MODELING THE LATENT PERIOD IN COMPARTMENTAL EPIDEMIOLOGICAL MODELS

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By

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We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

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ABSTRACT

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Two epidemiological models for the latent period are studied: the SEIR model and the SIR model with delay. Stability analysis of the endemic and the disease-free equilibria is performed for both models, and the basic reproduction number is determined. Using the meningococcal disease datasets of four countries, the best-fitted disease transmission rate is estimated by the least squares method, and the corresponding basic reproduction numbers are calculated for each country.

Keywords: Epidemic models, SEIR model, latent period, SIR model with delay, stability, basic reproduction number, parameter estimation.

ÖZET

KOMPARTIMAN BAZLI EPİDEMİYOLOJİK MODELLERDE LATENT DÖNEMİ MODELLEME

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Matematik, Yüksek Lisans
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Ocak 2023

Latent dönemi içeren iki epidemiyolojik model karşılaştırılmıştır: SEIR model ve gecikmeli SIR model. Her iki model için de endemik ve hastalıksız denge noktalarının kararlılık analizi yapılmış ve hastalık üretme temel eşik değeri belirlenmiştir. Dört ülkenin bakteriyel menenjit veri setleri kullanılarak, modele en uyumlu hastalık bulaşma oranı en küçük kareler yöntemiyle tahmin edilmiş ve her ülke için karşılık gelen hastalık üretme temel eşik değerleri hesaplanmıştır.

Anahtar sözcükler: Epidemik modeller, SEIR model, latent dönem, gecikmeli SIR model, kararlılık, hastalık üretme temel eşik değeri, parametre tahmini.

Acknowledgement

I want to start this page with a quote from Lynne Twist's book "The Soul of Money," which prompted me to think deeply about it when I read it. "I asked for strength, and God gave me difficulties to make me strong. I asked for wisdom, and God gave me problems to solve. I asked for prosperity, and God gave brawn and brain to work. I asked for patience, and God placed me in a situation where I was forced to wait. I asked for favors, and God gave me opportunities. I received nothing I wanted; I received everything I needed." So, I am sincerely thankful. Along with that, I could not have finished this thesis without the help of the people listed below.

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My father, ***Abbas***, who is my rock and my anchor...
My mom, ***Leyla***, who makes the world a better place just by being in it...
My brother, ***Erfan***, who has a good heart and gifted me with sibling love...

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Chapter 1

Introduction

Transmissible diseases are an unavoidable aspect of life. These diseases continue to cause suffering and mortality worldwide, and their spread threatens public health and places a financial and social development cost on society. Infectious diseases spread via two routes: horizontal transmission (direct contact from person to person) and vertical transmission (transmission to a newborn from an infected mother) [1]. However, the transmission mechanism of an infectious disease in a population is complex, and a mathematical model makes it possible to study the disease transmission dynamics. Among mathematical models, compartmental models are the typical types of models that use the role of one infectious individual to predict the spread of disease through the population. These models focus on either epidemic, endemic, or pandemic models. Epidemic models describe the transmission of disease that shows an outbreak, a rapid increase in the number of cases within a sufficiently short time. Endemic models explain the transmission mechanism of diseases that remain in the population over a long period. Pandemic models depict the transmission of a disease that spreads geographically across several nations and continents [1, 2, 3]. The first mathematical model in epidemiology was published in 1790 by Daniel Bernoulli. However, compartmental models for studying the transmission dynamics of a disease traced its history to 1927 when Kermack and McKendrick built the deterministic SIR (Susceptible, Infectious, Recovered) model to study the Black Death pandemic [4]. The SIR

model provides a description and groundwork for more complex models, which have been developed by adding additional compartments to the model, such as the effect of isolation and quarantine [5], vaccination [6], latent period [7] etc. The SIR model is based on the idea that an individual becomes infectious immediately once infected. However, this is unlikely for some diseases; a certain amount of time is needed for an individual to transmit the disease. This disease characteristic has been investigated via an extension of the SIR model, which is the SEIR (Susceptible, Infected, Infectious, Recovered); both the SIR and the SEIR model have been extensively studied [7, 8]. The SEIR model incorporates the process from being infected to becoming infectious by an additional compartment, E; in this model, an infected and infectious individual is distinguished. The process of becoming infected can also be represented by a constant time delay, such as the SIR model with delay [9]. The main objective of this thesis is to examine the models for the latent period: the SEIR model and the SIR model with delay and compare the results of the two models.

Chapter 2

The SIR Epidemiological Model and the Incidence of Disease

In 1927 Kermack and McKendrick proposed a model to describe the transmission dynamics of diseases. Today, this model is known as the SIR model and serves as a foundation of the compartmental approach in modeling infectious disease transmission. The SIR compartmental model divides the host population into three distinct compartments of people, such as Susceptible, Infected, and Recovered. An individual who is currently healthy yet subject to infection is classified as **Susceptible** individual denoted by the letter S. An individual who has already developed the disease and can spread the infections is classified as **Infectious** individual denoted by the letter I. An individual who is resistant to reinfection is referred to as **Recovered** individual denoted by the letter R. In the context of the SIR model, the number of individuals who become infectious per unit of time is referred to as the **Incidence** of the disease. The change in the number of hosts in each compartment in the interval $[t, t + \Delta t]$ when $\Delta t \to 0$ is denoted by $S'(t)$, $I'(t)$, and $R'(t)$.

2.1 Formulation of the SIR Model

The SIR model is built on the following assumptions:

- Infection is transmitted through direct person-to-person contact.
- Population is homogeneously mixed; the number of hosts in each compartment determines the number of contacts between hosts from different compartments.
- Parameter β is the transmission coefficient, and $\beta S(t)I(t)$ is the incidence of the disease.
- The rate at which transfer from a compartment occurs is proportional to the population size of the compartment. The rate of recovery (transfer rate from I to R) is written as γI for a constant positive rate γ.
- The population is assumed to be closed; in other words, there is no new susceptible input or removal from any compartment.
- There is no possibility of reinfection, which means the recovery from the disease is permanent.

The schematic illustration of the SIR model is given in Fig. 2.1

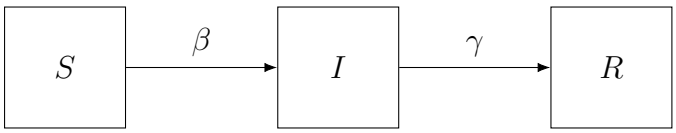


Fig. 2.1: Schematic illustration of the SIR model.

Based on the assumptions above, we obtain the following system of differential equations:

$$\begin{aligned} \frac{dS}{dt} &= -\beta S(t)I(t), \\ \frac{dI}{dt} &= \beta S(t)I(t) - \gamma I(t), \\ \frac{dR}{dt} &= \gamma I(t). \end{aligned} \tag{2.1}$$

At time $(t = 0)$ a certain number of infectious individuals is introduced to the population of susceptibles, and the system is started from the following nonnegative initial conditions;

$$S(0) = S_0, \quad I(0) = I_0, \quad \text{and} \quad R(0) = R_0.$$

The result Kermack and McKendrick obtained from model (2.1) is a threshold that the initial number of susceptible S_0 must exceed for an epidemic to occur; it explains the severity of the epidemic and gives a formula for the final size of an epidemic [1].

2.2 Modeling the Incidence of Disease

The chemical law of mass action states that the rate of a chemical reaction is proportional to the density of the reactants. This law makes the following assumptions: the mixture is homogeneous, so the density of the reactants only determines the contact rate, the total mass is conserved, and the reactant densities are low. In epidemiology, the law of mass action can be used to model the incidence under the same assumptions of homogeneously mixed population and small and conserved population size. In this case, the incidence is the mass action incidence [1]. In a population of size N, let λ denote the average contact number per capita per unit of time among the individuals; not all these contacts will lead to the infectious; let also p be the probability of the effective contact that leads to transmission. Then the incidence term is

$$p\lambda \frac{S(t)}{N(t)} I(t).$$

If we let p to be absorbed in λ, the incidence term will be given by

$$\lambda \frac{S(t)}{N(t)} I(t). \tag{2.2}$$

We consider two possibilities as follows:

- Case I: ***Incidence term when the total population size is constant***
  If the population size N is constant then we let $\frac{\lambda}{N} = \beta$ and the incidence term will be

  $$\beta S(t) I(t)$$

  which is the mass action incidence.

- Case II: ***Incidence term when the total population size is not constant***
  When population size changes over time, it is necessary to consider how the contract rate changes. We assume that the effective contact rate is proportional to the population density. There are two possibilities for the incidence term:

  - If population density is independent of population size, then the effective contact rate λ is independent of the population size, and the incidence term can be calculated as

    $$\frac{\lambda S(t) I(t)}{N(t)}.$$

    This is referred to as the standard incidence. This incidence is appropriate for modeling disease transmission in a rural area because the rural area expands to maintain a constant population density as the population grows.

  - If population density is proportional to population size, then the effective contact rate λ is proportional to the population size. That is

    $$\lambda(N) = \beta N(t).$$

    Then, by (2.2) the incidence term is

    $$\beta S(t) I(t).$$

Which is the mass action incidence. This incidence is suitable for modeling disease transmission in an urban area where the city is limited in space. We assume mass action incidence in all models examined in the following chapters.

We can see that the vital dynamics are ignored in model (2.1), as there is no recruitment and removal from the population. This is an unrealistic assumption; an expansion of this model includes vital dynamics. Under the vital dynamics, there are two assumptions about whether the population is constant or varies over time. The population size should be conserved to maintain the mass action incidence term in the model. If the population size varies, population density should be assumed to be proportional to population size. In model (2.3), we assume that population size is conserved, i.e., the birth and death rates are equal. The model's differential equation system is:

$$\begin{aligned} \frac{dS}{dt} &= \mu N - \beta S(t)I(t) - \mu S(t), \\ \frac{dI}{dt} &= \beta S(t)I(t) - \gamma I(t) - \mu I(t), \\ \frac{dR}{dt} &= \gamma I(t) - \mu R(t). \end{aligned} \tag{2.3}$$

The nonnegative initial condition at time $t = 0$ is

$$S(0) = S_0, \quad I(0) = I_0, \quad \text{and} \quad R(0) = R_0.$$

The death rate in the population is assumed to be constant μ and the recovery rate is assumed to be constant γ. To justify the reason for this assumption we present the following argument:

Suppose $N(a)$ is the number of individuals in a population who are alive until age a, and μ is the proportion of population who die and leave the population. The differential equation for this phenomenon is given by

$$\frac{dN(a)}{da} = -\mu N(a)$$

where the negative sign indicates that N decreases with respect to age due to death. Let $N(0) = N_0$, then

$$N(a) = e^{-\mu a} N_0$$

Hence, $\frac{N(a)}{N_0} = e^{-a\mu}$. The term $e^{-a\mu}$ is the probability of an individual entering the population at age $a = 0$ and surviving until age $a > 0$. Let X be the random variable of the age of an individual at death, according to the solution of the differential equation above we have

$$\begin{aligned}\mathbb{P}(0 \leq X \leq a) &= 1 - \mathbb{P}(X > a) \\ &= \int_0^a \mu e^{-\mu s} ds \\ &= 1 - e^{-\mu a} \\ &=: F(t).\end{aligned}$$

Where $F(a)$ is the probability distribution of the random variable X, and its probability density function is $f(a) = \frac{dF}{da} = \mu e^{-\mu a}$. The expected value of the random variable X is

$$\begin{aligned}\mathbb{E}[X] &= \int_0^\infty a\mu e^{-\mu a} da \\ &= \frac{1}{\mu}.\end{aligned} \tag{2.4}$$

Therefore, $\frac{1}{\mu}$ is the average lifespan of a population. In the same fashion, if the recovery rate is constant γ, then the average time spent in the infectious compartment is $\frac{1}{\gamma}$.

Chapter 3

Latent Period in Epidemiological Models

In Chapter 2, the basic compartmental model for the transmission dynamics of a disease, namely, the SIR model, is introduced. In the SIR model, an infected and an infectious individual has not been distinguished. However, the spread of an infectious disease begins with the pathogen moving from one host to another, i.e., individuals in epidemiological models. Once a pathogen reaches the host's body, a certain amount of time must pass for the pathogen to accumulate in sufficient numbers, allowing the human to become symptomatic and transmit the pathogen. Latent and incubation periods are phrases used to describe the time elapsed. On the other hand, the terms incubation and latent phases can be misleading; thus, defining them may be helpful.

- **Incubation Period:** The interval between being infected and the appearance of symptoms is referred to as the incubation period, as seen in Fig. 3.1 [1].
- **Latent Period:** The interval between being infected and capable of spreading the disease is referred to as the latent Period, as seen in Fig. 3.1[1].

Remark 1. *Latent period might be shorter or longer than the incubation period, depending on the disease.*

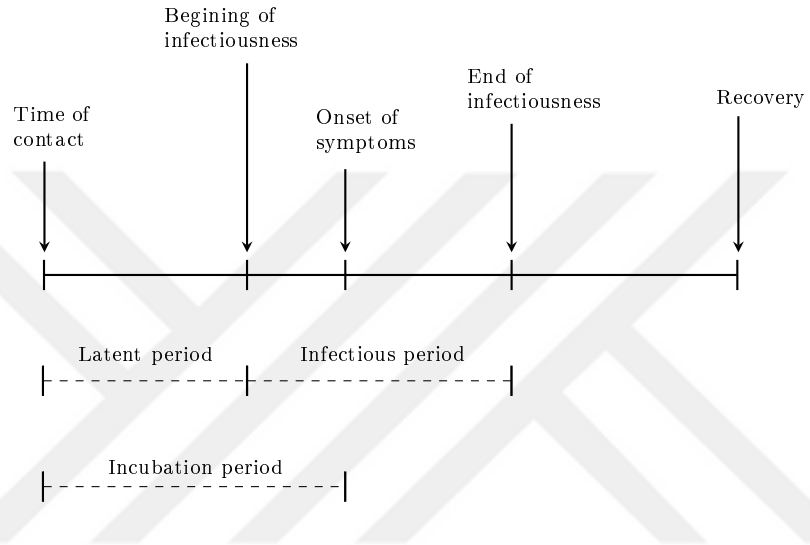


Fig. 3.1: Schematic illustration of latent and incubation period.

In the following section, we review the SEIR model, consisting of an additional compartment designated by the exposed compartment.

3.1 SEIR Epidemiological Model

A common approach in compartmental models to represent the latent period of the disease is to expand the SIR model and divide the infected compartment into two compartments: the latent compartment marked by the letter E and the infectious compartment I. The expanded model is the SEIR (Susceptible, Exposed, Infectious, Recovered) model, where the E compartment consists of exposed individuals who have come into contact with an infectious agent but cannot spread the disease yet; these individuals are infected but not infectious. Note that in this model, we adhere to the definition of susceptible, infectious, and recovered individuals described in the SIR model reviewed in Chapter 2.

3.2 Formulation of the SEIR Model

In the SEIR model, the following assumptions are made:

- The population is divided into four compartments: Susceptible (S), Exposed (E), Infectious (I), and Recovered (R).
- Population is sufficiently large that the size of each compartment is a continuous variable.
- The population is homogeneously mixed.
- β is the per capita per unit of time transmission rate of the disease.
- Effective contact rate is proportional to the population density, and population density is proportional to the population size. Therefore, the number of infectious cases per unit of time -$\beta S(t)I(t)$- follows the mass action law.
- Disease spreads through direct contact from person to person between hosts.
- The model incorporates vital dynamics, i.e., the birth rate a and death rate μ. It is assumed that the total inflow is constant and is proportional to the constant carrying capacity K. We have $aK = A$, where A is constant births in the population. The outflow is proportional to the size of the population size.
- The rate at which an infected individual becomes infectious is a constant σ, and the rate at which an infectious individual recovers from the disease is γ. The mean resident time in latent and infectious compartments are $\frac{1}{\sigma}$ and $\frac{1}{\gamma}$, respectively.
- The removal rates from the exposed compartment by both death and infectiousness, and the removal rates from the infectious compartment by both death and recovery, are $\mu+\sigma$ and $\mu+\gamma$, respectively. Therefore, the death-adjusted mean latent period and death-adjusted mean infectivity period are $\frac{1}{\mu+\sigma}$ and $\frac{1}{\mu+\gamma}$, respectively.

- Recovery is permanent, and there is no possibility of reinfection.
- Disease-induced death is neglected.

The incidence term of disease is $\beta S(t)I(t)$, which is the number of susceptible individuals who become ill at the rate of β and leave compartment S at time t. In this respect, the dynamics of susceptible individuals at time t include newborns who are naturally considered susceptible, those who are removed by death at the constant proportionality rate μ, and those who are removed by being ill at the rate of β. Likewise, the rate of change in the number of exposed individuals at time t is made up of individuals who become infected and join compartment E and those who exit the compartment due to becoming infectious at the rate of σ and dying naturally at the rate of μ at time t. Similarly, the dynamics of infectious and recovered individuals at time t are constructed based on the number of individuals who become infectious at the rate of σ and recover from the disease at the rate of γ at time t [10]. The schematic illustration of the SEIR model is given in Fig. 3.2.

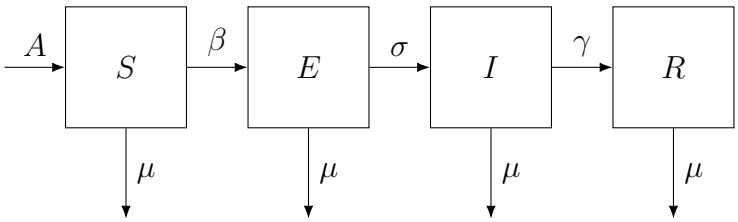


Fig. 3.2: Schematic illustration of the SEIR epidemiological model.

$$\frac{dS}{dt} = A - \beta S(t)I(t) - \mu S(t), \tag{3.1a}$$

$$\frac{dE}{dt} = \beta S(t)I(t) - (\mu + \sigma)E(t), \tag{3.1b}$$

$$\frac{dI}{dt} = \sigma E(t) - (\gamma + \mu)I(t), \tag{3.1c}$$

$$\frac{dR}{dt} = \gamma I(t) - \mu R(t). \tag{3.1d}$$

The total population size is $N(t) = S(t) + E(t) + I(t) + R(t)$ and at time $t = 0$ the system starts with the following nonnegative initial conditions:

$$S_0 = S(0), \quad E_0 = E(0), \quad I_0 = I(0), \quad R_0 = R(0), \quad N_0 = N(0). \tag{3.2}$$

3.3 Analysis of the SEIR Model

Proposition 3.1. *Solution to the initial value problem (3.1) - (3.2) exists and is unique. Starting from nonnegative initial conditions, and for nonnegative parameter values A, μ, β, σ, and γ solutions stay nonnegative.*

Proof. We refer to chapter 3 of [11] for proof of the existence and uniqueness of solutions, and continue with the proof of nonnegativity. Rewriting

$$S'(t) + (\mu + \beta I(t))S(t) = A,$$

multiplying both sides by the integrating factor $\Phi(t) = \exp\Big\{\int_0^t (\beta I(u) + \mu)du\Big\}$, we obtain

$$\frac{d}{dt}(\Phi(t)S(t)) = A\Phi(t). \tag{3.3}$$

Integrating (3.3) from 0 to t yields

$$\begin{aligned} S(t) = {} & S_0 \exp\Big\{-\int_0^t (\beta I(u) + \mu)du\Big\} \\ & + A\exp\Big\{-\int_0^t (\beta I(u) + \mu)du\Big\}\int_0^t \exp\Big\{\int_0^s (\beta I(u) + \mu)du\Big\}ds. \end{aligned} \tag{3.4}$$

Therefore, for $S_0 \geq 0$ we have $S(t) \geq 0$ for all $t \geq 0$. In a similar fashion, we integrate both sides of equations (3.1b) and (3.1c) and obtain

$$E(t) = E_0 e^{-(\mu+\sigma)t} + e^{-(\mu+\sigma)t}\beta\int_0^t e^{(\mu+\sigma)u}S(u)I(u)du. \tag{3.5}$$

$$I(t) = I_0 e^{-(\mu+\gamma)t} + e^{-(\mu+\gamma)t}\int_0^t e^{(\mu+\gamma)u}E(u)du. \tag{3.6}$$

Let $E_0 > 0$, then by continuity of the solutions there exists some neighborhood of $t = 0$ such that $E(t) > 0$. Define

$$t_1 = \sup\Big\{s > 0 : E(t) > 0 \text{ on } [0, s)\Big\}.$$

We will prove that $t_1 = \infty$. For contradiction, suppose $t_1 < \infty$, then $E(t) > 0$ for $0 \leq t < t_1$ and $E(t_1) = 0$. From (3.6) we conclude that $I(t) \geq 0$ for all $0 \leq t \leq t_1$. Therefore,

$$E(t_1) \geq E_0 e^{-(\mu+\sigma)t_1} > 0.$$

Hence, $E(t_1) > 0$ which is a contradiction. Therefore, t_1 cannot be finite and $E(t) > 0$ for all $t \geq 0$. To show that $I(t) \geq 0$ for all $t \geq 0$, we assume $I_0 > 0$ and let

$$t_2 = \sup\Big\{s > 0 : I(t) > 0 \text{ on } [0, s)\Big\}.$$

If $t_2 < \infty$, then $I(t) > 0$ for $0 \leq t < t_2$ and $I(t_2) = 0$. (3.5) implies that for $0 \leq t \leq t_2$ we have $E(t) \geq 0$. Solution for $I(t)$ gives the contradiction since

$$I(t_2) \geq I_0 e^{-(\mu+\gamma)t_2} > 0.$$

Hence $t_2 = \infty$. If $E_0 = I_0 = 0$, then from (3.5) and (3.6) we have $E(t) = I(t) = 0$ for $t = 0$, and

$$S(t) = S_0 e^{-\mu t} + \frac{A}{\mu} - \frac{A}{\mu} e^{-\mu t}.$$

Hence, the solution $(S(t), E(t), I(t)) = \big(S_0 e^{-\mu t} + \frac{A}{\mu} - \frac{A}{\mu} e^{-\mu t}, 0, 0\big)$ satisfies the system of equations, and from uniqueness this solution is then a solution of the system for initial conditions $E_0 = I_0 = 0$, which is nonnegative for $S_0 \geq 0$.
Solving (3.1d) gives

$$R(t) = R_0 e^{-\mu t} + \gamma e^{-\mu t} \int_0^t I(u) du.$$

Hence, $R(t) \geq 0$ for all $t \geq 0$ if $R_0 \geq 0$. Therefore, solutions are nonnegative for all $t \geq 0$. □

Definition 3.1. *A set Γ is forward invariant if $\psi_t(\Gamma) \subset \Gamma$ for all $t > 0$, where ψ_t is the solution of the initial value problem [11].*

It should be emphasized that we adopt the notation that variables S, E, I, and R are evaluated at time t inside of the sets given below.

Proposition 3.2. *The set*

$$\Gamma = \left\{(S, E, I, R) \in \mathbb{R}^4_{\geq 0} : 0 \leq S + E + I + R \leq \frac{A}{\mu}\right\}$$

is forward invariant for the system (3.1)*. Moreover, starting from nonnegative initial condition* (3.2) *solutions of the system are bounded for all* $t \geq 0$*.*

Proof. Let $N(t) = S(t) + E(t) + I(t) + R(t)$. Then taking time derivative of $N(t)$ and substituting $S'(t)$, $E'(t)$, $I'(t)$, and $R'(t)$ from (3.1), we get

$$N'(t) = A - \mu N(t).$$

Let $N(0) = N_0$, then solving for $N(t)$ yields

$$N(t) = \frac{A}{\mu} + e^{-\mu t}(N_0 - \frac{A}{\mu}).$$

Given the solution, $N(t)$, if $N_0 \leq \frac{A}{\mu}$, then $N(t) \leq \frac{A}{\mu}$ for all $t \geq 0$. Also for $N_0 \geq 0$ we have

$$\begin{aligned} N(t) &= \frac{A}{\mu} + e^{-\mu t} N_0 - \frac{A}{\mu} e^{-\mu t} \\ &\geq \frac{A}{\mu}(1 - e^{-\mu t}) \\ &\geq 0. \end{aligned}$$

Hence, starting from the set Γ solutions remain in Γ for all $t \geq 0$. Therefore, the set Γ is forward invariant. Boundedness of the solutions follows from the inequality $0 \leq S(t) + E(t) + I(t) + R(t) \leq \frac{A}{\mu}$ and nonnegativity of $S(t)$, $E(t)$, $I(t)$, and $R(t)$. □

Equations (3.1a)-(3.1c) are independent of $R(t)$. Therefore, without loss of generality, equation (3.1d) can be ignored. Hence, the reduced system is

$$\frac{dS}{dt} = A - \beta S(t) I(t) - \mu S(t), \tag{3.7a}$$

$$\frac{dE}{dt} = \beta S(t) I(t) - (\mu + \sigma) E(t), \tag{3.7b}$$

$$\frac{dI}{dt} = \sigma E(t) - (\gamma + \mu) I(t). \tag{3.7c}$$

The initial conditions at time $t = 0$ is:

$$S_0 = S(0) \geq 0, \quad E_0 = E(0) \geq 0, \quad I_0 = I(0) \geq 0.$$

The feasible region of the system (3.7) is the nonnegative orthant of $\mathbb{R}^3$

$$\mathbb{R}^3_{\geq 0} = \big\{(S, E, I) \mid S \geq 0, E \geq 0, I \geq 0\big\},$$

which is a forward invariant set for system (3.7), i.e., the vector field on the boundary of $\mathbb{R}^3_{\geq 0}$ is tangent to the boundary or point inward. Since we have $N(t) = S(t) + E(t) + I(t) + R(t)$ and $R(t) \geq 0$, then for all time t, we get $S(t) + E(t) + I(t) \leq N(t)$. Therefore, it suffices to consider the initial conditions in the bounded region

$$\Gamma_1 = \Big\{(S, E, I) \in \mathbb{R}^3_{\geq 0} : 0 \leq S + E + I \leq \frac{A}{\mu}\Big\}. \tag{3.8}$$

In a similar fashion presented in proposition 3.2, Γ_1 is forward invariant set for the system (3.7). For the rest of the analysis we restrict our attention to the system (3.7).

3.4 Equilibria of the SEIR Model

When working with nonlinear systems obtaining an analytical solution is sometimes challenging, if not impossible. However, there is a specific solution known as an equilibrium solution that does not change over time, and is easy to obtain. Hence, the first step in analyzing a system of differential equations is to determine the equilibrium solutions. This is accomplished by setting the rate of change equal to zero.

An equilibrium solution to the system (3.7) is (S^*, E^*, I^*) such that

$$A - \beta S^* I^* - \mu S^* = 0, \tag{3.9a}$$

$$\beta S^* I^* - (\mu + \sigma) E^* = 0, \tag{3.9b}$$

$$\sigma E^* - (\gamma + \mu) I^* = 0. \tag{3.9c}$$

The components of an equilibrium for the system (3.7) denote the system solutions, which are the number of individuals in each compartment, so an equilibrium with a negative component has no epidemiological significance. Epidemiological models possess two equilibria under two major conditions: $I^* = 0$ and $I^* > 0$. The equilibrium under the condition $I^* = 0$ is the disease-free equilibrium, and the equilibrium under the condition $I^* > 0$ is the endemic equilibrium.

- **Disease-free Equilibrium**

  The disease-free equilibrium is obtained by setting $I^* = 0$ in (3.9). Then we have

  $$E^* = 0 \qquad \text{and} \qquad S^* = \frac{A}{\mu}.$$

  Hence, the disease-free equilibrium denoted by P_1, is given by

  $$P_1 = \left(\frac{A}{\mu}, 0, 0\right). \tag{3.10}$$

- **Endemic Equilibrium**

  If $I^* > 0$, solving (3.9) for (S^*, E^*, I^*) yields

  $$S^* = \frac{(\mu+\sigma)(\mu+\gamma)}{\beta\sigma}.$$

  Substituting S^* in (3.9a) yields

  $$I^* = \frac{A\sigma\beta - \mu(\mu+\gamma)(\mu+\sigma)}{\beta(\mu+\gamma)(\mu+\sigma)}.$$

  Substituting I^* in (3.9c) gives

  $$E^* = \frac{A\sigma\beta - \mu(\mu+\gamma)(\mu+\sigma)}{\sigma\beta(\mu+\sigma)}.$$

  The equilibrium corresponding to the condition $I^* > 0$ denoted by P_2, is given by

  $$P_2 = \left(\frac{(\mu+\sigma)(\mu+\gamma)}{\beta\sigma}, \frac{A\sigma\beta - \mu(\mu+\gamma)(\mu+\sigma)}{\sigma\beta(\mu+\sigma)}, \frac{A\sigma\beta - \mu(\mu+\gamma)(\mu+\sigma)}{\beta(\mu+\gamma)(\mu+\sigma)}\right). \tag{3.11}$$

  The components of P_2 should be positive; since otherwise, it has no epidemiological meaning. Hence, the following condition should be satisfied.

  $$A\sigma\beta - \mu(\mu+\gamma)(\mu+\sigma) > 0.$$

In other words, the following condition must hold

$$\frac{A\sigma\beta}{\mu(\mu+\gamma)(\mu+\sigma)} > 1.$$

Let's define

$$\mathcal{R}_0 := \frac{A\sigma\beta}{\mu(\mu+\gamma)(\mu+\sigma)}.$$

Under the condition $\mathcal{R}_0 > 1$, P_2 is the endemic equilibrium. Rewriting (3.11) in terms of $\mathcal{R}_0$ gives

$$P_2 = \Big(\frac{A}{\mu\mathcal{R}_0}, \frac{\mu(\mu+\gamma)}{\sigma\beta}(\mathcal{R}_0 - 1), \frac{\mu}{\beta}(\mathcal{R}_0 - 1)\Big). \tag{3.12}$$

Remark 2. *It should be noted that both equilibria: P_1 and P_2 are mathematically valid independents of the value of $\mathcal{R}_0$. The condition on $\mathcal{R}_0$ is only required for the epidemiological significance of the equilibria.*

Remark 3. *If $\mathcal{R}_0 < 1$, then P_2 has negative components, which is invalid. Therefore, system (3.7) has only one equilibrium which is P_1. If $\mathcal{R}_0 > 1$, then both P_1 and P_2 are admissible and the system (3.7) has two equilibria: $P_1 \in \partial\Gamma_1$[1] and $P_2 \in \Gamma_1^\circ$[2]. If $\mathcal{R}_0 = 1$, then two equilibria are equal to the disease-free equilibrium.*

3.5 Local Stability of Equilibria

Linearization provides information on the behavior of the solution near equilibrium. It is used to examine the equilibrium's local stability and instability. Consider the following system, where F, G, H, and their partial derivatives are continuous.

$$S'(t) = F(S, I) = A - \beta S(t)I(t) - \mu S(t), \tag{3.13a}$$

$$E'(t) = G(S, I, E) = \beta S(t)I(t) - (\mu+\sigma)E(t), \tag{3.13b}$$

$$I'(t) = H(E, I) = \sigma E(t) - (\mu+\gamma)I(t). \tag{3.13c}$$

[1] $\partial\Gamma_1$ denotes the boundary of the set Γ_1.
[2] Γ_1° denotes the interior of the set Γ_1.

Let $X^*=(S^*, E^*, I^*)$ be any equilibrium of the system (3.7) and $(X(t), Y(t), Z(t))$ be perturbation of a solution starting from an initial condition close to (S^*, E^*, I^*) where

$$\begin{aligned} X(t) &= S(t) - S^*, \\ Y(t) &= E(t) - E^*, \\ Z(t) &= I(t) - I^*. \end{aligned} \tag{3.14}$$

Substituting (3.14) into (3.13) and expanding in Taylor series at (S^*, E^*, I^*) gives

$$\frac{dX}{dt} = F\Big(X(t)+S^*, Z(t)+I^*\Big) = F(S^*, I^*)+\frac{\partial F}{\partial S}(S^*, I^*)X(t)+\frac{\partial F}{\partial I}(S^*, I^*)Z(t) + \cdots,$$

$$\frac{dY}{dt} = G\Big(X(t)+S^*, Y(t)+E^*, Z(t)+I^*\Big) = G(S^*, E^*, I^*)+\frac{\partial G}{\partial S}(S^*, E^*, I^*)X(t) + \frac{\partial G}{\partial E}(S^*, E^*, I^*)Y(t) + \frac{\partial G}{\partial I}(S^*, E^*, I^*)Z(t) + \cdots,$$

$$\frac{dZ}{dt} = H\Big(Y(t)+E^*, Z(t)+I^*\Big) = H(E^*, I^*)+\frac{\partial H}{\partial E}(E^*, I^*)Y(t)+\frac{\partial H}{\partial I}(E^*, I^*)Z(t) + \cdots.$$

For small perturbation the higher order terms X^2, Y^2, Z^2, XY, XZ, and YZ are small; thus we ignore them. Hence, the linearized system is

$$\begin{aligned} \frac{dX}{dt} &= \Big(A - \beta S^* I^* - \mu S^*\Big) - (\beta I^* + \mu)X(t) - \beta S^* Z(t), \\ \frac{dY}{dt} &= \Big(\beta S^* I^* - (\mu+\sigma)E^*\Big) + \beta I^* X(t) - (\mu+\sigma)Y(t) + \beta I^* Z(t), \\ \frac{dZ}{dt} &= \Big(\sigma E^* - (\gamma+\mu)I^*\Big) + \sigma Y(t) - (\mu+\gamma)Z(t). \end{aligned}$$

Substituting equilibrium equation (3.9) gives

$$\begin{aligned} \frac{dX}{dt} &= -(\beta I^* + \mu)X(t) - \beta S^* Z(t), \\ \frac{dY}{dt} &= \beta I^* X(t) - (\mu+\sigma)Y(t) + \beta I^* Z(t), \\ \frac{dZ}{dt} &= \sigma Y(t) - (\mu+\gamma)Z(t). \end{aligned} \tag{3.15}$$

Rewriting the linear system (3.15) in matrix form we get

$$\begin{bmatrix} X' \\ Y' \\ Z' \end{bmatrix} = \begin{bmatrix} -\mu - \beta I^* & 0 & -\beta S^* \\ \beta I^* & -(\mu+\sigma) & \beta S^* \\ 0 & \sigma & -(\mu+\gamma) \end{bmatrix} \begin{bmatrix} X(t) \\ Y(t) \\ Z(t) \end{bmatrix}, \tag{3.16}$$

where

$$Df(X^*) = \begin{bmatrix} -\mu - \beta I^* & 0 & -\beta S^* \\ \beta I^* & -(\mu+\sigma) & \beta S^* \\ 0 & \sigma & -(\mu+\gamma) \end{bmatrix}, \tag{3.17}$$

is the Jacobian matrix of the nonlinear system (3.13) evaluated at equilibrium (S^*, E^*, I^*).

Definition 3.2. *An equilibrium X^* is said to be hyperbolic if for every eigenvalue λ of $Df(X^*)$ we have $\operatorname{Re}\lambda \neq 0$, and it is said to be nonhyperbolic if for at least one eigenvalue λ $Df(X^*)$ we have $\operatorname{Re}\lambda = 0$ [12].*

Rewriting the linearized system (3.16) in compact form yields

$$x'(t) = Df(X^*)x(t) \tag{3.18}$$

Let's define $Df(X^*) := J$, then the linear system is $x'(t) = Jx(t)$, where $\vec{x} := [X, Y, Z]^{\top 1}$. The objective is to find a vector $x(t)$ such that $x'(t) = Jx(t)$. Note that $Df(X^*) = J$ is a constant matrix; based on our knowledge of solving homogeneous equations with constant coefficients we speculate that the nontrivial solution is of the form

$$x(t) = \vec{u}e^{\lambda t}, \tag{3.19}$$

where λ is an eigenvalue value of the matrix J, and $\vec{u}$ is the eigenvector associated with the eigenvalue λ. To verify that (3.19) is, indeed, the nontrivial solution we substitute it into (3.18) and obtain

$$\lambda\vec{u}e^{\lambda t} = J\vec{u}e^{\lambda t}.$$

Then

$$(J - \lambda I)\vec{u}e^{\lambda t} = 0,$$

[1] $\top$ is transpose of the vector x.

where I is the identity matrix. System above is homogeneous linear system of three equations in the components of $\vec{u}e^{\lambda t}$. Therefore, the system has nontrivial solution $\vec{u}e^{\lambda t} \neq 0$ if and only if matrix $(J - \lambda I)$ is singular; in other words, we have

$$\det(J - \lambda I) = 0 \tag{3.20}$$

which is the characteristic equation of the Jacobian matrix evaluated at an equilibrium. Computing the characteristic polynomial of the Jacobian matrix at any equilibrium (S^*, E^*, I^*) gives

$$\det(J - \lambda I) = \det \begin{bmatrix} -\mu - \beta I^* - \lambda & 0 & -\beta S^* \\ \beta I^* & -(\mu + \sigma) - \lambda & \beta S^* \\ 0 & \sigma & -(\mu + \gamma) - \lambda \end{bmatrix}. \tag{3.21}$$

Then, the characteristic equation of any equilibrium (S^*, E^*, I^*) is

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0.$$

Where the coefficients are

$$\begin{aligned} A &= (\mu + \beta I^*) + (\mu + \gamma) + (\mu + \sigma), \\ B &= (\mu + \beta I^*)[(\mu + \gamma) + (\mu + \sigma)] + (\mu + \sigma)(\mu + \gamma) - \sigma\beta S^*, \\ C &= \beta^2 \sigma I^* S^* - (\mu + \beta I^*)(\sigma\beta S^*) + (\mu + \beta I^*)(\mu + \gamma)(\mu + \sigma). \end{aligned}$$

The following theorem states the condition under which the disease-free equilibrium is locally asymptotically stable.

Theorem 3.1. *If $0 < \mathcal{R}_0 < 1$, then the disease-free equilibrium is locally asymptotically stable.*

Proof. Evaluating the Jacobian matrix (3.17) at $P_1 = \left(\frac{A}{\mu}, 0, 0\right)$ yields

$$J = \begin{bmatrix} J_{11} & J_{12} & J_{13} \\ J_{21} & J_{22} & J_{23} \\ J_{31} & J_{32} & J_{33} \end{bmatrix} = \begin{bmatrix} -\mu & 0 & -\beta\dfrac{A}{\mu} \\ 0 & -(\mu + \sigma) & \beta\dfrac{A}{\mu} \\ 0 & \sigma & -(\mu + \gamma) \end{bmatrix}. \tag{3.22}$$

Since J_{21} and J_{31} are zero we can expand the matrix in terms of the first column which gives one of the eigenvalues $\lambda_1 = -\mu$. To find other eigenvalues it suffices to consider

$$J_1 = \begin{bmatrix} -(\mu+\sigma) & \beta\dfrac{A}{\mu} \\ \sigma & -(\mu+\gamma) \end{bmatrix}. \tag{3.23}$$

A 2×2 matrix has eigenvalues with negative real parts if and only if its determinant (D) is positive and its trace (Tr) is negative [13]. We see that sub-matrix J_1 satisfies these conditions:

$$\begin{aligned} Tr &= -(\mu+\gamma) - (\mu+\sigma) < 0, \\ D &= (\mu+\gamma)(\mu+\sigma) - \frac{\sigma\beta A}{\mu} \\ &= (\mu+\gamma)(\mu+\sigma)(1-\mathcal{R}_0). \end{aligned}$$

Since $\mathcal{R}_0 < 1$ we have $D > 0$. Hence, J_1 has two eigenvalues with negative real part. Therefore, the disease-free equilibrium is locally asymptotically stable. □

Theorem 3.2. *If $\mathcal{R}_0 > 1$, then the disease-free equilibrium is unstable. The endemic equilibrium (3.12) is locally asymptotically stable.*

Proof. To prove instability of the disease-free equilibrium when $\mathcal{R}_0 > 1$ it suffices to prove that the characteristic equation of the disease-free equilibrium has at least one root with positive real parts. The characteristic polynomial of sub-matrix J_1 is

$$\begin{aligned} P(\lambda) &= \lambda^2 + \lambda\Big[(2\mu+\sigma+\gamma)\Big] + \Big[(\mu+\gamma)(\mu+\sigma) - \frac{\sigma\beta A}{\mu}\Big] \\ &= \lambda^2 + \lambda\Big[(2\mu+\sigma+\gamma)\Big] + \Big[(\mu+\gamma)(\mu+\sigma)(1-\mathcal{R}_0)\Big]. \end{aligned}$$

The product[1] of roots of the characteristic equation $P(\lambda) = 0$ is

$$\lambda_1 \times \lambda_2 = (\mu+\gamma)(\mu+\sigma)(1-\mathcal{R}_0) < 0.$$

This implies that one of the roots is positive. Hence, the disease-free equilibrium is unstable. The endemic equilibrium (3.12) has a third degree characteristic

[1] Product of roots of a quadratic equation $a\lambda^2 + b\lambda + c = 0$ is $\lambda_1 \times \lambda_2 = \frac{c}{a}$.

polynomial as $\lambda^3 + \Delta\lambda^2 + \Sigma\lambda + \Psi = 0$ where the coefficients are

$$\begin{aligned}
\Delta &= \mu + \mu(\mathcal{R}_0 - 1) + 2\mu + \gamma + \sigma, \\
\Sigma &= \mu + \mu(\mathcal{R}_0 - 1)[(\mu + \gamma) + (\mu + \sigma)], \\
\Psi &= \mu(\mathcal{R}_0 - 1)(\mu + \gamma)(\mu + \sigma).
\end{aligned}$$

When $\mathcal{R}_0 > 1$, we have $\Delta > 0$, $\Sigma > 0$, and $\Psi > 0$. By Routh-Hurwitz criterion, a polynomial of degree three with real coefficients has three roots with negative real parts if and only if $\Delta > 0$, $\Sigma > 0$, and $\Psi > 0$, and the following Hurwitz matrix has positive determinant:

$$H = \begin{bmatrix} \Delta & 1 \\ \Psi & \Sigma \end{bmatrix}.$$

Determinant of the matrix H is

$$\begin{aligned}
\Delta\Sigma - \Psi = {} & \mu^2 + \mu^2(\mathcal{R}_0 - 1)(\mu + \gamma) + \mu^2(\mathcal{R}_0 - 1)(\mu + \sigma) + \mu^2(\mathcal{R}_0 - 1) + \mu^2(\mathcal{R}_0 - 1)^2(\mu + \gamma) \\
& + \mu^2(\mathcal{R}_0 - 1)^2(\mu + \sigma) + \mu(\mu + \gamma) + \mu(\mathcal{R}_0 - 1)(\mu + \gamma)^2 + \mu(\mu + \gamma)(\mu + \sigma)(\mathcal{R}_0 - 1) \\
& + \mu(\mu + \sigma) + \mu(\mathcal{R}_0 - 1)(\mu + \sigma)^2 + \mu(\mu + \gamma)(\mu + \sigma)(\mathcal{R}_0 - 1) - \mu(\mathcal{R}_0 - 1)(\mu + \gamma)(\mu + \sigma).
\end{aligned}$$

$$\begin{aligned}
\Delta\Sigma - \Psi = {} & \mu^2 + \mu^2(\mathcal{R}_0 - 1)(\mu + \gamma) + \mu^2(\mathcal{R}_0 - 1)(\mu + \sigma) + \mu^2(\mathcal{R}_0 - 1) + \mu^2(\mathcal{R}_0 - 1)^2(\mu + \gamma) \\
& + \mu^2(\mathcal{R}_0 - 1)^2(\mu + \sigma) + \mu(\mu + \gamma) + \mu(\mathcal{R}_0 - 1)(\mu + \gamma)^2 + \mu(\mu + \gamma)(\mu + \sigma)(\mathcal{R}_0 - 1) \\
& + \mu(\mu + \sigma) + \mu(\mathcal{R}_0 - 1)(\mu + \sigma)^2
\end{aligned}$$

For $\mathcal{R}_0 > 1$ we have $\Delta\Sigma - \Psi > 0$. Hence, by Routh-Hurwitz criterion for a third degree polynomial we conclude that the characteristic equation of the endemic equilibrium has three roots with negative real parts. Therefore, P_2 is locally asymptotically stable. □

3.6 Stability Analysis via Lyapunov Functions

Let

$$\dot{x} = f(x) \tag{3.24}$$

be a system of differential equations, where $f : D \to \mathbb{R}^n$ is a vector field and $D \subset \mathbb{R}^n$. The gradient vector of a real-valued $\mathcal{C}^1$ function, i.e., a continuous function with continuous first derivative $V : U \subset \mathbb{R}^n \to \mathbb{R}$ is

$$\nabla V(x) = \Big(\frac{\partial V}{\partial x_1}, \cdots, \frac{\partial V}{\partial x_n}\Big).$$

The Lie derivative of V in the direction of f at a point x is a real-valued function given by

$$L_f V(x) = \nabla V(x) \cdot f(x)$$

where "$\cdot$" denotes dot product. The function $V(x)$ is a Lyapunov function of system (3.24) near a point $x \in U$ if $L_f V(x) \leq 0$ for all $x \in U$. Let $x(t) \in U$ be a solution of (3.24). Then

$$\frac{d}{dt}V(x(t)) = \dot{V}(x) = \nabla V(x(t)) \cdot x'(t) = \nabla V(x(t)) \cdot f(x(t)) = L_f V(x(t)). \quad (3.25)$$

Hence, $\dot{V}(x) = L_f V(x)$. Indeed, the Lie derivative gives the rate of change of scalar function V along the solution of (3.24). V is called a Lyapunov function of (3.24) if $V(x(t))$ decreases along the solution of the (3.24), i.e., $\dot{V}(x) \leq 0$ for all $x \in U$.

Theorem 3.3. *[11] Let x^* be an equilibrium of the system (3.24). If there exists a Lyapunov function $V : U \to \mathbb{R}$, where, U is an open subset of $\mathbb{R}^n$ containing x^* such that*

- *$V(x^*) = 0$ and $V(x) > 0$ for all $x \in U \backslash \{x^*\}$*
- *$\dot{V}(x) \leq 0$ for all $x \in U \backslash \{x^*\}$*

Then the equilibrium x^* is stable. Moreover, if V also satisfies

- *$\dot{V}(x) < 0$ for all $x \in U \backslash \{x^*\}$*

Then the equilibrium x^* is asymptotically stable.

Proof. We refer to [11] for a proof. □

The following theorem allows us to determine the asymptotic stability of a stable equilibrium without requiring the Lyapunov function strictly decreasing for all $x \in U \backslash \{x^*\}$.

Theorem 3.4 (LaSalle's Invariance Principle [11]). *Let x^* be an equilibrium for $x' = f(x)$ and let $V : U \to \mathbb{R}$ be a Lyapunov function, where U is an open set containing x^*. Let $K \subset U$ be a compact neighborhood of x^*. Suppose also K is positively invariant and the largest invariant subset of the set $\{x \in K | \dot{V}(x) = 0\}$ is the equilibrium x^*. Then x^* is asymptotically stable and it attracts all the points in K.*

Remark 4. *If we know that the equilibrium x^* is stable, all solutions starting in U remain in U, and for a compact and positively invariant set $K \subset U$ the set $\mathcal{I} = \{x \in K | \dot{V}(x) = 0\}$ contains only the equilibrium x^*, then from the LaSalle's Invariance Principle the set $\{x^*\}$ attracts all the solutions, all the solutions that stay in U converge to x^* which implies that x^* is globally asymptotically stable in the region U.*

Theorem 3.5. *If $\mathcal{R}_0 > 1$, then the unique endemic equilibrium is globally asymptotically stable.*

Proof. We follow [14] in the proof. Define a Volterra type Lyapunov function $V : \mathbb{R}^3_{>0} \to \mathbb{R}$ and p, k, $r \in \mathbb{R}_{>0}$ such that

$$V(S, E, I) = p\Big(S - S^* - S^* \ln \frac{S}{S^*}\Big) + k\Big(E - E^* - E^* \ln \frac{E}{E^*}\Big) + r\Big(I - I^* - I^* \ln \frac{I}{I^*}\Big). \tag{3.26}$$

Where (S^*, E^*, I^*) is the endemic equilibrium. We claim that V is a positive definite function for p, k, $r \in \mathbb{R}_{>0}$. Consider

$$f(x) = x - 1 - \ln x. \tag{3.27}$$

Note that $f(x) > 0$ for $x > 0$ and $f(x) = 0$ for $x = 1$. Moreover, $f'(x) = 1 - \dfrac{1}{x} < 0$ for $x \in (0, 1)$. Thus, f attains a global minimum at $x = 1$, is strictly decreasing for $x \in (0, 1)$, and strictly increasing for $x > 1$. Therefore, for $S \in \mathbb{R}_{>0} \backslash \{S^*\}$ we have

$$S - S^* - S^* \ln \frac{S}{S^*} = S^*\Big(\frac{S}{S^*} - 1 - \ln \frac{S}{S^*}\Big) > 0.$$

The remaining two terms in (3.26) are also clearly positive for $E \in \mathbb{R}_{>0}\backslash\{E^*\}$ and $I \in \mathbb{R}_{>0}\backslash\{I^*\}$. Hence, V satisfies the following conditions:

- $V(S^*, E^*, I^*) = 0$
- $V(S, E, I) > 0, \quad \forall\, (S, E, I) \in \mathbb{R}^3_{>0}\backslash\{(S^*, E^*, I^*)\}$

If for all $(S, E, I) \in \mathbb{R}^3_{>0}$ we have $\dot{V}(S, E, I) \leq 0$, then V is a Lyapunov function for the endemic equilibrium.

Note that the system (3.7) evaluated at $X^* = (S^*, E^*, I^*)$ gives the equilibrium equation; therefore, multiplying both sides of the equations by any term has no effect. Hence, multiplying $\left.\frac{dE}{dt}\right|_{X^*}$ and $\left.\frac{dI}{dt}\right|_{X^*}$ by $\frac{E}{E^*}$ and $\frac{I}{I^*}$ gives:

$$\begin{aligned}
\left.\frac{dS}{dt}\right|_{X^*} &= A - \mu S^* - \beta S^* I^* = 0, \\
\left.\frac{dE}{dt}\right|_{X^*} &= \frac{E}{E^*}\Big(\beta S^* I^* - (\mu + \sigma)E^*\Big) = 0, \\
\left.\frac{dI}{dt}\right|_{X^*} &= \frac{I}{I^*}\Big(\sigma E^* - (\mu + \gamma)I^*\Big) = 0.
\end{aligned} \tag{3.28}$$

By (3.25) the general form of $\dot{V}$ is

$$\frac{dV}{dt} = \frac{\partial V}{\partial S}\frac{dS}{dt} + \frac{\partial V}{\partial E}\frac{dE}{dt} + \frac{\partial V}{\partial I}\frac{dI}{dt}. \tag{3.29}$$

Right hand side of (3.28) is zero; subtracting zero value from $\frac{dS}{dt}$, $\frac{dE}{dt}$, and $\frac{dI}{dt}$ in (3.29) does not change the value of $\dot{V}$. Rewriting $\dot{V}$ yields

$$\begin{aligned}
\frac{dV}{dt} &= \frac{\partial V}{\partial S}\left(\frac{dS}{dt} - \left.\frac{dS}{dt}\right|_{X^*}\right) + \frac{\partial V}{\partial E}\left(\frac{dE}{dt} - \frac{E}{E^*}\left.\frac{dE}{dt}\right|_{X^*}\right) + \frac{\partial V}{\partial I}\left(\frac{dI}{dt} - \frac{I}{I^*}\left.\frac{dI}{dt}\right|_{X^*}\right) \\
&= p\Big(1 - \frac{S^*}{S}\Big)\Big[(A - \mu S - \beta SI) - (A - \mu S^* - \beta S^* I^*)\Big] \\
&+ k\Big(1 - \frac{E^*}{E}\Big)\Big[\Big(\beta SI - (\mu + \sigma)E\Big) - \frac{E}{E^*}\Big(\beta S^* I^* - (\mu + \sigma)E^*\Big)\Big] \\
&+ r\Big(1 - \frac{I^*}{I}\Big)\Big[\Big(\sigma E - (\mu + \gamma)I\Big) - \frac{I}{I^*}\Big(\sigma E^* - (\mu + \gamma)I^*\Big)\Big].
\end{aligned} \tag{3.30}$$

By expanding the first term in (3.30) we obtain

$$
\begin{aligned}
&p\Big(1-\frac{S^*}{S}\Big)\Big[(A-\mu S-\beta SI)-(A-\mu S^*I^*-\beta S^*I^*)\Big]\\
&=pA-p\mu S-p\beta SI-pA\frac{S^*}{S}+p\mu S^*+p\beta S^*I-pA+p\mu S^*\\
&+p\beta S^*I^*+pA\frac{S^*}{S}-p\mu\frac{S^{*2}}{S}-p\beta\frac{S^{*2}}{S}I\\
&=-p\mu S+2p\mu S^*-\beta pSI+\beta pS^*I+p\beta S^*I^*-p\mu\frac{S^{*2}}{S}-p\beta\frac{S^{*2}}{S}I^*.
\end{aligned}
$$

Expansion of the second term in (3.30) is

$$
\begin{aligned}
&k\Big(1-\frac{E^*}{E}\Big)\Big[\Big(\beta SI-(\mu+\sigma)E\Big)-\frac{E}{E^*}\Big(\beta S^*I^*-(\mu+\sigma)E^*\Big)\Big]\\
&=k\beta SI-k(\mu+\sigma)E-k\frac{E^*}{E}\beta S^*I^*+k(\mu+\sigma)E-k\frac{E}{E*}\beta SI\\
&+k(\mu+\sigma)E^*+k\beta S^*I^*-k(\mu+\sigma)E^*\\
&=k\beta SI-k\frac{E^*}{E}\beta SI-k\frac{E}{E*}\beta S^*I^*+k\beta S^*I^*.
\end{aligned}
$$

Expanding the third term in (3.30) gives

$$
\begin{aligned}
&r\Big(1-\frac{I^*}{I}\Big)\Big[\Big(\sigma E-(\mu+\gamma)I\Big)-\frac{I}{I^*}\Big(\sigma E^*-(\mu+\gamma)I^*\Big)\Big]\\
&=r\sigma E-r(\mu+\gamma)I-r\sigma\frac{I}{I^*}E^*+r(\mu+\gamma)I-r\sigma\frac{I^*}{I}E-r(\mu+\gamma)I^*\\
&+r\sigma E^*+r(\mu+\gamma)I^*\\
&=r\sigma E-r\sigma\frac{I}{I^*}E^*-r\sigma\frac{I^*}{I}E+r\sigma E^*.
\end{aligned}
$$

Therefore,

$$
\begin{aligned}
\frac{dV}{dt}&=-p\mu S+2p\mu S^*-\beta pSI+\beta pS^*I+p\beta S^*I^*-p\mu\frac{S^{*2}}{S}-p\beta\frac{S^{*2}}{S}I^*\\
&+q\beta SI-q\frac{E^*}{E}\beta SI-q\frac{E}{E*}\beta S^*I^*+q\beta S^*I^*\\
&+r\sigma E-r\sigma\frac{I}{I^*}E^*-r\sigma\frac{I^*}{I}E+r\sigma E^*.
\end{aligned}
$$

Rewriting it gives

$$
\begin{aligned}
\frac{dV}{dt}&=p\mu S^*\Big[2-\frac{S^*}{S}-\frac{S}{S^*}\Big]+p\beta S^*I^*\Big[1-\frac{SI}{S^*I^*}-\frac{S^*}{S}+\frac{I}{I^*}\Big]\\
&+k\beta S^*I^*\Big[1+\frac{SI}{S^*I^*}-\frac{E^*}{E}\frac{SI}{S^*I^*}-\frac{E}{E^*}\Big]+r\sigma E^*\Big[1-\frac{I}{I^*}-\frac{E}{E^*}\frac{I^*}{I}+\frac{E}{E^*}\Big].
\end{aligned}
$$

If $p = k$ then we get

$$\frac{dV}{dt} = p\mu S^*\left[2 - \frac{S^*}{S} - \frac{S}{S^*}\right] + p\beta S^* I^*\left[2 - \frac{S^*}{S} + \frac{I}{I^*} - \frac{E^*}{E}\frac{SI}{S^*I^*} - \frac{E}{E^*}\right] + r\sigma E^*\left[1 - \frac{I}{I^*} - \frac{E}{E^*}\frac{I^*}{I} + \frac{E}{E^*}\right].$$

From equilibrium equation, $\beta S^* I^* = (\mu+\sigma)E^*$. Substituting $p = 1$ and $r = \dfrac{\mu+\sigma}{\sigma}$ we obtain

$$\begin{aligned}
\frac{dV}{dt} &= \mu S^*\left[2 - \frac{S^*}{S} - \frac{S}{S^*}\right] + \beta S^* I^*\left[3 - \frac{S^*}{S} - \frac{E^*}{E}\frac{SI}{S^*I^*} - \frac{E}{E^*}\frac{I^*}{I}\right] \\
&= -\mu S^*\left[\frac{S^*}{S} + \frac{S}{S^*} - 2\right] - \beta S^* I^*\left[\frac{S^*}{S} + \frac{E^*}{E}\frac{SI}{S^*I^*} + \frac{E}{E^*}\frac{I^*}{I} - 3\right] \\
&= -\mu S^*\left[\frac{S^*}{S} - 1 - \ln\frac{S^*}{S} + \frac{S}{S^*} - 1 - \ln\frac{S}{S^*}\right] \\
&\quad - \beta S^* I^*\left[\frac{S^*}{S} - 1 - \ln\frac{S^*}{S} + \frac{SIE^*}{S^*I^*E} - 1 - \ln\frac{SIE^*}{S^*I^*E} + \frac{EI^*}{E^*I} - 1 - \ln\frac{EI^*}{E^*I}\right].
\end{aligned}$$

Rewriting $\dot{V}$ in terms of function f defined in (3.27) yields

$$\frac{dV}{dt} = -\mu S^*\left[f\left(\frac{S^*}{S}\right) + f\left(\frac{S}{S^*}\right)\right] - \beta S^* I^*\left[f\left(\frac{S^*}{S}\right) + f\left(\frac{SIE^*}{S^*I^*E}\right) + f\left(\frac{EI^*}{E^*I}\right)\right].$$

$\dot{V}(S,E,I) < 0$ holds except at $(S,E,I) = (S^*,E^*,I^*)$. The set $\mathcal{I} = \left\{(S,E,I) \in \mathbb{R}^3_{>0}; \dot{V}(S,E,I) = 0\right\}$ contains only (S^*,E^*,I^*). Since the endemic equilibrium is locally asymptotically stable and $\mathcal{I}$ contains only the endemic equilibrium, by LaSalle's invariance principle we conclude that the endemic equilibrium attracts all the solutions and is globally asymptotically stable. Note that $\mathcal{R}_0 > 1$ guarantees the positiveness of the equilibrium. □

Stability analysis discussed above indicates that when $\mathcal{R}_0 < 1$ the disease dies out, and the epidemic does not occur; yet, when $\mathcal{R}_0 > 1$ the epidemic does occur, and the disease remains in the population. As a result, the $\mathcal{R}_0 = 1$ determines whether the disease is eradicated or persists in the population.

3.6.1 Epidemiological Interpretation of $\mathcal{R}_0$

In epidemiology, the basic reproduction number denoted by $\mathcal{R}_0$ is a dimensionless, important quantity that is defined as follows:

Definition 3.3. *The basic reproduction number is the number of secondary cases that one infectious individual produces in a completely susceptible population throughout its infection period [13].*

Based on the definition above, the basic reproduction number for the SEIR model is

$$\begin{aligned}\mathcal{R}_0 &= \text{transmission rate} \times \text{initial susceptible population in the absence of disease} \\ &\quad \times \text{probability of newly infected person surviving the latent period and death} \\ &\quad \times \text{mean period an individual remains alive and infectious} \\ &= \beta \times \frac{A}{\mu} \times \frac{\sigma}{\mu+\sigma} \times \frac{1}{\mu+\gamma}\end{aligned}$$

Therefore, the basic reproduction for the SEIR model is

$$\mathcal{R}_0 = \frac{\beta A \sigma}{\mu(\mu+\sigma)(\mu+\gamma)}. \tag{3.31}$$

3.7 Numerical Simulations

We provide simulations to support the analytical result. The parameter values are:

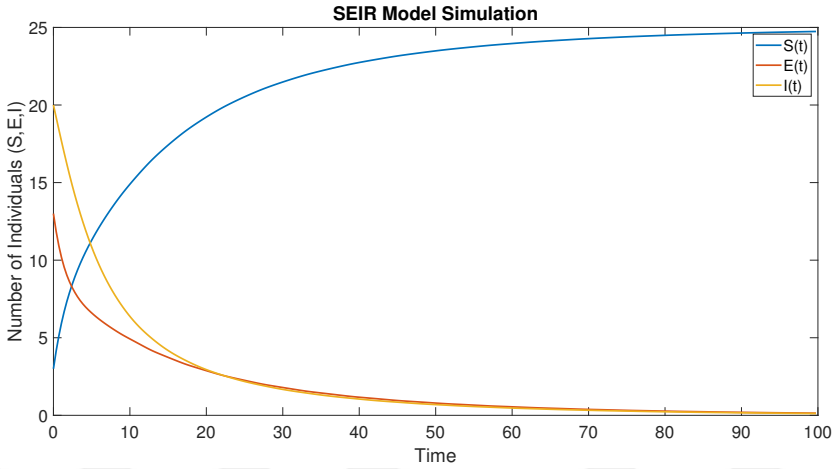
$$A = 5, \quad \beta = 0.015, \quad \mu = 0.2, \quad \gamma = 0.007, \quad S_0 = 3, \quad E_0 = 13, \quad I_0 = 20. \tag{3.32}$$

Note that solving for σ using the stability threshold, $\mathcal{R}_0 = 1$, gives

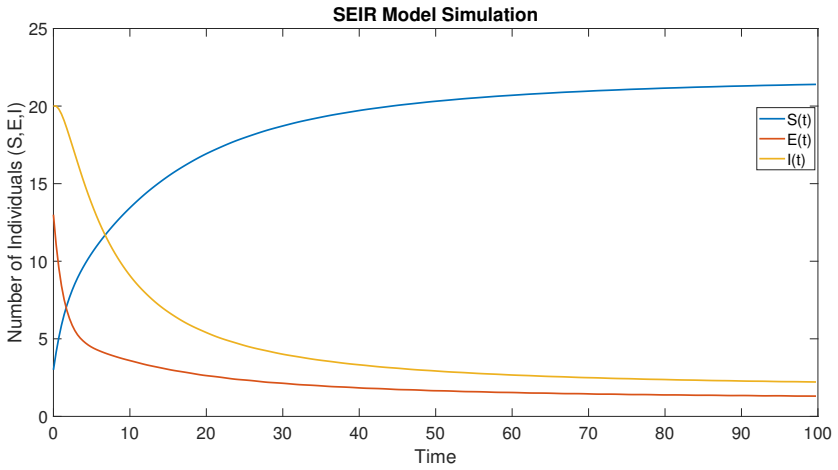
$$\sigma = \frac{\mu^2(\mu+\gamma)}{A\beta - \mu(\mu+\gamma)}.$$

We compute the value of σ using the parameter values given in (3.32), and obtain $\sigma = 0.2464$. This value is significant since it is the critical value for σ such that

$\mathcal{R}_0 = 1$ and any deviation from $\sigma = 0.2464$ gives the value of $\mathcal{R}_0$ either less or greater than one. To distinguish it from other values of σ, we denote it by $\sigma_0 = 0.2464$. Fig. 3.3a and Fig. 3.3b show the stability of the disease-free equilibrium and the endemic equilibrium for the threshold value of σ_0, respectively.



(a) Stable disease-free equilibrium $P_1 = (25, 0, 0)$ for $\sigma = 0.1464$ and $\mathcal{R}_0 = 0.7656$.



(b) Stable endemic equilibrium $P_2 = (21.76, 1.18, 1.97)$ for $\sigma = 0.3464$ and $\mathcal{R}_0 = 1.1485$.

Fig. 3.3: Stability of the disease-free and the endemic equilibrium for the SEIR model.

As value of σ increases from $\sigma_0 = 0.2464$, the endemic equilibrium becomes stable, and as its value decreases from $\sigma_0 = 0.2464$, the disease-free equilibrium becomes stable, see Fig. 3.4.

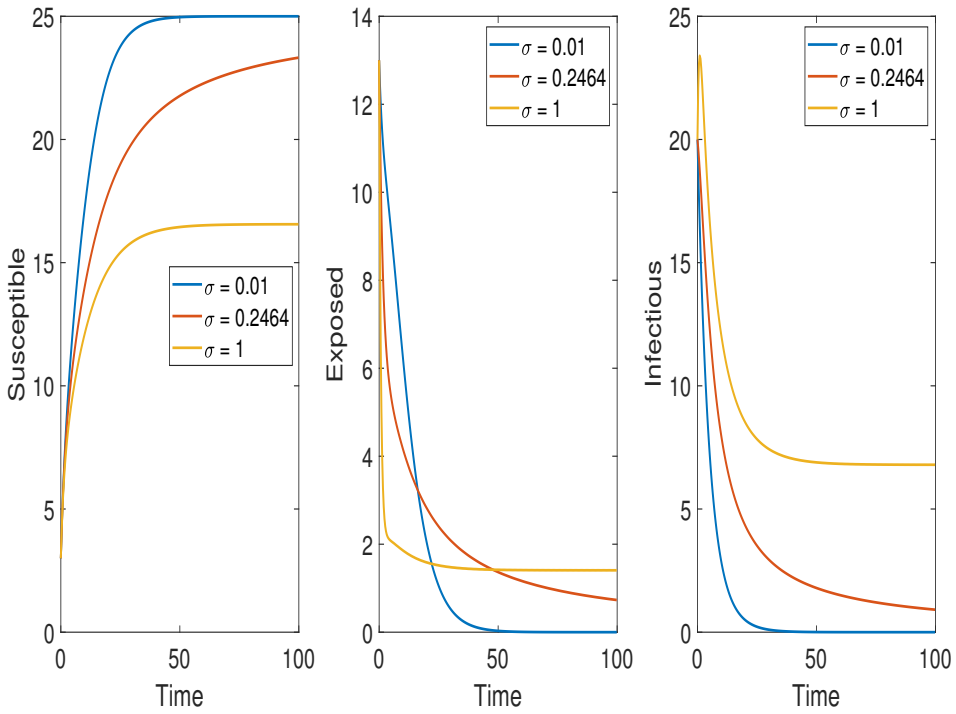


Fig. 3.4: Stability of the equilibria for different values of σ varied from $\sigma_0 = 0.2464$.

For parameter values given in (3.32) simulations show that solutions approach the disease-free equilibrium if the average time spent in the latent phase is greater than $1/\sigma_0$, i.e., $(\sigma < \sigma_0)$, whereas, for those with a latent period less than $1/\sigma_0$, i.e., $(\sigma > \sigma_0)$ solutions converge to the endemic equilibrium. The critical characteristic of an exponentially distributed residence time is that a large proportion of individuals have a short residence time and thus exit the exposed compartment quickly, while a smaller proportion exits after a long time [1].

Chapter 4

The SIR Epidemiological Model with Delay

A single constant time delay can be used to introduce the latent period. The SIR model with delay allows disease progression from latent to infectious to occur after a constant duration (delay) rather than following an exponential distribution, as was the case in the SEIR model. Unlike in the SEIR model, the initial state at a particular time does not solely determine a time-dependent solution of the SIR model with delay. Indeed, a description of the solution on an interval of length equal to the time delay is required. The model's dynamic behavior at time t is determined by the variables evaluated at time t and $t-\tau$, where τ is a positive constant number. In the case of the SEIR model, current information allows us to forecast the future of states at any time; however, in the SIR model, with delay, the past affects the present and future. In such a case, we must establish an infinite-dimensional set of initial conditions, referred to as initial functions, defined on a finite interval of time rather than a single point in time. As a result, the solution space for the SIR model with delay is the set of continuous functions mapping a finite interval to Euclidean space with the topology of uniform convergence. This space is the Banach space of continuous functions denoted by $C = \mathcal{C}([-\tau, 0], \mathbb{R}^n)$ [15]. The following theorem guarantees the existence and uniqueness of solutions for a differential equation with delay.

Theorem 4.1. *Consider the following initial value problem*

$$\frac{dx}{dt} = f(t, x(t), x(t-\tau)) \qquad t \geq s \tag{4.1}$$

$$x(t) = \phi(t) \qquad s - \tau \leq t \leq s. \tag{4.2}$$

where $s \in \mathbb{R}$ and $\tau > 0$. Let f be locally Lipschitz with respect to $x(t)$ and $x(t-\tau)$, and $\phi(t) : [s-\tau, s] \to \mathbb{R}$ be continuous, then there exists some $\alpha > s$ such that the initial value problem has a unique solution on $[s-\tau, \alpha]$.

Proof. We refer to [16] for a proof. □

Remark 5. *It is important to note that the value of α is not mentioned in the theorem. We continue solving the equation on succeeding intervals of length τ as long as the solution does not blow up (become discontinuous) as $t \to \alpha$. If a solution exists for each subsequent interval, we expand the solution to a global solution [16].*

4.1 Formulation of the SIR Model with Delay

The SIR model with delay is based on the following assumptions:

- Population is homogeneously mixed and is divided into three compartments S, I, and R. We comply with the definitions of susceptible, infectious, and recovered individuals discussed in the SIR model in chapter 2.
- The latent duration is a fixed value τ and $\beta S(t-\tau)I(t-\tau)$ is the number of infectious individuals that contact susceptible individuals at time $t-\tau$ and contribute to the transmission of the disease at the transmission rate, β.
- Infectious period has an exponential distribution with the rate parameter γ, i.e., the amount of time an individual spends in the infectious compartment is $\frac{1}{\gamma}$.

- Disease is not fatal, recovery is permanent, and disease transmits through direct contact from person to person.
- The model incorporates vital dynamics. It involves fixed births as the source of new susceptibles and exponential death with the rate parameter μ.
- The death-adjusted removal rate is $\mu+\gamma$. In other words, the average time spent in the infectious compartment given that individual is alive up to the time of removal from the infectious compartment is $\frac{1}{\mu+\gamma}$.
- q is defined as the survival probability of individuals during the constant latent duration τ.

The dynamics of state variables S, I, and R in the delayed SIR model are based on the above-mentioned assumptions. All newborns are considered susceptible in the population, and each compartment involves the removal of individuals at a rate μ proportional to the compartment size. A constant delay representing latent duration is incorporated into the variable $I(t)$, which means that a susceptible individual who comes into contact with an infectious person contributes to disease transmission after a constant τ unit of time. The survival term q illustrates that only those who have survived the latent duration τ can move to the infectious compartment; that is why we multiply it by the incidence term, $\beta S(t-\tau)I(t-\tau)$. The dynamics of the infectious compartment at time t includes those susceptible individuals who had direct interaction with an infectious at time $t-\tau$ at the rate of β and became exposed for the next τ unit of time and remained alive by the time they became infectious with the probability of q and joined the infectious compartment, as well as those infectious individuals who leave the compartment through natural death and disease recovery at the rates of μ and γ, respectively. A schematic illustration of the SIR model with delay is given in Fig. 4.1.

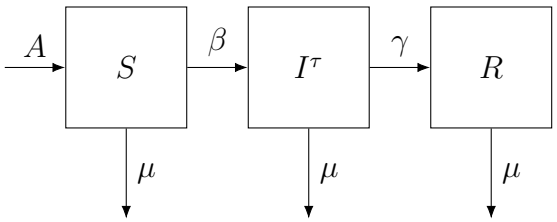


Fig. 4.1: Schematic illustration of the SIR model with delay.

$$\frac{dS}{dt} = A - \beta S(t)I(t) - \mu S(t), \tag{4.3a}$$

$$\frac{dI}{dt} = \beta S(t-\tau)I(t-\tau)q - (\mu+\gamma)I(t), \tag{4.3b}$$

$$\frac{dR}{dt} = \gamma I(t) - \mu R(t). \tag{4.3c}$$

We define a term q to be the probability of survival of individuals while being in the latent duration; this quantity is assumed as a fixed number. Given a solution $x(t) : D \subset \mathbb{R} \to \mathbb{R}^3$ to the system (4.3), we define $x_t \in \mathcal{C}$ as

$$x_t : [-\tau, 0] \to \mathbb{R}^3,$$
$$x_t := x(t+\theta) \qquad t \geq 0 \quad \text{and} \quad \theta \in [-\tau, 0].$$

Where $x(t) = [S(t), I(t), R(t)]^\top$, $x_t = [S_t, I_t, R_t]^\top$, and $\mathcal{C} = C([-\tau, 0], \mathbb{R}^3)$ is the Banach space of continuous functions mapping an interval $[-\tau, 0]$ into $\mathbb{R}^3$ with the norm $\|x\| = \max_{-\tau \leq \theta \leq 0} |x(\theta)|$. We define $f(t, x_t) = F(t, x(t), x(t-\tau))$, where F is the right hand side of system (4.3) and is continuous with respect to t, $x(t)$, and $x(t-\tau)$. The initial condition of the system (4.3) is defined as $x_0 = \Phi$ where $\Phi = (S_0(\theta), I_0(\theta), R_0(\theta))$ is given by

$$S_0(\theta) \geq 0, \quad I_0(\theta) \geq 0, \quad R_0(\theta) = R(0) \geq 0 \quad \text{where} \quad \theta \in [-\tau, 0]. \tag{4.4}$$

Before proceeding with the model analysis, we first justify the introduction of q as follows: as stated earlier in the chapter, during the latent period τ, an individual may be removed from the population; as a result, only those who have survived the latent period contribute to disease transmission. We assume two possibilities for q:

- Case I: First, we assume that all individuals will survive the latent duration τ, which means that the survival probability on $[0, \tau]$ is one. Thus, it is reasonable to assume that $q = 1$.

- Case II: Second, we assume an exponential probability distribution $e^{-\mu t}$, which is the probability of a person becoming infected at $t = 0$ and remaining infected at any time $t > 0$. To further illustrate this, let the number of infected individuals at time t be $P(t)$, and suppose that those individuals in the latent duration $0 \leq t \leq \tau$ can be removed at the constant rate μ. Constructing the rate of change in the number of infected individuals within $0 \leq t \leq \tau$ we get

$$\frac{dP}{dt} = -\mu P(t).$$

Let $P(0) = P_0$, we have $P(t) = P_0 e^{-\mu t}$, then

$$\frac{P(t)}{P_0} = e^{-\mu t}.$$

This expression indicates the fraction of infected population that remains infected. In fact, it is the probability of becoming infected for $t = 0$ and remaining infected at time $t > 0$ [1]. Since the latent duration is τ, we are interested in the probability of individuals becoming infected for time $t = 0$ and remain infected over the course of $\tau > 0$ so that we can say the individual survived the latent duration. Therefore, we have $q = e^{-\mu\tau}$.

4.2 Analysis of the SIR Model with Delay

Theorem 4.2. *The solution to the system (4.3) equipped with the initial conditions (4.4) exists and is unique for all $t \geq 0$. Moreover, if (4.4) holds, then $S(t) \geq 0$, $I(t) \geq 0$, and $R(t) \geq 0$ for all $t \geq 0$.*

Proof. Existence and uniqueness of the solutions follow from treating the equation by method of steps in each successive interval of length τ. All required is the integrability of the $F(t, x(t), \Phi(t - \tau))$ in each successive integral of length τ,

where $\Phi(t-\tau)$ is a given function, i.e., the solution obtained in the previous step that serves as the initial function for the current step and $F = [S', I', R']^\top$. Solving (4.3a) for $S(t)$ yields

$$S(t) = S(0)\exp\Big\{-\int_0^t (\beta I(u)+\mu)du\Big\} + A\exp\Big\{-\int_0^t (\beta I(u)+\mu)du\Big\}\int_0^t \exp\Big\{\int_0^s (\beta I(u)+\mu)du\Big\}ds.$$

Thus, for $S_0(\theta) \geq 0$ one obtains $S(t) \geq 0$ for all $t \geq 0$. Solving (4.3b) for $I(t)$ gives

$$I(t) = I(0)e^{-(\mu+\gamma)t} + e^{-(\mu+\gamma)t}\beta q\int_0^t e^{(\mu+\gamma)u} I(u-\tau)S(u-\tau)du. \tag{4.5}$$

Suppose $I_0(\theta) > 0$ for $-\tau \leq \theta \leq 0$, we will show that $I(t) > 0$ for all $t \geq 0$. Evaluating (4.5) at each successive interval of length τ the positivity of $I(t)$ follows. Note that $q > 0$ in both cases. If $I_0(\theta) = 0$ then the solution of the system is given by

$$S(t) = S(0)e^{-\mu t} + \frac{A}{\mu} - \frac{A}{\mu}e^{-\mu t}, \quad I(t) = 0.$$

Which satisfies the system of equations and from uniqueness it is then a solution of the system starting from the initial condition $I_0(\theta) = 0$ which is nonnegative for $S_0(\theta) = 0$. Also, $R(t)$ is

$$R(t) = R(0)e^{-\mu t} + \gamma e^{-\mu t}\int_0^t I(u)du.$$

for $R(0) \geq 0$ solution is nonnegative for all time $t \geq 0$. Based on the argument above starting from nonnegative initial condition solutions stay nonnegative. □

The equations (4.3a) and (4.3b) are independent of $R(t)$. Therefore, without loss of generality, equation (4.3c) can be dropped. Hence, the reduced system is

$$\begin{aligned} \frac{dS}{dt} &= A - \beta S(t)I(t) - \mu S(t), \\ \frac{dI}{dt} &= \beta S(t-\tau)I(t-\tau)q - (\mu+\gamma)I(t). \end{aligned} \tag{4.6}$$

The initial condition is

$$S(\theta) \geq 0, \quad I(\theta) \geq 0, \text{where} \quad \theta \in [-\tau, 0]. \tag{4.7}$$

And the feasible set for the solutions of the system is

$$\Gamma = \Big\{(S, I) \in \mathbb{R}^2_{\geq 0} : S(t) \geq 0, \quad I(t) \geq 0 \Big\}.$$

For the rest of the analysis, we restrict our attention to the system (4.6).

4.3 Equilibria of the SIR Model with Delay

An equilibrium of an equation with delay is a constant solution that does not change with time. Let (S^*, I^*) be an equilibrium solution for the system (4.6). Then, the equilibrium equation is

$$\begin{aligned} A - \beta S^* I^* - \mu S^* &= 0, \\ \beta S^* I^* q - (\mu + \gamma) I^* &= 0. \end{aligned} \tag{4.8}$$

- **Disease-free Equilibrium**

  If $I^* = 0$, then the disease-free equilibrium is

  $$P_1 = \Big(\frac{A}{\mu}, 0\Big). \tag{4.9}$$

- **Endemic Equilibrium**

  If $I^* > 0$ then the equilibrium is

  $$P_2 = \Big(\frac{\mu + \gamma}{\beta q}, \frac{A\beta q - \mu(\mu + \gamma)}{\beta(\mu + \gamma)}\Big). \tag{4.10}$$

  In order for P_2 to have positive components the following condition must hold

  $$A\beta q - \mu(\mu + \gamma) > 0. \tag{4.11}$$

  Rearranging (4.11) gives

  $$\frac{A\beta q}{\mu(\mu + \gamma)} > 1.$$

  Let

  $$\mathcal{R}_0 := \frac{A\beta q}{\mu(\mu + \gamma)}.$$

If $\mathcal{R}_0 > 1$, then P_2 is called the endemic equilibrium of the system. Therefore, the existence of the endemic equilibrium depends on $\mathcal{R}_0$. Thus, P_2 can be written as

$$P_2 = \Big(\frac{A}{\mu\mathcal{R}_0}, \frac{\mu}{\beta}(\mathcal{R}_0 - 1)\Big). \tag{4.12}$$

Remark 6. *If $\mathcal{R}_0 \leq 1$ the system (4.6) has only the disease-free equilibrium. If $\mathcal{R}_0 > 1$, the system has two equilibria; the disease-free and the endemic equilibrium.*

Remark 7. *It should be noted that both equilibria P_1 and P_2 are valid independently of the value of $\mathcal{R}_0$. The condition on $\mathcal{R}_0$ is solely necessary for epidemiological significance of the equilibria.*

4.4 Local Stability of Equilibria

Consider the following system of DDE

$$S'(t) = F(S, I) = A - \beta S(t)I(t) - \mu S(t), \tag{4.13a}$$

$$I'(t) = G(S(t-\tau), I(t-\tau), I(t)) = \beta S(t-\tau)I(t-\tau)q - (\mu + \gamma)I(t). \tag{4.13b}$$

Let $X^* = (S^*, I^*)$ be any equilibrium; we perturb solutions $S(t)$ and $I(t)$ starting from an initial condition close to X^* by functions $X(t)$ and $Y(t)$ as follows

$$X(t) = S(t) - S^*,$$
$$Y(t) = I(t) - I^*.$$

Substituting the perturbed solutions into (4.13) and expanding in Taylor series at X^* we obtain

$$\begin{aligned}\frac{dX}{dt} &= F\Big(X(t) + S^*, Y(t) + I^*\Big) \\ &= F(S^*, I^*) + \frac{\partial F}{\partial S}(S^*, I^*)X(t) + \frac{\partial F}{\partial I}(S^*, I^*)Y(t) + \cdots,\end{aligned}$$

$$\begin{aligned}\frac{dY}{dt} &= G\Big(X(t-\tau)+S^*, Y(t-\tau)+I^*, Y(t)+I^*\Big)\\ &= G(S^*,I^*)+\frac{\partial G}{\partial S(t-\tau)}(S^*,I^*)X(t-\tau)+\frac{\partial G}{\partial I(t-\tau)}(S^*,I^*)Y(t-\tau)\\ &\qquad\qquad +\frac{\partial G}{\partial I(t)}(S^*,I^*)Y(t)+\cdots\end{aligned}$$

For small perturbation we ignore the higher order terms X^2, XY, and Y^2 in Taylor expansion; thus, the linearized system is

$$\begin{aligned}\frac{dX}{dt} &= \Big(A-\beta S^*I^*-\mu S^*\Big)-(\beta I^*+\mu)X(t)-\beta S^*Y(t),\\ \frac{dY}{dt} &= \Big(\beta S^*I^*q-(\mu+\gamma)I^*\Big)+\beta I^*qX(t-\tau)+\beta S^*qY(t-\tau)-(\mu+\gamma)Y(t).\end{aligned} \tag{4.14}$$

Substituting (4.8) into the linearized system (4.14), and rewriting the linearized system in matrix form we obtain

$$\begin{bmatrix}X'\\ Y'\end{bmatrix}=\underbrace{\begin{bmatrix}-\mu-\beta I^* & -\beta S^*\\ 0 & -(\mu+\gamma)\end{bmatrix}}_{A_0}\begin{bmatrix}X(t)\\ Y(t)\end{bmatrix}+\underbrace{\begin{bmatrix}0 & 0\\ \beta I^*q & \beta S^*q\end{bmatrix}}_{A_1}\begin{bmatrix}X(t-\tau)\\ Y(t-\tau)\end{bmatrix}. \tag{4.15}$$

Writing (4.15) in compact form gives

$$x'(t)=A_0x(t)+A_1x(t-\tau). \tag{4.16}$$

The goal is to find a vector $x(t)$ that satisfies (4.16). Note that matrices A_0 and A_1 are constant; based on our experience of solving linear ODE, we speculate a solution of the form $x(t)=\vec{u}e^{\lambda t}$. Substituting $x(t)$ in (4.16) we obtain

$$\vec{u}\lambda e^{\lambda t}=A_0\vec{u}e^{\lambda t}+A_1\vec{u}e^{\lambda(t-\tau)}.$$

Factoring out $e^{\lambda t}$ and $\vec{u}$ gives

$$(A_0+A_1e^{-\lambda\tau}-\lambda I)\vec{u}e^{\lambda t}=0,$$

where I is the identity matrix. The equation above is a homogeneous linear system of equations; thus the system has nontrivial solution if and only if the matrix $A_0+A_1e^{-\lambda\tau}-\lambda I$ is singular. That is

$$\det\big(A_0+A_1e^{-\lambda\tau}-\lambda I\big)=0. \tag{4.17}$$

Equation (4.17) is the characteristic equation for the linearized DDE system (4.15). In the case of linear ODEs, the characteristic equation is a polynomial. According to the Fundamental Theorem of Algebra, the number of eigenvalues is limited to the degree of the polynomial. In linear DDEs, on the other hand, the characteristic equation is a transcendental equation with an infinite number of roots. The characteristic equation (4.17) at any equilibrium (S^*, I^*) is

$$\det \begin{bmatrix} -\mu - \beta I^* - \lambda & -\beta S^* \\ \beta I^* q e^{-\lambda\tau} & -(\mu+\gamma) + \beta S^* q e^{-\lambda\tau} - \lambda \end{bmatrix} = 0. \tag{4.18}$$

The characteristic equation for the disease-free equilibrium (4.9) is

$$\lambda^2 + \lambda(2\mu+\gamma) + \mu(\mu+\gamma) - q e^{-\lambda\tau}\Big(\frac{\beta A}{\mu}\lambda + \beta A\Big) = 0. \tag{4.19}$$

The characteristic equation for the endemic equilibrium (4.12) is

$$\lambda^2 + \lambda(\mu\mathcal{R}_0 + \mu + \gamma) + \mu\mathcal{R}_0(\mu+\gamma) - q e^{-\lambda\tau}\Big(\frac{\beta A}{\mu\mathcal{R}_0}\lambda + \frac{\beta A}{\mathcal{R}_0}\Big) = 0. \tag{4.20}$$

Theorem 4.3. *If $q = 1$ and $\mathcal{R}_0 < 1$, then the disease-free equilibrium of the system (4.6) is locally asymptotically stable for all $\tau \geq 0$.*

Proof. When $\tau = 0$ and $q = 1$ the characteristic equation (4.19) is

$$\lambda^2 + \lambda(\mu+\gamma)\Big[\frac{\mu}{\mu+\gamma} + 1 - \frac{\beta A}{\mu(\mu+\gamma)}\Big] + \mu(\mu+\gamma)\Big[1 - \frac{\beta A}{\mu(\mu+\gamma)}\Big] = 0. \tag{4.21}$$

Substituting $\mathcal{R}_0 = \dfrac{\beta A}{\mu(\mu+\gamma)}$ in equation (4.21) we get

$$\lambda^2 + \lambda(\mu+\gamma)\Big[\frac{\mu}{\mu+\gamma} + 1 - \mathcal{R}_0\Big] + \mu(\mu+\gamma)(1-\mathcal{R}_0) = 0. \tag{4.22}$$

A necessary and sufficient condition for asymptotic stability of the disease-free equilibrium is that all roots of equation (4.22) have negative real parts. Let λ_1 and λ_2 be the roots of (4.22); a necessary and sufficient conditions for equation (4.22) to have roots with negative real parts are $\lambda_1 \times \lambda_2 > 0$ and $\lambda_1 + \lambda_2 < 0$. The sum and products of roots are:

$$\lambda_1 \times \lambda_2 = \mu(\mu+\gamma)(1-\mathcal{R}_0) > 0, \tag{4.23}$$

and

$$\lambda_1 + \lambda_2 = (\mu + \gamma)\Big[\mathcal{R}_0 - \frac{\mu}{\mu + \gamma} - 1\Big] < 0. \tag{4.24}$$

By assumption $\mathcal{R}_0 < 1$; thus, inequalities (4.23) and (4.24) hold. Therefore, equation (4.22) has two roots with negative real parts, and the disease-free equilibrium is locally asymptotically stable for $\tau = 0$. When $\tau > 0$ the characteristic equation (4.19) is

$$\lambda^2 + \lambda(2\mu + \gamma) + \mu(\mu + \gamma) - e^{-\lambda\tau}\Big(\frac{\beta A}{\mu}\lambda + \beta A\Big) = 0. \tag{4.25}$$

We will prove that when $\mathcal{R}_0 < 1$ all roots of equation (4.25) are in the left half of the complex plane. Suppose, on the contrary, a purely imaginary root $\lambda = i\omega$, where $\omega \in \mathbb{R}$ satisfies equation (4.25). Substituting $\lambda = i\omega$ in (4.25) we obtain

$$-\omega^2 + i\omega[\mu + (\mu + \gamma)] - i\omega\frac{\beta A}{\mu}(\cos\omega\tau - i\sin\omega\tau) - \beta A(\cos\omega\tau - i\sin\omega\tau).$$

Separating the real and imaginary parts we get

$$-\omega^2 + \mu(\mu + \gamma) - \frac{\beta A\omega}{\mu}\sin\omega\tau - \beta A\cos\omega\tau = 0 \tag{4.26}$$

$$\omega[\mu + (\mu + \gamma)] - \frac{\beta A\omega}{\mu}\cos\omega\tau + \beta A\sin\omega\tau = 0 \tag{4.27}$$

Adding and squaring both sides of (4.26) and (4.27) gives

$$\omega^4 + \omega^2\Big[(\mu + \gamma)^2 + \mu^2 - (\frac{\beta A}{\mu})^2\Big] + \mu^2(\mu + \gamma)^2\Big[1 - \Big(\frac{\beta A}{\mu(\mu + \gamma)}\Big)^2\Big] = 0. \tag{4.28}$$

Substituting $\mathcal{R}_0 = \dfrac{A\beta}{\mu(\mu + \gamma)}$ in (4.28) we obtain

$$\omega^4 + \omega^2(\mu + \gamma)^2\Big[1 + \frac{\mu^2}{(\mu + \gamma)^2} - \mathcal{R}_0^2\Big] + \mu^2(\mu + \gamma)^2(1 - \mathcal{R}_0^2) = 0 \tag{4.29}$$

Let $T = \omega^2$. Equation (4.29) is then a quadratic equation in T

$$T^2 + T(\mu + \gamma)^2\Big[1 + \frac{\mu^2}{(\mu + \gamma)^2} - \mathcal{R}_0^2\Big] + \mu^2(\mu + \gamma)^2(1 - \mathcal{R}_0^2) = 0 \tag{4.30}$$

Let T_1 and T_2 be roots of equation (4.30). Since $\mathcal{R}_0 < 1$ we have

$$T_1 \times T_2 = \mu^2(\mu + \gamma)^2(1 - \mathcal{R}_0)^2 > 0,$$

and

$$T_2 + T_1 = (\mu+\gamma)^2\Big[\mathcal{R}_0^2 - 1 - \frac{\mu^2}{(\mu+\gamma)^2}\Big] < 0.$$

Hence, $T_1 < 0$ and $T_2 < 0$. We assumed that $T = \omega^2$ where $\omega \in \mathbb{R}$ which is invalid for negative T_1 and T_2; thus, ω does not exist and equation (4.25) has no purely imaginary roots. From local asymptotic stability of the disease-free equilibrium for $\tau = 0$ and the nonexistence of a purely imaginary root for $\tau > 0$, we conclude that by increasing values of τ roots are in the left half of the complex, and have negative real parts. Therefore, the disease-free equilibrium is locally asymptotically stable for any $\tau > 0$. □

Theorem 4.4. *If $q = e^{-\mu\tau}$ and $\mathcal{R}_0 < 1$, then the disease-free equilibrium of the system (4.6) is locally asymptotically stable.*

Proof. When $\tau = 0$ evaluating equation (4.18) at the disease-free equilibrium gives two roots: $\lambda_1 = -\mu$ and

$$\begin{aligned}\lambda_2 &= -(\mu+\gamma) + \frac{A\beta}{\mu} \\ &= (\mu+\gamma)\Big[\frac{A\beta}{\mu(\mu+\gamma)} - 1\Big] \\ &= (\mu+\gamma)(\mathcal{R}_0 - 1) \\ &< 0.\end{aligned} \tag{4.31}$$

Characteristic roots λ_1 and λ_2 have negative real parts. Therefore, the disease-free equilibrium is locally asymptotically stable for $\tau = 0$. When $\tau > 0$ equation (4.18) evaluated at the disease-free equilibrium and $q = e^{-\mu\tau}$ gives

$$(\lambda+\mu)\Big(\lambda + (\mu+\gamma) - \frac{A\beta}{\mu}e^{-\tau(\mu+\lambda)}\Big) = 0.$$

One of the roots is $\lambda_1 = -\mu$. Other roots are obtained by

$$\lambda + (\mu+\gamma) - \frac{A\beta}{\mu}e^{-\tau(\mu+\lambda)} = 0. \tag{4.32}$$

we will prove that all roots of equation (4.32) are in the left half of the complex plane. Suppose, on the contrary, that $\lambda = i\omega$, where $\omega \in \mathbb{R}$ satisfies equation

(4.32). Substituting it in the equation gives

$$\begin{aligned} i\omega &= -(\mu+\gamma) + \frac{A\beta}{\mu} e^{-\mu\tau}\Big[\cos\omega\tau - i\sin\omega\tau\Big] \\ &= -(\mu+\gamma) + (\mu+\gamma)\mathcal{R}_0\Big[\cos\omega\tau - i\sin\omega\tau\Big]. \end{aligned} \tag{4.33}$$

Separating the real and imaginary parts of (4.33) gives

$$(\mu+\gamma) = (\mu+\gamma)\mathcal{R}_0\cos\omega\tau,$$

$$\omega = -(\mu+\gamma)\mathcal{R}_0\sin\omega\tau.$$

Squaring and adding the real and imaginary parts we obtain

$$\omega^2 + (\mu+\gamma)^2(1-\mathcal{R}_0^2) = 0.$$

For $\mathcal{R}_0 < 1$, we have $\omega^2 < 0$, which is a contradiction for $\omega \in \mathbb{R}$; thus, ω does not exist. From the nonexistence of ω and the asymptotic stability of the disease-free equilibrium for $\tau = 0$, we conclude that by increasing the value of τ characteristic roots are in the left half of the complex plane. Therefore, the disease-free equilibrium is locally asymptotically stable. □

Theorem 4.5. *If $q = 1$, and $\mathcal{R}_0 > 1$, then the disease-free equilibrium is unstable, and the endemic equilibrium is locally asymptotically stable.*

Proof. **Instability of the disease-free equilibrium:** The disease-free equilibrium is unstable if and only if the characteristic equation has at least one root with positive real parts. When $\tau = 0$ and $\mathcal{R}_0 > 1$ from equation (4.23) we have $\lambda_1 \times \lambda_2 < 0$ which implies that the characteristic equation for the disease-free equilibrium (4.22) has a root with positive real parts; hence, the disease-free equilibrium is unstable. When $\tau > 0$ equation (4.18) at the disease-free equilibrium gives

$$(\lambda+\mu)\Big((\mu+\gamma) + \lambda - \frac{A\beta}{\mu}e^{-\lambda\tau}\Big) = 0 \tag{4.34}$$

One of the roots of (4.34) is $\lambda_1 = -\mu$. We should prove that the equation

$$(\mu+\gamma) + \lambda - \frac{A\beta}{\mu}e^{-\lambda\tau} = 0$$

has at least one root in the right half of the complex plane. To this end, we define

$$\begin{aligned} f(\lambda) &= \lambda + (\mu+\gamma) - \frac{A\beta}{\mu} e^{-\lambda\tau} \\ &= \lambda + (\mu+\gamma)(1 - \mathcal{R}_0 e^{-\lambda\tau}) \end{aligned}$$

We suppose $\lambda \in [0, \infty)$, by assumption $\mathcal{R}_0 > 1$; thus, for $\lambda = 0$ we have $f(0) < 0$. As $\lambda \to \infty$, we have $e^{-\lambda\tau} \to 0$, and $f(\lambda) \to \infty$. Hence, by continuity of the characteristic equation $f(\lambda)$, we conclude that a positive root exists, and the disease-free equilibrium is unstable.

Stability of the endemic equilibrium: For $\tau = 0$ and $q = 1$ the characteristic equation (4.20) is

$$\lambda^2 + (\mu+\gamma)\mu\mathcal{R}_0\lambda + (\mu+\gamma)(\mathcal{R}_0 - 1) = 0. \tag{4.35}$$

Let λ_1 and λ_2 be the roots of (4.35); for $\mathcal{R}_0 > 1$ we have $\lambda_1 \times \lambda_2 > 0$ and $\lambda_1 + \lambda_2 < 0$. Therefore, λ_1 and λ_2 are negative and the endemic equilibrium is locally asymptotically stable for $\tau = 0$. When $\tau > 0$ the characteristic equation (4.20) is

$$\lambda^2 + \lambda(\mu\mathcal{R}_0 + \mu + \gamma) + \mu\mathcal{R}_0(\mu+\gamma) - \lambda e^{-\lambda\tau}\frac{\beta A}{\mu\mathcal{R}_0} - e^{-\lambda\tau}\frac{\beta A}{\mathcal{R}_0} = 0. \tag{4.36}$$

Suppose $\lambda = i\omega$ is a root of (4.36), where $\omega \in \mathbb{R}$. Substituting it in the equation gives

$$-\omega^2 + \Big[\mu\mathcal{R}_0 + \mu + \gamma\Big] i\omega + \mu\mathcal{R}_0(\mu+\gamma) = (\cos\omega\tau - i\sin\omega\tau)(\mu+\gamma)(i\omega+\mu).$$

Separating the real and imaginary parts gives

$$-\omega^2 + \mu\mathcal{R}_0(\mu+\gamma) = \mu(\mu+\gamma)\cos\omega\tau + (\mu+\gamma)\omega\sin\omega\tau.$$

$$\omega(\mu\mathcal{R}_0 + \mu + \gamma) = (\mu+\gamma)\omega\cos\omega\tau - \mu(\mu+\gamma)\sin\omega\tau.$$

Let $p = \mu + \gamma + \mu\mathcal{R}_0$ and $q = \mu\mathcal{R}_0(\mu+\gamma)$; squaring and adding both sides yields

$$\Big[-\omega^2 + q\Big]^2 + \omega^2 p^2 = \mu^2(\mu+\gamma)^2 + (\mu+\gamma)^2\omega^2.$$

Expanding it yields

$$\omega^4 - 2\omega^2 q + q^2 + \omega^2 p^2 - \mu^2(\mu+\gamma)^2 - (\mu+\gamma)^2\omega^2 = 0. \tag{4.37}$$

Let's define $\omega^2 = T$; rewriting (4.37) in terms of T gives

$$T^2 + T(p^2 - 2q - (\mu+\gamma)^2) + q^2 - \mu^2(\mu+\gamma)^2 = 0, \tag{4.38}$$

Computing the coefficients yields

$$p^2 - 2q - (\mu+\gamma)^2 = \mu^2\mathcal{R}_0^2 > 0,$$

and

$$q^2 - \mu^2(\mu+\gamma)^2 = \mu^2(\mu+\gamma)^2(\mathcal{R}_0^2 - 1) > 0.$$

Let T_1 and T_2 be roots of the equation (4.38). Then, $T_1 \times T_2 > 0$ and $T_1 + T_2 < 0$; thus, T_1 and T_2 are roots with negative real parts; hence, the roots with negative real parts satisfy $T = \omega^2$, which is invalid for $\omega \in \mathbb{R}$. Therefore, ω does not exist, and roots never cross the imaginary axis. Moreover, we proved that the endemic equilibrium is stable when $\tau = 0$, which implies that the roots of the characteristic equation have negative real parts. Since a purely imaginary root does not exist, and for $\tau = 0$ the endemic equilibrium is asymptotically stable, we conclude that as values of τ increases from $\tau = 0$ roots are located in the left half of the complex plane. Therefore, the endemic equilibrium is locally asymptotically stable for $\tau > 0$. □

Theorem 4.6. *If $q = e^{-\mu\tau}$ and $\mathcal{R}_0 > 1$, then the disease-free equilibrium is unstable, and the endemic equilibrium of the system (4.6) is locally asymptotically stable.*

Proof. **Instability of the disease-free equilibrium:** Evaluating equation (4.18) at the disease-free equilibrium gives two roots: $\lambda_1 = -\mu$ and

$$\begin{aligned} \lambda_2 &= -(\mu+\gamma) + \frac{A\beta}{\mu} \\ &= (\mu+\gamma)(\mathcal{R}_0 - 1) \\ &> 0. \end{aligned} \tag{4.39}$$

There exists a characteristic root with positive real parts. Therefore, the disease-free equilibrium is unstable. When $\tau > 0$ the characteristic equation of the disease-free equilibrium for $q = e^{-\mu\tau}$ is

$$(\lambda+\mu)\Big((\mu+\gamma) + \lambda - \frac{A\beta}{\mu}e^{-\tau(\lambda+\mu)}\Big) = 0. \tag{4.40}$$

Clearly, one of the roots of (4.40) is $\lambda_1 = -\mu$. Other roots is obtained from

$$\begin{aligned} f(\lambda) &= (\mu+\gamma) + \lambda - \frac{A\beta e^{-\mu\tau}}{\mu} e^{-\tau\lambda} \\ &= \lambda + (\mu+\gamma)(1 - \mathcal{R}_0 e^{-\mu\tau}) \end{aligned} \tag{4.41}$$

For nonnegative real roots λ if $\lambda = 0$ and $\mathcal{R}_0 > 1$ we obtain $f(0) < 0$. As $\lambda \to \infty$ we have $e^{-\tau\lambda} \to 0$ and $f(\lambda) \to \infty$. By continuity of $f(\lambda)$, we conclude that a positive root satisfies the characteristic equation given in (4.40), and the disease-free equilibrium is unstable.

Stability of the endemic equilibrium: Substituting $q = e^{-\mu\tau}$ into the characteristic equation given in (4.20) we obtain

$$\lambda^2 + \lambda(\mu\mathcal{R}_0 + \mu + \gamma) + \mu\mathcal{R}_0(\mu+\gamma) - \lambda e^{-\lambda\tau}\frac{\beta A e^{-\mu\tau}}{\mu\mathcal{R}_0} - e^{-\lambda\tau}\frac{\beta A e^{-\mu\tau}}{\mathcal{R}_0} = 0. \tag{4.42}$$

We prove that when $\mathcal{R}_0 > 1$ (4.42) does not have any purely imaginary root. Suppose, on the contrary, that $\lambda = i\omega$ satisfies equation (4.42), where $\omega \in \mathbb{R}$. Substituting it into the equation we obtain

$$-\omega^2 + i\omega(\mu\mathcal{R}_0 + \mu + \gamma) + \mu\mathcal{R}_0(\mu+\gamma) - [\cos\omega\tau - i\sin\omega\tau]\left(i\omega\frac{\beta A e^{-\mu\tau}}{\mu\mathcal{R}_0} + \frac{\beta A e^{-\mu\tau}}{\mathcal{R}_0}\right) = 0. \tag{4.43}$$

Separating the real and imaginary parts of equation (4.43) we obtain

$$-\omega^2 + \mu\mathcal{R}_0(\mu+\gamma) - \frac{\beta A e^{-\mu\tau}}{\mathcal{R}_0}\cos\omega\tau - \frac{\beta A\omega e^{-\mu\tau}}{\mu\mathcal{R}_0}\sin\omega\tau = 0.$$

$$\omega(\mu\mathcal{R}_0 + \mu + \gamma) - \frac{\beta A\omega e^{-\mu\tau}}{\mu\mathcal{R}_0}\cos\omega\tau + \frac{\beta A e^{-\mu\tau}}{\mathcal{R}_0}\sin\omega\tau = 0.$$

Adding and squaring both sides of the real and imaginary parts we get

$$\omega^4 + \omega^2\left[(\mu\mathcal{R}_0)^2 + (\mu+\gamma)^2 - \left(\frac{\beta A e^{-\mu\tau}}{\mu\mathcal{R}_0}\right)^2\right] + \left[(\mu\mathcal{R}_0(\mu+\gamma))^2 - \left(\frac{\beta A e^{-\mu\tau}}{\mathcal{R}_0}\right)^2\right] = 0. \tag{4.44}$$

We know that $\mathcal{R}_0 = \dfrac{A\beta e^{-\mu\tau}}{\mu(\mu+\gamma)}$; thus simplifying (4.44) we get

$$\omega^4 + \omega^2(\mu\mathcal{R}_0)^2 + \mu^2(\mu+\gamma)^2(\mathcal{R}_0 - 1) = 0. \tag{4.45}$$

Let us define $T = \omega^2$; then (4.45) is a quadratic equation in T. Suppose T_1 and T_2 are the roots of equation (4.45). By assumption we have $\mathcal{R}_0 > 1$; thus,

$T_1 \times T_2 = \mu^2(\mu+\gamma)^2(\mathcal{R}_0 - 1) > 0$ and $T_1 + T_2 = -\mu^2\mathcal{R}^2 < 0$. Signs of sum and products of T_1 and T_2 imply that the roots of equation (4.45) have negative real parts. However, we assumed that $T = \omega^2$ where $\omega \in \mathbb{R}$; this, indeed, is a contradiction, and equation (4.42) has no purely imaginary root. The endemic equilibrium is locally asymptotically stable for $\tau = 0$, and no purely imaginary root satisfies the characteristic equation (4.42) for $\tau > 0$; thus, we conclude that the roots of the characteristic equation for $\tau > 0$ are in the left half of the complex plane. Therefore, the endemic equilibrium is locally asymptotically stable for $\tau > 0$. □

4.5 Stability Analysis via Lyapunov Functional

Lyapunov functions, like in the SEIR model, can be used to determine the local stability, asymptotic stability, and global stability of equilibria for the SIR model with delay. However, choosing the proper Lyapunov function for delayed models is more complex than a model without delay. In contrast to the local stability results obtained from the analysis of the characteristic equations, the stability results obtained by this method are global. This section will discuss the Lyapunov functional approach and the LaSalle invariance principle in the context of delayed differential equations used to establish global stability [15, 16].

4.5.1 Method of Lyapunov Functional for Autonomous Systems

Consider the system of autonomous equation

$$x'(t) = f(x_t), \tag{4.46}$$

where $f : \mathcal{C} \to \mathbb{R}^n$ is a continuous function and unique solutions of (4.46) depend continuously on initial data. We say $x(0, \phi)$ is a solution of (4.46) with initial value ϕ at 0, i.e., we denote the solution through $(0, \phi)$ by $x(\phi)$. For a continuous

functional $V : \mathcal{C} \to \mathbb{R}$, the derivative of V along the solution of (4.46) is defined as

$$\dot{V}(\phi) = \dot{V}_{(4.46)}(\phi) = \lim_{h \to 0^+} \frac{1}{h}[V(x_h(\phi)) - V(\phi)]$$

if the limit exits, where $x_h(\phi)$ satisfies (4.46). The function V is a Lyapunov functional on a set $G \subset \mathcal{C}$ relative to f if V is continuous on the closure[1] of G, denoted by $\bar{G}$ and $\dot{V}(\phi) \leq 0$ for $\phi \in G$ [17]. Define

$$E = \{\phi \in \bar{G} : \dot{V}(\phi) = 0\},$$
$$M = \text{The largest set in } E \text{ which is invariant with respect to (4.46).}$$

The following theorem is the LaSalle's invariance principle for equation (4.46).

Theorem 4.7. *If V is a Lyapunov functional on G and $x_t(\phi)$ is a bounded solution of (4.46) that stays in G, then $x_t(\phi) \to M$ as $t \to \infty$.*

Proof. We refer to [15] for a proof. □

Theorem 4.8. *If $q = 1$ and $\mathcal{R}_0 > 1$, then the unique endemic equilibrium of the system (4.6) is globally asymptotically stable.*

Proof. We follow [18] in construction of a Lyapunov functional for delay differential equations. Let $\mathcal{C} = C([-\tau, 0], \mathbb{R}^2)$ be the Banach space of continuous functions, $(S_t, I_t) = (S(t+\theta), I(t+\theta))$, and $\theta \in [-\tau, 0]$. We consider $C^+ = C([-\tau, 0], \mathbb{R}^2_{>0})$, and define a scalar function $V(S_t, I_t) : C^+ \to \mathbb{R}$ as

$$V(S, I) = \Big[S - S^* - S^* \ln \frac{S}{S^*}\Big] + \Big[I - I^* - I^* \ln \frac{I}{I^*}\Big] + \beta S^* I^* Q, \tag{4.47}$$

where

$$Q = \int_{t-\tau}^{t} \Big[\frac{S(u)I(u)}{S^*I^*} - 1 - \ln \frac{S(u)I(u)}{S^*I^*}\Big] du. \tag{4.48}$$

We define $f(x) = x - 1 - \ln x$. Based on the argument explained for the function f in Theorem 3.5 we know that for $S \in \mathbb{R}_{>0} \setminus \{S^*\}$ we have

$$S^*\Big(\frac{S}{S^*} - 1 - \ln \frac{S}{S^*}\Big) > 0.$$

[1] The closure of a subset G of a topological space consists of all the point of G and limit points of G.

Similarly, for $I \in \mathbb{R}_{>0} \setminus \{I^*\}$, the second term of (4.47) is positive, and for $(S, I) \in \mathbb{R}^2_{>0} \setminus \{(S^*, I^*)\}$ the function

$$\frac{S(u)I(u)}{S^*I^*} - 1 - \ln \frac{S(u)I(u)}{S^*I^*}$$

is positive. Hence, by monotonicity of integral, Q is positive. Therefore, V satisfies the following conditions:

- $V(S^*, I^*) = 0$,
- $V(S, I) > 0, \quad \forall\, (S, I) \in \mathbb{R}^2_{>0} \setminus \{(S^*, I^*)\}$.

If for all $(S, I) \in \mathbb{R}^2_{>0}$ the condition $\frac{d}{dt}V(S, I) \leq 0$ is satisfied, then V is a Lyapunov functional for the endemic equilibrium. Derivative of V is

$$\frac{dV}{dt} = \underbrace{\Big(1 - \frac{S^*}{S}\Big)S' + \Big(1 - \frac{I^*}{I}\Big)I'}_{L} + \beta S^* I^* Q'.$$

Computing Q' via Leibniz Integral rule yields

$$\begin{aligned}
Q' &= \Big[\frac{S(t)I(t)}{S^*I^*} - 1 - \ln \frac{S(t)I(t)}{S^*I^*}\Big] - \Big[\frac{S(t-\tau)I(t-\tau)}{S^*I^*} - 1 - \ln \frac{S(t-\tau)I(t-\tau)}{S^*I^*}\Big] \\
&= \frac{S(t)I(t)}{S^*I^*} - \frac{S(t-\tau)I(t-\tau)}{S^*I^*} - \ln \frac{S(t)I(t)}{S^*I^*} + \ln \frac{S(t-\tau)I(t-\tau)}{S^*I^*} \\
&= \frac{S(t)I(t)}{S^*I^*} - \frac{S(t-\tau)I(t-\tau)}{S^*I^*} + \ln \frac{S(t-\tau)I(t-\tau)}{S(t)I(t)} \\
&= \frac{S(t)I(t)}{S^*I^*} - \frac{S(t-\tau)I(t-\tau)}{S^*I^*} + \ln \Big[\frac{S(t-\tau)I(t-\tau)}{S^*I(t)} \times \frac{S^*}{S(t)}\Big] \\
&= \frac{S(t)I(t)}{S^*I^*} - \frac{S(t-\tau)I(t-\tau)}{S^*I^*} + \ln \frac{S(t-\tau)I(t-\tau)}{S^*I(t)} + \ln \frac{S^*}{S(t)},
\end{aligned} \tag{4.49}$$

and

$$L = \Big(1 - \frac{S^*}{S}\Big)\Big[A - \mu S - \beta SI\Big] + \Big(1 - \frac{I^*}{I}\Big)\Big[\beta S(t-\tau)I(t-\tau) - (\mu + \gamma)I(t)\Big].$$

Substituting $A = \mu S^* + \beta S^* I^*$ from equilibrium equation yields

$$L = \Big(1 - \frac{S^*}{S}\Big)\Big[\mu S^* + \beta S^* I^* - \mu S - \beta SI\Big]$$

$$+ \Big(1 - \frac{I^*}{I}\Big)\big[\beta S(t-\tau)I(t-\tau) - (\mu+\gamma)I(t)\Big]$$

$$= \mu S^* + \beta S^* I^* - \mu S - \beta SI - \mu\frac{S^{*2}}{S} - \beta\frac{S^{*2}I^*}{S} + \mu S^* + \beta S^* I + \beta S(t-\tau)I(t-\tau)$$

$$- (\mu+\gamma)I(t) - \beta\frac{S(t-\tau)I(t-\tau)I^*}{I} + (\mu+\gamma)I^*.$$

Substituting $(\mu+\gamma)I^* = \beta S^* I^*$ and simplifying some terms give

$$L = \mu S^*\Big[2 - \frac{S^*}{S} - \frac{S}{S^*}\Big]$$

$$+ \beta S^* I^*\Big[2 - \frac{SI}{S^*I^*} - \frac{S^*}{S} + \frac{\beta S(t-\tau)I(t-\tau)}{S^*I^*} - \frac{\beta S(t-\tau)I(t-\tau)}{S^*I}\Big]$$

$$+ \beta S^* I - (\mu+\gamma)I.$$

From endemic equilibrium (4.10) when $q = 1$ we obtain $S^* = \dfrac{\mu+\gamma}{\beta}$, and thus $\beta S^* I - (\mu+\gamma)I = 0$. Hence $\dot{V}$ is

$$\frac{dV}{dt} = \Big(1 - \frac{S^*}{S}\Big)S' + \Big(1 - \frac{I^*}{I}\Big)I' + \beta S^* I^* Q'$$

$$= \mu S^*\Big[2 - \frac{S^*}{S} - \frac{S}{S^*}\Big]$$

$$+ \beta S^* I^*\Big[2 - \frac{S(t)I(t)}{S^*I^*} - \frac{S^*}{S} + \frac{\beta S(t-\tau)I(t-\tau)}{S^*I^*} - \frac{\beta S(t-\tau)I(t-\tau)}{S^*I}\Big]$$

$$+ \beta S^* I^*\Big[\frac{S(t)I(t)}{S^*I^*} - \frac{S(t-\tau)I(t-\tau)}{S^*I^*} + \ln\frac{S(t-\tau)I(t-\tau)}{S^*I(t)} + \ln\frac{S^*}{S(t)}\Big]$$

$$= \mu S^*\Big[2 - \frac{S^*}{S} - \frac{S}{S^*}\Big]$$

$$+ \beta S^* I^*\Big[2 - \frac{S^*}{S} - \frac{\beta S(t-\tau)I(t-\tau)}{S^*I(t)} + \ln\frac{S(t-\tau)I(t-\tau)}{S^*I(t)} + \ln\frac{S^*}{S(t)}\Big]$$

Rewriting $\dot{V}$ in terms of function f we obtain

$$\frac{dV}{dt} = -\mu S^*\Big(f\Big(\frac{S^*}{S}\Big) + f\Big(\frac{S}{S^*}\Big)\Big) - \beta S^* I^*\left(f\Big(\frac{S^*}{S}\Big) + f\Big(\frac{S(t-\tau)I(t-\tau)}{S^*I(t)}\Big)\right).$$

Therefore, $\dot{V}$ satisfies $\dot{V}(S,I) \leq 0$ except at $(S,I) = (S^*, I^*)$. The set $\mathcal{I} = \left\{(S,I) \in \mathbb{R}^2_{>0}; \dot{V}(S,I) = 0\right\}$ contains only the endemic equilibrium (S^*, I^*). Since the endemic equilibrium is locally asymptotically stable, and $\mathcal{I}$ contains only the endemic equilibrium, by LaSalle's Invariance Principle the endemic equilibrium attracts all the solutions; thus, the endemic equilibrium is globally asymptotically stable. □

Theorem 4.9. *If $q = e^{-\mu\tau}$ and $\mathcal{R}_0 > 1$, then the unique endemic equilibrium of the system (4.6) is globally asymptotically stable.*

Proof. Define $V(S,I) : C^+ \to \mathbb{R}$ as

$$V(S,I) = \left[S - S^* - S^* \ln \frac{S}{S^*}\right] + e^{\mu\tau}\left[I - I^* - I^* \ln \frac{I}{I^*}\right] + \beta S^* I^* Q \tag{4.50}$$

Where

$$Q = \int_{t-\tau}^{t} \left[\frac{S(u)I(u)}{S^*I^*} - 1 - \ln \frac{S(u)I(u)}{S^*I^*}\right] du.$$

For the same reason illustrated in Theorem 4.8 function $V > 0$ for $(S,I) \in \mathbb{R}^2_{>0} \setminus \{(S^*, I^*)\}$, and $V(S^*, I^*) = 0$. If for all $(S,I) \in \mathbb{R}^2_{>0}$ the condition $\dot{V}(S,I) \leq 0$ is satisfied, then V is a Lyapunov functional for the endemic equilibrium. Calculating $\dot{V}$ we obtain

$$\frac{dV}{dt} = \underbrace{\left(1 - \frac{S^*}{S}\right)S' + e^{\mu\tau}\left(1 - \frac{I^*}{I}\right)I'}_{L} + \beta S^* I^* Q'. \tag{4.51}$$

In calculating L we use the following substitutions

$$A = \mu S^* + \beta S^* I^*$$

and

$$\beta S^* I^* = e^{\mu\tau}(\mu + \gamma) I^*$$

and also

$$I\left(\beta S^* - e^{\mu\tau}(\mu + \gamma)\right) = 0.$$

Last equation is obtained from the equilibrium equation given by

$$\beta S^* I^* e^{-\tau\mu} = (\mu + \gamma) I^* \Longrightarrow \beta S^* I^* = e^{\tau\mu}(\mu + \gamma) I^* \Longrightarrow \beta S^* - e^{\mu\tau}(\mu + \gamma) = 0.$$

Then, L is

$$\begin{aligned} L &= \Big(1-\frac{S^*}{S}\Big)\Big[\mu S^* + \beta S^* I^* - \mu S - \beta S I\Big] \\ &\quad + e^{\mu\tau}\Big(1-\frac{I^*}{I}\Big)\big[\beta S(t-\tau)I(t-\tau)e^{-\mu\tau} - (\mu+\gamma)I(t)\Big] \\ &= \mu S^* + \beta S^* I^* - \mu S - \beta S I - \frac{\mu S^{*2}}{S} - \frac{\mu S^{*2} I^*}{S} + \mu S^* + \beta S(t-\tau)I(t-\tau) \\ &\quad - \frac{\beta S(t-\tau)I(t-\tau)I^*}{I} + \beta S^* I^*. \end{aligned} \tag{4.52}$$

Q' is

$$\begin{aligned} Q' &= \Big[\frac{SI}{S^*I^*} - 1 - \ln\frac{SI}{S^*I^*}\Big] - \Big[\frac{S(t-\tau)I(t-\tau)}{S^*I^*} - 1 - \ln\frac{S(t-\tau)I(t-\tau)}{S^*I^*}\Big] \\ &= \frac{SI}{S^*I^*} - \frac{S(t-\tau)I(t-\tau)}{S^*I^*} + \ln\frac{S(t-\tau)I(t-\tau)}{S^*I} + \ln\frac{S^*}{S}. \end{aligned} \tag{4.53}$$

Hence, $\dot{V}$ is

$$\begin{aligned} \dot{V}(S,I) &= \mu S^*\Big[2 - \frac{S^*}{S} - \frac{S}{S^*}\Big] \\ &\quad + \beta S^* I^*\Big[2 - \frac{S(t)I(t)}{S^*I^*} + \frac{S(t-\tau)I^*(t-\tau)}{S^*I^*} + \frac{SI}{S^*I^*} - \frac{S(t-\tau)I^*(t-\tau)}{S^*I^*} \\ &\quad - \frac{S^*}{S} - \frac{\beta S(t-\tau)I(t-\tau)}{S^*I} + \ln\frac{S(t-\tau)I(t-\tau)}{S^*I} + \ln\frac{S^*}{S(t)}\Big] \\ &= -\mu S^*\Big[\frac{S^*}{S} + \frac{S}{S^*} - 2\Big] \\ &\quad - \beta S^* I^*\Big[\frac{S^*}{S} + \frac{\beta S(t-\tau)I(t-\tau)}{S^*I} - \ln\frac{S(t-\tau)I(t-\tau)}{S^*} - \ln\frac{S^*}{S}\Big] \end{aligned}$$

Rewriting $\dot{V}$ gives

$$\frac{dV}{dt} = -\mu S^*\Big(f\Big(\frac{S^*}{S}\Big) + f\Big(\frac{S}{S^*}\Big)\Big) - \beta S^* I^*\left(f\Big(\frac{S^*}{S}\Big) + f\Big(\frac{S(t-\tau)I(t-\tau)}{S^*I}\Big)\right).$$

Therefore, $\dot{V}$ satisfies $\dot{V}(S,I) \leq 0$ except at the $(S,I) = (S^*, I^*)$. The set $\mathcal{I} = \left\{(S,I) \in \mathbb{R}^2_{>0}; \dot{V}(S,I) = 0\right\}$ contains only the endemic equilibrium (S^*, I^*). Since the endemic equilibrium is locally asymptotically stable, and $\mathcal{I}$ contains only the equilibrium, by LaSalle's Invariance Principle, the endemic equilibrium attracts all the solutions; thus, the endemic equilibrium is globally asymptotically stable. □

Based on the analysis above, $\mathcal{R}_0 = 1$ is the threshold for the stability of the equilibria. A sufficient condition for a disease to be ended or continue in the population is $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$, respectively. Hence, the basic reproduction number and the stability threshold for the SIR model with time delay are identical for each case of q. This argument leads to the following biological interpretation of the stability threshold $\mathcal{R}_0$.

4.5.2 Epidemiological Interpretation of $\mathcal{R}_0$

The average time spent in the infectious compartment, given that the individual has survived the infectious phase, is $\frac{1}{\mu+\gamma}$, the total number of susceptibles in the absence of disease is $S = \frac{A}{\mu}$, and the transmission rate is β. Hence, according to Definition 3.3 given in Chapter 2 when $q = 1$

$$\mathcal{R}_0 = \frac{A\beta}{\mu(\mu+\gamma)}, \tag{4.54}$$

and when $q = e^{-\mu\tau}$

$$\mathcal{R}_0 = \frac{A\beta e^{-\mu\tau}}{\mu(\mu+\gamma)}, \tag{4.55}$$

are the basic reproduction number for the SIR model with time delay.

4.6 Numerical Simulations

We support theoretical results using numerical simulations. It is worth noting that for the comparison purpose yet to be discussed in the preceding chapter, we

keep the values of the parameters in the SIR models the same as in the simulation of the SEIR model. The fixed parameters are:

$$A = 5, \quad \beta = 0.015, \quad \mu = 0.2, \quad \gamma = 0.007, \quad S_0 = 3, \quad I_0 = 20. \tag{4.56}$$

The SIR model with delay when $q = 1$ has equal values of the basic reproduction number independent of the value of τ, see Fig.4.2. The basic reproduction is $\mathcal{R}_0 = 1.8116$, which is larger than unity for fixed parameters value, indicating that the endemic equilibrium, $(S^*, I^*) = (13.800, 10.821)$, is asymptotically stable.

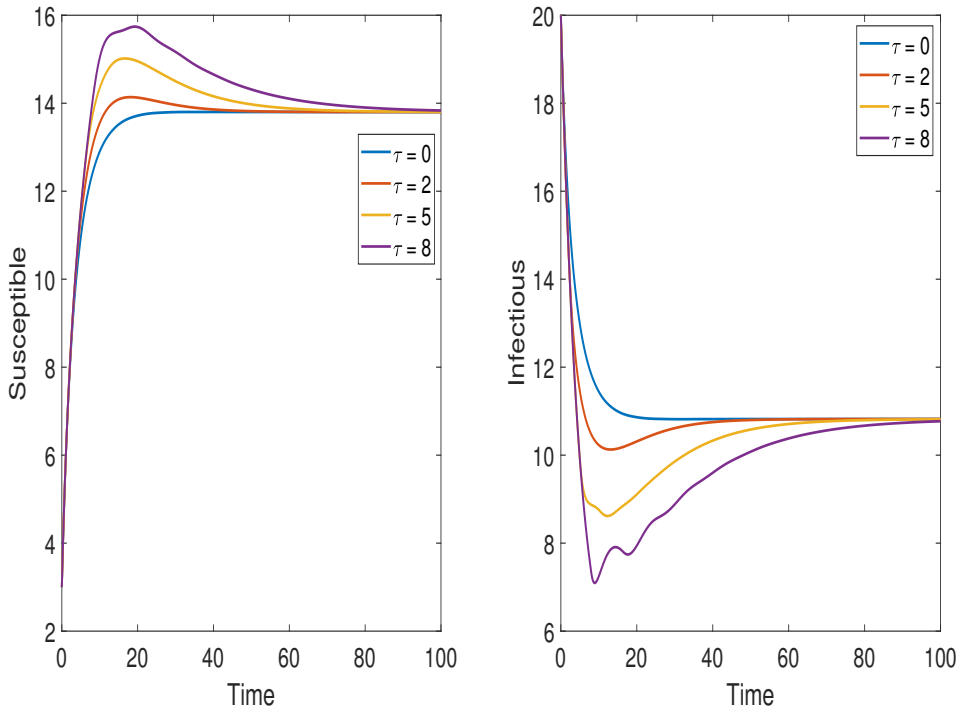


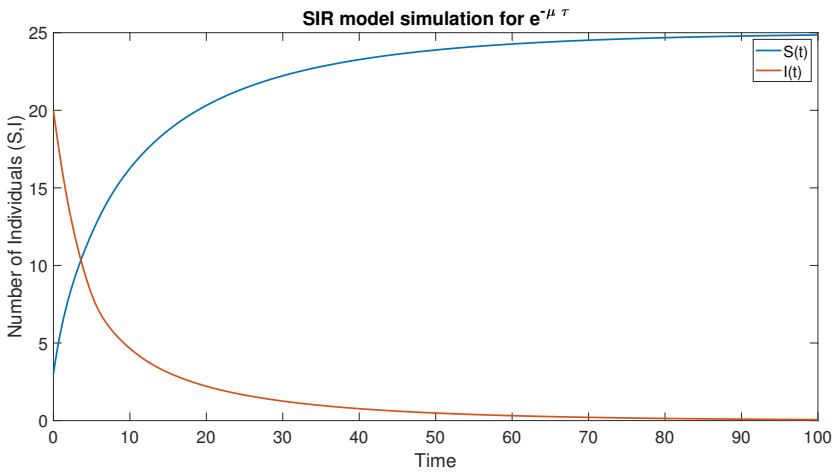
Fig. 4.2: Stability of the endemic equilibrium $(S^*, I^*) = (13.800, 10.821)$ for the SIR model with delay when $q = 1$ regardless of the value of τ.

When $q = e^{-\mu\tau}$, the basic reproduction number is given by (4.55) which depends on the value of the delay; solving for τ using the stability threshold, $\mathcal{R}_0 = 1$, yields

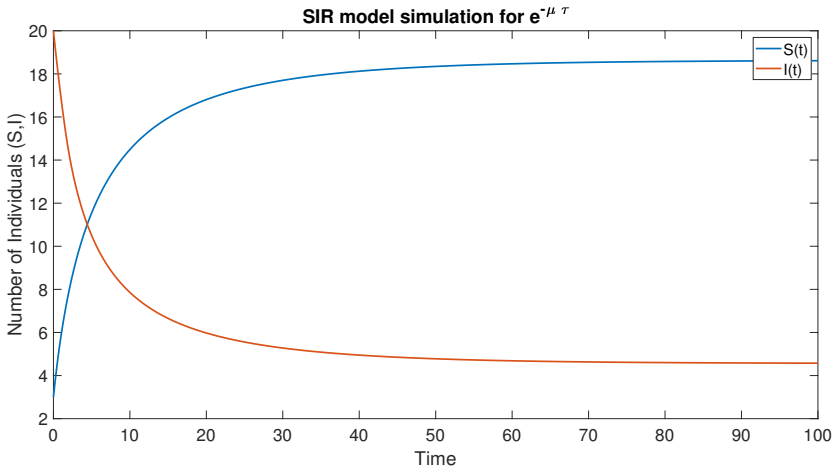
$$\tau = \frac{1}{\mu} \ln \frac{A\beta}{\mu(\mu + \gamma)}. \tag{4.57}$$

Using values given in (4.56) and equation (4.57) we obtain $\tau = 2.971$. This value is significant since it is the critical value for τ such that $\mathcal{R}_0 = 1$ and any deviation from $\tau = 2.971$ gives a value of $\mathcal{R}_0$ either less or greater than one. To distinguish it from the other values of τ, we denote it by $\tau_0 = 2.971$.

Fig. 4.3a and Fig. 4.3b show that the SIR models with delay exhibit stable disease-free equilibrium and endemic equilibrium for values of $\tau = 5$ and $\tau = 1.5$, respectively.



(a) Stable disease-free equilibrium $(S^*, I^*) = (25, 0)$ for $\tau = 5.00$ and $\mathcal{R}_0 = 0.6664$.



(b) Stable endemic equilibrium $(S^*, I^*) = (18.6281, 4.5608)$ for $\tau = 1.5$ and $\mathcal{R}_0 = 1.3421$.

Fig. 4.3: Stability of the disease-free and the endemic equilibrium for the SIR model with delay when $q = e^{-\mu\tau}$.

Moreover, as the value of delay increases from $\tau_0 = 2.971$, we have $\mathcal{R}_0 < 1$, implying that the disease-free equilibrium is stable. As the delay value decreases from the threshold value of τ, we get $\mathcal{R}_0 > 1$, implying that the endemic equilibrium is stable, see Fig. 4.4.

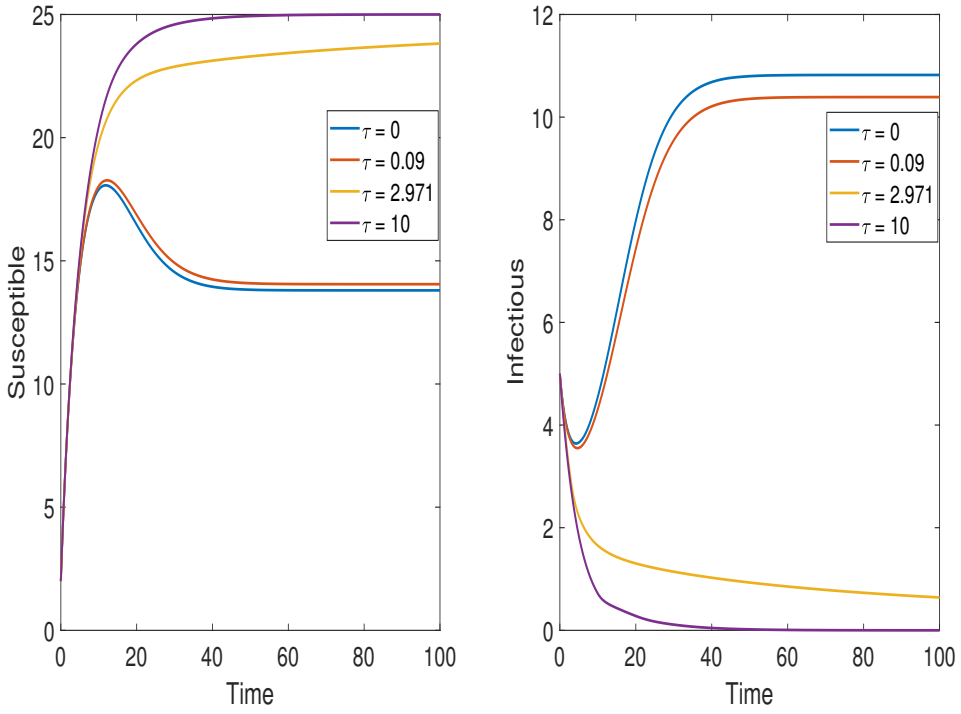


Fig. 4.4: Stability of the equilibria for different values of τ varied from $\tau_0 = 2.971$.

First, we assume $q = 1$, which implies the probability of surviving the latent phase of the duration τ is one. Based on this assumption, the basic reproduction number is independent of the delay value. The stated Theorems, together with the simulations, show that for $\mathcal{R}_0 < 1$, disease eradicates, and for $\mathcal{R}_0 > 1$, the disease persists in the population. Individuals may leave the population during the latent phase of some diseases, mainly due to death; we set $q = e^{-\mu\tau}$ to include this assumption. In this case, the model's basic reproduction number is affected by the delay value; thus, the threshold value of delay τ_0 can be determined. The increasing value of τ from its threshold τ_0, yields $\mathcal{R}_0 < 1$, implying that the disease has died out, whereas decreasing it from the threshold value τ_0 yields

$\mathcal{R}_0 > 1$, implying that the disease has persisted in the population. This is quite reasonable; when the latent period is extended, people remain inactive for a long time without contributing to disease transmission. Thus, the basic reproduction number is less than one. On the other hand, when we reduce the delay value, people spend less time in the latent period and contribute to the transmission sooner after being exposed; as a result, more people contribute to the transmission in a shorter period, allowing the basic reproduction number to be greater than one.

Chapter 5

Fitting the Epidemiological Models to Real Data

We discussed the SEIR and the SIR model with delay in Chapter 3 and Chapter 4, respectively, and mentioned that these two models can describe a disease's latent period. The SIR model investigated in Chapter 4 consists of two survival term choices: $q = e^{-\mu\tau}$ and $q = 1$. In this chapter, we compare these two models and investigate their suitability. We also validated our results by fitting the models to meningococcal data from four countries.

5.1 Comparison of the SEIR and the SIR Model with Delay

The basic reproduction number is a significant parameter as it provides information about disease spread in a population, and its value determines disease persistence or elimination. If the basic reproduction number is low, it indicates that the disease does not rapidly spread; if it is large, the disease quickly spreads in the population. Therefore, we compare the models using their basic reproduction numbers. Remember that the basic reproduction number for the SEIR

model is

$$\mathcal{R}_0^{SEIR} = \frac{A\beta\sigma}{\mu(\mu+\gamma)(\mu+\sigma)}. \tag{5.1}$$

The basic reproduction number for the SIR model with delay when $q = 1$ is

$$\mathcal{R}_0^{(1)} = \frac{A\beta}{\mu(\mu+\gamma)}. \tag{5.2}$$

The basic reproduction number for the SIR model with delay when $q = e^{-\mu\tau}$ is

$$\mathcal{R}_0^{(2)} = \frac{A\beta e^{-\mu\tau}}{\mu(\mu+\gamma)}. \tag{5.3}$$

The parameters representing the latent period in the SEIR model and the delayed SIR model are σ and τ, respectively. The SEIR model assumes that the latent period has an exponential distribution with the rate σ, whereas the SIR model assumes that the latent duration is constant τ. Thus, in the SEIR and SIR models, an individual's time in the latent phase is $1/\sigma$ and τ, respectively. These parameters appear in the formula for the basic reproduction numbers, (5.1) and (5.3), except in equation (5.2), which is the basic reproduction number for the SIR model with delay when $q = 1$. By assuming that the time an individual spends in a latent phase is the same in the SEIR and the SIR model when $q = e^{-\mu\tau}$ we get $\tau = 1/\sigma$. From (5.1) and (5.3) following Lemma results immediately.

Lemma 5.1. *Suppose $\sigma \neq 0$ and let $\tau = \dfrac{1}{\sigma}$, then*

$$\mathcal{R}_0^{SEIR} > \mathcal{R}_0^{(2)}.$$

for all positive fixed parameters A, μ, β, and γ.

Proof. It suffices to show that

$$\frac{\sigma}{\mu+\sigma} - e^{-\mu\tau} > 0. \tag{5.4}$$

By assumption $\tau = \dfrac{1}{\sigma}$; substituting it in (5.4) gives

$$\frac{1}{1+\mu\tau} - e^{-\mu\tau} > 0.$$

Let $\mu\tau = x$ where $x \in [0, \infty)$, and define the function $f(x)$ as

$$f(x) = \frac{1}{1+x} - e^{-x}.$$

To prove that $f(x) > 0$, it is enough to show that

$$e^x - x - 1 > 0$$

Let us define $g(x) = e^x - x - 1$, we have $g(0) = 0$. First derivative of g is $g'(x) = e^x - 1$. Therefore, g is positive for all $x > 0$. □

The fixed parameter values used in models simulations are:

$$A = 5, \quad \beta = 0.015, \quad \mu = 0.2, \quad \gamma = 0.007. \tag{5.5}$$

Using the parameter values given in (5.5) we compute the basic reproduction number for two models under the assumption of $\tau = 1/\sigma$. It is worth reminding the reader that $\sigma_0 = 0.2464$ and $\tau_0 = 2.971$ result in the basic reproduction numbers given by (5.1) and (5.3) reach the threshold value of one, respectively. As shown in Table 5.1, the basic reproduction number for the SIR model with delay when $q = 1$, is $\mathcal{R}_0^{(1)} = 1.8116$, which is greater than unity, regardless of the delay value; this implies that all solutions approach the endemic equilibrium in the long run. As seen in Table 5.1 and Table 5.2, for all values of τ and σ, the basic reproduction number for the SIR model with delay when $q = e^{-\mu\tau}$ is smaller than that of the SEIR model. Furthermore, if the latent duration is $\tau = 2.971$, the basic reproduction number for the SIR model when $q = e^{-\mu\tau}$ is equal to unity, implying that the disease-free equilibrium is stable. If we consider the SEIR model for the latent duration of $\tau = 2.971$, we obtain $\sigma = 0.3366$ which gives the basic reproduction number greater than one, implying that the endemic equilibrium is stable. Based on Table 5.1 and Table 5.2, we observe that for a value of delay $\tau \in (0, \tau_0)$, the basic reproduction number for both of the models is greater than one, for $\tau \in [\tau_0, \frac{1}{\sigma_0})$ the basic reproduction number is less than or equal to one for the SIR model. However, it is greater than one for the SEIR model, and for $\tau \in [\frac{1}{\sigma_0}, \infty)$, both models have the basic reproduction number less than or equal to one.

τ	1	1.5	$\tau_0 = 2.971$	3.00	3.2	3.5	4.0584	6.6667
$\mathcal{R}_0^{(2)}$	1.4832	1.3421	1.000	0.9942	0.9552	0.8996	0.8045	0.4775
$\mathcal{R}_0^{(1)}$	1.8116	1.8116	1.8116	1.8116	1.8116	1.8116	1.8116	1.8116

Table 5.1: Values of $\mathcal{R}_0$ for the SIR models with delay.

$\sigma = \frac{1}{\tau}$	1	0.6667	0.3366	0.3333	0.3125	0.2857	$\sigma_0 = 0.2464$	0.15
$\mathcal{R}_0$	1.5097	1.3936	1.1364	1.1322	1.1046	1.0656	1.000	0.7764

Table 5.2: Values of $\mathcal{R}_0$ for the SEIR epidemiological model.

5.2 Fitting Epidemiological Models to Data

We fit two epidemiological models to data and perform a validation, which establishes how well the mathematical models represent real-world data. Fitting the model to real-world data is essential since it allows us to acquire confidence in the model while obtaining realistic parameter estimates. We use the method of least squares to estimate the best-fitting transmission parameter β to the given data set [13]. This method is discussed in section 5.2.1.

5.2.1 Method of Least Squares

Let

$$\begin{aligned} x' &= f(x, \eta) \qquad x \in \mathbb{R}^d, \quad t \in [0, t_{\max}] \\ x(0) &= x_0 \end{aligned}$$

be the initial value problem for an epidemic model where $\eta \in \mathbb{R}^m$ is the m-dimensional parameter and $[0, t_{\max}]$ is the time interval in which the epidemic model is investigated. Data for the prevalence of the disease are given as

$t_1, \cdots, t_p \in [0, t_{\max}]$ such that

$$(t_1, g(x^{(1)})), \cdots, (t_p, g(x^{(p)})), \quad x^{(i)} \in \mathbb{R}^d.$$

The function $g(x) : \mathbb{R}^d \to \mathbb{R}^n$ represents the observable quantities of the state variable x. To fit the data we consider the values of the solution $x(t, \eta)$ at $t_1, \cdots, t_p$:

$$\big(x(t_1, \eta), \cdots, x(t_p, \eta)\big). \tag{5.6}$$

Let's denote the data points as

$$y = \big(g(x^{(1)}), \cdots, g(x^{(p)})\big), \quad x^{(i)} \in \mathbb{R}^d.$$

The squared sum of errors (SSE) can be measured by

$$SSE(\eta) = d(g(x(t, \eta)), y)^2 = \sum_{i=1}^{p} || \, g(x(t_i, \eta)) - g(x^{(i)}) \, ||^2$$

where $|| \, . \, ||$ is the Euclidean norm. SSE is a function of the parameters of the model. So, the problem is to identify parameters such that SSE is minimized. Since the dependence of a solution $x(t, \eta)$ on the parameter η is through a nonlinear system of differential equations, this minimization problem is a nonlinear least-squares problem [1].

5.2.2 Fitting the SEIR and the SIR Models to Meningococcal Disease Data

We minimize the SSE between the SEIR-SIR models, and the data points to find the best fit. Statistics for the models are derived from the World Bank, which can be found at https://data.worldbank.org/. We validate our findings using meningococcal disease published datasets from four countries: France, South Africa, the United States, and Australia. We use prevalence[1] of meningococcal diseases in France for twelve months throughout 2014 [19], prevalence of total serogroups (A, B, C, W, and Y) of meningococcal disease in South Africa from 2007 to 2016 [20], prevalence of five commonly identified bacterial meningitis

[1] The number of infectious individuals.

in the United States from 1997 to 2010 [21], and total cases of meningococcal disease of types (B, C, W, Y) in Australia from 2002 to 2015 [22]. The number of infectious cases is given per 100,000 for South Africa, the United States, and Australia; to calculate the actual number of cases, we use the formula below:

$$NC = \frac{NC_{per1000,000} \times TPZ}{100,000},$$

where NC is the number of cases for each year, and TPZ is the total population size for the starting year. In the formula above, we fix the total population size; for example, the TPZ for South Africa is the total population size in 2007, and we assume it is fixed for the preceding eleven years. Fixed parameters are total population size, natural death rate, number of newborns, and disease recovery rate. By the formula (2.4) given in Chapter 2, the death rate is estimated by considering the reciprocal of the life expectancy for each country. Number of newborns A, is obtained by $N_0 \approx A/\mu$. These parameter values are summarized in Table 5.3. We assume that the meningococcal diseases have a latent duration of 1-10 days [23], which implies that $\sigma = 1/\tau \in [0.1, 1]$ per capita per day or $\sigma \in [36, 365]$ per capita per year. It is also assumed that infectious individuals recover from the meningococcal disease in 21-30 days [24]; the recovery rate per capita per day is $\gamma \in [0.034, 0.047]$, which indicates that $\gamma \in [12.1, 17.15]$ per capita per year. We fix $\sigma = 0.82$ and $\gamma = 0.038$ per capita per day, which represents that $\sigma = 24.6$ and $\gamma = 1.14$ per capita per month, and $\sigma = 299.3 \approx 300$ and $\gamma = 13.8 \approx 14$ per capita per year.

Country	N_0	μ	A	γ
France in 2014	65057000	0.0010 month^{-1}	66840	1.14 month^{-1}
South Africa in 2007	49119766	1/54 year^{-1}	909630	14 year^{-1}
United States in 1997	272657000	1/77 year^{-1}	3541000	14 year^{-1}
Australia in 2002	19651400	1/80 year^{-1}	614	14 year^{-1}

Table 5.3: Fixed parameter values for the SEIR and the SIR model with delay.

Table 5.4 shows the estimated value of transmission rate and the rate at which individuals get infected for the SEIR model.

Country	σ (assumed)	β (fitted)
France	24.6 month^{-1}	1.434×10^{-8}
South Africa	300 year^{-1}	2.8524×10^{-7}
United States	300 year^{-1}	5.1033×10^{-8}
Australia	300 year^{-1}	7.0257×10^{-7}

Table 5.4: Best-fitted β and assumed σ values for the SEIR model.

Using parameter values given in Tables 5.3 and Table 5.4, we plotted Fig. 5.1, Fig. 5.2, Fig. 5.3, and Fig. 5.4. Estimated values of transmission rates for the delayed SIR model under the assumptions of $q = e^{-\mu\tau}$ and $q = 1$ are shown in Table 5.5.

Country	τ (assumed)	$\beta^{(2)}$ (fitted)	$\beta^{(1)}$ (fitted)
France	1/24.6 month	1.28×10^{-8}	1.28×10^{-8}
South Africa	1/300 year	2.8493×10^{-7}	2.8494×10^{-7}
United States	1/300 year	5.1007×10^{-8}	5.1009×10^{-8}
Australia	1/300 year	7.0198×10^{-7}	7.0196×10^{-7}

Table 5.5: Best-fitted values of β and assumed values of τ for the delayed SIR model. $\beta^{(2)}$ and $\beta^{(1)}$ is the transmission rate of the SIR model when $q = e^{-\mu\tau}$ and $q = 1$, respectively.

Using values given in Table 5.3 and Table 5.5, we plotted Fig. 5.5, Fig. 5.6, Fig. 5.7, and Fig. 5.8.

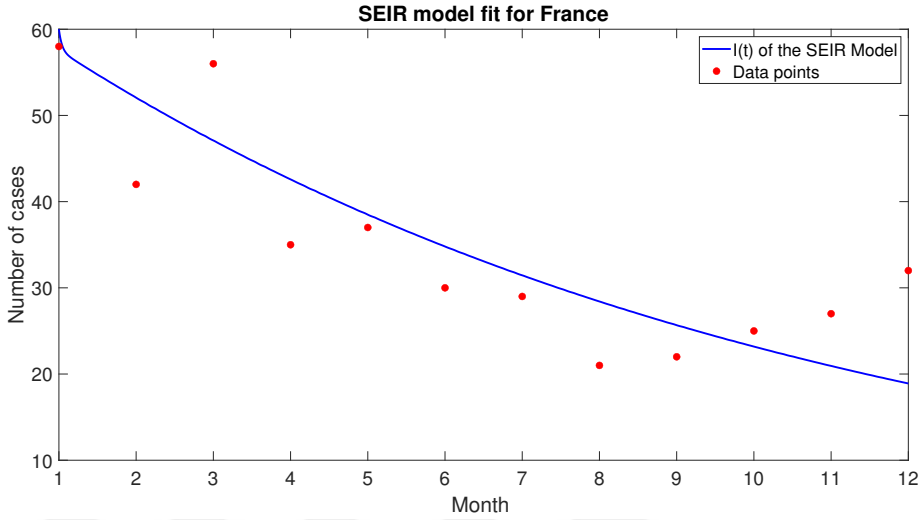


Fig. 5.1: Red points represent the prevalence of meningococcal diseases in France for twelve months in 2014, and the blue curve is the number of infectious cases estimated by $I(t)$ of the SEIR model.

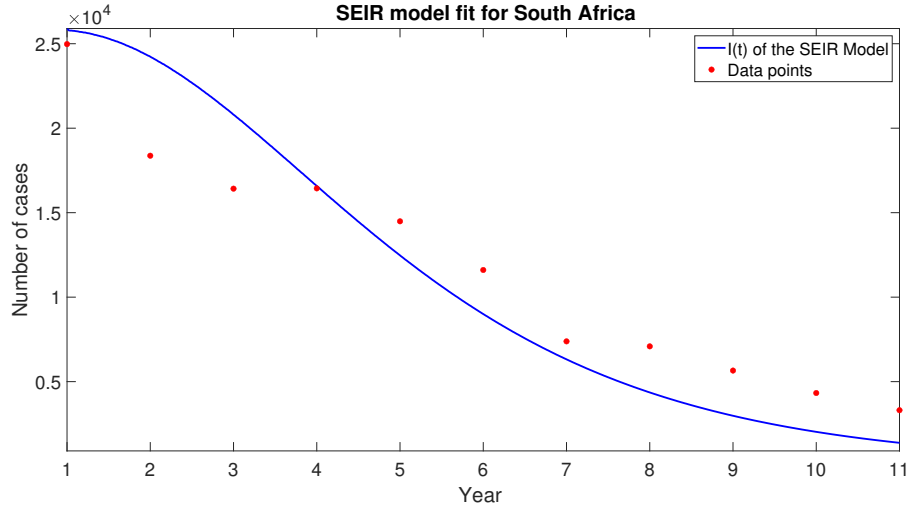


Fig. 5.2: Red points represent the prevalence of serogroups (A, B, C, W, and Y) of meningococcal disease in South Africa from 2007 to 2016, and the blue curve is the number of infectious cases estimated by $I(t)$ of the SEIR model.

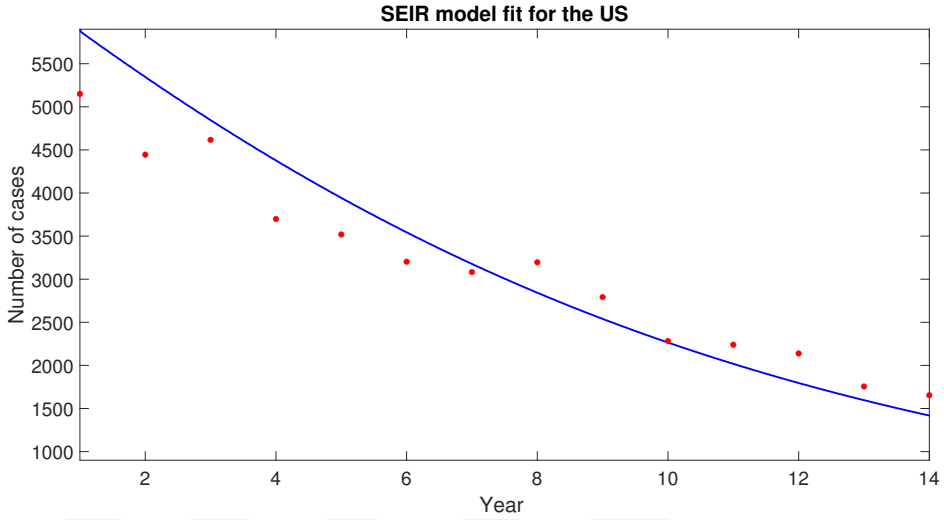


Fig. 5.3: Red points represent the prevalence of five commonly identified bacterial meningitis in the United States from 1997 to 2010, and the blue curve is the number of infectious cases estimated by $I(t)$ of the SEIR model.

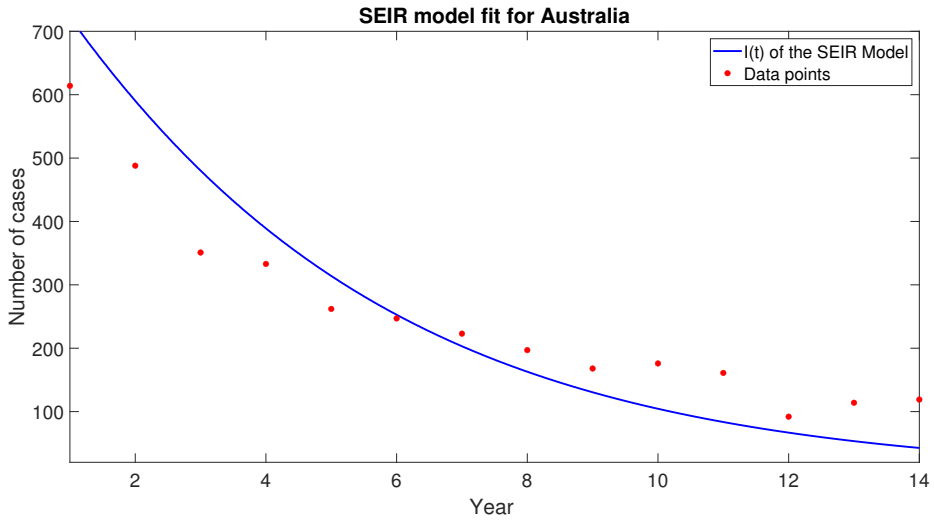
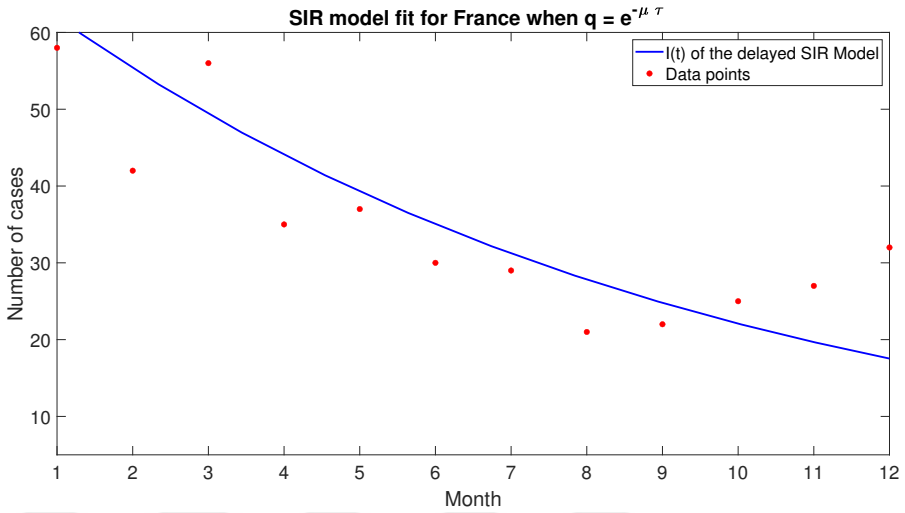
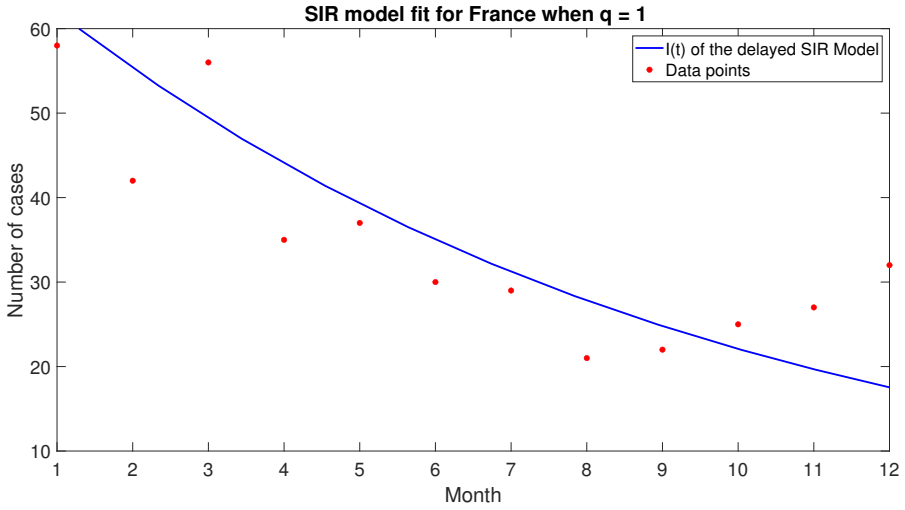


Fig. 5.4: Red points represent the prevalence of meningococcal disease of types (B, C, W, Y) in Australia from 2002 to 2015, and the blue curve is the number of infectious cases estimated by $I(t)$ of the SEIR model.

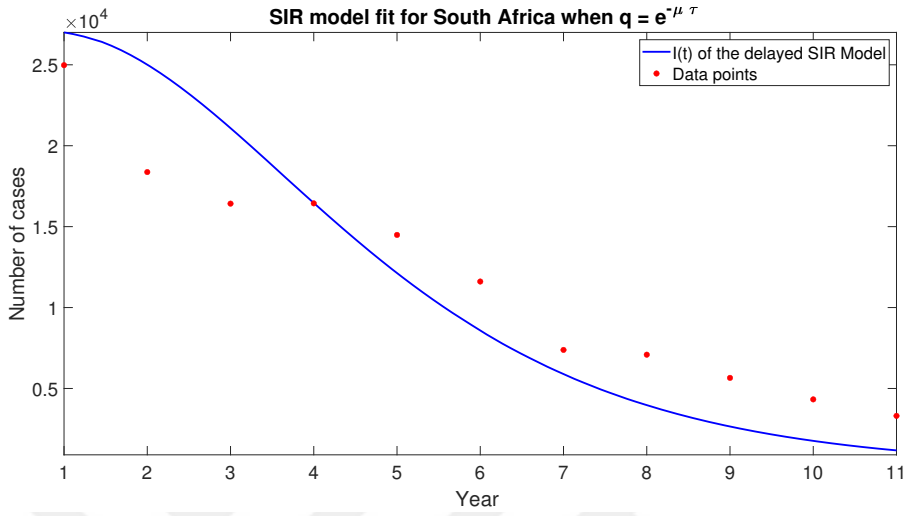


(a) The prevalence of meningococcal disease and number of infectious cases estimated by $I(t)$ of the SIR model when $q = e^{-\mu\tau}$.

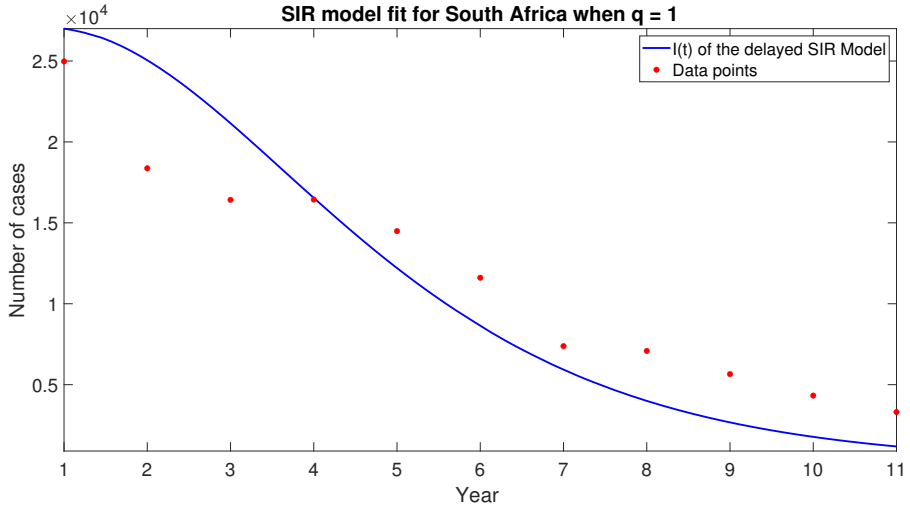


(b) The prevalence of meningococcal disease and number of infectious cases estimated by $I(t)$ of the SIR model when $q = 1$.

Fig. 5.5: Least squares fitting of the delayed SIR model for France monthly dataset in 2014.

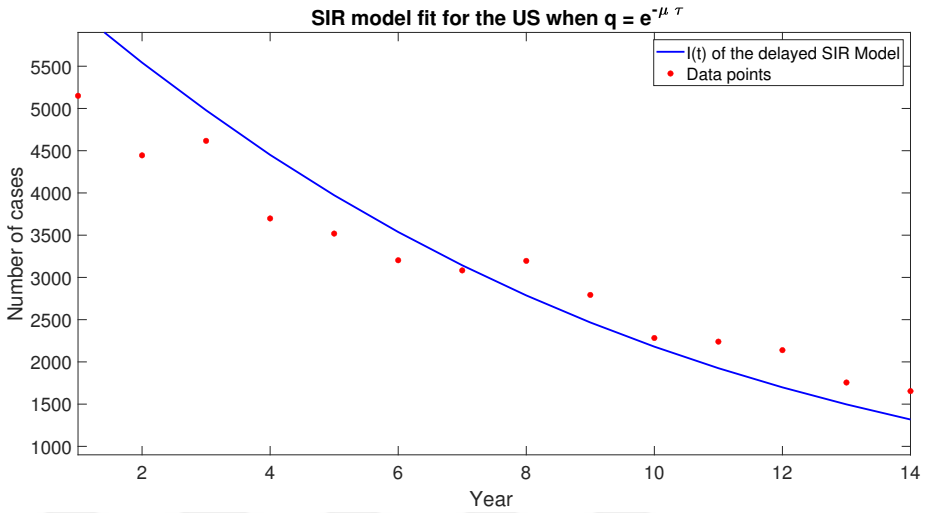


(a) The prevalence of total serogroups (A, B, C, W, and Y) of invasive meningococcal disease, and number of infectious cases estimated by $I(t)$ of the delayed SIR when $q = e^{-\mu\tau}$.

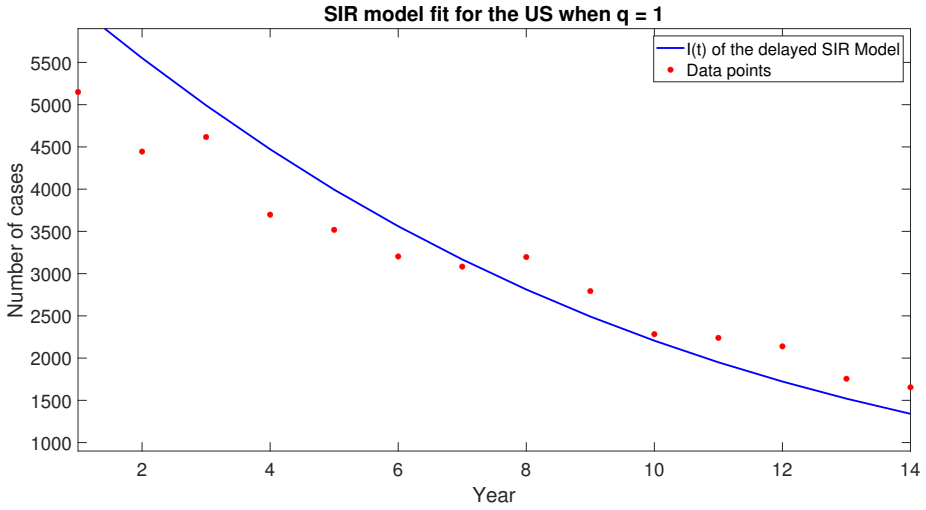


(b) The prevalence of total serogroups (A, B, C, W, and Y) of invasive meningococcal disease and number of infectious cases estimated by $I(t)$ of the delayed SIR when $q = 1$.

Fig. 5.6: Least squares fitting of the delayed SIR model for South Africa dataset from 2006 to 2017.

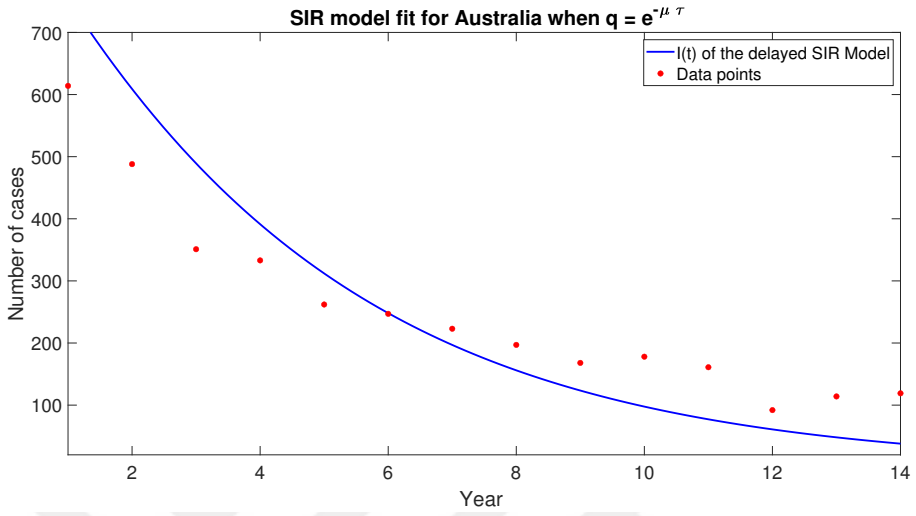


(a) The prevalence of five commonly identified bacterial meningitis types and the number of infectious cases estimated by $I(t)$ of the SIR model with delay when $q = e^{-\mu\tau}$.

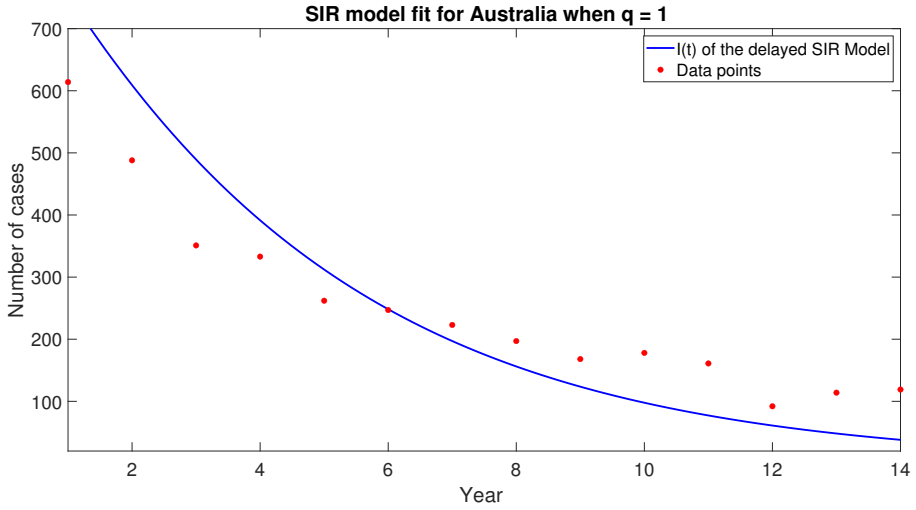


(b) The prevalence of five commonly identified bacterial meningitis types and the number of infectious cases estimated by $I(t)$ of the SIR model when $q = 1$.

Fig. 5.7: Least squares fitting of the delayed SIR model for the US dataset from from 1997 to 2010.



(a) Total cases of meningococcal disease of types (B, C, W, and Y) and the number of infectious cases estimated by $I(t)$ of the SIR model when $q = e^{-\mu\tau}$.



(b) Total cases of meningococcal disease of types (B, C, W, and Y) and the number of infectious cases estimated by $I(t)$ of the SIR model when $q = 1$.

Fig. 5.8: Least squares fitting of the delayed SIR model for Australia dataset from 2002 to 2015.

Table 5.6 and Table 5.7 summarize all estimated values of β and calculated values of $\mathcal{R}_0$ for two models, respectively.

Country	β (SEIR)	β (SIR$^{(2)}$)	β (SIR$^{(1)}$)
France	1.434×10^{-8}	1.28×10^{-8}	1.28×10^{-8}
South Africa	2.8524×10^{-7}	2.8493×10^{-7}	2.8494×10^{-7}
United States	5.1033×10^{-8}	5.1007×10^{-8}	5.1009×10^{-8}
Australia	7.0257×10^{-7}	7.0198×10^{-7}	7.0196×10^{-7}

Table 5.6: Best-fitted values of β for the SEIR and delayed SIR models. SIR$^{(2)}$ denotes the SIR model when $q = e^{-\mu\tau}$ and SIR$^{(1)}$ denotes the SIR model when $q = 1$.

Country	$\mathcal{R}_0^{SEIR}$	$\mathcal{R}_0^{(2)}$	$\mathcal{R}_0^{(1)}$
France	0.7387	0.7297	0.7298
South Africa	0.9994	0.9983	0.9984
United States	0.99293	0.99242	0.99251
Australia	0.98525	0.98443	0.98444

Table 5.7: Calculated values of $\mathcal{R}_0$ for the SEIR and the delayed SIR models. $\mathcal{R}_0^{(2)}$ and $\mathcal{R}_0^{(1)}$ is the basic reproduction number for the SIR model when $q = e^{-\mu\tau}$ and $q = 1$, respectively.

As shown in Table 5.6 the SIR model with delay has values of β smaller than the SEIR model. As seen in Table 5.7 two models show $\mathcal{R}_0$ less than one for all countries, which implies that the meningococcal disease is eradicated in these countries. When values of the basic reproduction number for each model are compared, we see that the SIR model with delay has a smaller basic reproduction number $\mathcal{R}_0$ than the SEIR model. When values of the basic reproduction number for the SIR model under two choices for q are compared, we observe that the basic reproduction number for the SIR model when $q = e^{-\mu\tau}$ is smaller than the choice of $q = 1$ for all countries. Based on the published datasets, we conclude that the SIR model with delay has a lower basic reproduction number.

Conclusion

We examined two distinct models, namely, the SEIR model and the delayed SIR model, to study how the latent duration affects the dynamics of infectious disease spread. The main difference between these two models is that the SEIR model describes the latent course with a separate compartment, whereas the delayed SIR model explains it with a fixed lag term. We discussed the structure of the two models under appropriate biological assumptions and proved the positivity and boundedness of the models' solutions for biological validity. The residence time in compartment E in the SEIR model has an exponential distribution with the rate parameter σ, and the mean amount of time spent in this compartment is $1/\sigma$. On the other hand, the SIR model with delay is based on a constant time elapse (τ) between pathogen exposure and disease transmission; this lag term is included in the infectious compartment. We introduced a survival term q in the delayed SIR model, describing the chance of surviving the latent duration τ. We analyzed the model under two scenarios: first, we assume $q = 1$, which means that no one dies while in the latent state and that everyone survives the duration τ. The second assumption is $q = e^{-\mu\tau}$; this implies that if the time spent in the latent phase of duration τ before dying is exponentially distributed, then q is the probability of an individual entering the latent phase at time $t = 0$ and remaining there for $\tau > 0$. We showed that all models have two equilibria: the disease-free equilibrium and the endemic equilibrium. From equilibria's stability analysis, we showed that the stability threshold and the basic reproduction number $\mathcal{R}_0$ are identical for both models. It is verified that the disease dies out if $\mathcal{R}_0 < 1$, but persists in the population if $\mathcal{R}_0 > 1$; this result holds for both two models. The basic reproduction number for the SEIR model and delayed SIR model when $q = e^{-\mu\tau}$ is affected by the latent parameters σ and τ, respectively. On the other hand, the basic reproduction number for the SIR model under the assumption of $q = 1$ is unaffected by the latent parameters τ. We demonstrated that assuming equal latent duration in both models ($\tau = 1/\sigma$), the basic reproduction number for the SEIR model is greater than the basic reproduction number for the delayed SIR when $q = e^{-\mu\tau}$. When we compared the basic reproduction number for the delayed SIR model, we observed that for $q = e^{-\mu\tau}$ and $q = 1$ the delayed SIR

model has almost the same values basic reproduction number. We used numerical simulations to support our analytical results and applied a model-fitting approach to real-world data. Using the least squares method and published datasets from four countries, we estimated the best-fitted transmission rate β of the models see Table 5.6 and calculated the basic reproduction number see Table 5.7.

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