Global stability analysis for a tick-borne model

by

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Submitted to the Department of Mathematics
in partial fulfillment of the requirements for the degree of

Master of Science in Applied Mathematics

at the

NAZARBAYEV UNIVERSITY

May 2019

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Abstract

This thesis consider three type of epidemiological models: SIR, SIS and SIRS with nonlinear incidence rate and piecewise constant delay of generalized type. In this paper the total population size is varied with time elapse. We study the global asymptotic stability of the disease-free and endemic equilibrium states of models by constructing suitable Lyapunov functions and Lyapunov–LaSalle technique. The main contribution of this master thesis is to develop more realistic compartmental models by extending the literature of models with piecewise constant delay. The theoretical findings are illustrated through numerical simulations.

Thesis Supervisor: Ardak Kashkynbayev
Title: Assistant Professor

Acknowledgments

Firstly, I would like to thank my thesis supervisor, Professor Ardak Kashkynbayev, for his guidance and help throughout my research work.

I would also like to express my gratitude to Professor Anastasios Bountis for his valuable help throught my graduate studies. Under his guidance, the second Summer School of Kazakhstan was held at Al Farabi Kazakh National University in Almaty between May 28th - June 8th, 2018, where I had an opportunity to participate in many research seminars. It is also worth emphasising, that with his help I had an individual study room equipped with computers, where I could study on my thesis. Moreover, I am very grateful for his comments and suggestions given during this term needed for improvements of my thesis paper.

I am also thankful to Professor Yang Kuang for his valuable comments, advice, and suggestions.

Finally, I would like to thank my family, my groupmates and friends for their moral support and motivation during this process.

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Chapter 1

Introduction

This thesis concentrates on developing more realistic modeling of epidemic dynamics. Mathematical epidemiological models help to investigate the rate of disease transmission in a given population. Numerical simulations help to analyze the spread characteristics of the diseases. Based on the results and simultaions, we may control the speed of disease transmission and take measures like vaccination to prevent or reduce epidemic outbreaks. With the help of mathematical modelling, we may get answers to many questions that concerns us, such as:

- how many people will require vaccination? How many living things such as animals, birds and insects will require treatment?
- how long will the epidemic last?
- when we should take measures in order to reduce epidemy?
- will the infection disappear after some time?

1.1 Contributions

Huang and Takeuchi [24] have recently studied diseases spread by vectors. They presented time delay as $t - \tau$, where $\tau > 0$ denotes time elapse for development of infection in a vector. The authors considered models with nonlinear incidence

rate and constant time delay. However, Busenberg and Cooke [31] considered vertically transmitted diseases, where disease is passed from parentage to their offsprings. To denote that an infection is transmitted with discrete generations they used the greatest integer functions to represent a time delay as $[t]$ [31]. In this thesis we consider models with nonlinear incidence rate and piecewise constant delay to make investigation more precise for the diseases that are transmitted with discrete generations. Usually the total population size is held constant in the literature; however, we consider the total population that is varied with time elapse. Using the next generation matrix technique [11], we compute the basic reproduction number and show that if $R_0 \leq 1$, there is only one equilibrium state, which is the disease-free equilibrium, and it is asymptotically stable, and if $R_0 > 1$, then there are two equilibrium states: disease-free equilibrium, which is unstable, and endemic equilibrium, which is asymptotically stable. We present the theoretical results through numerical simulations. Although the primary focus of this work is disease dynamics, researchers working in the fields such as biology, mathematical biology, bioengineering, and medicine will benefit from the results of this thesis.

1.2 Guide to the Thesis

Chapter 2

In this chapter, we give a general background to mathematical epidemiological modeling, introducing key concepts such as incidence rates, time delays, basic reproduction number, and asymptotic stability of equilibria.

Chapter 3

In the first half of this chapter, we discuss about delay differential equations, and in the second half, we discuss about differential equations with piecewise constant argument. Here we give definitions, theorems about existence and uniqueness of the solutions, and stability theorems.

Chapter 4

Here we consider SIR, SIS and SIRS models. We prove their global asymptotic stability by constructing suitable Lyapunov functions, and represent our results through

numerical simulations.

Chapter 5

In this final chapter, we make our conclusions and provide ideas for further study.

Chapter 2

Epidemic Modelling Background

2.1 Basic Compartmental Model

2.1.1 Kermack and McKendrick

The earliest formulation of epidemiological mathematical modeling was presented by Kermack-McKendrick [16] in 1926. Based on disease state of individuals at time t, a population of size N is separated into three distinct groups: S, I and R, where S denotes the number of susceptible individuals, who has no immunity against to the infection, I denotes the number of infected people, who is contagious and can transmit the disease, and R denotes the number of people, who has been recovered from a disease.

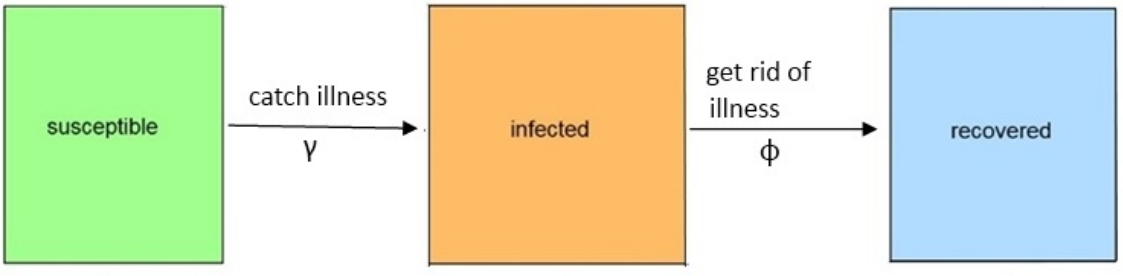

Figure 2-1: SIR diagram

This SIR model describes a disease process, where a susceptible individual from class S catches infection by a contact with infected individual; as a result, becomes contagious and moves from the compartment S to I, and after ful recovery from a

disease moves from the compartment I to R and gains an opportunity no longer get infected.

Because of movement of individuals between compartments, the change in each class is modelled as differential equations. Therefore, SIR model is a system that consists of three differential equations:

$$\begin{aligned} S'(t) &= -\gamma SI, \\ I'(t) &= \gamma SI - \phi I, \\ R'(t) &= \phi I, \end{aligned} \tag{2.1}$$

where $\gamma > 0$ is a transmission rate and $\phi > 0$ is a recovery rate.

An interaction between susceptibles with infected at transmission rate γ forms new infected individuals, and therefore the term γSI in the system (2.1) is negative for susceptible class and positive for infected class. The more susceptibles or the more infected individuals, the faster the disease spread. The recovery of infected individuals at rate ϕ forms new recovered individuals, and thus the term ϕI is negative for infected class and positive for recovered class.

The disease is assumed to be spread evenly between compartments and therefore the mixing of class members is homogeneous. The disease transmission process is shown by a diagram in Fig.2-1.

Later to make these models more realistic, the birth rate α and a natural mortality rate ρ were added to SIR model (2.1), where the recruitment rate of newborns into the susceptible class is directly proportional to the population $\alpha = \rho N$. This is biologically reasonable, since the larger population, the faster the growth of the population. SIR model with vital dynamics is illustrated in the Fig.2-2

SIR model with vital dynamics has the following form:

$$\begin{aligned} S'(t) &= \alpha - \rho S - \gamma SI, \\ I'(t) &= \gamma SI - \phi I - \rho I, \\ R'(t) &= \phi I - \rho R, \end{aligned} \tag{2.2}$$

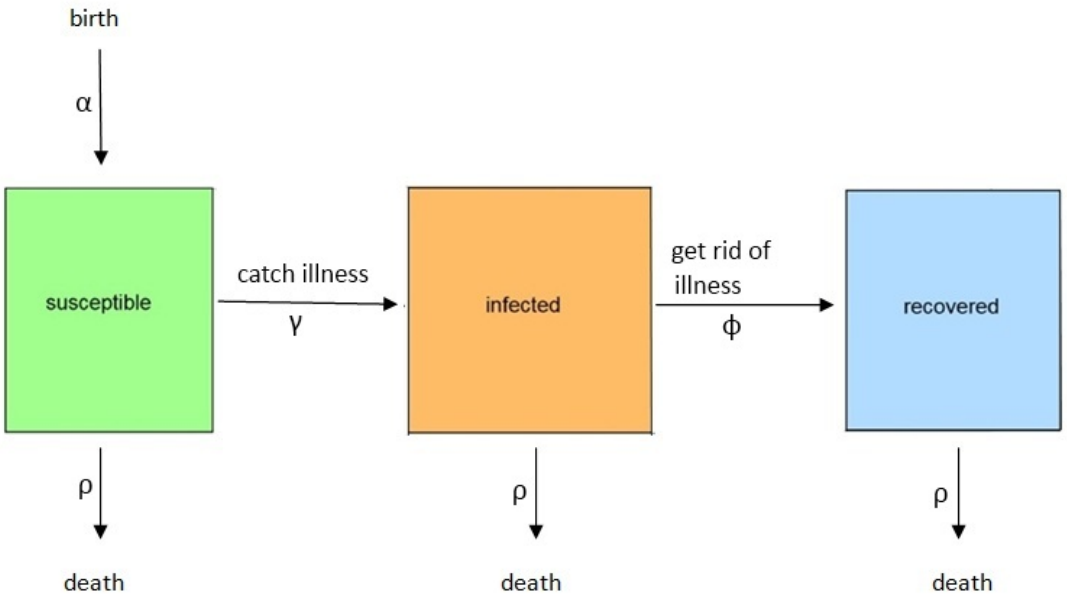

Figure 2-2: SIR model with vital dynamics

where the population size of the system (2.3) $N = S + I + R$ is constant, since $N'(t) = S'(t) + I'(t) + R'(t) = \alpha - \rho(S + I + R) = \rho N - \rho N = 0$. Hence, it is assumed that death rate is equal to the recruitment rate.

The population size is assumed to be constant, because it is considered only at the beginning of epidemy, that usually lasts for a few months for most of diseases, and during this period of time, a change in the number of births and deaths or in the number of migratted people (in and out of community) are too small, so that the change in population size is negligible.

To make a computation easier, the equations in the system (2.3) is divided by the constant population size N, and we obtain

$$\begin{aligned} s'(t) &= \alpha - \rho s - \gamma s i, \\ i'(t) &= \gamma s i - \phi i - \rho i, \\ r'(t) &= \phi i - \rho r, \end{aligned} \tag{2.3}$$

where $s = \dfrac{S}{N}$, $i = \dfrac{I}{N}$ and $r = \dfrac{R}{N}$ denote the fractions of classes in the population of normalized size 1.

Based on these formulations (2.1) and (2.3), other different epidemiological mod-

els, such as SIR, SIS, SEI, SI, SEIS, SEIR, SIRS and SEIRS have been developed and studied.

2.2 Incidence Rate

A transmission rate γ shown in Fig.2-1 is the rate of disease spread among susceptibles through their contacts with infected. Hence, the transmission rate γ together with s and i forms the class of new infected individuals. This term γsi in the systems (2.1) and (2.3) is called as bilinear incidence rate.

Epidemiological models with populations of homogeneous mixing are mostly used with bilinear incidence rate γsi and standard incidence rate γsI. However, if the model includes heterogeneous mixing, then a standard incidence and bilinear incidence rates might be irrelevant. In such case, nonlinear incidence rate should be added to the model.

If the proportion of infected individuals is too big, then the disease transmission rate may rise slower than a linear growth. This phenomenon also implies a nonlinear incidence rate and is called as saturation effect. Therefore, due to this effect Capasso and Serio [26] suggested a saturated incidence rate $\frac{\gamma is}{1+\alpha i}$, which seems more appropriate than the bilinear incidence rate γsi, since it keeps from unboundedness of the contact rate.

At the same time, Liu et al. [19, 20] considered a nonlinear incidence rate of the form $\gamma i^p s^q$, where p and q are positive constants. It was detected that SIR model with this rate might lead to Hopf bifurcation, saddle-node bifurcation, and bistable equilibria. Over last few decades, this form of a nonlinear incidence rate attracted much attention and have been studied later by Hethcote et al. [14], Derrick and van den Driessche [12, 13], Li and Muldowney [21], and others.

A functional form of nonlinear incidence rate was proposed by Hethcote and van den Driessche [15]. They introduced models with the rate $g(i)s$. The most general form of nonlinear incidence rate given by a function $f(s,i)$ was first studied by Feng and Thieme [27, 28] that satisfies the following conditions: "if there is no any susceptible or infected individuals in the population, then there is no disease trans-

mission". Later, Korobeinikov [2, 3, 4, 5] and Korobeinikov and Maini [6] added other two conditions: "the disease transmission rate with respect to susceptible or infected is positive", and "when the epidemy reaches its peak, the disease transmission will decrease". They also investigated the global properties of models with incidence rate $f(s)g(i)$ and $f(s,i)$ by constructing Lyapunov functions.

Taking into account the discussion above, SIR model (2.3) with nonlinear incidence rate has the following form:

$$\begin{aligned} s'(t) &= \alpha - \rho s - f(s,i), \\ i'(t) &= f(s,i) - \phi i - \rho i, \\ r'(t) &= \phi i - \rho r. \end{aligned} \tag{2.4}$$

2.3 Time Delay

Usually, viral diseases progress slower than other diseases. It takes time untill an infected person becomes infectious for others to spread the disease, and time elapse between an injection of the virus to a human body and a development of this infection is called as the latent period. This period may last for a few days, months, and even several years. For instance, smallpox virus develops in a human organism for 10 - 14 days, and the first symptoms appear only after this incubation period [42]. The latent period for genital warts is between 2 weeks and 8 months [43]; whereas, the latent period for AIDS is about 10 years [44]. Thus, the latent period is worth considering in epidemic dynamics, and therefore time delay due to latent period in host is usually added to the models.

The transmission of diseases such as malaria, yellow fever, African sleeping sickness is much slower than others, because they are not transmitted directly from a person to person. They are spread due to vectors (agents like mosquitoes, tsetse flies, birds and insects). There is time elapse for agents to be infected first by people and then to transmit this infection to others. For instance, malaria parasites develops within the mosquito at least 9 days, and only then this mosquito is able to transmit an infection [41]. This is known as time delay due to the latency in a vector. The

first epidemic model with discrete delay was proposed by Cooke [30] in his work on a vector-born disease. He presented time delay as $t - T$, where $T > 0$ denotes time elapse for development of infection in a mosquito.

2.4 Basic Reproduction Number and Stability

There are two equilibrium states of the system: **disease free equilibrium** and **endemic equilibrium**. For example, set the right-hand side of the second equation of the system (2.2) to zero and obtain $S = \frac{\phi + \rho}{\gamma}$ or $I = 0$.

First, let us consider $I = 0$. Now setting the first equation of the system (2.2) to zero and substituting $I = 0$ yields $S = \frac{\alpha}{\rho}$, whereas, setting the third equation of the system (2.2) to zero and substituting $I = 0$ yields $R = 0$. Hence $(S_0, I_0, R_0) = (\frac{\alpha}{\rho}, 0, 0)$ is called as disease free equilibrium (DFE), because at this state there is no infected population, $I = 0$.

Now let us consider $S = \frac{\phi + \rho}{\gamma}$. Setting the first equation of (2.2) to zero gives $I = \frac{\alpha - \rho S}{\gamma S}$. Plugging in S yields $I = \frac{\alpha\gamma - \rho(\phi + \rho)}{\gamma(\phi + \rho)}$. Setting the last equation of (2.2) to zero gives $R = \frac{\phi I}{\rho}$. Plugging in I yields $R = \frac{\phi}{\rho} \cdot \frac{\alpha\gamma - \rho(\phi + \rho)}{\gamma(\phi + \rho)}$. Hence, the endemic equilibrium is at

$$\big(S^*, I^*, R^*\big) = \big(\frac{\phi + \rho}{\gamma}, \quad \frac{\alpha\gamma - \rho(\phi + \rho)}{\gamma(\phi + \rho)}, \quad \frac{\phi}{\rho} \cdot \frac{\alpha\gamma - \rho(\phi + \rho)}{\gamma(\phi + \rho)}\big).$$

The endemic equilibrium exists if the numerators of the fractions are strictly positive. Hence, it exists if $\alpha\gamma > \rho(\phi + \rho)$ or $\mathcal{R}_0 = \frac{\alpha\gamma}{\rho(\phi + \rho)} > 1$.

To analyze the local stability of these equilibria, we compute the Jacobian matrix.

Jacobian matrix of (2.2) is

$$J(S,I,R) = \begin{bmatrix} \frac{\partial S'}{\partial S} & \frac{\partial S'}{\partial I} & \frac{\partial S'}{\partial R} \\ \frac{\partial I'}{\partial S} & \frac{\partial I'}{\partial I} & \frac{\partial I'}{\partial R} \\ \frac{\partial R'}{\partial S} & \frac{\partial R'}{\partial I} & \frac{\partial R'}{\partial R} \end{bmatrix} = \begin{bmatrix} -\rho - \gamma I & -\gamma S & 0 \\ \gamma I & \gamma S - \phi - \rho & 0 \\ 0 & \phi & -\rho \end{bmatrix}$$

We compute Jacobian at DFE that is:

$$J\big|_{(S_0, I_0, R_0)} = \begin{bmatrix} -\rho & -\frac{\gamma\alpha}{\rho} & 0 \\ 0 & \frac{\gamma\alpha}{\rho} - \phi - \rho & 0 \\ 0 & \phi & -\rho \end{bmatrix}$$

To analyze the local stability, we calculate eigenvalues of $J\big(S_0, I_0, R_0\big)$

$$\det(J - \lambda I) = \begin{bmatrix} -\rho - \lambda & -\frac{\gamma\alpha}{\rho} & 0 \\ 0 & \frac{\gamma\alpha}{\rho} - \phi - \rho - \lambda & 0 \\ 0 & \phi & -\rho - \lambda \end{bmatrix}$$

$$= -\rho - \lambda \begin{bmatrix} -\rho - \lambda & -\frac{\gamma\alpha}{\rho} \\ 0 & \frac{\gamma\alpha}{\rho} - \phi - \rho - \lambda \end{bmatrix}$$

$$= (\rho + \lambda)^2 \big(\frac{\gamma\alpha}{\rho} - \phi - \rho - \lambda\big) = 0.$$

This characteristic equation yields $\lambda_1 = -\rho$, $\lambda_2 = -\rho$, and $\lambda_3 = \frac{\gamma\alpha}{\rho} - \phi - \rho$.
If $\lambda_3 < 0$, then an equilibrium state is locally asymptotically stable. Thus, the disease free equilibrium is **locally asymptotically stable** if $\frac{\gamma\alpha}{\rho} - \phi - \rho < 0$ or $\mathcal{R}_0 = \frac{\gamma\alpha}{\rho(\phi + \rho)} < 1$. If $\mathcal{R}_0 > 1$, then it is unstable.

Now to analyze local stability of endemic equilibrium, we compute the Jacobian matrix at $\big(\ S^*, I^*, R^*\big)$.

$$J\big|_{(S^*, I^*, R^*)} = \begin{bmatrix} -\rho - \gamma I^* & -(\phi + \rho) & 0 \\ \gamma I^* & 0 & 0 \\ 0 & \phi & -\rho \end{bmatrix}$$

We calculate the determinant of the matrix $\det(J - \lambda I) = 0$ in terms of the last column, and obtain the first eigenvalue $\lambda_1 = -\rho$. The other two eigenvalues can be obtained from this submatrix:

$$J_1\big|_{(S^*, I^*, R^*)} = \begin{bmatrix} -\rho - \gamma I^* & -(\phi + \rho) \\ \gamma I^* & 0 \end{bmatrix}$$

The computation of eigenvalues from the characteristic equation of the submatrix J_1 is not straightforward, because of complicated expression of I^*, so we consider $\mathrm{tr}(J_1)$ and $\det(J_1)$. We need $\mathrm{tr}(J_1) < 0$ and $\det(J_1) > 0$ for the equilibrium state to be an asymptotically stable. So, $\mathrm{tr}(J_1) = -\rho - \gamma I^* = -\rho - \dfrac{\alpha\gamma - \rho(\phi + \rho)}{(\phi + \rho)}$ and $\det(J_1) = \alpha\gamma - \rho(\phi + \rho)$. Since the endemic equilibrium exists only if $\mathcal{R}_0 = \dfrac{\gamma\alpha}{\rho(\phi + \rho)} > 1$, then $\mathrm{tr}(J_1) < 0$ and $\det(J_1) > 0$. Thus, if the endemic equilibrium exists, it is always **locally asymptotically stable**.

Taking into account all analyses above, we conclude our results in the following lemma:

Lemma 2.1. if $\mathcal{R}_0 \leq 1$, then there is only one equilibrium, disease-free equilibrium $E_0(S_0, I_0, R_0)$, which is locally asymptotically stable, and if $\mathcal{R}_0 > 1$, then there are equilibrium states: disease-free equilibrium, which is unstable, and endemic equilibrium, $E^*(S^*, I^*, R^*)$, which is locally asymptotically stable.

Although there are many parameters involved in the analyses above, there is only one parameter $\mathcal{R}_0$, which is important in stability analyses, since it determines whether an epidemy will occur or not. So later on, van den Driessche and Watmough [11] provided a general approach to calculate the basic reproduction number, that is known as the next generation matrix. They showed that the basic reproduction number is the largest eigenvalue of this matrix.

According to this approach, $\mathcal{R}_0$ for a system (2.4) is obtained as

$$\mathcal{R}_0 = \frac{1}{\phi + \rho} \frac{\partial f(s_0, 0)}{\partial i}. \tag{2.5}$$

Even though obtained the basic reproduction number is different for different models, they all obey the same lemma above.

2.5 Motivation

Tick-borne diseases are a serious health problem throughout the world, and demand an attention, since they have rapidly increased over last few years. In 2004 the number of tickborne disease cases was 22527, while by 2017, it significantly increased up to 59349 [46]. In 1920 there was one case per million and in 2015 there were 13 cases per million [47]. One of the examples of the tick-borne disease is Crimean-Congo hemorrhagic fever, that occurs in Central Asia, China, Eastern Europe, Africa, and the Middle East [51]. Omsk Hemorrhagic Fever (OHF) is another tickborne disease found in Omsk, Tyumen, and Novosibirsk.

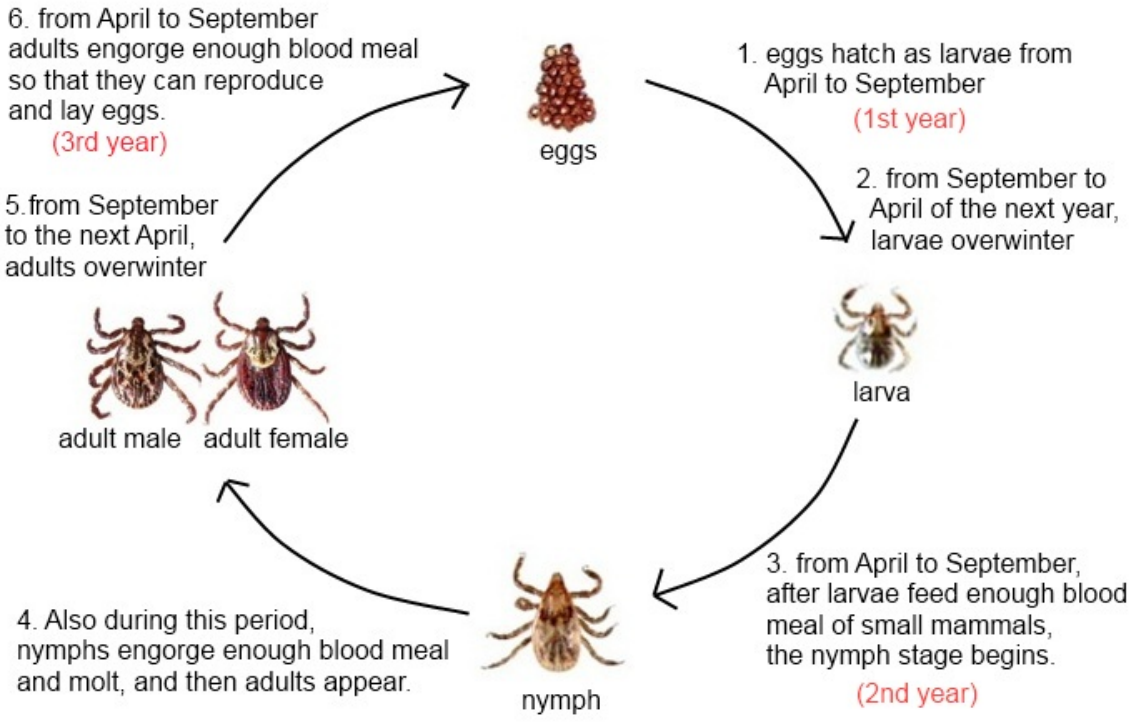

Figure 2-3: Seasonal life stages of tick

The most prevalent tick-borne disease in the United States is Rocky Mountain Spotted Fever [47]. It occurs mostly in Oklahoma, Missouri, Arkansas, Tennessee, and North Carolina. 5-10 % of Rocky Mountain spotted fever cases are fatal if treatment is not taken on time [47]. The agent that cause Rocky Mountain spotted fever is known as Rickettsia rickettsi. It is transmitted by three species of ticks: brown dog tick (Rhipicephalus sanguineus), Rocky Mountain wood tick (Dermacentor andersoni), and American dog tick (Dermacentor variabilis) [48].

One of the dangerous tick-borne disease in Kazakhstan is Crimean-Congo Hemorrhagic Fever (CCHF). CCHF cases mostly occur in Taraz, Kyzylorda, and South Kazakhstan regions [55]. 704 cases of CCHF were reported in Kazakhstan between 1948 and 2013 with mortality rate of 14.8% [55]. From 5% to 30% of hospitalized individuals can ended up with death [56]. In Kazakhstan at most 10 CCHF cases occur annually [56]. CCHF virus among people is transmitted by ixodid ticks [52].

Usually ticks pass through four stages of the life cycle: eggs, larvae, nymphs, and adults [45]. To pass from one stage to the next, it need to feed blood meal of the host. As we can see from the Fig.2-3, usually ticks feed blood meal of host from April to September and the rest of the time they overwinter. Brown dog tick usually engorge blood meal of the same host during all its life stages. At the stage of nymphs and adults, they can even bite and feed on humans, and transmit Rickettsia rickettsi, if they are infected. As a result, a contact with infected ticks may cause a Rocky Mountain spotted fever among people [31]. However, unlike brown dog ticks, American dog ticks engorge different hosts at their different life stages (See Fig.2-4). Usually, larvae prefer blood of mice and voles, nymphs prefer opossum and raccoons, and adults prefer dogs and deers [49]. Only at this stage, ticks can also bite and engorge blood of humans, and transmit Rickettsia rickettsi, if they are infected. Whereas, larvae and nymphs of ixodid tick species require blood meal of birds, mice and hares, and adult ticks engorge livestock such as goats and sheep [52, 53]. Similarly as American dog ticks, only infected adult ticks can bite and feed humans, and may transmit CCHF virus (See Fig.2-5).

These diseases takes time until ticks grow up as adults to pass an infection to humans. Different species of ticks need different time period to complete their life

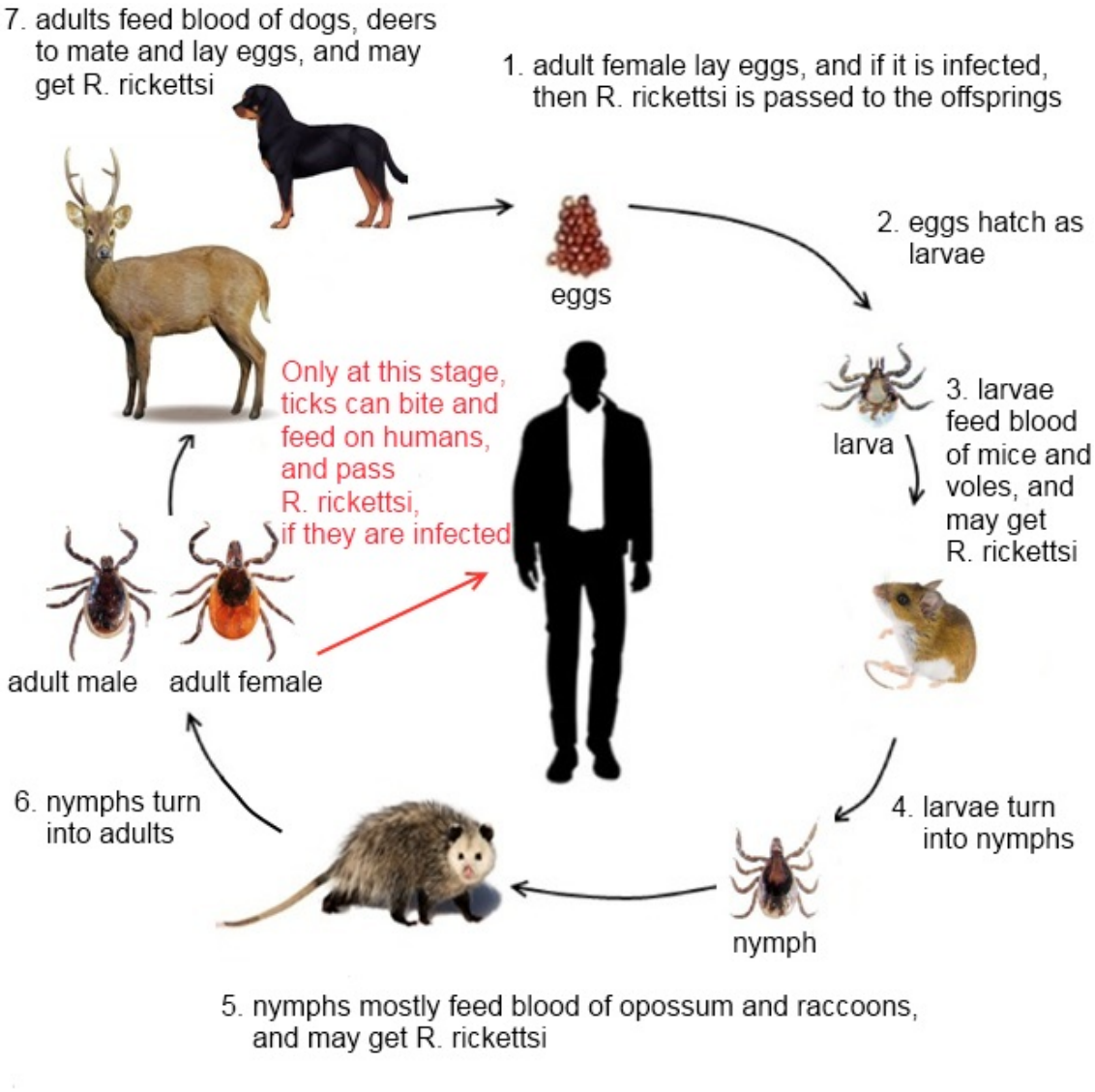

Figure 2-4: Life cycle of the American dog tick and the spread of Rickettsia rickettsii

cycle. For example, in Nova Scotia it occurs for two years; whereas, in Virginia it would be one year [31]. To model Rocky Mountain spotted fever and to make a computation easier, Busenberg and Cooke normalized the time variable so that each generation is considered for one unit of time. They used the greatest integer functions to represent a time delay as $[t]$ to denote that an infection is handed down with discrete generations [31].

The present study generalizes this idea by considering so-called $\beta-$type argument functions. One of the advantages of the current study is that we do not normalize the

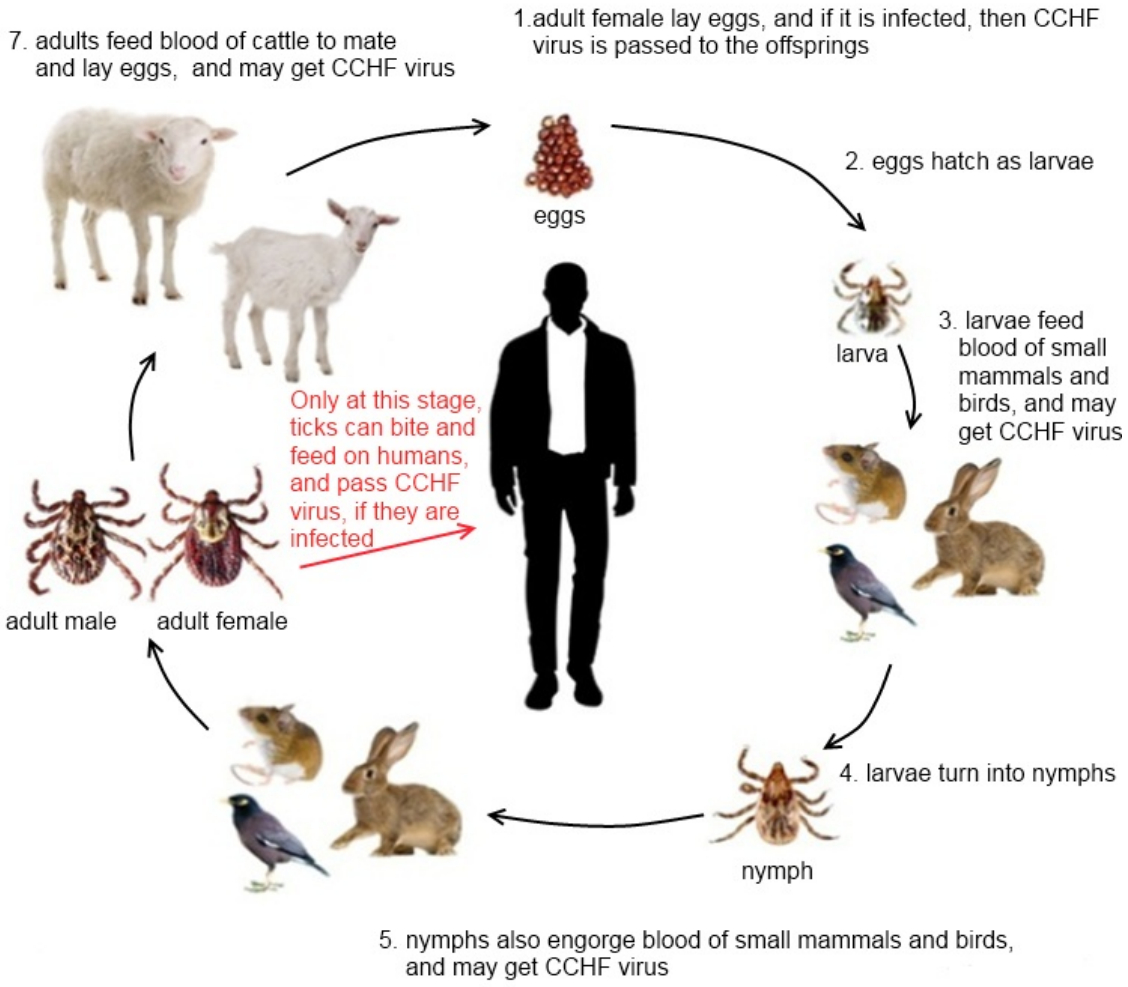

Figure 2-5: Life cycle of the ixodid tick and the spread of CCHF virus

time variable and consider epidemic models with piecewise constant arguments of generalized type which have features of both discrete and continuous time dynamics.

Chapter 3

Differential Equation Theory

3.1 Delay Differential Equations

We consider a delay differential equation:

$$x'(t) = f(t, x_t). \tag{3.1}$$

$C := C([-k, 0], \mathbb{R}^n)$ is a set of continuous functions mapping $[-k, 0]$ to $\mathbb{R}^n$, where k is a positive constant. Assume Ω is an open subset of $\mathbb{R} \times C$ [23], $x(t) : \Omega \to \mathbb{R}^n$, define the function $x_t : [-k, 0] \to \mathbb{R}^n$ by $x_t(\sigma) := x(t + \sigma), \quad \sigma \in [-k, 0]$.

3.1.1 Existence and Uniqueness

Theorem 3.1. [23] Let $f : \Omega \to \mathbb{R}^n$ be continuous on Ω. If $(r, \delta) \in \Omega$, then there is a solution of (3.1) passing through (r, δ).

Definition 3.1. [23] $f(t, \delta)$ is *Lipschitz* in δ in a compact set M of $\mathbb{R} \times C$ if $\exists$ a constant $m > 0$ such that, for $\forall (t, \delta_i) \in M, \quad i = 1, 2,$

$$|f(t, \delta_1) - f(t, \delta_2) \leq m|\delta_1 - \delta_1|.$$

Theorem 3.2. [23] Let Ω be an open set in $\mathbb{R} \times C$, $f : \Omega \to \mathbb{R}^n$ be continuous, and $f(t, \delta)$ is Lipschitz in δ in each compact set in Ω. If $(r, \delta) \in \Omega$, then there is a

unique solution of (3.1) passing through (r, δ).

3.1.2 Stability Theorems

Suppose

$$x'(t) = f(x_t), \tag{3.2}$$

where $f : \mathbb{C} \to \mathbb{R}^n$ is continuous, and $x(\delta)$ is a solution through $(0, \delta)$.
For a continuous functional $V : \mathbb{C} \to \mathbb{R}$, define

$$V'(\delta) = \overline{\lim}_{h \to 0^+} \frac{1}{h}[V(x_h(\delta)) - V(\delta)],$$

the derivative of V along a solution of (3.2).

Definition 3.2. [23] $V : \mathbb{C} \to \mathbb{R}$ is a *Lyapunov functional* on a set J in C for Eq. (3.2), if it is continuous on $\bar{J}$ (the closure of J) and $V' \leq 0$ on J.
Define $E = \{\delta \in \bar{J} : V'(\delta) = 0\}$ and M is the largest set in E that is invariant with respect to Eq. (3.2).

Lyapunov-LaSalle theorem 3.3. [23] If V is a Lyapunov functional on J and $x_t(\delta)$ is a bounded solution of (3.2) in J, then $x_t(\delta) \to M$ as $t \to +\infty$.

3.2 Differential Equations with Piecewise Constant Argument

3.2.1 Notations and Definitions

The first model with piecewise constant argument, studied by Busenberg and Cooke in 1982, was of the following form [7]:

$$x'(t) = f(t, x(t), x([t])), \tag{3.3}$$

where $x \in \mathbb{R}^n, t \in \mathbb{R}$, and $[\cdot]$ is the greatest integer function.

According to Arugaslan [9], adding piecewise constant arguments to models means that the rate of the population depends on the present size and the memorized values of the population.

Many differential equations with piecewise constant argument are investigated by reducing them into discrete equations. However, stability analysis may not be evaluated completely for this class of equations of the initial-value problems. So, Akhmet [7] generalized these differential equations by considering any piecewise constant functions as arguments. This new approach helped to solve stability problems. Later, Akhmet, Arugaslan, and Yilmaz [10] developed the following form of Lyapunov method for these equations with piecewise constant arguments of generalized type:

$$x'(t) = f(t, x(t), x(\beta(t))), \tag{3.4}$$

where $x \in B(h),\ B(h) = \{x \in \mathbb{R}^n : \|x\| < h\},\ t \in \mathbb{R}^+,\ \beta(t) = \theta_i \quad \text{for } t \in [\theta_i, \theta_{i+1}),\ i \in \mathbb{N}$, and $\theta_i,\ i \in \mathbb{N}$, is a fixed real-valued increasing sequence such that $\theta_i \to \infty$ as $i \to \infty$. It is assumed that there exists a positive number θ such that $\theta_{i+1} - \theta_i \leq \theta,\ i \in \mathbb{N}$.

This new method is more effective, because it does not require the reduction to discrete equations and it considers nonlinear systems.

3.2.2 Existence and Uniqueness

Definition 3.3. [7] A function $x(t)$ is a solution of (3.4) on $\mathbb{R}^n$ if

i. $x(t)$ is continuous on $\mathbb{R}^n$;

ii. the derivative $x'(t)$ exists for $t \in \mathbb{R}^n$ with the possible exception of the points $\theta_i,\ i \in \mathbb{N}$, where one-sided derivatives exist;

iii. (3.4) is satisfied by $x(t)$ on each interval $(\theta_i, \theta_{i+1}),\ i \in \mathbb{N}$ and it holds for the right derivative of $x(t)$ at the points $\theta_i,\ i \in \mathbb{N}$.

The following conditions will be needed throughout the section:

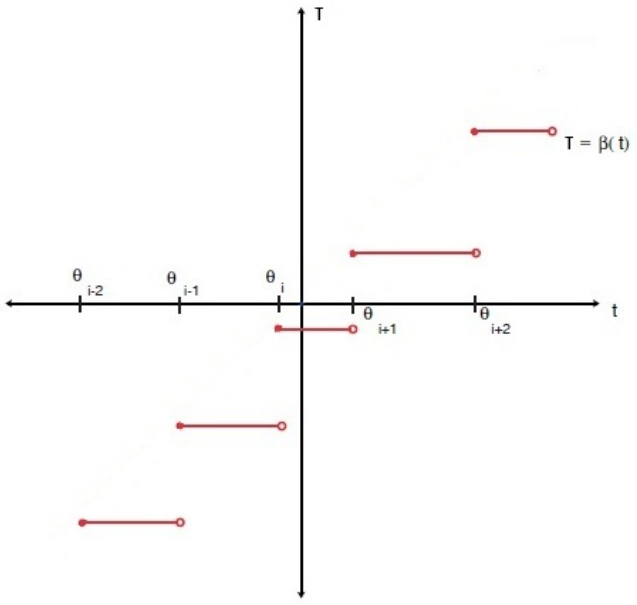

Figure 3-1: The graph of β - time delay [7]

(C1) $f(t, y, z) \in (\mathbb{R}^+ \times B(h) \times B(h))$ is an $n \times 1$ real valued function;

(C2) $f(t, y, z)$ satisfies the condition:

$$\|f(t, y_1, z_1) - f(t, y_2, z_2)\| \leq l(\|(y_1 - y_2)\| + \|(z_1 - z_2)\|)$$

for $\forall t \in \mathbb{R}^+$ and $y_1, y_2, z_1, z_2 \in B(h)$, where $l > 0$ is a Lipschitz constant;

(C3) $\exists$ a positive number θ such that $\theta_{i+1} - \theta_i \leq \theta$, $i \in \mathbb{N}$;

(C4) $l\theta[1 + (1 + l\theta)e^{l\theta}] < 1$;

(C5) $3l\theta e^{l\theta}] < 1$.

Theorem 3.4. [7] If the conditions $(C1) - (C5)$ hold, then for $\forall (t_0, x_0) \in \mathbb{R}^+ \times B(h)$ there exists a unique solution $x(t) = x(t, t_0, x_0)$ of (3.4) on $\mathbb{R}^+$ such that $x(t_0) = x_0$.

3.2.3 Stability

Definition 3.4. [7] The zero solution of (3.4) is

(C1) stable if for $\forall \epsilon > 0$ and $t_0 \in \mathbb{R}^+$, there exists a $\nu = \nu(t_0, \epsilon) > 0$ such that $\|x_0\| < \nu$ implies $\|x(t, t_0, x_0)\| < \epsilon$ for $\forall t \geq t_0$;

(C2) uniformly stable if ν is independent of t_0.

Definition 3.5. [7] The zero solution of (3.4) is uniformly asymptotically stable if it is uniformly stable and there is a $\nu_0 > 0$ such that for $\forall \epsilon > 0$ and $t_0 \in \mathbb{R}^+$, there exists $T = T(\epsilon) > 0$ such that $\|x(t, t_0, x_0)\| < \epsilon$ for $\forall t > t_0 + T$ whenever $\|x_0\| < \nu_0$.

Chapter 4

Epidemiological Models with Nonlinear Incidence Rate and Generalized Piecewise Constant Argument

In this thesis, we consider SIR, SIRS and SIS models with generalized piecewise constant argument. In most of the existing compartmental models in the literature population size is considered to be constant. However, in the reality these are merely the case. Thus, the population size, $N(t) = s(t) + i(t) + r(t)$, is varied for all these three models. Once infected an individual is shifted from s, susceptible population, to i, infected population. Upon a recovery if an individual gains permanent immunity against the disease then the individual is shifted to r, recovered population. These assumptions lead us to consider SIR model that takes the following form.

$$\begin{aligned} s'(t) &= \alpha - \kappa s(t) - f(s(t), i(\beta(t))), \\ i'(t) &= f(s(t), i(\beta(t))) - (\omega + \kappa + d)i(t), \\ r'(t) &= \omega i(t) - \kappa r(t). \end{aligned} \tag{4.1}$$

Further, if we assume that a compartmental model that does not have an immune period then, after the recovery an individual is moved from class i to the class s again. This model is known as SIS model in the literature. We consider SIS in the following form.

$$\begin{aligned} s'(t) &= \alpha - \kappa s(t) - f(s(t), i(\beta(t))) + \omega i(t), \\ i'(t) &= f(s(t), i(\beta(t))) - (\omega + \kappa + d) i(t). \end{aligned} \tag{4.2}$$

If, however, the gained immunity is not permanent then after recovery the individual becomes susceptible again. Thus, we consider SIRS model which takes the following form.

$$\begin{aligned} s'(t) &= \alpha - \kappa s(t) - f(s(t), i(\beta(t))) + \varepsilon r(t), \\ i'(t) &= f(s(t), i(\beta(t))) - (\omega + \kappa + d) i(t), \\ r'(t) &= \omega i(t) - (\kappa + \varepsilon) r(t). \end{aligned} \tag{4.3}$$

In the above models, α is the recruitment rate, ω is the recovery rate, κ is the natural death rate, $1/\varepsilon$ is an average period of immunity, d is the disease-induced death rate, and the nonlinear function $f(s, i)$ is used to model an incidence rate. We impose the following conditions on this function.

(C1) $f(s, 0) = f(0, i) = 0$;

(C2) $f(s, i)$ is a positive, continuous, differentiable and monotonically increasing function, i.e.,

$$\frac{\partial f(s, i)}{\partial i} > 0, \quad \frac{\partial f(s, i)}{\partial s} > 0 \quad \text{for all } s, i > 0;$$

(C3) $f(s, i)$ is concave with respect to i, i.e.,

$$\frac{\partial^2 f(s, i)}{\partial i^2} \leq 0 \quad \text{for all } s, i > 0.$$

It can be easily seen that all incidence rate functions such as the bilinear function,

the saturated function, and Holling type II functions mentioned in Introduction satisfy these conditions. Thus, the models (4.1),(4.3) with the nonlinear function $f(s,i)$ are the generalizations of the existing models in the literature.

In the models (4.1) and (4.2), r is decoupled from the previous equations. Thus, we ignore r component in these models. Further, by means of the condition (C1) one can easily show that the systems (4.1) and (4.2) have an equilibrium state $E_0 = (s_0, i_0)$, where $s_0 = \alpha/\kappa$ and $i_0 = 0$. Moreover, the models (4.1) and (4.2) may have a positive equilibrium state $E^* = (s^*, i^*)$, called as an endemic equilibrium, where for (4.1) its coordinates satisfy:

$$f(s^*, i^*) = \alpha - \kappa s^* = (\omega + \kappa + d)i^*,$$

and for (4.2) its coordinates satisfy:

$$f(s^*, i^*) = \alpha - \kappa s^* + \omega i^* = (\omega + \kappa + d)i^*.$$

To ensure the uniqueness of the endemic equilibrium which satisfy the above equations and for the further analysis we should need the following conditions:

(C4)

$$\lim_{i \to 0} \frac{f(s_0, i)}{f(s, i)} > 1 \quad \text{for all } s \in (0, s_0);$$

(C5)

$$\frac{i}{i^*} \leq \frac{f(s,i)}{f(s,i^*)} \leq 1 \quad \text{for } 0 < i \leq i^*,$$

$$1 \leq \frac{f(s,i)}{f(s,i^*)} \leq \frac{i}{i^*} \quad \text{for } i \geq i^*.$$

In what follows, asymptotic behavior of the compartmental models considered in this paper essentially depend on a threshold value, $\mathcal{R}_0$, so-called the basic reproduction number. By virtue of the next generation matrix technique [11] we compute the basic reproduction number for the models (4.1)-(4.2) as follows.

$$\mathcal{R}_0 = \frac{1}{\omega + \kappa + d} \frac{\partial f(s_0, 0)}{\partial i}. \tag{4.4}$$

The following lemma [6] ensures the uniqueness of the positive equilibrium $E^*(s^*, i^*)$ if $\mathcal{R}_0 > 1$.

Lemma 4.1. If the conditions $(C2)-(C4)$ hold, and if $\mathcal{R}_0 > 1$, then in addition to the disease-free equilibrium state, systems (4.1), (4.2) and (4.3) have a unique positive endemic equilibrium state $E^*(s^*, i^*)$. If $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium $E_0(s_0, i_0)$ is the only nonnegative equilibrium state of systems (4.1), (4.2) and (4.3).

To prove that the endemic positive equilibrium state $E^*(s^*, i^*)$ of SIR model is globally asymptotically stable, we define Lyapunov function as follows:

$$V_1(s,i) = s(t) - s^* - \int_{s^*}^{s(t)} \frac{f(s^*, i^*)}{f(\rho, i^*)} d\rho + i(t) - i^* - i^* \ln \frac{i(t)}{i^*}.$$

Differentiating $V_1(s,i)$ with respect to s and i, we obtain:

$$\frac{\partial V_1}{\partial s} = 1 - \frac{f(s^*, i^*)}{f(s, i^*)}, \qquad \frac{\partial V_1}{\partial i} = 1 - \frac{i^*}{i},$$

where $(s,i) = (s^*, i^*)$ is a stationary point of the function. Since $f(s, i^*)$ grows monotonically, $\dfrac{\partial V_1}{\partial s}$ grows monotonically too. Thus, $E^*(s^*, i^*)$ is the only extremum of the function. Moreover,

$$\frac{\partial^2 V_1}{\partial s^2} = \frac{f(s^*, i^*) f'(s, i^*)}{(f(s, i^*))^2} > 0, \qquad \frac{\partial^2 V_1}{\partial i^2} = \frac{i^*}{i^2} > 0,$$

while

$$\frac{\partial^2 V_1}{\partial s \partial i} = \frac{\partial^2 V_1}{\partial i \partial s} = 0,$$

$E^*(s^*, i^*)$ is the minimum. The point $E^*(s^*, i^*)$ is the only internal stationary point of the function, which is also a minimum, and $V_1(s,i) \to \infty$ as $s \to \infty$ and $i \to \infty$. Hence, $E^*(s^*, i^*)$ is the global minimum and the function is bounded from below. Therefore, $V_1(s,i)$ is indeed a Lyapunov function [50].

To prove that the disease-free positive equilibrium state $E_0(s_0, i_0)$ of SIR model is globally asymptotically stable, we define Lyapunov function as follows:

$$V_2(s,i) = s(t) - s_0 - \int_{s_0}^{s(t)} \lim_{i \to 0} \frac{f(s_0, i)}{f(u, i)} du + (\omega + \kappa + d) \int_0^{t-\theta_i} i(t-u) du + i(t),$$

for all $t \in [\theta_i, \theta_{i+1})$.

Represent $V_2(s,i)$ as the functions $G(i)$ and $F(s)$.

$G(i) = (\omega + \kappa + d)\int_0^{t-\theta_i} i(t-u)du + i(t)$ is non-negative, since $i(t)$ is non-negative, and it is zero for $i(t) = 0$.

For $F(s) = s(t) - s_0 + \int_{s(t)}^{s_0} \lim_{i \to 0} \frac{f(s_0,i)}{f(u,i)} du$, we can apply the first and second derivative test to show that s_0 is a stationary and global minimum point of the function. So, $V_2(s,i)$ is indeed a Lyapunov function.

4.1 Stability of SIR model

Considering the system (4.1), we may skip the third equation, since the last variable does not appear in the equations for $s(t)$ and $i(t)$. We notice that

$$s'(t) + i'(t) + r'(t) = \alpha - \kappa s(t) - \kappa i(t) - \kappa r(t) - di(t) \leq \alpha - \kappa\big[s(t) + i(t) + r(t)\big].$$

The last inequality implies that $\limsup_{t \to \infty} \big[s(t) + i(t) + r(t)\big] \leq \alpha/\kappa$. Thus, we study the system (4.1) in a biologically feasible region

$$\Omega = \{(s,i,r) |\ \ s > 0,\ \ i \geq 0,\ \ r \geq 0;\ \ s + i + r \leq \alpha/\kappa\}.$$

One can easily show that Ω is positively invariant with respect to SIR model (4.1), i.e., every solution which starts in Ω will remain in Ω for $t \geq 0$. Further, with the help of Lemma 4.1 we know that (4.1) has two steady states: disease-free positive equilibrium state $E_0(s_0, i_0)$ and endemic positive equilibrium state $E^*(s^*, i^*)$. In what follows, we analyze global stability of these equilibrium points by constructing appropriate Lyapunov functions.

Theorem 4.1.

i. If $(C1) - (C3)$ hold, and if $\mathcal{R}_0 \leq 1$, then the disease-free positive equilibrium state $E_0(s_0, i_0)$ is globally asymptotically stable.

ii. If $(C2) - (C5)$ hold, and if $\mathcal{R}_0 > 1$, then the endemic positive equilibrium state

$E^*(s^*, i^*)$ is globally asymptotically stable.

Proof. To prove the first part of the theorem we define another Lyapunov function as:

$$V_1(s,i) = s(t) - s^* - \int_{s^*}^{s(t)} \frac{f(s^*, i^*)}{f(\rho, i^*)} d\rho + i(t) - i^* - i^* \ln \frac{i(t)}{i^*}.$$

$$\frac{dV_1}{dt} = \alpha - \kappa s(t) - \frac{f(s^*, i^*)}{f(s(t), i^*)} \cdot s'(t) - (\omega + \kappa + d)i(t)$$

$$- \frac{i^*}{i(t)}\Big(f(s(t), i(\beta(t))) - (\omega + \kappa + d)i(t)\Big)$$

$$= \kappa s^* + f(s^*, i^*) - \kappa s(t) - \frac{f(s^*, i^*)}{f(s(t), i^*)} \cdot s'(t) - (\omega + \kappa + d)i(t)$$

$$- \frac{i^*}{i(t)}\Big(f(s(t), i(\beta(t))) - (\omega + \kappa + d)i(t)\Big)$$

$$= \kappa s^*\Big(1 - \frac{s(t)}{s^*}\Big) + f(s^*, i^*)$$

$$- \frac{f(s^*, i^*)}{f(s(t), i^*)}\Big(\kappa s^* + f(s^*, i^*) - \kappa s(t) - f(s(t), i(\beta(t)))\Big) - (\omega + \kappa + d)i(t)$$

$$- \frac{i^*}{i(t)} f(s(t), i(\beta(t))) + (\omega + \kappa + d)i^*$$

$$= \kappa s^*\Big(1 - \frac{s(t)}{s^*}\Big)\Big(1 - \frac{f(s^*, i^*)}{f(s(t), i^*)}\Big) + f(s^*, i^*) - f(s^*, i^*)\frac{f(s^*, i^*)}{f(s(t), i^*)}$$

$$+ f(s^*, i^*)\frac{f(s(t), i(\beta(t)))}{f(s(t), i^*)} - (\omega + \kappa + d)i(t) - \frac{i^*}{i(t)} f(s(t), i(\beta(t))) + f(s^*, i^*)$$

$$= \kappa s^*\Big(1 - \frac{s(t)}{s^*}\Big)\Big(1 - \frac{f(s^*, i^*)}{f(s(t), i^*)}\Big)$$
$$+ f(s^*, i^*)\Big(2 - \frac{f(s^*, i^*)}{f(s(t), i^*)} + \frac{f(s(t), i(\beta(t)))}{f(s(t), i^*)} - \frac{i(t)}{i^*} - \frac{i^*}{i(t)}\frac{f(s(t), i(\beta(t)))}{f(s^*, i^*)}\Big)$$

$$= \kappa s^*\Big(1 - \frac{s(t)}{s^*}\Big)\Big(1 - \frac{f(s^*, i^*)}{f(s(t), i^*)}\Big)$$
$$+ f(s^*, i^*)\Big(3 - \frac{f(s^*, i^*)}{f(s(t), i^*)} - \frac{i^*}{i(t)}\frac{f(s(t), i(\beta(t)))}{f(s^*, i^*)} - \frac{i(t)}{i^*}\frac{f(s(t), i^*)}{f(s(t), i(\beta(t)))}\Big)$$
$$+ f(s^*, i^*)\Big(\frac{f(s(t), i(\beta(t)))}{f(s(t), i^*)} - \frac{i(t)}{i^*} - 1 + \frac{i(t)}{i^*}\frac{f(s(t), i^*)}{f(s(t), i(\beta(t)))}\Big).$$

From the monotonicity of $f(s,i)$ with respect to s, we have

$$\Big(1-\frac{s(t)}{s^*}\Big)\Big(1-\frac{f(s^*,i^*)}{f(s(t),i^*)}\Big)\leq 0.$$

Also, from the concavity of $f(s,i)$ with respect to i, and by theorem hypotheses:

$$\frac{f(s(t),i(\beta(t)))}{f(s(t),i^*)}-\frac{i(t)}{i^*}-1+\frac{i(t)}{i^*}\frac{f(s(t),i^*)}{f(s(t),i(\beta(t)))}$$

$$=\left(\frac{i(t)}{i^*}-\frac{f(s(t),i(\beta(t)))}{f(s(t),i^*)}\right)\left(\frac{f(s(t),i^*)}{f(s(t),i(\beta(t)))}-1\right)$$

$$\leq 0.$$

Moreover,

$$3\ \leq\ \frac{f(s^*,i^*)}{f(s(t),i^*)}+\frac{i^*}{i(t)}\frac{f(s(t),i(\beta(t)))}{f(s^*,i^*)}+\frac{i(t)}{i^*}\frac{f(s(t),i^*)}{f(s(t),i(\beta(t)))}$$

for $\forall s,i>0$, since the geometric mean is less than or equal to the arithmetic mean. Hence, $\frac{dV_1}{dt}\leq 0$ holds for $\forall s,i>0$. The equality holds if and only if $s(t)=s^*$ and $i(t)=i^*$. Thus, $E^*(s^*,i^*)$ is the largest invariant set in $\Lambda_2=\Big\{(s,i)|\ \ \frac{dV_1}{dt}=0\Big\}$. This asserts that the endemic equilibrium $E^*(s^*,i^*)$ is indeed globally asymptotically stable by Lyapunov-LaSalle theorem [17, 23].

To prove the second part of the theorem we define another Lyapunov function as:

$$V_2(s,i)=s(t)-s_0-\int_{s_0}^{s(t)}\lim_{i\to 0}\frac{f(s_0,i)}{f(u,i)}du+(\omega+\kappa+d)\int_0^{t-\theta_i}i(t-u)du+i(t),$$

for all $t\in[\theta_i,\theta_{i+1})$.

Differentiating $V_2(t)$ along the trajectories of (4.1) for $t \in [\theta_i, \theta_{i+1})$ yields:

$$\frac{dV_2(t)}{dt} = \alpha - \kappa s(t) - f(s(t), i(\theta_i)) - \lim_{i\to 0} \frac{f(s_0, i(t))}{f(s(t), i(t))}\Big(\alpha - \kappa s(t) - f(s(t), i(\theta_i))\Big)$$

$$+ (\omega + \kappa + d)i(t) - (\omega + \kappa + d)i(\theta_i) + f(s(t), i(\theta_i)) - (\omega + \kappa + d)i(t)$$

$$= \alpha\Big(1 - \frac{\kappa}{\alpha}s(t)\Big)\left(1 - \lim_{i\to 0} \frac{f(s_0, i(t))}{f(s(t), i(t))}\right)$$

$$+ f(s(t), i(\theta_i)) \lim_{i\to 0} \frac{f(s_0, i(t))}{f(s(t), i(t))} - (\omega + \kappa + d)i(\theta_i)$$

$$= \alpha\Big(1 - \frac{s(t)}{s_0}\Big)\left(1 - \lim_{i\to 0} \frac{f(s_0, i(t))}{f(s(t), i(t))}\right)$$

$$+ (\omega + \kappa + d)i(\theta_i)\left(\frac{f(s(t), i(\theta_i))}{(\omega + \kappa + d)i(\theta_i)} \lim_{i\to 0} \frac{f(s_0, i(t))}{f(s(t), i(t))} - 1\right).$$

By theorem hypotheses, and from the monotonicity of $f(s, i)$ with respect to s, we have

$$\Big(1 - \frac{s(t)}{s_0}\Big)\left(1 - \lim_{i\to 0} \frac{f(s_0, i(t))}{f(s(t), i(t))}\right) \leq 0.$$

The concavity of $f(s, i)$ with respect to i leads to $f(s, i) \leq i\dfrac{\partial f(s, 0)}{\partial i}$, and hence we have

$$f(s(t), i(\theta_i)) \;\leq\; i(\theta_i)\frac{\partial f(s(t), 0)}{\partial i}.$$

Therefore,

$$\frac{f(s(t), i(\theta_i))}{(\omega + \kappa + d)i(\theta_i)} \lim_{i\to 0} \frac{f(s_0, i(t))}{f(s(t), i(t))} = \frac{f(s(t), i(\theta_i))}{(\omega + \kappa + d)i(\theta_i)} \frac{\frac{\partial f(s_0, 0)}{\partial i}}{\frac{\partial f(s(t), 0)}{\partial i}}$$

$$\leq \frac{i(\theta_i)}{(\omega + \kappa + d)i(\theta_i)} \frac{\partial f(s_0, 0)}{\partial i} = \mathcal{R}_0.$$

Hence, $\dfrac{dV_2}{dt} \leq 0$ for all $s, i > 0$. This proves that $E_0(s_0, i_0)$ is stable. On the other hand, the equality $\dfrac{dV_2}{dt} = 0$ holds if and only if $s(t) = s_0$ and $i(t) = 0$. Thus, $E_0(s_0, i_0)$ is the largest invariant set in $\Lambda_1 = \Big\{(s, i)|\ \dfrac{dV_2}{dt} = 0\Big\}$. Therefore, we conclude by Lyapunov-Lasalle theorem [17, 23] that the disease-free equilibrium $E_0(s_0, i_0)$ is globally asymptotically stable. □

4.2 Stability of SIS model

For convenience, let us rewrite SIS model.

$$\begin{aligned} s'(t) &= \alpha - \kappa s(t) - f(s(t), i(\beta(t))) + \omega i(t), \\ i'(t) &= f(s(t), i(\beta(t))) - (\omega + \kappa + d) i(t). \end{aligned}$$

Since $s'(t) + i'(t) = \alpha - \kappa s(t) - \kappa i(t) - d i(t) \leq \alpha - \kappa\big[s(t) + i(t)\big]$, it follows that $\limsup_{t\to\infty} \big[s(t) + i(t)\big] \leq \alpha/\kappa$. Thus, we consider SIS model the biologically feasible region

$$\widetilde{\Omega} = \{(s, i)|\ \ s > 0,\ \ i \geq 0;\ \ s + i \leq \alpha/\kappa\}.$$

It can be easily shown that the set $\widetilde{\Omega}$ is positively invariant. Since we are interested in the dynamics of the solutions to SIS model we can take $i(t) = \alpha/\kappa - s(t)$. Set $\widetilde{\alpha} = \alpha + \omega\alpha/\kappa$, $\widetilde{\kappa} = \kappa + \omega$, and $\widetilde{\phi} = \omega + \kappa + d$. Then, SIS model (4.2) is reduced to the following system.

$$\begin{aligned} s'(t) &= \widetilde{\alpha} - \widetilde{\kappa} s(t) - f(s(t), i(\beta(t))), \\ i'(t) &= f(s(t), i(\beta(t))) - \widetilde{\phi} i(t). \end{aligned} \tag{4.5}$$

The above system is the same as SIR model (4.1) with different coefficients. We note that $s_0 = \dfrac{\alpha}{\kappa} = \dfrac{\widetilde{\alpha}}{\widetilde{\kappa}}$ implies that (4.5) has the same the disease-free equilibrium $E_0(s_0, i_0)$ as SIR model (4.1) as well as $\mathcal{R}_0 = \dfrac{1}{\widetilde{\phi}} \dfrac{\partial f(s_0, 0)}{\partial i} = \dfrac{1}{\omega + \kappa + d} \dfrac{\partial f(s_0, 0)}{\partial i}$. Thus, Lemma 4.1 implies that if $\mathcal{R}_0 > 1$, then there exist an unique positive equilib-

rium $\widetilde{E}^*(s^*, i^*)$. Further, following the proof of Theorem 4.1, we conclude that the disease-free equilibrium $E_0(s_0, i_0)$ is globally asymptotically if $\mathcal{R}_0 \leq 1$, whereas the endemic equilibrium $\widetilde{E}^*(s^*, i^*)$ is globally asymptotically stable if $\mathcal{R}_0 > 1$.

4.3 Stability of SIRS model

Let us consider SIRS model (4.3).

$$\begin{aligned} s'(t) &= \alpha - \kappa s(t) - f(s(t), i(\beta(t))) + \varepsilon r(t), \\ i'(t) &= f(s(t), i(\beta(t))) - (\omega + \kappa + d) i(t), \\ r'(t) &= \omega i(t) - (\kappa + \varepsilon) r(t). \end{aligned}$$

It is clear that if $\varepsilon = 0$, then this model is reduced to the SIR model.

Since $s'(t)+i'(t)+r'(t) = \alpha-\kappa s(t)-\kappa i(t)-\kappa r(t)-di(t) \leq \alpha-\kappa\big[s(t)+i(t)+r(t)\big]$, we have that $\limsup_{t\to\infty} \big[s(t)+i(t)+r(t)\big] \leq \alpha/\kappa$. Therefore, as in the previous section we consider SIRS model (4.3) in the biologically feasible region Ω which is positively invariant.

Set $\bar{\alpha} = \alpha + \varepsilon\alpha/\kappa$, $\bar{\kappa} = \kappa + \varepsilon$, $\bar{\phi} = \omega + \kappa + d + \varepsilon$, and $\bar{f}(s(t), i(\beta(t))) = f(s(t), i(\beta(t))) + \varepsilon i$. Moreover, since we are interested in the asymptotic behavior of the solutions we assume that $s(t)+i(t)+r(t) = \alpha/\kappa$ so that $r(t) = \alpha/\kappa - s(t) - i(t)$. Thus, we omit the third equation of SIRS model in our analysis. Then, SIRS model (4.3) is reduced to following system of equations:

$$\begin{aligned} s'(t) &= \bar{\alpha} - \bar{\kappa} s(t) - \bar{f}(s(t), i(\beta(t))), \\ i'(t) &= \bar{f}(s(t), i(\beta(t))) - \bar{\phi} i(t). \end{aligned} \tag{4.6}$$

The last system of equations have the same form as SIR model (4.1) in the previous section. Further, one can easily show that the disease-free equilibrium point of (4.6) and SIR model (4.1) are the same since $s_0 = \dfrac{\alpha}{\kappa} = \dfrac{\bar{\alpha}}{\bar{\kappa}}$. However, different from SIS model, the basic reproduction number the reduced SIRS model (4.6) is not equal to

$\mathcal{R}_0$, i.e.,

$$\overline{\mathcal{R}}_0 = \frac{1}{\bar{\phi}} \frac{\partial \bar{f}(s_0, 0)}{\partial i} = \frac{1}{\omega + \kappa + d + \varepsilon} \left(\frac{\partial f(s_0, 0)}{\partial i} + \varepsilon \right) \neq \mathcal{R}_0.$$

Nonetheless, we note that the relation $\overline{\mathcal{R}}_0 = \dfrac{(\omega + \kappa + d)\mathcal{R}_0 + \varepsilon}{\omega + \kappa + d + \varepsilon}$ holds. Thus, one can see that $\overline{\mathcal{R}}_0 > 1$ if and only if $\mathcal{R}_0 > 1$, $\overline{\mathcal{R}}_0 < 1$ if and only if $\mathcal{R}_0 < 1$, and $\overline{\mathcal{R}}_0 = 1$ if and only if $\mathcal{R}_0 = 1$. In other words, the threshold values of (4.3) and (4.6) are equal. Hence, by means of Lemma 4.1 we deduce that there exist an unique positive equilibrium $\overline{E}^*(s^*, i^*)$ if $\mathcal{R}_0 > 1$. Finally, we conclude that the disease-free equilibrium $E_0(s_0, i_0)$ is globally asymptotically if $\mathcal{R}_0 \leq 1$, whereas the endemic equilibrium $\overline{E}^*(s^*, i^*)$ is globally asymptotically stable if $\mathcal{R}_0 > 1$.

4.4 Simulations

For the simulation part we use Holling type II function, $f(s, i) = \dfrac{\gamma si}{1 + i}$, as an incidence rate for our SIR model (4.1). Assume the following set of parameters in the system (4.1) are as follows:

$$\alpha = 0.5811, \qquad \kappa = 0.0298, \qquad w = 0.0238, \qquad d = 0.0953.$$

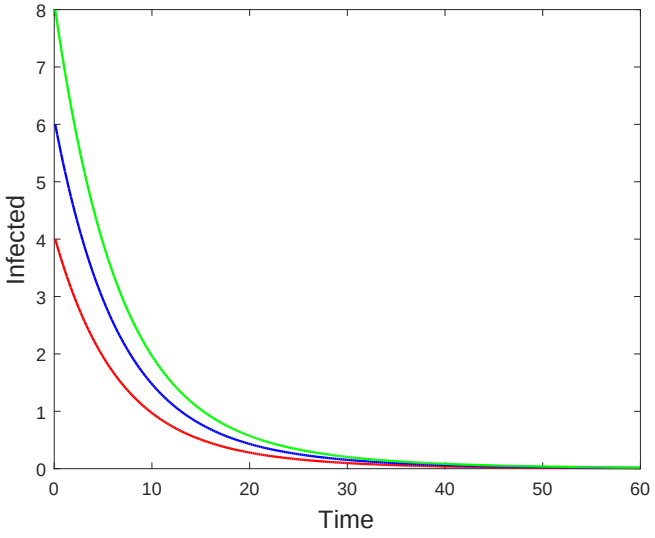

Figure 4-1: We choose $\gamma = 0.005$, so that $\mathcal{R}_0 < 1$. The disease disappears eventually.

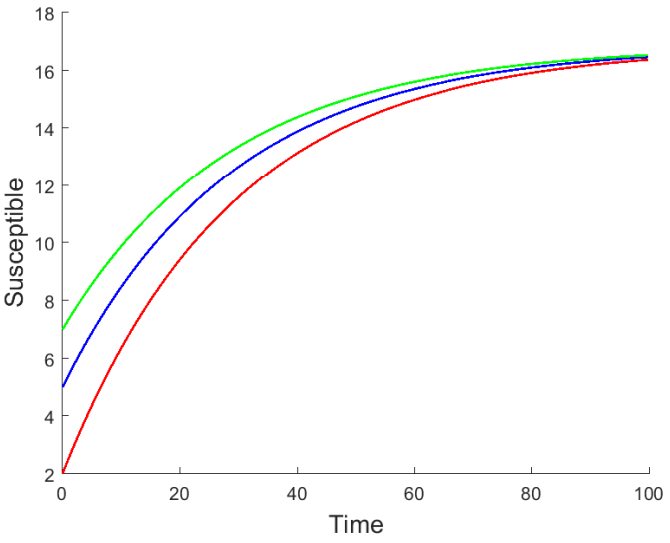

Figure 4-2: The disease disappears eventually at $\mathcal{R}_0 < 1$ and $\gamma = 0.005$.

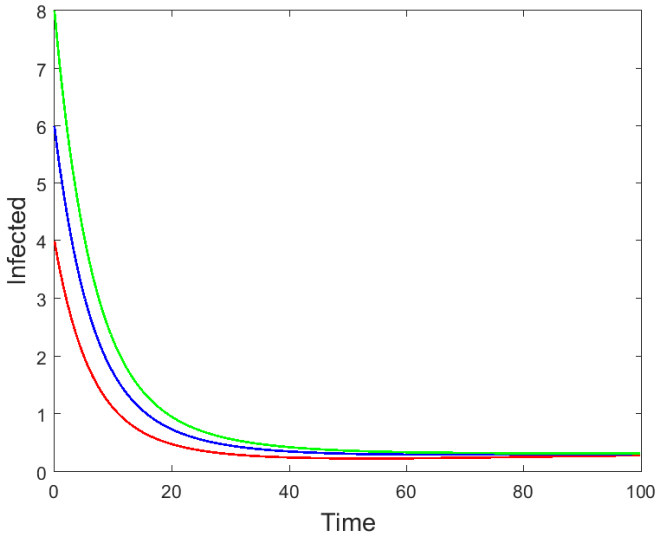

Figure 4-3: We choose $\gamma = 0.015$, so that $\mathcal{R}_0 > 1$. The disease remains persistent.

Estimated parameter values were taken arbitrarily. If we further choose $\gamma = 0.005$, then $\mathcal{R}_0 = 0.65477 < 1$. By Theorem 4.1, the disease eventually dies out. A numerical simulation illustrates this result (see Fig.4-1).

On the other hand, if we choose $\gamma = 0.015$, then $\mathcal{R}_0 = 1.96430 > 1$. By Theorem 4.1, the disease remains persistent (see Fig.4-3).

Substituting $\mathcal{R}_0 = 1$ into (4.4) and solving for γ gives $\gamma = \gamma^* = 0.00764$, where γ^* is chosen as the threshold of transmission rate.

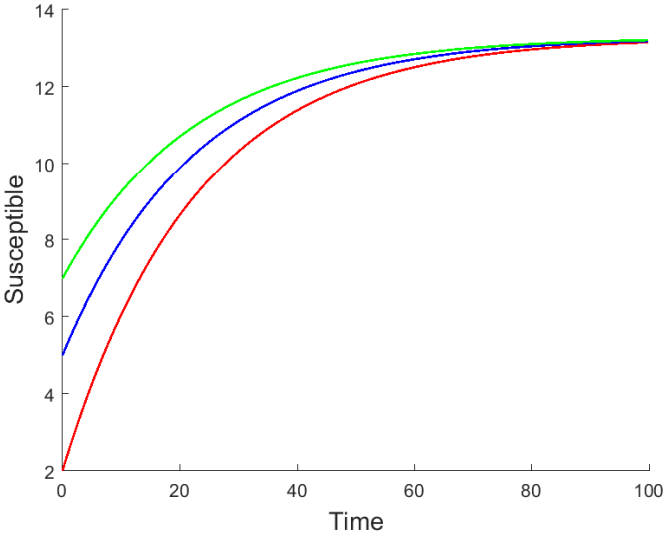

Figure 4-4: The disease remains persistent at $\mathcal{R}_0 > 1$ and $\gamma = 0.015$.

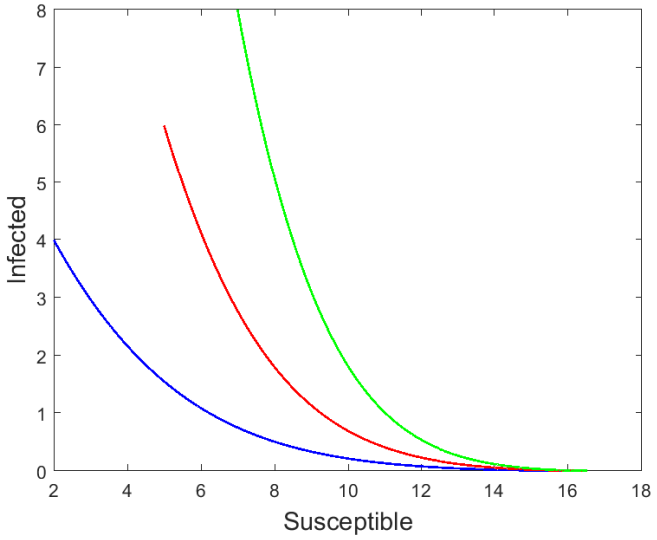

Figure 4-5: The phase diagram of $S - I$ with $\gamma = 0.005$, so that $\mathcal{R}_0 < 1$.

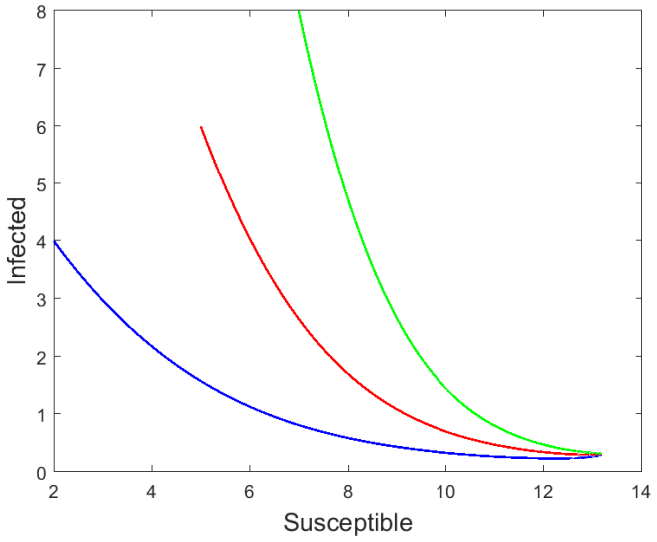

Figure 4-6: The phase diagram of $S - I$ with $\gamma = 0.015$, so that $\mathcal{R}_0 > 1$.

Chapter 5

Conclusions and Future Work

5.1 Conclusions

In this thesis we considered the diseases that are transmitted with discrete generations. We studied three type of epidemiological models with nonlinear incidence rate and piecewise constant delay, where the total population is varied with time elapse.

We computed the basic reproduction number, using the next generation matrix technique [11], and showed that if $R_0 \leq 1$, then there is only one equilibrium state, which is disease-free equilibrium and it is asymptotically stable, and if $R_0 > 1$, then in addition to the disease-free equilibrium which is unstable, the model has also an endemic equilibrium that is asymptotically stable. Moreover, we studied the global asymptotic stability of the disease-free and endemic equilibrium states of models by constructing suitable Lyapunov functions and Lyapunov–LaSalle technique.

We supported theoretical results with numerical simulations.

5.2 Future Work

In the future, we would like to consider the total population as logistic population $\upsilon N(1-\frac{N}{C})$, where υ is an intrinsic population growth rate, N is the population size, and C is population carrying capacity. Because of space limitations, food resources and other factors, the logistic population seems more realistic and reasonable to

consider it in the models. When initial population size N grows up to some threshold upper bound C, the recruitment rate of individuals into the susceptible class is a directly proportional to the population. This is biologically reasonable, since the larger initial population size, the faster the growth of the population. Therefore, initially it behaves like an exponential population growth (Fig. 5-1). When population reaches the bound $N \approx C$, there is a negligible population growth after that.

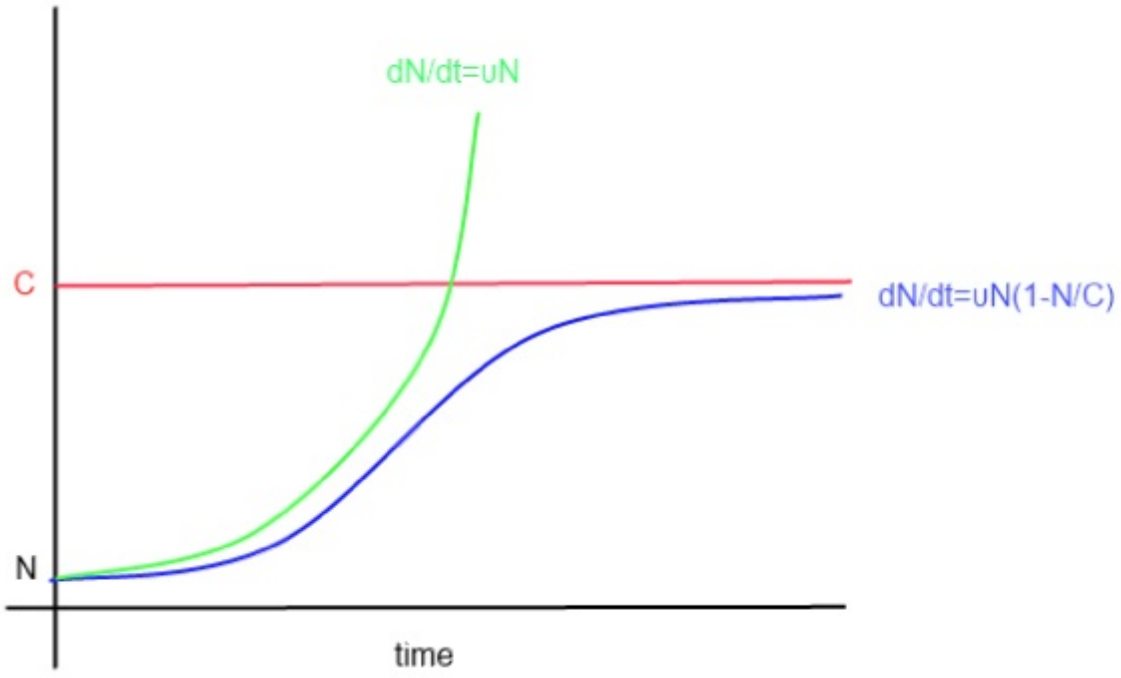

Figure 5-1: Exponential and logistic population growth

According to statistics, people at age 45 and above are more subject to Rocky Mountain Spotted Fever [47]. Therefore, we would also like to consider age-structured epidemic models in the future.

Bibliography

[1] L.J.S. Allen, Some discrete-time SI, SIR, and SIS epidemic models. Mathematical Biosciences **124** 1994, 83–105.

[2] A. Korobeinikov, Lyapunov functions and global stability for SIR and SIRS epidemiological models with non-linear transmission, Bull. Math. Biol., **68** (2006), 615–626.

[3] A. Korobeinikov, Global Properties of Infectious Disease Models with Nonlinear Incidence, Bull. Math. Biol., **69** (2007), 1871–1886.

[4] A. Korobeinikov, Global asymptotic properties of virus dynamics models with dose-dependent parasite reproduction and virulence, and non-linear incidence rate, Math. Med. Biol., **26** (2009), 225–239.

[5] A. Korobeinikov and P.K. Maini, A Lyapunov function and global properties for SIR and SEIR epidemiological models with nonlinear incidence, Math. Biosci. Eng. , **1** (2004), 57–60.

[6] A. Korobeinikov and P.K. Maini, Nonlinear incidence and stability of infectious disease models, Math. Med. Biol., **22** (2005), 113–128.

[7] M. Akhmet, Nonlinear hybrid continuous/discrete-time models, Atlantis Press, Paris, 2011.

[8] M. Akhmet and D. Arugaslan, Lyapunov-Razumikhin method for differential equations with piecewise constant argument, Discrete Cont. Dyn. Systems, **25** (2009), 457–466.

[9] D. Arugaslan, Dynamics of a harvested logistic type model with delay and piecewise constant argument, J. Nonlinear Sci. Appl. **8** (2015), 507–517.

[10] M. U. Akhmet, D. Arugaslan, and E. Ylmaz, Method of Lyapunov functions for differential equations with piecewise constant delay, J. Comput. Appl. Math., **235**, (2011) 4554–4560.

[11] Van den Driessche and J. Watmough, Reproduction Numbers and Sub-Threshold Endemic Equilibria for Compartmental Models of Disease Transmission, Mathematical Biosciences, **180** (2002), 29–48.

[12] W.R. Derrick and van den Driessche, A disease transmission model in a nonconstant population, J. Math. Biol., **31** (1993), 495–512.

[13] W.R. Derrick and Van den Driessche, Homoclinic orbits in a disease transmission model with nonlinear incidence and nonconstant population, Discrete Cont. Dyn. Systems Ser. B, **3** (2003), 299–309.

[14] H.W. Hethcote, M.A. Lewis and van den Driessche, An epidemiological model with delay and a nonlinear incidence rate, J.Math. Biol., **27** (1989), 49–64.

[15] H.W. Hethcote and van den Driessche, Some epidemiological models with nonlinear incidence, J.Math. Biol., **29** (1991), 271–287.

[16] W.O. Kermack and A.G. McKendrick, A contribution to the mathematical theory of epidemics, Proc. R. Soc. A, **115** (1927), 700–721.

[17] J.K. Hale and S.M.V. Lunel, Introduction to Functional Differential Equations, Springer, (1993).

[18] X. Liu and P. Stechlinski, Infectious Disease Modeling: A Hybrid System Approach Springer, (2017).

[19] W.M. Liu, S.A. Levin and Y. Isawa, Influence of nonlinear incidence rates upon the behaviour of SIRS epidemiological models, J. Math. Biol., **23** (1986), 187–204.

[20] W.M. Liu, H.W. Hethcote and S.A. Levin, Dynamical behavior of epidemiological models with nonlinear incidence rates, J. Math. Biol., **25** (1987), 359–380.

[21] M.Y. Li and J.S. Muldowney, Global stability for the SEIR model in epidemiology, Math. Biosci., **125** (1995), 155–64.

[22] E. Beretta, T. Hara, W. Ma, and Y. Takeuchi, Global asymptotic stability of an SIR epidemic model with distributed time delay, Nonlinear Anal., **47** (2001), 4107–4115.

[23] Y. Kuang, Delay Differential Equations with Applications in Population Dynamics, Academic Press, 1993.

[24] G. Huang, Y. Takeuchi, W. Ma and D. Wei, Global stability for delay SIR and SEIR epidemic models with nonlinear incidence rate, Bull. Math. Biol., **72** (2010), 1192–1207.

[25] G. Huang and Y. Takeuchi, Global analysis on delay epidemiological dynamic models with nonlinear incidence, J. Math. Biol., **63** (2011), 125–139.

[26] V. Capasso and G. A. Serio, Generalization of the KermackâĂŞMcKendrick deterministic epidemic model, Math. Biosci., **42** (1978), 43–61.

[27] Z. Feng and H.R. Thieme, Endemic models with arbitrarily distributed periods of infection I: fundamental properties of the model, SIAM J Appl. Math., **61** (2000), 803–833.

[28] Z. Feng and H.R. Thieme, Endemic models with arbitrarily distributed periods of infection II: fast disease dynamics and permanent recovery, SIAM J Appl. Math., **61** (2000), 983–1012.

[29] Y. Zhao, D.T. Wood, H.V. Kojouharov, Y. Kuang and D.T. Dimitrov, Impact of Population Recruitment on the HIV Epidemics and the Effectiveness of HIV Prevention Interventions, Bull. Math. Biol., **78(10)** (2016), 2057–2090.

[30] K.L. Cooke, Stability analysis for a vector disease model, Rocky Mountain J. Math., **9** (1979), 31–42.

[31] S. Busenberg and K.L. Cooke, Models of vertically transmitted diseases with sequential continuous dynamics, Nonlinear Phenomena in Mathematical Sciences, Academic Press, New York, (1982), 179–187.

[32] K.L. Cooke and J. Wiener, Retarded differential equations with piecewise constant delays, J. Math. Anal. Appl., **99** (1984), 265–297.

[33] S.M. Shah and J. Wiener, Advanced differential equations with piecewise constant argument deviations, Int. J. Math. Math. Sci., **6** (1983), 671–703.

[34] Y. Muroya, Persistence, contractivity and global stability in logistic equations with piecewise constant delays, J. Math. Anal. Appl., **270** (2002), 602–635.

[35] Y. Arugaslan Y. and A. Ozer, Stability analysis of a predatorâĂŞprey model with piecewise constant argument of generalized type using Lyapunov functions, Journal of Mathematical Sciences, **203 (3)** (2014), 297–305.

[36] Q. Xi, Global Exponential Stability of Cohen-Grossberg Neural Networks with Piecewise Constant Argument of Generalized Type and Impulses, Neural computation, **28** (2015), 1–27.

[37] F. Gurcan, S. Kartal, I. Ozturk and F. Bozkurt, Stability and bifurcation analysis of a mathematical model for tumorâĂŞimmune interaction with piecewise constant arguments of delay, Chaos, Solitons & Fractals, **68** (2014), 169–179.

[38] I. Ozturk, F. Bozkurt and F. Gurcan, Stability analysis of a mathematical model in a microcosm with piecewise constant arguments, Mathematical Biosciences, **240 (2)** (2012), 85–91.

[39] I. Győri, On approximation of the solutions of delay differential equations by using piecewise constant arguments, International Journal of Mathematics and Mathematical Sciences, **14 (1)** (1994), 111–126.

[40] I. Győri, F. Hartung, On numerical approximation using differential equations with piecewise-constant arguments, Period Math Hung, **56** (2008), 55–69.

[41] CDC - Malaria - About Malaria - Biology. (2018, November 14). Retrieved from https://www.cdc.gov/malaria/about/biology/index.html

[42] Clinical Disease - Smallpox - CDC. (2016, December 5). Retrieved from https://www.cdc.gov/smallpox/clinicians/clinical-disease.html

[43] Anic, G. and Giuliano, A., Genital HPV infection and related lesions in men. Preventive Medicine, **53** (2011), S36 – S41. doi: 10.1016/j.ypmed.2011.08.002

[44] Epidemiology of Disease Progression in HIV. (1998). Retrieved from http://hivinsite.ucsf.edu/InSite?page=kb-03-01-04S2X

[45] Information on the Tick Life Cycle - Terminix. (n.d.). Retrieved from https://www.terminix.com/pest-control/ticks/life-cycle/

[46] Tickborne Disease Surveillance Data Summary - Ticks - CDC. (2019). Retrieved from https://www.cdc.gov/ticks/data-summary/index.html

[47] Epidemiology and Statistics - Rocky Mountain Spotted Fever (RMSF) - CDC. (2019). Retrieved from https://www.cdc.gov/rmsf/stats/

[48] Retrieved from https://www.cdc.gov/rmsf/transmission/index.html

[49] American Dog Tick - Cooperative Extension: Tick Lab - University of Maine Cooperative Extension. (n.d.). Retrieved from https://extension.umaine.edu/ticks/maine-ticks/american-dog-tick/

[50] A. M. Lyapunov, The General Problem of the Stability of Motion, London: Taylor Francis (1992).

[51] Tickborne Diseases Abroad - Ticks - CDC. (2019). Retrieved from https://www.cdc.gov/ticks/diseases/abroad.html

[52] Transmission - Crimean-Congo Hemorrhagic Fever (CCHF) - CDC. (2019). Retrieved from https://www.cdc.gov/vhf/crimean-congo/transmission/index.html

[53] S. Aslam et al., Crimean-Congo Hemorrhagic Fever: Risk Factors And Control Measures For The Infection Abatement, Biomedical Reports, **4** (2015), 15 – 20.

[54] Outbreak Distribution Map - Crimean-Congo Hemorrhagic Fever (CCHF) - CDC. (2019). Retrieved from https://www.cdc.gov/vhf/crimean-congo/outbreaks/distribution-map.html

[55] T. Nurmakhanov et al., Crimean-Congo haemorrhagic fever virus in Kazakhstan (1948-2013), International Journal Of Infectious Diseases, **38** (2015), 19 – 23.

[56] B. Knust et al., Crimean-Congo Hemorrhagic Fever, Kazakhstan, 2009âĂŞ2010, Emerging Infectious Diseases, **18** (2012), 643 – 645.