DOKUZ EYLÜL UNIVERSITY
GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

FUNDEMENTALS OF BIOMATHEMATICS AND ITS APPLICATIONS

by
Gürcihan ZAMAN

August, 2022
İZMİR

FUNDEMENTALS OF BIOMATHEMATICS AND ITS APPLICATIONS

A Thesis Submitted to the
Graduate School of Natural And Applied Sciences of Dokuz Eylül University
In Partial Fulfillment of the Requirements for the Degree of Master of Science in Mathematics

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August, 2022
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M.Sc THESIS EXAMINATION RESULT FORM

We have read the thesis entitled “**FUNDEMENTALS OF BIOMATHEMATICS AND ITS APPLICATIONS**” completed by **GÜRCIHAN ZAMAN** under supervision of **ASSOC. PROF. DR. BURCU SİLİNDİR YANTIR** and we certify that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

Assoc. Prof. Dr. Burcu SİLİNDİR YANTIR

Supervisor

Assoc. Prof. Dr. Refet POLAT	Asst. Prof. Dr. Meltem ADIYAMAN
Jury Member	Jury Member

Prof. Dr. Okan FISTIKOĞLU
Director
Graduate School of Natural and Applied Sciences

ACKNOWLEDGEMENTS

First, I would like to thank my supervisor Assoc. Prof. Dr. Burcu SİLİNDİR YANTIR for the motivation, encouragement, endless patience and all her helps she provided during my study.

I would like to express my profound gratitude to my mother, my brother and my sister for providing me their support and all their helps whenever I need.

Finaly, I would like to thank to my friends Şule KILIÇASLAN and Mustafa Kutay KUTLU for the motivation and support they gave.

Gürcihan ZAMAN

FUNDEMENTALS OF BIOMATHEMATICS AND ITS APPLICATIONS

ABSTRACT

In this thesis, we study on simplest epidemiological models. SIR and SIS model are a few of these models. We first build these models by making some assumptions and we examine in which cases a disease disappears from population or becomes endemic in mathematical approaches. We also incorporate demography into SIR epidemic model and discuss the stability of the equilibria of this model. In addition, we develop a model of a disease which is transmitted by a vector. We observe that models of vector-borne diseases admit delay differential equations. Finally, we present more realistic models about infectious diseases.

Keywords: Epidemiological models, SIR model, SIS model, vector-borne diseases, delay differential equations

BİYOMATEMATİĞİN TEMELLERİ VE UYGULAMALARI

ÖZ

Bu tezde, en basit epidemiyolojik modeller üzerinde çalıştık. SIR ve SIS modeli bu modellerden birkaçıdır. İlk olarak bu modelleri bazı varsayımlar yaparak oluşturduk ve bir hastalığın hangi durumlarda popülasyondan yok olduğunu veya endemik hale geldiğini matematiksel yaklaşımlarla inceledik. SIR modele demografiyi de ekledik ve bu modelin denge noktalarının kararlılığını tartıştık. Ayrıca taşıyıcı kaynaklı hastalıkların modellerini geliştirdik. Taşıyıcı kaynaklı hastalıkların modellerinin gecikmeli diferansiyel denklemler formunda olduğunu gözlemledik. Son olarak, bulaşıcı hastalıklarla ilgili daha gerçekçi modeller sunduk.

Anahtar kelimeler: Epidemiyolojik modeller, SIR model, SIS model, taşıyıcı kaynaklı hastalıklar, gecikmeli diferansiyel denklemler

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CHAPTER ONE
INTRODUCTION

Throughout history, there have been epidemics of infectious diseases. Ancient Greece and Egypt civilizations were affected by smallpox, leprosy, tuberculosis, meningococcal infections, and diphtheria. One of the most chronicled epidemics was the Black death, which swept across Europe in 1345. However, the Black death reemerged in several regions of Europe in the nineteenth century. In 16th century, smallpox epidemic devastated the Aztec population and it caused the death of about 35 million people. At the beginning of 20th century, an epidemic of influenza caused the death of about 20 million people all around the world. The recent significant outbreaks of epidemics are Bombay plague (1905), SARS (2003) and H1N1 (2009).

Although infectious diseases date back to long history, the mathematical analysis is 350 years old. The first statistical study related to infectious diseases was introduced by John Graunt (1663) “Natural and Political Observations Made upon the Bills of Mortality”. In 1760, D. Bernoulli carried out a mathematical model for smallpox (Bernoulli (2004)) which is now considered the first mathematical modeling of an infectious disease. His approach was reformulated in Dietz & Heesterbeek (2002).

Scientific view accepts the idea that the diseases are spread due to a bacterium or virus contact. The precense of microorganisms was proven by A. Leeuwenhoek (1632) when he invented the microscope. Since then L. Pasteur (1822), J. Lister (1827) and R. Koch (1843) established the germ theory of infectious diseases. The notion of transmission of bacterial disease via contact between healthy individual and infected one provided a basis to the mathematical modeling of infectious diseases.

In the early 20th century, W. Hamer suggested a mass action law in a mathematical model to explain the measles. R. Ross was interested in malaria epidemic and he was awarded by the Nobel Prize (1902) for his demonstration that malaria is transmitted between mosquitoes and humans. In 1911, he developed a simple compartmental model for transmission of malaria and derived the concept of reproduction number.

The mathematical modeling about infectious diseases improved with the paper published by Kermack & Mckendrick (1927). This paper had the first deterministic model including susceptible, infected and removed compartments. Following this article to describe the model of transmission of infectious diseases, Kermack and McKendrick published a sequence of two more papers in 1932 and 1933 respectively.

In the 1980's, the occurrence of HIV epidemics gave importance to mathematical modeling of infectious diseases. Since then, scientists have constructed and analyzed mathematically a vast variety of models. Nowadays, mathematical modeling, which contributes to public health significantly, have an important place.

The book by Martcheva (2015) is one of the landmark sources in mathematical modeling of epidemiology. In this thesis, our aim is to present an introductory mathematical approach for infectious diseases. This thesis is a survey based on Martcheva (2015).

This thesis is organized as follows: Chapter 2 presents some basic definitions and concepts used in of the epidemiological models. Chapter 3 is devoted to simple epidemiological models, which are SIR model and SIS model. Here, we investigate the SIR model with its mathematical properties and analyze stability of the equilibrium points of the SIS model. Chapter 4 includes SIR model with demography and discussion of stability of the equilibrium points of SIR model with demography. In Chapter 5, we present vector-borne disease models expressed in terms of delay differential equations. Chapter 6 consists of more realistic models. For that reason, we give essential stages of infectious diseases with examples.

CHAPTER TWO

INFECTIOUS DISEASES: CLASSIFICATION AND BASIC NOTIONS

In this chapter, we first present the basic definitions of epidemiological mathematical models.

Definition 2.1. The study of health, illness and related patterns is called as *epidemiology*.

Until the twentieth century, epidemiological studies were generally interested in infectious disease. Nowadays, there are diseases which cause death worldwide such as cronery heart disease. These dieases that do not transmit from one person to person take place as a center of attention of the epidemiological studies. In this thesis, our primary goal is to present the mathematical modeling of infectious diseases.

Definition 2.2. A clinically evident illness steaming from the existence of a viral, bacterial, parasitic or viral agent is defined as an *infectious disease*.

Definition 2.3. The infectious diseases that are spread from person to person are called as *communicable diseases*. Although most of the infectious diseases are communicable diseases, there are infectious ones such as tetanus but not communicable.

Definition 2.4. The infectious diseases that are transmitted unnaturally from one person to person are called as *transmittable diseases* . Malaria is a transmittable disease.

Infectious diseases are generally as communicable or transmittable since there is a high risk of transmission. Infectious diseases are based on the way of transmission as follows:

1. *Person-to-person transmitted diseases* occur direct or indirect contact, for example HIV and influenza.
2. *Airbone transmission* is transmitted through breathing in infected air, such as influenza, smallpox, tuberculosis

3. *Water- and foodborne diseases* is spread by consuming contaminated water or food, for example cholera, stomach flu.
4. *Vertical trasmission* refers to a infection that is spread from a mother to the offspring through placenta. Hepatitis B, syphilis and HIV are examples of vertical transmission.
5. *Vector-borne diseases* are spread by a vector, such as mosquito, tick, and snail. For instance west Nile virus, dengue, malaria are vector-borne diseases.

In epidemiology, consepts associated with infectious diseases have a significant role to develop mathematical models. They add a variety of features to models. A few of the widely used concepts are given below.

Definition 2.5. Here, we list the most frequent consepts that appear the terminology of the diseases.

***Exposed individuals*:** An exposed individual is a healthy person with the potential to make disease-transmitting contact. In mathematical models, it is generally assumed that all exposed individuals get caught the disease eventually.

***Infectious and infected individuals*:** Whenever a pathogen enters the body of exposed individual, then that host becomes infected. Such hosts are called as infected individuals and they are capable of transmitting the disease. Throughout the infection, infected individuals may or may not be infectious.

***Latent individuals*:** Individuals who have infection without being infectious are called latent individuals. The time between when an individual exposures to a pathogen and when he/she can transmit the pathogen to another individuals is defined as *latent period*.

***Incubation period*:** The period between being infected and appearance of the first symptoms is called incubation period.

***Incidence*:** Incidence refers to the number of new cases over a specified period of time.

***Prevalence*:** The prevalence is called as the number of new cases and existing cases of a disease at a particular time.

***Case fatality proportion(CFP)*:** The ratio of people who end up dying with a disease to all individuals contracting it is defined as the fatality proportion.

***Disease-induced mortality*:** It is given by the proportion of individuals dying from a certain disease per unit of time to the total population.

See Nelson & Williams (2014) for the complete list of terminology for the epidemiology of infectious diseases.

A mathematical modeling is a construction of a system that are expressed in terms of differential equations, functional equations or stochastic equations. The process of mathematical modeling is described in Figure 2.1 (see Martcheva (2015)). Mathematical modeling that gained importance with HIV is used in studying of infectious disases. Throughout in this thesis, we will be interested in modeling diseases in a population. A mathematical model may help to obtain information about behavior of a system, which can be classified as follows:

i. A model that has a nonlinear dependence on the variables is classified as *nonlinear*, otherwise it is called *linear model*.

ii. Models with discrete or system states are called as *discrete models* and *continuos models* represent time and system states in a continuous manner.

iii. If the system depends on the change of time, then the model is called as *dynamic*. *Static model* is classified as a model which has time-invariant quantities.

iv. A *deterministic model* describes the uniquely determination of the variable states without randomness. A *stochastic* model is characterized by the variable states with randomness.

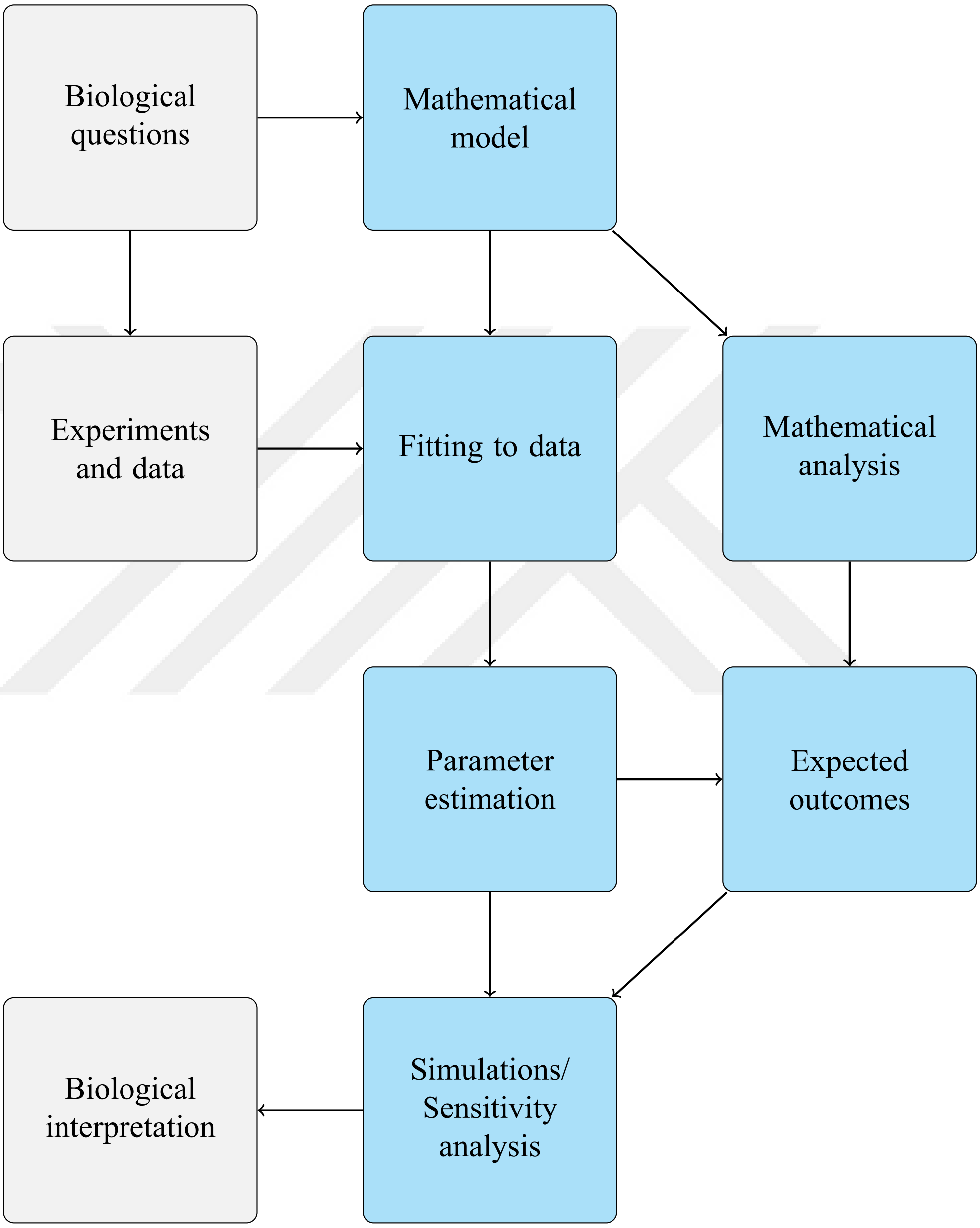


Figure 2.1 Modeling process

CHAPTER THREE
EPIDEMIC MODELS

3.1 SIR Epidemic Model

In the litature, Kermack & Mckendrick (1927) introduced the so-called *SIR epidemic model* which is one of the first epidemic models. The model represents the childhood diseases such as smallpox, chickenpox, mups and rubella.

In the SIR model, a population decomposes into 3 classes depending on time t.

Definition 3.1. We define the class of individuals as follows.

i. Individuals who are healthy but have a risk of contracting the disease are called as *susceptible class*, denoted by $S(t)$.

ii. Individuals who harbor an disease-causing agent and are currently sick belong to *infected compartment*, denoted by $I(t)$. In the SIR epidemic model, we assume that infected class also as to be infectious.

iii. The class of individuals who have pulled through the illness and cannot become sick again is said to be *removed or recovered individuals*. This class is denoted by $R(t)$.

We denote M as the total population size which is equivalent the sum of S, I and R. In order to find the change in such classes depending on time, we need to derive a epidemiological model comprising system of ODEs. For the SIR model, the number of susceptible individuals decreases since newly infected population pass to $I(t)$. *Incidence* is the number of individuals who get infected per time. Thus, the rate of change of $S(t)$ becomes $S'(t) = -$incidence. We consider how we can represent the incidence. In order to formulate SIR model, we need the following assumptions:

i. Infected individuals are infectious.

ii. M is constant.

iii. The number of contacts of an infectious individual per time is given by rM. Here, r is per capita contact rate.

iv. The probability of a contact with a susceptible individual is denoted by S/M

v. The number of contacts with susceptible individuals per time is given by $rM\frac{S}{M}$. Note that not every contact with a susceptible produces spread of the disease.

vi. prS is the number of susceptible individuals who become infected per time per infectious individual, where p refers to the probability of a contact with a susceptible which occurs in spread.

Therefore, $prSI$ stands for the number of individuals who become infected per time. Let us set $pr = \delta$. Hence, we derive the following differential equation for susceptible individual

$$S'(t) = -\delta I(t)S(t),$$

where δ is called the transmission rate constant and $\delta I(t)$ refers to the force of infection. The susceptible individuals who are infected pass to infected compartment while the infected individuals who are recovered do not belong to the infected class and pass to the recovered class. To sum up, the model is expressed by the coupled system of ODE's

$$S'(t) = -\delta IS, \tag{3.1}$$

$$I'(t) = \delta IS - \gamma I, \tag{3.2}$$

$$R'(t) = \gamma I, \tag{3.3}$$

where γ is the recovery rate. Note that the system (3.1)-(3.2)-(3.3) is called as SIR model. For well-definedness, we have to impose initial conditions at time $t = 0$, i.e., $S(0) := S_0$, $I(0) := I_0$ and $R(0) := R_0$. A differential equation is said to be well-posed if there exists a unique solution at every initial point. In order to be both mathematically and biologically consistent, a model given by a system of ODE must be well-posed. Furthermore, many biological and epidemiological models necessarily admit nonnegative solutions if initial conditions are nonnegative.

Properties. We list the mathematical properties of SIR model:

1. $\lim\limits_{t\to\infty} S(t) = \widetilde{S}$. Since $S(t) > 0$ and $S'(t) < 0$, then $S(t)$ is decreasing. That's why $S(t)$ has a limit point, say $\widetilde{S}$. Such $\widetilde{S}$ is called as *final size* of the epidemic.

2. $\lim\limits_{t\to\infty} R(t) = \widetilde{R}$. The number of recovered individuals is always increasing, since $R'(t) > 0$ for all t. Because $R(t)$ is monotone and bounded by M, $R(t)$ has also a limit, say $\widetilde{R}$.

3. An initial increase in the infected class implies that

$$I'(0) = (\delta S(0) - \gamma)I(0) > 0,$$

   which produces $\frac{\delta S(0)}{\gamma} > 1$. Therefore, the prevelance has a sudden increase and then a decline to zero. This is a classial behavior of an outbreak.

4. Combining (3.1) and (3.3), we obtain

$$\frac{dS}{dR} = -\frac{\delta}{\gamma}S,$$

   which admits a solution

$$S(t) = S(0)e^{\frac{-\delta}{\gamma}R(t)-R(0)} \geq S(0)e^{\frac{-\delta}{\gamma}M} > 0. \tag{3.4}$$

   Integrating (3.1) on $[0,\infty)$, one can obtain

$$\int_0^\infty S'(t)dt = -\gamma\int_0^\infty S(t)I(t)dt,$$

   which implies by Fundamental Theorem of Calculus

$$-\widetilde{S} + S(0) = \gamma\int_0^\infty S(t)I(t)dt \geq \gamma\widetilde{S}\int_0^\infty I(t)dt.$$

5. Since $S(0) - \widetilde{S} \geq \gamma\widetilde{S}\int_0^\infty I(t)dt$, then $I(t)$ is integrable on $[0,\infty)$.

Proposition 3.1. *Let* $I(t)$ *be convergent to L. If* $I(t)$ *is integrable on* $[0, \infty)$ *then* $L = 0$.

Proof. Clearly $I(t) > 0$. Let $I(t)$ be integrable on given interval and $\lim_{t \to \infty} I(t) = L \neq 0$. Then, for all $\frac{L}{2} > 0$, there exists $M > 0$ such that for all $t > M$

$$|I(t) - L| < \frac{L}{2},$$

from which we derive

$$I(t) > \frac{L}{2}, \qquad \forall t > M.$$

Therefore,

$$\int_0^\infty I(t)dt = \int_0^M I(t)dt + \int_M^\infty I(t)dt > \int_0^M I(t)dt + \int_M^\infty \frac{L}{2}dt.$$

Due to the second term at the right-hand side, $I(t)$ is not integrable. This contradicts with our assumption. Hence, $\lim_{t \to \infty} I(t) = 0$. □

Proposition 3.2. *The maximum number of infectious individuals is obtained by*

$$I_{max} = -\frac{\delta}{\gamma} + \frac{\delta}{\gamma} \ln \frac{\delta}{\gamma} + I_0 + S_0 - \frac{\delta}{\gamma} \ln S_0, \tag{3.5}$$

where $S(0) := S_0$ *and* $I(0) := I_0$.

Proof. First, we aim to solve (3.1) and (3.3). Dividing these two equation, we obtain

$$\frac{I'(t)}{S'(t)} = \frac{\delta SI - \gamma I}{-\delta SI} = -1 + \frac{\gamma}{\delta S},$$

or

$$I' = -S' + \frac{\gamma}{\delta} \frac{S'}{S}. \tag{3.6}$$

Integrating with respect to t leads to

$$I(t) = -S(t) + \frac{\gamma}{\delta} \ln S(t) + c$$

where c is arbitrary constant. Imposing the initial conditions $S(0) = S_0$ and $I(0) = I_0$, and using $\lim_{t\to\infty} S(t) = \widetilde{S}$ and $\lim_{t\to\infty} I(t) = 0$, we obtain

$$c = I_0 + S_0 - \frac{\gamma}{\delta}\ln S_0 = \widetilde{S} - \frac{\gamma}{\delta}\ln \widetilde{S},$$

from which we deduce

$$\frac{\gamma}{\delta} = \frac{\ln \frac{S_0}{\widetilde{S}}}{I_0 + S_0 - \widetilde{S}}. \tag{3.7}$$

The maximum number of infected individuals is calculated for $I'(t) = 0$. Therefore,

$$I'(t) = \delta SI - \gamma I = 0,$$

which implies that $S = \frac{\gamma}{\delta}$. We notice that the implicit solution is $I = -S + \frac{\gamma}{\delta}\ln S + I_0 + S_0 - \frac{\gamma}{\delta}\ln S_0$. To get I_{max}, we substitute $S = \frac{\gamma}{\delta}$ into the equation

$$I(t) + S(t) - \frac{\gamma}{\delta}\ln S(t) = I_0 + S_0 - \frac{\gamma}{\delta}\ln S_0, \tag{3.8}$$

we end up with (3.5). We remark that during the epidemic the maximum number of infected individuals is calculated by I_{max}. After that number, the number of infectious individuals will begin to decrease. □

Our next goal is to estimate the recovery rate of the SIR model. In order to estimate the recovery rate, we assume that there is no inflow in $I(t)$ and at $t = 0$, which implies

$$I'(t) = -\gamma I, \qquad I(0) = I_0, \tag{3.9}$$

whose solution can be easily derived as

$$I(t) = I_0 e^{-\gamma t}. \tag{3.10}$$

Then the probability of being still infectious can be represented as

$$\frac{I(t)}{I_0} = e^{-\gamma t}, \qquad t \geq 0.$$

Similarly, it is possible to obtain the probability of recovering or leaving the infectious class in terms of probability distribution function

$$F(t) = 1 - e^{-\gamma t}, \qquad t \geq 0. \tag{3.11}$$

Note that, $F(t) = 0$ for $t < 0$. Let X be a random variable, which denotes the time to exiting the infectious class, then X is continuous, and the probability distribution function has a probability density function.

Definition 3.2. (Ross (2009)) If the random variable X is continuous, then the probability distribution function of X, say F, will be differentiable and

$$\frac{dF(t)}{dt} := f(t) \geq 0,$$

where f(t) is the probability density function.

Consequently, the probability density function of (3.11) is

$$f(t) = \gamma e^{-\gamma t}. \tag{3.12}$$

Moreover, the average time being in the infectious class is described by the expected value of the random variable X.

Definition 3.3. (Ross (2009)) Let X be a continuous random variable and $f(t)$ be the probability density function of X, then the expected value of a continuous random variable X is defined by

$$E[X] = \int_{-\infty}^{\infty} t f(t) dt.$$

In this context,

$$\begin{aligned} E[X = t] &= \int_{-\infty}^{\infty} t f(t) dt = \int_{-\infty}^{\infty} t \gamma e^{-\gamma t} dt \\ &= -te^{-\gamma t}\Big|_0^{\infty} + \int_0^{\infty} e^{-\gamma t} dt = \frac{1}{\gamma}. \end{aligned}$$

Therefore, we conclude that the average time in the infectious class can be found as $\frac{1}{\gamma}$.

For instance, for smallpox, an individual is infectious for 21 days. Indeed, the recovery rate is $1/21$.

Example 3.1. (Brauer & Castillo-Chavez (2012)) In England, an epidemic occured because of a plague between 1665 and 1666. The values of susceptibles and infectives are given in Table 3.1. The initial points become $S(0) = 254$ and $I(0) = 7$, the final number of susceptibles $\widetilde{S} = 83$. From the equation (3.7), we obtain $\frac{\gamma}{\delta} = 153$. The infective period of plague was estimated by 11 days or 0.3667 month, which implies $\gamma = 2.73$ and then $\delta = 0.0178$. We can also obtain the maximum number of infectious individuals $I_{max} = 30.4$. In Figure 3.1, we see that similar results occur between our estimation and data.

Table 3.1 Data for Plague of Eyam

Date 1666	Infectives	Susceptibles
Mid-May	7	254
July 19	22	201
August 3/4	29	153.5
August 19	21	121
September 19	8	97
October 20	0	83

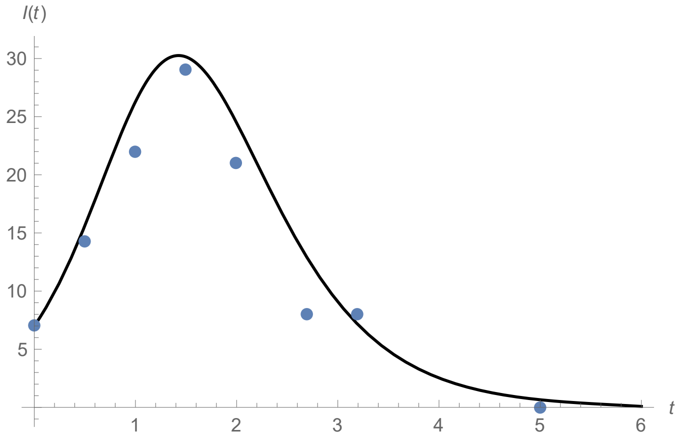


Figure 3.1 Function of $I(t)$ with data

3.2 SIS Epidemic Model

There are cases when individuals who recover become immediately susceptible again. In such cases such as influenza, the model turns out to be

$$S'(t) = -\delta IS + \gamma I, \tag{3.13}$$

$$I'(t) = \delta IS - \gamma I. \tag{3.14}$$

The system (3.13) and (3.14) is called SIS epidemic model. Assume $S(0) := S_0$ and $I(0) := I_0$. Since M is constant, we can write $M = S_0 + I_0$. Thus, SIS model reduces to the following equation

$$I'(t) = \delta I(t)(M - I(t)) - \gamma I(t), \tag{3.15}$$

which is a variant of the *Logistic equation* written as the form

$$I'(t) = rI\left(1 - \frac{I}{K}\right), \tag{3.16}$$

where $r = \delta M - \gamma$ and $K = r/\delta$. The logistic equation, which is a model of population growth, is one the classical models in the population dynamics. The parameter r is usually called as the *growth rate*. The logistic equation, which is a Bernoulli equation, can be solved by using the trasformation $\frac{K}{I(t)} = -V(t)$

$$V' + rV = -r,$$

which becomes a linear differential equation and the solution can be determined by

$$V(t) = -1 + ce^{rt},$$

where c is arbitrary constant. The general solution of $I(t)$ can be derived as

$$I = \frac{K}{1 - ce^{-rt}}.$$

Imposing the initial condition $I(0) := I_0$, we get

$$c = \frac{I_0 - K}{I_0}.$$

Thus, the unique solution for $I(t)$ is

$$I(t) = \frac{K}{1 - \left(\frac{I_0 - K}{I_0}\right) e^{-rt}}.$$

Remark 1. Let us analyze the growth rate r.

i. When $r < 0$, $I(t) \to 0$ as $t \to \infty$. That is, the disease disappears from the population on its own.

ii. When $r > 0$, $I(t)$ goes to K as $t \to \infty$, which means that the disease remains in the population indefinitely, and the number of infecteds stabilizes around K.

The threshold condition $r > 0$ can be written as $\mathcal{R}_0 > 1$, where

$$\mathcal{R}_0 = \frac{\delta M}{\gamma},$$

and it is so-called *basic reproduction number* of the disease.

Remark 2. The reproduction number stands for the number of secondary cases produced by one infectious individual in an entirely susceptible population. If a population is composed of only susceptible individuals, then $S = M$. Since the incidence is δSI, the number of secondary cases caused by one infectious individual per unit of time is δM. An individual who belongs to infectious compartment remains infectious for $1/\gamma$. Hence, the number of secondary infections caused by one infectious individual during the period when that individual remains infectious is $\frac{\delta M}{\gamma} = \mathcal{R}_0$.

Now, we investigate the qualitative analysis of the Logistic equation. Several biological models cannot be solved explicitly, however we can observe the behaviour of solutions in the long-term. Equilibrium points, which are constant solutions in time, are significant tools providing the analysis of the behavior of the solutions in the long-term.

Definition 3.4. For an autonomous differential equation i.e.,

$$\frac{dy}{dx} = g(y),$$

the values of y for which $\frac{dy}{dx} = 0$ are called *equilibruim points*.

Let us find the equilibrium points of SIS model:

$$I'(t) = I(\delta M - \delta I - \gamma) = f(I) = 0. \tag{3.17}$$

We have two equilibria: $I_1 = 0$ and $I_2 = \frac{\delta M - \gamma}{\delta} = K$. The equilibrium point I_1 is called as a *disease-free equilibrium* in the mathematical epidemiology and it always exists since the disease does not exist in the population and the whole population is susceptible.

The equilibrium I_2 is called an *endemic equilibrium* and it exists only if $\mathcal{R}_0 > 1$. When $\mathcal{R}_0 > 1$, both $I_1 = 0$ and $I_2 = K$ are solutions of (3.15). On $(0, K)$ interval, $\frac{dI}{dt} > 0$ for every $t \geq 0$. This means that the solutions in that interval are increasing. Since $I(t)$ is bounded and increasing, $I(t)$ converges as $t \to \infty$. Using the following corollary, the behavior of its derivative can be analyzed.

Corollary 3.1 (Thieme (2003))**.** Assume that $f(t)$ converges as $t \to \infty$ and $f'(t)$ is uniformly continuous on $[0, \infty)$. Then $f'(t) \to 0$ as $t \to \infty$.

Proof. By the definition of uniform continuity of f', for every $\frac{\epsilon}{2} > 0$, there exists $\delta > 0$ such that whenever $|t - y| < \delta$, for every $t, y \in [0, \infty)$ we have

$$|f'(t) - f'(y)| < \epsilon.$$

Assume $f \to L$ as $t \to \infty$ i.e.,

$$|f(t) - L| < \frac{\delta\epsilon}{4}, \qquad \forall t > M, \exists M > 0.$$

Therefore, for every $t, y \in \mathbb{N}$, we deduce that

$$\begin{aligned}|f(t) - f(y)| &= |f(t) - f(y) + L - L| \\ &\leq |f(t) - L| + |f(y) - L| < \frac{\delta\epsilon}{2}.\end{aligned}$$

Now, we use the Mean Value Theorem, for $t > M$, there exists $c \in (t, t + \delta)$ such that

$$\frac{f(t + \delta) - f(t)}{\delta} = f'(c).$$

Then,

$$\begin{aligned}|f'(t)| &= |f'(t) - f'(c) + f'(c)| \\ &\leq |f'(t) - f'(c)| + \frac{|f(t + \delta)|}{\delta} < \frac{\epsilon}{2} + \frac{\delta\epsilon}{2\delta} = \epsilon.\end{aligned} \tag{3.18}$$

This proves that for every $\epsilon > 0$, there exists $M > 0$ such that $|f'(t)| < \epsilon$ for every $t > m$ i.e., $f'(t) \to 0$ as $t \to \infty$. ☐

Since $I(t)$ converges as $t \to \infty$ and $I'(t)$ is uniformly continuous, then $I'(t) \to 0$ as $t \to \infty$ by above corollary. This can be interpreted as the number of infected individuals remain constant after a certain time, say $\lim_{t\to\infty} I(t) = L$. Clearly, L satisfies the equilibrium equation $f(L) = 0$. Now,

$$\lim_{t\to\infty} I'(t) = \delta L(M - L) - \gamma L$$

implies that $L = 0$ or $L = K$. As seen Figure 3.2, $I'(t) > 0$ on $(0, K)$ while $I'(t) < 0$ on (K, ∞), which implies that K is the absolute maximum value of $I(t)$.

We can investigate the concavity of the solutions for $\frac{d^2I}{dt^2} = 0$. Let us find the second

	0		K	
I'	0	$+$	0	$-$

Figure 3.2 Sign table of first derivative of I

derivative of I

$$\begin{aligned}\frac{d^2I}{dt^2} &= \frac{d}{dt}(\delta MI - \delta I^2 - \gamma I) \\ &= r^2\left(1 - \frac{2I}{K}\right)\left(1 - \frac{I}{K}\right)I.\end{aligned}$$

Then, $I = 0$, $I = \frac{K}{2}$ and $I = K$. As given Figure 3.3, on $(0, K/2)$, $I''(t) > 0$ i.e., $I(t)$ is concave up and increasing while on $(K/2, K)$, it is concave down and increasing. Similarly, on (K, ∞), $I(t)$ is decreasing and concave up. All this results is illustrated in Figure 3.4.

	0		$K/2$		K		∞
I''	0	$+$	0	$-$	0	$+$	

Figure 3.3 Sign table for second derivative of I

3.3 Stability Analysis of Models

The stability of equilibrium poinst determines whether solutions nearby the equilibrium points, remain themselves, get closer or go further away.

Definition 3.5. If all solutions of a differential equation converge to its equilibrium point for every initial condition, we say that this equilibrium point is *globally stable*.

The equilibrium points of the Logistic equation (3.15) are $I_1 = 0$ and $I_2 = K$. Then,

i. If $\mathcal{R}_0 < 1$ then $r < 0$ and $K < 0$, so that all solutions get closer the unique

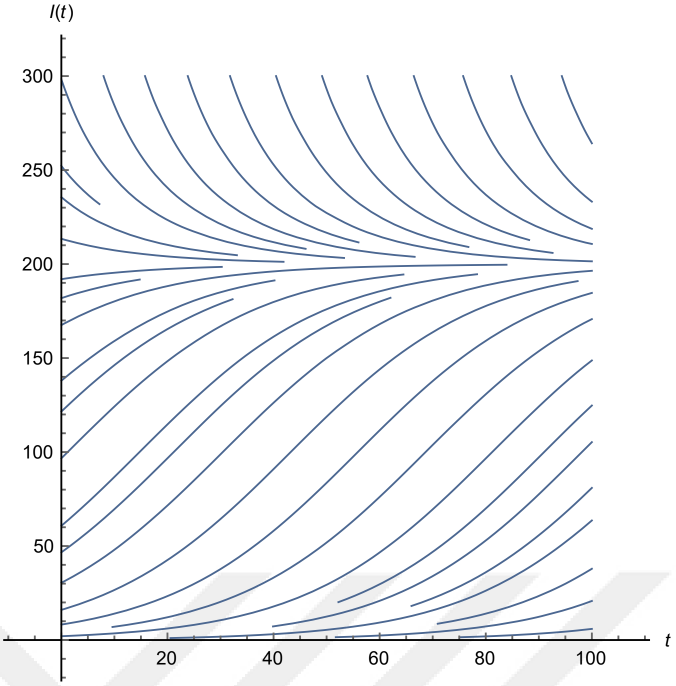


Figure 3.4 Solutions of logistic equation converging to endemic equilibrium

equilibrium $I_1 = 0$. In other words, all solutions $I(t) \to 0$ as $t \to \infty$ and $I(0) > 0$ which means that the disease-free equilibrium is *globally stable*.

ii. If $\mathcal{R}_0 > 1$, we have two equilibria: $I_1 = 0$ and $I_2 = K$. In this case, starting from $I(0) > 0$, all solutions diverge from $I_1 = 0$ which means that the disease-free equilibrium is *unstable*. Moreover, all solutions starting from $I(0) > 0$ converge to the endemic equilibrium $I_2 = K$. Hence, the endemic equilibrium is *globally stable*.

We may not have globally stable equilibrium when there are several endemic equilibria. In such cases, we use the concept of a *locally asymptotically stable* equilibrium.

Definition 3.6. If solutions close to the equilibrium converge to the equilibrium then such equilibrium is said to be *locally asymtotically stable*.

In order to investigate the stability of a nonlinear system, we make use of the following *linearization Theorem*.

Theorem 3.1. *(Martcheva (2015)) An equilibrium x^* of the differential equation $x'(t) = f(x)$ is locally asymtotically stable if $f'(x^*) < 0$ and is unstable if $f'(x^*) > 0$.*

Note that, if $f(x^*) = 0$, the theorem provides no information for the stability of x^*. Furthermore, we say that an equilibrium is *hyperbolic* for which $f'(x^*) \neq 0$ and *nonhyperbolic* for which $f'(x^*) = 0$.

Proof. Consider the following ODE

$$x'(t) = f(x), \tag{3.19}$$

x^* is an equilibrium point iff $f(x^*) = 0$. Let us denote the perturbation by $u(t) := x(t) - x^*$. Solutions of (3.19) that start from a neighborhood x^* converge to x^* if $u(t) \to 0$. We assume that the perturbation of $u(t)$ is very small. Now, we expand f around x^* as a Taylor series if $f \in \mathcal{C}'(I)$, $I \subset \mathbb{R}$. Then,

$$f(x) = u'(t) = f(x^*) + f'(x^*)u(t) + \frac{f''(\xi)}{2!}(u(t))^2, \tag{3.20}$$

where $\xi \in (x^*, x^* + u(t))$. Assume $f \in \mathcal{C}^2(I)$. Then $f''(x) < N$ for some $N > 0$. The term $(u(t))^2$ is neglicable. We also have $f(x^*) = 0$ since x^* is equilibrium. Thus, the expansion (3.20) becomes

$$u'(t) = f'(x^*)u(t), \tag{3.21}$$

which is the linearized form of the equation (3.19), whose solution eqquipped with the initial condition $u(0) = u_0$ can be derived as

$$u(t) = u_0 e^{f'(x^*)t}. \tag{3.22}$$

If $f'(x^*) > 0$, $u(t) \to \pm\infty$, depending on u_0, and $u(t) \to 0$ if $f'(x^*) < 0$. This implies that $u(t) = x(t) - x^* \to 0$ i.e., $x(t) \to x^*$. We conclude that solutions of (3.19) converge to this equilibrium if $f'(x^*) < 0$. Hence, the equilibrium x^* is locally asymtotically stable if $f'(x^*) < 0$. When $f'(x^*) > 0$, $|u(t)| \to \infty$, which means that $x(t)$ moves away from x^*. Hence, the equilibrium x^* is unstable. $\square$

Remark 3. We investigate the stability analysis of the Logistic equation (3.15) by Theorem 3.1. For $\mathcal{R}_0 < 1$, the only equilibrium is computed as $I_1 = 0$ and for $\mathcal{R}_0 > 1$, the equilibrium points are $I_2 = 0$ and $I_2 = K$. By (3.16)

$$f(I) = rI\left(1 - \frac{I}{K}\right)$$

from which we find

$$f'(I) = r\left(1 - \frac{I}{K}\right) - \frac{rI}{K}.$$

It is clear that

$$f'(0) = r \qquad \text{and} \qquad f'(K) = -r.$$

If $\mathcal{R}_0 = \frac{\delta M}{\gamma} < 1$ then $r < 0$ and endemic equilibrium does not exist. Hence, the disease-free equilibrium is locally asymtotically stable by the linearization Theorem 3.1. If $\mathcal{R}_0 > 1$ then $r > 0$. Therefore, the disease-free equilibrium is unstable and the endemic equilibrium is locally asymtotically stable.

The stability of each equilibrium can be interpreted from the slope of the graph through which the equilibrium passes. As illustration, see Figure 3.5.

3.4 A Simple Model with Treatment

In a simple SIS model, suppose that recovery rate γ depends on treatment. If treatment resources are limited, then recovery rate γ depends on I and it is decreasing. To be more precise, assume

$$\gamma(I) = \frac{\gamma}{1 + I}, \tag{3.23}$$

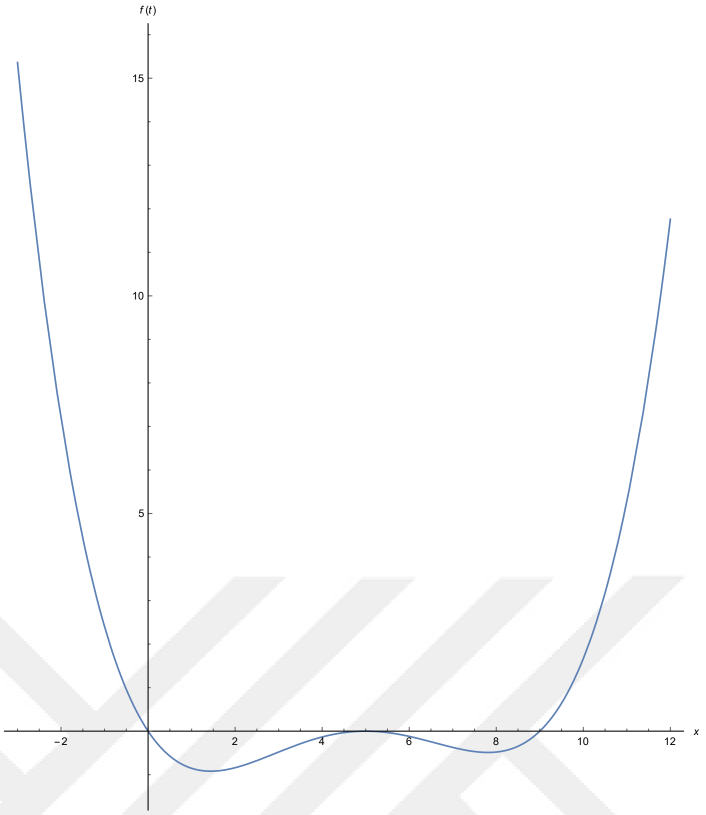


Figure 3.5 Function $f(x)$ for stability of its equilibrium points

where γ is the constant recovery rate if there are few infectives. We substitute (3.23) into SIS model (3.13)-(3.14).

$$\begin{aligned} S'(t) &= -\delta IS + \frac{\gamma I}{1+I}, \\ I'(t) &= \delta IS - \frac{\gamma I}{1+I}. \end{aligned} \tag{3.24}$$

The system (3.24) is called as an SIS epidemic model with treatment. Since the total population size is M, then $M(t) = S(t) + I(t)$. Since also $M' = 0$, we obtain $M(t)$ to be constant. Thus, $S(t) = M - I(t)$. Therefore, the system (3.24) implies

$$I'(t) = \delta I(M - I) - \frac{\gamma I}{1+I}, \tag{3.25}$$

which can be solved easily. Let us analyze the stability of its equilibria. Let us denote

$$f(I) := I \left[\delta(M - I) - \frac{\gamma}{1+I} \right] = 0.$$

Clearly, we find $I_1 = 0$ is a equilibrium, which is the disease-free equilibrium. Moreover, we obtain a quadratic equation

$$(M - I)(1 + I) = \frac{\gamma}{\delta}, \tag{3.26}$$

which has 2 roots by Fundamental Theorem of Arithmetic. To investigate graphically, set $g(I) := (M - I)(1 + I)$, where $g(I)$ is a parabola that opens downward. We see that $g(0) = M$ and in this case we have a horizontal line $y = \frac{\gamma}{\delta}$.

i. If $g(0) = M > \frac{\gamma}{\delta}$, then the horizontal line cuts the graph at a positive point. Hence, we have a unique positive equilibrium. This situation is illustrated in Figure 3.6. If $\mathcal{R}_0 = \frac{\delta M}{\gamma} > 1$, then there is a unique endemic equilibrium.

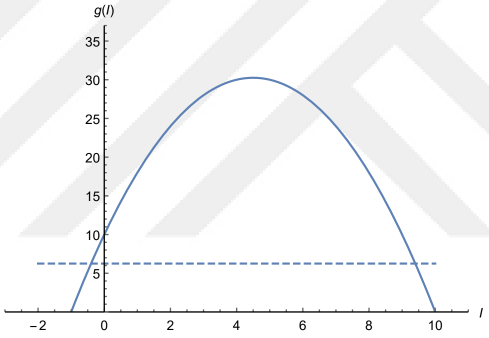


Figure 3.6 Graphic for function $g(I)$

ii. If $g(0) = M < \frac{\gamma}{\delta}$, we have either two or zero solutions since the horizontal line cuts the graph either at two points or at no point. We illustrate these two conditions in Figure 3.7.

iii. We see that the parabola cuts the horizontal axis M and -1. Therefore, its maximum appears at their average,

$$I_m = \frac{M-1}{2} > 0,$$

which implies $M > 1$.

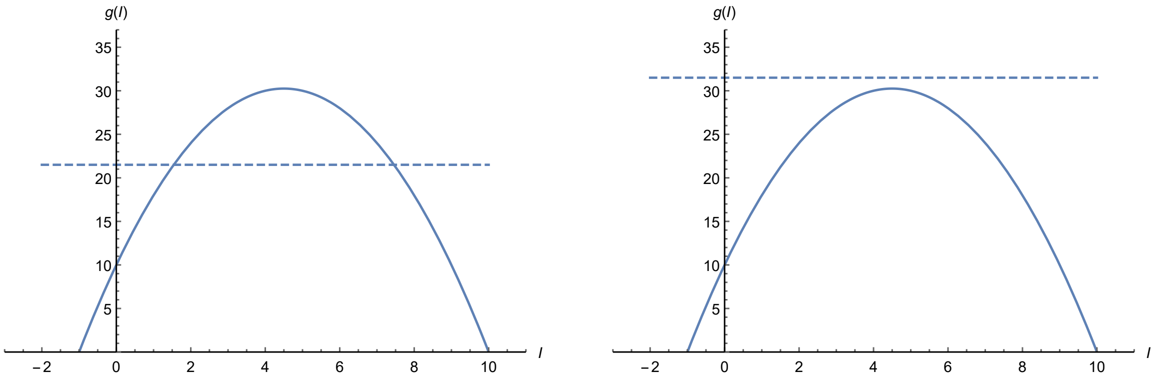


Figure 3.7 Left : There are two positive equilibria. Right: there is no positive equilibria

iv. If the line $y = \frac{\gamma}{\delta}$ is below the maximum of the parabola, then

$$(M - I_m)(1 + I_m) > \frac{\gamma}{\delta}. \tag{3.27}$$

Therefore, the system (3.24) has two endemic equilibrium points if $\mathcal{R}_0 < 1$, $M > 1$ and condition (3.27) is satisfied. Otherwise, it has no endemic equilibria.

3.5 Bistability

In order to analysis the stability of equilibria, we discuss the below cases seperately.

i. If $\mathcal{R}_0 < 1$ and there are no nontrivial equilibrium points, all solutions of (3.26) approach disease-free equilibrium, because

$$f'(I) = \delta(M - I) - \delta I + \frac{-\gamma(1 + I) + \gamma I}{(1 + I)^2}$$
$$f'(0) = \delta M - \gamma < 0$$

Hence, for every initial condition $I(0) = I_0 > 0$, the disease-free equilibrium is globally stable.

ii. If $\mathcal{R}_0 > 1$, we have $f'(0) > 0$. This means that the disease-free equilibrium $I_1 = 0$ is unstable. For $\mathcal{R}_0 > 1$, we found one more equilibrium point I_2. For solutions starting from $I(0) = I_0 > 0$ and satisfying $0 < I(t) < I_2$ for all t, $I(t)$

is increasing since $f(I) = \frac{dI}{dt} > 0$ in that interval. Hence, $I(t) \to I_2$ as $t \to \infty$. Furthermore, for solutions that start from $I_0 > I_2$ and satisfying $I(t) > I_2 \; \forall t$, $I(t)$ is decreasing since $f(I) < 0$. So, we have $I(t) \to I_2$ as $t \to \infty$.

Therefore, the endemic equilibrium I_2 is locally stable. Furthermore, it is also globally stable since all solutions approach the endemic equilibrium for every initial condition $I_0 > 0$.

iii. When $\mathcal{R}_0 < 1$, there are two equilibria $I_{11} < I_{12}$ apart from $I_1 = 0$. Since $\frac{dI}{dt} < 0$ on $(0, I_{11})$, $I(t)$ is decreasing. Hence, for solutions starting from initial condition $I_0 > 0$ and satisfying $0 < I(t) < I_{11}$ for all t, we have that $I(t) \to 0$ as $t \to \infty$. Because $\frac{dI}{dt} > 0$ on (I_{11}, I_{12}), $I(t)$ is increasing. Therefore, for solutions starting from I_0 satisfying $I_{11} < I_0, I(t) < I_{12} \; \forall t$, we get $\lim\limits_{t \to \infty} I(t) = I_{12}$. Furthermore, $I(t)$ is decreasing since $\frac{dI}{dt} < 0$ on (I_{12}, ∞). Hence, for solutions starting from I_0 which satisfies the condition $I_{12} < I_0, I(t)$ for all t, we obtain $\lim\limits_{t \to \infty} I(t) = I_{12}$.

Thus, we have solutions converging to both disease-free and the endemic equilibria. This situation is called as *bistability*. Note that, we cannot discuss global stability.

CHAPTER FOUR
THE SIR MODEL WITH DEMOGRAPHY

Let us first recall what we mean by demography.

Definition 4.1. *Demography* is the study of humans population with respect to their process of changing, density, distribution e.t.c.

SIR and SIS models established before did not include births and deaths occuring in the population. They are beneficial for epidemic modeling on a short period of time, such as influenza. If there does not exists a significant change in population size and disease develops on a short time period, it is possible to ignore the population change. This is valid for *fast diseases*, for example; childhood disease,influenza. On the other side, HIV and tuberculosis are the so-called *slow diseases*. In this situation, we cannot ignore the demography of the population since the population changes for a long period of time. In this chapter, we will incorproate the population change in the epidemic models.

Example 4.1. As an illustration, we first focus on the Logistic model as a model of population growth. Here, we assume that

i. K is the upper limit of the population growth, which is called as carrying capacity,

ii. $K - M$ is the number of individuals that can be added to the population before it reaches carrying capacity,

iii. $\frac{K-M}{K}$ is the ratio of the carrying capacity for further growth.

Then,

$$\frac{dM}{dt} = rM\left(1 - \frac{M}{K}\right),$$

which is the Logistic model.

Remark 4. 1. At low densities $M(t) \equiv 0$, which implies $\frac{K-M}{K} = 1$, thus the population growth rate becomes maximal and is equal to r.

2. The population growth rate decreases if population number exceeds K.

3. When $M = K$, the population growth rate reaches zero.

The Logistic model is seldomly used to model human population since carrying capacity may not be constant. However, when it is used for short periods of time, it usually gives admirable results.

Example 4.2. We present a simple Logistic model which depends on the birth and death rate

$$M'(t) = \Theta - \kappa M, \tag{4.1}$$

where Θ is the total birth rate and κ is the per capita natural death rate. One can compute the solution as

$$M(t) = M_0 e^{-\kappa t} + \frac{\Theta}{\kappa}\left(1 - e^{-\kappa t}\right), \tag{4.2}$$

where $M(0) = M_0$. Clearly, as $t \to \infty$, $M \to \frac{\Theta}{\kappa}$.

We can compute the per capita rate at which the individuals leave a class is $\frac{1}{T}$, where T is the time spent in that class. If κ is the natural death rate, then the average lifespan should be $\frac{1}{\kappa}$.

4.1 The SIR Model with Demography

In order to establish the SIR model with demography, we first assume that

i. All individuals are born susceptible from birth.

ii. Per capita death rate is κ and the total death rate in each class is κS, κI and κR respectively.

Then, the SIR model with demography is given by

$$\begin{aligned}S'(t) =&\Theta - \delta I(t)S(t) - \kappa S(t),\\ I'(t) =&\delta I(t)S(t) - \gamma I(t) - \kappa I(t),\\ R'(t) =&\gamma I(t) - \kappa R(t),\end{aligned}$$

where δ and γ are transmission and recovery rates, respectively. Similar to the discussion in Example 4.2, $M(t) \to \frac{\Theta}{\kappa}$ as $t \to \infty$, which can be interpreted as population size is asymptotically constant. Otherwise, the incidence is proportional to SI i.e., δSI and it is called *mass action incidence*. When mass action incidence is normalized, the incidence $\frac{\delta SI}{M}$ is called as *the stantard incidence*.

Remark 5. In some diseases, disease-relevant contact increases as the the population size increases. In such cases mass action incidence is used e.g., the size of population would impact the number of contacts in influenza. In some diseases, contact rate is limited and cannot grow further than a specific rate regardless of the size of the population. In such cases standard incidence is used e.g., sexually transmitted diseases.

Let us write the SIR model with demography as follows

$$S'(t) =\Theta - \delta IS - \kappa S := f(S, I), \tag{4.3}$$

$$I'(t) =\delta IS - \gamma I - \kappa I := g(S, I), \tag{4.4}$$

where $R = N - S - I$ and the functions f and g are nonlinear. Since f and g are independent of time, the system (4.3) and (4.4) is autonomous. In order to reduce the parameters in the system (4.3) and (4.4), we use the transformation

$$\tau := (\gamma + \kappa)t. \tag{4.5}$$

Then

$$\begin{aligned}M(t) =& M\left(\frac{\tau}{\gamma+\kappa}\right) = \tilde{M}(\tau),\\ I(t) =& I\left(\frac{\tau}{\gamma+\kappa}\right) = \tilde{I}(\tau),\\ S(t) =& S\left(\frac{\tau}{\gamma+\kappa}\right) = \tilde{S}(\tau).\end{aligned}$$

Thus, the reduced system turns out to be

$$\begin{aligned}\frac{d\tilde{S}}{d\tau} =& \frac{\Theta}{\gamma+\kappa} - \tilde{S}(\tau)\frac{(\delta\tilde{I}(\tau)+\kappa)}{\gamma+\kappa},\\ \frac{d\tilde{I}}{d\tau} =& \frac{\delta\tilde{I}(\tau)\tilde{S}(\tau)}{\gamma+\kappa} - \tilde{I}(\tau).\end{aligned}$$

Rescaling the variables $\tilde{S}$ and $\tilde{I}$ with the total limiting population size, we define

$$x(\tau) := \frac{\kappa\tilde{S}}{\Theta}, \qquad y(\tau) := \frac{\kappa\tilde{I}}{\Theta},$$

which implies

$$\begin{aligned}x'(\tau) =& \frac{\kappa}{\gamma+\kappa}(1-x(\tau)) - \frac{\Theta\delta}{\kappa(\gamma+\kappa)}x(\tau)y(\tau),\\ y'(\tau) =& \left(\frac{\delta\Theta}{\kappa(\gamma+\kappa)}x(\tau)-1\right)y(\tau).\end{aligned}$$

One can rewrite the system for $x'(\tau)$ and $y'(\tau)$ as

$$\begin{aligned}x' &= \zeta(1-x) - \mathcal{R}_0 xy,\\ y' &= (\mathcal{R}_0 x - 1)y,\end{aligned} \tag{4.6}$$

where $\zeta = \frac{\kappa}{\gamma+\kappa}$ and $\mathcal{R}_0 = \frac{\Theta\delta}{\kappa(\gamma+\kappa)}$. The system (4.6) is the dimensionless form of the SIR model with demography. We emphasize that the number of parameters are reduced. Moreover, the system (4.6) is equivalent to original one since the long-term behavior of the solutions of both systems is the same.

Now, we investigate equiblirium points of the dimensionless SIR model with demography. From the system (4.6), the equilibrium can be computed.

$$x' = \zeta(1-x) - \mathcal{R}_0 xy = 0, \tag{4.7}$$

$$y' = (\mathcal{R}_0 x - 1)y = 0. \tag{4.8}$$

i. If $y = 0$, there are no infectives. By (4.7), we conclude that $x = 1$, which means that all individuals are susceptible. Hence, the equilibrium $(x, y) = (1, 0)$ is the disease-free equilibrium.

ii. If $y \neq 0$, by (4.8) $x = \frac{1}{\mathcal{R}_0}$ and by (4.7), $y = \zeta\left(1 - \frac{1}{\mathcal{R}_0}\right)$. Therefore, the second equilibrium $(x, y) = \left(\frac{1}{\mathcal{R}_0}, \zeta\left(1 - \frac{1}{\mathcal{R}_0}\right)\right)$ is the endemic equilibrium provided that $\mathcal{R}_0 > 1$.

4.2 Linearization

In order to investigate the behavior of solutions close to an equilibrium, we can use linearization. Suppose the general system is given by

$$\begin{aligned} x' &= f(x, y), \\ y' &= g(x, y). \end{aligned} \tag{4.9}$$

Let (x^*, y^*) be an equilibrium point of (4.9) and we perturbate the solution near the equilibrium by setting $k(\tau) := x(\tau) - x^*$ and $l(\tau) := y(\tau) - y^*$. The system (4.9) can be rewritten as

$$\begin{aligned} k' &= f(k + x^*, l + y^*), \\ l' &= g(k + x^*, l + y^*). \end{aligned} \tag{4.10}$$

Assume $f, g \in \mathcal{C}^2$ and expand the Taylor series of f and g near the point (x^*, y^*)

$$\begin{aligned} f(k + x^*, l + y^*) = \; & f(x^*, y^*) + f_x(x^*, y^*)k(\tau) + f_y(x^*, y^*)l(\tau) + \tfrac{1}{2}f_{xx}(x^*, y^*)k^2(\tau) \\ & + f_{xy}(x^*, y^*)k(\tau)l(\tau) + \tfrac{1}{2}f_{yy}(x^*, y^*)l^2(\tau) + \ldots, \end{aligned}$$

$$
\begin{aligned}
g(k+x^*,l+y^*) = \ & g(x^*,y^*)+g_x(x^*,y^*)k(\tau)+g_y(x^*,y^*)l(\tau)+\tfrac{1}{2}g_{xx}(x^*,y^*)k^2(\tau) \\
& +g_{xy}(x^*,y^*)k(\tau)l(\tau)+\tfrac{1}{2}g_{yy}(x^*,y^*)l^2(\tau)+\dots
\end{aligned}
$$

If the perturbations are very small, i.e., $k \approx 0$ and $l \approx 0$, then k^2, kl, l^2 are also very small. So, we can ignore at least second-order terms. Since the point (x^*, y^*) is an equilibrium $f(x^*, y^*) = 0$ and $g(x^*, y^*) = 0$. Then the linearized system (4.10) leads to obtaining

$$
\begin{pmatrix} k'(\tau) \\ l'(\tau) \end{pmatrix} = \begin{pmatrix} f_x(x^*,y^*) & f_y(x^*,y^*) \\ g_x(x^*,y^*) & g_y(x^*,y^*) \end{pmatrix} \begin{pmatrix} k(\tau) \\ l(\tau) \end{pmatrix} = J \begin{pmatrix} k(\tau) \\ l(\tau) \end{pmatrix}, \tag{4.11}
$$

where J is the Jacobian matrix.

Hartman-Grobman Theorem gives us important results about a nonlinear system. Before presenting the theorem, we give some of definitions.

Definition 4.2. Let $X : \mathcal{A} \to \mathcal{A}$ and $Y : \mathcal{M} \to \mathcal{M}$ be two functions. If there exists a homeomorphism $h : \mathcal{A} \to \mathcal{M}$ such that

$$
h \circ X = Y \circ h \quad \text{or} \quad h(X(a)) = Y(h(m)).
$$

Here, $a \in \mathcal{A}$ and $m \in \mathcal{M}$, then the functions X and Y are *topologically conjugate*.

Definition 4.3. Let $\phi : \mathcal{A} \times \mathbb{R} \to \mathcal{A}$ be a mapping. The map ϕ is a flow such that $\forall a \in \mathcal{A}$ and $y, z \in \mathbb{R}$

$$
\begin{aligned}
\phi(a,0) &= a, \\
\phi\left(\phi(a,z),y\right) &= \phi(a,y+z).
\end{aligned}
$$

Theorem 4.1 (Hartman-Grobman)**.** *(Chicone (2006)) Let $x(t)$ be in $\mathbb{R}^n$, and it satisfies the differential equation $\frac{dx}{dt} = g(x)$, for some smooth map $g : \mathbb{R}^n \to \mathbb{R}^n$. Suppose that $g(x^*) = 0$ and none of eigenvalues the Jacobian matrix $A = [\partial g_i/\partial x_j]$ of g at x^* have zero real part. Then, there exists an open set $\mathcal{M}$ containing x^* and a homeomorphism $h : \mathcal{M} \to \mathbb{R}^n$ such that the flow of $\frac{dx}{dt} = g(x)$ is topologically conjugate by h to the flow of its linearization $\frac{dx}{dt} = Ax$ in the set $\mathcal{M}$.*

The Theorem 4.1 can be interpreted as the solutions of an autonomous system in a domain near a hyperbolic equilibrium point behave qualitatively the same as the solutions of its linearized system close to the point $(0,0)$.

Since the Jacobian matrix J is evaluated at the equilibrium points, it is a constant matrix. Now for the equilibrium points, we discuss

$$\begin{pmatrix} k' \\ l' \end{pmatrix} = J \begin{pmatrix} k \\ l \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \begin{pmatrix} k \\ l \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}. \tag{4.12}$$

The homogenous system (4.12) has trivial solution if and only if $\det J = 0$. Let us set

$$k(\tau) = \bar{k}e^{\lambda\tau} \quad , \quad l(\tau) = \bar{l}e^{\lambda\tau},$$

where $\bar{k}$ and $\bar{l}$ are nonzero constants. Then

$$\begin{pmatrix} a-\lambda & b \\ c & d-\lambda \end{pmatrix} \begin{pmatrix} k \\ l \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} = A\vec{u},$$

whose characteristic polynomial is obtained by

$$p(\lambda) = \lambda^2 - (a+d)\lambda + (ad-bc) = 0,$$

which has 2-eigenvalues, say λ_1 and λ_2. Here, $\operatorname{tr} J = a + d = \lambda_1 + \lambda_2$, $\det J = ad - bc = \lambda_1\lambda_2$.

Theorem 4.2. *An equilibrium is locally asymptotically stable iff all eigenvalues of the Jacobian matrix have negative real part.*

Proof. For the proof, we investigate the seperate cases for the eigenvalues.

i. If λ_1 and λ_2 are distinct and real then the solution of the system becomes

$$\begin{aligned} k(\tau) &= \bar{c_1}e^{\lambda_1\tau} + \bar{c_2}e^{\lambda_2\tau}, \\ l(\tau) &= \bar{c_3}e^{\lambda_1\tau} + \bar{c_4}e^{\lambda_2\tau}, \end{aligned}$$

where $\bar{c_1}, \ldots, \bar{c_4}$ are arbitrary constants. Clearly, k, $l \to 0$ as $\tau \to \infty$ iff $\lambda_1 < 0$ and $\lambda_2 < 0$.

ii. If $\lambda_1 = \lambda_2 = \lambda$ are real numbers,

$$\begin{aligned} k(\tau) =& d_1 e^{\lambda\tau} + d_2 \tau e^{\lambda\tau}, \\ l(\tau) =& d_3 e^{\lambda\tau} + d_4 \tau e^{\lambda\tau}, \end{aligned}$$

where $d_1, \ldots, d_4$ are arbitrary constants. Also here, k, $l \to 0$ as $\tau \to \infty$ iff $\lambda < 0$.

iii. If the eigenvalues are complex, then $\lambda_1 = \xi + \theta i$ and $\lambda_2 = \xi - \theta i$, for $\xi, \theta \in \mathbb{R}$. Thus, the solution of the system is found as

$$\begin{aligned} k(\tau) =& m_1 e^{\xi\tau} \sin\theta\tau + m_2 e^{\xi\tau} \cos\theta\tau, \\ l(\tau) =& m_3 e^{\xi\tau} \sin\theta\tau + m_4 e^{\xi\tau} \cos\theta\tau, \end{aligned}$$

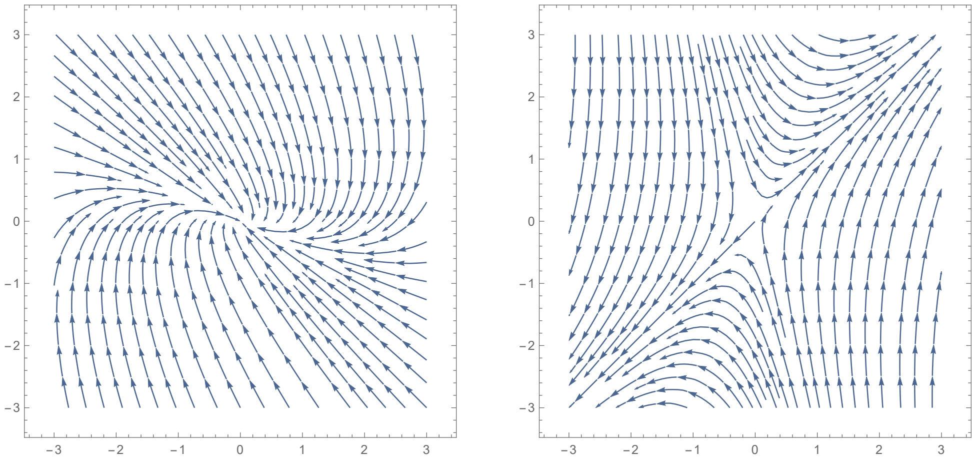
where $m_1, \ldots, m_4$ are arbitrary constants. Similarly, k, $l \to 0$ as $\tau \to \infty$ iff $\xi < 0$.

Thus, all cases show that the eigenvalues must have negative real part in order to have a locally asymptotically stable equilibrium. □

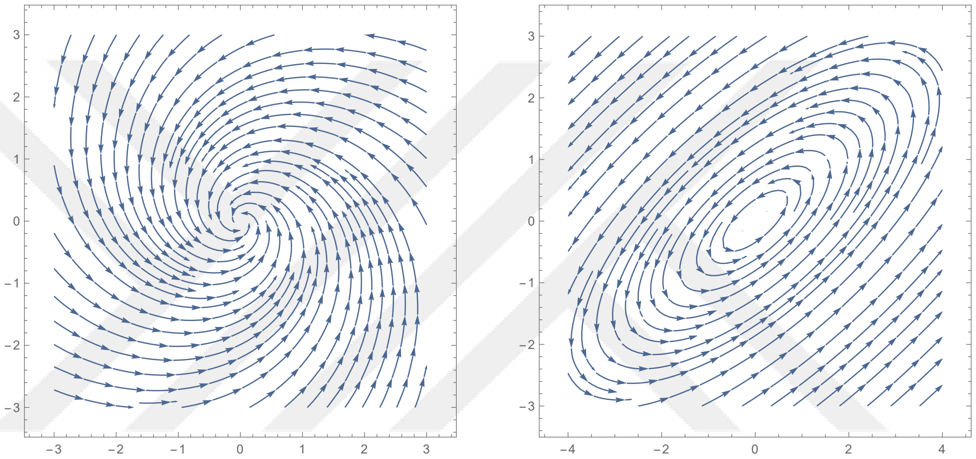
Corollary 4.1. Assume that J is a constant 2×2 matrix with nonzero determinant. Then the equilibrium (x^*, y^*) is locally asymtotically stable iff tr $J < 0$ and det $J > 0$ and unstable iff tr $J > 0$ or det $J < 0$.

Remark 6. In general, the asymptotic stability of the equilibrium (x^*, y^*) of the nonlinear system is equivalent to the asymptomtic stability of the equilibrium (x^*, y^*) of the linearized system. However, there is an exceptional case whenever det $J > 0$ and tr $J = 0$. In such case, the eigenvalues have zero real part, which does not imply stability precisely.

Remark 7. $(0, 0)$ - equilibrium of the linearized system can be classified based on the eigenvalues λ_1 and λ_2 as follows.



(a) Stable node (b) Saddle



(c) Stable spiral (d) Center

Figure 4.1 Classification of origin

i. If $\lambda_1, \lambda_2 \in \mathbb{R}$ and $\lambda_1 \lambda_2 > 0$, then the origin is said to be a *node*. The node is unstable when both eigenvalues are positive and it is stable when eigenvalues are negative. If additionally $\lambda_1 = \lambda_2$, then the node is called as *degenerate*.

ii. If $\lambda_1, \lambda_2 \in \mathbb{R}$ and $\lambda_1 \lambda_2 < 0$, then the origin is called as a *saddle*, which is always unstable.

iii. If $\lambda_1, \lambda_2 \in \mathbb{C}$ and $\mathrm{Re}(\lambda_1) \neq 0$, $\mathrm{Re}(\lambda_2) \neq 0$, then the origin said to be *spiral*. The spiral is stable if $\mathrm{Re}(\lambda_1) < 0$ and $\mathrm{Re}(\lambda_2) < 0$. Otherwise, it is unstable.

iv. A *center* occurs when $\lambda_1, \lambda_2 \in \mathbb{C}$ and $\mathrm{Re}(\lambda_1) = \mathrm{Re}(\lambda_2) = 0$. This case provides that every orbit is periodic and the center is stable.

Table 4.1 Types of the equilibrium based on the tr J, det J and Δ

Type	tr J	det J	Δ
Center	0	positive	
Stable node	negative	positive	nonnegative
Unstable node	positive	positive	nonnegative
Stable spiral	negative	positive	negative
Unstable spiral	positive	positive	negative
Saddle		negative	

We sum up equilibrium types related to Jacobian of a system in Table 4.1 and present illustrations for types of origin in Figure 4.1.

Example 4.3. Let us investigate local stability of the equilibria of the dimensionless SIR model.

Theorem 4.3. *We summarize the stability of equilibrium points as follows.*

i. If $\mathcal{R}_0 < 1$, then the disease-free equilibrium $(1,0)$ is locally stable.

ii. If $\mathcal{R}_0 < 1$, then the endemic equilibrium is asymptotically stable and $(1,0)$ is unstable.

Proof. For the disease-free equilibrium, the Jacobian of dimensionless SIR model at the point $(1,0)$ is obtained as

$$J = \begin{pmatrix} -\zeta & -\mathcal{R}_0 \\ 0 & \mathcal{R}_0 - 1 \end{pmatrix}.$$

Since J is an upper triangular, $\lambda_1 = -\zeta$ and $\lambda_2 = \mathcal{R}_0 - 1$. Therefore, the disease-free equilibrium is a stable node if $\mathcal{R}_0 < 1$ and it is a saddle if $\mathcal{R}_0 > 1$.
For endemic equilibrium , the Jocabian at $\left(\frac{1}{\mathcal{R}_0}, \zeta(1 - \frac{1}{\mathcal{R}_0})\right)$ becomes

$$J = \begin{pmatrix} -\zeta - \mathcal{R}_0\zeta\left(1 - \frac{1}{\mathcal{R}_0}\right) & -1 \\ \mathcal{R}_0\zeta\left(1 - \frac{1}{\mathcal{R}_0}\right) & 0 \end{pmatrix}.$$

In this case, $\operatorname{tr} J < 0$ and $\det J > 0$, so the endemic equilibrium is locally asymtotically stable by the corollary 4.1.

In order to investigate the type of the endemic equilibrium, we compute the characteristic equation of the endemic equilibrium

$$\lambda^2 + \mathcal{R}_0\zeta\lambda + \zeta(\mathcal{R}_0 - 1) = 0,$$

which provides the eigenvalues as $\lambda_{1,2} = \frac{(-\zeta\mathcal{R}_0 \pm \sqrt{\Delta})}{2}$, where $\Delta = (\zeta\mathcal{R}_0)^2 - 4\zeta(\mathcal{R}_0 - 1)$. We have two cases

a. When $\Delta > 0$, then λ_1, $\lambda_2 < 0$ since $-\zeta\mathcal{R}_0 + \sqrt{\Delta} < 0$. So, the endemic equilibrium is a stable node.

b. When $\Delta < 0$, then λ_1, $\lambda_2 \in \mathbb{C}$ and $\mathrm{Re}(\lambda_1) < 0$, $\mathrm{Re}(\lambda_2) < 0$. In this case, the endemic equilibrium is a stable spiral. Moreover, $x(\tau)$ and $y(\tau)$ tend to oscillate, which means that the model may have periodic solution.

$\square$

Remark 8. The reproduction number $\mathcal{R}_0$ refers to the number that an infected person will generate secondary cases if the population is full of susceptibles. Therefore $\mathcal{R}_0$ can be represented as

$$\mathcal{R}_0 = \frac{\delta\Theta}{\kappa(\gamma + \kappa)}, \tag{4.13}$$

because when the population is mode of susceptibles, the number of transmissions is generated by an infected person.

4.3 Global Stability of SIR Model

In this section, we analyze the global stability of the disease-free equilibrium of SIR model with demography. Note that an equilibrium can be globally stable if it is stable for almost initial condition, which cannot be proven in general. However, the global stability of a disease-free equilibrium of the SIR model can be proved if $\mathcal{R}_0 < 1$ and the only equilibrium point is disease-free equilibrium.

Theorem 4.4. *Let* $\mathcal{R}_0 < 1$. *Then the equilibrium point* $(1,0)$ *of SIR model* (4.6) *is globally stable.*

Proof. **Claim 1**: $\lim_{t\to\infty} y(t) = 0$.
Proof of claim 1: Note that $x'(t) < 0$ if $x(0) > 1$ and $x(t) > 1$ for all t. Therefore, $x(t)$ is decreasing if $x > 1$. Let us assume $t_0 > 0$ such that $x(t_0) = 1$ and $x(t) \leq 1$ for all $t > t_0$. We can take the initial condition $t_0 = 0$ when $x(0) \leq 1$.
Let us consider $y' = (\mathcal{R}_0 x - 1)y$. For $t > t_0$ and $x(t) \leq 1$, we have a linear inequality

$$y'(t) \leq (\mathcal{R}_0 - 1)y(t). \tag{4.14}$$

If we multiply (4.14) by $e^{-(\mathcal{R}_0-1)(t-t_0)}$, we obtain

$$e^{-(\mathcal{R}_0-1)(t-t_0)}y'(t) - (\mathcal{R}_0 - 1)e^{-(\mathcal{R}_0-1)(t-t_0)}y(t) \leq 0, \tag{4.15}$$

which can be written

$$\frac{d}{dt}\left[e^{-(\mathcal{R}_0-1)(t-t_0)}y(t)\right] \leq 0.$$

Integrating on (t_0, t) interval and using Fundamental Theorem of Calculus, we obtain

$$e^{-(\mathcal{R}_0-1)(t-t_0)}y(t) - e^{-(\mathcal{R}_0-1)(t-t_0)}y(t_0) \leq 0, \tag{4.16}$$

which implies

$$y(t) \leq y(t_0)e^{(\mathcal{R}_0-1)(t-t_0)} \tag{4.17}$$

by multiplying (4.16) by $e^{(\mathcal{R}_0-1)(t-t_0)}$. Now if $\mathcal{R}_0 < 1$, $y(t) \to 0$ as $t \to \infty$.
Claim 2: $\lim_{t\to\infty} x(t) \to 1$.
Proof of claim 2: By system (4.6), we obtain a similar inequality for x

$$x' = \zeta(1-x) - \mathcal{R}_0 xy \leq \zeta(1-x), \qquad \text{for} \quad t \geq 0.$$

whose solution can be found similar to previous procedure

$$x(t) \leq e^{-\zeta t}x(0) + \zeta e^{-\zeta t}\int_0^t e^{\zeta s}ds,$$

which implies

$$\limsup_{t\to\infty} x(t) \leq 1. \tag{4.18}$$

On the other hand, since $\lim_{t\to\infty} y(t) = 0$, $\forall\epsilon > 0\ \exists t_0 > 0$, $t > t_0$ such that $y(t) < \epsilon$. So,

$$x' \geq \zeta(1-x) - \epsilon\mathcal{R}_0 x,$$

whose solution gives rise to

$$x(t) \geq e^{-(\zeta+\epsilon\mathcal{R}_0)t}x(0) + \zeta\int_0^t e^{-(\zeta+\epsilon\mathcal{R}_0)(t-s)}ds,$$

which implies

$$\liminf_{t\to\infty} x(t) \geq \frac{\zeta}{\zeta+\epsilon\mathcal{R}_0}.$$

For every value ϵ, the inequality holds. So

$$\liminf_{t\to\infty} x \geq 1 \geq \limsup_{t\to\infty} x \tag{4.19}$$

Therefore, $\lim_{t\to\infty} x = 1$. To be more precise, $\lim_{t\to\infty}(x(t), y(t)) = (1, 0)$. □

The global stability of the endemic equilibrium of the SIR model with demography is given by the following Theorem. We do not present its highly abstract proof given in Martcheva (2015).

Theorem 4.5. *Assume that* $\mathcal{R}_0 > 1$ *and* $I(0) > 0$. *Then the endemic equilibrium of the system* (4.6) *is globally stable.*

CHAPTER FIVE
MATHEMATICAL MODELS OF VECTOR-BORNE DISEASES

A vector-borne disease is a disease that the pathogenic microorganism is transmitted from an infected individual to another individual by an arthropod or other agent. In vector-borne diseases, the transmission depends on the following three factors: Pathogenic agent or arthropod agent or human host.

Definition 5.1. A *vector* is an organism that transfers an infectious agent from one individual to another.

Vectors are generally considered to be invertebrate animal. For instance arthropods are the most common vectors. Neverthless, some vertebrates such as foxes, raccouns are also vectors. Vectors do not suffer from the diseases even if they are permanently infected. Vector-borne diseases are generally transferred by pathogens such as protozoa, bacteria, virus, helminth. For some vector-borne diseases, data is given in Table 5.1

Table 5.1 Some data for vector-borne diseases

Disease	Agent	Vector type	Population at risk (millions)	Prevelance of the disease (millions)
Malaria	Plasmodium spp.	Anopheles mosquito	2100	270
Schistosomiasis	Schistosome flatworms	Water snails	600	260
Dengue	Dengue virus	Aedes mosquitoes	2000	50–100
Leishmaniasis	Leishmania spp.	Sand flies	12	350
Lymphatic filariasis	Nematode worms	Mosquito	900	65.5

The first mathematical model for a vector-borne disease was introduced by Ross (1911) in order to analyze the dynamics of malaria.

5.1 SI Model for Malaria

Malaria is one of the most contagious diseases from which approximately 241 million people suffered and 627 000 people died in 2020. Malaria is transmitted by the vector mosquito to a human host. Once a mosquito is infected it can not recover. For that reason, there are only a susceptible class denoted by S_m and an infected class I_m. Let b be the biting rate at which a susceptible mosquito becomes infected by biting an infected human denoted by I_h. The probability of transmission of the disease is given by p. Then the system of the mosquito is described by

$$\begin{aligned} S_m' &= \Theta_m - pbS_mI_h - \kappa S_m, \\ I_m' &= pbS_mI_h - \kappa I_m, \end{aligned} \tag{5.1}$$

where Θ_m is the birth rate of the mosquitos and κ is the death rate. Since mosquitos live in a short period, the system should include demography. The size of the total mosquito population is given by $M_m = S_m + I_m$. Then we have a simplified logistic initial value problem

$$M_m' = \Theta_m - \kappa M_m, \qquad M_m(0) = M_0,$$

which admits the solution

$$M_m(t) = \frac{\Theta_m}{\kappa} + e^{-\kappa t}\left(M_m(0) - \frac{\Theta_m}{\kappa}\right).$$

We can reduce the system (5.1) by expressing the number of susceptible mosquitos in terms of infected mosquitos $S_m = M_m - I_m$:

$$I_m'(t) = pb(M_m(t) - I_m(t))I_h(t) - \kappa I_m(t). \tag{5.2}$$

When it comes to the system of the human hosts, we should note that even if humans get recovered they can be infected again. The simplest human model is an SIS model without demography. Let us denote the susceptible humans S_h and infected humans

I_h. Susceptible humans get infected when they are bitten by a mosquito at the same rate b as susceptible mosquitos and the probability of transmission is called $\tilde{p}$. Then the model of humans is represented by

$$\begin{aligned} S_h' &= -\tilde{p}bS_hI_m + \gamma I_h, \\ I_h' &= \tilde{p}bS_hI_m - \gamma I_h, \end{aligned} \tag{5.3}$$

where γ is the recovery rate. Since the size of the total human population M_h is constant, the system (5.3) can be reduced to one equation

$$I_h' = \tilde{p}b(M_h - I_h)I_m - \gamma I_h. \tag{5.4}$$

Hence combining (5.2) and (5.4), we derive the system

$$\begin{aligned} I_m'(t) &= pb(M_m(t) - I_m(t))I_h(t) - \kappa I_m(t), \\ I_h'(t) &= \tilde{p}b(M_h - I_h(t))I_m(t) - \gamma I_h(t). \end{aligned} \tag{5.5}$$

The model (5.5) is nonautonomous because $M_m(t)$, $I_m(t)$, $I_h(t)$ all depend on time t. Nonautomous models are not easy to analyze as autonomous models. However $\lim\limits_{t\to\infty} M_m(t) = \frac{\Theta_m}{\kappa} = M_m$. Hence the system (5.5) becomes asymptotically autonomous, which is easier to analyze. Here, the main question is whether the global dynamics of the asymptotically autonomous system show similarity with the dynamics of the original nonautonomous system. In order to answer this question, we take advantage of the following theorem.

Definition 5.2. Let the omega limit set of point v^0 be denoted by $\omega(v^0)$. There exists a sequence $(t_i)_{i\in\mathbb{N}}$ in $\mathbb{R}^2$ and $a \in \mathbb{R}^2$ such that $v(t_i) \to a$ as $t_i \to \infty$. Then $\omega(v^0)$ consists of all points a.

Theorem 5.1 (Thieme (1994)). *Let $u' = h(t,u)$ be a nonautonomous system such that $u \in \mathbb{R}^2$ and its limiting autonomous system be $v' = f(v)$. Let ω be omega limit set of a forward bounded solution u of the nonautonomous system. Assume there are finitely many equilibria of the autonomous system in a neighborhood of ω. Then the followings similtaneously hold:*

i. *ω consists of an equilibrium of the autonomous system.*

ii. *ω is a union of periodic orbits of the autonomous system and possible centers surrounded by periodic orbits lying in ω.*

iii. *ω contains equilibria of the autonomous system that are cyclically chained to each other in ω by orbits.*

It is clear that $I_m(t)$ and $I_h(t)$ are bounded. By Theorem 5.1, the ω-limit set of the nonautonomous system can be obtained from investigation of the ω-limit set of autonomous system.

We discuss equilibria of limiting autonomous sytem of the system (5.5) and reproduction numbers. Clearly, the disease-free equilibrium of the system is the point $(0,0)$. In order to analyze the stability of the disease-free equilibrium, the Jacobian of the system can be computed

$$J = \begin{pmatrix} -\kappa & pbM_m \\ \tilde{p}bM_h & -\gamma \end{pmatrix}.$$

The disease-free equilibrium is stable if det $J > 0$ and tr $J < 0$. Here, tr $J = -(\kappa + \gamma) < 0$ and det $J = \kappa\gamma - p\tilde{p}b^2 M_m M_h > 0$ if we introduce the reproduction number

$$\mathcal{R}_0 := \frac{p\tilde{p}b^2 M_m M_h}{\kappa\gamma} < 1.$$

Hence, the disease-free equilibrium is locally stable if $\mathcal{R}_0 < 1$ and unstable otherwise.

The reproduction number $\mathcal{R}_0$ provides the number secondary infections of humans that may be generated in an entirely susceptible human population. Transmission of vector-borne disease includes two transmission cycles which are vector to human and human to vector. For that reason each transmission process should be characterized by seperate the reproduction numbers, $\mathcal{R}_m$ and $\mathcal{R}_h$, where $\mathcal{R}_m$ stands for the reproduction number of secondary infected vectors and $\mathcal{R}_h$ refers to the one for infected vector in a susceptible human population:

$$\mathcal{R}_h = \frac{\tilde{p}bM_h}{\kappa}, \qquad \mathcal{R}_m = \frac{pbM_m}{\gamma}.$$

In order to compute the secondary human infections, note that one infected human will generate $\mathcal{R}_m$ infected vectors and each of these will generate $\mathcal{R}_h$ infected humans. Thus, the reproduction number $\mathcal{R}_0$ of secondary human infections is given by

$$\mathcal{R}_0 = \mathcal{R}_h\mathcal{R}_m = \frac{p\tilde{p}b^2M_mM_h}{\gamma\kappa}.$$

Proposition 5.1. *The endemic equilibrium of the system* (5.5) *exists iff* $\mathcal{R}_0 > 1$ *and it is a stable node.*

Proof. For the endemic equilibrium of (5.5), let us simplify the system the use of change of variable $y = \frac{1}{I_h}$, $u = \frac{1}{I_m}$, which leads to

$$\begin{aligned} u' =& [pb(M_mu - 1) - \kappa y]\frac{-u}{y}, \\ y' =& [\tilde{p}b(M_hy - 1) - \gamma u]\frac{-y}{u}, \end{aligned}$$

whose equilibrium are as follows

$$I_h = M_h\frac{\mathcal{R}_0 - 1}{\frac{pbM_h}{\kappa} + \mathcal{R}_0}, \qquad I_m = M_m\frac{\mathcal{R}_0 - 1}{\frac{\tilde{p}bM_m}{\gamma} + \mathcal{R}_0}.$$

Clearly, the endemic equilibrium exists iff $\mathcal{R}_0 > 1$.

In order to analyze local stability of endemic equilibrium, we compute the Jacobian of the system (5.5)

$$J = \begin{pmatrix} -pbI_h - \kappa & pb(M_m - I_m) \\ \tilde{p}b(M_h - I_h) & -\tilde{p}bI_m - \gamma \end{pmatrix}.$$

Here, $\operatorname{tr} J < 0$. Notice that

$$pb(M_m - I_m) = \kappa I_m/I_h, \tag{5.6}$$

$$\tilde{p}b(M_h - I_h) = \gamma I_h/I_m. \tag{5.7}$$

The product of the equations (5.6) and (5.7) is equal to $\gamma\kappa$. Thus

$$\det J = (pbI_h + \kappa)(\tilde{p}bI_m + \gamma) - pb\tilde{p}b(M_m - I_m)(M_h - I_h) = (pbI_h + \kappa)(\tilde{p}bI_m + \gamma) - \gamma\kappa > 0,$$

which implies that the endemic equilibrium is locally stable. To examine the endemic equilibrium point, we compute

$$\det(J - \lambda I) = \lambda^2 + (pbI_h + \kappa + \tilde{p}bI_m + \gamma)\lambda + (pbI_h + \kappa)(\tilde{p}bI_m + \gamma) - \kappa\gamma = 0,$$

whose discriminant can be obtained as

$$\begin{aligned} \Delta = \; & (pbI_h + \kappa + \tilde{p}bI_m + \gamma)^2 - 4(pbI_h + \kappa)(\tilde{p}bI_m + \gamma) + 4\kappa\gamma \\ & = (pbI_h + \kappa - \tilde{p}bI_m - \gamma)^2 + 4\kappa\gamma > 0, \end{aligned}$$

which implies that there are two negative real roots. Hence, the endemic equilibrium is a stable node. □

5.2 Delay-Differential Models

The incubation period of the pathogen in the vectors and also humans affects significantly the dynamics of the infectious disease. For that reason delays naturally occur in vector-borne diseases. Inclusion of the incubation period in the vector is called *extrinsic incubation period*, which is particularly important since the vector may or not live longer during the incubation period.

5.2.1 Delay Differential Model with Unique Delay

Let t_1 be the duration of the incubation period of the pathogen in a vector. The vectors have been infected t_1 units of time ago. Only a proportion of those vectors infected t_1 units of time ago are infectious at the present time t and this proportion is

$$pb[M_m - I_m(t-t_1)]I_h(t-t_1)e^{-\kappa t_1},$$

where $e^{-\kappa t_1}$ is the probability that the vector survives the extrinsic incubation period. In a similar way, let t_2 be the duration of the incubation period of the pathogen in the human. The proportion of humans infected t_2 units of time ago can be calculated as

$$\tilde{p}b[M_h - I_h(t-t_2)]I_m(t-t_2)e^{-\gamma t_2},$$

where $e^{-\gamma t_2}$ is the probability that a human remains infected during the whole incubation period. Under such circumstances the delay vector-borne model can be presented as (Ruan et al. (2008)).

$$\begin{aligned} I_m' &= pbe^{-\kappa t_1}\left(-I_m(t-t_1) + M_m\right) I_h(t-t_1) - \kappa I_m, \\ I_h' &= \tilde{p}be^{-\gamma t_2}\left(-I_h(t-t_2) + M_h\right) I_m(t-t_2) - \gamma I_h. \end{aligned} \tag{5.8}$$

Since we specifically focus on the case of malaria, let us assume $t_1 = t_2 = \tau$, namely the extrinsic incubation period is equivalent to the incubation periof of humans. Additionally, we assume that the average lifespan of mosqitos is shorter than the infection period of humans i.e., $\kappa > \gamma$. The related model was given by Martcheva & Prosper (2013). When the vector dynamics reach equilibrium, we have $I_m' = 0$. The number of population at time t and $t-\tau$ are equal at equilibrium, approximately. We obtain

$$I_m = \frac{pbe^{-\kappa\tau} M_m I_h(t-\tau)}{pbe^{-\kappa\tau} I_h(t-\tau) + \kappa}.$$

Substituting I_m in I_h', the following single delay equation is obtained

$$I_h' = \frac{pb^2\tilde{p}e^{-\gamma\tau}e^{-\kappa\tau} M_m I_h(t-\tau)}{pbe^{-\kappa\tau} I_h(t-\tau) + \kappa}\left(M_h - I_h(t-\tau)\right) - I_h,$$

which can be simplified as

$$z' = \frac{pb^2\tilde{p}ne^{-\gamma\tau}e^{-\kappa\tau} z(t-\tau)}{pbe^{-\kappa\tau} z(t-\tau) + \kappa}\left(1 - z(t-\tau)\right) - \gamma z(t), \tag{5.9}$$

where we set $z = I_h/M_h$, $n = \frac{M_m}{M_h}$ and replace b by bM_h. In order to compute equilibrium points of the delay equation (5.9), we assume that z^* is an equilibrium of (5.9). Then we obtain

$$z^* \left(\frac{pb^2 \tilde{p} n e^{-\gamma\tau} e^{-\kappa\tau}}{pbe^{-\kappa\tau} z^* + \kappa} (1 - z^*) - \gamma \right) = 0, \tag{5.10}$$

which provides that $z^* = 0$ is the disease-free equilibrium. We linearize the equation to analyze the stability of the disease-free equilibrium. Let us call $z' = f(z(t), z(t-\tau))$, and let $x(t) = z(t) - z^*$ be perturbation solution, where $z^* = 0$. The linearization of the delay equation around z^* is given by

$$x' = \left.\frac{\partial f}{\partial z(t-\tau)}\right|_{z(t-\tau)=z^*} x(t-\tau) + \left.\frac{\partial f}{\partial z(t)}\right|_{z(t)=z^*} x(t),$$

which implies

$$x' = \frac{pb^2 \tilde{p} n e^{-\gamma\tau} e^{-\kappa\tau} x(t-\tau)}{\kappa} - \gamma x(t).$$

We look for an exponential solution $x(t) = \bar{x} e^{\lambda t}$. Then,

$$\lambda + \gamma = \frac{pb^2 \tilde{p} n e^{-\gamma\tau} e^{-\kappa\tau} e^{-\lambda\tau}}{\kappa}, \tag{5.11}$$

which is a *transcendental equation*. Let us define the reproduction number $\mathcal{R}_0$ as

$$\mathcal{R}_0 := \frac{pb^2 \tilde{p} n e^{-\gamma\tau} e^{-\kappa\tau}}{\kappa\gamma}.$$

Theorem 5.2. *For delay differential equation* (5.9)*, if* $\mathcal{R}_0 < 1$ *then there exists locally asymptotically stable disease-free equilibrium. If* $\mathcal{R}_0 > 1$*, the equation* (5.9) *has unstable disease-free equilibrium. In addition* (5.9) *has locally asymptotically stable endemic equilibrium* z^* *if* $\mathcal{R}_0 z^* < 1$.

For the proof of theorem, we need the following auxiliary lemmas.

Lemma 5.1. The equation (5.11) has a unique positive real solution iff $\mathcal{R}_0 > 1$.

Proof. First, we assume that $\mathcal{R}_0 < 1$ and the unique eigenvalue $\lambda \in \mathbb{R}^+$. Then,

$$\lambda + \gamma = \gamma \mathcal{R}_0 e^{-\lambda\tau} \leq \gamma \mathcal{R}_0.$$

Then $\lambda \leq \gamma(\mathcal{R}_0 - 1)$. Since $\mathcal{R}_0 - 1 < 0$, $\lambda < 0$, which contradicts with our assumption. Secondly, suppose that $\mathcal{R}_0 > 1$ and $\lambda \in \mathbb{R}^-$. Then,

$$\lambda + \gamma = \gamma \mathcal{R}_0 e^{-\lambda\tau}.$$

By our assumption $\lambda < 0$, therefore

$$\lambda \geq \gamma(\mathcal{R}_0 - 1) > 0,$$

which is a contradiction with our assumption. □

Lemma 5.2. If $\mathcal{R}_0 < 1$ and for (5.11) all other eigenvalues $\lambda \in \mathbb{C}$ then $\mathrm{Re}(\lambda) < 0$.

Proof. Let λ be a root such that $\lambda = u + vi$, $u, v \in \mathbb{R}$. Assume that $u \geq 0$. Then,

$$|\lambda + \gamma| = \sqrt{(u+\gamma)^2 + v^2} \geq u + \gamma \geq \gamma. \tag{5.12}$$

On the other hand,

$$\begin{aligned} \left| \frac{pb^2 \tilde{p} n e^{-\gamma\tau} e^{-\kappa\tau} e^{-\lambda\tau}}{\kappa} \right| &= \frac{pb^2 \tilde{p} n e^{-\gamma\tau} e^{-\kappa\tau} \left| e^{-\lambda\tau} \right|}{\kappa} \\ &= \frac{pb^2 \tilde{p} n e^{-\gamma\tau} e^{-\kappa\tau} e^{-u\tau}}{\kappa} \leq \frac{pb^2 \tilde{p} n e^{-\gamma\tau} e^{-\kappa\tau}}{\kappa} \end{aligned} \tag{5.13}$$

Combining (5.12) and (5.13), we obtain

$$\frac{pb^2 \tilde{p} n e^{-\gamma\tau} e^{-\kappa\tau}}{\kappa} \geq \gamma,$$

which means $\mathcal{R}_0 > 1$ contradicting with our assumption. □

Reconsidering the equation (5.10), one can find the endemic equilibrium

$$z^* = \frac{\mathcal{R}_0 - 1}{\frac{pb}{\kappa}e^{-\kappa\tau} + \mathcal{R}_0}$$

iff $\mathcal{R}_0 > 1$. For the stability of the endemic equilibrium, let $y(t)$ be perturbation solution, that is, $y(t) = z(t) - z^*$. To simplify the notation, let us call

$$pb^2\tilde{p}ne^{-\gamma\tau}e^{-\kappa\tau} = H \qquad \text{and} \qquad pbe^{-\kappa\tau} = F.$$

Therefore, the linearization of the endemic equilibrium is computed via

$$y' = \left(\frac{\kappa H(1 - z^*)}{(Fz^* + \kappa)(Fz^* + \kappa)} - \frac{Hz^*}{Fz^* + \kappa}\right) y(t - \tau) - \gamma y(t).$$

We notice that $\frac{H(1-z^*)}{Fz^*+\kappa} = \gamma$ and $\mathcal{R}_0 = \frac{H}{\gamma\kappa}$, which implies the equation

$$y'(t) = \frac{\kappa\gamma}{Fz^* + \kappa}(1 - \mathcal{R}_0 z^*)y(t - \tau) - \gamma y(t). \tag{5.14}$$

Seeking for an exponential type solution $y(t) = \bar{y}e^{\lambda t}$, the form of the characteristic equation is obtained by

$$\lambda + \gamma = \frac{\gamma\kappa}{Fz^* + \kappa}(1 - \mathcal{R}_0 z^*)e^{-\lambda\tau}. \tag{5.15}$$

Lemma 5.3. Assume $\mathcal{R}_0 > 1$. All roots of the equation (5.15) have negative real parts if $\mathcal{R}_0 < \frac{1}{z^*}$.

Similar discussion can provide the proof of Lemma 5.3. Consequently proof of Theorem 5.2 follows.

5.2.2 Delay Differential Model with Two Different Delays

Let us consider the time delays $t_1 \neq t_2$. Then, the system (5.8) has the disease-free equilibrium $(0, 0)$. We linearize the disease-free equilibrium by perturbations $I_m :=$

$y+0$ and $I_h := z+0$, and let us call $I_m' = F(I_m(t), I_m(t-t_1), I_h(t), I_h(t-t_1))$ and $I_h' = G\left(I_m(t), I_m(t-t_2), I_h(t), I_h(t-t_2)\right)$. Then,

$$\begin{aligned}F =&F_{I_m(t)}(\varepsilon_0)y(t) + F_{I_m(t-t_1)}(\varepsilon_0)y(t-t_1) + F_{I_h(t)}(\varepsilon_0)z(t) + F_{I_h(t-t_1)}(\varepsilon_0)z(t-t_1),\\ G =&G_{I_m(t)}(\varepsilon_0)y(t) + G_{I_m(t-t_2)}(\varepsilon_0)y(t-t_2) + G_{I_h(t)}(\varepsilon_0)z(t) + G_{I_h(t-t_2)}(\varepsilon_0)z(t-t_2),\end{aligned}$$

where $\varepsilon_0 = (0,0,0,0)$. Therefore, the perturbations become

$$\begin{aligned}y' =&pbe^{-\kappa t_1}M_m z(t-t_1) - \kappa y(t),\\ z' =&\tilde{p}be^{-\gamma t_2}M_h y(t-t_2) - \gamma z(t).\end{aligned}$$

Setting exponential solutions $y = \bar{y}e^{\lambda t}$ and $z = \bar{z}e^{\lambda t}$, the following eigenvalue problem is obtained

$$\begin{pmatrix} -(\lambda+\kappa) & pbe^{-\kappa t_1}M_m e^{-\lambda t_1} \\ \tilde{p}be^{-\gamma t_2}M_h e^{-\lambda t_2} & -(\lambda+\gamma) \end{pmatrix} \begin{pmatrix} y \\ z \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \tag{5.16}$$

which can be written as $A\vec{u} = \vec{0}$. This linear system has nontrivial solution iff $\det A = 0$. In this case, the characteristic equation follows

$$(\lambda+\kappa)(\lambda+\gamma) = pbe^{-\kappa t_1}M_m e^{-\lambda t_1}\tilde{p}be^{-\gamma t_2}M_h e^{-\lambda t_2}. \tag{5.17}$$

Let us define

$$\mathcal{R}_0 := \frac{pbe^{-\kappa t_1}M_m\tilde{p}be^{-\gamma t_2}M_h}{\gamma\kappa}.$$

Theorem 5.3. *If $\mathcal{R}_0 < 1$, the disease-free equilibrium of the system* (5.8) *is locally asymptotically stable and unstable otherwise.*

Proposition 5.2. *If $\mathcal{R}_0 < 1$ then all roots of the equation* (5.17) *have negative real parts.*

Proof. Let $\mathcal{R}_0 < 1$ and $\lambda \in \mathbb{R}^+$. Then

$$(\lambda+\kappa)(\lambda+\gamma) = \gamma\kappa\mathcal{R}_0 e^{-\lambda(t_1+t_2)} \leq \gamma\kappa\mathcal{R}_0,$$

which implies $\lambda(\lambda+\kappa+\gamma) \leq 0$. Then,

$$\lambda+\kappa+\gamma \leq 0.$$

Hence, λ must be negative, which gives a contradiction to our assumption.
Now, we assume that $\mathcal{R}_0 < 1$ and $\lambda \in \mathbb{C}$ and $\mathrm{Re}(\lambda) \geq 0$. Thus, $(\lambda+\kappa)(\lambda+\gamma) \geq \kappa\gamma$. At the same time,

$$|\mathcal{R}_0\gamma\kappa e^{-\lambda(t_1+t_2)}| \leq \gamma\kappa\mathcal{R}_0.$$

Therefore, we obtain $\gamma\kappa \leq \gamma\kappa\mathcal{R}_0$, which implies $1 \leq \mathcal{R}_0$. This gives a contradiction to $\mathcal{R}_0 < 1$. $\square$

Utilizing the previous proposition, the proof of Theorem 5.3 is clear.

CHAPTER SIX
COMPLEX EPIDEMIOLOGICAL MODELS

In order to present infectious diseases in a more realistic level, additional situations and corresponding conditions should be embedded to related models. For this purpose, we need to investigate a detailed classification of infectious diseases. Modeling of infectious diseases can be classified

1. according to stages of diseases
    i. latent stage,
    ii. passive immunity stage,
    iii. asymptomatic stage,
    iv. carrier stage
2. according to control strategies of diseases
    i. isolation or quarantina,
    ii. treatment,
    iii. vaccination
3. according to the heterogeneities of the host and the vector of the diseases
    i. host heterogeneities,
    ii. pathogen genetic heterogeneities,
    iii. age and space.

In this chapter, we present such realistic models with examples. However, the reader should note that as the model becomes more realistic, the system gets higher dimensional and techniques get more advanced.

6.1 Stages of Infectious Diseases

In the SI, SIS, SIR models, the transmission process is based on the presence of susceptible and infectious individuals. However, there are additional stages that affect the transmission of infectious diseases. The most essential stages of the disease are given by the following.

i. **Latent Stage:**

   When a pathogen enters a hosts body, it takes time to reproduce and establish itself inside the host cell. The time that passes between being infected and becoming infectious is called the *latent period*, which is denoted by $L(t)$. There is also another period, called as *incubation period*, which refers to the duration between being infectious and showing symptoms of the disease. The incubation and latent period need not to have the same duration. For instance, for influenza we show symptoms one day after getting infectious. If we add latent period of an SIR model, it becomes an SLIR model

$$\begin{aligned} S'(t) &= \Theta - \delta SI - \kappa S, \\ L'(t) &= \delta SI - (\beta + \kappa)L, \\ I'(t) &= \beta L - (\gamma + \kappa)I, \\ R'(t) &= \gamma I - \kappa R, \end{aligned} \tag{6.1}$$

   where Θ is the total birth rate, δ is the transmission rate, κ is the natural death rate, β is the per capita rate of becoming infectious and γ is the recovery rate. We notice that the lenght of the latent period is approximately $1/\beta$.

ii. **Passive Immunity Stage:**

   Passive immunity is the transfer of antibodies to a non-immune individual from another individual that has active immunity. It can be induced artificially or occur naturally, such as maternal antibodies transferred to the offspring by the placenta. Mathematical model with passive immunity stage is denoted by $M(t)$ and admit the form

$$\begin{aligned} M'(t) &= \Theta - \alpha M - \kappa M, \\ S'(t) &= \alpha M - \delta S I - \kappa S, \\ I'(t) &= \delta S I - (\gamma + \kappa) I, \\ R'(t) &= \gamma I - \kappa R, \end{aligned} \tag{6.2}$$

where α is the per unit of time rate of loss of maternal antibodies and the other parameters are the same as above. We assume that maternal antibodies completely protect the newborn babies.

iii. **Asymptomatic Stage:**

Asymptomatic infection is called as the infection without showing any symptoms of a disease. Individuals with asymptomatic infection affect the distribution of the disease since they are infectious. The diseases such as HIV, malaria, influenza are examples for asymptomatic infection. We refer $A(t)$ for asymptomatic class. After an infected individual leave the latent compartment, he/she passes to the symptomatic infectious or to the asymptomatic infectious compartment. We assume that p is the probability of passing to the symptomatic class and $1 - p$ is the probability of passing to asymptomatic class. Asymptomatic individuals are infectious with a reduced transmission rate $q\delta$, which produces the following model

$$\begin{aligned} S'(t) &= \Theta - \delta S(I + qA) - \kappa S, \\ L'(t) &= \delta S(I + qA) - (\beta + \kappa) L, \\ I'(t) &= p\beta L - (\gamma + \kappa) I, \\ A'(t) &= (1 - p)\beta L - (\xi + \kappa) A, \\ R'(t) &= \gamma I + \xi A - \kappa R, \end{aligned} \tag{6.3}$$

where ξ is the recovery rate of the asymptomatic individuals. The symptomatic infectious period is usually longer than asymptomatic period, that is, $1/\xi < 1/\gamma$.

iv. **Carrier Stage:**

Individuals who transmit the disease microorganisms without showing symptoms belong to carrier stage. Several viral diseases, (e.g., viral hepatitis) and bacterial diseases (e.g., diphtheria and meningococcal meningitis) exhibit a carrier stage. We denote carrier compartment by $C(t)$ and the model turns out to be

$$\begin{aligned} S'(t) &= \Theta - \delta S(I + qC) - \kappa S + \alpha R, \\ C'(t) &= \delta S(I + qC) - (\beta + \xi + \kappa)C, \\ I'(t) &= \beta C - (\gamma + \kappa)I, \\ R'(t) &= \gamma I + \xi C - (\alpha + \kappa)R, \end{aligned} \tag{6.4}$$

where α is the rate of loss of immunity, β is the rate at which carrier indivudals pass to infected class and ξ is the recovery rate of the carrier individuals without being infected.

6.2 Control Stragies of Infectious Diseases

In order to control the spread of diseases, there are disease control strategies that can be involved in models, which are discussed as follows.

i. **Isolation or Quarantina:**
   Quarantine is for individuals who may have been exposed to an infectious individual. Isolation is the restriction of the contact of an infectious individual with a healthy individual. Let us denote the class of isolated or quarantine by $Q(t)$. An SIQR model given below assumes standard incidence. (See Feng & Thieme (1995).)

$$\begin{aligned} S'(t) &= \Theta - \delta SI/A - \kappa S, \\ I'(t) &= \delta SI/A - (\gamma + \xi + \kappa)I, \\ Q'(t) &= \xi I - (\alpha + \kappa)Q, \\ R'(t) &= \gamma I + \alpha Q - \kappa R, \end{aligned} \tag{6.5}$$

where A is the size of the active class. The goal of quarantine and isolation is to prevent the spread of the disease. Quarantine is a complete isolation no matter individuals are infectious or not. The word quarantina dates back to 17th century when ships were made to wait 40 days before entering the harbours of Venice. Childhood diseases such as chickenpox, smallpox are the examples for the model (6.5).

ii. **Treatment:**

Treatment is the care provided to cure or mitigate symptoms that a disease cause. We assume that an individual is successfully treated with probability q and relapses to the latent class with probability p, where $p + q = 1$. The model with treatment SLIT, which captures the dynamics of a disease such as tuberculosis, is given below. (See Feng et al. (2000).)

$$\begin{aligned}
S'(t) &= \Theta - \delta_1 SI/M - \kappa S, \\
L'(t) &= \delta_1 SI/M + \delta_2 TI/M - (\kappa + \rho + n_1)L + pn_2 I, \\
I'(t) &= \rho L - (n_2 + \kappa)I, \\
T'(t) &= n_1 L + qn_2 I - \delta_2 TI/M - \kappa T,
\end{aligned} \tag{6.6}$$

where $T(t)$ stands for treatment class, n_1 is the treatment rate of latent individuals, n_2 is the treatment rate of infectious individuals and ρ is the rate of passing to infectious state.

iii. **Vaccination:**

Vaccination is the transfer of weakened/dead microorganisms into the body to provide immunity. Individuals may acquire partial/complete immunity due to vaccination. Vaccination can be incorporated in models by two ways: vaccination at recruitment and continuous vaccination. An SIS model with vaccination is given below

$$\begin{aligned}
S'(t) &= \Theta - \delta SI/M - (\kappa + \eta)S + \upsilon\gamma I, \\
I'(t) &= \delta SI/M + \delta qVI/M - (\kappa + \gamma)I, \\
V'(t) &= \eta S - \delta qVI/M + (1 - \upsilon)\gamma I - \kappa V,
\end{aligned} \tag{6.7}$$

where $V(t)$ refers to vaccination class, η is the per capita vaccination rate, υ is the proportion of individuals who recover to the vaccinated class, $1-\upsilon$ is the proportion of individuals who recover to the susceptible compartment and δq is the reduced transmission rate of vaccinated individuals. Note that vaccinated individuals can get infectious again but with a reduced transmission rate.

6.3 Heterogeneity of Infectious Disease

Host or pathogen heterogeneities can also affect the dynamics of the disease, which are classified as follows.

i. **Host Heterogeneities:**
A pathogen can infect multiple host species. For instance, the pathogen of avian infulenza can infect both wild birds and domestic birds which have different population characteristics. A simple SI model includes two susceptible populations S_w and S_d and two infected populations I_w and I_d. The form of the multihost model with single-pathogen becomes

$$\begin{aligned} S_w'(t) &= \Theta_w - \delta_{11} S_w I_w - \delta_{12} S_w I_d - \kappa_w S_w, \\ I_w'(t) &= \delta_{11} S_w I_w + \delta_{12} S_w I_d - (\kappa_w + \gamma_w) I_w, \\ S_d'(t) &= \Theta_d - \delta_{21} S_d I_w - \delta_{22} S_d I_d - \kappa_d S_d, \\ I_d'(t) &= \delta_{21} S_d I_w + \delta_{22} S_d I_d - (\kappa_d + \gamma_d) I_d. \end{aligned} \tag{6.8}$$

ii. **Pathogen Genetic Heterogeneities:**
Many pathogens have several genetically distinct variants. The existence of the variants can lead to different control measures. An SIS model with two strains is of the form

$$\begin{aligned} S'(t) &= \Theta - \delta_1 S I_1 - \delta_2 S I_2 - \kappa S + \gamma_1 I_1 + \gamma_2 I_2, \\ I_1'(t) &= \delta_1 I_1 - (\kappa + \gamma_1) I_1, \\ I_2'(t) &= \delta_2 I_2 - (\kappa + \gamma_2) I_2, \end{aligned} \tag{6.9}$$

where I_1 and I_2 refer to infectious classes with first and second strains repectively.

iii. **Space and Age:**

Different than other species insects and plants have discrete population dynamics which produces age heterogeneities. In this case, mathematical models turn out to be discrete models.

If the population lives on an isolated island or immigrate to different countries, the spatial heterogeneity occurs which affects the transmission of the disease. In this case, models are expressed in terms of systems of partial differential equations such as diffusion equation.

CHAPTER SEVEN

CONCLUSION

In this thesis, we presented simple mathematical epidemic models. Firstly to construct SIR and SIS model, we made some assumptions and analyzed their properties mathematically. Next we included births and deaths that occur in the population into SIR model. Moreover, we expressed modeling of vector-borne diseases with delay differential equations. We saw that the reproduction number of a disease was a critical value for the disease to die out from the population. Then we ended up with complex models which are more realistic but harder to analyze.

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