

Epidemiological Models For Mutating Pathogens With Temporary Immunity

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**EPIDEMIOLOGICAL MODELS FOR MUTATING PATHOGENS
WITH TEMPORARY IMMUNITY**

by

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A dissertation submitted in partial fulfillment of the requirements
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ABSTRACT

Significant progress has been made in understanding different scenarios for disease transmissions and behavior of epidemics in recent years. A considerable amount of work has been done in modeling the dynamics of diseases by systems of ordinary differential equations. But there are very few mathematical models that deal with the genetic mutations of a pathogen. In-fact, not much has been done to model the dynamics of mutations of pathogen explaining its effort to escape the host's immune defense system after it has infected the host.

In this dissertation we develop an *SIR* model with variable infection age for the transmission of a pathogen that can mutate in the host to produce a second infectious mutant strain. We assume that there is a period of temporary immunity in the model. A temporary immunity period along with variable infection age leads to an integro-differential-difference model. Previous efforts on incorporating delays in epidemic models have mainly concentrated on inclusion of latency periods (this assumes that the force of infection at a present time is determined by the number of infectives in the past).

We begin with reviewing some basic models. These basic models are the building blocks for the later, more detailed models. Next we consider the model for mutation of pathogen and discuss its implications. Finally, we improve this model for mutation of pathogen by incorporating delay induced by temporary immunity. We examine the influence of delay as we establish the existence, and derive the explicit forms of disease-free, boundary and endemic equilibriums. We will also investigate the local stability of each of these equilibriums. The possibility of Hopf bifurcation using delay as the bifurcation parameter is studied using both analytical and numerical solutions.

To my parents, for making it possible to embark on this journey.

To my husband, for making it possible to conclude it.

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CHAPTER 1: INTRODUCTION

Disease has played an important role in the history of mankind. The spread of communicable diseases has influenced the growth of populations, the success of invading armies, and the economies of countries. A famous example of the effect that a disease can have on society is the 14th century plague known as the Black Death. This disease, also known as the bubonic plague, occurred in Europe starting around 1346. From that time until about 1350, it is estimated that one-third of the continent's 85 million people died as a result of this plague. Like many diseases, the Black Death recurred periodically, striking various regions for the next 300 years. Of course this had a tremendous impact on the political and economic development of the area, as the plague devastated certain cities, but left others unscathed.

This example illustrates how a disease can suddenly affect the demography of a human population due to the mortality caused by the disease. Hence the need to study how diseases spread, a branch of science known as epidemiology. Ever since the time of Aristotle (384 BC - 322 BC), Hippocrates (400 BC) scientists have studied the transmission of disease in an effort to better understand the processes involved. Germ theory of disease was first expressed by Jacob Henle in 1840, and then developed by Robert Koch, Joseph Lister, and Louis Pasteur in the late 19th/early 20th centuries. In the initial stages of this development the focus tended to be on modeling the spread of certain diseases. For example, Daniel Bernoulli formulated a model for smallpox in 1760 to examine the effect of variolation of healthy subjects with the virus and showed that inoculation against small pox would lengthen life expectancy. However the first contributions of modern mathematics to epidemiology are due to P.D En'ko between 1873 and 1894. Sir R. A. Ross, W. H. Hamer, A.G Mckendrick, and W. O Kermack laid the foundation to

the approach of epidemiology based on compartmental models between 1900 and 1935. See [11, 14, 20, and 45] During the same time statistical contributions were made by J Brownlee. Ross demonstrated the dynamics of the transmission of malaria between mosquitoes and humans, which was widely accepted by medical community.

An important result concerning the idea of epidemic thresholds was published in 1926 by Kermack and Mckendrick. An epidemic represents the sudden outbreak of a disease, often occurring on a short temporal scale and affecting a significant portion of a population. Epidemics also may exhibit some periodic behavior, as opposed to endemics, which are diseases that are always present to some extent in a population. Kermack and McKendrick illustrated that diseases showed a threshold type of behavior. In other words, if a single person infected by a particular disease passed on the infection to more than one person in turn, an epidemic would occur, while if less than one secondary infection occurred for each primary one, the disease would die out. This threshold quantity, which will be discussed in more detail later, is an important characteristic of a disease, and is based on the parameters that are part of the disease model. Since the time of Kermack and McKendrick mathematical epidemiology has grown rapidly, with a large variety of models having been created, analyzed, and applied to infectious diseases, [11, 20, 39, and 46].

Obviously epidemiology is concerned with not only the study of disease transmission, but also controlling the spread of disease. As a matter of fact, disease brings about more death than any other cause, including war and natural disasters. As infectious agents continue to adapt and evolve, the importance of epidemiology has increased. Factors that contribute to the emergence and spread of infection include human/animal invasions of ecosystems, global warming,

environmental degradation, increased travel, and resistance of bacteria and other microorganisms to antibiotics. Epidemiology attempts to sort out the factors of relevance to a particular disease and helps governments plan, in order to be prepared for future.

In general, traits which are to be transmitted in a population could include: disease, genetic characteristics, cultural characteristics. Among the things to be considered when attempting to understand the impact of a disease, one of the most important aspect is how the disease is actually spread. Transmission of a disease is carried out by different agents. A disease transmitted by a virus, such as influenza or measles, generally confers immunity against reinfection while diseases caused by bacteria, such as tuberculosis, typhoid or gonorrhea, offer no immunity. Another form of transmission is due to vectors, which are agents infected by humans which then transfer the disease to another human. A common example of a vector is the mosquito, which spreads malaria and filariasis. Other disease carrying agents include protozoa, helminths (worms), and the recently discovered prions, which are thought to cause infections such as mad cow disease. See [3, 10, 21, 22, 47, and 50].

Epidemiology is the branch of science which essentially deals with the mathematical modeling of spread of diseases. The interest here lies in formulating a model which will explain the population dynamics of disease causing agents, and can then be analyzed with a view to controlling or eradicating the spread of those agents. The formulation of a model is a process which includes statement of the relevant assumptions, relationship among variables, and parameters and relations governing their behaviors. Of course, the choice of these factors is critical to the model and depends largely on the particular disease to be modeled and the intended purpose of that model. A simple model, by its nature, simplifies the situation by making many

assumptions but may still describe qualitative behavior to a reasonable extent, while a more detailed model may provide quantitative predictions, but are usually impossible to solve analytically. See [38].

The transmission dynamics of a disease could be studied from different perspectives, such as at various levels of a spatial, temporal, or organizational scale. One of the important aspects of the modeling process is how much organizational detail like population structure, immunity, and genetic variability will be included in the model. Then the model builder decides a strategy to model these details to effectively describe the disease spread. We will generally see that ordinary differential equations, partial differential equations as well as integro-differential equations are the mathematical tools of choice.

In this dissertation we consider a time-delayed SIR model with variable infection age, governed by partial differential equation for the transmission of pathogen that mutates to produce a second mutant strain. The time delay is introduced in the form of temporary immunity. The main purpose of this study is to investigate the effect of time delay on the model. Various authors have previously shown that time delay can sometimes destabilize the unique endemic equilibrium if the time delay is large enough, and usually we find that periodic solutions can arise by Hopf bifurcation. We will investigate the possibility of Hopf bifurcation for endemic equilibrium both numerically and analytically.

In chapter 2, we do some background study related to modeling. We review and develop some results for basic models. We begin with analyzing the most basic SIR and SIS model. These models establish the broad principle of epidemiology. We find the reproductive number and establish the criteria for existence and stability of disease-free and endemic equilibrium. We

also examine some basic time-delayed models and investigate the occurrence of periodic solutions.

With all this knowledge in hand, in chapter 3 we propose an improvement of model originally developed by Li, Ma, Zhou and Hyman. The original model is based on SIR model with variable infection age for the transmission of a pathogen that can mutate in the host to create a second infectious mutant strain. The model is modified by addition of time delay. The time delay is incorporated in the form of temporary immunity, which means that after recovery an individual acquires temporary immunity from the second mutant strain, for some period of time and then moves to susceptible class again. We will derive the explicit formulas and establish the local stability of disease-free, boundary and endemic equilibriums under the influence of time delay.

In chapter 4, to gain insight in the transmission dynamics of the time-delayed model we consider a special case. We make some assumptions which changes the PDE governed model into DDE governed model. For this DDE governed model we do the Hopf bifurcation analysis for endemic equilibrium. It's been shown that introducing time delay destabilizes the unique endemic equilibrium. We find the conditions under which the Hopf bifurcation occurs. The Hopf bifurcation is illustrated using numerical simulations.

In chapter 5, we summarize the results of the model and derive the conclusions based on the analysis. Some ideas for future work are also presented.

CHAPTER 2: BACKGROUND STUDY

2.1: Basic SIR Model

We will first consider a simple epidemic model developed by Kermack and McKendrick in 1927. This model establishes the broad principles of epidemiology and is a building block for the later, more detailed, models. See [11, 14, 20, 45, and 46]. Even though there are several assumptions made, this model has been shown to predict the behavior of many diseases. Many highly relevant observations can be made about the spread of such diseases. Also, by looking at some simple models it will be possible to compare the results from a more detailed model later on, as far as the kind of differences that may exist in the qualitative behavior of the epidemics.

First of all, consider a population which remains constant. The population is divided into three classes: the susceptibles, S , who can catch the disease; the infectives, I , who are infected and can transmit the disease to the susceptibles, and the removed class, R , who either had the disease and recovered (or died), or have developed immunity, or have been removed from contact with the other classes. Of course, from the point of view of studying a disease, exactly how an individual is 'removed' is important. But at least from the modeling perspective only the overall state of a person with respect to the disease is relevant. The progress of individuals is schematically described by



These types of models are known as *SIR* models in general. Depending on the actual disease, more or less of these three classes may be used. For example, some disease models only include the *S* and *I* classes (models), while others may have a fourth class which represents a state in which a disease is latent (models). See [10]. Diseases like Gonorrhoea, Chagas and Rocky Mountain Spotted fever are modeled using type of models because people become susceptible as soon as they recover from infection. For disease like AIDS, model is more appropriate as there is a latent period, when the virus is present in the host but has still not infected the host.

Several assumptions will be made for model. One is that the number of people in each class is a differentiable function of time. This is not unreasonable as long as there are enough people in each class. Because of the use of differential equations in the model, the epidemic behavior is deterministic, meaning that the state of each class is completely determined by the previous states as well as the rules governing the development of the model. For a model that describes classes with small populations, the modeling process may be stochastic instead, meaning that random variations may greatly affect the behavior of the disease. See [28]. Although, this may be an appropriate way to model certain situations, we will only consider the deterministic types of models in this thesis. Some of the first analyses of stochastic and deterministic continuous-time models are due to Bailey (1957) and Barlett (1956).

Now some assumptions must be made about the transmission of the disease and the period of incubation. These assumptions will determine the terms and parameters that are included in the model equations. The assumptions made are as follows:

- (i) The rate of gain of the infective class is proportional to both *I* and *S* at time. This is expressed by the term rSI , where $r > 0$ is a constant parameter. r is known as the infection rate.

The susceptibles have an equivalent rate of loss.

(ii) The rate of loss of the infective class is proportional to I , represented by the term aI , where a is a constant. The recovery rate of gain is equivalent to this. The number $1/a$ is the average time of infection where a is called the removal rate.

(iii) The incubation period is very short; in other words, a susceptible who gets the disease is immediately put into the infective class.

(iv) The different classes are uniformly mixed, meaning that each person has an equal opportunity of coming into contact with another person. This assumption depends greatly on the type of disease to be modeled. For example, for most sexually transmitted diseases, it is unreasonable to assume this kind of uniform contact.

Based on the above assumptions, the model is:

$$S' = -rSI \tag{1}$$

$$I' = rSI - aI \tag{2}$$

$$R' = aI \tag{3}$$

where $S' = \frac{dS}{dt}$, $I' = \frac{dI}{dt}$ and $R' = \frac{dR}{dt}$, t being the time. This is known as the classic

Kermack-McKendrick model. Of course, only non-negative solutions for S , I , and R are of

interest. The fact that the total population being considered is constant is embedded in the model, since upon adding (1) - (3) we get

$$S' + I' + R' = 0 \quad \longrightarrow \quad S(t) + I(t) + R(t) = N, \quad 4$$

where N is the population size. To complete the model, initial conditions are required for S , I and R ; for example

$$S(0) = S_0 > 0, \quad I(0) = I_0 > 0, \quad R(0) = R_0. \quad 5$$

Because the population is constant, determining S and I will also determine R . Thus the model is reduced to a system of only two differential equations. Solving this system is not possible analytically; however the behavior of the solutions can still be analyzed using a qualitative approach. Note that $S' < 0$ for all t and $I' > 0$ as long as $S_0 > \frac{a}{r}$. This means that I will initially increase to some maximum if $S_0 > \frac{a}{r}$, but eventually must decrease and approach zero, since S is always decreasing. The possibility of I increasing is what is of interest, since that indicates an epidemic. Otherwise, if $S_0 < \frac{a}{r}$ then I will simply head to zero, indicating no epidemic. We thus have threshold phenomena. If $S_0 > \frac{a}{r}$ there is an epidemic while if $S_0 < \frac{a}{r}$ there is not. Obviously, the behavior of the disease depends on the value of the number $\frac{S_0 r}{a}$, known as a threshold quantity. We will define the basic reproductive number

$R_0 = \frac{S_0 r}{a}$, which is the number of secondary infections produced by one primary infection in the population of susceptibles. In terms of this parameter, if $R_0 < 1$ the disease dies out, and if $R_0 > 1$ there is an epidemic. See [39].

To obtain the trajectories (curves in the S - I plane, or phase plane) we first divide equations and of the model to get

$$\frac{dI}{dS} = \frac{(rS - a)I}{-rSI} = -1 + \frac{a}{rS} \quad 6$$

Integrating the above equation with respect to S we have,

$$I = -S + \frac{a}{r} \ln S + c \quad 7$$

where c is an arbitrary constant of integration. The orbits can now be described by defining a function of the form,

$$V(S, I) = S + I - \frac{a}{r} \ln S \quad 8$$

Here each trajectory is determined implicitly by the equation for some constant. The constant c can be obtained if the initial values of S_0 , I_0 of S and I are known. Therefore,

$$c = V(S_0, I_0) = S_0 + I_0 - \frac{a}{r} \ln S_0 \quad 9$$

Let us assume a population of size K . Introduce a small number of infectives in the population,

so that $S_0 \approx K$, $I_0 \approx 0$, and $R_0 = \frac{rK}{a}$. Using that fact that $I(t) \rightarrow 0$ as $t \rightarrow \infty$, and

$S_0 < \frac{a}{r}$ let the relation $V(S_0, I_0) = V(S_\infty, 0)$, gives

$$K - \frac{a}{r} \ln S_0 = S_\infty - \frac{a}{r} \ln S_\infty, \quad 10$$

$$K - S_\infty = \frac{a}{r} \ln \frac{S_0}{S_\infty}, \quad 11$$

using which we can evaluate r/a in terms of the measurable quantities S_∞ and S_0 , as

$$\frac{r}{a} = \frac{\ln \frac{S_0}{S_\infty}}{K - S_\infty}, \quad 12$$

Here $0 < S_\infty < K$, that is part of the population escapes infection. It is difficult to estimate the contact rate r as it depends on the disease being studied and also on social and behavioral factors. S_∞ and S_0 can be estimated by serological studies before and after the

epidemic, and using this data the basic reproductive number $R_0 = \frac{rK}{a}$ may be obtained using equation (12).

The maximum number of infectives at any time can be obtained by substituting

$S = \frac{a}{r}$, $I = I_{\max}$ in equation (7). This maximum is given by

$$I_{\max} = S_0 + I_0 - \frac{a}{r} \ln S_0 - \frac{a}{r} + \frac{a}{r} \ln \frac{a}{r} \quad 13$$

Example: The village of Eyam, England suffered an outbreak of bubonic plague in 1665-1666.

The community was asked to quarantine itself so that the disease could be prevented from spreading to other communities. A thorough record was kept according to which it is believed that out of an initial population of 350 persons only 83 survived the Eyam plague. The disease in Eyam has been used as a case study for modeling. Here we try to fit the model given by equations (1) – (3) over the period from mid-May to mid-October 1666, measuring time in months with an initial population of 7 infectives and 254 susceptibles and a final population of 83. Using equation (12) with $S_0 = 254, I_0 = 7, S_\infty = 83$ we get

$$\frac{r}{a} = 6.54 * 10^{-3} \Rightarrow \frac{a}{r} = 153 \quad 14$$

The infective period was 11 days, so $\alpha = 2.73$ and $r = 0.0178$. Using equation (13), the maximum number of infectives comes out to be 30.4. We use the values obtained for the

parameters α and r in the model and then plot the phase plane, the (S, I) plane. We also graph S and I as a function of t .

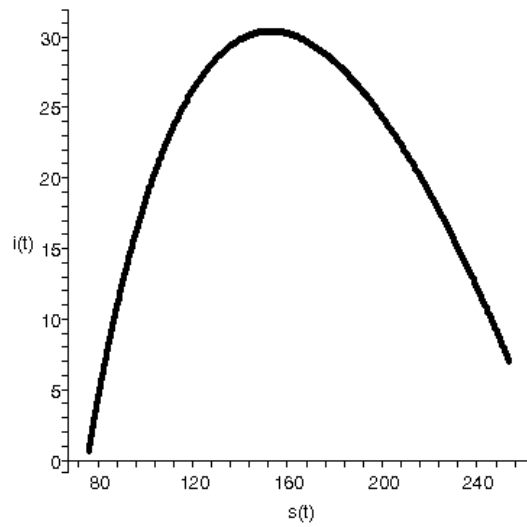


Figure 1: Phase Portrait ($S - I$ plane)

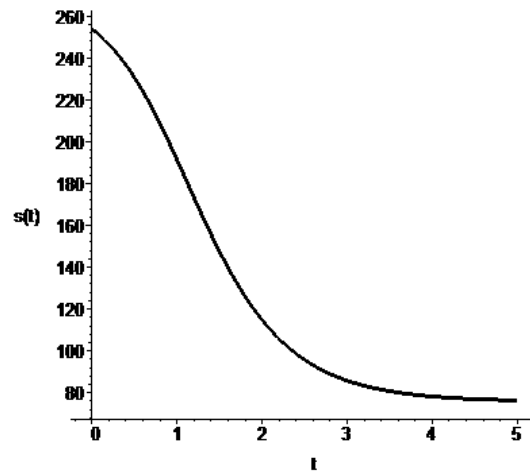


Figure 2: S as a function of t

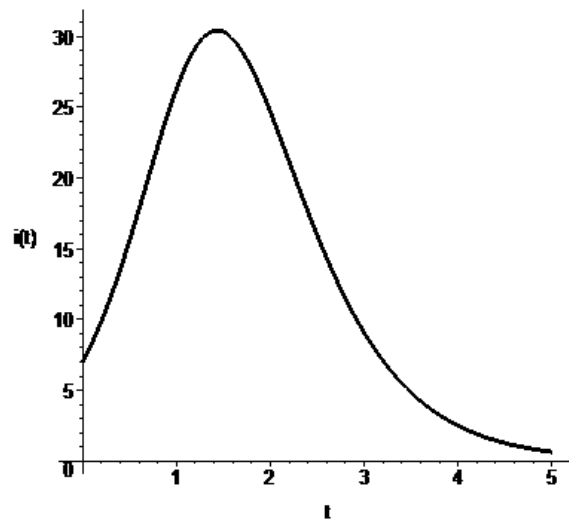


Figure 3: I as a function of t

The prediction of this model and the actual data of Eyam epidemic are very close because our model assumes that the infection is spread from person to person. This may be possible but bubonic plague is mostly transmitted by rat fleas. The fleas first spread the infection among rats. As the availability of rats decreases the fleas then move to human host. In medieval times the trading ships were infested with rats and that led to the spread the infection among rats. As the availability of rats decreases the fleas then move to human host. In the medieval times the trading ships were infested with rats and that led to the spread of plague from Asia into Europe. To get a correct model of plague transmission one would have to include flea and rat populations, as well as movements in space. This kind of model is very complicated and the predictions might not be any better than our simple model described here.

In the village of Eyam the community was asked to quarantine itself so that the infection doesn't spread. But this did not help much to prevent the infection as the infected rats moved to other communities and as a result there was an epidemic. It is clear that the control strategy based on false models models may be harmful, and hence it is necessary to distinguish between

assumptions that simplify but do not change the predicted effects substantially, and wrong assumptions which make an important difference. To prevent an epidemic break out, if the infectives are introduced into a population it is important to reduce the basic reproductive number R_0 so that R_0 is below one.

2.2: Basic SIS Model

In this type of model, the infectives return to the susceptible class on recovery because the disease confers no immunity against reinfection. Such models are more effective for disease caused by bacteria or helminth agents and also for most sexually transmitted diseases. See [20, 38, 45, 52]. The simplest model given by Kermack and Mckendrick to describe this, is

$$S' = rSI - \gamma I \tag{15}$$

$$I' = rSI - \gamma I \tag{16}$$

This model is different from *SIR* model as in this model the recovered members return to the class *S* at a rate of γI instead of moving to class *R*. Here also the total populations $S + I$ is constant, since $(S + I)' = 0$. Let this constant population be K . This model can now be reduced to a single differential equation by replacing S by $K - I$ to give,

$$I' = rI(K - I) - \gamma I = (rK - \gamma)I - rI^2 \quad 17$$

$$= (rK - \gamma)I \left(1 - \frac{1}{K - \frac{\gamma}{r}}\right) \quad 18$$

This is a logistic equation with growth rate $= rK - \gamma$ and carrying capacity $= K - \frac{\gamma}{r}$.

The qualitative analysis tells us that if $rK - \gamma < 0$ or $\frac{rK}{\gamma} < 1$, then for any $I_0 > 0$,

$$I(t) \rightarrow 0 \quad \text{as} \quad t \rightarrow \infty, \quad 19$$

and

$$S(t) \rightarrow K \quad \text{as} \quad t \rightarrow \infty \quad 20$$

If $\frac{rK}{\gamma} > 1$, then for any $I_0 > 0$,

$$I(t) \rightarrow K - \frac{\gamma}{r} \quad \text{as} \quad t \rightarrow \infty \quad 21$$

$$S(t) \rightarrow \frac{\gamma}{r} \quad \text{as} \quad t \rightarrow \infty \quad 22$$

The analysis shows that there is always a single limiting value for I . The value of the quantity $\frac{rK}{\gamma}$ decides which limiting value is approached, irrespective of the initial rate of the spread of the disease. From an epidemiological perspective, if $\frac{rK}{\gamma} < 1$ the infection dies out or in other words the number of infectives approach to zero. Hence the equilibrium $I = 0$, which corresponds to $S = K$, is named as the *disease-free equilibrium*. Alternatively, if $\frac{rK}{\gamma} > 1$, the infection persists. Therefore the equilibrium $I = K - \frac{r}{\gamma}$, that corresponds to $S = \frac{\gamma}{r}$, is known as the endemic equilibrium.

As mentioned in the previous model, the dimension less quantity $\frac{rK}{\gamma}$ is called the basic reproductive number, symbolized as R_0 . The determination of basic reproductive number is of utmost importance in the study of infectious diseases as it determines if the disease will persist or not. The value one of R_0 characterizes a threshold quantity at which the path of the infection varies between disappearance and persistence. Hence $R_0 = \frac{rK}{\gamma}$ (rK is the number of contacts made by an average infective per unit time and $\frac{1}{\gamma}$ is the mean infective period) defines the average number of secondary infection produced when one infected individual is introduced in the host population of susceptibles. Hence it is easy to see that if $R_0 < 1$ the infection must vanish, whereas if $R_0 > 1$ the infection continues. In more refined models the estimation of R_0 is much more complex. See [39].

2.3: SIS Model with Infective Periods of Fixed Length

In all the previous models we have assumed that all rates of transition out of compartment (class) are proportional to the number of members in the compartment. In this model we assume an infective period of fixed length. This assumption leads to differential-difference equations which are more complicated mathematically than the systems of differential equations we have studied so far. See [11, 17].

Distributed delays have been included in a variety of constant population models. For example, *SIS* model with time delay in infective class were analyzed by Cooke and Yorke (1973), and Greenberg and Hoppensteadt (1975). Several *SEIS* models with time delays have been analyzed by Busenberg and Cooke (1980), and Hethcote et al. (1981b). In all these cases a disease either dies out or approaches an endemic steady state. Later on, we will look at models for diseases with more general infective period distribution which will lead to a Volterra integral equation. We will perform the qualitative analysis and shall look at the qualitative behavior of systems of differential equations as a special case.

We start by finding the equilibrium points of the model. We then linearize equilibrium by translating the equilibrium to the origin and expanding in a Taylor series. At equilibrium the constant terms always cancel out and we retain all linear terms but get rid of the terms of higher order. This gives a linear system of differential equations in the case of ordinary differential equations whose coefficient matrix is the matrix of partial derivatives of the right sides of the equations of the original system with respect to the variable.

To get the characteristic equation at equilibrium, the linearization at the equilibrium must have a solution whose components are constant multiple of $e^{\lambda t}$. For an ordinary differential

equation, the characteristic equation is the polynomial equation which determines the eigen values of the coefficient matrix; however, in general the characteristic equation is transcendental. The asymptotic stability of equilibrium depends on whether all the roots of the characteristic equation have negative real parts. We demonstrate the process with the help of some examples, making use of *SIS* model with an infected period of fixed length, as they have fewer compartments and hence easier to analyze. See [16, 40].

We start with the basic *SIS* model with no births or deaths (including disease related death), making the following assumptions:

- (i) An average infective makes contact enough to transmit infection with rN others per unit time rN unit time, where N represents total population size.
- (ii) The population size remains constant given by a contact given by a constant K , that is there are no births or deaths.
- (iii) Infectives in infected class remain infective for a fixed time τ , where τ is defined as the infected period of fixed length and then return to the susceptible class.

The rate of new infection at time t is given by $rS(t)I(t)$. Since we have assumed that the total population size is a constant K , we have $S + I = K$, and hence we can formulate the model in terms of single variable I , replacing S by $K - I$. Therefore,

$$rS(t)I(t) = rI(t)[K - I(t)]. \quad 23$$

Now the rate at which the infectives return to the susceptible class after recovery is

$$rS(t - \tau)I(t - \tau) = rI(t - \tau)[K - I(t - \tau)]. \quad 24$$

The infective population size is only affected by new infections and recoveries, so we have

$$I'(t) = rI(t)[K - I(t)] - rI(t - \tau)[K - I(t - \tau)]. \quad 25$$

To find equilibrium we try to solve equation (25) with $I(t) = \text{constant}$, but we see that we have no condition to solve, infact every constant value of I is a solution of equation (25). Therefore to find the equilibria we need to add some additional conditions. We do that by including initial data $-\tau \leq t \leq 0$, into the model by writing it in the integrated form,

$$I(t) = \int_{t-\tau}^t rI(x)[K - I(x)] dx \quad 26$$

Here $I(t)$ describes the integral sum of members infected at time x between $t - \tau$ and t .

Solving (26) we get

$$I = 0 \text{ or } 1 = r\tau(K - I). \quad 27$$

We have disease-free equilibrium $I = 0$ and an endemic equilibrium $I = K - \frac{1}{r\tau}$.

For linearization at equilibrium, I_∞ we substitute $I = I_\infty + u(t)$ in (26), giving

$$I(t) = \int_{t-\tau}^t r[I_\infty + u(x)][K - I_\infty - u(x)] dx . \quad 28$$

Neglecting the quadratic term, we get

$$u(t) = \int_{t-\tau}^t r[K - 2I_\infty]u(x) dx \quad 29$$

The characteristic equation is

$$e^{\lambda t} = \int_{t-\tau}^t r[K - 2I_\infty]e^{\lambda x} dx \quad 30$$

$$= \frac{r(K - 2I_\infty)[e^{\lambda t} - e^{\lambda(t-\tau)}]}{\lambda} \quad 31$$

$$\text{or } \frac{r(K - 2I_\infty)[1 - e^{-\lambda\tau}]}{\lambda} = 1 \quad 32$$

The characteristic equation at the disease free equilibrium i.e. $I_\infty = 0$, is given by

$$\frac{rK [1 - e^{-\lambda\tau}]}{\lambda} = 1 \quad 33$$

We make use of the following proposition to establish the asymptotic stability of the disease-free equilibrium.

2.3.1 Proposition: If $\tau > 0$ and $\Re \lambda \geq 0$ then $\frac{1 - e^{-\lambda\tau}}{\lambda} \leq \tau$

If $r\tau K < 1$, then for $\Re \lambda \geq 0$ absolute value of the left side of the equation (33) is not

Greater than 1 and thus there can be no root of the equation (33) with $\Re \lambda \geq 0$ and thus the disease – free equilibrium is asymptotically stable if $R_0 = r\tau K < 1$,

At the endemic equilibrium

$$I = K - \frac{1}{r\tau}, K - 2I = K - 2K + \frac{2}{r\tau} = \frac{2}{r\tau} - K, \quad 34$$

and the characteristic equation (32) becomes

$$\left(\frac{2}{r\tau} - K \right) \frac{1 - e^{-\lambda\tau}}{\lambda} = 1. \quad 35$$

The absolute value of the left side of (35) is at most $r\left(\frac{2}{r\tau} - K\right)\tau = 2 - R_0$. The equilibrium

is asymptotically stable for $R_0 > 1$ because there are no roots with $\Re \lambda \geq 0$.

Hence we see that the disease-free equilibrium is asymptotically stable if $R_0 < 1$ and if

$R_0 > 1$, the endemic equilibrium exists and is asymptotically stable.

Next we include birth and death into the model. Because of this the total population may be constant. For this case we use the variables I and N . We use N instead of S , to facilitate the extension to models which incorporate a density-dependent contact rate. We assume that there are no deaths due to disease and μ is the natural death rate then μK is the birth rate and μN is the death rate.

Then the differential equation for N is given by

$$N' = \mu K - \mu N \tag{36}$$

To obtain the differential equations for I we make use of the following facts:

- (i) The rate of new infection is given by $rS(t)I(t) = rI(t)[N(t) - I(t)]$.
- (ii) The rate of the recoveries at time t is the rate of new infections $rS(t - \tau)I(t - \tau)$ at time $t - \tau$ times the fraction $e^{-\mu\tau}$ of these new infectives who survive until time t .

Therefore the differential-difference equation is

$$I'(t) = rI(t)[N(t) - I(t)] - e^{-\mu\tau} rI(t - \tau)[N(t - \tau) - I(t - \tau)] \tag{37}$$

and thus the model is

$$N' = \mu K - \mu N(t) \quad 38$$

$$I'(t) = rI(t)[N(t) - I(t)] - e^{-\mu\tau} rI(t - \tau)[N(t - \tau) - I(t - \tau)] \quad 39$$

We skip the equilibrium analysis as it is similar to the case $\mu = 0$, but somewhat complicated as we now have a two dimensional system. Since not all constants are solutions of the system we need not use the integrated form to carry out the equilibrium analysis. We have disease-free equilibrium $I = 0, N = K$, and an endemic equilibrium $I = K - \frac{\mu}{r(1 - e^{-\mu\tau})}$,

$N = K$, this exists if

$$R_0 = \frac{rK(1 - e^{-\mu\tau})}{\mu} > 1 \quad 40$$

At equilibrium i.e. $I = I_\infty, N = K$, the characteristic equation is

$$\frac{r[K - 2I_\infty](1 - e^{-(\lambda + \mu)\tau})}{\lambda + \mu} = 1 \quad 41$$

We generalize the Proposition 1 used earlier for the analysis of *SIS* model without births and deaths to analyze equation (41).

2.3.2 Proposition 2: If $\tau > 0$ and $\Re \lambda \geq 0$ then

$$\frac{(1 - e^{-(\lambda + \mu)\tau})}{\lambda + \mu} \leq \frac{1 - e^{-\mu\tau}}{\mu}. \quad 42$$

Proof: For $\mu > 0$ and $\Re \lambda \geq 0$, we have

$$\left| \int_0^\tau e^{-(\lambda + \mu)x} dx \right| \leq \int_0^\tau |e^{-(\lambda + \mu)x}| dx = \int_0^\tau |e^{-\lambda x}| e^{-\mu x} dx \quad 43$$

$$\leq \int_0^\tau e^{-\mu x} dx = \frac{1 - e^{-\mu\tau}}{\mu} \quad 44$$

The integral is,

$$\int_0^\tau e^{-(\lambda + \mu)x} dx = \frac{1 - e^{-(\lambda + \mu)\tau}}{\lambda + \mu} \quad 45$$

hence,

$$\frac{1 - e^{-(\lambda + \mu)\tau}}{\lambda + \mu} \leq \frac{1 - e^{-\mu\tau}}{\mu} \quad 46$$

(We need not prove Proposition 1 separately because it is the limiting case of Proposition 2 as $\mu \rightarrow 0$.)

If $R_0 = \frac{rK(1 - e^{-\mu\tau})}{\mu} < 1$ then for $\Re \lambda \geq 0$ the absolute value of the left side of the equation

(42) with $I_\infty = 0$ is no greater than one and consequently there can be no root of the equation with $\Re \lambda \geq 0$ and hence the disease-free equilibrium is asymptotically stable if $R_0 < 1$. At the endemic equilibrium

$$r(K - 2I_\infty) = \frac{2\mu}{1 - e^{-\mu\tau}} - rK \quad 47$$

hence the absolute value of the side of the equation (42) is no greater than $2 - R_0$, which is not greater than one since $R_0 > 1$. Note also that no root of characteristic equation is possible with $\Re \lambda \geq 0$ and as a result the endemic equilibrium is asymptotically stable if $R_0 > 1$.

Next we include the deaths due to the disease into the model by making the assumption that at the end of a fixed infective period a fraction p of infectives dies while the remainder returns to the susceptible class. In this case the model is,

$$I'(t) = rI(t)[N(t) - I(t)] - e^{-\mu\tau} rI(t - \tau)[N(t - \tau) - I(t - \tau)] - \mu I(t) \quad 48$$

$$N'(t) = \mu K - \mu N(t) - p e^{-\mu\tau} rI(t - \tau)[N(t - \tau) - I(t - \tau)] \quad 49$$

The value of R_0 obtained here is same as the R_0 obtained for the model given by (38 - 39).

The characteristic equation is

$$\frac{r[N_\infty - (2 - p)I_\infty][1 - e^{-(\lambda + \mu)\tau}]}{\lambda + \mu} = 1 + \frac{p\beta I_\infty}{\lambda + \mu} \quad 50$$

Here we establish that for every p , $0 \leq p \leq 1$, the disease-free equilibrium is asymptotically stable if $R_0 > 1$.

The case $p = 1$ is similar to the *SIR* model. We will not analyze the *SIR* model here as the general ideas are analogous to the *SIS* models [9].

2.4: SIRS Model with Fixed Period of Temporary Immunity

Delays in population dynamics models can destabilize equilibrium so that the periodic solutions arise by a Hopf bifurcation. To analyze this situation consider an *SIRS* model with an assumption that instead of exponentially distributed period of temporary immunity, we have a constant period of temporary immunity following recovery from infection. See [13, 15, and 55].

Hethcote et al. (1981a, 1989) has shown that *SIRS* model with time delay in the removed class (i.e. a constant period of temporary immunity) can exhibit periodic solutions for some parameter values.

We shall include all the usual assumption mentioned previously and one additional assumption in this model. The assumptions are as follows:

- (i) Birth rate is μK
- (ii) μ is the proportional death rate is each class
- (iii) The rate of new infections is rSI .
- (iv) γ is the proportional recovery rate
- (v) α is the proportional disease death rate per unit time.
- (vi) ω is the temporary immunity period of fixed length, after which the infectives return to the susceptible class.

Thus the model based on these assumptions is given by,

$$S'(t) = \mu K - \mu S(t) - rS(t)I(t) + \gamma I(t - \omega)e^{-\mu(t-\omega)} \quad 51$$

$$I'(t) = rS(t)I(t) - (\mu + \gamma + \alpha)I(t) \quad 52$$

$$R'(t) = \gamma I(t) - \gamma I(t - \omega)e^{-\mu(t-\omega)} - \mu R(t) \quad 53$$

We only analyze the special case with $\mu = 0$ and $\alpha = 0$ with no births, natural deaths, or disease deaths. We can analyze the general case in a similar way. In this case we have,

$$S'(t) = -rS(t)I(t) + \gamma I(t - \omega) \quad 54$$

$$I'(t) = rS(t)I(t) - \gamma I(t) \quad 55$$

$$R'(t) = \gamma I(t) - \gamma I(t - \omega) \quad 56$$

Since $S(t) + I(t) + R(t) = \text{constant}$, we can discard R and the model reduces to a two dimensional system

$$S'(t) = -rS(t)I(t) + \gamma I(t - \omega) \quad 57$$

$$I'(t) = rS(t)I(t) - \gamma I(t) \quad 58$$

Equilibria are given by $I = 0$ or $rS = \gamma$. The characteristic equation at an equilibrium (S_∞, I_∞) is found using the same approach as used in the previous model and is given by

$$r\gamma I_{\infty} \frac{1 - e^{-\omega\lambda}}{\lambda} = -\lambda - (\gamma + rI_{\infty} - rS_{\infty}). \quad 59$$

Equation (59) reduces to a linear equation with a single root $\lambda = rK - \gamma$ at the disease-free equilibrium $S_{\infty} = K, I_{\infty} = 0$, which is negative if and only if $R_0 = \frac{rK}{\gamma} < 1$. Next we analyze the equation (59) at the endemic equilibrium condition; hence we need an additional equation. This additional equation can be obtained by writing the equation of R in the integrated form

$$R(t) = \int_{t-\omega}^t \gamma I(x) dx \quad 60$$

From this equation we get $R_{\infty} = \omega\gamma I_{\infty}$. We also have $rS_{\infty} = \gamma$, from $S_{\infty} + I_{\infty} + R_{\infty} = K$ we get

$$rK = rS_{\infty} + r(1 + \omega\gamma)I_{\infty} = \gamma + r(1 + \omega\gamma)I_{\infty} \quad 61$$

$$rI_{\infty} = \frac{rK - \gamma}{(1 + \omega\gamma)}. \quad 62$$

Rewriting equation (59) at the endemic equilibrium we have,

$$\gamma \frac{rK - \gamma}{(1 - \omega\gamma)} \frac{1 - e^{-\omega\lambda}}{\lambda} = -\lambda - \frac{rK - \gamma}{(1 - \omega\gamma)} \quad 63$$

Consider r and γ as parameters and keep ω and K fixed. For $\gamma = 0$ the equation (63) is linear and its only root is $-\omega K < 0$. As a result there is a region in (r, γ) parameter space including the r -axis in which all the roots have negative real part. We use the information that the roots of equation (63) continuously depend in r and γ to find the size of the stability region. A root can move to the right half plane either by crossing the imaginary axis or by passing through the value zero as r and γ vary.

Hence, the stability region contains the r -axis and extends into the plane until there is a root $\lambda = 0$ or until there is a pair of imaginary roots $\lambda = \pm iy, y > 0$. As the left hand side of equation (63) is positive and the right side is negative for real $\lambda \geq 0$, there cannot be a root at $\lambda = 0$.

To have $\lambda = iy$ as a root the condition is,

$$\gamma \frac{rK - \gamma}{(1 - \omega\gamma)} \frac{1 - e^{-\omega iy}}{iy} = -iy - \frac{rK - \gamma}{(1 - \omega\gamma)} \quad 64$$

Separating real and imaginary parts we get pair of equations,

$$\gamma \frac{\sin(\omega y)}{y} = -1, \quad \gamma \frac{rK - \gamma}{(1 - \omega\gamma)} \frac{1 - \cos(\omega y)}{y} = y. \quad 65$$

Since $|\sin(\omega y)| \leq |\omega y|$ for all y , it is essential to have $\omega y > 1$ in order to satisfy the first condition. This means that the endemic equilibrium is asymptotically stable if $\omega y < 1$. Also, we require $\sin \omega y < 0$. There are infinite sequences of intervals on which $\sin \omega y < 0$. For each of these intervals the equation (65) defines a curve in the (r, γ) plane parametrically with y as a parameter. The region in the plane below the first of these curves is the region of asymptotic stability.

Here we see that the endemic equilibrium is not asymptotically stable for all parameter values. What happens if the endemic equilibrium is unstable? The loss of stability generally occurs because of the root $\lambda = iy$ of the characteristic equation which gives periodic solutions to the model. This is very similar to the Hopf bifurcation theorem which states that when the roots of the characteristic equation cross the imaginary axis a stable periodic orbit rises [15, 55]. The periodic behavior is unpleasant from epidemiological point of view. This means that the number of infectives vary which makes it difficult to allocate resources for treatment. If the data was measured over a small time interval, and the oscillations have long period, then the actual behavior may not be displayed. Hence the situation where endemic equilibrium is unstable is very important.

2.5: Basic SIS Model with Arbitrarily Distributed Infective Periods

The previous models were formulated either with assumption of exponentially distributed infective periods or with infective periods of fixed length. In real life the assumption of exponentially distributed infective period is quite unrealistic. In fact, a more plausible or realistic

assumption would be to have an arbitrarily distributed infective periods [40]. This assumption leads to volterra integral equation which is more complicated to analyze than ordinary differential equations. Hoppensteadt in 1974, 1975 introduced a model framework that incorporates almost arbitrary length distributions for various disease stage. After that quite a few models have been considered where the infection period is arbitrarily distributed.

Stech and Williams (1981) show a noteworthy global stability result for the endemic equilibrium in a model with an arbitrarily distributed immunity period. Their result was recently extended to diseases that cause fatalities. Lin and van den Driessche (1992) prove threshold results for models with an arbitrarily distributed infective period and a nonlinear incidence. Castillo Chavez et al. (1989) analyze the global stability of the disease free equilibrium and the local stability of the endemic equilibrium for an AIDS model with arbitrarily distributed infectivity and a general contact function.

We begin the formulation of this model with arbitrarily distributed infective periods, making the assumption that there is a function $P(s)$, which represents the fraction of those infectives who became infected s time units in the past and are still alive and remain infective. The function $P(s)$ is of the form,

$$P(s) = e^{-(\alpha+\gamma)s} \tag{66}$$

for the exponentially distributed case and for the fixed infective period it is

$$P(s) = \begin{cases} 1, & \text{for } 0 \leq s \leq \tau \\ 0, & \text{for } s > \tau \end{cases} \quad 67$$

We also assume function $P(s)$ to have following properties:

(i) $P(s)$ is a non-negative, a non-increasing function,

(ii) $P(0) = 1$

(iii) $\tau = \int_0^{\infty} P(s) ds$, the mean infective period is finite.

We consider a simple *SIS* model with no births or deaths and a total population size of constant K and $S + I = K$. This model has the form

$$I(t) = \int_{-\infty}^t rI(x)[K - I(x)] p(t-x) dx \quad 68$$

Here S is replaced by $K - I$.

Equilibria are given by

$$rI(K - I) \int_{-\infty}^t P(t-x) dx = rI(K - I)\tau \quad 69$$

The disease-free equilibrium is $I_\infty = 0$ and endemic equilibrium is $I_\infty = K - \frac{1}{r\tau}$. The characteristic equation is determined following the same procedure as followed for *SIS* model with an infective period fixed length. The characteristic equation thus obtained is,

$$1 = rI (K - I) \int_0^\infty e^{-\lambda u} P(u) du \quad 70$$

The term $\int_0^\infty e^{-\lambda u} P(u) du$ is the laplace transform of P and will be denoted by $\hat{P}(\lambda)$. Using the property of laplace transform, if $P(u)$ is a non negative function and if $\Re \lambda \geq 0$ we have

$$\hat{P}(\lambda) = \int_0^\infty e^{-\lambda u} P(u) du \leq \int_0^\infty P(u) du = \hat{P}(0) = \tau \quad 71$$

(Since $e^{-\lambda u} \leq e^{-\Re \lambda u} \leq 1$)

This property helps us to analyze the characteristic equation. The analysis here yields similar results as obtained earlier for other models. The disease-free equilibrium $I = 0$ is an asymptotically stable if and only if $R_0 = r\tau K < 1$ and the endemic equilibrium exists only if $R_0 = r\tau K > 1$, and is asymptotically stable if $R_0 > 1$. Similar results are obtained when birth and deaths are included.

The analysis of *SIR* model can be carried out following the procedure for *SIS* model but it is more complicated due to increase in dimension. For this model also we obtain similar results i.e. the disease-free equilibrium is asymptotically stable if and only if $R_0 < 1$ and the endemic equilibrium which exists only if $R_0 > 1$, and is asymptotically stable.

CHAPTER 3: EPIDEMIOLOGICAL MODEL FOR MUTATING PATHOGEN WITH TEMPORARY IMMUNITY

3.1: Introduction

Significant progress has been made in understanding different scenarios for disease transmissions and behavior of epidemics in recent years. Considerable amount of work has been done in modeling the dynamics of diseases by systems of ordinary differential equations. But there are very few mathematical models that deal with the genetic mutations of a pathogen. See [3, 23, and 35]. In-fact, not much has been done to model the dynamics of mutations of pathogen explaining its effort to escape the host's immune defense system after it has infected the host.

The memory immune responses enable humans and animals to rapidly clear, or even prevent altogether, infection by a pathogen with which they have previously been infected. For example, we typically contract chicken pox only once in our life time. This is because of the effectiveness of the memory response and vaccines designed around the knowledge that our immune system will efficiently fight foreign invaders if already exposed to something similar. As a result it is easy to imagine why some pathogens such as influenza virus, use the strategy of disguise to survive in a host population. With enough mutation, a pathogen will ultimately be unrecognizable to the immune system of a host that previously has been infected with one of its ancestors. This ability of pathogen to mutate, allows them to escape partially the host immunity acquired from previous infections. In a few diseases, such as influenza A and canine parvovirus,

new antigenic variants arise continuously affecting significantly the epidemiology of the disease. In our model the pathogen mutates to produce a second strain. We will concentrate on the analysis with respect to these two strains.

We develop an *SIR* model with variable infection age for the transmission of a pathogen that can mutate in the host to produce a second infectious mutant strain [21, 41]. We also assume that there is a period of temporary immunity in the model [3, 39]. Temporary immunity period along with variable infection age leads to integro-differential-difference equation model. Previous efforts on incorporating delays in epidemic models have been mainly concentrated on inclusion of latency periods (this assumes that the force of infection at a present time is determined by the number of infectives in the past). Temporary immunity means that after recovery an individual acquires immunity from the disease for some period of time and then it moves into the susceptible class again. The diseases with temporary immunity are influenza, Salmonella infection (with partial immunity) and respiratory syncytial. In case of influenza we see that there is a long (but not lifelong) immunity to the same strain of the disease but no immunity against other strains, [21, 46, and 50].

We find the explicit formulas for the reproductive number of infection and will describe the threshold conditions of the epidemic which establishes the stability of disease-free equilibrium in section 4.3. Boundary equilibrium (only one strain persists) under the influence of delay will be studied and its local stability will be examined in section 4.4. The formulas for the endemic equilibrium (stationary coexistence solution) and its characteristic equation will be developed and local stability will be analyzed in section 4.5, [3]. The main purpose of our study is to investigate the influence of time-delay on the analysis of the model. We will show that the endemic equilibrium when unstable gives rise to periodic solutions and as a result leads to Hopf

bifurcation. The Hopf bifurcation will be demonstrated using numerical simulations in section 5.3, [6, 7, 15, 30, 32, 37, 43, 44, and 55].

3.2: Formulation of the model with temporary immunity

The model of interest here is based on *SIR* model for the transmission of pathogen. We assume that after a certain period of infection, the pathogen mutates in the host to produce a second mutant strain. The original strain is called strain A and the second strain is called strain B. As a result, the individuals infected by strain A are then bearing strain B. Let $S(t)$ be the susceptibles and $i(t, \tau)$ be the distribution of infectives infected by strain A with

τ being the time since infection. $\int_{\tau_1}^{\tau_2} i(t, \tau) d\tau$ represents the total number of infectives between

τ_1 and τ_2 . Let $J(t)$ be the infectives infected by strain B and let $R(t)$ be the recovered individuals from both the strains. We also assume that after recovery from strain B an individual has a temporary immunity against the disease and therefore, it moves to the susceptible class after some period of time. We incorporate temporary immunity in our model by introducing the term $e^{-\mu\omega} J(t - \omega)$, where ω the length of immunity period, t is the time and μ is a constant indicating total remove rate.

The mathematical model described above has the following form:

$$\frac{dS(t)}{dt} = \mu(K - S(t)) - \left(\int_0^{\infty} r_1(\tau) i(t, \tau) d\tau + r_2 J(t) \right) S(t) + \gamma_2 J(t - \omega) e^{-\mu\omega}, \quad 72$$

$$\frac{\partial i(t, \tau)}{\partial t} + \frac{\partial i(t, \tau)}{\partial \tau} = -(\mu + \gamma_1)i(t, \tau) - \kappa(\tau)i(t, \tau), \quad 73$$

$$i(t, 0) = S(t) \int_0^{\infty} r_1(\tau) i(t, \tau) d\tau, \quad 74$$

$$i(0, \tau) = \psi(\tau), \quad 75$$

$$\frac{dJ(t)}{dt} = r_2 J(t) S(t) - (\mu + \gamma_2) J(t) - \int_0^{\infty} \kappa(\tau) i(t, \tau) d\tau, \quad 76$$

$$\frac{dR(t)}{dt} = \gamma_1 \int_0^{\infty} i(t, \tau) d\tau + \gamma_2 J(t) - \mu R(t) - \gamma_2 J(t - \omega) e^{-\mu\omega}, \quad 77$$

where μ is the total removal rate, ω is the length of the immunity period, γ_1 and γ_2 are the recovery rates of the strains A and B, $\kappa(\tau)$ is the rate at which strain A is converted to strain B, $r_1(\tau)$ and r_2 are the transmission rates of strain A and strain B, μK is the influx in the susceptible population, and $\psi(\tau)$ is the initial distribution of infectives infected by strain A. Since $i(t, \tau)$ is a function of two independent continuous variables we have a PDE in the model which makes the model more complicated than the models based on ODE. In ODE governed

models the variables of interest are functions of one independent variable, usually time t , hence they are easier to analyze.

This model integrates many of the previous models given in chapter 2. For example, by setting $i=0, \psi=0, r_1=0$ and $\mu=0$ in the system of equations (72 – 77), our model reduces to a simple time delayed SIR model, which is given by,

$$\frac{dS(t)}{dt} = -r_2 J(t)S(t) + \gamma_2 J(t - \omega), \quad 78$$

$$\frac{dJ(t)}{dt} = r_2 J(t)S(t) - \gamma_2 J(t), \quad 79$$

$$\frac{dR(t)}{dt} = \gamma_2 J(t) - \gamma_2 J(t - \omega), \quad 80$$

The analysis of this model is analogous to the analysis done for *SIS* model with fixed period of immunity mentioned in chapter 2, section 2.3.

3.3: Disease-Free Equilibrium

The disease-free equilibrium corresponds to both strains not being present. Consider the case where there is no infection, i.e. $i(t, \tau) = 0$ and $J = 0$ then the system of equations (72 – 77) reduces to

$$\frac{dS(t)}{dt} = \mu(K - S(t)) \quad 81$$

Setting $\frac{dS(t)}{dt} = 0$ here shows equilibrium of system (72 – 77) at $E_0 = (K, 0, 0)$. This is the disease-free equilibrium. Thus, in the absence of infectives the susceptible have an equilibrium value of K . Investigation of the stability of this equilibrium will derive the so-called reproductive number, R_0 .

3.3.1: Reproductive Number

The stability analysis of disease-free equilibrium determines the thresholds (reproductive number) of the epidemic. We drop the equation for $R(t)$ for the study of growth of epidemics as it does not have an effect on the development of S , I and J . Linearizing the system of equations (72 – 77) about E_0 , by defining the perturbation variables

$$x(t) = S(t) - K, y(t, \tau) = i(t, \tau), z(t) = J(t) \quad 82$$

This gives us the new system of equations,

$$\frac{dx(t)}{dt} = -\mu x(t) - \left(\int_0^{\infty} r_1(\tau) y(t, \tau) d\tau + r_2 z(t) \right) K + \gamma_2 z(t - \omega) e^{-\mu\omega}, \quad 83$$

$$\frac{\partial y(t, \tau)}{\partial t} + \frac{\partial y(t, \tau)}{\partial \tau} = -(\mu + \gamma_1) y(t, \tau) - \kappa(\tau) y(t, \tau), \quad 84$$

$$y(t, 0) = K \int_0^{\infty} r_1(\tau) y(t, \tau) d\tau, \quad 85$$

$$\frac{dz(t)}{dt} = r_2 z(t) K - (\mu + \gamma_2) z(t) - \int_0^{\infty} \kappa(\tau) y(t, \tau) d\tau, \quad 86$$

Let $x(t) = x_0 e^{\lambda t}$, $y(t, \tau) = p(\tau) e^{\lambda(t-\tau)}$, and $z(t) = z_0 e^{\lambda t}$, where x_0 , $p(\tau)$, z_0 and λ are to be determined. Substituting this ansatz in system (83 – 86), we get

$$\lambda x_0 = -\mu x_0 - K \int_0^{\infty} r_1(\tau) p(\tau) e^{-\lambda\tau} d\tau - r_2 z_0 K + \gamma_2 z_0 e^{-\omega(\lambda+\mu)}, \quad 87$$

$$p'(\tau) = p(\tau)(-(\mu + \gamma_1) - \kappa(\tau)), \quad 88$$

$$p(0) = K \int_0^{\infty} r_1(\tau) p(\tau) e^{-\lambda\tau} d\tau, \quad 89$$

$$\lambda z_0 = r_2 K z_0 - (\mu + \gamma_2) z_0 + \int_0^{\infty} \kappa(\tau) p(\tau) e^{-\lambda\tau} d\tau, \quad 90$$

for $x_0 \neq 0$, $p(\tau) \neq 0$, $z_0 \neq 0$ and λ .

Note that the equations (88) and (89) have no connection with equations (87) and (90).

Integrating (88) from 0 to τ , we get

$$\int_0^{\tau} \frac{p'(v)}{p(v)} dv, = \int_0^{\tau} -(\mu + \gamma_1) dv - \int_0^{\tau} \kappa(v) dv, \quad 91$$

$$p(\tau) = p(0) e^{-(\mu + \gamma_1)\tau - \int_0^{\tau} \kappa(v) dv}, \quad 92$$

Substituting (92) into (89) gives the characteristic equation,

$$p(0) = p(0)K \int_0^{\infty} r_1(\tau) \left(e^{-\left(\mu + \gamma_1\right)\tau - \int_0^{\tau} \kappa(v) dv} \right) e^{-\lambda t} d\tau, \quad 93$$

Define

$$C(\lambda) = K \int_0^{\infty} r_1(\tau) \left(e^{-\left(\mu + \gamma_1\right)\tau - \int_0^{\tau} \kappa(v) dv} \right) e^{-\lambda \tau} d\tau, \quad 94$$

From equation (93), it is easy to conclude that $p(0) \neq 0$ if and only if there exists a unique λ , say λ_0 , such that $C(\lambda) = 1$. The sign of λ is determined by the size of $C(0)$.

We consider two cases for λ , first when λ is a real number and second when λ is a complex number.

Case 1: λ is a real number:

Since the integral in equation (94) is uniformly convergent in λ ,

$$C'(\lambda) = -K \int_0^{\infty} r_1(\tau) \left(e^{-\left(\mu + \gamma_1\right)\tau - \int_0^{\tau} \kappa(v) dv} \right) e^{-\lambda \tau} \tau d\tau < 0, \quad 95$$

by differentiating inside the intergral sign.

Hence $C(\lambda)$ is a decreasing function of λ . Also,

$$C(\lambda) \rightarrow \infty \quad \text{as} \quad \lambda \rightarrow -\infty \quad 96$$

$$C(\lambda) \rightarrow 0 \quad \text{as} \quad \lambda \rightarrow \infty \quad 97$$

Hence if we define

$$R_1 := C(0) = K \int_0^{\infty} r_1(\tau) \left(e^{-\left(\mu + \gamma_1\right)\tau - \int_0^{\tau} \kappa(v) dv} \right) d\tau, \quad 98$$

then there exists a unique solution to λ from the equation $C(\lambda) = 1$, which is negative if

$R_1 < 1$ and positive if $R_1 > 1$.

Case 2: λ is a complex number. Let $\lambda = \lambda_1 + i\lambda_2$, separating real and imaginary part of $C(\lambda) = 1$ we get,

$$\text{Real part: } K \int_0^{\infty} r_1(\tau) \left(e^{-\left(\mu + \gamma_1\right)\tau - \int_0^{\tau} \kappa(v) dv} \right) e^{-\lambda_1\tau} \cos(\lambda_2\tau) d\tau \quad 99$$

$$\text{Img part: } K \int_0^{\infty} r_1(\tau) \left(e^{-\left(\mu + \gamma_1\right)\tau - \int_0^{\tau} \kappa(v) dv} \right) e^{-\lambda_1\tau} \sin(\lambda_2\tau) d\tau \quad 100$$

The real part λ_1 satisfies

$$1 = K \int_0^{\infty} r_1(\tau) \left(e^{-\left(\mu + \gamma_1\right)\tau - \int_0^{\tau} \kappa(\tau) dv} \right) e^{-\lambda_1 \tau} \cos(\lambda_2 \tau) d\tau \quad 101$$

Note that

$$K \int_0^{\infty} r_1(\tau) \left(e^{-\left(\mu + \gamma_1\right)\tau - \int_0^{\tau} \kappa(\tau) dv} \right) e^{-\lambda_1 \tau} \cos(\lambda_2 \tau) d\tau \leq K \int_0^{\infty} r_1(\tau) \left(e^{-\left(\mu + \gamma_1\right)\tau - \int_0^{\tau} \kappa(\tau) dv} \right) e^{-\lambda_1 \tau} d\tau \quad 102$$

which means the solution λ_1 to equation (101) must be negative if $R_1 < 1$. Hence for equation $C(\lambda) = 1$ to have a solution with negative real part only when λ is a complex number, we must have $R_1 < 1$.

The number R_1 defined in (98) is the reproductive number for strain A because $R_1 > 1$ epidemic persists for strain A while if $R_1 < 1$ it decays and eventually dies out. It is also the number of secondary infections caused by strain A. The solution λ of $C(\lambda) = 1$ can be used to determine $p(\tau)$ (See page Appendix A.3.1). The initial values, x_0 and z_0 can be define from (87) and (90).

Initially if no one is infected with strain A, that is $i(t, \tau) = 0$, and $p(\tau) = 0$ for all τ .

Under this condition the equations (87) and (90) reduce to

$$\lambda x_0 = -\mu x_0 - r_2 z_0 K + \gamma_2 z_0 e^{-\omega(\lambda+\mu)}, \quad 103$$

$$\lambda z_0 = r_2 K z_0 - (\mu + \gamma_2) z_0, \quad 104$$

They determine the threshold for the strain B. Notice for all solutions λ of system (103 – 104) to be negative the required condition is

$$r_2 K < \mu + \gamma_2, \quad 105$$

Define

$$R_2 := \frac{r_2 K}{\mu + \gamma_2} \quad 106$$

Hence system (103 – 104) has negative solutions if and only if $R_2 < 1$. The number R_2 is the reproductive number (threshold value) for strain B. It is also the number of secondary infections caused by strain B.

The two reproductive numbers R_1 and R_2 found for strain A and strain B respectively can be summarized as follows:

Lemma 4.3.1.1: Define a reproductive number, R_0 , of infection in the total population by

$$R_0 = \max\{ R_1, R_2 \} \quad 107$$

that is

$$R_0 = \max \left\{ K \int_0^{\infty} r_1(\tau) \left(e^{-\int_0^{\tau} (\mu + \gamma_1) dv} e^{-\int_0^{\tau} \kappa(\tau) dv} \right) d\tau, \frac{r_2 K}{\mu + \gamma_2} \right\} \quad 108$$

Then the disease-free equilibrium E_0 is asymptotically stable for all values of ω if $R_0 < 1$ and is unstable if $R_0 > 1$.

3.4: Boundary Equilibrium

When the disease is endemic, there is a possibility that the disease is caused by strain A only, by strain B only or by both strains. In this section we establish the existence of boundary equilibrium (where only one strain is present) and find its explicit form. We will also perform its stability analysis.

3.4.1: Existence of Boundary Equilibrium

Let $(S, i(\tau), J)$ be the equilibrium of the system.

Therefore the equilibrium of system, $(S, i(\tau), J)$ satisfies

$$\mu(K - S) - \int_0^{\infty} r_1(\tau)i(\tau)d\tau + r_2JS + \gamma_2Je^{-\mu\omega} = 0 \quad 109$$

$$\frac{\partial i(\tau)}{\partial \tau} = -(\mu + \gamma_1)i(\tau) - \kappa(\tau)i(\tau) \quad 110$$

$$i(0) = S \int_0^{\infty} r_1(\tau)i(\tau)d\tau \quad 111$$

$$r_2JS - (\mu + \gamma_2)J - \int_0^{\infty} \kappa(\tau)i(\tau)d\tau = 0 \quad 112$$

From (112) if $J = 0 \Rightarrow \int_0^{\infty} \kappa(\tau)i(\tau)d\tau = 0 \quad 113$

Since $\kappa(\tau)i(\tau) \geq 0$ and $\kappa(\tau) > 0$, we conclude that

$$i(\tau) = 0 \text{ for all } \tau . \quad 114$$

This means that the only boundary equilibrium has $i(\tau) = 0$ for all τ . When $J \neq 0$ the boundary equilibrium is denoted as $E_1 = (S_1, 0, J_1)$. Solving (112) at the equilibrium point yields,

$$r_2 J_1 S_1 - (\mu + \gamma_2) J_1 = 0 \quad 115$$

Since $J_1 \neq 0$, (115) gives,

$$r_2 S_1 - (\mu + \gamma_2) = 0 \quad 116$$

$$S_1 = \frac{(\mu + \gamma_2)}{r_2} \quad 117$$

Then at the equilibrium equation (109) yields,

$$\mu(K - S_1) - r_2 J_1 S_1 + \gamma_2 J_1 e^{-\mu\omega} = 0 . \quad 118$$

Hence,

$$J_1 = \frac{\mu(K - S_1)}{(r_2 S_1 - \gamma_2 e^{-\mu\omega})} \quad 119$$

i.e. which on substituting (117) in (119) yields,

$$J_1 = \left(\frac{\mu K - \mu \left(\frac{\mu + \gamma_2}{r_2} \right)}{\left(r_2 \left(\frac{\mu + \gamma_2}{r_2} \right) - \gamma_2 e^{-\mu\omega} \right)} \right), \quad 120$$

which simplifies further to,

$$J_1 = \frac{\mu(\mu + \gamma_2)}{r_2[\mu + \gamma_2(1 - e^{-\mu\omega})]} (R_2 - 1). \quad 121$$

The explicit form of boundary equilibrium is given by

$$E_1 = \left(\frac{\mu + \gamma_2}{r_2}, 0, \frac{\mu(\mu + \gamma_2)}{r_2[\mu + \gamma_2(1 - e^{-\mu\omega})]} (R_2 - 1) \right). \quad 122$$

and it exists if and only if $R_2 > 1$. The infectives with strain B, is exponentially decaying function of the delay parameter ω . Note that when ω is large, corresponding to life long immunity then the form of boundary equilibrium reduces exactly to that form in appendix A.3

3.4.2: Stability Analysis of Boundary Equilibrium

To study the stability of the boundary equilibrium we linearize the system of equations (72 – 77) about $E_1 = (S_1, 0, J_1)$ by letting,

$$x(t) = S(t) - S_1, y(t) = J(t) - J_1, z(t, \tau) = i(t, \tau) \quad 123$$

We obtain the following system of equations

$$\frac{dx(t)}{dt} = -\mu x(t) - r_2 J_1 x(t) - r_2 S_1 y(t) - \int_0^{\infty} r_1(\tau) z(t, \tau) d\tau + \gamma_2 y(t - \omega) e^{-\mu\omega} \quad 124$$

$$\frac{\partial z(t, \tau)}{\partial t} + \frac{\partial z(t, \tau)}{\partial \tau} = -(\mu + \gamma_1) z(t, \tau) - \kappa(\tau) z(t, \tau) \quad 125$$

$$z(t, 0) = S_1 \int_0^{\infty} r_1(\tau) z(t, \tau) d\tau \quad 126$$

$$\frac{dy(t)}{dt} = r_2 J_1 x(t) + r_2 S_1 y(t) - (\mu + \gamma_2) y(t) - \int_0^{\infty} \kappa(\tau) z(t, \tau) d\tau \quad 127$$

Using the same approach (the one used to derive the characteristic equation and reproductive number R_1 for disease-free equilibrium (See section 3.3.1)) we derive the characteristic equation for E_1 :

$$1 = S_1 \int_0^{\infty} r_1(\tau) e^{-\lambda\tau} e^{-(\mu+\gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau \quad 128$$

Defining

$$R_b = S_1 \int_0^{\infty} r_1(\tau) e^{-\lambda\tau} e^{-(\mu+\gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau \quad 129$$

then if $R_b < 1$, $z(t, \tau) \rightarrow 0$ as $t \rightarrow \infty$.

Under the above condition the stability of system (124-127) reduces to the study of the stability of

$$\frac{dx(t)}{dt} = Ax(t) + Cy(t) + Ey(t - \omega) \quad 130$$

$$\frac{dy(t)}{dt} = Bx(t) \quad 131$$

for large t .

where , $A = -(\mu + r_2 J_1)$, $C = r_2 S_1$, $E = -\gamma_2 e^{-\mu\omega}$ and $B = -r_2 J_1$

Now equations (130) and (131) can be expressed as second order delay differential equation.

$$\frac{d^2 y(t)}{dt^2} = B[Ax(t) + By(t) + Ey(t - \omega)], \quad 132$$

Eliminating $x(t)$ in (132) we get,

$$\frac{d^2 y(t)}{dt^2} - A \frac{dy(t)}{dt} - BCy(t) - BEy(t - \omega) = 0 \quad 133$$

Letting $y(t) = e^{\lambda t}$ in (133), yields the characteristic equation

$$\Delta(\lambda, \omega) = \lambda^2 - A\lambda - BC - BEe^{-\omega\lambda} = 0 \quad 134$$

The steady state solution (boundary equilibrium) is asymptotically stable provided that all roots of the characteristic equation (134) have negative real part and it is unstable if there exists a root with positive real part. To establish the stability of boundary equilibrium we need to show that roots of the characteristic equation (134) has negative real parts. Since the characteristic equation is transcendental it is a very complicated task. However with the help of Nyquist criteria we are able to prove the local stability of boundary equilibrium under certain conditions.

Substitute $\lambda = \alpha + i\beta$ in (134) and separating the real and imaginary parts we obtain the system of transcendental equations

$$\alpha^2 - \beta^2 - A\alpha - BC - BEe^{-\alpha\omega} \cos \beta\omega = 0 \quad 135$$

$$2\alpha\beta - A\beta + BEe^{-\alpha\omega} \sin \beta\omega = 0 \quad 136$$

The stability of the system is determined by the sign of those λ satisfying equation (134) if λ is real or the sign of α satisfying equations (135 – 136) if λ is complex.

Now, we mention two results from [19], which will be used later

THEOREM 1: The following are necessary and sufficient conditions for E_1 to be asymptotically stable for every $\omega \geq 0$:

- (a) The real part of every root of $\Delta(\lambda, 0) = 0$ is negative
- (b) For all real β_0 and $\omega \geq 0$, $\Delta(i\beta_0, 0) = 0$

THEOREM 2: As $A < 0$ and $B < 0$, then in the parametric region $-E < C$.

the interior equilibrium E_1 of system (132) is locally asymptotically stable for $0 < \omega < \frac{\pi}{\beta_0}$.

Proof: From (134) it is clear that boundary equilibrium is asymptotically stable for $\omega = 0$ if $-E < C$.

Consider equation (134) and $C[-\omega, \infty)$, the space of all real-valued continuous functions satisfying the initial condition $x(t) = 0$ for $-\omega \leq t < 0$, $x(0^+) = P_1 > 0$, and $\dot{x}(0^+) = P_2 > 0$.

After taking the Laplace transform of (133) and simplifying, we have

$$L(y(s)) \equiv L(s) = \frac{P_1 s + P_2 - AP_1}{s^2 - As - BC - BEe^{-\omega s}} \quad 137$$

The inverse Laplace transform of $L(s)$ will have terms which increase exponentially with t if $L(s)$ has poles with positive real part. Thus it is clear that a condition for stability of boundary equilibrium is that all poles of $L(s)$ have negative real parts. The simplest way of finding whether any poles are located in the right half plane is by use of the Nyquist – plot technique which states that if we let s traverse a curve encircling the right half plane, the curve $L(s)$ will encircle the origin a number of times which is equal to the difference between number of poles and a number of zeros of $L(s)$ in the right half plane. We apply the Nyquist criterion (See appendix A.1, [4], Thingstad and Langeland) to conclude whether $L(s)$ has any pole in the right half-plane. This criterion leads us to the conditions

$$\text{Im } \psi(i\beta_0) > 0 \quad 138$$

$$\text{Re } \psi(i\beta_0) = 0 \quad 139$$

where

$$\psi(s) = s^2 - As - BC - BEe^{-\omega s} = 0, \quad 140$$

β_0 being the smallest positive value of β for which (139) holds. Now,

$$\psi(i\beta_0) = -\beta_0^2 - iA\beta_0 - BC - BE(\cos \beta_0\omega - i \sin \beta_0\omega). \quad 141$$

$$\text{Im } \psi(i\beta_0) = -A\beta_0 + BE \sin \beta_0\omega \quad 142$$

and

$$\text{Re } \psi(i\beta_0) = -\beta_0^2 - BC - BE \cos \beta_0\omega \quad 143$$

Using conditions (138) and (139) using the expressions (142) and (143) and taking account of the fact that $B < 0$ and $E < 0$, we obtain

$$\frac{A}{BE\omega} < \frac{\sin \beta_0\omega}{\beta_0\omega} \quad 144$$

and

$$\beta_0^2 = -BC - BE \cos \beta_0 \omega. \quad 145$$

Since $A < 0$ and $-(CE) < 0$, condition (139) is satisfied for $0 < \omega < \frac{\pi}{\beta_0}$.

Further since $B < 0, E < 0$ we have

$$-BC - BE < -BC - BE \cos \beta_0 \omega < -BC + BE. \quad 146$$

Hence $z = \beta_0^2$ and $z = -BC - BE \cos \beta_0 \omega$ intersect on $0 < \beta_0 < \frac{\pi}{\omega}$.

From equations (143) and (144) we also have (in the parametric region $-E < C$)

$$0 < -BC - BE < \beta_0^2 < -BC + BE, \text{ for } 0 < \beta_0 < \frac{\pi}{\omega}. \quad 147$$

Hence, the upper bound of β_0 given by $\sqrt{BE - BC} = \sqrt{J_1 r_2^2 S_1}$.

Hence we can conclude that in our case the Nyquist criterion holds and the boundary equilibrium of the system (130 – 131) is locally asymptotically stable for all values of ω satisfying

$$0 < \omega < \frac{\pi}{\beta_0}.$$

Combining the results from the existence and stability of boundary equilibrium as mentioned above, we obtain the following,

THEOREM 3: The unique boundary equilibrium

$$E_1 = (S_1, 0, J_1) = \left(\frac{\mu + \gamma_2}{r_2}, 0, \frac{\mu(\mu + \gamma_2)}{r_2[\mu + \gamma_2(1 - e^{-\mu\omega})]}(R_2 - 1) \right) \quad 148$$

exists if and only if $R_2 > 1$. It is locally asymptotically stable for all delay values ω satisfying

$$0 < \omega < \frac{\pi}{\beta_0} \text{ if}$$

$$R_b = \frac{\mu + \gamma_2}{r_2} \int_0^{\infty} r_1(\tau) e^{-\lambda\tau} e^{-(\mu + \gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau < 1 \quad 149$$

and is unstable if $R_b > 1$ for all ω .

This result can be interpreted in the following way: When the temporary immunity is not too large and the reproductive number for A is less than one, then strain B persists. Also, when the reproductive number for strain A is greater than one strain B will not persist for any immunity period.

3.5: Endemic Equilibrium

It is known that the co-circulating strains of pathogen can coexist. See references [3, 8, 21, 23, 36, 49, 51, 57]. The stationary coexistence solution is an endemic equilibrium whose components we assume to be positive, [3, 9, 22, 53]. In this section we establish the existence of endemic equilibrium and locate its explicit form. We also study its local stability.

3.5.1: Existence of Endemic Equilibrium

Let $E^* = (S^*, i^*(\tau), J^*)$ be an endemic equilibrium of system (72 – 77). It follows from (110) that

$$\frac{\partial i^*(\tau)}{\partial \tau} = -(\mu + \gamma_1)i^*(\tau) - \kappa(\tau)i^*(\tau), \quad 150$$

which can be integrated to get,

$$i^*(\tau) = i^*(0)e^{-(\mu + \gamma_1)\tau - \int_0^\tau \kappa(v) dv}, \quad 151$$

Substituting in (111), we find

$$i^*(0) = i^*(0) S^* \int_0^{\infty} r_1(\tau) e^{-\lambda\tau} e^{-(\mu + \gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau \quad 152$$

$$= i^*(0) S^* \frac{R_1}{K}. \quad 153$$

which has a solution $i^*(0) > 0$ if and only if

$$S^* = \frac{R_1}{K}. \quad 154$$

We can express equation (111) as

$$i^*(0) = S^* W_1, \quad 155$$

where, $W_1 := \int_0^{\infty} r_1(\tau) i^*(\tau) d\tau$. 156

Using (155) in (151) we get,

$$i^*(\tau) = S^* W_1 e^{-(\mu + \gamma_1)\tau - \int_0^{\tau} \kappa(v) dv}. \quad 157$$

Define

$$W_2 := \int_0^{\infty} \kappa(\tau) i^*(\tau) d\tau = S^* W_1 \int_0^{\infty} \kappa(\tau) e^{-(\mu + \gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau \quad 158$$

$$= S^* W_1 G, \quad 159$$

$$\text{where } G := \int_0^{\infty} \kappa(\tau) e^{-(\mu + \gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau. \quad 160$$

Now, (109) and (112) can be expressed simply as

$$\mu K = (\mu + W_1 + r_2 J^*) S^* - \gamma_2 J^* e^{-\mu\omega} \quad 161$$

$$W_2 = ((\mu + \gamma_2) - r_2 S^*) J^* \quad 162$$

From (162),

$$W_2 = (\mu + \gamma_2) \left(1 - \frac{r_2 S^*}{\mu + \gamma_2} \right) J^* \quad 163$$

Using (154) and (106) in (166), we get

$$W_2 = (\mu + \gamma_2) \left(1 - \frac{R_2}{R_1}\right) J^* \quad 164$$

Since $W_2 > 0$, there exists a positive solution of (164) if and only if

$$\frac{R_2}{R_1} < 1 \text{ i.e. } R_2 < R_1 \quad 165$$

When $R_2 < R_1$, solving equation (164) for J^* , we have

$$0 < J^* = \frac{W_2}{(\mu + \gamma_2) \left(1 - \frac{R_2}{R_1}\right)}. \quad 166$$

Substituting (166) in (161) we get

$$\mu K = \left((\mu + W_1) + r_2 \frac{W_2 R_1}{(\mu + \gamma_2)(R_1 - R_2)} \right) S^* - \frac{\gamma_2 e^{-\mu\omega} W_2 R_1}{(\mu + \gamma_2)(R_1 - R_2)}. \quad 167$$

Using $W_2 = S^* W_1 G$ from (159) we get

$$\mu K = \left((\mu + W_1) + r_2 \frac{S^* W_1 G R_1}{(\mu + \gamma_2)(R_1 - R_2)} \right) S^* - \frac{\gamma_2 e^{-\mu\omega} S^* W_1 G R_1}{(\mu + \gamma_2)(R_1 - R_2)} \quad 168$$

Now dividing both the sides by S^* and using $S^* = \frac{K}{R_1}$, we obtain

$$\mu R_1 = \mu + W_1 + \frac{r_2 W_1 G K}{(\mu + \gamma_2)(R_1 - R_2)} - \frac{\gamma_2 e^{-\mu\omega} W_1 R_1 G}{(\mu + \gamma_2)(R_1 - R_2)}. \quad 169$$

From (169), simplifying we get,

$$\mu R_1 - \mu = W_1 + W_1 \left(\frac{r_2 G K}{(\mu + \gamma_2)(R_1 - R_2)} - \frac{\gamma_2 e^{-\mu\omega} R_1 G}{(\mu + \gamma_2)(R_1 - R_2)} \right) \quad 170$$

that leads to,

$$\mu(R_1 - 1) = W_1 + W_1 \left(\frac{r_2 G K - \gamma_2 e^{-\mu\omega} R_1 G}{(\mu + \gamma_2)(R_1 - R_2)} \right), \quad 171$$

which implies that $W_1 > 0$ if $R_1 > 1$, assuming $r_2 K > \gamma_2 R_1$. This means that the number of people in susceptible population is always going to be bigger than the reproductive number for strain A or strain B.

Solving (171) for w_1 yields

$$W_1 = \frac{\mu(R_1 - 1)(\mu + \gamma_2)(R_1 - R_2)}{\left[((\mu + \gamma_2)(R_1 - R_2)) + (r_2 GK - \gamma_2 e^{-\mu\omega} R_1 G) \right]} \quad 172$$

We know $w_2 = S^* w_1 G$ and $S^* = \frac{K}{R_1}$ therefore

$$W_2 = \frac{KG \mu(R_1 - 1)(\mu + \gamma_2)(R_1 - R_2)}{R_1 \left[((\mu + \gamma_2)(R_1 - R_2)) + (r_2 GK - \gamma_2 e^{-\mu\omega} R_1 G) \right]} \quad 173$$

This leads to,

THEOREM 4: If $R_1 > 1$, $R_1 > R_2$ and $r_2 K > \gamma_2 R_1$, then there exists a unique endemic equilibrium $E^* = (S^*, i^*(\tau), J^*)$ given by

$$S^* = \frac{R_1}{K}, \quad i^*(\tau) = \frac{KW_1}{R_1} e^{-(\mu + \gamma_1)\tau - \int_0^\tau \kappa(v) dv} \quad \text{and} \quad J^* = \frac{W_2}{(\mu + \gamma_2) \left(1 - \frac{R_2}{R_1} \right)} \quad 174$$

Note that the infectives with strain A and strain B, are exponentially decaying functions of the delay parameter ω . Furthermore when ω is large, corresponding to life long immunity then the form of endemic equilibrium reduces exactly to that form in appendix A.3

3.5.2: Stability Analysis of the Endemic Equilibrium

We investigate the local stability of the endemic equilibrium E^* , by linearizing the basic system (72 – 77) about $E^* = (S^*, i^*(\tau), J^*)$.

Let

$$x(t) = S(t) - S^*, y(t, \tau) = i(t, \tau) - i^*(\tau), z(t) = J(t) - J^* \quad 175$$

The linearization results in the perturbed equations

$$\frac{dx(t)}{dt} = -(\mu + W_1 + r_2 J^*)x(t) - r_2 S^* z(t) - S^* \int_0^\infty r_1(\tau) y(t, \tau) d\tau + \gamma_2 z(t - \omega) e^{-\mu\omega} \quad 176$$

$$\frac{\partial y(t, \tau)}{\partial t} + \frac{\partial y(t, \tau)}{\partial \tau} = -(\mu + \gamma_1) y(t, \tau) - \kappa(\tau) y(t, \tau) \quad 177$$

$$y(t, 0) = S^* \int_0^\infty r_1(\tau) y(t, \tau) d\tau + W_1 x(t) \quad 178$$

$$\frac{dz(t)}{dt} = r_2 J^* x(t) + r_2 S^* z(t) - (\mu + \gamma_2) z(t) - \int_0^\infty \kappa(\tau) y(t, \tau) d\tau \quad 179$$

Suppose $x(t) = x_0 e^{\lambda t}$, $y(t, \tau) = \hat{y}(\tau) e^{\lambda(t-\tau)}$, and $z(t) = z_0 e^{\lambda t}$. Substituting these variables into system (176 – 179) and solving for $\hat{y}(\tau)$, with initial condition $\hat{y}(0)$, leads to the system,

$$(\lambda + \mu + W_1 + r_2 J^*) x_0 + r_2 S^* z_0 - S^* \int_0^{\infty} r_1(\tau) \hat{y}(\tau) e^{-\lambda \tau} d\tau + \gamma_2 z_0 e^{-\omega(\lambda+\mu)} = 0, \quad 180$$

$$-r_2 J^* x_0 + (\lambda + \mu + \gamma_2 - r_2 S^*) z_0 - \int_0^{\infty} \kappa(\tau) \hat{y}(\tau) e^{-\lambda \tau} d\tau = 0, \quad 181$$

$$\hat{y}(\tau) = \left(S^* \int_0^{\infty} r_1(\tau) \hat{y}(\tau) e^{-\lambda \tau} d\tau + W_1 x_0 \right) e^{-(\lambda + \mu)\tau - \int_0^{\tau} \kappa(v) dv}. \quad 182$$

These expressions can be simplified by defining the functions

$$H(\lambda) := \int_0^{\infty} r_1(\tau) \hat{y}(\tau) e^{-\lambda \tau} d\tau, \quad 183$$

$$Q(\lambda) := \int_0^{\infty} \kappa(\tau) \hat{y}(\tau) e^{-\lambda \tau} d\tau, \quad 184$$

$$P_1(\lambda) := \int_0^{\infty} r_1(\tau) e^{-\lambda\tau} e^{-(\mu+\gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau, \quad 185$$

$$P_2(\lambda) := \int_0^{\infty} \kappa(\tau) e^{-\lambda\tau} e^{-(\mu+\gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau, \quad 186$$

Multiply $r_1(\tau)e^{-\lambda\tau}$ with $\hat{y}(\tau)$ in (182) and integrating from 0 to ∞ , we get

$$\begin{aligned} \int_0^{\infty} e^{-\lambda\tau} r_1(\tau) \hat{y}(\tau) d\tau &= \left(S^* \int_0^{\infty} r_1(\tau) \hat{y}(\tau) e^{-\lambda\tau} d\tau \int_0^{\infty} e^{-\lambda\tau} e^{-(\lambda+\mu)\tau - \int_0^{\tau} \kappa(v) dv} r_1(\tau) d\tau \right) \\ &+ \left(W_1 x_0 \int_0^{\infty} e^{-\lambda\tau} r_1(\tau) \hat{y}(\tau) d\tau e^{-(\lambda+\mu)\tau - \int_0^{\tau} \kappa(v) dv} \right). \end{aligned} \quad 187$$

Using (183) through (186), the above equation can be written as

$$H(\lambda) = S^* H(\lambda) P_1(\lambda) + W_1 P_1(\lambda) x_0, \quad 188$$

which leads to

$$H(\lambda) = \frac{W_1 P_1(\lambda) x_0}{1 - S^* P_1(\lambda)}. \quad 189$$

Now multiply $\kappa(\tau)e^{-\lambda\tau}$ with $\hat{y}(\tau)$ in (182) and integrate from 0 to ∞ . We get

$$\int_0^{\infty} e^{-\lambda\tau} r_1(\tau) \hat{y}(\tau) d\tau = \left(S^* \int_0^{\infty} r_1(\tau) \hat{y}(\tau) e^{-\lambda\tau} d\tau \int_0^{\infty} e^{-\lambda\tau} e^{-\lambda\tau} e^{-\int_0^{\tau} \kappa(v) dv} r_1(\tau) d\tau \right) + \left(W_1 x_0 \int_0^{\infty} e^{-\lambda\tau} r_1(\tau) \hat{y}(\tau) d\tau e^{-\int_0^{\tau} \kappa(v) dv} \right). \quad 190$$

Again using (183) through (186),

$$Q(\lambda) = S^* H(\lambda) P_2(\lambda) + W_1 P_2(\lambda) x_0, \quad 191$$

$$Q(\lambda) = \left(\frac{S^* W_1 P_1(\lambda)}{1 - S^* P_1(\lambda)} + W_1 \right) P_2(\lambda) x_0. \quad 192$$

Using (183) through (186) in equations (180) and (181) can be written as

$$S^* H(\lambda) = (\gamma_2 e^{-\omega(\lambda+\mu)} - r_2 S^*) z_0 - (\lambda + \mu + W_1 + r_2 J^*) x_0, \quad 193$$

$$Q(\lambda) = -r_2 J^* x_0 + (\lambda + \mu + \gamma_2 - r_2 S^*) z_0. \quad 194$$

Substituting (189) and (192) in (193) we get

$$\left(\frac{W_1}{1-S^*P_1(\lambda)} + \lambda + \mu + r_2J^* \right) x_0 = (\gamma_2 e^{-\omega(\lambda+\mu)} - r_2S^*) z_0. \quad 195$$

Substituting (189) and (192) in (194) we get

$$\left[\frac{W_1P_2(\lambda)}{1-S^*P_1(\lambda)} + r_2J^* \right] x_0 = (\lambda + \mu + \gamma_2 - r_2S^*) z_0. \quad 196$$

From (195) and (196) we obtain the characteristic equation for the endemic equilibrium

$$(r_2S^* - \gamma_2 e^{-\omega(\lambda+\mu)}) \left[\frac{W_1(\omega)P_2(\lambda)}{1-S^*P_1(\lambda)} + r_2J^*(\omega) \right] + (\lambda + \mu + \gamma_2 - r_2S^*) \left[\lambda + \mu + r_2J^*(\omega) + \frac{W_1(\omega)}{1-S^*P_1(\lambda)} \right] = 0. \quad 197$$

This is the characteristic equation of the endemic equilibrium. The equation is transcendental and hence it is difficult to determine when all the roots of the characteristic equation have negative real parts which determines stability of the endemic equilibrium. In order to gain insight into the stability of endemic equilibrium we consider a special case where the rate of mutation and rate of transmission are constants i.e. they are no longer dependent on infection stages. This assumption leads to a delay differential equation (DDE) governed model.

CHAPTER 4: CONSTANT MUTATION CASE

To explore deeper into the transmission dynamics of the disease we must investigate stability of endemic equilibrium. In chapter 3, we found the characteristic equation of the endemic equilibrium to be very complicated and as result difficult to analyze, hence we make the following assumptions. In this chapter, we consider the system which is independent of the infection stages. We also assume that the rate of mutation is constant. Due to these new assumptions the system no longer contains a PDE and it is now governed by DDE's. We find the explicit form of endemic equilibrium, reproductive numbers and develop the criteria for a Hopf bifurcation to arise.

We assume that the mutation rate from Strain A to Strain B is constant and the infection rate of Strain A is independent of the infection stages. We define these constant rates as

$$\kappa(\tau) := k \text{ and } r_1(\tau) := r_1 \tag{198}$$

Also, let the total infectives be $I(t) := \int_0^{\infty} i(t, \tau) d\tau$. Integrating the equation for $i(t, \tau)$ in (73) with respect to τ and using the initial conditions $i(t, 0)$ eliminates the PDE to give the system of DDE's,

$$\frac{dS(t)}{dt} = \mu(K - S(t)) - r_1 I(t) S(t) - r_2 J(t) S(t) + \gamma_2 J(t - \omega) e^{-\mu\omega} \tag{199}$$

$$\frac{dI(t)}{dt} = r_1 S(t)I(t) - (\mu + \gamma_1 + k)I(t) \quad 200$$

$$\frac{dJ(t)}{dt} = r_2 J(t)S(t) - (\mu + \gamma_2)J(t) + kI(t) \quad 201$$

The reproductive numbers of Strains A and B, R_1 and R_2 , for system (199 – 201), are now

$$R_1 = \frac{r_1 K}{(\mu + \gamma_1 + k)}, \text{ and } R_2 = \frac{r_2 K}{(\mu + \gamma_2)}. \quad 202$$

The only boundary equilibrium with $I = 0$ and $J > 0$ exists if $R_2 > 1$. This boundary equilibrium is stable if $R_1 < R_2$ and unstable if $R_1 > R_2$.

4.1: Existence of Endemic Equilibrium

For $\kappa(\tau) = k$, the term defined in (160), now becomes

$$G := \int_0^{\infty} \kappa(\tau) e^{-(\mu + \gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau \quad 203$$

$$G := \frac{k}{(\mu + \gamma_1 + k)} \quad 204$$

From (174) we have,

$$S^* = \frac{K}{R_1}, \quad i^*(\tau) = \frac{KW_1}{R_1} e^{-(\mu + \gamma_1 + k)\tau}, \quad J^* = \frac{GKW_1}{(\mu + \gamma_2)(R_1 - R_2)} \quad 205$$

Using (202) in (173)

$$S^* = \frac{\mu + \gamma_1 + k}{r_1}, \quad 206$$

Using $W_1 = \frac{\mu(R_1 - 1)(\mu + \gamma_2)(R_1 - R_2)}{[(\mu + \gamma_2)(R_1 - R_2)] + (r_2 GK - \gamma_2 e^{-\mu\omega} R_1 G)}$, in 205

$$J^* = \frac{k\mu(R_1 - 1)K}{(\mu + \gamma_1 + k)[(\mu + \gamma_2)(R_1 - R_2)] + (r_2 GK - \gamma_2 e^{-\mu\omega} R_1 G)}. \quad 207$$

Next, we find I^* for $i^*(\tau)$ given in (173) as,

$$i^*(\tau) = \frac{KW_1}{R_1} e^{-(\mu + \gamma_1 + k)\tau}. \quad 208$$

Integrating (208) from 0 to ∞ , yields

$$\int_0^{\infty} i^*(\tau) d\tau = \frac{KW_1}{R_1} \int_0^{\infty} e^{-(\mu + \gamma_1 + k)\tau} d\tau, \quad 209$$

$$I^* = \frac{KW_1}{R_1} \frac{1}{(\mu + \gamma_1 + k)}. \quad 210$$

Using $R_1 = \frac{r_1 K}{(\mu + \gamma_1 + k)}$ in (210) we get,

$$I^* = \frac{W_1}{r_1} = \frac{1}{r_1} \cdot \frac{\mu(R_1 - 1)(\mu + \gamma_2)(R_1 - R_2)}{[(\mu + \gamma_2)(R_1 - R_2)] + (r_2 GK - \gamma_2 e^{-\mu\omega} R_1 G)}, \quad 211$$

The endemic equilibrium so obtained is

$$S^* = \frac{\mu + \gamma_1 + k}{r_1}, \quad J^* = \frac{k\mu(R_1 - 1)K}{(\mu + \gamma_1 + k)[(\mu + \gamma_2)(R_1 - R_2)] + (r_2 GK - \gamma_2 e^{-\mu\omega} R_1 G)} \quad \text{and}$$

$$I^* = \frac{1}{r_1} \cdot \frac{\mu(R_1 - 1)(\mu + \gamma_2)(R_1 - R_2)}{[(\mu + \gamma_2)(R_1 - R_2)] + (r_2 GK - \gamma_2 e^{-\mu\omega} R_1 G)}. \quad 212$$

We see that the endemic equilibrium $E^* = (S^*, I^*, J^*)$ exists if and only if $R_1 > 1$, $R_1 > R_2$ and $r_2 K > \gamma_2 R_1$ for all values of ω .

Note that the infectives with strain A and strain B, are exponentially decaying functions of the delay parameter ω . Furthermore when ω is large, corresponding to life long immunity the form of endemic equilibrium reduces exactly to that form in appendix A.3

4.2: Hopf Bifurcation Analysis of Endemic Equilibrium

In this section we determine criteria for Hopf bifurcation using the time delay as the bifurcation parameter. Let $E^* = (S^*, I^*, J^*)$ denote the unique endemic equilibrium point where $S^*, I^*, J^* \geq 0$.

Setting $\frac{dS}{dt} = 0$ in equation (199) we get,

$$\mu(K - S^*) - r_1 I^* S^* - r_2 J^* S^* + \gamma_2 J^* e^{-\mu\omega} = 0 \tag{213}$$

Dividing throughout by S^* and using $S^* = \frac{K}{R_1}$, the above equation can be written as

$$r_2 J^* + \mu = \mu \frac{K}{S^*} - r_1 I^* - \gamma_2 \frac{J^*}{S^*} e^{-\mu\omega} \tag{214}$$

Using (214), and the assumption of constant mutation and transmission rates, we obtain the characteristic equation for the system (199 – 201):

$$(r_2 S^* - \gamma_2 e^{-\alpha(\lambda+\mu)}) \left[r_2 J^* + r_1 I^* \frac{k}{\lambda} \right] + (\lambda + \mu + \gamma_2 - r_2 S^*) \left[\lambda + \mu \frac{K}{S^*} - (e^{-\mu\omega} \gamma_2) \frac{J^*}{S^*} + r_1 I^* \frac{(\mu + \gamma_1 + k)}{\lambda} \right] = 0 \quad 215$$

Simplifying equation (215) we get,

$$\lambda^3 + \lambda^2 \left(\frac{\mu K}{S^*} - \frac{\gamma_2 J^* e^{-\mu\omega}}{S^*} + \frac{k I^*}{J^*} \right) + \lambda \left(r_1^2 J^* S^* + \frac{\mu k K I^*}{S^* J^*} - \frac{\gamma_2 k I^* e^{-\mu\omega}}{S^*} + r_2^2 J^* S^* \right) + r_1^2 k S^* I^* + k r_1 r_2 I^* S^* = e^{-\lambda\omega} \left[\lambda (r_2 \gamma_2 J^* e^{-\mu\omega}) + k \gamma_2 r_1 I^* e^{-\mu\omega} \right] \quad 216$$

Note that for large ω that this transcendental equation reduces to the cubic equation given in appendix A.3. Equation (216) can be expressed as

$$\lambda^3 + A_1 \lambda^2 + A_2 \lambda + A_3 = e^{-\omega\lambda} (T_1 \lambda + T_2). \quad 217$$

where $A_1 = \frac{\mu K}{S^*} - \frac{\gamma_2 J^* e^{-\mu\omega}}{S^*} + \frac{k I^*}{J^*}$, $A_2 = r_1^2 J^* S^* + \frac{\mu k K I^*}{S^* J^*} - \frac{\gamma_2 k I^* e^{-\mu\omega}}{S^*} + r_2^2 J^* S^*$, $A_3 = r_1^2 k S^* I^* + k r_1 r_2 I^* S^*$,

$T_1 = r_2 \gamma_2 J^* e^{-\mu\omega}$ and $T_2 = k \gamma_2 r_1 I^* e^{-\mu\omega}$.

It is the sign of $\text{Re}(\lambda)$ for equation (217) that determines the stability.

We set $\lambda = \alpha + i\beta$ in equation (217) and separating real and imaginary parts, we obtain the following equations,

$$(\alpha^3 - 3\alpha\beta^2) + A_1(\alpha^3 - \beta^2) + A_2\alpha + A_3 = e^{-\alpha\omega} [\cos \omega\beta(T_1\alpha + T_2) + \sin \omega\beta(T_1\beta)], \quad 218$$

$$3\alpha^2\beta^2 - \beta^3 + 2A_1\alpha\beta + A_2\beta = e^{-\alpha\omega} [\sin \omega\beta(-(T_1\alpha + T_2)) + (T_1\beta)\cos \omega\beta], \quad 219$$

Let ω_1^* be such that $\alpha(\omega_1^*) = 0$. Then equations (218 – 219) reduce to

$$-A_1\beta_1^{*2} + A_3 = [\cos \omega_1^*\beta_1^*(T_2) + \sin \omega_1^*\beta_1^*(T_1\beta_1^*)], \quad 220$$

$$-\beta_1^{*3} + A_2\beta_1^* = [\cos \omega_1^*\beta_1^*(T_2) + \sin \omega_1^*\beta_1^*(T_1\beta_1^*)], \quad 221$$

where $\beta_1^* = \beta_1(\omega_1^*)$.

Squaring and adding the equations (220 – 221) and simplifying we arrive at

$$\beta_1^{*6} + \beta_1^{*4}(A_1^2 - 2A_2) + \beta_1^{*2}(A_2^2 - 2A_1A_3 + T_1^{*2}) + A_3^2 - T_2^2 = 0 \quad 222$$

Since E^* is stable for ω large, the roots of the corresponding characteristic equation,

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0 \tag{223}$$

must have negative real parts and hence satisfy the Routh-Hurwitz conditions for a cubic polynomial. (See Appendix A.3). See references [1, 32, 45, 46]. Equation (222) is a cubic equation in β_1^{*2} that has one or more real roots, β_0^{*2} , since when $\beta_1^* = 0$, the left-hand side of equation (222) is negative if $A_3^2 < T_2^2$, while for sufficiently large values of β_1^* it is positive. The left hand side of the equation (222) is positive for sufficiently large values of β_1^* and also $\beta_1^* = 0$ if $A_3^2 > T_2^2$. Hence equation (222) has at least one positive real root for β_1^{*2} .

We need the following result:

Lemma 1: Define

$$\Delta = \frac{4}{27}b_2^3 - \frac{1}{27}b_1^2b_2^2 + \frac{4}{27}b_1^3b_3 - \frac{2}{3}b_1b_2b_3 + b_3^2. \tag{224}$$

Suppose $b_3 > 0$. Then necessary and sufficient conditions for the cubic equation

$$w^3 + b_1w^2 + b_2w + b_3 = 0 \tag{225}$$

to have at least one simple positive root for w are:

(i) Either (a) $b_1 < 0, b_2 \geq 0$, and $b_1^2 > 3b_2$ or (b) $b_2 < 0$,

and

(ii) $\Delta < 0$.

Proof: Write

$$f(w) = w^3 + b_1 w^2 + b_2 w + b_3, \quad 226$$

then

$$f'(w) = 3w^2 + 2b_1 w + b_2. \quad 227$$

If $f(w) = 0$ has a real positive simple root it must have three simple real roots, one negative and two strictly positive. Hence $f(w)$ must have two real turning points, one at $w = \alpha$ and one at $w = \beta$, and the second turning point must occur at a positive value of w . For $f'(w)$ to have two strictly positive real roots (or one strictly positive and one zero real root) we must have $b_1 < 0, b_2 \geq 0$ and $b_1^2 > 3b_2$, and for $f'(w)$ to have one strictly negative real root we must have $b_2 < 0$. In addition as $f(\alpha) > f(0) > 0$ and $f(\beta) < 0$ we must have

$$\Delta = f(\alpha)f(\beta) < 0.$$

Now

$$\alpha + \beta = -\frac{2b_1}{3}, \quad \alpha\beta = -\frac{b_2}{3}. \quad 228$$

Hence

$$\Delta = f(\alpha)f(\beta) \quad 229$$

$$= (\alpha^3 + b_1\alpha^2 + b_2\alpha + b_3)(\beta^3 + b_1\beta^2 + b_2\beta + b_3) \quad 230$$

$$= (\alpha\beta)^3 + b_1(\alpha\beta)^2(\alpha + \beta) + b_2(\alpha\beta)(\alpha^2 + \beta^2) + b_3(\alpha^3 + \beta^3)$$

$$+ b_1^2(\alpha\beta)^2 + b_1b_2(\alpha\beta)(\alpha + \beta) + b_1b_3(\alpha^2 + \beta^2) + b_2b_3(\alpha + \beta) + b_3^2 + b_2^2(\alpha\beta). \quad 231$$

Using equations (229) and the relationships

$$\alpha^2 + \beta^2 = (\alpha + \beta)^2 - 2\alpha\beta, \quad 232$$

$$\alpha^3 + \beta^3 = (\alpha + \beta)^3 - 3\alpha\beta(\alpha + \beta), \quad 233$$

we deduce that

$$\Delta = \frac{4}{27}b_2^3 - \frac{1}{27}b_1^2b_2^2 + \frac{4}{27}b_1^3b_3 - \frac{2}{3}b_1b_2b_3 + b_3^2. \quad 234$$

It is straightforward to show that the conditions of Lemma are also sufficient for $f(w) = 0$ to have a simple root.

We need to show that with this value of β_1^* there is a ω_1^* such that $\alpha(\omega_1^*) = 0$ and

$\beta_1^* = \beta_1(\omega_1^*)$. Given β_1^* the equations (220 - 221) can be written as

$$P \cos \omega_1^* \beta_1^* + Q \sin \omega_1^* \beta_1^* = M, \quad 235$$

$$Q \cos \omega_1^* \beta_1^* - P \sin \omega_1^* \beta_1^* = N \quad 236$$

where $M^2 + N^2 = P^2 + Q^2 = L_1^2$ with $L_1 > 0$. The equations

$$P = L_1 \cos \xi \quad 237$$

$$Q = L_1 \sin \xi \quad 238$$

determine a unique $\xi \in [0, 2\pi)$, and with this ξ we have

$$L_1 \cos(\omega_1^* \beta_1^* - \xi) = M \quad 239$$

$$L_1 \sin(\omega_1^* \beta_1^* - \xi) = M \quad 240$$

These equations determine $\omega_1^* \beta_1^* - \xi$ uniquely in $[0, 2\pi)$ and hence β_1^* uniquely in $\left[\frac{\xi}{\beta_1^*}, \frac{(2\pi + \xi)}{\beta_1^*} \right]$.

We prove the following theorem analogous to [6, 7, 43], to study Hopf bifurcation.

THEOREM 5: Suppose that β_1^* is the largest positive root of equation (222). Then $i\beta(\omega_1^*) = i\beta_1^*$ is a simple root of equation (217) and $\alpha(\omega) + i\beta(\omega)$ is differentiable with respect to ω in a neighbourhood of $\omega = \omega_1^*$.

Proof: To show that $i\beta(\omega_1^*) = i\beta_1^*$ is a simple root of the equation (217) can be written as $f(\lambda) = 0$ where

$$f(\lambda) = \lambda^3 + A_1 \lambda^2 + A_2 \lambda + A_3 - e^{-\omega \lambda} (T_1 \lambda - T_2) \quad 241$$

Any double root λ satisfies

$$f(\lambda) = 0, \quad f'(\lambda) = 0, \quad 242$$

where

$$f'(\lambda) = 3\lambda^2 + 2A_1\lambda + A_2 - e^{-\omega\lambda}(T_1) + \omega e^{-\omega\lambda}(T_1\lambda - T_2) \quad 243$$

Substituting $\lambda = i\beta_1^*$ and $\omega = \omega_1^*$ in equations (242) and (243) and equating real and imaginary parts,

$$-A_1\beta_1^{*2} + A_3 = T_2 \cos(\omega_1^*\beta_1^*) + T_1\beta_1^* \sin(\omega_1^*\beta_1^*) \quad 244$$

$$-\beta_1^{*3} + A_2\beta_1^* = -T_2 \sin(\omega_1^*\beta_1^*) + T_1\beta_1^* \cos(\omega_1^*\beta_1^*) \quad 245$$

$$-3\beta_1^{*2} + A_2 = (T_1 - \omega_1^*T_2) \cos(\omega_1^*\beta_1^*) - \omega_1^*T_1\beta_1^* \sin(\omega_1^*\beta_1^*) \quad 246$$

$$2A_1\beta_1^{*2} = -(T_1 - \omega_1^*T_2) \sin(\omega_1^*\beta_1^*) - \omega_1^*T_1\beta_1^* \cos(\omega_1^*\beta_1^*) \quad 247$$

Equation (222) can be written as $F(\beta) = 0$, where

$$F(\beta) = (-A_1\beta^2 + A_3)^2 + (\beta^3 - A_2\beta)^2 - (T_2^2 + T_1^2\beta^2) \quad 248$$

$$F(\beta_1^*) = (T_2 \cos(\omega_1^*\beta_1^*) + T_1\beta_1^* \sin(\omega_1^*\beta_1^*))^2 + (T_2 \sin(\omega_1^*\beta_1^*) - T_1\beta_1^* \cos(\omega_1^*\beta_1^*))^2 - (T_2^2 + T_1^2\beta_1^{*2}) = 0 \quad 249$$

$$F'(\beta_1^*) = 2(-A_1\beta_1^{*2} + A_3)(-2A_1\beta_1^*) + 2(\beta_1^{*3} - A_2\beta_1^*)(3\beta_1^{*2} - A_2) - (2T_1^2\beta_1^*) \quad 250$$

Using equation (244 – 247) in equation (250) we get,

$$F'(\beta_1^*) = 0 \quad 251$$

As $F(\beta_1^*) = F'(\beta_1^*) = 0$, β_1^* is a double root of $F(\beta_1^*) = 0$, which is a contradiction as we have assumed that β_1^* is a simple root of equations (218 – 219), which is an analytic equation. So, using the analytic version of the implicit function theorem (Chow & Hale, 1982), $\alpha(\omega) + i\beta(\omega)$ is defined and analytic in a neighbourhood of $\omega = \omega_1^*$.

This completes the proof of Theorem 6.

Now to establish the Hopf bifurcation at $\omega = \omega_1^*$, we need to show that $\frac{d\alpha(\omega_1^*)}{d\omega} \neq 0$.

From equations (218 – 219), differentiating with respect to ω , setting $\omega = \omega_1^*$, $\beta = \beta_1^*$, $\mu = 0$ we get,

$$\begin{aligned} \frac{d\alpha}{d\omega} & \left(-3\beta_1^2 + A_2 + \omega_1^* T_2 \cos(\omega_1^* \beta_1^*) + \omega_1^* T_1 \beta_1^* \sin(\omega_1^* \beta_1^*) - T_1 \cos(\omega_1^* \beta_1^*) \right) \\ & + \frac{d\beta}{d\omega} \left(-2A_1\beta + \omega_1^* T_2 \sin(\omega_1^* \beta_1^*) - \omega_1^* T_1 \beta_1^* \cos(\omega_1^* \beta_1^*) - T_1 \sin(\omega_1^* \beta_1^*) \right) \end{aligned}$$

$$= \left(-\beta_1^* T_2 \sin(\omega_1^* \beta_1^*) - T_1 \beta_1^{*2} \cos(\omega_1^* \beta_1^*) \right), \quad 252$$

$$\frac{d\alpha}{d\omega} \left(2A_1 \beta - \omega_1^* T_2 \sin(\omega_1^* \beta_1^*) + \omega_1^* T_1 \beta_1^* \cos(\omega_1^* \beta_1^*) + T_1 \sin(\omega_1^* \beta_1^*) \right)$$

$$\frac{d\beta}{d\omega} \left(-3\beta_1^2 + A_2 + \omega_1^* T_2 \cos(\omega_1^* \beta_1^*) + \omega_1^* T_1 \beta_1^* \sin(\omega_1^* \beta_1^*) - T_1 \cos(\omega_1^* \beta_1^*) \right)$$

$$= \left(-\beta_1^* T_2 \cos(\omega_1^* \beta_1^*) - T_1 \beta_1^{*2} \sin(\omega_1^* \beta_1^*) \right) \quad 253$$

Let

$$V_1 = \left(-3\beta_1^2 + A_2 + \omega_1^* T_2 \cos(\omega_1^* \beta_1^*) + \omega_1^* T_1 \beta_1^* \sin(\omega_1^* \beta_1^*) - T_1 \cos(\omega_1^* \beta_1^*) \right) \quad 254$$

$$V_2 = \left(2A_1 \beta - \omega_1^* T_2 \sin(\omega_1^* \beta_1^*) + \omega_1^* T_1 \beta_1^* \cos(\omega_1^* \beta_1^*) + T_1 \sin(\omega_1^* \beta_1^*) \right) \quad 255$$

Using V_1 and V_2 , and solving for $\frac{d\alpha}{d\omega}$ we get,

$$\frac{d\alpha}{d\omega} = \frac{3\beta_1^{*6} + \beta_1^{*4} (2A_1^2 - 4A_2) + \beta_1^{*2} (A_2^2 - 2A_1 A_3 - T_1^2)}{V_1^2 + V_2^2} \quad 256$$

Let $\psi = \beta_1^{*2}$, then equation (222) reduces to

$$\varphi(\psi) = \psi^3 + \psi^2(A_1^2 - 2A_2) + \psi(A_2^2 - 2A_1A_3 - T_1^2) + A_3^2 - T_2^2 \quad 257$$

So

$$\frac{d\varphi}{d\psi} = 3\psi^2 + 2\psi(A_1^2 - 2A_2) + (A_2^2 - 2A_1A_3 - T_1^2) \quad 258$$

As β_1^* is the largest single root of equation (222), we have

$$\left. \frac{d\varphi}{d\psi} \right|_{\beta=\beta_1^*} > 0. \quad 259$$

Hence

$$\left. \frac{d\alpha}{d\omega} \right|_{\omega=\omega_1^*} = \frac{\beta_1^{*2} \cdot \left. \frac{d\varphi}{d\psi} \right|_{\beta=\beta_1^*}}{V_1^2 + V_2^2} > 0. \quad 260$$

This leads to the following theorem:

THEOREM 6: Suppose that

- (i) $R_1 > 1$, $R_1 > R_2$, $r_2 K > \gamma_2 R_1$ and the unique endemic equilibrium E^* exists; and
- (ii) Let the conditions of Lemma be satisfied and let β_1^* be the largest simple positive root for equation (222).

Then there is a Hopf bifurcation for the system of equations (199 – 201) as ω passes through ω_1^* leading to a periodic solution that bifurcates from E^* .

We will illustrate the Hopf bifurcation using numerical simulations in the next section.

We will consider a few examples with ω as the bifurcation parameter.

4.3: Numerical Results

Our theoretical results have so far examined Hopf bifurcation in a general *SIR* epidemic model for transmission of pathogen mutation. Although we have shown that Hopf is theoretically possible we have not shown that it can occur at realistic parameter values. In this section we address this question for our model. We consider four examples to illustrate bifurcation. In each of these four examples ω will be our bifurcation parameter. Other parameters are the same as in examples in [23]. Also, in each example will first look at the portraits and graph of the system without delay and then the system with the delay. We have used the `dde23` function of MATLAB to run numerical simulations for our time-delayed system, [29].

Example 1: Let $\gamma_1 = \gamma_2 = \gamma = 0.49$, $\mu = 1/100$, $R_1 = 3$, $R_2 = 2$, $r_1 = 0.2$, $r_2 = 0.01$.

System (199 – 201) becomes

$$\frac{dS(t)}{dt} = \frac{1}{100}(S^0 - S) - \left(\frac{3+6k}{2S^0}I - \frac{1}{S^0}J \right)S + \gamma J(t-\omega)e^{-\mu\omega}, \quad 261$$

$$\frac{dI(t)}{dt} = \frac{3+6k}{2S^0}SI - \frac{1+2k}{2}I, \quad 262$$

$$\frac{dJ(t)}{dt} = \frac{1}{S^0}JS - \frac{1}{2}J + kI, \quad 263$$

and has the endemic equilibrium

$$E^* = \left(\frac{\mu + \gamma + k}{r_1}, \frac{W_1}{r_1}, \frac{GKW_1}{(\mu + \gamma)(R_1 - R_2)} \right) \quad 264$$

where $W_1 = \frac{\mu(R_1 - 1)(\mu + \gamma_2)(R_1 - R_2)}{[(\mu + \gamma_2)(R_1 - R_2)] + (r_2 GK - \gamma_2 e^{-\mu\omega} R_1 G)}$ 265

The linearization of system (199 – 201) at E^* has the characteristic equation

$$f(\lambda) = \lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 - e^{-\mu\lambda}(T_1\lambda + T_2) = 0 \quad 266$$

If all the roots of equation (266) have negative real parts, the endemic equilibrium is stable.

Substituting $\lambda = i\beta_1^*$ in equation (266) we get,

$$\beta_1^{*6} + \beta_1^{*4}(A_1^2 - 2A_2) + \beta_1^{*2}(A_2^2 - 2A_1A_3 + T_1^{*2}) + A_3^2 - T_2^2 = 0 \quad 267$$

If Lemma 1 is satisfied, then β_1^* is the largest positive root and Hopf bifurcation occurs for some ω_1^* .

First we look at the phase plane portraits for the system of equations (See Appendix A.3) without delay.

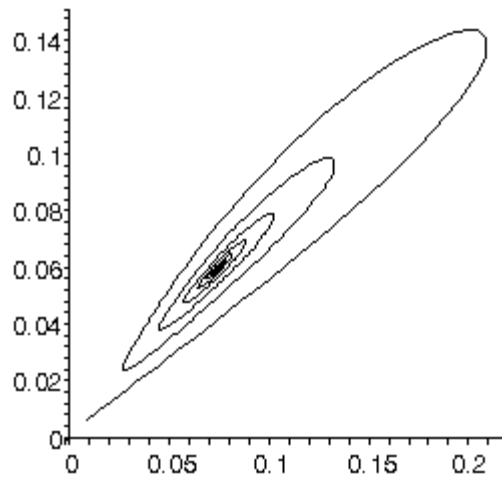


Figure 4: Projected $I - J$ phase plane ($k = 0.135$.)

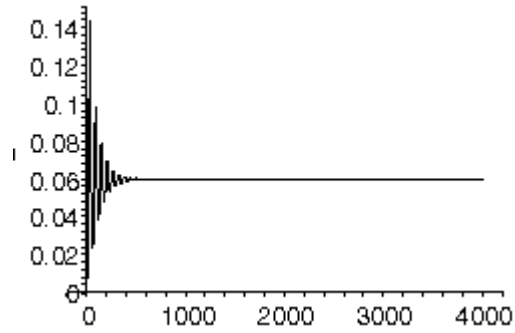


Figure 5: Infectives infected with strain A ($k = 0.135$) vs. time

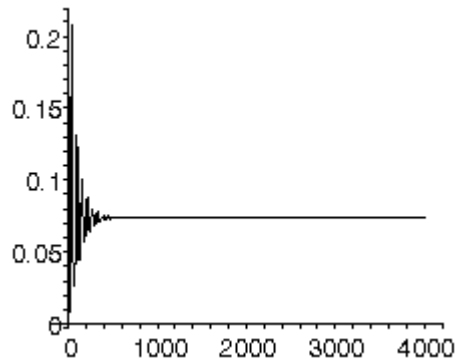


Figure 6: Infectives infected with strain B ($k = 0.135$) vs. time

We see that the endemic equilibrium is asymptotically stable for the system with no delay.

Next we consider the system with delay, and look at the stability of endemic equilibrium.

Table 1: Bifurcation conditions, $k = 0.135$.

ω	b_1	b_2	b_3	$b_1^2 > 3b_2$	Δ
30	0.2436	-0.0017	2.4801e-006	yes	-9.788e-010
50	0.2442	-0.0015	2.3874e-006	yes	6.0743e-011

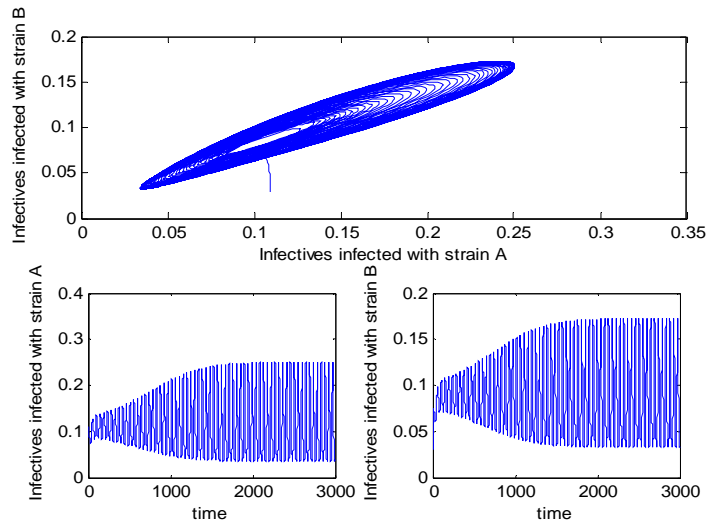


Figure 7: $I - J$ phase plane and graphs (with respect to time) for $\omega = 30$.

The endemic equilibrium is unstable and a stable periodic solution is bifurcated from the endemic equilibrium. The bottom two figures show how the solutions with initial values near the unstable endemic equilibrium rapidly converge to the stable periodic solution. In chapter 3, using the same parameters, for the system without delay it's been shown that the endemic equilibrium is stable and there is no bifurcation. We see that incorporating delay in the system destabilizes the endemic equilibrium, as is seen in the above figures. In the next figure when we increase $\omega = 30$ to $\omega = 50$, we see that the periodic solutions disappear and the endemic equilibrium regains its stability.

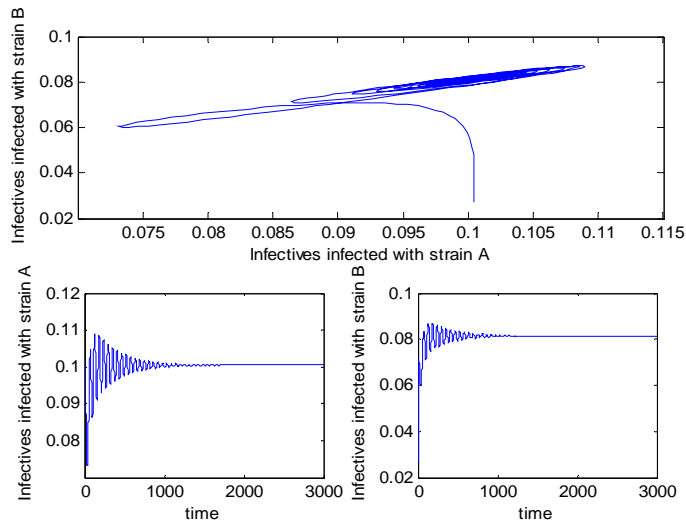


Figure 8: $I - J$ phase plane and graphs (with respect to time) for $\omega = 50$.

The bottom two figures shows transient period of rapid initial oscillations which damp down to the steady persistent equilibrium, showing that endemic equilibrium is stable.

Example 2: We use all the parameters from example 1, except $k = 0.9846$

In this example, again we first look at the graphs for the system without delay.

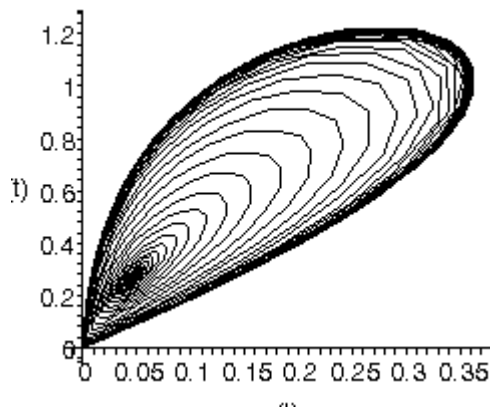


Figure 9: Projected $I - J$ phase plane ($k = 0.9846$.)

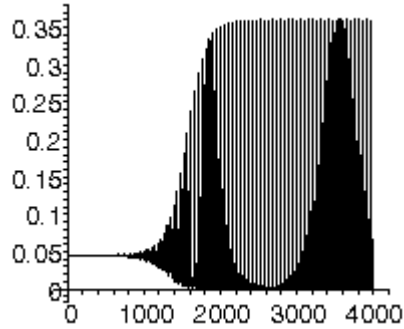


Figure 10: Infectives infected with strain A ($k = 0.9846$) vs. time

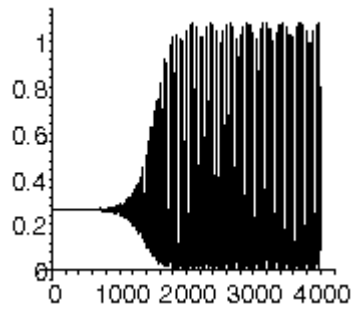


Figure 11: Infectives infected with strain B ($k = 0.9846$) vs. time

We see that the system without delay is unstable. Next we look at the system with delay. We get the plots for $\omega = 30$ and $\omega = 100$.

Table 2: Bifurcation conditions, $k = 0.9846$.

ω	b_1	b_2	b_3	$b_1^2 > 3b_2$	Δ
30	-0.3710	0.0282	0.0011	Yes	-1.056e-007
100	-0.1903	0.0056	3.5905e-004	Yes	-5.951e-010

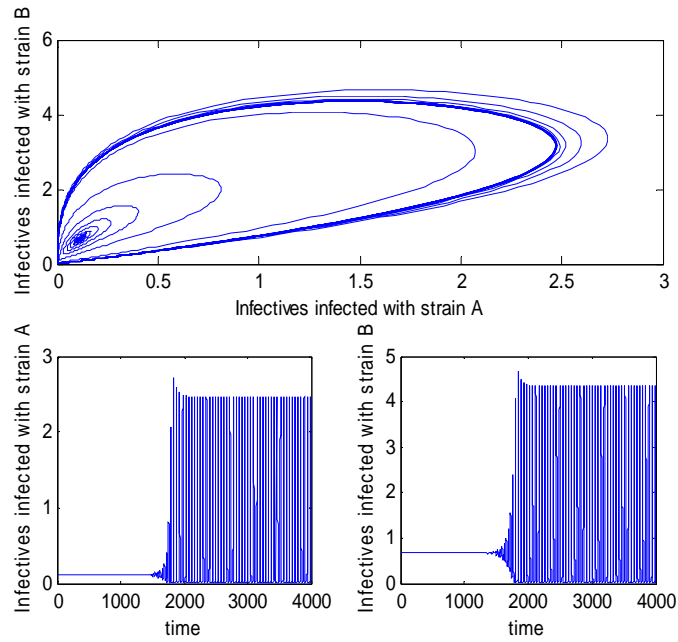


Figure 12: $I - J$ phase plane and graphs (with respect to time) for $\omega = 30$.

The endemic equilibrium $E^* = (7.4230, 0.1134, 0.6698)$ is unstable and a stable periodic solution is bifurcated from the endemic equilibrium. The bottom two figures show how the solutions with initial values near the unstable endemic equilibrium rapidly converge to the stable periodic solution. For this example where the mutation rate $k = 0.9846$, it's been shown for the system without delay, the endemic equilibrium is unstable and there is a stable periodic solution. We run the numerical simulation for a variety of delay values, by randomly picking values from the interval $\omega = 1$ to $\omega = 200$. We observe that for each of the delay value, the lemma is satisfied and there is a Hopf bifurcation. The phase plane portrait and graphs of I (infectives infected with strain A) and J (infectives infected with strain B) with respect to time for $\omega = 30$ and $\omega = 100$ is shown in Fig 21 and Fig 22.

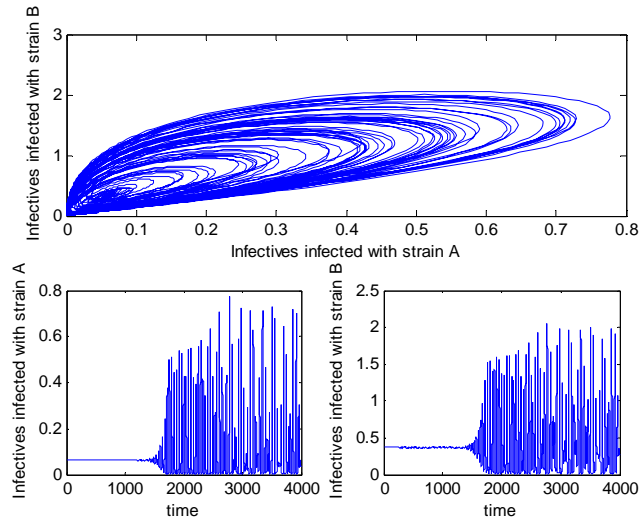


Figure 13: $I - J$ phase plane and graphs (with respect to time) for $\omega = 100$.

The endemic equilibrium $E^* = (7.4230, 0.0621, 0.3671)$ is unstable but we see stable periodic solution.

Example 3: All the parameters same as in example 2 except $k = 9/10$, $R_2 = 0.2$.

The system with out delay has following graphs,

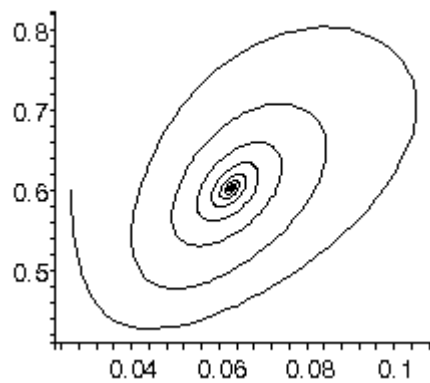


Figure 14: Projected $I - J$ phase plane ($R_2 = 0.2$)

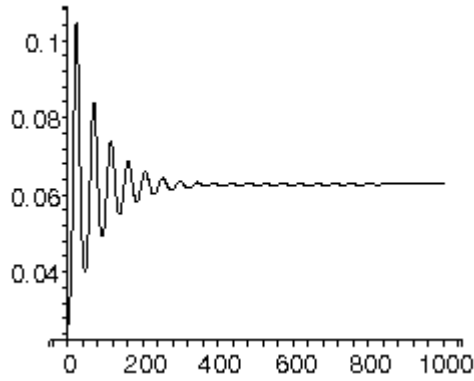


Figure 15: Infectives infected with strain A ($R_2 = 0.2$) vs. time

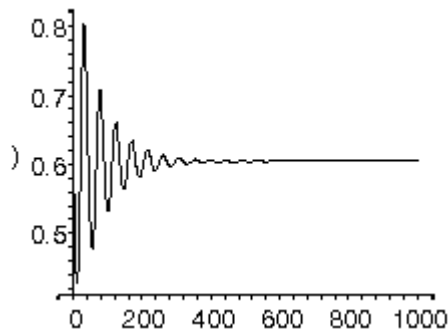


Figure 16: Infectives infected with strain B ($R_2 = 0.2$) vs. time

For the system with out delay we see that the endemic equilibrium is asymptotically stable. Lets see what happens to the system with delay included.

Table 3: Bifurcation conditions, $R_2 = 0.2$.

ω	b_1	b_2	b_3	$b_1^2 > 3b_2$	Δ
10	-1.3731	0.4657	0.0042	Yes	1.6389e-005
50	-0.7083	0.1223	0.0011	Yes	6.8919e-008

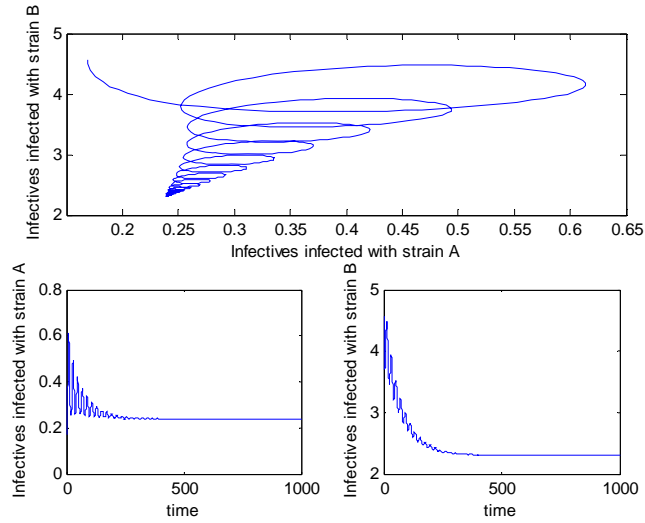


Figure 17: $I - J$ phase plane and graphs (with respect to time) for $\omega = 10$.

The condition for the lemma is not satisfied and we see there are some initial rapid oscillations which damp down to steady equilibrium. Again for this choice of parameters, it's been shown in Appendix A.3 that the endemic equilibrium is asymptotically stable for the system without delay and the same thing can be observed for the system with delay. We see in fig 17, the endemic equilibrium $E^* = (3.3333, 0.2389, 2.3040)$ for $\omega = 10$ is asymptotically stable. Also for $\omega = 50$, examining the bottom two figures in fig 18, we see rapid oscillations which eventually damp down. Note that for both delay values the endemic equilibrium is asymptotically stable.

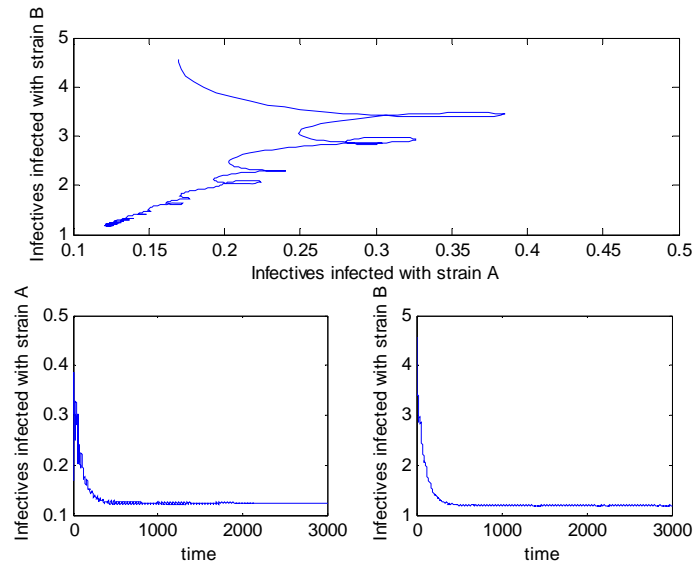


Figure 18: $I - J$ phase plane and graphs (with respect to time) for $\omega = 50$.

In the Fig 24, the bottom two figures show rapid oscillations which damps down to steady equilibrium. The endemic equilibrium $E^* = (3.3333, 0.1239, 1.1951)$ is stable.

Example 4: All the parameters same as in example 3 except $R_2 = 2$.

For the system without delay, we have following phase portraits,

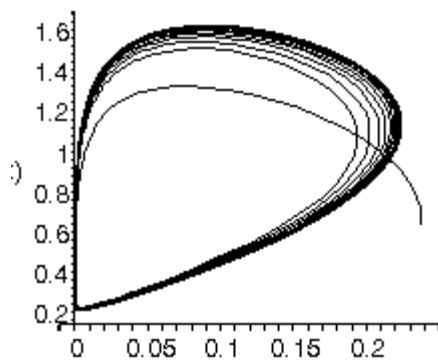


Figure 19: Projected $I - J$ phase plane ($R_2 = 2$)

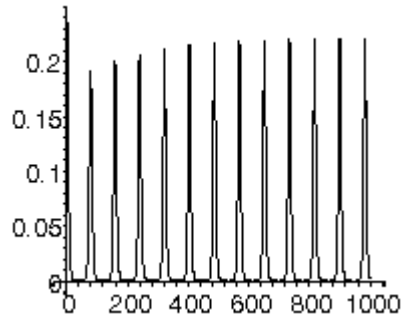


Figure 20: Infectives infected with strain A ($R_2 = 2$) vs. time

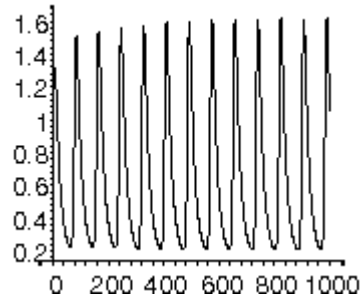


Figure 21: Infectives infected with strain B ($R_2 = 2$) vs. time

The endemic equilibrium for the system without delay is unstable and stable periodic solutions arise. Lets establish stability of endemic equilibrium for the system with delay.

Table 4: Bifurcation conditions, $R_2 = 2$

ω	b_1	b_2	b_3	$b_1^2 > 3b_2$	Δ
25	-1.1941	0.3558	4.4567e-004	Yes	2.2463e-006
100	-0.5676	0.0803	1.0137e-004	Yes	9.6972e-008

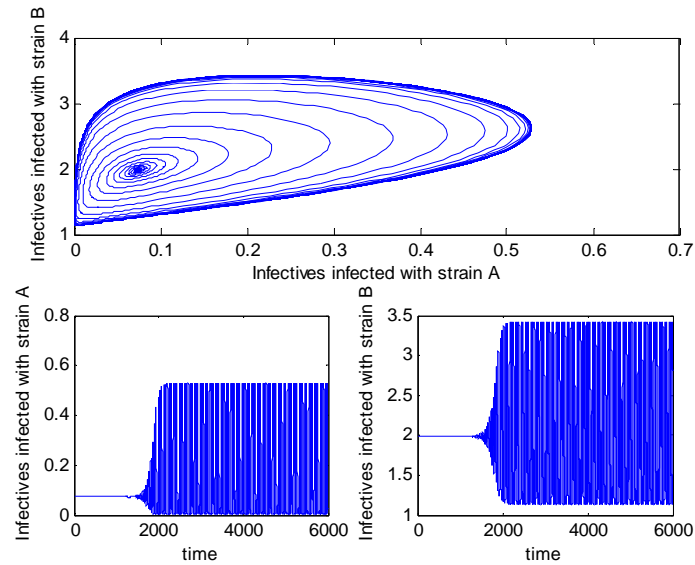


Figure 22: $I - J$ phase plane and graphs (with respect to time) for $\omega = 25$.

The endemic equilibrium $E^* = (3.3333, 0.0735, 1.9834)$ is unstable and a stable periodic solution is bifurcated from the endemic equilibrium. The bottom two figures show how the solutions with initial values near the endemic equilibrium rapidly converge to the stable periodic solution. In this example for the choice of parameter values, the lemma is not satisfied. But still we see Hopf bifurcation in both fig 23 and fig 23. We see that for realistic parameters though the conditions for Hopf bifurcation to occur are not satisfied but it still occurs, which leads us to believe that the instability is arising due to the delay. For the example with similar parameters the system without delay has unstable endemic equilibrium and a stable periodic solution. See figures 19, 20 and 21. Incorporating delay in the system produces similar results.

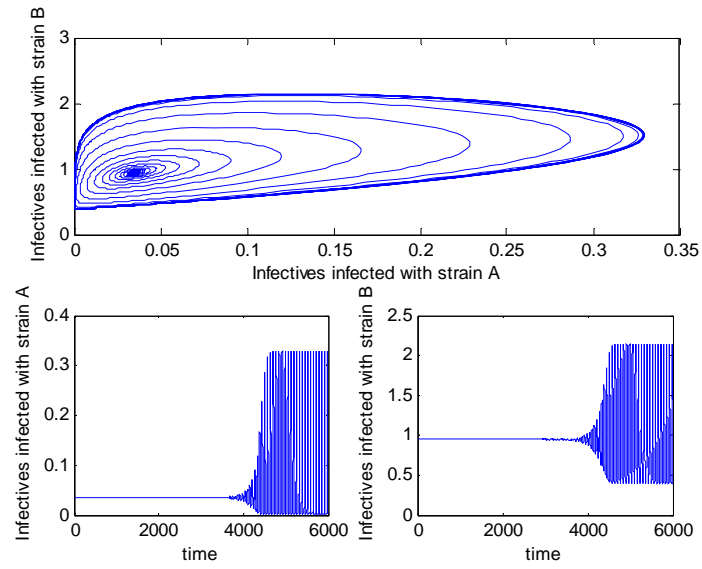


Figure 23: $I - J$ phase plane and graphs (with respect to time) for $\omega = 100$.

The endemic equilibrium $E^* = (3.3333, 0.0350, 0.9444)$ is unstable and a stable periodic solution is bifurcated from the endemic equilibrium.

CHAPTER 5: SUMMARY AND CONCLUSIONS

In this dissertation we have examined a delayed SIR model for the mutation of a pathogen. The delay introduced is due to temporary immunity which for this particular model means that after recovery from the second mutant strain, an individual is immune for some period of time, and then returns to being susceptible again. Our model is based on models previously studied by Li, Ma, Zhou and Hyman.

We have derived the explicit formulas for the reproductive numbers for both the strains and have also established the existence and local asymptotic stability of disease-free equilibrium. We see that incorporating delay does not change the threshold or the asymptotic behavior of disease free equilibrium for this model. We also derive the explicit form of boundary equilibrium, which is the steady state solution when only one strain is present, and establish conditions for its existence. Using Nyquist stability criterion we prove that the boundary equilibrium is locally asymptotically stable for a range of delays bounded by a constant.

The existence of the endemic equilibrium is shown for the model. For the endemic equilibrium we see that the characteristic equation is a transcendental equation and therefore difficult to determine the stability. To investigate the stability of endemic equilibrium we consider a special case which leads to a DDE governed model. For this special case we analyze the stability of the endemic equilibrium. We have also derived the conditions for the possibility of Hopf bifurcation theoretically. Numerical simulations were performed using delay as the bifurcation parameter. Hopf bifurcation has helped us determine the existence of a region of

instability in the neighbourhood of a nonzero endemic equilibrium where the population will survive undergoing regular fluctuations.

It has been shown that for some parameter values the conditions for the occurrence of Hopf bifurcation are met theoretically and the numerical simulations are in conformity with it. We look at four different examples where we fix all the parameter except the ω . In example 6, for $\omega = 50$ the two strains can coexist and eventually stay at constant steady state level. But when $\omega = 30$ we see that there can be sustained periodic oscillations of the two pathogen strains. In examples 7 and 9, for most of the delay parameter choices, there are persistent periodic oscillations of two pathogen strains.

From the analytical and numerical investigations, we observe that the introduction of delay induced by temporary immunity has enormous effect on the dynamics of a disease governed by our model. We found that the delay does destabilize the endemic equilibrium in most of the examples considered in chapter 5. These examples illustrate a wide range of behavior which can exist when a pathogen mutates in the host to create a second mutant strain.

5.1 Future Work

1. Investigating the stability of other special cases where the transcendental equation of endemic equilibrium can be analyzed both analytically and numerically.
2. Generalize the immunity to distributed delay for this model.
3. Applying the method outlined in this dissertation for a particular disease by choosing appropriate functions and parameters.

APPENDIX: A

A.1: Nyquist Criteria

The classical method to investigate ordinary linear differential equations consists of determining the roots of the characteristic equation and computing the response to some special input functions, such as step or a pulse. Often one is interested only in the nature of the possible oscillations of the system. The frequency method developed by Nyquist permits the stability investigation of very complicated linear systems without an excessive amount of labor. From the Nyquist diagram of the system, it can be readily determined whether the system is stable or not.

Nyquist recognized that for rational functions of the form,

$$H(z) \equiv \frac{P(z)}{Q(z)}, \quad 268$$

where $P(z)$ and $Q(z)$ are polynomials in z with no common factors, owing to the Argument Principle, the relationship

$$\frac{1}{2\pi} \Delta_C \arg H(z) = N_P - N_Q \quad 269$$

= total number of zeros of $P(z)$ within C less the total number of zeros of zeros of $Q(z)$ within C

must hold. Since the zeros of Q are the pole singularities H^* , the right-hand side of (2) is merely the difference between the number of zeros and the number of poles of $H(z)$ within C . The left hand side of this expression, of course, can be viewed as the net number times Γ , the image

contour in the w -plane of C under the mapping $w = H(z)$, winds around the origin while s traverses the original contour in the positive direction.

For a stability calculation C becomes the fundamental contour depicted in Fig 24 and the resulting image contour Γ is termed the *Nyquist diagram*.

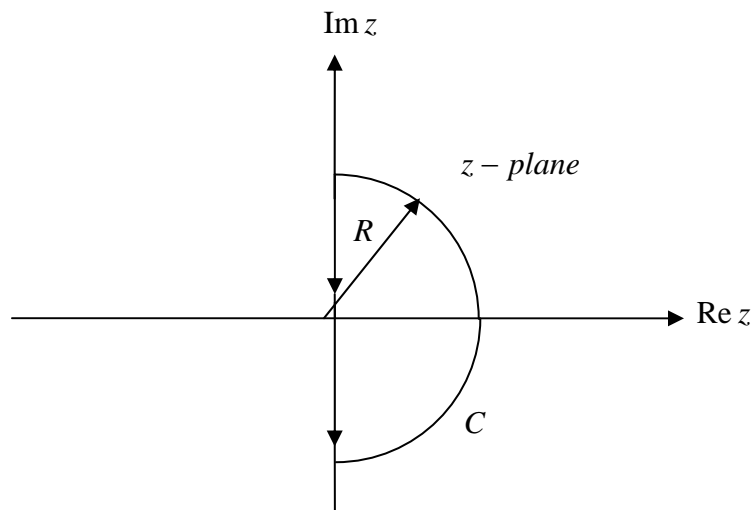


Figure 24: Appropriate contour in the z plane for stability calculation

Nyquist stability criterion: Let $F(z)$ and $G(z)$ be rational functions of z and assume that in the product FG the only cancellation that occur involve poles and zeros in the left half of the complex z -plane. If $w = FG$ has N poles in the right half-plane, then the single-loop feedback system is strictly stable if and only if the Nyquist diagram in the w -plane encircles the point $w = -1$ in the negative or clockwise sense exactly N times.

A.2: Routh-Hurwitz Stability Criterion

For higher order polynomials it is usually easier to employ an indirect approach that tests for the position of all zeros simultaneously. Two variants of such a procedure were developed independently in the late 19th century by Edward Routh (1831 – 1907) and Adolf Hurwitz (1859 – 1919). These methods depend upon inequalities involving the so-called Hurwitz determinants.

$$D_k \equiv \begin{vmatrix} a_1 a_0 & 0 & \cdots & \cdots & \cdots & 0 \\ a_3 a_2 & a_1 a_0 & 0 & \cdots & 0 & \cdots & 0 \\ \cdot & & & & & & \\ \cdot & & & & & & \\ \cdot & & & & & & \\ a_{2k-1} a_{2k-2} & \cdots & \cdots & \cdots & a_k & & \end{vmatrix} \quad k = 1, 2, \dots, n \quad 270$$

(where $a_j = 0$ for $j > n$) associated with the coefficients of $Q(s)$. In its most general and perhaps most efficient) from the Routh – Hurwitz criterion may be stated as

THEOREM 7: If the polynomial

$$Q(s) = a_0 s^n + a_1 s^{n-1} + \cdots + a_{n-1} s + a_n \quad 271$$

has real coefficients, with $a_0 > 0$, then any one of the following conditions is necessary and sufficient for every zero of $Q(s)$ to have negative real part:

(i) $a_n > 0, a_{n-2} > 0, a_{n-4} > 0, \dots; D_1 > 0, D_3 > 0, \dots$

(ii) $a_n > 0, a_{n-2} > 0, a_{n-4} > 0, \dots; D_2 > 0, D_4 > 0, \dots$

(iii) $a_n > 0, a_{n-1} > 0, a_{n-3} > 0, \dots; D_1 > 0, D_3 > 0, \dots$

(iv) $a_n > 0, a_{n-1} > 0, a_{n-3} > 0, \dots; D_2 > 0, D_4 > 0, \dots$

A. 3: EPIDEMIOLOGICAL MODELS FOR MUTATION PATHOGEN

A.3.1: Model Formulation

The model formulation for the origin of the pathogen strain is based on a susceptible-infective-recovered (*SIR*) model with variable infection ages and is governed by partial differential equations (PDEs). The dynamics of mutant are based on an ordinary differential equation. The model is based on the spread of pathogen which can mutate to produce a second, co circulating mutant strain. The original strain is called strain 1 and the second mutant is called to strain 2. We assume that after some time the pathogen mutates and produces strain 2, therefore individuals infected with strain 1 are then carrying strain 2. Let $S(t)$ be the susceptible and $i(t, \tau)$ be the distribution of infectives infected by strain 1 with τ being the time since

infection. $\int_{\tau_1}^{\tau_2} i(t, \tau) d\tau$ represents the total number of infectives between τ_1 and τ_2 . Let $J(t)$

be the infectives infected by strain 2 and let $R(t)$ be the recovered individuals who have recovered and immune to both strains. We further assume that genetic difference between the two strains, or the drift of the mutation is relatively small so that there is perfect cross-immunity; that is, once and individual is recovered from infection by one of the two strains, the individual is immune to both strains.

The dynamics of the transmission in this model are governed by the system

$$\frac{dS(t)}{dt} = \mu(S^0 - S(t)) - \left(\int_0^{\infty} \beta_1(\tau) i(t, \tau) d\tau + \beta_2 J(t) \right) S(t), \quad 272$$

$$\frac{\partial i(t, \tau)}{\partial t} + \frac{\partial i(t, \tau)}{\partial \tau} = -(\mu + \gamma_1)i(t, \tau) - \kappa(\tau)i(t, \tau), \quad 273$$

$$i(t, 0) = S(t) \int_0^{\infty} \beta_1(\tau) i(t, \tau) d\tau, \quad 274$$

$$i(0, \tau) = \psi(\tau), \quad 275$$

$$\frac{dJ(t)}{dt} = \beta_2 J(t) S(t) - (\mu + \gamma_2) J(t) - \int_0^{\infty} \kappa(\tau) i(t, \tau) d\tau, \quad 276$$

$$\frac{dR(t)}{dt} = \gamma_1 \int_0^{\infty} i(t, \tau) d\tau + \gamma_2 J(t) - \mu R(t), \quad 277$$

where μ is the total removal rate which accounts for both natural death and people moving in or out of the susceptible population, γ_1 and γ_2 are the recovery rates of strains 1 and 2, $\kappa(\tau)$ is the rate at which strain 1 is converted to strain 2, $\beta_1(\tau)$ and β_2 are the transmission rates of strain 1 and strain 2, μK is the influx in the susceptible population, and $\psi(\tau)$ is the initial distribution of infectives infected by strain 1.

A.3.2: Threshold of the Epidemics

Assume that the initial distribution of the infectives is zero. Then $E^0 = (S^0, 0, 0)$ is the infection-free equilibrium. The stability of infection free equilibrium determines the thresholds of the epidemic. We investigate the local stability of E^0 as follows.

Since the dynamics of $R(t)$ do not affect the evolution of S , i , and J , we omit the equation for $R(t)$ when studying the growth of the epidemic. Linearizing system (272 – 277) about E^0 , by defining the perturbation variables $x(t) = S(t) - S^0$, $y(t, \tau) = i(t, \tau)$, $z(t) = J(t)$, and using $x(t) = x_0 e^{\rho t}$, $y(t, \tau) = p(\tau) e^{\rho(t-\tau)}$, and $z(t) = z_0 e^{\rho t}$, where x_0 , $p(\tau)$, z_0 and ρ are to be determined, we get

$$\lambda x_0 = -\mu x_0 - \left(\int_0^{\infty} \beta_1(\tau) p(\tau) e^{-\rho\tau} d\tau - \beta_2 z_0 \right) S^0, \quad 278$$

$$p'(\tau) = p(\tau) (-(\mu + \gamma_1) - \kappa(\tau)), \quad 279$$

$$p(0) = S^0 \int_0^{\infty} \beta_1(\tau) p(\tau) e^{-\rho\tau} d\tau, \quad 280$$

$$\lambda z_0 = \beta_2 S^0 z_0 - (\mu + \gamma_2) z_0 + \int_0^{\infty} \kappa(\tau) p(\tau) e^{-\rho\tau} d\tau, \quad 281$$

for $x_0 \neq 0, p(\tau) = 0, z_0 = 0$ and ρ .

Using (279) and (280) we obtain the reproductive number

$$R_1 := K \int_0^{\infty} r_1(\tau) \left(e^{-\left(\mu + \gamma_1\right)\tau - \int_0^{\tau} \kappa(\tau) d\nu} \right) d\tau, \quad 282$$

The number R_1 is the threshold value for strain 1 because if $R_1 > 1$ the epidemic for strain 1 grows, while if $R_1 < 1$ it delays. It is also the number of secondary infective cases generated by infection of strain 1.

If initially no one is infected with strain 1, i.e. $i(t, \tau) = 0$, then $p(\tau) = 0$ for all τ .

Equations (178) and (281) can be reduced to

$$\lambda x_0 = -\mu x_0 - \beta_2 z_0 S^0, \quad 283$$

$$\lambda z_0 = \beta_2 S^0 z_0 - (\mu + \gamma_2) z_0, \quad 284$$

and they determine the threshold conditions for strain 2. Define

$$R_2 := \frac{r_2 K}{\mu + \gamma_2}. \quad 285$$

All solutions ρ of system (278 – 281) are negative if and only if $R_2 < 1$. Therefore, R_2 is the reproductive number for strain 2 and is the number infective cases generated by infection strain 2.

A.3.3: Existence and Stability of the Boundary Equilibrium

Equilibrium of system (272 – 277), $(S, i(\tau), J)$, satisfies the system

$$\mu(S^0 - S) - \left(\int_0^\infty \beta_1(\tau) i(\tau) d\tau + r_2 J \right) S = 0 \quad 286$$

$$\frac{\partial i(\tau)}{\partial \tau} = -(\mu + \gamma_1) i(\tau) - \kappa(\tau) i(\tau) \quad 287$$

$$i(0) = S \int_0^\infty \beta_1(\tau) i(\tau) d\tau \quad 288$$

$$\beta_2 JS - (\mu + \gamma_2) J - \int_0^\infty \kappa(\tau) i(\tau) d\tau = 0 \quad 289$$

From (289) it follows if $J = 0$, then $i(\tau) = 0$ for all τ . The only boundary equilibrium that exists has $i(\tau) = 0$ for all τ and $J = 0$. We denote it as $E^1 = (S_1, 0, J_1)$

Solving (286) and (289), we have

$$S_1 = \frac{(\mu + \gamma_2)}{\beta_2}, J_1 = \frac{\mu}{\beta_2} \left(\frac{S^0 \beta_2}{\mu + \gamma_2} - 1 \right) = \frac{\mu}{\beta_2} (R_2 - 1) \quad 290$$

The boundary equilibrium E^1 exists if and only if $R_2 > 1$.

To study the stability of this boundary equilibrium, we linearize system (272 – 277) about E^1 by letting $x(t) = S(t) - S_1$, $y(t) = J(t) - J_1$, $z(t, \tau) = i(t, \tau)$. Using the same approach (the one used to derive the characteristic equation and reproductive number R_1 for disease-free equilibrium we obtain,

$$R_b = S_1 \int_0^{\infty} r_1(\tau) e^{-\lambda \tau} e^{-(\mu + \gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau \quad 291$$

If $R_b < 1$, then as $z(t, \tau) \rightarrow 0$ as $t \rightarrow \infty$

Next we locate the eigenvalues of the following matrix from system:

$$\begin{bmatrix} -\mu - \beta_2 J_1 & -\beta_2 S_1 \\ \beta_2 J_1 & 0 \end{bmatrix} \quad 292$$

The trace and determinant of this matrix are negative and positive, respectively. Therefore, its eigen values both have negative real part.

Hence the unique boundary equilibrium exists if and only if $R_2 > 1$. It is locally asymptotically stable if $R_b < 1$ and is unstable if $R_b > 1$.

A.3.4: Existence and Stability of the Endemic Equilibrium

Let $E^* = (S^*, i^*(\tau), J^*)$ be an endemic equilibrium of system (272 – 277). Solving the system for S^* , $i^*(\tau)$ and J^* we get unique endemic equilibrium which exists if $R_1 > 1$ and $R_1 > R_2$. The expression for the unique positive endemic equilibrium is given by

$$S^* = \frac{R_1}{K}, \quad i^*(\tau) = \frac{S^0 W_1}{R_1} e^{-(\mu + \gamma_1)\tau - \int_0^\tau \kappa(v) dv}, \quad J^* = \frac{KS^0 W_1}{(\mu + \gamma_2)(R_1 - R_2)}, \quad 293$$

where

$$W_1 = \frac{\mu(R_1 - 1)(\mu + \gamma_2)(R_1 - R_2)}{[(\mu + \gamma_2)(R_1 - R_2)] + \beta_2 KS^0}, \quad 294$$

$$W_2 = S^* W_1 K = \frac{KS^0 \mu(R_1 - 1)(\mu + \gamma_2)(R_1 - R_2)}{R_1 [(\mu + \gamma_2)(R_1 - R_2)] + \beta_2 KS^0}, \quad 295$$

and

$$K := \int_0^{\infty} \kappa(\tau) e^{-(\mu + \gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau \quad 296$$

We investigate the local stability of the endemic equilibrium, E^* by linearizing system (272 – 277) about E^* using the perturbation variables

$$x(t) = S(t) - S^*, y(t, \tau) = i(t, \tau) - i^*(\tau), z(t) = J(t) - J^* \quad 297$$

and then letting $x(t) = x_0 e^{\rho t}$, $y(t, \tau) = \hat{y}(\tau) e^{\rho(t-\tau)}$, and $z(t) = z_0 e^{\rho t}$, we obtain the characteristic equation

$$\left[\rho + \mu + \beta_2 J^* + \frac{W_1}{1 - S^* P_1(\rho)} \right] (\rho + \mu + \gamma_2 - \beta_2 S^*) + \left[\beta_2 J^* + \frac{W_1 P_2(\rho)}{1 - S^* P_1(\rho)} \right] (\beta_2 S^*) = 0 \quad 298$$

The endemic equilibrium, given in (393), is locally asymptotically stable if all roots, ρ of the characteristic equation (298) have negative real parts.

Table 5: Stability conditions for infection-free, boundary and endemic equilibrium.

	$R_2 < 1, R_1 < 1$	$R_2 < 1 < R_1$	$R_1 < 1 < R_2$	$1 < R_1 < R_2$	$1 < R_2 < R_1$
E^0	Stable	Unstable	Unstable	Unstable	Unstable
E^1	Does not exist	Does not exist	Stable	Stable	Unstable
E^*	Does not exist	Exists	Does not exist	Does not exist	Exists

The existence condition for the boundary equilibria, E^1 and E^* , and stability conditions for the infection-free and boundary equilibria, E^* and E^1 . These conditions are based on the relations between the two reproductive numbers.

A.3.5: Constant Mutation Case

As the characteristic equation obtained for the endemic equilibrium is a transcendental equation, it is difficult to determine when all the roots of the characteristic equation will have a negative real part and hence, whether the endemic equilibrium is stable. To gain insight into the transmission dynamics of the disease governed by system (272 – 277), we consider the special case where the mutation rate from strain 1 to strain 2 is constant and where the infection rate of strain 1 is independent of the infection stages. Lets define these constant rates as $\kappa(\tau) := k$ and $\beta_1(\tau) := \beta_1$.

Let the total infectives be $I(t) := \int_0^\infty i(t, \tau) d\tau$. Integrating the equation for $i(t, \tau)$ in (273)

with respect to τ and using the initial conditions $i(t, 0)$ reduces the system of PDEs to the system of ODE's,

$$\frac{dS(t)}{dt} = \mu(S^0 - S) - \beta_1 IS - \beta_2 JS \quad 299$$

$$\frac{dI(t)}{dt} = \beta_1 SI - (\mu + \gamma_1 + k)I \quad 300$$

$$\frac{dJ(t)}{dt} = \beta_2 JS - (\mu + \gamma_2)J + kI \quad 301$$

The reproductive numbers of Strains 1 and 2, R_1 and R_2 , for system (299 – 301) are

$$R_1 = \frac{r_1 S^0}{(\mu + \gamma_1 + k)}, \text{ and } R_2 = \frac{r_2 K}{(\mu + \gamma_2)} \quad 302$$

The only boundary equilibrium with $I = 0$ and $I > 0$ exists if $R_2 > 1$, and it has the same expression as in section A.3.3. This boundary equilibrium is stable if $R_1 < R_2$ and is unstable if $R_1 > R_2$.

A.3.5.1: Existence and Stability of the Endemic Equilibrium

For $\kappa(\tau) = k$, the term defined in (296) becomes

$$K := \int_0^{\infty} \kappa(\tau) e^{-(\mu + \gamma_1)\tau - \int_0^{\tau} \kappa(v) dv} d\tau = \frac{k}{\mu + \gamma_1 + k} \quad 303$$

By solving for an endemic equilibrium, we have the equivalent solution

$$S^* = \frac{K}{R_1} \quad , \quad 304$$

$$I^* = \frac{\mu}{\beta_1} \cdot \frac{(R_1 - 1)(\mu + \gamma_1 + k)(R_1 - R_2)}{[(\mu + \gamma_2)(R_1 - R_2)] + kR_1} \quad 305$$

$$J^* = \frac{\mu k S^0 (R_1 - 1)}{(\mu + \gamma_2)[(\mu + \gamma_2)(R_1 - R_2)] + kR_1} \quad 306$$

We see that the endemic equilibrium $E^* = (S^*, I^*, J^*)$ exists if and only if $R_1 > 1$ and $R_1 > R_2$.

Using $\beta_2 J^* + \mu = \mu \frac{K}{S^*} - \beta_1 I^*$, the characteristic equation for system (299 – 301) has the

form,

$$\left[\rho + \mu R_1 + \beta_1 I^* \frac{(\mu + \gamma_1 + k)}{\rho} \right] (\rho + \mu + \gamma_2 - \beta_2 S^*) + \left[\beta_2 J^* + \beta_1 I^* \frac{k}{\rho} \right] (\beta_2 S^*) = 0 \quad 307$$

The above equation can be expressed as

$$\rho^3 + a_1 \rho^2 + a_2 \rho + a_3 = 0, \quad 308$$

where

$$a_1 := \mu + \gamma_2 - r_2 S^* + \mu R_1 = \mu \frac{S^0}{S^*} + k \frac{I^*}{J^*}, \quad 309$$

$$a_2 := \mu R_1 (\mu + \gamma_2 - \beta_2 S^*) + \beta_2^2 J^* S^* + \beta_1 I^* (\mu + \gamma_1 + k) \quad 310$$

$$= \beta_1^2 S^* I^* + \beta_2^2 J^* S^* + \mu \frac{S^0}{S^*} k \frac{I^*}{J^*} \quad 311$$

$$a_3 := ((\mu + \gamma_2) \beta_1 + \beta_2 (\mu + \gamma_1)) (\mu + \gamma_1 + k) I^* = \beta_1 S^* k \frac{I^*}{J^*} (\beta_1 I^* + \beta_2 J^*) \quad 312$$

Since $a_1 > 0$ and $a_3 > 0$, it follows from the Routh-Hurwitz criterion that all characteristic roots of (308) have negative real part if and only if $a_1 a_2 > a_3$.

Then,

$$a_1 a_2 - a_3 = \frac{\mu(R_1 - 1)(R_1 - R_2)}{R_1^2((\sigma_1 + k)R_1 - \sigma_1 R_2)}(c_2 k^2 + c_1 k + c_0) \quad 313$$

where,

$$\sigma_1 := \mu + \gamma_1, \sigma_2 := \mu + \gamma_2, \quad 314$$

$$c_0 := \sigma_1^2 \mu R_1^3 + \sigma_2 R_1 (\mu R_1^2 + \sigma_2 (R_1 - R_2)) \frac{\sigma_1 (R_1 - R_2)}{R_1 - 1}, \quad 315$$

$$c_1 := 2\sigma_1 \mu R_1^3 + \frac{\mu \sigma_2 R_1^2 R_2^2}{R_1 - R_2} + \frac{\sigma_2 R_1^2 (\mu R_1^2 + \sigma_2 (R_1 - R_2))}{R_1 - 1} - \sigma_2 R_2 (\sigma_1 R_1 - \sigma_2 R_1), \quad 316$$

$$c_2 := \mu R_1^3 - \sigma_2 R_1 R_2. \quad 317$$

Hence all roots of (313) have negative real part if $c_2 k^2 + c_1 k + c_0 > 0$, and at least one of the roots of (313) has positive real part if $c_2 k^2 + c_1 k + c_0 < 0$.

Lets summarize the result in the following theorem.

THEOREM 8: When the mutation rate is constant, the dynamical behavior of epidemic model (299 – 301) can be described as one of the following cases:

1. If we define $R_0 := \max\{R_1, R_2\}$ and $R_0 < 1$, then the infection-free equilibrium, $E^0 := (S^0, 0, 0)$, is locally asymptotically stable. If $R_0 > 1$, then E^0 is unstable.
2. If $R_1 < 1 < R_2$, or $1 < R_1 < R_2$, the only boundary equilibrium, given by

$$E^1 = (S_1, 0, J_1) = \left(S^0 R_2, 0, \frac{\mu S^0}{\sigma_2 R_2} (R_2 - 1) \right), \quad 318$$

exist and is locally asymptotically stable. In this case, the endemic equilibrium E^* does not exist.

3. If $R_2 < 1 < R_1$, the endemic equilibrium E^* , exists and is the only nontrivial equilibrium. It is locally asymptotically stable if $c_2 k^2 + c_1 k + c_0 > 0$ and unstable if $c_2 k^2 + c_1 k + c_0 < 0$.

4. If $1 < R_2 < R_1$, the boundary equilibrium, E^1 exists but is unstable. The endemic equilibrium, E^* exists and is locally asymptotically stable if $c_2 k^2 + c_1 k + c_0 > 0$ and unstable if $c_2 k^2 + c_1 k + c_0 < 0$.

APPENDIX: B

B 1: Matlab Code

Omega as the bifurcation parameter.

```
function [sol1]=revisedFinalhopf2
omega = input('Enter the delay value for omega:');
% Explicit values for endemic equilibrium are calculated.

c = 0.4900;
sigma = 0.5;
r1 = 3;
r2 = 2;
k = 0.135;
mu = 0.01;
beta1 = 0.190330606;
beta2 = 0.01;
w1 = ((mu * (r1 - 1)* sigma * (r1 - r2))/ (sigma * (r1 - r2)+((( k * sigma *
r2)/( sigma + k))-((c * exp(-mu*omega) * r1 * k)/(sigma+k))));
x = ((mu + c + k)/ beta1)
a = r1 * x
y = (w1/beta1)
z = ((k * w1 * a)/(sigma * (r1 - r2) * (sigma + k)))

% Establish the Hopf bifurcation criteria

A1 = ((mu * a)/ x)-(( c * z * exp(-mu*omega))/ x)+(( k * y)/ z));
A2 = ( ( ((beta1^2)+(beta2^2)) * z * x )+ ( (mu * k * a * y) / ( x * z))-(( c
* k * y * exp(-mu*omega)) / x) );
A3 = ( (( beta1^2) *k * x* y )+ ( k * beta1 * beta2 * y * x));
T1 = ( beta2 * c * z * exp(-mu*omega));
T2 = ( k * c * beta1 * y *exp(-mu*omega));
b1 = ((A1^2) - (2* A2))
b2 = ((A2^2) - (2 * A1 * A3 ) +( T1^2))
b3 = ((A3^2) - (T2^2))
if ( (b1^2) > (3 * b2))
    display('yes')
end
delta = ( ((4/27 )*( b2^3)) - ((1/27) *( b1^2)* (b2^2)) +(( 4/27 )*
(b1^3)*b3) -(( 2/3 )*( b1*b2*b3)) + (b3^2))

% Plots

history = [x; y; z];
tspan = [0;3000];
opts = ddeset('RelTol',1e-5,'AbsTol',1e-8);
d=omega;
sol1 = dde23(@hopf1f,omega,history,tspan,opts,a,k,c,d);
```

figure

```
subplot(2,2,1:2),plot(sol1.y(2,:),sol1.y(3,:))  
xlabel('Infectives infected with strain A')  
ylabel('Infectives infected with strain B')
```

```
subplot(2,2,3),plot(sol1.x,sol1.y(2,:))  
xlabel('time')  
ylabel('Infectives infected with strain A')
```

```
subplot(2,2,4),plot(sol1.x,sol1.y(3,:))  
xlabel('time')  
ylabel('Infectives infected with strain B')
```

```
function v=hopf1f(t,y,Z,a,k,c,d)
```

```
    v=zeros(3,1);
```

```
    ylag = Z(:,1);
```

```
    v(1) = 0.01 * ( a - y(1)) - (((3+6*k)/(2*a)) * y(2) + (1/a) * y(3)) * y(1) +  
           c * ylag(3) * exp(-(0.01*d));
```

```
    v(2) = ( (3+6*k) / (2*a) ) * y(2) * y(1) - ( (1+2*k) / 2 ) * y(2);
```

```
    v(3) = (1/a) * y(1) * y(3) - 0.5 * y(3) + k * y(2);
```

```
%-----
```

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