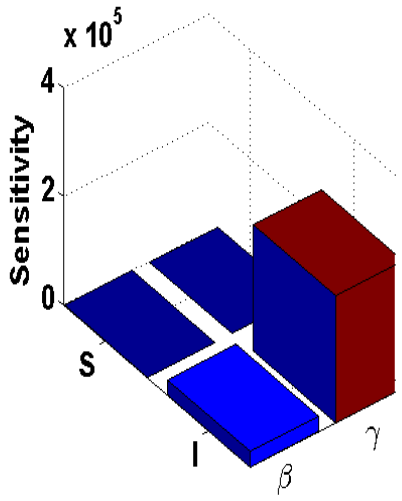


c) $N = 20, \gamma = 0.3, R_0 = 3.$

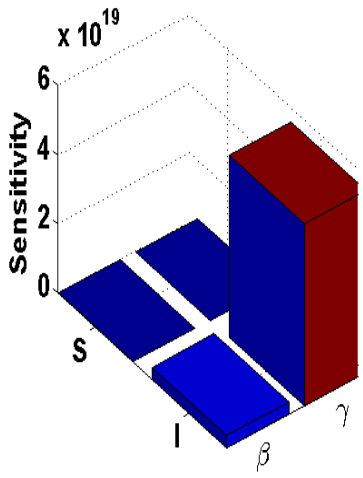


d) $N = 20, \gamma = 1, R_0 = 0.5.$

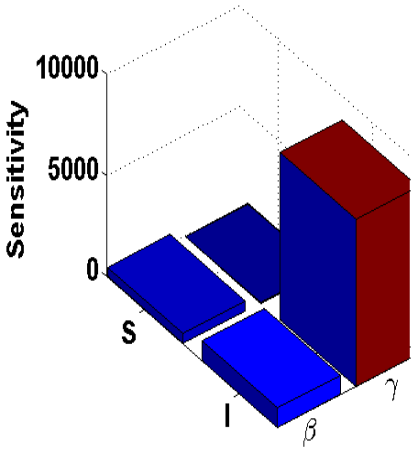
Figure 6.3. Dynamics and numerical simulations of the SIS model with initial condition $I(0) = 20$.



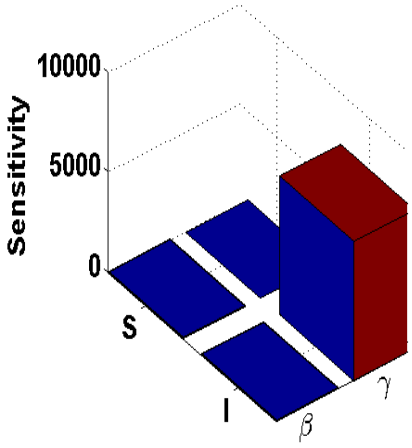
a) $\boldsymbol{\beta = 0.2,\ \gamma = 0.6.}$



b) $\boldsymbol{\beta = 0.324,\ \gamma = 4.}$



c) $\boldsymbol{\beta = 0.7,\ \gamma = 0.7.}$



d) $\boldsymbol{\beta = 0.234,\ \gamma = 0.037.}$

Figure 6.4. The local sensitivity of all variables with respect to a set of parameters using the SimBiology Toolbox for Matlab of the SIS model with initial condition $S(0) = 100,\ I(0) = 20$.

6.3. Susceptible-Infected-Recovered (SIR model)

The SIS model can be further extended. In 1927, Kermack and McKendrick proposed SIR model. This model is surely the one of basic mathematical models for the disperse of an infectious disease. According to this model people are characterized into three classes: susceptible S, infective I and removed R. Removed individuals are no longer susceptible nor infective (Abramson (2011), Hethcote (2000), Kot (2001) and Murray (2001)).
The model may be diagrammed as:

$$\begin{cases} S + I \xrightarrow{\beta} 2I, \\ I \xrightarrow{\gamma} R\,. \end{cases} \tag{40}$$

where β is an infective rate constant and γ is a recovered rate constant.

6.3.1. Mathematical Formulation

Using mass action law, we have the following differential equations

$$\begin{cases} \dfrac{dS}{dt} = -\beta SI, \\ \dfrac{dI}{dt} = \beta SI - \gamma I, \\ \dfrac{dR}{dt} = \gamma I. \end{cases} \tag{41}$$

We have the following initial conditions

$$S(0) = S_0, \qquad I(0) = I_0, \qquad R(0) = 0.$$

The system (41) has surely a conservation law

$$S + I + R = N, \tag{42}$$

where N is a constant model population. The dimensionless form for SIR equations is then given as:

$$\begin{cases} \dfrac{dS^*}{d\tau} = -\delta S^* I^*, \\ \dfrac{dI^*}{d\tau} = \delta S^* I^* - I^*, \\ \dfrac{dR^*}{d\tau} = I^*. \end{cases} \tag{43}$$

where

$$S^* = \frac{S}{N}, \qquad I^* = \frac{1}{N}\,, \qquad R^* = \frac{R}{N}\,, \qquad \tau = \gamma t, \qquad \delta = \frac{\beta N}{\gamma}.$$

Thus, the conservation law (42) then becomes

$$S^* + I^* + R^* = 1. \tag{44}$$

In addition, the system (43) is then reduced to

$$\begin{cases} \dfrac{dS^*}{d\tau} = -\delta S^* I^*, \\ \dfrac{dI^*}{d\tau} = \delta S^* I^* - I^*. \end{cases} \tag{45}$$

with initial conditions

$$S^*(0) = S_0^* \text{ and } I^*(0) = I_0^*.$$

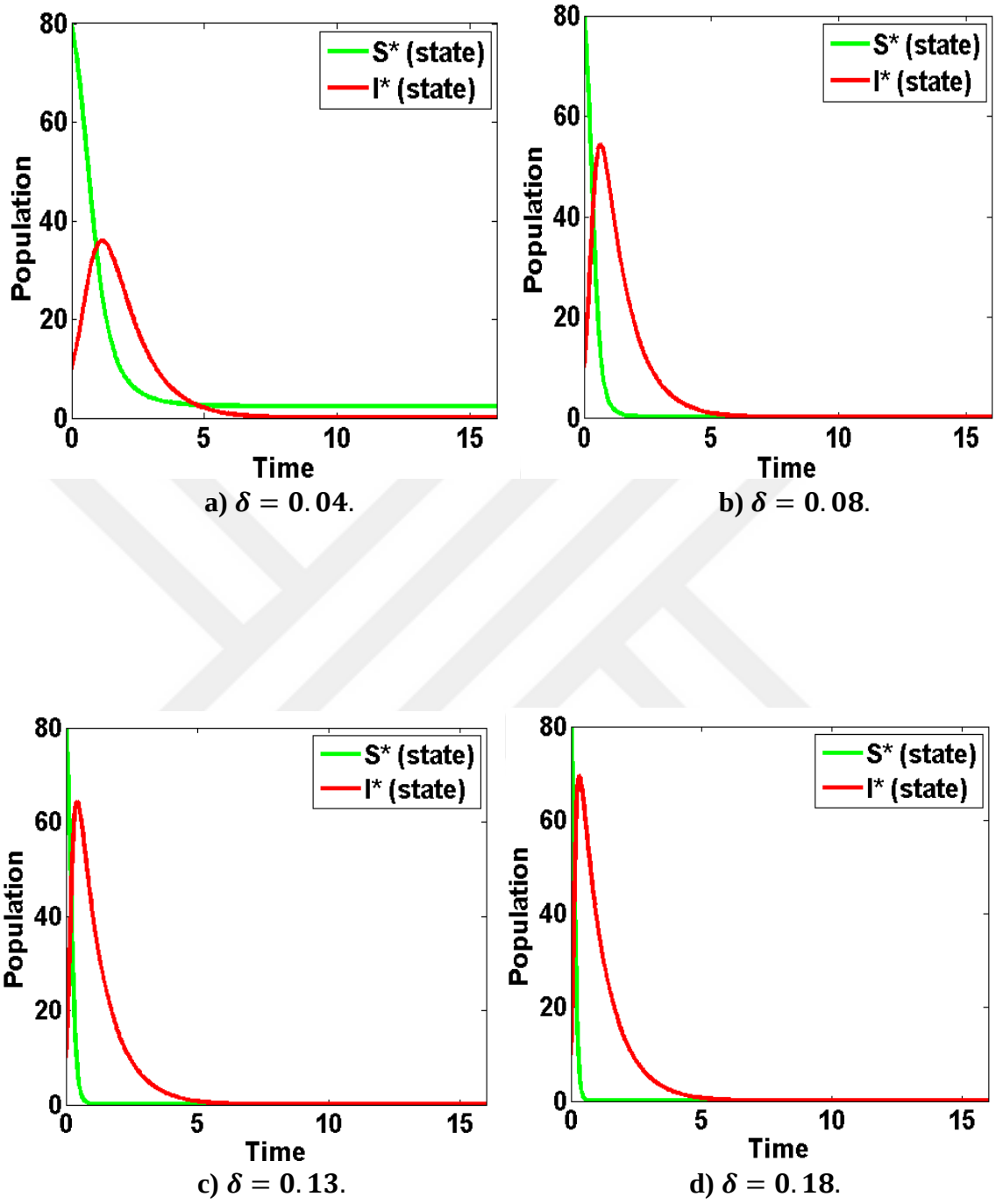
From (45), we can find the following single differential equation as:

$$\frac{dI^*}{dS^*} = \left(-1 + \frac{1}{\delta S^*}\right).$$

The above equation is a separable differential equation that can be solved analytically. Then, the soultion becomes

$$I^*(\tau) = -\tau + I^*{}_0 + \frac{\ln(S^*{}_0\, S^*)}{\delta}.$$

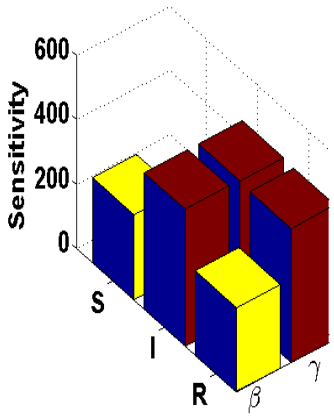
We use Matlab codes for numerical simulations in order to have some approximate solutions for the reduced model (45) for different parameters. The approximate solutions of the reduced model (45) for different values of parameters can be expressed in Figure 6.5. We simulate the reduced model for different values of the remaining parameter. Generally, we can conclude that for different values of the remaining parameters there is a different dynamic.



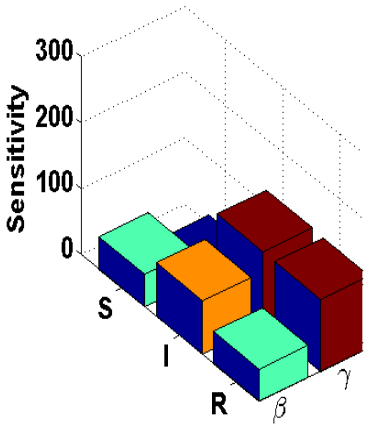
a) $\delta = 0.04$. b) $\delta = 0.08$.

c) $\delta = 0.13$. d) $\delta = 0.18$.

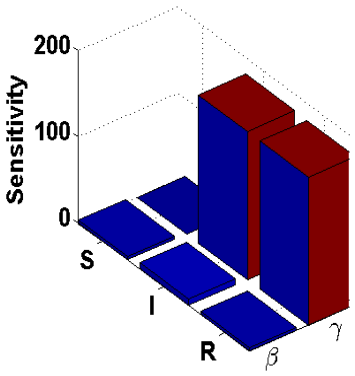
Figure 6.5. Dynamics of the reduced model and numerical simulations of the SIR model with initial conditions: $S^*(0) = 80$ and $I^*(0) = 10$.



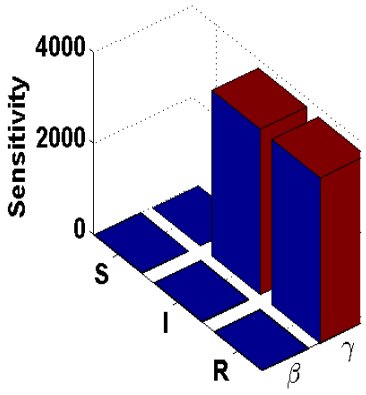
a) $\boldsymbol{\beta = 0.1,\ \gamma = 0.5.}$



b) $\boldsymbol{\beta = 0.231,\ \gamma = 1.}$



(c) $\boldsymbol{\beta = 0.8,\ \gamma = 0.8.}$



d) $\boldsymbol{\beta = 0.347,\ \gamma = 0.063.}$

Figure 6.6. The local sensitivity of all variables with respect to a set of parameters using the SimBiology Toolbox for Matlab of the SIR model with initial conditions $S(0) = 80$ and $I(0) = 10$.

7. MATHEMATICAL MODEL FOR THE EBOLA VIRUS DISEASE (EVD)

7.1. Introduction

The SIR model was suggested by Kermack and McKendrick in 1927. This is certainly the most famous mathematical model of an infectious disease. According to this model, people are divided into three classes: the first class is susceptible S, the second one is infective I and the last one is recovered R.

An Ebola outbreak recently has influence on some countries in West Africa. The first case was reported in Guinea by the world health organization on March 23, 2014. And the diseases disperse in the neighboring countries of Liberia and Sierra Leone, Later the outbreak become more widespread travel-associated case emerged in Nigeria, Mali, Senegal, even united states. In general, nine countries have declared cases Ebola more than 27000 people have had suspected, probable, or, confirmed Ebola, and more than 11000 have died. Considerable attention has been concentrated upon preventing the outbreak from extra-spread out and the size and scope of this epidemic illustrate the need for stronger, sustainable illness detection and prohibition capacity word wide, (Shen, et al., 2015).

Ebola, or, Ebola hemorrhagic fever (EHF), is resulted by infection with one of the Ebola virus spices, Ebola can lead to disease not only humans, but non-human pirates such as (Monkeys, Gorilla, and Chimpanzees). Ebola virus symptoms, usually get at two to twenty days after contracting the virus with a fever, sore throat, muscle hurts and headaches as usual nausea vomiting, and diarrhea with reduced functioning of kidneys and liver, even to get to have breeding problems. This virus is basically localized to the rain forests of central and western Africa, and also. Philippines whereas the exact mechanism of natural virus transmittal to both humans and non-human pirates is ambiguous, but thought that Bats may constitute the natural reservoir and basic source of infection.

A mathematical model can be used to provide an account of the development of the Ebola outbreak to date. It provides short term projections for its future development and controlling the outbreak. For example, "increased contact tracing", improved reach to "PPE" for health care personnel and the use of a pharmaceutical intervention to treat survival in hospitalized patients.

In short, the population here is classified into eight compartments. The first group is susceptible people S, then this group could become exposed people E after contact with and infected individual. Then, they become infectious I class after the diseases incubation period.

At that stage, individuals may be hospitalized H. Both untreated patients in I and hospitalized patients in H may experience one of two results: patients may die, with a chance of infecting others during the resulting funeral F before being removed from the model R, or they may recover, at which point they are similarly. (Shen, et al., 2015).

7.2. Mathematical Modeling

The population of this model is classified into eight classes: S is susceptible people who can be infected by Ebola virus , V is vaccinated individuals, E_1 is latent undetectable individuals, E_2 is latent detectable individuals, I is infectious individuals with symptoms, J is isolated individuals, D is individuals who are dead but have not been buried, and R is recovered individuals. We assume that N denoted by the total population size,

$$N = S + V + E_1 + E_2 + I + J + D + R. \tag{46}$$

The model diagram can be shown as:

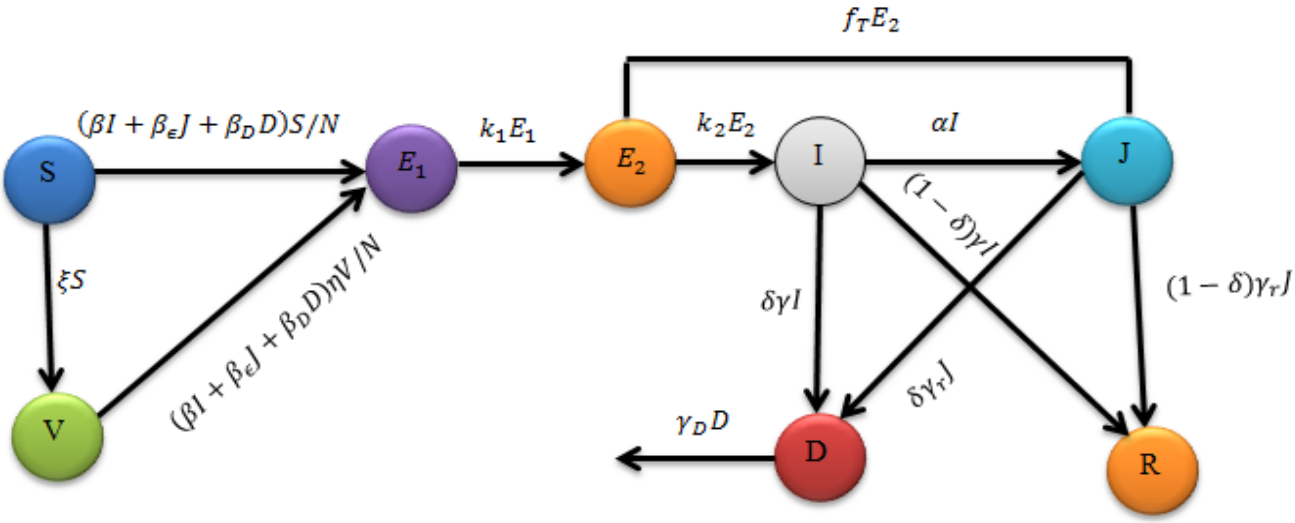


Figure 7.1. A schematic rate of flow diagram of Ebola infection with isolation, media impact, post-death transmission and vaccination. (Shen, et al., 2015).

The chemical reactions of the model are given as:

$$\begin{cases} \mathrm{S} \xrightarrow{\xi S} V, \\ S \xrightarrow{(\beta I+\beta_\epsilon J+\beta_D D)S/N} \mathrm{E}_1, \\ V \xrightarrow{(\beta I+\beta_\epsilon J+\beta_D D)\eta V} \mathrm{E}_1, \\ \mathrm{E}_1 \xrightarrow{k_1 E_1} \mathrm{E}_2, \\ \mathrm{E}_2 \xrightarrow{k_2 E_2} I, \\ I \xrightarrow{\alpha I} J, \\ E_2 \xrightarrow{f_T \mathrm{E}_2} J, \\ I \xrightarrow{(1-\delta)\gamma I} R, \\ I \xrightarrow{\delta\gamma I} D, \\ J \xrightarrow{\delta\gamma_r J} D, \\ J \xrightarrow{(1-\delta)\gamma_r J} R, \\ D \xrightarrow{\gamma_D D}. \end{cases} \tag{47}$$

We have the following stoichiometric vectors of the model

$$\gamma_1 = \begin{pmatrix} -1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \ \gamma_2 = \begin{pmatrix} -1 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \gamma_3 = \begin{pmatrix} 0 \\ -1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \ \gamma_4 = \begin{pmatrix} 0 \\ 0 \\ -1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \gamma_5 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ -1 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \gamma_6 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ -1 \\ 1 \\ 0 \\ 0 \end{pmatrix},$$

$$\gamma_7 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ -1 \\ 0 \\ 1 \\ 0 \\ 0 \end{pmatrix}, \gamma_8 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ -1 \\ 0 \\ 0 \\ 1 \end{pmatrix}, \gamma_9 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ -1 \\ 0 \\ 1 \\ 0 \end{pmatrix}, \gamma_{10} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ -1 \\ 1 \\ 0 \end{pmatrix}, \gamma_{11} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ -1 \\ 0 \\ 1 \end{pmatrix}, \gamma_{12} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ -1 \\ 0 \end{pmatrix}.$$

The reaction rates are

$$\begin{cases} v_1 = \xi S, \\ v_2 = \dfrac{\left(\beta I + \beta_\epsilon J + \beta_D D\right) S}{N}, \\ v_3 = \dfrac{\left(\beta I + \beta_\epsilon J + \beta_D D\right) \eta V}{N}, \\ v_4 = k_1 E_1, \\ v_5 = k_2 E_2, \\ v_6 = \alpha I, \\ v_7 = f_T E_2, \\ v_8 = (1-\delta)\gamma I, \\ v_9 = \delta\gamma I, \\ v_{10} = \delta\gamma_r J, \\ v_{11} = (1-\delta)\gamma_r J, \\ v_{12} = \gamma_D D. \end{cases} \tag{48}$$

By applying mass action Law, we have a set of differential equations.

$$\frac{d}{dt}\begin{bmatrix} S \\ V \\ E_1 \\ E_2 \\ I \\ J \\ D \\ R \end{bmatrix} = \sum_{p=1}^{12} \gamma_p v_p . \tag{49}$$

Then the system becomes

$$
\begin{cases}
\dfrac{dS}{dt} = -\xi S - \dfrac{\left(\beta I + \beta_{\epsilon} J + \beta_{D} D\right) S}{N}, \\
\dfrac{dV}{dt} = \xi S - \dfrac{\left(\beta I + \beta_{\epsilon} J + \beta_{D} D\right) \eta V}{N}, \\
\dfrac{dE_1}{dt} = \dfrac{\left(\beta I + \beta_{\epsilon} J + \beta_{D} D\right)(S + \eta V)}{N} - k_1 E_1, \\
\dfrac{dE_2}{dt} = k_1 E_1 - (k_2 + f_T) E_2, \\
\dfrac{dI}{dt} = k_2 E_2 - \alpha I - \gamma I, \\
\dfrac{dJ}{dt} = \alpha I + f_T E_2 - \gamma_r J, \\
\dfrac{dD}{dt} = \delta \gamma_r J + \delta \gamma I - \gamma_D D, \\
\dfrac{dR}{dt} = (1 - \delta)\gamma_r J + (1 - \delta)\gamma I.
\end{cases}
\tag{50}
$$

Table 7.1. Model parameters and values for simulation and data fitting values for a model of an Ebola disease in Guinea, Sierra Leone and Liberia. (Shen, et al., 2015).

Parameter	Description	Default or estimated mean value with 95% confidence interval		
		Guinea	Sierra Leone	Liberia
N	Size of the total Population.	11,745,189	6,092,075	4,294,077
$\frac{1}{k_1}$	Mean time from latent undetectable class to latent detectable class.	4 days	4 days	4 days
$\frac{1}{k_2}$	Mean time from latent detectable class to infectious symptomatic class.	3 days	3 days	3 days
$\frac{1}{\alpha}$	Mean time from infectious symptomatic class to isolated class.	3 days	3 days	3 days
$\frac{1}{\gamma}$	Mean time that infectious individuals are removed by recovery or induced death.	6 days	6 days	6 days
$\frac{1}{\gamma_\gamma}$	Mean time that isolated individuals are removed by recovery or disease induced death.	6.7981 days [6.5617,7.0522]	6.9979 days [6.6578,7.3746]	7.2 days [7.0522,7.3529]
$\frac{1}{\gamma_D}$	Mean time from death to traditional burial.	2 days	2 days	2 days
β	Pre-media human to human transmission rate.	$0.2896\ \text{day}^{-1}$ [0.2487,0.3305]	$0.4652\ \text{day}^{-1}$ [0.4056,0.5247]	$0.3500\ \text{day}^{-1}$ [0.3371,0.3628]
β_ϵ	Post-media human to human transmission rate.	0.2275day^{-1} [0.2088,0.2462]	$0.2355\ \text{day}^{-1}$ [0.2069,0.2641]	$0.1701\ \text{day}^{-1}$ [0.1644,0.1758]
β_D	Pre-media transmission rate during funeral.	$0.2373\ \text{day}^{-1}$ [0.1926,0.2820]	$0.1669\ \text{day}^{-1}$ [0.1266,0.2071]	0.2986day^{-1} [0.2693,0.3279]
f_T	The rate at which latent detectable Individuals progress to the isolation class.	$0.7136\ \text{day}^{-1}$ [0.6238,0.8033]	0.8291day^{-1} [0.7509,0.9072]	$0.4898\ \text{day}^{-1}$ [0.4636,0.5160]
ξ	The vaccination rate.	1.0002	0.8671	1.3×10^{-3} $[0.7389,1.8611]\times10^{-3}$
η	The efficacy of Vaccination.	0.4572	0.5649	0.5487 [0.4649,0.6325]
δ	The case fatality rate.	0.6728 [0.6573,0.6884]	0.3143 [0.3014,0.3272]	0.4765 [0.4738,0.4792]

7.3. Computational Simulations

We use the SBToolbox for Matlab to simulate the population of the model states of Ebola virus disease (EVD). A set of parameters and fitted values are used in Guinea, Sierra Leone and Liberia, 2015. There are some interesting results based on computational simulations for these three countries. If we make a fitted assessment for Guinea, we see the susceptible population reduces gradually and becomes zero after 5 days; see Figure 7.2.a. While, the vaccinated population for its initial days increase quickly, reaches maximum level after 5 days, later its value falls and become stable, see Figure; 7.2.b. Also, if we notice the individual population value, in commencement, rises surprisingly and reaches to maximum level between the days of 20-25 days. Reversely, it decreases to zero in the days of 100 days; see Figure 7.2.c. In Sierra Leone, the significant transforms can be seen. The susceptible falls sharply and become zero in the 5 days, see Figure 7.3.a, whereas, the vaccinated population increases quickly from initial days and continues to maximum level form 15-20 days, then it gradually decreases see Figure 7.3.b, while, the infectious population, rises to peak value later it reduces. On the other hand, it starts to rise again but not as much as the initial days. Contrary to it decreases quickly between the days 60-70 and become zero in the days of 200 days; see figure 7.3.e. In Liberia, the latent undetectable population falls at the begin while it increases from the days 5-10, whereas it decreases again, in the days between 60-70, and becomes zero in the days of 200 see Figure 7.4.d, reversely. The recovered population rises quickly and stayed steadily, between days 90-110; see Figure 7.4.h.

After we use the SimBiology Toolbox for Matlab, to simulate population of the model states of these three mentioned countries. The sensitivity value for state variables$\{S,\ V,\ E_1,\ E_2,\ I,\ J,\ D,\ R\}$, showswith respect to the parameters of $\{\beta,\ \beta_\epsilon,\ \beta_D,\ k_1,\ k_2,\ \gamma,\ \gamma_r,\ \gamma_D,\ f_T,\ \xi,\ \eta,\ N\}$, most variables have sensitivity for the parameters, but the variable V has more sensitivity for the parameter β_ϵ, and variable E_1 for parameter k_1; see Figure 7.5.a. In spite of that, most state variables have a little sensitivity for the parameters, but it's clear that the state variables S and V have much sensitivity for parameter ξ, and variable J for parameter γ_r, see Figure 7.5.b. In Sierra Leone, most state variables have sensitivity for the parameters obviously, the state variable V has much sensitivity for parameter β_ϵ, the state variable E_1 for parameter k_1; see Figure 7.6.a, and the state variables S and V for parameter ξ; see Figure 7.6.b. There more, In Liberia, some of the state variables have sensitivity for the parameters. The state variable of S has more sensitivity for the parameter β_ϵ; see figure 7. 7.a, vice versa, the state variables have a little or, non-sensitivity for the parameters, except the state variables of S and V for parameter ξ, see Figure 7.7.b.

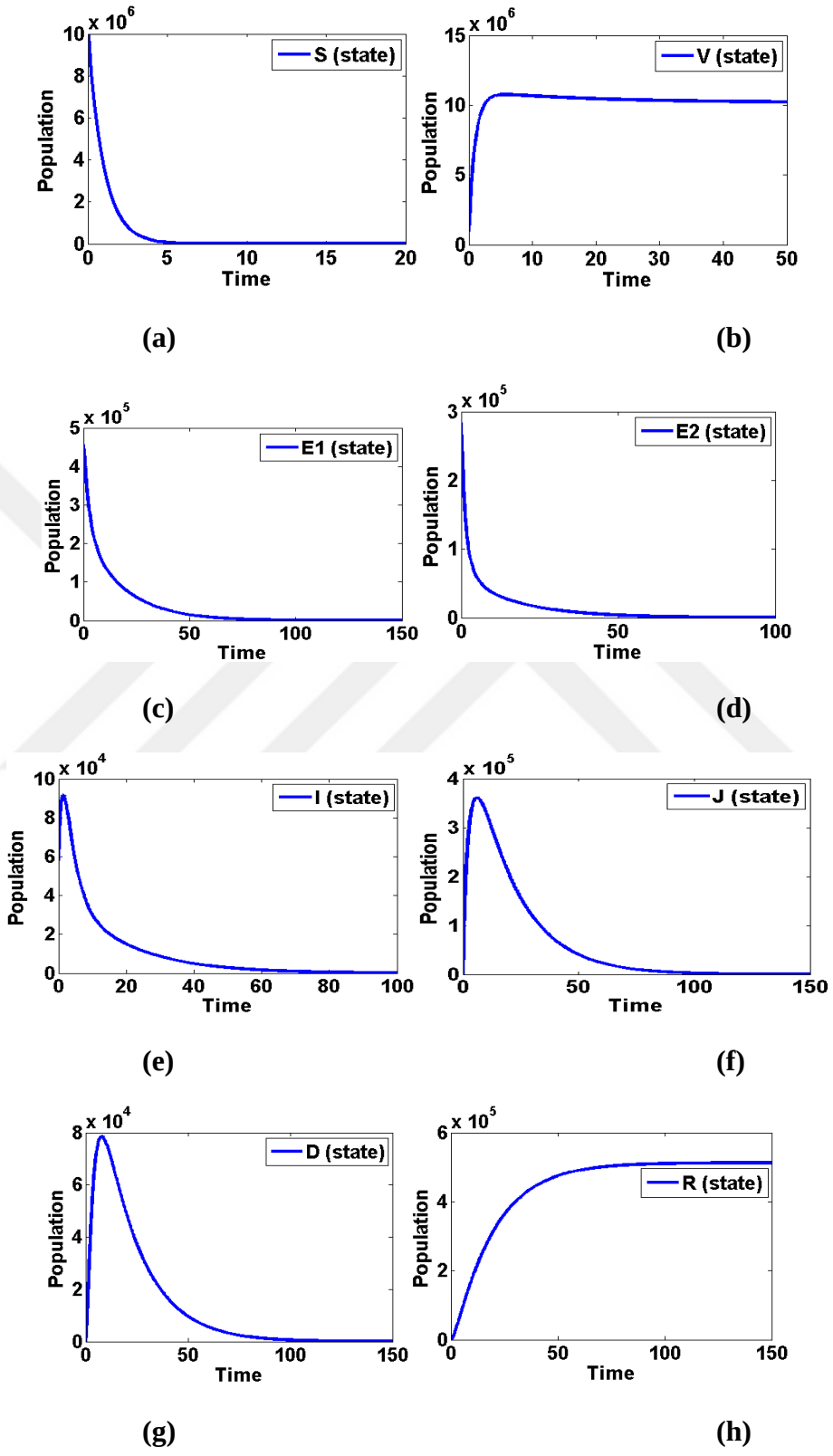


Figure 7.2. The dynamics of state variables of the Ebola Virus disease model using the SBToolbox for Matlab for parameters and fitted values for Guinea, 2015.

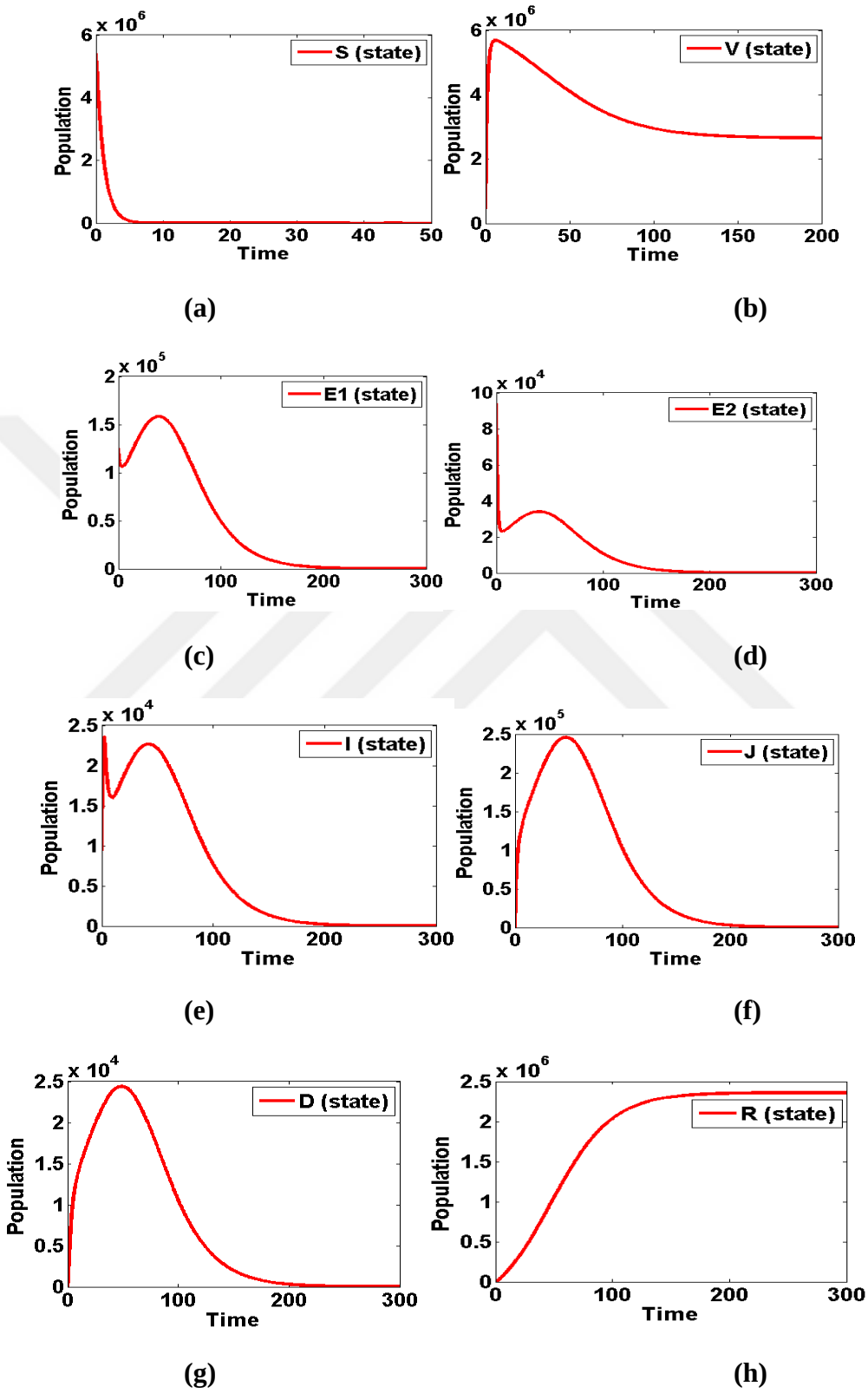


Figure 7.3. The dynamics of state variables of the Ebola Virus disease model using the SBToolbox for Matlab for parameters and fitted values for Sierra Leone, 2015.

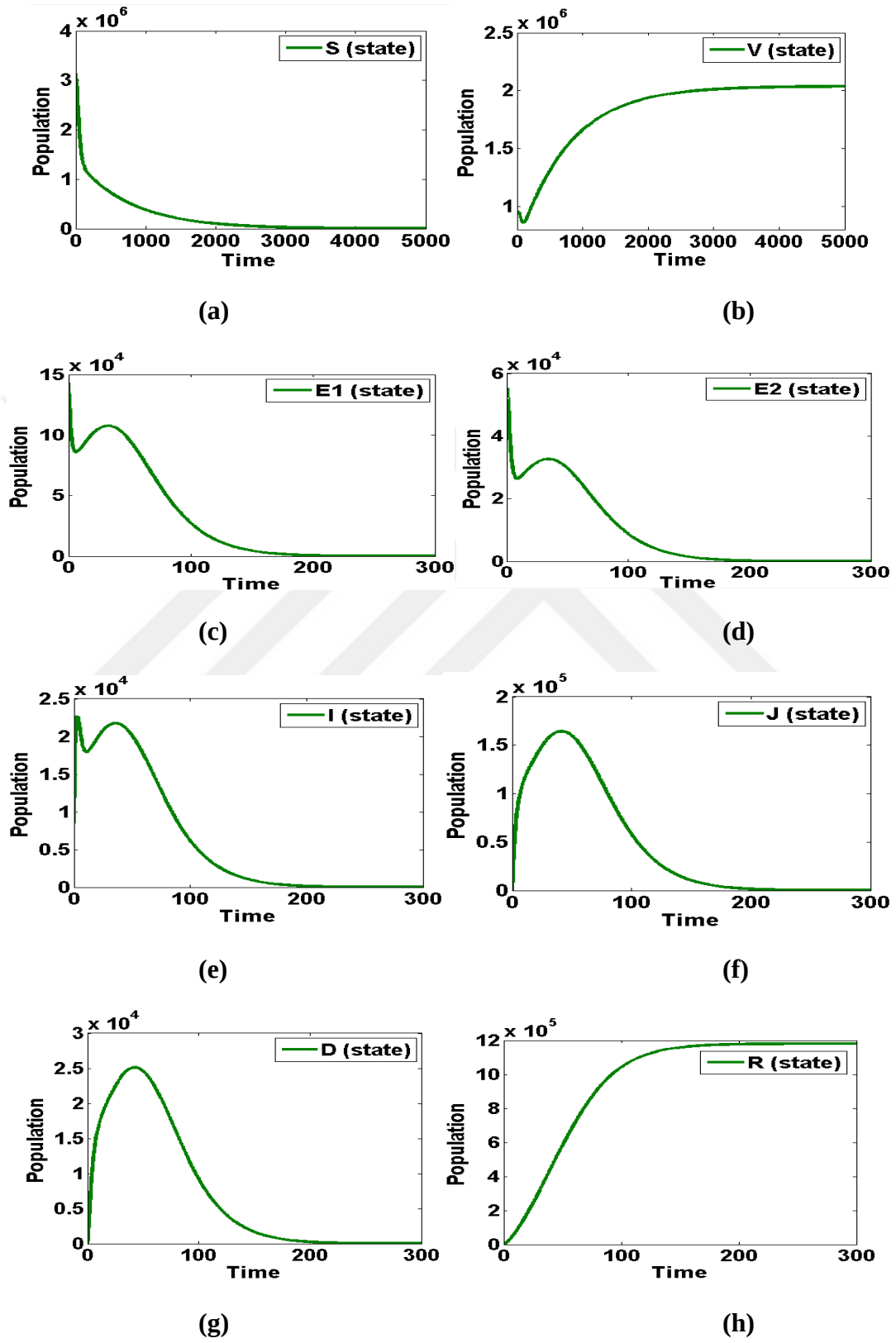
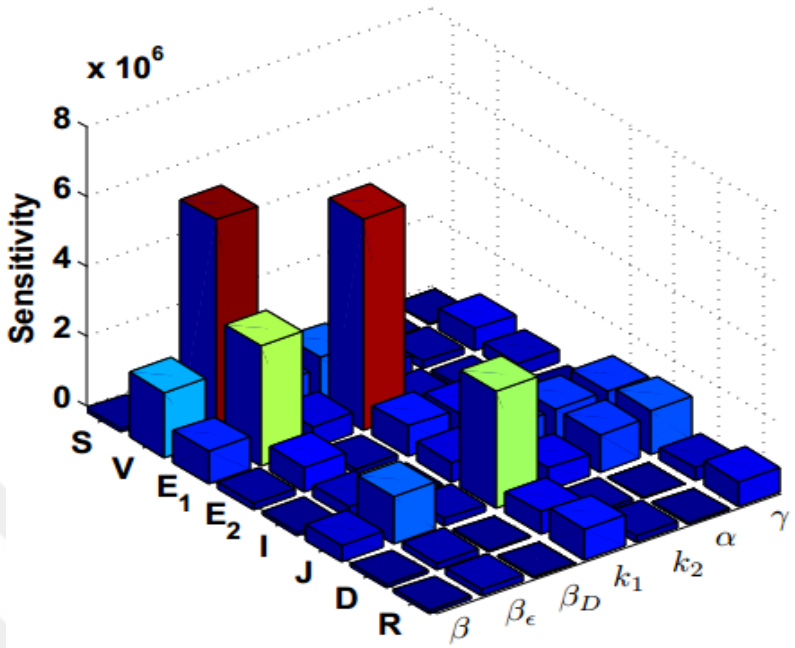
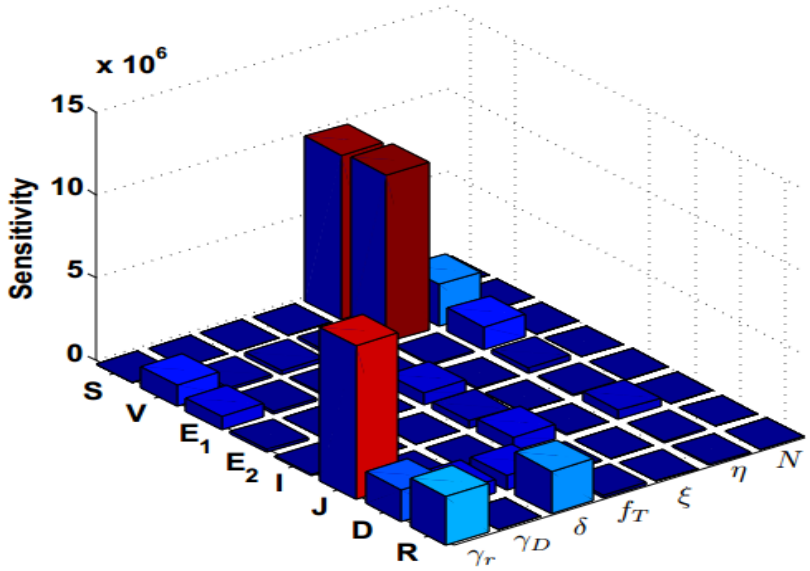


Figure 7.4. The dynamics of state variables of the Ebola Virus disease model using the SBToolbox for Matlab for parameters and fitted values for Liberia, 2015.

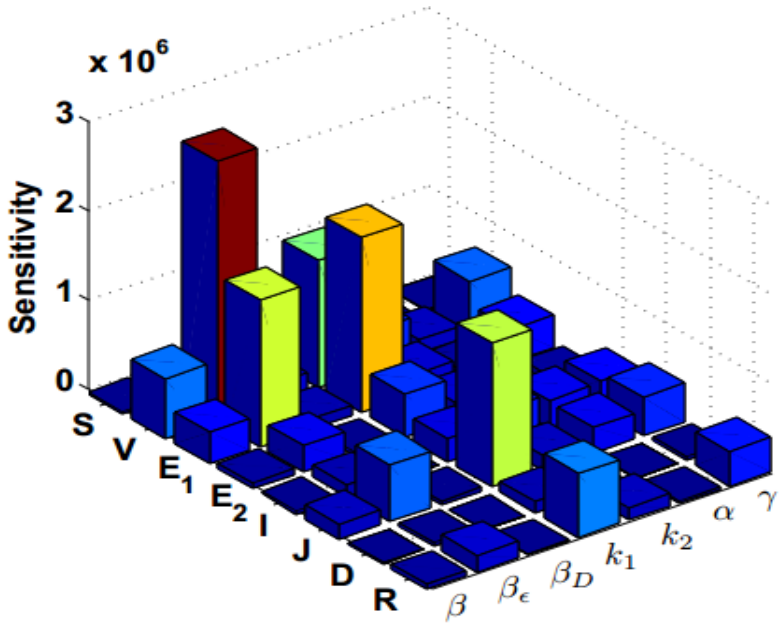


(a) $\boldsymbol{\beta = 0.2231,\ \beta_\epsilon = 0.1374,\ \beta_D = 0.1373,\ k_1 = 0.25,\ k_2 = 0.3333,\ \alpha = 0.3333,\ \gamma = 0.1666.}$

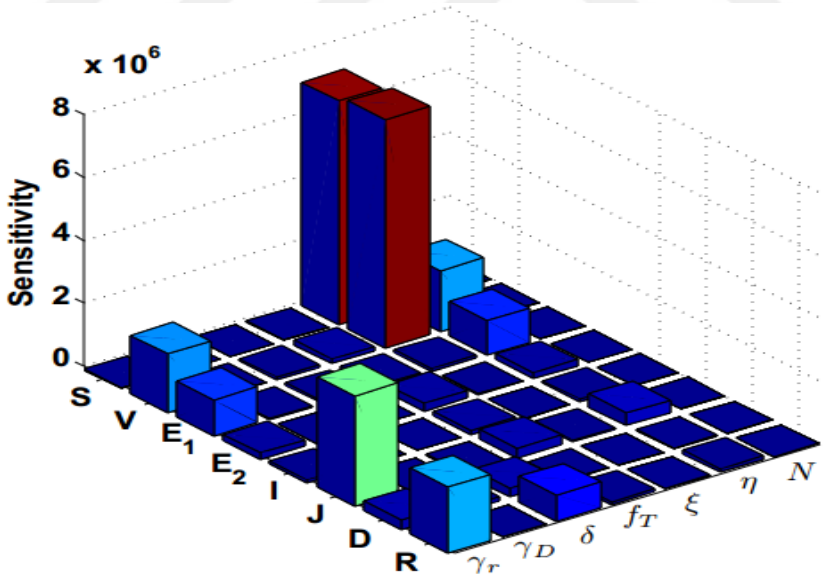


(b) $\boldsymbol{\gamma_r = 0.1470,\ \gamma_D = 0.5,\ \delta = 0.6728,\ f_T = 0.7136,\ \xi = 1.0002,\ \eta = 0.4572,\ N = 11745189.}$

Figure 7.5. The local sensitivity of all variables with respect to a set of parameters using the SimBiology Toolbox for Matlab for fitted parameters values for Guinea, 2015.With initial conditions: $\boldsymbol{S(0) = 10000000,\ V(0) = 946000,\ E_1(0) = 457262,\ E_2(0) = 283743,\ I(0) = 58184,\ J(0) = 0,\ D(0) = 0,\ R(0) = 0.}$

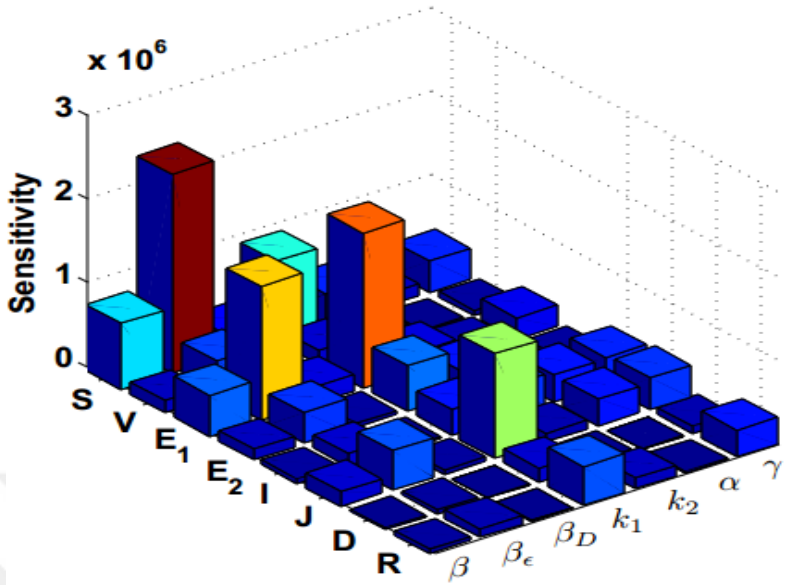


(a) $\boldsymbol{\beta = 0.5237,\ \beta_{\epsilon} = 0.3323,\ \beta_D = 0.1243,\ k_1 = 0.25,\ k_2 = 0.3333,\ \alpha = 0.3333,\ \gamma = 0.1666.}$

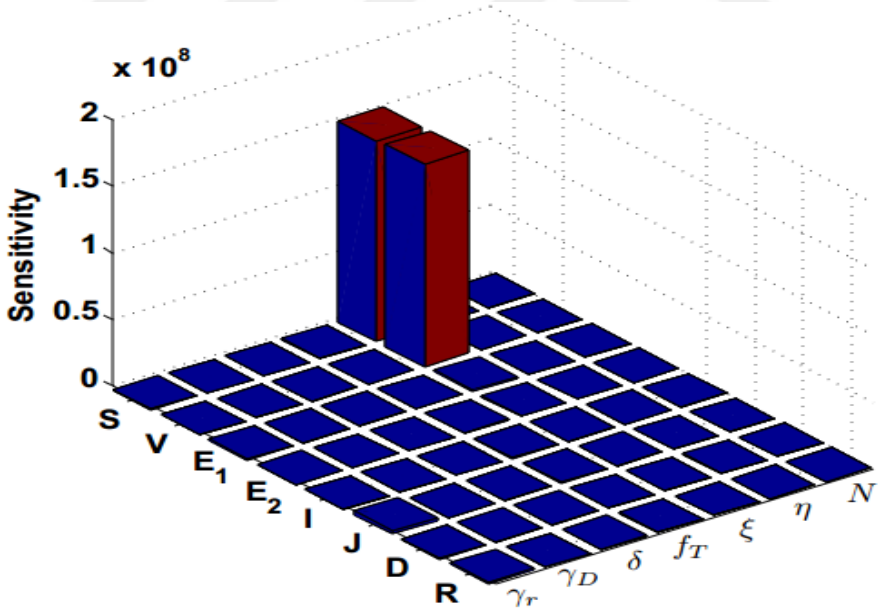


(b) $\boldsymbol{\gamma_r = 0.1429,\ \gamma_D = 0.5,\ \delta = 0.3143,\ f_T = 0.8291,\ \xi = 0.8671,\ \eta = 0.5649,\ N = 6092075.}$

Figure 7.6. The local sensitivity of all variables with respect to a set of parameters using the SimBiology Toolbox for Matlab for fitted parameters values for Sierra Leone, 2015. With initial conditions: $\mathbf{S(0) = 5404728,\ V(0) = 458218,\ E_1(0) = 125464,\ E_2(0) = 94213,\ I(0) = 9452,\ J(0) = 0,\ D(0) = 0,\ R(0) = 0.}$



(a) $\boldsymbol{\beta = 0.3126,\ \beta_{\epsilon} = 0.17351,\ \beta_D = 0.2239,\ k_1 = 0.25,\ k_2 = 0.3333,\ \alpha = 0.3333,\ \gamma = 0.1666.}$



(b) $\boldsymbol{\gamma_r = 0.1388,\ \gamma_D = 0.5,\ \delta = 0.4765,\ f_T = 0.4898,\ \xi = 0.0013,\ \eta = 0.5487,\ N = 4294077.}$

Figure 7.7. The local sensitivity of all variables with respect to a set of parameters using the SimBiology Toolbox for Matlab for fitted parameters values for Liberia, 2015.With initial conditions: $\mathbf{S(0) = 3139652, V(0) = 947386, E_1(0) = 143163, E_2(0) = 55378,\ I(0) = 8498,\ J(0) = 0, D(0) = 0, R(0) = 0.}$

8. CONCLUSION AND RECOMMENDATIONS

Mathematical modeling and computational simulations of epidemic models are important tools in systems biology. Studying the behavior of diseases model frequently needs some methods of model analysis. In this thesis, we studied some epidemic disease models such as SI model, SIS model, SIR model and Ebola virus disease model. We proposed two computational tools of model analysis. The suggested computational tools of model analysis here significantly play in calculating some numerical approximate solutions and also identifying critical model elements. The suggested mathematical model of Ebola virus diseases helps us for further studying and understanding the disease in many ways. First of all, the mathematical representation of the model becomes a great step forward to integrate experimental knowledge into a coherent picture. Secondly, calculating model population of state variables provides suggestions for its future development. Finally, identifying critical model parameters in this study is another way to study the model practically and give some suggestions for future improvements of the disease. Furthermore, the results in this project will help international efforts to control the Ebola in countries in West Africa. More interestingly, the proposed computational tools here of model analysis will be applied to a wide range of complex infectious disease models in systems of biology.

9. APPENDIX A

Dynamic System Simulations Using Systems Biology Toolbox (SBToolbox) for Matlab

A.1. SBToolbox file for Matlab containing the Ebola virus disease Model for Guinea

********** MODEL NAME

The Ebola virus disease Model for Guinea

********** MODEL NOTES

beta=b1

beta epsilon=b2

betaD=b3

xi=x

eta=e

alpha=a

gamma=g1

gammar=g2

gammaD=g3

delta=d

population=N

********** MODEL STATES

d/dt(S)=-(b1*I+b2*J+b3*D)*S/N-x*S

d/dt(V)=x*S-(b1*I+b2*J+b3*D)*e*V/N

d/dt(E1)=(b1*I+b2*J+b3*D)*(S+e*V)/N-K1*E1

d/dt(E2)=K1*E1-(K2+ft)*E2

d/dt(I)=K2*E2-(a+g1)*I

d/dt(J)=ft*E2+a*I-g2*J

d/dt(D)=d*g1*I+d*g2*J-g3*D

d/dt(R)=(1-d)*g1*I+(1-d)*g2*J

S(0)=10000000

V(0)=946000

E1(0)=457262

E2(0)=283743

I(0)=58184

J(0)=0

D(0)=0

R(0)=0

********** MODEL PARAMETERS

b1=0.2231

b2=0.1374

b3=0.1373

K1=0.25

K2=0.3333

a=0.3333

g1=0.1666

g2=0.1470

g3=0.5

d=0.6728

ft=0.7136

x=1.0002

e=0.4572

N=11745189

A.2. SBToolbox file for Matlab containing the Ebola virus disease Model for Sierra Leone

********** MODEL NAME

The Ebola virus disease Model for Sierra Leone

********** MODEL NOTES

beta=b1

beta epsilon=b2

betaD=b3

xi=x

eta=e

alpha=a

gamma=g1

gammar=g2

gammaD=g3

delta=d

population=N

********** MODEL STATES

d/dt(S)=-(b1*I+b2*J+b3*D)*S/N-x*S

d/dt(V)=x*S-(b1*I+b2*J+b3*D)*e*V/N

d/dt(E1)=(b1*I+b2*J+b3*D)*(S+e*V)/N-K1*E1

d/dt(E2)=K1*E1-(K2+ft)*E2

d/dt(I)=K2*E2-(a+g1)*I

d/dt(J)=ft*E2+a*I-g2*J

d/dt(D)=d*g1*I+d*g2*J-g3*D

d/dt(R)=(1-d)*g1*I+(1-d)*g2*J

S(0)=5404728

V(0)=458218

E1(0)=125464

E2(0)=94213

I(0)=9452

J(0)=0

D(0)=0

R(0)=0

********** MODEL PARAMETERS

b1=0.5237

b2=0.3323

b3=0.1243

K1=0.25

K2=0.3333

a=0.3333

g1=0.1666

g2=0.1429

g3=0.5

d=0.3143

ft=0.8291

x=0.8671

e=0.5649

N=6092075

A.3. SBToolbox file for Matlab containing the Ebola virus disease Model for Liberia

********** MODEL NAME

The Ebola virus disease Model for Liberia

********** MODEL NOTES

beta=b1

beta epsilon=b2

betaD=b3

xi=x

eta=e

alpha=a

gamma=g1

gammar=g2

gammaD=g3

delta=d

population=N

********** MODEL STATES

d/dt(S)=-(b1*I+b2*J+b3*D)*S/N-x*S

d/dt(V)=x*S-(b1*I+b2*J+b3*D)*e*V/N

d/dt(E1)=(b1*I+b2*J+b3*D)*(S+e*V)/N-K1*E1

d/dt(E2)=K1*E1-(K2+ft)*E2

d/dt(I)=K2*E2-(a+g1)*I

d/dt(J)=ft*E2+a*I-g2*J

d/dt(D)=d*g1*I+d*g2*J-g3*D

d/dt(R)=(1-d)*g1*I+(1-d)*g2*J

S(0)=3139652

V(0)=947386

E1(0)=143163

E2(0)=55378

I(0)=8498

J(0)=0

D(0)=0

R(0)=0

********** MODEL PARAMETERS

b1=0.3126

b2=0.17351

b3=0.2239

K1=0.25

K2=0.3333

a=0.3333

g1=0.1666

g2=0.1388

g3=0.5

d=0.4765

ft=0.4898

x=0.0013

e=0.5487

N=4294077

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