A MATHEMATICAL MODELING OF OPTIMAL VACCINATION STRATEGIES IN EPIDEMIOLOGY.

by

Lutendo Nemaranzhe

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Supervisor: **Prof P.J. Witbooi**

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Abstract

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L. Nemaranzhe

M.Sc thesis, Department of Mathematics, University of Western Cape.

We review a number of compartmental models in epidemiology which leads to a nonlinear system of ordinary differential equations. We focus an SIR, SEIR and SIS epidemic models with and without vaccination. A threshold parameter R_0 is identified which governs the spread of diseases, and this parameter is known as the basic reproductive number. The models have at least two equilibria, an endemic equilibrium and the disease-free equilibrium.

We demonstrate that the disease will die out, if the basic reproductive number $R_0 < 1$. This is the case of a disease-free state, with no infection in the population. Otherwise the disease may become endemic if the basic reproductive number R_0 is bigger than unity. Furthermore, stability analysis for both endemic and disease-free steady states are investigated and we also give some numerical simulations.

The second part of this dissertation deals with optimal vaccination strategy in epidemiology. We use optimal control technique on vaccination to minimize the impact of the disease. Hereby we mean minimizing the spread of the disease in the population, while also minimizing the effort on vaccination roll-out. We do this optimization for the cases of SIR and SEIR models, and show how optimal strategies can be obtained which minimize the damage caused by the infectious disease. Finally, we describe the numerical simulations using the fourth-order Runge-Kutta method.

These are the most useful references: [G. Zaman, Y.H Kang, II. H. Jung. *BioSystems* 93, (2008), 240 − 249], [K. Hattaf, N. Yousfi. *The Journal of Advanced Studies in Biology, Vol.* 1(8), (2008), 383 − 390.], [Lenhart, J.T. Workman. *Optimal Control and Applied to Biological Models.* Chapman and Hall/CRC, (2007).], [P. Van den Driessche, J. Watmough. *Math. Biosci.*, 7, (2005)], and [J. Wu, G. Röst. *Mathematical Biosciences and Engineering, Vol* 5(2), (2008), 389 − 391].

Keywords

Basic reproductive number

Disease-free equilibrium

Epidemiology

Endemic model

Numerical simulation

Population model

Optimization

Stability analysis

Vaccination

Declaration

Thesis Title: Mathematical modeling of optimal vaccination strategies in epidemiology.

I hereby declare that:

- the above thesis is my own work and design, apart from the normal guidance from my supervisor,
- neither the above thesis has been submitted in the past, or is being, or is to be submitted for another degree or examination at this or any other University or Institution of higher learning,
- and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

L. Nemaranzhe December 2010

Signed.....

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Chapter 1

1. Introduction

1.1 Historical overview

Infectious diseases such as measles, influenza, smallpox, tuberculosis, malaria, etc., have been having a great influence on human life. Almost every year millions of people die from different infectious diseases. This motivated the development of modern epidemiological theory. The most important concerns about any infectious disease is the ability to invade a population. The goal of the study of infectious diseases via mathematical population models is to understand how infections diseases are propagated in terms of numbers of people affected and also to find the best possible strategies to control the spread of a disease or to eradicate it. Mathematical modeling approaches therefore also provide powerful tools for epidemiological policy decision making in many countries, and among other health authorities. These models are often the only practical approach for answering questions about which prevention or control procedure is most effective.

There is on record, in relatively distant history, some interesting mathematical intervention in epidemiological situations. In 1760, Daniel Bernoulli carried out the first application of mathematical modeling to the spread of infectious disease which was described in the paper of Zhou and Liu [69]. Even though his work existed before the identification of the agent responsible for the transmission of smallpox by a century, he formulated and solved a differential equation which described the dynamics of the infection which is still of great importance even today. In 1906, Hamer [20] formulated and analyzed a discrete time model in attempting to understand the recurrence of measles

epidemics. His model may have been the first to assume that the incidence depends on the product of the densities of the susceptibles and infectives. Ross [48] developed differential equation models for malaria as a host-vector disease in 1911 because he was interested in the incidence and control of malaria.
The serious development of mathematical epidemiology was delayed by lack of understanding of the mechanism of infectious spread until the beginning of 20th century.

The first stochastic theory was developed in 1926 by McKendrick [38]. The extremely important threshold theorem was established in 1930 by Kermack and McKendrick, which showed that the density of susceptible individuals must exceed a certain critical value in order for an epidemic outbreak to occur, was described in the textbook of Bailey [5]. Most traditional compartmental models descend from the classical SIR model of Kermack and McKendrick, where the population is divided into the classes of susceptible, infected, and recovered (S, I and R) individuals. For some diseases, such as influenza and tuberculosis, on sufficient contact with an infectious individual, a susceptible becomes exposed for a while, that is, infected but not yet infectious. Thus, it is reasonable to introduce a latent compartment, leading to an SEIR model. Such models have been widely discussed in the literature. Anderson and May [2] showed that the well known standard mathematical models of the spread of infectious diseases have been useful for many different diseases in various regions all over the world. The models proposed by Kermack and McKendrick [39], published in 1927, had a great influence on the modeling framework. Their SIR model tracks the numbers of susceptible, infective and recovered individuals during an epidemic with the help of ordinary differential equations.

1.2 Models and their analysis

Mathematical modeling can be used for comparing different diseases in the same population, the same diseases at different times or the same diseases in different population. Epidemiological models are helpful when comparing the effects of prevention or control procedures. Hethcote and Yorke [66] used models for comparing gonorrhea control procedures such as screening, tracing infectors, post translational and general vaccination. In most mathematical biology literature, various researchers have proposed several mathematical models for modeling the spread of infectious diseases. The model formulation process clarifies assumptions, parameters and variables. Furthermore, models provide conceptual results such as basic reproductive numbers, contact rate and other

numerical thresholds. Computer simulations and mathematical models are very useful experimental tools for building and testing theory, assessing quantitative conjectures, answering specific questions, determining sensitivities to changes in parameter values, and estimating key parameters from data.

The most common methods for intervention in the spread of infectious diseases include either the removal of susceptible individuals or the application of treatments to infected individuals in order to prevent further spread of a disease. For example, in the case of foot-and-mouth disease, the susceptible individuals may be selected from the host population to avoid contact with the infected individuals (Tildesley et al. [58]; Enserink [15]). When it comes to contagious disease such as severe acute respiratory syndrome, infected individuals may be quarantined (see Lloyd et al. [35]). Furthermore, susceptibles individuals may be vaccinated as in case of smallpox or influenza as shown by Ferguson et al. [17] and Halloran et al. [19].

Each one of the actions above involves a cost. For selection, the cost is determined by the additional number of deaths. In case of vaccination the cost may be measured in both monetary units and additional vaccine-induced infection. For quarantine, the cost is mostly measured in units rather than deaths, and for medical treatment also the cost is monetary. In addition, each of these actions associated with costs can be dependent upon the state or intensity of the disease within the host population. From this arose fundamental questions of epidemiological modeling on how to find optimal epidemiological interventions in such a way that is adaptively dependent upon a state of the epidemic. There is also the problem of how to find threshold conditions which determine whether an infectious disease will spread or will die out in a host population.

Numerous epidemiological models have a disease-free equilibrium at which the population remains free of the disease. These models usually have the threshold parameter which governs the spread of diseases, and is also related to the long term behaviours and the level of intervention necessary for eradication. This parameter is known as the basic reproductive number R_0. We define R_0 as the average number of secondary infectious cases produced by an infectious individual in a totally susceptible population during the entire infectious period. If $R_0 < 1$, then the disease eventually dies out from the population because on average, each infected cannot guarantee transmission of the infectious agent to one susceptible. Therefore the disease-free equilibrium is asymptotically stable and the population cannot be invaded by the disease. On the other hand if $R_0 > 1$, then each infected individual produces,

on average, more than one new infection, and the disease can spread in the population. Therefore the disease-free equilibrium is unstable and invasion is always possible, see for instance [22] of Hethcote.

Local and global stability analysis of the disease-free and endemic equilibrium have been carried out using different assumptions and contact rates, this can be seen in Castillo-Chavez and Feng [9]. Other important references are for examples Enatsu et al. [14], Korobeinikov et al. [30], Li and Jin [33], Zaman et al. [67] and [69]. Bailey [5] reported that the number of references to mathematical epidemiology had quintupled to 500 in a space of 18 years in 1975.

1.3 Scope of this dissertation

In this work we use optimal control strategies on vaccination to control the number of susceptible and infective individuals and increase the number of recovered individuals. With the help of an iterative method and the Maximum principle of Pontryagin as for example in Kamien and Schwartz [28], we shall develop some new model. The goal of this work is not to consider a special disease but to present a method of how to treat this *class* of optimization problems.

Firstly, we consider a general SIR epidemic model of Zaman et. al. [67], and apply stability analysis theory to understand the equilibria for the model (see the paper [7] by Brauer and Castillo-Chavez). After investigating the equilibria of the model without vaccination, then we present a SIR model with a vaccination and we show how to optimally control the vaccination. Furthermore, we also consider the SEIR model proposed by Tessa [57], and SIS models [69]. Again we analyze stability and study the control of the vaccination.

We consider vaccination strategies defined by a fraction of the current susceptible population to be targeted for vaccination. The optimal vaccination strategy is to control the total number of susceptible, exposed and recovered individuals and also to minimize the probability that the infected individuals spread the disease in the population. Then we demonstrate how the optimal control of the vaccination variable $u(t)$ can be applied to minimize the number of infected individuals. We shall also briefly refer to an alternate approach to modeling of vaccination, which is the so-called pulse vaccination strategy.

Finally we use the fourth-order Runge-Kutta numerical procedure to solve the optimal system with interactive method. Starting with an initial guess for the adjoint variables, the state equations are solved by a forward Runge-Kutta scheme in time. Then those state values are used to solve the adjoint equations by a backward Runge-Kutta scheme, because of the transversality conditions.

1.4 Description of the chapters

The remainder of the thesis is organized as follows. In chapter 2 we introduce some mathematical preliminaries and basics that are important prerequisites to the study epidemiological models. This chapter is arranged to familiarize the reader with the mathematical definitions, methods and theorems that are used in epidemiological models.

In chapter 3 we discuss some mathematical models of the epidemiology used by the researchers over the past years, including some very recent papers. In addition, we presented some continuous mathematical model for the transmission of infectious diseases, as a higher order system of ordinary differential equations.

In chapter 4 we describe the SIR model for the transmission of infectious diseases in the population. The basic reproductive number is identified and shown to be a threshold parameter. Furthermore, we study and determine the equilibrium points, and their stability is analyzed.

Chapter 5 extends the results of chapter 4 to cover the control of vaccination for SIR epidemiological models. The optimal control problem is formulated and we also provide the main method for solving these highly nonlinear control problem. The significance of our analytical and numerical simulations are discussed. The SIR model that we consider is the one used in Hattaf and Yousfi. The method is similar to that in the paper [67] by Zaman et al. Therefore we have some marginal novelty in this chapter.

In chapter 6 we demonstrate the stability analysis for both SEIR and SIS models. Local and global stabilities for the disease-free equilibrium and endemic equilibrium are described. In this case we present a Lyapunov function in order to establish global stability of the disease-free equilibrium.

In addition, we also formulated the optimal control problem for the SEIR model in chapter 7 as we did in chapter 5 for the SIR model. This is an independent piece of work, at least, the author does not know of such a piece of

work. We use an SEIR model similar to that of Ngwenya [42]. Then, we give the procedure for solving the nonlinear control problem. We present different computer simulations of the dynamic system and discuss their outcomes. Finally, the conclusion are summarized in chapter 8.

Chapter 2

Preliminaries and basics

2.1 Modeling

This dissertation entails a study of deterministic compartmental models of population dynamics in epidemiology. In this introductory chapter, we briefly review some several definitions, methods, theorems and results that are important mathematical prerequisites to the study of epidemiology. This chapter serves only as a short summary and convenient reference. We include some definitions and results on stability of solutions of ordinary differential equations which we mainly take from the textbook of Jordan and Smith [26]. Other useful references in this regard are the books [47] by Rao and [3] of Arrowsmith and Place. Another important mathematical method we shall be using, is optimal control theory. Our basic result is taken from Seierstadt and Sydsaeter [50]. The books by Kamien and Schwartz [28] and Lenhart and Workman [31] are also useful references. Technical terminology on epidemiology such as basic reproductive number, transmission coefficient, endemic equilibrium, etc will be picked up along the way, mostly in chapter 3 where we look at a variety of epidemiological models.

2.2 Systems of ordinary differential equations

Our main references for this section are the textbook [26] by Jordan and Smith, [3] of Arrowsmith and Place and [47] Rao.

Definition 2.2.1. Given a non-empty subset A of $\mathbb{R}^n$ and a point $x \in \mathbb{R}^n$, the *distance* $\text{dist}(x, A)$ from x to A is defined as $\text{dist}(x, A)$=inf $\{\|x - a\| : a \in A\}$.

Note that due to the infimum property, for a non-empty set A, the distance will always exist.

Definition 2.2.2. For a function $x : \mathbb{R} \to \mathbb{R}^n$, for $t_0 \in \mathbb{R}$ and for $b \in \mathbb{R}^n$, the *half-path* of $x(t)$ starting at b when $t = t_0$, is the set $H(x, b, t_0) = \{x(t) : \quad t \geq b\}$.

In what follows we assume that we have a differential equation $\dot{x} = f(x)$, with x being a function $x : \mathbb{R} \to \mathbb{R}^n$, and $f : \mathbb{R}^n \to \mathbb{R}^n$.

Definition 2.2.3. (Poincaré or orbital stability). Let $H^* = H(x^*, a^*, t_0)$ be the half-path for the solution $x^*(t)$ of $\dot{x} = f(x)$ which starts at a^* at $t = t_0$. Suppose that for every $\epsilon > 0$ there exists $\delta > 0$ such that

$$|a - a^*| < \delta \Rightarrow \sup_{x \in H} \text{dist } (x, H^*) < \epsilon.$$

Then x^* is said to be *Poincaré stable.*

Definition 2.2.4. (Lyapunov stability). Let $x^*(t)$ be a given real or complex solution of the system. Then $x^*(t)$ is a *Lyapunov stable* on $t \geq t_0$ if, for any $\epsilon > 0$, there exists $\delta(\epsilon, t_0)$ such that for a solution $x(t)$, we have:

(a). $\|x(t_0) - x^*(t_0)\| < \delta \Rightarrow \|x(t) - x^*(t)\| < \epsilon$, for all $t \geq t_0$.

Otherwise $x^*(t)$ is said to be unstable.

Remark 2.2.5. As remarked in Jordan and Smith [26], if (a) of the defination (2.2.4) is satisfied for initial conditions at t_0, then a similar condition is satisfied when any $t_1 > t_0$ is substituted for t_0: that is, if $x^*(t)$ is stable for $t \geq t_0$, it is stable for $t \geq t_1 > t_0$.

Definition 2.2.6. (Uniform stability). If a solution is stable for $t \geq t_0$ and the δ of Lyapunov stability is independent of t_0, then the solution is said to be *uniformly stable* on the interval $t \in [t_0, \infty)$.

Definition 2.2.7. (Asymptotic stability). Let x^* be a stable (or uniformly stable) solution for $t \geq t_0$. If additionally there exists $\eta(t_0) > 0$ such that

$$|x(t_0) - x^*(t_0)| \leq \eta \Rightarrow \lim_{t\to\infty} |x(t) - x^*(t)| = 0,$$

then the solution is said to be *asymptotically stable* (or uniformly and asymptotically stable).

Some solutions of a system of the form $\dot{x} = f(x)$ are particularly important and requires special mention, especially in epidemiology. We now define these points, the so-called equilibrium solutions, also sometimes referred to as fixed points or critical points.

Definition 2.2.8. An *equilibrium* solution of $\dot{x} = f(x)$ is a function $x_0(t)$ satisfying the condition $0 = f(x_0(t))$ for all t.
A point which is an equilibrium solution is also called a *fixed point.*

Consider a fixed point x_0 of the system of differential equations

$$\dot{x} = f(x), \tag{2.1}$$

assuming that $x(.) : [0, \infty) \to \mathbb{R}^n$ is differentiable. Let $Df(y)$ be the derivative of f at the point y, regarding $Df(y)$ as an $n \times n$ matrix (a_{ij}) with

$$a_{ij} = \frac{\partial f_i}{\partial x_j}. \tag{2.2}$$

The special case when the system is of the form $\dot{x} = Ax$ for some matrix A with constant coefficients, have received much attention in the literature, e.g. Jordan and Smith [26]. In particular there is the following theorem.

Theorem 2.2.9. *Let A be constant matrix in the system $\dot{x} = Ax$, with eigenvalues λ_i, $i = 1, 2, ..., n$.*

(i) If the system is stable , then Re $\{\lambda_i\} \leq 0$, $i = 1, 2, ..., n$.

(ii) If either Re $\{\lambda_i\} < 0$, $i = 1, 2, ..., n$.*; or if* Re $\{\lambda_i\} \leq 0$, $i = 1, 2, ..., n$. *and there is no zero repeated eigenvalues, then the system is uniformly stable.*

(iii) The system is asymptotically stable if and only if Re $\{\lambda_i\} < 0$, $i = 1, 2, ..., n$. *(and then it is also uniformly stable, by (ii)).*

This theorem is reasonably easily generalized, to obtain the so-called linearization theorem. A version of the following theorem can be found in, e.g.

the book of Lomen and Lovelock [36] or Hirsch and Smale [24]. For the proof we refer to Hirsch and Smale.

Theorem 2.2.10. *Let $\bar{x}$ be an equilibrium solution of the system $\dot{x} = f(x)$ and let $t_0 \geq 0$. Suppose that for every eigenvalue of $Df(\bar{x})$, the real part is negative. Then there exists an open subset U of $\mathbb{R}^n$ with $\bar{x} \in U$, such that for every solution x of $\dot{x} = f(x)$ for which $x(t_0) \in U$, we have $x(t) \to \bar{x}$ as $t \to \infty$.*

This theorem will be applied in a number of cases to analyze stability. If $\bar{x}$ is as in the theorem above, then we say that $\bar{x}$ is *locally* asymptotically stable.

2.3 Optimization

Our main reference in this section is the book [50] by Seierstadt and Sydsaeter. other relevant books are [31] by Lenhart and Workman and [28] by Kamien and Schwartz.

Definition 2.3.1. A function $f : D \to \mathbb{R}$ is said to be *concave* over a suitable subset of the domain $D \subseteq \mathbb{R}^n$ if for any $a, b \in D$ and any for $t \in [0, 1]$ we have $f(a + t(b - a)) \geq f(a) + t(f(b) - f(a))$.

We consider the problem of finding a piecewise continuous control vector $u(t) = [u_1(t), ..., u_m(t)]$ and an associated continuous and piecewise differentiable state vector $x(t) = [x_1(t), ..., x_n(t)]$, defined on the fixed time interval $[t_0, t_1]$, that will maximize the functional $J(u(t))$ (over a suitable set of *admissible* real-valued functions $u(\cdot)$),

$$J(u(t)) = \int_{t_0}^{t_1} f(t, x(t), u(t))dt \tag{2.3}$$

subject to the differential equations,

$$\dot{x}_i(t) = g_i(t, x(t), u(t)), \quad i = 1, ..., n, \tag{2.4}$$

initial conditions,

$$x_i(t_0) = x_{i0}, \quad i = 1, ..., n, (x_{i0}, \text{ fixed}), \tag{2.5}$$

terminal conditions,

$$x_i(t_1) = x_{i1}, \quad i = 1, ..., p,$$

$x_i(t_1) \geq x_{i1}, \quad i = p+1, ..., q$, ($x_{i1}, \quad i = 1, ..., q$, fixed),

$x_i(t_1)$ free $\quad i = q+1, ..., n$,

and control variable restriction $u(t) \in U$, for some $U \subset \mathbb{R}^m$.

We assume that f, g_i, $\partial f/\partial\ x_j$, and $\partial g_j/\partial x_j$ are continuous functions of all their arguments, for all $i = 1, ..., n$ and $j = 1, ..., n$.

The Hamiltonian function H is defined by

$$H(t, x, u, \lambda) = \lambda_0 f(t, x, u) + \sum_{i=1}^{n} \lambda_i g_i(t, x, u). \tag{2.6}$$

Theorem 2.3.2. *In order that $u^*(t)$ be optimal for the above problem, it is necessary that there exist a constant λ_0 and continuous functions $\lambda(t) = (\lambda_1(t), ..., \lambda_n(t))$, where for all $t_0 < t < t_l$ we have $(\lambda_0, \lambda(t)) \neq (0, 0)$ such that for every $t_0 < t < t_1$,*

$$H(t, x^*(t), u, \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t)). \tag{2.7}$$

Except at points of discontinuity of $u^*(t)$, we have

$$\dot{\lambda}_i(t) = -\partial H(t, x^*(t), u^*(t), \lambda(t))/\partial x_i, \quad i = 1, ...n. \tag{2.8}$$

Also

$$\lambda_0 = 1 \quad or \quad \lambda_0 = 0. \tag{2.9}$$

Finally, the transversality conditions are satisfied:

$\lambda_i(t_1)$ *no conditions,* $i = 1, ..., p$,

$\lambda_i(t_1) \geq 0 \quad (= 0$ *if* $x_i^*(t_1) > x_{i1})$ $i = p+1, ..., q$,

$\lambda_i(t_1) = 0, \quad i = q+1, ..., n$.

It is also known [28] that if $f(t, x(t), u(t))$ is a concave function, then in Theorem 2.2.2 above, we have $\lambda_0 = 1$.

Definition 2.3.3. A set S is an *invariant set* for a dynamic system $\dot{x} = f(x)$ if every trajectory $x(t)$ which has a point in S remains in S for all time.
A set S is a *positively invariant set* for a dynamic system $\dot{x} = f(x)$ if every trajectory $x(t)$ which starts from a point $x(0)$ in S remains in S for all time $t > 0$.

Theorem 2.3.4. (La Salle's principle to establish asymptotic stability). *Let* $V(x) : \mathbb{R}^n \to \mathbb{R}$ *be such that on* $\Omega_l = \{x \in \mathbb{R}^n : V(t) \leq l\}$, *we have* $\dot{V}(t) \leq 0$. *Define* $R = \left\{x \in \mathbb{R}^n : \dot{V}(t) = 0\right\}$. *Then, if* R *contains no other trajectories other than* $x = 0$, *then the zero solution is asymptotically stable.*

Chapter 3

Mathematical models in epidemiology

In this chapter, we briefly review some of the mathematical models of epidemiology used by the researchers over the past years. We start off with the landmark model of Kermack and McKendrick (1927) and work through models becoming increasingly more sophisticated and accurate.

3.1 The work of Kermack and McKendrick

In 1927, Kermack and McKendrick proposed a model in which they considered a fixed population with only three compartments: namely susceptible individuals $S(t)$, infective individuals $I(t)$ and recovered individuals $R(t)$. Birth rate, death rate and migration was not considered in this model, and they assume that the population is constant such that, $N = S(t) + I(t) + R(t)$. Therefore they described the model by way of the following differential equations:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI, \\ \frac{dI}{dt} &= \beta SI - \gamma I, \\ \frac{dR}{dt} &= \gamma I. \end{aligned} \tag{3.1}$$

Here β is the product of contact rate and transmission probability, and γ is the

recovery rate or removal rate constant. From this model many assumptions were made in the formulation of these equations. The first assumption was that the probability within the population amongst individuals is equal to every other individual of contracting the disease with a rate of β, which is considered as infection rate of the disease. Therefore, infected individuals I cause a total number $\beta SI/N$ of infections per unit time. The final assumption is that the rate of infection and recovery is much faster than the time scale of births and deaths and therefore, these factors are ignored in this model.

Remark 3.1.1. It can be easily proved that in this system the total population is preserved for any time t. Since $\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0$, it follows that: $S(t) + I(t) + R(t) = N =$ constant.

Remark 3.1.2. If the birth rate μ equal to the death rate are included in the model, we get the following system, which is the same as in, for instance [67] by Zaman et al.

$$\begin{aligned} \frac{dS}{dt} &= \mu N - \mu S - \frac{\beta SI}{N}, \\ \frac{dI}{dt} &= \frac{\beta SI}{N} - (\mu + \gamma)I, \\ \frac{dR}{dt} &= \gamma I - \mu R, \end{aligned} \tag{3.2}$$

with initial conditions:

$$S(0) = S_0, \quad I(0) = I_0, \quad R(0) = R_0.$$

We demonstrate some numerical simulations of the epidemiological models for the system 3.2 where birth and death are included in the population. In Figure 3.1, the parameters are chosen as $\beta = 0.4$, $\gamma = 0.02$ and $\mu = 0.008$. Furthermore, the initial population are $S_0 = 6000$, $I_0 = 3000$ and $R_0 = 1000$. The dynamic of the model is determined by the fluctuating of the number of individuals in each compartment over time, as implied by the variable function of t. We observe that the number of susceptible individuals falls rapidly as more of them are infected during epidemic, and thus enter the infectious and recovered compartments. The number of infected individuals are more than susceptible individuals in the host population. Therefore the disease cannot invade the population until the number of susceptible individuals has built back up again.

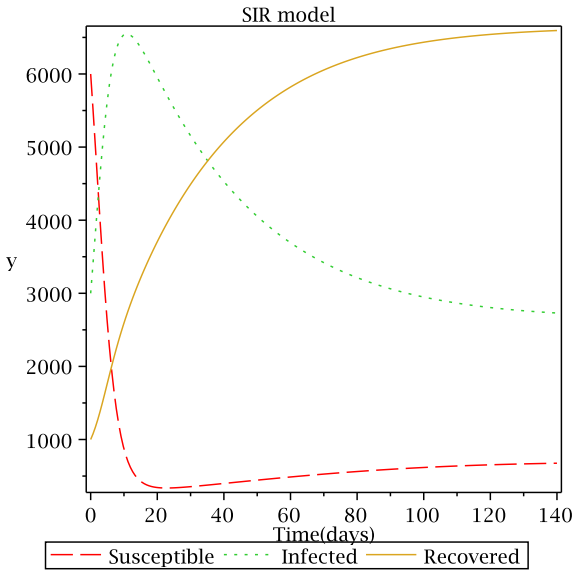

Figure 3.1: An epidemiological graph for the SIR model.

3.2 Birth, mortality and vaccination

The model of McKendrick and Kermack serves more or less as the basis for the modern, more sophisticated SIR models. Subsequent models also consider birth and death. Hattaf and Yousfi [21] introduces the simple model for the transmission of influenza. They assume that an individual can be infected only through contacts with the infectious individuals. Therefore the model parameters are defined by,

- β is the effective contact rate,
- Λ is the recruitment rate,
- r is the recovery rate,
- μ is the natural mortality rate,
- m is the H1N1 induced mortality rate.

Their model is given by the following nonlinear system of differential equations

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \mu S - \frac{\beta SI}{N}, \\ \frac{dI}{dt} &= \frac{\beta SI}{N} - (\mu + m + r)I, \\ \frac{dR}{dt} &= rI - \mu R, \end{aligned} \tag{3.3}$$

where initial conditions are given by $S(0) = S_0$, $I(0) = I_0$, and $R(0) = R_0$.

It is claimed in Hattaf and Yousfi [21] that the set

$$\Omega = \left\{ (S, I, R) \in \mathbb{R}^3_+ : 0 \leq N \leq \frac{\Lambda}{\mu} \right\}$$

is dissipative, i.e., that every solution will eventually have a point in Ω. Furthermore, Ω is positively invariant. Therefore all the solutions will be eventually in Ω. We give our own proof that Ω is in an absorbing set. Furthermore it is shown in Hattaf and Yousfi how to compute the equilibria and the basic reproductive ratio. In a later chapter, we shall study optimal vaccination on this model.

Proposition 3.2.1. *Consider any solution $(S(t), I(t), R(t))$ of the system (3.3). Then there exist some $t_0 > 0$ such that $(S(t), I(t), R(t)) \in \Omega$ for all $t > t_0$.*

Proof. We note that, by adding the differential equations,

$$\frac{dN}{dt} = \Lambda - \mu N - mI \leq \Lambda - \mu N \text{ (since } I \geq 0).$$

This means that, whenever $N > \frac{\Lambda}{\mu}$, then $\frac{dN}{dt} \leq 0$. This means that if outside of Ω, N will decrease until $(S, I, R) \in \Omega$ and once (S, I, R) has hit the set Ω, it will never be able to escape again. □

Proposition 3.2.2. *The value of the basic reproductive number is $R_0 = \frac{\beta}{\mu+m+\gamma}$.*

Proof. The argument uses simply the definition of the different entities. The rate at which infectives are being removed through recovery or death is $(\mu + m + \gamma)$. Therefore the average duration of the infection in a given person is $(\mu + m + \gamma)^{-1}$. The transmission rate being β yields the asserted value for R_0. □

3.3 A model with incubation

The SIR model were modified to capture an incubation or latent compartment, usually denoted by E, in certain cases. This was necessary for diseases in which the pathogen undergoes a phase of incubation in the body of a newly infected host, before the symptoms start to show. Example of such diseases are malaria, measles and smallpox. Example of the papers discussing such SEIR model are Li and Jin [33], Li et al. [32], and d'Onofrio [11]. We pay particular intention to a measles study. Tessa [57] formulated a compartmental mathematical model to describe the transmission dynamics of measles in the presence of vaccine within the population. Since measles virus is highly regarded as one of the most contagious diseases, a vaccination strategy was applied in order to control the transmission of measles in the population.

We have four different compartments in this model (S, E, I, R), and the population is assumed to be homogeneous-mixed. Thus the host population of a size $N(t)$ at a time t is divided into four epidemiological compartments: Susceptible individuals $S(t)$, exposed individuals $E(t)$ but not yet infectious, infectious individuals $I(t)$, and recovered individuals $R(t)$. If β is the average number of the contact rate of a person per unit time, then $\beta I(t)/N(t)$ is the average number of contacts with infectives per unit time of one susceptible, and the number of new cases per unit time due to the $S(t)$ susceptibles is $\beta S(t)[I(t)/N(t)]$. The model parameters are defined as follows:

- β is the contact rate,
- b is the birth rate,
- μ is the mortality rate,
- p is the proportion of those successively vaccinated at birth,
- σ is the differential mortality due to measles,
- $\frac{1}{\gamma}$ is the average infectious period,
- $\frac{1}{\sigma}$ is the average latent period.

The diagram below represent the SEIR model during horizontal transmission,

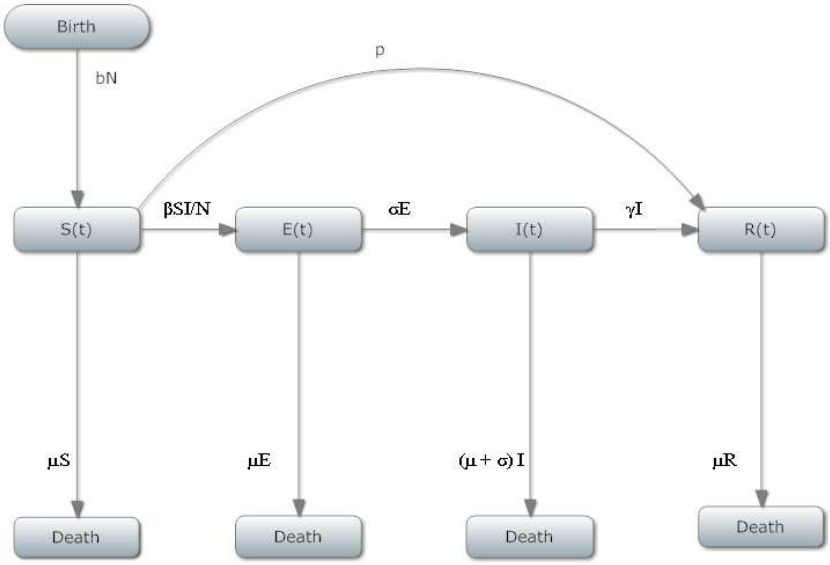

Figure 3.2: A flowchart of possible states in an SEIR epidemic model.

The dynamics of measles transmission in the presence of vaccine within the population is governed by the following differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= b(1-p)N - \frac{\beta SI}{N} - \mu S, \\
\frac{dE}{dt} &= \frac{\beta SI}{N} - (\sigma + \mu)E, \\
\frac{dI}{dt} &= \sigma E - (\gamma + \mu + \sigma)I, \\
\frac{dR}{dt} &= bpN + \gamma I - \mu R,
\end{aligned} \tag{3.4}$$

Remark 3.3.1. *Notice that the system* (3.4) *has the reproductive number of*

$$R_0 = \frac{b\beta\sigma}{\mu(\sigma+\mu)(\gamma+\mu+\sigma)}.$$

3.4 Multiple pathogen strains

Ackleh and Allen [1] studied SIR and SIS epidemic models with multiple pathogen strains. In their models they assume total cross immunity, stan-

dard incidence and density-dependent host mortality. The main aim of this model is to study and investigate the effect of demography on competitive exclusion and coexistence of multiple pathogen strains. Therefore, they derive conditions in an SIR epidemic model with n strains. In this model, we define the parameter as:

- b is the per capita birth rate,
- $f(N)$ is the per capita growth rate,
- β_j is the transmission rate for the jth strain,
- γ_j is the recovery rate from infection with strain j,
- μ_j is the disease-related death rate for strain j,
- $d(N)$ is the density-dependent death rate.

The SIR model with standard incidence is given by:

$$\begin{aligned}
\dot{S}(t) &= S\left(f(N) - \sum_{k=1}^{n} \beta_k \frac{I_k}{N}\right) + \sum_{k=1}^{n} bI_k + bR, \\
\dot{I}_j(t) &= I_j\left(f(N) - b + \beta_j \frac{S}{N} - \gamma_j - \mu_j\right), \quad j = 1, 2, ..., n, \qquad (3.5) \\
\dot{R}(t) &= R(f(N) - b) + \sum_{k=1}^{n} \gamma_k I_k, \\
N &= S + R + \sum_{k=1}^{n} I_k.
\end{aligned}$$

Then we have $f(N) = b - d(N)$. If we let $d(N)$ to be the density-dependent death rate, therefore $-d(N) = f(N) - b$. Subtracting and adding the term bS in all equations of system (3.5), then we obtain the differential equation for S as,

$$\dot{S}(t) = S\left(f(N) - b - \sum_{k=1}^{n} \beta_k \frac{I_k}{N}\right) + b(N).$$

Note that in an SIS model there is no recovery state. Therefore the spreading of diseases is based only on the cycle of diseases within the host population. Thus the SIS epidemic model with n strains is of the form,

$$\begin{aligned}
\dot{S}(t) &= S\left(f(N) - \sum_{k=1}^{n} \beta_k \frac{I_k}{N}\right) + \sum_{k=1}^{n} (b + \gamma_k) I_k, \\
\dot{I}_j(t) &= I_j\left(f(N) - b + \beta_j \frac{S}{N} - \gamma_j - \mu_j\right), \quad j = 1, 2, ..., n, \qquad (3.6) \\
\dot{R}(t) &= R(f(N) - b) + \sum_{k=1}^{n} \gamma_k I_k, \\
N &= S + \sum_{k=1}^{n} I_k.
\end{aligned}$$

Furthermore, subtracting and adding the term bS in equation (3.6), then we obtain the differential equation for S as,

$$\dot{S}(t) = S\left(f(N) - b - \sum_{k=1}^{n} \beta_k \frac{I_k}{N}\right) + \sum_{k=1}^{n} (\gamma_k) I_k + b(N),$$

where $\gamma_j = 0$ for $j = 1, 2, ..., n$.

Note that the basic reproductive number calculated in proposition 3.2.2 is also valid for this multi-strain SIR. Of course now each strain is considered separately, and for the k^{th} strains we have R_k as,

$$R_k = \frac{\beta_k}{b + \gamma_k + \mu_k}.$$

The proof that a necessary condition that must hold in order that the two strains k^{th} and l^{th} will both be endemic is that $R_k = R_l$. This "exact" identity is of course mathematically highly unlikely. Therefore, at most one of the strains can become endemic. It will necessarily be the strain with the highest R_k-value that will dominate. In fact it turns out that for the system, the basic reproductive ratio is

$$R = \max\{R_k : k = 1, 2, ..., n\}.$$

3.5 An age-structured model

Inaba [25] considered a mathematical model for the spreading of a directly transmitted infectious disease in an age-structured population. In his model, he assume that infected individuals in a population is recovered with permanent immunity or quarantined by an age-specific times, and infectious disease can also be transmitted vertically from adult individuals to their newborns, but not only horizontally. The population is assumed to be demographic stable. First he consider a closed one-sex age-structured population under the demographic stable growth. Let $P(t, a)$ denote the age-density at time t of the host population, where $\mu(a)$ is the age-specific natural death rate, and $f(a)$ the age-specific fertility rate. Then he used McKendrick equation to describe the host population dynamics, which is thus given by,

$$\left(\frac{\partial}{\partial(t)} + \frac{\partial}{\partial(a)}\right) P(t,a) = -\mu(a)P(t,a), \tag{3.7}$$

$$P(t,0) = \int_0^\omega f(a)P(t,a)da, \tag{3.8}$$

$$P(0,a) = P_0(a). \tag{3.9}$$

Where $\omega < \infty$ is the upper bound of age and the initial data is given by $P_0(a)$. Therefore the system has a stable population model in demography.
From the stability of population model in demography, it follows that both equations (3.7) and (3.8) has a unique lasting age profile as

$$\psi(a) := \frac{e^{-r_0 a}\ell(a)}{\int_0^\omega e^{-r_0 a}\ell(a)\ da},$$

where the survival rate is denoted by $\ell(a)$, which is defined by

$$\ell(a) := \quad exp\left(-\int_0^a \mu(\sigma)\ d\sigma\right),$$

and r_0 denote the intrinsic rate of natural increase, which is given by the dominant real root of the Euler-Lotka characteristic equation

$$\int_0^{\omega} e^{-ra} f(a)\ell(a)da \;=\; 1. \tag{3.10}$$

Therefore the age density of the host population is given by

$P(t,a) = N(t)\psi(a)$, where $N(t) = \int_0^{\omega} P(t,a)da$ is the total size of the population.

The host population is divided into three epidemiological classes:
namely

- $S(t,a)$ = Susceptible individuals,
- $I(t,a)$ = Infectious individuals,
- $R(t,a)$ = Recovered individuals.

Then the age-structured SIR epidemic model with vertical transmission is given by the following nonlinear system of differential equestions:

$$\begin{aligned}
\left(\frac{\partial}{\partial(t)} + \frac{\partial}{\partial(a)}\right) S(t,a) &= -\left(\lambda(t,a) + \theta(a) + \mu(a)\right) S(t,a), \\
\left(\frac{\partial}{\partial(t)} + \frac{\partial}{\partial(a)}\right) I(t,a) &= \left(\lambda(t,a)S(t,a) - \left(\gamma(a) + \mu(a)\right) I(t,a), \right. \\
\left(\frac{\partial}{\partial(t)} + \frac{\partial}{\partial(a)}\right) R(t,a) &= \theta(a)S(t,a) + \gamma(a)I(t,a) - \mu(a)R(t,a), \qquad (3.11) \\
S(t,0) &= \int_0^{\omega} f(a)[S(t,a) + (1-q)I(t,a) + R(t,a)]da, \\
I(t,0) &= q\int_0^{\omega} f(a)I(t,a)da, \\
R(t,0) &= R_a(t).
\end{aligned}$$

The force of infection $\lambda(t,a)$ is given by

$$\lambda(t,a) = \frac{1}{N(t)} \int_0^{\omega} \beta(a,\sigma) I(t,\sigma) d\sigma. \tag{3.12}$$

The above model parameters are defined by,

- $\beta(a,\sigma)$ is the transmission rate between the susceptible individuals aged a,
- σ is the age of infective individuals,
- $\gamma(a)$ is the rate of recovery at age a,
- $\theta(a)$ is the rate of removal at age a.

3.6 Discrete model with delay

Enatsu et al. [14] proposed the class of discrete SIR epidemic epidemic models with distributed delays using backward Euler method. They used a discrete mathematical model to elaborate the following continuous SIR model with distributed delays,

$$\begin{aligned} \frac{ds(t)}{dt} &= b - \beta s(t) \int_0^h f(\tau) i(t-\tau)\, d\tau - \mu_1 s(t), \\ \frac{di(t)}{dt} &= \beta s(t) \int_0^h f(\tau) i(t-\tau)\, d\tau - (\mu_2 + \lambda) i(t), \\ \frac{dr(t)}{dt} &= \lambda i(t) - \mu_3 r(t), \end{aligned} \tag{3.13}$$

where $s(t)$, $i(t)$ and $r(t)$ are the proportions of the population which belong to the classes S, I and R respectively to time t. In this model, they assume that the parameters of the model are positive and constant, which are defined by,

- b is the constant rate,

- β is the mass action coefficient rate,
- μ_1, μ_2 and μ_3 are the death rates of susceptible, infectious and recovered individuals,
- h is the duration rate,
- τ is the infection rate,
- $f(\tau)$ is the fraction of vector population.

They also assume that $\int_0^h f(\tau)\ d\tau = 1$, such that the function is positive and continuous on $[0, h]$. Furthermore, from the above information, we propose the discrete SIR epidemic model derived from system (3.13) by employing a variation of the backward Euler method.

$$\begin{aligned} s(p+1) - s(p) &= b - \beta s(p+1) \sum_{j=0}^{m} f(j) i(p-j) - \mu_1 s(p+1), \\ i(p+1) - i(p) &= \beta s(p+1) \sum_{j=0}^{m} f(j) i(p-j) - (\mu_2 + \lambda) i(p+1), \\ r(p+1) - r(p) &= \lambda i(p+1) - \mu_3 r_(p+1). \end{aligned} \tag{3.14}$$

The initial conditions of the system (3.14) are,

$$\begin{aligned} s(p) &= \phi(p) \geq 0,\ i(p) = \psi(p) \geq 0,\ r(p) = \sigma(p) \geq 0, \\ p &= -m,\ -(m-1),\ \ldots,\ -1, \end{aligned}$$

and $s(0) > 0, \quad i(0) > 0, \quad r(0) > 0.$

Here b, β, μ_i for all $(i = 1, 2, 3), \lambda$ and m are positive constants, and $f(j) \geq 0$ for some $j = 0,\ 1,\ \ldots\ m$. Therefore we have that,

$$\sum_{j=0}^{m} f(j) = 1.$$

Thus there exist nonnegative integer such that $0 \leq j \leq m$.

3.7 Age model with delay

Wu and Röst [64] derived a new SEIR model with distributed infinite delay whereby infectivity depends on the age of infection in the population. They distinguish the basic reproductive number R_0, which is considered as the threshold quantity of the equilibria for the stability analysis. Furthermore, they also mention that if $R_0 < 1$, then the disease-free equilibrium is globally asymptotically stable and if $R_0 > 1$, then an endemic equilibrium is locally asymptotically stable.

We take $i(t, a)$ to represent the density of infected individuals with respect to the age of infection a at the given time t. Then $I(t) = \int_0^\infty i(t, a)da$ and we also introduce the kernel function $0 \leq k(a) \leq 1$ in order to show the infectivity of infection according to the age a. The parameters of this model are defined by,

- β is the baseline transmission rate,
- a is the age of infection,
- $\frac{1}{\mu}$ is the average latency period,
- $\frac{1}{r}$ is the average infectivity period,
- δ is the disease-induced death rate,
- Λ is the constant recruitment rate,
- d is the natural death rate.

The SEIR model with distributed infinite infectivity is given by the following differential equations:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - \beta S(t)\int_0^\infty k(a)i(t,a)da - ds(t), \\
\frac{dE(t)}{dt} &= \beta S(t)\int_0^\infty k(a)i(t,a)da - (\mu + d)E(t), \\
\frac{dI(t)}{dt} &= \mu E(t) - (\gamma + \mu + \delta)I(t), \\
\frac{dR(t)}{dt} &= rI(t) - dR.
\end{aligned} \tag{3.15}$$

Therefore the development of the density is given by the following equation,

$$\left(\frac{\partial}{\partial(t)} + \frac{\partial}{\partial(a)}\right) i(t,a) = (d+\delta+r)i(t,a), \tag{3.16}$$

which is subjected to the following boundary condition $i(t,0) = \mu E(t)$.

Solving equation (3.16) results to

$i(t,a) = i(t-a,0)e^{-(d+\delta+r)a} = \mu E(t-a)e^{-(d+\delta+r)a}$, for $t \geq a$.

Thus, we obtain the deterministic model of delay differential equations as follows

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - \beta S(t)\int_0^\infty k(a)\mu E(t-a)e^{-(d+\delta+r)a}da - ds(t), \\
\frac{dE(t)}{dt} &= \beta S(t)\int_0^\infty k(a)\mu E(t-a)e^{-(d+\delta+r)a}da - (\mu+d)E(t), \\
\frac{dI(t)}{dt} &= \mu E(t) - (\gamma+\mu+\delta)I(t), \\
\frac{dR(t)}{dt} &= rI(t) - dR.
\end{aligned} \tag{3.17}$$

An interesting problem following on this work of Wu and Röst would be to introduce vaccination into this age structured model, and search for optimal vaccination strategies.

3.8 Polynomial solutions

The general practice for solving differential equations in epidemiology is to resort to numerical solutions. The textbook of Lenhart and Workman [31] gives procedures of solving such systems. Otherwise, there are sporadic attempts at finding closed form solutions. We present one case here. Makinde [37] developed an SIR model which controls the temporal dynamics of a childhood disease in the presence of preventive vaccine.

This covers diseases such as chicken pox, influenza, mumps, polio, rubella, measles, etc. This types of disease can be spread quickly because young children have maturing immune systems and are often in close proximity to one

another, such as in day-care centers, homes, classrooms, and at school. This makes the transmission of contagious diseases particularly easy.

Therefore the development of vaccines against infectious childhood diseases is a blessing to mankind and children, because vaccines have proven among the most cost-effective strategies for preventing infectious diseases. In his model, he employed the Adomian decomposition method to compute an estimation to the solution of the non-linear system of differential equations ruling the problem. The SIR model is a standard compartmental model that has been used to describe many epidemiological disease. Then we have the following,

- S is the susceptible group,
- I is the infected group,
- R is the removed group.

He also assume that the efficacy of the vaccine is 100 percent, and the proportion of those newborn infants who are vaccinated successfully each year is given by $P($ with $0 < P < 1)$. We define the model parameters as follows,

- β is the average contact rate,
- γ is the recovery rate,
- μ is the natural death rate,
- π is the constant birth rate.

Now the system of integral equations for the SIR model are,

$$\begin{aligned} s(t) &= s(0) + (1-P)\pi t - \beta \int_0^t si\ dt - \pi \int_0^t s\ dt, \\ i(t) &= i(0) + \beta \int_0^t si\ dt - (\gamma + \pi) \int_0^t i\ dt, \\ r(t) &= r(0) + P\pi t + \gamma \int_0^t i\ dt - \pi \int_0^t r\ dt. \end{aligned} \tag{3.18}$$

We consider the Adomian decomposition method of the system (3.18) as the sum the following series,

$$s = \sum_{n=0}^{\infty} s_n, \quad i = \sum_{n=0}^{\infty} i_n, \quad r = \sum_{n=0}^{\infty} r_n. \tag{3.19}$$

Then we estimate the non-linear terms in the system as follows,

$$si = \sum_{k=0}^{\infty} F_n(s_0, ..., s_0, i_0, ..., i_n), \tag{3.20}$$

where,

$$F_n = \frac{1}{n!}\left[\frac{d^n(\sum_{k=0}^{\infty} s_k\lambda^k)(\sum_{k=0}^{\infty} i_k\lambda^k)}{d\lambda^n}\right]_{\lambda=0}. \tag{3.21}$$

The function F_n is a non-linear and is called Adomian's polynomials. Now substituting equations (3.19), (3.20) and (3.21) into system (3.18) we obtain

$$\begin{aligned}
\sum_{n=0}^{\infty} s_n &= s(0) + (1-P)\pi t - \beta\int_0^t \sum_{n=0}^{\infty} F_n\, dt - \pi\int_0^t \sum_{n=0}^{\infty} s_n\, dt,\\
\sum_{n=0}^{\infty} i_n &= i(0) + \beta\int_0^t \sum_{n=0}^{\infty} F_n\, dt - (\gamma+\pi)\int_0^t \sum_{n=0}^{\infty} i_n\, dt,\\
\sum_{n=0}^{\infty} r_n &= r(0) + P\pi t + \gamma\int_0^t \sum_{n=0}^{\infty} i_n\, dt - \pi\int_0^t \sum_{n=0}^{\infty} r_n\, dt.
\end{aligned} \tag{3.22}$$

Hence, we define the system (3.22) as follows,

$$\begin{aligned}
s_{n+1} &= -\beta\int_0^t F_n\, dt - \pi\int_0^t s_n\, dt \quad (\text{for } n \geq 0),\\
i_{n+1} &= \beta\int_0^t F_n\, dt - (\gamma+\pi)\int_0^t i_n\, dt \quad (\text{for } n \geq 0),\\
r_{n+1} &= \gamma\int_0^t i_n\, dt - \pi\int_0^t r_n\, dt \quad (\text{for } n \geq 0),
\end{aligned} \tag{3.23}$$

where,

$$s_0 = s(0) + (1 - P)\pi t, \quad i_0 = i(0), \quad r_0 = r(0) + P\pi t.$$

Thus Makinde [37] has obtained a closed form approximate solution to an SIR model.

Chapter 4

Stability of epidemiological models

We first consider the general SIR epidemic model. As seen up to now, there are different versions of SIR-model. We consider the model of Hattaf and Yousfi, which we treated in chapter 3 and which gives other models such as that of Zaman et al. [67], as special cases. We assume that there is an equality of interaction of individual within the population. In standard formulations of disease dynamics, the time evolution of the different classes of hosts is described by a simple set of ordinary differential equations, and stability criteria for first-order systems or for higher-order difference equations depend on the behavior of the system. Upon this assumption, the population is assumed to be homogeneous and sufficiently large such that stochastic events are negligible. As in an SIR model, we assume that the host population is divided into three compartments. For convenience we recall the model of Hattaf and Yousfi [21] from chapter 3:

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \mu S - \frac{\beta SI}{N}, \\ \frac{dI}{dt} &= \frac{\beta SI}{N} - (\mu + m + r)I, \\ \frac{dR}{dt} &= rI - \mu R. \end{aligned} \tag{4.1}$$

We assume that birth and death rates are not necessarily equal. This implies that the population size N is not constant, i.e., $N = N(t)$ is a function

of time,

$$S(t) + I(t) + R(t) = N(t).$$

A susceptible host can get infected at rate β when in contact with infected individuals. By γ we denote the rate of recovery from the infection and β is a transmission coefficient, the meaning of which is as follows. Susceptible individuals acquire the infection at a per capita rate $\beta I(t)$ and therefore, the migration from the S-class to the I-class takes place at a rate $\beta SI/N$. The symbol Λ corresponds to the birth rate, ν corresponds to the natural mortality rate in the classes S, I and R. The transfer diagram and the equations were given in chapter 3 and will not be repeated here.

Remark 4.0.1. In Proposition 3.2.2 we proved that the system (3.3) has basic reproductive ratio

$$R_0 = \frac{\beta}{\mu + r + m}.$$

In this chapter the basic reproductive number R_0 will be used to describe stability of the an equilibrium point.

4.1 The disease-free equilibrium

In this section, we study and analyze the stability status of the equilibrium solutions. We show that there exist a disease-free equilibrium point and an endemic equilibrium.

Proposition 4.1.1. *The disease-free equilibrium is the point* **F** *with S-value* $S_F = \frac{\Lambda}{\mu}$ *and the unique endemic equilibrium solution is the point* $\mathbf{D} = (S_D(t), I_D(t), R_D(t))$, *given by*

$$S_D = \tfrac{1}{K} N^*,$$

$$I_D = \tfrac{\mu(K-1)}{K(\mu+\gamma+m)} N^*$$

$$R_D = \tfrac{\gamma(K-1)}{K(\mu+\gamma+m)} N^*,$$

$$N_D = \tfrac{\Lambda K(\mu-\gamma)}{\mu[(K-1)+K(\mu+\gamma+m)]}.$$

Sketch of proof. To this end, we set $dS(t)/dt = 0$ and $dI(t)/dt = 0$. We obtain the said value of S_F by setting $I(t) = 0$. Next we take $I_D(t) \neq 0$ and we obtain the value of (S_D, I_D, R_D) as declared in the proposition. □

For stability analysis we shall use the linearization theorem and we shall compute the Jacobian matrix.

$$W = \begin{bmatrix} \frac{\partial X}{\partial S} & \frac{\partial X}{\partial I} & \frac{\partial X}{\partial R} \\ \frac{\partial Y}{\partial S} & \frac{\partial Y}{\partial I} & \frac{\partial Y}{\partial R} \\ \frac{\partial Z}{\partial S} & \frac{\partial Z}{\partial I} & \frac{\partial Z}{\partial R} \end{bmatrix}.$$

This matrix comes up as follows,

$$W = \begin{bmatrix} -\mu - \frac{\beta I}{N} & -\frac{\beta S}{N} & 0 \\ \frac{\beta I}{N} & \frac{\beta S}{N} - \gamma - \mu - m & 0 \\ 0 & \gamma & -\mu \end{bmatrix}.$$

The characteristic equation of this matrix is given below, and here $\mathbf{I}_3$ denotes the 3×3 identity matrix :

$$\mathrm{Det}(\lambda \mathbf{I}_3 - W) = 0.$$

Proposition 4.1.2. *For the number* $K = \frac{\beta\Lambda}{\mu(w+\gamma+m)N}$ *we have:*

(i) If $K < 1$*, then the disease-free equilibrium* $\mathbf{F}$ *is locally asymptotically stable.*

(ii) If $K > 1$*, then the disease-free equilibrium* $\mathbf{F}$ *is unstable.*

Proof. At the disease-free equilibrium point, we take $S_F = \frac{\Lambda}{\mu}$ and $I_D = 0$ and then the characteristic equation reduces to

$$(\lambda + \mu)^2 (\beta - \mu - \gamma - m - \lambda) = 0. \tag{4.2}$$

Therefore the eigenvalues are $\lambda_1 = -\mu$, $\lambda_2 = -\mu$, and $\lambda_3 = \beta - \mu - \gamma - m$.

Note that $\lambda_3 < 0$ if and only if $\beta < \mu + \gamma + m$, i.e., if

$$\frac{\beta}{(\mu + \gamma + m)} < 1.$$

Clearly λ_1 and λ_2 are negative. Thus, if $K < 1$, then all the eigenvalues are negative when $K < 1$ and so $\mathbf{F}$ is locally asymptotically stable. This proves (i). The proof of (ii) is simple. □

Next we turn to equilibrium point.

Proposition 4.1.3. *(i) If $K < 1$, then the point* $\mathbf{D}$ *does not exist.*

(ii) If $K > 1$, then $\mathbf{D}$ *is locally asymptotically stable.*

Proof. If $K < 1$, it is easy to show that $\mathbf{D}$ does not exist. We now turn to proving (ii). We assume that $K > 1$. Then matrix W can be computed and the characteristic equations comes up as follows

$$(\mu + \lambda)(\lambda^2 + a_1\lambda + a_2) = 0, \tag{4.3}$$

with,

$$a_1 = \mu + \frac{\mu\beta(K-1)}{K(\mu + \gamma + m)} \text{ and } a_2 = \frac{\mu\beta(K-1)}{K^2}[\mu + \beta(K-1)].$$

Therefore the characteristic roots are $\lambda_1, \lambda_2, \lambda_3$. Where $\lambda_1 = -\mu$, while λ_2 and λ_3 are the solutions of the quadratic equation

$$\lambda^2 + a_1\lambda + a_2. \tag{4.4}$$

It is clear that when $K > 1$, then both a_1 and a_2 are positive, so that all the roots of equation (4.3) have negative real parts. Therefore, $\mathbf{D}$ is locally asymptotically stable whenever $K > 1$. □

4.2 The endemic equilibrium

We now simulate the SIR model using Euler methods to demonstrate the dynamics of the system. The numerical simulation was done using Maple. The table below shows the parameters used in the simulations and the parameters are chosen arbitrarily.

Table 4.1: The parameter values for SIR model

Position	Parameter	Values
1.	Λ	0.21
2.	β	[0.36, 0.95]
3.	μ	0.21
4.	γ	[0.32, 0.43]
5.	S	0.26
6.	I	0.6
7.	R	0.14
8.	N	600

Firstly, we set the parameter values used in Figure 4.1 as follows: $\mu = 0.21$ $\beta = 0.36$, $\gamma = 0.32$ and $\Lambda = 0.21$. On the vertical axis y represent the number of individuals in the population. In our simulation, we assume that population size is constant with natural mortality rate of individuals μ being equal to the birth rate Λ $(\mu = \Lambda = 0.21)$.

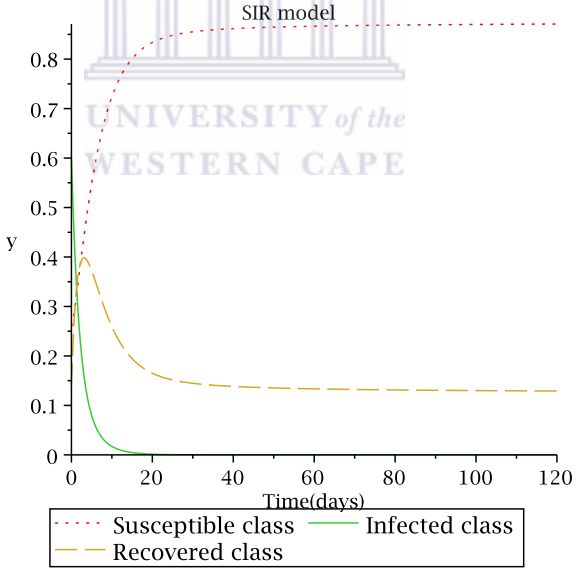

Figure 4.1: The plot shows the global stability of the SIR epidemic model, when $R_0 = 0.7$. [Programmed in Maple (2010)].

From Figure 4.1 above, we can easily see that when $R_0 < 1$, the number of susceptible individuals and recovered individuals starts to increase from the first day while the number of infected individuals decreases from the first day to zero. When recovered individuals approaches day 10 it also decreases until it reaches day 20, where it becomes constant. In this case the disease seems to disappears from the population after 18 days, and there will be no infection in the host population. Thus disease-free equilibrium is globally stable.

In Figure 4.2 below, we also simulate the dynamic model for SIR when $R_0 > 1$. We obtain $R_0 = 1.5$ if $\mu = 0.21$, $\beta = 0.95$, $\gamma = 0.43$, and $\Lambda = 0.21$. Therefore figure 4.2 shows that the number susceptible and recovered individuals increase in their very first days, while on the other side the number of infected individuals sharply decreases during the first 10 days. From day 11 infected individuals started to increase until it approaches day 21, and it reaches its steady state. This shows that there is a unique positive epidemic equilibrium in the host population.

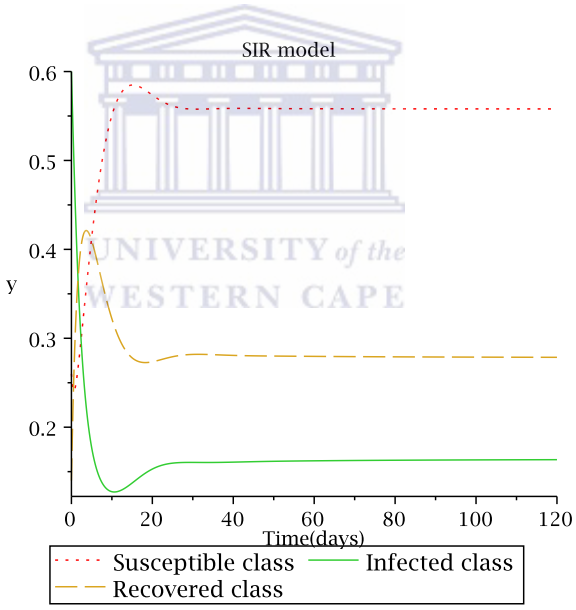

Figure 4.2: The plot shows unstable SIR epidemic model, when $R_0 = 1.5$. [Programmed in Maple (2010)].

Chapter 5

Control of vaccination in SIR model

5.1 The SIR model

We continue with the general SIR model of an epidemic, impose vaccination on it, and determine an optimal strategy for rolling out the vaccination. The model in this form has been used by Hattaf and Yousfi [21] for instance, and a similar control problem was studied for a simpler model in [67] by Zaman et al. The textbook [31] of Lenhart and Workman is a very useful reference for this kind of problem.

We solve a control problem similar to that done in [67]. We identify some properties that were not observed by Zaman et al. Essentially we observed that one of the Lagrange multipliers become identical to zero. This simplifies, in particular, the description of the optimal control. Our presentation is in detail.

We have shown in chapter 3 that all the viable solutions of the system (3.3) enters the region

$$\Omega = \left\{ (S, I, R) \in \mathbb{R}^3_+ : \ 0 \leq N \leq \tfrac{\Lambda}{\mu} \right\}.$$

It is sufficient to consider solutions in Ω. It has been shown that all the solutions of system (3.3) beginning in Ω remains in Ω for all $t \geq 0$, i.e., Ω is positively invariant. The derivatives of the system (3.3) of the right hand side implies that there exist a unique solution on the maximal interval. In this

case, the solutions are eventually bounded and exist for $t \geq 0$ when they enter and approaches Ω. Hence the model is mathematically and epidemiology well posed. We calculate the basic reproductive number R_0. Also in chapter 3, we have noted that the value of the basic reproductive number is $R_0 = \frac{\beta}{\gamma+\mu+m}$.

In the next section we introduce vaccination into the model.

5.2 The model with vaccination

At this point we assume further that the model has constant population size, i.e., there is no extra disease-induced mortality ($m = 0$), as in [67] of Zaman et al. We modify our basic model by imposing vaccination. We assume that at any point in time, susceptibles are being vaccinated at a rate of $u(t) \times 100$ % of the $S(t)$. Hereby we mean that the number of susceptibles that are being vaccinated during a short time period dt is $u(t)S(t)dt$. Then it follows that the population will satisfy the following system of equations:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - (\mu + u(t))S(t) - \frac{\beta I(t)S(t)}{N}, \quad S(0) = S_0 \geq 0, \\
\frac{dI(t)}{dt} &= \frac{\beta I(t)S(t)}{N} - (\gamma + \mu)I(t), \quad I(0) = I_0 \geq 0, \\
\frac{dR(t)}{dt} &= \gamma I(t) - \mu R(t) + u(t)S(t), \quad R(0) = R_0 \geq 0.
\end{aligned} \tag{5.1}$$

The idea is now to find some optimal way of rolling out the vaccination. To this end we shall consider the objective functional $J = J(u)$ below, in which τ is a constant parameter. We intend to choose a vaccination strategy $u^*(t)$ in such a way as to minimize the value of J. Note that this is modeled on the functional in Zaman et al. Our analysis follows also as in [67], with some new observations, essentially that a certain co-state variable vanishes.

$$J(u) = \int_0^{t_{end}} [I(t) + \frac{1}{2}\tau u^2(t)] \quad dt. \tag{5.2}$$

Thus we have the problem, present in the next section.

5.3 The Optimal vaccination problem

We consider an optimal control problem to minimize the objective function $J(u)$ with respect to u and subject to the conditions above. Let us further assume that $0 < u(t) < A$ for some fixed constant A.

Now we continue towards the solution of the optimization problem. We note that the Hamiltonian of the problem is

$$H(S, I, R, u, \lambda_1, \lambda_2, \lambda_3, t) = I(t) + \tfrac{1}{2}\tau u^2(t) + \lambda_1(t)\tfrac{dS}{dt} + \lambda_2(t)\tfrac{dI}{dt} + \lambda_3(t)\tfrac{dR}{dt}.$$

Theorem 5.3.1. *Let $S^*(t)$, $I^*(t)$, $R^*(t)$ and $u^*(t)$ be optimal for the optimal control problem. Then the adjoint variables satisfy the following equations:*

$$\lambda_1(t) = \left(u + \mu - \tfrac{\beta I^*(t)}{N}\right)\lambda_1(t) + I^*(t)\lambda_2(t),$$

$$\lambda_2(t) = 1 - \left(\tfrac{\beta S^*(t)}{N}\right)\lambda_1(t) + \left(\tfrac{\beta S^*(t)}{N} - \gamma - \mu\right)\lambda_2(t),$$

$$\lambda_3(t) \equiv 0,$$

with transversality conditions (or boundary conditions),

$$\lambda_1(t_{end}) = 0,\ \lambda_2(t_{end}) = 0.$$

Furthermore, the optimal control $u^*(t)$ is given by,

$$u^*(t) = \max\{\min\{\tfrac{\lambda_1(t)S(t)}{\tau}, A\}, 0\}.$$

Proof. We apply the Pontryagin maximum principle, Theorem 2.2.2. We calculate the partial derivatives of H with respect to S, I and R in order to obtain the time derivatives $\dot{\lambda}_i$ of the costate variables. In particular, since $S(t_{end})$, $I(t_{end})$, and $R(t_{end})$ are free, the following terminal conditions hold:

$$\lambda_1(t_{end}) = 0,\ \lambda_2(t_{end}) = 0,\ \lambda_3(t_{end}) = 0.$$

We start noting that,

$$\dot{\lambda}_3(t) = \frac{dH}{dR} = -\mu\lambda_3(t),$$

which means that $\lambda_3(t)$ is an exponential function of time. This together with the condition $\lambda_3(t_{end}) = 0$ means that,

$$\lambda_3(t) \equiv 0.$$

Hereafter we can calculate,

$$\dot{\lambda}_1(t) = \frac{dH}{dS} \text{ and } \dot{\lambda}_2(t) = \frac{dH}{dI}.$$

and obtain the values as asserted.

The function u^* must optimize H. So, we calculate,

$$\frac{dH}{du} = \tau u^* - \lambda_1 S(t).$$

When $\tau u^* - \lambda_1 S(t) = 0$, then of course we choose $u^* = \frac{\lambda_1(t)S(t)}{\tau}$.

When $\tau u^* - \lambda_1 S(t) \geq 0$, then H is an increasing function of u and so we must choose u^* at its least possible value. A similar argument holds for the case $\tau u^* - \lambda_1 S(t) \leq 0$. Thus u^* is as given. □

We characterized $u^*(t)$ for the optimal control by substituting the value of $u^*(t)$ into the control system (5.1), and we obtain the following differential equations,

$$\begin{aligned}
\frac{dS^*(t)}{dt} &= \Lambda - \left(\mu + \max\left\{\min\left\{\frac{S^*(t)\lambda_1(t)}{\tau}, A\right\}, 0\right\}\right) S^*(t) - \frac{\beta S^*(t) I^*(t)}{N}, \\
\frac{dI^*(t)}{dt} &= \frac{\beta S^*(t) I^*(t)}{N} - (\gamma + \mu) I^*, \qquad (5.3) \\
\frac{dR^*(t)}{dt} &= \gamma I^*(t) - \mu R^*(t) + \left(\max\left\{\min\left\{\frac{S^*(t)\lambda_1(t)}{\tau}, A\right\}, 0\right\}\right) S^*(t).
\end{aligned}$$

N the Hamiltonian H^* at $(S^*, I^*, R^*, u^*, \lambda_1, \lambda_2, \lambda_3, t)$ csn be expressed as:

$$
\begin{aligned}
H^* &= I^*(t) + \frac{1}{2}\left[\tau\left(\max\left\{\min\left\{\frac{S^*(t)\lambda_1(t)}{\tau}, A\right\}, 0\right\}\right)^2\right] \\
&+ \lambda_1(t)\left[\Lambda - \left(\mu + \max\left\{\min\left\{\frac{S^*(t)\lambda_1(t)}{\tau}, A\right\}, 0\right\}\right)S^*(t) - \frac{\beta S^*(t)I^*(t)}{N}\right] \\
&+ \lambda_2(t)\left(\frac{\beta S^*(t)I^*(t)}{N} - (\gamma+\mu)I^*(t)\right).
\end{aligned}
$$

5.4 Numerical simulation and discussion for the SIR model

In this section, we demonstrate some numerical simulations of the epidemiological models which illustrates the theoretical results and predict the evolution of infectious diseases in the population at host and we also studied the dynamical behavior of the models. We were very general when setting up these simulations thinking of an infectious disease in the human population, for example infectious disease such as H1N1(influenza), chickenpox, measles, mumps, etc.

The dynamics behavior of the epidemic model cannot only be studied by using analytical methods or normal forms. Therefore we have performed the simulations by computer. Thus we use the optimal vaccination strategy to control the total number of susceptible and recovered individuals and also to minimize the probability that the infected individuals spread the disease in the host population. Vaccination is regarded as one of the most primary strategies used by public health authorities to control human infectious diseases, and these strategy can also provide with some several clear benefits. In real life this strategy can be useful for epidemics such as malaria, rubella, chickenpox, ebola, measles, mumps, influenza, etc.

We use the Runge-Kutta procedure to solve the optimal system with interactive method. Firstly, we solve for the state variable of the system of equations with an initial guess forward Runge-Kutta procedure in time and then we also use the backward Runge-Kutta procedure to solve the adjoint equations in time because of the transversality conditions. The table below shows the parameters used in the simulations and the parameters are chosen arbitrarily.

Table 5.1: The parameters values for SIR model

Position	Parameters	Value
1.	Λ	0.002
2.	β	0.9
3.	μ	0.002
4.	m	0
5.	γ	0.07
6.	S	0.5
7.	I	0.3
8.	R	0.2
9.	N	1

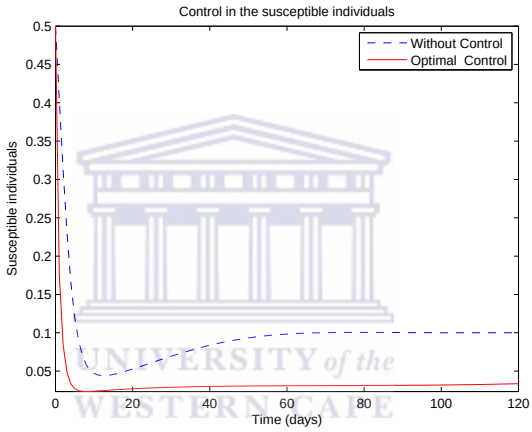

Figure 5.1: The plot represent the population of susceptible individuals (S) with optimal control vaccination. [Programmed in MATLAB (2010)].

Note that we display the quantities S, I and R as fractions rather than the numbers themselves.

In Figure. 5.1, we plot the susceptible individuals using system (5.1). In our graph, note that the solid line represent the population of susceptible individuals with control. We observe that the number of susceptible individuals sharply decreases in the first 13 days, while the number of recovered individuals increases from the first day after vaccination. The population of susceptible become stable at day 22 until it reaches day 120, this is the case of a disease-free state.

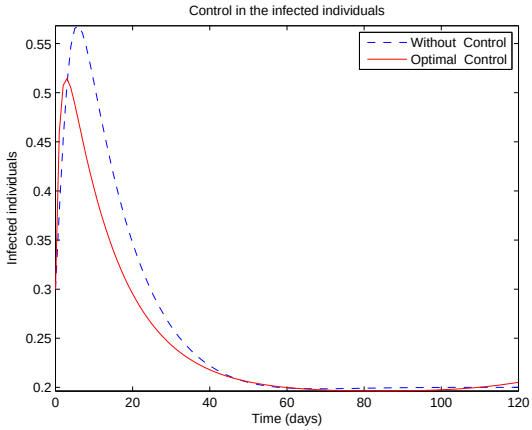

Figure 5.2: The plot represent the population of infected individuals (I) with optimal control vaccination. [Programmed in MATLAB (2010)].

The plot in Figure.5.2, shows that the population of infected individuals with control and without vaccination control increases from the first day until they reach day 20. Furthermore, the number of infected individuals decreases to zero, this shows that the disease dies out and only the susceptible remain in the population. This is a case of a disease-free state, with no infection in the population.

In Figure. 5.3, we plot the recovered individuals using system 5.1. The population number of infected individuals decreases after 20 days of vaccination. We observe that when vaccination control was introduced in the population, the number of recovered individuals increases. This also show the impact the vaccination have brought in the population.

Now we consider Figure 5.4 and Figure 5.5. The graphs represent the adjoint variables λ_1, λ_2 and λ_3 in the optimal system. Firstly, we solve the state of the system equations with an initial guess forward Runge-Kutta procedure in time and then we also use the backward Runge-Kutta procedure to solve the adjoint equations in reverse time because of the transversality conditions.

Figure 5.6 shows the control variable $u(t)$ plotted as a function of S and λ_1 for the weight factor $\tau = 6$ in the population. We observe that the control

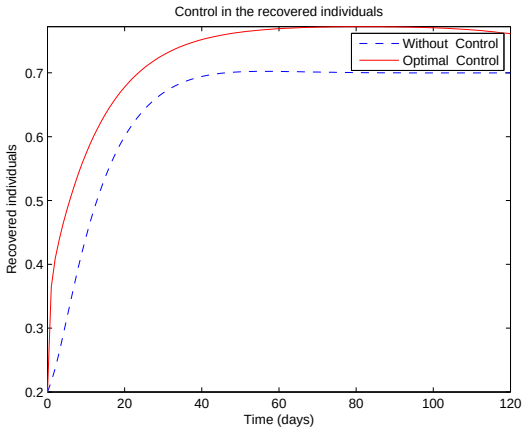

Figure 5.3: The plot represent the population of recovered individuals (R) with optimal control vaccination. [Programmed in MATLAB (2010)].

variable u at a time t play a significant role in minimizing the probability that the infected individuals spread the disease in the host population.

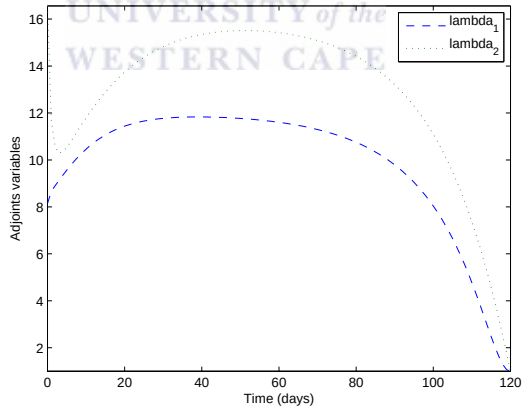

Figure 5.4: The plot represent the adjont variables λ_1 and λ_2 . [Programmed in MATLAB (2010)].

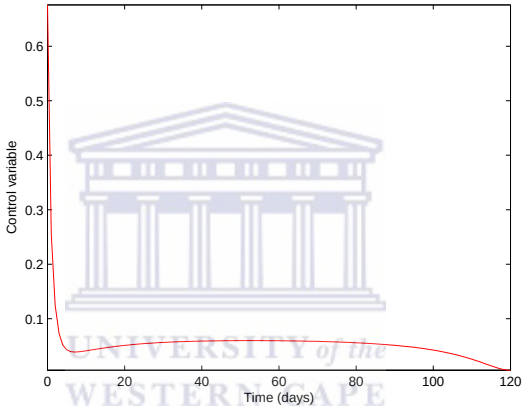

Figure 5.5: The plot represent the population of susceptible individuals (S) with optimal control vaccination. [Programmed in MATLAB (2010)].

Chapter 6

Stability analysis for SEIR model

The SIR model we discussed in earlier chapters considers only the diseases which can cause an individual to infect others immediately upon their infection. In many infectious diseases there is an exposed period, during which the individual is said to be infected but not infectious. In this chapter we use an SEIR model to describe the spread of infectious diseases from susceptibles to potentially infective members in the population.

The compartment denoting the exposed phase is denoted by E. This phase is also known as the incubation period for the pathogen in the body of the host, or the latent period. Diseases for which there is such an incubation period of the pathogen includes HIV/AIDS, tuberculosis, malaria and others. In some cases, such as malaria, a so-called *vector* facilitates the transmission between an infected human and a susceptible, and then the latter becomes infected. In the case of malaria the vector is the Anopheles mosquito, see for instance the paper [43] of Okosun et al. In this dissertation we avoid working with vector-borne diseases.

Therefore we add an exposed class E in the SIR model, and now SEIR is our new model. We assume that the population size N is constant over time with no new entries from births, as we did in the SIR model, such that $N = S+E+I+R$. The accompanying transfer diagram shows the propagation of the disease through the various compartments, and the definitions of model parameters are listed in Table 6.1. The specific model we use in our analysis is the one featuring in [42] by Ngwenya.

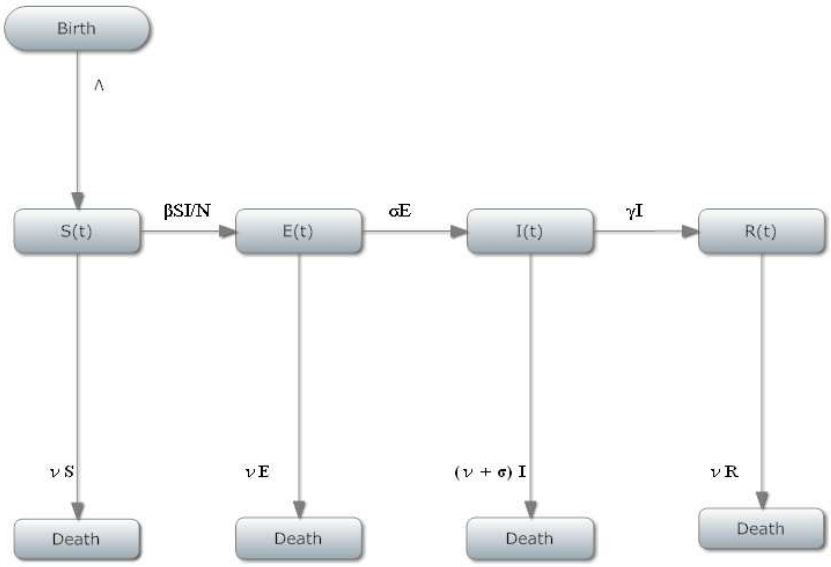

Figure 6.1: A flowchart of possible states in an SEIR epidemic model

Table 6.1: The parameter definitions for SEIR model

Position	Parameters	Definition
1.	Λ	Recruitment rate
2.	β	Transmission coefficient/ Effective contact rate
3.	ν	Natural mortality rate
4.	σ	Disease outcome rate
5.	γ	Recovery rate
6.	t	The total population at time t

One of the most important concerns in infectious disease modeling is to estimate the transition rates (σ, ν and γ) between the corresponding compartments. The rate of infection β can be expressed in terms of the probability of effective contact and the number of infectious at time t. The number of newly infected or exposed individuals at each time step depends on the contact between infectious and susceptible individuals. Therefore the new infections is given by $\frac{\beta SI}{N}$.

The transfer diagram together with the assumptions lead to the following system of differential equations,

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - \nu S - \frac{\beta SI}{N}, \\
\frac{dE(t)}{dt} &= \frac{\beta SI}{N} - (\sigma + \nu)E, \\
\frac{dI(t)}{dt} &= \sigma E - (\gamma + \nu)I, \\
\frac{dR(t)}{dt} &= \gamma I - \nu R,
\end{aligned} \tag{6.1}$$

with initial conditions:

$$S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0.$$

The basic reproductive number R_0 is considered as the threshold quantity that determines when an infection can invade and persist in a new population. If $R_0 < 1$, then the infection in the population dies out, while if $R_0 > 1$, then there is a unique positive epidemic equilibrium.

If each individual effectively contacts c individuals per unit time, then we have $\beta = \frac{c}{N}$ in a population of size N. We also assume that individuals mix at random within the population, there is no stratification of individuals according to age group and sex. Then the average number of individuals effectively contacted by each person per unit time is given by
$c = R/(\text{average duration of infectiousness } \sigma)$. Substituting this expression into that for β above, we obtain $\beta = \frac{R}{N*\sigma}$.

Given a steady process over a time period, the rate at which the process occurs is determined by the inverse of the waiting time attached to the process (duration). The transition rate σ by which exposed become infectious can be derived from the average latent period, and the recovery rate γ can be obtained from the average duration of the infectivity period as follows: $1/\sigma$ can be regarded as the mean latent period latent period, $1/\gamma$ the mean infectious period and $1/\nu$ the mean immune period.

Since $N = S+E+I+R$ is constant, therefore an equation of R is a surplus in this model. Furthermore we assume that all the parameters and variables of the model in system (6.1) are positive, since we are dealing with a human population.

Theorem 6.0.1. *For the SEIR-model above we have the following:*

(i) *The equilibrium value of* N *is* $N = \frac{\Lambda}{\nu}$,
(ii) *The general solution for* N *is,*

$$N = \frac{\Lambda}{\nu} - \frac{(\Lambda - N(t_0)\nu)e^{-\nu(t-t_0)}}{\nu},$$

(iii) *If* $N(t_0) < \frac{\Lambda}{\nu}$, *then* $N < \frac{\Lambda}{\nu}$ *for all time* t.

Proof. By adding the equations of system 6.1, we obtain

$$\frac{dN}{dt} = \Lambda - \nu S - \frac{\beta SI}{N} + \frac{\beta SI}{N} - \sigma E - \nu E + \sigma E - \gamma I - \nu I + \nu I + \nu R,$$

$$= \Lambda - \nu S - \nu E - \nu I - \nu R,$$

$$= \Lambda - \nu(S + E + I + R),$$

$$= \Lambda - \nu N.$$

This yields,

$$\frac{dN}{dt} = \Lambda - \nu N. \tag{6.2}$$

Therefore the equilibrium value of N is $N = \frac{\Lambda}{\nu}$ and so (i) is proved.

When $N(t_0) \geq 0$, we get the general solution of the same equation (6.2) as,

$$
\begin{aligned}
\int_{N(t_0)}^{N} \frac{1}{(\Lambda - \nu N)}\, dN &= \int_{t_0}^{t} dt, \\
-\frac{1}{\nu} \ln(\Lambda - \nu N)|_{N(t_0)}^{N} &= t - t_0, \\
-\frac{1}{\nu} \ln(\Lambda - \nu N) + \frac{1}{\nu} \ln(\Lambda - \nu N(t_0)) &= t - t_0, \\
-\frac{1}{\nu} \ln\left[(\Lambda - \nu N) - (\Lambda - \nu N(t_0))\right] &= t - t_0, \\
\ln\left[\frac{(\Lambda - \nu N)}{(\Lambda - \nu N(t_0))}\right] &= -\nu(t - t_0), \qquad (6.3) \\
\left[\frac{(\Lambda - \nu N)}{(\Lambda - \nu N(t_0))}\right] &= e^{-\nu(t-t_0)}, \\
(\Lambda - \nu N) &= (\Lambda - N(t_0))e^{-\nu(t-t_0)}, \\
N &= \frac{\Lambda}{\nu} - \frac{(\Lambda - N(t_0))e^{-\nu(t-t_0)}}{\nu}.
\end{aligned}
$$

Thus we have proved (ii). The assertion (iii) easily follows from (ii). □

Therefore all the feasible solutions of system (6.1) enters the region,

$$\Omega = \left\{ (S, E, I, R) \in \mathbb{R}_+^4 : \ 0 \leq N \leq \frac{\Lambda}{\nu} \right\},$$

and stays inside it. In particular, Ω is a positively invariant set for the model.

6.1 Local stability for the disease-free equilibrium F

Let us assume henceforth that the population size N of our model is constant, $N = \frac{\Lambda}{\nu}$. The system (6.1) always has a disease-free equilibrium of the form $\mathbf{F} = (\frac{\Lambda}{\nu}, 0, 0)$, corresponding to the disappearance of the disease. We show the stability for the disease-free equilibrium $\mathbf{F}$. Since the first three equations of system (6.1) are all independent of the variable R, thus the equation of R can be omitted. Therefore we consider the following reduced model:

$$\begin{aligned} \dot{S} &= \Lambda - \nu S - \frac{\beta SI}{N}, \\ \dot{E} &= \frac{\beta SI}{N} - (\sigma + \nu)E, \\ \dot{I} &= \sigma E - (\gamma + \nu)I. \end{aligned} \tag{6.4}$$

We note the following.

Proposition 6.1.1. *The disease-free equilibrium is the point* $F = (\frac{\Lambda}{\nu}, 0, 0)$ *with disease-free total population* $N_F = \frac{\Lambda}{\nu}$.

Proof. This is clear. □

The Jacobian of the system (6.4) at the equilibrium point (S, E, I) is,

$$J = \begin{bmatrix} -\nu - \frac{\beta I}{N} & 0 & -\frac{\beta S}{N} \\ \frac{\beta I}{N} & -(\sigma + \nu) & \frac{\beta S}{N} \\ 0 & \sigma & -(\gamma + \nu) \end{bmatrix}.$$

In absence of infection, $\dot{I} = 0$, and then the Jacobian of system (6.4) at the disease-free equilibrium $\mathbf{F} = (\frac{\Lambda}{\nu}, 0, 0)$ is,

$$J = \begin{bmatrix} -\nu & 0 & -\beta \\ 0 & -(\sigma + \nu) & \beta \\ 0 & \sigma & -(\gamma + \nu) \end{bmatrix}.$$

Thus, $-\nu$ is one of the eigenvalues, and the other two are the roots of,

$$x^2 + (\sigma + \gamma + 2\nu)x + (\nu + \sigma)(\nu + \gamma) - \beta\sigma = 0. \tag{6.5}$$

If all eigenvalues are negative, then

$$\frac{\beta\sigma}{(\nu+\sigma)(\nu+\gamma)} < 1,$$

and the disease-free equilibrium is locally asymptotically stable. Since the basic reproductive number is given by,

$$R_0 = \frac{\beta\sigma}{(\nu+\sigma)(\nu+\gamma)}.$$

Then we have the following result.

Theorem 6.1.2. *The disease-free equilibrium* $\mathbf{F}$ *is asymptotically locally stable if* $R_0 < 1$*, and unstable if* $R_0 > 1$*.*

6.2 Global stability for the disease-free equilibrium F

We consider the Lyapunov function,

$$\mathbf{L} = \sigma E + (\sigma+\nu)I,$$

for establishing the global stability of the disease-free equilibrium $\mathbf{F}$.

Proposition 6.2.1. *The disease-free equilibrium* $\mathbf{F}$ *is global asymptotically stable if* $R_0 < 1$*.*

Proof. Now the derivative of this Lyapunov function is as follows.

$$\dot{\mathbf{L}} = \sigma\dot{E} + (\sigma+\nu)\dot{I},$$

$$= \sigma\left(\tfrac{\beta SI}{N} - (\sigma+\nu)E + (\sigma+\nu)(\sigma E - (\gamma+\nu)I\right),$$

$$= \left(\tfrac{\beta\sigma SI}{N} - (\sigma+\nu)\sigma E\right) + (\sigma+\nu)\sigma E - (\sigma+\nu)(\gamma+\nu)I,$$

$$= \frac{\beta\sigma SI}{N} - (\sigma+\nu)\sigma E + (\sigma+\nu)\sigma E - (\sigma+\nu)(\gamma+\nu)I,$$

$$= \frac{\beta\sigma SI}{N} - (\sigma+\nu)(\gamma+\nu)I,$$

$$= I\left(\frac{\beta\sigma S}{N} - (\sigma+\nu)(\gamma+\nu)\right),$$

$$\leq I\left(\sigma\beta - (\sigma+\nu)(\gamma+\nu)\right), \text{ since } S \leq \frac{\Lambda}{\nu} \text{ in } \Omega,$$

$$\leq I\left(\frac{\sigma\beta}{(\sigma+\nu)(\gamma+\nu)} - 1\right)(\sigma+\nu)(\gamma+\nu),$$

$$\leq I\left(R_0 - 1\right)(\sigma+\nu)(\gamma+\nu).$$

When $R_0 \leq 1$, then $\dot{\mathbf{L}} \leq 0$; and equality itself holds only for,

(i) $R_0 = 1$ and $E = I = R = 0$ or (ii) $I = 0$.

The one-point set $(E, I, R) = (0, 0, 0)$ is the largest positively invariant subset of the set defined by (i) and (ii) above, where $\dot{\mathbf{L}} = 0$.

Hence, by the Lyapunov-LaSalle theorem, the disease-free equilibrium is globally asymptotically stable. □

6.3 Endemic equilibrium D

We set the endemic equilibrium $\mathbf{D} = (S, E, I)$ as follows,

$$\begin{aligned} \Lambda - \nu S - \frac{\beta SI}{N} &= 0, \\ \frac{\beta SI}{N} - (\sigma+\nu)E &= 0, \\ \sigma E - (\gamma+\nu)I &= 0. \end{aligned} \tag{6.6}$$

We have $E = \frac{(\gamma+\nu)I}{\sigma}$. Substituting E into the second equation of the system (6.6), we obtain

$$\frac{\beta SI}{N} - \frac{(\sigma+\nu)(\gamma+\nu)I}{\sigma} = 0,$$

$$I\left(\frac{\beta S}{N} - \frac{(\sigma+\nu)(\gamma+\nu)}{\sigma}\right) = 0.$$

This implies that,

$$I = 0 \text{ or } \frac{\beta S}{N} = \frac{(\sigma+\nu)(\gamma+\nu)}{\sigma}.$$

Now, $S = \frac{N(\sigma+\nu)(\gamma+\nu)}{\sigma\beta} = \frac{N}{R_0} = \frac{\Lambda}{\nu R_0}$.

Substituting S into the first equation of the system (6.6), we obtain

$$\Lambda = S\left(\frac{\beta I}{N} + \nu\right),$$

$$\Lambda = \frac{\Lambda}{\nu R_0}\left(\frac{\beta I}{N} + \nu\right),$$

$$\Lambda\nu R_0 = \frac{\Lambda\beta I}{N} + \Lambda\nu,$$

$$\Lambda\nu(R_0 - 1) = \frac{\Lambda\beta I}{N},$$

$$\Lambda\nu(R_0 - 1) = \frac{\Lambda\beta I}{\frac{\Lambda}{\nu}},$$

$$\Lambda\nu(R - 1) = \beta I\nu,$$

$$I = \frac{\Lambda}{\beta}(R_0 - 1).$$

Therefore we have the following result,

Theorem 6.3.1. *Endemic equilibrium* **D** *exists if and only if* $R_0 > 1$. □

6.4 Local stability for endemic equilibrium D

The Jacobian matrix at **D** is given by,

$$J(\mathbf{D}) = \begin{bmatrix} -\nu - \frac{\beta I}{N} & 0 & -\frac{\beta S}{N} \\ \frac{\beta I}{N} & -(\sigma+\nu) & \frac{\beta S}{N} \\ 0 & \sigma & -(\gamma+\nu) \end{bmatrix}.$$

Substituting S and I into the Jacobian matrix at **D**, we get

$$J(\mathbf{D}) = \begin{bmatrix} -\nu R_0 & 0 & -\frac{\beta}{R_0} \\ \nu(R_0-1) & -(\sigma+\nu) & \frac{\beta}{R_0} \\ 0 & \sigma & -(\gamma+\nu) \end{bmatrix}.$$

The characteristic equation for this matrix is,

$$-(\nu R_0+x)\left[(\sigma+\nu)(\gamma+\nu)+((\sigma+\nu)+(\gamma+\nu))x+x^2-\frac{\sigma\beta}{R_0}\right]+(\nu-\nu R_0)\frac{\sigma\beta}{R_0}=0,$$

and is of the form $x^3 + a_0x^2 + a_1x + a_2 = 0$. The coefficients are as below.

$a_0 = (\sigma+\nu)+(\gamma+\nu)+\nu R_0 > 0,$

$a_1 = (\sigma+\nu)(\gamma+\nu)+[(\sigma+\nu)+(\gamma+\nu)]\,\nu R_0 - \frac{\sigma\beta}{R_0},$

$= (\sigma+\nu)(\gamma+\nu)+[(\sigma+\nu)+(\gamma+\nu)]\,\nu R_0 - \sigma\beta\left(\frac{(\sigma+\nu)(\gamma+\nu)}{\sigma\beta}\right),$

$= (\sigma+\nu)(\gamma+\nu)+[(\sigma+\nu)+(\gamma+\nu)]\,\nu R_0 - (\sigma+\nu)(\gamma+\nu),$

$$= [(\sigma + \nu) + (\gamma + \nu)]\, \nu R_0 > 0,$$

$$a_2 = \nu R_0(\sigma + \nu)(\gamma + \nu) - \tfrac{\sigma\beta\nu}{R_0},$$

$$= \nu R_0(\sigma + \nu)(\gamma + \nu) - \sigma\beta\nu \left(\tfrac{(\sigma+\nu)(\gamma+\nu)}{\sigma\beta}\right),$$

$$= \nu R_0(\sigma + \nu)(\gamma + \nu) - \nu(\sigma + \nu)(\gamma + \nu),$$

$$= \nu(\sigma + \nu)(\gamma + \nu)[R_0 - 1],$$

which implies that,

$$a_2 = \begin{cases} > 0 & \text{if } R_0 > 1, \\ < 0 & \text{if } R_0 < 1. \end{cases} \tag{6.7}$$

Now evaluating $a_0a_1 - a_2$, we have:

$$a_0a_1 - a_2 = ((\sigma + \nu) + (\gamma + \nu) + \nu R_0)\,([(\sigma + \nu) + (\gamma + \nu)]\, \nu R_0) - \nu((\sigma + \nu)(\gamma + \nu)) > 0.$$

This implies that,

$$a_0a_1 - a_2 = 2\nu^3R_0^2 + \gamma\nu^2R_0^2 + \sigma\nu^2R_0^2 + 4\nu^3R_0 + 4\gamma\nu^2R_0 + 4\sigma\nu^2R_0 + \gamma^2\nu R_0 + 2\sigma\gamma\nu R_0 + \sigma^2\nu R_0 - \nu^3 - \gamma\nu^2 - \sigma\nu^2 - \sigma\gamma\nu > 0.$$

According to the Routh-Hurwitz criterion, the eigenvalues of the matrix have negative real parts if and only if the following inequalities hold,

$$a_0, a_1, a_2 > 0,$$

$$a_0a_1 - a_2 > 0.$$

For $R_0 > 1$, we have $a_0, a_1, a_2 > 0$ and $a_0a_1 - a_2 > 0$, and this shows that the endemic equilibrium $\mathbf{D}$ is locally asymptotically stable.

Hence, we have proved the following result.

Theorem 6.4.1. *The unique endemic equilibrium is locally asymptotically stable.* □

6.5 Numerical solutions for SEIR

We simulate the SEIR model using Euler methods to illustrate the dynamics of the system. The numerical simulation was carried out using Maple. The table below shows the parameters used in the simulations and the parameters are chosen arbitrarily.

Table 6.2: The parameters values for SEIR model

Position	Parameter	Value
1.	Λ	0.08
2.	β	[0.09, 0.3]
3.	ν	0.08
4.	σ	[0.76, 0.90]
5.	γ	[0.048, 0.062]
6.	S	0.073
7.	E	0.25
8.	I	0.53
9.	R	0.15
10.	N	700

We firstly consider the numerical simulation of the SEIR model when $R_0 < 1$. Therefore we obtain $R_0 = 0.64$, when $\nu = 0.08$, $\beta = 0.09$, $\sigma = 0.76$, $\gamma = 0.048$, and $\Lambda = 0.08$. In our simulation, we also assume that population size is constant with natural mortality rate of individuals ν is equal to the birth rate Λ $(\nu = \frac{\Lambda}{N} = 0.08)$.

Now in Figure 6.2 above, we observe that the number of susceptible individuals and recovery individuals increases during the first 10 days. This graph also shows that the number of infected individuals and exposed individuals sharply decreases to zero. After 50 days the disease seems to disappears form

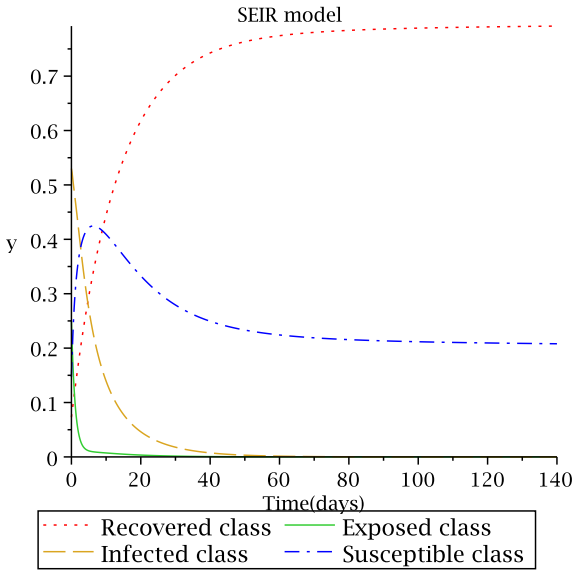

Figure 6.2: The plot shows the global stability of the SEIR epidemic model, when $R_0 = 0.64$. [Programmed in Maple (2010)].

the host population. Our numerical simulations indicate that the disease-free equilibrium in these model is globally stable.

Furthermore, we simulate the SEIR model using different parameters, we get $R = 1.9$. where, $\nu = 0.08$, $\beta = 0.3$, $\sigma = 0.90$, $\gamma = 0.062$, and $\Lambda = 0.08$. Figure 6.3 below shows that the number of susceptible individuals and recovered individuals also increase from the first 10 days of the model, while exposed individuals and infected individuals decreasing. The exposed and infected individuals still exist in the host population, this shows that there is an endemic disease within the population. therefore the disease-free equilibrium seems to be in an unstable state as the time increases.

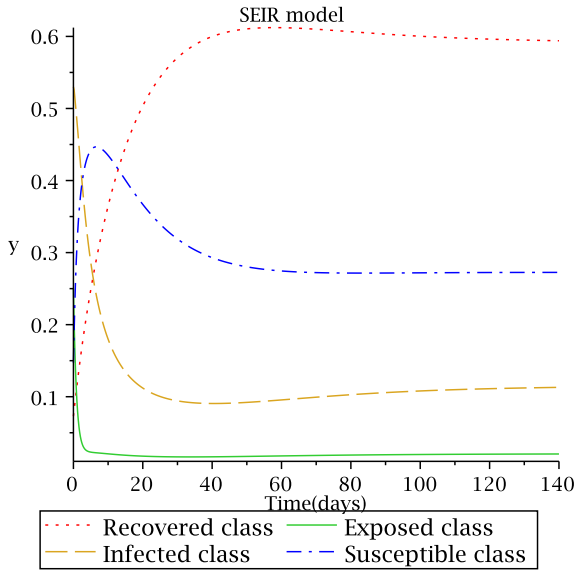

Figure 6.3: The plot shows unstable SEIR epidemic model, when $R_0 = 1.9$. [Programmed in Maple (2010)].

6.6 The SIS model

In this subsection, we introduce the simple SIS epidemic model for the transmission of various infectious diseases through a population. Disease for which there is no immunity after recovery are modeled as SIS, and include diseases such as influenza, pneumonia, meningitis and streptococcal sore throat etc. Some infections diseases , for example diseases of those responsible for the common cold, do not grant any long lasting immunity. Such infections, individuals become susceptible again after infection. Therefore in this model there is no recovered state, thus an SIS model for the spread of a diseases is only based on the cycle of disease in a host population.

A number of papers have contributed to our understanding of the SIS-disease. Examples see papers by [69] Zhou and Liu, [56] Tassier and [61] Van den Driessche and Watmough. The particular model that we study is the one featuring in [8] of Brauer and Van den Driessche. Let S be the number of susceptible individuals, and let I be the number of infected individuals with a constant population size N. The diagram below shows the SIS model during horizontal transmission:

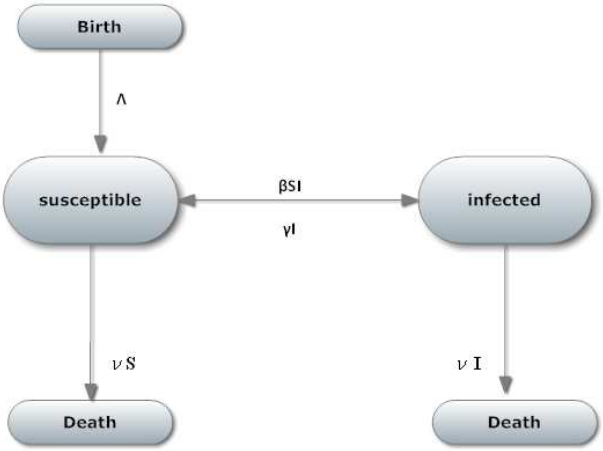

Figure 6.4: A flowchart of possible states in an SIS epidemic model

The simplest SIS model is given by the following differential equations,

$$\begin{aligned} \frac{dS}{dt} &= \Lambda N - \nu S - \frac{\beta SI}{N} + \gamma I, \\ \frac{dI}{dt} &= \frac{\beta SI}{N} - (\gamma + \nu)I, \end{aligned} \tag{6.8}$$

with initial conditions, $S(0) = S_0 > 0, \quad I(0) = I_0 > 0.$

We also assume that the birth rate Λ is equal to the death rate ν, an average infected individual in the host population makes contact sufficient to infect βN others per unit time. Now we have S/N as the probability that a given individual that each infected individual comes in contact with a susceptible. Therefore, each infected individual causes $(SN)(\beta/N) = \beta S$ infections per unit time. Thus the total number of infections per unit time of βSI is caused by infected individuals I. The parameter γ is the recovery rate from infection. This is the rate at which individuals who recover per unit time and re-enter the susceptible class. We have that,

$$\frac{d}{dt}(S + I) = 0, \tag{6.9}$$

since $S(t) + I(t) = N = 1$ is constant. Substituting $S = N - I$ into the second equation of the system (6.8), we get,

$$\frac{dI}{dt} = \beta I(1 - \frac{I}{N}) - (\gamma + \nu)I, \tag{6.10}$$

Then solving the $dI/dt = 0$, we can easily see that there are two possible equilibria for this SIS model. The first one is $I = 0$ and the other is

$$I = \left[1 - \tfrac{(\gamma+\nu)}{\beta}\right] N.$$

Proposition 6.6.1. *The basic reproductive number is given by,* $R_0 = \frac{\beta}{\gamma+\nu}$.

Proof. The proof follows very much along the same lines as in the case of SIR model, which was done in section 3.2. □

In [8] it is shown that the disease-free equilibrium **F**is globally asymptotically stable if $R_0 < 1$, and on the other hand, the disease-free equilibrium **F** is unstable and the endemic equilibrium **D** is globally asymptotically stable if $R_0 > 1$.

Chapter 7

Control of vaccination in SEIR model

Optimal control theory has been used successfully in making decisions relating to biological models. The aim of this optimal vaccination strategy is to reduce the number of infected individuals, while keeping the vaccination effort sufficiently low. We use the method of Lenhart and Workman [31] to analyze the optimal control including vaccination for the SEIR model. This method had been used by other such as [67] Zaman et al., [27] Joshi, [50] Seierstadt and Sydsaeter. The epidemiological model itself is the one of Ngwenya [42]. We try to find an optimal control $u^*(t)$, such that,

$$J(u^*(t)) = \min\ J(u), \tag{7.1}$$

where J is an objective functional to be defined.

7.1 The optimal control problem

The problem is to minimize the objective functional,

$$J(u) = \int_0^T [CI(t) + \frac{1}{2}\tau u^2(t)]\ dt, \tag{7.2}$$

subject to the following,

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - (\nu + u(t))S - \frac{\beta S(t)I(t)}{N}, \\
\frac{dE(t)}{dt} &= \frac{\beta S(t)I(t)}{N} - (\sigma + \nu)E(t), \\
\frac{dI(t)}{dt} &= \sigma E(t) - (\gamma + \nu)I(t), \\
\frac{dR(t)}{dt} &= \gamma I(t) - \nu R(t) + uS(t),
\end{aligned} \tag{7.3}$$

and with the given initial conditions,

$$S(0) = S_0 \geq 0, E(0) = I_0 \geq 0, I(0) = E_0 \geq 0, R(0) = Z \geq 0. \tag{7.4}$$

We shall assume that u is bounded above by some constant α, such that for all t, we have $0 \leq u(t) \leq \alpha < 1$. The Pontryagin's maximum principle gives us essential conditions for an optimal control problem, and converts system (7.1), (7.2) and (7.3) into a problem of minimizing a Hamiltonian, with respect to u. The Hamiltonian is,

$$\begin{aligned}
H(S, E, I, R, u, \lambda_1, \lambda_2, \lambda_3, \lambda_4, t) &= [CI(t) + \frac{1}{2}\tau u^2(t)] \\
&+\lambda_1(t)\frac{dS}{dt} + \lambda_2(t)\frac{dE}{dt} + \lambda_3(t)\frac{dI}{dt} + \lambda_4(t)\frac{dR}{dt}.
\end{aligned} \tag{7.5}$$

Thus, by applying the Pontryagin maximum principle and the existence result for the optimal control $u^*(t)$, we obtain the following theorem.

Theorem 7.1.1. *There exists an optimal control $u^*(t)$ and corresponding solution, $S^*(t)$, $E^*(t)$, $I^*(t)$, $R^*(t)$ and J^*, that minimizes $J(u)$. Then there exist adjoint functions, $\lambda_1(t), \lambda_2(t), \lambda_3(t)$ and $\lambda_4(t)$, such that*

$$\lambda_1'(t) = \tfrac{\beta I(t)}{N}(\lambda_1(t) - \lambda_2(t)) + u\lambda_1,$$

$$\lambda_2'(t) = \lambda_2(t)(\sigma + \nu) - \sigma\lambda_3(t),$$

$$\lambda_3'(t) = -C + \tfrac{\beta S(t)}{N}(\lambda_1(t) - \lambda_2(t)) + \lambda_3(t)(\gamma + \nu),$$

$$\lambda_4'(t) \equiv 0,$$

with transversality conditions (or boundary conditions)

$$\lambda_1(T) = \ \lambda_2(T) = \lambda_3(T) = 0.$$

Furthermore, the explicit formula for $u^*(t)$ is given by,

$$u^*(t) = \max\left\{\min\left\{\frac{\lambda_1 S(t)}{\tau}, \alpha\right\}, 0\right\}.$$

Proof. We apply the Pontryagin maximum principle as in [31] or [28]. We calculate the partial derivatives of H with respect to S, E, I and R in order to obtain the time derivatives $\dot{\lambda}_i$ of the costate variables. In particular, since $S(T), E(T), I(T)$, and $R(T)$ are free, the following terminal conditions hold:

$$\lambda_1(T) = 0, \ \lambda_2(T) = 0, \ \lambda_3(T) = 0 \text{ and } \ \lambda_4(T) = 0.$$

We start noting that,

$$\dot{\lambda}_4(t) = \frac{dH}{dR} = -\nu\lambda_4(t),$$

which means that $\lambda_4(t)$ is an exponential function of time. This together with the condition $\lambda_4(T) = 0$ means that,

$$\lambda_4(t) \equiv 0.$$

Hereafter we can calculate,

$$\dot{\lambda}_1(t) = \frac{dH}{dS} \ , \ \dot{\lambda}_2(t) = \frac{dH}{dE} \text{ and } \dot{\lambda}_3(t) = \frac{dH}{dI},$$

and obtain the values as asserted.

The function $u^*(t)$ must optimize H. So, we calculate

$$\begin{aligned}\frac{dH}{du} &= \tau u^*(t) - \lambda_1 S(t), \\ &= \tau u^*(t) - \lambda_1 S(t).\end{aligned}$$

Therefore when $\tau u^*(t) - \lambda_1 S(t) = 0$, then of course we choose,

$$u^*(t) = \frac{\lambda_1 S(t)}{\tau},$$

When $\tau u^*(t) - \lambda_1 S(t) \geq 0$, then H is an increasing function of u, and so we must choose $u^*(t)$ at its least possible value. A similar argument holds for the case $\tau u^*(t) - \lambda_1 S(t) \leq 0$.

Thus $u^*(t) = \max\left\{\min\left\{\frac{\lambda_1 S(t)}{\tau}, \alpha\right\}, 0\right\}$. □

Furthermore, note that the second derivative of the Hamiltonian with respect to u is non-negative. This implies that the optimal problem is minimum at control $u^*(t)$. Therefore we substitute the value of $u^*(t)$ in the control system (7.3), and we have the new system:

$$\begin{aligned}
\frac{dS^*(t)}{dt} &= \Lambda - \left(\nu + \max\left\{\min\left\{\frac{\lambda_1 S^*(t)}{\tau}, \alpha\right\}, 0\right\}\right) S^*(t) - \frac{\beta S^*(t) I^*(t)}{N}, \\
\frac{dE^*(t)}{dt} &= \frac{\beta S^*(t) I^*(t)}{N} - (\sigma + \nu) E^*(t), \\
\frac{dI^*(t)}{dt} &= \sigma E^*(t) - (\nu + \gamma) I^*(t), \\
\frac{dR^*(t)}{dt} &= \gamma I^*(t) - \nu R^*(t) + \left(\max\left\{\min\left\{\frac{\lambda_1 S^*(t)}{\tau}, \alpha\right\}, 0\right\}\right),
\end{aligned} \tag{7.6}$$

where the Hamiltonian H^* at $(S^*, E^*, I^*, R^*, u^*, \lambda_1, \lambda_2, \lambda_3, \lambda_4, t)$ is given by,

$$\begin{aligned}
H^* &= I^*(t) + \frac{1}{2}\left[\tau\left(\max\left\{\min\left\{\frac{\lambda_1 S^*(t)}{\tau}, \alpha\right\}, 0\right\}\right)^2\right] \\
&+ \lambda_1(t)\left[\Lambda - \left(\nu + \max\left\{\min\left\{\frac{\lambda_1 S^*(t)}{\tau}, \alpha\right\}, 0\right\}\right) S^*(t) - \frac{\beta S^*(t) I^*(t)}{N}\right] \\
&+ \lambda_2(t)\left(\frac{\beta S^*(t) I^*(t)}{N} - (\sigma + \nu) E^*(t)\right) + \lambda_3(t)[\sigma E^*(t) - (\nu + \gamma) I^*(t)] \\
&+ \lambda_4(t)\left[\gamma I^*(t) - \nu R^*(t) + \left(\max\left\{\min\left\{\frac{\lambda_1 S^*(t)}{\tau}, \alpha\right\}\right\}, 0\right) S^*(t)\right]
\end{aligned} \tag{7.7}$$

7.2 Numerical simulations of the SEIR model

In this section, we give the numerical simulation which demonstrate the theoretical results for the SEIR model. We also use the Runge-Kutta procedure to solve the optimal problem for the SEIR model, as we did for the SIR model in chapter 5. Note that the individuals with control are marked by the solid line. The table below shows the parameters used in the simulations and the parameters are chosen arbitrarily.

Table 7.1: The parameters values for SEIR model

Position	Parameter	Value
1.	Λ	0.0002
2.	β	0.08
3.	ν	0.0002
4.	σ	0.4
5.	γ	0.2
6.	S	0.5
7.	E	0.20
8.	I	0.2
9.	R	0.1
10.	N	1

Figure 7.1: The plot represent the population of susceptible individuals (S) with optimal control vaccination. [Programmed in MATLAB (2010)].

In Figure. 7.1, we use system (7.3) to plot the graph of susceptible individuals. We observe that the population of susceptible individuals in system (7.3) decreases from the first days of the disease outbreak, while the population number of recovered individuals increases from the first day after vaccination.

From day 60 the the population of susceptible become stable. At day 120 the disease dies out and only susceptible remains in the population.

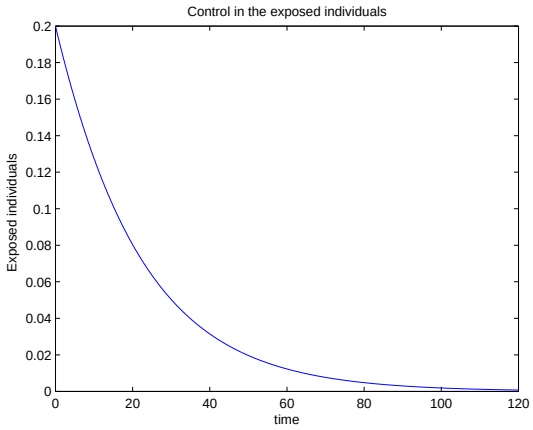

Figure 7.2: The plot represent the population of exposed individuals (E) with optimal control vaccination. [Programmed in MATLAB (2010)].

In figure.7.2, we plot the exposed individuals using system (7.3). We can easily see that the population of exposed individuals with vaccination control decreases to zero. The disease dies out at day 120, and thus the vaccination ends. Therefore this shows the impact of vaccination in the host population.

We consider Figure.7.3 below, we observe that the population of infected individuals with vaccination control increases from the first day of vaccination. Infected individuals become stable from day 18 to day 25. In system (7.3) the population of infected individuals decrease to zero. This implies that the disease dies out and only the susceptible individuals remain. Therefore there is no infection in the population.

Figure.7.4, the population number of recovered individuals in the system of equations (7.3) is very large with vaccination control, this implies that there are few infected individuals in the population. We observe that when vaccination control was implemented or introduced in the population, the number of recovered individuals increases. This also show the impact which the vaccination brought in the population.

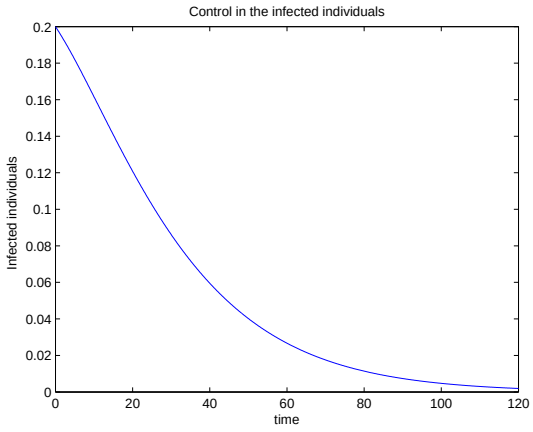

Figure 7.3: The plot represent the population of infected individuals (I) with optimal vaccination. [Programmed in MATLAB (2010)].

In Figure. 7.5, Figure. 7.6 and Figure. 7.7. The graphs represent the adjoint variables λ_1, λ_2 and λ_3 of the optimal system. Firstly, we solve the state of the system equations with an initial guess forward Runge-Kutta procedure in time and then we also use the backward Runge-Kutta procedure to solve the adjoint equations in time because of the transversality conditions.

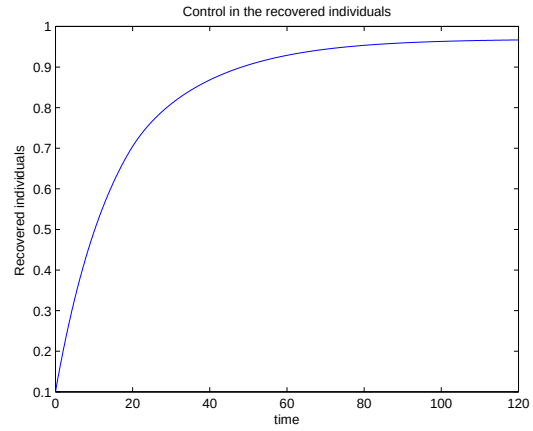

Figure 7.4: The plot represent the population of recovered individuals (R) with optimal vaccination. [Programmed in MATLAB (2010)].

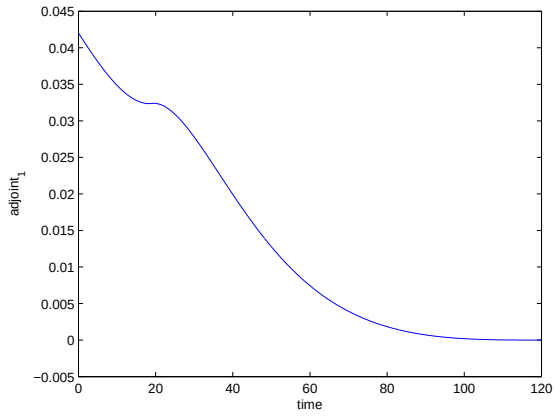

Figure 7.5: The plot represent the four adjoint variable λ_1, λ_2, and λ_3 in the population, and we solve these adjoint by a backward fourth-order Runge-Kutta procedure. [Programmed in MATLAB (2010)].

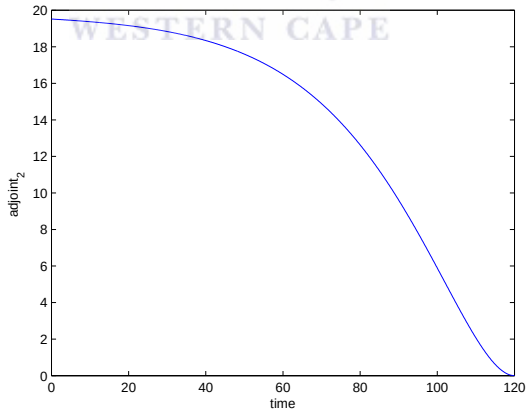

Figure 7.6: The plot represent the four adjoint variable λ_1, λ_2, and λ_3 in the population, and we solve these adjoint by a backward fourth-order Runge-Kutta procedure. [Programmed in MATLAB (2010)].

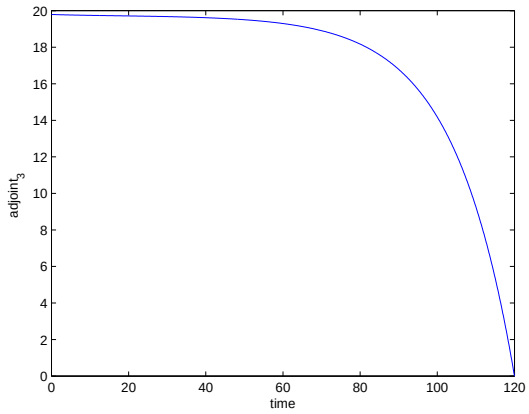

Figure 7.7: The plot represent the four adjoint variable λ_1, λ_2, and λ_3 in the population, and we solve these adjoint by a backward fourth-order Runge-Kutta procedure. [Programmed in MATLAB (2010)].

Figure 7.8, represent the control variable $u(t)$ plotted as a function of S, λ_1 for the weight factor $\tau = 500$ in the population. the present of the $\tau = 500$ plays an important role in keeping the population size in balanced. Furthermore, we observe that the control variable u at a time t play a significant role in minimizing the probability that the infected individuals spread the disease in the host population.

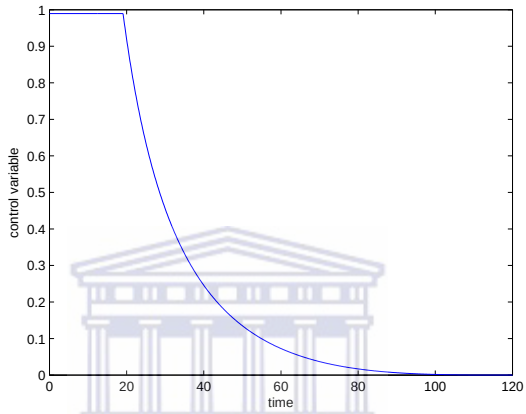

Figure 7.8: The plot represent the control variable $u(t)$ plotted as a function of S, λ_1 and λ_4 for the weight factor $\tau = 58$ in the population. [Programmed in MATLAB (2010)].

Chapter 8

Conclusion

There is no doubt that mathematical modeling is essential in planning and formulation of policy on contagious diseases. As is the case with modeling in general, there will always be the quest for more appropriate and accurate models. The kind of models we have been studying in this dissertation can be refined in many different ways. Many such improvements already exists in the literature, and we might have even briefly touched on such. *Delay* differential equations is sometimes used and they can, for instance, accommodate the phenomenon of an incubation period in a different manner as in the usual SEIR model. Such models can be found for instance in [68] of Zaman et al. See also section 3.

Pulse vaccination is a strategy that is also incorporated into modeling. Shulgin et al. [51] conducted a study about the way a disease, such as measles can be efficiently controlled by looking at and analyzing a simple SIR model. They proposed pulse vaccination method which vaccinates the susceptible population of people in a series of pulses in order to stop the spread of the virus in the network. Other useful references in this regard are [34], [10], [11] and [40].

Up to now we have only studied models which assumes that population sizes are so large and the process associated with the relevant diseases and so uniform that it is not necessary to allow for uncertainty or randomness. There are however models that do take such stochasticity into account. Interesting reading in this regard can be found in the paper [41] of Merl et al. or the textbook [8] of Brauer and Van den Driessche.

In this dissertation we have briefly reviewed a number of epidemiological

models. We focused on SIR models, but also featured the SEIR and briefly also SIS models. In particular we studied their stability properties, paying particular attention to basic reproductive number. We also studied vaccination and determined optimal vaccination strategies for SIR and SEIR models. We were able to expand on the existing literature by way of supplying missing detail and making sharper observation especially in chapter 4.

We can remark at this point that the objective functional used in the optimization can be interpreted or adapted to reflect the actual cost associated with the public health endeavor of fighting a contagious disease. An exciting follow-up on the optimization work done here, would be to pursue such problem in a stochastic setting.

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