ADAMA SCIENCE AND TECHNOLOGY UNIVERSITY

SCHOOL OF APPLIED NATURAL SCIENCES

DEPARTMENT OF MATHEMATICS

MATHEMATICAL MODELLING OF MALARIA TRANSMISSION WITH WANING IMMUNITY

By

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Abstract

We present a deterministic mathematical model for malaria transmission with waning immunity in humans. The model consists of five non-linear differential equations where the first three equations describes the human population and the mosquito population is described by the last two equations. We used next generation method to drive the basic reproduction number $\mathscr{R}_0$. The disease free equilibrium has been computed and its local stability has been shown by the virtue of the Jacobean matrix. Moreover, using Lyapunov function theory and LaSalle Invariance Principle we have proved that the disease free equilibrium is globally asymptotically stable whenever $\mathscr{R}_0$ is less than unity. Conditions for existence of endemic equilibrium point have been established. A qualitative study based on bifurcation theory reveals that backward bifurcation may occur. The stable disease free equilibrium of the model coexists with the stable endemic equilibrium when the basic reproduction number is less than one. We have shown that bringing the number of disease induced death rate below some threshold is enough to eliminate backward bifurcation. Numerical simulations were carried out using Matlab to support our analytical results.

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Finally, I would like to thank Ministry of Education; for the grant.

Glossary

DFE disease free equilibrium

EEP endemic equilibrium point

SI susptible infected

SIRS susptible infected recoverd susptible

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For,
Absar!

Chapter 1
Introduction

1.1 Background of the Study

Malaria is an infectious disease caused by the parasitic infections of red blood cells by a protozoan of the genus *Plasmodium* that are transmitted to people through the bites of infected female *Anopheles*[1] mosquitoes [1]. The name malaria was derived from the Medieval Italian word, *mal aria*(bad air), thinking that the foul vapours emanating from the stagnate water and swamps were the cause of fever, a major symptom of the disease. Surprisingly, the cause of malaria was not known from the dawn of history until the later part of the 19th century, when Charles Laveran discovered the malaria parasite in human blood in Africa. Consequently, Giovanni Grassi and Raimondo Filetti used the word Plasmodium to name the malaria parasite and in 1897, Ronald Ross demonstrated that Plasmodium parasite can be transmitted from infected human to mosquitoes.

The malaria parasite requires two hosts to complete its life cycle, the vector female *Anopheles* mosquito and human. *Anopheles* mosquitoes become infected when they feed and ingest human blood that contains mature gametocytes. The gametocytes develop into male and female gametes that fertilize to become zygotes in the mid-gut wall of the mosquito. The zygote elongates to become ookinete and penetrates the mid-gut epithelium that later develops and ultimately produces sporozoites, which become infective when they migrate to the salivary glands [2].

The development of malaria parasites in a human host commences inside the liver cells where the malaria parasites undergo asexual multiplication to produce merozoites that are eventually released into the bloodstream to invade red blood cells. Then

the infected red blood cells burst after 2 – 3 days to release merozoites and gametocytes into the blood stream. This is associated with the clinical symptoms such as fever, pain, chills and sweats may develop a few days after infected mosquito bites. The infection can lead to serious complications affecting the brain, lungs, kidneys and other organs [3].

About 3.2 billion people, nearly half of the world's population, are at risk of malaria. In 2015, there were roughly 214 million malaria cases and an estimated 438,000 malaria deaths. Increased prevention and control measures have led to a 60% reduction in malaria mortality rates globally since 2000. Sub-Saharan Africa continues to carry a disproportionately high share of the global malaria burden. In 2015, the region was home to 89% of malaria cases and 91% of malaria deaths [1]. The environmental conditions in the tropics are the prime factor for malaria being endemic. The moderate-to-warm temperatures, high humidity and water bodies allow mosquito and parasites to reproduce. The epidemiological patterns of malaria usually vary with season because of the dependence of transmission on mosquito. Malaria control is chal-

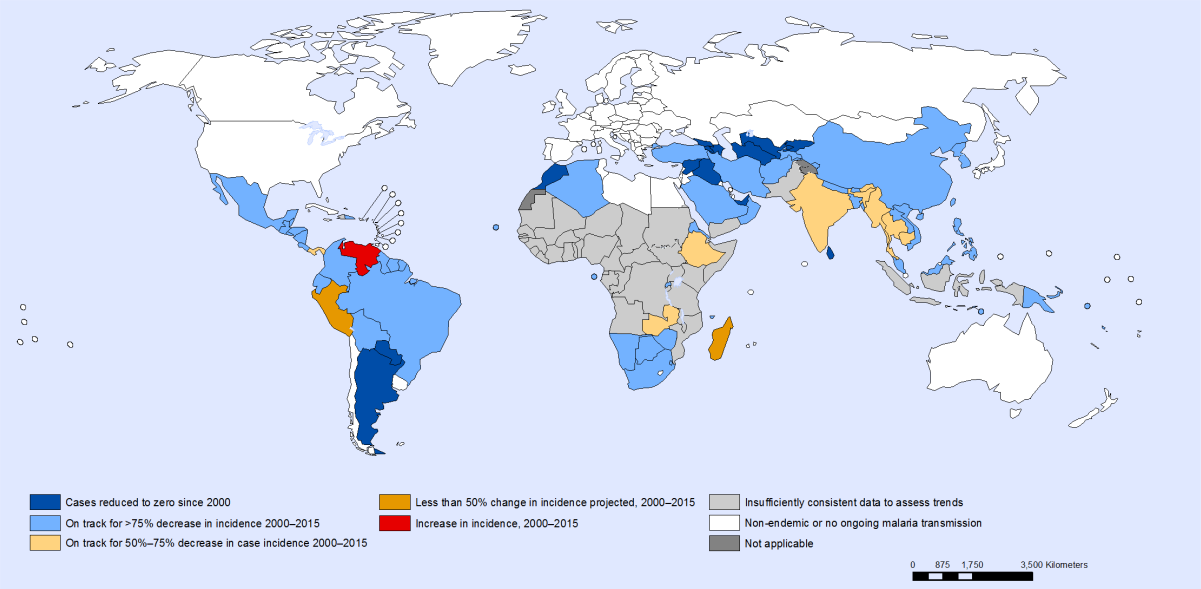


Figure 1.1: Malaria incidence rate 2000-2015, Source: World Malaria Report 2015, [1].

lenging due to many factors. The complexity of the disease control process, the cost of the control program and resistance of the parasite to anti-malarial drugs, and vectors to insecticides, are some of the challenges. There is a variation in disease patterns and transmission dynamics from place to place, by season and according to varying environmental circumstances. The approaches in the planning and implementation

of prevention and control activities also vary based on local realities.

Since malaria increases morbidity and mortality, it continues to inflict major public health and socioeconomic burdens in developing countries. It is clear that poverty, while not a disease in itself, is a contributing factor not only for malaria, but also for almost all diseases that face mankind. Because of poverty, communities may have poor sanitation and poor drainage, and these two factors allow the mosquitoes to breed in ever greater numbers. Poverty also means that people will not be able to afford the simple protection of a mosquito net or even screens for their windows. A favourite hiding place for the Anopheles is in a dark, moist room. With an increased number of vectors living with human becomes an increased chance of being bitten by an infected mosquito, which will in turn infect the person with the parasite [4].

Malaria has for several years been thought of as a worldwide issue, and several epidemiologists and different scientists spent their endeavour in learning the dynamics of malaria to control its spread.

1.2 Statement of the Problem

Malaria has for many years been considered as a global issue, and many epidemiologists and other scientists invest their effort in learning the dynamics of malaria and to control its transmission. From interactions with those scientists, mathematicians have developed a significant and effective tool, namely mathematical models of malaria, giving an insight into the interaction between the host and vector population, the dynamics of malaria, how to control malaria transmission, and eventually how to eradicate it. Mathematical modelling of malaria has flourished since the days of Ronald Ross, who received the *Nobel Prize* in Physiology or Medicine in 1902 for his work on the life cycle of the malaria parasite. Ross developed a simple SIS-model. After many years, Yang et al. [5] proposed SIR for the human and SI for the vector compartment model. But in their model, Yang et. al. assumed that the number of births for human and mosquito are independent of the total human and mosquito population. This assumption was later modified by Abadi and Krogstad [6] by making the number of births for human and mosquito dependent of the total human and mosquito population. However, Abadi and Krogstad made an assumption that, once the humans enter the recovered class they never go to the susceptible class again. Yet malaria does not confer permanent immunity [7]. The recovered humans have a chance to be susceptible again. So we will modify the model in [6] by replacing the assumption of permanent immunity by an immunity which wanes through time. Therefore, this research work will try to address the following basic questions

1. What are the dynamics of malaria transmission?
2. What are the basic assumptions to develop a mathematical model which describes the dynamics of the transmission of malaria?
3. What are the mathematical models, which describe the dynamics of malaria and its transmission?
4. Which parameter plays greater role in the dynamics of malaria transmission?
5. What are the biological interpretations of the solution of the mathematical model which describes the dynamics?

1.3 Objectives of the Study

1.3.1 General Objective

The general objective of this research work is to understand the dynamics of malaria and its transmission.

1.3.2 Specific Objectives

The specific objectives of the study are to

- Develop a mathematical model which describes the dynamics of malaria and its transmission.
- Investigate the qualitative behaviour of the mathematical model.
- Examine the biological implications of the analysis.
- Interpret the biological implication of the solutions.

1.4 Significance of the Study

The significance of this study is to

- Develop awareness about the dynamics of malaria and its transmission.
- Suggest the possible intervention mechanisms.
- Improve our understanding of the dynamical properties of malaria and its transmission.

Chapter 2

Literature Review

Mathematical modelling of malaria began with Ronald Ross while working at the Indian Medical Service in 1911 [8, 9]. He developed a simple model, now known as the classical "Ross model" [10], which explained the relationship between the number of mosquitoes and incidence of malaria in humans. From the Ross's model, several models have been developed by researchers who extended his model by considering different factors such as latent period of infection in mosquitoes and humans [11, 12], age-related differential susceptibility to malaria in human population [11, 13, 14], acquired immunity [13, 15, 16], and genetic heterogeneity of host and parasite [17–21].

Ross in his first mathematical model of malaria used the word "pathometry" to mean "quantitative study of a disease either in the individual or in the community". Through his model, he showed that reduction of mosquito numbers "below a certain figure" (transmission threshold) was sufficient to control malaria [10]. The major advantage in Ross's models was his ability to provide a suitable control strategy through the transmission threshold criterion which is based on the reproductive capacity of the parasite and is termed as the basic reproductive number (R_0). Although the idea of threshold was first introduced by Ross, it originated from Fisher's "net reproductive value" for a parasite [22].

In 1911, Ross introduced the first deterministic differential equation model of malaria by dividing the human population into susceptible (S_h) and infected (I_h) compartments, with the infected class returning to susceptible class again leading to the SIS structure. The mosquito population also has only two compartments susceptible(S_m) and infected (I_m), but they do not recover from infection due to their short lifespan, and thereby follow the SI structure.

Ross did not consider the latency period of the parasite in mosquitoes and their sur-

vival during that period in his model. This resulted in the model predicting a rapid progress of the epidemic in human and a higher equilibrium prevalence of infectious mosquitoes. After about 40 years, George Macdonald, in the 1950s, reasserted the value of mathematical epidemiology based on 20 years of fieldwork. He modified Ross's model and obtain the so-called Ross-Macdonald model, which still is the basis for much malarial epidemiology [13]. This Ross-Macdonald model is defined as

$$\begin{aligned} \frac{dx}{dt} &= \left(\frac{abM}{N}\right) y(1-x) - rx \\ \frac{dy}{dt} &= ax(1-y) - \mu y \end{aligned} \tag{2.0.1}$$

where x is the fraction of infectious humans; y is the fraction of infectious female mosquitoes; a is the number of bites on humans by a single female mosquito per unit time, usually day; b is the probability of transmission of infection from an infected mosquito to a susceptible human per bite; M is the size of the total female mosquito population; N is the size of the total human population; r is the rate of recovery for infectious humans; and μ is the death rate of the female mosquito population [23]. He develop (2.0.1) by integrating biological information of latency in the mosquito due to malaria parasite development, and concerned the survivorship of adult female mosquito as the weakest element in the malaria cycle. This provided the basis for a massive World Health Organization (WHO) coordinated campaign, which focused on using the insecticide dichlorodiphenyltrichloroethane (DDT) that killed mosquitoes, which resulted in the elimination of malaria transmission among 500 million people in Africa .

Macdonald termed the latency period as t_m, and introduced the Exposed (E_m) class in the mosquitoes. Therefore, in his model the mosquito population is divided into three compartments (SEI), and the model studies the time evolution of the exposed (E_m) and infected (I_m) classes in mosquito [12].

Total population size was assumed to be constant for all malaria models which came before Ngwa and Shu's model. Ngwa and Shu [24] proposed an immunity model in which disease related death rate is considered to be significantly high, and the total population is not constant. The Ngwa-Shu model consists of four compartments in humans Susceptible (S_h), Exposed (E_h), Infected (I_h) and Immune (R_h) and three com-

partments in mosquitoes Susceptible (S_m), Exposed (E_m), Infected (I_m). Mathematical analysis of the model shows that the basic Reproductive number, R_0, can describe the malaria transmission dynamics of the disease, where a globally stable disease-free state exists if $R_0 < 1$, while for $R_0 > 1$, the endemic equilibrium becomes globally stable. This model explicitly shows the role of inclusion of demographic effects (net population growth) in predicting the number of fatalities that may arise as a result of the disease.

Yang et al. [5] proposed SIR for the human and SI for the vector compartment model. But in their model, Yang et. al. assumed that the number of births for human and mosquito are independent of the total human and mosquito population. This flaw was modified afterwards by Abadi and Krogstad [6] by making the number of births for human and mosquito dependent of the total human and mosquito population. However, Abadi and Krogstad made an assumption that, once the humans enter the recovered class they never go to the susceptible class again. Yet malaria does not confer permanent immunity [7]. After some period, the recovered humans lose their immunity and return to the susceptible class. So we will modify the model in [6] by replacing the assumption of permanent immunity by an immunity which wanes as time goes. Thus, our model is SIRS for human population and SI for mosquito population.

Chapter 3

Model Formulation and Analysis

3.1 Model Formulation

In this section, we formulate a mathematical model of malaria transmission with waning immunity. Because humans might repeatedly infected due to not acquiring permanent immunity, the human population is assumed to be described by the SIRS model. Mosquitoes are assumed not to recover from the parasites due to their short lifespan so the mosquito population is described by the SI model. Recovered human hosts have temporary immunity that can be lost and are again susceptible to reinfection. All newborns are susceptible to infection, and the development of malaria starts when the infectious female mosquito bites the human host. The vectors do not die from the infection or are otherwise harmed. The flowchart of the model is shown in Figure 3.1.

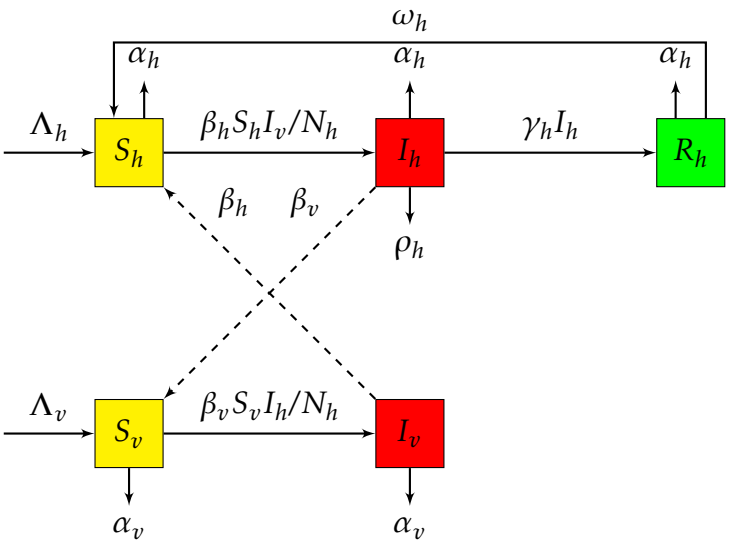


Figure 3.1: Malaria model flowchart

Table 3.1: State variables of malaria model

Symbol	Description
S_h	The number of susceptible human population
I_h	The number of infected human population
R_h	The number of recovered human population
S_v	The number of susceptible mosquito population
I_v	The number of infected mosquito population

Table 3.2: Parameters of malaria model

Symbol	Description
Λ_h	The recruitment rate of humans
α_h	The natural death rate of humans
β_h	The human contact rate
γ_h	Per capita recovery rate for humans
ρ_h	Per capita disease-induced death rate for humans
ω_h	The per capita rate of loss of immunity in humans
Λ_v	The recruitment rate of mosquitoes
α_v	The natural death rate of mosquitoes
β_v	The mosquito contact rate

The flowchart leads to the following system of non-linear ordinary differential equations

$$\left.\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h - \frac{\beta_h S_h I_v}{N_h} + \omega_h R_h - \alpha_h S_h \\
\frac{dI_h}{dt} &= \frac{\beta_h S_h I_v}{N_h} - \gamma_h I_h - \rho_h I_h - \alpha_h I_h \\
\frac{dR_h}{dt} &= \gamma_h I_h - \omega_h R_h - \alpha_h R_h \\
\frac{dS_v}{dt} &= \Lambda_v - \frac{\beta_v S_v I_h}{N_h} - \alpha_v S_v \\
\frac{dI_v}{dt} &= \frac{\beta_v S_v I_h}{N_h} - \alpha_v I_v
\end{aligned}\right\} \tag{3.1.1}$$

subjected to the initial condition

$$S_h(0) = S_{h0}, I_h(0) = I_{h0}, R_h(0) = R_{h0}, S_v(0) = S_{v0}, I_v(0) = I_{v0}$$

where $S_h, I_h, R_h, S_v, I_v, N_h$ and N_v represent the number of susceptible humans, infectious humans, recovered humans, susceptible mosquitoes, infectious mosquitoes, the total size of the human population, and the total size of the mosquito population, respectively. All the parameters can be found in Table 3.2.

In the model, the term $\frac{\beta_h S_h I_v}{N_h}$ denotes the rate at which the human hosts S_h get infected by infected mosquitoes I_v and $\frac{\beta_v S_v I_h}{N_h}$ refers to the rate at which the susceptible mosquitoes S_v are infected by the infected human hosts I_h.

The total population sizes N_h and N_v can be determined by $N_h = S_h + I_h + R_h$ and $N_v = S_v + I_v$ or from the differential equations

$$\frac{dN_h}{dt} = \Lambda_h - \alpha_h N_h - \rho_h I_h, \tag{3.1.2}$$

$$\frac{dN_v}{dt} = \Lambda_v - \alpha_v N_v \tag{3.1.3}$$

which are derived by adding the first three equations of the system (3.1.1) for the human population and the last two equations of the system (3.1.1) for mosquito vector population.

3.1.1 Invariant Region

The model represented by the system (3.1.1) will be analyzed in the feasible region and since we are working with population all state variables and parameters are assumed to be positive. The invariant region can be obtained by the following theorem.

Theorem 3.1.1 The solutions of the system (3.1.1) are feasible for all $t > 0$ if they enter the invariant region $\Omega = \Omega_h \times \Omega_v$.

Proof: Let $(S_h, I_h, R_h, S_v, I_v) \in \mathbb{R}^5_+$ be any solution of the system (3.1.1) with non-negative initial conditions. For simplicity, we split the solution into two parts; the human population, N_h and the mosquito vector population, N_v. In the absence of the disease(malaria), i.e $I_h = 0$, equation (3.1.2) becomes

$$\frac{dN_h}{dt} + \alpha_h N_h \leq \Lambda_h$$

Solving for N_h yields

$$N_h \leq \frac{\Lambda_h}{\alpha_h} + Ce^{-\alpha_h t}, \qquad \text{where } C \text{ is constant.}$$

Using the initial conditions at $t = 0$, $N_h(0) = N_{h0}$

$$N_h \leq \frac{\Lambda_h}{\alpha_h} + \left(N_{h0} - \frac{\Lambda_h}{\alpha_h}\right)e^{-\alpha_h t}$$

Which can be easily obtained by applying the theorem for differential inequality [25]. Then

$$0 \leq N_h \leq \frac{\Lambda_h}{\alpha_h}$$

Therefore, as $t \to \infty$ the human population N_h approaches the parameter $K = \frac{\Lambda_h}{\alpha_h}$ which is usually called the carrying capacity. Hence all feasible solutions set of the human population of the model (3.1.1) enters the region

$$\Omega_h = \left\{(S_h, I_h, R_h) \in \mathbb{R}^3_+ : S_h + I_h + R_h \leq \frac{\Lambda_h}{\alpha_h}\right\}$$

Similarly, the feasible solutions set of the mosquito enters the region

$$\Omega_v = \left\{(S_v, I_v) \in \mathbb{R}^2_+ : S_v + I_v \leq \frac{\Lambda_v}{\alpha_v}\right\}$$

Therefore, the feasible solution set for the malaria model (3.1.1), given by $\Omega = \Omega_h \times \Omega_v$ is positively invariant and hence the model is biologically meaningful and mathematically well-posed in the domain Ω. □

3.1.2 Positivity of Solutions

For the system (3.1.1) with a non-negative initial data to be epidemiologically meaningful and consistent, we need to prove that all the state variables must remain non-negative $\forall t \geq 0$.

Theorem 3.1.2 Let the initial conditions of system (3.1.1) be positive. Then the solutions $(S_h(t), I_h(t), R_h(t), S_v(t), I_v(t))$ of the system is non-negative for all $t \geq 0$.

Proof: From the first equation of the system (3.1.1), we have

$$\begin{aligned}\frac{dS_h}{dt} &= \Lambda_h - \lambda_h S_h + \omega_h R_h - \alpha_h S_h, \qquad \text{where } \lambda_h = \beta_h I_v / N_h, \\ &\geq -(\lambda_h + \alpha_h) S_h\end{aligned}$$

Then

$$\frac{dS_h}{S_h} \geq -(\lambda_h + \alpha_h) dt$$

which implies

$$\ln S_h \geq -(\lambda_h + \alpha_h)t + c, \qquad \text{where } c \text{ is constant.}$$

Hence, using the initial condition we obtain

$$S_h(t) \geq S_h(0) e^{-(\lambda_h + \alpha_h)t} \geq 0$$

And from the second equation of the system (3.1.1), we have

$$\frac{dI_h}{dt} = \lambda_h S_h - \gamma_h I_h - \rho_h I_h - \alpha_h I_h \geq -(\gamma_h + \rho_h + \alpha_h) I_h$$

In a similar manner, we get

$$I_h(t) \geq I_h(0) e^{-(\gamma_h + \rho_h + \alpha_h)t} \geq 0$$

From the third equation of the system (3.1.1), we have

$$\frac{dR_h}{dt} = \gamma_h I_h - \omega_h R_h - \alpha_h R_h \geq -(\omega_h + \alpha_h) R_h$$

Thus,

$$R_h(t) \geq R_h(0) e^{-(\omega_h + \alpha_h)t} \geq 0$$

From the fourth equation of the system (3.1.1), we have

$$\begin{aligned}\frac{dS_v}{dt} &= \Lambda_v - \lambda_v S_v - \alpha_v S_v, \qquad \text{where } \lambda_v = \beta_v I_h / N_h, \\ &\geq -(\lambda_v + \alpha_v) S_v\end{aligned}$$

Hence,

$$S_v(t) \geq S_v(0)e^{-(\lambda_h+\alpha_h)t} \geq 0$$

Finally, from the fifth equation of the system (3.1.1), we have

$$\frac{dI_v}{dt} = \lambda_v S_v - \alpha_v I_v \geq -\alpha_v I_v$$

Thus,

$$I_v(t) \geq I_v(0)e^{-\alpha_v t} \geq 0$$

□

3.2 Model Analysis

3.2.1 The Basic Reproduction Number

Intuitively from the epidemiological point of view, the basic reproduction number(R_0)[2] is the average number of new cases(infections), that one infected case will generate during their entire infectious lifetime [26]. It is very important in determining whether the disease persist in the population or die out.

We use the next generation method[3] to compute R_0. Let us assume that there are n compartments of which the first m compartments correspond to infected individuals. Let

- ➔ $\mathscr{F}_i(x)$ be the rate of appearance of new infections in compartment i,
- ➔ $\mathscr{V}_i^+(x)$ be the rate of transfer of individuals into compartment i by all other means, and
- ➔ $\mathscr{V}_i^-(x)$ be the rate of transfer of individuals out of compartment i.

It is assumed that each function is continuously differentiable at least twice in each variable. The disease transmission model consists of nonnegative initial conditions together with the following system of equations:

$$\frac{dx_i}{dt} = f_i(x) = \mathscr{F}_i(x) - \mathscr{V}_i(x), \quad i = 1, \ldots, n, \tag{3.2.4}$$

where $\mathscr{V}_i(x) = \mathscr{V}_i^-(x) - \mathscr{V}_i^+(x)$.

The next step is the computation of the $m \times m$ square matrices F and V which are defined by

$$F = \left[\frac{\partial \mathscr{F}_i}{\partial x_j}(x_0)\right] \text{ and } V = \left[\frac{\partial \mathscr{V}_i}{\partial x_j}(x_0)\right] \text{ with } 1 \leq i, j \leq m.$$

such that F is non-negative, V is a non-singular M-matrix[4] and x_0 is the disease free equilibrium point (DFE) of (3.2.4). Since F is non-negative and V is non-singular, then of V^{-1} is nonnegative and also of FV^{-1} is non-negative. The matrix FV^{-1} is called the next generation matrix [27]. Finally, the basic reproduction number is given by

$$R_0 = \rho(FV^{-1})$$

where $\rho(A)$ denotes the spectral radius[5] of a matrix A and the spectral radius, $\rho(FV^{-1})$, is the biggest non-negative eigenvalue of the next generation matrix.

To determine the basic reproduction number, let us rewrite the system (3.1.1) starting with the infected compartments for both populations; I_h, I_v and followed by uninfected classes; S_h, R_h, S_v also from the two populations, then the system becomes

$$\left.\begin{aligned}
\frac{dI_h}{dt} &= \frac{\beta_h S_h I_v}{N_h} - \gamma_h I_h - \rho_h I_h - \alpha_h I_h \\
\frac{dI_v}{dt} &= \frac{\beta_v S_v I_h}{N_h} - \alpha_v I_v \\
\frac{dS_h}{dt} &= \Lambda_h - \frac{\beta_h S_h I_v}{N_h} + \omega_h R_h - \alpha_h S_h \\
\frac{dR_h}{dt} &= \gamma_h I_h - \omega_h R_h - \alpha_h R_h \\
\frac{dS_v}{dt} &= \Lambda_v - \frac{\beta_v S_v I_h}{N_h} - \alpha_v S_v
\end{aligned}\right\} \tag{3.2.5}$$

From the system (3.2.5), $\mathscr{F}$ and $\mathscr{V}$ are defined as

$$\mathscr{F} = \begin{pmatrix} \frac{\beta_h S_h I_v}{N_h} \\ \\ \frac{\beta_v S_v I_h}{N_h} \end{pmatrix} \tag{3.2.6}$$

and

$$\mathscr{V} = \begin{pmatrix} (\gamma_h + \rho_h + \alpha_h) I_h \\ \\ \alpha_v I_v \end{pmatrix} \tag{3.2.7}$$

The Jacobian matrix of (3.2.6) at the DFE $E_0 = (S_h^0, I_h^0, R_h^0, S_v^0, I_v^0) = \left(\frac{\Lambda_h}{\alpha_h}, 0, 0, \frac{\Lambda_v}{\alpha_v}, 0\right)$ is

$$F = \begin{pmatrix} 0 & \beta_h \\ \\ \frac{\beta_v \Lambda_v / \alpha_v}{\Lambda_h / \alpha_h} & 0 \end{pmatrix}$$

Similarly, the Jacobian matrix of (3.2.7) at the DFE E_0 is

$$V = \begin{pmatrix} \gamma_h + \rho_h + \alpha_h & 0 \\ \\ 0 & \alpha_v \end{pmatrix}$$

The inverse of V is

$$V^{-1} = \begin{pmatrix} \frac{1}{\gamma_h + \rho_h + \alpha_h} & 0 \\ \\ 0 & \frac{1}{\alpha_v} \end{pmatrix}$$

Therefore, our next generation matrix is

$$FV^{-1} = \begin{pmatrix} 0 & \frac{\beta_h}{\alpha_v} \\ \\ \frac{\beta_v \Lambda_v \alpha_h}{\alpha_v \Lambda_h (\gamma_h + \rho_h + \alpha_h)} & 0 \end{pmatrix}$$

The eigenvalues of the next generation matrix are

$$-\sqrt{\frac{\beta_h \beta_v \Lambda_v \alpha_h}{\Lambda_h \alpha_v^2 (\gamma_h + \rho_h + \alpha_h)}}, \qquad \text{and} \qquad \sqrt{\frac{\beta_h \beta_v \Lambda_v \alpha_h}{\Lambda_h \alpha_v^2 (\gamma_h + \rho_h + \alpha_h)}}$$

Which were computed using Maple^{TM}.

Since R_0 is the biggest non-negative eigenvalue of the next generation matrix, we have

$$R_0 = \sqrt{\frac{\beta_h \beta_v \Lambda_v \alpha_h}{\Lambda_h \alpha_v^2 (\gamma_h + \rho_h + \alpha_h)}}$$

Then the reproduction number is given by

$$R_0 = \sqrt{R_{0v} R_{0h}}$$

where

- $R_{0v} = \frac{\beta_v \Lambda_v}{\alpha_v^2}$ is the contribution of the mosquito population when it infects the humans, and
- $R_{0h} = \frac{\beta_h \alpha_h}{\Lambda_h (\gamma_h + \rho_h + \alpha_h)}$ is the human contribution when they infect the mosquitoes.

The square root represents the geometric mean of the average number of secondary host infections produced by one vector, and the average number of secondary vector infections produced by one host. The basic reproduction number can be used to determine the local stability of the disease free equilibrium point.

3.2.2 Stability of Disease Free Equilibrium Point

The equilibria are obtained by equating the right hand side of the system (3.1.1) to zero. Disease-free equilibrium (DFE) of the model is the steady-state solution of the model in the absence of the disease (malaria). Hence, the DFE of the malaria model (3.1.1) is given by

$$E_0 = (S_h^0, I_h^0, R_h^0, S_v^0, I_v^0) = \left(\frac{\Lambda_h}{\alpha_h}, 0, 0, \frac{\Lambda_v}{\alpha_v}, 0 \right)$$

Local Stability of DFE

Theorem 3.2.1 The DFE, E_0, of the system (3.1.1) is *locally asymptotically stable* if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof: The Jacobian matrix of (3.1.1) at the disease-free equilibrium E_0 is

$$J(E_0) = \begin{pmatrix} -\alpha_h & 0 & \omega_h & 0 & -\beta_h \\ 0 & -(\gamma_h + \rho_h + \alpha_h) & 0 & 0 & \beta_h \\ 0 & \gamma_h & -(\alpha_h + \omega_h) & 0 & 0 \\ 0 & -\frac{\beta_v \Lambda_v \alpha_h}{\alpha_v \Lambda_h} & 0 & -\alpha_v & 0 \\ 0 & \frac{\beta_v \Lambda_v \alpha_h}{\alpha_v \Lambda_h} & 0 & 0 & -\alpha_v \end{pmatrix} \tag{3.2.8}$$

The eigenvalues of (3.2.8) are the solutions of the characteristic equation

$$|J(E_0) - \lambda I_5| = 0$$

where I_5 is the identity matrix of order 5. Then we have

$$\begin{vmatrix} -\alpha_h - \lambda & 0 & \omega_h & 0 & -\beta_h \\ 0 & -(\gamma_h + \rho_h + \alpha_h) - \lambda & 0 & 0 & \beta_h \\ 0 & \gamma_h & -(\alpha_h + \omega_h) - \lambda & 0 & 0 \\ 0 & -\frac{\beta_v \Lambda_v \alpha_h}{\alpha_v \Lambda_h} & 0 & -\alpha_v - \lambda & 0 \\ 0 & \frac{\beta_v \Lambda_v \alpha_h}{\alpha_v \Lambda_h} & 0 & 0 & -\alpha_v - \lambda \end{vmatrix} = 0 \tag{3.2.9}$$

The first column of (3.2.9) is all zero except the first entry, which is $-\alpha_h - \lambda$. Thus, we have the first eigenvalue; $\lambda_1 = -\alpha_h$. The rest of the eigenvalues are computed from the

following equation

$$\begin{vmatrix} -(\gamma_h+\rho_h+\alpha_h)-\lambda & 0 & 0 & \beta_h \\ \gamma_h & -(\alpha_h+\omega_h)-\lambda & 0 & 0 \\ -\frac{\beta_v\Lambda_v\alpha_h}{\alpha_v\Lambda_h} & 0 & -\alpha_v-\lambda & 0 \\ \frac{\beta_v\Lambda_v\alpha_h}{\alpha_v\Lambda_h} & 0 & 0 & -\alpha_v-\lambda \end{vmatrix} = 0 \tag{3.2.10}$$

The third column of (3.2.10) has only one non-zero entry which is in its diagonal, i.e. $-\alpha_v-\lambda$. Then $\lambda_2=-\alpha_v$ is the second eigenvalue of (3.2.8). The other eigenvalues are computed using the equation

$$\begin{vmatrix} -(\gamma_h+\rho_h+\alpha_h)-\lambda & 0 & \beta_h \\ \gamma_h & -(\alpha_h+\omega_h)-\lambda & 0 \\ \frac{\beta_v\Lambda_v\alpha_h}{\alpha_v\Lambda_h} & 0 & -\alpha_v-\lambda \end{vmatrix} = 0 \tag{3.2.11}$$

The second column is zero except in its diagonal. In a similar manner, the third eigenvalue of (3.2.8) found to be $\lambda_3=-(\alpha_h+\omega_h)$. Note that all of the eigenvalues we have found so far are all negative. The remaining eigenvalues are found using the equation

$$\begin{vmatrix} -(\gamma_h+\rho_h+\alpha_h)-\lambda & \beta_h \\ \frac{\beta_v\Lambda_v\alpha_h}{\alpha_v\Lambda_h} & -\alpha_v-\lambda \end{vmatrix} = 0 \tag{3.2.12}$$

The algebraic simplification of (3.2.12) gives

$$\lambda^2+(k+\alpha_v)\lambda+k\alpha_v\left(1-R_0^2\right)=0 \tag{3.2.13}$$

where $k=\gamma_h+\rho_h+\alpha_h>0$. Routh-Hurwitz criteria [28], gives a necessary and sufficient condition for the negativity of the roots (eigenvalues) of (3.2.13). In our case, the

condition of Routh-Hurwitz criteria is reduced to the condition

$$k\alpha_v\left(1-R_0^2\right)>0 \tag{3.2.14}$$

But we know that $k>0$ and $\alpha_v>0$. Hence, if we need equation (3.2.14) to hold, then R_0 should be less than a unity. Therefore, the DFE E_0 is locally asymptotically stable of $R_0<1$ and unstable if $R_0>1$.[7] □

In order for disease elimination to be independent of the initial sizes of the sub-populations of the model when $R_0<1$, a global asymptotic stability property must be established for the DFE when $R_0<1$. This is explored below.

Global Stability of DFE

[8]

Theorem 3.2.2 If $R_0<1$, the DFE E_0 of the system (3.1.1) is *globally asymptotically stable*.

Proof: To establish the global[9][10] stability of the DFE E_0, we choose the following Lyapunov function[11]

$$L=\frac{\alpha_v}{\beta_h}I_h+I_v$$

Differentiating the Lyapunov function with respect to t, we obtain

$$\begin{aligned}
\frac{dL}{dt}&=\frac{\alpha_v}{\beta_h}\frac{dI_h}{dt}+\frac{dI_v}{dt}=\frac{\alpha_v}{\beta_h}\left(\frac{\beta_h S_h I_v}{N_h}-(\gamma_h+\rho_h+\alpha_h)I_h\right)+\frac{\beta_v S_v I_h}{N_h}-\alpha_v I_v\\
&=\alpha_v\frac{S_h I_v}{N_h}-\frac{\alpha_v}{\beta_h}(\gamma_h+\rho_h+\alpha_h)I_h+\frac{\beta_v S_v I_h}{N_h}-\alpha_v I_v\\
&=\left(\beta_v\frac{S_v}{N_h}-\frac{\alpha_v}{\beta_h}(\gamma_h+\rho_h+\alpha_h)\right)I_h-\alpha_v\left(1-\frac{S_h}{N_h}\right)I_v\\
&\leq\left(\beta_v\frac{S_v}{N_h}-\frac{\alpha_v}{\beta_h}(\gamma_h+\rho_h+\alpha_h)\right)I_h\\
&\leq\left(\beta_v\frac{\Lambda_v/\alpha_v}{\Lambda_h/\alpha_h}-\frac{\alpha_v}{\beta_h}(\gamma_h+\rho_h+\alpha_h)\right)I_h\\
&=\frac{\beta_h}{\alpha_v(\gamma_h+\rho_h+\alpha_h)}\left(R_0^2-1\right)I_h
\end{aligned}$$

Thus we have established that $\frac{dL}{dt}<0$ if $R_0<1$ and $\frac{dL}{dt}=0$ if and only if $I_h=0$, $I_v=0$.

Therefore, the largest compact invariant set in $\{(S_h, I_h, R_h, S_v, I_v) \in \Omega : \frac{dL}{dt} = 0\}$ is the singleton set $\{E_0\}$ in Ω. From LaSalle's invariant principle [29], every solution that starts in the region Ω approaches E_0 as $t \to \infty$ and hence, the DFE E_0 is globally asymptotically stable for $R_0 < 1$ in Ω.[12] □

3.2.3 Existence of Endemic Equilibrium Point

Endemic equilibrium point (EEP) is a steady state solution where the disease persists in the population. The EEP $E_* = (S_h^*, I_h^*, R_h^* S_v^*, I_v^*)$ can be determined by setting the right hand side of the model (3.1.1) equal to zero.

Solving the third equation of (3.1.1) gives

$$R_h^* = \frac{\gamma_h}{\alpha_h + \omega_h} I_h^*$$

From the fourth equation of (3.1.1) we get

$$S_v^* = \frac{\Lambda_v N_h}{\alpha_v N_h + \beta_v I_h^*} \tag{3.2.15}$$

The fifth equation of the model (3.1.1) gives

$$I_v^* = \frac{\beta_v}{\alpha_v N_h} S_v^* I_h^* \tag{3.2.16}$$

By substituting (3.2.15) into (3.2.16) we obtain

$$I_v^* = \frac{\alpha_v R_{0v} I_h^*}{\alpha_v N_h + \beta_v I_h^*} \tag{3.2.17}$$

where $R_{0v} = \frac{\beta_v \Lambda_v}{\alpha_v^2}$.

When we substitute (3.2.17) in the second equation of (3.1.1) we get

$$\frac{\beta_h S_h^*}{N_h} \left(\frac{\alpha_v R_{0v} I_h^*}{\alpha_v N_h + \beta_v I_h^*} \right) - (\gamma_h + \rho_h + \alpha_h) I_h^* = 0$$

Which implies $I_h^* = 0$ or

$$\beta_h \alpha_v R_{0v} S_h^* - N_h(\gamma_h + \rho_h + \alpha_h)(\alpha_v N_h + \beta_v I_h^*) = 0$$

Then

$$\frac{\alpha_h \beta_h \alpha_v R_{0v} S_h^*}{\Lambda_h(\gamma_h + \rho_h + \alpha_h)} - \left(\alpha_v \frac{\Lambda_h}{\alpha_h} + \beta_v I_h^*\right) = 0$$

Thus, we get[13]

$$S_h^* = \frac{\alpha_v \Lambda_h + \alpha_h \beta_v I_h^*}{\alpha_h \alpha_v R_0^2}$$

where $R_0^2 = R_{0v} R_{0h}$, $R_{0h} = \frac{\beta_h \alpha_h}{\Lambda_h(\gamma_h + \rho_h + \alpha_h)}$ and I_h^* is obtained by solving the equation

$$A(I_h^*)^2 + BI_h^* + C = 0 \tag{3.2.18}$$

where

$$\left.\begin{aligned} A &= \alpha_h \alpha_v \beta_h \gamma_h \omega_h R_0^2 N_h - \alpha_h \alpha_v \beta_h \beta_v R_{0v} - \alpha_h^2 \alpha_v \beta_v (\alpha_h + \omega_h) N_h^2 \\ B &= \alpha_h \alpha_v \beta_h \Lambda_h (\alpha_h + \omega_h) R_0^2 N_h + \alpha_h \alpha_v^2 \gamma_h \omega_h R_0^2 N_h^2 \\ &\quad - \alpha_h \alpha_v \beta_h \Lambda_h (\alpha_h + \omega_h) N_h - \alpha_h^2 \alpha_v \beta_v (\alpha_h + \omega_h) N_h^2 - \alpha_v^2 \beta_h \Lambda_h R_{0v} \\ C &= \alpha_h \alpha_v^2 \Lambda_h (\alpha_h + \omega_h) N_h^2 \left(R_0^2 - 1\right) \end{aligned}\right\} \tag{3.2.19}$$

From (3.2.19) it follows that $C > 0$ whenever $R_0 > 1$. Thus, the number of possible positive real roots for (3.2.18) depends on the signs of A and B. This can be analyzed using the Descartes' Rule of Signs on the quadratic

$$f(I_h^*) = A(I_h^*)^2 + BI_h^* + C$$

The different possibilities for the roots $f(I_h^*)$ are tabulated in Table 3.3[14].

Hence, we have established the following result

Theorem 3.2.3 The system (3.1.1) has a unique endemic equilibrium E_* if Cases 2, 4, 5 and 7 are satisfied.

The existence of multiple endemic equilibria when $R_0 < 1$ is shown in Table 3.3 which

Table 3.3: Number of possible positive real roots of $f(I_h^*)$ for $R_0 < 1$ and $R_0 > 1$.

Cases	A	B	C	R_0	Number of sign changes	Number of positive real roots
1	+	+	+	>1	0	0
2	+	+	-	<1	1	1
3	+	-	+	>1	2	2
4	+	-	-	<1	1	1
5	-	+	+	>1	1	1
6	-	+	-	<1	2	2
7	-	-	+	>1	1	1
8	-	-	-	<1	0	0

suggests the possibility of backward bifurcation [30], where the stable DFE coexists with a stable endemic equilibrium, when the reproduction number is less than unity. Thus, the occurrence of a backward bifurcation has an important implications for epidemiological[15] control measures, since an epidemic may persist at steady state even if $R_0 < 1$. This will be explored in the next section.

3.2.4 Existence of Backward Bifurcation

We shall use the following theorem[16] in [31], to show that the system (3.1.1) exhibits backward bifurcation at $R_0 = 1$.

Theorem 3.2.4 Consider the following general system of ordinary differential equations with a parameter ϕ

$$\frac{dx}{dt} = f(x, \phi), \qquad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \text{ and } f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}) \tag{3.2.20}$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (3.2.20) for all values of the parameter ϕ, (that is $f(0, \phi) \equiv 0$). Assume

(A1) $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ is the linearized matrix of system (3.2.20) around the equilibrium 0 with ϕ evaluated at 0.

(A2) Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;

(A3) Matrix A has a non-negative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue. Let f_k be the k^{th} component of f and

$$\begin{aligned} a &= \sum_{i,j,k=1}^{5} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ b &= \sum_{k,i=1}^{5} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0) \end{aligned} \tag{3.2.21}$$

The local dynamics of system (3.2.20) around 0 are totally determined by a and b.

i. $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium.

ii. $a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;

iii. $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears;

iv. $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

Particularly, if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

To apply the above result, the following simplification and change of variables are made on the system (3.1.1). Let $S_h = x_1, I_h = x_2, R_h = x_3, S_v = x_4$ and $I_v = x_5$. So,

$$N_h = x_1 + x_2 + x_3 \quad \text{and} \quad N_v = x_1 + x_2$$

Moreover, by using vector notation $x = (x_1, x_2, x_3, x_4, x_5)^T$, the system (3.1.1) can be written in the form $\frac{dx}{dt} = (f_1, f_2, f_3, f_4, f_5)^T$ as follows

$$\left.\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda_h - \frac{\beta_h x_1 x_5}{x_1 + x_2 + x_3} + \omega_h x_3 - \alpha_h x_1 \\
\frac{dx_2}{dt} &= f_2 = \frac{\beta_h x_1 x_5}{x_1 + x_2 + x_3} - (\gamma_h + \rho_h + \alpha_h) x_2 \\
\frac{dx_3}{dt} &= f_3 = \gamma_h x_2 - \omega_h x_3 - \alpha_h x_3 \\
\frac{dx_4}{dt} &= f_4 = \Lambda_v - \frac{\beta_v x_4 x_2}{x_1 + x_2 + x_3} - \alpha_v x_4 \\
\frac{dx_5}{dt} &= f_5 = \frac{\beta_v x_4 x_2}{x_1 + x_2 + x_3} - \alpha_v x_5
\end{aligned}\right\} \tag{3.2.22}$$

Choose $\beta_h = \beta_h^*$ as a bifurcation parameter. Solving for β_h^* from $R_0 = 1$ gives

$$\beta_h^* = \frac{\Lambda_h \alpha_v^2 (\gamma_h + \rho_h + \alpha_h)}{\beta_v \Lambda_v \alpha_h}$$

The Jacobian matrix of the system (3.2.22) evaluated at the disease free equilibrium E_0 with $\beta_h = \beta_h^*$ is given by

$$J_* = \begin{pmatrix}
-\alpha_h & 0 & \omega_h & 0 & -\beta_h \\
0 & -k & 0 & 0 & \beta_h \\
0 & \gamma_h & -(\alpha_h + \omega_h) & 0 & 0 \\
0 & -d & 0 & -\alpha_v & 0 \\
0 & d & 0 & 0 & -\alpha_v
\end{pmatrix}$$

where $k = \gamma_h + \rho_h + \alpha_h$ and $d = (\beta_v \Lambda_v \alpha_h)/(\alpha_v \Lambda_h)$.

The Jacobian J_* of the linearized system has a simple zero eigenvalue[17] with all other eigenvalues having negative real part. For the case when $R_0 = 1$, using the technique in Castillo-Chavez and Song [31], it can be shown that the matrix J_* has a right eigen-

vector (corresponding to the zero eigenvalue), given by $w = [w_1\ w_2\ w_3\ w_4\ w_5]^T$, where

$$w_1 = -\frac{\alpha_h^2 + (\gamma_h + \omega_h + \rho_h)\alpha_h + \omega_h\rho_h}{\gamma_h\alpha_h}w_3, \quad w_2 = \frac{\omega_h + \alpha_h}{\gamma_h}w_3, \quad w_3 = w_3 > 0,$$
$$w_4 = -\frac{\alpha_h\beta_h\Lambda_v(\omega_h + \alpha_h)}{\gamma_h\alpha_v^2\Lambda_h}w_3, \quad w_5 = \frac{\alpha_h\beta_h\Lambda_v(\omega_h + \alpha_h)}{\gamma_h\alpha_v^2\Lambda_h}w_3$$

Similarly, the components of the left eigenvector of J_* (corresponding to the zero eigenvalue), denoted by $v = [v_1\ v_2\ v_3\ v_4\ v_5]$, are given by

$$v_1 = v_3 = v_4 = 0, \quad v_2 = v_2 > 0, \quad v_5 = \frac{\Lambda_h\alpha_v(\gamma_h + \rho_h + \alpha_h)}{\beta_v\Lambda_v\alpha_h}v_2$$

Computation of a

By computing[18] the second-order partial derivatives at the disease free equilibrium point we have

$$\frac{\partial^2 f_2}{\partial x_1\partial x_j} = 0, \quad \text{for } j = 1, 2, 3, 4, 5$$
$$\frac{\partial^2 f_2}{\partial x_2\partial x_j} = 0, \quad \text{for } j = 1, 2, 3, 4$$
$$\frac{\partial^2 f_2}{\partial x_3\partial x_j} = 0, \quad \text{for } j = 1, 2, 3, 4$$
$$\frac{\partial^2 f_2}{\partial x_4\partial x_j} = 0, \quad \text{for } j = 1, 2, 3, 4, 5$$
$$\frac{\partial^2 f_2}{\partial x_5\partial x_j} = 0, \quad \text{for } j = 1, 4, 5$$

where as

$$\frac{\partial^2 f_2}{\partial x_2\partial x_5} = \frac{\partial^2 f_2}{\partial x_5\partial x_2} = -\frac{\beta_h\alpha_h}{\Lambda_h}$$
$$\frac{\partial^2 f_2}{\partial x_3\partial x_5} = \frac{\partial^2 f_2}{\partial x_5\partial x_3} = -\frac{\beta_h\alpha_h}{\Lambda_h}$$

Similarly,

$$\begin{aligned}
\frac{\partial^2 f_5}{\partial x_1 \partial x_j} &= 0, \quad \text{for } j = 1,3,4,5 \\
\frac{\partial^2 f_5}{\partial x_2 \partial x_j} &= 0, \quad \text{for } j = 5 \\
\frac{\partial^2 f_5}{\partial x_3 \partial x_j} &= 0, \quad \text{for } j = 1,3,4,5 \\
\frac{\partial^2 f_5}{\partial x_4 \partial x_j} &= 0, \quad \text{for } j = 1,3,4,5 \\
\frac{\partial^2 f_5}{\partial x_5 \partial x_j} &= 0, \quad \text{for } j = 1,2,3,4,5
\end{aligned}$$

while

$$\begin{aligned}
\frac{\partial^2 f_5}{\partial x_1 \partial x_2} = \frac{\partial^2 f_5}{\partial x_2 \partial x_1} = -\frac{\beta_v \Lambda_v \alpha_h^2}{\alpha_v \Lambda_h^2} = \frac{\partial^2 f_5}{\partial x_2 \partial x_3} = \frac{\partial^2 f_5}{\partial x_3 \partial x_2} \\
\frac{\partial^2 f_5}{\partial x_2^2} = -\frac{2\beta_v \Lambda_v \alpha_h^2}{\alpha_v \Lambda_h^2}, \ \frac{\partial^2 f_5}{\partial x_2 \partial x_4} = \frac{\partial^2 f_5}{\partial x_4 \partial x_2} = \frac{\beta_v \alpha_h}{\Lambda_h}
\end{aligned}$$

Then

$$\begin{aligned}
a =& v_2 \sum_{i,j=1}^{5} w_i w_j \frac{\partial^2 f_5}{\partial x_i \partial x_j}(0,0) + v_5 \sum_{i,j=1}^{5} w_i w_j \frac{\partial^2 f_5}{\partial x_i \partial x_j}(0,0) \\
=& 2v_2 \left(-w_2 w_5 \frac{\beta_h \alpha_h}{\Lambda_h} - w_3 w_5 \frac{\beta_h \alpha_h}{\Lambda_h} \right) \\
& + 2v_5 \left(-w_1 w_2 \frac{\beta_v \Lambda_v \alpha_h^2}{\alpha_v \Lambda_h^2} - w_2^2 \frac{2\beta_v \Lambda_v \alpha_h^2}{\alpha_v \Lambda_h^2} - w_2 w_3 \frac{\beta_v \Lambda_v \alpha_h^2}{\alpha_v \Lambda_h^2} + w_2 w_4 \frac{\beta_v \alpha_h}{\Lambda_h} \right) \\
=& \frac{2(\gamma_h + \rho_h + \alpha_h)(\alpha_h^2 + (\gamma_h + \omega_h + \rho_h)\alpha_h + \omega_h \rho_h)(\omega_h + \alpha_h) v_2 w_3^2}{\Lambda_h \gamma_h^2} \\
& - \frac{4\alpha_h (\gamma_h + \rho_h + \alpha_h)(\omega_h + \alpha_h)^2 v_2 w_3^2}{\Lambda_h \gamma_h^2} - \frac{2\alpha_h (\omega_h + \alpha_h)(\gamma_h + \rho_h + \alpha_h) v_2 w_3^2}{\Lambda_h \gamma_h} \\
& - \frac{2\alpha_h \alpha_v \beta_h (\gamma_h + \rho_h + \alpha_h)(\omega_h + \alpha_h)^2 v_2 w_3^2}{\gamma_h^2} \\
=& \frac{2(\alpha_v (\gamma_h + \rho_h + \alpha_h)(\omega_h + \alpha_h))^2}{\gamma_h^2 \beta_h \beta_v \alpha_h \Lambda_v} \left[\frac{\beta_v \Lambda_v \rho_h}{\Lambda_h^2 \alpha_v^3 (\gamma_h + \rho_h + \alpha_h)} - R_0^2 \right] v_2 w_3^2
\end{aligned}$$

Computation of b

To compute b we need to find the second order derivatives of f_2 and f_5 with respect to x_i and β_h at the disease free equilibrium point. Direct computation shows

$$\frac{\partial^2 f_2}{\partial x_i \partial \beta_h} = 0, \quad \text{for } i = 1,2,3,4$$
$$\frac{\partial^2 f_5}{\partial x_i \partial \beta_h} = 0, \quad \text{for } i = 1,2,3,4,5$$

and

$$\frac{\partial^2 f_2}{\partial x_5 \partial \beta_h} = \beta_h$$

$$b = \sum_{i,k=1}^{5} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_h}(0,0) = \beta_h v_2 w_5 > 0$$

Hence the following result holds

Theorem 3.2.5 The malaria model (3.1.1) exhibits backward bifurcation at $R_0 = 1$ whenever a is positive.

Notice that $a > 0 \Leftrightarrow R_0 < \sqrt{M}$ where $M = \frac{\beta_v \Lambda_v \rho_h}{\Lambda_h^2 \alpha_v^3 (\gamma_h + \rho_h + \alpha_h)}$. Moreover, $M = 1$ gives

$$\rho_h = \frac{\Lambda_h^2 \alpha_v^3 (\gamma_h + \alpha_h)}{\beta_v \Lambda_v - \Lambda_h^2 \alpha_v^3} := \rho_h^*$$

Hence, if the disease induced death rate satisfies $0 \leq \rho_h \leq \rho_h^*$, then the disease can be eradicated provided that $R_0 < 1$.

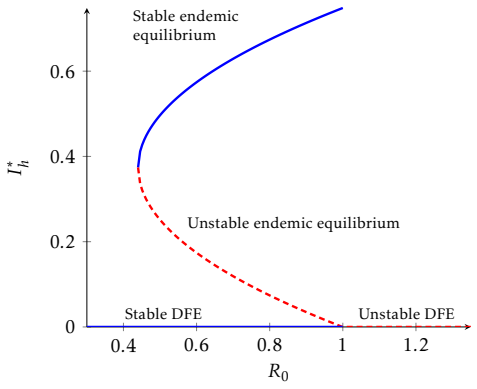


Figure 3.2: Backward bifurcation phenomenon

Chapter 4

Numerical Simulations and Result

In this chapter we present a numerical simulations of the model which is carried out using a fourth order Rung-Kutta scheme in Matlab ode45. The values of the parameter used in the model are given in Table 4.1.

Table 4.1: Parameter values

Parameter	Values	Reference
Λ_h	2.5	[32]
β_h	0.01	[5]
α_h	0.05	[12]
ρ_h	0.0001	Assumed
γ_h	0.9	[6]
Λ_v	500	[32]
β_v	0.005	[5]
α_v	0.06	[12]
ω_h	0.9	Assumed

The initial conditions $S_h(0) = 19413000$, $I_h(0) = 3797000$, $R_h(0) = 3790000$, $S_v(0) = 16800000$, $I_v(0) = 38200000$ were used for the simulations. In Figure 4.1, the fractions of the populations, S_h, I_h and R_h are plotted versus time. The susceptible populations will initially decreases with time and then increases and the fractions of infected human populations decrease. The reproduction number is below one and the disease-free equilibrium point $E_0 = (\Lambda_h/\alpha_h, 0, 0)$ is stable. The susceptible and infected

mosquito population decreases over time as shown in Figure 4.2.

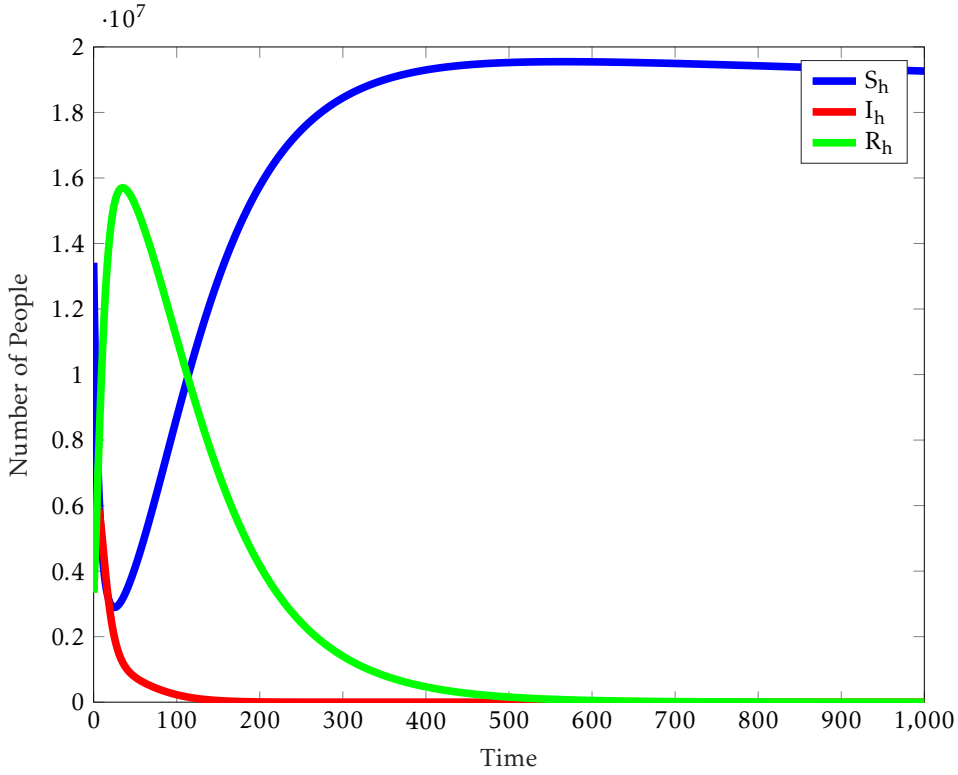


Figure 4.1: Simulations of the model (3.1.1) for susceptible, infected and recovered human population

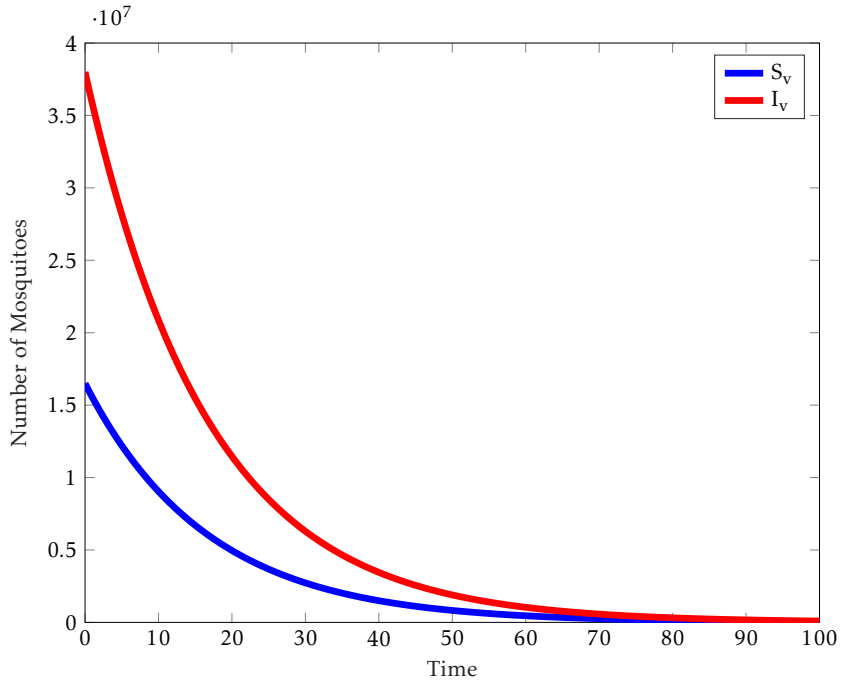


Figure 4.2: Simulations of the model (3.1.1) for susceptible and infected mosquito population

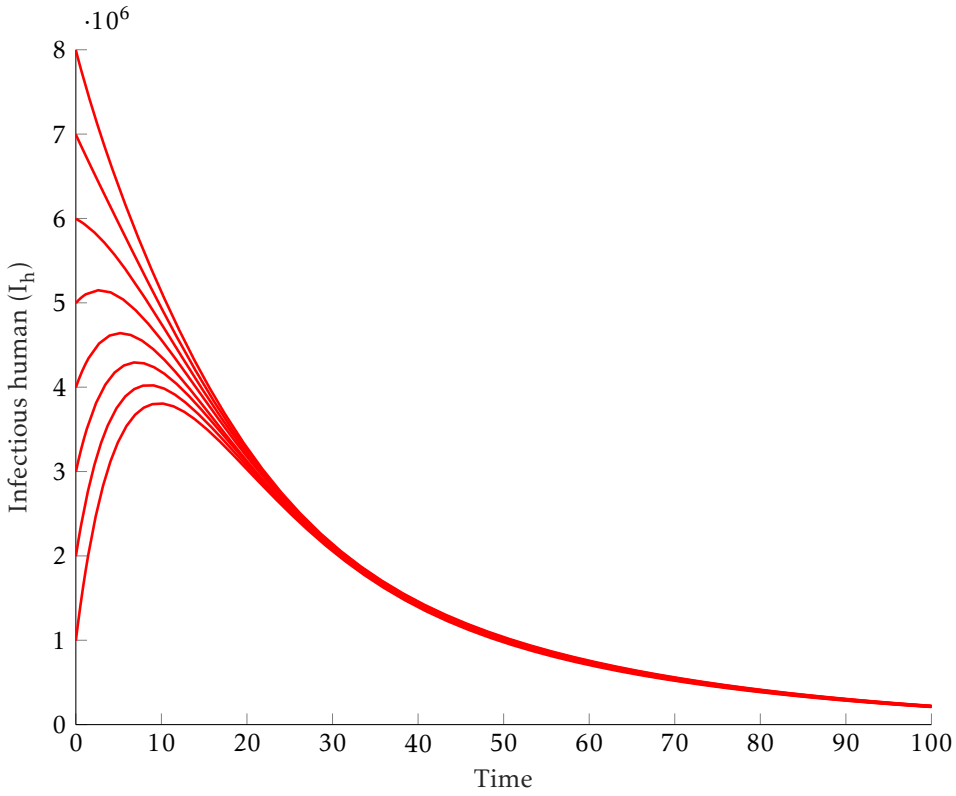


Figure 4.3: Time series plot of the model (3.1.1) with different initial conditions.

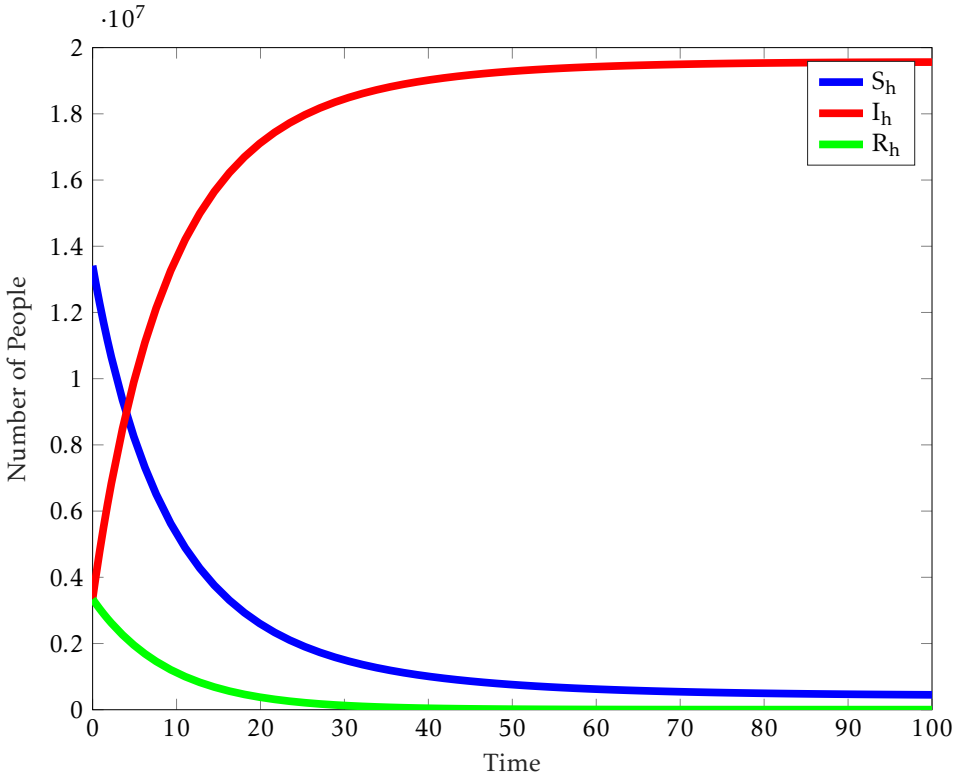


Figure 4.4: Simulations of the model (3.1.1) for $R_0 = 47.6631$ with parameter values $\Lambda_h = 0.000091, \Lambda_v = 0.071, \beta_h = 0.0714285, \beta_v = 0.09091, \gamma_h = 0.000014285, \alpha_h = 0.00004278, \alpha_v = 0.04, \rho_h = 0.0000027, \omega_h = 0.109$

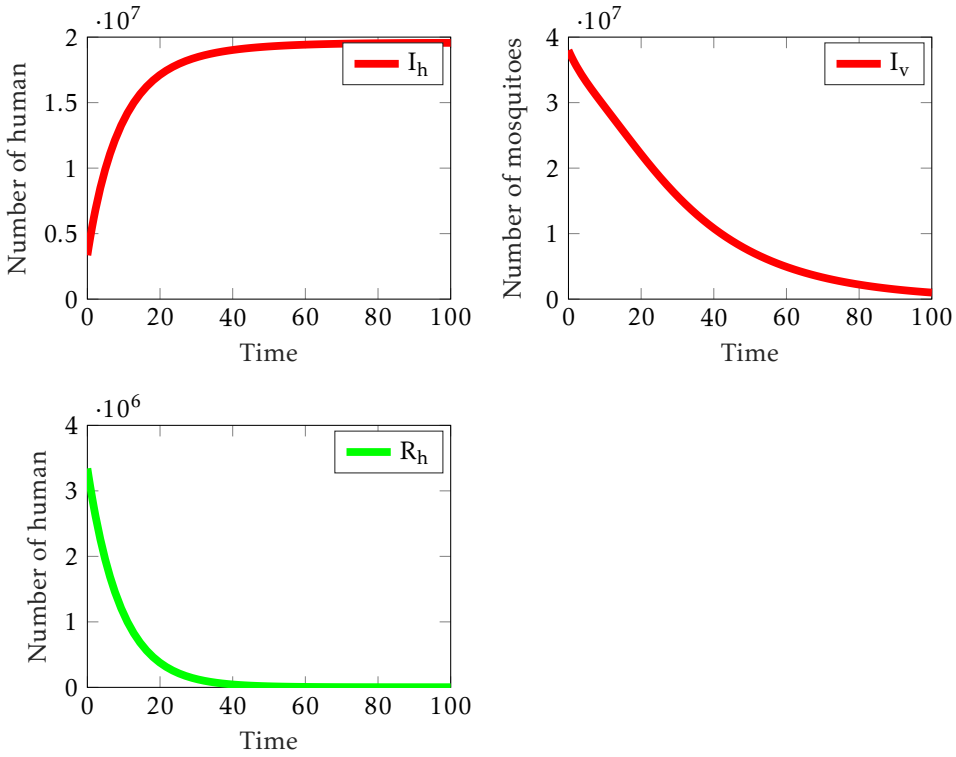


Figure 4.5: Simulations of the model (3.1.1) for $R_0 = 47.6631$ showing infected human, infected mosquito and recovered human.

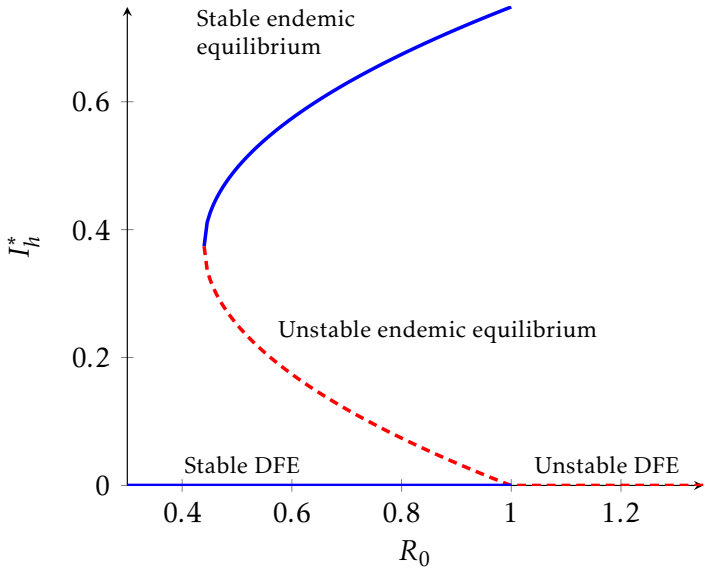


Figure 4.6: Backward bifurcation phenomenon

The following parameter values were used to simulate the bifurcation diagram $\Lambda_h = 7, \Lambda_v = 0.071, \alpha_h = 0.23, \alpha_v = 0.54, \beta_v = 0.82, \gamma_h = 0.143, \rho_h = 0.27, \omega_h = 0.011$. It is important to note that these parameter values were used for illustrative purpose only, and may not be realistic epidemiologically.

Chapter 5

Discussions and Conclusion

5.1 Discussions

House spraying with residual Insecticides and mosquito bed nets are the major intervention measures used in these days to prevent malaria transmission. These methods reduce the contact rates between the mosquitoes and humans. Other measures employ the use of anti-malarial drugs which have the effect of reducing the infectivity of the human host. Indoor Residual Spraying (IRS) reduces mosquito longevity and it also reduces mosquito fertility. This strategy is also likely to kill mosquitoes that rest indoors after feeding so it would increase the chances of killing infected mosquitoes. Indoor residual spraying increases the mosquito death rate α_v, and reduces the number of mosquitoes. Increasing α_v can be effective in reducing the malaria burden. The other intervention measure, Insecticide-Treated bed Nets, prevent mosquito-human contacts which reduce the number of bites per mosquito. Reducing the number of blood meals that each female mosquito gets would also lower the mosquito recruitment rate, Λ_v, which in turn reduces the number of mosquitoes. This is found to be the most effective control strategy in reducing disease transmission. Therefore, all these control strategies are an effective way of controlling most of the parameters which are involved in our model. In order to determine the efficient way to tackle malaria, and reduce malaria mortality, it is necessary to know the relative importance of the different factors responsible for its transmission and prevalence. The basic reproduction number is such an important tool, which allows us to determine the importance of

the parameters in the disease transmission. From our computation of the basic reproduction number we have noticed that R_0 is independent of the rate of immunity loss. We have also noticed that an increasing mosquito to human contact rate β_h, the mosquito recruitment rate Λ_v, and the human to mosquito contact rate β_v, leads to an increase in the basic reproduction number and this leads to for disease to be hard controlling. Furthermore, we have seen that bringing R_0 less than unity is necessary but not sufficient condition for the disease eradication.

5.2 Conclusion

In this study, a deterministic mathematical model for malaria transmission has been presented. It was showed that there exists a domain in which the model is mathematically and epidemiologically well posed. The next generation matrix was used to derive the basic reproduction number R_0, which is the average number of new cases that one infected case will generate. The disease free equilibrium of the model was proved to be locally asymptotically stable whenever R_0 is less than unity. It is also showed that the disease free equilibrium is globally asymptotically stable provided that the basic reproduction number is less than some threshold. The unique endemic equilibrium point was shown to exist under certain conditions. The possibility of multiple endemic equilibrium point was discussed. It was shown that the model undergo backward bifurcation phenomenon. The stable disease free equilibrium coexist with the stable endemic equilibrium. Bringing the disease (malaria) induced death rate below some threshold was shown to be sufficient to eliminate backward bifurcation. Thus along with treated bed nets, and insecticides that would reduce the mosquito population there is a need for effective drug and efficient treatment which reduce the number of malaria induced death rate.

Appendix A

Mathematical Preliminaries

A.1 Basic Definitions and Results

In this section, we provide the basic mathematical definitions and results, which are crucial for a better understanding of this thesis work.

An autonomous system of ordinary differential equation have the form

$$\begin{aligned} \frac{dx_1}{dt} &= f_1(x_1, \cdots, x_n), \\ &\vdots \\ \frac{dx_n}{dt} &= f_n(x_1, \cdots, x_n) \end{aligned}$$

Which can be written concisely in vector form

$$\frac{dx}{dt} = f(x), \qquad x \in \mathbb{R}^n \tag{A.1.1}$$

where $x = (x_1, \cdots, x_n)^T$ and $f = (f_1, \cdots, f_n)^T$ [33].

Definition A.1.1 Let $x(0) = x_0$ be the initial condition of (A.1.1), by a solution of (A.1.1) we mean a continuously differentiable function $x : I(x_0) \to \mathbb{R}^n$ satisfying (A.1.1), where $I(x_0)$ is an interval in $\mathbb{R}$ containing the origin.

Definition A.1.2 ([34]) Equation (A.1.1) defines a dynamical system[19] on $E \subset \mathbb{R}^n$ if, for every $x \in E$, there exists a unique solution of (A.1.1) defined for all $t \in \mathbb{R}_+$.

A simple condition which permits one to imply uniqueness is the Lipschitz condition.

Definition A.1.3 ([29]) A function $f(x)$ is said to be *locally Lipschitz* on a domain[20] $\Omega \subset \mathbb{R}^n$ if each point of Ω has a neighborhood Ω_0 such that f satisfies

$$\|f(x) - f(y)\| \leq L\|x - y\| \qquad \text{for all } x, y \in \Omega_0.$$

f is *globally Lipschitz* if it is locally Lipschitz for every neighborhood Ω_0 of $\mathbb{R}^n$.

Lemma A.1.4 If $f(t,x)$ and $[df/dx](t,x)$ are continuous on $[a,b]\times\Omega$, for some domain $\Omega \subset \mathbb{R}^n$, then f is locally Lipschitz in x on $[a,b]\times\Omega$.

Theorem A.1.5 (PicardLindelöf Theorem [29]) Let $f(t,x)$ be a piecewise continuous in t and satisfy the Lipschitz condition

$$\|f(t,x) - f(t,y)\| \leq L\|x - y\|$$

$\forall x, y \in B = \{x \in \mathbb{R}^n : \|x - x_0\| \leq r\}, \forall t \in [t_0, t_1]$. Then, there exists some $\delta > 0$ such that the state equation $\dot{x} = f(t,x)$ with $x(t_0) = x_0$ has a unique solution over $[t_0, t_0 + \delta]$.

Theorem A.1.6 (Gronwall's Lemma) Let $x(t)$ satisfy

$$\frac{dx}{dt} \leq px + q, \quad x(0) = x_0,$$

for p, q constants. Then for $t \geq 0$

$$x(t) \leq e^{pt}x_0 + \frac{q}{p}\left(e^{pt} - 1\right), \quad p \neq 0$$

and

$$x(t) \leq x_0 + qt, \quad p = 0.$$

A.2 Equilibria and Stability

Definition A.2.1 (Equilibrium Point, [35]) An equilibrium point (fixed point, stationary point, rest point, singularity, critical point, steady state) of the system (A.1.1) is a point $x_* \in \mathbb{R}^n$ such that

$$f(x_*) = 0$$

i.e., a solution which does not change in time.

Stability properties characterize how a system behaves if its state is initiated close to, but not precisely at a given equilibrium point.

Definition A.2.2 (Stable, [35]) A critical point x_* is *stable*[21] provided that, for each $\varepsilon > 0$, there exists $\delta > 0$ such that

$$\|x_0 - x_*\| < \delta \quad \Rightarrow \quad \|x(t) - x_*\| < \varepsilon \text{ for all } t > 0.$$

The critical point x_* is called *unstable* if it is not stable.

Definition A.2.3 (Asymptotically Stable, [35]) A critical point x_* is *asymptotically stable*[22] if there exists $\delta > 0$ such that

$$\|x_0 - x_*\| < \delta \quad \Rightarrow \quad \lim_{t\to\infty} x(t) = x_*.$$

A.2.1 Descartes' Rule of Signs

Theorem A.2.4 [36] [23]Given a polynomial

$$P(\lambda) = a_0\lambda^n + a_\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n, \qquad a_i \in \mathbb{R},\ a_0 \neq 0. \tag{A.2.2}$$

Consider the sequence of coefficients of (A.2.2):

$$a_n, a_{n-1}, \ldots, a_, a_0.$$

Let k be the total number of sign changes from one coefficient to the next in the sequence. Then the number of positive real roots of the polynomial is either equal to k, or k minus a positive even integer. (Note: if $k = 1$ then there is exactly one positive real root.)

A.2.2 The Routh-Hurwitz Criteria

Theorem A.2.5 [37] Given a polynomial

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + \cdots + a_n$$

where the coefficients a_i are real constants,$i = 1, 2, \ldots, n$ define the n Hurwitz matrices using the coefficients of the characteristic polynomial:

$$H_1 = \begin{pmatrix} a_1 \end{pmatrix}, H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}, H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix}, \cdots$$

and

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & 1 & \cdots & 0 \\ a_5 & a_4 & a_3 & a_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & a_n \end{pmatrix}$$

where $a_j = 0$ for $j > n$. All the roots of polynomial $P(\lambda)$ are negative or have negative real parts iff the determinants of all Hurwitz matrices are positive:

$$\det H_j > 0, \quad j = 1, 2, \ldots, n$$

For $n = 2$, $\det H_1 = a_1 > 0$ and $H_2 = \begin{pmatrix} a_1 & 1 \\ 0 & a_2 \end{pmatrix} = a_1 a_2 > 0$ or $a_1 > 0$ and $a_2 > 0$. For polynomials of degree $2, 3, 4$ and 5, the Routh Hurwitz Criteria are summarized as follows:

$$\begin{aligned}
&n = 2 : a_1 > 0 \text{ and } a_2 > 0 \\
&n = 3 : a_1 > 0, a_3 > 0 \text{ and } a_1 a_2 - a_3 > 0 \\
&n = 4 : a_1 > 0, a_3 > 0, a_4 > 0 \text{ and } a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 > 0 \\
&n = 5 : a_i > 0, i = 1, 2, 3, 4 \text{ and } 5, a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 > 0, \text{ and} \\
&\qquad (a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) - a_5 (a_1 a_2 - a_3)^2 - a_1 a_5^2 > 0
\end{aligned}$$

A.3 Linear Systems and Linearization

A.3.1 Linear Systems

Consider a linear systems

$$\frac{dx}{dt} = Ax, \qquad x \in \mathbb{R}^n, \tag{A.3.3}$$

where A is a matrix of order n. Then the solutions of (A.3.3) is given by

$$x(t) = \sum_{i=1}^{n} c_i e^{\lambda_i t} x_i, \qquad c_i\text{'s are arbitrary constants}$$

where λ_i's are the eigenvalues of A and x_i' are the corresponding eigenvectors.

The stability of the solutions of a linear systems is determined by the *sign* of the eigenvalues of its coefficient matrix. Particularly, we have the following characterization

theorem for a linear systems

Theorem A.3.1 The equilibrium point $x = 0$ of (A.3.3) is stable if and only if all eigenvalues of A satisfy $\mathfrak{Re}[\lambda_i] < 0$.

A much simpler characterization of stability in a planar system is given by the following result.

Theorem A.3.2 Let A be a 2×2 matrix and consider the system

$$\dot{x} = Ax,$$

where $x \in \mathbb{R}^2$, then stability is equivalent to

$$\text{trace}A < 0 \text{ and } \det A > 0$$

The trace-determinant diagram shown in Figure A.1 gives the general classification of stability of the linear systems.

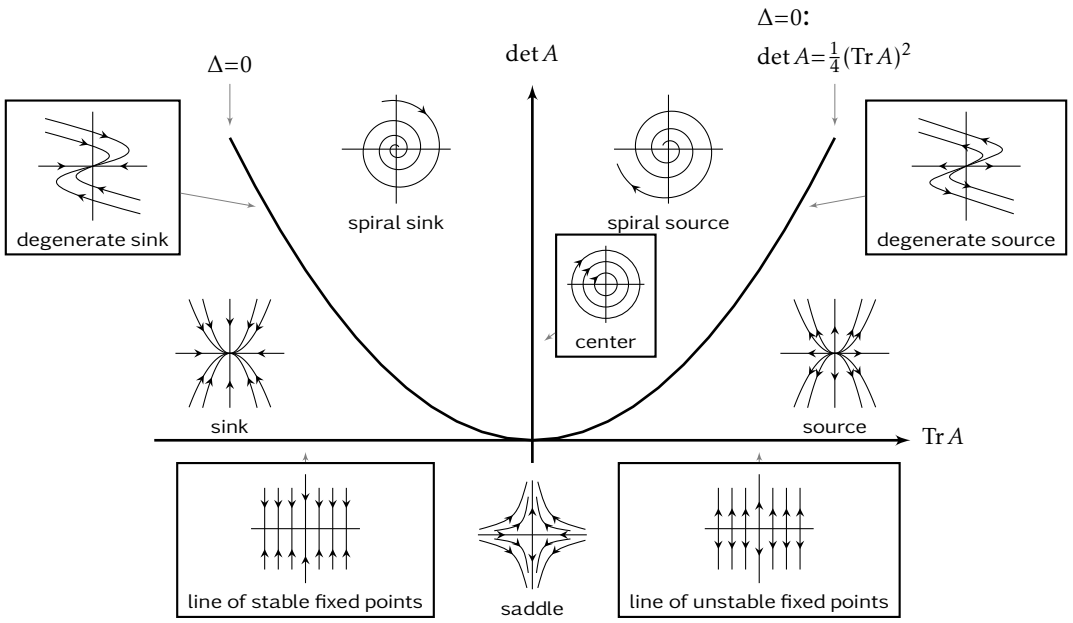


Figure A.1: Trace-Determinant diagram

A.3.2 Linearization

To determine the behavior near a critical point, we will linearize[24] the non-linear system around the critical point and use our knowledge of linear systems.
The linearization of the non-linear system (A.1.1) around the equilibrium point x_* is

$$\frac{dx}{dt} = Jx \tag{A.3.4}$$

where J is the jacobian matrix evaluated at x_*, i.e.

$$J := J(x_*) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(x_*) & \frac{\partial f_1}{\partial x_2}(x_*) & \cdots & \frac{\partial f_1}{\partial x_n}(x_*) \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1}(x_*) & \frac{\partial f_n}{\partial x_2}(x_*) & \cdots & \frac{\partial f_n}{\partial x_n}(x_*) \end{pmatrix}$$

The local behavior of the solutions near a critical point is described by the following theorems.

Theorem A.3.3 (Poincaré - Lyapunov) Suppose x_* is a critical point of the non-linear system (A.1.1), and suppose the $Re(\lambda)$, the real part of the eigenvalues of J (the linearization) are negative. Then the critical point is *locally asymptotically stable*.

Theorem A.3.4 Suppose x_* is a critical point, and the real part of *at least one* eigenvalue of J is positive. Then the critical point is *unstable*.

A.3.3 Hartman-Grobman Theorem

Definition A.3.5 (Hyperbolic Equilibrium Point, [38]) A critical point is called *hyperbolic*[25] if the real part of the eigenvalues of the Jacobian matrix J are nonzero.

The next theorem is a guarantee that the non-linear system inherits the behavior of the linearized system.

Theorem A.3.6 (Hartman-Grobman, [39]) Suppose that x_* is a hyperbolic critical point

of system the nonlinear system (A.1.1). Then, in a neighborhood of x_*, the system (A.1.1) and its corresponding linearization are equivalent; i.e., there is a homeomorphism h that maps trajectories in (A.1.1) near x_* onto trajectories in (A.3.4).

A.4 Lyapunov Theory

A powerful method for analyzing the stability of an equilibrium point is based on the use of Lyapunov functions [40].

Definition A.4.1 A function $V : \mathbb{R}^n \to \mathbb{R}$ is said to be a positive-definite function if

- $V(x) > 0$ for all $x \neq 0$,
- $V(x) = 0$ if and only if $x = 0$.

Definition A.4.2 Let x_* be an equilibrium point of (A.1.1) and let $V : U \to \mathbb{R}$ be a $\mathbb{C}^1$ function defined on some neighbourhood U of x_* such that

(i) V is positive-definite,

(ii) $\dot{V}(x) \leq 0$ in $U \backslash \{x\}$.

Any function, V, that satisfies the Conditions (i) and (ii) above is called a Lyapunov Function [36, 40].

Definition A.4.3 (Invariant Set) A set M is an invariant set with respect to (A.1.1) if

$$x(0) \in M \Rightarrow x(t) \in M, \forall t \in \mathbb{R}$$

Definition A.4.4 (Positively Invariant) A set M is a positively invariant set

$$x(0) \in M \Rightarrow x(t) \in M, \forall t \geq 0$$

Theorem A.4.5 (LaSalle's,) Let $f(x)$ be a locally Lipschitz function defined over a domain $D \subset \mathbb{R}^n$ and $\Omega \subset D$ be a compact set that is positively invariant with respect

to (A.1.1). Let $V(x)$ be a continuously differentiable function defined over D such that $V'(x) \leq 0$ in Ω. Let E be the set of all points in Ω where $V'(x) = 0$, and M be the largest invariant set in E. Then every solution starting in Ω approaches M as $t \to \infty$.

A.5 Bifurcation

Bifurcation[26] is the qualitative changes in the dynamics of a system, which occurs when the system parameters are changed [41]. The parameter values where bifurcation occurs are called bifurcation values (bifurcation point) [38]. A standard definition of bifurcation at a point is given below.

Definition A.5.1 Let

$$\frac{dx}{dt} = f(x, \mu), \; x \in \mathbb{R}, \mu \in \mathbb{R}, \tag{A.5.5}$$

be a one-parameter family of one-dimensional ODEs. An equilibrium solution of (A.5.5) given by $(x, \mu) = (0, 0)$ is said to undergo bifurcation at $\mu = 0$ if the flow for μ near zero and x near zero is not qualitatively the same as the flow near $x = 0$ at $\mu = 0$.

There are several types of bifurcation which includes; Saddle-node bifurcation[27]: which occurs when fixed points exist and are destroyed[28] by changing the values of some parameters. Transcritical bifurcation[29]: which corresponds to the case where the fixed points change stability with the change of the values of some parameter. Pitchfork bifurcation[30]: where equilibrium points appear and disappear in symmetrical pairs. Hopf bifurcation[31]: which happens when a fixed point of a dynamical system loses stability as a pair of complex conjugate eigenvalues of the linearization around the fixed point cross the imaginary axis of the complex plane. Two of these, forward and backward bifurcations, are relevant to this thesis.

Appendix B

Mathematicians

The true method of foreseeing the future of mathematics is to study its history and its actual state.

Poincaré

Ronald Ross ~ ***amateur mathematician***

(a)

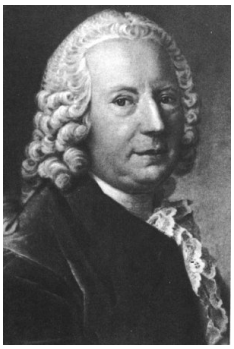
(b)

Figure B.1: Ronald Ross

Born in Almora, India, Sir Ronald Ross (13 May 1857 - 16 September 1932), was a British medical doctor who received the Nobel Prize for Physiology or Medicine in 1902 for his work on the transmission of malaria, becoming the first British Nobel laureate, and the first born outside of Europe. His discovery of the malarial parasite in the gastrointestinal tract of a mosquito proved that malaria was transmitted by mosquitoes, and laid the foundation for the method of combating the disease. He was a polymath, writing a number of poems, published several novels, and composed songs. He was also an amateur artist and mathematician. He developed the mathematical foundation for epidemiology, and used insights gained from his mathematical models to reduce the transmission of malaria. He also published over a dozen papers in pure mathematics.

Daniel Bernoulli ~ *a pioneer in mathematical epidemiology*

(a)



(b)

Figure B.2: Daniel

Daniel Bernoulli (8 February 1700 - 17 March 1782) was a Swiss mathematician and physicist and was one of the many prominent mathematicians in the Bernoulli family. He is particularly remembered for his applications of mathematics to mechanics, especially fluid mechanics, and for his pioneering work in probability and statistics. His name is commemorated in the Bernoulli's principle[32], a particular example of the conservation of energy, which describes the mathematics of the mechanism underlying the operation of two important technologies of the 20th century: the carburetor[33] and the airplane wing.

Daniel was the son of Johann Bernoulli (one of the "early developers" of calculus), nephew of Jacob Bernoulli (who "was the first to discover the theory of probability"). He had two brothers, Niklaus and Johann II. He is said to have had a bad relationship with his father. Between 1725 and 1749 Daniel won 10 prizes from the Paris Academy of Sciences for work on astronomy, gravity, tides, magnetism, ocean currents, and the behaviour of ships at sea. He also made substantial contributions in probability. He shared the 1735 prize for work on planetary orbits with his father, who, it is said, threw him out of the house for thus obtaining a prize he felt should be his alone. Daniel's prizewinning papers reflected his success on the research frontiers of science and his ability to set forth clearly before an interested public the scientific problems of the day. In 1732 he accepted a post in botany and anatomy at Basel; in 1743, one in physiology; and in 1750, one in physics.

Despite his ground breaking contribution to physics, which also gave him the honor to be called the father of mathematical physics, Daniel was a pioneer in mathematical epidemiology. In 1760, he showed the effectiveness of inoculation against smallpox, which was first known result in mathematical epidemiology. Now, smallpox is the only infectious disease that affects humans has been eradicated.

Henri Poincaré ~ *the father of dynamical systems*

(a)

(b)

Figure B.3: Poincaré

The opponent of Georg Cantor's theory of transfinite numbers[34], Jules Henri Poincaré (29 April 1854 - 17 July 1912) was born in Cité Ducale neighborhood, Nancy, Meurthe-et-Moselle into an influential family. His father Leon Poincaré (1828-1892) was a professor of medicine at the University of Nancy. His cousin, Raymond Poincaré was the President of France from 1913 to 1920. Poincaré was the greatest man France had ever produced in modern times.

Poincaré grew up in Nancy and studied mathematics from 1873 to 1875 at the École Polytechnique in Paris. He continued his studies at the Mining School in Caen before receiving his doctorate from the École Polytechnique in 1879 under the supervision of Charles Hermite. His doctoral thesis was in the field of differential equations. Poincaré devised a new way of studying the properties of these equations. He not only faced the question of determining the integral of such equations, but also was the first person to study their general geometric properties. He introduced a new point of view that emphasized qualitative rather than quantitative questions. Particularly, in attacking the *three body problem*[35] Poincaré developed a powerful geometric approach, which has flowered into the modern subject of dynamics [41, 42].

Poincaré 's *Analysis situs*, published in 1895, is an early systematic treatment of topology. He can be said to have been the originator of algebraic topology and, in 1901, he claimed that his researches in many different areas such as differential equations and multiple integrals had all led him to topology. For 40 years after Poincaré published the first of his six papers on algebraic topology in 1894, essentially all of the ideas and techniques in the subject were based on his work. The *Poincaré conjecture*[36] remained as one of the most baffling and challenging unsolved problems in algebraic topology until it was settled by Grigori Perelman in 2002. He is also described as a polymath, and in mathematics as The Last Universalist by Eric Temple Bell, since he excelled in all fields of the discipline as it existed during his lifetime [43].

Aleksandr Lyapunov ~ ***a stable lover***

(a)

(b)

Figure B.4: Lyapunov

A student of Chebyshev, Aleksandr Mikhailovich Lyapunov was born in Yaroslavl, Russian Empire. His surname is sometimes romanized as Ljapunov, Liapunov, Liapounoff or Ljapunow. He was the son of astronomer Mikhail Lyapunov and his brother, Sergei Lyapunov, was a gifted composer and pianist. After the death of his father in 1868, Aleksandr Lyapunov was educated by his uncle R. M. At his uncle's family, Lyapunov studied with his distant cousin Natalia Rafailovna, who became his wife in 1886 [36].

In 1892, Lyapunov completed his doctoral thesis *The general problem of the stability of motion* in which the original problem was proposed by his mentor Chebyshev. Afterwards, he contributed to several fields, including differential equations, potential theory, dynamical systems and probability theory. His main preoccupations were the stability of equilibria and the motion of mechanical systems, and the study of particles under the influence of gravity. His work in the field of mathematical physics regarded the boundary value problem of the equation of Laplace. In the theory of potential, his work from 1897 *On some questions connected with Dirichlet's problem* clarified several important aspects of the theory. Lyapunov developed many important approximation methods. His methods, which he developed in 1899, make it possible to define the stability of sets of ordinary differential equations. He created the modern theory of the stability of a dynamic system. In the theory of probability, he generalised the works of Chebyshev and Markov, and proved the Central Limit Theorem under more general conditions than his predecessors [29].

By the end of June 1917, Lyapunov traveled with his wife to his brother's place in Odessa. Lyapunov's wife was suffering from tuberculosis so they moved following her doctor's orders. She died on October 31, 1918. The same day, Lyapunov shot himself in the head, and three days later he died.

Appendix C

Matlab Codes

C.1 Malaria model

```
function start
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% Starting script to the module 'SIR models of epidemics'
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

% Implements the basic SIR model, and plots simulation results

%-------------------------------------------------------
% User Section 1: Definition of model parameters
%-------------------------------------------------------
%
% These parameters are passed to the function that calculates
    the
% derivatives.
%
% NOTE: Do not change the name 'param'!
%
param.beta = 1e-3; % set the parameter 'beta' of the model
param.r = 1e-1;    % set the parameter 'r' of the model
```

```
19
20 % This is the title string for the plot window.
21 model_title = 'SIR Epidemics';
22
23 %----------------------------------------------------
24 % User Section 2: Definition of initial conditions
25 %----------------------------------------------------
26 %
27 % Initial conditions are the values of all variables at time
     zero.
28 %
29 % NOTE: Do not change the name 'initial'! Define the initial
     values
30 %       in the same order as the derivatives
31 %
32 initial.S = 499;        % set the initial value of 'S'
33 initial.I = 1;  % set the initial value of 'I'
34 initial.R = 0;  % set the initial value of 'R'
35
36 %----------------------------------------------------
37 % User Section 3: Definition of the simulation time
38 %----------------------------------------------------
39 end_time = 100;
40
41 %----------------------------------------------------
42 % User Section 4: Definition of the ODE system
43 %----------------------------------------------------
44 function deriv = ode_system (t, x, param)
45 % Function to calculate derivatives of the SIR model
46 %
47 % Input:
48 % t: Time (not used in this example because there is no
```

```
    explicit
% time dependence).
% x: Vector of the current values of all variables in the same
%    order as you defined the inital values: S, I, R
%    param: Used to pass parameter values.
% Output:
% deriv: Column vector of derivatives, must be the same order
    as the
%    input vector x.

S = x(1);
I = x(2);
R = x(3);
dS = -param.beta * S * I;
dI = +param.beta * S * I - param.r * I;
% Note: because S+I+R=constant, this equation could actually
    be omitted,
% and R at any time point could simply be calculated as N-S-I.
dR = param.r * I;
deriv = [dS; dI; dR];
end

%-------------------------------------------------------
% Now we solve the ODE system and plot the results
%-------------------------------------------------------

% Calculate and print R_0 on the screen
N = initial.S + initial.R + initial.I;
R_0 = param.beta * N / param.r

% Extract initial values from the 'initial' structure and
    collect them
```

```
77 % in a column vector for use in 'ode45'.
78 initial_values = [];
79 variable_names = fieldnames(initial);
80 for i=1:length(variable_names)
81     initial_values = [initial_values; initial.(variable_names{
       i})];
82 end
83
84 % integrate the ODE system
85 [t, y] = ode45(@(t, x) ode_system(t, x, param), ...
86                [0 end_time], ...
87                initial_values, ...
88                []);
89
90 % prepare legend texts
91 legend_texts = cell(length(variable_names), 1);
92 for i=1:length(variable_names)
93     text = [variable_names{i} '(t)'];
94     legend_texts{i} = text;
95 end
96
97 % plot the results
98 plot(t, y);
99 xlabel('time');
100 ylabel('number of individuals');
101 title(model_title);
102 legend(legend_texts);
103
104 end
```

Notes

[1]Anopheles is derived from the Greek word for useless (”without advantage”)

[2]”One of the foremost and most valuable ideas that mathematical thinking has brought to epidemic theory” (Heesterbeek & Dietz, 1996).

[3]Other methods include the survival function, rearranging the largest eigenvalue of the Jacobian matrix, the next-generation method, calculations from the intrinsic growth rate, existence of the endemic equilibrium, the number of susceptibles at the endemic equilibrium, the average age of infection and the final size equation.

[4]An M-matrix is a Z-matrix with eigenvalues whose real parts are positive. An $n \times n$ real matrix $A = [a_{ij}]$ is a Z-matrix if its off-diagonal elements are nonpositive, i.e., if $a_{ij} \leq 0$ for all $i, j = 1, \ldots, n$ with $i \neq j$. The name M-matrix was seemingly originally chosen by Alexander Ostrowski in reference to Hermann Minkowski.

[5]the largest of the absolute values of the eigenvalues is called the spectral radius of A

[6]Local stability of an equilibrium point means that if you put the system somewhere nearby the point then it will move itself to the equilibrium point in some time.

[7]This concludes that the infected mosquitoes and humans eventually vanish and the disease dies out.

[8]To ensure that disease elimination is independent of the initial sizes of the subpopulations, it is necessary to show that the DFE is globally asymptotically stable (GAS) if $R_0 < 1$.

[9]Global stability means that the system will come to the equilibrium point from any possible starting point (i.e., it is indpendent of the initial condition).

[10]If the origin $x = 0$ is a *globally asymptotically stable* equilibrium point of a system, then it must be the ***unique*** equilibrium point of the system. For if there were another equilibrium point $\bar{x}$, the trajectory starting at $\bar{x}$ would remain at $\bar{x}$ for all $t > 0$; hence, it would not approach the origin, which contradicts the claim that the origin is globally asymptotically stable. Therefore, global asymptotic stability is not studied for multiple equilibria systems like the pendulum equation [29].

[11]A Lyapunov function is a scalar function $V(y)$ defined on a region Ω that is **continuous**, **positive definite**, $V(y) > 0$ for all $y \neq 0$), and has continuous first-order partial derivatives at every point of Ω.

[12]The epidemiological implication of this result is that malaria will be eliminated from the population if R_0 can be brought to (and maintained at) a value less than unity.

[13]We use the first equation of system 3.1.1 to compute I_h^* with $N_h \leq \Lambda_h/\alpha_h$.

[14]This table is just the same as ”truth table” in Set Theory (Logic) where the ”+” and ”−” signs correspond to ”True” and ”False”. Thus since there are 3 statements, namely A, B and C the possible number of rows in this case will be $2^3 = 8$.

[15]the branch of medicine that deals with the incidence, distribution, and possible control of diseases and other factors relating to health.

[16]The center manifold theorem is the rigorous formulation that allows us to reduce a large problem to a small and manageable one.

[17]The Jacobian matrix has a simple zero eigenvalue because of the parameter β_h, which is chosen in a particular way, $\beta_h^* = \frac{\Lambda_h \alpha_v^2 (\gamma_h + \rho_h + \alpha_h)}{\beta_v \Lambda_v \alpha_h}$. For any other choice of β_h there won't be a zero eigenvalue.

[18]we need the partial derivatives of f_2 and f_5 since $v_1 = v_3 = v_4 = 0$.

[19]A dynamical system is a semigroup G acting on a space M. That is, there is a map $T : \underset{(g,x)}{G \times M} \to \underset{T_g(x)}{M}$ such that $T_{g \circ T_h} = T_{g \circ h}$ -[G. Tschl].

[20]open and connected set

[21]An equilibrium point is stable whenever the system state is initiated near that point, the state remains near it, perhaps even tending towards the equilibrium point as time increases.

[22]"Asymptotically Stable" is stronger than the notion of "Stable". Because asymptotically stable if it is stable and δ can be chosen such that [29]

[23]This result is believed to have been first described by Réné Descartes in his 1637 work *La Géométrie*. In 1828, Carl Friedrich Gauss improved the rule by proving that when there are fewer roots of polynomials than there are variations of sign, the parity of the difference between the two is even.

[24]approximating the non-linear system with a linear system close to the equilibrium point

[25]a hyperbolic critical point (i.e. the real part of the eigenvalues of J are not zero)

[26]was coined by Poincaré

[27] $\frac{dx}{dt} = \mu - x^2$

[28]the two equilibria existing on one side of the bifurcation disappear on the other side of the bifurcation. This means that as the parameter varies, two equilibria move towards each other, coincide and are destroyed

[29]

$$\frac{dx}{dt} = \mu x - x^2$$
$$\frac{dy}{dt} = -y$$

[30]

$$\frac{dx}{dt} = \mu x - x^3$$
$$\frac{dy}{dt} = -y$$

$$\frac{dx}{dt} = \mu x - y + (x + 3/2y)(x^2 + y^2)$$
$$\frac{dy}{dt} = x + \mu y + (3/2x - y)(x^2 + y^2)$$

[32]In fluid dynamics, Bernoulli's principle states that an increase in the speed of a fluid occurs simultaneously with a decrease in pressure or a decrease in the fluid's potential energy. The principle is named after Daniel Bernoulli who published it in his book Hydrodynamica in 1738.

[33]a device that blends air and fuel for an internal combustion engine in the proper ratio for combustion.

[34]Poincaré was dismayed by Georg Cantor's theory of transfinite numbers, and referred to it as a "disease" from which mathematics would eventually be cured. Poincaré said, "There is no actual infinite, the Cantorians have forgotten this, and that is why they have fallen into contradiction.

[35]It is the problem of taking an initial set of data that specifies the positions, masses, and velocities of three bodies for some particular point in time and then determining the motions of the three bodies, in accordance with Newton's laws of motion and of universal gravitation which are the laws of classical mechanics.

[36]Every simply connected, closed 3-manifold is homeomorphic to the 3-sphere.

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