MATHEMATICAL MODELING AND CONTROL OF MERS-COV EPIDEMICS

A THESIS

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF MASTER OF SCIENCE

IN THE GRADUATE SCHOOL OF THE

TEXAS WOMAN'S UNIVERSITY

DEPARTMENT OF MATHEMATICS AND COMPUTER SCIENCE

COLLEGE OF ARTS AND SCIENCES

BY

NARJES S. ALSHAKHOURY B.S.

DENTON, TEXAS

DECEMBER 2017

DEDICATION

I would like to dedicate this thesis to my lovely mother Amenah AL Musa and my father Shubber Alshakhoury. To my siblings and all the members of my family that I left in my country to achieve this degree.

This work couldn’t have been completed without the continuous support from my lovely family, my husband Abdulla Albahrani, my sweet son Muhtada, and my two beautiful daughters Hawra and Israa, Thus, I would like to devote my success to them.

ACKNOWLEDGMENTS

I would like to express my deep appreciation to my academic advisor Dr. Ellina Grigorieva, who supported and helped me kindly throughout my research journey.

Secondly, I would like to send special thanks to Dr. Don E. Edwards and Dr. Junalyn Navarra-Madsen, who dedicated their time to review my thesis and gave me helpful feedbacks.

ABSTRACT

NARJES ALSHAKHOURY

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Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a viral infectious disease that can be transmitted to humans through interaction with infected animals or humans. In this thesis, we will investigate the basic compartment models for infectious diseases qualitatively and quantitatively. The equilibrium points and their stability will be explored by using differential equations methods. Based on the available data on the Middle East Respiratory Syndrome, this research study will clarify the model of MERS-CoV analytically and numerically. Additionally, this proposed study will explore the optimal control to reduce the spread of MERS-CoV disease as well as its threshold. Mathematical software, such as MAPLE, will be used to investigate the model.

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CHAPTER I

INTRODUCTION

Recently, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) has concerned the Arabian Peninsula. MERS-CoV is believed to be an infectious disease transmitted to humans by contact with either infected animals or humans. As a first virus that related to lineage C Betacoronavirus (βCoV) and the sixth Coronavirus (CoV), MERS-CoV is a virus transmitted to humans [2]. In 2012, the first case of MERS-CoV was recognized in the Kingdom of Saudi Arabia. The case symptoms included fever, short breath, cough, and expectoration [29]. Before MERS-CoV had emerged, the outbreak of the zoonotic coronavirus known as Sever Acute Respiratory Syndrome (SARS) spread in 26 countries, which exceeded 8000 cases in 2003 [30]. In fact, SARS was the first known coronavirus infection at that time. Before that time, Coronavirus infections caused no more than a moderate upper respiratory tract infection which was not considered as major public health issue [5]. Early large nosocomial epidemic events are significant characteristic for both SARS and MERS, nosocomial infectious diseases that have a reproduction number declining to be less than 1 for 3 to 5 disease generations [3]. MERS-CoV related viruses have been discovered in bats that have indirect contact with humans [26]. Considerable indications assumed that the main source of MERS-CoV transmission is dromedary camels [18,23, 9]. It is suggested that there might be a viral connection between bats, camels and humans, whereas there is no specific evidence of the main sources of MERS-CoV [27]. The result of the zoonotic transmission events that have generated MERS-CoV

with clusters of reported human to human transmission of the virus is that animal is a preceding source of MERS-CoV [12]. In early 1992, the antibodies of MERS existed in dromedaries, whereas the first case of MERS-CoV reported in humans was in 2012 [23]. Even though some evidence suggested that camels are one of the sources of MERS-CoV transmissions, the precise sources of its outbreak are still unknown [9]. Even though MERS-CoV was spread first in the Arabian Peninsula, the outbreak spread around the world in many countries. An Italian adult man who traveled to Jordan was reported as a first case of MERS-CoV in Italy in May 2013 [21]. In 2014, many cases of MERS-CoV were reported in Saudi Arabia and in United Arab Emirates. At that time, the cases of MERS-CoV that were reported outside the Middle East had a history of visiting either United Arab Emirates (UAE) or the Kingdom of Saudi Arabia (KSA) [1]. MERS-CoV outbreaks are increasing since 2012. According to the World Health Organization (WHO), globally, 2079 cases have been reported, with 722 cases experiencing death as of September 6th, 2017.

The lack of understanding of the dynamics of MERS-CoV transmission would lead to a fatal dramatic outbreak. Some factors, also, would assist in its spread, such as the pilgrims to the holy places in KSA. Annually, about 2 to 3 million Muslim pilgrims coming from approximately 180 countries travel to Mecca in KSA to perform the pilgrimage or Hajj, which affects the Saudi Arabia's health system [17]. The Hajj event might be a factor of increasing the spread of MERS-CoV around the world. Until now, there is no antivirus for MERS-CoV infection to prevent its spread. The only precaution taken to limit the spread of the disease is isolation and hospitalization of the infected patients. The visitors coming back from the Middle East area must be investigated and isolated if they are suspected of

having any contact with MERS-CoV cases, or having the disease symptoms as the incubation period of the MER-CoV is 12 days [8].

With this uncertain dynamic of MERS-CoV transmission, mathematical model and optimal control can assist epidemiologists to investigate the spread of the disease and behavior so that they can discover the strategies to limit the spread. In 2013, a stochastic model including nine compartments for MERS-CoV was approached by Chowella et al. [4]. Their results indicate that the average reproduction number is 0.45 if all the reported zoonotic cases are severe, while about 57% of secondary cases are symptomatic. The major result in [4] was that the hospitalized cases should be more considered by epidemiologists because hospitalized transmission is four times higher than community transmission. On the other side, during the largest outbreak which happened outside the Middle East in 2015 in the Republic of South Korea, [26] studied the mathematical model of MERS-CoV. The study indicates a higher basic reproduction number that equals to 4.422. Using SIR model and Bayesian method, [25] studied the epidemic level of MERS and the reproduction values in western, central, and eastern regions of Saudi Arabia between May 2013 and May 2015. In 2017, a stability method of ordinary differential equation was used by Al-Asouad N. et al. in [20] to study the analytical investigation of MERS-CoV mathematical model, resulting the endemic steady state which is stable with isolation method for preventing the spread of MERS-CoV. Also, [28] studied the mathematical dynamic transmission model for MERS-CoV in two areas by analyzing the sensitivity indices of the reproduction number to reduce the infected cases. However, these studies only focused on the mathematical models of MERS, but did not investigate the optimal control of MERS-CoV. Indeed, an optimal

control objective function can be introduced to reduce and limit the factors of MERS-CoV outbreak.

This paper contains five chapters. In Chapter II, we will investigate the properties of the two basic compartment models for infectious diseases, which are Susceptible-Infectious-Recovery (SIR) model and Susceptible-Exposed-Infectious-Recovery (SEIR) model. In Chapter III, a model of MERS-CoV will be created and investigated using methods of nonlinear differential equations. Also, it contains developed model of MERS-CoV with evaluation its reproduction ratio using next-generation method. Numerical solutions will be presented based on available data for MERS-CoV outbreak in Chapter IV. Mathematical software, such as MAPLE will be used to explore the model. Numerical control problem of reductions of the spread of MERS-CoV disease will be also presented. An optimal control problem of minimization of infected individuals at the terminal time T is stated and solved numerically. In the last chapter, the result of our study will be discussed and the conclusion will be made.

CHAPTER II

MATHEMATICAL COMPARTMENT MODELS FOR INFECTIOUS DISEASES: (SIR) AND (SEIR) MODELS

The main consideration in epidemiology is studying the spread of diseases. Epidemiology deals with tracing and analyzing the factors that cause the spread of diseases over time, and seeks out finding possible control. Besides epidemiology, mathematical modeling is a contributory aspect of the study of infectious diseases. Mathematical modeling assists in understanding and predicting the behavior of infectious diseases. Mathematical epidemiology models have been studied for long time. The first compartment model for epidemic infectious diseases was derived by Kermarck and McKendrick [14]. In epidemic models, the population usually is divided into classes or compartments. In order to study the dynamics of the infectious diseases, the basic SIR epidemic model is used to divide the population into three various classes, which are susceptible S, infected I, and recovered R individuals. In this model, the movement of individuals from one compartment to another is determined by their capability to fight the diseases and the individuals' interactions with infected people [22]. The basic SIR model represents a system with three non-linear 1st order differential equations. Addition of an exposed compartment to SIR model leads to another model called SEIR model.

In this chapter, investigation of the properties of the basic SIR and SEIR models will be explored. The SIR model will be first represented with a diagram, and an

explanation of its compartments and its parameters that show the connection between the compartments. Then, its equilibria and its basic reproduction ratio will be explored. Also,

the stability of its equilibria will be discovered according to the theory of stability. In the numerical solution for the SIR model, the trajectory of the model and the Jacobian matrix after linearizing the system of the SIR model will be explored. With selected initial value, the behavior of the spread of the infectious disease will be discovered. The same process will be followed for the SIR model, and by adding Exposed individuals compartment make it SEIR model.

2.1 Susceptible-Infectious-Recovery (SIR) Model

In SIR model, the population size is divided into three different states or compartments, which are Susceptible $S(t)$, Infectious $I(t)$, and Recovered individuals $R(t)$. The assumptions of our SIR model are stated below:

- The population size is N, which contains all three compartments as mentioned before; therefore $N = S(t) + I(t) + R(t)$
- The population size is fixed
- In this model, the demographics (the natural birth and death of individuals) will be considered; The rate of birth equals the death rate and they are denoted by μ; the birth rate enters the susceptible class as μN
- The rate of death is independent of the disease
- The rate of the interactions between susceptible class and infectious class is β

- Individuals who transferred from the infectious class to the recovery class are represented by α

The flowchart below explains the movement from each class and the rate of their interactions.

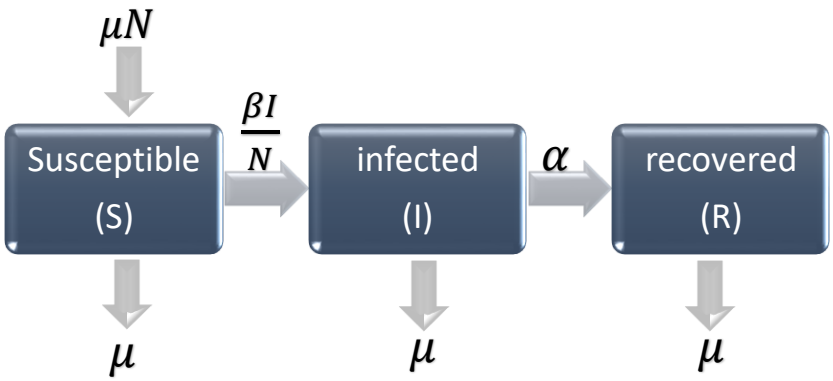


Figure 2.1 SIR compartment model

The diagram above can be represented by the system of nonlinear differential equations. Indeed, in SIR model, it is difficult to find the precise solutions of $S(t)$ and $I(t)$ analytically, while this model assists to describe the behavior of their interactions [16]. The formulas in (2.1) show the system of SIR model:

$$\begin{cases} \frac{dS(t)}{dt} = \mu N - \mu S(t) - \frac{1}{N}\beta S(t)I(t) \\ \frac{dI(t)}{dt} = \frac{1}{N}\beta S(t)I(t) - \alpha I(t) - \mu I(t) \\ \frac{dR(t)}{dt} = \alpha I(t) - \mu R(t) \end{cases} \quad (2.1)$$

Because of our assumption that the population is constant and $N = S(t) + I(t) + R(t)$, the system can be reduced to the two nonlinear differential equations. Moreover, by

considering that $s = \frac{S}{N}$, $i = \frac{I}{N}$, and, $r = \frac{R}{N}$ the SIR model would be written as new system (2.2) after substituting and dividing all the equations by N. For convenience, returning to original variables we have:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \mu - \mu S(t) - \beta S(t)I(t) = f(S(t), I(t), t) \\
\frac{dI(t)}{dt} &= \beta S(t)I(t) - (\alpha + \mu)I(t) = g(S(t), I(t), t) \\
\frac{dR(t)}{dt} &= \alpha I(t) - \mu R(t) = h(I(t), R(t), t)
\end{aligned} \tag{2.2}$$

In the system (2.2), when the infectious compartment increases, the epidemic would occur [10]. Therefore, when $\frac{dI(t)}{dt} > 0$, then $\beta S(t)I(t) > (\alpha + \mu)I(t)$. That leads to

$$\frac{\beta S(t)I(t)}{(\alpha + \mu)} > I(t) \tag{2.3}$$

If the number of susceptible approximately equals to 1, the upcoming quantity would be approved after substituting $S(t) \approx 1$.

$$\frac{\beta}{(\alpha + \mu)} > 1 \tag{2.4}$$

The left-hand side of (2.4) is known as the basic reproduction ratio (R_0).

Definition. The basic reproduction ratio is the number of secondary infections that are caused by a single infectious case so that the disease would spread continuously.

The definition of the ratio R_0 is considered by [11,13], and it is found as well for SIR model.

In the next section, we will explore the equilibrium points of SIR model to investigate more about its behavior. To find its equilibria, the linearization of the system must be conducted.

In order to linearize the system (2.2), the equations below need to be solved:

$$f(S(t), I(t), t) = 0 \quad , \quad g(S(t), I(t), t) = 0 \quad , \quad h(I(t), R(t), t) = 0$$

Thus,

$$\begin{cases} \mu - \mu S(t) - \beta S(t) I(t) = 0 \\ \beta S(t) I(t) - (\alpha + \mu) I(t) = 0 \\ \alpha I(t) - \mu R(t) = 0 \end{cases} \qquad (2.5)$$

From (b), the equation $\beta S(t) I(t) = (\alpha + \mu) I(t)$ can be substituted in the first equation above to have

$$\mu(1 - S(t)) - (\alpha + \mu) I(t) = 0$$

The left-hand side of this equation must be zero when $S(t) = 1$, and $I(t) = 0$, by substituting the last equation in (2.5), $R(t) = 0$. Thus, the first equilibrium point is $(S^*, I^*, R^*) = (1,0,0)$. In addition to this equilibrium point for SIR model illustrated by (2.2), the second equilibrium point would be found by solving the equation the second equation in (2.5). After dividing the equation by $I(t)$ on both sides, we will have:

$\beta S(t) = (\alpha + \mu)$, which will lead to $S^* = \frac{\alpha + \mu}{\beta}$. After substituting this value in the first equation in (2.5) we will have:

$\mu - \mu\left(\frac{\alpha+\mu}{\beta}\right) - \beta I(t)\left(\frac{\alpha+\mu}{\beta}\right) = 0$. By solving for $I(t)$, I^* would be equal to $\frac{\mu}{\alpha+\mu} - \frac{\mu}{\beta}$. Also, R^* would be found by substituting the value of I^* into last equation in (2.5).

Thus, $R^* = \frac{\alpha}{\mu}\left(\frac{\mu}{\alpha+\mu} - \frac{\mu}{\beta}\right) = \alpha\left(\frac{1}{\alpha+\mu} - \frac{1}{\beta}\right)$. The second equilibrium point for our system, therefore, would be equal to $\left(\frac{\alpha+\mu}{\beta}, \frac{\mu}{\alpha+\mu} - \frac{\mu}{\beta}, \alpha\left(\frac{1}{\alpha+\mu} - \frac{1}{\beta}\right)\right)$.

Definition. Endemic equilibrium (EE) occur when $I^* > 0$ so the disease keeps spreading in the population while the Disease-Free equilibrium (DFE) occurs when $I^* = 0$.

It is also possible for EE equilibrium to be written in terms of R_0 , which is

$$\left(\frac{1}{R_0}, \frac{(R_0-1)\mu}{\beta}, \frac{\alpha(R_0-1)}{\beta}\right)$$

Definition. The $(k \times k)$ matrix of partial derivatives of nonlinear system of k first order equations is called **Jacobian** (***J***) of the system.

The Jacobian for SIR model (2.2) is evaluated as:

$$J(S,I,R) = \begin{bmatrix} \frac{\partial f}{\partial S} & \frac{\partial f}{\partial I} & \frac{\partial f}{\partial R} \\ \frac{\partial g}{\partial S} & \frac{\partial g}{\partial I} & \frac{\partial g}{\partial R} \\ \frac{\partial h}{\partial S} & \frac{\partial h}{\partial I} & \frac{\partial h}{\partial R} \end{bmatrix} = \begin{bmatrix} -\beta I(t) - \mu & -\beta S(t) & 0 \\ \beta I(t) & \beta S(t) - (\alpha+\mu) & 0 \\ 0 & \alpha & -\mu \end{bmatrix}$$

To investigate more about the behavior of epidemic models near equilibrium points, it is helpful to evaluate the eigenvalues of Jacobian matrix at the equilibrium points of the system of nonlinear equations.

Theorem. (Stability Theorem) If J is a $(k\times k)$ matrix, the Jacobian matrix for a nonlinear system of k first-order equations, then the eigenvalues $(\lambda_i, i = 1 \dots k)$ of J at the equilibrium points have five different possible behaviors depending on its value. The table below denotes these cases:

Table 1. Possible Behaviors Depending on The Values of Eigenvalues

λ_i **value**	**equilibria**
Real part for all eigenvalues is negative	Stable
At least one eigenvalue has negative real part value and at least one eigenvalue has positive real part eigenvalue	Saddle
Real part for all eigenvalues is positive	Unstable
At least a complex conjugate pair eigenvalues	Stable or unstable (Spiral)
All eigenvalues are real	Stable or unstable (Node)
A pair of complex eigenvalues with real part equals to zero	Linear center

For more information about this theorem, see [19, 22]. To find the characteristic equation for the Jacobian matrix at equilibrium points, $\det(J - \lambda I) = 0$ must be solved. Before finding the characteristic equation, we will evaluate the Jacobian matrix at DFE= $(1,0,0)$.

$$J(1,0,0) = \begin{bmatrix} -\mu & -\beta & 0 \\ 0 & \beta - (\alpha + \mu) & 0 \\ 0 & \alpha & -\mu \end{bmatrix}$$

Thus, the characteristic equation of Jacobian matrix at DFE point $(1,0,0)$ is shown below:

$$\det(J-\lambda I)=\begin{vmatrix}-\mu-\lambda & -\beta & 0\\ 0 & \beta-(\alpha+\mu)-\lambda & 0\\ 0 & \alpha & -\mu-\lambda\end{vmatrix}=0$$

$$(-\mu-\lambda)^2\,(\beta-(\alpha+\mu)-\lambda)=0$$

The eigenvalues are

$$\lambda_{1,2}=-\mu,\ \lambda_3=\beta-(\alpha+\mu)$$

Because $\mu>0$, there are two cases for equilibrium behavior:

- If $\beta-(\alpha+\mu)<0$, then DFE is a stable node
- If $\beta-(\alpha+\mu)>0$, then DFE is a saddle point

The case $I^*=0$ is discussed above resulting the DFE. In addition to DFE, let us discuss the other cases.

Case 1: when $I^*>0$

As mentioned in the definition of **EE**, the infections would occur in this case. Therefore, $\frac{dI}{dt}>0$, which leads to $\beta S(t)I(t)-(\alpha+\mu)I(t)>0$.

Then,

$$[\beta S(t)-(\alpha+\mu)]I(t)>0 \qquad (2.6)$$

After writing the EE point in term of R_0, we have $(S^*, I^*, R^*) = \left(\frac{1}{R_0}, \frac{(R_0-1)\mu}{\beta}, \frac{\alpha}{\beta}(R_0-1)\right)$.

In this case, we will have

$$\frac{(R_0-1)\mu}{\beta} > 0$$

Because $\frac{\mu}{\beta} > 0$, $R_0 > 1$. This makes a stable EE and unstable DFE.

Case 2: when $I^* < 0$

In this case, $\frac{(R_0-1)\mu}{\beta} < 0$, and this happens when $R_0 < 1$. Moreover, in this case, we obtain unstable EE and stable DFE.

These cases will be next shown numerically.

2.2 Numerical Explanation of SIR Model using MAPLE

Using computer software and programs for simulating models make the explorations easier. In this section, I will investigate the SIR model numerically by setting initial values for SIR model.

MAPLE software can also assist in finding the Jacobian matrix for SIR model. The output of Jacobian matrix of (a, b, c) equations mentioned above is shown as:

$$J := \begin{bmatrix} -\mu - \beta\, In & -\beta\, S & 0 \\ \beta\, In & \beta\, S - \alpha - \mu & 0 \\ 0 & \alpha & -\mu \end{bmatrix}$$

Figure 2.2. The output of Jacobian matrix of SIR model

Also, the output of equilibrium points is the same as what is found analytically above, which is:

$$sol := \{ In = 0, R = 0, S = 1 \}, \{ R = -\frac{\alpha\,(-\beta + \alpha + \mu)}{\beta\,(\alpha + \mu)}, In = -\frac{\mu\,(-\beta + \alpha + \mu)}{\beta\,(\alpha + \mu)}, S = \frac{\alpha + \mu}{\beta} \}$$

Figure 2.3. The output of equilibrium points of SIR model

These outputs in MAPLE allow us to evaluate the numerical solutions for our system easily. Moreover, the eigenvalues and the eigenvectors can also be evaluated by MAPLE. (See Appendix-A (a) for the inputs). After substituting these two values on the Jacobian matrix, we obtain the Jacobian evaluated at DFE equilibria and its eigenvalues are:

$$\begin{bmatrix} -\mu & -\beta & 0 \\ 0 & \beta - \alpha - \mu & 0 \\ 0 & \alpha & -\mu \end{bmatrix}$$

$$eigenvalue1 := -\mu, -\mu, \beta - \alpha - \mu$$

Figure 2.4. The output of the Jacobian matrix at DFE and its eigenvalues

While Jacobian at EE point is:

$$\begin{bmatrix} -\mu + \frac{\mu(-\beta+\alpha+\mu)}{\alpha+\mu} & -\alpha-\mu & 0 \\ -\frac{\mu(-\beta+\alpha+\mu)}{\alpha+\mu} & 0 & 0 \\ 0 & \alpha & -\mu \end{bmatrix}$$

Figure 2.5. The output of the Jacobian matrix at EE

Let us explore the case $R_0 < 1$ for SIR model. Figure (2.6) below shows the trajectory for susceptible and infectious individuals with $\mu = 0.6, \beta = 0.5, \alpha = 0.3$ by using MAPLE, (see Appendix-A, Figure (2.6)).

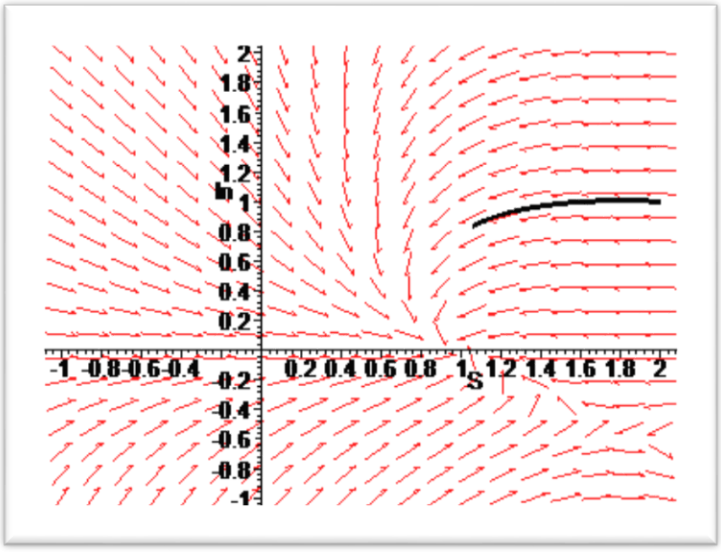


Figure 2.6. The plot of the trajectory for susceptible and infectious individuals of SIR model using MAPLE

In Figure (2.6) above, it is obvious that the behavior of DFE is stable node because the equilibrium points in this case are real negative values.

Figures (2.7) below show the 3D plotting for SIR model. (See Appendix-A, (Figure 2.7).

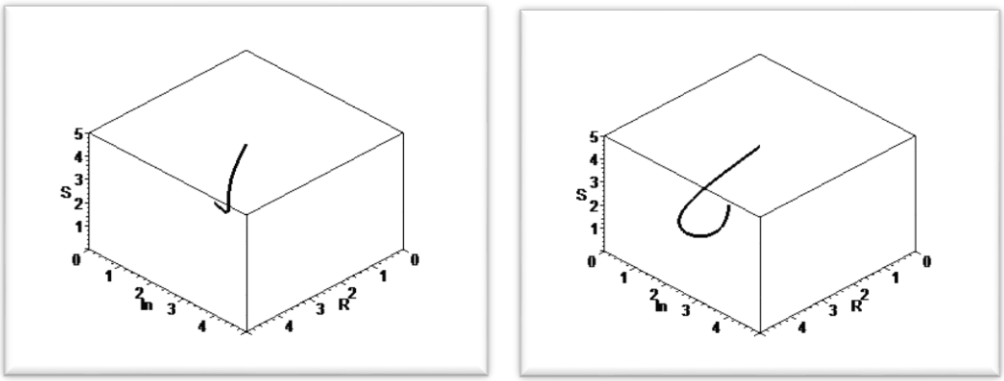


Figure 2.7. The 3D plot of SIR model

Case 2: when $R_0 > 1$, the behavior of DFE is a saddle equilibria while EE is stable spiral equilibria. Let set $\mu = 0.3$, $\beta = 0.7$, $\alpha = 0.2$, the trajectory of susceptible and infectious classes is shown in Figure (2.8). (See Appendix-A, (Figure 2.8)).

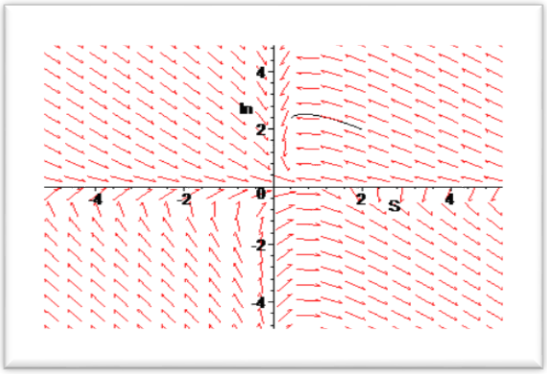


Figure 2.8. The trajectory of susceptible and infectious classes of SIR model when $R_0 > 1$

To see how the number of infected individuals increase or decrease for each case, the plot of the solution of the system must be conducted. The plots below show the two cases in selected time.

$R_0 < 1$

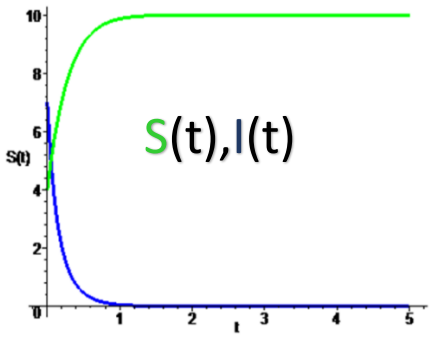


Figure 2.9

$R_0 > 1$

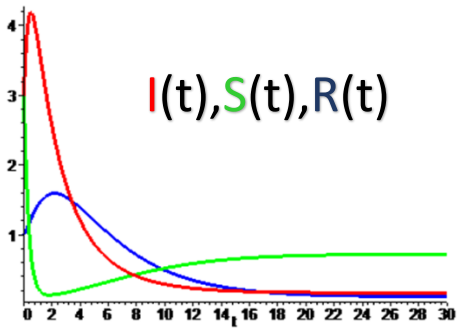


Figure 2.10

Figure 2.9. The plot of susceptible and infected individuals of SIR model when $R_0 < 1$

Figure 2.10. The plot of susceptible, infected, and recovered classes of SIR model when $R_0 > 1$

These plots illustrate that the number of infected individuals would decrease until the infection dies out when $R_0 < 1$, while the spread of infection would increase, causing an epidemic when $R_0 > 1$.

2.3 Susceptible-Exposed-Infectious-Recovery (SEIR) Model

In the SEIR model, the population with size N is divided into four compartments which are susceptible S, exposed E, infected I, and recovered R.Thus, the population N can be written as $N = S + E + I + R$. Let us suppose that

- The contacts between susceptible and infected individuals cause the transmission of the pathogen during a period (t) with a rate β individuals/unit time. Then, the exchange rate for individuals from being in the susceptible category to the exposed category is obtained by rate βI.
- The parameter α illustrates the rate of movement of people from the exposed class to the infected class.
- The parameter γ illustrates the rate of moving from being in the infected class to recovered class.
- The demographics (natural birth and death) are considered in this model, and μ represents death and birth.
- The population size is constant.

The flowchart below illustrates the interaction between each class in the SEIR model**.**

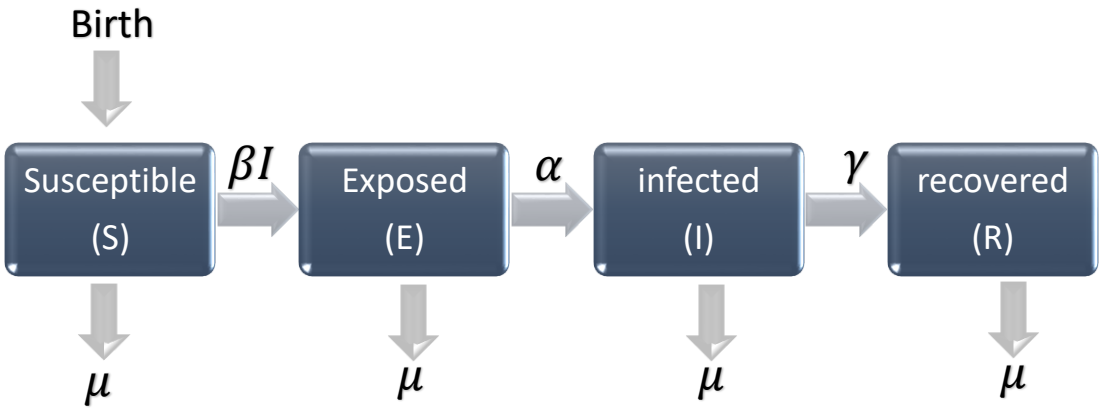


Figure 2.11. SEIR compartments model

This diagram is the illustration of a first order non-linear differential equations system (2.7):

$$\begin{cases} \dfrac{dS(t)}{dt} = \mu N - \dfrac{\beta}{N} S(t)I(t) - \mu S(t) \\ \dfrac{dE(t)}{dt} = \dfrac{\beta}{N} S(t)I(t) - \alpha E(t) - \mu E(t) \\ \dfrac{dI(t)}{dt} = \alpha E(t) - \gamma I(t) - \mu I(t) \\ \dfrac{dR(t)}{dt} = \gamma I(t) - \mu R(t) \end{cases} \tag{2.7}$$

In the SEIR system shown in (2.7), $\frac{dR(t)}{dt}$ can be reduced as well as in the SIR model because it depends only on $I(t)$. Also, $\frac{dR(t)}{dt} = -(\frac{dS(t)}{dt} + \frac{dE(t)}{dt} + \frac{dI(t)}{dt})$ because

$N = S + E + I + R$ and N is constant as it is mentioned in our assumption above. Therefore, instead of discussing the system (2.7), I will discuss the reduced system below:

$$\begin{cases} \dfrac{dS(t)}{dt} = \mu N - \dfrac{\beta}{N} S(t)I(t) - \mu S(t) = f(S(t), E(t), I(t), t) \\ \dfrac{dE(t)}{dt} = \dfrac{\beta}{N} S(t)I(t) - \alpha E(t) - \mu E(t) = g(S(t), E(t), I(t), t) \\ \dfrac{dI(t)}{dt} = \alpha E(t) - \gamma I(t) - \mu I(t) = h(S(t), E(t), I(t), t) \end{cases} \quad (2.8)$$

After linearizing (2.8), the Diseases Free Equilibria can be found by substituting $I^* = 0$ in the linearized system (2.9) below. Thus, $\frac{dI^*}{dt} = \alpha E^*(t) = 0$, obtained when $E^* = 0$. Also, by substituting $(I^* = 0)$ into $\mu N - \frac{\beta}{N} S(t)I(t) - \mu S(t) = 0$, S^* must be equal to the size of the population N. Therefore, DFE= $(N, 0, 0)$.

$$\begin{cases} \mu N - \frac{\beta}{N} S(t)I(t) - \mu S(t) = 0 \\ \frac{\beta}{N} S(t)I(t) - \alpha E(t) - \mu E(t) = 0 \\ \alpha E(t) - \gamma I(t) - \mu I(t) = 0 \end{cases} \quad (2.9)$$

For more illustration, the second equation in (2.9) can be rewritten as:

$$\mu N - \left(\frac{\beta}{N} I(t) + \mu\right) S(t) = 0$$

And from last equation we have

$$E(t) = \frac{(\gamma + \mu)\, I(t)}{\alpha} \quad (2.10)$$

After substituting (2.10) in the second equation in the system (2.9), we will have

$$\frac{\beta}{N}S(t)I(t) - \frac{1}{\alpha}(\alpha+\mu)(\gamma+\mu)\,I(t) = 0$$

After factor $I(t)$, the previous equation can be written as

$$\left(\frac{\beta}{N}S(t) - \frac{1}{\alpha}(\alpha+\mu)(\gamma+\mu)\right)I(t) = 0 \quad (2.11)$$

To solve this equation either $I(t) = 0$ or

$$S(t) = \frac{N(\alpha+\mu)(\gamma+\mu)}{\alpha\beta} \quad (2.12)$$

For $I(t) = 0$ we will have the DFE that it is found earlier, which is $(N, 0,0)$. In addition, the endemic equilibria will be found by substituting (2.12) in the first equation in the system (2.9) to find the value of $I(t)$. Thus,

$$\mu N - \frac{N\beta(\alpha+\mu)(\gamma+\mu)}{N\beta\alpha}I(t) - \frac{N\mu(\alpha+\mu)(\gamma+\mu)}{\beta\alpha} = 0$$

By multiplying and dividing the previous equation by $\alpha\beta$ and by simplifying the above equation, we will have:

$$\mu N\alpha\beta - \beta(\alpha+\mu)(\gamma+\mu)I(t) - N\mu(\alpha+\mu)(\gamma+\mu) = 0$$

By solving for $I(t)$, we have:

$$\mu N\alpha\beta - N\mu(\alpha+\mu)(\gamma+\mu) = \beta(\alpha+\mu)(\gamma+\mu)I(t)$$

Then,

$$I(t) = \frac{\mu N\alpha\beta - N\mu(\alpha+\mu)(\gamma+\mu)}{\beta(\alpha+\mu)(\gamma+\mu)}$$

$$I(t) = \frac{\mu N(\alpha\beta - (\alpha+\mu)(\gamma+\mu))}{\beta(\alpha+\mu)(\gamma+\mu)} \tag{2.13}$$

$E(t)$, also, can be found by substituting (2.13) into (2.10)

$$E(t) = \frac{\mu N(\alpha\beta - (\alpha+\mu)(\gamma+\mu))}{\alpha\beta(\alpha+\mu)}$$

Thus, the endemic equilibrium point for SEIR model is

$$(S^*, E^*, I^*) = \left(\frac{N(\alpha+\mu)(\gamma+\mu)}{\alpha\beta}, \frac{\mu N\left(\alpha\beta - (\alpha+\mu)(\gamma+\mu)\right)}{\alpha\beta(\alpha+\mu)}, \quad \frac{\mu N\left(\alpha\beta - (\alpha+\mu)(\gamma+\mu)\right)}{\beta(\alpha+\mu)(\gamma+\mu)}\right)$$

This is the same result that I found using MAPLE software:

$$\{S=N, In=0, Ex=0, R=0\}, \left\{S=\frac{N(\alpha\gamma+\alpha\mu+\mu\gamma+\mu^2)}{\beta\alpha}, Ex=\frac{\mu N(\beta\alpha-\alpha\gamma-\alpha\mu-\mu\gamma-\mu^2)}{\alpha(\alpha+\mu)\beta}, In=\frac{\mu N(\beta\alpha-\alpha\gamma-\alpha\mu-\mu\gamma-\mu^2)}{\beta(\alpha\gamma+\alpha\mu+\mu\gamma+\mu^2)}, R=\frac{\gamma N(\beta\alpha-\alpha\gamma-\alpha\mu-\mu\gamma-\mu^2)}{\beta(\alpha\gamma+\alpha\mu+\mu\gamma+\mu^2)}\right\}$$

Figure 2.12. The output of EE for SEIR model

(See Appendix-B, (b)).

The Jacobian for SEIR model (2.8) is evaluated as:

$$J(S,E,I) = \begin{bmatrix} \frac{\partial f}{\partial S} & \frac{\partial f}{\partial E} & \frac{\partial f}{\partial I} \\ \frac{\partial g}{\partial S} & \frac{\partial g}{\partial E} & \frac{\partial g}{\partial I} \\ \frac{\partial h}{\partial S} & \frac{\partial h}{\partial E} & \frac{\partial h}{\partial I} \end{bmatrix} = \begin{bmatrix} -\frac{\beta}{N}I(t) - \mu & -\frac{\beta}{N}S(t) & 0 \\ \frac{\beta}{N}I(t) & -(\alpha+\mu) & \frac{\beta}{N}S(t) \\ 0 & \alpha & -(\gamma+\mu) \end{bmatrix}$$

The Jacobian of the SEIR model at DFE is shown below:

$$J(N,0,0) = \begin{bmatrix} -\mu & -\beta & 0 \\ 0 & -(\alpha+\mu) & \beta \\ 0 & \alpha & -(\gamma+\mu) \end{bmatrix}$$

To find its eigenvalues, $\det\left(J_{(N,0,0)} - \lambda I\right) = 0$ must be solved.

$$\det(J - \lambda I) = \begin{vmatrix} -\mu-\lambda & -\beta & 0 \\ 0 & -(\alpha+\mu)-\lambda & \beta \\ 0 & \alpha & -(\gamma+\mu)-\lambda \end{vmatrix} = 0$$

After the expanding the determinant, we obtain

$$(\mu+\lambda)\Big(\big(\,(\alpha+\mu)+\lambda\big)\big((\gamma+\mu)+\lambda\big) - \alpha\beta\Big) = 0$$

$$\lambda_1 = -\mu \quad , \lambda_{2,3} = \frac{-(\alpha+2\mu+\gamma) \pm \sqrt{\big((\alpha+\mu)-(\gamma+\mu)\big)^2 + 4\alpha\beta}}{2}$$

According to the stability theorem, the trajectory of the system will have stable behavior when

$$\sqrt{\big((\alpha+\mu)-(\gamma+\mu)\big)^2 + 4\alpha\beta} < (\alpha+2\mu+\gamma)$$

Let us find the eigenvalue at the endemic equilibria for SEIR model later in this chapter with numerical solution.

Next, the basic reproduction ratio of the SEIR model will be found by two different ways.

2.4 The Basic Reproduction Ratio R_0 for SEIR Model

R_0 is useful to investigate the spread of the disease and helps to predict if the disease will increase and become an endemic disease or if it will decrease. The basic reproduction ratio R_0, also known as the threshold parameter, for the SEIR model, can be found if the infectious disease is increasing. In the SEIR model the infections would happen when $\frac{dE(t)}{dt} > 0$. To explore this, the right-hand side of equation (2.11), that it is written previously, must be more than zero,

$$\left(\frac{\beta}{N}S(t) - \frac{1}{\alpha}(\alpha+\mu)(\gamma+\mu)\right)I(t) > 0$$

let $S(t) \approx N$, and solve this quantity to have:

$$\beta I(t) > \frac{1}{\alpha}(\alpha+\mu)(\gamma+\mu)I(t)$$

$$\frac{\beta\alpha}{(\alpha+\mu)(\gamma+\mu)} > 1$$

Thus, $R_0 = \frac{\beta\alpha}{(\alpha+\mu)(\gamma+\mu)}$

Another way to calculate R_0 is the next-generation method. See [24, p.32] for more illustration.

The next-generation method

In next-generation method, we need to consider both the ways of creating new infections and the ways of moving between states. In SEIR model, “exposed” and “Infectious” are two different disease states. In the exposed and infectious states, by looking at (2.8), it is obvious that there is one way to create new infections, which is the interaction between susceptible and infectious individuals, while there are many ways to move between infectious and exposed classes. By using the next-generation method, there are two matrices F and V, where

$$F = \frac{\partial f_i}{\partial x_j}$$

and

$$V = \frac{\partial v_i}{\partial xj}$$

f_i : the rate of having new infections

$(v_i = v_i^- - v_i^+)$: v_i^- is the rate of moving individuals out compartment i and v_i^+ is the rate of moving individuals into the compartment.

In SEIR model (2.8),

$$F = \begin{bmatrix} 0 & \frac{\beta}{N} S_0 \\ 0 & 0 \end{bmatrix} = \begin{bmatrix} 0 & \beta \\ 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} (\mu + \alpha) & 0 \\ -\alpha & (\gamma + \mu) \end{bmatrix}$$

The next-generation method shows that R_0 is the largest eigenvalue of matrix $G = FV^{-1}$.

After evaluating V^{-1} and multiplying it by F matrix,

$$G = \begin{bmatrix} \dfrac{\beta\alpha}{(\mu+\alpha)(\gamma+\mu)} & \dfrac{\beta}{(\gamma+\mu)} \\ 0 & 0 \end{bmatrix}$$

In this matrix G, $R_0 = \frac{\beta\alpha}{(\mu+\alpha)(\gamma+\mu)}$, which is the largest eigenvalue of next-generation matrix. In fact, the result here is the same as what was found earlier.

2.5 Numerical Solution of SEIR

As I mentioned before, software such as MAPLE assists to find the Jacobian matrix more easily. For the SEIR model without reducing $\frac{dR}{dt}$, the output of the Jacobian matrix using MAPLE is shown below.

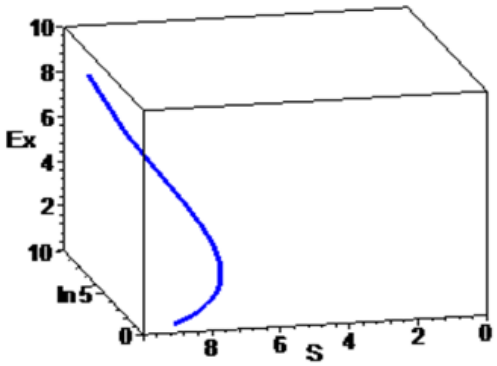
$$J := \begin{bmatrix} -\mu - \frac{\beta\, In}{N} & 0 & -\frac{\beta\, S}{N} & 0 \\ \frac{\beta\, In}{N} & -\alpha - \mu & \frac{\beta\, S}{N} & 0 \\ 0 & \alpha & -\gamma - \mu & 0 \\ 0 & 0 & \gamma & -\mu \end{bmatrix}$$

Figure 2.13. The output of Jacobian matrix of SEIR model

This shows the same result as I found earlier.

Let us suppose the initial values for SEIR model and analyze the plots of both cases $R_0 < 1$, and $R_0 > 1$.

Case: $(R_0 < 1)$



$\boldsymbol{\mu = 0.2}$ $\boldsymbol{\beta = 0.2}$
$\boldsymbol{\alpha = 0.4}$ $\boldsymbol{\gamma = 0.1}$
$\boldsymbol{N = 10}$

Initial values

$S(0) = 10$
$E(0) = 9$
$I(0) = 7$

Figure 2.14. The 3D plot of SEIR model with selected initial values when $R_0 < 1$

Figure (2.14) above shows the 3d plot of SEIR model (2.8) with selected initial values when $(R_0 < 1)$.

To understand more about the dynamics of this system with these initial values, the phase portraits will explain more about the spread of the infectious disease when the threshold is less than one. Figure (2.15) below indicates that the infections individuals will die out until there is no more endemic, while the number of the susceptible individuals will be equal to the number of the populations.

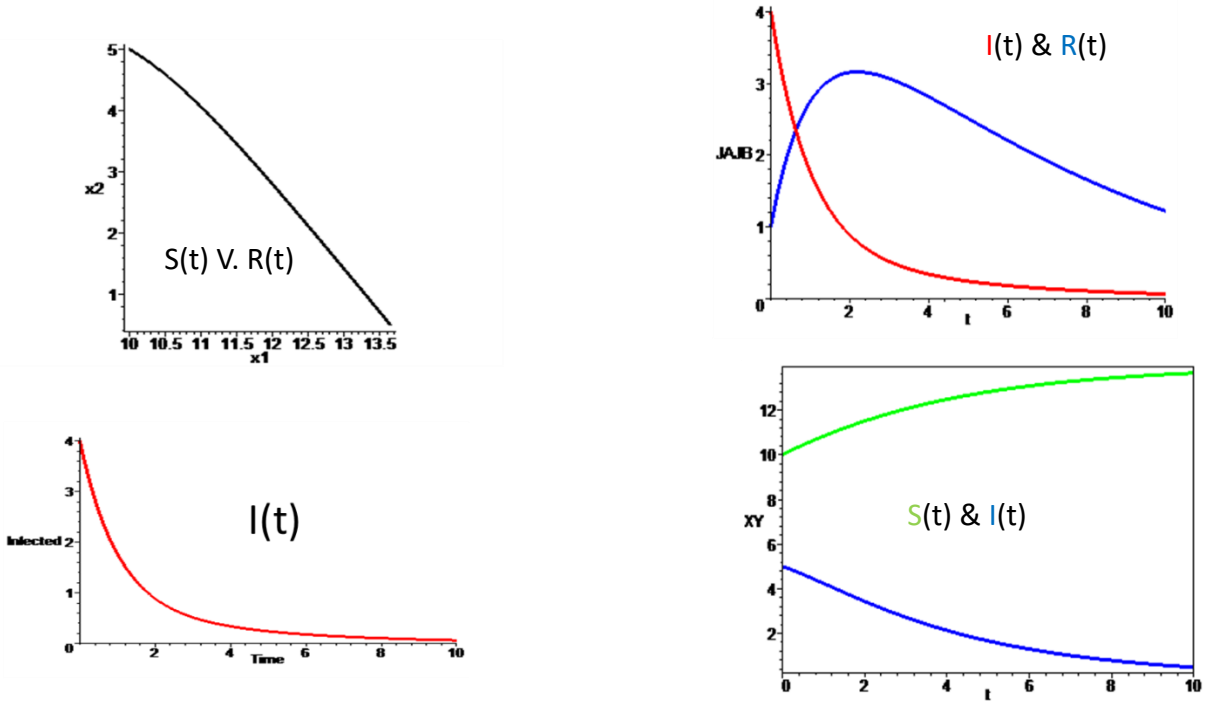
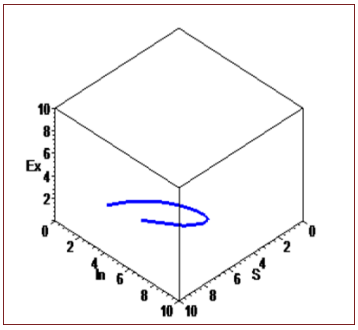


Figure 2.15. Different plots of S, I, and E classes of SEIR model when $R_0 < 1$

Case: $(R_0 > 1)$

The 3d plot of SEIR model (2.8) is shown in figure (2.3).



$\boldsymbol{\mu = 0.2}$ $\boldsymbol{\beta = 0.4}$
$\boldsymbol{\alpha = 0.8}$ $\boldsymbol{\gamma = 0.1}$
$\boldsymbol{N = 10}$

Initial values

$S(0) = 20$
$E(0) = 5$
$I(0) = 7$

Figure 2.16. The 3D plot of SEIR model when $R_0 > 1$

Figure (2.17) below shows the plot for each susceptible, infected, and exposed individual during one month with the same initial and parameter value above.

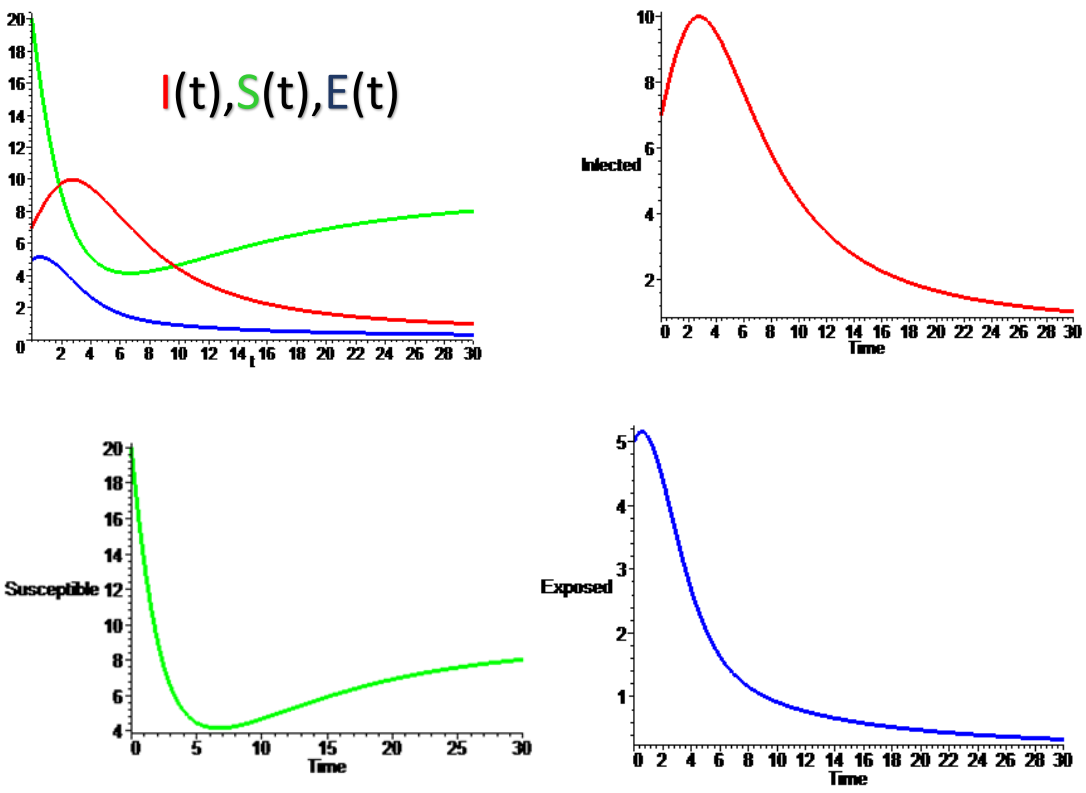


Figure 2.17. Different plots of S, I, E classes of SEIR model when $R_0 > 1$

In this chapter, the basic models of epidemics are represented. Both SIR and SEIR models are investigated to see how the epidemics spread during a period of time. There are similar results for both models, which state that the spread of the disease is mostly dependent on the interaction between susceptible and infected individuals. However, the spread of infectious individuals in the SEIR model is slower than the spread in the SIR model. It is mostly about the exposed compartment on SEIR model. If the contact between susceptible and infected people increase, the spread will be

increased as well. Therefore, it is found that to control epidemics, we must impose preventive measures that would decrease the rate of interaction between infectious and susceptible individuals. Also, we found the criteria of the stability for each model using the Jacobian matrix and the theorem of stability.

CHAPTER III

MERS-CoV MODEL INVESTIGATION

DESCRIPTION OF THE MODEL

By adding more compartments to SEIR model, we created the SEIHR model to investigate the spread of MERS-CoV infectious disease. Based in MERS models that were studied in [4, 20, 26], I use a similar model to explore the MERS infection in humans. The proposed model studied in this chapter has five compartments indicated below:

S the susceptible individuals

E the exposed individuals who have the pathogen but haven't be infected yet

I the infected individuals

H the hospitalized individuals

R the removed or recovery individuals

The assumption of this model is illustrated below:

- We assume that the population size is constant and $\mathrm{N} = \mathrm{S}(\mathrm{t}) + \mathrm{E}(\mathrm{t}) + \mathrm{I}(\mathrm{t}) + \mathrm{H}(\mathrm{t}) + \mathrm{R}(\mathrm{t})$.
- The natural death and birth rates are also considered in our model.
- MERS-CoV has a latency period evaluated to be 2-14 days [15], which allows us to use the exposed individuals in our model. Thus, we consider the latency or exposed individuals in our model.

- We assume that the virus of MERS transfers to humans by either contacting with exposed, infected, or hospitalized individuals.
- The parameters below indicate the interaction between compartments that are included in our model:

β_1 the rate of the interaction between susceptible and exposed individuals

β_2 the rate of the interaction between susceptible and infectious individuals

β_3 the rate of the interaction between susceptible and hospitalized individuals

α the rate of the movement from being exposed to be in infectious calss

ε the rate of the movement form being infected to be in hospitalized class

d_1 the death rate from infected individuals

d_2 the death rate from hospitalized individuals

r_1 the recovery rate from infected individuals

r_2 the recovery rate from hospitalized individuals

Based on the assumptions above, the proposed model of MERS-CoV is indicated in (3.1) as a nonlinear differential equations system.

$$\begin{cases} \frac{dS(t)}{dt} = \theta N - \frac{(\beta_1 E(t)+\beta_2 I(t)+\beta_3 H(t))S(t)}{N} - \mu S(t) \\ \frac{dE(t)}{dt} = \frac{(\beta_1 E(t)+\beta_2 I(t)+\beta_3 H(t))S(t)}{N} - (\alpha+\mu)E(t) \\ \frac{dI(t)}{dt} = \alpha E(t) - (\varepsilon + d_1 + r_1 + \mu)I(t) \\ \frac{dH(t)}{dt} = \varepsilon I(t) - (d_2 + r_2 + \mu)H(t) \\ \frac{dR(t)}{dt} = r_1 I(t) + r_2 H(t) - \mu R(t) \end{cases} \quad (3.1)$$

To linearize system (3.1), we solved system (3.2) to find the equilibria for the model.

$$\begin{aligned} &\theta N - \frac{(\beta_1 E(t)+\beta_2 I(t)+\beta_3 H(t))S(t)}{N} - \mu S(t) = 0 \\ &\frac{(\beta_1 E(t)+\beta_2 I(t)+\beta_3 H(t))S(t)}{N} - (\alpha+\mu)E(t) = 0 \\ &\alpha E(t) - (\varepsilon + d_1 + r_1 + \mu)I(t) = 0 \\ &\varepsilon I(t) - (d_2 + r_2 + \mu)H(t) = 0 \\ &r_1 I(t) + r_2 H(t) - \mu R(t) = 0 \end{aligned} \quad (3.2)$$

It is easier to find the disease-free equilibria first, which there is no more infections $(I^* = 0)$. Consequently, there will be no more exposed, hospitalized, and recovered individuals $(E^* = H^* = R^* = 0)$. By substituting these values in the first equation in (3.2), we will have

$\theta N - \mu S(t) = 0$. Thus, $S^* = \frac{\theta N}{\mu}$. Thus, the disease-free equilibrium is

$DFE = (S^*, E^*, I^*, H^*,\ R^*) = (\frac{\theta N}{\mu}, 0, 0, 0, 0)$. To find the endemic equilibrium point we need to solve the linearized system (3.2).

Before finding the endemic equilibria, I would consider the first four equations in (3.2) because from the first system (3.1), we can reduce the last equation that depends on only infected and hospitalized individuals.

I would also eliminate N from the system by substituting

$S(t) = NS,\ E(t) = NE,\ I(t) = NI,\ and\ H(t) = NH$

Then, by dividing both sides by N, we have the system (3.3) shown below.

$$\begin{aligned} &\theta - (\beta_1 E + \beta_2 I + \beta_3 H + \mu)S = 0 \\ &(\beta_1 E + \beta_2 I + \beta_3 H)S - (\alpha + \mu)E = 0 \\ &\alpha E - (\varepsilon + d_1 + r_1 + \mu)I = 0 \\ &\varepsilon I - (d_2 + r_2 + \mu)H = 0 \end{aligned} \qquad (3.3)$$

From third equation in system (3.3), we have

$$I = \frac{\alpha E}{(\varepsilon + d_1 + r_1 + \mu)} \qquad (3.4)$$

From last equation in system (3.3), we have

$$I = \frac{(d_2 + r_2 + \mu)H}{\varepsilon} \qquad (3.5)$$

The left-hand side of (3.4) and (3.5) are equal. Hence,

$$H = \frac{\varepsilon \alpha E}{(\varepsilon + d_1 + r_1 + \mu)(d_2 + r_2 + \mu)} \qquad (3.6)$$

Also, by adding the first and the second equations in system (3.3), and solving for E, we have,

$$E = \frac{\theta - \mu S}{(\alpha + \mu)} \qquad (3.7)$$

By substituting (3.4), (3.5), and (3.6) into equation the second equation in (3.3),

$$[(\beta_1 + \frac{\beta_2 \alpha}{(\varepsilon + d_1 + r_1 + \mu)} + \frac{\beta_3 \varepsilon \alpha}{(\varepsilon + d_1 + r_1 + \mu)(d_2 + r_2 + \mu)})S - (\alpha + \mu)]E = 0$$

To solve this equation, either $E = 0, or\ S = \frac{(\alpha + \mu)}{\beta_1 + \frac{\beta_2 \alpha}{(\varepsilon + d_1 + r_1 + \mu)} + \frac{\beta_3 \varepsilon \alpha}{(\varepsilon + d_1 + r_1 + \mu)(d_2 + r_2 + \mu)}}$

Thus, the susceptible value of the endemic equilibria is evaluated below:

$$S^* = \frac{(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)}{\beta_1(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)+\beta_2\alpha(d_2+r_2+\mu)+\beta_3\varepsilon\alpha}$$

By substituting S^* into (3.7),

$$E^* = \frac{\theta}{(\alpha+\mu)} - \frac{\mu(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)}{[\beta_1(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)+\beta_2\alpha(d_2+r_2+\mu)+\beta_3\varepsilon\alpha]}$$

And by substituting E^* into (3.4) and (3.5), we have

$$I^* = \frac{\alpha}{(\varepsilon+d_1+r_1+\mu)}\left[\frac{\theta}{(\alpha+\mu)} - \frac{\mu(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)}{[\beta_1(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)+\beta_2\alpha(d_2+r_2+\mu)+\beta_3\varepsilon\alpha]}\right]$$

$$H^* = \frac{\varepsilon\alpha}{(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)}\left[\frac{\theta}{(\alpha+\mu)} - \frac{\mu(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)}{[\beta_1(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)+\beta_2\alpha(d_2+r_2+\mu)+\beta_3\varepsilon\alpha]}\right]$$

Let $D = \beta_1(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)+\beta_2\alpha(d_2+r_2+\mu)+\beta_3\varepsilon\alpha$

Then, the endemic equilibria for MERS-CoV is

$$(S^*, E^*, I^*, H^*) = \left(\frac{(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)}{D}, \right.$$

$$\frac{\theta}{(\alpha+\mu)} - \frac{\mu(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)}{D},$$

$$\frac{\alpha\theta}{(\varepsilon+d_1+r_1+\mu)(\alpha+\mu)} - \frac{\alpha\mu(d_2+r_2+\mu)}{D},$$

$$\left. \frac{\varepsilon\alpha\theta}{(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)} - \frac{\varepsilon\alpha\mu}{D} \right)$$

3.1 The Jacobian Matrix for MERS-CoV:

To find the stability of MERS-CoV, the Jacobian matrix must be evaluated as well as its equilibrium points. The Jacobian matrix for the MERS-CoV model at any equilibrium point (S^*, E^*, I^*, H^*) is presented below:

$$J_{(S^*,\ E^*,\ I^*,\ H^*)}$$

$$= \begin{bmatrix} -(\beta_1 E + \beta_2 I + \beta_3 H + \mu) & -\beta_1 S^* & -\beta_2 S^* & -\beta_3 S^* \\ \beta_1 E^* + \beta_2 I^* + \beta_3 H^* & \beta_1 S^* - (\alpha+\mu) & \beta_2 S^* & \beta_3 S^* \\ 0 & \alpha & -(\varepsilon+d_1+r_1+\mu) & 0 \\ 0 & 0 & \varepsilon & -(d_2+r_2+\mu) \end{bmatrix}$$

$$J_{(\frac{\theta}{\mu},\ 0,\ 0,\ 0)} = \begin{bmatrix} -\mu & -\beta_1\frac{\theta}{\mu} & -\beta_2\frac{\theta}{\mu} & -\beta_3\frac{\theta}{\mu} \\ 0 & \beta_1\frac{\theta}{\mu} - (\alpha+\mu) & \beta_2\frac{\theta}{\mu} & \beta_3\frac{\theta}{\mu} \\ 0 & \alpha & -(\varepsilon+d_1+r_1+\mu) & 0 \\ 0 & 0 & \varepsilon & -(d_2+r_2+\mu) \end{bmatrix}$$

$$\det(J-\lambda I)=\begin{vmatrix} -\mu-\lambda & -\beta_1\frac{\theta}{\mu} & -\beta_2\frac{\theta}{\mu} & -\beta_3\frac{\theta}{\mu} \\ 0 & \beta_1\frac{\theta}{\mu}-(\alpha+\mu)-\lambda & \beta_2\frac{\theta}{\mu} & \beta_3\frac{\theta}{\mu} \\ 0 & \alpha & -(\varepsilon+d_1+r_1+\mu)-\lambda & 0 \\ 0 & 0 & \varepsilon & -(d_2+r_2+\mu)-\lambda \end{vmatrix}$$

$$=0$$

$$-(\mu+\lambda)\Big[\Big(\frac{\beta_1\theta}{\mu}-(\alpha+\mu)-\lambda\Big)\big((\varepsilon+d_1+r_1+\mu)+\lambda\big)\big((d_2+r_2+\mu)+\lambda\big)$$

$$+\frac{\beta_2\theta\alpha}{\mu}\big((d_2+r_2+\mu)+\lambda\big)+\frac{\beta_3\theta\alpha\varepsilon}{\mu}\Big]=0$$

Instead of solving this equation, the numerical solution using data of MERS-CoV will be evaluated in this chapter after finding the reproduction ratio of our system using the next-generation method. Simulating our model on MAPLE software and evaluating the eigenvalues around our equilibrium point would ease the outcome of its stability.

3.2 The Reproduction Ratio $(\boldsymbol{R_0})$ of MERS-Cov Model

The next-generation method is used here to find the reproduction ratio or the threshold for our model of MERS-CoV. The illustrations of finding (R_0) is presented for MERS-CoV model system (3.1). In this model, the exposed, Infected and hospitalized compartments make-up the infectious disease. Thus, we will consider the three differential equations shown below:

$$\frac{dE(t)}{dt} = (\beta_1 E(t) + \beta_2 I(t) + \beta_3 H(t))S(t) - (\alpha + \mu)E(t)$$
$$\frac{dI(t)}{dt} = \alpha E(t) - (\varepsilon + d_1 + r_1 + \mu)I(t)$$
$$\frac{dH(t)}{dt} = \varepsilon I(t) - (d_2 + r_2 + \mu)H(t)$$

Let $f_i, i = 1,2,3$ are the compartments that have a rate of having new infections from each equation respectively. And $v_i = v_i^- - v_i^+$, v_i^- is the rate of moving individuals out of the compartment and v_i^+ is the rate of moving individuals into the compartment.

Hence,

$$f_1 = (\beta_1 E(t) + \beta_2 I(t) + \beta_3 H(t))S(t)$$

$$f_2 = 0$$

$$f_3 = 0$$

Let

$$F_{(S^*,\ E^*, I^*, H^*)} = \begin{bmatrix} \frac{\partial f_1}{\partial E} & \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial H} \\ \frac{\partial f_2}{\partial E} & \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial H} \\ \frac{\partial f_3}{\partial E} & \frac{\partial f_3}{\partial \mathrm{I}} & \frac{\partial f_3}{\partial H} \end{bmatrix}$$

$$= \begin{bmatrix} (\beta_1 + \beta_2 I^* + \beta_3 H^*)S^* & (\beta_1 E^* + \beta_2 + \beta_3 H^*)S^* & (\beta_1 E^* + \beta_2 I^* + \beta_3)S^* \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

By substituting the free-disease endemic equilibrium in the previous matrix, we will have

$$F_{\left(\frac{\theta}{\mu},\ 0,\ 0,\ 0\right)} = \begin{bmatrix} \beta_1\frac{\theta}{\mu} & \beta_2\frac{\theta}{\mu} & \beta_3\frac{\theta}{\mu} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} = F$$

Now, let

$$v_1 = (\alpha + \mu)E^*$$

$$v_2 = (\varepsilon + d_1 + r_1 + \mu)I^* - \alpha E^*$$

$$v_3 = (d_2 + r_2 + \mu)H^* - \varepsilon I^*$$

Hence,

$$V_{(S^*,\ E^*, I^*, H^*)} = \begin{bmatrix} \frac{\partial v_1}{\partial E} & \frac{\partial v_1}{\partial I} & \frac{\partial v_1}{\partial H} \\ \frac{\partial v_2}{\partial E} & \frac{\partial v_2}{\partial I} & \frac{\partial v_2}{\partial H} \\ \frac{\partial v_3}{\partial E} & \frac{\partial v_3}{\partial \mathrm{I}} & \frac{\partial v_3}{\partial H} \end{bmatrix} = \begin{bmatrix} (\alpha+\mu) & 0 & 0 \\ -\alpha & (\varepsilon + d_1 + r_1 + \mu) & 0 \\ 0 & -\varepsilon & (d_2 + r_2 + \mu) \end{bmatrix} = V$$

To find R_0 that we are looking for, we need to find the largest eigen value of FV^{-1}.

$\det(V), V^T\ and\ dj(V)$ are evaluated to find the inverse of V.

$$\det(V) = (\alpha + \mu)(\varepsilon + d_1 + r_1 + \mu)(d_2 + r_2 + \mu)$$

$$V^T = \begin{bmatrix} (\alpha+\mu) & -\alpha & 0 \\ 0 & (\varepsilon + d_1 + r_1 + \mu) & -\varepsilon \\ 0 & 0 & (d_2 + r_2 + \mu) \end{bmatrix}$$

$$adj(V)$$

$$= \begin{bmatrix} (\varepsilon + d_1 + r_1 + \mu)(d_2 + r_2 + \mu) & 0 & 0 \\ \alpha\,(d_2 + r_2 + \mu) & (\alpha+\mu)(d_2 + r_2 + \mu) & 0 \\ \alpha\varepsilon & \varepsilon(\alpha+\mu) & -(\alpha+\mu)(\varepsilon + d_1 + r_1 + \mu) \end{bmatrix}$$

$$V^{-1} = \frac{1}{\det(V)} \cdot adj(V)$$

$$= \begin{bmatrix} \frac{1}{(\alpha+\mu)} & 0 & 0 \\ \frac{\alpha}{(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)} & \frac{1}{(\varepsilon+d_1+r_1+\mu)} & 0 \\ \frac{\alpha\varepsilon}{(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)} & \frac{\varepsilon}{(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)} & \frac{1}{(d_2+r_2+\mu)} \end{bmatrix}$$

$$F \cdot V^{-1} = \begin{bmatrix} \beta_1\frac{\theta}{\mu} & \beta_2\frac{\theta}{\mu} & \beta_3\frac{\theta}{\mu} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{(\alpha+\mu)} & 0 & 0 \\ \frac{\alpha}{(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)} & \frac{1}{(\varepsilon+d_1+r_1+\mu)} & 0 \\ \frac{\alpha\varepsilon}{(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)} & \frac{\varepsilon}{(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)} & \frac{1}{(d_2+r_2+\mu)} \end{bmatrix}$$

$$= \begin{bmatrix} \frac{\beta_1\theta}{\mu(\alpha+\mu)} + \frac{\beta_2\theta\alpha}{\mu(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)} + \frac{\beta_3\theta\alpha\varepsilon}{\mu(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)} & \frac{\theta\beta_2}{\mu(\varepsilon+d_1+r_1+\mu)} + \frac{\beta_3\theta\varepsilon}{\mu(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)} & \frac{\beta_3\theta 1}{\mu(d_2+r_2+\mu)} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

The largest eigenvalue for $F \cdot V^{-1}$ represents the reproduction number for MERS-CoV disease, which is shown below:

$$R_0 = \frac{\beta_1\theta}{\mu(\alpha+\mu)} + \frac{\beta_2\theta\alpha}{\mu(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)} + \frac{\beta_3\theta\alpha\varepsilon}{\mu(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)}$$

$$R_0 = \frac{\beta_1\theta(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu) + \beta_2\theta\alpha(d_2+r_2+\mu) + \beta_3\theta\alpha\varepsilon}{\mu(\alpha+\mu)(\varepsilon+d_1+r_1+\mu)(d_2+r_2+\mu)}$$

3.3 Developed Model of MERS-CoV

In this model, similar assumptions to our previous model (3.1) were used to create the model. In this model, it is assumed that the infected cases have two different categories, one of them had either direct or indirect contact with infected camels while another case be infected by contacting other infected cases and I_c, and I_h represent these compartments respectively.

$$
\begin{aligned}
\frac{dS(t)}{dt} &= \theta N - \frac{(\beta_1 E(t)+\beta_2 I_h(t)+\beta_3 I_c(t)+\beta_4 H(t))S(t)}{N} - \mu S(t)\\
\frac{dE(t)}{dt} &= \frac{(\beta_1 E(t)+\beta_2 I_h(t)+\beta_3 I_c(t)+\beta_4 H(t))S(t)}{N} - (\alpha+\gamma+\mu)E(t)\\
\frac{dI_h(t)}{dt} &= \alpha E(t) - (\varepsilon_h + d_1 + r_1 + \mu)I_h(t)\\
\frac{dI_c(t)}{dt} &= \gamma E(t) - (\varepsilon_c + d_2 + r_2 + \mu)I_c(t)\\
\frac{dH(t)}{dt} &= \varepsilon_h I_h(t) + \varepsilon_c I_c(t) - (d_3 + r_3 + \mu)H(t)\\
\frac{dR(t)}{dt} &= r_1 I_h(t) + r_2 I_c(t) + r_3 H(t) - \mu R(t)
\end{aligned}
\tag{3.8}
$$

Numerical solution using MAPLE is used in the next chapter for system (3.1).

Before moving to the numerical simulations of MERS-CoV model, the reproduction ratio of system (3.8) is found after reducing the model and eliminating N, using similar method that was used to find R_0 for previous model (3.1).

Thus, by applying the next-generation method for (3.8), we have:

$$f_1 = (\beta_1 E(t) + \beta_2 I_h(t) + \beta_3 I_c(t) + \beta_4 H(t))S(t)$$

$$f_2 = 0, \quad f_3 = 0, \quad f_4 = 0$$

Let

$$
F_{(S^*,\ E^*,\ I_h^*,\ I_c^*, H^*)} = \begin{bmatrix}
(\beta_1 + \beta_2 I_h^* + \beta_3 I_c^* + \beta_4 H^*)S^* & (\beta_1 E^* + \beta_2 + \beta_3 I_c^* + \beta_4 H^*)S^* & (\beta_1 E^* + \beta_2 I_h^* + \beta_3 + \beta_4 H^*)S^* & (\beta_1 E^* + \beta_2 I_h^* + \beta_3 I_c^* + \beta_4)S^* \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{bmatrix}
$$

By evaluating this matrix at free disease equilibrium, we have

$$F_{\left(\frac{\theta}{\mu},\ 0,\ 0,\ 0,\ 0\right)} = \begin{bmatrix} \beta_1\frac{\theta}{\mu} & \beta_2\frac{\theta}{\mu} & \beta_3\frac{\theta}{\mu} & \beta_4\frac{\theta}{\mu} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} = F$$

Now, let

$$v_1 = (\alpha + \gamma + \mu)E^*$$

$$v_2 = (\varepsilon_h + d_1 + r_1 + \mu)I_h^* - \alpha E^*$$

$$v_3 = (\varepsilon_c + d_2 + r_2 + \mu)I_c^* - \gamma E^*$$

$$v_4 = (d_3 + r_3 + \mu)H^* - (\varepsilon_h I_h^* + \varepsilon_c I_c^*)$$

Hence,

$$V_{(S^*,\ E^*, I^*, H^*)} = \begin{bmatrix} (\alpha + \gamma + \mu) & 0 & 0 & 0 \\ -\alpha & (\varepsilon_h + d_1 + r_1 + \mu) & 0 & 0 \\ \gamma & 0 & (\varepsilon_c + d_2 + r_2 + \mu) & 0 \\ 0 & -\varepsilon_h & -\varepsilon_c & (d_3 + r_3 + \mu) \end{bmatrix} = V$$

MAPLE software was used to find the inverse of matrix V and then by multiplying the result by matrix F, (see Appendix-C (3. a)). The output is shown below:

$$F * V^{-1}$$

$$= \begin{bmatrix} \frac{\beta_1\theta}{\mu Nk} + \frac{\beta_2\theta\alpha}{\mu Nkk_1} - \frac{\beta_3\theta\gamma}{\mu Nkk_2} - \frac{\beta_4\theta(-\alpha k_2\varepsilon_h + \gamma k_1\varepsilon_c)}{\mu Nkk_1k_2k_3} & \frac{\beta_2\theta}{\mu Nk_1} + \frac{\beta_4\theta\varepsilon_h}{\mu Nk_1k_3} & \frac{\beta_3\theta}{\mu Nk_2} + \frac{\beta_4\theta\varepsilon_c}{\mu Nk_2k_3} & \frac{\beta_4\theta}{\mu Nk_3} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

where, $k = (\alpha + \gamma + \mu),\ k_1 = (\varepsilon_h + d_1 + r_1 + \mu),\ k_2 = (\varepsilon_c + d_2 + r_2 + \mu),$

$k_3 = (d_3 + r_3 + \mu)$

The largest eigenvalue for $F * V^{-1}$ is known as the reproduction ratio according to the next-generation method. Thus, $R_0 = \frac{\beta_1\theta}{\mu Nk} + \frac{\beta_2\theta\alpha}{\mu Nkk_1} - \frac{\beta_3\theta\gamma}{\mu Nkk_2} - \frac{\beta_4\theta(-\alpha k_2\varepsilon_h + \gamma k_1\varepsilon_c)}{\mu Nkk_1k_2k_3}$.

With more evidence and information about being infected by contacting infected camels, this would be a helpful approached to optimal control MERS infectious disease.

CHAPTER IV

NUMERICAL INVESTIGATION OF MERS-CoV MODEL AND ITS CONTROL

For better understanding of the dynamics of our models, numerical simulations using MAPLE of our MERS-CoV model are presented in this chapter. The stability of system (3.1) around the disease-free equilibria is investigated first. Data of MERS-CoV were collected from [31], and it is reported that the incubation period is 5 days and infected move to be hospitalized for 4 days [32]. We estimated that infected individuals must recover during one week and 6 days for hospitalization while the death for both infected and hospitalized individuals would be during 14 days. Because MERS-CoV is central in the Middle East, the data used are focused on patients reported in The Kingdom of Saudi Arabia, where the most cases of MERS-CoV were confirmed. It is found that 179 MERS-CoV cases were reported in Saudi Arabia from January 2, 2017 until August 12, 2017.

Table 2. The Value of Parameters in MERS-CoV System (3.1)

N	Population size in KSA	32783206
θ	The birth rate during 2017	0.016
μ	The death rate during 2017	0.03
β_1	The rate of contacting exposed individuals	0.4
β_2	The rate of contacting infected individuals	0.4
β_3	The rate of contacting hospitalized individuals	0.2
α	The rate of moving from being exposed to be infected	0.2
ε	The rate of moving from being infected to be hospitalized	0.25
r_1	The rate of recovered from infected class	0.07
r_2	The rate of recovered from hospitalized	0.14
d_1	The death rate of infected class	0.07
d_2	The death rate of hospitalized class	0.07

To investigate the stability of MERS-CoV using MAPLE software, the eigenvalues around DFE point is found below:

$$[-.03,\ 2.082970223,\ -.5166459217,\ -.3229909645]$$

Figure 4.1. The output of the eigenvalues at DFE for MERS model

(See appendix-C, (4.1)).

These values show that the MERS-CoV trajectory for our model makes a saddle or unstable node around DFE, according to stability theory stated in chapter one.

Using values on Table (2), the plot of infected individuals related to our differential equation system (3.1) is shown below in Figure (4.2):

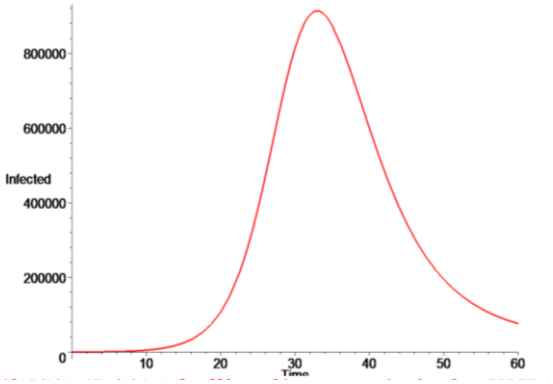
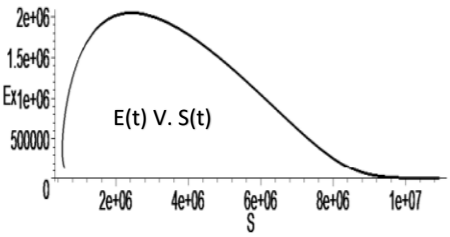
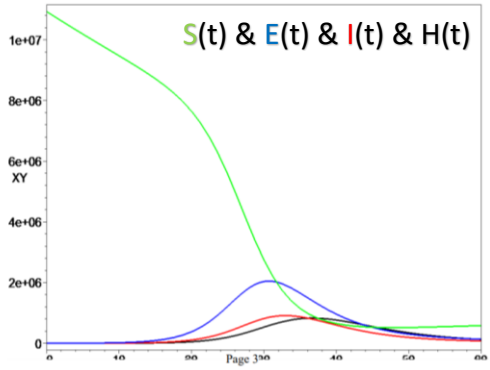


Figure 4.2. The plot of infected individuals of MERS

Figure (4.4) below shows the plots for susceptible, exposed, infected, and hospitalized classes of MERS-CoV system (3.1). (See Appendix-C, (4.2)).





(4.3) **(4.4)**

Figure 4.3. The plot of E V. S of MERS

Figure 4.4. Plots of S, E, I, and H individuals for system (3.1)

The reproduction ratio for MERS-CoV model using vlues on Table (2) is represented below:

$$R\_0 := 1.599263860$$

Figure 4.5. The output of R_0 for MERS model

The reproduction ratio is more than one, which makes concern of having epidemic in the future. To control this, we need to optimally control our model by decreasing the rate of contact between suscitple and exposed classes. By subsituting different values of parameters, it is found that when β_1 is decreased to be 0.01, R_0 will be less than one so that the infections will die out.

When β_1 is reduced to be equal to 0.01, the reproduction ratio is evaluated below:

$$R\_0 := .4740740738$$

Figure 4.6. The output of R_0 when $\beta_1 = 0.01$

The plot of infected and hospitalized indiviudals of model (3.1) after changing β_1 is shown below in Figure (4.7).

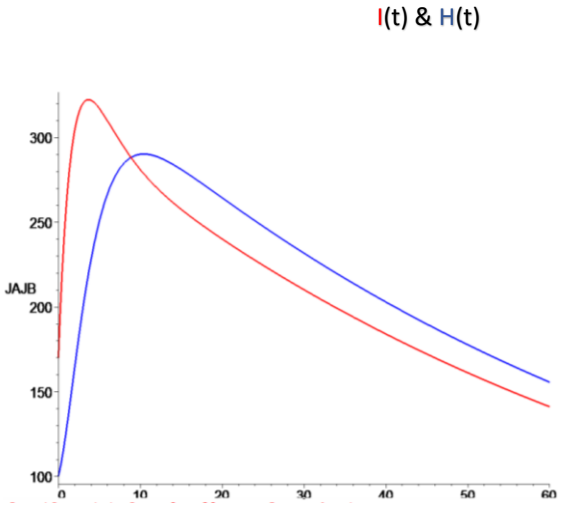


Figure 4.7. Plot of I, and H individuals of MERS model when $R_0 < 1$

While the source of the spread of MERS-CoV is still studied and the vaccine has not been developed yet, informing people to follow some instructions is a useful tool to manage the spread of MERS-CoV. Washing hands regularly, avoiding contact with other patients having MERS-CoV, and preventing the contact with camels are advantageous to avoid having MERS virus.

It seems that the spread of MERS-CoV is labile during the time. Therefore, introducing control problem to the model when $R_0 > 1$ can assist in preventing the spread of the disease. MERS model can be controllable by introducing a function $u(t)$ to system (3.1), when $u(t)$ implies the way of preventing the spread of disease by contact the exposed, infected and hospitalized individuals. Our model after using the control problem is represented as

$$\begin{cases} \frac{dS(t)}{dt} = \theta N - \frac{u(t)(\beta_1 E(t)+\beta_2 I(t)+\beta_3 H(t))S(t)}{N} - \mu S(t) \\ \frac{dE(t)}{dt} = \frac{u(t)(\beta_1 E(t)+\beta_2 I(t)+\beta_3 H(t))S(t)}{N} - (\alpha+\mu)E(t) \\ \frac{dI(t)}{dt} = \alpha E(t) - (\varepsilon + d_1 + r_1 + \mu)I(t) \\ \frac{dH(t)}{dt} = \varepsilon I(t) - (d_2 + r_2 + \mu)H(t) \\ \frac{dR(t)}{dt} = r_1 I(t) + r_2 H(t) - \mu R(t) \end{cases} \quad (4.1)$$

Where, $0 < u_{min} \leq u(t) \leq u_{max}$.

The objective function is $I(T) \rightarrow min$. Our goal of this control problem is minimizing the infected individuals at time T. Since our model is similar to Ebola model in the work of Grigorieva and Khailov in [6,7], then we assumed that the type of optimal control model would be similar. Therefore, we introduced control function $u(t)$ into the system (3.1) and assumed that optimal control is piece wise constant function with at most two switchings. Instead of solving complex two point boundary value problem for the maximum principle, this reduced our problem to a simpler one of finite dimensional optimization.

Let $u_{min} = 0.4$ and $u_{max} = 1$ in our numerical control model, and the time interval be 20 days. The best optimal control obtained numerically for model (3.1) using original program written in MAPLE is shown in Figure (4.8).

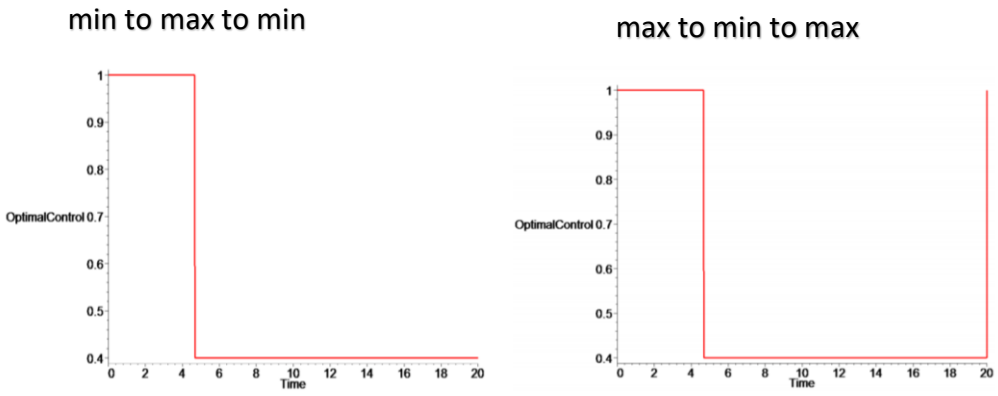
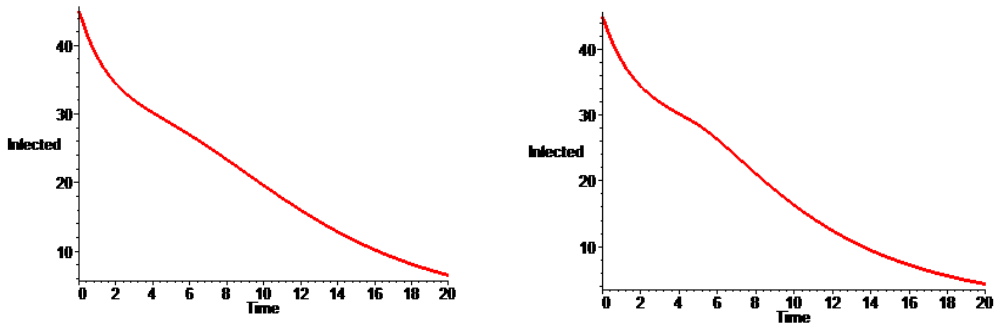


Figure 4.8. Plot of optimal control $u(t)$ for MERS model

By using data on Table 2 and changing the intial values to flexible find the optimal control, the plot of Inftected indiviuals of MERS model before and after adding the control function $u(t)$ for $t \in [0, 20]$ is shown in Figure(4.9). See (Appendix-C (control model)).



Without control with control

Figure 4.9. Plot of $I(t)$ for MERS model with and without the optimal solution

We observed that to minimize the number of infected individual at the end of the time interval, to have only 7 infected individuals at time $T = 20$ days, the best optimal strategy is the following:

For the first 4 days of the planning period of 20 days, the optimal control can take its maximum value (hence, no precocious measures should be used, for example, in order to not make population panic), then for the remaining 16 days, the optimal control takes its minimal value that indicates that the maximal precocious measures must be taken, such as quarantine, marketing and educational efforts and even closing of public events .

For more effective control to prevent the spread of MERS, the methods used by Grigorieva and Khailov in [6, 7] can be also used for MERS model. Three optimal control functions can be introduced to control our model (3.1), and four optimal control functions for MERS model (3.8). In future study, an analytical optimal control investigation will be explored and investigated.

CHAPTER V

CONCLUSION

In this paper, the basic SIR and SEIR models are represented in Chapter II. The knowledge of investigating these basic models for infectious disease assists in understanding the dynamic of the spread of disease, which is a useful tool to apply this study for any infectious disease by creating model that appropriate with understanding the sources of its outbreak. Analytical and numerical solutions were investigated in this paper for both SIR and SEIR model. The Jacobian matrix was evaluated as well as threshold. It is found that if $R_0 > 1$, the disease will continue distributed and the spread of the disease will be increased, while if $R_0 < 1$, the disease will die out. To optimal control these model, the contact between susceptible and infected or exposed individuals must be minimized to prevent the spread of the disease. In Chapter III, the same methods used in chapter II were applied to investigate the model of MERS that is similar to [4, 20, 26]. Developed model was created by divided the infected individuals of MERS to two categories, infected people who had contact with camels and infected having contact with infected cases. The reproduction ratio was evaluated using next-generation method. In Chapter IV, numerical investigation and numerical optimal control of MERS were studied using MAPLE software after selected data for reported cases in KSA during 2017. It is found that $R_0 \approx 1.59$, which show that MERS should be considerable as a pandemic in the future. For our selected data, it is found that if β_1 decreased to be 0.01, then MERS outbreak will die out. A control function is

added to our system to minimize the rate of interaction between susceptible and exposed, infected and hospitalized individuals so that the infected individuals will be decreased consequently. By having more data and knowledge about MERS, the analytical investigation of the optimal control will be a future study.

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[31] http://www.who.int/csr/don/12-september-2017-mers-oman/en/

[32] https://www.cdc.gov/coronavirus/mers/clinical-features.html

Appendix-A

(a) Jacobian and eigenvalues for SIR

```
> restart:with(linalg):with(tensor):with(plots):
> N:=S+In+R:
> eq1:=mu-mu*S-beta*S*In:
> eq2:=beta*S*In-(alpha+mu)*In:
> eq3:=alpha*In-mu*R:
> A:=vector([eq1,eq2,eq3]):
> J:=jacobian(A,[S,In,R]);
```

$$J := \begin{bmatrix} -\mu - \beta In & -\beta S & 0 \\ \beta In & \beta S - \alpha - \mu & 0 \\ 0 & \alpha & -\mu \end{bmatrix}$$

```
> sol:=solve({eq1=0,eq2=0,eq3=0},{S,In,R});
```

$$sol := \{R = 0, In = 0, S = 1\}, \{R = -\frac{\alpha(-\beta+\alpha+\mu)}{\beta(\alpha+\mu)}, In = -\frac{\mu(-\beta+\alpha+\mu)}{\beta(\alpha+\mu)}, S = \frac{\alpha+\mu}{\beta}\}$$

```
> J_1:=eval(jacobian(A,[S,In,R]),[S=subs(sol[1],S),In=subs(sol[1],In),R=subs(sol[1],R)]);
```

$$J\_1 := \begin{bmatrix} -\mu & -\beta & 0 \\ 0 & \beta - \alpha - \mu & 0 \\ 0 & \alpha & -\mu \end{bmatrix}$$

```
> J_2:=eval(jacobian(A,[S,In,R]),[S=subs(sol[2],S),In=subs(sol[2],In),R=subs(sol[2],R)]);
```

$$J\_2 := \begin{bmatrix} -\mu + \frac{\mu(-\beta+\alpha+\mu)}{\alpha+\mu} & -\alpha-\mu & 0 \\ -\frac{\mu(-\beta+\alpha+\mu)}{\alpha+\mu} & 0 & 0 \\ 0 & \alpha & -\mu \end{bmatrix}$$

```
> eigvalue1:eigenvalues(J_1);
```

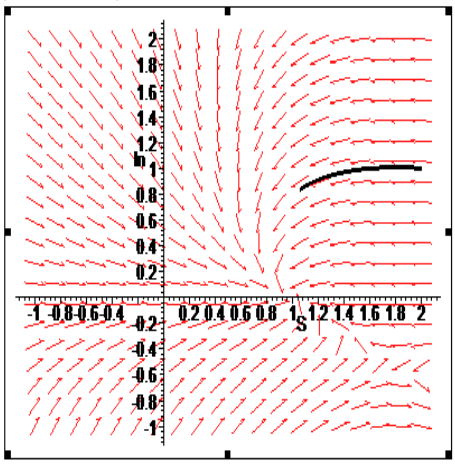
$$-\mu, -\mu, \beta - \alpha - \mu$$

```
> eigvalue2:=eigenvalues(J_2);
```

$$eigvalue2 := -\mu, \frac{1}{2}\frac{-\mu\beta + \sqrt{\mu^2\beta^2 + 4\mu\alpha^3 + 12\mu^2\alpha^2 - 4\mu\beta\alpha^2 - 8\alpha\mu^2\beta + 12\alpha\mu^3 - 4\mu^3\beta + 4\mu^4}}{\alpha+\mu}, \frac{1}{2}\frac{-\mu\beta - \sqrt{\mu^2\beta^2 + 4\mu\alpha^3 + 12\mu^2\alpha^2 - 4\mu\beta\alpha^2 - 8\alpha\mu^2\beta + 12\alpha\mu^3 - 4\mu^3\beta + 4\mu^4}}{\alpha+\mu}$$

(Figure 2.6) The trajectory of S and I classes ($R_0 < 1$)

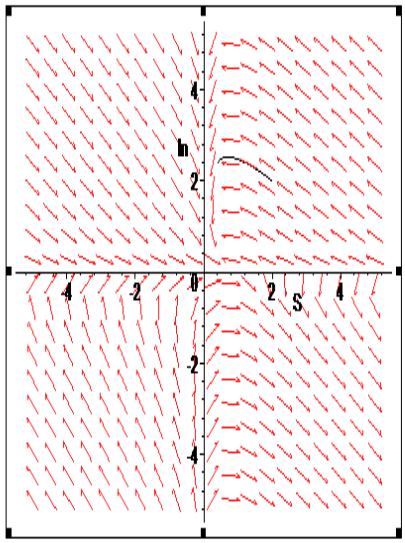
```
> restart:with(plots):with(DEtools):
> eq1:=diff(S(t),t)=mu-mu*S(t)-beta*S(t)*In(t):
> eq2:=diff(In(t),t)=beta*S(t)*In(t)-(alpha+mu)*In(t):
> eq3:=diff(R(t),t)=alpha*In(t)-mu*R(t):
> beta:=0.5: alpha:=0.3: mu:=0.6:
> ini:=S(0)=10,In(0)=0:
> sys:=[eq1,eq2]:
> DEplot(sys,[S(t),In(t)],t=0..1,S=-1..2,In=-1..2,[[S(0)=2,In(0)=1]],linecolor=black);
```




```
>
```

(Figure 2.8) the trajoctory of S and I classes ($R_0 > 1$)

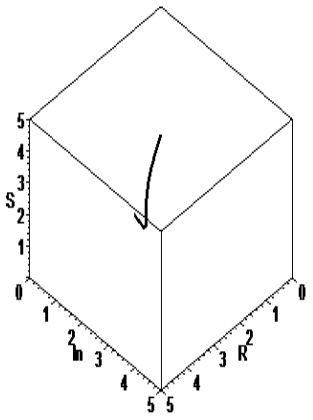
```
> restart:with(plots):with(DEtools):
> eq1:=diff(S(t),t)=mu-mu*S(t)-beta*S(t)*In(t):
> eq2:=diff(In(t),t)=beta*S(t)*In(t)-(alpha+mu)*In(t):
> eq3:=diff(R(t),t)=alpha*In(t)-mu*R(t):
> beta:=0.7: alpha:=0.2: mu:=0.3:
> ini:=S(0)=10,In(0)=0:
> sys:=[eq1,eq2]:
> DEplot(sys,[S(t),In(t)],t=0..1,[[S(0)=2,In(0)=2]],stepsize=0.05,S=-5..5,In=-5..5,thickness=1,linecolor=black);
```



>

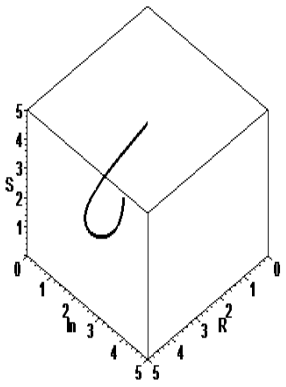
(Figure 2.7)

```
> restart:with(plots):with(DEtools):
> eq1:=diff(S(t),t)=mu-mu*S(t)-beta*S(t)*In(t):
> eq2:=diff(In(t),t)=beta*S(t)*In(t)-(alpha+mu)*In(t):
> eq3:=diff(R(t),t)=alpha*In(t)-mu*R(t):
> beta:=0.5: alpha:=0.3: mu:=0.6:
> ini:=S(0)=10,In(0)=0:
> sys:=[eq1,eq2,eq3]:
> DEplot3d(sys,{S(t),In(t),R(t)},t=0..100,[[S(0)=2,In(0)=2,R(0)=3]],stepsize=0.05,S=0..5,In=0..5,R=0..5,thickness=3,linecolor=black);
```



>

```
> restart:with(plots):with(DEtools):
> eq1:=diff(S(t),t)=mu-mu*S(t)-beta*S(t)*In(t):
> eq2:=diff(In(t),t)=beta*S(t)*In(t)-(alpha+mu)*In(t):
> eq3:=diff(R(t),t)=alpha*In(t)-mu*R(t):
> beta:=0.7: alpha:=0.8: mu:=0.3:
> ini:=S(0)=10,In(0)=0:
> sys:=[eq1,eq2,eq3]:
> DEplot3d(sys,{S(t),In(t),R(t)},t=0..100,[[S(0)=2,In(0)=2,R(0)=3]],stepsize=0.05,S=0..5,In=0..5,R=0..5,thickness=3,linecolor=black);
```




```
>
```

Appendix-B

The Jacobian matrix and its equilibria

```
> restart:with(linalg):with(tensor):with(plots):
> eq1:=mu*N-mu*S-(beta/N)*S*In:
> eq2:=(beta/N)*S*In-(alpha+mu)*Ex:
> eq3:=alpha*Ex-gamma*In-mu*In:
> eq4:=gamma*In-mu*R:
> A:=vector([eq1,eq2,eq3,eq4]):
> J:=jacobian(A,[S,Ex,In,R]);
```

$$J := \begin{bmatrix} -\mu - \frac{\beta In}{N} & 0 & -\frac{\beta S}{N} & 0 \\ \frac{\beta In}{N} & -\alpha - \mu & \frac{\beta S}{N} & 0 \\ 0 & \alpha & -\gamma - \mu & 0 \\ 0 & 0 & \gamma & -\mu \end{bmatrix}$$

```
> sol:=solve({eq1=0,eq2=0,eq3=0,eq4},{S,Ex,In,R});
```

$$sol := \{S = N, In = 0, Ex = 0, R = 0\}, \left\{ S = \frac{N(\alpha\gamma+\alpha\mu+\mu\gamma+\mu^2)}{\beta\alpha}, Ex = \frac{\mu N(\beta\alpha-\alpha\gamma-\alpha\mu-\mu\gamma-\mu^2)}{\alpha(\alpha+\mu)\beta}, In = \frac{\mu N(\beta\alpha-\alpha\gamma-\alpha\mu-\mu\gamma-\mu^2)}{\beta(\alpha\gamma+\alpha\mu+\mu\gamma+\mu^2)}, R = \frac{\gamma N(\beta\alpha-\alpha\gamma-\alpha\mu-\mu\gamma-\mu^2)}{\beta(\alpha\gamma+\alpha\mu+\mu\gamma+\mu^2)} \right\}$$

```
> J_1:=eval(jacobian(A,[S,Ex,In,R]),[S=subs(sol[1],S),Ex=sub(sol[1],Ex),In=subs(sol[1],In),R=subs(sol[1],R)]);
```

$$J\_1 := \begin{bmatrix} -\mu & 0 & -\beta & 0 \\ 0 & -\alpha - \mu & \beta & 0 \\ 0 & \alpha & -\gamma - \mu & 0 \\ 0 & 0 & \gamma & -\mu \end{bmatrix}$$

```
> J_2:=eval(jacobian(A,[S,Ex,In,R]),[S=subs(sol[2],S),Ex=sub(sol[2],Ex),In=subs(sol[2],In),R=subs(sol[2],R)]);
```

$$J\_2 := \begin{bmatrix} -\mu - \frac{\mu(\beta\alpha-\alpha\gamma-\alpha\mu-\mu\gamma-\mu^2)}{\alpha\gamma+\alpha\mu+\mu\gamma+\mu^2} & 0 & -\frac{\alpha\gamma+\alpha\mu+\mu\gamma+\mu^2}{\alpha} & 0 \\ \frac{\mu(\beta\alpha-\alpha\gamma-\alpha\mu-\mu\gamma-\mu^2)}{\alpha\gamma+\alpha\mu+\mu\gamma+\mu^2} & -\alpha - \mu & \frac{\alpha\gamma+\alpha\mu+\mu\gamma+\mu^2}{\alpha} & 0 \\ 0 & \alpha & -\gamma - \mu & 0 \\ 0 & 0 & \gamma & -\mu \end{bmatrix}$$

Appendix-C

(3.a) evaluated R_0 for developed model

```
> with(linalg):
> F:=linalg[matrix](4,4,[beta1*(theta/N),beta2*(theta/N),beta3*(thet
  a/N),beta4*(theta/N),0,0,0,0,0,0,0,0,0,0,0,0]);
```

$$F := \begin{bmatrix} \frac{\beta 1\,\theta}{N} & \frac{\beta 2\,\theta}{N} & \frac{\beta 3\,\theta}{N} & \frac{\beta 4\,\theta}{N} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

```
> V:=linalg[matrix](4,4,[k,0,0,0,-alpha,k1,0,0,gamma,0,k2,0,0,-epsil
  on*h,-epsilon*c,k3]);
```

$$V := \begin{bmatrix} k & 0 & 0 & 0 \\ -\alpha & k1 & 0 & 0 \\ \gamma & 0 & k2 & 0 \\ 0 & -\varepsilon\,h & -\varepsilon\,c & k3 \end{bmatrix}$$

```
> V1:= inverse(V);
>
```

$$V1 := \begin{bmatrix} \frac{1}{k} & 0 & 0 & 0 \\ \frac{\alpha}{k\,k1} & \frac{1}{k1} & 0 & 0 \\ -\frac{\gamma}{k\,k2} & 0 & \frac{1}{k2} & 0 \\ -\frac{\varepsilon\,(-\alpha\,k2\,h+\gamma\,k1\,c)}{k\,k1\,k2\,k3} & \frac{\varepsilon\,h}{k1\,k3} & \frac{\varepsilon\,c}{k2\,k3} & \frac{1}{k3} \end{bmatrix}$$

```
> multiply(F,V1);
```

$$\left[\frac{\beta 1\,\theta}{N\,k}+\frac{\beta 2\,\theta\,\alpha}{N\,k\,k1}-\frac{\beta 3\,\theta\,\gamma}{N\,k\,k2}-\frac{\beta 4\,\theta\,\varepsilon\,(-\alpha\,k2\,h+\gamma\,k1\,c)}{N\,k\,k1\,k2\,k3},\ \frac{\beta 2\,\theta}{N\,k1}+\frac{\beta 4\,\theta\,\varepsilon\,h}{N\,k1\,k3},\ \frac{\beta 3\,\theta}{N\,k2}+\frac{\beta 4\,\theta\,\varepsilon\,c}{N\,k2\,k3},\ \frac{\beta 4\,\theta}{N\,k3}\right]$$

$$[0,0,0,0]$$

$$[0,0,0,0]$$

$$[0,0,0,0]$$

(4.1) evaluated the eigenvalue of system (3.1) around DFE

```
> restart:with(linalg):with(tensor):with(plot
  s):
> eq1:=0.016-(0.4*Ex+.4*In+.2*H+.03)*S:
> eq2:=(0.4*Ex+.4*In+.2*H)*S-(.2+.03)*Ex:
> eq3:=.2*Ex-(0.25+.07+.07+.03)*In:
> eq4:=0.25*In-(.07+.14+.03)*H:
> A:=vector([eq1,eq2,eq3,eq4]):
> J:=jacobian(A,[S,Ex,In,H]);
```

$$J := \begin{bmatrix} -.4\,Ex - .4\,In - .2\,H - .03 & -.4\,S & -.4\,S & -.2\,S \\ .4\,Ex + .4\,In + .2\,H & .4\,S - .23 & .4\,S & .2\,S \\ 0 & .2 & -.42 & 0 \\ 0 & 0 & .25 & -.24 \end{bmatrix}$$

```
> 
> sol:=solve({eq1=0,eq2=0,eq3=0,eq4},{S,Ex,In
  ,H});
```

$$sol := \{In = 0, H = 0, S = .5333333333, Ex = 0\}, \{S = .3334867664, Ex = .02606694351, In = .01241283024, H = .01293003150\}$$

```
> J_1:=eval(jacobian(A,[S,Ex,In,H]),[S=0.16/0
  .03,Ex=0,In=0,H=0]);
```

$$J\_1 := \begin{bmatrix} -.03 & -2.133333333 & -2.133333333 & -1.066666667 \\ 0 & 1.903333333 & 2.133333333 & 1.066666667 \\ 0 & .2 & -.42 & 0 \\ 0 & 0 & .25 & -.24 \end{bmatrix}$$

```
> J_2:=eval(jacobian(A,[S,Ex,In,H,R]),[S=subs
  (sol[2],S),Ex=sub(sol[2],Ex),In=subs(sol[2]
  ,In),H=subs(sol[2],H),R=subs(sol[2],R)]);
```

$$[-.4\,\mathrm{sub}(\{S = .3334867664, Ex = .02606694351, In = .01241283024, H = .01293003150\}, Ex) - .03755113840 , -.1333947066 , -.1333947066 , -.06669735328 , 0]$$
$$[.4\,\mathrm{sub}(\{S = .3334867664, Ex = .02606694351, In = .01241283024, H = .01293003150\}, Ex) + .007551138396 , -.0966052934 , .1333947066 , .06669735328 , 0]$$
$$[0 , .2 , -.42 , 0 , 0]$$
$$[0 , 0 , .25 , -.24 , 0]$$

```
> evalf(Eigenvals(J_1,vecs));
```

$$[-.03, 2.082970223, -.5166459217, -.3229909645]$$

(4.2) the plot of MERS Model

```
> restart:
> with(plots):
> with(DEtools):
> alpha:=0.2:theta:=0.016:N:=32783206:beta1:=0.4: beta2:=0.4:
  beta3:=0.2: mu:=0.03: epsilon:=0.25: r1:=.07: r2:=.14: d1:=.07:
  d2:=.07:
> N := S(t)+Ex(t)+In(t)+H(t)+R(t);
>
```

$$N := S(t) + Ex(t) + In(t) + H(t) + R(t)$$

```
> eq1:=diff(S(t),t)=theta*N-(1/N)*(beta1*Ex(t)+beta2*In(t)+beta3*H(t
  ))*S(t)-mu*S(t);
```

$$eq1 := \frac{\partial}{\partial t} S(t) = -.014\,S(t) + .016\,Ex(t) + .016\,In(t) + .016\,H(t) + .016\,R(t) - \frac{(.4\,Ex(t) + .4\,In(t) + .2\,H(t))\,S(t)}{S(t) + Ex(t) + In(t) + H(t) + R(t)}$$

```
> eq2:=diff(Ex(t),t)=(1/N)*(beta1*Ex(t)+beta2*In(t)+beta3*H(t))*S(t)
  -(alpha+mu)*Ex(t);
```

$$eq2 := \frac{\partial}{\partial t} Ex(t) = \frac{(.4\,Ex(t) + .4\,In(t) + .2\,H(t))\,S(t)}{S(t) + Ex(t) + In(t) + H(t) + R(t)} - .23\,Ex(t)$$

```
> eq3:=diff(In(t),t)=alpha*Ex(t)-(epsilon+d1+r1+mu)*In(t);
```

$$eq3 := \frac{\partial}{\partial t} In(t) = .2\,Ex(t) - .42\,In(t)$$

```
> eq4:=diff(H(t),t)=epsilon*In(t)-(d2+r2+mu)*H(t);
```

$$eq4 := \frac{\partial}{\partial t} H(t) = .25\,In(t) - .24\,H(t)$$

```
> eq5:=diff(R(t),t)=r1*In(t)+r2*H(t)-mu*R(t);
```

$$eq5 := \frac{\partial}{\partial t} R(t) = .07\,In(t) + .14\,H(t) - .03\,R(t)$$

```
> sys:=[eq1,eq2,eq3,eq4];
```

$$sys := \left[\frac{\partial}{\partial t} S(t) = -.014\,S(t) + .016\,Ex(t) + .016\,In(t) + .016\,H(t) + .016\,R(t) - \frac{(.4\,Ex(t) + .4\,In(t) + .2\,H(t))\,S(t)}{S(t) + Ex(t) + In(t) + H(t) + R(t)},\ \frac{\partial}{\partial t} Ex(t) = \frac{(.4\,Ex(t) + .4\,In(t) + .2\,H(t))\,S(t)}{S(t) + Ex(t) + In(t) + H(t) + R(t)} - .23\,Ex(t),\ \frac{\partial}{\partial t} In(t) = .2\,Ex(t) - .42\,In(t),\ \frac{\partial}{\partial t} H(t) = .25\,In(t) - .24\,H(t)\right]$$

```
> ics:=S(0)=10927735,Ex(0)=1000,In(0)=170,H(0)=100,R(0)=60;
```

```
#ics:=S(0)=0,Ex(0)=0,In(0)=0,H(0)=0,R(0)=0;
```

$$ics := S(0) = 10927735, Ex(0) = 1000, In(0) = 170, H(0) = 100, R(0) = 60$$

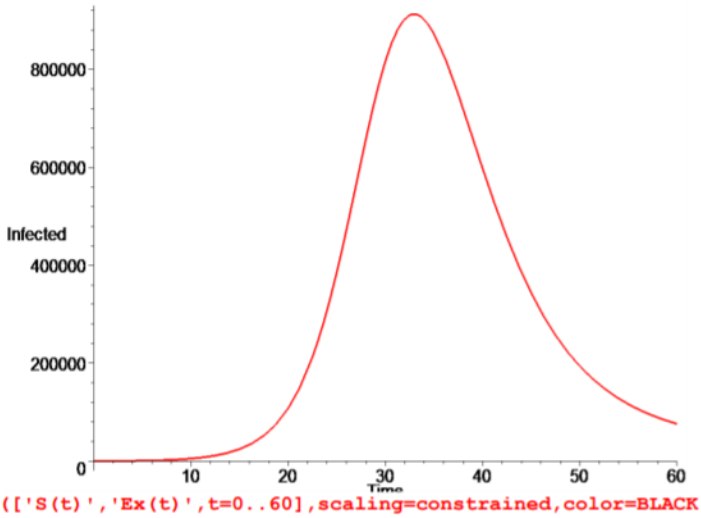
```
> sol:=dsolve({eq1,eq2,eq3,eq4,eq5,ics},{S(t),Ex(t),In(t),H(t),R(t)}
  ,type=numeric,
   startinit=true,output=listprocedure);
```

$$sol := [t = (\mathbf{proc}(t)\ \ldots\ \mathbf{end}), H(t) = (\mathbf{proc}(t)\ \ldots\ \mathbf{end}), Ex(t) = (\mathbf{proc}(t)\ \ldots\ \mathbf{end}), In(t) = (\mathbf{proc}(t)\ \ldots\ \mathbf{end}), R(t) = (\mathbf{proc}(t)\ \ldots\ \mathbf{end}), S(t) = (\mathbf{proc}(t)\ \ldots\ \mathbf{end})]$$

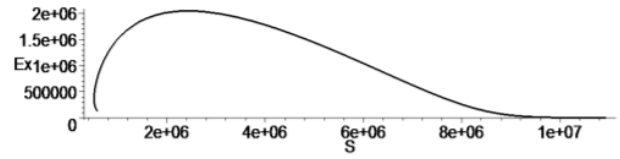
```
> assign(sol);
> S:=S(t);
  Ex:=Ex(t);
  In:=In(t);
  H:=H(t);
  R:=R(t);
```

$$S := \mathbf{proc}(t)\ \ldots\ \mathbf{end}$$
$$Ex := \mathbf{proc}(t)\ \ldots\ \mathbf{end}$$
$$In := \mathbf{proc}(t)\ \ldots\ \mathbf{end}$$
$$H := \mathbf{proc}(t)\ \ldots\ \mathbf{end}$$
$$R := \mathbf{proc}(t)\ \ldots\ \mathbf{end}$$

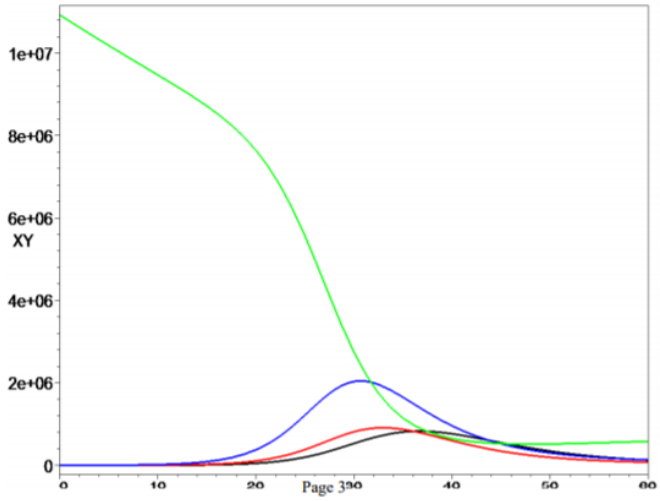
```
> plot('In'(t),t=0..60,thickness=3, labels=['Time', 'Infected']);
```

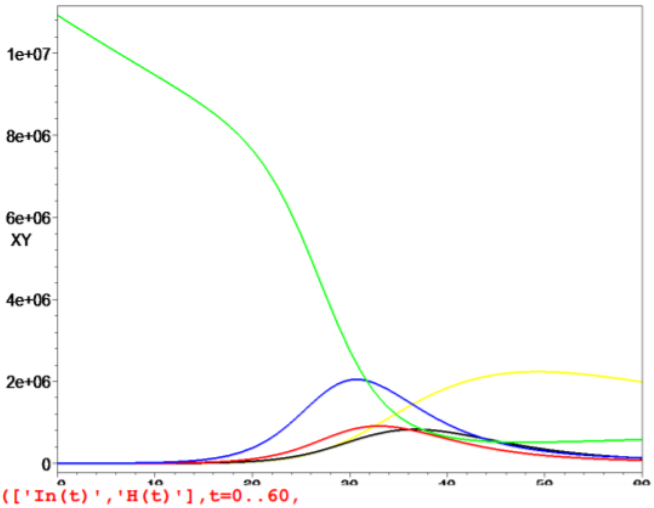



```
> plot(['S(t)','Ex(t)',t=0..60],scaling=constrained,color=BLACK,thic
  kness=3,labels=['S','Ex']);
```

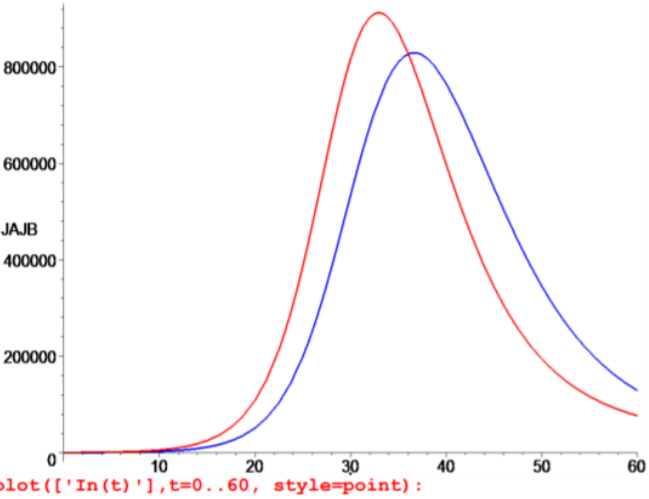



```
> plot(['S(t)','Ex(t)','In(t)','H(t)'],t=0..60,axes=box,labels=['t',
  'XY'],thickness=3,color=[green,blue,red,black]);
> plot(['S(t)','Ex(t)','In(t)','H(t)','R(t)'],t=0..60,axes=box,label
  s=['t','XY'],thickness=3,color=[green,blue,red,black,yellow]);
```



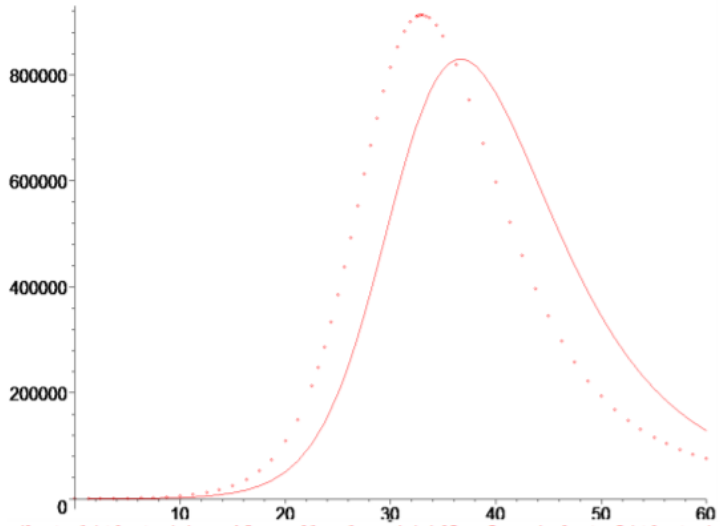



```
> plot(['In(t)','H(t)'],t=0..60,
labels=['t','JAJB'],thickness=3,color=[red,blue]);
```




```
> P1:=plot(['In(t)'],t=0..60, style=point):
> P2:=plot(['H(t)'],t=0..60, style=line):
```

```
> 
> plots[display]({P1,P2});
```




```
> R_0:=(beta1*theta*(epsilon+d1+r1+mu)*(d2+r2+mu)+beta2*theta*alpha*
  (d2+r2+mu)+beta3*theta*alpha*epsilon)/(mu*(alpha+mu)*(epsilon+d1+r
  1+mu)*(d2+r2+mu));
```

$$R\_0 := 1.599263860$$

```
> 
```

(Control MERS)

```
> restart:
> with(plots):
> with(DEtools):
> umin:=0.4;
  umax:=1;
  u2min:=0;
  u2max:=1000;
```

$$umin := .4$$

$$umax := 1$$

$$u2min := 0$$

$$u2max := 1000$$

```
> alpha:=0.2:theta:=0.016:N:=32783206:beta1:=0.4: beta2:=0.4:
  beta3:=0.2: mu:=0.03: epsilon:=0.25: r1:=.07: r2:=.14: d1:=.07:
  d2:=.07:
> N := S(t)+Ex(t)+In(t)+H(t)+R(t);
>
```

$$N := \mathrm{S}(t) + \mathrm{Ex}(t) + \mathrm{In}(t) + \mathrm{H}(t) + \mathrm{R}(t)$$

```
> eq1:=diff(S(t),t)=theta*N-(1/N)*u(t)*(beta1*Ex(t)+beta2*In(t)+beta
  3*H(t))*S(t)-mu*S(t);
```

$$eq1 := \frac{\partial}{\partial t}\mathrm{S}(t) = -.014\,\mathrm{S}(t) + .016\,\mathrm{Ex}(t) + .016\,\mathrm{In}(t) + .016\,\mathrm{H}(t) + .016\,\mathrm{R}(t) - \frac{\mathrm{u}(t)\,(.4\,\mathrm{Ex}(t) + .4\,\mathrm{In}(t) + .2\,\mathrm{H}(t))\,\mathrm{S}(t)}{\mathrm{S}(t) + \mathrm{Ex}(t) + \mathrm{In}(t) + \mathrm{H}(t) + \mathrm{R}(t)}$$

```
> eq2:=diff(Ex(t),t)=(1/N)*u(t)*(beta1*Ex(t)+beta2*In(t)+beta3*H(t))
  *S(t)-(alpha+mu)*Ex(t);
```

$$eq2 := \frac{\partial}{\partial t}\mathrm{Ex}(t) = \frac{\mathrm{u}(t)\,(.4\,\mathrm{Ex}(t) + .4\,\mathrm{In}(t) + .2\,\mathrm{H}(t))\,\mathrm{S}(t)}{\mathrm{S}(t) + \mathrm{Ex}(t) + \mathrm{In}(t) + \mathrm{H}(t) + \mathrm{R}(t)} - .23\,\mathrm{Ex}(t)$$

```
> eq3:=diff(In(t),t)=alpha*Ex(t)-(epsilon+d1+r1+mu)*In(t);
```

$$eq3 := \frac{\partial}{\partial t}\mathrm{In}(t) = .2\,\mathrm{Ex}(t) - .42\,\mathrm{In}(t)$$

```
> eq4:=diff(H(t),t)=epsilon*In(t)-(d2+r2+mu)*H(t);
```

$$eq4 := \frac{\partial}{\partial t}\mathrm{H}(t) = .25\,\mathrm{In}(t) - .24\,\mathrm{H}(t)$$

```
> eq5:=diff(R(t),t)=r1*In(t)+r2*H(t)-mu*R(t);
```

$$eq5 := \frac{\partial}{\partial t}\mathrm{R}(t) = .07\,\mathrm{In}(t) + .14\,\mathrm{H}(t) - .03\,\mathrm{R}(t)$$

```
> sys:=[eq1,eq2,eq3,eq4];
```

$$sys := \left[\frac{\partial}{\partial t}\mathrm{S}(t) = -.014\,\mathrm{S}(t) + .016\,\mathrm{Ex}(t) + .016\,\mathrm{In}(t) + .016\,\mathrm{H}(t) + .016\,\mathrm{R}(t)\right.$$

$$-\frac{u(t)\,(.4\,Ex(t)+.4\,In(t)+.2\,H(t))\,S(t)}{S(t)+Ex(t)+In(t)+H(t)+R(t)},$$

$$\frac{\partial}{\partial t}Ex(t)=\frac{u(t)\,(.4\,Ex(t)+.4\,In(t)+.2\,H(t))\,S(t)}{S(t)+Ex(t)+In(t)+H(t)+R(t)}-.23\,Ex(t),\ \frac{\partial}{\partial t}In(t)=.2\,Ex(t)-.42\,In(t),$$

$$\frac{\partial}{\partial t}H(t)=.25\,In(t)-.24\,H(t)\Big]$$

```
> ics:=S(0)=100,Ex(0)=50,In(0)=45,H(0)=10,R(0)=10;
  #ics:=S(0)=0,Ex(0)=5,In(0)=0,H(0)=1,R(0)=0;
```

$$ics := S(0)=100,\ Ex(0)=50,\ In(0)=45,\ H(0)=10,\ R(0)=10$$

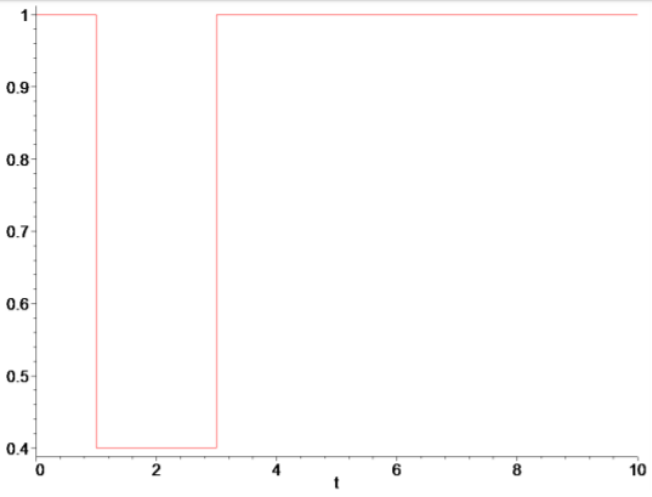
```
> sol:=dsolve({eq1,eq2,eq3,eq4,eq5,ics},{S(t),Ex(t),In(t),H(t),R(t)}
  ,type=numeric,
   startinit=true,output=listprocedure);
```

$$sol := [t=(\mathbf{proc}(t)\ \ldots\ \mathbf{end}),\ R(t)=(\mathbf{proc}(t)\ \ldots\ \mathbf{end}),\ H(t)=(\mathbf{proc}(t)\ \ldots\ \mathbf{end}),$$
$$S(t)=(\mathbf{proc}(t)\ \ldots\ \mathbf{end}),\ Ex(t)=(\mathbf{proc}(t)\ \ldots\ \mathbf{end}),\ In(t)=(\mathbf{proc}(t)\ \ldots\ \mathbf{end})]$$

```
> assign(sol);
> S:=S(t);
  Ex:=Ex(t);
  In:=In(t);
  H:=H(t);
  R:=R(t);
```

$$S := \mathbf{proc}(t)\ \ldots\ \mathbf{end}$$
$$Ex := \mathbf{proc}(t)\ \ldots\ \mathbf{end}$$
$$In := \mathbf{proc}(t)\ \ldots\ \mathbf{end}$$
$$H := \mathbf{proc}(t)\ \ldots\ \mathbf{end}$$
$$R := \mathbf{proc}(t)\ \ldots\ \mathbf{end}$$

```
>
> v:=proc(tau1,tau2)
   unapply(piecewise(t<tau1,umax,t<tau2,umin,umax),t);
  end:
>
> plot(v(1,3)(t),t=0..10,numpoints=100);
```




```
> J:=proc(T,tau1,tau2)
   global u;
   u:=v(tau1,tau2):
   print(tau1,tau2,S(T),Ex(T),In(T), H(T),R(T));
   print(tau1,tau2,S(5),Ex(5),In(5), H(5),R(5)); RETURN(In(T));
  end:
> J(20,3,8);
```

3, 8, 19.85579902325121, 12.53052345005799, 7.502249814494355, 11.35476572123126, 64.68192669127045

3, 8, 51.58119732899810, 42.86005189969034, 26.97148069083125, 26.63502224448333, 33.67561886490530

7.502249814494355

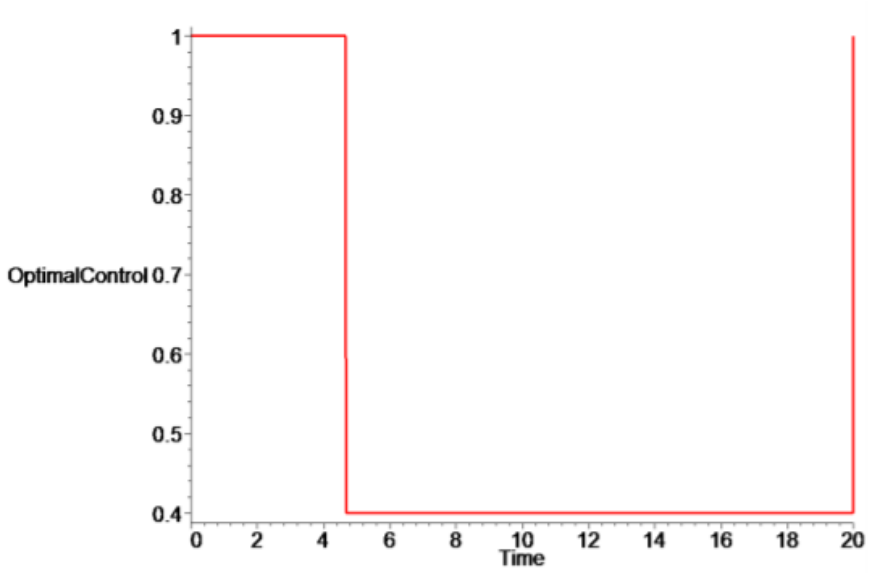
```
> T:=20;
```

$$T := 20$$

```
>  Jmin:=10:
  Tau1:=-infinity:
  Tau2:=-infinity:
  N:=30;
  h:=evalhf(T/N);
  for i from 0 to N do
```

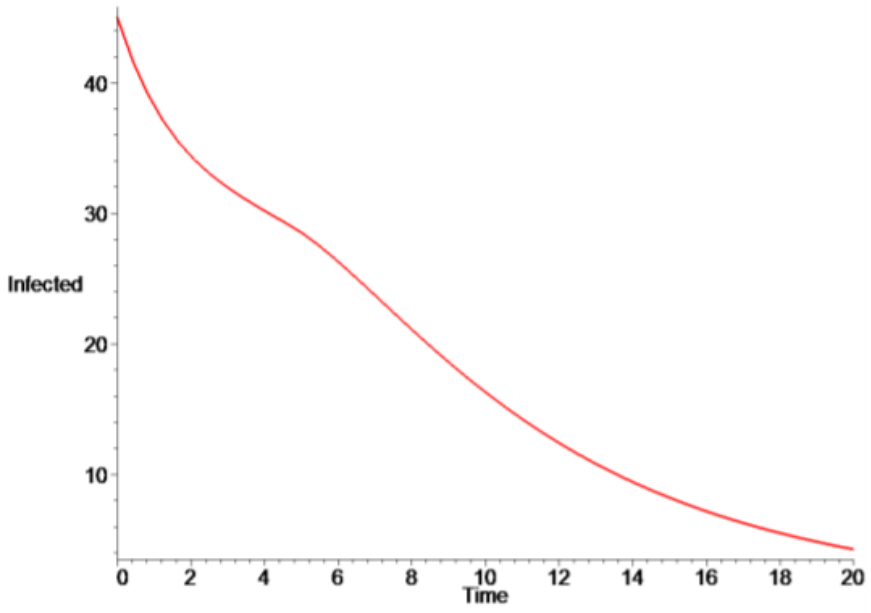
```
   tau1:=i*h;
   for j from 0 to N do
    tau2:=j*h;
    if (tau1 < tau2) then
     Jtemp:=J(T,tau1,tau2);
        if (Jmin > Jtemp) then
      Jmin:=Jtemp;
      Tau1:=tau1;
      Tau2:=tau2;
     fi:
    fi:
   od
  od:
> 'Jmin'=Jmin;
  'Tau1'=Tau1;
  'Tau2'=Tau2;
```

```
> plot(v(Tau1,Tau2)(t),t=0..T, thickness=3,labels=['Time',
  'OptimalControl'] );
```

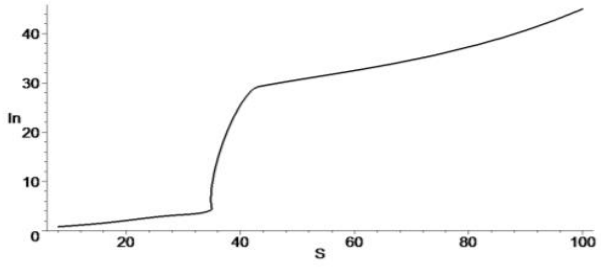



```
> u:=v(Tau1,Tau2);
> plot('In'(t),t=0..T,thickness=3, labels=['Time', 'Infected']);
```

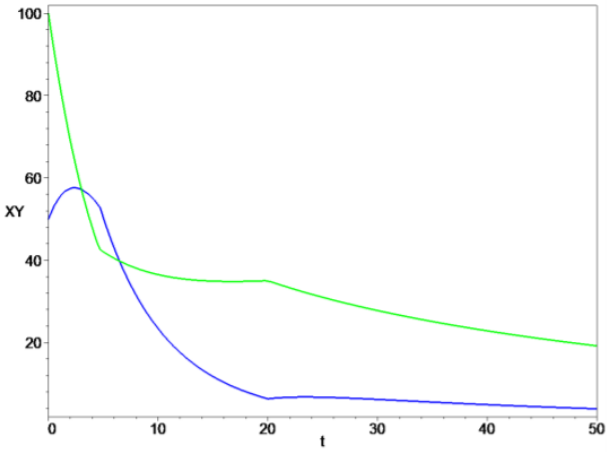
$$u := t \rightarrow \text{piecewise}(t < 4.666666667,\ 1,\ t < 20.00000000,\ .4,\ 1)$$



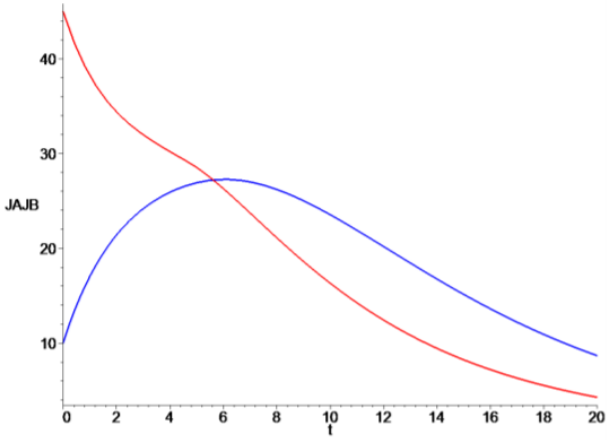
```
> plot(['S(t)','In(t)',t=0..100],scaling=constrained,color=BLACK,thi
  ckness=3,labels=['S','In']);
```




```
>
> plot(['S(t)','Ex(t)'],t=0..50,axes=box,labels=['t','XY'],thickness
  =3,color=[green,blue]);
```

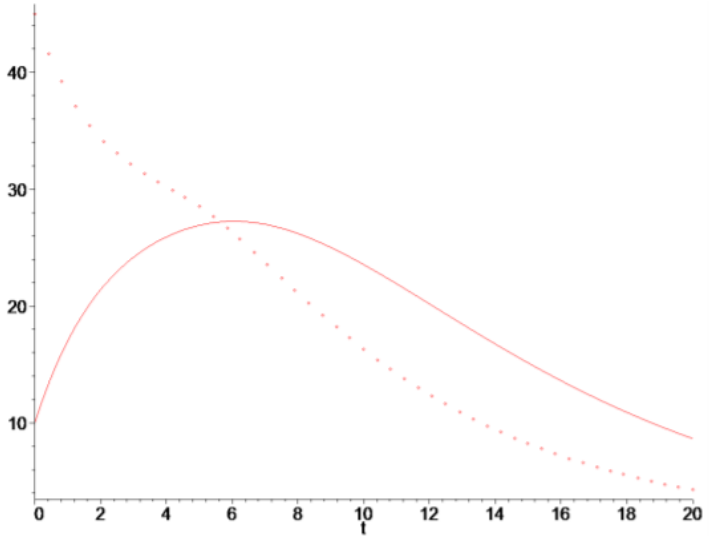



```
> plot(['In(t)','H(t)'],t=0..T,
  labels=['t','JAJB'],thickness=3,color=[red,blue]);
```




```
> P1:=plot(['In(t)'],t=0..T, style=point):
> P2:=plot(['H(t)'],t=0..T, style=line):
```

```
>
> plots[display]({P1,P2});
```




```
> R_0:=(beta1*theta*(epsilon+d1+r1+mu)*(d2+r2+mu)+beta2*theta*alpha*
  (d2+r2+mu)+beta3*theta*alpha*epsilon)/(mu*(alpha+mu)*(epsilon+d1+r
  1+mu)*(d2+r2+mu));
```

$$R\_0 := 1.599263860$$

```
>
```