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PROJECT REPORT

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Mathematical Modeling of Visceral Leishmaniasis And Disease Spread Control

By

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Dhiraj Sain.C

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Chapter - 1

INTRODUCTION

Leishmaniasis results from infection by various species of Leishmania, a protozoan parasite of the family *Trypanosomatidae* (order Kinetoplastida) and is a vector borne disease transmitted by the *Phlebotomine* flies. Among different leishmania species at least 16 species and subspecies are pathogenic for mammals. The pathogenic New World species include the *L. braziliensis* complex (*L. braziliensis, L. panamensis, L. guyanensis*), *L. Mexicana* complex (*L. mexicana, L. amazonensis, L. venezuelensis*), *L. peruviana*, and *L. chagasi* [1].

Human Cutaneous Leishmaniasis occurs along the Mediterranean coast and in parts of Central and South America, Asia, Africa, the Middle East, China, and India, and in the Dominican Republic in the Caribbean [1]. Human Visceral Leishmaniasis (VL) is found in Bangladesh, India, Nepal, Guadeloupe, Martinique, along the Mediterranean coast, and in parts of Africa, Central Asia, China, the Middle East, and South America [1]. Texts from the Inca period in the 15th and 16th centuries, and then during the Spanish colonization, mention the risk run by seasonal agricultural workers who returned from the Andes with skin ulcers in the form of disfigurements of the nose and mouth later known as "white leprosy" because of their strong resemblance to the lesions caused by leprosy. In the Old World, Indian physicians termed kala azar to an ancient disease later defined as Visceral Leishmaniasis. In 1901, Leishman identified certain organisms in smears taken from the spleen of a patient who had died from "dum-dum fever". At the time, "Dum-dum", a town near Calcutta, was considered to be particularly unhealthy. In 1903, Captain Donovan described these organisms as being new. The link between these organisms and kala azar was eventually discovered by Major Ross, who named them *Leishmania donovani*. The Leishmania genus had been discovered.

Visceral Leishmaniasis (VL), commonly known as kala azar, is a silent killer, invariably killing almost all untreated patients. VL affects not only the weakest in the community, such as children and those weakened by other diseases such as HIV and tuberculosis, but also healthy adults and economically productive social groups [2]. Incidence of VL varies from place to place depending on the epidemiological characteristics. High incidence rates of VL are common in areas where human populations are despoiled by social instability, war, and migration. Progress towards the discovery of an effective vaccine against leishmaniasis has become a snail's race. Therefore, control of leishmaniasis by vaccines remains only a long term goal [3].

1.1 The Vector - Phlebotomine sandfly

Adult female sand fly (Figure 1.1) is bloodsucker, usually feeding at the night on sleeping prey. Sandflies breed in dark corners in the crevices of the walls having rich humus and moisture [4]. It is about 1/3 rd size of mosquito, Active in twilight evening and night time hours (from dusk to dawn) and less active during the hottest time of the day. The infection of sand flies with leishmaniasis starts upon the release of amastigotes from infected macrophages ingested by the fly during the blood meal [5]. Viseral Leishmaniasis is seasonal, and cases fluctuate with changes in the vector populations i.e. sand fly populations.

Figure 1.1. Picture of Phlebotomine sandfly, vector for Visceral leishmaniasis [2]

1.2 The Parasite - *Leishmania donovani*

Leishmania donovani is 3-6 micrometers long, 1.5-3 micrometers in diameter. Amastigotes are found in the blood host organism (Figure 1.2). It is round, non-motile and 3-7 micrometers in diameter.

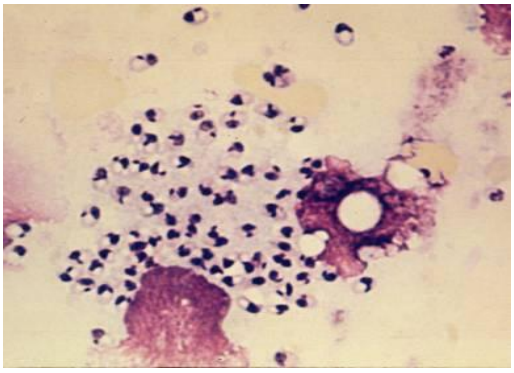


Figure 1.2 Amastigote form of *Leishmania donovani* obtained from spleen of human being [6].

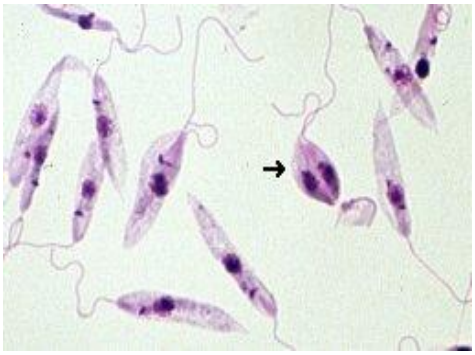


Figure 1.3 Promastigotes found in the gut of vector [7].

Amastigote transforms into second *Leishmania donovani* form called promastigote, when it enters back into the sand fly to complete its life cycle. Promastigotes are found in the gut region of the sand fly (Figure 1.3). They are spindle shaped and triple the size of amastigotes. Interestingly they have a single flagella for motility. Promastigotes live extracellularily in sandfly's alimentary canal, where they reproduce asexually, then they migrate with the help of flagella to proximal end of the gut for their invasion into next host when sand fly visits for a blood meal.

1.3 Life Cycle Of *Leishmania donovani*

The transmission cycle begins with female sandflies as they need protein to develop eggs. The figure 1.4 shows the life cycle of the Leishmaniasis in the host, human and vector, sandfly.

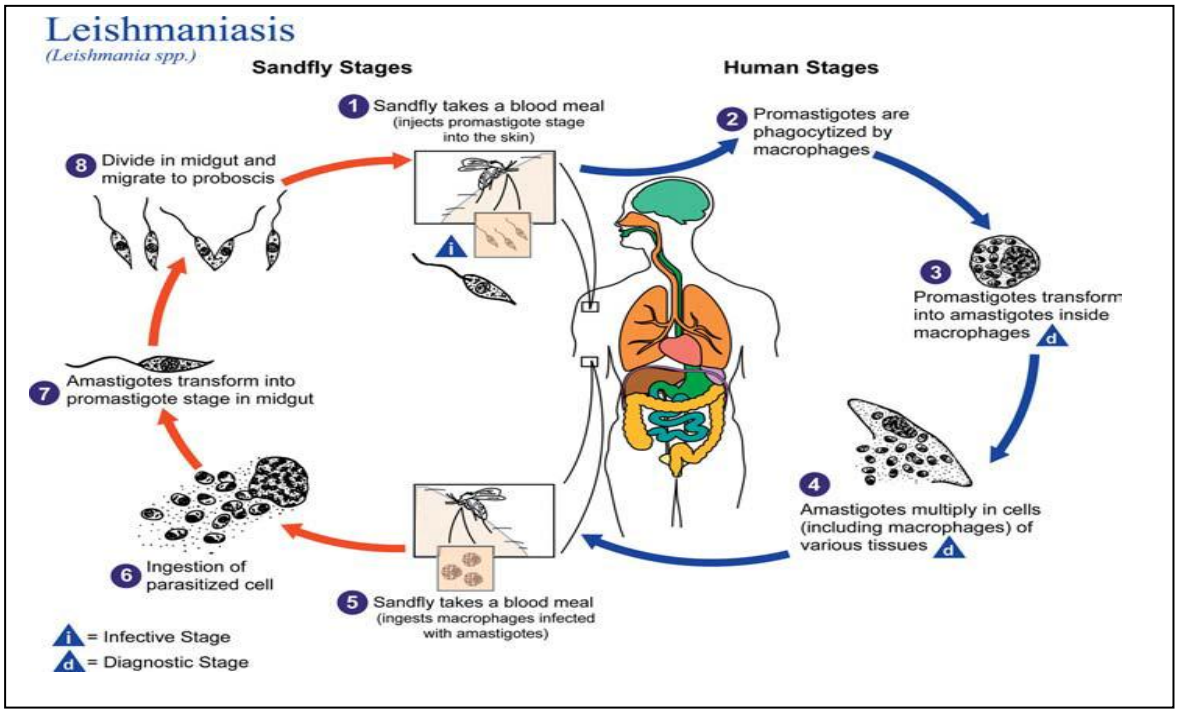


Figure 1.4 The Life Cycle of Leishmania donovani [2].

1.4 Symptoms Of The Disease

The most common symptoms of Visceral Leishmaniasis are a prolonged undulant fever, weight loss, decreased appetite, signs of anemia, and abdominal distension with splenomegaly and hepatomegaly i.e enlargement of the spleen and liver. Other symptoms may include coughing, chronic diarrhea, darkening of the skin, lymphadenopathy, and in many cases, signs of chronic kidney disease [8].

1.5 Treatment

For many decades, the treatment of VL has been based on Pentavalent antimonials, given intramuscularly or intravenously for one month.But currently drugs those are administered such as allupurinol, Amphotericin B which is highly efficacious but is associated with serious side effects and can only be given in a hospital setting. Liposomal amphotericin B is expensive and has to be administered intravenously, making treatment more difficult under field conditions. Miltefosine is effective against VL but is expensive and cannot be used to treat women of childbearing age. Miltefosine is registered in India for first-line treatment of VL [8].

1.6 Preventive Measures

Preventative measures against sandflies include using insect repellents such as DEET, covering exposed skin, and staying on higher floors of buildings in the evening or at night, as these insects are poor fliers. Fans can also be helpful, and insecticidal sprays can be used to kill the insects inside houses. Insecticide-treated bed nets decrease bites from these insects at night. Untreated bed nets are not generally useful: sandflies are very tiny and can pass through the mesh of most nets, while bed nets with a very narrow mesh may be too hot in warmer climates. Insecticide-treated bed sheets; window curtains and slow release paint have also been used. Insecticide spraying programs have been conducted in some countries [8].

Incidence of VL varies from place to place depending on the epidemiological characteristics. High incidence rates of VL are common in areas where human populations are despoiled by social instability, war, and migration. Progress towards the discovery of an effective vaccine against leishmaniasis has become snail's race. Therefore, control of leishmaniasis by vaccines remains only a long term goal [3].

1.7 Mathematical Modelling:

Mathematical modelling is a series of steps taken to convert an idea first into a conceptual model and then into a quantitative model. A conceptual model represents our ideas about how the system works. It is expressed visually in a model diagram, typically involving boxes (state variables) and arrows (causal effects).

Progress of epidemic through a population is amenable to mathematical modelling. In particular, the first attempt to model and predict or explain patterns dates back over 100 years [9], although it was the work of Kermack and McKendrick [10] that established the basic foundations of the subject by proposing a series of compartmental models such as

Susceptible-Infected-Recovered (SIR), Susceptible-Infected (SI), Susceptible-Exposed-Infected-Recovered (SEIR) and different combination of these. These early models, and many subsequent revisions and improvements [11, 12] operated on the principle that individuals can be classified by their epidemiological status—most simply susceptible to the infection, infected and therefore infectious, and recovered and hence no longer infectious and etc. Equations are developed for the rates of each process and are combined to form a quantitative model consisting of dynamic (i.e., varying with time) equations for each state variable. Epidemiologists use various developed mathematical models to understand previous outbreaks of diseases and to better understand the dynamics of how infections spread through populations.

Mathematical Model-

Mathematical Models are simplified representations of some real world entity in form of simple equations. They are characterized by assumptions about:

i) Variables (the things which change)
ii) Parameters (the things which do not change)
iii) Functional forms (the relationship between the above two)

So far our knowledge is concerned most of the studies on leishmaniasis epidemiology were qualitative and descriptive. But now that the natural history of many Leishmania parasites is quite well known, there is growing interest in quantitative analysis and vector control has the potential to efficiently reduce transmission of parasites [13]. Mathematical models are necessary tools in the study of diseases; they provide the means to explore and understand regulatory mechanisms of a system. The mathematical modelling of the dynamics of transmission of Leishmaniasis has been poorly developed if we compare it with other infectious diseases.

1.8 Objective Of The Project

The main objective of the project is to study the basic epidemiological models such as SIR, SI, and SIRS, in order to understand the dynamics across each of the compartmental class and look at persistence of VL infection with a mathematical modelling approach, which is different from previous studies in this direction. We plan to develop a simple Susceptible-Exposed-Infected-Recovered (SEIR) type mathematical model considering the Human, Animal and Fly population and to analyse it for identification of important parameters relevant for an efficient control of infection and transmission.

Chapter - 2

STUDY OF BASIC EPIDEMIOLOGICAL MODELS

In order to model the progress of an epidemic in a large population, comprising many different individuals in various fields, the population diversity must be reduced to a few key characteristics which are relevant to the infection under consideration. One of the most basic procedures in the modelling of diseases is to use a compartmental model, in which the population is divided into different groups called compartments.

Namely,

(S) Susceptible: Individuals those able to contract the disease

(E) Exposed: Individuals those who have been infected but are not yet infectious

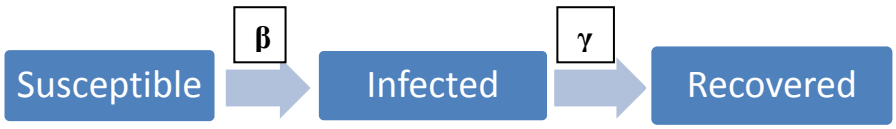
(I) Infected: Individuals those capable of transmitting the disease

(R) Recovered: Individuals those who have become immune.

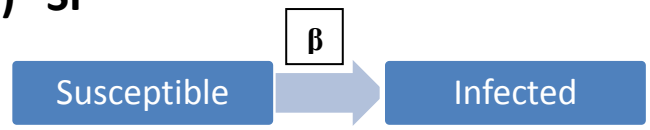
Below we show the structures and combinations of these compartmental models.

Basic epidemiological models

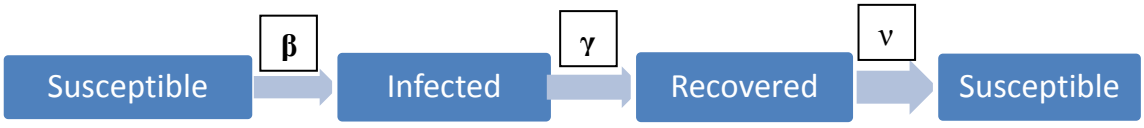
(i) SIR



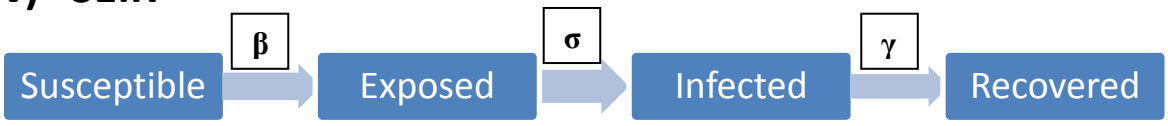
(ii) SI



(iii) SIRS



(iv) SEIR



Here:

β Rate of infection(Contact rate)

γ Recovery rate

ν Rate of immunity loss

σ Rate of incubation

METHODOLOGY AND SOFTWARE/TOOLS:

Matlab R2008a was used to perform numerical simulation of Ordinary Differential Equations using Runge-Kutta Fourth Order technique. Numerical simulation of simple basic models were performed to standardize the software.

2.1 SIR Model

The SIR Model is used in epidemiology to compute the amount of susceptible, infected, and Recovered people in a population. This simple model incorporates Humans, who are firstly susceptible (S) to the disease, and those individuals who are infected are termed as infecteds (I) and are infectious, another class of humans who are recovering are termed as recovered (R). Whereas, infection rate (β) and recovery rate (γ) are important parameters. It is also used to explain the change in the number of people needing medical attention during an epidemic. For the SIR model to be appropriate, once a person has recovered from the disease, they would receive lifelong immunity. The SIR model is also not appropriate if a person was infected but is not infectious [14, 15]. Chicken pox and influenza are the best examples of SIR epidemiological models.

MODEL EQUATIONS:

$$dS/dt = -\beta IS, \quad S(0) = So \geq 0,$$
$$dI/dt = \beta IS - \gamma I, \quad I(0) = Io \geq 0,$$
$$dR/dt = \gamma I, \quad R(0) = Ro \geq 0,$$

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

- **N - Total no. of individuals, S - No. of susceptible individuals**
- **I - No. of infected individuals, R - No. of recovered individuals**
- **β – Contact rate, γ - Recovery rate**

SOLUTION OF SIMPLE SIR MODEL - Variation of Parameters and Time

A solution to the simple SIR model, a plot with the differential equations with beta(**β**) = 0.01/day ,gamma(**γ**) = 0.1/day and with the initial values S(0) = 760, I(0) = 3 and R(0) = 0 is shown in Figure 2.1.

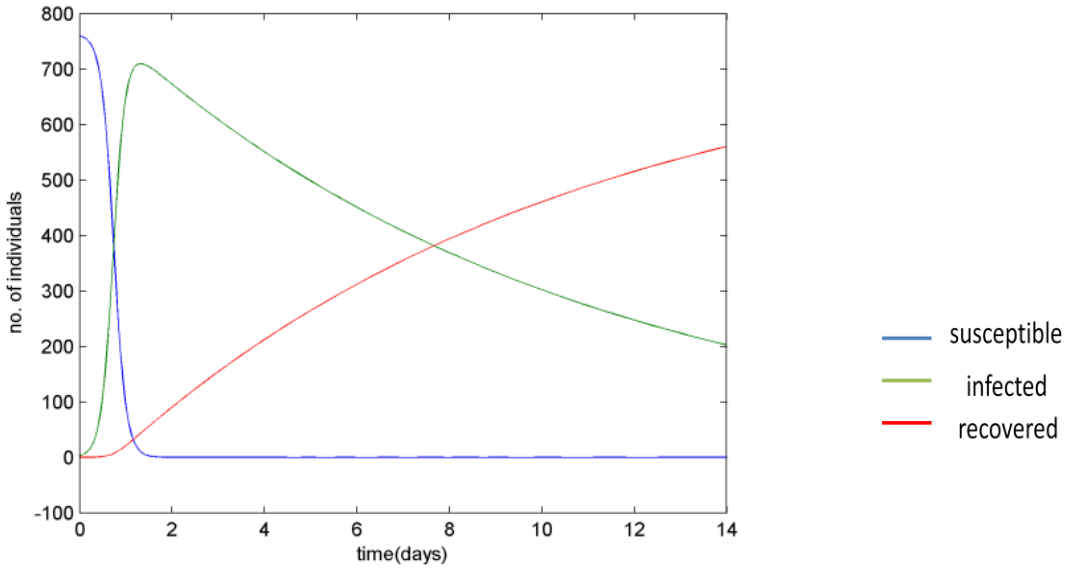


Figure 2.1 Time dynamics of SIR population individuals

When time span was decreased by 10 fold and increased by 10 fold & 100 fold,the graphical solution plotted:

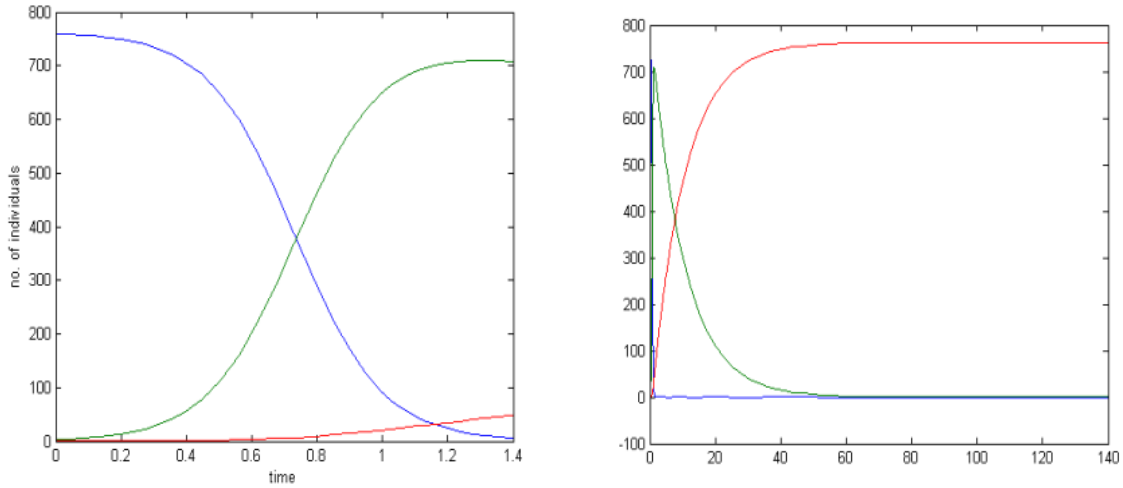


Figure 2.2 Short time dynamics of SIR population individuals

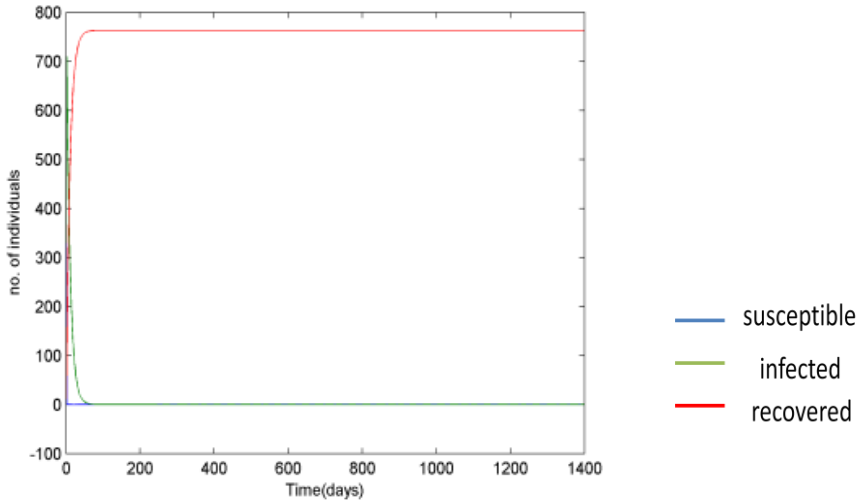


Figure 2.3 Time dynamics of SIR population individuals for a longer run

When time span was decreased by 10 fold (Figure 2.2) w.r.t basal time, we observed the rate of change in the compartmental classes clearly. Rate of change among the the susceptible individuals decreases along the time,simulataneously it is clearly observed that the infecteds increase intially and drop where in the the recovered class individuals increase as when plotted on longer time span (Figure 2.3).

When the infection rate (β) and recovery rate(γ) were increased by 10 fold,it was observed that the change among these compartments were relatively faster.There was a decline in the individuals of the susceptible group and intial optimisation by reaching peak of the infected class and an increased number of individuals in the recovered class was relatively quicker (Figure 2.4). When the same was plotted on longer time span (1400 days) it showed no recurrence of the disease (Figure 2.5).

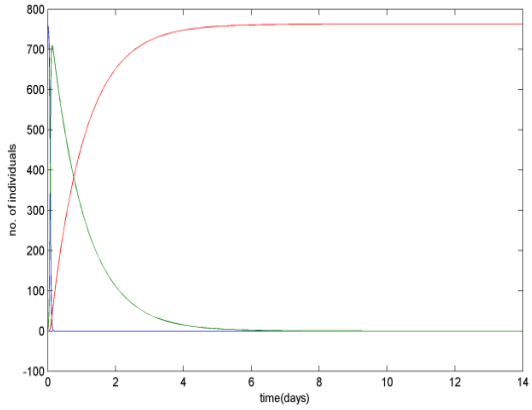


Figure 2.4 Time dynamics when infection and recovery rate both were increased

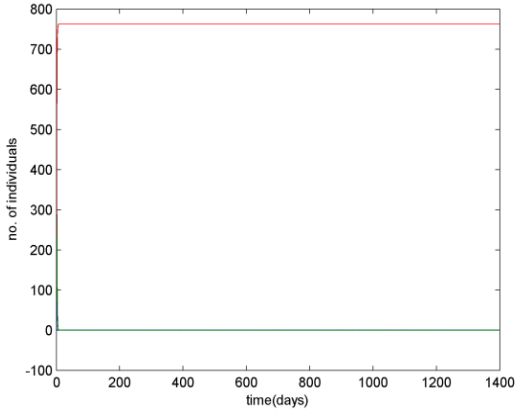


Figure 2.5 Time dynamics of SIR population individuals on longer run

Similarly when, both the infection rate (β) and recovery rate (γ) were decreased by 10 fold we observed the lag in each of the compartmental class taking more time relatively in

transformation from one class to another. And it is notable that the the recovered class is just rising when the rate of recovery was lowered by 10 fold (Figure 2.6). The same when plotted for longer time span (Figure 2.7), clearly shows the difference when Figure 2.5 and Figure 2.7 are compared.

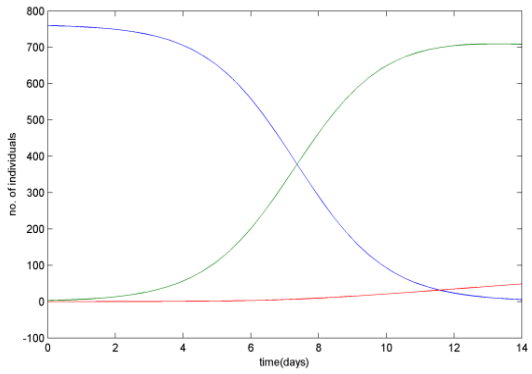


Figure 2.6 Time dynamics when infection and recovery rate both were decreased

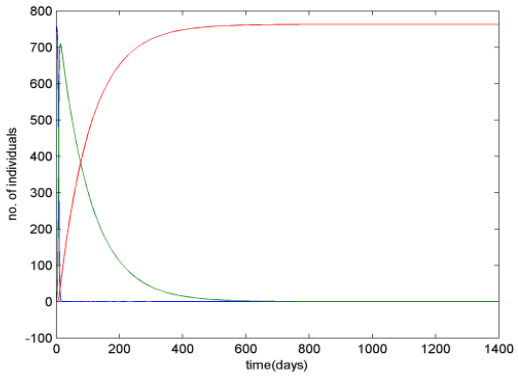


Figure 2.7 Time dynamics of SIR population individuals on longer run which got delayed

When the rate of infection (β) was decreased by 10 fold , i.e. β = 0.001/day and on keeping gamma (γ) constant we observe, the rate of change in the susceptible class to infected class has been diminished, as the contact rate was lowered (Figure 2.8). On plotting to the longer time span (1400 days) we see no recurrence of the disease and steady states are achieved in less than 100 days (Figure 2.9).

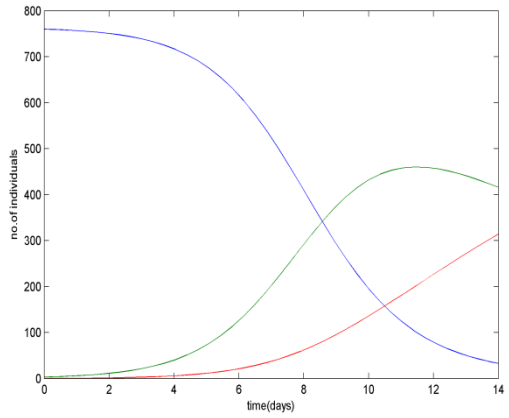


Figure 2.8 Time dynamics on decreasing the contact rate by 10 fold

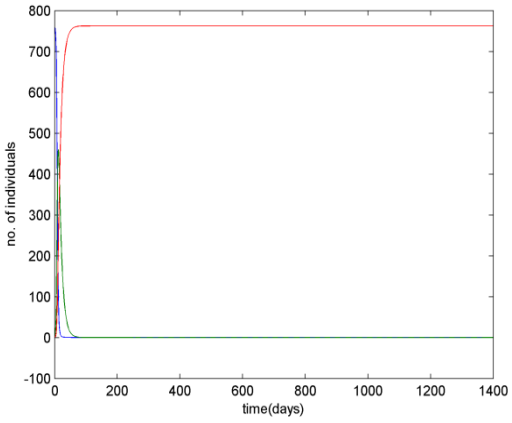


Figure 2.9 Time dynamics when ran for longer time

Similarly when the recovery rate (γ) was decreased by 10 fold, i.e. γ = 0.01/day and on keeping beta (β) constant we observe, the increase in the recovery class individuals was very slow as the rate of recovery was lowered (Figure 2.10) and the number of infected individuals are slowly being declined. The same when plotted on longer time span (1400

days) we observe the infected class declines slowly and in approximately 600 days it reaches steady state (Figure 2.11).

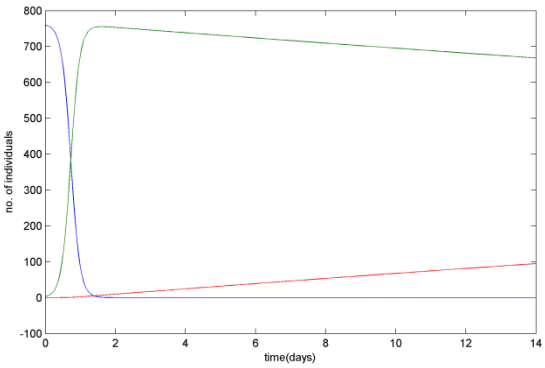


Figure 2.10 Time dynamics on decreasing the recovery rate by 10 fold

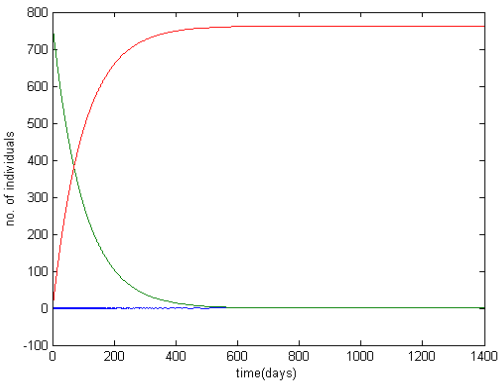


Figure 2.11 Time dynamics when ran for longer time

When the rate of infection (β) was increased by 10 fold, i.e. β = 0.1/day and on keeping gamma (γ) constant we observe, the rate of change in the susceptible class to infected class has been maximised, as the contact rate was increased (Figure 2.12). And the curve representing the susceptible class shows a steep decline in very short span of time. Plotting on the longer time span (1400 days) we see no recurrence of the disease and steady states are achieved in less than 50 days (Figure 2.13).

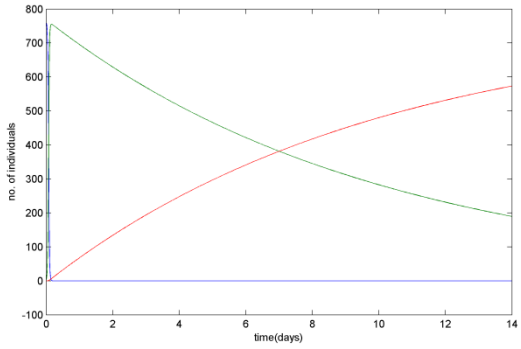


Figure 2.12 Time dynamics on increasing the contact rate by 10 fold

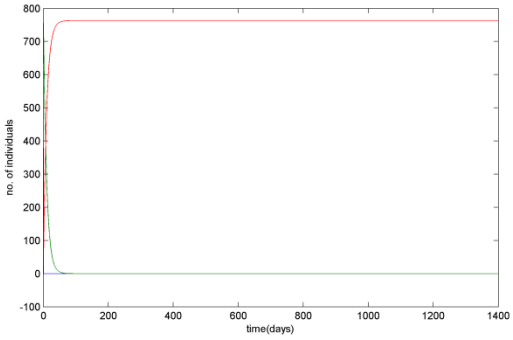


Figure 2.13 Time dynamics when plotted for longer time

Similarly when the recovery rate (γ) was increased by 10 fold, i.e. γ = 1/day and on keeping the infection rate constant (β), We observed the infected individuals number has come down and number of infected people are getting recovered faster (Figure 2.14).

When the same was plotted for longer time span (1400 days), it is very clearly notable of the susceptible group being reduced very low and subsequently the decrement in infected class

and especially the infected class is completely recovered by comparing the infected and recovered curves (Figure 2.15).

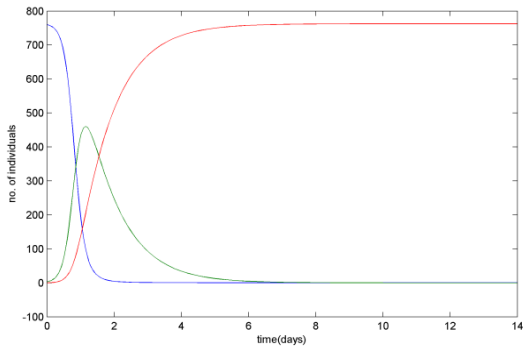


Figure 2.14 Time dynamics on increasing the recovery rate by 10 fold

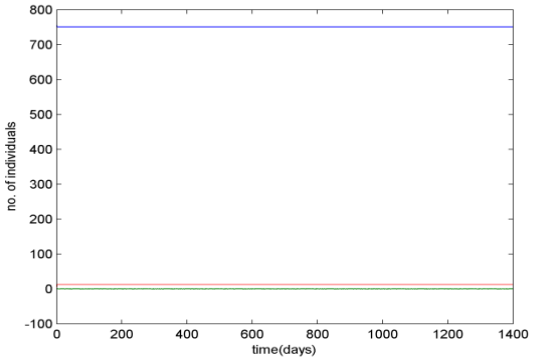


Figure 2.15 Time dynamics when plotted for longer time

2.2 SI Model

Mainly the SI model incorporates humans those are Susceptible to the disease and transformation of susceptible into infected class, model clearly indicates that all the individuals in a class are susceptible (S) to the disease and after being exposed the individual become infectious and is called infected (I) and the rate at which susceptible is being transformed to infected class is given by the parameter termed as contact rate (β). This model also assumes that there is no incubation period and no recovery i.e. they remain infectious throughout their life.

MODEL EQUATIONS:

$$dS/dt = -\beta IS, \quad S(0) = So \geq 0,$$

$$dI/dt = \beta IS, \quad I(0) = Io \geq 0,$$

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

- **N - Total no. of individuals**
- **S - No. of susceptible individuals**
- **I - No. of infected individuals**
- **β - Contact rate**

SOLUTION OF A SIMPLE SI MODEL

A solution to the simple SI model, a plot with the differential equations with beta (**β**) = 0.00013/day and with the initial values S(0) = 2000, I(0) = 1 are shown in Figure 2.16.

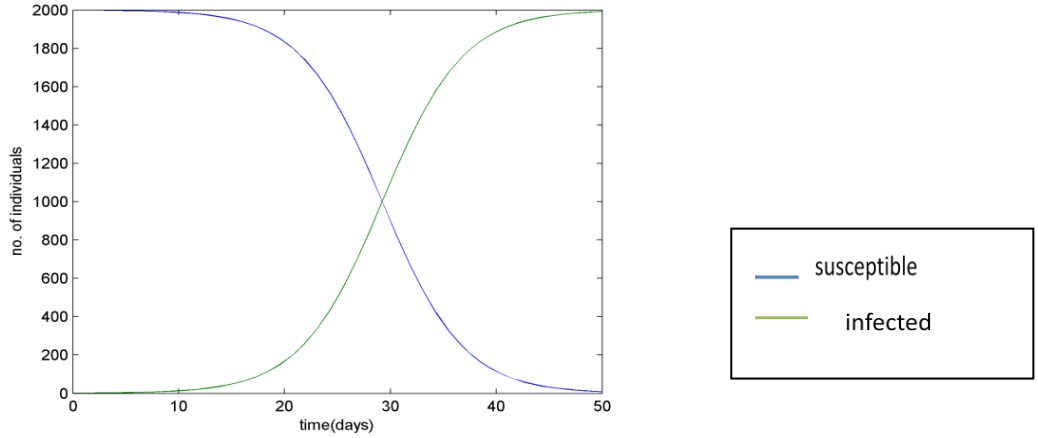


Figure 2.16 Time dynamics of susceptible and infected population

When the timespan was increased by 10 fold and 100 fold (Figures 2.17 & 2.18), we observed no recurrence of the disease firstly.

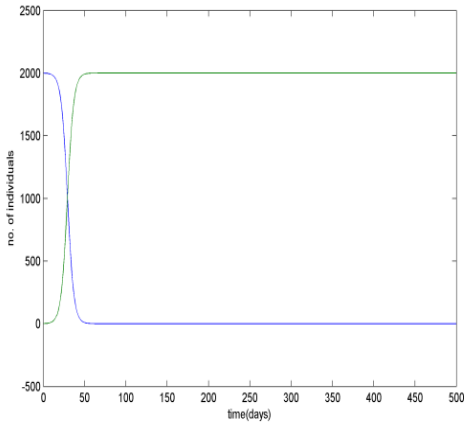


Figure 2.17 Time dynamics of susceptible and infected population when increased by 10 fold

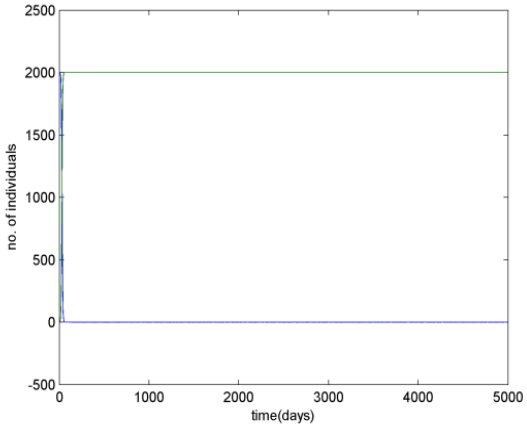


Figure 2.18 Time dynamics of susceptible and infected population when increased by 100 fold

When the rate of contact has been increased by 10 fold i.e. (β = 0.0013/day) w.r.t basal β value, It is clearly notable that the infection rate is higher and the transformation from susceptible to infected class rate has become quicker. Similarly when the contact rate was decreased by 10 fold i.e. (β = 0.000013/day) w.r.t basal value, we observed the infection rate being lower and on longer time span (500 days) it is notable that the susceptible class slowly transforms into infected class.

2.3 SIRS Model

In this epidemiological model, we have humans being susceptible for the disease (S) and are infected (I) and become infectious to spread disease based on important parameter termed as contact rate (β). Recovered individuals (R) lose their immunity against the infection in short span of time i.e. this model will follow the SIR model except that the immunity gained is only temporary and after a small period of time the individual will again enter the susceptible category. Other two important parameters are rate of immunity loss (γ) that is held responsible for recovered individuals being transformed into susceptible again and Rate of recovery (ν) for infected individuals to recover.

MODEL EQUATIONS:

$$dS/dt = -\beta IS + \gamma R, \quad S(0) = So \geq 0,$$

$$dI/dt = \beta IS - \nu I, \quad I(0) = Io \geq 0,$$

$$dR/dt = \nu I - \gamma R, \quad R(0) = Ro \geq 0,$$

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

- **N - Total no. of individuals; S - No. of susceptible individuals**
- **I - No. of infected individuals; R - No. of recovered individuals**
- **β - Contact rate/ rate constant for infection; γ - Rate constant for immunity loss**
- **ν - Rate constant for recovery**

SOLUTION OF SIMPLE SIRS MODEL

A solution to the simple SIRS model, a plot with the differential equations with beta(**β**) = 0.33/day ,gamma(**γ**) = 0.7/day, nu(ν) = 0.9/day and with the initial values S(0) = 500, I(0) = 1 and R(0) = 0 is performed (Figure 2.19)

We observed change in each of the specific classes when there is increment by 10 fold and decrement by 10 fold w.r.t basal parameter values when compared.

As the time span being same but when the parameters are increased, we observe the rate of change happening quicker in short time. And similarly when parameters were decreased, we did observe variation among each class being slower and lags on the same time span.

When the infection rate was decreased by 10 fold i.e. β = 0.033/day, it is clearly observable that the susceptible class declination was slow and the time taken for the transformation of susceptible class to infected class was also relatively low, and when plotted on longer time span it showed no recurrence of the disease.

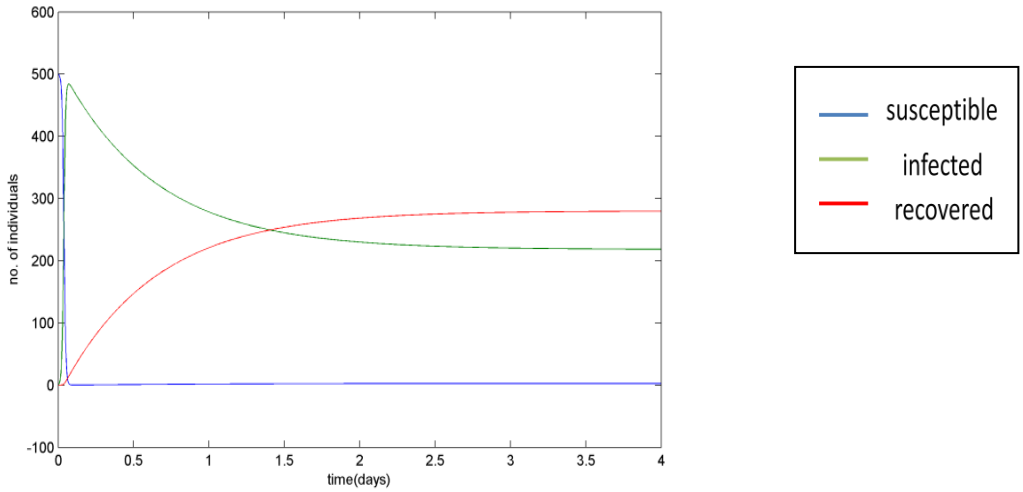


Figure 2.19 Time dynamics of SIRS population

VARIATION OF INFECTION RATE (β) BY 10 FOLD [KEEPING RATE OF IMMUNITY LOSS (γ) & RATE OF RECOVERY (ν) CONSTANT]

Similarly when the infection rate was increased by 10 fold i.e. β = 3.3/day, we observed that the susceptible class individuals had a steep decline in their population and transformation rates into the infected class was quick and very high, and when plotted on longer time span it showed no recurrence of the disease.

VARIATION OF IMMUNITY LOSS (γ) BY 10 FOLD [KEEPING INFECTION RATE (β) & RATE OF RECOVERY (ν) CONSTANT]

When the rate of immunity loss was decreased by 10 fold i.e. γ = 0.07/day, we observe the change where in number of people being susceptible after being recovered will reduce. Similarly when the rate of immunity loss was increased by 10 fold i.e. γ = 7/day, we observed the change where in number of the people being susceptible after being recovered increased i.e. people being infected also increased certainly and we observe the rate of infection being increased and doesn't decrease linearly and completely, rather it decreases by small extent and continues to be in steady state. And when plotted for longer time span (400 days) we didn't observe any recurrence of the disease.

VARIATION OF RECOVERY RATE (ν) BY 10 FOLD [KEEPING INFECTION RATE (β) & RATE OF IMMUNITY LOSS (γ) CONSTANT]

When the recovery rate was decreased by 10 fold i.e. ν = 0.09/day w.r.t basal value, we observed the inclination in the recovery curve to be very slow and linear, which rose slowly and the infected individuals population hardly decreased. Similarly when the recovery rate was increased by 10 fold i.e. ν = 9/day w.r.t basal value, we observed the rate at which infected people were recovering was rapid and quick in very short span of time. The transformation of infected individuals to recovered class individuals was high. When the same was plotted on longer time span (400 days), we observed no recurrence of the disease.

Chapter - 3

BASIC DETERMINISTIC SEIR MODEL DEVELOPED FOR VISCERAL LEISHMANIASIS

Following the basic models discussed in the previous chapter, a biologically realistic model incorporating Human (H), Reservoirs (A) and Flies (F) is developed. This follow the structure of the basic Susceptible - Latent – Infected – Recovered (SEIR) type with suitable modification according to the biology of the disease.

The Human population is initially considered as Susceptible (S_H) with a birth rate (α_H) to a constant population of N_H and transmitted to Latent class (E_H). This population then goes different class such as Symptomatic infection (I_{Hs}), Asymptomatic infection (I_{Ha}), and Co-infected (I_{Hc}) with certain proportion according to the nature of the disease. There is a transmission of symptomatic patients developing PKDL (I_{Hp}). All these infected groups are then enter into the respective recovered classes R_{Hs}, R_{Ha}, R_{Hp} and R_{Hc}, Which further becomes susceptible with a rate K_H. Similarly the Reservoir population is also classified as susceptible animal (S_A), Latent animal (E_A), infected animal (I_A) and recovered animal (R_A).

The fly population is also classified accordingly to Susceptible (S_F), Latent fly (E_F), and Infected fly (I_F). The model equations describing all these classes are given below.

Basic SEIR type model for human population

- $dS_H/dt=\alpha_H N_H + K_H(R_{Hs}+R_{Ha}+R_{Hp}+R_{Hc})- \beta(P_{Hi}S_H I)/(N_H+N_A)-\mu_H S_H$
- $dE_H/dt=\beta(P_{HI}S_H I)/(N_H+N_A)-[b_{Hs}\sigma_{Hs}+b_{Hc}\sigma_{Hc}+(1-b_{Hc}-b_{Hs})\sigma_{Ha}]E_H-\mu_H E_H$
- $dI_{Hs}/dt=b_{Hs}\sigma_{Hs}E_H-(\mu_H+\gamma_{Hs}+b_{Hp}\rho_{Hp})I_{Hs}$
- $dI_{Ha}/dt=(1-b_{Hc}-b_{Hs})\sigma_{Ha}E_H-(\mu_H+\gamma_{Ha})I_{Ha}$
- $dI_{Hp}/dt=b_{Hp}\rho_{Hp}I_{Hs}-(\mu_H+\gamma_{Hp})I_{Hp}$
- $dI_{Hc}/dt=b_{Hc}\sigma_{Hc}E_H-(\mu_H+\gamma_{Hc}+\mu_{Hc})I_{Hc}$
- $dR_{Hs}/dt=\gamma_{Hs}I_{Hs}-(\mu_H+K_H)R_{Hs}$
- $dR_{Ha}/dt=\gamma_{Ha}I_{Ha}-(\mu_H+K_H)R_{Ha}$
- $dR_{Hp}/dt=\gamma_{Hp}I_{Hp}-(\mu_H+K_H)R_{Hp}$
- $dR_{Hc}/dt=\gamma_{Hc}I_{Hc}-(\mu_H+K_H)R_{Hc}$

Basic SEIR type model for animal population

- $dS_A/dt=\alpha_A N_A + K_A R_A - \beta(P_{Ai} S_A I)/(N_H+N_A)-\mu_A S_A$
- $dE_A/dt=\beta(P_{Ai} S_A I)/(N_H+N_A)- (\sigma_A +\mu_A)E_A$
- $dI_A/dt= \sigma_A E_A-(\mu_A+\gamma_A)I_A$
- $dR_A/dt=\gamma_A I_A -(\mu_A+K_A)R_A$

Basic SEI type model for fly population

- $dS_F/dt=\alpha_F N_F - \beta P_{fi}(f_{Hc} I_{Hc} + f_{Hp} I_{Hp} + f_{Hs} I_{Hs} + f_{Ha} I_{Ha}) S_F/(N_H+N_A)-\mu_F S_F - \beta(P_{Fi} I_A f_A S_F)/(N_H+N_A)-\mu_F S_F$
- $dE_F/dt= \beta P_{fi}(f_{Hc} I_{Hc} + f_{Hp} I_{Hp} + f_{Hs} I_{Hs} + f_{Ha} I_{Ha}) S_F/(N_H+N_A)+\beta(P_{Fi} I_A f_A S_F)/(N_H+N_A)-(\sigma_F+\mu_F) E_F$
- $dI_F/dt= \sigma_F E_F-\mu_F I_F$

Parameter values used in this model for simulation are mentioned in Table 1.

Table 1: Parameter values used for model simulation [13]

Parameters	Symbols	Values
Total No. of Humans	N_H	100000
Total No. of Animals	N_A	0
Total No. of Flies	N_F	500000
Birth rate of Human	α_H	$6.35*10^{-5}$/person/day
Birth Rate of Animal/Dog	α_A	0
Birth Rate of Flies	α_F	0.07
Mortality rates of Human	μ_H	$6.35*10^{-5}$/person/day
Mortality rates of Flies	μ_F	0.07
Human Excess mortality caused by Co-infection (e.g. HIV)	μ_{Hc}	$6.35*10^{-5}$/person/day
Total biting rates of Fly[bites/day]	β	10
Probability that the bite of an infected Fly infects Human	P_{Hi}	1
Probability that the bite of an infected Fly infects Animal/Dog	P_{Ai}	1
Probability that the Fly becomes infected from a infectious blood meal	P_{Fi}	1
Proportion of human who become Symptomatic infected	b_{Hs}	0.1
Proportion of Human who become Co-infected	b_{Hc}	0.1
Duration of the latent stage of Human who becomes Symptomatic carriers	$1/\sigma_{Hs}$	1/100
Duration of the latent stage of Human who becomes Asymptomatic carriers	$1/\sigma_{Ha}$	1/100
Duration of the latent stage of Human becomes Co-	$1/\sigma_{Hc}$	1/100

infected		
Proportion of symptomatic patients develop PKDL	b_{Hp}	0.1
Duration between developing symptoms and becoming PKDL	$1/\rho_{Hp}$	1/1000
Duration of the latent stage of Fly	$1/\sigma_F$	1
Duration of the latent stage of Animal/Dog	$1/\sigma_A$	0
Duration of the infectious period of Human Symp. Patients	$1/\gamma_{Hs}$	1/100
Duration of the infectious period of Human Asymp. Patients	$1/\gamma_{Ha}$	1/100
Duration of the infectious period of Human PKDL patients	$1/\gamma_{Hp}$	1/100
Duration of the infectious period of Human Co-infected Patients	$1/\gamma_{Hc}$	1/100
Duration of the infectious period of Animal/Dog	$1/\gamma_A$	0
Duration of the Human immunity to VL	$1/\kappa_H$	1/100
Duration of the Animal/Dog immunity to VL	$1/\kappa_A$	0
Weight for infection of flies from Human Co-infected patients = parasite density as measured as diagnostic	$(f_{Hc} = d_{Hc}/D)$ d_{Hc}	100
Weight for infection of flies from Human PKDL patients	$(f_{Hp} =$ $d_{Hp}/D)$ d_{Hp}	100
Weight for infection of flies from Human Symptomatic patients	$(f_{Hs} = d_{Hs}/D)$ d_{Hs}	10
Weight for infection of flies from Human Asymptomatic patients	$(f_{Ha} =$ $d_{Ha}/D)$ d_{Ha}	0
Weight for infection of flies from Animal/Dog	$(f_A = d_A)$ d_A	0
$D = d_{Hc} + d_{Hp} + d_{Hs} + d_{Ha}$		

SOLUTION OF SEIR MODEL FOR HUMANS:

A solution to the simple SEIR model, a plot with the differential equations with beta (**β**) = 10/day, and respective parameters mentioned above in the table, with the initial values $S_H(0)$ = 10000,E_H (0) =7500, $I_{Hs}(0)$ = 1200, I_{Ha} (0) = 600, I_{Hp} (0) = 300, I_{Hc} (0) = 0, R_{Hs} (0) = 0, R_{Ha} (0) = 0, R_{Hp} (0) = 0, R_{Hc} (0) = 0. Time span = 300 minutes (5 hours).

I. Susceptible and Exposed Curves for short time span:

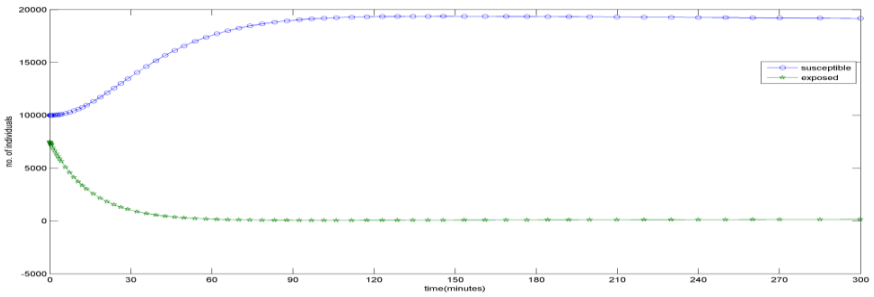


Figure 3.1 Short time dynamics of susceptible and exposed individuals

II. Infected class curves for short time span:

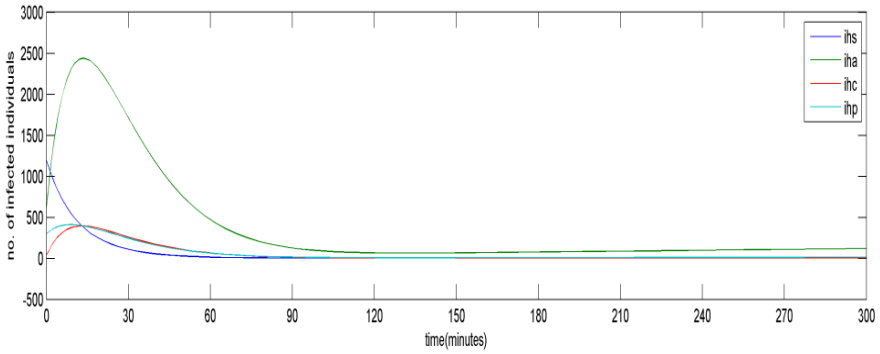


Figure 3.2 Short time dynamics of infected group individuals

III. Recovered class curves for short time span:

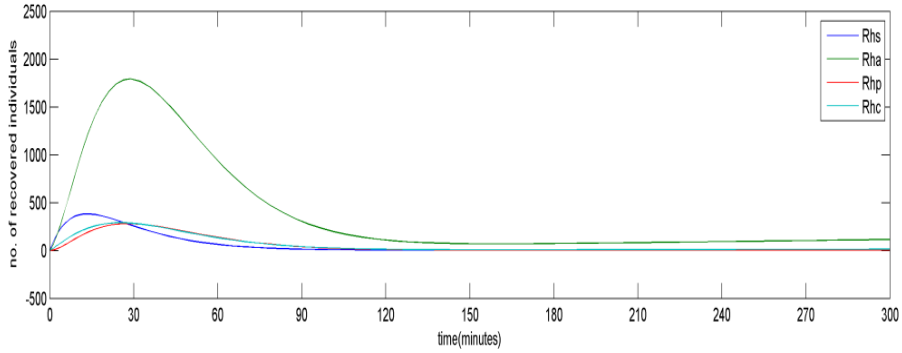


Figure 3.3 Short time dynamics of recovered group individuals

When plotted for 10 days, we observed the following observations (Figure 3.4 – 3.6).

i. Susceptible and exposed plots for humans:

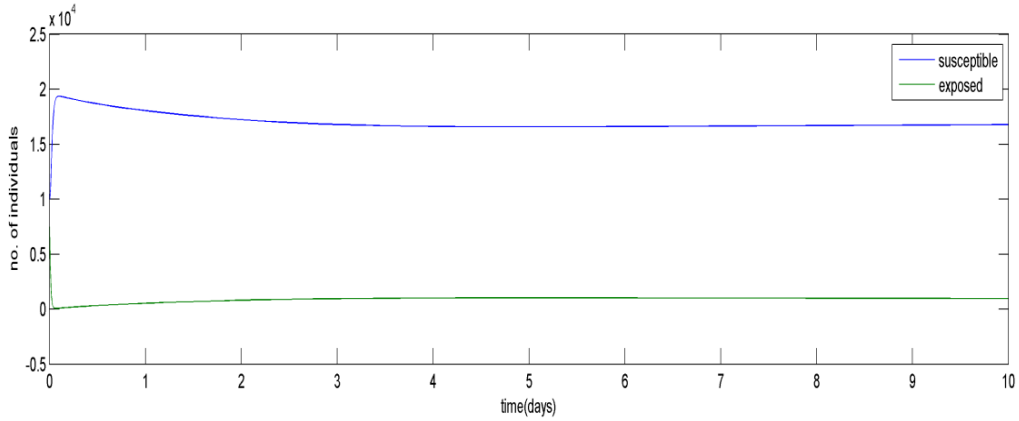


Figure 3.4 Time dynamics of susceptible and exposed individuals

ii. Infected Class plots for Humans:

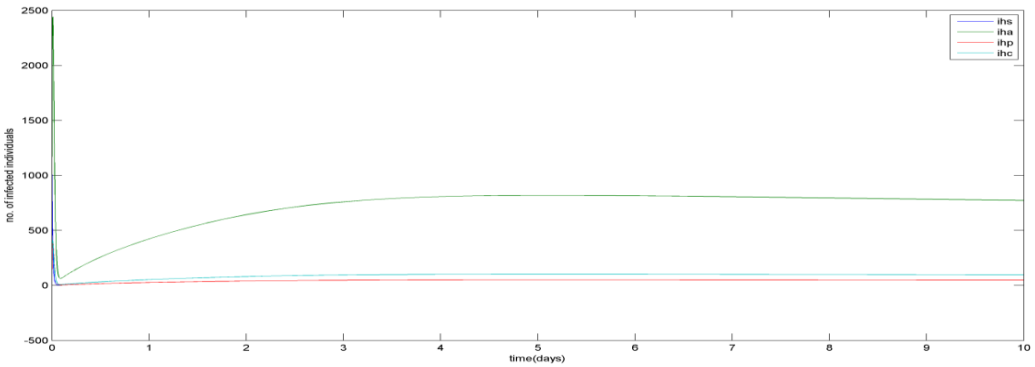


Figure 3.5 Time dynamics of infected group individuals

iii. Recovered Class plots for Humans:

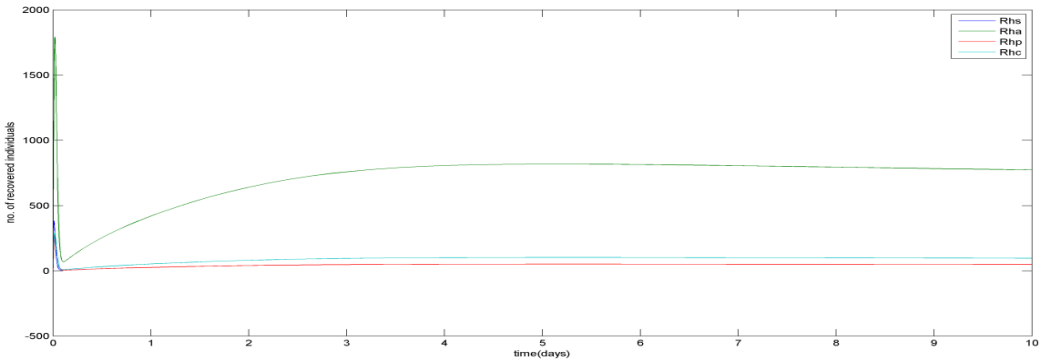


Figure 3.6 Time dynamics of recovered group individuals

From the above figures related to SEIR model for Humans, We observe the variation in the susceptible and exposed classes' individuals as we considered initial population of susceptible class to be 10000 individuals and exposed to be 7500 individuals. When plotted for time frames short span of 5 hours and 10 days, we observed the incline in the susceptible class individuals initially (Figure 3.1) and similarly it increased and followed by linear decrement when time frame was considered to be 10 days (Figure 3.4)

The Exposed class individuals were linearly being decreased (Figure 3.1) as they were being transformed into infected classes. Figure 3.4 clearly depicts the variation in the Exposed class being infected and stabilising by reaching the steady state.

Similarly the infected classes have also been subsequently rising initially, reached its peak (Figure 3.2) and after some time it was observed that the infected population number decreased, and reached steady state (Figure 3.5). Of all the infected sub classes asymptomatic infected individuals raised to the maximum extent comparatively to other sub infected classes. Whereas, the symptomatic infected individuals were linearly decreasing on the both the time spans (Figure 3.2 and Figure 3.5).

When the Recovered classes were observed, we noticed increment in all the sub classes of the Recovered group of Humans (Figure 3.3). There was a similar kind of pattern observed in both the infected and recovered sub groups where in both the plots we observed initial rise in the curves reaching peaks and drop certainly followed by gradual increment again and steady state arrival (Figure 3.6).

SOLUTION OF SEI MODEL FOR FLIES:

A solution to the simple SEI model, a plot with the differential equations and respective parameters mentioned above in the table 1, with the initial values $S_F(0) = 40000$, $E_F(0) = 35000$, $I_F(0) = 0$.

1. Time span = 300 minutes (5 hours)

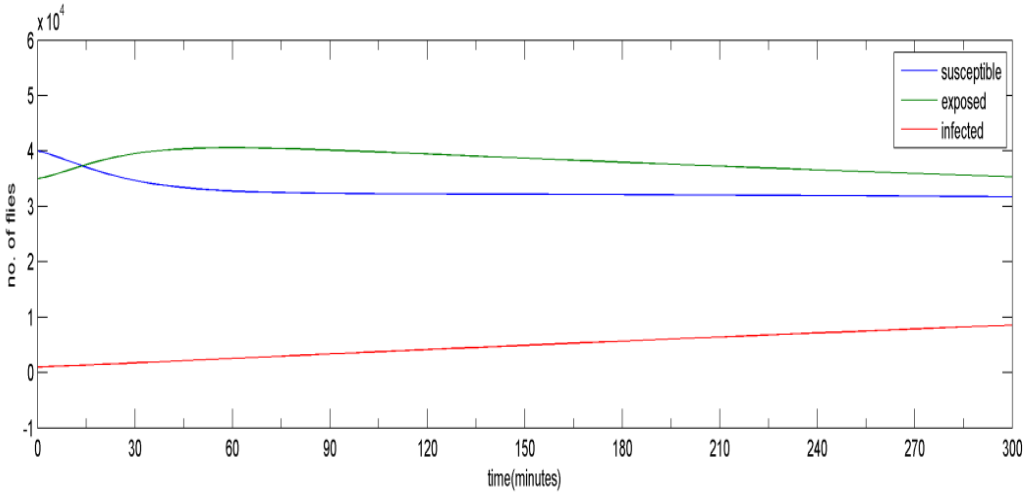


Figure 3.7 Short time dynamics for the fly population individuals

2. Time span = 10 days

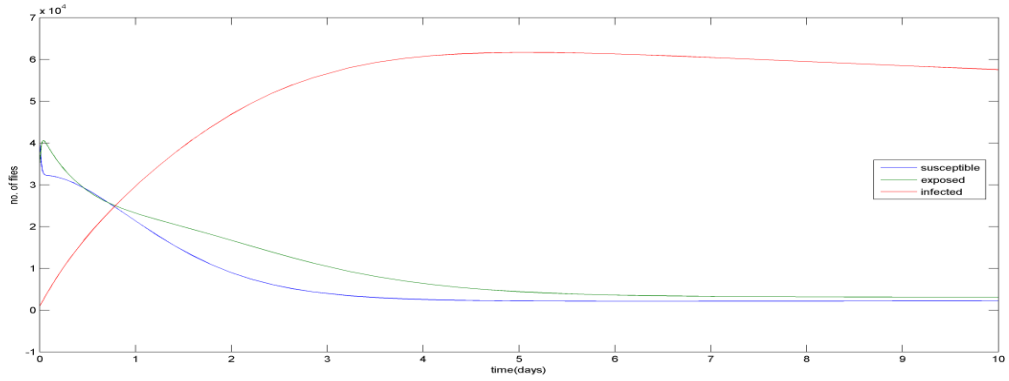


Figure 3.8 Time dynamics for the fly population individuals

3. Time span = 500 days

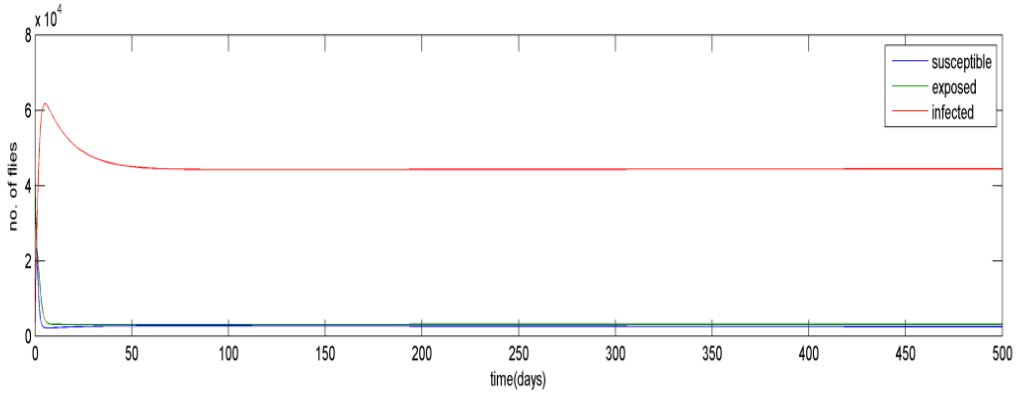


Figure 3.9 Time dynamics for the fly population individuals for longer run

In the above figures, we observe the rate of change among each compartmental class respectively in its various time frames. We see the susceptible class flies marginally decrease in the Figure 3.7, but when looked at it in the increasing time span (10 days and 500 days) Figure 3.8 and Figure 3.9, it clearly portrays the decrement in the susceptible population of flies as they are being exposed gradually, and ultimately being infected. Since there is no recovery possible in these flies they remain infected throughout their life span.

Figure 3.8, depicts the exposed class decreasing and infected class of flies increasing linearly on the time scale of 10 days which was considered as the basal time span while plotting the results. Whereas, the Figure 3.9 portrays the steady state condition of each compartmental class of the flies on time span 500 days.

SOLUTION OF SEIR MODEL FOR HUMANS

After varying the biting rates (**β**) given in Table 2, we solved the above equations and plotted figures 3.10-3.19.

Table 2: BETA (β) BITES/DAY VALUES

Notations	Beta(β) bites/day	color
Beta1	1	Black
Beta2	10	Red
Beta3	50	Green
Beta4	100	Blue

(i) Susceptible Human (S_H)

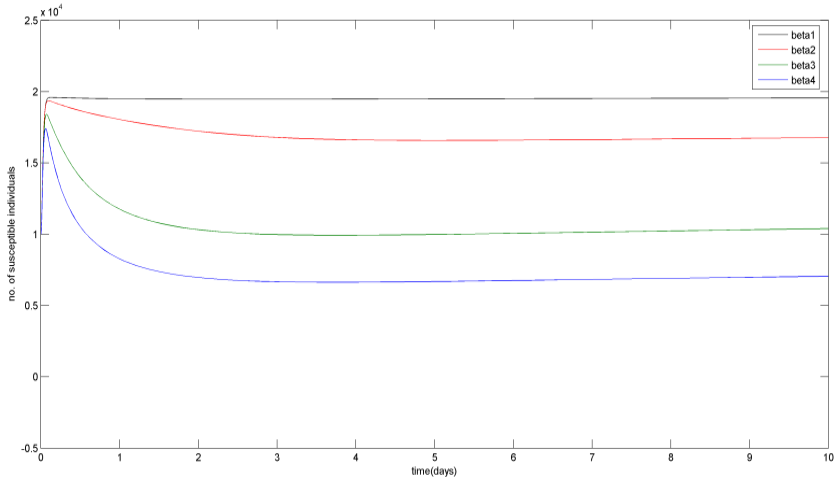


Figure 3.10 Time dynamics of susceptible human population for various beta values.

(ii) Exposed human (E_H)

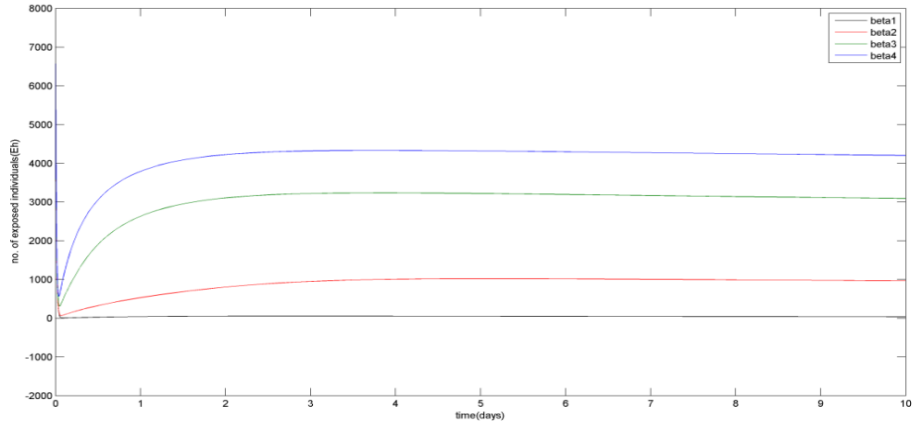


Figure 3.11 Time dynamics of exposed human population for various beta values

(iii) Infected symptomatic individuals (I_{Hs})

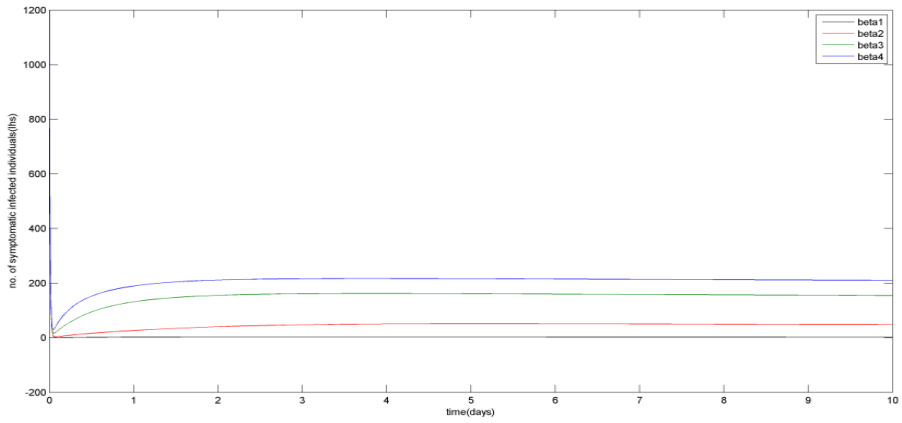


Figure 3.12 Time dynamics of infected symptomatic individuals for various beta values

(iv) Infected asymptomatic individuals (I_{Ha})

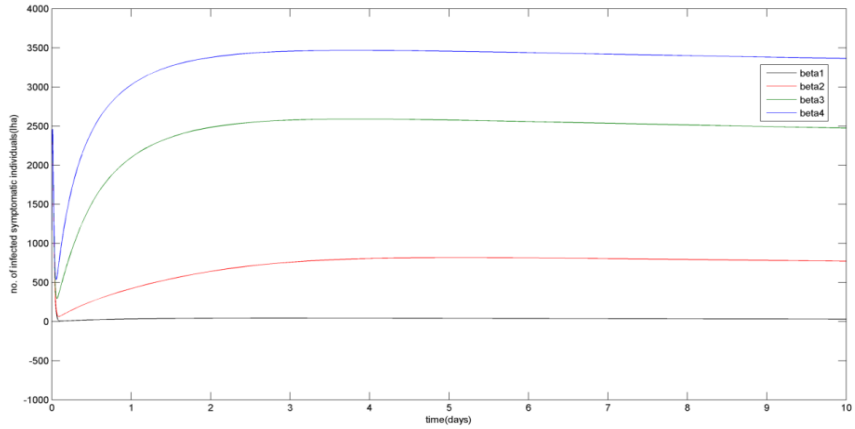


Figure 3.13 Time dynamics of infected asymptomatic individuals for various beta values

(v) Infected PKDL individuals (I_{Hp})

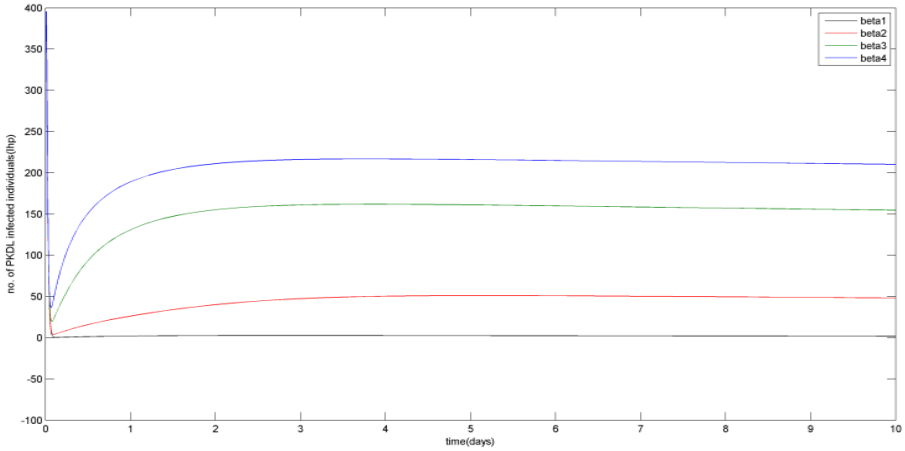


Figure 3.14 Time dynamics of infected PKDL individuals for various beta values

(vi) Co- infected individuals (I_{Hc})

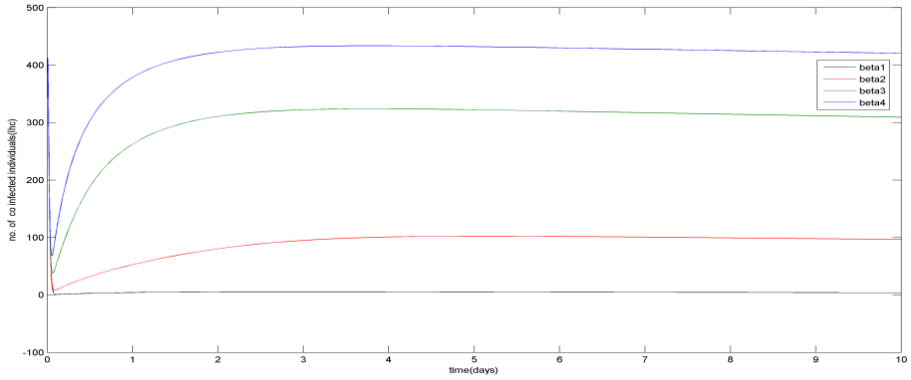


Figure 3.15 Time dynamics of co-infected individuals for various beta values

(vii) Recovered symptomatic individuals (R_{Hs})

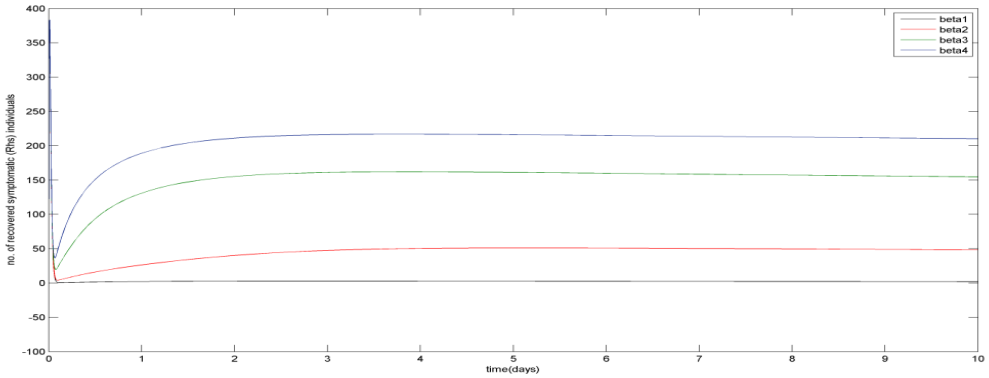


Figure 3.16 Time dynamics of recovered symptomatic individuals for various beta values

(viii) Recovered asymptomatic individuals (R_{Ha})

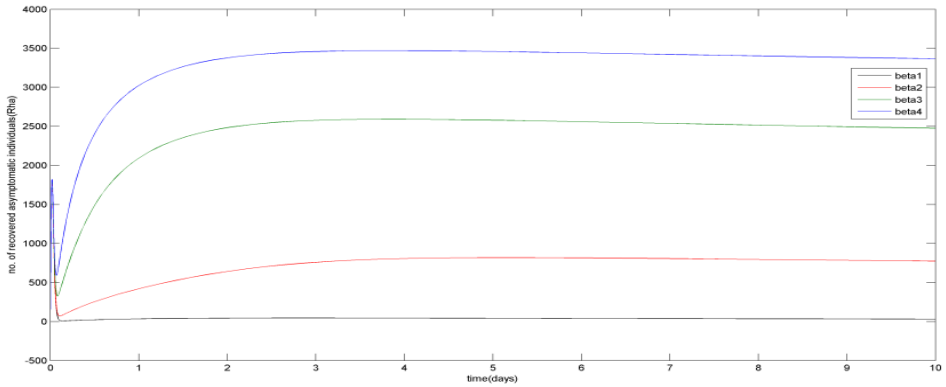


Figure 3.17 Time dynamics of recovered asymptomatic individuals for various beta values

(ix) Recovered PKDL individuals (R_{Hp})

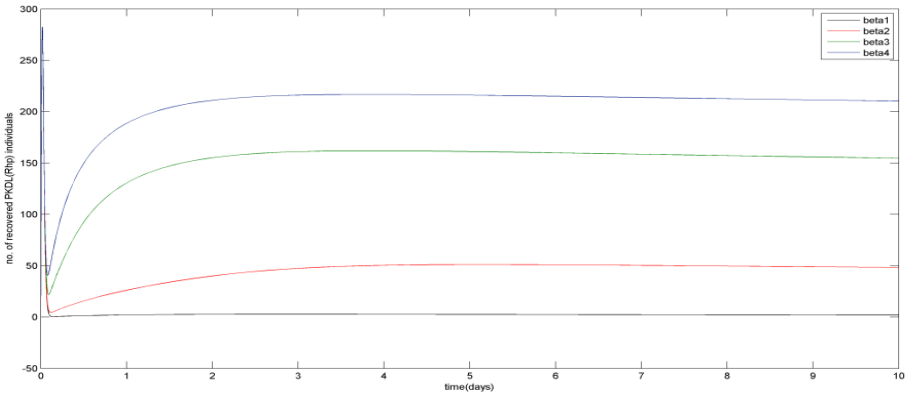


Figure 3.18 Time dynamics of recovered PKDL individuals for various beta values

(x) Recovered co- infected individuals (R_{Hc})

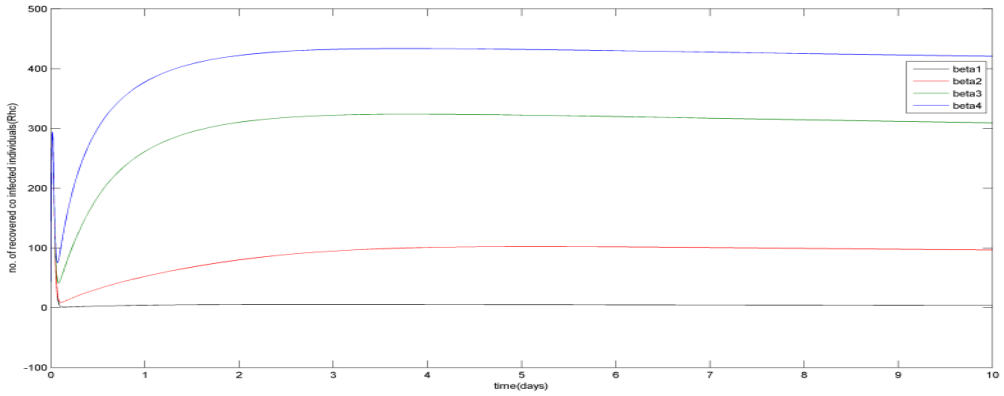


Figure 3.19 Time dynamics of recovered co-infected individuals for various beta values

From the above graphs we could clearly see the importance of the beta (β) the biting rate per day, as it was considered as the crucial parameter and plots were obtained for individual class of compartmental modelling for Humans and Flies, in order to understand the variation and its influence on the dynamics of the disease spread with the time span (10 days).

For the Susceptible class of humans when the biting rate (β) was altered with 1, 10, 50 and 100. We observed the variation in the Susceptible class to be increasing initially irrespective of the beta value but as time passed by, On considering beta 1(β=1), we could hardly see the decrement in the individuals number entering into the exposed class and the curve seemed to be reaching steady state without any declination.

The figure clearly depicts fall in the susceptible curve with increase in the beta value which is expected to be (Figure 3.10). Similarly for the exposed class of humans when the biting rate (β) was varied and observed, we noticed a steep drop from the initial value of exposed (E_H = 7500) for beta1 =1, as the beta value was increased we observed a declination in the curve initially and according raised. And it was clearly depicted, increase in the beta value increases the rate of infection and individuals moving from exposed class to infected class also subsequently increases and steady states were obtained (Figure 3.11).

Variation observed in the infected individuals with varied beta values, was similar to that of exposed class of humans, we observed increase in beta value increases the number of infected individuals which is expected to be (Figure 3.12 – Figure 3.15). Of which significant variation in the increment of infected individuals was observed in the sub class of infected individuals (Asymptomatic infected individuals) (Figure 3.13)

Variation observed in the recovered individuals with varied beta values, we observed increase in beta value brought about change in the rise of the curves, initially recovered class has zero individuals, but as time passed by the increased in the number hit the maximum peak and dropped to an extent depending on the beta value. Higher the beta value sooner was the declination or drop and it continued to stay steady (Figure 3.16 – Figure 3.19).

Steady state analysis for the SEIR of humans

In order to obtain the steady state values we simulated this model for time span of 1000 days with Initial Susceptible (S_H) population of 10000, and considering exposed population (E_H) of 7500, infected symptomatic (I_{Hs}) individuals being 1200, infected asymptomatic (I_{Ha}) individuals being 600 co Infected (I_{Hc}) being 300 individuals and 30 PKDL infected individuals (I_{Hp}). All the recovered classes i.e. recovered symptomatic (R_{Hs}), recovered asymptomatic (R_{Ha}), recovered Co Infected (R_{Hc} , recovered PKDL infected (R_{Hp}) individuals were 0. The summary of the analysis is shown in Table 3 and 4.

Table 3: Steady state values obtained from individual class of humans

Beta (per day)	Sh ($x10^4$)	Eh ($x10^4$)	Ihs ($x10^4$)	Iha ($x10^4$)	Ihp ($x10^4$)	Ihc ($x10^4$)	Rhs ($x10^4$)	Rha ($x10^4$)	Rhp ($x10^4$)	Rhc ($x10^4$)
10	2.1667	0.096	0.0048	0.0774	0.0048	0.0097	0.0048	0.0774	0.0048	0.0097
50	1.4451	0.3367	0.0168	0.2694	0.00168	0.0337	0.0168	0.2694	0.0168	0.0337
100	1.0225	0.4773	0.0239	0.3819	0.0239	0.0477	0.0239	0.3819	0.0239	0.0477

Table 4: Percentage Variation in susceptible and infected classes with respect to beta variation

Beta (per day)	Variation (%) of Sh	Variation (%) of Ihs	Variation (%) of Iha	Variation (%) of Ihp	Variation (%) of Ihc
10	0	0	0	0	0
50	-33.3%	250%	248%	-96.5%	247.4%
100	-52.8%	397%	393.4%	397.9%	384.5%

When steady states were obtained and recorded to calculate the variation in the increment or decrement in each of the sub classes of their respective compartments. We observed when beta was increased to 50 bites/day there was a decrement in the susceptible human population by 33.3% and similarly when beta was increased to 100 bites/day we observed decrement in the susceptible human population by 52.8%.

Interestingly when infected sub classes were observed, we found on increasing beta value to 50 bites/day that symptomatic infected individuals increased by 250% and the same when beta was increased to 100 bites/day it was noted to be increased by 397% .Similarly asymptomatic infected individuals increased by 248% when beta was 50 bites/day and increased by 393.4% when beta was 100bites/day.

It was interesting to note the variation in the post kala azar infected individuals as they were decreased by 96.5% when beta was 50 bites/day, but seemingly when beta value was increased to 100 bites/day, we noted the increase by 397.9%

On observing the co-infected individuals, when beta value was increased to 50 bites/day we observed the variation to be increased by 247.4% and when beta was 100 bites/day, we noted the percentage increment of co-infected individuals to be 384.5.

Chapter - 4

DISCUSSION

Modeling is an essential way to determine dynamics of a population. Creating a model to analysis a population lets us see how transmission/removal rates affect the compartmental classes. Parameters responsible for the change in the rates of transformation among the compartmental classes play major role in understanding the variation of the disease spread. Thus a simple deterministic Susceptible-Exposed-Infected-Recovered (SEIR) model for Visceral Leishmaniasis was developed with various parameters. This project is an attempt to understand the basic variation among the compartments when set of parameters were varied and draw understanding of disease spread.

In this project, we primarily worked on basic compartmental models of epidemiology such as SIR (Susceptible- Infected- Recovered), SI (Susceptible-Infected) and SIRS (Susceptible-Infected-Recovered-Susceptible) which benefited us in knowing the basics clearly. To observe the alterations in the population transformation we changed the parameter values by either increasing or decreasing with specific folds and plotted to various time frames in order to see if there was any recurrence of disease. Variation among the parameters was done by varying an individual parameter keeping the other parameters constant to clearly see the difference in the outcome.

On working with basic deterministic SEIR model for human, on considering the initial values when plotted we observed the change in the transformation compartmental classes and on labelling beta (no. of fly bites/day) as important parameter, we altered it from beta1 = 1, beta2 = 10, beta3 = 50, beta4 = 100, and plotted graphs for each compartmental class to observe the variation that was brought about in each compartmental class.

Similarly when worked on the basic deterministic SEI (Susceptible- Exposed- Infected) model that was developed for fly, we observed the variation in each of its compartmental class with respect to the time frames.

Our observations suggest that in order to decrease the disease spread we shall work on the implementation of policies that would be enforced on the vector control methods which would certainly decrease the beta (fly biting rate) value and helps in decreasing the disease spread.

REFERENCES

[1] The Center for food security and Public Health- report (2004)- Leishmaniasis (cutaneous and visceral), http://www.ivis.org/advances/Disease_Factsheets/leishmaniasis.pdf

[2] Asrat Hailu, Ahmed Mudawi Musa, Catherine Royce, Monique Wasunna (2005) Visceral Leishmaniasis: New Health Tools Are Needed. PLoS Med 2(7):e211. doi:10.1371/journal.pmed.0020211.

[3] Desjeux P (1996) Leishmaniasis. Public Health Aspects And Control. Clin Dermatol 14(5): 417– 423.

[4] K. Kishore, V. Kumar, S. Kesari, D.S. Dinesh, A.J. Kumar, P. Das & S.K. Bhattacharya (2006),Visceral leishmaniasis, Indian J Med Res 123: 467-472.

[5] Marcelo Ramalho-Ortigao, Elvira M. Saraiva and Yara M. Traub-Csekö (2010) Sand Fly-Leishmania Interactions: Long Relationships are Not Necessarily Easy, The Open Parasitology Journal, 195-204.

[6] http://home.btconnect.com/neqasteach/blood_methods.htm

[7] https://www.msu.edu/course/zol/316/lsppscope.htm

[8] The Center for food security and Public Health- report (2009)- Leishmaniasis (cutaneous and visceral), http://www.cfsph.iastate.edu/Factsheets/pdfs/leishmaniasis.pdf

[9] Hamer W (1906) Epidemic diseases in England—the evidence of variability and of persistency of type. Lancet 1, 733-739.

[10] Kermack WO, McKendrick AG (1927) Contribution to the mathematical theory of epidemics. Proc R Soc Lond A 115, 700-721.

[11] Anderson RM, May RM (1991) Infectious Diseases of Humans. Oxford, UK: Oxford University Press.

[12] Keeling MJ, Rohani P (2008) Modelling Infectious Diseases. New Jersey, USA: Princeton University Press.

[13] Anette Stauch , Ram Rup Sarkar , Albert Picado ,Bart Ostyn ,Shyam Sundar et. Al. (2011) Visceral Leishmaniasis In The Sub Continent: Modelling Epidemiology And Control. PLoS Neglected Tropical Diseases 5(11):e1405.

[14] Bauch, Chris, and David Earn (2003) "Interepidemic Intervals in Forced and Unforced SEIR models." Dynamical Systems and Their Applications in Biology. Ed. Shigui Ruan, Gail S. Wolkowicz and Jianhong Wu. New York: American Mathematical Society, 33-43.

[15] Rhodes, John A., and Elizabeth S. Allman (2003) Mathematical Models in Biology : An Introduction. New York: Cambridge UP, pp. 280-301.