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ANALYSIS OF MALARIA MODEL WITH TWO INFECTIOUS CLASSES AND SEASONAL MOSQUITO BIRTH RATE

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BY

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Thesis submitted to the Department of Mathematics and Statistics of the School of Physical Sciences, University of Cape Coast in partial fulfilment of the requirements for the award of Doctor of Philosophy degree in Mathematics

June 2014

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DECLARATION

Candidate's Declaration

I hereby declare that this thesis is the result of my own original work and that no part of it has been presented for any other degree in this university or elsewhere.

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Supervisors' Declaration

We hereby declare that the preparation and presentation of the thesis were supervised in accordance with the guidelines on supervision of thesis laid down by the university of Cape Coast.

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ABSTRACT

Malaria is a complex and deadly infectious disease that puts approximately 3.3 billion people at risk in 109 countries and territories around the world. A mathematical model for malaria was analysed to better understand the transmission and spread of this disease. The goal was to use this model to estimate human malaria infection for a given data set.

The model was analysed for the existence and stability of disease-free and endemic (malaria persisting in the population) equilibria. In some cases essential parameters (i.e., parameters with significant influence on the endemic equilibrium) was determined and also bifurcation parameter K was calculated.

It was shown that a scaled version of the model has a unique endemic equilibrium for certain values of the ratio of mosquito to human population, which is always a global attractor. Otherwise, there is no endemic equilibrium and the disease-free equilibrium is a global attractor. When the ratio of mosquito to human population changes the endemic equilibrium changes and forms a curve C_e in the phase space parameterized by this ratio. For a certain range of the rate of human population entering the susceptible class (either by birth or migration) the original model has an equilibrium on the curve C_e. This equilibrium is a saddle with a four-dimensional stable and a one-dimensional unstable manifold. The unstable manifold is well approximated by this curve.

A new version of periodicity was introduced and applied it to two malaria models. The results of the analyses of these models with the periodicity on how they estimate human malaria infection was compared with the results of the models without periodicity.

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DEDICATION

To my family for their understanding, love and support

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CHAPTER ONE

INTRODUCTION

Background of the Study

Malaria is a complex and deadly disease, globally, an estimated 3.3 billion people were at risk of malaria in 2011, with populations living in sub-Saharan Africa having the highest risk of acquiring malaria: approximately 80% of cases and 90% of deaths are estimated to occur in this region, with children under five years of age and pregnant women most severely affected (World Malaria Reports 2012).

In 2000, there were between 350 and 500 million cases of malaria and at least one million deaths world-wide, most of them in African children. In addition to its health toll, malaria places a heavy economic burden on many endemic countries, contributing to the cycle of poverty and limiting economic development. For example, Africa alone is estimated to lose at least US$ 12 billion per year in direct losses (e.g., illness, treatment, premature death), and many times more than that in lost economic growth (World Malaria Reports 2001).

Malaria is endemic and perennial in all parts of Ghana, with seasonal variations that are more pronounced in the north. Ghana's entire population of 25.4 million is at risk of malaria infection, but children under five years of age and pregnant women are at higher risk of severe illness due to lowered immunity. Transmission tends to be less intense in large urban centers (World Malaria Reports 2013).

According to Ghana Health Service (GHS) health facility data, malaria is the number one cause of morbidity and mortality in children under five years of age, accounting in recent years for 33% of hospital deaths in children under five years and about 38% of all outpatient illnesses and 36% of all admissions.

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Between 3.1 and 3.5 million cases of clinical malaria are reported in public health facilities each year, of which 900,000 cases are in children under five years and 3,000-4,000 result in inpatient deaths. The World Health Organisation (WHO) recently estimated total malaria-attributable child deaths at 14,000 per year in Ghana (WHO World Malaria Report 2008). The verbal autopsy component of the 2008 Demographic and Health Survey (DHS) household survey found that roughly half of the deaths in children under five occurred at home, which helps to explain the discrepancy between facility versus total deaths.

The normal duration of the intense malaria transmission season ranges from approximately 6-7 months in the northernmost part of the country (May-October), up to 10-11 months in the forest zone. Peak levels of malaria infection and malaria associated anemia in the population persist for two to three months into the dry season. Plasmodium falciparum accounts for 85-90% of all infections. Plasmodium malariae is also found and more rarely Plasmodium ovale (0.15%). The major vectors are Anopheles gambiae species complex and Anopheles funestus. These species generally bite late in the night, are indoor resting, and are most common in the rural and peri-urban areas. Outdoor biting is common in the northern savannah (e.g., more than 50% outdoor biting pre-Indoor Residual Spraying, was documented at several monitoring sites in Northern Region). Anopheles melas is found in the mangrove swamps of the southwest and Anopheles arabiensis in savannah areas of northern Ghana.

The incidence of malaria has been fluctuating recently due to increasing parasite drug-resistance, mosquito insecticide-resistance and other numerous unaccountable factors. Therefore, it is important to understand the important parameters in the transmission of the disease and develop effective solution strategies for its prevention and control.

Mathematical modelling involves the use of mathematics to describe, explain, or predict behaviour or phenomena in the real world. It can be particularly

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useful in investigating questions or testing ideas within complex systems. A mathematical model is an abstraction of a physical system that uses precise language to describe the systems behaviour. The model is then analysed, solved, or simulated on a computer. The results can be interpreted in physical terms to aid understanding of the underlying system or to point to parts of the system that might be targeted for change.

Infectious disease elimination like malaria is a unique situation that requires specific considerations in modelling. The most frequently employed modelling technique to investigate infectious disease dynamics is deterministic modelling.

In this thesis we develop a deterministic mathematical malaria model with two infectious classes to better understand the transmission and spread of malaria. We model the disease through ordinary differential equations (ODEs) where humans and mosquitoes interact and infect each other. This model is used to determine which factors are most responsible for the spread of malaria. The model divides the human population into four classes: susceptible, infectious, recovered and re-infectious. Humans enter the susceptible population through natural birth. Susceptible humans get infected at a certain probability when they are bitten by infectious mosquitoes. They then progress through the infectious, recovered and re-infectious classes, before reentering the susceptible class. Humans leave the population through natural death in all classes, and through additional disease-induced death out of the infectious and the re-infectious class. There are two classes for the mosquito population: susceptible and infectious. Mosquitoes enter the susceptible class through natural birth. Susceptible mosquitoes get infected at a certain probability when they bite infectious or re-infectious humans (at a lower probability) and then move to the infectious class. Both species follow a logistic model for their population growth, with humans having additional disease-induced death.

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The model contains a system of six coupled nonlinear ODEs with one dependent variable representing each population class. For ease of analysis, we convert the population variables to fractional quantities to create a new system of six ODEs with four variables representing the fractions of the human population (susceptible, infectious, recovered and re-infectious) and two variables representing the fractions of the mosquito population (susceptible and infectious).

We first show that there exists a domain, Ω, in the positive region of R^6, where the model is epidemiologically and mathematically well-posed. Disease-free equilibrium point is a steady state solution where there is no malaria in either the human or mosquito populations. There is one disease-free equilibrium point in Ω, on the boundary of the positive region and this happens when we have only susceptible humans and mosquitoes.

We will give detailed explanation of terms transition between population classes that will be encounter in the thesis, this includes: incidence, recovery, loss of immunity, and birth, death and immigration. Endemic equilibrium points are steady state solutions where the disease persist in a population. Using numerical simulations of the main and scaled systems we establish the presence of endemic equilibrium. We also calculate the endemic equilibrium analytically and compare it with the simulated values.

We write some algorithms for "Wxmaxima" calculating analytically the sizes of populations at equilibrium, this is used to determine a set of parameters that has greater influence on the dynamics of the system at the endemic equilibrium and name them essential parameters.

According to Koella (1991), as one includes more details into a model, the number of assumptions about the interactions increases exponentially. Therefore, the probability of making a wrong and critical assumptions increases rapidly, and it has been found that the predictive power of a model usually declines after some level of detail has been exceeded. Based on this fact, we performed

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a rough estimation of the endemic equilibrium by neglecting the non-essential parameters.

Since the numerical simulations indicate the presence of endemic equilibrium, it goes to suggest the presence of transicrical bifurcation. Therefore, we calculated the bifurcation condition by requiring the determinant of the Jacobian matrix of the simplified scaled system to be zero.

We reviewed the Ross' model, Chitnis' model and Ngwa and Shu's model in comparison with the NDM−model. Tables of typical values of parameters from these three models are presented together with their ranges.

Seasonality plays very important role in the transmission of malaria. According to a research conducted on Patterns and seasonality of malaria transmission in the forest-savannah transitional zones of Ghana by Dery et al. (2010). They reported in their discussions that, mosquito (Anopheles gambiae and Anopheles funestus) abundance was greatly influenced by rainfall and the abundance of both vectors correlated with monthly rainfall patterns, and the prevalence of malaria was highest during the rainy seasons (May-October). Another group (Kasasa et al., 2013) also examined the Spatio-temporal malaria transmission patterns in Navrongo demographic surveillance site, northern Ghana. They indicated in their results that, for the entire research period, mean biting rates per month varied with seasonal changes. For both species (Anopheles gambiae and Anopheles funestus), most bites were observed during the wet season (July to November). Highest bites occurred in the month of September for all the three years. During the dry period of January to April, fewer monthly bites were recorded. Considering the results of these two publications, we proceeded to incorporate a seasonal mosquito birth rate into the Ross model and analysed it. We compared the average human infection obtained by the usual Ross model to mean human infection obtained from the Ross model with seasonal mosquito birth rate.

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The NDM−model was modified by including an exposed (latency) class for the mosquito population and analysed. Further work was done by incorporating seasonal mosquito birth rate and comparing the average infection to mean infection.

Statement of the Problem

1. A commonly adopted method of parsimony in developing mathematical models is to accept the simplest possible theoretical description consistent with the data available at a given time. However, these simple models often have limited predictability and are not satisfactory when new data becomes available, and more complexities of interactions are considered.

2. According to a research conducted on Patterns and seasonality of malaria transmission in the forest-savannah transitional zones of Ghana by (Dery et al., 2010) and another research which examined the Spatio-temporal malaria transmission patterns in Navrongo demographic surveillance site, northern Ghana by (Kasasa et al., 2013), seasonality plays very important role in the transmission of malaria.

Research Objectives

The purpose of this study includes the following:

1. To derive the conditions necessary for disease free and endemic equilibria of a deterministic differential equation model involving two infectious classes.

2. To compare this model and three other malaria models and further establish tables of realistic parameter values ranges.

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3. To introduce a new version of periodicity in malaria modelling, where the mosquito rate attain different values in a given time interval within the year.

4. To analyse Ross (1911) model incorporating this version of periodicity and compare to the Ross (1911) model on how the two models estimate human malaria infectivity.

5. To analyse the modified version of Nortey, Danso-Addo, and Marijani (2008) model incorporating seasonal mosquito birth rate and compare to the Nortey et al. (2008) model on how the two models estimate human malaria infectivity.

Methodology

1. We shall study the models analytically (using manual calculations and 'Wxmaxima') or computer numerical simulations (Using 'octave' and 'Wx-maxima').

2. Formulation of the original model using system of differential equations.

3. Transform the original model for easy analysis by scaling the compartmental populations with the total host population and vector population (which we call scaled version).

4. Employed concepts from dynamical systems to check for the existence of equilibrium states either analytically or computer simulation.

5. If the equilibria exists we examine them for stability, either analytically or computer simulation.

6. We will calculate relative populations and use it to compare the original model and the scaled version.

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7. We examine the equilibria for global stability by computer simulations.

8. Identify parameters that greatly influence the stability of an equilibrium both analytically and computer simulation.

9. Calculate the bifurcation parameter analytically.

10. Explain the nature of the bifurcation parameter analytically.

Scope and Limitation of the Study

In this study the source of all the data we used are from authentic published papers and books. We did not go to field to collect any data.

Emphasis is more on the numerical analysis of the deterministic system of differential equations based on epidemiological compartment models with no discussion on data based statistical models.

Significance of the Study

In this study, we presented a comprehensive survey in malaria modelling, the approach has been to summarize the modelling activity in this area so that it helps reach a wider range of researchers working on epidemiology, transmission, and other aspects of malaria. This may facilitate the mathematicians to further develop suitable models in this direction relevant to the present scenario, and help the biologists and public health personnel to adopt better understanding of the modelling strategies to control the malaria disease

Outline of the Study

We present some description of the biological and medical background of malaria in the Appendix.

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In Chapter two, we presented a survey on mathematical modelling in malaria since Ross (1909) and also brief description of mathematical epidemiology and its importance in the control of infectious diseases.

Chapter three deals with some concepts in dynamical systems, that includes: equilibrium and stability, bifurcation theory, some epidemic models and the reproduction number of a disease R_0.

In Chapter four, we present the formulation and the analysis of a malaria model with two infectious classes (which we called the NDM−model). We describe the model, the state variables, and the parameters. We review three other known models and compared them with the model under discussion. We further prepared tables parameter values and their ranges which are very useful for references.

Chapter five reviews the fundamental derivation of Ross (1911) model with some analysis and then introduces a new version of periodicity (with seasonal mosquito birth rate) in malaria modelling. We then incorporate this periodicity into the Ross (1911) model (we call this periodic model) and analysed it. A comparison is made between the Ross (1911) model and the periodic model on how they estimate human malaria infectivity.

In Chapter six, we modified the NDM−model introduced in Chapter three by including latency in the mosquito population. We then analyse this modified version of the NDM−model. In addition, we incorporated the seasonal mosquito birth rate into the modified NDM−model (we call this periodic model) and analysed it. A comparison is made between the modified NDM−model and the periodic model on how they estimate human malaria infectivity.

The last but not the least, Chapter seven summaries the entire work, presents some discussions and draws some conclusions

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CHAPTER TWO

LITERATURE REVIEW

Introduction

This chapter presents a detailed review of mathematical modelling of malaria from the basic model of Ross (1909) to the current complicated models by Ngwa and Shu (2000), and Chitnis, Cushing, and Hyman (2006). We also included a review of mathematical epidemiology and its importance in the spread and control of infectious diseases.

Review of Mathematical Modelling of Malaria

A commonly adopted method of parsimony in developing mathematical models is to accept the simplest possible theoretical description consistent with the data available at a given time. However, these simple models often have limited predictability and are not satisfactory when new data becomes available, and more complexities of interactions are considered. Therefore, subsequently, several models have been developed by researchers who extended Ross's model (Ross, 1909, 1911) by considering different factors, such as latent period of infection in mosquitoes and humans (Macdonald, 1957; Anderson & May, 1991), age-related differential susceptibility to malaria in human population (Macdonald, 1957; Aron & May, 1982; Dietz, 1988) acquired immunity (Aron & May, 1982; Aron, 1988; Dietz, Molineaux, & Thomas, 1974), spatial and genetic heterogeneity of host and parasite (Hasibeder & Dey, 1988; Gupta, Swinton, & Anderson, 1974; Gupta & Hill, 1995; Torres-Sorando & Rodriguez, 1997, 2001; Yang, 2000), varying human population size (Ngwa & Shu, 2000; Chitnis et al., 2006), immunity as function (Filipe, Riley, Darkeley, Sutherland, & Ghani, 2007) and socio-economic factors (Yang, 2000).

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Many epidemiological models divide the population into distinct classes called *compartments*. These divisions is cause by the presence of a pathogen in a host community and the classes depends on parasite density inside them and the type of infection. These compartments are represented by standard notation of $S-E-I-R$ after the pioneering work of W. O. Kermack and McKendrik (1922). Definitions of the classes are as follows: S is the fraction of the host population that is *Susceptible* to the infection; E is *Exposed* class, the fraction of the population whose individuals are infected by the pathogen, but not capable of passing on infection to others (during a latent period). The next is the I class, the fraction of the population that are *Infectious*, who give rise to more infected individuals through interaction with the Susceptible. Finally, those individuals who *Recover* from the infection make up the R class. There may be variations in the compartment structure depending on the type of disease. Using these notations, eight classes of compartmental models are possible- $SI, SIS, SEI, SEIS, SIR, SIRS, SEIR$ and $SEIRS$. In case of malaria, the plasmodium parasite requires both human and mosquito for its life cycle to complete, and the infection is transferred between susceptible human individuals through the bite of infected mosquitoes, which acquire infection through a blood meal from infected humans. Therefore, in malaria models, these compartments have been applied to both human (hosts) and mosquito (vector).

We note that, different stages of infection which are significant to the dynamics of transmission are considered. This follows the fact that, the levels of infectious agent that replicates inside in a host may develop from small inoculum to a higher level, and later decline and/or disappear altogether as it passes through these compartments.

Ronald Ross, the man who proved that mosquitoes transmit malaria, developed the first mathematical model for the disease (Ross, 1909, 1911), and later extended by Macdonald (1957) and Anderson and May (1991). He divided the

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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, that is, S_m and I_m, but they do not recover from infection due to their short life span, and thereby follow the *SI* structure. Time evolution of the fraction of individuals in the infected classes I_h and I_m is studied using the following two differential equations, one each for the human and mosquito.

$$\begin{aligned} \frac{dh_h}{dt} &= (abM/N)I_m(1-I_h) - rI_h \\ \frac{dI_m}{dt} &= acI_h(1-I_m) - \mu I_m, \end{aligned} \tag{2.1}$$

where a is the number of bites on humans by a single female mosquito per unit time (usually in a 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 recover for infectious humans ($1/r$ is the average duration of the infectious period); c is the proportion of bites by susceptible mosquitoes on infected people that produce a patent infection, and μ is the death rate of the female mosquito population ($1/\mu$ is the average life span of an adult mosquito).

In this simple model, the total population of both humans and mosquitoes is assumed constant, so that the dynamical variables are the proportion infected in each population (I_h and I_m). The first equation of (2.1) describes changes in the proportion of infected humans. New infections are acquired at a rate that depends on the number of mosquito bite per person per unit time, aM/N, on the probabilities that the biting mosquito is infected, I_m, and that a bitten human is uninfected, $1 - I_h$, and on the chance that an uninfected person thus bitten will actually develop a patent infection. The ratio M/N which we denote as m arises as a direct consequence of the fact that female mosquitoes only take a fixed number of blood meals per unit time. Thus the net rate of transmission is held to an upper limit, irrespective of the absolute densities of mosquitoes and

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people, by the biting rate times the number of female mosquitoes per person. Infections are lost by infected people returning to the uninfected class at a net recover rate rI_m. In this simple model it is assumed that recovered individuals have no immunity to reinfection. Human recovery is assumed to occur at a much faster rate than human mortality such that the rate of mortality is of negligible importance in loss of infected people.

The second equation of (2.1) describes changes in the proportion of mosquitoes infected. The gain term depends on the number of bites per mosquito per unit of time a, on the probabilities that the biting mosquito is uninfected, $1 - I_m$, and that the bitten human is infected, I_h, and on the chance that an uninfected mosquito acquires infection from biting an infectious person, c. The loss term arises from the death of infected mosquitoes, μI_m (mosquitoes do not appear to recover from malaria infection). In the book of Anderson and May, the derivation of the reproductive number R_0 is given as

$$R_0 = \frac{ma^2bc}{\mu r} \tag{2.2}$$

The reproductive number, R_0, is defined as the number of secondary infections that one infectious person would produce in a fully susceptible population through the entire duration of the infectious period.

For simple homogeneous models, the reproductive number can be defined as the product of the number of contacts that one individual has per unit time, the probability of transmission per contact and the duration of the infectious period. In the case of (2.1), R_0 is defined as the product of the number of mosquitoes that one infectious human infects and the number of humans that one infectious mosquito infects, through the duration of their infectious periods. Now, take a single primary case with a recovery rate of r; the average time spent in an infectious state is $1/r$. During this time, the average number of mosquito bites received from m susceptible mosquitoes each with a biting rate a is ma/r; of these bites a proportion c are actually infectious, which gives a total of mac/r

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mosquitoes infected by the primary human case. Each of these mosquitoes survive for an average time $1/\mu$ and makes a total of ab/μ infectious bites. The total number of secondary cases is thus $(ab/\mu)(mac/r)$.

It is clear that the parameters, m, a, b, and c, that contribute to the increase of R_0 in this model, are related to mosquitoes and humans, and any change in them can significantly affect malaria transmission. Increasing mosquito mortality and reducing mosquito biting rate can R_0. The Ross model outlines the basic features of malaria transmission, and puts the main burden of transmission on mosquito-specific features, thereby paving the way for mosquito-based malaria control programmes.

The malaria parasite spends approximately 10 days inside a mosquito during its life cycle. The simple Ross model did not consider this latency period of the parasite in the mosquitoes and their survival during that period. This resulted in the model predicting a rapid progress of the epidemic in human, and a higher equilibrium prevalence of infectious mosquitoes.

Macdonald extended Ross's simple model by introducing latent period t_m, and introduced the *Exposed* E_m class in the mosquitoes (Macdonald, 1957). Therefore, the mosquitoes population in this model is divided into three compartments, that is, *SEI* structure and the model studies the time evolution of the exposed E_m and infected I_m classes in mosquito and the Infected I_h class in human. The extended model then becomes

$$\begin{aligned}
\frac{dh_h(t)}{dt} &= ab\frac{M}{N}I_m(t)(1-I_h(t)) - rI_h(t) \\
\frac{dE_m(t)}{dt} &= acI_h(t)(1-E_m(t)-I_m(t)) - acI_h(t-\tau_m) \\
&\quad [1-E_m(t-\tau_m)-I_m(t-\tau_m)]e^{-\mu\tau_m} - \mu E_m(t) \\
\frac{dI_m(t)}{dt} &= acI_h(t-\tau_m)[1-E_m(t-\tau_m)-I_m(t-\tau_m)]e^{-\mu\tau_m} - \mu I_m(t)
\end{aligned} \tag{2.3}$$

The corresponding R_0 is given as

$$R_0 = \frac{Ma^2bc}{N\mu r}e^{-\mu\tau_m}. \tag{2.4}$$

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It could now be observed that, the R_0 for this model is consequently scaled down with increasing latency period.

Anderson and May (1991) made an obvious modification to the Macdonald model by incorporating latency period in human population during which infected humans are infected but not infectious. They now denote the latency periods as τ_h and τ_m in human and mosquito host respectively. They further represent mortality in the human population as occurring at a rate μ_h, and that in the mosquito population as occurring at a rate μ_m. The proportion of infected but not yet infectious hosts are defined as E_h and E_m for humans and mosquitoes respectively. The variables I_h and I_m maintain their formal definitions.
The model then takes the form

$$\begin{aligned}
\frac{dE_h(t)}{dt} &= ab\frac{M}{N}I_m(t)(1-E_h(t)-I_h(t)) - ab\frac{M}{N}I_m(t-\tau_h) \\
&\quad [1-E_h(t-\tau_h)-I_h(t-\tau_h)]e^{-(r+\mu_h)\tau_h} - rE_h(t) - \mu_h E_h(t) \\
\frac{I_h(t)}{dt} &= ab\frac{M}{N}I_m(t-\tau_h)[1-E_h(t-\tau_h)]e^{-(r+\mu_h)\tau_h} - rE_h(t) - \mu_h I_h(t) \\
\frac{dE_m(t)}{dt} &= acI_h(t)[1-E_m(t)-I_m(t)] - acI_h(t-\tau_m) \\
&\quad [1-E_m(t-\tau_m)-I_m(t-\tau_m)]e^{-\mu_m\tau_m} - \mu_m E_m \\
\frac{dI_m(t)}{dt} &= acI_h(t-\tau_m)[1-E_m(t-\tau_m)-I_m(t-\tau_m)]e^{-\mu_m\tau_m} - \mu_m I_m(t)
\end{aligned} \tag{2.5}$$

It is here assumed that latent and infectious hosts has identical mortality rates. The basic reproductive rate of malaria infection for model then becomes

$$R_0 = \frac{Ma^2bc}{N\mu_m r}e^{-\mu_h\tau_h-\mu_m\tau_m}. \tag{2.6}$$

The introduction of latent periods diminishes the value of R_0 compare with that derived from the basic model, Equation (2.2), by a factor $e^{[-(\mu_h\tau_h+\mu_m\tau_m)]}$. The importance is therefore very much dependent on the magnitudes of the death rates μ_h and μ_m and the latent periods τ_h and τ_m.

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It is clear that, the Ross, Macdonald and, Anderson and May's models form the three basic models upon which many other models are build. We conclude the review on these three models by looking at their predicting the effects of interventions. The parameters mosquito density m, biting rate a and mosquito mortality rate μ_m are important in regulating the fraction of human population that will enter into the exposed E and infected I classes. The most important fact for any epidemiologist or public health person is to have an idea about the relative effects of interventions in these parameters to the intensity of transmission, the measure of which is R_0. Given the expressions of R_0 in all three models it is clear that, the square dependence of the biting rate a implies that halving the biting rate is more effective than halving the coefficients b or c in all three models. Thus, reducing the biting rate (by using bed nets, or any other method) will be an effective method of controlling the transmission. But this is not so obvious for all parameters. For example, the relative effect of reducing the adult mosquito mortality μ_m in comparison to biting rate a is different in these models due to the presence of the exponential function of μ_m. Due to higher disease prevalence predicted by Ross model the R_0 is always higher compared to that of the Anderson-May model. When $R_0 = 1$ shows that onset of epidemic happens at higher values of parameters in Ross model compared to Anderson-May model. These results indicate that compared to the reduction in biting rate a, reducing the length of life of adult mosquitoes is most effective in decreasing malaria cases, in the latter two of the three basic models. As mentioned before, these model results provided rationale for control of malaria transmission through the mosquitoes, using insecticides (DDT) and insecticide-impregnated bed nets, since they affect m, a, and μ_m. Thus, even at this low level of complexity, these models had been successful in describing the factors that influence the transmission of the disease, which were useful in control and eradication of malaria from many areas in the world including Europe, North America, Aus-

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tralia, North Africa and the Caribbean, and parts of South America, Asia and Southern Africa.

Over and above the simple scenario described in the basic models, many other factors such as, host factors, demographic heterogeneity, geographic distribution of populations, rules of social interactions including migration/visitation, climate and environmental influences, and the ecology of the area play important roles in the development of malaria in space and time. Age-specific host immunity, parasite diversity, DDT and drug resistance dynamics, vector population dynamics, effect of global warming are also interacting factors and variables that influence disease dynamics at different scales. There has not been a model that has been able to incorporate all factors and variables because of the overwhelming complexity of the system. Also, a model's utility may not always lie in its mathematical analysis or incorporating finer details. The ability to base it on relevant details and ask specific questions that can be tested, are the hallmark of useful models. Along with fitting the past data and predicting the future, it should also be able to point to areas where data needs to be generated in order to increase our conceptual grasp. Such improvements in modelling generally occur in multiple steps, one leading to the other, as more information become available. In the next few pages we consider the review of some of the current and past malaria models that have incorporated some of the above mentioned factors.

Torres-Sorando and Rodriguez (1997) considered the effects of migration and visitation on transmission of malaria and decided to modify the Ross model to include space that is fragmented into a number of patches. Only humans are assumed to move among the patches and mosquitoes are evenly distributed. The equations describing the system are themselves. The number of infected humans and mosquitoes in patch $i(i = 1,2,...,A)$ at time t are, $I_{hi}(t)$ and $I_{mi}(t)$, respectively, and e_{ij} is the fraction of humans that migrate per unit time from patch i to patch j, and do not return. So, to incorporate the effect of migration in this

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model, an extra term related to infected people due to movement between the patches is added to the human dynamics equation. For visitation, the individuals visit from patch i to patch j during a time, which is a fraction T_{ij} of the time unit, and then return to their patch of origin. The number of newly infected people added during visitation is the corresponding equations for the visitation model. The model results show that increase in mobility between patches enhances the persistence of the disease. Even though migration of humans does not change the equilibrium prevalence, equilibrium is reached faster for higher levels of migration. When there is visitation, the equilibrium prevalence increases with visitation time, and the time to reach the equilibrium decreases with increase in the intensity of visitation.

An important advance for the mathematical modelling of malaria was the inclusion of acquired immunity in the model proposed by Dietz et al. (1974). They proposed a model with two different classes of humans: one without immunity to malaria and one class with some immunity. As the non-immune class falls sick, some people recover with immunity. The immune class can get infected, but does not fall clinically ill and cannot be infectious. The model by Dietz et al. (1974) also included superinfection, a phenomenon usually associated with macroparasites. The model has shown a good fit to the data obtained from northern Nigeria. The changes on each compartment in this model were presented using difference equations. Due to lack of confirmed markers of immunological protection, different processes that determine the immunity acquisition to clinical disease and to asymptomatic carriage of malaria parasites are poorly understood. The models discussed in the earlier section consider the immune individuals as a separate class, with no consideration of the types of processes that drive acquisition of immunity and its role in disease progression. In an insightful approach, Filipe et al. (2007) introduced three age-specific "immunity-functions" in their *SEI* model for the human host, in which the infected humans are divided into

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three classes - infected with severe disease I_{h1}, asymptomatic patent infection I_{h2}, and infected with undetectable parasite density I_{h3}. The effect of mosquito density is incorporated through the force of infection h. The three immunity functions IF introduced in the Filipe model are:

(i) Reducing the susceptibility to clinical disease, $\phi IF1$,

(ii) speeding up of the clearance of detectable parasites, $r_A(IF2)$, and

(iii) increasing tolerance to sub-patent infections, $r_{ij}(IF3)$. These functions depend on age and disease transmission intensity (i.e., Entomological Inoculation Rate) in a complex manner. They base their model assumptions on the fact that the rates at which both types of immunity - clinical and anti-parasite - develop are different. All these processes have widely varied time scales, which make the disease transmission in this age-structured population quite complex. Susceptibility to clinical disease (effect of $IF1$) develops early in life and then decreases with age, and is inversely proportional to the inoculation rate. Anti-parasite immunity, on the other hand, develops later in life and results in more rapid clearance of parasite. This shows that, the rate of recovery from detectable parasite (effect of $IF2$) increases with age and force of infection h. These clearly show that these two distinct acquired immunity processes are required to demonstrate:

(i) reduction in clinical susceptibility and

(ii) a parasite immunity process that develops substantially in later life, and, which increases the rate of natural recovery. In addition, this also explains the duration of clinical and parasite immunity from the age-prevalence pattern.

The spread of drug-resistant Plasmodium was considered by Koella and Antia (2003) they discussed a model where, starting with the Macdonald model and moving to more complicated models, they include a strain of disease that is resistant to treatment. Their results show that in their simplest models, there is a threshold value of fraction of infectious humans treated, below which there is no resistance to drugs, and above which, resistance to treatment spreads. In the

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more complicated models, this kind of resistance is usually not fixed, but there is some level of sensitivity to drugs that is maintained in the population.

Yang (2000) was able to show that in most endemic areas of malaria, changes in social and economic conditions are considered to be far more important than temperature shift. The economic and social burdens from factors such as fertility, population growth, premature mortality, misdiagnosis, inflicted by the disease on the society have been studied by many authors. Given the nature of the factors, most investigations are case studies, and there are only few differential equation based models that incorporate socio-economic structure. Using a mathematical model, Yang showed how the basic reproductive number R_0 of malaria transmission changes with global warming and local social and economic conditions (Yang, 2000). In this model, good, intermediate and poor economic conditions among human community have been considered and each condition is further divided into three temperature zones. A host of factors control disease transmission rates in this model such as, differential immunity, endemicity, resistance, economic conditions and temperature dependence of mosquito development. These lead to different R_0 for three temperature zones with different socio-economic structures. These modelling results point out the requirement of proper management of the surrounding environment, along with good health care system, in disease transmission. From the point of view of designing field research, it is shown in a mosquito based model (Chitnis, Schapira, Smith, & Steketee, 2010), that the effectiveness of malaria control through different types of intervention methods (insecticide-treated nets and indoor residual spraying) can have differential protection, with the former being more protective. The socio-economic scenario for large scale deployment of interventions at the population level has also been addressed using modelling studies (Killeen & Smith, 2007).

The environment has become an important factor in the modelling of malaria

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transmission as the basic reproductive numbers R_0 for the basic models depend crucially on the parameters related to mosquito density. Environmental factors, such as temperature, humidity, rainfall and wind patterns have great impact on mosquito reproduction, development and longevity and the parasite survival in its life cycle in mosquito. It is known that mosquito breeding is influenced by temperature – a change in temperature from 12°C to 31°C reduces the number of days required for breeding from 65 days to 7.3 days (Li et al., 2002). The sporogony of the parasites in vector is completed in 55 days at 16°C, which reduces to 7 days at 28°C (Martens, Niessen, Rotmans, Jetten, & McMichael, 1995). With recent surge of interest on the effects of global warming on malaria incidence, modelling the effects of environmental factors in malaria transmission has become quite relevant and topical. As humidity is conducive to mosquito growth, rainfall and stagnant water bodies also influence mosquito density. Owing to these facts about the environment and the dynamics of mosquito population, Parham and Michael (2010) proposed a model, to study the dynamics of the mosquito population by considering simultaneous effects of rainfall and temperature. The model consists of three compartments in humans S_h, I_h and R_h with fixed duration of latency, and three compartments in mosquitoes S_m, E_m and I_m. Different environmental factors are introduced in this model through parameters related to mosquitoes. The birth rate of adult mosquito is considered to be a function of rainfall and temperature, whereas, mosquito mortality rate, biting rate, duration of sporogonic cycle and survival probability of infected mosquitoes over the incubation period of the parasite are considered to be dependent on temperature variation. The major finding of this model is that changes in rainfall patterns not only influence vector abundance, but also strongly govern malaria endemicity, invasion and extinction. However, when sufficient rainfall exists to sustain vector development and survival, then the temperature affects the pathogen life cycle, and has stronger influence on the rate of disease spread.

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One of the features that has been consistently followed in all the models discussed above is the constancy of population size. Mortality and migrations are major factors in changing the population size in an area and the inclusion of varying population size in the model makes them more realistic. Ngwa and Shu proposed an immunity model in which disease related death rate is considered to be significantly high, and the total population is not constant. The model proposed by Ngwa and Shu (2000) consists of four compartments in humans – Susceptible S_h, Exposed E_h, Infected I_h and Immune R_h - and three compartments in mosquitoes - Susceptible S_m, Exposed E_m, and 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.

In a similar style, Chitnis (2005) derived and analysed a mathematical model to give a better understanding of the transmission and spread of malaria. Their main goal was to use this model to compare intervention strategies for malaria control for two representative areas of high and low transmission. They modelled malaria using ordinary differential equations that captures the property of constant immigration of susceptible human population. Considering immigration of people and excluding direct human recovery from the infectious to susceptible class. They analysed this model for the existence and stability of disease-free and endemic (malaria persisting in the population) equilibria. The key to their analysis is the definition of a reproductive number, R_0 (the number of new infections caused by one individual in an otherwise fully susceptible population through the duration of the infectious period). They proved the loss of stability of the disease-free equilibrium as R_0 increases through $R_0 = 1$. Using

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global bifurcation theory developed by Rabinowitz, they showed the bifurcation of endemic equilibria at $R_0 = 1$. This bifurcation was shown to be either supercritical (leading to stable endemic equilibria for $R_0 > 1$) or subcritical (leading to stable endemic equilibria for $R_0 < 1$ in the presence of hysteresis). They compiled two reasonable sets of values for the parameters in the model: for areas of high and low transmission. Computed sensitivity indices of R_0 and the endemic equilibrium to the parameters around the baseline values. They established that R_0 is most sensitive to the mosquito biting rate in both high and low transmission areas. They also found out that the fraction of infectious humans at the endemic equilibrium is most sensitive to the mosquito biting rate in low transmission areas, and to the human recovery rate in high transmission areas. This sensitivity analysis allowed them to compare the effectiveness of different control strategies. According to their model, the most effective methods for malaria control are the use of insecticide-treated bed nets and the prompt diagnosis and treatment of infected individuals.

One of the most prominent feature in the models discussed above, however, depend on the unrealistic assumption of quasi-static vector numbers and unvarying parasite development rates. It must be noted that, variation in mosquito population plays very important role in the transmission of malaria and these variation are dependent of climatic conditions.

In order to be able to predict within-season and between year variation in weather-related malaria risk, Hoshen and Morse (2004) propose a model is driven weather variation and described in detail the development of a weather-driven dynamic mathematical malaria model, the final output of which is new infections in the human host. Their preliminary results from numerical evaluation in time and space are presented. They chose a causal mathematical model rather than a statistical model is basing their argument on the fact that, the former is better suited to extrapolations to novel situations (e.g., when interventions are

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introduced), and for investigating the non-linear impacts of short-lived changes in driving meteorological determinants. Their malaria model is designed to be used for two distinct but related functions:

(i) To determine the impact of whether variables on model output (malaria cases/ infection) for given interventions and

(ii) To determine the impact of specific control interventions on model outputs by modifying model parameters.

For the former function, the model can be driven with meteorological variables, from ground-based observations, satellite or modelled weather data, seasonal climate forecasts (and potentially) climate change scenarios. In the second function, the value of a malaria early warning system (MEWS) in terms of triggering earlier or scaling up intervention efforts (e.g., residual spraying) in epidemic years may be assessed. In both cases, the biological processes are included as a series of interlinked sub-models and thus represented as coupled delay differential equations.

Each new item of knowledge (such as improvements in the structure of the dynamic equations, due to novel experimental or field data) may be immediately used in the model. New developments such as, for example, the ominous spread of drug resistance may also be immediately incorporated into the model, as, in this example, a reduction in the parasite clearance rate. The implications of all such changes may then be assessed as a quantitative amendment to the prediction. This is done independently for each location and, therefore, the model can be fitted to local conditions, where relevant data are available, or to regional parameters when such data are lacking.

Sensitivity analysis can also be used to establish the relative importance of obtaining more accurate data on each parameter. Thus, central to their analysis is the development of a new weather-dependent mathematical dynamic model which no longer attempts to calculate a single constant epidemiological per-case

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multiplication rate, but follows the temporal progress of the prevalence of infection within a population through seasons and years. To simulate the stochastic elements of their model, they constructed a delay differential equations based on probabilistic transition between groups rather than on Monte Carlo modelling.

Seasonality may come from various sources, for example, seasonality by varying the transmission rates and the fluctuations in birth rates are the most common ones. These two factors have been known to cause complex dynamics. The mathematical models that describe these diseases are seasonally forced. For such models, R_0 depends on the the time of invasion, and thus is a function of time.

Ma and Ma (2006) derived a threshold conditions for eradication of diseases that can be described by seasonally forced susceptible, exposed, infectious and recovered (SEIR) models or their variants. For autonomous models, according them, the basic reproduction number $R_0 < 1$ is usually both necessary and sufficient for the extinction of diseases, but seasonality forced models, R_0 is a function of time t. They found out that,

(i) for models without recruitment of susceptible individuals (via births or loss of immunity), $max_t\{R_0\} < 1$ is required to prevent outbreaks no matter when and how the disease is introduced,

(ii) for models with recruitment, if the latent period can be neglected, the disease goes extinct if and only if the basic reproduction number $\bar{R}_0$ of the time average systems (the autonomous systems obtained by replacing the time-varying parameters with their long-term time averages) is less than 1. Otherwise, $\bar{R}_0 < 1$ is sufficient but not necessary for extinction. Thus, reducing $\bar{R}_0$ of the average system to less than 1 is sufficient to prevent or curtail the spread of an endemic disease.

Wang and Zhao (2008) analysed the global dynamics of a periodic epidemic model with patch structure in order to study the impact of periodic con-

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tacts or periodic immigrations on the malaria disease transmission.

They established the basic reproduction ratio and its computational formulae for a large class of compartmental epidemic models in periodic environments. They proved that, a disease cannot invade the disease–free state if the ratio is less than unity and can invade if it is greater than unity. They also showed that, the basic reproduction number of the time–averaged autonomous system is applicable in the case where both the matrix of new infection rate and the matrix of the transition and dissipation within infectious compartments are diagonal, but conceded that, it may underestimate and overestimate infection risks in other cases.

Review of Mathematical Epidemiology

The epidemiology of a disease deals with the reasons for the prevalence of the disease and the nature and causes of its variation. Its aim is to understand the dynamics of the disease transmission well enough to manage control programs efficiently. In the case of malaria, biological studies in the field and the laboratory have greatly increased our knowledge of the life cycle of the malaria parasite and its interactions with its mosquito vector and its final host. However, since the beginning of malaria research (Ross, 1911; Macdonald, 1957), it has been clear that even the most detailed biological knowledge of the parasite's life-cycle cannot lead to a complete understanding of what causes such radical differences in malaria patterns in different parts of the world. Such understanding can only be reach by synthesizing the many factors controlling transmission, integrating detailed biological information into one coherent picture. This integration is the aim of mathematical epidemiology.

According to Smith (2008), mathematical epidemiology has its roots in 1760, when Daniel Bernoulli formulated and solved a model for smallpox. In 1906, Hamer used a discrete time model of measles to understand recurrent epi-

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demics. In 1911, Sir Ronald Ross used mathematics models to help demonstrate that malaria is spread by mosquitoes (later wining a Nobel prize for his work). This work was later followed up by public-health physician William Kermack and biologist Anderson McKendrick in 1927, who showed that mortality rates were much more dependent on the year of birth than the year of death, as previously thought.

As Macdonald (1957) writes; "Mathematical epidemiology gives a sense of proportion, relating the various factors of the transmission cycle to each other and to relevant biological characteristics of the mosquito. It can show the scale of changes in infection rates to be expected following changes in one of the transmission factors, and why this scale should differ greatly under different conditions. It can supply the principle which connects happenings in two countries and explain the detail of happenings in any individual country".

Mathematical models have become important tools in analysing the spread and control of infectious diseases. The model formulation process clarifies assumptions, variables, and parameters; moreover, models provide conceptual results such as thresholds, basic reproduction numbers, contact numbers, and replacement numbers. Mathematical models and computer simulations are useful experimental tools for building and testing theories, assessing quantitative conjectures, answering specific questions, determining sensitivities to changes in parameter values, and estimating key parameters from data. Understanding the transmission characteristics of infectious diseases in communities, regions, and countries can lead to better approaches to decreasing the transmission of these diseases. Mathematical models are used in comparing, planning, implementing, evaluating, and optimizing various detection, prevention, therapy, and control programs. Epidemiology modelling can contribute to the design and analysis of epidemiological surveys, suggest crucial data that should be collected, identify trends, make general forecasts, and estimate the uncertainty in forecasts. Often

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the work of a mathematical epidemiologist consists of

- model building,
- estimation of parameters,
- investigation of the sensitivity of the model to changes in the parameters and
- simulations.

All these activities are expected to tell us something about the spread of the disease in the population, the possibility to control this spread and maybe how to make the disease disappear from the population.

The diseases which are modelled most often are the so called infectious diseases, that is, diseases that are contagious and can be transferred from one individual to another through contact. Examples of such diseases are the childhood diseases: measles, rubella, chicken pox and mumps, the vector borne diseases includes: malaria, dengue fever, leishmaniasis, African horse sickness, chagas disease, and the sexually transmitted diseases: HIV/AIDS, gonorrhea, syphilis and others. Other examples of infectious diseases are hepatitis, tuberculosis, and we are all very much familiar with: influenza. What constitutes a contact so that the disease can be transmitted in each case is different. For example, you know that the common flu can be obtained by just being physically close to a person who already has it. In sexually transmitted diseases, in most cases a sexual contact is necessary for transmission.

Despite the early recognition by Ross and Macdonald of the importance of a quantitative description of malaria transmission, mathematical epidemiology has encountered many difficulties in gaining general acceptance by epidemiologists and public health workers. One of the reasons for this lack of acceptance may lie in the increasing complexity of the models published since 1960's

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till date. According to Koella (1991), these models are not only difficult for non−mathematicians to understand, but the interpretation of their results may sometimes actually be misleading. On the one hand, the more variables included in a model, the closer the predictions of the model often agree with observations, simply because more degrees of freedom are involved. However, a close agreement between prediction and observation does not necessarily imply an agreement between the structure of the model and the biological processes. Therefore, the qualitative predictions of simple models may be more biologically meaningful than the precise quantitative predictions of complex models involving many parameters. On the other hand, more detailed models do not necessarily result in greater predictive power. In fact, the results of more complex models may be less reliable than those of simple ones (Lee, 1973; O'Neil, 1973). According to Koella (1991), as one includes more detail into a model, the number of assumptions about interactions increases exponentially. Therefore, the probability of making a wrong and critical assumptions increases rapidly, and it has been found that the predictive power of a model usually declines after some level of detail has been exceeded.

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CHAPTER THREE

SOME CONCEPTS IN DYNAMICAL SYSTEMS

Introduction

In this chapter, we deal with equilibrium points and their stability in linear and non−linear systems, treat the concept of bifurcations and explain two types of bifurcations into details. We will also introduce some epidemic models and analyse them using the concept of equilibrium and stability as well as bifurcations. The last section will deal with the fundamental concept in mathematical biology, that is, the basic reproductive ratio, denoted as R_0.

Equilibrium and Stability in System of Differential Equations

The notion of a dynamical system is the mathematical formalization of the general scientific concept of a *deterministic process*. The future and past states of many physical, chemical, biological, ecological, economical, and social systems can be predicted to a certain extent by knowing their present state and the laws governing their evolution. Provided these laws do not change in time, the behaviour of such a system could be considered as completely defined by its initial state. Thus, the notion of a dynamical system includes a set of its possible states (*state space*) and a law of the *evolution* of the state in *time* (Kuznetsov, 1998).

Definition 3.1. *A dynamical system is a triple* T, X, φ^t, *where* T *is a time set,* X *is a state space, and* $\varphi^t : X \to X$ *is a family of evolution operators parameterized by* $t \in T$ *and satisfying the following properties:*

1. The system does not change its state spontaneously and

2. The law governing the behaviour of the system does not change in time: That

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is, system is autonomous.

The most common way to define a continuous-time dynamical system is by differential equations. Under very general conditions, solutions of ordinary differential equations define smooth continuous-time dynamical systems. Few types of differential equations can be solved analytically (in terms of elementary functions). However, for smooth right-hand sides, the solutions are guaranteed to exist according to Propositions 3.1 and 3.2.

A standard epidemiological model for disease prevalence is a set of differential equations that categorizes percentages of the population. So, it is therefore necessary to consider the concept of equilibria and stability when dealing with epidemiological models.

It is well known that most differential equations cannot be solved like in ground courses in calculus so that the solutions are given by expressions of elementary functions. Even in the cases where there is a formula for the solutions it might be so complicated that it is hard to use in practice. This is the reason why the qualitative theory of differential equations started to develop. The qualitative theory examines the properties of solutions without knowing the exact solution. In general, one does not seek detailed solutions either in numerical or analytical form, but rather one seeks to characterize some aspects of system behaviour. For example, one might ask whether there are equilibrium points and whether they are stable. In this section, we will consider treating equilibrium and stability under the following headings: Existence and uniqueness, one−dimensional system, linear system and non−linear system.

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Existence and uniqueness

Definition 3.2. *Let $X(t,x)$ be a real-valued function of the real variables t and x, with domain $D \subseteq R^2$. A function $x(t)$, with t in some open interval $I \subseteq R$, which satisfies*

$$\dot{x}(t) = \frac{dx}{dt} = X(t,x(t)) \tag{3.1}$$

is said to be a solution of the differential equation (3.1).

A necessary condition for $x(t)$ to be a solution is that $(t,x(t)) \in D$ for each $t \in I$; so that D limits the domain and range of $x(t)$. If $x(t)$, with domain I, is a solution to (3.1) then so is its restriction to any interval $J \subset I$. To prevent any confusion in this thesis, we will always take 1 to be the largest interval for which $x(t)$ satisfies (3.1). Solutions with this property are called maximal solutions.

The existence of solutions is determined by the properties of X. The following proposition is stated without proof (Arrowsmith & Place, 1992).

Proposition 3.1. *If X is continuous in an open domain, $D' \subseteq D$, then given any pair $(t_0,x_0) \in D'$, there exists a solution $x(t)$, $t \in I$, of $\dot{x} = X(t,x)$ such that $t_0 \in I$ and $x(t_0) = x_0$.*

For example, consider

$$\dot{x} = 2|x|^{1/2}, \tag{3.2}$$

where $D = R^2$. Any pair (t_0,x_0) with $x_0 \geq 0$ is given by $(t_0,x(t_0))$ when $x(t)$ is the solution

$$X = \begin{cases} 0, & t \in (-\infty, C) \\ 1, & t \in (C, -\infty) \end{cases} \tag{3.3}$$

and $C = t_0 - \sqrt{x_0}$. A solution can similarly be found for pairs (t_0,x_0) when $x_0 < 0$.

Observe that Proposition 3.1 does not exclude the possibility that $x(t_0) = x_0$ for more than one solution $x(t)$. For example, for (3.2), infinitely many solutions $x(t)$ satisfy $x(t_0) = 0$, namely every solution of the form (3.3) for which $C > t_0$ and solution $x(t) \equiv 0$.

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The following proposition gives a sufficient condition for each pair in D' to occur in one and only one solution of (3.1).

Proposition 3.2. *If X and $\partial X/\partial x$ are continuous in an open domain $D' \subseteq D$, then given any $(t_0, x_0) \in D'$ there exists a unique solution $x(t)$ of $\dot{x} = X(t,x)$ such that $x(t_0) = x_0$.*

Notice that, while $X = 2|x|^{1/2}$ is continuous on $D(= R^2)$, $\partial X/\partial x(= |x|^{-1/2}$ for $x > 0$ and $= -|x|^{-1/2}$ for $x < 0$) is continuous only on $D' = \{(t,x)|x \neq 0\}$; it is undefined for $x = 0$. We have already observed that the pair $(t_0, 0)$, $t_0 \in R$ occurs in infinitely many solutions of $\dot{x} = 2|x|^{1/2}$. On the other hand, $X(t,x) = x - t$ and $\partial X/\partial x = 1$ are continuous throughout the domain $D = R^2$. Any (t_0, x_0) occurs in one and only one solution of $\dot{x} = x - t$, namely

$$x(t) = 1 + t + Ce^t, \tag{3.4}$$

when $C = (x_0 - t_0 - l)e^{-t_0}$.

We observe that the Propositions 3.1 and 3.2 are satisfied for the main model under discussion in this thesis, the usual exception are piecewise continuous models.

+textbfOne−dimensional systems

We will here employ the qualitative method of examining the solutions for one−dimensional systems of differential equations of the type

$$\dot{x} = f(x), \tag{3.5}$$

where $x \in R$. Such differential equations are called autonomous. We will always assume that the function $f(x)$ is sufficiently smooth that the existence and uniqueness theorem studied above is valid, and there is a unique solution of the differential equation (3.5) through each initial point. An autonomous differential equation is always separable, but if the integral $\int \frac{dx}{df(x)}$ is difficult or impossible to evaluate, solution by separation of variables is impractical. We note that, there

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is the possibility to obtain constant solutions which do not come from separation of variables. It will turn out that examination of these constant solutions is of central importance in the qualitative analysis.

We note the following property of constant solution. That is, if $\tilde{x}$ is a solution of the equation $f(x) = 0$, then the constant function $x = \tilde{x}$ is a solution of the differential equation $\dot{x} = f(x)$. Conversely, if $x = \tilde{x}$ is a constant solution of the differential equation $\dot{x} = f(x)$ then $\tilde{x}$ is a solution of the equation $f(x) = 0$.

To establish this property, we need only observe that because the derivative of a constant function is the zero function, a constant function $x = \tilde{x}$ is a solution of (3.5) if and only if $f(x) = 0$. A solution $\tilde{x}$ of $f(x) = 0$ is called an equilibrium or critical point of the differential equation (3.5), and the corresponding constant solution of (3.5) is called an equilibrium solution.

The behaviour of the solutions can be summarized in the so called *phase portrait*. By the phase portrait we mean a collection of trajectories (solution curves) with time direction giving the general geometrical behaviour of the solutions.

The phase portrait of a one−dimensional system (3.5) consist of equilibria and trajectories between them going from one equilibrium to another. If on an interval between two equilibria $f(x) > 0$, then the trajectory tends to the left equilibrium for $t \to -\infty$ and to the right for $t \to \infty$. This happens because $x_0 > 0$ means that x is increasing. Analogously, if $f(x) < 0$ on an interval between two equilibria, then the trajectory tends to the right equilibrium for $t \to -\infty$ and to the left for $t \to \infty$.

Example 3.1. *To examine the equilibrium point of* $\dot{x} = \lambda x$, *when* $\lambda > 0$ *and* $\lambda < 0$

We that If $\lambda > 0$, the equilibrium point is $x = 0$, clearly the solutions decrease for $x < 0$ (then $\dot{x} < 0$) and tend to negative infinity and increase for $x > 0$ (then $\dot{x} > 0$) and tend to positive infinity. The equilibrium point $x = 0$ is unstable. The phase portrait is given in Figure 1a.

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If $\lambda < 0$ The solutions decrease for $x > 0$ (then $\dot{x} < 0$) and tend to zero from above and increase for $x < 0$ (then $\dot{x} > 0$) and in tend to zero from below. The equilibrium point $x = 0$ is said to be stable. The phase portrait is given Figure 1b.

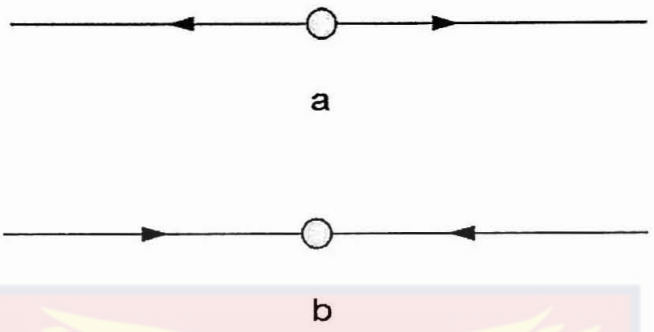


Figure 1: **Phase portraits of** $\dot{x} = \lambda x$

We use Figure 2 to illustrate typical equilibria in one−dimensional system and conclude as follows: Let x_0 be an equilibrium point. If near x_0, $f(x) > 0$ for $x > x_0$ and $f(x) < 0$ for $x < x_0$ then x_0 is unstable (in both directions). If the derivative at x_0 is positive it means that $f(x)$ is positive above the equilibrium and negative below. This means that if $f(x_0) = 0 < f'(x_0)$, then x_0 is an unstable equilibrium see Figure 2A.

If near $x_0, f(x) < 0$ for $x > x_0$ and $f(x) > 0$ for $x < x_0$ then x_0 is stable. This means that if $f(x_0) = 0 > f'(x_0)$, then x_0 is a stable equilibrium see Figure 2B.

If $f(x) > 0$ for all x near $x_0, x \neq x_0$ or if $f(x) < 0$ for all x near $x_0, x \neq x_0$ then x_0 is a so called shunt. It is unstable but if we start from one side of the equilibrium it is attracting although small (in practice always existing) perturbations when we are near to the equilibrium will push it to the other side after which we will move away see Figure 2 C and D.

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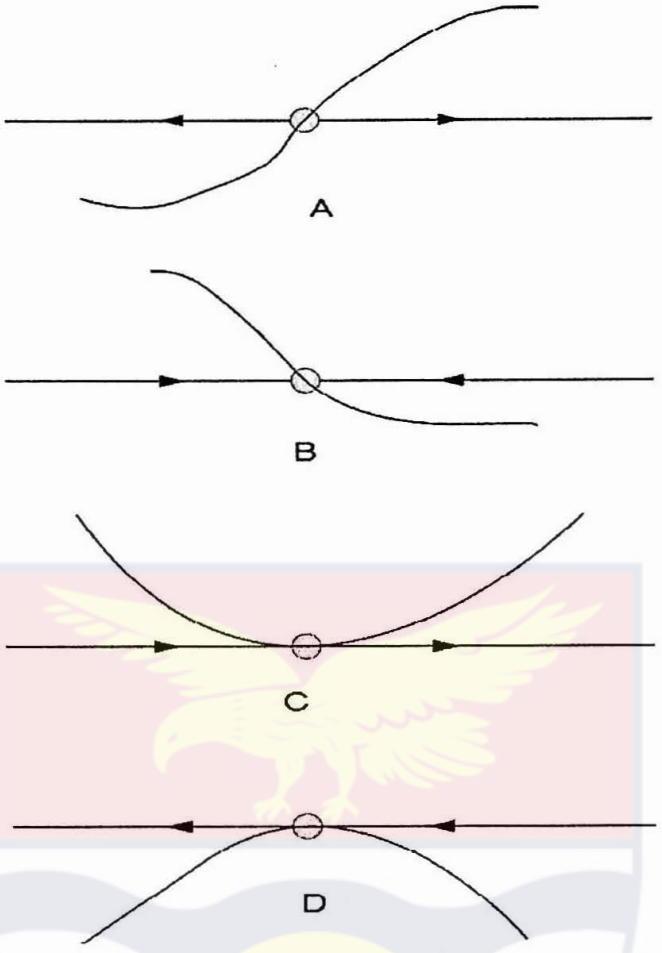


Figure 2: **Phase portraits illustrating types of equilibria**

Multi−dimensional systems

In this subsection, we develop a qualitative theory for multi−dimensional systems of differential equations, much in the spirit of immediate past subsection, where we introduced phase-line and vector field analysis. Here, we will use phase-plane analysis, vector-field analysis and the phase portrait. With these methods, the qualitative behaviour of a system of equations can be understood without solving the equations explicitly. However, for the sake easy explanation and clear understanding we used two−dimensional systems to illustrate the qualitative theory for multi−dimensional systems.

Consider a system of two differential equations,

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$$\begin{aligned} \dot{x_1} &= f_1(x_1, x_2) \\ \dot{x_2} &= f_2(x_1, x_2) \end{aligned} \tag{3.6}$$

At each $x = (x_1, x_2) \in R^2$, the vector field $f(x) = (f_1(x), f_2(x))$ represents a vector. A solution $x(t) = (x_1(t); x_2(t))$ represents a parametric curve in the $(x_1, x_2)-$plane, called a trajectory or an orbit, whose tangent vector $\dot{x}(t) = (\dot{x}_1(t), \dot{x}_2(t))$ is specified by the vector field $f(x(t)) = (f_1(x_1(t), x_2(t)), f_2(x_1(t), x_2(t)))$.

Since solution curves are tangential to the vector field, f, we often can follow trajectories just by following the arrows. The vector field can be used to sketch more than one typical solutions, starting at different initial conditions. The sketch of the $(x_1, x_2)-$plane with a number of typical solutions is called a phase portrait. Another helpful tool for obtaining insight into the phase portrait are *nullclines* (or 0-*isoclines*). The x_1-nullcline, which we call n_1, is the set of points (x_1, x_2) such that $\dot{x}_1 = f(x_1, x_2) = 0$, that is,

$$n_1 := \{(x_1, x_2) | f_1(x_1, x_2) = 0\}$$

.

Similarly, the x_2-nullcline, n_2, is given by

$$n_2 := \{(x_1, x_2) | f_2(x_1, x_2) = 0\}$$

.

On n_1, all vectors of the vector field are vertical (since $\dot{x}_1 = 0$). Similarly, on n_2, all vectors are horizontal (since $\dot{x}_2 = 0$). At intersections of n_1 and n_2, we have $\dot{x}_1 = 0$ and $\dot{x}_2 = 0$. Hence, a steady state or equilibrium point exists at any intersection of n_1 and n_2.

Example 3.2. *To draw the phase portrait of*

$$\begin{aligned} \dot{x_1} &= 0.12x_2(1 - x_1) - 0.01x_1 \\ \dot{x_2} &= 0.05x_1(1 - x_2) - 0.04x_2 \end{aligned} \tag{3.7}$$

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and to indicate where the equilibrium solutions are,

we find the nullclines by equating $\dot{x_1}$ and $\dot{x_2}$ to zero. We get the nullclines to be

$$n_1 : 0.12x_2(1-x_1) - 0.01x_1 = 0$$

and

$$n_2 : 0.05x_1(1-x_2) - 0.04x_2 = 0$$

We then plot the nullclines as shown in Figure 3 and observe that there are two points of intersections, one at the origin and another at P. These two points are the steady points or the equilibria for the system (3.7).

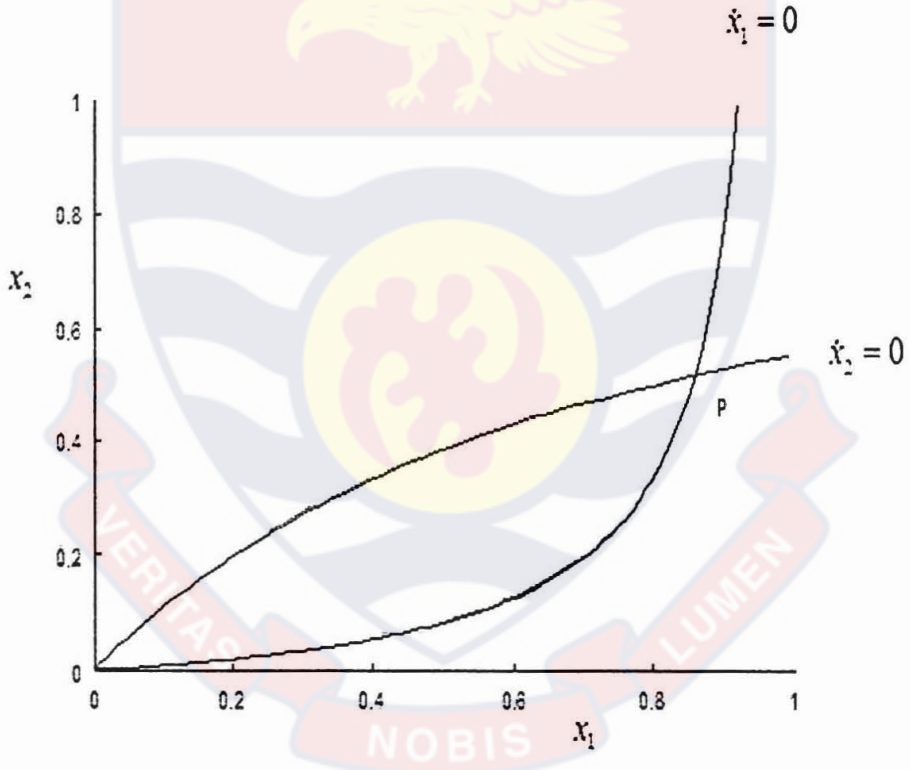


Figure 3: **Phase portrait of system (3.7)**

In general, equilibria, or steady states of the system (3.6) are solutions of

$$f_1(x_1, x_2) = 0 \text{ and } f_2(x_1, x_2) = 0,$$

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which we will denote by $(\bar{x}_1, \bar{x}_2)$. The steady states play an important role in the understanding of the model dynamics. In many cases, if the behaviour near each steady state is known, then the global behaviour of solutions can be understood quite well. It turns out that we can classify all possible types of behaviour which can occur near a steady state. We will do so under the following headings: Specific linear systems, generalized linear systems and non−linear systems.

Specific linear systems

We first treat specific linear systems, that is, we will treat the system with specific case of real eigenvalues and specific case of complex eigenvalues. After that, we generalize to arbitrary linear systems.

Case 1: Real distinct eigenvalues

Consider the linear system,

$$\begin{aligned} \dot{x}_1 &= \lambda_1 x_1, \\ \dot{x}_2 &= \lambda_2 x_2, \end{aligned} \tag{3.8}$$

whose unique steady state is the origin, $(\bar{x}_1, \bar{x}_2) = (0,0)$. In matrix form, we can write

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}.$$

Note that λ_1 and λ_2 are the eigenvalues of the matrix

$$A = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix}$$

Solutions to the system (3.8) are

$$x_1(t) = C_1 e^{\lambda_1 t}, \; x_2(t) = C_2 e^{\lambda_2 t}$$

Plotting the parametric curves $(x_1(t), x_2(t))$ for different initial values (C_1, C_2), we arrive at three distinct phase portraits, depending on the signs of λ_1 and λ_2, as shown in Figures 4, 5 and 6.

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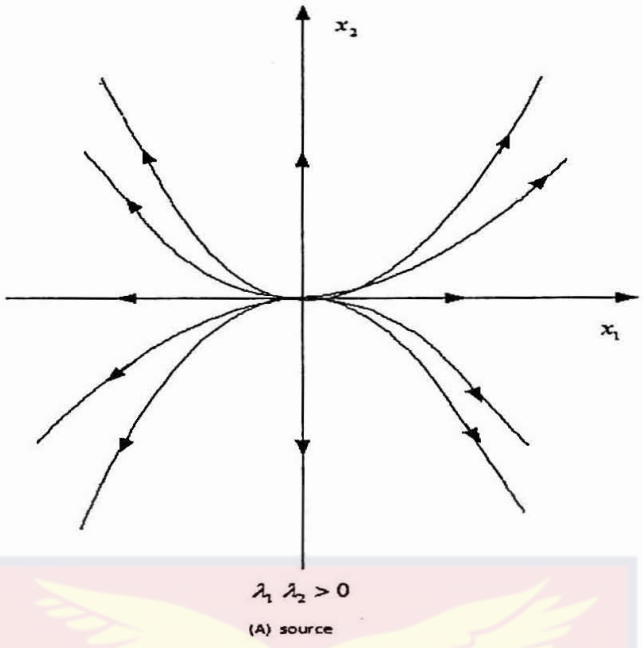


Figure 4: **Phase portrait of System (3.8) for $\lambda_1, \lambda_2 > 0$**

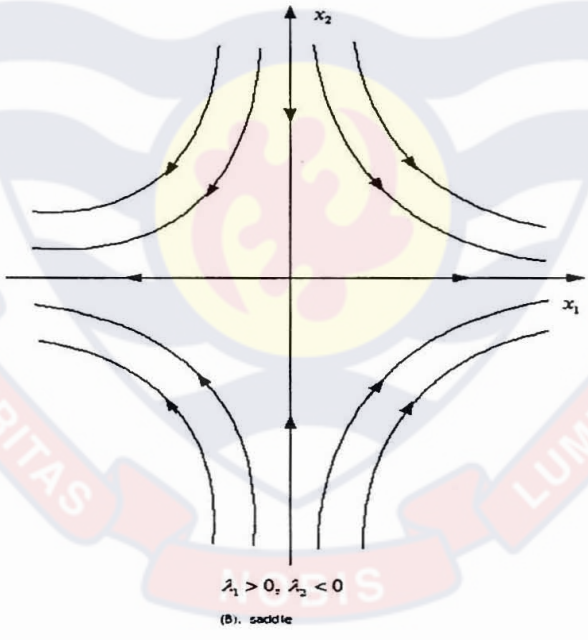


Figure 5: **Phase portrait of System (3.8) for $\lambda_1 > 0, \lambda_2 < 0$**

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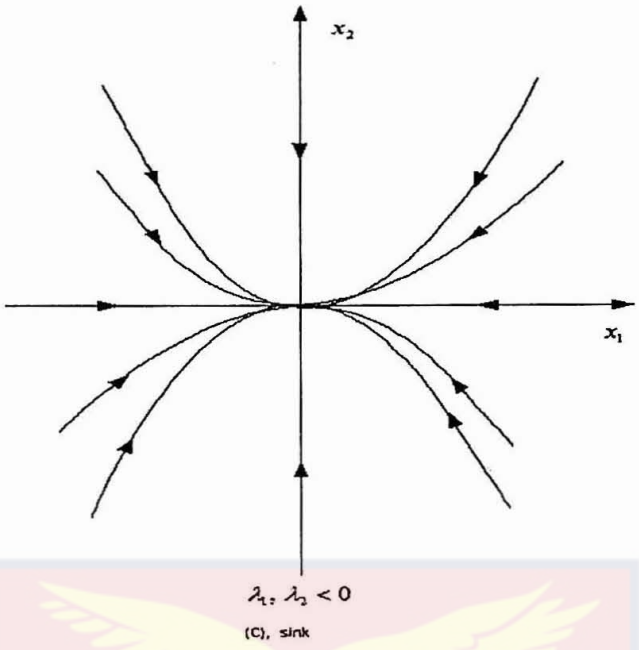


Figure 6: **Phase portrait of System (3.8) for $\lambda_1, \lambda_2 < 0$**

We now consider analysing the different phase portraits of the same system, which depends on the nature of the eigenvalues:

If both eigenvalues λ_1 and λ_2 are positive, then all solutions diverge from the steady state $(0,0)$. In Figure 3, several trajectories are shown for positive, negative, or mixed initial conditions. In this case, the steady state $(0,0)$ is called a source or an unstable node.

If the eigenvalues have opposite signs, $\lambda_1 > 0$ and $\lambda_2 < 0$, say, then $x_1(t)$ is exponentially increasing, while $x_2(t)$ is decreasing. All solutions approach the x_1-axis, as shown in Figure 4. In this case, the steady state $(0,0)$ is called a saddle.

If both eigenvalues are negative, then all solutions converge to the steady state $(0,0)$, as shown in Figure 5. The steady state is called a sink or stable node.

Case 2: Equal eigenvalues

When we have equal eigenvalues two forms of the coefficient matrix arises, giving rise to two forms of phase portraits.

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If the coefficient matrix appears in the form

$$A = \begin{pmatrix} \lambda & 0 \\ 0 & \lambda \end{pmatrix},$$

the system is given by

$$\begin{aligned} \dot{x}_1 &= \lambda x_1, \\ \dot{x}_2 &= \lambda x_2, \end{aligned} \tag{3.9}$$

with solution $x_1 = C_1 e^{\lambda t}$, $x_2 = C_2 e^{\lambda t}$, where (C_1, C_2) is the initial value for trajectory of the system (3.8) and (3.9). If $\lambda < 0$ both x_1 and x_2 tend to zero as $t \to \infty$ and $\frac{x_2}{x_1} = \frac{C_2}{C_1}$. Thus, every orbit is a straight line going to the origin, and slopes as the orbit approaches the origin are possible. The phase portrait is as shown in Figure 7. If $\lambda > 0$, the phase portrait is the same except that the arrows are reversed.

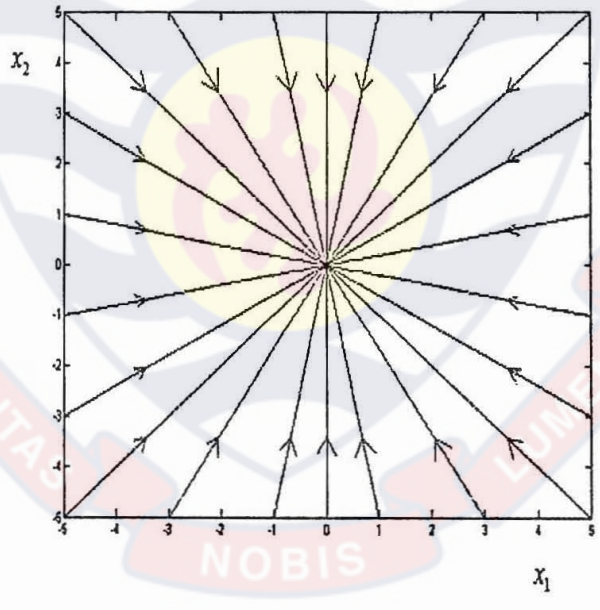


Figure 7: **Phase portrait of System (3.9) for $\lambda < 0$**

The coefficient matrix appears in the form

$$A = \begin{pmatrix} \lambda & 1 \\ 0 & \lambda \end{pmatrix},$$

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the system is given by

$$\begin{aligned} \dot{x}_1 &= \lambda x_1 + x_2, \\ \dot{x}_2 &= \lambda x_2. \end{aligned} \tag{3.10}$$

The solution of the second equation of System (3.10) is $x_2 = C_2 e^{\lambda t}$. Substituting into the first equation gives the first order linear differential equation

$$\dot{x}_1 = \lambda x_1 + C_2 e^{\lambda t}$$

whose solution is

$$x_1 = (C_1 + C_2 t) e^{\lambda t}.$$

If $\lambda < 0$, both x_1 and x_2 tend to zero as $t \to \infty$ and $\frac{x_2}{x_1} = \frac{C_2}{C_1 + C_2 t}$ tends to zero unless $C_2 = 0$, in which case the orbit is the x_1-axis. Thus, except for the orbits on the x_1-axis, every orbit has a maximum or minimum x_1-value and then turns back towards to the origin. The phase portrait is as shown in Figure 8. If $\lambda > 0$ the portrait is the same except that the arrows are reversed.

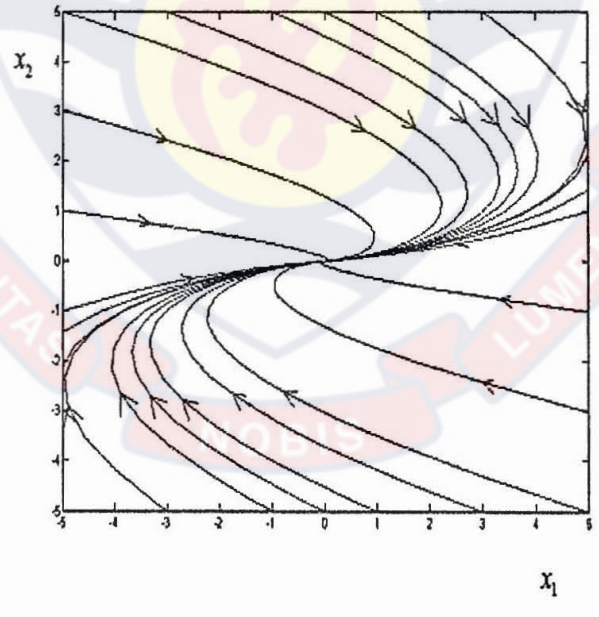


Figure 8: **Phase portrait of System (3.10) for $\lambda > 0$**

Case 3: Complex eigenvalues

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Consider the linear system,

$$\begin{aligned} \dot{x}_1 &= \alpha x_1 + \beta x_2, \\ \dot{x}_2 &= -\beta x_1 + \alpha x_2. \end{aligned} \tag{3.11}$$

For $\beta \neq 0$, the system has the origin, $(0,0)$, as its only steady state. In the matrix form, the system (3.11) is given as

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} \alpha & \beta \\ -\beta & \alpha \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}.$$

The coefficient matrix

$$A = \begin{pmatrix} \alpha & \beta \\ -\beta & \alpha \end{pmatrix}$$

has

$$\lambda_1 = \alpha + \beta i$$

and

$$\lambda_2 = \alpha - \beta i.$$

as the eigenvalues.

The system (3.11) has two special solutions, given by

$$x^{(1)}(t) = e^{\alpha t} \begin{pmatrix} cos\beta t \\ -sin\beta t \end{pmatrix}, \; x^{(2)}(t) = e^{\alpha t} \begin{pmatrix} sin\beta t \\ cos\beta t \end{pmatrix}.$$

The superposition principle of linear systems implies that all solutions to (3.11) are of the form

$$x(t) = x_1(0)x^{(1)}(t) + x_2(0)x^{(2)}(t) = ae^{\alpha t} \begin{pmatrix} cos(\beta t + \theta) \\ -sin(\beta t + \theta) \end{pmatrix}$$

or

$$\begin{aligned} x_1(t) &= ae^{\alpha t} cos(\beta t + \theta), \\ x_2(t) &= -ae^{\alpha t} sin(\beta t + \theta), \end{aligned} \tag{3.12}$$

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where a and θ are determined by the initial conditions, $(x_1(0), x_2(0))$.

Using (3.12), we can classify three distinct cases, shown in Figures 6, 9 and 10.

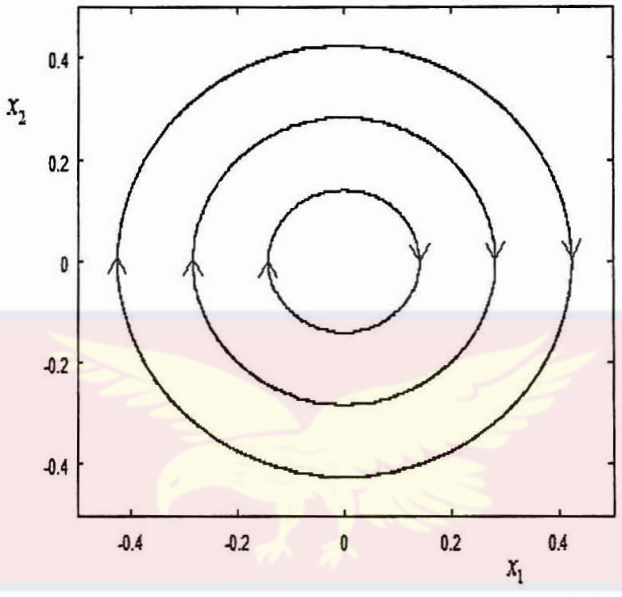


Figure 9: **Phase portrait of System (3.11) for $\alpha = 0$**

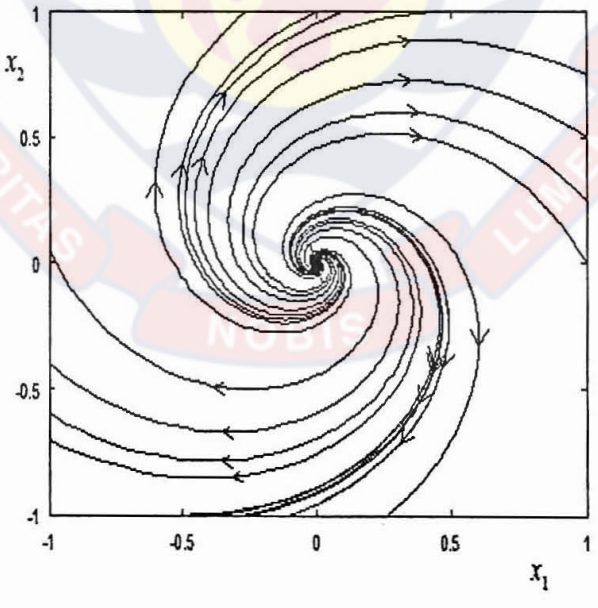


Figure 10: **Phase portrait of System (3.11) for $\alpha > 0$**

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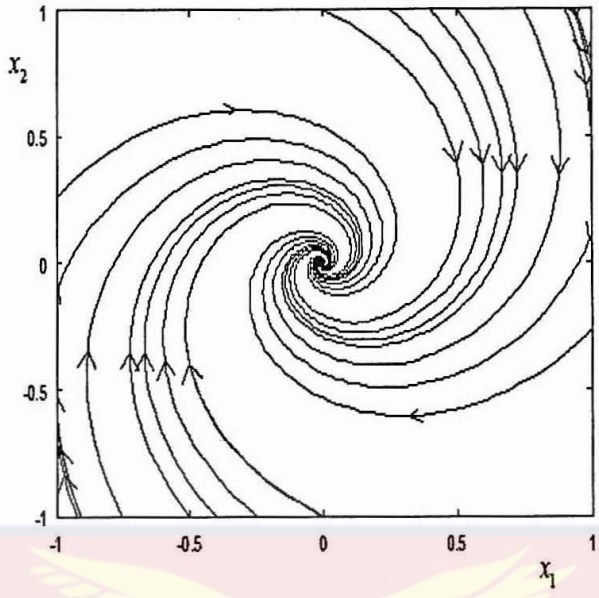


Figure 11: **Phase portrait of System (3.11) for $\alpha < 0$**

We analyse the phase portraits as follows:

If $\alpha = 0$, both eigenvalues are purely imaginary. All solutions are periodic, and all trajectories are closed orbits surrounding the steady state $(0,0)$, clockwise if $\beta > 0$ and counterclockwise if $\beta < 0$. The phase portrait for $\beta > 0$ is as shown in Figure 9. The steady state is called a centre.

If $\alpha > 0$, both eigenvalues have positive real parts. The exponential function $e^{\alpha t}$ grows for $t > 0$. All trajectories spiral away from the steady state $(0,0)$, as shown in Figure 10. The steady state is called an unstable spiral or a spiral source.

If $\alpha < 0$, both eigenvalues have negative real parts. The exponential function $e^{\alpha t}$ decays for $t > 0$. All trajectories spiral towards the steady state $(0,0)$, as shown in Figure 11. The steady state is called a stable spiral or a spiral sink.

We observe that the parameters α and β play very important role in the development of the phase portrait for the system with complex eigenvalues. The parameter α represents the speed of attraction or repulsion and β represents the direction of rotation and can be seen also from the solution forms. For instance,

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from Figure 9, when α is zero it shows there is no attraction nor repulsion, hence, the solution curves remain in their tracts equidistance from the centre.

General linear systems

We now consider the concept of the two−dimensional linear system, state a theorem that govern the behaviour of such linear systems and give a short summary of the possible types of behaviours.

Consider a two−dimensional general linear system

$$\begin{aligned} \dot{x}_1 &= ax_1 + bx_2, \\ \dot{x}_2 &= cx_1 + dx_2, \end{aligned} \tag{3.13}$$

In the matrix form we have the system (3.13) as

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}. \tag{3.14}$$

The coefficient matrix is given as

$$A = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

If we make the transformation (by linear change of variables, see pages 35 to 43 (Arrowsmith & Place, 1992) for detailed explanation).

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = P^{-1} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix},$$

where P is a 2×2 invertible matrix, then $y = (y_1, y_2)$ satisfies the system

$$\begin{pmatrix} \dot{y}_1 \\ \dot{y}_2 \end{pmatrix} = B \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}, \tag{3.15}$$

where $B = P^{-1}AP$. Systems (3.13) and (3.15) have the same phase portraits.

It is known from linear algebra (see pages 270 to 278 of (EdwardsJr & Penney, 1986)) that if A has two distinct real eigenvalues λ_1 and λ_2 such that

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$\lambda_1 \neq \lambda_2$, then we can choose P such that

$$B = \begin{pmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{pmatrix}.$$

If A has two complex conjugate eigenvalues $\lambda_1 = \alpha + \beta i$ and $\lambda_2 = \alpha - \beta i$, then we can choose P such that

$$B = \begin{pmatrix} \alpha & \beta \\ -\beta & \alpha \end{pmatrix}.$$

We then conclude that the phase portraits of (3.13) will be the same as those of Systems (3.8), (3.9), (3.10) or (3.11).

So far, we have seen that we can classify the equilibria of a linear system according to the eigenvalues of the corresponding coefficient matrix,

$$A = \begin{pmatrix} a & b \\ c & d \end{pmatrix}.$$

Sometimes, it is more convenient to use two other characteristic values of A, namely the *trace* of A, written as $trA = a + d$, and the *determinant* of A, written as $detA = ad - bc$. It is known that the trace is always the sum of the eigenvalues, $trA = \lambda_1 + \lambda_2$, and the determinant is the product of eigenvalues, $detA = \lambda_1 \lambda_2$. Moreover, one can use the trace and determinant to calculate the eigenvalues. That is,

$$\lambda_{1,2} = \frac{trA}{2} \pm \frac{\sqrt{(trA)^2 - 4detA}}{2} \tag{3.16}$$

Note that the formula in (3.16) holds only for 2×2 matrices. For higher-order matrices, there is no formula of this form.

From (3.16), we see that it is necessary to have $trA < 0$ in order to have a steady state that is asymptotically stable (otherwise at least one eigenvalue would have a positive real part). If $trA < 0$, then the discriminant, $(trA)^2 - 4detA$, is either negative or smaller than $(trA)^2$. Hence the real part of the eigenvalues

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is always negative, and $(0,0)$ is asymptotically stable. We can summarize our conclusions in the following theorem.

Theorem 3.1. *For a linear system,* (3.13), *the following are equivalent:*

- *The equilibrium* $(0,0)$ *is asymptotically stable,*
- *All eigenvalues of A have negative real parts and*
- $detA = ad - bc > 0$ *and* $trA = a + d < 0$.

We can consider all different combinations for the sign of trace and determinant, and obtain a complete picture of possible behaviour near an equilibrium point. Figure 12 gives a complete picture of all possible types of behaviours for the equilibrium states of two-dimensional systems.

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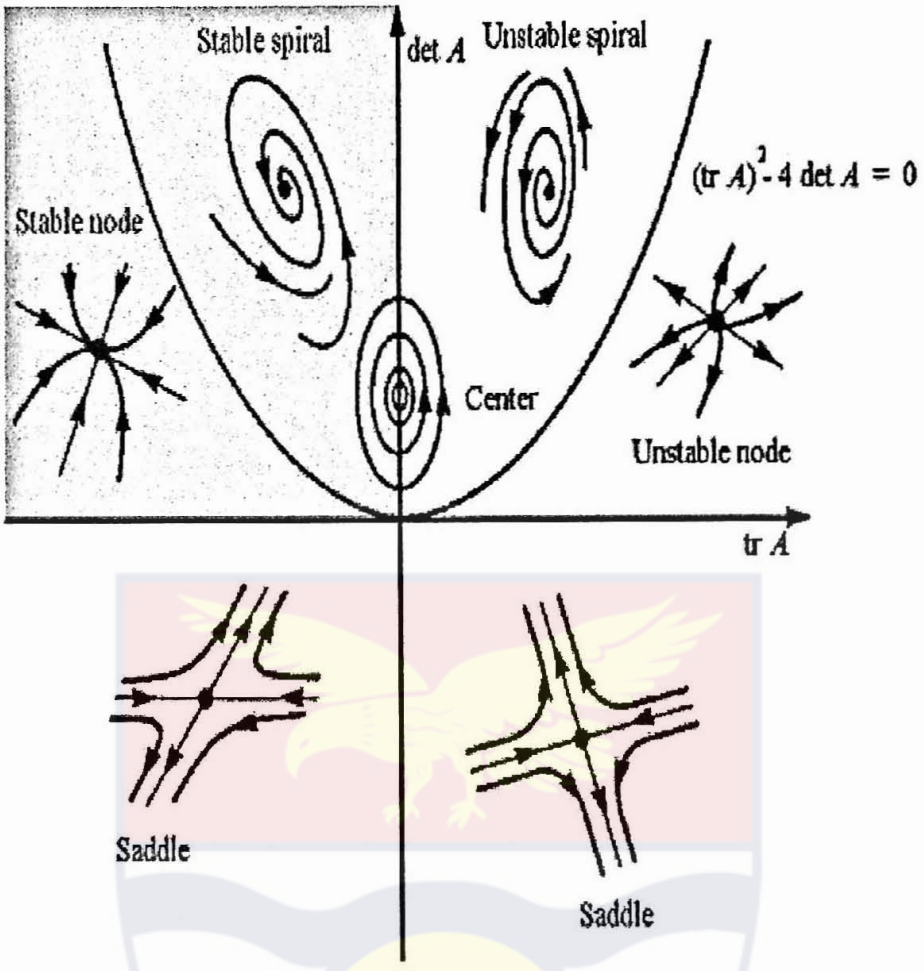


Figure 12: **Summary of how the phase portraits of System (3.13) depend on the trA and the $detA$**

We can summarize the possible types of behaviour as follows:

- If $detA < 0$, then $(trA)^2 - 4detA > (trA)^2$. From Formula 3.16, it follows that there is one positive and one negative eigenvalue, $\lambda_1 > 0$ and $\lambda_2 < 0$, say. Hence, $(0,0)$ is a saddle point. Moreover, solutions grow as $e^{\lambda_1 t}$ in the direction of the eigenvector φ_1 corresponding to λ_1, and solutions decay as $e^{\lambda_2 t}$ in the direction of the eigenvector φ_2 corresponding to λ_2. In Figure 12, the stable and unstable eigenvectors are shown.

- If $detA > 0$ and $trA < 0$, then $(trA)^2 < 4detA$ (above the parabola in Figure 12). Then λ_1 and λ_2 are complex conjugate eigenvalues with real part

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$\frac{trA}{2} < 0$, and $(0,0)$ is a stable spiral. If $(trA)^2 > 4detA$ (below the parabola), then λ_1 and λ_2 are real, but they have the same sign, and $(0,0)$ is a stable node.

- If $detA > 0$ and $trA > 0$, depending on the sign of $(trA)^2 - 4detA$, we have either an unstable spiral or an unstable node.

- If $detA > 0$ and $trA = 0$, then we have a centre in this case.

Non−linear system

In this subsection we will look at some particular non−linear systems, generally inspired from physics and biology. We will then use the linearization method to try to understand the behaviour of these systems. One of the classical examples of a non−linear system is the Lotka-Volterra model of competition between two species (let us take them to be rabbits and kangaroos). Both species are competing for the same food supply (say the grass) and there is a limited amount of this resource.

Consider a non−linear system in R^2,

$$\begin{aligned} \dot{x}_1 &= f_1(x_1, x_2) \\ \dot{x}_2 &= f_2(x_1, x_2), \end{aligned} \tag{3.17}$$

where f_1 and f_2 are continuously differentiable functions.

In general, each pair $(\bar{x}_1, \bar{x}_2)$ satisfying $f_1(\bar{x}_1, \bar{x}_2) = f_2(\bar{x}_1, \bar{x}_2) = 0$ is called an equilibrium or a steady state for (3.17). We would like to understand the behaviour of the solutions near equilibria.

For linear systems, we observed that solutions converge to $(0,0)$, they diverge away from $(0,0)$, or, in the centre case, they stay close by. Before we can generalize these observations to non−linear systems, we need some definitions from dynamical systems theory, see Arrowsmith and Place (1992).

Definition 3.3. *An equilibrium point $\bar{x} = (\bar{x}_1, \bar{x}_2)$ of the System (3.17) is said to be stable if, for every neighborhood N of $\bar{x}$, there is a smaller neighborhood*

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$N' \subseteq N$ of $\bar{x}$ such that every trajectory which passes through N' remains in N as t increases.

Definition 3.4. *An equilibrium point $\bar{x}$ of the System (3.17) is said to be asymptotically stable if it is stable and there is a neighborhood N of $\bar{x}$ such that every trajectory passing through N approaches $\bar{x}$ as t tends to infinity.*

Definition 3.5. *An equilibrium point of the System (3.17) which is not stable is said to be unstable*

This means that there is a neighborhood N of the equilibrium point such that for every neighborhood $N' \subseteq N$ there is at least one trajectory which passes through N' and does not remain in N.

We will now examine the stability of an equilibrium point $(\bar{x}_1, \bar{x}_2)$ by linearizing (3.17).

Let

$$\begin{aligned} x_1(t) &= \bar{x}_1 + y_1(t) \\ x_2(t) &= \bar{x}_2 + y_2(t), \end{aligned}$$

where $y_1(t)$ and $y_2(t)$ are assumed to be small, so that they can be thought of as perturbations to the steady state. We denote $\bar{x} = (\bar{x}_1, \bar{x}_2)$ and $y = (y_1, y_2)$, and write the Taylor expansion of $f = (f_1, f_2)$ about $(\bar{x}_1, \bar{x}_2)$ as

$$f(\bar{x} + y) = f(\bar{x}) + Df(\bar{x}) \cdot y + \text{higher} - \text{order terms},$$

where

$$Df(\bar{x}_1, \bar{x}_2) = \begin{pmatrix} a & b \\ c & d \end{pmatrix} = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} \end{pmatrix}$$

contains the partial derivatives of f evaluated at $(\bar{x}_1, \bar{x}_2)$. The matrix $Df(\bar{x}_1, \bar{x}_2)$ is called the Jacobian matrix of f at $(\bar{x}_1, \bar{x}_2)$.

We substitute the Taylor expansion into (3.17) and we drop the higher-order terms. Since $\dot{x}_1 = \frac{d}{dt}(\bar{x}_1 + y_1(t)) = \dot{y}_1$ and $\dot{x}_2 = \frac{d}{dt}(\bar{x}_2 + y_2(t)) = \dot{y}_2$, and

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since $f(\bar{x}) = 0$, we obtain a linear system governing the dynamics of the perturbation (y_1, y_2):

$$\begin{pmatrix} \dot{y}_1 \\ \dot{y}_2 \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} \tag{3.18}$$

We recall how we examine linear systems in our previous work. For most (but not all) equilibrium points, conclusions obtained for the linearized system indeed carry over to the original non−linear system.

Definition 3.6. *The equilibrium point* $(\bar{x}_1, \bar{x}_2)$ *is called hyperbolic if all eigenvalues of the Jacobian* $Df(\bar{x}_1, \bar{x}_2)$ *have nonzero real part.*

Theorem 3.2. *(Hartman-Grobmann). Assume that* $(\bar{x}_1, \bar{x}_2)$ *is a hyperbolic equilibrium point. Then, in a small neighborhood of* $(\bar{x}_1, \bar{x}_2)$*, the phase portrait of the non−linear system,* (3.17)*, is the same as that of the linearized system,* (3.18).

We conclude this section by noting that:

(1) By Theorems 3.1 and 3.2, at a hyperbolic equilibrium $\bar{x}$, stability properties are determined by the eigenvalues of the Jacobian matrix, $Df(\bar{x}_1, \bar{x}_2)$. This method of linearization may fail for nonhyperbolic equilibria.

(2) The phrase "the same as" in Theorem 3.2 refers to topological equivalence of vector fields. This means that in a neighborhood of $(\bar{x}_1, \bar{x}_2)$, there is a homeomorphism (a continuous one-to-one map between open sets) which maps the vector field of the non−linear system to the vector field of its linearization. In that case, the phase portrait near the stationary point is one of those shown in Figure 12.

Topological equivalent

In this subsection we want to specify when we define two dynamical systems as being qualitatively similar or equivalent. Such a definition must meet some general intuitive criteria. For instance, it is natural to expect that two equivalent systems have the same number of equilibria and cycles of the same

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stability types. The relative position of these invariant sets and the shape of their regions of attraction should also be similar for equivalent systems. In other words, we consider two dynamical systems as equivalent if their phase portraits are qualitatively similar, namely, if one portrait can be obtained from another by a continuous transformation.

Definition 3.7. *A dynamical system* $\{T, R^n, \varphi^t\}$ *is called topologically equivalent to a dynamical system* $\{T, R^n, \psi^t\}$ *if there is a homeomorphism* $h : R^n \to R^n$ *mapping orbits of the first system onto orbits of the second system, preserving the direction of time (Kuznetsov, 1998).*

A *homeomorphism* is an invertible map such that both the map and its inverse are continuous. The definition of the topological equivalence can be generalized to cover more general cases when the state space is a complete metric or, in particular, is a Banach space. The phase portraits of topologically equivalent systems are often also called topologically equivalent. The above definition applies to both continuous- and discrete-time systems. It also fulfills the following properties.

- Reflection: $\{T, R^n, \varphi^t\}$ is topologically equivalent to $\{T, R^n, \varphi^t\}$.
- Symmetry: $\{T, R^n, \varphi^t\}$ is topologically equivalent to $\{T, R^n, \psi^t\}$ implies that $\{T, R^n, \psi^t\}$ is topologically equivalent to $\{T, R^n, \varphi^t\}$.
- Transitivity: If $\{T, R^n, \varphi^t\}$ is topologically equivalent to $\{T, R^n, \psi^t\}$ and $\{T, R^n, \psi^t\}$ is topologically equivalent to $\{T, R^n, \phi^t\}$, then $\{T, R^n, \varphi^t\}$ is topologically equivalent to $\{T, R^n, \phi^t\}$

Very often we study system dynamics locally and not in the whole state space R^n, but in some region $U \subset R^n$. Such a region may be, for example, a neighborhood of an equilibrium (fixed point) or a cycle. The above definitions of topological equivalences can be easily localized by introducing appropriate

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regions. For example, in the topological classification of the phase portraits near equilibrium points, the following modification of Definition 3.7 is useful.

Definition 3.8. *A dynamical system* $\{T, R^n, \varphi^t\}$ *is called locally topologically equivalent near an equilibrium* x_0 *to a dynamical system* $\{T, R^n, \psi^t\}$ *near an equilibrium* y_0 *if there exists a homeomorphism* $h : R^n \to R^n$ *that*

(i) is defined in a small neighborhood $U \subset R^n$ *of* x_0*;*

(ii) satisfies $y_0 = h(x_0)$*;*

(iii) maps orbits of the first system in U *onto orbits of the second system in* $V = f(U) \subset R^n$*, preserving the direction of time (Kuznetsov, 1998).*

If U is an open neighborhood of x_0, then V is an open neighborhood of y_0. Let us also remark that equilibrium positions x_0 and y_0, as well as regions U and V, might coincide.

In the case of non−linear systems the phase portrait are topologically equivalent if

1. they have the same number of equilibrium points with the same stability properties;

2. they have the same number of periodic orbits with the same stability properties;

3. they have the same invariant in one−to−one correspondence.

Therefore, for non−linear systems a local equivalence (Definition 3.8) is of course more useful.

In the case of topological equivalence in linear systems, according to Arnold (1974) two linear systems are topologically equivalent if they present spectrums with no eigenvalues on the imaginary axis and the same number of eigenvalues having positive and negative real parts respectively.

We remark that, the non−linear system in U is topologically equivalent to the associate linearized system in V if the latter is hyperbolic (this is another way to state Hartman-Grobmann theorem, see Theorem 3.2).

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Bifurcation Theory

In scientific fields as diverse as fluid mechanics, electronics, chemistry and theoretical ecology, there is the application of what is referred to as bifurcation analysis; the analysis of a system of ordinary differential equations (ODEs) under parameter variation. In general, in a dynamical system, a parameter is allowed to vary, then the differential system may change. An equilibrium can become unstable and a periodic solution may appear or a new stable equilibrium may appear making the previous equilibrium unstable. The value of parameter at which these changes occur is known as "bifurcation value" and the parameter that is varied is known as the "bifurcation parameter". Performing a local bifurcation analysis is often a powerful way to analyse the properties of such systems, since it predicts the kind of behaviour (system is in equilibrium, or there is cycling) that occurs in parameter space. With local bifurcations linearisation in state space at the critical point of the parameter space provides sufficient information. The main goal of this section is then that the results bifurcation can be understood in terms of biology.

In order to lay good foundation for our discussions on bifurcations we will give some definitions upon which we build our arguments.

Definition 3.9. *The appearance of a topologically nonequivalent phase portrait under variation of parameters is called a bifurcation (Kuznetsov, 1998).*

Thus, a bifurcation is a change of the topological type of the system as its parameters pass through a bifurcation (critical) value.

We also consider another definition of an important concept known as structural stability, whose global and local definitions form the basis of the global and local definitions of bifurcation.

Definition 3.10. *A system* $\dot{x} = f(x, \mu_0)$ *is structurally stable (with respect to the parameter) if and only if there exists* $\varepsilon > 0$ *such that its phase portrait is*

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topologically equivalent to that of the system $\dot{x} = f(x, \mu)$ *for any* μ *such that* $\|\mu - \mu_0\| < \varepsilon$.

We remark that,

1. a hyperbolic equilibrium is structurally stable under smooth perturbations,
2. a sufficiently small perturbation of the vector field does not induce a qualitatively change of a structurally stable dynamical system, and
3. a local version of the Definition 3.10 is of course available.

Now if we consider an ordinary differential equation that depends on one parameter α

$$\dot{x} = f(x, \alpha), \tag{3.19}$$

where $x \in R^n$ and $\alpha \in R^m$ represent phase variables and parameters, respectively and for simplicity, we assume α to be one parameter only. Consider the phase portrait of the System (3.19). As the parameter varies, the phase portrait also varies. There are two possibilities: either the system remains topologically equivalent to the original one, or its topology changes.

In this section, we will discuss three types of bifurcations, tangent(saddle node), transcritical and pitchfork. These three occur in both one− and higher−dimensional systems. However, we note that there are many types of other bifurcations, but these are those mostly occurring in the systems we considered in the thesis.

Bifurcation in one−dimensional system

In this subsection we will consider bifurcations in one−dimensional system. This includes: Tangent (saddle node) bifurcation, transcritical bifurcation and pitchfork bifurcation.

Tangent (saddle node) bifurcation

Let us study the system

$$\dot{x} = x^2 - \alpha. \tag{3.20}$$

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The System (3.20) is structurally stable for a $\alpha \neq 0$ and has a bifurcation at $\alpha = 0$. For $\alpha > 0$ there are two equilibria $p\pm = \pm\sqrt{\alpha}$, where $p+$ is attracting and $p-$ is unstable. For $\alpha < 0$ there are no equilibria and all trajectories go to minus infinity. For $\alpha = 0$ there is a bifurcation and for this parameter value there is exact one equilibrium at zero which is a shunt. Of course, in most systems there will be another attractor somewhere. In a biological setting, this other attractor will often be $x = 0$, while the two equilibria involved in the tangent bifurcation are both positive. We then interpret the tangent bifurcation as a sudden extinction of the species. The phase portraits are seen in Figure 13 and summarized as a bifurcation diagram in Figure 14.

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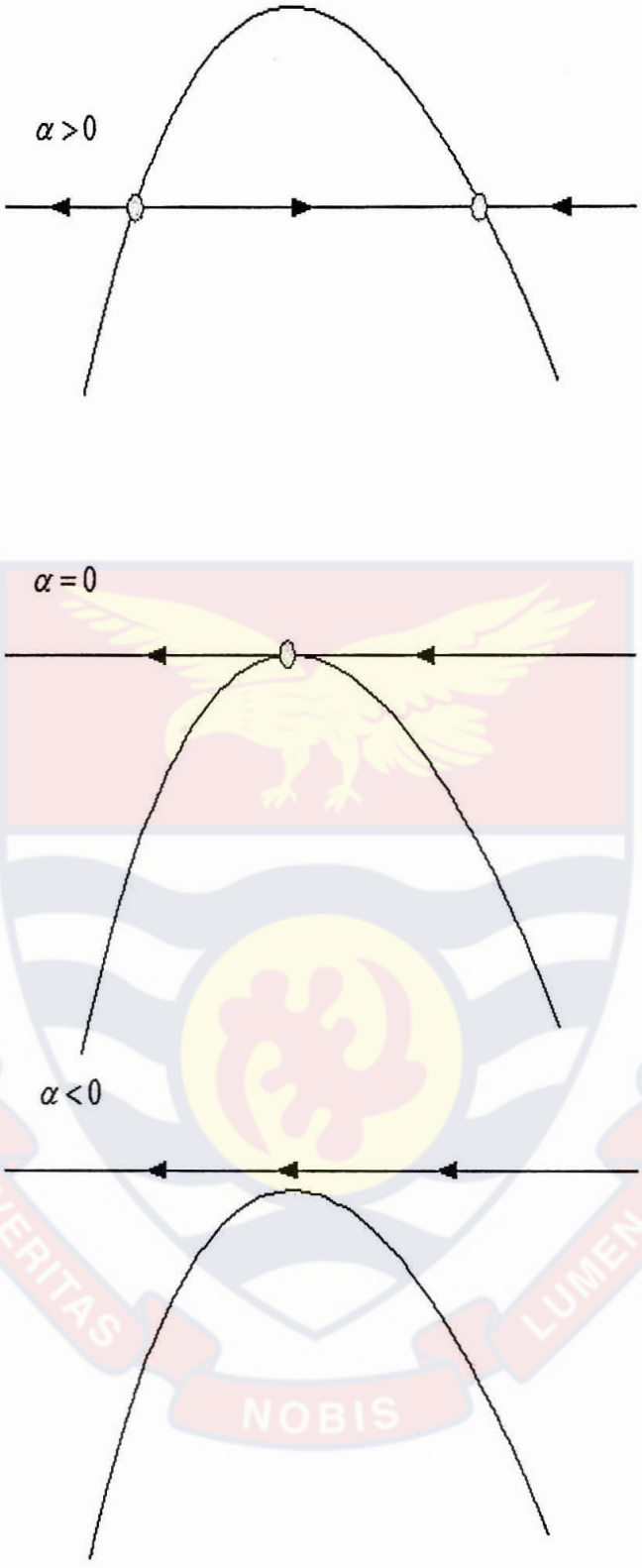


Figure 13: **Phase portraits of (3.20)**

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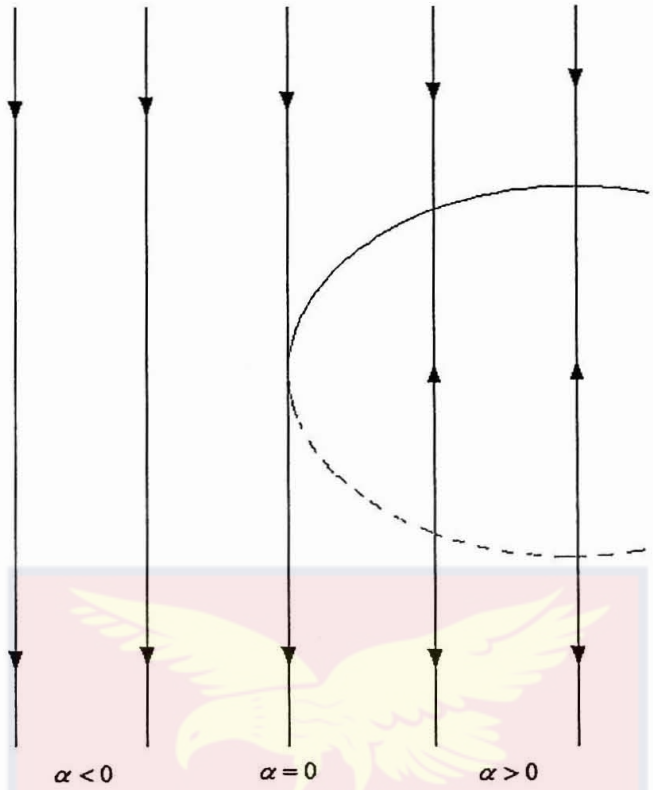


Figure 14: **Tangent bifurcation diagram**

In general, we have an often occurring bifurcation at an equilibrium with the following behaviour. For some parameter value α_0 the system has an equilibrium at p_0 and for parameter values a little above (or a little below) has no equilibria near p_0 and for parameter values a little below (or a little above) there are two equilibria near to p_0, one stable and the other unstable. This a called a fold or saddle-node bifurcation. It means equilibria either suddenly appear or disappear. There is always a fold bifurcation at an equilibrium p_0 for a parameter value α_0 if

$$f'(p_0) = 0,$$

$$f''(p_0) \neq 0$$

and

$$\frac{\partial}{\partial \alpha} f(p_0, \alpha_0) \neq 0.$$

The proof is based on implicit function theorem.

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Transcritical bifurcation

Let us study another system, now written as

$$\dot{x} = x(\alpha - x) \tag{3.21}$$

This system has two equilibria, one for $x = 0$ and the other for $x = \alpha$. For $\alpha = 0$ these equilibria coincide otherwise they are different. For $\alpha > 0$ the equilibrium at $x = 0$ is unstable and the equilibrium at $x = \alpha$ is stable. The interval $(0, \alpha)$ is attracted by α. For $\alpha < 0$ the equilibrium at $x = 0$ is stable and the equilibrium at $x = \alpha$ is unstable. The interval $(\alpha, 0)$ is attracted by 0. For $\alpha = 0$ the only equilibrium is $x = 0$ is a shunt. We call this point a transcritical bifurcation. At this point, the two equilibria exchange stability.

See Figure 15 for phase portraits and Figure 16 for summarizing a bifurcation diagram.

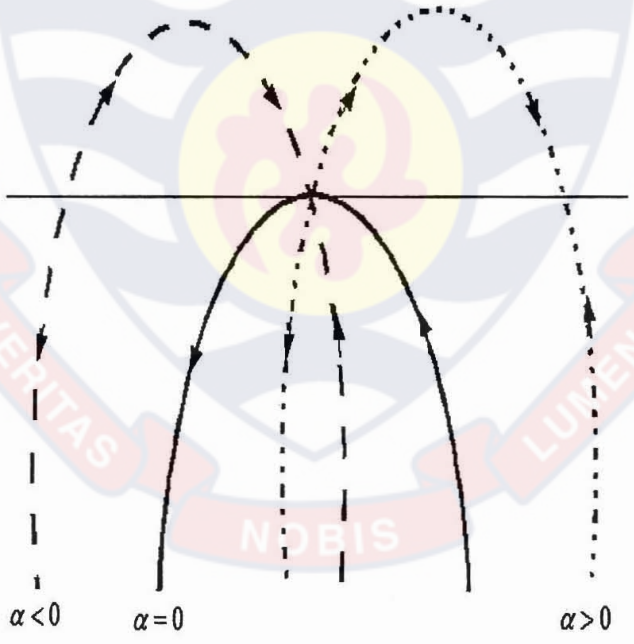


Figure 15: **Phase portraits of (3.21)**

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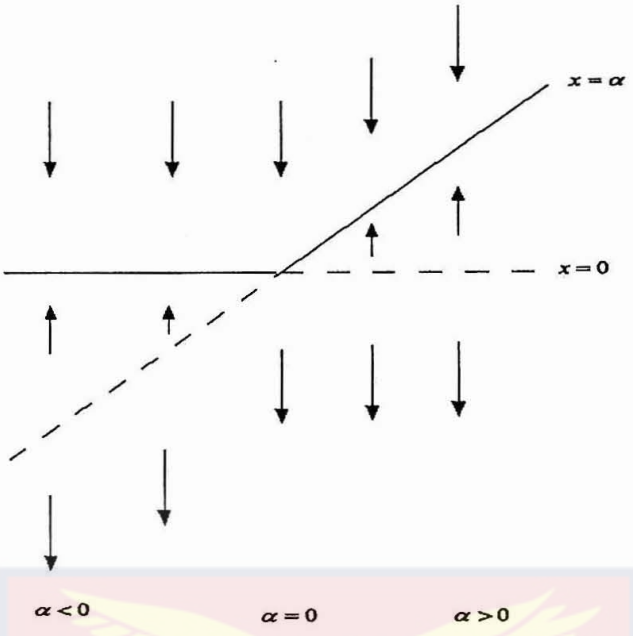


Figure 16: **Transcritical bifurcation diagram**

From a biological perspective we associate this behaviour with the invasion of a species x. The transcritical bifurcation is said to be the invasion boundary of this species. For $\alpha < 0$ the stable equilibrium is zero, which means the species does not survive (for infinite time; it might stick around a while though before it inevitably disappears). For $\alpha > 0$ the stable equilibrium is larger than zero, which means a population can be maintained always.

In general this is an often occurring bifurcation where for a fixed point p is a shunt for a given parameter value α_0 and for parameter values near to α_0 there are two branches $p_1(\alpha)$ and $p_2(\alpha)$ of equilibria and no other equilibria and the branches intersect for $\alpha = \alpha_0$. Further p_1 is stable and p_2 is unstable for parameter values a little below (above) α_0 and p_1 is unstable and p_2 is stable for parameter values a little above (below) α_0 and p_1 is attracting the interval between p_1 and p_2 for parameter values a little below (above) α_0 and p_2 is attracting the interval between p_1 and p_2 for parameter values a little above (below) α_0.

Such bifurcations are called transcritical and they always occur if p_0 is an

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equilibrium and the following are satisfied:

$$f'_x(p_0, \alpha_0) = 0, \tag{3.22}$$

$$f''_{xx}(p_0, \alpha_0) \neq 0, \tag{3.23}$$

$$f''_{x\alpha}(p_0, \alpha_0) \neq 0, \tag{3.24}$$

and

$$f''_{xx}(p_0, \alpha_0) f''_{\alpha\alpha}(p_0, \alpha_0) < (f''_{x\alpha}(p_0, \alpha_0))^2. \tag{3.25}$$

Derivatives are taken at bifurcation values. Proof is based on series expansion around bifurcation values.

Then, depending on the signs of the expression (3.23) and (3.24):

- the equilibrium p_0 is stable (unstable) when $\alpha < \alpha_0$, $(\alpha > \alpha_0)$; and
- the equilibrium p_0 becomes unstable (stable) for each parameter value $\alpha > \alpha_0$, $(\alpha < \alpha_0)$, and a branch of additional stable (unstable) equilibria p emerges.

Pitchfork bifurcation

Now we consider a one−dimensional system of the form

$$\dot{x} = x\alpha - x^3 \tag{3.26}$$

For $\alpha > 0$ there are three equilibria $x = 0$ and $x = p\pm = \pm\sqrt{\alpha}$. The equilibrium $x = 0$ is unstable and the equilibria p are stable and $p-$ attracts the whole interval $(p-, 0)$ and $p+$ attracts the whole interval $(0, p+)$. For $\alpha \leq 0$ there is only one equilibrium $x = 0$ and it is stable.

See Figure 17 for phase portraits and Figure 18 for summarizing a bifurcation diagram.

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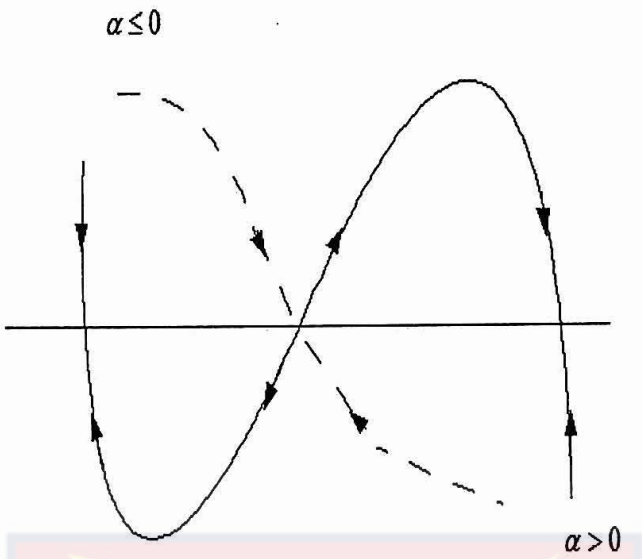


Figure 17: **Phase portraits of (3.26)**

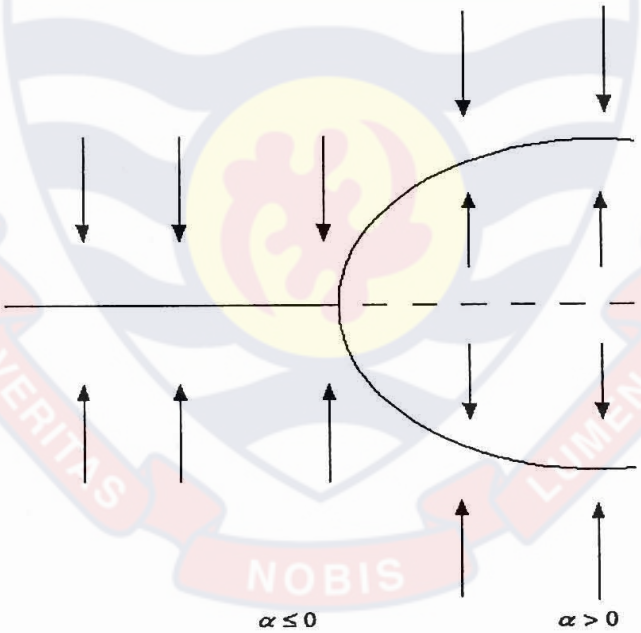


Figure 18: **Pitchfork bifurcation diagram**

A bifurcation where for parameter values there are one stable (unstable) equilibrium on one side near to the bifurcation parameter and three equilibria on the other side, one unstable (stable) and two stable (unstable) is called a pitchfork

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bifurcation. Such a bifurcation always occurs if $f' = 0$, $f'_\alpha = 0$, $f''_{xx} = 0$ and

$$f''_{x\alpha} \neq 0, \tag{3.27}$$

$$f'''_{xxx} \neq 0. \tag{3.28}$$

Derivatives are taken at bifurcation values. Proof is based on series expansion around bifurcation values.

Then, depending on the signs of the expression (3.27) and (3.28)

- the equilibrium p_0 is stable (unstable) when $\alpha_0 < \alpha$, $(\alpha_0 > \alpha)$; and
- the equilibrium p_0 becomes unstable (stable) for each parameter value $(\alpha_0 > \alpha)$, $\alpha_0 < \alpha$, and two branches of additional stable (unstable) equilibria p emerges.

Bifurcation in higher−dimensional systems

In the last subsection on bifurcation in one−dimensional systems we discussed three bifurcations (tangent, transcritical and pitchfork) that can also occur in higher−dimensional systems. This is possible in the case that the linearization of the system at the bifurcation point (which is necessarily singular) has a zero eigenvalue with a corresponding eigenspace of dimension one and other eigenvalues with real part zero. Then the reduction theorem tells us that near the equilibrium point the dynamical system is topologically equivalent to the product of a standard saddle with the restriction of the system to one−dimensional centre manifold. This center manifold is by definition tangent to the eigenspace of the linearization corresponding to the zero eigenvalue of the linearization at the bifurcation point. In higher−dimensions there is an invariant curve on which the system behaves like in the one−dimensional cases which the main connection from centre manifold theory. It is now rather clear what has to be done in order to analyse this type of situation. It is necessary to determine an approximation of

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sufficiently high order to the centre manifold and to carry out a qualitative analysis of the dynamics in the centre manifold. In practice this leads to cumbersome calculations. A method of doing these calculations are well treated in Kuznetsov (1998).

In thesis, we will mostly be confronted with transcritical bifurcations and one of the most usual indication of its presence is when exactly one eigenvalue is zero (i.e. determinant of the Jacobian matrix is zero). We also note that, next after transcritical bifurcation, tangent (saddle−note) bifurcation is the most usual one, but as common as pitchfork.

Some Epidemic Models

This section provides an overview of some epidemic models to explain how epidemiology of infectious diseases are transmitted and how to asses the potential benefits of purpose of control strategies. We categories epidemic models into two types, deterministic models and stochastic models.

When dealing with models of infectious disease in a large populations, where the behaviour of the disease in the population is determined completely by its history, and by the rules which govern the development of the model, then deterministic models are used. In the deterministic model, individuals in the population are assigned to different subgroups or compartments, each representing specific stage of the epidemic.

When the transition rates from one compartment to another are mathematically expressed as derivatives, then the model is formulated using differential equations. While building such models, it must be assumed that the population size in a compartment is differentiable with respect to time and that the epidemic process is deterministic. In other words, the changes in population of a compartment can be calculated using only the history used to develop the model.

Another approach is through discrete analysis, where relationships be-

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tween quantities as they change over discrete intervals of time, space, and so on. This applied frequently to populations whose generations do not overlap. For example, when adults die and are replaced by their progeny, the population size from one generation to the next generation, x_t to x_{t+1}, can be modelled with difference equations.

We can also consider the inclusion of time delay terms in the differential equations. The delays or lags can represent gestation times, incubation periods, transport delays, or can simply lump complicated biological processes together, accounting only for the time required for these processes to occur. Such models have the advantage of combining a simple, intuitive derivation with a wide variety of possible behaviour regimes for a single system. On the negative side, these models hide much of the detailed workings of complex biological systems, and it is sometimes precisely these details which are of interest.

When it comes to analysing spatiotemporal processes we require partial differential equations. To some extend, partial differential equations are sufficiently realistic to be in ecological models but they are usually difficult to solve than ordinary differential equations. However, the advantage for using partial differential equations is that, they allow the modeller to incorporate both temporal and spatial processes simultaneously into the equation governing population dynamics.

The word stochastic means being or having a random variable. A stochastic model is a tool for estimating probability distributions of potential outcomes by allowing for random variation in one or more inputs over time. Stochastic models depend on the chance variations in risk of exposure, disease and other illness dynamics. They are used when these fluctuations are important, as in small populations.

Assumptions and notation

The population under consideration is divided into disjoint classes which

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change with time t. The susceptible class consist of those individuals who can incur the disease but are not yet infective. The infective class consists of those who are transmitting the disease to others. The removed class consists of those who are removed from the susceptible-infective interaction by recovery with immunity, isolation, or death. The fraction of the total population in these classes are denoted by $S(t)$, $I(t)$ and $R(t)$.

In the epidemiological models we shall consider here, the following assumptions are made:

1. The population considered has constant size N which is sufficiently large so that the sizes of each class can be considered as continuous variables. If the model is to include vital dynamics, then it is assumed that births and natural deaths occur at equal rates and that all newborns are susceptible. Individuals are removed by death from each class at a rate proportional to the class size with proportionality constant μ which is called the daily death rate. This corresponds to a negative exponential age structure with an average lifetime of $\frac{1}{\mu}$.

2. The population is homogenously mixing. The daily contact rate λ is the average number of adequate contacts per infective per day. An adequate contact of an infective is an interaction which results in infection of the other individual if he is susceptible. Thus, the average number of susceptibles infected by an infective per day is λS, and the average number of susceptibles infected by the infective class with size NI per day is λSNI. The daily contact rate λ is fixed and does not vary on the specific disease. The number of cases per day λSNI, which is called the incidence, is a mass action law since it involves the product of S and I.

3. Individuals recover and are removed from the infective class at a rate proportional to the number of infectives with proportionality constant γ, called the daily recovery removal rate. The latent period is zero (it is define as the period between the time of exposure and the time when infectiousness begins).

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Thus the proportion of individuals exposed (and immediately infective) at time t_0 who are still infective at time $t_0 + t$ is $\exp(-\gamma t)$, and the average period of infectivity is $\frac{1}{\gamma}$.

The SIS model

The first model is for diseases for which infection does not confer immunity. It is called an *SIS* model since individual return to the susceptible class when they recover from infection.

Assume a town is suffering an epidemic, the chance of a person catching the disease is proportional to the probability that you will meet a carrier of the disease. That is, the probability of catching the disease is proportional to the probability that you will be in a given place at a given time multiplied by the probability that a carrier will also be in that given place at a given time. If we represent the probability of an encounter simply by the sheer number of susceptible individuals (S) times the number of infected individuals (I), then we can represent this mathematically as

$$\begin{aligned} \frac{dS}{dt} &\propto -SI \\ \frac{dI}{dt} &\propto SI, \end{aligned} \tag{3.29}$$

where I increases due to the encounters (more people get sick) and S decreases by the same amount (the susceptible people have now become infected).

Of course, these are not really probabilities; for one thing, they are always greater than than 1. But we can scale them out by replacing the proportionality with constant multiple. That is, we replace the $\propto$ with an "$= \beta$", where β is some parameter that reflects how easy the disease is to transmit and the average person's ability to resist the disease. Each equation must use the same β, and since βSI represents the same increase in infected people as the loss of susceptible people.

What is fundamentally happening here is that, people start off susceptible and then they leave the susceptible class and move into the infected class. We

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represent this visually as shown in Figure 19.

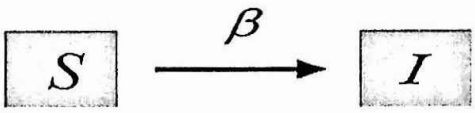


Figure 19: **An SI model**

This is known as an *SI* model, partly because it only has Susceptible and Infected classes, but also because individuals move from S to I and that is it. The corresponding system of equations is

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI \end{aligned}$$

We now examine the *SIS* epidemic model, which stands for Susceptible → Infected → Susceptible. These epidemics represent diseases such as common cold, which generally cause a person to be sick for a time and then recover, but without immunity to the disease. Graphically, this can be represented in Figure 20.

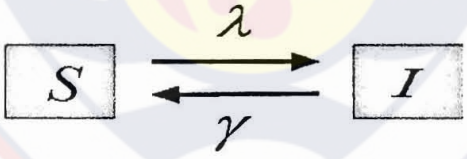


Figure 20: **An SIS model**

The system of equations follows quite nicely from Figure 20:

$$\begin{aligned} \frac{dS}{dt} &= \gamma I - \lambda SI \\ \frac{dI}{dt} &= \lambda SI - \gamma I \end{aligned} \tag{3.30}$$

What is happening here is that, individuals move into the Susceptible compartment only by when they recover (γI) and move out when they become infected

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$(-\lambda SI)$. Individuals move into the infected compartment when they become infected (λSI) and move out when they recover (γI).

Let $N = S + I$ be the total population. Note that if we add the equations together, then $\frac{dS}{dt} + \frac{dI}{dt} = \frac{dN}{dt} = 0$. Thus, the total population is constant (since the derivative of a constant is zero).

To analyse the System (3.30), we have two options. We can attempt to solve the system directly and find the *time series*: the time-course of the disease, where the time variable is explicit. Or, we can make time an implicit variable and discuss solutions in state-space consisting of only S and I.

Solving System (3.30) directly

It is important to stress that dynamic modelling is more suited to large populations of similar and well-mixed individuals. If we assume that the number of people in this town stays the same (no one enters, leaves, is born or dies), then the total number of people in the town will be some constant number N. Since everyone is either susceptible or infectious, $S + I = N$. We substitute $S + I = N$ into the second equation of system (3.30) to obtain

$$\frac{dI}{dt} = (\lambda N - \gamma - \lambda I)I.$$

Since $\lambda N - \gamma$ is just some constant number, we can represent it by a constant A. Thus,

$$\frac{dI}{dt} = (A - \lambda I)I. \tag{3.31}$$

By separation of variables, we rearrange Equation (3.31) to get

$$\frac{dI}{A - \lambda I} I = dt. \tag{3.32}$$

To solve Equation (3.32), we integrate both sides and use partial fractions to get

$$\begin{aligned} \int \tfrac{1}{A}\left(\tfrac{\lambda}{A-\lambda I} + \tfrac{1}{I}\right) dI &= \int dt \\ \tfrac{1}{A}[-\ln(A - \lambda I) + \ln I] &= t + C \end{aligned}$$

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Expanding and simplifying, we obtain

$$\frac{I}{A-\lambda I} = e^{At+AC}$$

we substitute B for e^{AC} which is a constant to obtain

$$\frac{I}{A-\lambda I} = Be^{At}$$

and solving for I, we have

$$I = \frac{ABe^{At}}{1+\lambda Be^{At}}. \tag{3.33}$$

We now solve for B (our integration constant). When $t = 0$, $I = I_0$. Substituting these in Equation (3.33) and noting that $(A = \lambda N - \gamma)$, we have

$$B = \frac{I_0}{(\lambda N - b) - \lambda I_0}.$$

Substituting in Equation (3.33) and rearranging to simplify the equation somewhat, we obtain

$$I = \frac{(\lambda N - \gamma) I_0 e^{(\lambda N-\gamma)t}}{(\lambda N - \gamma) + \lambda I_0 [e^{(\lambda N-\gamma)t} - 1]}.$$

Finally, since $S = N - I$, we have

$$S = N - \frac{(\lambda N - \gamma) I_0 e^{(\lambda N-\gamma)t}}{(\lambda N - \gamma) + \lambda I_0 [e^{(\lambda N-\gamma)t} - 1]}.$$

We have derived the time-series equations for the dynamics within the susceptible and the infectious classes. This shows how the system changes over time (See Figure 21). In both graphs, $N = 3000000, I_0 = 1000000$ and $\lambda = 0.2$. In the left hand graph $\gamma = 0.1$ and in the right hand graph, $\gamma = 0.7$.

Thus, we see that sometimes the infected individuals die out and everyone becomes susceptible again (see Figure 21 rihgt). In this case, there is no epidemic and the disease disappears on its own. However, at other times, the population reaches a steady states in both infected and susceptible individuals. In this case, the diseases has taken hold within the population and has become endemic.

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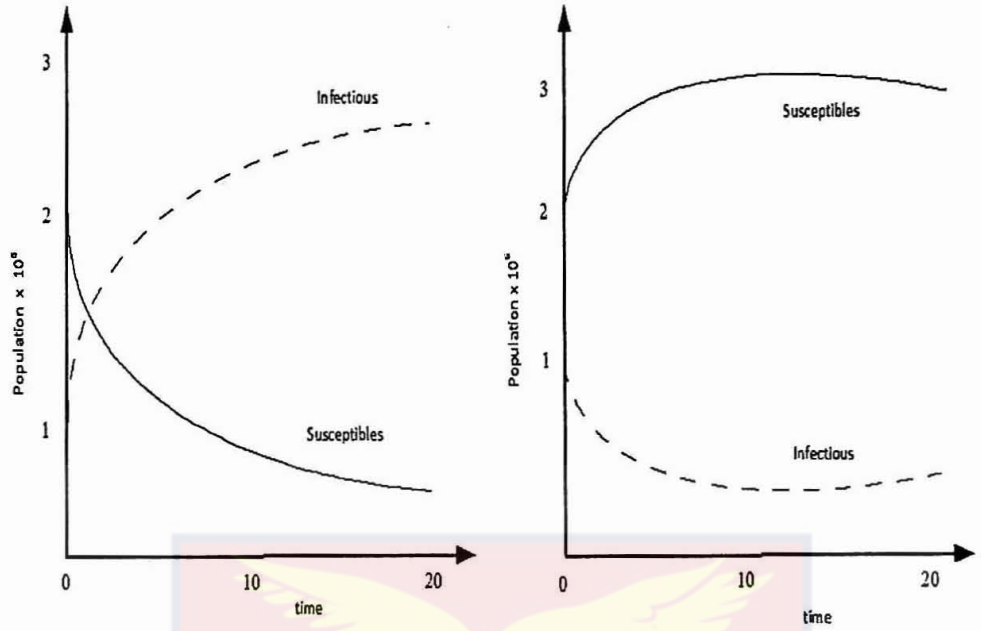


Figure 21: **The time series of the infection. Left** $\gamma = 0.1$. **Right** $\gamma = 0.7$

The time-series is the best if it is possible to calculate, because it gives us the complete solution, at every point in time. So if we want to know what happens at the beginning, middle or end of an endemic, we simply have to pick a time we are interested in and plug it into the equations.

Phase portrait of System (3.30)

We know that phase portrait involves only spatial variables, making time an implicit part of the solution. This gives us less overall information, but is able to tell what happens at the beginning and the end of the endemic.

Since $N = S + I$, it follows that $I = N - S$, which, when graphed in the $S - I$ plane, is a straight line. See (Figure 22). We have thus parameterized our equations so that they are independent of time. The population must travel along the line—although, since we eliminated time, we have no idea how it does so.

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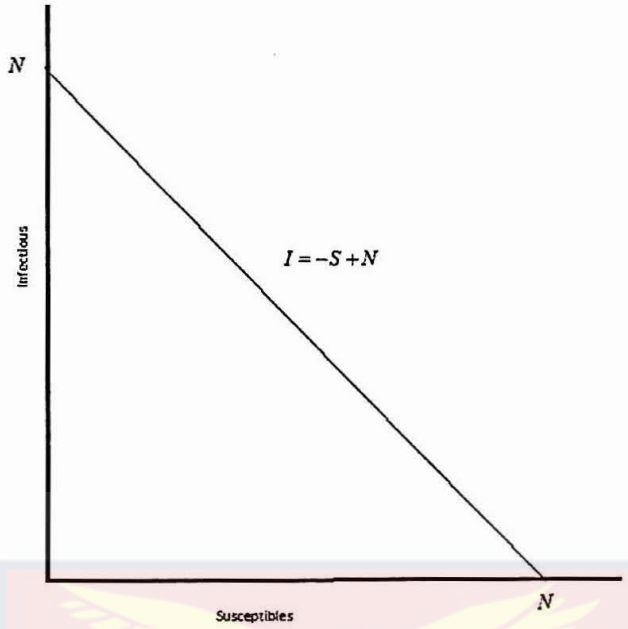


Figure 22: **The linear relationship between S and I**

We now consider calculating the equilibrium points, and as define earlier in this chapter, these are points the system experience no change, thus the derivatives are zero. Hence, we set the right hand sides of System (3.30) to zero to obtain

$$\begin{aligned} \gamma I - \lambda SI &= 0 \\ \lambda SI + \gamma I &= 0 \end{aligned} \tag{3.34}$$

Since the equations in System (3.29) are identical, they will hold when either (i) $S = \frac{\gamma}{\lambda}$ and $I = N - \frac{\gamma}{\lambda}$ (since $S + I = N$); or (ii) $I = 0$ and $S = N$ (since $S + I = N$). We let $p = \frac{\gamma}{\lambda}$. Then our equilibrium point becomes

$$(\bar{S}, \bar{I}) = (p, N - p) \text{ or } (\bar{S}, \bar{I}) = (N, 0).$$

Next, we look at the existence of these two steady solutions. In terms of realistic solutions, the equilibrium $(N, 0)$ will always exist, but the equilibrium $(p, N - p)$ only exists when $p < N$ (if $P > N$) then the second equilibrium would have $S > N$, so this equilibrium is not biologically realistic). Now this gives us two cases to study. Case I: when $p < N$ and Case II: $p > N$.

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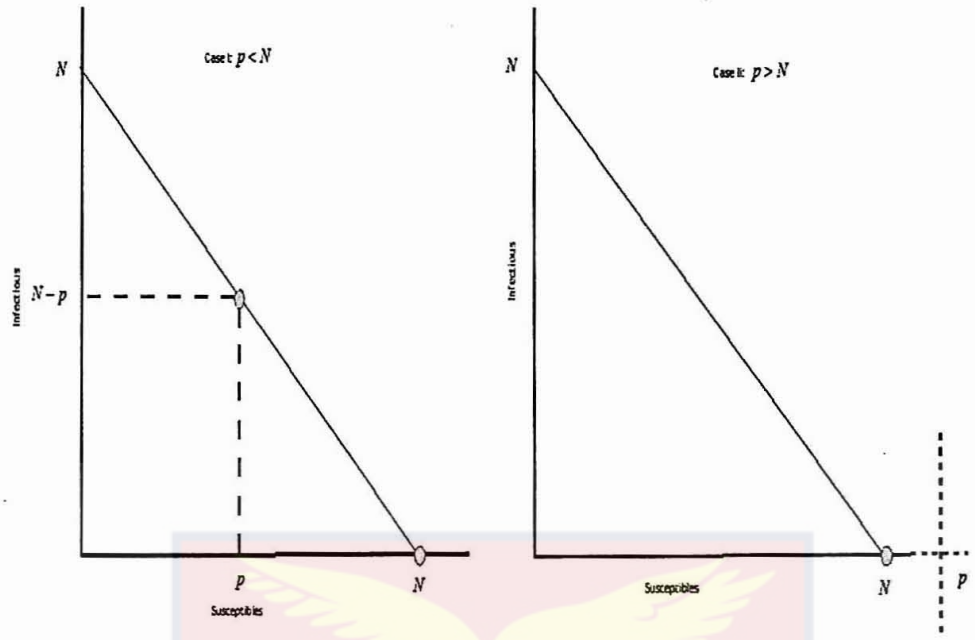


Figure 23: **Equilibria for the two cases**

In Case I, there will be two equilibrium points, whereas in Case II, there will only be one equilibrium in the positive plane (See Figure 23).

These two cases correspond exactly to the times-series solution in Figure 21. In the case $P < N$ (which was when $\gamma = 0.1$ in Figure 21 Left), there is an interior equilibrium, with both susceptibles and the infectious. In the case $p > N$ (which was when $\gamma = 0.7$ in Figure 21 Right), there is only one equilibrium, which is when the infection has died out and only susceptible remain.

The major question now is about the stability of the equilibrium points. We can rewrite the System (3.30) as

$$\begin{aligned} \frac{dS}{dt} &= \lambda(p-S)I \\ \frac{dI}{dt} &= \lambda(S-p)I, \end{aligned} \tag{3.35}$$

where $p = \frac{\gamma}{\lambda}$. If $S < p$, then clearly $\frac{dS}{dt} > 0$ and $\frac{dI}{dt} < 0$ (since $p - N > 0$). Conversely, if $S > p$, then $\frac{dS}{dt} < 0$ and $\frac{dI}{dt} > 0$ (since $p - N < 0$).

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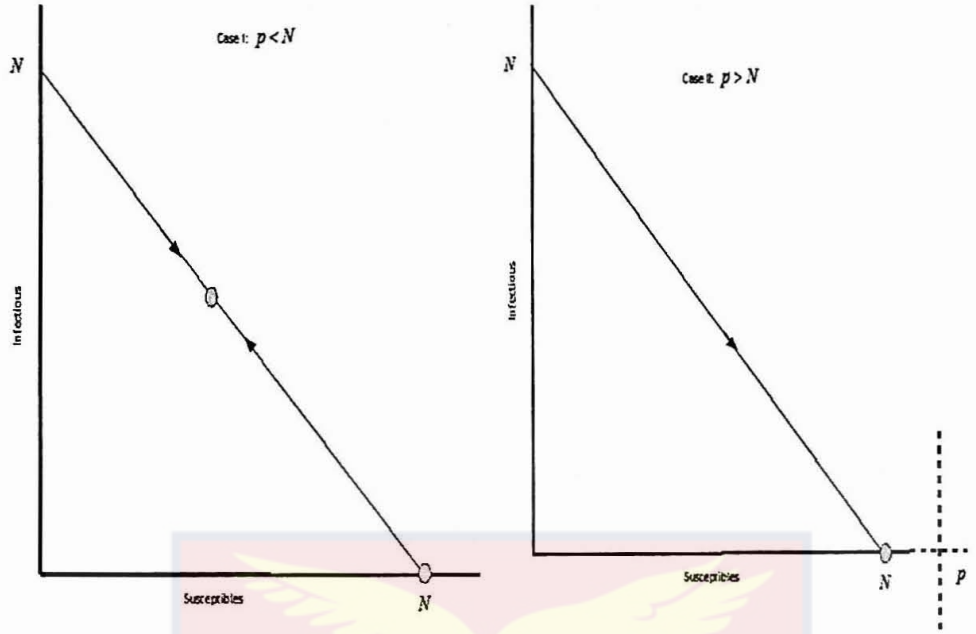


Figure 24: **The stability of the equilibrium points**

We observe in Figure 24 that, for Case I: $p < N$ the portion of of the line to the left of the equilibrium $(p, N-p)$, S is increasing and I is decreasing. Trajectories must therefore be moving down the line. For the portion of the line to the right of the equilibrium $(p, N-p)$, S is decreasing and I is increasing. Trajectories must therefore be moving up the line. It follows that the equilibrium $(p, N-p)$ is stable while $(N, 0)$ is unstable.

On the other hand Case II: $p > N$, we have $S < p$ and along the line S is increasing and I is decreasing. Thus, the equilibrium $(N, 0)$ is stable. We note that there is this unrealistic unstable equilibrium represented by p outside the real plane, any slight change will drive the dynamics away from this point and towards the stable point. Thus, biologically, when $p > N$ it tells us that more people are recovering compared to those getting infected and the number of infected people will decrease, approaching zero. When $p < N$, there is a stable endemic equilibrium where there are p susceptible and $N-p$ infectious people. There is unstable disease free equilibrium at $(N, 0)$, where even one infectious

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person leads to an increase in the number of infectious people until the stable endemic equilibrium $(p, N-p)$ is reached.

We remark here that, for the *SIS* model, the stability of the equilibria depends on the ratio $\frac{\gamma}{\lambda}$. So, if the recovery rate γ is very high compared to the rate of infection λ, then the infectious recover quickly and the population moves to a population of suscepibles to establish a disease free equilibrium. If λ is very high compared to the γ, then the infection stabilizes at an endemic equilibrium.

We also note that naturally occurring births and deaths (vital dynamics) are excluded, but the behaviour of the solutions is similar when vital dynamics are included.

The SIR model

SIR stands for Susceptible $\rightarrow$ Infectious $\rightarrow$ Removed. This is one of the simplest models that was proposed by Kermack and McKendrick in 1927. The term "removed" is a general term which allows for infectious individuals to be no longer infectious, yet not susceptible either. Practically, this could mean that the person gets better (either through treatment or natural immunity) or that the person dies (the ultimate removal). We might represent this process visually as in Figure 25.

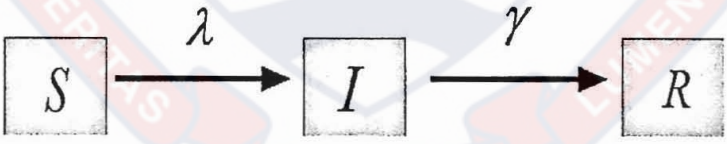


Figure 25: **An SIR model**

The system of equations from Figure 25 is given as

$$\begin{aligned} \frac{dS}{dt} &= -\lambda SI \\ \frac{dI}{dt} &= \lambda SI - \gamma I \\ \frac{dR}{dt} &= \gamma I \end{aligned} \tag{3.36}$$

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This is based on the following assumptions (see Brauer and Castilo-Chavez (2001) for justification):

(i) An average infective makes contact sufficient to transmit infection with λN others per unit time, where N represents total population size.

(ii) A fraction γ of infectives leave the infective class per unit time.

(iii) There is no entry into or departure from the population, except possibly through death from the disease.

The sum of all classes gives the total population size $N = S+I+R$. On the other hand, if we add all three differential equations we obtain the differential equation of the total population size, namely $\dot{N}(t) = 0$. Consequently, the total population size is a constant N.

To solve the System (3.36) directly, we first notice that the variable R does not participate in the first two equations. Thus, we can consider only the equations for S and I, which are coupled, and leave out the equation for R. The variable R can then be obtained from the relation $R = N-S-I$.

$$\begin{aligned} \frac{dS}{dt} &= -\lambda SI \\ \frac{dI}{dt} &= \lambda SI - \gamma I \end{aligned} \tag{3.37}$$

Dividing the two equations, we obtain

$$\frac{dI}{dS} = \frac{\lambda SI - \gamma I}{-\lambda SI} = -1 + \frac{\gamma}{\lambda S}.$$

Separating the variables, we have

$$dI = (-1 + \frac{\gamma}{\lambda S})dS.$$

Integrating leads to

$$I = -S + \frac{\gamma}{\lambda}\ln S + C,$$

where C is an arbitrary constant. Thus, the orbits of the solution are given implicitly by the equation

$$I + S - \frac{\gamma}{\lambda}\ln S = C.$$

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The Kermack-McKendrick model is equipped with initial conditions: $S_0 = S(0)$ and $I_0 = I(0)$. Those are assumed given. We assume also that $\lim_{t\to\infty} I(t) = 0$ while $S_\infty = \lim_{t\to\infty} S(t)$ gives the final number of susceptible individuals after the epidemic is over. The above equality holds both for (S_0, I_0) and for $(S_\infty, 0)$. Thus,

$$I_0 + S_0 - \frac{\gamma}{\lambda}\ln S_0 = C.$$

Consequently,

$$I_0 + S_0 - \frac{\gamma}{\lambda}\ln S_0 = S_\infty - \frac{\gamma}{\lambda}\ln S_\infty.$$

Rearranging terms, we obtain

$$I_0 + S_0 - S_\infty = \frac{\gamma}{\lambda}(\ln S_0 - \ln S_\infty).$$

Therefore,

$$\frac{\lambda}{\gamma} = \frac{\ln \frac{S_0}{S_\infty}}{I_0 + S_0 - S_\infty}. \tag{3.38}$$

We note that since the population is constant $S_\infty < S_0 + I_0$. The implicit solution also allows us to compute the maximum number of infected individuals that is attained. This number occurs when $\frac{dI}{dt} = 0$, that is, when

$$S = \frac{\gamma}{\lambda}.$$

From

$$I + S - \frac{\gamma}{\lambda}\ln S = I_0 + S_0 - \frac{\gamma}{\lambda}\ln S_0,$$

substituting the expression for S and moving all terms but I to the right-hand side leads to

$$I_{max} = S_0 + I_0 - \frac{\gamma}{\lambda}\ln S_0 - \frac{\gamma}{\lambda} + \frac{\gamma}{\lambda}\ln\frac{\gamma}{\lambda} \tag{3.39}$$

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Estimating the parameters

We use an example from the book of (Brauer & Castilo-Chavez, 2001), dubbed the "The Great Plague of Eyam" to illustrate how to estimate parameters.

The village of Eyam near Sheffield, England suffered an outbreak of bubonic plague in 1665-1666. The source of that plague was believed to be the Great Plague of London. The community was persuaded quarantine itself. Detailed records were preserved.

The initial population of Eyam was 350. In mid-May, 1666 there were 254 susceptibles and 7 infectives. The data about the epidemic are given in the table below.

Table 1: **Eyam Plague data**

Data(1666)	Susceptibles	Infectives
Mid-May	254	7
July 3/4	235	14.5
July 19	201	22
August 3/4	153.5	29
August 19	121	21
September 3/4	108	8
September 19	97	8
October 4/5	Unknown	Unknown
October 20	83	0

These data give the following values: $S_0 = 254$, $I_0 = 7$, $S_\infty = 83$. From Equation (3.38) we have

$$\frac{\lambda}{\gamma} = \frac{\ln \frac{254}{83}}{261 - 83} = 0.00628. \tag{3.40}$$

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We measure time in months. We take $t_0 = 0$ to be the mid-May, 1666. We have that $t_{final} = 5$ is the mid-October, 1666.

Figure 26 shows the graph of the function $S(t)$ obtained through simulation with the model. The parameters are taken as follows: $\gamma = 2.82$, $\lambda = 0.0177$, $S_0 = 254$, $I_0 = 7$. The dots give the number of susceptible individuals in the data. The two show a remarkable agreement.

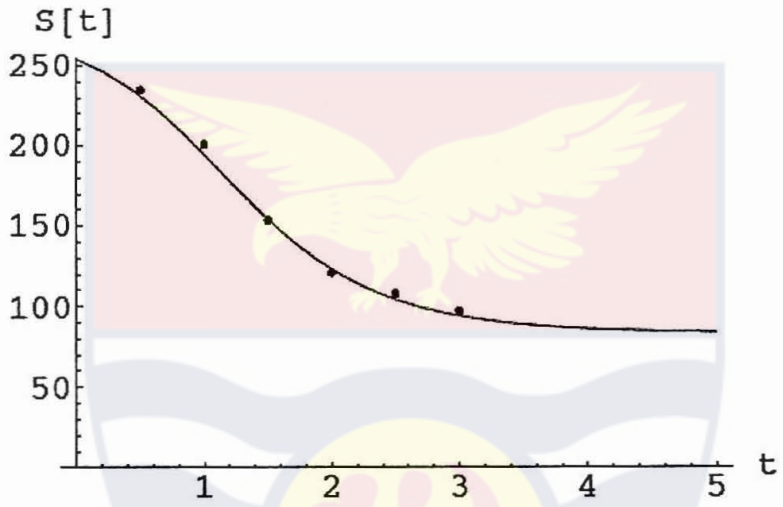


Figure 26: S as function of t

The infective period of bubonic plague is about 11 days. We convert 11 days into months: 11 days $= \frac{11}{31} = 0.3548387$ months. From this information we can estimate γ as the reciprocal of the time spent as an infectious individual (infectious period): $\gamma = \frac{1}{0.3548387} = 2.82$.

From Equation (3.40) and using the value for γ, we can obtain the value for λ: $\lambda = 0.00628$, $\gamma = 0.00628 \times 2.82 = 0.0177$.

From the equation for the I_{max} we can estimate the maximum number of infectives during the epidemic. First, notice that $\frac{\gamma}{\lambda} = 159$. Thus, $I_{max} = -159 + 159\ln 159 + 261 - 159\ln 254 = 27.5$. We observe that from the data give the maximum number of infective individuals as 29.

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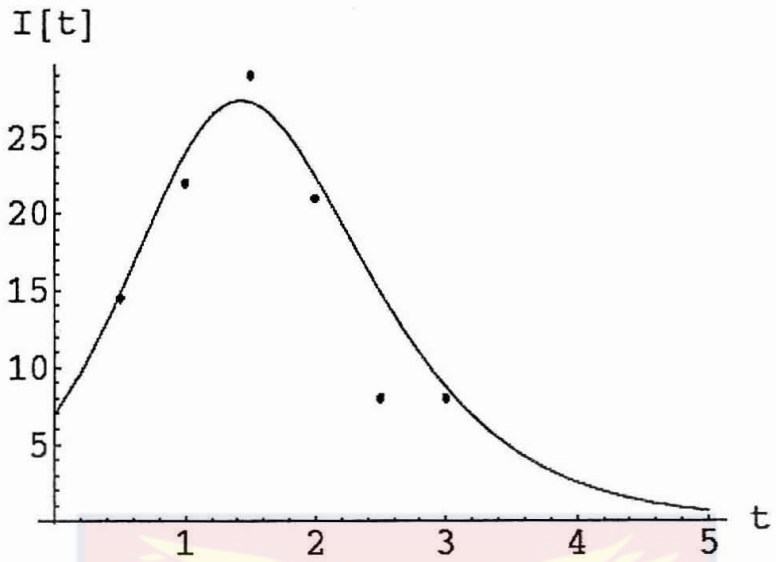


Figure 27: I **as function of** t

Figure 27 shows the graph of the function $I(t)$ obtained through simulation with the model. The parameters are taken as follows: $\gamma = 2.82$, $\lambda = 0.0177$, $S_0 = 254$, $I_0 = 7$. The dots give the number of infected individuals in the data. The two show a significant agreement.

The Reproduction Number of a Disease R_0

This section deals with the basic reproductive ratio, R_0 is a key concept in mathematical epidemiology. Originally developed for the study of demographics, it was independently studied for vector-borne diseases such as malaria (Ross, 1911; MacDonald, 1952) and directly transmitted human infections (W. Kermack & McKendrick, 1927). It is now widely used in the study of infectious disease, and more recently, in models of in-host population dynamics.

We will also review the various methods currently in use for the derivation of R_0, highlighting the difference between R_0 and surrogate parameters with equivalent threshold behaviour. We then discuss methods commonly used to

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estimate R_0 from incidence data, this includes: the method of Anderson and May, The Jacobian matrix method, The survival function method and The next-generation method. Finally, we give an overview of the recent use of R_0 in assessing emerging and endemic disease.

Threshold parameters

As a general definition, R_0 is the expected number of secondary individuals produced by an individual in its lifetime. The interpretation of secondary, however, depends on context. In demographics and ecology, R_0 is taken to mean the lifetime reproductive success of a typical member of the species. In epidemiology, we take R_0 to mean the number of individuals infected by a single infected individual during his or her entire infectious period, in a population which is entirely susceptible. For in-host dynamics, R_0 gives the number of newly infected cells produced by one infected cell during its lifetime, assuming all other cells are susceptible. (Heffernan, Smith, & Wahl, 2005)

From this definition, it is immediately clear that when $R_0 < 1$, each infected individual produces, on average, less than one new infected individual, and we therefore predict that the infection will be cleared from the population, or the microparasite will be cleared from the individual. If $R_0 > 1$, the pathogen is able to invade the susceptible population. This threshold behaviour is the most important and useful aspect of the R_0 concept. In an endemic infection, we can determine which control measures, and at what magnitude, would be most effective in reducing R_0 below one, providing important guidance for public health initiatives.

When measuring data in the field, we may occasionally have the chance to measure the average number of secondary infections cause by a single individual. If so, that is fine. However, it is rare that we get to study a disease in its very earliest stages of infection and disease are often not noticed until they are well underway. When this happens, we would not be able to measure R_0 precisely,

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because spatial considerations get in the way. A single infectious individual may be able to infect any susceptible individual, but multiple infectious individuals may "use up" their infectivity on those already infected. If 90% of a village is infected, then a single infected individual may have a fairly remote chance of infecting a susceptible individual, even if $R_0 > 1$, because they may never come into contact with them.

However, it is also possible that we may not actually want the true value of the R_0. Often, what we would really like to know are two things:

1. Will the disease become endemic or will it die out of its own accord?
2. If the disease is endemic, will our control strategies be sufficient?

Both of these questions are really concerned with the threshold, not the true value of R_0. Of course, we know that R_0 is a threshold, but it turns out that there are many surrogate thresholds that are not R_0.

These values will also have the property that if they are less than 1 then the disease will die out, whereas if they are greater than 1 the disease will take hold. What they cannot do is allow comparison of different diseases; for example if SARS has a threshold value of 6 and HIV has threshold value of 4, we can not actually conclude that SARS is a worse disease than HIV unless the same method was used to calculate each of them.

The Anderson and May method

Probably, this is the most well-known version of R_0 which comes from Anderson and May (1991), who basically posit that

$$R_0 = \beta c D,$$

where β is the transmissibility (i.e., probability of infection given contact between a susceptible and infected individual), c is the average rate of contact between susceptible and infected individuals and D is the average time spent being infectious. This formula turns out to be very useful and applies quite widely,

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under a very important restriction, namely, that there should be no background death rate.

For instance, HIV is a disease that eventually kills a person if the person is infected with it, but not for a long time, especially if the person is on antiretroviral drugs. So if a person is infected with HIV, the chances that the person will get killed in a motor accident rather than die from AIDS is non−negligible, because the person has a small, but nonzero chance of getting killed in a motor accident in the intervening five years or more. So this formula would not work here.

However, in the case of disease like Ebola, which occurs on a very timescale, the background death rate could be negligible. If village is infected with Ebola, the disease will rage through and quickly kill everyone it is going to kill in a matter of weeks. So the chance of a person dying from motor accident, old age or any other disease during this time is quite small. So, in this case, it would be reasonable to use the formula.

Anderson and May (1991) gave another simpler version for estimating R_0 with some further restrictions. In the previous formula the methods of formulating R_0 was in terms of the parameters of some deterministic model. In order to estimate the value of R_0 from incidence data, however, we require numerical estimates of a number of these parameters. Typically, it is clear that, the contact rate or transmission probability are difficult to determine from direct measures.

This new method assumes that an endemic equilibrium is attained and uses the prevalence of the infection at this equilibrium to estimate R_0. Following derivation, we consider a single infected individual and note that the number of successful contacts (in which the infection is passed on) for that individual should be given by R_0x^*, where x^* is the probability that a given contact is with a susceptible. At equilibrium, the average number of new infections per infected individual must be exactly one, allowing us to write $R_0 = \frac{1}{x^*}$. Under the assumption of homogenous mixing, the unknown probability, x^* can be estimated as the

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fraction of the host population that is susceptible at the endemic equilibrium.

Jacobian and stability conditions

A predictive threshold is often found through the study of the eigenvalues of the Jacobian at the disease-free equilibrium. This is a simple, widely used method for system of ordinary differential equations. Using this method, a parameter is derived from the condition that all of the eigenvalues of the Jacobian have a negative real part. This can easily be done using the characteristic polynomial and the Routh Hurwitz stability conditions.

The Jacobian method clearly allows us to derive a parameter that reflects the stability of the disease-free equilibrium. The parameter obtained in this way, however, may or may not reflect the biologically meaningful value of R_0.

Similarly, we can often derive a condition based on parameter values such that when the condition holds, the endemic equilibrium exists, whereas when the condition is false, only the disease-free equilibrium exists. Mathematically, we are referring to a transcritical bifurcation, and we know that the condition must switch from being false to true at parameter values which give $R_0 = 1$.

For more complex models, the characteristic equation may be of the form $\lambda^n + p_{n-1}\lambda^{n-1} + \cdots + p_1\lambda + p_0 = 0$ with $p_1, p_2, \cdots, p_{n-1} > 0$. In this special case, $n-1$ roots of the polynomial have negative real part. When $p_0 = 0$, the nth root, or largest eigenvalue, is zero, when $p_0 > 0$, all eigenvalues are negative, whereas when $p_0 < 0$, the largest eigenvalue has positive real part. Thus, the stability is determined solely by the sign of the constant term of the characteristic equation.

Survival function

The method we describe as the survival function approach is, in essence, a first-principles definition of R_0, and thus, has a rich history of use. It always gives the correct R_0 but can be difficult to apply in practice (Smith, 2008).

Consider a large population and let $F(a)$ be the probability that a newly infected individual remains infectious for at least time a. This is called the survival

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probability. Also, let $b(a)$ denote the average number of newly infected individuals that an infectious individual will produce per unit time when infected for total time a. Then, R_0 is given by

$$R_0 = \int_0^\infty b(a)F(a)da. \tag{3.41}$$

As this expression yields R_0 by definition, this approach will be appropriate for any model in which closed-form expressions can be given for the underlying survival probability, $F(a)$, and the infectivity as a function of time, $b(a)$. In particular, it is straightforward to handle situations in which infectivity depends on time, since infection, or other transmission probabilities between states, vary with time. Thus, this derivation of R_0 is not restricted to systems described by ordinary differential equations.

This method can also be naturally extended to describe models in which a series of states are involved in the reproduction of an infected individual. As an example of the latter technique, consider epidemic modelling of malaria. An infected human may pass the infection to a mosquito, which may in turn infect more humans. This complete cycle must be taken into account in our derivation of R_0, which we might expect to yield the total number of infected humans produced by one infected human. In general, if only two distinct infectious states are involved in such an infection cycle, $F(a)$ can be defined as the probability that an individual in state 1 at time zero produces an individual who is in state 2 until at least time a. Similarly, $b(a)$ is the average number of new individuals in state 1 produced by an individual who has been in state 2 for time a. In modelling malaria, $F(a)$ could be the probability that a human infected at time zero produces an infected mosquito which remains alive until at least time a. In more

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concrete terms, $F(a)$ would be the integral of the following product:

$$\begin{aligned} F(a) \;=\; & \int_0^{\infty} \texttt{probability(human infected at time 0 exist at time } t\texttt{)} \\ & \times \texttt{probability(human infected for total time} \\ & t \texttt{ infects mosquito)} \\ & \times \texttt{probability(infected mosquito lives to be age } a-t\texttt{)} dt \end{aligned} \tag{3.42}$$

while $b(a)$ would simply be the average number of humans newly infected by a mosquito which has been infected for time a. (Note that we could also take the infected mosquito as state 1, deriving an analogous expression which would yield the same value of R_0.)

Unfortunately, derivations of equations such as Equation (3.42) become increasingly cumbersome as this method is extended to infection cycles involving three or more states. In these situations, the next generation operator offers an elegant solution.

Next-generation method

The next generation method, introduced by Diekmann et al. (as cited by (Heffernan et al., 2005)), is a general method of deriving R_0 in such cases, encompassing any situation in which the population is divided into discrete, disjoint classes. The next generation operator can thus be used for models with underlying age structure or spatial structure, among other possibilities. For typical implementations, continuous variables within the population are approximated by a number of discrete classes. This approximation assumes that transmission probabilities between states are constant, or equivalently, that the distribution of residence times in each state is exponential.

In the next generation method, R_0 is defined as the spectral radius of the next generation operator. The formation of the operator involves determining two compartments, infectious and non−infectious, from the model.

Suppose there are n infectious compartments and m non−infectious com-

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partments, and let $x \in R^n$ and $y \in R^m$ be the sub-populations in each of these compartments. Further, denote by F_i the rate secondary infections increase the i^{th} disease compartment and by ν_i the rate disease progression, death and recovery decrease the i^{th} compartment. The compartmental model can then be written in the following form

$$\begin{aligned} \dot{x}_i &= F_i(x, y) - \nu_i(x, y), \; i \cdots n \\ \dot{y}_i &= g_j(x, y), \; i \cdots m \end{aligned} \tag{3.43}$$

Note that the decomposition of the dynamics into F and ν and the designation of compartments as infectious or non−infectious may not be unique; different decompositions correspond to different epidemiological interpretations of the model.

Assuming F_i and ν_i meet the conditions outlined by Driessche and Watmough (2008). Then this conditions ensures that the disease-free set, which consists of all points of the form $(0, y)$, is invariant. That is, any solution with no infected individuals at some point in time will be free of infection for all time. This in turn ensures that the disease-free equilibrium is also an equilibrium of the full system.

Suppose a single infected person is introduced into a population originally free of disease. The initial ability of the disease to spread through the population is determined by an examination of the linearization of the first equation of System (3.43) about the disease-free equilibrium $(0, y_o)$. Still using the assumptions, it can be shown that

$$\frac{\partial F_i}{\partial y_j}(0, y_0) = \frac{\nu_i}{\partial y_j}(0, y_0) = 0$$

for every pair (i, j). This implies that the linearized equations for the disease compartments, x, are decoupled from the remaining equations and can be written as

$$\dot{x} = (F - V)x, \tag{3.44}$$

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where F and V are $n \times n$ matrices with entries

$$F = \frac{\partial F_i}{\partial x_j}(0, y_0) \text{ and } V = \frac{\nu_i}{\partial x_j}(0, y_0).$$

We can now form the next generation matrix FV^{-1}, whose entries give the rate at which infectious individuals in x_j produce new infections in x_i, times the average length of time an individual spends in a single visit to compartment j. R_0 is given by the largest eigenvalue of the matrix FV^{-1}.

We now consider an example from Smith (2008), for a model of malaria. Let us describe the rate of change of the infected human, H_I, and mosquito, M_I, populations by the following equations:

$$\begin{aligned} \dot{H}_I &= \beta_{MH} M_I H_S - (\mu_H + \alpha + \sigma) H_I \\ \dot{M}_I &= \beta_{MH} M_S H_I - \mu_M M_I. \end{aligned}$$

Infected humans are produced by the infection of susceptible humans, H_S, by an infected mosquito with efficacy β_{MH}. We assume that they die with natural death rate μ_H, die due to infection with rate σ and recover from the infection with rate α. Infected mosquitoes are produced when susceptible mosquitoes, M_S, bite infected humans. We further assume that this process has efficacy β_{HM} and assume that infected mosquitoes can only leave the infected compartment by dying naturally with rate μ_M. For this system, we find that

$$F = \begin{pmatrix} 0 & \beta_{MH} H_S(0) \\ \beta_{HM} M_S(0) & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \mu_H + \alpha + \sigma & 0 \\ 0 & \mu_M \end{pmatrix}.$$

Since V is non−singular matrix, we can determine V^{-1} :

$$V^{-1} = \begin{pmatrix} \frac{1}{\mu_H + \alpha + \sigma} & 0 \\ 0 & \frac{1}{\mu_M} \end{pmatrix}.$$

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We then have

$$FV^{-1} = \begin{pmatrix} 0 & \frac{\beta_{MH} H_S(0)}{\mu_M} \\ \frac{\beta_{HM} M_S(0)}{\mu_H + \alpha + \sigma} & 0 \end{pmatrix}.$$

and

$$det(FV^{-1} - \lambda I) = \lambda^2 - \frac{\beta_{MH}\beta_{HM} H_S(0) M_S(0)}{\mu_M(\mu_H + \alpha + \sigma)}.$$

Thus,

$$R_0 = \sqrt{\frac{\beta_{MH}\beta_{HM} H_S(0) M_S(0)}{\mu_M(\mu_H + \alpha + \sigma)}}.$$

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CHAPTER FOUR

DESCRIPTION AND ANALYSIS OF MATHEMATICAL MODEL

Introduction

In this chapter, we describe and analyse a malaria model with two infectious classes (Naandam, Essel, Nortey, & Soderbacka, 2013) which we call NDM−model from (Nortey et al., 2008). In addition, we will compare the parameters and the general dynamics of this model to three other models from (Ross, 1911; Chitnis, 2005; Ngwa & Shu, 2000). We start the chapter by presenting general notations and preliminaries from malaria modelling, followed by the detail description of the model and preliminary analysis of the model. The rest of the sections will be as follows: presenting the main results of the model, the review of some known models in comparison to the model, typical values of parameters and their ranges, the summary on how the calculations of the parameter values and ranges was done and finally give a conclusion on the chapter.

Notations and Preliminaries from Malaria Modelling

In comparing the parameters and the general behavior of the model with some other malaria models, we find it prudent to give a general overview of notations and preliminaries from general malaria modelling, especially those pertaining to the models we shall be discussing.

Description of variables and parameters

In epidemic modelling the populations are divided into classes forming the variables in a system of differential equations. The terms in the equations give the transition rates between the population classes. The population classes

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we used and their notations are given in Table 2. These population classes are explained in details in Chapter one, but specific population classes involved in the NDM−model are also explained when the NDM−model is introduced in this chapter.

Table 2: **Description of variables for the malaria model**

Variables	Description
S_H	Susceptible human population
E_H	Latent human population
I_H	Infectious human population
R_H	Recovered with clinical immunity
S_M	Susceptible mosquitoes
E_M	Latent mosquito population
I_M	Infectious mosquitoes
I_{H1}	Infectious human (clinical malaria cases resulting from completely susceptible individuals)
I_{H2}	Re-infectious individuals from clinical immunity
N_H	Total human population
N_M	Total mosquito population
$m = \frac{N_M}{N_H}$	Ratio of mosquito and human population

In addition to the above population class notations, the equations also contain five types of parameters which include: the incidence parameters given in Table 3, the recovery parameters given in Table 4, loss of immunity parameters given in Table 5, birth and death parameters given in Table 6 and latency parameters given in Table 7. The meaning of these parameters are explained in

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more details under the subsection titled: Terms for transition between population classes and the possible ranges of them are given in Tables 15, 16 and 17.

Table 3: **Incidence parameters and descriptions**

Parameters	Description
β_H	Contact rate between susceptible humans and infectious mosquitoes
β_M	Contact rate between susceptible mosquitoes and infectious humans
c	Constant of proportionality
k	Resistance factor

Note that the following parameters: σ_h, σ_v, a, β_{hv}, C, β_{vh}, b, $\tilde{\beta}_{vh}$ and $\tilde{C}_{hv}$ are in the incidence terms of Chitnis' model and Ngwa's model (for full meanings we refer to Chitnis et al. (2006); Ngwa and Shu (2000)) .

Table 4: **Recovery parameters and descriptions**

Parameters	Description
γ	Rate of recovery from infectious class
α	Rate of recovery from re−infectious

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Table 5: **Loss of immunity parameter and descriptions**

Parameters	Description
ω	Rate of loss of clinical immunity

Table 6: **Birth and death parameters and descriptions**

Parameters	Description
b	Rate of human population entering into susceptible class (i.e., birth and migration)
b_M	Birth rate for the mosquito population entering into susceptible class
μ_H	Natural death rate of human
δ_1	Death rate due to clinical malaria
δ_2	Death rate due to re−infection of malaria
μ_M	Natural death rate of mosquitoes

Table 7: **Latency parameters and descriptions**

Parameters	Description
ν_H	Latency rate in human
ν_M	Latency rate in mosquitoes

The NDM−model (Nortey et al., 2008) and the Ross (1911) model have no latent classes but Chitnis (2005) and Ngwa and Shu (2000) models include these classes.

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Terms for transition between population classes

For easy reading we explain the following transitional terms which will be encountered in the thesis: incidence, recovery, loss of immunity, birth, death and migration and latency.

Incidence

All epidemic models have an incidence term that measures the rate at which individuals in a population get infectious. For example, the incidence term in the SI model (Hethcote, 2000) is βIS (i.e., the rate at which individuals move from susceptible to infectious class.)

In general, we can have different such incidence terms:

Type 1 is of the form $b(I,S)$. Here, S represents a susceptible host or vector population and I an infectious vector or host population correspondingly. The function $b(I,S)$ is increasing in both variables.

Type 2 is of the form $b(R,S)$. Sometimes there is supposed to be possibilities for recovered also to be infectious as in (Chitnis, 2005). Here R is the recovered host and S is the susceptible vector (Chitnis, 2005; Ngwa & Shu, 2000) and the function $b(R,S)$ is increasing in both variables.

Type 3 is of the form $b(I,R)$. Here the recovered individual is not fully immune and therefore capable of being infected. Here I is the infectious vector population, whilst R is the recovered but not fully immune host population and the function $b(I,R)$ is increasing in both variables.

In some cases the incidence function is written as a product of two increasing functions g and h in the form $b(I,S) = g(I)h(S)$. The most usual incidence function is the case when g and h are linear and this is called linear incidence. A general class of non-linear incidence functions in a simple model are studied in (Akoto, Essel, & Soderbacka, 2012).

Usual non-linear types of g and h are $h(S) = S^r$ and $g(I) = kI^p$, where p and r are positive numbers. Another type of non-linear incidence function is given

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by $g(I) = \frac{kI^p}{1+aI^q}$. Many incidence functions are of the special type $b(I,S) = \beta IS$ where β often also depends on host and vector sizes. For example, the mosquito population size usually oscillates between the rainy season and dry season and is bigger during the rainy season and this can then have an effect also on the coefficient β.

In the models we have considered here, the incidence function is written in the form $b(I,S) = \frac{\beta_H}{N_H} IS$ in host equations and $b(I,S) = \frac{\beta_M}{N_H} IS$ in vector population equations.

In Chitnis (2005) model, β-parameters are dependent on population sizes in a natural way. Where N_H is far larger than N_M, the incidence function in Chitnis (2005) model coincides with the incidence functions in the other models named above. More precise, Chitnis (2005) finds the coefficients for term with $I_M S_H$ and $I_H S_M$ consequently in the form

$$B_H = \frac{\lambda_h}{I_M} = b_h(N_H,N_M)\frac{\beta_{hv}}{N_M} = \frac{b(N_H,N_M)}{N_H}\frac{\beta_{hv}}{N_M} = \frac{\sigma_h\sigma_v N_M}{\sigma_v N_M+\sigma_h N_M}\frac{\beta_{hv}}{N_M} = \frac{\sigma_v\sigma_h\beta_{hv}}{\sigma_v N_M+\sigma_h N_H} \tag{4.1}$$

$$B_M = \frac{\lambda_v}{I_H} = b_v(N_H,N_M)\frac{\beta_{vh}}{N_H} = \frac{b(N_h,N_H)}{N_M}\frac{\beta_{vh}}{N_H} = \frac{\sigma_h\sigma_v N_H}{\sigma_v N_M+\sigma_h N_H}\frac{\beta_{vh}}{N_H} = \frac{\sigma_v\sigma_h\beta_{vh}}{\sigma_v N_M+\sigma_h N_H} \tag{4.2}$$

For N_M small and N_H considerable large, we then get approximately

$$B_H = \frac{\sigma_v\beta_{hv}}{N_H},\ B_M = \frac{\sigma_v\beta_{vh}}{N_H}, \tag{4.3}$$

which corresponds to NDM−system with $B_H = \frac{\beta_H}{N_H}$ and $B_M = \frac{\beta_M}{N_H}$, where $\beta_H = \sigma_v\beta_{hv}$ and $\beta_M = \sigma_h\beta_{vh}$. However, for N_H small and N_M considerable large we then obtain approximately

$$B_H = \frac{\sigma_h\beta_{hv}}{N_M},\ B_M = \frac{\sigma_h\beta_{vh}}{N_M}, \tag{4.4}$$

which is quite an opposite situation. As we interpret it, Chitnis (2005) suggested that dividing by small N_H in these cases will make an unrealistic big β-factor.

Chitnis (2005) has incidence terms with combinations $I_M S_H$, $I_H S_M$ and $R_H S_M$ as NDM−system has incidence terms for $I_M S_H$, $I_M R_H$, $I_{H1} S_M$ and $I_{H2} S_M$.

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NDM−system does not have the possibility for mosquitoes to get infectious from recovered class.

Recovery

The recovery rate is denoted by γ. Most models, except the NDM−model which has one type of recovery. The recovery terms are all linear. The average time spent in recovery is $\frac{1}{\gamma}$, if γ is the coefficient in the linear term. In the NDM−model there are two recovery rates, one of them representing the recovery from the infectious class is denoted by γ whiles the other representing the recovery from the re−infectious class is denoted by α. Also, here, the terms are linear. Usually after the recovery, the infectious are moved to a recovered class with some immunity but in Ross model the infectious move directly to the susceptible class whiles in the Ngwa and Shu (2000) model some of the infectious move to the susceptible whiles the rest move to recovered class.

Loss of immunity

The loss of immunity is denoted by ω. It was observed that with the exception of the Ross model, all the other models have rates of loss of immunity. These terms are also linear. The quantity $\frac{1}{\omega}$ is the average time in loosing immunity. Here, ω is the coefficient of the linear term.

Birth, death and migration

The birth and death coefficients are $b, b_M, \mu_H, \mu_M, \delta_1, \delta_2$ and comes from linear terms in the NDM−system. The parameters b and μ_H are the birth and death rates for the host population respectively. The number $\frac{1}{\mu_H}$ is the average life expectancy of humans and $\frac{1}{b}$ is the average time to give birth. Likewise, the parameters b_M and μ_M are the birth and death rates for the mosquito population respectively.

In NDM−model we assume linear birth and death terms, whereas in Chitnis (2005) and Ngwa and Shu (2000) models, they assumed quadratic birth terms, whilst death has both linear and quadratic terms. The disease-induced death rates

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δ_1 and δ_2 add an extra linear term for infectious classes. Chitnis (2005) also includes a migration factor into the susceptible host class which is a constant term.

Latency

The rate of becoming infectious in latent classes are denoted by ν_H and ν_M for the host and mosquito populations respectively. Some models have separate class for latency and is usually denoted by E, whereas in the NDM−model this latency class is accounted for by decreasing β values. Identifying how the latency values are included in the decreasing β values may be quite difficult. Nevertheless, latency can be included in the model in two ways, either with a latent population E, but if included more exact it should be included by making a delay system. Not withstanding, there can be a lot of mathematical difficulties associated with this type of system. The need for having a latency term in the model becomes very important if the life span of the vector is relatively short and less important in the case of the host which has a longer life span. For individuals (e.g., host) with longer life span, the latency term may often be excluded from the model.

In the case of malaria the latency period can be very different (Anderson & May, 1991) and thus there is no clear latency period used in the delay equations but must be taken in average. This means that delay-equations are not so much better than models with a latent population included.

The NDM−Model

In this chapter, we review and analyse the NDM−model which is the main subject of investigation in this thesis. In the paper published by Ricardo, White, Snow, and Gomes (2008), the authors identified an interesting phenomenon. This phenomenon was further investigated by the authors of the NDM−model in (Nortey et al., 2008). Ricardo et al. (2008) claimed that a characteristic of plasmodium falciparum is the gradual acquisition of clinical immunity, resulting

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from repeated exposures to the parasite. However, any given infection produces a clinical outcome that depends on a combination of parasite, vector, host and environmental factors. Also, in highly endemic regions, both prevalence of infection and incidence of severe malaria are high in young children and pregnant women, whereas in older children and adults, prevalence of infection is higher while incidence of severe cases is lower. Thus, even after many exposures, humans are not resistant to infection, but develop clinical immunity that prevents symptomatic disease which is not solely dependent on host intrinsic age factors. In low endemic regions, however, malaria infection and morbidity shows less age dependence, with infections being commonly symptomatic even in adults, due to less frequent immunologic simulation. In the work done by the authors of the NDM−model (Nortey et al., 2008), a model was created consisting of a system of ODE's for the host and vector populations.

The NDM−model, divides the host populations into four classes: Susceptible, S_H, Infectious, I_{H1}, Recovered, R_H and Re-infectious, I_{H2}. Human beings enter the susceptible class either through birth (at a constant rate) or from the recovered class (at a constant rate). When an infectious mosquito bites a susceptible human, there is some probability that the parasite (in the form of sporozoite) will be passed on to the human and the person will move to the infectious class and become infectious. After some time the infectious humans recover and move to the recovered class. In NDM−model a proportion of the recovered humans could move back into the susceptible class and the remaining become re−infectious and move to the re−infectious class. In addition, some of the re−infectious humans recover and return to the recovered class (at a constant rate). Humans leave the population through a density−dependent natural death rate, μ_H and through a disease−induced death rates, δ_1 and δ_2.

In the NDM−model, we divide the vector (mosquito) population into two classes: the Susceptible S_M, and the Infectious class, I_M. Female mosquitoes

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(we do not include male mosquitoes because only female mosquitoes bite human for blood meals) enter the susceptible S_M class through birth. The parasite (in the form of gametocytes) enters the mosquito, after biting an infectious human with some probability. When this happens the mosquito then moves from the susceptible S_M class to the infectious I_M class. The mosquito remains infectious for life. Mosquitoes leave the population through a density-dependent natural death rate, μ_M.

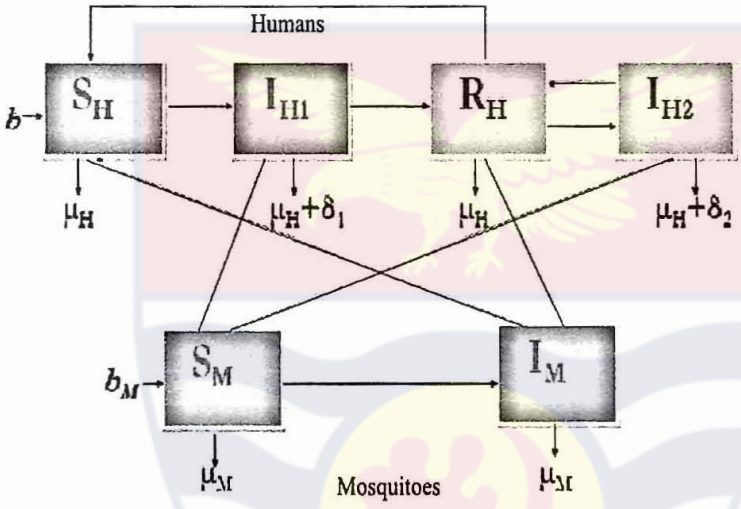


Figure 28: **Flow diagram of malaria model**

In Figure 28 , we present a schematic diagram of the mathematical model for malaria transmission. Susceptible humans, S_H, get infectious at a certain probability, when they are bitten by an infectious mosquito. They then progress to infectious class, I_{H1}, and later into the recovered class R_H. These also progress from recovered to the re−infectious, I_{H2} or re-enter the susceptible S_H class.

Susceptible mosquitoes S_M get infectious at a certain probability when they come in contact with infectious I_{H1} or re−infectious I_{H2} humans and then progress to the infectious class I_M.

The state variables of the model are shown in Table 2 and the parameters

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used in the model are shown in Tables 3, 4, 5, 6 and 7. All parameters are assumed to be strictly positive with the exception of the disease-induced death rates, δ_1 and δ_2 , which we assume to be nonnegative. We now present the system of equations for the NDM malaria model from Figure 28.

$$\begin{aligned}
\dot{S}_H(t) &= bN_H - \frac{\beta_H S_H I_M}{N_H} + \omega R_H - \mu_H S_H \\
\dot{I}_{H1}(t) &= \frac{\beta_H S_H I_M}{N_H} - \gamma I_{H1} - (\mu_H + \delta_1) I_{H1} \\
\dot{R}_H(t) &= \gamma I_{H1} + \alpha I_{H2} - \frac{c\beta_H R_H I_M}{N_H} - (\omega + \mu_H) R_H \\
\dot{I}_{H2}(t) &= \frac{c\beta_H R_H I_M}{N_H} - \alpha I_{H2} - (\mu_H + \delta_2) I_{H2} \\
\dot{S}_M(t) &= b_M N_M - \frac{\beta_M S_M (I_{H1} + k I_{H2})}{N_H} - \mu_M S_M \\
\dot{I}_M(t) &= \frac{\beta_M S_M (I_{H1} + k I_{H2})}{N_H} - \mu_M I_M \\
\dot{N}_H &= (b - \mu_H) N_H - \delta_1 I_{H1} - \delta_2 I_{H2} \\
\dot{N}_M &= (b_M - \mu_M) N_M
\end{aligned} \tag{4.5}$$

To carry out a serious mathematical investigation, it is usual to scale the equations to variables representing proportions of population classes, compared with total host or mosquitos classes. Sometimes after that, total host and mosquito populations are assumed constant. This often gives good approximations in short time behavior, even if not always, especially for the mosquito population which can change faster. Ngwa and Shu (2000) and Chitnis et al. (2006) have pointed out this problem. Anyhow, a lot can be obtained from scaled models assuming at least the host population is constant. The populations can be considered as slow variables thereby simplifying the general investigation.

We now start the scaling of system of equations (4.5) by using the the scaled variables

$$s = \frac{S_H}{N_H},\ x = \frac{I_{H1}}{N_H},\ r = \frac{R_H}{N_H},\ y = \frac{I_{H2}}{N_H}$$

and

$$u = \frac{S_M}{N_M},\ z = \frac{I_M}{N_M}$$

and notation

$$m = \frac{N_M}{N_H}.$$

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We assume $\dot{N}_H \cong \dot{N}_M \cong 0$. Differentiating the scaling equations, simplifying and neglecting these terms, we have

$$\begin{aligned} \dot{s} &= \frac{\dot{S}_H N_H - S_H \dot{N}_H}{N_H^2} = \frac{\dot{S}_H}{N_H} = \frac{1}{N_H}(bN_H - \frac{\beta_H S_H I_M}{N_H} + \omega R_H - \mu_H S_H) \\ &= b - \beta_H s z \frac{N_M}{N_H} + \omega r - \mu_H s \end{aligned} \tag{4.6}$$

$$\begin{aligned} \dot{x} &= \frac{\dot{I}_{H1} N_H - I_{H1} \dot{N}_H}{N_H^2} = \frac{\dot{I}_{H1}}{N_H} = \frac{1}{N_H}(\frac{\beta_H S_H I_M}{N_H} - (\gamma + \mu_H + \delta_1) I_{H1}) \\ &= \beta_H s z \frac{N_M}{N_H} - (\gamma + \mu_H + \delta_1) x \end{aligned} \tag{4.7}$$

$$\begin{aligned} \dot{r} &= \frac{\dot{R}_H N_H - R_H \dot{N}_H}{N_H^2} = \frac{\dot{R}_H}{N_H} = \frac{1}{N_H}(\gamma I_{H1} + \alpha I_{H2} - \frac{c\beta_H R_H I_M}{N_H} - (\omega + \mu_H) R_H) \\ &= \gamma x + \alpha y - \frac{N_M}{N_H} \beta_H c r z - (\omega + \mu_H) r \end{aligned} \tag{4.8}$$

$$\begin{aligned} \dot{y} &= \frac{\dot{I}_{H2} N_H - I_{H2} \dot{N}_H}{N_H^2} = \frac{\dot{I}_{H2}}{N_H} = \frac{1}{N_H}(\frac{c\beta_H R_H I_M}{N_H} - \alpha I_{h2} - (\mu_H + \delta_2) I_{H2}) \\ &= \frac{N_M}{N_H} \beta_H c r z - (\alpha + \mu_H + \delta_2) y \end{aligned} \tag{4.9}$$

$$\begin{aligned} \dot{u} &= \frac{\dot{S}_M N_M - S_M \dot{N}_M}{N_M^2} = \frac{\dot{S}_M}{N_M} = \frac{1}{N_M}(b_M N_M - \frac{\beta_M S_M (I_{H1} + k I_{H2})}{N_H} - \mu_M S_M) \\ &= b_M - \beta_M u(x + ky) - \mu_M u \end{aligned} \tag{4.10}$$

$$\begin{aligned} \dot{z} &= \frac{\dot{I}_M N_M - I_M \dot{N}_M}{N_M^2} = \frac{\dot{I}_M}{N_M} = \frac{1}{N_M}(\frac{\beta_M S_M (I_{H1} + k I_{H2})}{N_H} - \mu_M I_M) \\ &= \beta_M u(x + ky) - \mu_M z \end{aligned} \tag{4.11}$$

Now the scaled system is given as

$$\begin{aligned} \dot{s} &= b - \beta_H m s z + \omega r - \mu_H s \\ \dot{x} &= \beta_H m s z - (\gamma + \mu_H + \delta_1) x \\ \dot{r} &= \gamma x + \alpha y - \beta_H m c r z - (\omega + \mu_H) r \\ \dot{y} &= \beta_H m c r z - (\alpha + \mu_H + \delta_2) y \\ \dot{u} &= b_M - \beta_M u(x + ky) - u\mu_M \\ \dot{z} &= \beta_M u(x + ky) - \mu_M z \end{aligned} \tag{4.12}$$

with $s + x + r + y = 1$ and $u + z = 1$.

For numerical verification of how System (4.12) estimate System (4.5), we refer to the section headed Error Analysis in this chapter.

For this model, (4.12), there exists a domain where the system of equations is epidemiologically and mathematically well-posed. We define this domain, Ω,

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as:

$$\Omega = \{ \begin{pmatrix} s \\ x \\ r \\ y \\ u \\ z \end{pmatrix} \in R^6 : s > 0, x \geq 0, r \geq 0, y \geq 0, u \geq 0, z \geq 0, s+x+r+y \leq 1, u+z \leq 1 \}$$

This domain, Ω, is valid epidemiologically as the fractional populations, s, x, r, y, u and z are all nonnegative and have sums over their species type that are less than or equal to 1. The human population, N_H, is positive, while the mosquito population, N_M, is nonnegative.

Preliminary Analysis of NDM−Model

In this section, we calculate the endemic equilibrium analytically and compare the values with the numerical simulations values. The parameters have different impact on the dynamics of the system, we will determine the set parameters that have greater influence on the endemic equilibrium and call them essential parameters. A rough estimation of the endemic equilibrium will be done neglecting the non-essential parameters for both the scaled and the main systems. The system undergoes a form of transcritical bifurcation, we will use the Jacobian method to calculate this bifurcation parameter. The comparison between the main system and the scaled system will be determined by estimating maximum difference between them and where it occurs. We use the standard parameter values for the NDM−model given in Table 8.

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Table 8: **Parameter values for NDM−model**

Parameter	Value
β_H	0.06
β_m	0.05
γ	0.04
ω	0.01
μ_H	0.000055
μ_m	0.05
α	0.04
δ_1	0.000018
δ_2	0.00001
k	0.12
c	0.25
b_m	0.05
b	0.000055

Simulation results of the main system

To analyse the main System (4.5) using Octave, we assume that we have 700 susceptible humans, 100 infected humans, 100 recovered humans with temporal clinical immunity, 100 re−infected humans, 700 susceptible mosquitoes and 300 infected mosquitoes. This gives an initial condition (700, 100, 100, 100, 700, 300), the parameter values are those given in Table 8 and the time span is 15000 days. The system seems to stabilize to an equilibrium point with values (678.1, 60.18, 239.4, 5.311, 941.7, 58.27) in a period from three to five years. The solution curves are shown in Figure 29 indicating how the system gets stabilized.

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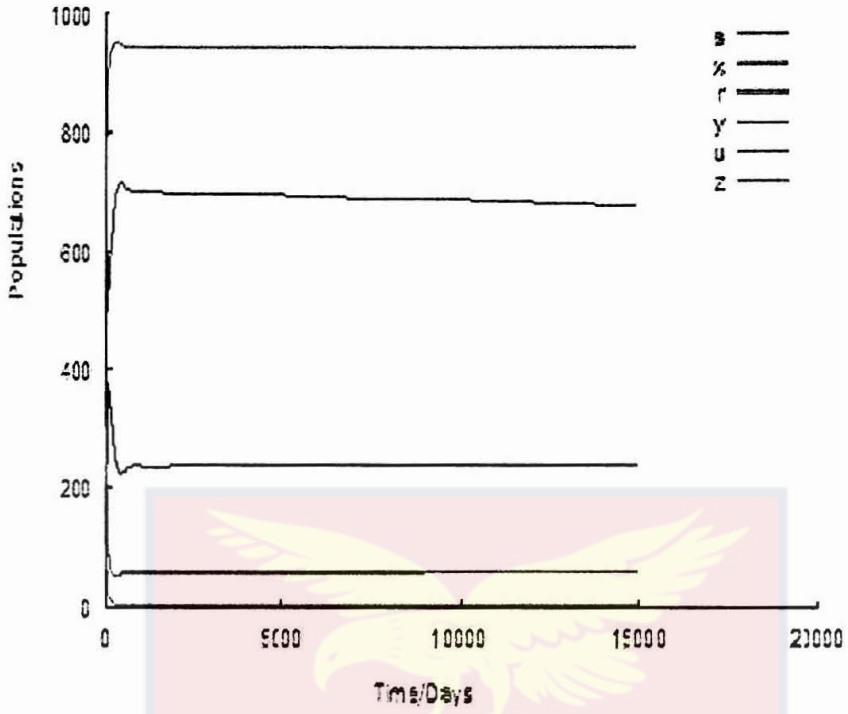


Figure 29: **Solution curves for main system**

Simulation results of the scaled system

The scaled System (4.12) was also analysed using Octave. The initial condition was (0.7, 0.1, 0.1, 0.1, 0.7, 0.3), these are relative values corresponding to the original model's initial conditions. The same parameter values were used and the time span is 1500 days. The system stabilizes to an equilibrium point (0.6996, 0.0571, 0.2274, 0.0046, 0.9454, 0.0545) after three years up to infinity. Figure 30 shows how the system stabilizes after three years.

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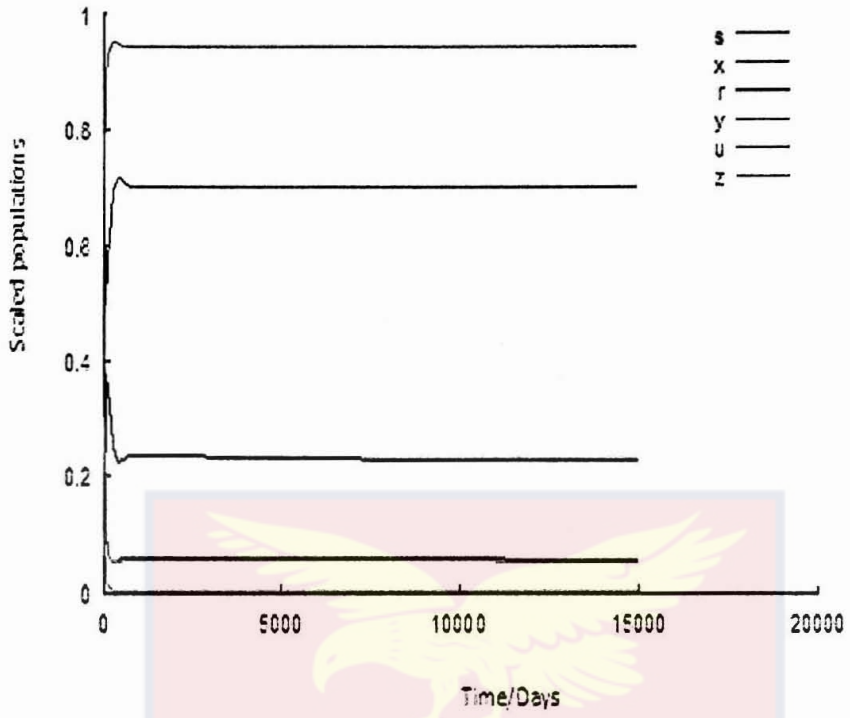


Figure 30: **Solution curves for the scaled system**

Determination of endemic equilibrium of the scaled system using "WxMaxima"

In this subsection, we present an analytic algorithm and give some numerical values for some parameters to determine the endemic equilibrium of the scaled system. To determine the endemic equilibrium of the system, the right hand side of the scaled system equations are equated to zero. From the system of equations in (4.12), we add the third and fourth equations to obtain a formula for r at the equilibrium, in terms of x and y, and no other variables, only parameters.

$$r = -\frac{(\mu_H + \delta_2)y - \gamma x}{(\mu_H + \omega)} \tag{4.13}$$

Secondly, we add the first two equations and substitute the expression for r to obtain a formula for s at the equilibrium, in terms of x and y, and this is given by

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$$s = -\frac{(\omega(\mu_H + \delta_2)y - \gamma x)}{\mu_H(\mu_H + \omega)} - \frac{\mu_H + \delta_1 + \gamma)x - b}{\mu_H} \tag{4.14}$$

The sum of the last two equations is zero and we see that $u = 1 - z$. Then we substitute $u = 1 - z$ into the fifth equation and solve for z as a function of x and y. This gives

$$z = \frac{\beta_M(ky + x)}{\beta_M(ky + x) + \mu_M} \tag{4.15}$$

By substituting the expressions for s and z into the second equation we obtain a second order equation in x and y given in the form

$$a_{x2}x^2 + a_{xy}xy + a_{y2}y^2 + a_x x + a_y y = 0 \tag{4.16}$$

Note that we consider only the numerator and the coefficients of the equation and they are given as:

$$\begin{aligned}
a_{x2} &= -\beta_M(\mu_H^3 + \delta_1\mu_H^2 + \beta_H\mu_H^2 + \omega\mu_H^2 + \gamma\mu_H^2 + \beta_H\delta_1\mu_H + \omega\delta_1\mu H \\
&+ \omega\beta_H\mu_H + \gamma\beta_H\mu_H + \gamma\omega\mu_H + \omega\beta_H\delta_1) \\
a_{xy} &= -\beta_M(k\mu_H^3 + \delta_1 k\mu_H^2 + \beta_H k\mu_H^2 + \omega k\mu_H^2 + \gamma k\mu_H^2 + \beta_H\delta_1 k\mu_H \\
&+ \omega\delta_1 k\mu_H + \omega\beta_H k\mu_H + \gamma\beta_H k\mu_H + \gamma\omega k\mu_H + \omega\beta_H\mu_H \\
&+ \omega\beta_H\delta_1 k + \omega\beta_H\delta_2) \\
a_{y2} &= -\omega\beta_H\beta_M k(\mu_H + \delta_2 \\
a_x &= (-\mu_H - \omega)(\mu_H^2\mu + M + \delta_1\mu_H\mu_M + \gamma\mu_H\mu_M - b\beta_H\beta_M) \\
a_y &= b\beta_H\beta_M k(\mu_H + \omega)
\end{aligned} \tag{4.17}$$

Substituting the expressions for s and z into the fourth equation we find a second order equation in x and y given in the form

$$b_{x2}x^2 + b_{xy}xy + b_{y2}y^2 + b_y y = 0 \tag{4.18}$$

Note also that we take only the numerator and the coefficients of the equation and they are given as:

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$$\begin{aligned}
b_{x2} &= \gamma\beta_H\beta_M c \\
b_{xy} &= -\beta_M(\mu_H^2+\delta_2\mu_H+\beta_H c\mu_H+\omega\mu_H+\alpha\mu_H-\gamma\beta_H ck+\beta_H c\delta_2 \\
&+ \omega\delta_2+\alpha\omega) \\
b_{y2} &= -\beta_M k(\mu_H^2+\delta_2\mu_H+\beta_H c\mu_H+\omega\mu_H+\alpha\mu_H+\beta_H c\delta_2 \\
&+ \omega\delta_2+\alpha\omega) \\
b_y &= (-\mu_H-\omega)(\mu_H+\delta_2+\alpha)\mu_M
\end{aligned} \tag{4.19}$$

We establish that $a_{x2} = a_{xy}k - a_{x2}k^2$, and $b_{y2} = b_{xy}k - b_{x2}k^2$. We add Equations (4.16) and (4.18) to eliminate the y^2 terms and solve for y as a function of x and substitute this expression for y in (4.18). The numerator gives an equation in x which occurs in the form

$$c_4x^4 + c_3x^3 + c_2x^2 + c_1x = 0 \tag{4.20}$$

In calculating the coefficients we find only $c_4 = 0$ and we indeed have a quadratic in x for a nonzero solutions. We now solve for x to obtain

$$x = \frac{-c_2 \pm \sqrt{c_2^2 - 4c_1c_3}}{2c_3}, \tag{4.21}$$

where

$$\begin{aligned}
c_1 &= a_x b_y(a_{x2}b_y k - a_y b_{x2}k - a_{xy}b_y + a_y b_{xy}) \\
c_2 &= -a_x^2 b_{x2}^2 k^3 + 2a_x^2 b_{x2}b_{xy}k^2 + a_{x2}^2 b_y^2 k + 2a_x a_{x2}b_{xy}b_y k \\
&- 2a_{x2}a_y b_{x2}b_y k - a_x a_{xy}b_{x2}b_y k - a_x^2 b_{xy}^2 k - a_x a_y b_{x2}b_{xy}k \\
&+ a_y^2 b_{x2}^2 k - a_{x2}a_{xy}b_y^2 + a_{x2}a_y b_{xy}b_y - a_x a_{xy}b_{xy}b_y \\
&+ a_{xy}a_y b_{x2}b_y + a_x a_y b_{xy}^2 - a_y^2 b_{x2}b_{xy} \\
c_3 &= (a_{x2}b_{xy} - a_{xy}b_{x2})(2a_x b_{x2}k^2 + 2a_{x2}b_y k - a_{xy}b_y + a_y b_{xy}).
\end{aligned} \tag{4.22}$$

We use the sign in (4.21) given positive x.

The formula for y in terms of x is given as

$$y = -\frac{(a_{x2}by2 - a_{y2}b_{x2})x^2 + a_x b_{y2}x}{(a_{xy}b_{y2} - a_{y2}b_{xy})x + a_y b_{y2} - a_{y2}b_y} \tag{4.23}$$

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The algebraic expressions for the Formulae (4.21) and (4.23) give the x and y values at equilibrium respectively. Substituting x and y in Equations (4.13), (4.14) and (4.15), we obtain the values of r, s and z at equilibrium respectively.

To find numerical values for the population classes at equilibrium, we substitute the parameter values from Table 8 into Equations (4.17) and (4.19) to obtain concrete values for $a_{x2}, a_{xy}, a_{y2}, a_x, a_y, b_{x2}, b_{xy}, b_{y2}, b_y$ which depends on the parameters of the system. Substituting values of the parameters into Equation (4.22) we obtain the values for the coefficients c_1, c_2 and c_3. Now, substituting the values of c_1, c_2 and c_3 in Equation (4.21), we obtain two values for x, they are -1.801855169922222 and 0.055784152314704. Since x is positive we discard -1.801855169922222. Now we substitute the value of x into (4.23) to get numerical value of y, the values of x and y are then substituted into (4.13), (4.14) and (4.15) to obtain the numerical values of r, s and z respectively. We used the fact that $u = 1 - z$ to get numerical value of u. Hence, the numerical values at the endemic equilibrium point is given as

$(0.6988, 0.0558, 0.2219, 0.0044, 0.9467, 0.0533)$.

To compare the values of endemic equilibrium obtained from three different approaches, we present Table 9. The first column gives the population classes, the second column headed main system is the estimated values for the endemic equilibrium for the corresponding populations from the simulation of the main system. The third column is the estimated values for the endemic equilibrium from the simulation of the scaled system, so is headed "scaled system". The fourth column is the estimated values of the endemic equilibrium using algorithms in "wXmaxima" to solve the scaled system and headed by "direct calculations".

It is observed that the values of the endemic equilibrium from the direct calculations estimate the scaled system simulated values very close since they both used the same system of equations. The scaled system has better estimate

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to the main system than the direct calculations.

Table 9: **Table of endemic points from different approaches**

Population classes	Main system (Scaled)	Scaled system	Direct calculation
Susceptible humans	678.1 (0.6781)	0.6996	0.6988
Infectious humans	60.18 (0.0602)	0.0571	0.0558
Recovered humans	239.4 (0.2394)	0.2274	0.2215
Re-infectious humans	5.311 (0.0053)	0.0046	0.0044
Susceptible mosquitoes	941.7 (0.9410)	0.9454	0.9467
Infectious mosquitoes	58.27 (0.0583)	0.0505	0.0533

The simulations and calculations were done by varying the initial populations, especially the ratio between mosquito population and human population, m. What is presented in this section is a sample of one of the simulations. We then conclude that, in moderate time, the solution curves of system (4.5) are close to the solution curves of the scaled System (4.12) and after that, slowly move close to a curve of equilibria of the scaled system where parameter m changes.

Determination of essential parameter by graphical method

We present a graphical method of determining parameters that can impact the endemic equilibrium point when they are varied. We recall that we developed an algorithm in the immediate past subsection using "wXmaxima" to calculate the endemic equilibrium of the scaled system. By using the parameter values from Table 9, we obtain the endemic point to be

$(0.6988, 0.0558, 0.2219, 0.0044, 0.9467, 0.0533)$.

At this point we write another algorithm that varies for a selected parameter and holding the rest of the constant as in Table 9. This produces a sequence of endemic equilibria, where each equilibrium corresponds to each value of the var-

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ied parameter. As the endemic equilibrium changes with respect to the changes in the selected parameter, the values of the population classes (state variables) also changes accordingly.

As part of the algorithm, we plot the population classes (state variables) against the selected varied parameter. This generate graphs for each population class (state variable) with different steepness and directions.

From geometry we know strength of any functional relation between two quantities is described by the gradient function. The absolute value of the gradient function at given point will tell how strong one of the quantities can influence the other. In addition, the sign (positive or negative) of the value of the gradient function at a point informs the nature of the relationship. In this section, we are going are to consider the relationship between some parameters of the scaled system of the NDM−model and the state variables of the model. We will examine the nature of the graphs generated by inspection and try to draw a conclusion as to whether the given parameter is essential or not.

Varying the re−infectious recovery rate

Figure 31 illustrates the response by the state variables to the variation of recovery rate from the re−infectious class. It is observed that the graphs in this figures are eventually horizontal, indicating that variation in α thus have very little or no effect in the developments in the state variables. Hence, we conclude that α is not an essential parameter.

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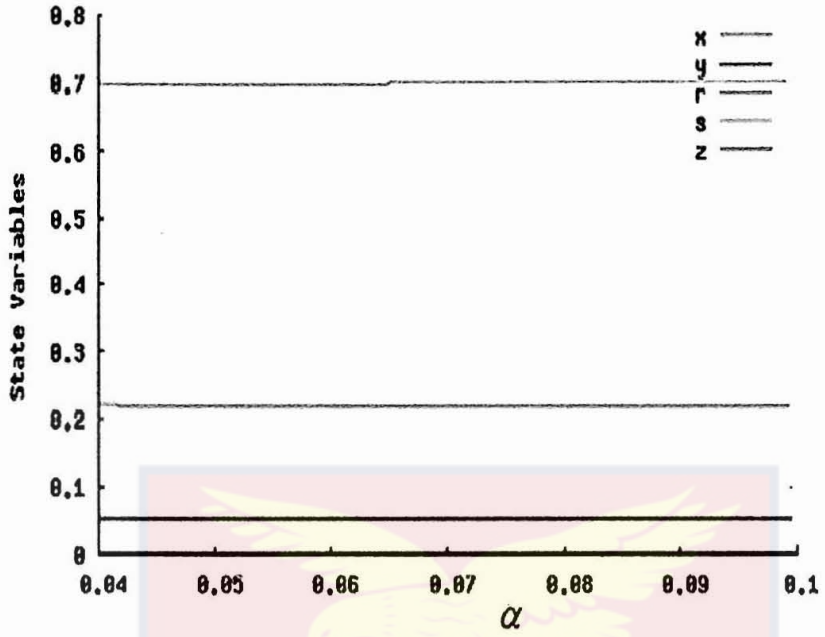


Figure 31: **State variables against re−infectious recovery rate**

Varying the contact rate of susceptible humans to infectious mosquitoes

Figure 32 illustrates the response by the state variables to the variation of the contact rate between susceptible humans and infectious mosquitoes. In this figure, it is observed that the graphs of susceptible and recovery variables had a strong response, whilst the infectious humans and mosquitoes variables responded slightly weaker. The re−infectious class response is almost horizontal. On the average, we conclude that β_H is an essential parameter.

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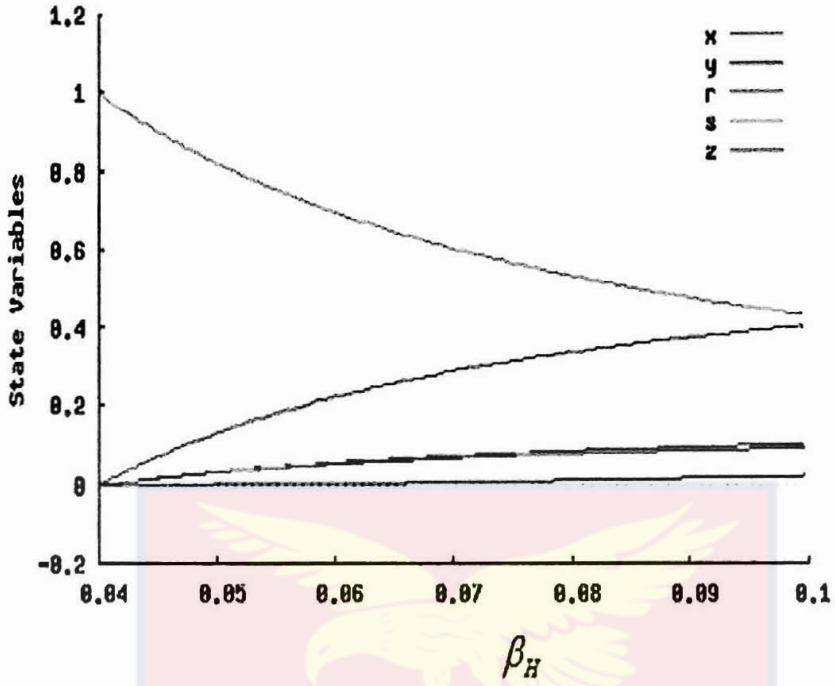


Figure 32: **State variables against contact rate of susceptible humans to infectious mosquitoes**

Varying the contact rate of infectious humans to susceptible mosquitoes

Figure 33 illustrates the response by the state variables to the variation of the contact rate between infectious humans and susceptible mosquitoes. The observation is almost the same as in Figure 32 except that the response in each variable appears to be stronger than their corresponding variables in Figure 32, indicating the significance of β_M in the transmission of malaria. Hence, we conclude β_M is an essential parameter.

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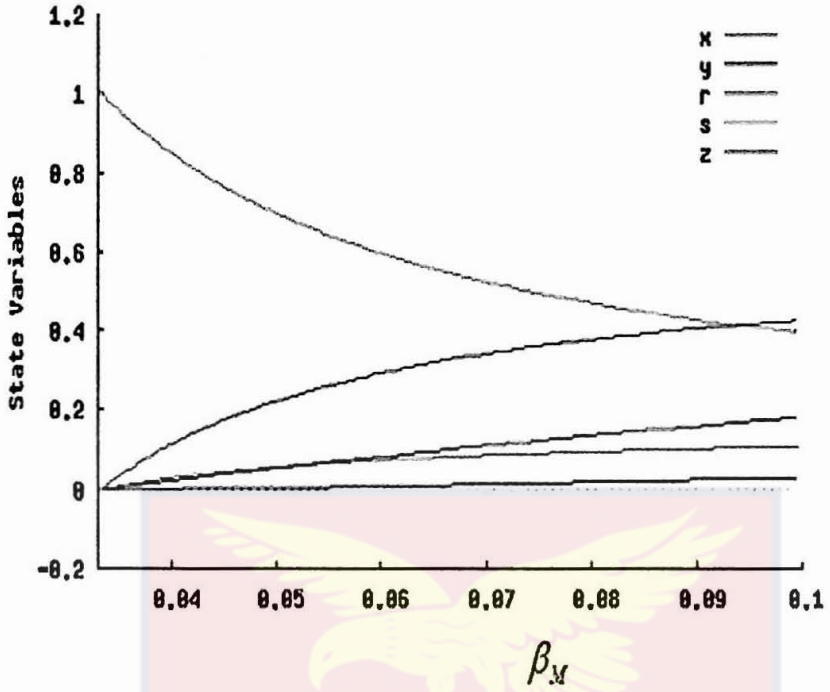


Figure 33: **State variables against contact rate of infectious human to susceptible mosquito**

Varying the recovery rate from infectious class

Figure 34 illustrates the response by the state variables to the variation of the recovery rate from the infectious class. It appears the response from the susceptible, infectious and recovered human variables are very strong and this should be expected since they are directly affected by the recovery rate. The infectious mosquitoes variable also shows equivalent strong response by decreasing as the recovery rate increases. The re−infectious humans variable shows a weaker and decreasing response to the increasing recovery rate.

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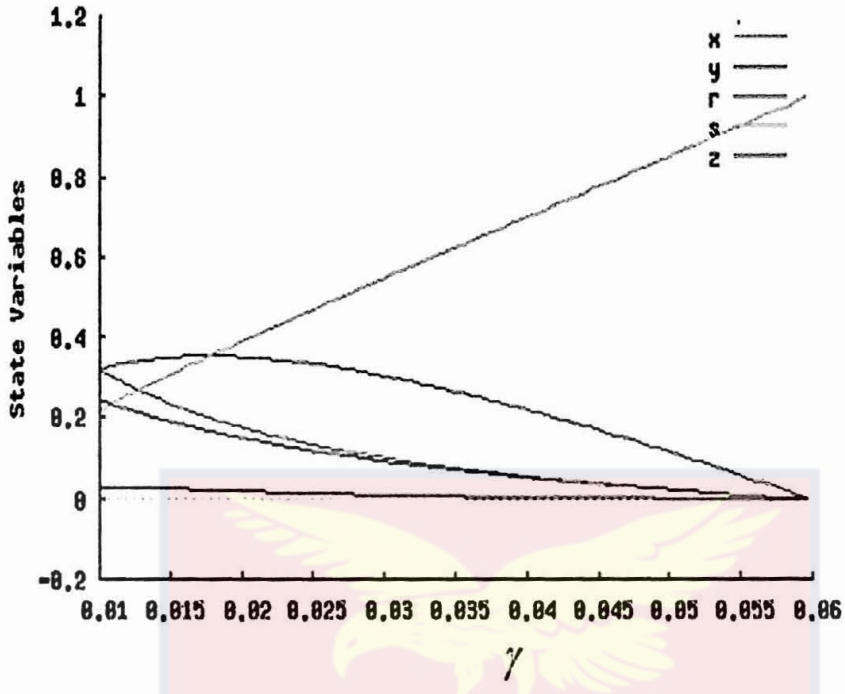


Figure 34: **State variables against recovery rate from infectious class**

Varying the mortality rate of mosquitoes

Figure 35 illustrates the response by the state variables to the variation of the mortality rate of mosquitoes. It is observed that the susceptible humans variable shows a strong and increasing response to the increasing mosquito mortality rate, whilst the recovered humans variable shows strong and decreasing response. The remaining three response is slightly weaker and decreasing to the increasing mosquito mortality rate.

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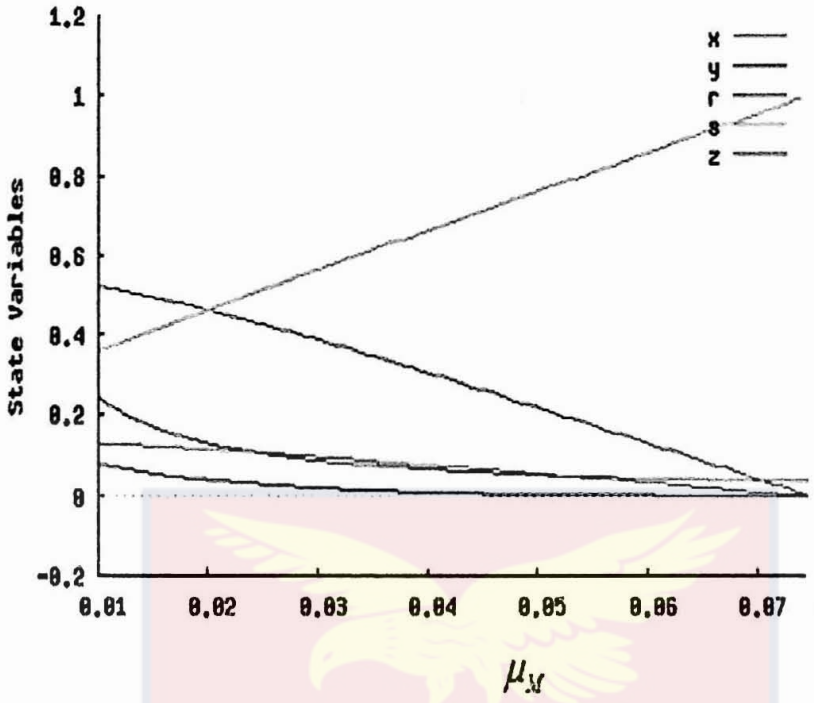


Figure 35: **State variables against mortality rate of mosquitoes**

Varying the rate of loss of clinical immunity

Figure 36 illustrates the response by the state variables to the variation of rate of loss of clinical immunity. The response by the susceptible humans, infectious humans and infectious mosquitoes variables are slightly weaker and increasing with increasing rate of loss of clinical immunity. The recovery variable shows a strong but decreasing response to the increasing rate of loss of clinical immunity. There seems to be virtually no response from the re−infectious variable.

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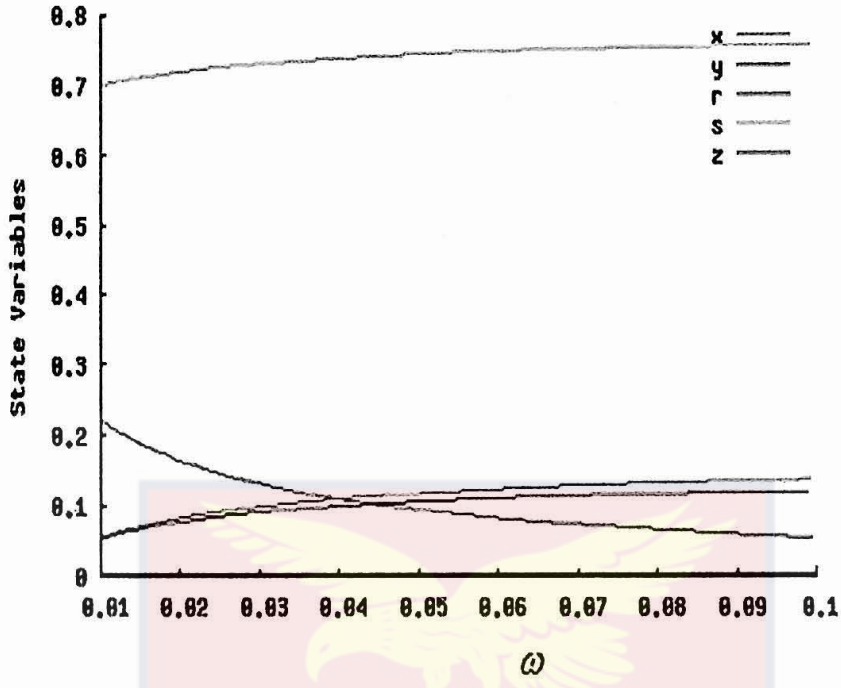


Figure 36: **State variables against rate of loss of clinical immunity**

We note that similar graphs were prepared for δ_1, δ_2, k and c but the responses from the state variables were the same as in Figure 31, so we declared them to be non−essential parameters.

Rough approximation of endemic equilibrium

In this subsection, we seek for good approximations to endemic equilibrium of the main NDM−system and its scaled version in the case of constant mosquito population. It is hard to solve for endemic equilibrium of the main System (4.5) and thus we are here going to look for approximations to it by assuming some of the non-essential parameters such as δ_1, δ_2 and k, and b and μ_H to be negligible.

The endemic equilibrium of a scaled version is possible to calculate, but the formulae are long and heavy so there will be the need to make use of simpler approximations.

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Simplified scaled system

In the NDM−model, we scaled the population sizes in each class by the total population sizes to derive a simplified version of the model above, by introducing the following new variables we obtained the scaled system (4.12). By neglecting the four small parameters and letting $m = 1$ we obtain

$$\begin{aligned} s' &= -\beta_H sz + \omega r \\ x' &= \beta_H sz - \gamma x \\ r' &= -c\beta_H zr + \alpha y + \gamma x - \omega r \\ y' &= c\beta_H zr - \alpha y \\ u' &= b_M - \beta_m u(x + ky) - \mu_m u \\ z' &= \beta_M u(x + ky) - \mu_m z \end{aligned} \tag{4.24}$$

We now find a rough approximation for the variables s, x, y, r, u and z at the endemic equilibrium. Assuming ky is small compared with x and u is approximately one in $z' = 0$ we obtain the relation $z = \frac{\beta_m}{\mu_m} x$. Using this relation in $x' = 0$ we obtain an approximation for s: $s = \frac{\gamma\mu_m}{\beta_h\beta_m}$. Using relation $x' + s' = 0$ we obtain the relation $r = \frac{\gamma}{\omega} x$. Substituting the relation for r and s into equality $s + x + r + y = 1$ we obtain the equation

$$\frac{\gamma\mu_m}{\beta_h\beta_m} + x + \frac{\gamma}{\omega} x + y = 1 \tag{4.25}$$

substituting the relation for z into $y' = 0$ we obtain

$$\alpha y - \frac{\gamma\beta_h\beta_m c x^2}{\mu_m \omega} \tag{4.26}$$

Solving for y from (4.25) and substituting into (4.26) we obtain a second order in x:

$$-\frac{\gamma\beta_h\beta_m c x^2}{\mu_m \omega} + \left(-\frac{\gamma\alpha}{\omega} - \alpha\right) x - \frac{\gamma\alpha\mu}{\beta_h\beta_m} + \alpha. \tag{4.27}$$

The positive solution will give the value of the approximation of the x-

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value at endemic and resuming the other coordinates are got from

$$\begin{aligned} s &= \frac{\gamma\mu_m}{\beta_h\beta_m} \\ r &= \frac{\gamma}{\omega}x \\ y &= 1-\left(\frac{\gamma\mu_m}{\beta_h\beta_m}+x+\frac{\gamma}{\omega}x\right) \\ u &= 1-z \\ z &= \frac{\beta_m}{\mu_m}x \end{aligned} \tag{4.28}$$

For the standard values of parameters

$$\beta_h = 0.06, \beta_m = 0.05, c = 0.25, \omega = 0.01, \gamma = 0.04, \alpha = 0.04, \mu_m = 0.05$$

we obtain

$$s = 0.67, x = 0.065, r = 0.26, y = 0.008, u = 0.93, z = 0.065$$

to be compared with the exact values

$$s = 0.7, x = 0.056, r = 0.22, y = 0.0044, u = 0.95, z = 0.053$$

Simplified main system

In this section, we assume $b_M = \mu_M$ and thus the mosquito population is constant and neglecting some small terms, the equations of the main System (4.5) become

$$\begin{aligned} \dot{S}_H(t) &= -\frac{\beta_H S_H I_M}{N_H} + \omega R_H \\ \dot{I}_{H1}(t) &= \frac{\beta_H S_H I_M}{N_H} - \gamma I_{H1} \\ \dot{R}_H(t) &= \gamma I_{H1} + \alpha I_{H2} - \frac{c\beta_H R_H I_m}{N_H} - \omega R_H \\ \dot{I}_{H2}(t) &= \frac{c\beta_H R_H I_M}{N_H} - \alpha I_{H2} \\ \dot{S}_M(t) &= b_M N_M - \frac{\beta_M S_M (I_{H1}+kI_{H2})}{N_H} - \mu_M S_M \\ \dot{I}_M(t) &= \frac{\beta_M S_M (I_{H1}+kI_{H2})}{N_H} - \mu_M I_M \end{aligned} \tag{4.29}$$

For simplifying we in calculations use the notations

$$S = S_H, X = I_{H1}, R = R_H, Y = I_{H2}, U = S_M, Z = I_M.$$

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Anyhow for calculating the value of N_H at endemic we do not use these equations but the main NDM system and get

$$N_H = \frac{\delta_1 X + \delta_2 Y}{b - \mu_H}. \tag{4.30}$$

Assuming kY is small compared with X and U is approximately N_M in $Z' = 0$ we obtain relation $Z = \frac{\beta_M N_M}{\mu_M N_H} X$.

Using this relation in $X' = 0$ we obtain an approximation for S: $S = \frac{\gamma \mu_M N_H^2}{\beta_H \beta_M N_M}$.

Using relation $X' + S' = 0$ we obtain the relation $R = \frac{\gamma}{\omega} X$.

Substituting the relation for R and S into equality $S + X + R + Y = N_H$ we obtain the equation

$$\frac{\gamma \mu_M N_H^2}{\beta_H \beta_M N_M} + X + \frac{\gamma}{\omega} X + Y = N_H \tag{4.31}$$

and substituting the relation for Z into $Y' = 0$ we obtain

$$\alpha Y - \frac{\gamma \beta_H \beta_M c N_M X^2}{\mu_M \omega N_H^2} = 0 \tag{4.32}$$

Solving for N_H^2 from (4.31) and substituting into (4.32) and finally using (4.30) we obtain an equation with only quadratic terms in X and Y:

$$a_{yy} Y^2 + a_{xy} X Y + a_{xx} X^2 = 0 \tag{4.33}$$

$$\begin{aligned} a_{yy} &= \alpha \omega \mu_H + \alpha \omega \delta_2 - \alpha \omega b \\ a_{xy} &= (\alpha \omega + \gamma \alpha) \mu_H + \alpha \omega \delta_1 + (-\alpha \omega - \gamma \alpha) b \\ a_{xx} &= \gamma^2 c \mu_H - \gamma^2 b c \end{aligned} \tag{4.34}$$

Solving (4.34), we obtain relations of type $Y = AX$ and substituting the one with positive A into (4.31) we obtain a second order equation for X without constant term.

Using $Y = AX$ and (4.30) and $S = \frac{\gamma \mu_M N_H^2}{\beta_H \beta_M N_M}$, $R = \frac{\gamma}{\omega} X$, $Z = \frac{\beta_M N_M}{\mu_M N_H} X$ and $U = N_M = 1000$ we obtain all the coordinates for the approximation of the endemic equilibrium.

For the standard values

$$\beta_h = 0.06, \beta_m = 0.05, c = 0.25, \omega = 0.01, \gamma = 0.04, \alpha = 0.04, \mu_m = 0.05$$

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$$b = 0.00006, \mu_H = 0.000055, \delta_1 = 0.000018, \delta_2 = 0.00001$$

and $N_M = 1000$, we obtain

$$S = 7.3, X = 14.1, R = 56.4, Y = 27.1, U = 865.6, Z = 134.4, N_H = 105$$

to be compared with the exact values

$$S = 7.96, X = 15.1, R = 60.1, Y = 28.7, U = 857.5, Z = 142.5, N_H = 112$$

Error analysis

We now consider to determine how good the scaled system could be used to estimate the main system by measuring the maximum error between them at the endemic equilibrium as the initial conditions are varied.

Error made when initial populations are varied

We present tables and graphs to summaries the error analysis of the main NDM−model and the scaled NDM−model when initial populations are varied. We assume a community of 1000 susceptible human beings and 1000 susceptible mosquitoes. First we assumed one re−infective human being is introduced into the community, the results of the dynamics of the human and mosquito population for five years is given in Table 10 and Figure 37.

It is observed from Figure 37 that the solution curves for both the main and the scaled systems attains endemicity in three years. The solution curves of the corresponding classes for systems almost lie in the same line after three years and from Table 10 we estimated the relative error each class makes in the scaled system with respect to the corresponding class in the main system. It is observed from the table that the highest error occurs between the re−infectious classes, which is approximately 0.8%.

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Table 10: **Relative Error made at endemic equilibrium for varying initial populations (1 re−infectious introduced)**

Population classes	Relative error
Susceptible host	0.00008
Infectious host	0.0044
Recovered host	0.0004
Re-infectious	0.0008
Susceptible vector	0.0002
Infectious vector	0.0004

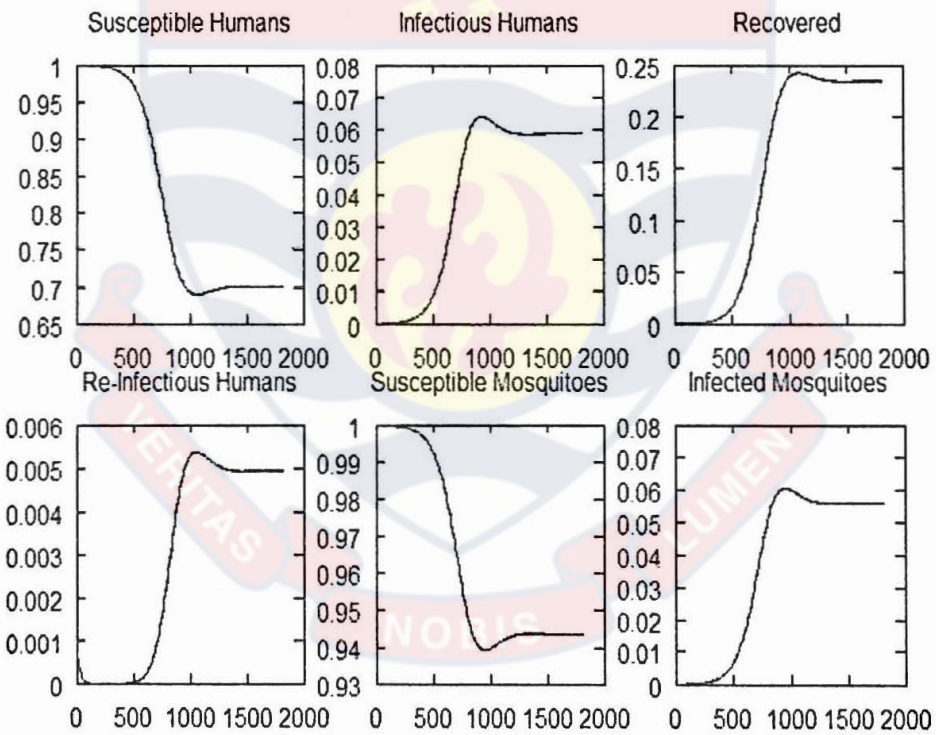


Figure 37: **Solution curves for the scaled and main NDM systems (1 re−infectious introduced)**

There is a pattern of increasing relative error as the number of re−infectious

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humans are being introduced into the community. Table 11 and Figure 38 illustrates the results of 10 re−infectious humans beings introduced into the community.

It is observed from Figure 38 that, the solution curves for both the main and the scaled systems attain endemicity in three years. However, the solution curves of the corresponding classes for the systems in completely different trajectories and from Table 11 we estimated the relative error each class makes in the scaled system with respect to the corresponding class in the main system. It is observed from the table that the highest error occurs between the re−infectious classes, which is approximately 20%.

Table 11: **Relative Error made at endemic equilibrium for varying initial populations (10 re−infectious introduced)**

Population classes	Relative error
Susceptible host	0.0202
Infectious host	0.0970
Recovered host	0.0934
Re-infectious	0.2073
Susceptible vector	0.0034
Infectious vector	0.0948

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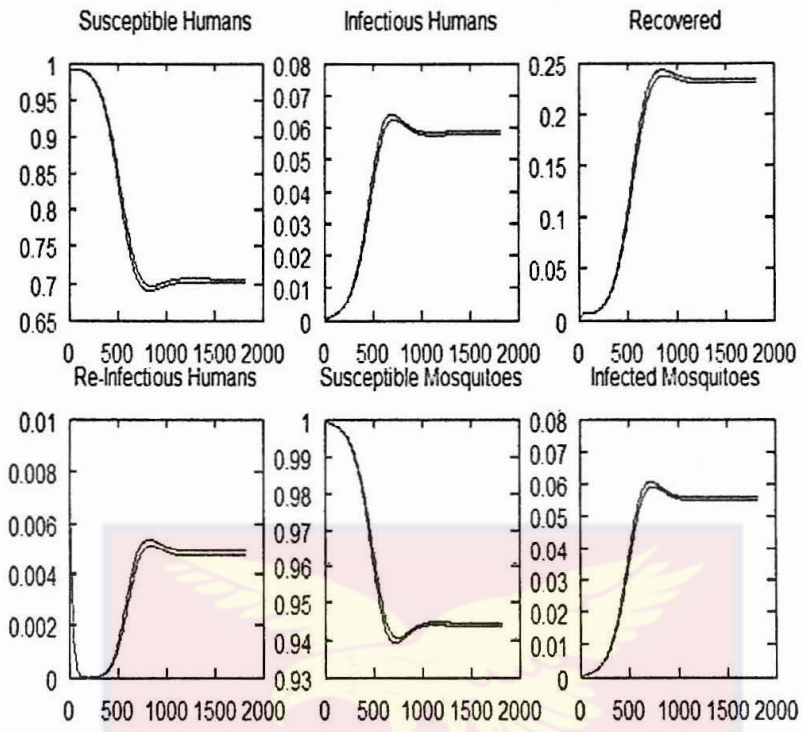


Figure 38: **Solution curves for the scaled and main NDM systems (10 re−infectious introduced)**

Main Results

In this section, we present and prove our main results. Before we do that, we introduce the following notations.

Notations

$$r_x = \frac{\gamma}{\omega+\mu_H}, r_y = \frac{\mu_H+\delta_2}{\omega+\mu_H}, \gamma_1 = \gamma+\mu_H+\delta_1,$$
$$\triangle b = \frac{\delta_2}{1+kc\gamma_1 r_y/\alpha_1 - r_y}, B = \frac{\beta_H \beta_M}{\gamma_1 \mu_M}. \tag{4.35}$$

We have the following main results:

Results for scaled system

The scaled system has a unique endemic equilibrium for $m > \frac{1}{B}$, which is always a global attractor. For $m \leq \frac{1}{B}$, there is no endemic equilibrium and the disease-free equilibrium where $x = r = y = z = 0$ (and thus, $s = u = 1$) is a global

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attractor. When m changes the endemic equilibria form a curve C_e in the phase space parameterized by m.

Results for main system

For $\mu_H < b < \triangle b + \mu_H$, the original NDM−system has an equilibrium on the curve C_e which is a saddle with a four−dimensional stable and a one−dimensional unstable manifold. The unstable manifold is well approximated by the curve C_e. On one side of the stable manifold of the saddle point the total host population slowly decreases to zero and on the other side, the population increases to infinity and getting to disease-free situation after the value of m has passed $\frac{1}{B}$. If $b \leq \mu_H$, the host population will decrease to zero near the curve C_e and if $b > \triangle b + \mu_H$, the host population will go to infinity near the curve C_e, becoming disease-free when m has passed $\frac{1}{B}$.

Calculations of endemic equilibrium for scaled system In this subsection, we examine the model algebraically for the existence and uniqueness of an endemic equilibrium.

Existence of endemic equilibrium solution

We now show how to get the expressions for the curve C_e by solving for the equilibria for (4.12). We also prove that this equilibrium is unique provided it exists. From (4.12) we see that if

$x' = 0$ then

$$x = \frac{\beta_H}{\gamma_1} msz. \tag{4.36}$$

$y' = 0$ then

$$y = \frac{c\beta_H}{\alpha_1} mrz, \tag{4.37}$$

where $\alpha_1 = \alpha + \mu_H + \delta_2$.

$r' + y' = 0$ then

$$r = r_x x - r_y y. \tag{4.38}$$

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$z' = 0$ and using $u = 1 - z$ then

$$z = \frac{\beta_M(x+ky)}{\beta_M(x+ky)+\mu_M}. \tag{4.39}$$

Using these formulae, we deduce an expression also for s. Some calculations give

$$s = \frac{1}{Bm} + C_1 x + C_2 y, \tag{4.40}$$

where $C_1 = \frac{\gamma_1}{\beta_H m} - \frac{kc\gamma_1 r_x}{\alpha_1}$ and $C_2 = \frac{kc\gamma_1 r_y}{\alpha_1} + \frac{k\gamma_1}{\beta_H m}$.

From $s+x+r+y = 1$, using (4.38) and (4.40), we can solve for y as a linear expression of x (that is, $y = L - Qx$) and substituting into (4.37) we obtain a second order equation for x given by

$$\eta_2 x^2 + \eta_1 x + \eta_0 = 0, \tag{4.41}$$

where

$$\begin{aligned}
\eta_2 &= \beta_M(kQ-1)(r_y AQ + Q + r_x A)\\
\eta_1 &= -2\beta_M k r_y ALQ - 2\beta_M kLQ - \mu Q + \beta_M r_y AL - \beta_M k r_x AL + \beta_M L\\
\eta_0 &= L(\beta_M k r_y AL + \beta_M KL + \mu_M),
\end{aligned} \tag{4.42}$$

with $Q = \frac{1+C_1+r_x}{1+C_2-r_y}$, $L = \frac{1-\frac{1}{Bm}}{1+C_2-r_y}$ and $A = \frac{c\beta_H m}{\alpha_1}$. Knowing x, we can easily calculate the other variables at equilibrium. Variable y is calculated from the linear expression in x and r from (4.38) and finally, we have $s = 1-x-r-y$, $u = 1-z$.

Uniqueness of endemic equilibrium solution

We now prove the uniqueness of the endemic equilibrium of the simplified system. Here, we show that there is exactly one endemic equilibrium for the simplified system in the case $m > \frac{1}{B}$ and otherwise no endemic equilibrium.

For our range (see, Tables 12 to 17) of parameters Q must be positive. For y to be positive we need $x < \frac{L}{Q}$. For our range of parameters $L < Q$ and $\frac{L}{Q} < 1$. We show that there is exactly one solution of Equation (4.41) for $0 < x < \frac{L}{Q}$ when $m > \frac{1}{B}$. From $m > \frac{1}{B}$, it follows that $L > 0$. Equation (4.41) is quadratic

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or linear and as the value on the left hand side is positive for $x = 0$ and negative ($-\frac{\beta_M r_x A L^2}{Q^2}$) for $x = \frac{L}{Q}$ it must have exactly one solution in the interval from 0 to $\frac{L}{Q}$. For $m \leq \frac{1}{B}$, we obtain $L \leq 0$ and there is then no positive solution for y if $Q > 0$. Using the x value found for $m > \frac{1}{B}$ and calculating y and inserting these into the expressions for s, r, y, z and u, we see that all of them will be positive and less than one.

The solution considered as a function of m will be a parameter form for the curve C_e. If we have parameters a little bit outside our parameter ranges, then Q might become negative and we have in the case $m < \frac{1}{B}$ the possibility of two endemic equilibria for the simplified system, one stable and the other unstable.

Calculations of the equilibrium for the main NDM−system

In this subsection, we take a look at equilibrium for the main NDM−system. In order to find the equilibrium we let $N_H' = 0$. For this equilibrium, the relations (4.36), (4.37), (4.38), (4.39) and (4.40) are valid. From (4.12), we see that if $N_H' = 0$ then

$$\delta_1 x + \delta_2 y = b - \mu_H. \tag{4.43}$$

From $x + y + r + s = 1$, using (4.38) and (4.40) we obtain

$$(1 + C_1 + r_x)x + (1 + C_2 - r_y)y = 1 - \frac{1}{Bm}. \tag{4.44}$$

Solving (4.43) and (4.44) with respect to x and y, we obtain

$$\begin{aligned} x &= \frac{x_{n1}m + x_{n0}}{x_{d1}m + x_{d0}} \\ y &= \frac{y_{n1}m + y_{n0}}{x_{d1}m + x_{d0}} \end{aligned}, \tag{4.45}$$

where $x_{n1}, x_{n0}, y_{n1}, y_{n0}, x_{d1}, x_{d0}$ do not depend on m and are given by the following expressions

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$$
\begin{aligned}
x_{n1} &= (c\gamma_1 k\mu_H r_y - \alpha_1\mu_M y_y - bc\alpha_1 k r_y + \alpha_1 b r_y + \alpha_1\mu_H + \alpha_1\delta_2 - \alpha_1 b)\beta_H B \\
x_{n0} &= (\gamma_1 k\mu_H B - b\gamma_1 kB - \beta_H\delta_2)\alpha_1 \\
x_{d1} &= (c\delta_1\alpha_1 k r_y - \alpha_1\delta_1 r_y + c\delta_2\gamma_1 k r_x - \alpha_1\delta_2 + \alpha_1\delta_1)\beta_H B \\
x_{d0} &= (\delta_1 k - \delta_2)\alpha_1\gamma_1 B \\
y_{n1} &= (c\gamma_1 k\mu_H r_x - \alpha_1\mu_H r_x - bc\gamma_1 k r_x + \alpha_1 b r_x - \alpha_1\mu_H - \alpha_1\delta_1 + \alpha_1 b)\beta_H B \\
y_{n0} &= (-\gamma_1\mu_H B + b\gamma_1 B + \beta_H\delta_1)\alpha_1
\end{aligned}
\tag{4.46}
$$

By substituting (4.39) into (4.37), we obtain

$$
y(\beta_M(x+ky)+\mu_M) = \frac{c\beta_H}{\alpha_1}\beta_M m(r_x x - r_y y)(x+ky). \tag{4.47}
$$

Calculations show that $\beta_M(x_{n0}+ky_{n0})+\mu_M x_{d0} = 0$ and thus, substituting (4.45) into (4.47), the numerator gives a third order equation in m as follows:

$$
q_3 m^3 + q_2 m^2 + q_1 m = 0, \tag{4.48}
$$

where the coefficients are given by

$$
\begin{aligned}
q_3 &= \beta_H\beta_M c(ky_{n1} + x_{n1})(r_y y_{n1} - r_x x_{n1}) \\
q_2 &= \alpha_1\beta_M k {y_{n1}}^2 + 2\beta_H\beta_M ckr_y y_{n0} y_{n1} + \alpha_1\beta_M x_{n1} y_{n1} + \beta_H\beta_M c r_y x_{n0} y_{n1} \\
&\quad - \beta_H\beta_M ckr_x x_{n0} y_{n1} + \alpha_1\mu_M x_{d1} y_{n1} + \beta_H\beta_M c r_y x_{n1} y_{n0} \\
&\quad - \beta_H\beta_M ckr_x x_{n1} y_{n0} - 2\beta_H\beta_M c r_x x_{n0} x_{n1} \\
q_1 &= 2\alpha_1\beta_M k y_{n0} y_{n1} + \alpha_1\beta_M x_{n0} y_{n1} + \alpha_1\mu_M x_{d0} y_{n1} + \beta_H\beta_M ckr_y {y_{n0}}^2 \\
&\quad + \alpha_1\beta_M x_{n1} y_{n0} + \beta_H\beta_M c r_y x_{n0} y_{n0} - \beta_H\beta_M ckr_x x_{n0} y_{n0} + \alpha_1\mu_M x_{d1} y_{n0} \\
&\quad - \beta_H\beta_M c r_x {x_{n0}}^2.
\end{aligned}
\tag{4.49}
$$

Solving Equation (4.48), we obtain three values of the ratio m between the mosquito and host population at equilibrium. We consider the positive value of m and substituting this value into (4.45) we obtain the values of x and y, after which

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we can calculate the values of the other variables from (4.38), (4.39) and from $s = 1-x-y-r$ and $u = 1-z$. The Equations (4.43) and (4.44) have positive solutions only for $\mu_H < b < \triangle b + \mu_H$.

Approximate bifurcation parameter K

Numerical experiments indicates there is a transcritical bifurcation, so, we will calculate the bifurcation condition K by requiring that the determinant of the Jacobian matrix of the scaled system (neglecting the nonessential parameters) is zero at the disease free equilibrium. The Jacobian matrix is given by

$$\begin{pmatrix} -J_{11} & -J_{12} & -J_{13} & J_{14} \\ J_{21} & -J_{22} & J_{23} & -J_{24} \\ 0 & J_{32} & -J_{33} & J_{34} \\ J_{41} & 0 & J_{43} & -J_{44} \end{pmatrix},$$

where

$$\begin{aligned}
J_{11} &= \beta_H mz + \gamma \\
J_{12} &= \beta_H mz \\
J_{13} &= \beta_H mz \\
J_{14} &= \beta_H m(-y-x-r+1) \\
J_{21} &= \gamma \\
J_{22} &= \beta_H cmz + \omega \\
J_{23} &= \alpha \\
J_{24} &= \beta_H cmr \\
J_{32} &= \beta_H cmz \\
J_{33} &= \alpha \\
J_{34} &= \beta_H cmr \\
J_{41} &= \beta_M(-z+1) \\
J_{43} &= \beta_M k(-z+1) \\
J_{44} &= \beta_M(ky+x)+\mu.
\end{aligned}$$

We now evaluate the disease−free equilibrium, that is, when $(x = 0, r =$

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$0, y = 0, z = 0$). We have

$$\begin{pmatrix} -\gamma & 0 & 0 & \beta_H m \\ \gamma & -\omega & \alpha & 0 \\ 0 & 0 & -\alpha & 0 \\ \beta_M & 0 & \beta_M k & -\mu_M \end{pmatrix}$$

The determinant of this matrix is given as

$$\alpha\omega(\gamma\mu_M - \beta_H\beta_M m)$$

Equating this quantity to zero, we obtain

$$\frac{\beta_H\beta_M m}{\gamma\mu_M} = 1$$

and the bifurcation condition is given by

$$K = \frac{\beta_H\beta_M m}{\gamma\mu_M} \tag{4.50}$$

Since the infectious host and vector leaves their various populations through recovery γ and mortality rate μ_M, we have the duration of infections for each of them to be $\frac{1}{\gamma}$ and $\frac{1}{\mu_M}$ respectively. The quantities β_H and β_M defines the contact rates for the infectious host and infectious vector respectively. At $K = 1$, there is a transcritical bifurcation where the disease-free and endemic equilibrium point collide and exchange stability. Hence, there is stable disease free and unstable endemic when $K < 1$, and unstable disease free and stable endemic when $K > 1$.

Numerical results

Extensive numerical experiments indicate that the endemic equilibrium for the simplified system is a global attractor when it exists and the disease-free equilibrium is globally attracting when there is no endemicity.

From numerical solutions of Equation (4.48) we observe there is exactly one solution when $\mu_H < b < \triangle b + \mu_H$ and calculating the eigenvalues of the Jacobian matrix, we find that the equilibrium is a saddle with one−dimensional unstable set.

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For other systems (like Chitnis (2005) and Ngwa and Shu (2000)) there might be a stable equilibrium on the slow motion curve attracting all solutions. Whether this equilibrium can be reached in realistic time, depends on the concrete parameter values and the initial conditions. In Chitnis (2005), there is sometimes the possibility for more than one equilibrium.

The ratio $K = \frac{\beta_H \beta_M m}{\gamma \mu_M}$ is an important approximative bifurcation parameter, so that there is a transcritical bifurcation for the scaled system at $K = 1$ and endemic solution exists only for $K > 1$. The proportion of susceptible population is approximately $1/K$.

Experiments show that by varying different parameters and initial conditions for the first 3 years, the scaled NDM−model approximates well, to the main NDM−model with a relative error of less than two percent. This situation occurs if the scaled model has an endemic equilibrium with a size not too small (i.e., the value of K is not too near to the bifurcation value) and in addition the sizes of some of the populations are not less than one percent of the total population.

Experiments also show that in the long term the dynamics follows the curve C_e which might have a saddle point on it. Figures 39 and 40 depict the long term behavior of the system.

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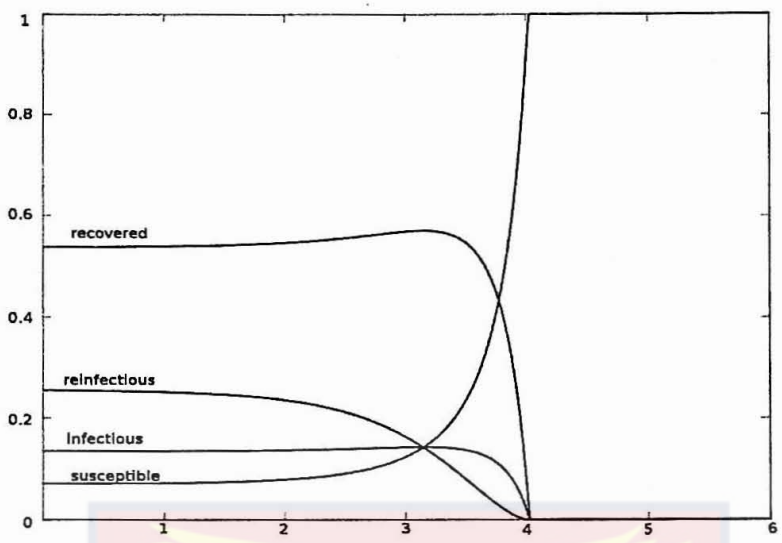


Figure 39: **Relative coordinates on slow motion curve when host population grows**

By using the standard values of the NDM system and varying the b parameter, a saddle point is seen to exist in the interval for b and this is found to be approximately in the range $[0.000055, 0.000065]$. In Figure 39, we see the result of simulations of the NDM system with standard values but parameter $b = 0.00006$ for initial value a little bit above the stable set of the saddle point. The coordinates are in relative host populations. First there is slow movement out from the saddle point along the unstable set showing almost constant values of variables, but growing faster when population grows and then changing slowly until the population is so great that we have the disease-free situation. In this part of the unstable set, the relative size of the susceptible host population, starts from a low value near the saddle point and grows until it approaches a disease free situation.

The relative size of all other host populations decrease until they disappear for disease-free cases. Also, the total host population is growing, implying a decrease in the mosquito-host ratio m, leading to disease-free in the long run.

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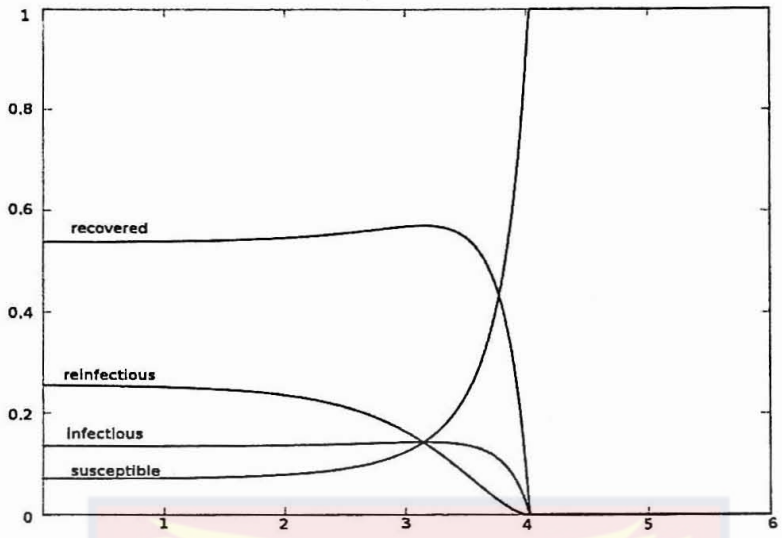


Figure 39: **Relative coordinates on slow motion curve when host population grows**

By using the standard values of the NDM system and varying the b parameter, a saddle point is seen to exist in the interval for b and this is found to be approximately in the range $[0.000055, 0.000065]$. In Figure 39, we see the result of simulations of the NDM system with standard values but parameter $b = 0.00006$ for initial value a little bit above the stable set of the saddle point. The coordinates are in relative host populations. First there is slow movement out from the saddle point along the unstable set showing almost constant values of variables, but growing faster when population grows and then changing slowly until the population is so great that we have the disease-free situation. In this part of the unstable set, the relative size of the susceptible host population, starts from a low value near the saddle point and grows until it approaches a disease free situation.

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In Figure 40, we see the result of simulations of the NDM system with standard values but parameter $b = 0.00006$ for an initial value a little bit below the stable set of the saddle point. We see slow movement to the situation when total population is zero and the mosquito-host ratio m grows to infinity. The relative size of all other host populations, except the re−infectious is decreasing and for small total host population the re−infectious class is dominating. The susceptible host population is always low.

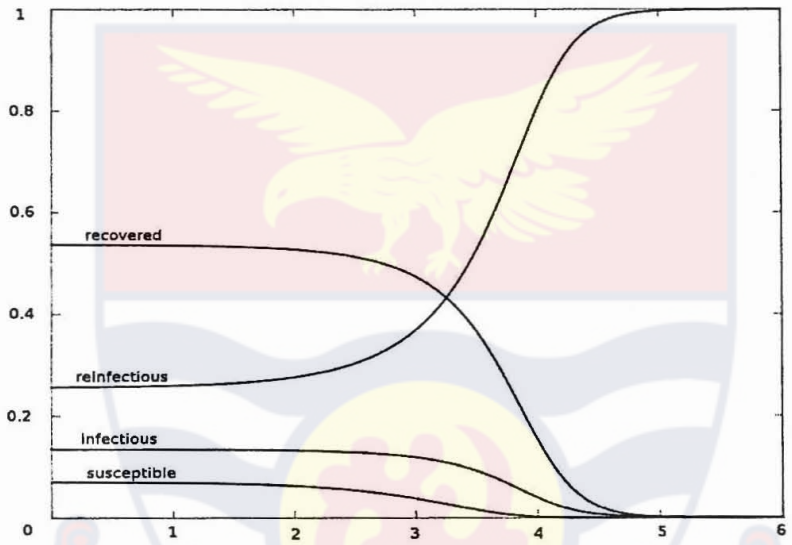


Figure 40: **Relative coordinates on slow motion curve when host population decreases**

In both of these cases there is a good agreement with the curve C_e and a point on that curve corresponds to the sizes of the populations at a given time in the figures.

Review of Some Known Models in Comparison to NDM−Model

We hereby compare the NDM−model with some known models which have important connections with the model we consider. We have chosen three

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very known models. The first one is the historical Ross model which is an SI-model with no recovery class, only two population classes for host and vector. The two other models are the Chitnis (2005) and Ngwa and Shu (2000) models which also have latency classes for both host and vector, but only one infectious class for host. We rewrite all the models in notations corresponding to the notations used in the NDM−model. In the earlier sections of this chapter, we gave a list of ranges for parameters used in known publications and discuss the form of different transition terms between classes, which includes: incidence, latency, recovery and other terms.

Ross model

In this model, we have only four population classes; the susceptible host population S_H and mosquito population S_M and the infectious human population I_H and infectious mosquito population I_M. For details see (Anderson & May, 1991).

We expect the total host and mosquito populations to be constant. Thus, the model is given by the equations for the infectious populations.

$$\begin{aligned} \dot{I}_H &= ab\frac{I_M S_H}{N_H} - \gamma I_H \\ \dot{I}_M &= aC\frac{I_H S_M}{N_H} - \mu I_M \end{aligned} \tag{4.51}$$

The equations for susceptible populations follow from the relations $S'_H = -I'_H$ and $S'_M = -I'_M$.

Parameters γ and μ are the host recovering rate and mosquitos death rate correspondingly. The incidence rates we described before as β_H and β_M are now represented by ab and aC respectively (we use C instead of c in the model described in (Anderson & May, 1991) so as not to get confused with the constant c in the NDM−model) and the meaning of a, b and C are given in the tables of parameter values in Section 2.

Chitnis' model

Here, we introduce a known model of Chitnis (2005) and discuss some

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connections with the NDM−model. In our notation, the equation of the model takes the form:

$$\begin{aligned}
\dot{S}_H &= \Lambda_H + bN_H + \omega R_H - \frac{\beta_H S_H I_M}{N_H} - \mu_H S_H \\
\dot{E}_H &= \frac{\beta_H S_H I_M}{N_H} - \nu_H E_H - \mu_H E_H \\
\dot{I}_H &= \nu_H E_H - \gamma I_H - \mu_H I_H - \delta I_H \\
\dot{R}_H &= \gamma I_H - \omega R_H - \mu_H R_H \\
\dot{S}_M &= b_M N_M - \frac{\beta_M S_M I_H + \tilde{\beta}_M S_M R_H}{N_H} - \mu_M S_M \\
\dot{E}_M &= \frac{\beta_M S_M I_H + \tilde{\beta}_M S_M R_H}{N_H} - \nu_M E_M - \mu_M E_M \\
\dot{I}_M &= \nu_M E_M - \mu_M I_M
\end{aligned} \tag{4.52}$$

We have the following relations between our notations and Chitnis (2005) notations.

For Population Variables:

$S_H = S_h, E_H = E_h, I_H = I_h, R_H = R_h, S_M = S_v, E_M = E_v$ and $I_M = I_v$.

$$N_H = N_h = S_h + E_h + I_h + R_h \text{ and } N_M = N_v = S_v + E_v + I_v.$$

The latency classes E_H and E_M are added in this model.

For the Parameters:

$$\Lambda_H = \Lambda_h, b = \psi_h, b_M = \psi_v, \omega = \rho_h, \nu_H = \nu_h, \nu_M = \nu_v, \gamma = \gamma_h, \delta = \delta_h,$$

$$\beta_H = \frac{\lambda_h N_h}{I_v} = \frac{\sigma_v \sigma_h \beta_{hv} N_h}{\sigma_v N_v + \sigma_h N_h}, \beta_M = \frac{b_v \beta_{vh} N_h}{N_v} = \frac{\sigma_v \sigma_h \beta_{vh} N_h}{\sigma_v N_v + \sigma_h N_h}, \tilde{\beta}_M = \frac{b_v \tilde{\beta}_{vh} N_h}{N_v} = \frac{\sigma_v \sigma_h \tilde{\beta}_{vh} N_h}{\sigma_v N_v + \sigma_h N_h},$$

$\mu_H = f_h(N_h) = \mu_{1h} + \mu_{2h} N_h$ and $\mu_M = f_v(N_v) = \mu_{1v} + \mu_{2v} N_v$.

We have linear transmission terms from latency to infectious and quadratic death terms, except terms which are familiar from NDM−model. We also have the possibility that mosquitoes can get the disease from recovered host. We observe that β_H, β_M and $\tilde{\beta}_M$ are not constant but have complicated form as explained in the earlier sections of this chapter in connection to incidence.

Ngwa and Shu's model

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Here, we introduce a known model of Ngwa and Shu (2000) and discuss some connections with the NDM−model. In our notation, the equations of the model takes the form:

$$\begin{aligned}
\dot{S}_H(t) &= bN_H + \omega R_H + r_H I_H - \mu_H S_H - \frac{\beta_H S_H I_M}{N_H} \\
\dot{E}_H(t) &= \frac{\beta_H S_H I_M}{N_H} - (\nu_H + \mu_H) E_H \\
\dot{I}_H(t) &= \nu_H E_H - (r_H + \gamma + \delta + \mu_H) I_H \\
\dot{R}_H(t) &= \gamma I_H - (\omega + \mu_H) R_H \\
\dot{S}_M(t) &= b_M N_M - \mu_M S_M - \frac{\beta_M S_M I_H}{N_H} - \frac{\tilde{\beta}_M S_M R_H}{N_H} \\
\dot{E}_M(t) &= \frac{\beta_M S_M I_H}{N_H} + \frac{\tilde{\beta}_M S_M R_H}{N_H} - (\nu_M + \mu_M) E_M \\
\dot{I}_M(t) &= \nu_M E_M - \mu_M I_M
\end{aligned} \tag{4.53}$$

We have the following relations between our notations and Ngwa and Shu (2000) notations:

For Population Variables:

$S_H = S_h, E_H = E_h, H_H = I_h, R_H = R_h, S_M = S_v, E_M = E_v$, and $I_M = I_v$

$N_H = N_h = S_h + E_h + I_h + R_h$ and $N_M = N_v = S_v + E_v + I_v$

For parameters:

$b = \lambda_h, \omega = \beta_h, \beta_H = c_{vh} a_v, \nu_H = \nu_h, r_H = r_h, \gamma = \alpha_h, \delta = \gamma_h, b_M = \lambda_v, \nu_M = \nu_v,$ $\beta_M = c_{hv} a_v, \tilde{\beta}_M = \tilde{c}_{hv} a_v$, $\mu_H = f_h(N_h) = \mu_h + \mu_{2h} N_h$ and $\mu_M = f_v(N_v) = \mu_v +$ $\mu_{2v} N_v$.

The model has the same population classes as in Chitnis (2005). The term $r_H I_H$ for the transition from infectious directly to susceptible, with immediate loss of immunity is present in Ross equation but not present in NDM−model nor in Chitnis (2005) model. The incidence terms are the same as in Chitnis (2005) but β_M and β_H do not depend on the population size. They also used logistic death terms.

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Typical Values of Parameters and Their Ranges

Some typical parameter values and the possible ranges of the parameters in the models are given in six tables below. Two of them give values for incidence parameters, two of them give values for transmission parameters between population classes and two tables give birth, death and migration parameter values.

The columns in Tables 12 to 14 refer to different sets of parameter values used in different papers. Standard values of the NDM−model are given in column 2 of the tables. The C06 refers to values in tables taken from Chitnis et al. (2006) and C08 refers to values from Chitnis, Hyman, and Cushing (2008) with different sets for low and high transmission of the disease. N00 refers to values from Ngwa and Shu (2000). ROSS refers to values from Ross model in Anderson and May (1991). The ranges for the parameter values are taken or calculated from the same references.

In Table 12, we see the values for the incidence parameters.

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Table 12: **Incidence Parameters**

Parameters	NDM	C06	C08 Low	C08 High	N00	ROSS
β_H	0.06	0.011	0.0055	0.0088	-	0.055
β_M	0.05	0.48	0.06	0.19	0.4167	0.03
c	0.25	-	-	-	-	-
k	0.12	-	-	-	-	-
σ_h	-	18	4.3	19	-	-
σ_v, a	-	0.6	0.33	0.5	-	0.055
β_{hv}, C	-	0.02	0.022	0.022	-	0.5
β_{vh}, b	-	0.83	0.24	0.48	-	1
$\tilde{\beta}_{vh}, \tilde{C}_{hv}$	-	0.083	0.024	0.048	-	-
m	-	2	4	10	-	25

The parameters β_H and β_M are present in all models. In Chitnis (2005) model, they are not constant and depend on human and mosquito population sizes. In this case, we give the values of β_H and β_M for population sizes corresponding to disease free equilibrium. The following constants $\sigma_h, \sigma_v, \beta_{hv}, \beta_{vh}, \tilde{\beta}_{vh}$ are present in the incidence expressions in Chitnis (2005) model, whiles the constants c and k are present only in the NDM−model. The parameters a, b, C are constants in the incidence expressions in the Ross model. The parameters $C_{vh}, \tilde{C}_{hv}$ are constants in the incidence expressions in the (Ngwa & Shu, 2000) model.

Finally, $m = \frac{\mu_M}{\mu_H}$ is the ratio between the mosquito and human population used in the incidence expressions in the Chitnis et al. (2006) and Ross models. Columns 2 to 7 of Table 13 are the values associated with transition parameters in column 1, (see, Nortey et al. (2008); Ngwa and Shu (2000); Chitnis et al.

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(2006, 2008)).

Table 13: **Transition parameters**

Parameters	NDM	C06	C08 Low	C08 High	N00	ROSS
$\gamma(I_H \rightarrow R_H)$	0.04	0.0037	0.0035	0.0035	0.0124	-
$\omega(R_H \rightarrow S_H)$	0.01	0.015	0.0027	0.00055	0.0146	-
$\alpha(I_{H_2} \rightarrow R_H)$	0.04	-	-	-	-	-
$\nu_H\ (E_H \rightarrow I_H)$	-	0.083	0.10	0.10	0.0833	-
e $\nu_M\ (E_M \rightarrow I_M)$	-	0.1	0.083	0.091	0.10	-
$r_H(I_H \rightarrow S_H)$	-	-	-	-	0.00833	0.011

We have constants for the rates of recovery, loss of immunity and transition from latency to infectious.

In Table 14 we see the values for the birth, death and migration parameters in the following: (see, Nortey et al. (2008); Ngwa and Shu (2000); Chitnis et al. (2006, 2008)).

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Table 14: **Birth, death and migration parameters**

Parameters	NDM	C06	C08Low	C08High	N00	ROSS
Λ_H	-	0.033	0.041	0.033	-	-
b	0.000055	0.000078	0.00011	0.000055	0.000077	-
b_M	0.05	0.4	0.13	0.13	0.04175	-
μ_H	0.000055	0.00012	0.00012	0.00016	-	-
μ_M	0.05	0.17	0.13	0.0.13	-	0.137
δ_1, δ	0.000018	0.00035	0.000018	0.00009	0.0000417	-
δ_2	0.00001	-	-	-	-	-
μ_{1h}	-	0.000042	0.0000088	0.000016	0.000056	-
μ_{1v}	-	0.1429	0.033	0.033	0.0417	-
μ_{2h}	-	0.0000001	0.0000002	0.0000003	-	-
μ_{2v}	-	0.00023	0.00004	0.00002	-	-

The parameters b and b_M are the birth rates for human and mosquito populations correspondingly. The parameters μ_H and μ_M are the death rates for human and mosquito populations correspondingly. The parameters $\delta_1, \delta_2, \delta$ are disease induced death rates for human population. In the Chitnis (2005) and Ngwa and Shu (2000) models, quadratic expressions are used for the death terms, with constants $\mu_{1h}, \mu_{2h}, \mu_{1v}, \mu_{2v}$ in the expressions.

From Tables 15 to 17, we present possible realistic ranges for the various parameters. In Table 15, we see the values for the ranges of the incidence parameters.

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Table 15: **Ranges for incidence parameters**

Parameters	Range
β_H	0-0.27
β_M	0- 0.63
c	0.125-0.5
k	0.06-0.24
σ_h	0.10-50
σ_v, a	0.055-1.0
β_{hv}, C	0.01-0.5
β_{vh}, b	0.072-1.0
$\tilde{\beta}_{vh}$	0.024-0.64
m	2-40

Ranges for $\sigma_h, \sigma_v, \beta_{hv}, \beta_{vh}, \tilde{\beta}_{vh}, a, b, C, m$ are taken directly from Chitnis et al. (2006), Ngwa and Shu (2000) and Anderson and May (1991). The maximal β_H, β_M are calculated from Chitnis et al. (2006). The ranges for c and k are simply taken as the half and double values of the corresponding values in the standard parameter set.

In Table 16, we present ranges for the values of the transition parameters.

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Table 16: **Ranges for transition parameters**

Parameters	Range
$\gamma\,(I_H \rightarrow R_H)$	0.0014-0.04
$\omega\,(R_H \rightarrow S_H)$	0.00055-0.0146
$\alpha\,(I_{H_2} \rightarrow R_H)$	0.01-0.04
$\nu_H\,(E_H \rightarrow I_H)$	0.067-0.20
$\nu_M\,(E_M \rightarrow I_M)$	0.029-0.33
$r_H\,(I_h \rightarrow S_h)$	0.008-0.011

The ranges are obtained as follows:

- γ, lowest value taken from (Chitnis et al., 2008) and upper value taken from (Nortey et al., 2008)
- ω, lowest value taken from (Chitnis et al., 2008) and upper value taken from (Ngwa & Shu, 2000)
- α, lowest value is half the value in (Nortey et al., 2008) and upper value is double the value in (Nortey et al., 2008),
- ν_H and ν_M directly from table in (Chitnis et al., 2008),
- r_H lowest value take from (Ngwa & Shu, 2000) and upper value taken from (Ross, 1911) in (Anderson & May, 1991).

Table 17 depicts the values for the ranges of the birth, death and migration parameters.

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Table 17: **Ranges for birth, death and migration parameters**

Parameters	Range
Λ_H	0.0027-0.27
b	0.000027-0.00014
b_M	0.020-0.4
μ_H	0.00003-0.00009
μ_M	0.02-0.12
δ_1, δ	0-0.0004
δ_2	0.000005-0.000015
μ_{1h}, μ_h	0.000001-0.001
μ_{2h}	0.00000001-0.000001
μ_{1v}, μ_v	0.001-0.1
μ_{2v}	0.000001-0.001

The ranges are obtained as follows:

- Λ_H and b are taken directly from (Chitnis et al., 2008),
- b_M lowest value taken from (Chitnis et al., 2008) and upper value from (Chitnis et al., 2006),
- μ_H taken from the average life expectancy between about 30 to 90 years,
- μ_M taken from average life expectancy between 8 to 50 days,
- δ_1 and δ from (Chitnis et al., 2008),
- δ_2 lowest value is half the value in (Nortey et al., 2008) and upper value is double the value in (Nortey et al., 2008),
- $\mu_{1h}, \mu_{1v}, \mu_{2h}$ and μ_{2v} taken directly from (Chitnis et al., 2008).

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Summary of Parameter Values and Ranges Calculations

In this section, we give a summary of how the typical parameter values and ranges in the immediate past section were calculated from Anderson and May (1991), Chitnis et al. (2006), Chitnis et al. (2008), and Ngwa and Shu (2000).

Parameters from Ngwa and Shu (2000)

We have rewritten the system of Ngwa and Shu (2000) in our notations for comfortable comparison in the equations of (4.53). In the experiments in the paper of (Ngwa & Shu, 2000), the authors used parameter values we describe below and the description of them are done in our notations. The main information for calculating the parameters were given in pages 757-8 using Formulae (8) on page 751 of the paper.

The authors use μ_M (a death rate of mosquitoes) as scaling parameter, but we prefer to interprets them in a more direct way so that the values of the parameters can be compared with the corresponding or similar parameters for other often used systems.

We give their values for death and birth parameters. We have three kinds of death parameters. The death rate for mosquitoes μ_v, the natural death rate for human μ_H and the disease-induced death rate δ.

Parameter μ_v, which is the death rate for small mosquito populations, is taken to be $\mu_v = 1/24 = 0.0417$ corresponding to average life time of 24 days for mosquitoes. The real μ_M could not be calculated as we do not have information about the parameter μ_{2v}.

Parameter μ_h, which is the death rate for small mosquito populations, is taken to be $\mu_H = 0.0000558$. This can be obtain from the formula $\mu_h = \varepsilon\mu_v$, assuming that the value of $\lambda - \varepsilon$ in the text to their Figure 5 to be 0.0005. The real μ_H could not be calculated as we do not have information about the parameter μ_{2h}.

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Parameter δ (in their notation γ_h) is taken to be $\delta = \frac{1.52}{365 \cdot 100} = 0.000042$, corresponding to a death rate of 1.52 percentages per year. This parameter is corresponding to the parameter δ_1 in the NDM−model as Ngwa and Shu (2000) include the death rate induced by re−infected in the natural death rate of human.

There are two births rates in (Ngwa & Shu, 2000), one for human b and the other for mosquitoes b_M. Parameter b (in their notation λ_h) is taken to be $\mu_H = \frac{28}{365 \cdot 1000} = 0.000077$, corresponding to a death rate of 2.8 percentages per year. Parameter b_M (in their notation λ_v) is taken to be $b_M = 0.04175$, a little bit greater than the death rate μ_M.

We have five kinds of transition parameters in (Ngwa & Shu, 2000), parameter for loss of immunity ω, parameters for recovering r_H and γ of human infective, two parameters for latency ν_H and ν_M for human and mosquitoes correspondingly.

Parameter ω (in their notations β_h) is taken to be $\omega = 0.0146$, corresponding to an average time of 68.5 days for loosing immunity. Parameter r_H (in their notations r_h) is taken to be $r_H = 0.00833$, corresponding to an average time of 120 days for recovering. Those human who recovered at this parameter rate do not have immunity so they move to the susceptible class immediately. Parameter γ (in their notations α_h) is taken to be $\gamma = 0.0125$, corresponding to an average time of 80 days for recovering. Those humans who recover at this parameter rate have some temporal immunity, so they move to the recovered class.

Parameter ν_H (in their notations ν_h) is taken to be $\nu_H = 0.08333$, corresponding to average latency of 12 days for humans. Parameter ν_M (in their notations ν_v) is taken to be $\nu_M = 0.01$, corresponding to average latency of 10 days for mosquitoes.

From the incidence parameters only β_M can be calculated from given information. It takes the value $\beta_M = c_{hv} a_v = b\mu_v = \frac{10}{24} = 0.4167$. We were unable

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to calculate the values of β_H and $\tilde{\beta}_M$ as the parameters $a_v, c_{hv}, \tilde{c}_{hv}, c_{vh}, \mu_{2h}$ and μ_{2v} were lumped in the parameter ξ and there was no information about them.

Thus, we have found all parameters in the Equations (4.53), except β_H and $\tilde{\beta}_M$ and the death rates μ_H and μ_M. The parameter $\tilde{\beta}_H$ corresponds to incidence parameter $k\beta_M$ in the the NDM−model as the re−infective are included in the recovered in model of Ngwa and Shu (2000).

Parameters for Ross (1911) from Anderson and May (1991)

The Ross (1911) model as described in Anderson and May (1991) uses only four essential parameters. The recovery rate for human γ, the death rate for mosquitoes μ_M and the incidence rates β_H and β_M. The incidence rate β_H is a product of the parameters a and b, and β_M is a product of parameters a and c. The quantities a, b and c are well described in (Anderson & May, 1991). The parameters we calculate from data that are given in Figure 14.22 and 14.23, and $a = 0.055, b = 1$ and $c = 0.5$ are taken from pages 404 and 409.

Thus,

- $\gamma = \frac{4}{365} = 0.011$ which takes the average time for recovering is here assumed to be 90 days.
- $\mu_M = \frac{50}{365} = 0.137$ which takes the average life expectancy for mosquitoes is taken to be 7 days.

The corresponding values of β_H and β_M in Anderson and May (1991) were calculated as follows:

- $\beta_H = ab = \frac{20}{365} \cdot 1 = 0.0548$
- $\beta_M = ac = \frac{20}{365} \cdot 0.5 = 0.027$

As their standard value of parameter m (which is the ratio of mosquito population to host population) we consider the average value of 25 used in Figure 14.23 in

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(Anderson & May, 1991). (We here wish also to inform that Anderson and May (1991) have an interesting list of life expectancy of different mosquito types).

Parameters from Chitnis et al. (2006)

The values of all parameters in the case C06 are taken directly from Table 4.1 in (Chitnis et al., 2006) except the incidence parameters β_M and β_H and death rates μ_H and μ_M which we calculated using the following formulae:

- $\beta_H = \frac{\sigma_v \sigma_h \beta_{hv}}{\frac{\sigma_v N_v^*}{N_h^*} + \sigma_h}$
- $\beta_M = \frac{\sigma_v \sigma_h \beta_{vh}}{\frac{\sigma_v N_v^*}{N_h^*} + \sigma_h}$
- $\mu_H = \mu_{1h} + \mu_{2h} N_h^*$
- $\mu_M = \mu_{1v} + \mu_{2v} N_v^*$,

where N_h^* is the host population at disease-free equilibrium and where N_v^* is the mosquito population at disease-free equilibrium got from simulations of (Chitnis et al., 2006) system with parameter values from the table indicated.

Parameters from Chitnis et al. (2008)

The values for parameters in cases Chitnis low and high endemic baselines are all taken from Table 3 in Chitnis et al. (2008). The corresponding values of β_M and β_H in NDM−model were calculated as follows:

- $\beta_H = \frac{\sigma_v \sigma_h \beta_{hv}}{\frac{\sigma_v N_v^*}{N_h^*} + \sigma_h}$
- $\beta_M = \frac{\sigma_v \sigma_h \beta_{vh}}{\frac{\sigma_v N_v^*}{N_h^*} + \sigma_h}$.

Calculations of incidence parameter ranges

Table 18 explains how incidence parameter ranges were obtained from (Anderson & May, 1991), (Chitnis et al., 2006) and (Chitnis et al., 2008).

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Table 18: **Incidence parameters ranges calculations**

Incidence Parameters	Description on how it was obtained
β_H	Using the parameter ranges in Chitnis et al. (2008) in Table 3 and $\beta_H = \frac{\sigma_v \sigma_h \beta_{hv}}{\sigma_v \frac{N_v^*}{N_h^*} + \sigma_h}$
β_M	Using the parameter ranges in Chitnis et al. (2008) in Table 3 and $\beta_M = \frac{\sigma_v \sigma_h \beta_{vh}}{\sigma_v \frac{N_v^*}{N_h^*} + \sigma_h}$
c	One-half the original value is added to original value for upper boundary and also subtracted from the original value for lower boundary.
k	One-half the original value is added to original value for upper boundary and also subtracted from the original value for lower boundary.
σ_h	Taken from Chitnis et al. (2008) Table 3.
σ_v, a	Lower boundary from Anderson and May (1991) page 409 and upper boundary from Chitnis et al. (2008), Table 3.
β_{hv}, C	Lower boundary from Chitnis et al. (2008), Table 3 and upper boundary from Anderson and May (1991) page 409
β_{vh}, b	Lower boundary from Chitnis et al. (2008), Table 3 and upper boundary from Anderson and May (1991) page 409
$\tilde{\beta}_{vh}$	Taken from Chitnis et al. (2008) Table 3.
m	Lower boundary from Chitnis et al. (2006), Figure 4.2 and upper boundary from Anderson and May (1991) page 404, Figure 14.23

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Conclusion

Most mathematical models of malaria can be divided into two classes. Those scaled, assuming total host and vector population constant, and those allowing at least the host population to change. In general the change in the size of the total host populations are slow compared with the other developments and then the system can be very well approximated by a scaled system. An exception is when the migration factor is greater as in Chitnis et al. (2006) and Chitnis et al. (2008), and then affecting essentially the dynamics for some initial conditions. Here, we assumed the mosquito population to be constant and thus did not consider the interesting question of oscillating mosquito population.

In scaled models, we have at least one equilibrium that is the disease-free situation. Disease-free equilibrium points are steady state solutions where there is no malaria in either the human or mosquito populations.

In most models for some parameter ranges we also have endemic equilibria, where the disease persists in the population (all state variables are positive). In some models (and this is usual in models with non-linear incidence terms) we can have more than one endemic equilibrium.

In the model where the host population changes, the motion can often be divided into fast motion and slow motion. First, there is a fast motion as a result of coming near to an attracting point of a corresponding scaled system with constant host populations (often about 3 years). This fast motion is often very well approximated by the solution curve of the corresponding scaled system. After that there is a slow motion along approximately a curve of endemic equilibria for scaled systems for different total host populations. On this curve, the system with changing host population can have one or more equilibria which are saddles or attractors, or the motion will increase the host population to infinity or decrease it to zero. In reality only a small part of this curve is seen to be realized

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as it might take millions of days to move far away.

The equilibrium points are usually either stable or saddle points. If they are stable they have a basin of attraction determining global behavior. In the scaled Ross model and NDM−model and the full Ngwa and Shu (2000) model we have only two possibilities. Either there is no endemic and the disease-free is a global attractor and we have no possibility for endemic or there is endemic and the endemic equilibrium is attracting everything except the disease-free equilibrium, so we will reach endemic independently of the initial situation.

In other models there is the possibility that both disease-free and endemic equilibria are stable. Between the stable equilibria there is usually a saddle endemic equilibria, determining the boundary of the basins of attractions of equilibria. In these cases it depends on the initial conditions whether we obtain endemic or disease-free situation.

Usually, the endemic equilibrium appears at a transcritical bifurcation at the disease-free equilibrium. This is the case for the scaled Ross and NDM−model and full Ngwa and Shu (2000) model and usually also for the Chitnis et al. (2006) model. There is also a possibility for saddle-node bifurcations where two endemic equilibria arise suddenly, one stable and the other of a saddle type. This can happen in the Chitnis et al. (2006) model and is usually in models with non-linear incidence. In Chitnis et al. (2006), this sometimes happens on the slow motion curve but never for the scaled versions. In the NDM−model the existence of a real endemic equilibria depends approximately on the value of a quantity of four essential parameters and the ratio between mosquitoes and host populations and this is also usual for many other models.

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CHAPTER FIVE

ROSS MODEL AND SEASONAL MOSQUITO BIRTH RATE

Introduction

In this chapter, we study the effect of seasonal variations (wet and dry seasons) on the spread of malaria. Literature indicates that, in Ghana malaria is endemic and perennial in all parts of Ghana, with seasonal variations that are more pronounced in the north. Ghanas entire population of 24.2 million (2010 Census) is at risk of malaria infection, but children under five years of age and pregnant women are at higher risk of severe illness due to lowered immunity. Transmission tends to be less intense in large urban centers (Ghana malaria report 2013). A research was conducted on "Patterns and seasonality of malaria transmission in the forest-savannah transitional zones of Ghana" by Dery et al. (2010). They reported in their discussions that, mosquito(Anopheles gambiae and Anopheles funestus) abundance was greatly influenced by rainfall and the abundance of both vectors correlated with monthly rainfall patterns, and the prevalence of malaria was highest during the rainy seasons (May-October). Another group (Kasasa et al., 2013) also examined the "Spatio-temporal malaria transmission patterns in Navrongo demographic surveillance site, northern Ghana". They indicated in their results that for the entire research period, mean biting rates per month varied with seasonal changes. For both species (Anopheles gambiae and Anopheles funestus), most bites were observed during the wet season (July to November). Highest bites occurred in the month of September for all the three years. During the dry period of January to April, fewer monthly bites were recorded. Mosquitoes in the area became more abundant after the first three months of

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the rainy season. Similar spatio-temporal variation has been observed in coastal Kenya (Mbogo et al., 2003), in Kilombero valley in Tanzania (Drakeley et al., 2003), in some selected Ugandan villages (Okello et al., 2006) and in a low transmission zone in Sudan (Hamad et al., 2002).

Since the mosquito population varies periodically, we extend the simple Ross model (Figure 41) by introducing a seasonal variation into the birth rate of the mosquito population. We however, refer to several papers in the literature which discuss the role of seasonal variations in malaria modeling and other disease models (Dembele, Friedman, & Yakubu, 2009; Hoshen & Morse, 2004; Ma & Ma, 2006; Wang & Zhao, 2008). For example, Greenhalgh and Moneim (2003) studied an SIRS epidemic model with a general seasonal variation in the contact rate; their model was motivated by diseases such as measles, chickenpox, mumps, and rubella.

Derivation of Ross Model

In this section, we give a detail derivation of Ross model (Figure41), describing the transmission of malaria. The model divides the human population into 2 classes: susceptible, S_H, and infectious, I_H. People enter the susceptible class, either through birth (at a constant per capita rate) or through immigration (at a constant rate). When an infectious mosquito bites a susceptible human, there is some finite probability that the parasite (in the form of sporozoites) will be passed on to the human and the person will move to the infectious class. After some time, the infectious humans recover and move back to the susceptible. The total human population is assumed to be constant.We divide the mosquito population into two classes: susceptible, S_M, and infectious, I_M. Female mosquitoes (we do not include male mosquitoes in our model because only female mosquitoes bite animals for blood meals) enter the susceptible class through birth. The parasite (in the form of gametocytes) enters the mosquito,

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with some probability, when the mosquito bites an infectious human and the mosquito moves from the susceptible to the infectious class. The mosquito remains infectious for life. Mosquitoes leave the population through a per capita density-dependent natural death rate.

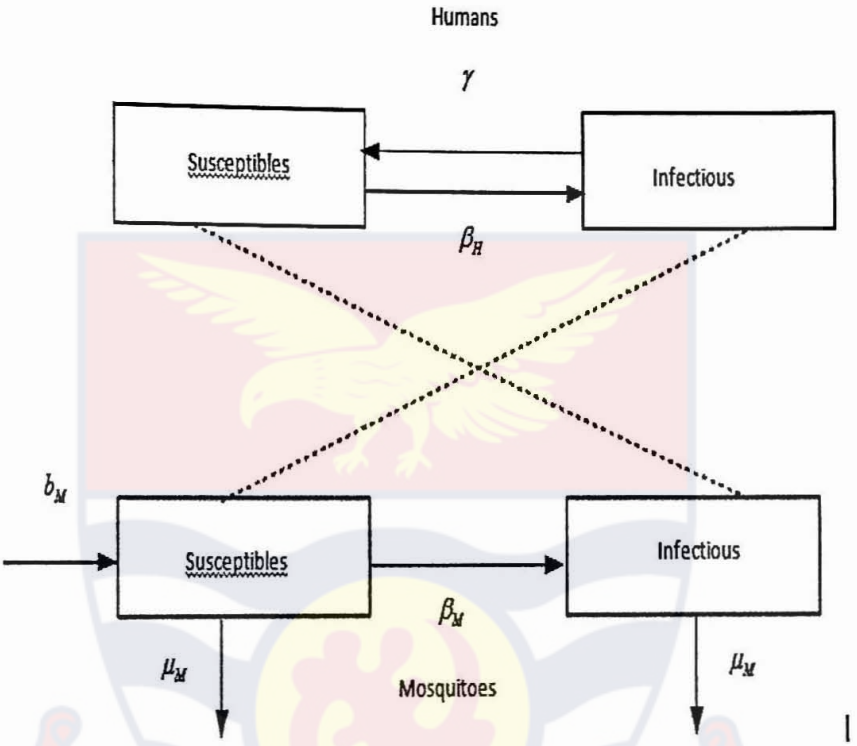


Figure 41: **Flow diagram of the Ross malaria model**

The equations for the malaria model, Figure 41 are shown in Equation (5.1). The state variables of the model are shown in Table 2 and the parameters used in the model are shown in Tables 3, 4, 5, 6 and 7. All parameters are assumed to be strictly positive.

$$\begin{aligned}
\dot{S}_H &= \frac{-\beta_H S_H I_M}{N_H} + \gamma I_H \\
\dot{I}_H &= \frac{\beta_H S_H I_M}{N_H} - \gamma I_H \\
\dot{S}_M &= b_M N_M - \frac{\beta_M S_M I_H}{N_H} - \mu_M S_M \\
\dot{I}_M &= \frac{\beta_M S_M I_H}{N_H} - \mu_M I_M
\end{aligned} \tag{5.1}$$

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We note that in this model, β_H corresponds to the product of rate of bitting on humans by a single mosquito and the proportion of infectious bites on humans that produces a patent infection in the Ross basic model. The β_M corresponds to product of rate of bitting of humans by a single mosquito and the proportion of bites susceptible mosquitoes on infected people that produce a patent infection in the Ross basic model.

To analyse the malaria model (5.1) more easily, we work with fractional quantities instead of actual populations by scaling the population of each class by the total species population. We let,

$$s = \frac{S_H}{N_H}, x = \frac{I_H}{N_H}, u = \frac{S_M}{N_M}, z = \frac{I_M}{N_M}$$

$$\dot{N}_M = \dot{S}_M + \dot{I}_M = b_M N_M - \mu_M(S_M + I_M) = (b_M - \mu_M)N_M$$

We have

$$\dot{s} = \frac{\dot{S}_H N_H - S_H \dot{N}_H}{N_H^2} = \frac{\dot{S}_H}{N_H} = \frac{-\beta_H S_H I_M}{N_H^2} + \frac{\gamma I_H}{N_H} = -\beta_H s z \frac{N_M}{N_H} + \gamma x \tag{5.2}$$

$$\dot{x} = \frac{\dot{I}_H N_H - I_H \dot{N}_H}{N_H^2} = \frac{\dot{I}_H}{N_H} = \frac{\beta_H S_H I_M}{N_H^2} - \frac{\gamma I_H}{N_H} = \beta_H s z \frac{N_M}{N_H} - \gamma x \tag{5.3}$$

$$\dot{u} = \frac{\dot{S}_M N_M - S_M \dot{N}_M}{N_M^2} = \frac{\dot{S}_M}{N_M} - \frac{\dot{N}_M}{N_M} u = \frac{1}{N_M}(b_M N_M - \frac{\beta_M S_M I_H}{N_H} - \mu_M S_M) - (b_M - \mu_M)u$$
$$= b_M - \beta_M u x - b_M u \tag{5.4}$$

$$\dot{z} = \frac{\dot{I}_M N_M - I_M \dot{N}_M}{N_M^2} = \frac{\dot{I}_M}{N_M} - \frac{\dot{N}_M}{N_M} z = \frac{1}{N_M}(\frac{\beta_M S_M I_H}{N_H} - \mu_M I_M) - (b_M - \mu_M)z \tag{5.5}$$
$$= \beta_M u x - b_M z$$

and the transform system is given as

$$\begin{aligned} \dot{s} &= -\beta_H s z \tfrac{N_M}{N_H} + \gamma x \\ \dot{x} &= \beta_H s z \tfrac{N_M}{N_H} - \gamma x \\ \dot{u} &= b_M - \beta_M u x - b_M u \\ \dot{z} &= \beta_M u x - b_M z. \end{aligned} \tag{5.6}$$

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We now reduced the transformed system into two−dimensional system. Since $s+x=1$, $u+z=1$ and $m=\frac{N_M}{N_H}$, we have

$$\begin{aligned}\dot{x} &= \beta_H m z(1-x)-\gamma x \\ \dot{z} &= \beta_M x(1-z)-b_M z\end{aligned} \tag{5.7}$$

Analysis of Ross Model

The Ross model (5.7) has zero isoclines to be $z=\frac{\gamma x}{\beta_H m(1-x)}$ and $x=\frac{b_M z}{\beta_M(1-z)}$. Solving these two zero isoclines simultaneously, we obtain two equilibrium points at $(0,0)$, which is disease−free and at $\left(\frac{\beta_H\beta_M m-b_M\gamma}{\beta_M(\beta_H m+\gamma)}, \frac{\beta_H\beta_M m-b_M\gamma}{\beta_H m(\beta_M+b_M)}\right)$, which is endemic. To check the stability of these equilibria, we use the sign analysis method as described in (Akoto et al., 2012).

We start by plotting the isoclines as shown in Figure 42 and we can see that the isoclines intersect at the two equilibria and divide the xz−plane into four regions. To the left of $x'=0$, the sign of x' is negative and to the right is positive. For the upper of $z'=0$, the sign of z' is negative and the bottom is positive. We describe the regions as follows

- Region 1 is where $z'<0<x'$
- Region 2 is where $z', x'>0$
- Region 3 is where $z', x'<0$
- Region 4 is where $x'<0<z'$

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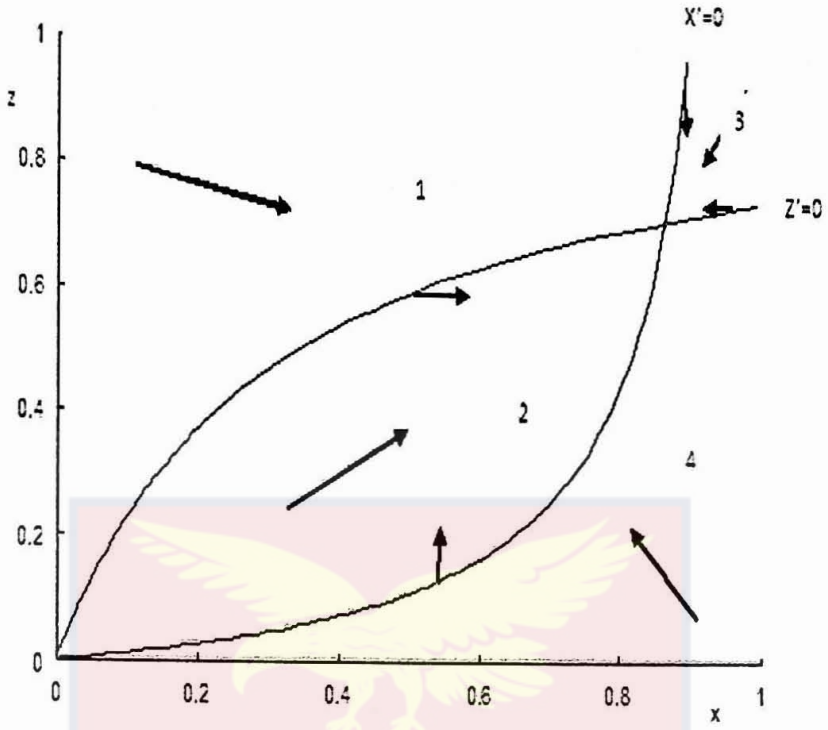


Figure 42: **Isoclines depicting** $\omega > 0$

In Region 1 the $x-$coordinate of the trajectory is increasing and the $z-$coordinate is decreasing. Thus, the trajectory cannot remain in the region, it has to hit the isocline $z' = 0$ or isocline $x' = 0$ entering Region 2 or Region 3 respectively after some time or hit the endemic point directly, but cannot leave Region 2 since the x and z coordinates of the trajectory are both increasing.

In Region 4 the $x-$coordinate of the trajectory is decreasing and the $z-$coordinate is increasing. Thus the trajectory cannot remain in the region, it has to hit the isocline $x' = 0$ or $z' = 0$ entering Region 2 or Region 3 respectively after some time or hit the endemic point directly, but cannot leave region 2 since the x and z coordinates of the trajectory are both increasing.

In Region 2, the $x-$ and $z-$coordinates are increasing and the trajectory cannot escape from Region 2 against the direction field on the boundaries $x' = 0$ and $z' = 0$. In Region 2, all trajectories can be attracted only to the endemic

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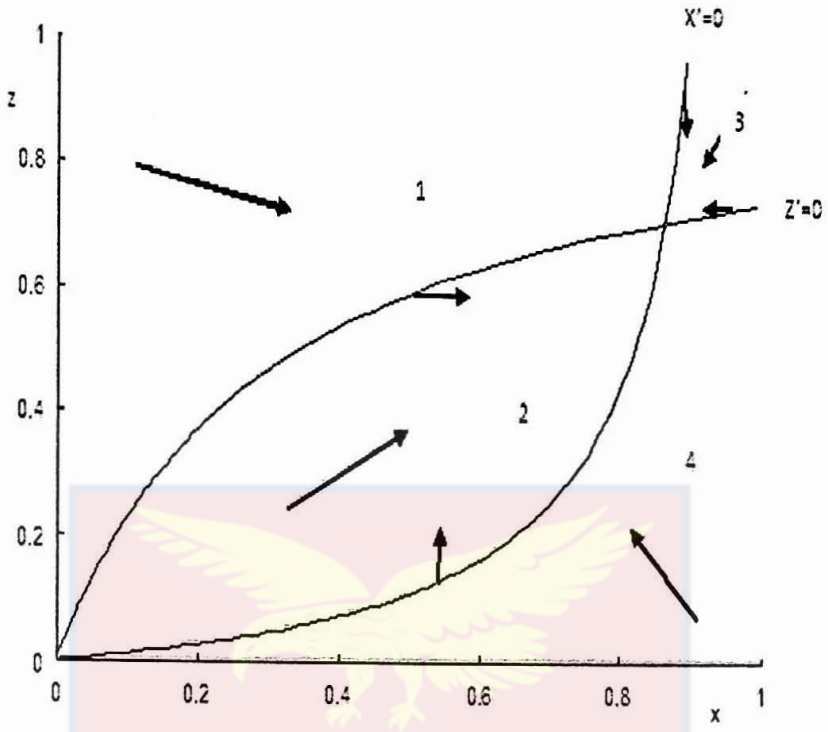


Figure 42: **Isoclines depicting $\omega > 0$**

In Region 1 the $x-$coordinate of the trajectory is increasing and the $z-$coordinate is decreasing. Thus, the trajectory cannot remain in the region, it has to hit the isocline $z' = 0$ or isocline $x' = 0$ entering Region 2 or Region 3 respectively after some time or hit the endemic point directly, but cannot leave Region 2 since the x and z coordinates of the trajectory are both increasing.

In Region 4 the $x-$coordinate of the trajectory is decreasing and the $z-$coordinate is increasing. Thus the trajectory cannot remain in the region, it has to hit the isocline $x' = 0$ or $z' = 0$ entering Region 2 or Region 3 respectively after some time or hit the endemic point directly, but cannot leave region 2 since the x and z coordinates of the trajectory are both increasing.

In Region 2, the $x-$ and $z-$coordinates are increasing and the trajectory cannot escape from Region 2 against the direction field on the boundaries $x' = 0$ and $z' = 0$. In Region 2, all trajectories can be attracted only to the endemic

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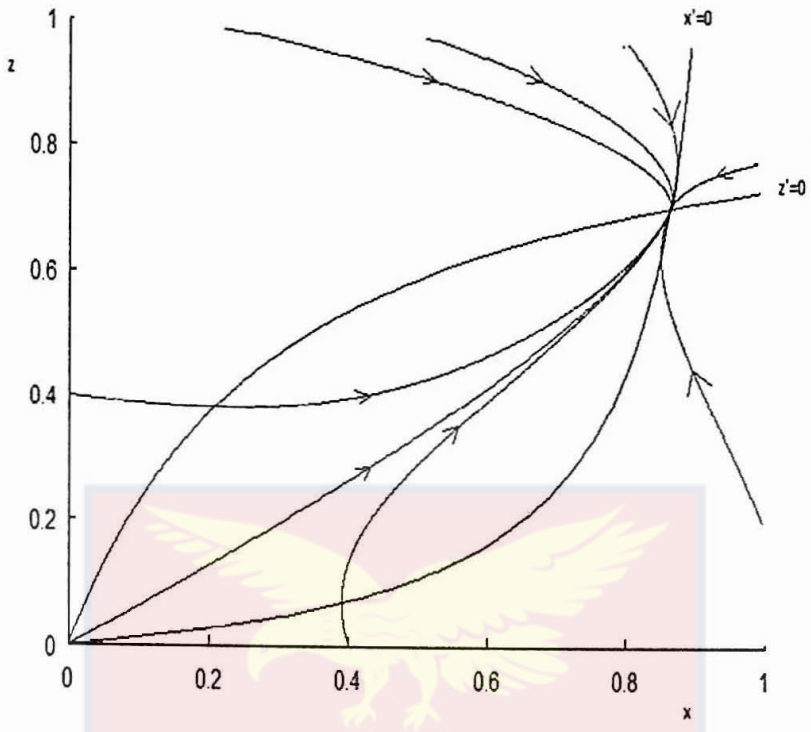


Figure 43: **Phase portrait of Ross model**

In the second case, if the quantity ω is relatively small even though still positive, the z−isocline will have the shallow form depicted in Figure 44 and the equilibrium is likely going to move towards the origin. In this case, small changes in mosquito density or the biting rate are more likely to result in substantial changes in the proportion of humans infected. The third case is when ω is less than zero, then the zero isoclines do not intersect and all the trajectories are directed towards the origin and the disease can not maintain itself, see Figure 45.

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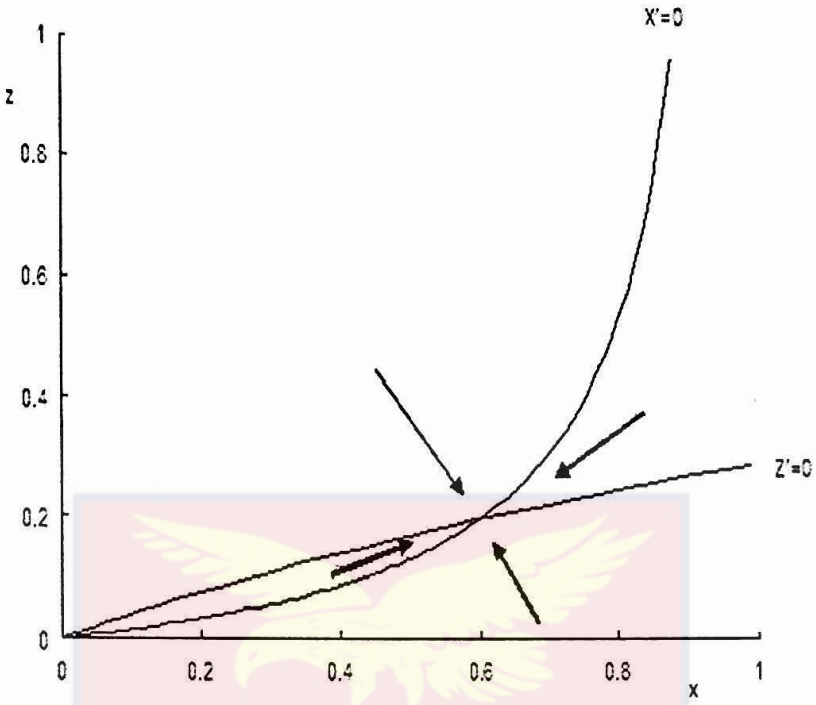


Figure 44: **Isoclines depicting relatively small ω**

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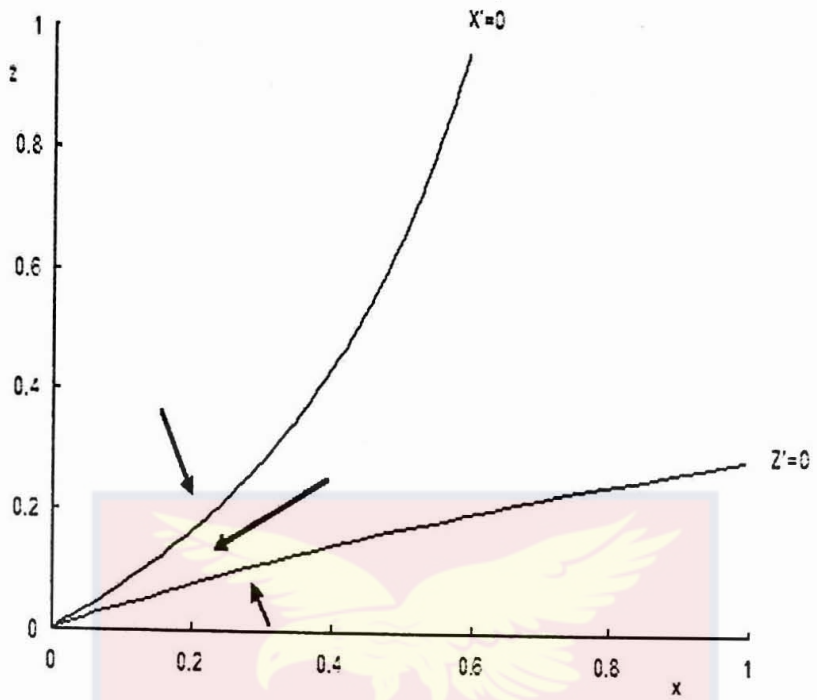


Figure 45: **Isoclines depicting $\omega < 0$**

Bifurcation analysis of Ross model

Here, we illustrate the behavior of the endemic and the disease−free equilibria by using bifurcation analysis. As stated earlier the Ross system has two equilibria one at $(0,0)$ and the other at $\left(\frac{\beta_H\beta_M m-b_M\gamma}{\beta_M(\beta_H m+\gamma)}, \frac{\beta_H\beta_M m-b_M\gamma}{\beta_H m(\beta_M+b_M)}\right)$. For $\omega = 0$ these equilibria coincide otherwise they are different. For $\omega > 0$ the equilibrium at $(0,0)$ is unstable and the equilibrium at $\left(\frac{\beta_H\beta_M m-b_M\gamma}{\beta_M(\beta_H m+\gamma)}, \frac{\beta_H\beta_M m-b_M\gamma}{\beta_H m(\beta_M+b_M)}\right)$ is stable. For $\omega < 0$ the equilibrium at $(0,0)$ is stable and the equilibrium at $\left(\frac{\beta_H\beta_M m-b_M\gamma}{\beta_M(\beta_H m+\gamma)}, \frac{\beta_H\beta_M m-b_M\gamma}{\beta_H m(\beta_M+b_M)}\right)$ is unstable, but really does not exits. For $\omega = 0$, the only equilibrium is $(0,0)$ and is a shunt. See Figure 46 for summarizing in a bifurcation diagram. The full line in the diagram denotes stable equilibrium and the broken line denote unstable equilibrium.

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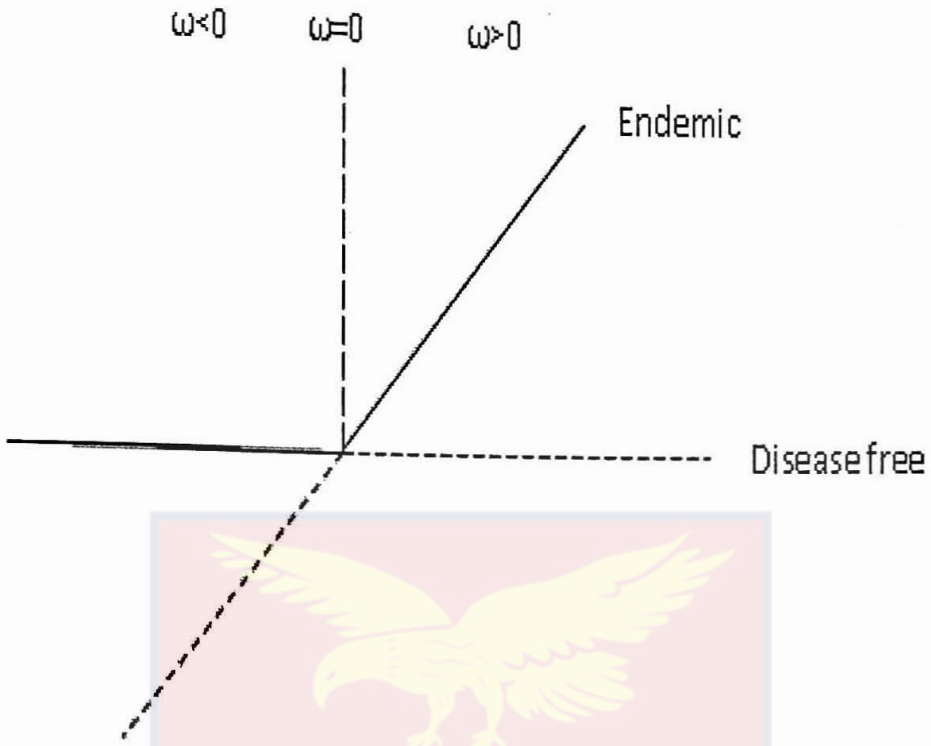


Figure 46: **Bifurcation diagram showing behaviour of equilibria**

Ross Model with Seasonal Mosquito Birth Rate (Periodic Model)

The Ross model gives a good overview of the dynamics of malarial infection, particularly the basic factors that underlie 'stable' and 'unstable' malaria. However, many of its predictions are extremely different from reality. One notable prediction is that if an area has endemic malaria, it means the area attains a certain value of prevalence of human infection throughout the year. It is clear that in reality the malaria prevalence is associated with the abundance of mosquito population, which is seasonal. From the work of Dery et al. (2010) and Kasasa et al. (2013), the mosquito population at any time in the year depends on the amount of rainfall. So we divide the year into three seasons, that is, the dry season (November to April) that takes half of the year, T_1, with constant mosquito birth rate b_1, the heavy wet season (May to August) that covers four months, T_2,

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with constant mosquito birth rate b_2 and the light wet season (September to October) that takes covers two months, T_3, with a linearly declining mosquito birth rate that depends on time and the previous mosquito birth rates b_1 and b_2. This start with b_2 from the heavy wet season and ends with b_1 at the beginning of the dry season.

We start here by describing the dynamics of total mosquito population over a period of one year and their development from one season to another. This will include calculating mosquito population in the dry season, heavy wet season and light wet season. We use a modified system of System (5.1), where the parameter b_M is equal to b_1 during the dry season, b_2 during the heavy wet season and $b_3(t)$ during the light wet season.

Mosquito population in the dry season

The differential equation for mosquito population during the dry season is given by

$$\dot{N}_M = (b_1 - \mu_M)N_M,\ 0 \leq t \leq T_1,\ b_1 < \mu_M. \tag{5.8}$$

By separation of variables, we have a solution

$$N(t) = N_0 e^{(b_1-\mu_M)t},$$

where N_0 is the mosquito population at the beginning of the dry season. The mosquito population at the end of the dry season is given as

$$N_1 = N_0 e^{(b_1-\mu_M)T_1}. \tag{5.9}$$

Mosquito population in the heavy wet season

The differential equation for mosquito population during the heavy wet season is given by

$$\dot{N}_M = (b_2 - \mu_M)N_M,\ 0 \leq t \leq T_2,\ b_2 > \mu_M. \tag{5.10}$$

By separation of variables, we have a solution

$$N(t) = N_1 e^{(b_2-\mu_M)t}.$$

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The mosquito population at the end of the heavy wet season is given as

$$N_2 = N_1 e^{(b_2-\mu_M)T_2}. \tag{5.11}$$

Mosquito population in the light wet season

The differential equation for mosquito population during the light wet season is given by

$$\dot{N}_M = (b(t)-\mu_M)N_M,\ 0 \le t \le T_3, \tag{5.12}$$

where

$$b(t) = b_2 + (b_1 - b_2)t/T_3.$$

By separation of variables, we have a solution

$$N(t) = N_2 e^{B(t)-\mu_M t},$$

where

$$B(t) = b_2 t + (b_1 - b_2)t^2/2T_3.$$

The mosquito population at the end of the light wet season is given as

$$N_3 = N_2 e^{[(b_1+b_2)/2-\mu_M]T_3}. \tag{5.13}$$

Now, if we require $N_3 = N_0$ then we obtain

$$b_1T_1 + b_2T_2 + (b_1+b_2)T_3/2 = \mu_M(T_1+T_2+T_3).$$

Finally, knowing b_1 we can calculate b_2 from

$$b_2 = [\mu_M T_1 - b_1(T_1 + T_3/2)]/(T_2 + T_3/2). \tag{5.14}$$

The mean mosquito population

In this subsection, we want to calculate the mean mosquito population over the year. To do this, we need to find the mosquito population by integrating the population over a year and divide by the length of the year. We start by integrating the population over the periods.

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By integrating over the period of the dry season, we obtain

$$\int_0^{T_1} N_0 e^{(b_1-\mu_M)t}dt = \frac{N_0}{b_1-\mu_M}[e^{(b_1-\mu_M)T_1}-1] = I_1. \tag{5.15}$$

Population at the end of the first period is

$$N_1 = N_0 e^{(b_1-\mu_M)T_1}.$$

By integrating over the period of the heavy wet season, we obtain

$$\int_0^{T_2} N_1 e^{(b_2-\mu_M)t}dt = \frac{N_1}{b_2-\mu_M}[e^{(b_2-\mu_M)T_2}-1] = I_2. \tag{5.16}$$

Population at the end of second period is

$$N_2 = N_1 e^{(b_2-\mu_M)T_2}.$$

By integrating over the period of the light dry season, we have

$$\int_0^{T_3} N_2 e^{(B(t)-\mu_M t)}dt = I_3. \tag{5.17}$$

It should be noted that I_3 cannot be integrated analytical, so we will therefore employ numerical integration during the calculation of the mean population. The sum of the three integrals will be the integral of the mosquito population in a year. By denoting the mean population as I_{mean}, we calculate it as

$$I_{mean} = \frac{I_1+I_2+I_3}{T_1+T_2+T_3}. \tag{5.18}$$

Analysis of the Periodic Model

In this section, we will consider analysing the periodic model as follows:

1. To describe and estimate the development of the various populations in the compartments with time.
2. To describe and estimate the development of infection with time,
3. To compare the periodic system and the average system and finally and
4. Describe the trap region using some typical diagrams from our simulations.

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The dynamics of mosquito and human population when malaria is introduced in a free zone

In this subsection, we will consider describing a special case of the dynamics of the populations in the compartments of the periodic model when infection have just been introduced and yet to be stabilized. In this case, we note that the infection was introduced at the beginning of the dry season.

Development of susceptible host population

From Figure 47 we observe the susceptible host population continue to decrease from the introduction of the infection up to the end of February where the infectious mosquito population is minimal. The susceptible host population begin to increase due to more recovery and less infections from infectious mosquitoes. It becomes steady around July due to the onset of rains in May and increase in mosquito population lead to the increase in infectious mosquito population, and from August the susceptible host population begin to fall much faster, since many people will be getting many more infectious bites leading to malaria disease.

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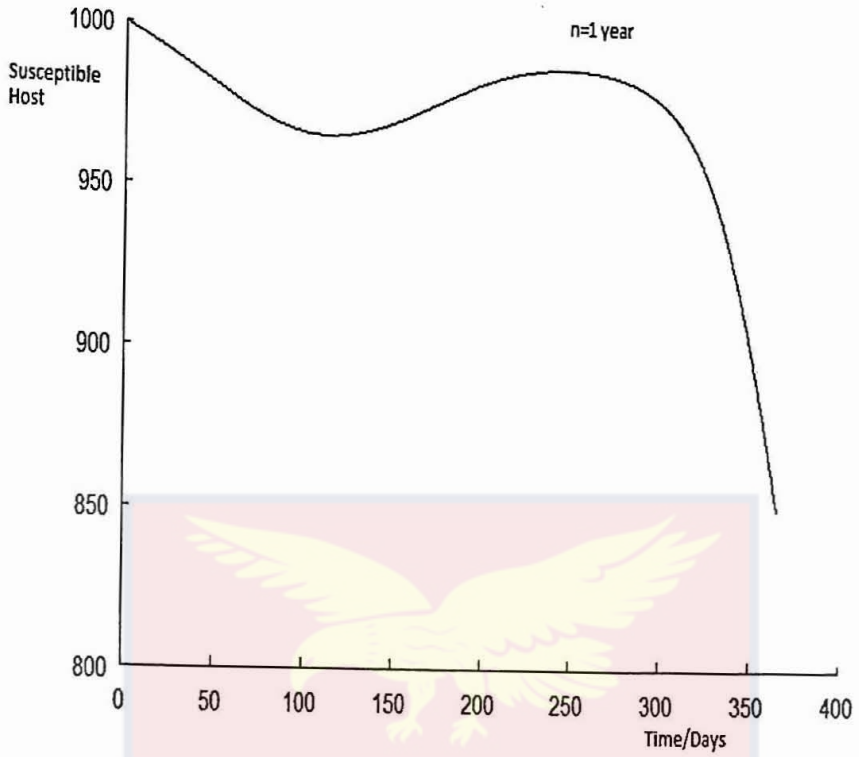


Figure 47: **Development of susceptible host population against time**

Development of infectious host population

From Figure 48, the infectious host population continue to increase (at a reducing rate) from the introduction of the infection to attain a local maximum around February, this is due to the remaining infectious mosquitoes from the rainy season. But because the rate of birth of mosquitoes has dropped, there is less new born mosquitoes into the susceptible class leading to a gradual dropping in the rate of infection. From February, because the rate of infection is at the barest minimum, the rate of recovery on the part of the host, even though remains constant, gets a major boost since less people are getting infected and leads to a decrease in the infectious host population. This decrease continues until around July where it becomes flat and start to increase afterwards since the onset of rains in May would have brought about more new born mosquitoes which have gotten infected over the time. From here the infection rate begin to exceed the rate of

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recovery leading to a sharp increase to the infectious host population through September.

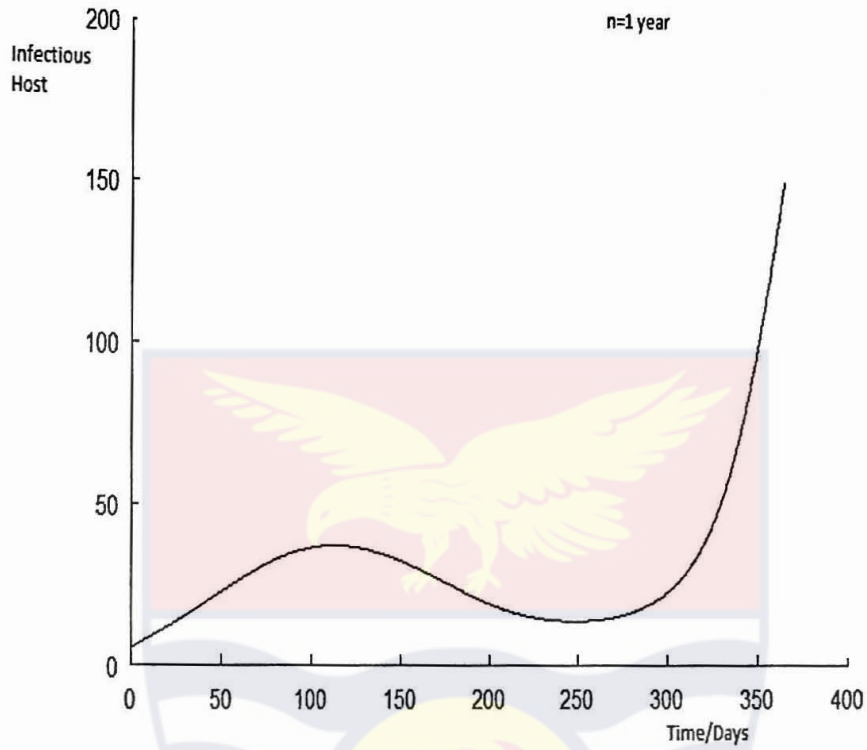


Figure 48: **Development of infectious host population against time**

Development of susceptible mosquito population

The susceptible mosquito population continue to decrease from the introduction of the infection to attain a local minimum around the end of April. This is due to the reduction in the rate of birth of and the fact that the adult mosquitoes die with very little or in some cases no replacement. From the onset of rains around May enhancing breeding grounds, there is a sharp increase in the susceptible population due to the new born mosquitoes which are not yet infected. As a matter of fact, the rate of birth of new mosquitoes is extremely higher than the rate at which they get infected. By September, it is possible susceptible mosquito population would have reach a saturation level and could have infection rate higher than the rate of birth, leading to the drop in the susceptible population and

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increasing infectious mosquito population.

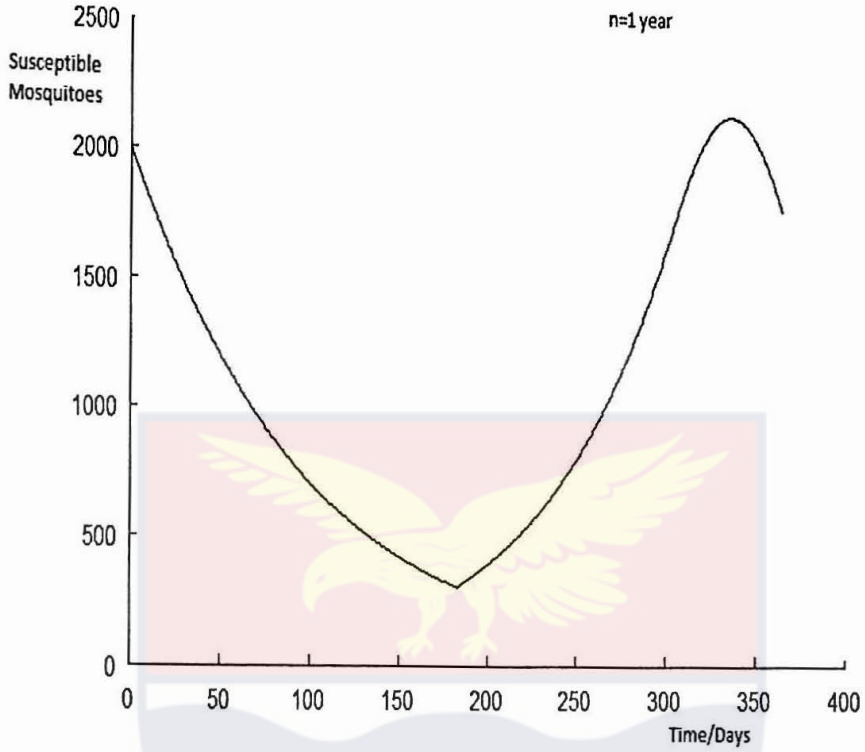


Figure 49: **Development of susceptible mosquito population against time**

Development of infectious mosquito population

From Figure 50, we can observe that there is a slight increases in the infectious mosquito population due to the excess susceptible mosquitoes that are infected by the excess infectious human population. However, this slight increase attains a local maximum around December and begin to fall and become steady flat around April ending until the end of May. The possible reason for this behavior could be due to the fact that we have more susceptible humans and the few susceptible mosquitoes biting these susceptible humans leads to no infections. From the end of May, the infectious mosquito population increases and because more susceptible mosquitoes are introduced into the system, the mosquito to human density becomes very high, leading to the susceptible mosquitoes to be able to reach the few infectious humans. These mosquitoes get infected and intend

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infecting susceptible humans and this cycle continues so rapidly within June and July leading to a surge in infectiousness in both the host and the vector populations through August and September.

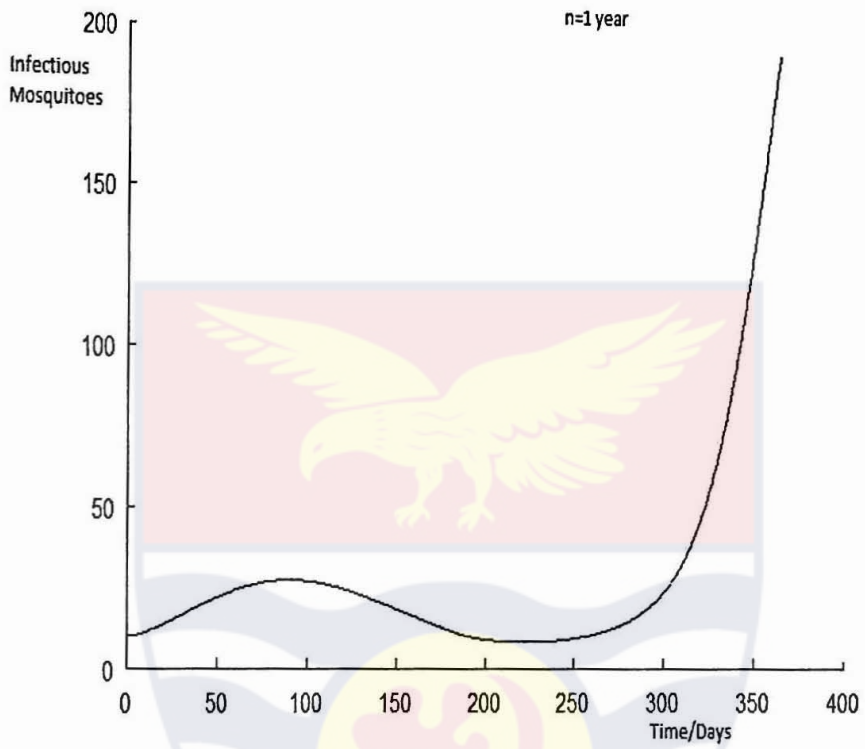


Figure 50: **Development of infectious mosquito population against time**

Dynamics of infectious mosquito population against infectious human population

From Figure 51, it could be observed that from $p1$ to $p2$ there is a gradual increase in both vector and host infections but at a reducing rate. This happen or seems to happen around November to February. During this time there are less mosquito breeding places, and the mortality rate is higher than the birth rate. From $p2$ to $p3$ occurs around March to April where both populations in the infectious classes decreases. Here, more humans recover and less get infected, and most of the infectious mosquitoes die out and less are born to infected. The mortality of the infectious mosquitoes continue to decrease, given rise to the

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dynamics from $p3$ to $p4$ but at this time the rains had set in and we have more new born mosquito into the system ready to be infected and more humans might have also recovered. Finally, from p4 to p5 there is a sudden surge of infections in both classes.

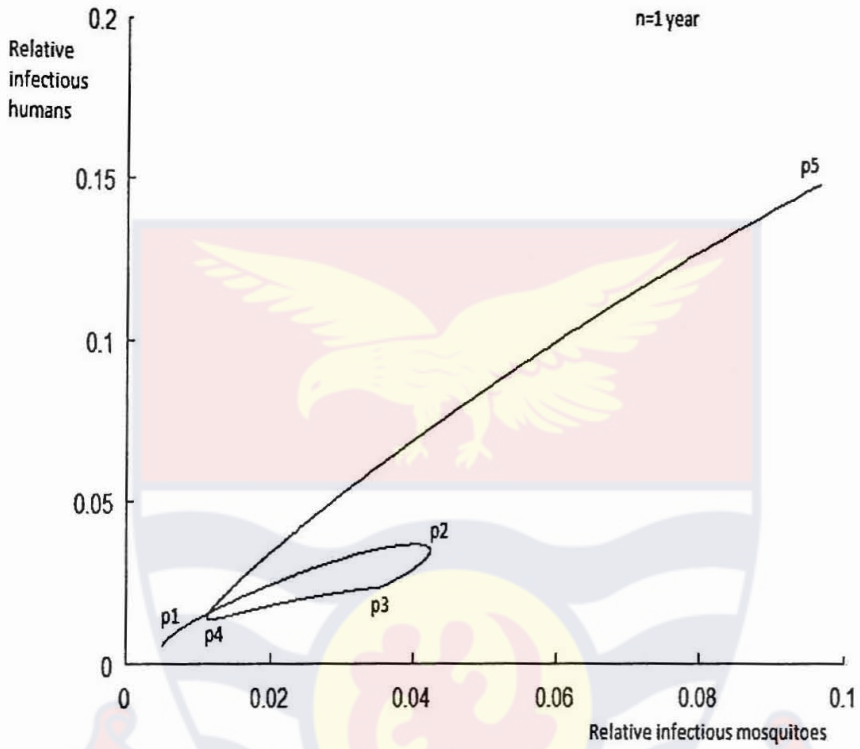


Figure 51: **Dynamics of infectious mosquito population against infectious human population**

The dynamics of mosquito and human population in endemic situation

It is important to observe how a disease will behave in a community over a period of time, that is, the time the disease stabilizes and to examine whether the disease will establish itself in the community (endemic) or it will die out (disease−free). Also to examine the stability of these endemic and disease−free situations, and to what extent does the variation of some of the parameters affect these stabilities. We are also interested to know the parameters for which it can be endemic (not disease−free) and the size of endemicity for periodic mosquito

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population.

In this subsection, we discuss the development in the total mosquito population, the development of infection and then compare the results of the periodic system to average system. We use $\tilde{\beta}$ to scale β_H and β_M so that by varying $\tilde{\beta}$ we will always have β_H and β_M maintaining their right proportions. We therefore set $\tilde{\beta} = 1$ and simulate the system using $\gamma = 0.01$, $\mu_M = 0.05$ and $b_1 = 0.04$. In this simulations the year begins in January.

Development of infection

The initial populations and time for simulation remain the same as above. Figure 52a illustrate the development of relative infectious human and mosquito populations over the period of one year after it has stabilized to pure periodic behavior.

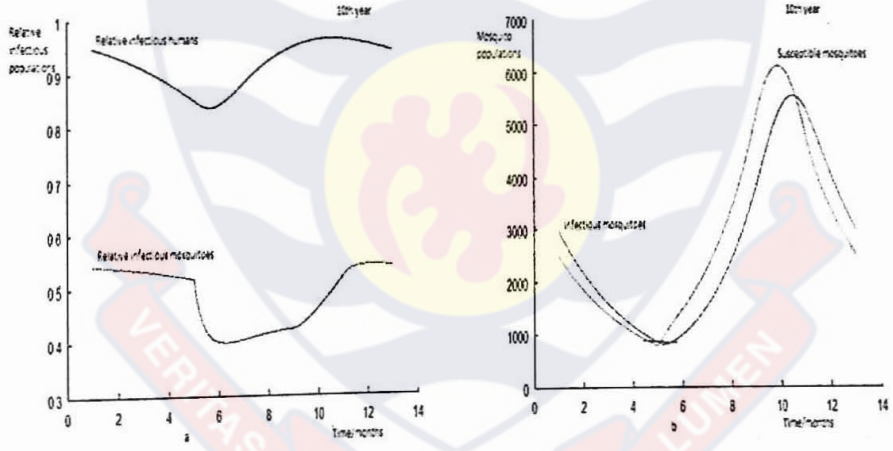


Figure 52: **Development of infection**

The following are the estimates of the relative infectious populations in time: the minimum relative infectious host population is 0.84 and is attained in June; the maximum relative infectious host is 0.97 and is attained in October/November; the minimum relative infectious vector is 0.40 and is attained in June; and the maximum relative infectious vector is 0.54 and is attained in December/January. The other estimates includes: the maximum increase in in-

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fectious host is 1.6, occurring in July; maximum increase in infectious vector is 57.1, occurring in August; and the mean relative infectious host is 0.92.

The estimate from Figure 52a and the plots in Figure 52b are best explained by the detailed studies that was reported by Boyd (1949) and Christophers (1949). They stated that the peak of mosquito density occurs either before or during the peak of human malaria cases, but that the maximum prevalence among mosquitoes follows both the peak in prevalence within humans and the peak of mosquito abundance. We give the explanation to this dynamics using the views of Anderson and May (1991), which puts the sequence of events as follows: at first, mosquito density rise due to the seasonal increase in the number of emerging adults. As the total density rises, the density of infected mosquitoes also rises, followed by a peak in human cases. The rise in prevalence among mosquitoes occurs after the peak in human cases, not just from latent period delays, but because by then fewer mosquitoes are emerging into the population to swell the ranks of the uninfected vectors, thus causing the proportion infected to increase.

Now, we compare the Ross model and the periodic model (an extension of Ross model) using one of the most important predictions. The Ross model predicts a relative infectious host population at endemic as 0.94 and the periodic model reports a mean relative infectious host population as 0.92. This goes to buttress the earlier statement we made about Ross model, that, many of its predictions are extremely different from reality.

We also consider the development of infectious host against infectious vector within the tenth year using Figure 53.

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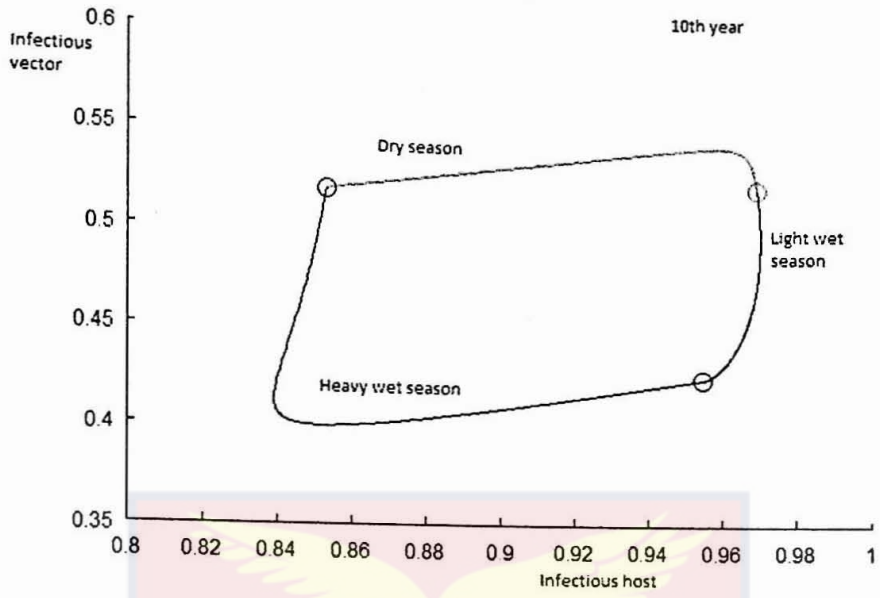


Figure 53: **Total mosquito population development**

The green curve indicates the development in the dry season, starting from the light wet season which is the blue curve, it shows some amount of increase in both infectious populations and immediately start to decrease in both populations but faster in the infectious host population. The red curve represents heavy wet season and takes off from dry season with a short period of continual decrease in both populations, but faster in the infectious vector population and suddenly turns where both populations increase but now faster in infectious host population. The heavy wet gives way to light wet season with a continual increase in both populations but faster in infectious vector population and this ends at the beginning of the dry season, and the cycle continues.

Bifurcation analysis of the periodic model

The definition of bifurcation is not different from what we defined in Ross basic model. In the case of the periodic model, we use the mean mosquito population as given in Equation (5.18) to calculate the mosquito density m. We define

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the bifurcation parameter here to be

$$\Psi = \frac{\beta_H \beta_M m}{\mu_M \gamma}. \tag{5.19}$$

We consider β_H and β_M to be very important since they each depends on one of the most influential factors in malaria transmission, which is the bitting rate. We again use the scaling $\tilde{\beta}$ to vary β_H and β_M while maintaining their proportions.

Next, we performed numerical simulation by varying $\tilde{\beta}$ between 0.1763 and 0.1725, $\mu_M = 0.05$ and $\gamma = 0.01$. We observed that $\Psi > 1$ for $\tilde{\beta} > 0.1763$ and $\Psi < 1$ for $\tilde{\beta} < 0.1725$. We then concluded that $\tilde{\beta}$ is between 0.1763 and 0.1725 for which $\Psi = 1$, we also observed endemic for $\tilde{\beta} > 0.1763$ and disease−free for $\tilde{\beta} < 0.1725$. This proves the existence of bifurcation. As $\Psi = 1$ is the bifurcation condition of Ross basic model, the bifurcation leading to endemic arises for the same condition for the periodic model.

Endemicity in the periodic system

In the Ross basic model analysis we demonstrated that the endemic equilibrium was a global attractor and we also demonstrated in the bifurcation analysis of the periodic model that the conditions that gave rise to the endemic equilibrium in the basic model is the same conditions for the periodic model. Here, we want to illustrate using diagrams that given a periodic model with b_M, the birth rate of mosquitoes varying between two values, *bmin* and *bmax*, and m the mosquito density varying between two values, *mmin* and *mmax*. Then there is a region which we call the ***trapregion*** where the periodic endemic equilibrium will be located and it will be a periodic attractor.

We simulate the Ross basic model, varying b_M and m between the maximum and minimum values generated by the periodic model. Thus, we plot the $x' = 0$ isoclines for $m = 2$ and $m = 11$, and $z' = 0$ isoclines for $b_M = 0.04$ and $b_M = 0.064$.

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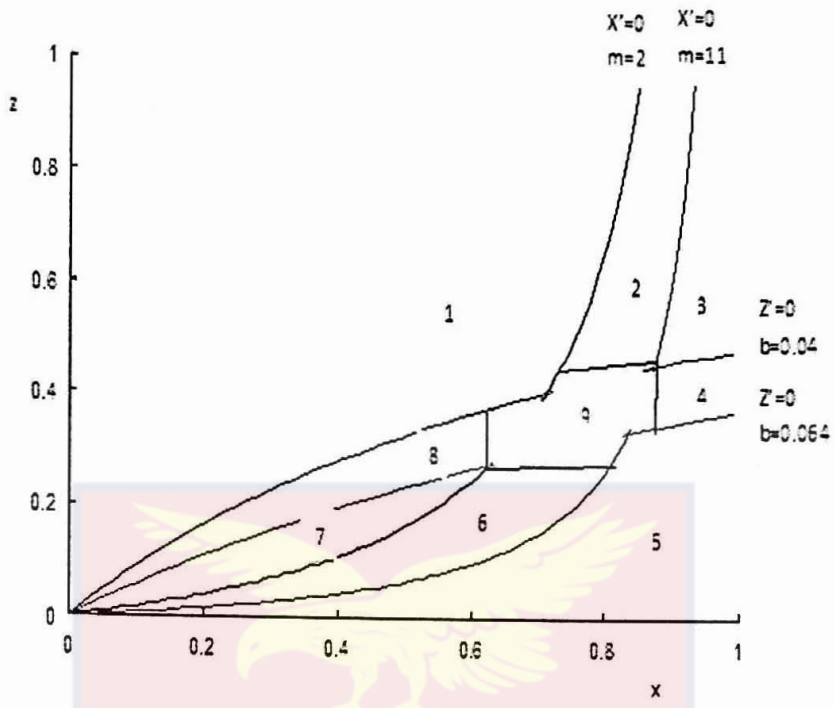


Figure 54: **Region of endemicity**

These four isoclines divides the $xz-$ plane into nine regions, see Figure 54. By sign analysis, when a trajectory leaves Region 1, it will either go into Region 2 or Region 8 or Region 9. If it goes into Region 2 it will either go into Region 9 or continue into Region 3 and go into Region 9 or go into Region 4 and eventually go into Region 9 because it can not leave Region 4 into Region 5. If the trajectory goes into 8, it will either go into Region 9 or continue into Region 7 and go into Region 9 or continue into Region 6 and eventually go into Region 9 because it can not leave Region 6 into Region 5. On the other hand, when a trajectory leaves region 5, it will either go into Region 4 or Region 6 or Region 9. If it goes into Region 4 it will either continue into Region 9 or Region 3 and go into Region 9 or continue into Region 2 and eventually go into Region 9 because it can not leave Region 2 into Region 1. If it goes into Region 6 it either go into Region 9 or continue into Region 7 and go into Region 9 or continue into Region

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8 and eventually go into Region 9 because it cannot leave Region 8 into Region 1. General observation proves that any starting from any region eventually ends up in Region 9 but no trajectory leaves Region 9 for any Region. We therefore conclude that, if there is any endemic periodic attractor it will be found in Region 9 and the trapregion is a global attractor.

Comparing the Ross Model with the Periodic Model

We present Figure 55 to compare Ross model with constant mosquito population (which we will refer to as Ross model) and the Ross model with seasonal mosquito birth rate (which we refer to as the periodic model) on how they estimate human infection in a given period. This illustrates the plots of human malaria infection estimated by Ross model and the periodic model against the variation of minimal mosquito birth rate parameter b_{min}. A point on each line is the estimate of the human infection corresponding to a particular value b_{min} in the period, except the points on the curve represented Ross model estimate which takes a constant birth rate.

The Ross model presents only one estimate for the human infection and it represented by the black curve in the figure, which we will call average infection denoted 'xave'. The periodic model presents the following three estimates.

1. The highest infection recorded in the period, which we call the maximal infection, denoted as 'xmax' and is represented by the red curve.

2. The lowest infection recorded in the period, which we call minimum infection, denoted as 'xmin' and represented by the curve with the magenta colour and

3. The mean infection which we denote as 'xmean' and is represented by the green curve.

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From Figure 55, the numerical average infection (xave) of the Ross model estimates the human infection to be about 94.6%. The maximal infection (xmax) estimates the human infection to be 97% when the minimal mosquito birth rate is 0.04 and decreases with increasing minimal mosquito birth rate. The minimal infection (xmin) estimates the human infection to be about 85% when the minimal mosquito birth rate is 0.04 and increases with increasing minimal mosquito birth rate. The mean infection (xmean) estimate the human infection to be about 93% when the minimal mosquito birth rate is about 0.04 and increases with increasing minimal mosquito birth rate.

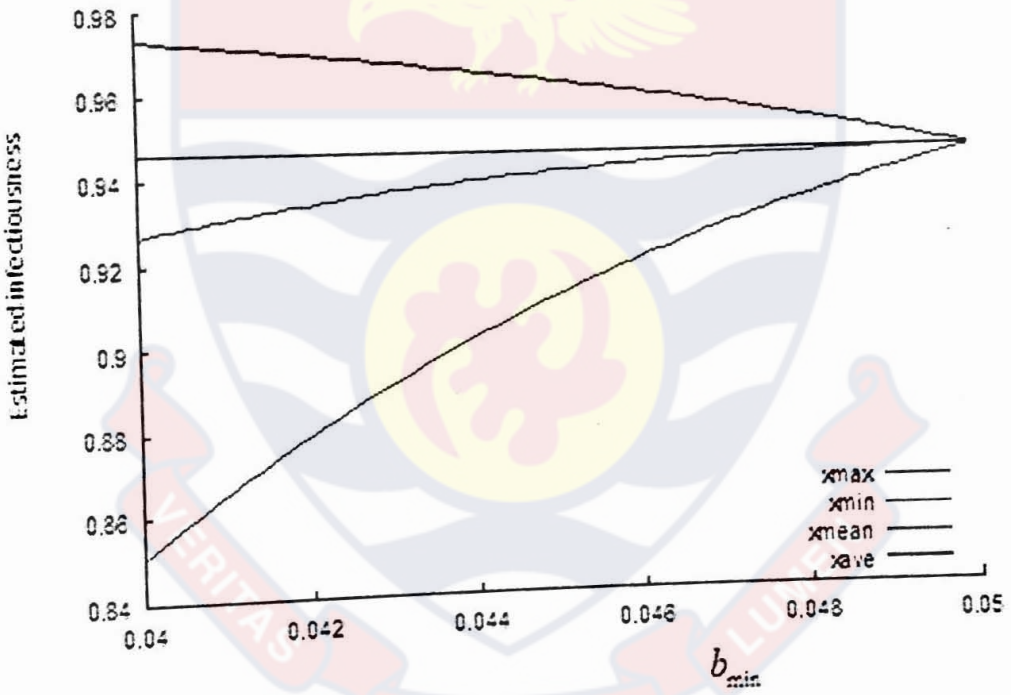


Figure 55: **Estimated infectiousness against mosquito birth rate** $(b_{min} < \mu_M)$

Here, it is clear that the difference between the average infectious estimate by Ross model and mean infectious estimate from the periodic model in the dry season is about 1.6%, and can make a tremendous impact on malaria control strategies. On the other hand, in the wet season where we have high minimal

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mosquito birth rate like $b_{min} = 0.049999$ which is close to the mortality rate, we have both the Ross model average infection and the periodic model mean infection estimating the same amount of human infection.

Figure 56 presents another situation by varying the contact rates β_H and β_{min} through a scaling quantity $\tilde{\beta}$ so that the contact rates can maintain their proportions at any point in time. The mosquito birth rate follows the seasonality explained in section four of this chapter. The figure presents a plot of estimated human malaria infection by Ross model and the periodic model against the scaling quantity $\tilde{\beta}$ which represents the variation in contact between infectious humans and susceptible mosquitoes or infectious mosquitoes and susceptible humans. The curves and their colors maintains the same meaning as in Figure 55. A point on each curve represents an estimated infection corresponding to the scaling quantity $\tilde{\beta}$.

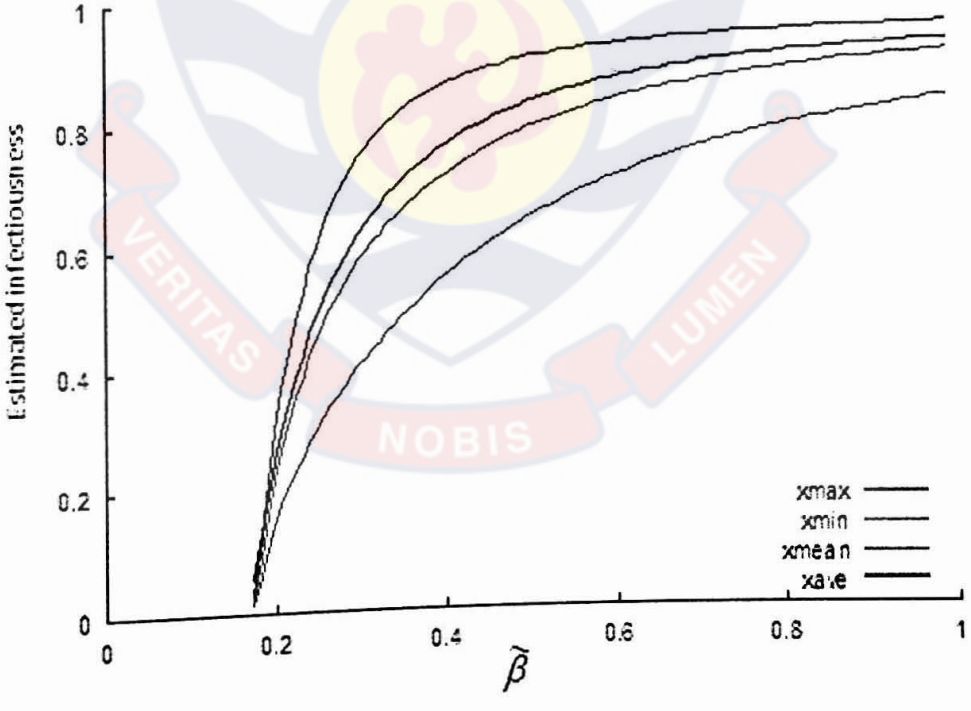


Figure 56: **Estimated infectiousness against scaling quantity $\tilde{\beta}$**

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It is observed from Figure 56 that in general, the estimated infectious increases with increasing scaling quantity $\tilde{\beta}$ (increasing mosquito and human contact in any form). The minimal infection continue to estimate lower infection and the maximal infection continue to estimate higher infection. The most important feature on the figure is that the mean infection estimated by the periodic model continue to estimate lower than the average infection which is estimated by Ross model. However, we note that the difference between the mean infection estimates and the average infection estimates decreases after sufficient increases in the contact rate.

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CHAPTER SIX

MODIFIED NDM–MODEL WITH SEASONAL MOSQUITO BIRTH RATE

Introduction

The NDM–model discussed in Chapter Three was developed to capture one most important class (re–infectious) in the transmission and control of malaria. In this chapter, we modify the NDM–model by assuming the host population to be constant and extending the model by introducing an exposed class for the mosquito population and a seasonal mosquito birth rate. This kind of modification is necessary because latency and seasonal birth rate of the mosquito play very important roles in the dynamics of malaria infection. The need for having a latency term in the model becomes very important since the life span of the vector is relatively short. The prevalence of malaria is associated with the abundance of adult mosquitoes, which depends on the amount of rainfall and this is seasonal. The outline of this chapter includes:

1. The derivation of the modified NDM–model and its analysis,
2. The introduction of the seasonal mosquito birth rate into the modified NDM–model and its analysis and
3. To compare the modified NDM–model with the periodic modified NDM–model (modified NDM–model with seasonal mosquito birth rate) on how they each estimate human malaria infection/recovery when certain parameters are varied.

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Modified NDM–model

We divide the host population into four classes, that is, susceptible, S_H, infectious, I_{H1}, recovered, R_R and reinfectious, I_{H2}. The vector population is divided into three classes, that is, susceptible, S_M, exposed, E_M and infectious, I_M. We make following assumptions:

1. Latency in host is considered to have small effect compared with the latency of mosquitoes so we consider the latency population class only for mosquitoes.

2. The host population is assumed constant but mosquito population follows the periodicity discussed in the previous chapter.

The flow diagram for the model is similar to the one in Figure 28 and can easily be replicated. We note that all the parameters are strictly positive. The equations are given as

$$\begin{aligned} S'_H &= -\frac{\beta_H I_M S_H}{N_H} + \omega R_H \\ I'_{H1} &= \frac{\beta_H I_M S_H}{N_H} - \gamma I_{H1} \\ R'_H &= -\frac{c\beta_H I_M R_H}{N_H} + \gamma I_{H1} + \alpha I_{H2} - \omega R_H \\ I'_{H2} &= \frac{c\beta_H I_M R_H}{N_H} - \alpha I_{H2} \\ S'_M &= b_M N_M - \frac{\beta_M (I_{H1} + kI_{H2}) S_M}{N_H} - \mu_M S_M \\ E'_M &= \frac{\beta_M (I_{H1} + kI_{H2}) S_M}{N_H} - (\nu + \mu_M) E_M \\ I'_M &= \nu E_H - \mu_M I_M \end{aligned} \tag{6.1}$$

We denote the form of the incidence functions as B_{H1}, B_{H2} and B_M and they are given as

$$B_{H1} = \frac{\beta_H I_M S_H}{N_H}, \; B_{H2} = \frac{c\beta_H I_M R_H}{N_H}, \; B_M = \frac{\beta_M (I_{H1} + kI_{H2}) S_M}{N_H}, \tag{6.2}$$

where N_H is the total host population and N_M is the total mosquito population. To enable us refer easily, Tables 2, 3, 4, 5, 6 and 7 present the description of the

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state variables and parameters of which the modified NDM−model parameters are included.

To analyse the malaria model (6.1) more easily, we work with fractional quantities instead of actual populations by scaling the population of each class by the total species population. We let

$$s = \frac{S_H}{N_H},\ x = \frac{I_{H1}}{N_H},\ r = \frac{R_H}{N_H},\ y = \frac{I_{H2}}{N_H}$$

and

$$u = \frac{S_M}{N_M},\ e = \frac{E_M}{N_M},\ z = \frac{I_M}{N_M}$$

with

$$N_M' = (b_M - \mu_M)N_M$$

Differentiating the scaling equations and simplifying, we have

$$\begin{aligned} \dot{s} &= \frac{\dot{S}_H N_H - S_H \dot{N}_H}{N_H^2} = \frac{\dot{S}_H}{N_H} = \frac{-\beta_H S_H I_M}{N_H^2} + \frac{\omega I_H}{N_H} \\ &= -\beta_H s z \frac{N_M}{N_H} + \omega x \end{aligned} \tag{6.3}$$

$$\begin{aligned} \dot{x} &= \frac{\dot{I}_H N_H - I_H \dot{N}_H}{N_H^2} = \frac{\dot{I}_H}{N_H} = \frac{\beta_H S_H I_M}{N_H^2} - \frac{\gamma I_H}{N_H} \\ &= \beta_H s z \frac{N_M}{N_H} - \gamma x \end{aligned} \tag{6.4}$$

$$\begin{aligned} \dot{r} &= \frac{\dot{R}_H N_H - R_H \dot{N}_H}{N_H^2} = \frac{\dot{R}_H}{N_H} \\ &= \frac{1}{N_H}\left(\frac{-c\beta_H I_M R_H}{N_H} + \gamma I_{H1} + \alpha I_{H2} - \omega R_H\right) \\ &= -\frac{N_M}{N_H} c\beta_H z r + \gamma x + \alpha y - \omega r \end{aligned} \tag{6.5}$$

$$\begin{aligned} \dot{y} &= \frac{\dot{I}_{H2} N_H - I_{H2} \dot{N}_H}{N_H^2} = \frac{\dot{I}_{H2}}{N_H} = \frac{1}{N_H}\left(\frac{c\beta_H I_M R_H}{N_H} - \alpha I_{H2}\right) \\ &= \frac{N_M}{N_H} c\beta_H z r - \alpha y \end{aligned} \tag{6.6}$$

$$\begin{aligned} \dot{u} &= \frac{\dot{S}_M N_M - S_M \dot{N}_M}{N_M^2} = \frac{\dot{S}_M}{N_M} - \frac{\dot{N}_M}{N_M} u \\ &= \frac{1}{N_M}\left(b_M N_M - \frac{\beta_M (I_{H1} + k I_{H2}) S_M}{N_H} - \mu_M S_M\right) - (b_M - \mu_M) u \\ &= b_M - \beta_M (x + ky) u - b_M u \end{aligned} \tag{6.7}$$

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$$\begin{aligned}\dot{e} &= \frac{\dot{E}_M N_M - E_M \dot{N}_M}{N_M^2} = \frac{\dot{E}_M}{N_M} - \frac{\dot{N}_M}{N_M} e \\ &= \frac{1}{N_M}\left(\frac{\beta_M (I_{H1} + k I_{H2}) S_M}{N_H} - (\nu + \mu_M) E_M\right) - (b_M - \mu_M) e \\ &= \beta_M (x + ky) u - (\nu + b_M) e \end{aligned} \tag{6.8}$$

$$\begin{aligned}\dot{z} &= \frac{\dot{I}_M N_M - I_M \dot{N}_M}{N_M^2} = \frac{\dot{I}_M}{N_M} - \frac{\dot{N}_M}{N_M} z = \frac{1}{N_M}(\nu E_H - \mu_M I_M) \\ &= \nu e - \mu_M z \end{aligned} \tag{6.9}$$

The transformed system is given as

$$\begin{aligned}\dot{s} &= -\beta_H m s z + \omega r \\ \dot{x} &= \beta_H m s z - \gamma x \\ \dot{r} &= -\beta_H m c r z + \gamma x + \alpha y - \omega r \\ \dot{y} &= \beta_H m c r z - \alpha y \\ \dot{u} &= b_M - \beta_M u (x + ky) - b_M u \\ \dot{e} &= \beta_M u (x + ky) - (\nu + \mu_M) e \\ \dot{z} &= \nu e - \mu_M z, \end{aligned} \tag{6.10}$$

where $m = \frac{N_M}{N_H}$.

Analysis of Modified NDM−Model

Bifurcation condition and the endemic equilibrium point

Numerical experiments indicates that there is a transcritical bifurcation, so, we will calculate the bifurcation condition B by requiring that the determinant of the Jacobian matrix of the scaled system (6.10) is zero at the disease−free equilibrium.

The system (6.10) is a five−dimensional system, since $s = 1 - x - r - y$ and $u = 1 - e - z$. We define a disease−free to be a situation where we have only susceptible humans and susceptible mosquitoes but no disease ($x = 0$, $r = 0$, $y = 0$, $e = 0$, $z = 0$). If we calculate the determinant for the Jacobian matrix for (6.10) at the disease-free equilibrium $(0,0,0,0,0)$, we obtain a bifurcation condition which will be used to analyse the behavior of the equilibria.

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The Jacobian matrix for System (6.10) is given by

$$\begin{pmatrix} -J_{11} & -J_{12} & -J_{13} & 0 & J_{15} \\ J_{21} & -J_{22} & J_{23} & 0 & -J_{25} \\ 0 & J_{32} & -J_{33} & 0 & J_{35} \\ J_{41} & 0 & J_{43} & -J_{44} & -J_{45} \\ 0 & 0 & 0 & J_{54} & -J_{55} \end{pmatrix},$$

where

$$\begin{aligned}
J_{11} &= \beta_H mz+\gamma \\
J_{12} &= \beta_H mz \\
J_{13} &= \beta_H mz \\
J_{15} &= \beta_H m(-y-x-r+1) \\
J_{21} &= \gamma \\
J_{22} &= \beta_H cmz+\omega \\
J_{23} &= \alpha \\
J_{25} &= \beta_H cmr \\
J_{32} &= \beta_H cmz \\
J_{33} &= \alpha \\
J_{35} &= \beta_H cmr \\
J_{41} &= \beta_M(-z-e+1) \\
J_{43} &= \beta_M k(-z-e+1) \\
J_{44} &= \beta_M(ky+x)+\nu+\mu_M \\
J_{45} &= \beta_M(ky+x) \\
J_{54} &= \nu \\
J_{55} &= \mu_M
\end{aligned}$$

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When we evaluate the Jacobian matrix at the disease–free, we obtain

$$\begin{pmatrix} -\gamma & 0 & 0 & 0 & \beta_H m \\ \gamma & -\omega & \alpha & 0 & 0 \\ 0 & 0 & -\alpha & 0 & 0 \\ \beta_M & 0 & \beta_M k & -\nu-\mu_M & 0 \\ 0 & 0 & 0 & \nu & -\mu_M \end{pmatrix}$$

So calculating the Jacobian matrix determinant and equating the result to zero, we obtain the bifurcation condition to be

$$B = \frac{\beta_H \beta_M m \nu}{\gamma \mu_M (\nu + \mu_M)}. \tag{6.11}$$

For the non-periodic system we always have $b_M = \mu_M$ and we can calculate the coordinates for the endemic equilibrium.

Theorem 6.1. *If the determinant of a Jacobian matrix is greater than zero, then there exist an endemic equilibrium.*

Proof

From $r' + y' = 0$ and $z' = 0$, we obtain

$$r = \frac{\gamma x}{\omega}, e = \frac{\mu_M z}{\nu} \tag{6.12}$$

Substituting the right hand side of r and e from (6.12) into $s = 1 - x - r - y$ and $u = 1 - e - z$ we obtain

$$s = 1 - \left(1 + \frac{\gamma}{\omega}\right) x - y, u = 1 - \left(1 + \frac{\mu}{\nu}\right) z \tag{6.13}$$

From $x' = 0$ and $y' = 0$, we obtain

$$x = \frac{\beta_H m s z}{\gamma}, y = \frac{\beta_H m c z r}{\alpha} \tag{6.14}$$

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and

$$z = \frac{\gamma x}{\beta_H m s}, z = \frac{\alpha y}{\beta_H m c r} \tag{6.15}$$

Substituting (6.14) into $\frac{e'}{z} = 0$, we obtain

$$\frac{\beta_H \beta_M m \nu(\alpha s + ck\gamma r)u - \gamma\alpha\mu_M(\mu_M + \nu)}{\alpha\gamma\nu} = 0 \tag{6.16}$$

Substituting the expression for u from (6.13) into the numerator of the left hand side of equation (6.16) we obtain a new equation given by

$$\beta_H \beta_M m \nu(\alpha s + ck\gamma r) - \gamma\alpha\mu(\mu + \nu) - \beta_H \beta_M m(\mu + \nu)(\alpha sz + \gamma ckrz) = 0 \tag{6.17}$$

Now, substituting the expression for s from (6.13) and the expression for r from (6.12) into $sz - rz$ from (6.14), we obtain

$$-Dy - Lx + Q = 0, \tag{6.18}$$

where

$$\begin{aligned} D &= \alpha\beta_M(\nu\beta_H m + \gamma k(\nu + \mu)) \\ L &= (\gamma^2 \nu \beta_H mck - \beta_H m\alpha\nu(\omega + \gamma) - \gamma\alpha\omega(\nu + \mu))\frac{\beta_M}{\omega} \\ Q &= \alpha(\beta_H \beta_M m\nu - \gamma\mu(\nu + \mu)) \end{aligned} \tag{6.19}$$

We observe that $Q > 0$ if the condition

$$\beta_H \beta_M m\nu - \gamma\mu_M(\nu + \mu_M) > 0 \tag{6.20}$$

is satisfied. We now proceed to calculate the endemic equilibrium. From (6.15) we obtain

$$\frac{\gamma x}{\beta_H m s} - \frac{\alpha y}{\beta_H m c r} = 0. \tag{6.21}$$

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Now, substituting the expression for s in (6.13) and the expression for r in (6.12), we obtain the equation

$$\alpha\omega y^2+\alpha(\omega+\gamma)xy+\gamma^2cx^2-\alpha\omega y=0 \tag{6.22}$$

Solving for y in Equation (6.18) and substituting into (6.22) we obtain a second order equation for x given by

$$q_2x^2+q_1x+q_0=0, \tag{6.23}$$

where

$$\begin{aligned}
q_2 &= (\gamma^2ck^2-\alpha k(\omega+\gamma)+\alpha\omega)(\gamma^2\mu^2cB^2+\alpha\mu B\beta_M(\omega+\gamma)+\alpha\omega\beta_M^2)\\
q_1 &= \alpha\omega(q_{12}\gamma^2+q_{11}\gamma+q_{10})\\
q_0 &= -\alpha^2\mu\omega^2(\beta_Mk+\mu)(B-1),\\
q_{10} &= \alpha\omega(2\mu\beta_MkB-\mu\beta_MB+\mu^2B\beta_M^2k-\mu\beta_Mk+2\mu\beta_M)\\
q_{11} &= \alpha\mu(2\beta_MkB+\mu B-\beta_Mk)\\
q_{12} &= \mu ckB(\mu B-\beta_Mk-2\mu)
\end{aligned} \tag{6.24}$$

and

$$B=\frac{\beta_H\beta_Mm\nu}{\mu\gamma(\nu+\mu)}. \tag{6.25}$$

By solving (6.23), we obtain a formula for x at equilibrium. This is given by

$$x=\frac{-q_1\pm\sqrt{q_1^2-4q_2q_0}}{2q_2}. \tag{6.26}$$

Now, substituting x into (6.18) and (6.12), we obtain the formulae of y and r at equilibrium respectively. Substituting the expressions for y and r in (6.15) we obtain the formula for z at equilibrium. Substituting x, y and z into (6.13) we obtain formulae for s and u at equilibrium and using the fact that $u=1-e-z$ we obtain a formula for e at equilibrium.

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Using the parameter values, $\beta_H = 0.06$, $\beta_M = 0.05$, $\gamma = 0.01$, $\alpha = 0.04$, $\omega = 0.01$, $c = 0.25$, $k = 0.12$, $\mu_M = 0.05$, $\nu = 0.15$ with $m = 5$, we calculate the numerical values for the population classes at equilibrium. We substitute these parameter values into (6.24) and (6.25) to obtain the numerical values for q_0, q_1 and q_2. The values of q_0, q_1 and q_2 are then substituted into (6.26) to get $x = 0.3904$ and $x = -1.0441$. We discard the negative value of x, since x is suppose to be non-negative. We again substitute the parameter values into (6.19) to obtain the values of D, L and Q. Then substitute the values of D, L and Q, together with value of x into (6.18) and solve for y to get $y = 0.1590$. We substitute the values of x and y into (6.13) to get $s = 0.0597$. Substituting the value of x into (6.12), we obtain $r = 0.3904$. Substituting the values of x and s or y and r into (6.15) we obtain $z = 0.2179$ and substituting the value of z into (6.13) we obtain $u = 0.7095$. Using the fact that $u = 1 - e - z$, we calculate the value of e to be 0.0726.

Hence, the numerical values of the population classes at equilibrium is given as $(0.0597, 0.3904, 0.3904, 0.1595, 0.7095, 0.0726, 0.2179)$.

Development of endemic equilibrium when β_H and β_M are changing

We use Figure 57 to illustrate how the dynamics of the infectious populations classes develop when we are varying the contact rates β_H and β_M through a scaling quantity $\tilde{\beta}$ so that the contact rates can maintain their proportion at any point in time.

At the endemic equilibrium we obtained the following formulae for the infectious classes which are explicitly functions of β_H or β_M or both:

$$\begin{aligned} x &= \frac{-q_1 \pm \sqrt{q_1^2 - 4q_2q_0}}{2q_2} \\ y &= \frac{Q - Lx}{D} \\ r &= \frac{\gamma x}{\omega} \\ z &= \frac{\alpha y}{\beta_H mcr} \\ e &= \frac{\mu_M z}{\nu} \end{aligned} \tag{6.27}$$

We use the following parameter values for the simulation of (6.27) by varying the

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scaling $\tilde{\beta}$: $\beta_H = 0.06\tilde{\beta}$, $\beta_M = 0.05\tilde{\beta}$, $\gamma = 0.04$, $\alpha = 0.04$, $\omega = 0.01$, $c = 0.25$, $k = 0.12$, $\mu_M = 0.15$, $\nu = 0.15$ with $m = \frac{10110}{1010}$.

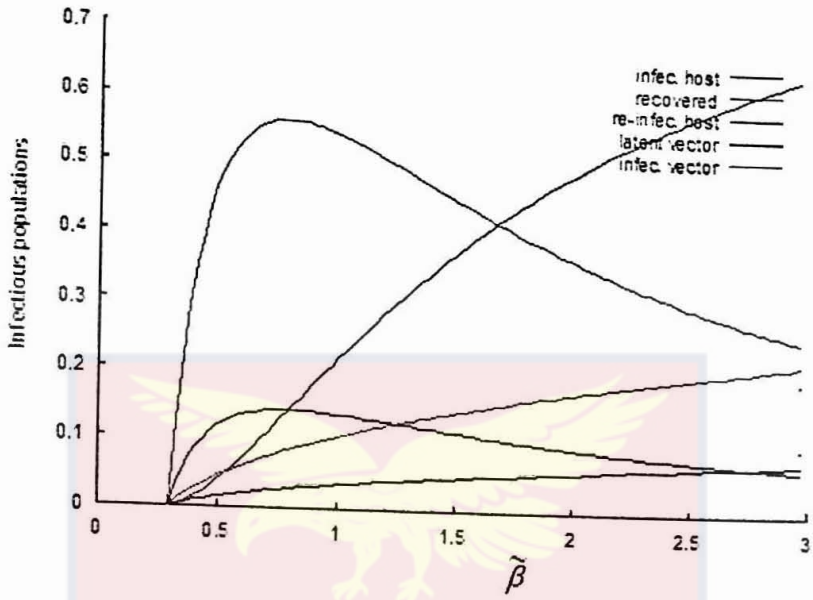


Figure 57: **Development of total mosquito population in time**

The various populations are represented by the plots. From Figure 57, it is observed that the infectious human population represented by the red curve increases sharply as the scaling $\tilde{\beta}$ increases for a short while and begin to decrease as the scaling $\tilde{\beta}$ continue to increase. This dynamics could be due to the fact that as more people get infected, we reach a saturation where almost everybody is infected and the only development will either be recovery or re−infectiousness. It is observed that the recovery population development is represented by a green curve also increases sharply from the beginning and starts to decrease after a while. However, the re−infectious population which is represented by a blue curve continue to increase throughout the period. The vector population shows a gradual but steady increase throughout the period.

Development of endemic equilibrium when m is changing

We now consider studying the development of infectious population classes

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at endemic equilibrium as functions of m supposing the other parameters remain constant. We use the following parameter values for the simulation of (6.27) by varying the mosquito to human ratio m: $\beta_H = 0.06$, $\beta_M = 0.05$, $\gamma = 0.04$, $\alpha = 0.04$, $\omega = 0.01$, $c = 0.25$, $k = 0.12$, $\mu_M = 0.15$, $\nu = 0.15$. All the formulae in (6.27) giving the population classes depends on m either directly or indirectly.

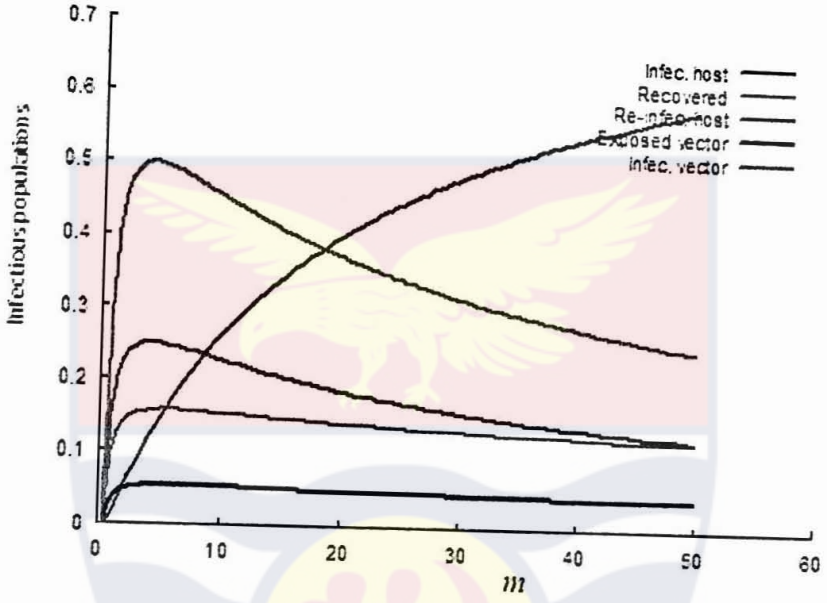


Figure 58: **Development of endemic equilibrium with m is varied**

Figure 58 illustrate the development of the endemic equilibrium when the mosquito to human ratio m is changing. The curves with different colours represents the developments of the various populations at endemic equilibrium when m is varied. The blue curve represents the re−infectious human class and it indicates a continuous gentle increase in the reinfection as the ratio of mosquito to human continue to increase. The infectious vector population class is represented by the curve with colour magenta, it indicates a sharp increase at the beginning and assumes a constant value as m increases. The exposed class of the vector population which is represented by the black curve shows a slight increase at the beginning and also assumes almost a constant value as m increases. The infectious and recovered host populations development are represented by

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the red and green curves respectively. They both indicate sharp increase at the beginning followed by a gradual but gentle continuous decrease as m increases.

General observation for Figures 57 and 58 show that, whatever the case may be, as we increase the chances of mosquitoes to have contact with humans or the vice versa, the re−infectious human class will continue to increase while the infectious human class will increase shortly and begin to decrease and finally assume a constant value.

Estimation of maximal infections

At this stage we want to estimate the maximal infection in both the host and vector populations at a given mosquito to human ratio m. So we start by using System (6.10) to calculate the formulae for the infectious population classes as functions of m at the endemic equilibrium. At the endemic equilibrium, we have the following relations:

$$x = \frac{\mu_M Z}{\beta_M U} \tag{6.28}$$

$$z = \frac{\beta_M U \nu x}{\mu_M(\nu + \mu_M)} \tag{6.29}$$

$$s = \frac{1}{BU} \tag{6.30}$$

$$y = ABUmx^2 \tag{6.31}$$

$$y + 1 + \Gamma x + s = 1, \tag{6.32}$$

where

$$A = \frac{c\gamma^2}{\alpha\omega} \tag{6.33}$$

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$$B = \frac{\beta_H \beta_M}{\gamma \mu_M} \frac{\nu}{\nu + \mu_M} \tag{6.34}$$

$$U = u(1 + k\frac{y}{x}) \tag{6.35}$$

$$m = \frac{N_M}{N_H} \tag{6.36}$$

$$\Gamma = \frac{\gamma}{\omega} \tag{6.37}$$

Now, substituting (6.28), (6.30), and (6.31) into (6.32), we obtain

$$ABVx^2 + (1+\Gamma)x + \frac{1}{BV} = 1, \tag{6.38}$$

where $V = Um$.

To obtain the maximal infection in x with respect to m we differentiate (6.38) with respect to m and equate to zero. This gives

$$ABV'x^2 + 2ABVxx' + (1+\Gamma)x' - \frac{V'}{BV^2} = 0. \tag{6.39}$$

Solving for x' we obtain

$$x' = \frac{V'\left[\frac{1}{BV^2} - ABx^2\right]}{2ABVx + 1 + \Gamma} \tag{6.40}$$

At maximal x, we have $x' = 0$ (with respect to m). This implies that

$$ABVx^2 = \frac{1}{BV} \tag{6.41}$$

Using (6.41) and also substituting it into (6.38), we obtain a relation for maximal x:

$$x = \frac{1 - \frac{2}{BV}}{1 + \Gamma} = \frac{1}{\sqrt{A}BV} \tag{6.42}$$

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Solving (6.42) with respect to V, we obtain

$$V = \frac{2 + \frac{1+\Gamma}{\sqrt{A}}}{B} \tag{6.43}$$

Using substituting (6.43) into (6.42), we obtain an explicit expression for maximal x given by

$$x = \frac{1}{\sqrt{A}\left(2 + \frac{1+\Gamma}{\sqrt{A}}\right)} = x^* \tag{6.44}$$

At maximal x, we also obtain

$$\frac{y}{x} = ABVx = \sqrt{A},$$

where we have used (6.41) for the second equality. We thus obtain an expression for y for maximal x given as

$$y = \frac{1}{\left(2 + \frac{1+\Gamma}{\sqrt{A}}\right)} \tag{6.45}$$

We also get $U = u(1 + k\sqrt{A})$ and from (6.43) we obtain a relation for m at maximal x:

$$m = \frac{2 + \frac{1+\Gamma}{\sqrt{A}}}{Bu(1 + k\sqrt{A})} \tag{6.46}$$

Using the relation for Z in (6.28), we obtain the equation

$$Z = \frac{\beta_M}{\mu_M} xU = \frac{\beta_M}{\mu_M} x(1 - Z)(1 + k\sqrt{A}) \tag{6.47}$$

Solving for Z, gives for maximal x, the relation

$$Z = \frac{D}{1 + D} = Z^*, \tag{6.48}$$

where $D = \frac{\beta_M}{\mu_M} x^*(1 + k\sqrt{A})$.

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Using $u = 1 - Z$ and substituting into (6.46) we obtain an explicit expression for the value of m, where x is maximal, to be

$$m = \frac{2 + \frac{1+\Gamma}{\sqrt{A}}}{B(1-Z^*)(1+k\sqrt{A})}. \tag{6.49}$$

We now find lower bounds for u and upper bounds for x valid for any m. From $e' = z' = 0$, we obtain

$$Z < \frac{\beta_M(x+ky)}{\beta_M(x+ky)+\mu_M} < \frac{\beta_M((1-k)x+k)}{\beta_M(x(1-k)+k)+\mu_M} \tag{6.50}$$

because $y < 1 - x$. As $u = 1 - Z$, using (6.44) and (6.50), we obtain a lower bound for u:

$$u > \frac{\mu_M}{\mu_M + \beta_M((1-k)x^* + k)} = u^* \tag{6.51}$$

Using (6.38), we obtain an upper estimate for x given as

$$x < \frac{1 - \frac{1}{Bu^*m}}{1+\Gamma} \tag{6.52}$$

This upper estimate gives sense only for m less than the value where we have maximal x. However, we also calculate another estimate which has some meaning for greater m.

Using the expression for y in (6.31), we obtain

$$y = ABmu\left(1 + k\frac{y}{x}\right)x^2 < ABmuyx$$

and we arrive at a new estimate for x given by

$$x < \frac{1}{ABu^*m} = x_m \tag{6.53}$$

For big m, we have $y \sim 1$ and $\frac{y}{x}$ is large and $U \sim uk\frac{y}{x}$, leading to

$$u = \sim \frac{\mu_M}{\mu_M + \beta_M k} = u_\infty,\ x \sim \frac{1}{ABu_\infty m},\ \frac{y}{x} = \sim ABu_\infty m,\ s \sim \frac{1}{Bu_\infty m} \tag{6.54}$$

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and from (6.12) and $y = 1 - x - r - s$ and $u = 1 - e - z$, we easily obtain approximations for r, y, e and z.

Analysis of Modified NDM−Model with Seasonal Mosquito Birth Rate

In the immediate past Section, we used an average value for the birth rate to calculate the equilibrium points of the System (6.1) and to estimate average infection over the period. In this section, we will incorporate seasonal birth rate into the System (6.1) and analyse some figures from the simulations of the system for a one-year stabilized cycle. The seasonal mosquito birth rate follows the same pattern as explained in the fourth section of Chapter Four. We use the following parameter values: $\beta_H = 0.06, b_1 = 0.04, \gamma = 0.01, \alpha = 0.04, \omega = 0.01, c = 0.25, k = 0.12, \mu_M = 0.05$ and $\nu = 0.15$ with initial populations $(1000, 10, 0, 0, 10000, 10, 100)$ for all the simulations in this section. We however note that the value of the initial m is changing in Figures 60 to 62 by scaling the initial condition for mosquito population to get the same average m in all cases.

Development in total mosquito population

As reported in Chapter Four, the development of mosquito population in a year always follow the rain pattern and could be observed that, the NDM−periodic model also gives the same results. From Figure 59, it is observe that the mosquito population attains its minimum around May with numerical value of 1622 mosquitoes and maximum in October with numerical value of 11480 mosquitoes.

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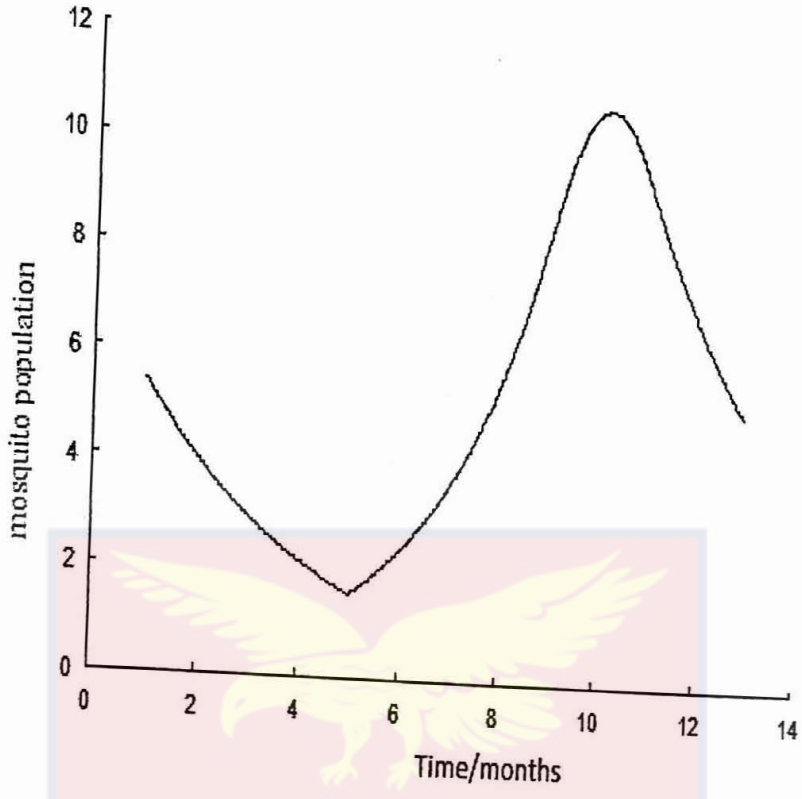


Figure 59: **Development of total mosquito population in time**

Development of host populations

The development in the host populations appears to be a bit complicated because of the number of classes involved. From Figure 60 both the infectious and the re−infectious decrease slowly to attain minimum populations around June and begin to increase. This is due to the onset of rains in May. The infectious class population rises faster to attain maximum population around August and the re−infectious rises slowly to attain maximum population around November. The possible reason for this dynamics is that, some of the infectious host who might have recovered could have been reinfected and goes into the re−infectious class. So, as the infectious class population decreases after August the re−infectious continue to increase and attains maximum population in early November, almost the same time as recovered attains minimum population.

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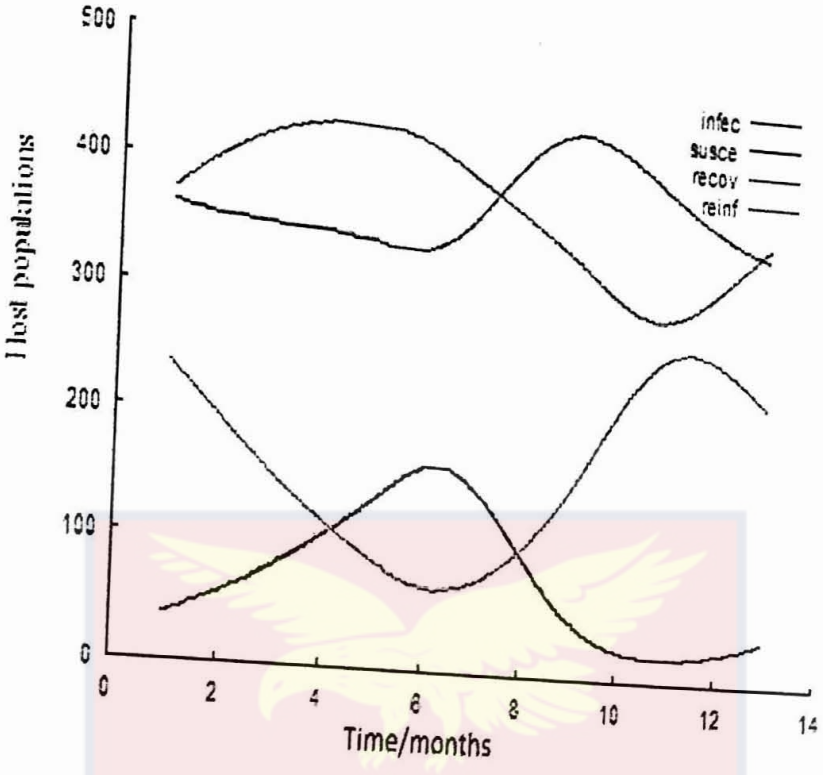


Figure 60: **Development of host populations in time**

On the other hand, the recovered and the susceptible classes increase to attain their maximum around May and June respectively. The susceptible decreases much faster and attains its minimum around October, whilst, the recovered decreases slowly to attain minimum around November. This dynamics is expected, since one has to get infected before recovery. There is a sharp rise in the recovery class from November, since some of the members in the infectious class would have started recovering. Because of the temporal immunity in the recovery class the susceptible class remain slightly constant until December before it start to increase gradually.

Development of vector populations

Figure 61 illustrates the development of the various classes in the vector population in a given year. These classes includes: susceptible represented by black curve, exposed represented by yellow curve and infectious represented by

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red curve.

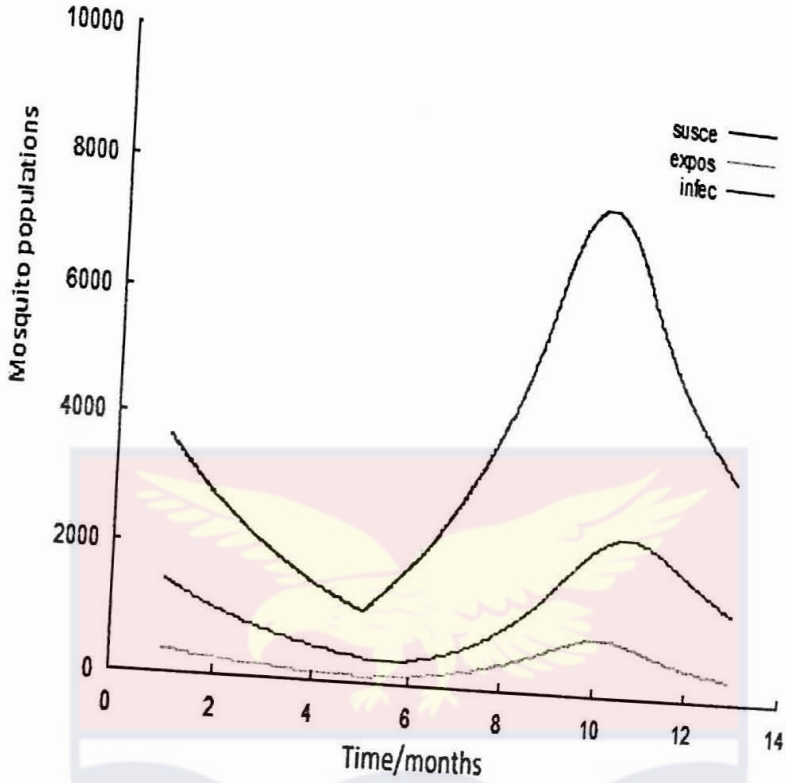


Figure 61: **Development of mosquito populations in time**

We observe that from January the populations in the three classes decreases, indicating that, in the dry season the mortality rate is higher than the birth rate. This means the mosquitoes are dying, but few or no replacement because of lack of breeding places. However, from May there is a sudden increase in the population of the susceptible class signifying the onset of the heavy rain season and this increase continue until it attains its maximum in August as reported by Kasasa et al. (2013) and Dery et al. (2010). Meanwhile, the increase in the exposed and infectious classes are slow and gentle, and continued to be less than the susceptible class throughout the year. This behavior of the exposed and the infectious class in relation to the susceptible is well explained by Anderson and May (1991), that, "virtually without exception the prevalence of infection within vector populations is very low, irrespective of the type of disease agent

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or species of vector. In general, this is a direct consequence of the short life expectancies of vector species relative to the duration of infection in the human host and the latent period of infection in the vector".

Development of infectious populations

Figure 62 illustrates the development of infectious populations in a given year. These populations include: infectious human population represented by the red curve, re−infectious human population represented by the curve with colour magenta and the infectious mosquito population represented by the curve with cyan colour.

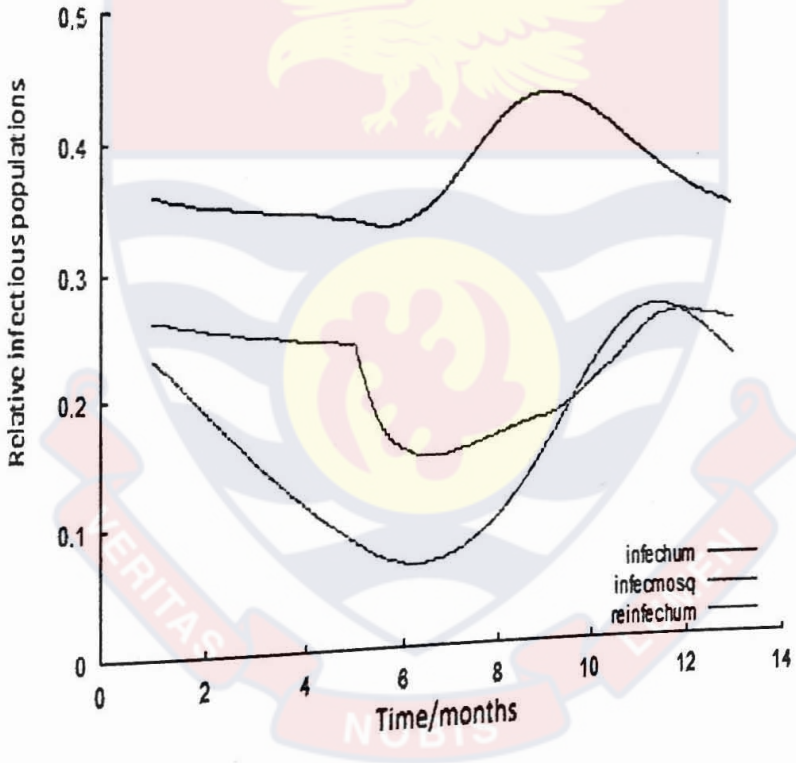


Figure 62: **Development of relative infectious populations in time**

The three infectious populations continue to decrease throughout the dry season to attain their minimum populations from late May to mid June. We notice that the infectious mosquito population takes sudden dive in May. This is due to the onset of rains and more susceptible mosquitoes are introduced into

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the system as compared to the mosquitoes that are infected daily. So, the daily proportion of the infectious mosquitoes to the total mosquito population has to fall drastically. Since there is an increase in susceptible mosquitoes, certainly there will be an increase in β_M leading to an increase in infectious mosquitoes which also leads to an increase in β_H and the subsequent effect is an increase in infectious and re−infectious humans.

Since the human population is assumed constant the infectious and re−infectious humans continue to increase till they attain maximum in September and November respectively. However, the relative increment in the infectious mosquito population is gradual due to non constant total population and the latency factor.

Dynamics of relative infectious vector with relative infectious host

We use Figure 63 to explain the cyclic nature of malaria infection (this includes infectious and re−infectious humans). We plot the relative infectious vector against the relative infectious host. The green curve indicates the relationship between the relative vector infection and the relative host infection during the dry season. It takes off from the light wet season with a continuous increase in mosquito infection and a gradual decrease in host infection. After a while both infections begin to decrease, but faster in the host infection compared to the vector infection. The dry season gives way to the heavy wet season represented by the red curve where both infections continue decrease but this faster in the vector infection. After a short while, both infections begin to increase with the host infection growing much faster. The heavy wet season gives way to the light wet season represented by the blue curve, it could be observed that, both infections increases but faster in the vector infection compared to the host infection. This season also gives way to the dry season and the cycle continues.

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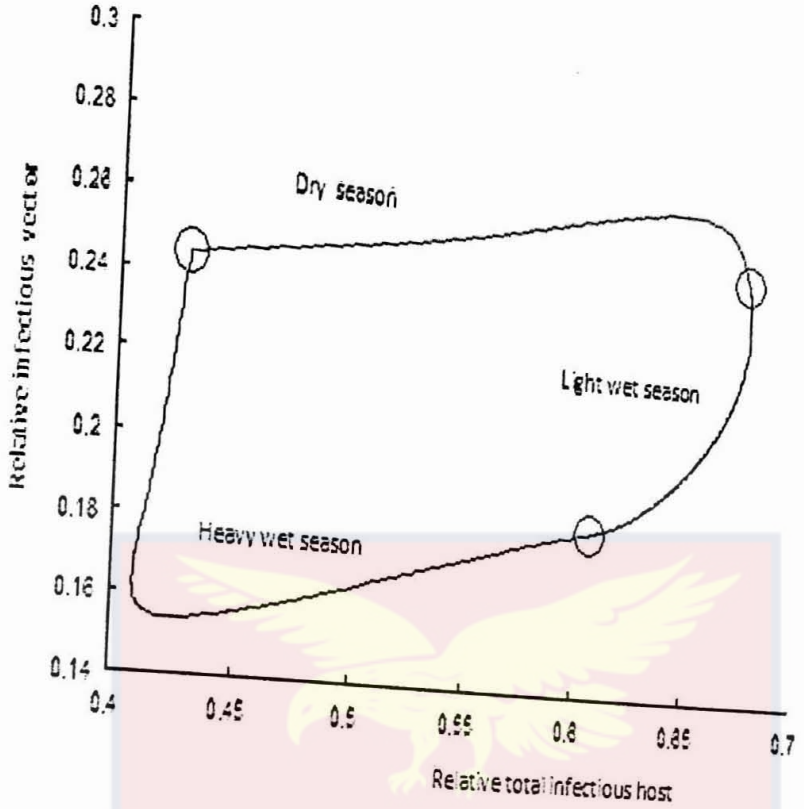


Figure 63: **Relative infectious vector against relative infectious host**

Dynamics of relative infectious vector with relative severe infectious host

Figure 64 explains the cyclic nature of severe malaria infections. Similar to Figure 63, the green curve represents the relationship between relative infections in the vector and the relative severe infections in the host during the dry season and begins from the light wet season. It indicates relative severe host infection is decreasing whilst there is a continuous increase in the vector infection. After a while both infections decreases but faster in the host infections. This season gives way to the heavy wet season and vector and host infections relationship is represented by a red curve. The curve indicates both infections decreasing for a short time, but faster in the vector infection. There is an increase in both infections, but this time faster in the host infection. The red curve gives way to the blue curve which represents the relationship in the light wet season. This curve indicates an increase in the vector infection as against decreases in the host

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infections. This cycle continue as the blue hands over to the green curve.

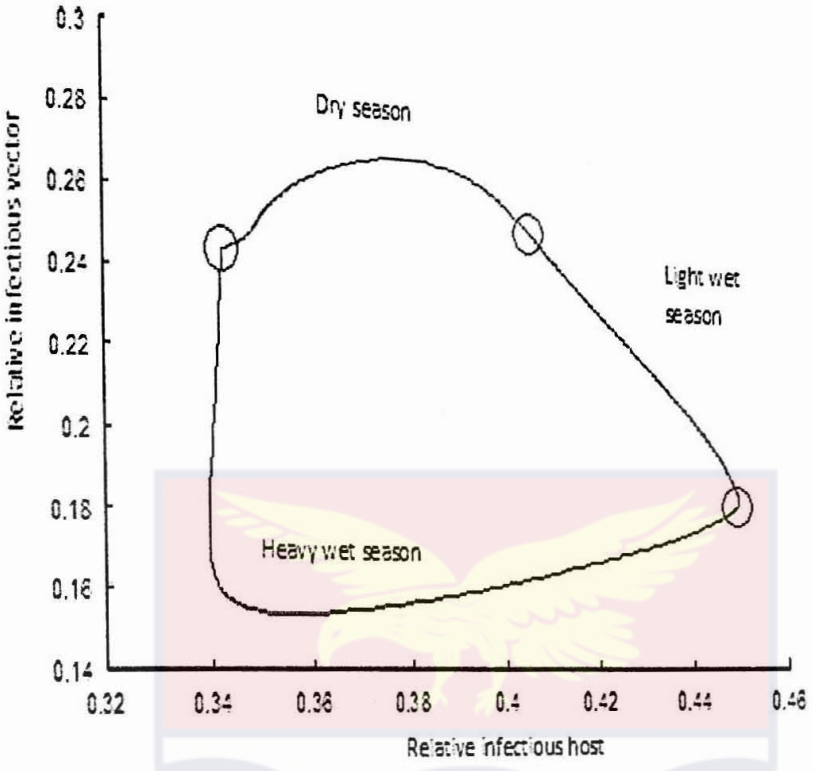


Figure 64: **Relative infectious vector against relative severe infectious host**

Malaria incidence per month

We here define the incidence of malaria as the number of new cases of malaria reported per month. In the NDM−model there are two types of incidence:

1. The rate at which new cases are reported for severe malaria and
2. The rate at which new cases reported for re−infected malaria.

Figure 65 shows the incidence of malaria per month in a given year. The red curve represents the rate at which new cases of malaria are reported in a given month in a year and the blue curve represents the re−infected cases reported in a given month of the year.

We observe from Figure 65 that for the reported severe cases of malaria remains relatively steady from January to May. The highest is reported in July

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and from there it begin to decrease. On the other hand, the lowest reported re−infected cases occurs in April and the highest in October. It is further observed that in general, we have more reported cases of re−infection than severe infection even though the lowest of the re−infection is less than the lowest severe malaria case.

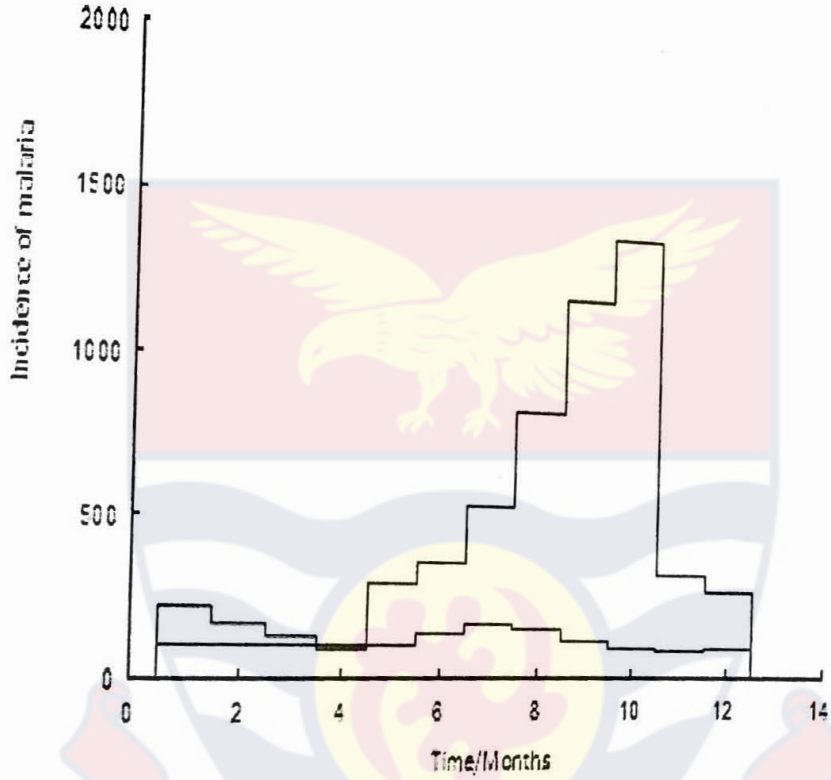


Figure 65: **Incidence per month**

Comparing the Modified NDM−model with the Periodic Model

In this section, we present a number of figures to compare the modified NDM−model with constant mosquito population (which we will refer to as Modified NDM−model) and the Modified NDM−model with seasonal mosquito birth rate (which we refer to as the periodic model) on how they estimate human malaria infection in a given period. We will consider this comparison in two forms.

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1. We compare the plots of human malaria infection/recovery estimated by modified NDM−model and the periodic model against the variation of minimal mosquito birth rate parameter b_{min}. A point on each curve is the estimates of the human infection corresponding to a particular value b_{min} in the period, except the points on the curve represented modified NDM−model estimates which takes a constant birth rate.

2. We compare the plots of human malaria infection/recovery estimated by modified NDM−model and the periodic model against the variation of the ratio of mosquito population to human population (m) for a given minimal mosquito birth rate parameter b_{min}.

We use the parameter values $\beta_H = 0.06$, $b_1 = 0.04$, $\gamma = 0.01$, $\alpha = 0.04$, $\omega = 0.01$, $c = 0.25$, $k = 0.12$, $\mu_M = 0.05$ and $\nu = 0.15$ with initial populations $(1000, 10, 0, 0, 10000, 10, 100)$ for all the simulations in this section, except when a particular parameter is varied for the purpose of comparison.

Comparing the modified NDM−model with the periodic model when b_{min} is varied

The Figures 66, 67 and 68 are presented to compare the modified NDM−model with the periodic model on how they estimate human malaria infection/recovery in a given period for a given minimal mosquito birth rate. We plot the estimated human malaria infection by the modified NDM−model and the periodic model against the mosquito birth rate to obtain Figure 66. The estimated re−infectiousness by the modified NDM−model and the periodic model are plotted against the mosquito birth rate to obtain Figure 67 and the estimated recovery by the modified NDM−model and the periodic model are also plotted against the mosquito birth rate to obtain Figure 68.

A point on each curve is a particular estimate of human malaria infection/recovery corresponding to a particular value of b_{min} in the period, except

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the points on the curves represented by the estimates of modified NDM−model which takes a constant mosquito birth rate equal to the mortality rate.

The modified NDM−model gives only one estimate of human infection/ recovery in each case. That is denoted by 'xave' for average infection, 'yave' for average re−infection and 'rave' for average recovery. All of them are represented by a black curves in the figures. The periodic model gives three estimates in each case. These include:

1. The highest infection/recovery recorded in the period denoted by 'xmax' for maximum infection, 'ymax' for maximum re−infection and 'rmax' for maximum recovery all represented by red curve in the figures,

2. The mean infection/recovery recorded over the entire period is denoted by 'xmean' for mean infection, 'ymean' for mean re−infection and 'rmean' for mean recovery all represented by green curve in the figures and

3. The lowest infection/recovery recorded in the period denoted by 'xmin' for minimum infection, 'ymin' for minimum re−infection and 'rmin' for minimum recovery all represented by blue curve in the figures.

From the Figure 66, the numerical average infection (xave) of the modified NDM−model estimates the human infection to be about 14%. The maximal infection (xmax) of the periodic model estimates the human infection to be 25% when the mosquito birth rate is 0.04 and decreases with increasing mosquito birth rate. The minimal infection (xmin) of the periodic model estimates the human infection to be about 7% when the mosquito birth rate is 0.04 and increases with increasing mosquito birth rate. The mean infection (xmean) of the periodic model estimates the human infection to be about 12% when the mosquito birth rate is about 0.04 and increases with increasing mosquito birth rate.

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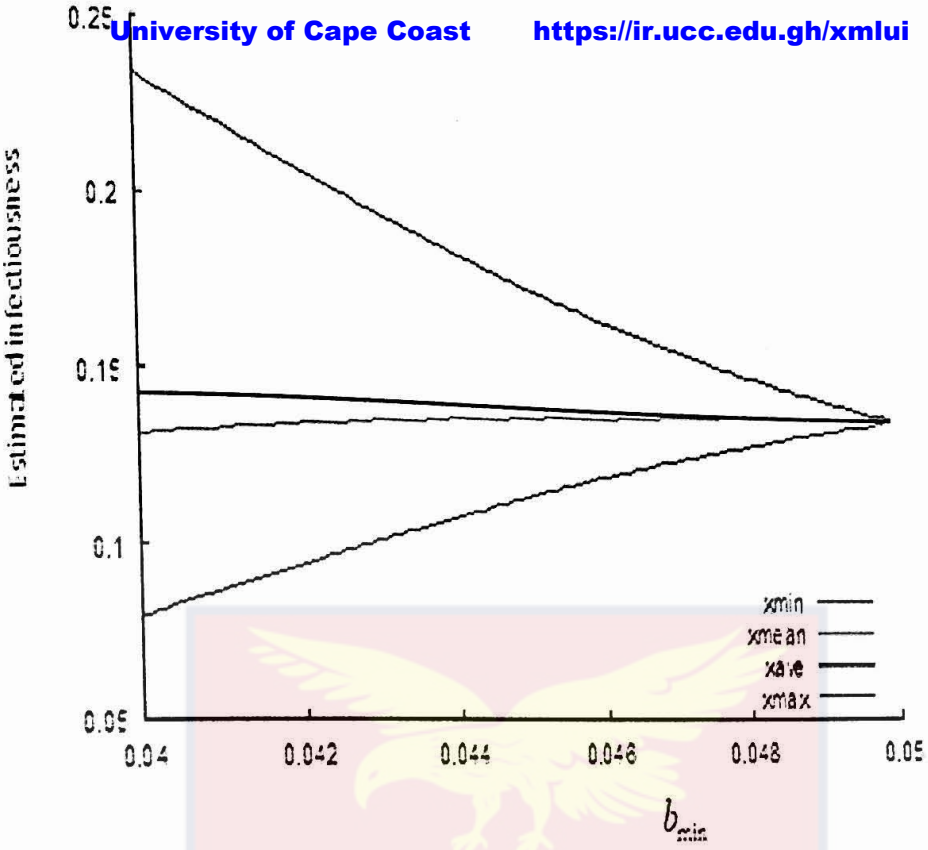


Figure 66: **Comparing estimated infectious by modified NDM−model and periodic model**

Here, it is clear that the difference between the average infection estimated by modified NDM−model and mean infection estimated by the periodic model when the cycle starts with low mosquito birth rate is about 2%, and can make a tremendous impact on malaria control strategies. On the other hand, when the cycle starts with high mosquito birth rate like $b_{min} = 0.049999$, which is close to the mortality rate, then we have both the modified NDM−model's average infection and the periodic model's mean infection estimating the same amount of human malaria infection.

From Figure 67, the numerical average re−infection 'yave' of the modified NDM−model estimates the human re−infection to be about 10%. The maximal re−infection 'ymax' of the periodic model estimates the human re−infection to be 25% when the mosquito birth rate is 0.04 and decreases with increasing

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mosquito birth rate. The minimal re−infection 'ymin' of the periodic model estimates the human re−infection to be about 2% when the mosquito birth rate is 0.04 and increases with increasing mosquito birth rate. The mean re−infection 'ymean' of the periodic model estimates the human re−infection to be about 10% when the mosquito birth rate is about 0.04 and remain constant with increasing mosquito birth rate.

We observe that the average re−infection estimated by the modified NDM−model is equal to the mean re−infection estimated by the periodic model for whatever mosquito birth rate considered.

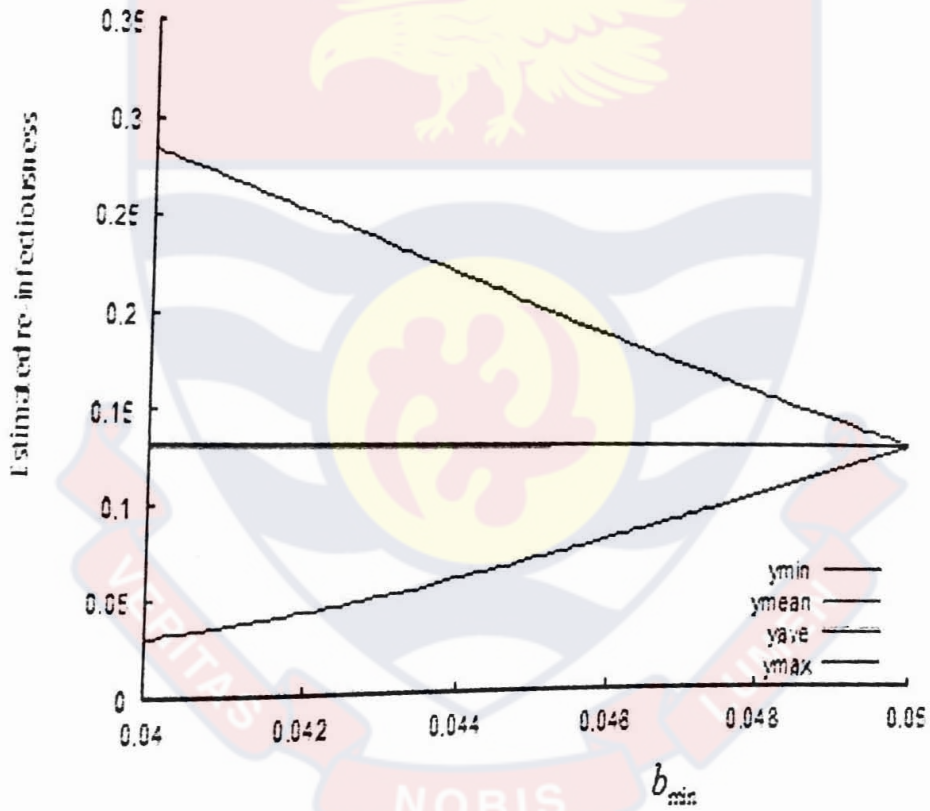


Figure 67: **Comparing estimated re−infectious by modified NDM−model and periodic model**

From Figure 68, the numerical average recovery (rave) of the modified NDM−model estimates the human recovery to be about 57%. The maximal recovery (rmax) of the periodic model estimates the human recovery to be 60%

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when the mosquito birth rate is 0.04 and decreases with increasing mosquito birth rate. The minimal recovery (rmin) of the periodic model estimates the human recovery to be about 41% when the mosquito birth rate is 0.04 and increases with increasing mosquito birth rate. The mean recovery (rmean) of the periodic model estimates the human recovery to be about 51% when the mosquito birth rate is about 0.04 and remain constant with increasing mosquito birth rate.

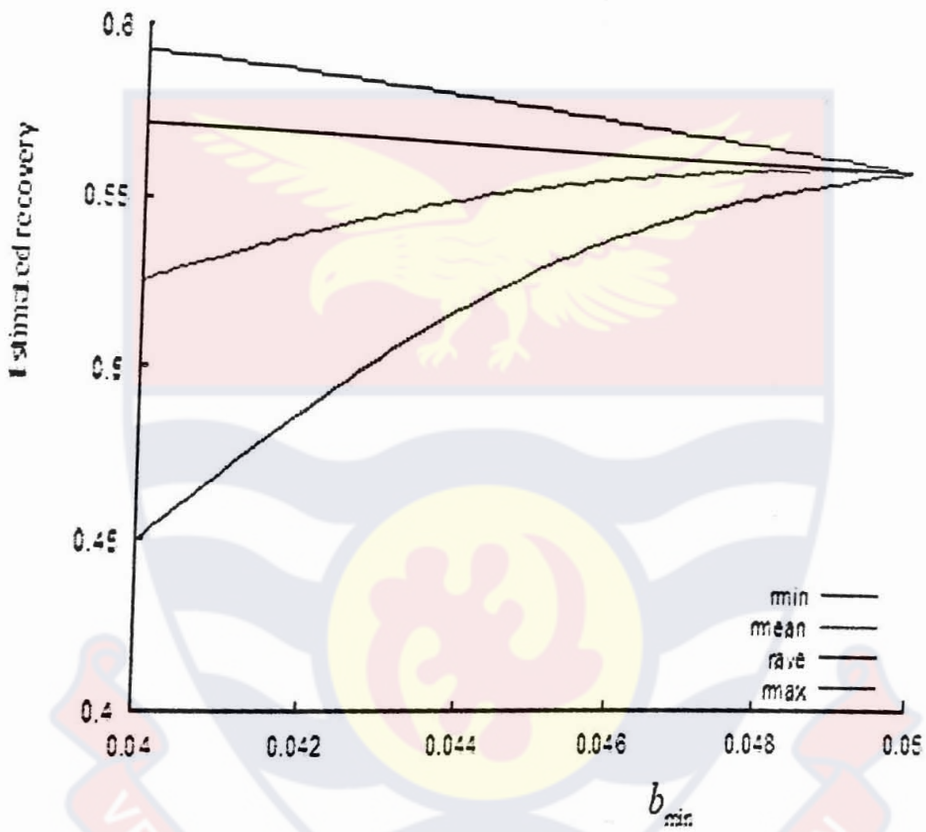


Figure 68: **Comparing estimated recovery by modified NDM−model and periodic model**

Similar to Figure 66, the difference between the average recovery estimated by modified NDM−model and mean recovery estimated by the periodic model when the cycle starts with low mosquito birth rate is about 16%, and can make a tremendous impact on malaria control strategies. On the other hand, when the cycle starts with high mosquito birth rate like $b_{min} = 0.049999$, which is close to the mortality rate, then we have both the modified NDM−model's

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average recovery and the periodic model's mean recovery estimating the same amount of human malaria recovery.

Comparing the modified NDM−model with the periodic model when m varied for a given b_{min}

Figures 69, 70 and 71 illustrate how the modified NDM−model and the periodic model estimate human malaria infection, re−infection and recovery respectively. The upper red curve represents maximal infection in Figure 69, maximal re−infection in Figure 70 and maximal recovery in Figure 71. The lower red curve represents minimal infection in Figure 69, minimal re−infection in Figure 70 and minimal recovery in Figure 71. The green curve represents mean infection in Figure 69, mean re−infection in Figure 70 and mean recovery in Figure 71. These three curves (the two red curves and the green curve) represents estimates from the periodic model. The fourth curve which is blue, represents average infection in Figure 69, average re−infection in Figure 70 and average recovery in Figure 71. This blue curve is obtained from the modified NDM−model.

We observe in Figure 69 that there is a general trend in the estimation of the relative infectiousness for any given b_{min} when m is varied. All infectious estimates attain their maximum when $0 < m < 15$ and after that they all decrease equally as m increases. We also see that for lower birth rates the maximal and the minimal infection differ so much from the average infection, especially for lower m and the mean infection slightly differ from the average infection. However, at higher mosquito birth rate the maximal and the minimal infection closely estimate the average infection and the mean infection is almost on the same trajectory as the average infection.

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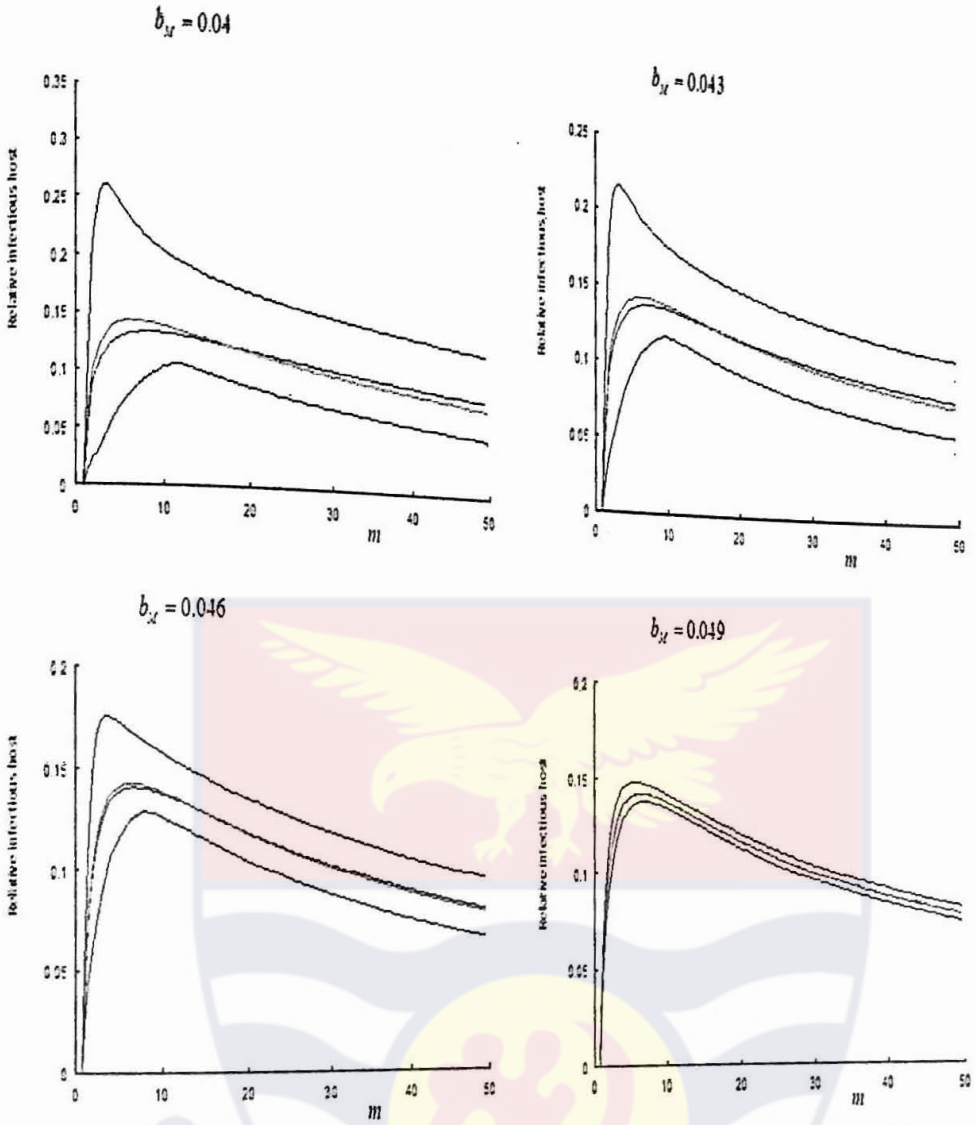


Figure 69: **Estimation of human malaria infection**

In Figure 70, there is a general exponential increase in the re−infectious estimates for any given b_{min}, as m increases. We observed that the estimation of the maximal and the minimal re−infection differ significantly from the average re−infection for lower b_{min} and seems to even increase as m increases. The mean re−infection shows similar behavior to the average re−infection. However, at higher mosquito birth rate the maximal and the minimal re−infection closely estimates the average re−infection and the mean re−infection is almost on the same trajectory as the average infection.

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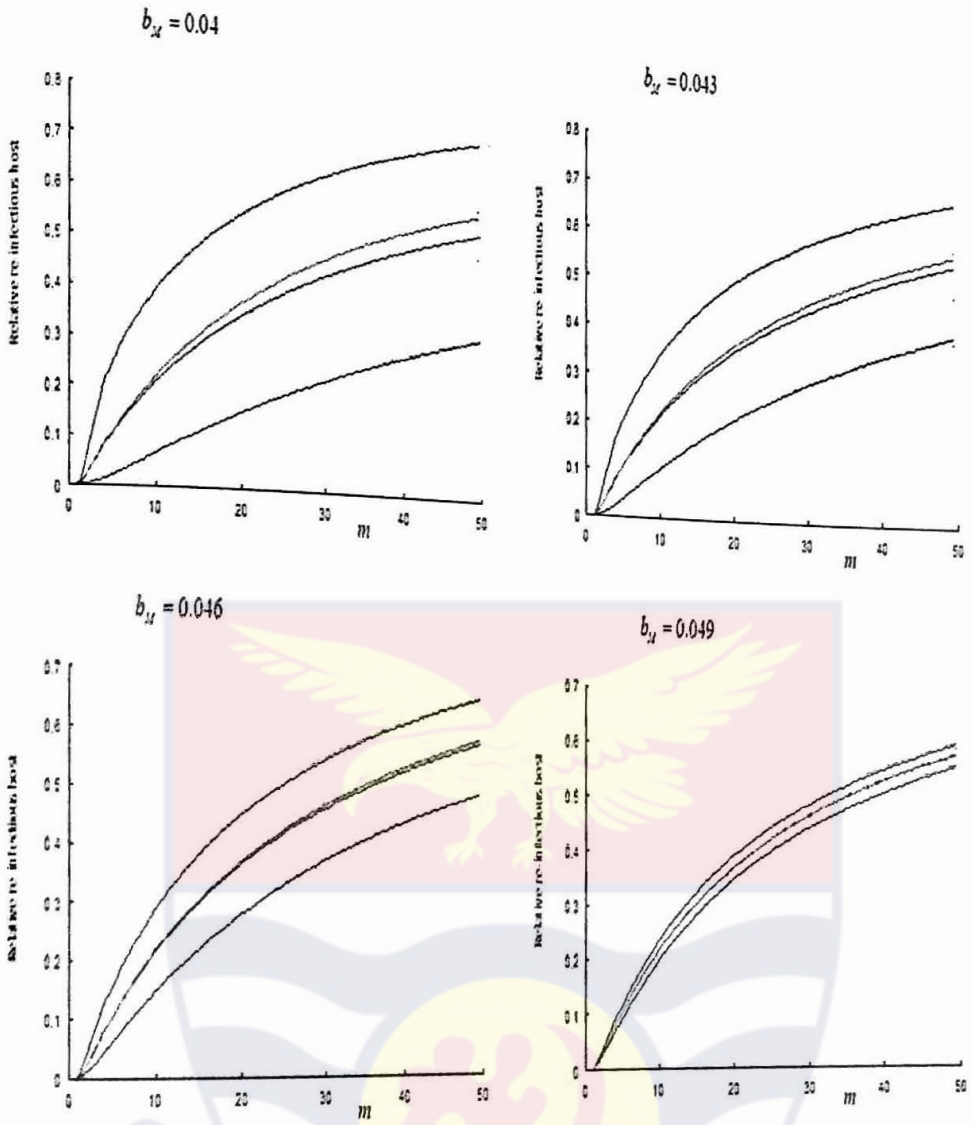


Figure 70: **Estimation of human malaria re−infection**

Similar to Figures 69 and 70, Figure 71 also show a general trend in the estimation of human malaria recovery by the modified NDM−model and the periodic model. For any given b_{min}, as m is varied, all the various recovery estimates attain their maximum within $0 < m < 15$ and there after decreases as m increases. We observe that for lower birth rates the maximal and the minimal recovery differ significantly from the average recovery, especially for lower m and the mean recovery slightly differ from the average recovery. However, at higher mosquito birth rate the maximal and the minimal recovery closely estimate the average recovery and the mean recovery is almost on the same trajectory as the average recovery.

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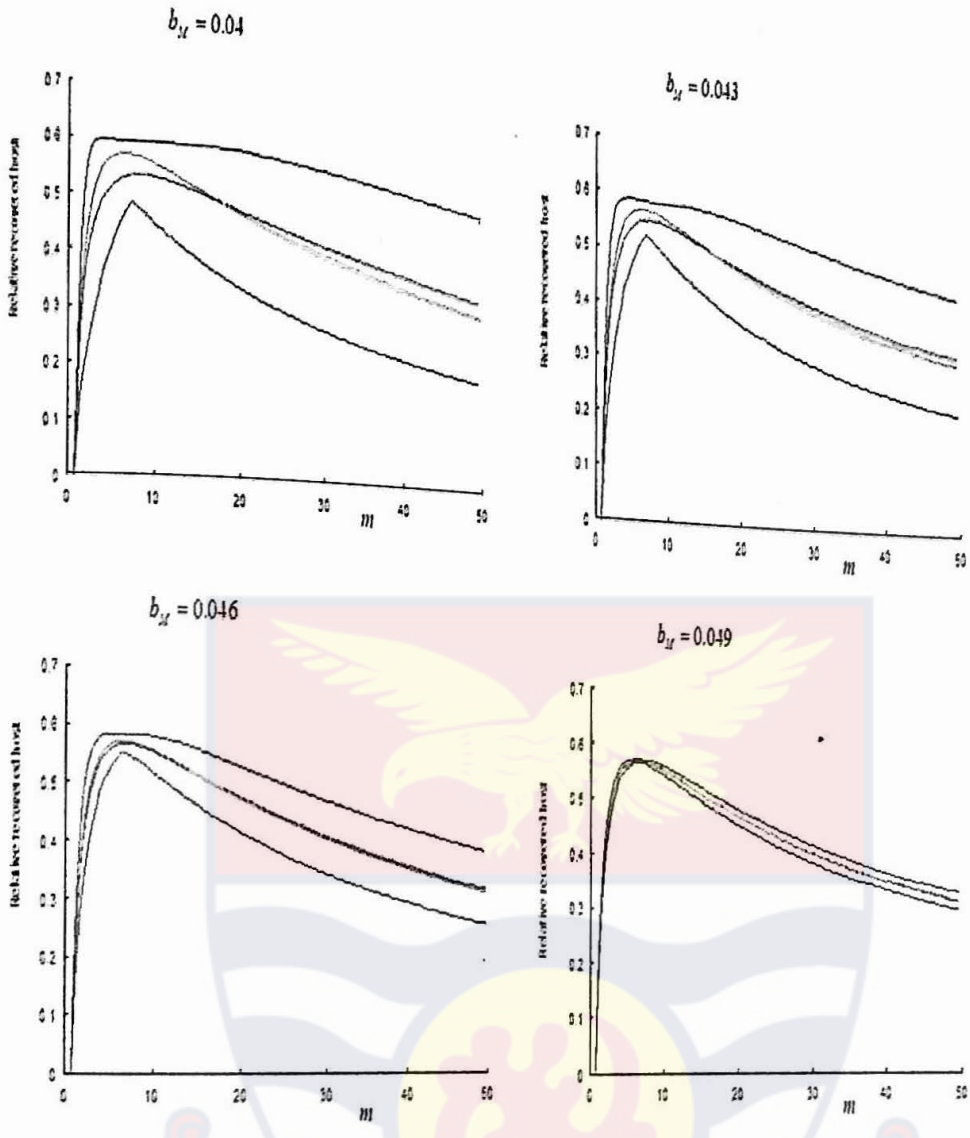


Figure 71: **Estimation of human malaria recovery**

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CHAPTER SEVEN

SUMMARY, DISCUSSION AND CONCLUSION

Summary

The main thrust of this thesis is to analyse six deterministic malaria models. This includes: the NDM−model, the simplified version of the NDM−model, the Ross model, the periodic verson of the Ross model, the modified NDM−model and the periodic version of the modified NDM−model.

The NDM−model is a system having two infectious host classes (clinically infectious and reinfectious) , one recovered and susceptible class for host population and one infectious and susceptible class for mosquitos. The parameters are the incidence parameters, recovery parameter and parameter for loosing immunity in the host population. The other parameters in host equations are: the natural (background) death rates and the disease-induced death rate. The parameters involve in the vector equations are: incidence, birth and death parameters. The mosquito population is assumed constant but the host population can change. The simplified NDM−model is obtained from the NDM−model by assuming constant host population.

The main results for the simplified NDM−model are that, the disease-free is a global attractor for the bifurcation parameter $K < 1$ and the unique endemic equilibrium is a global attractor for $K > 1$ and the endemic equilibrium arises through a transcritical bifurcation for $K = 1$. The parameter K depends mainly on the incidence rates, the recovering rate for the clinically infectious, the mortality rate for mosquitos and the constant ratio m between the total mosquito and host populations. Also the infectious populations depend mainly on these parameters where $1/K$ estimates the part of susceptible host populations.

The main results for the NDM−model are that at the beginning for a pe-

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riod of 3-5 years the dynamics is well estimated by the dynamics of the simplified NDM−model. After that the dynamics is a slow motion near the curve of endemic equilibria of the simplified NDM system depending on the parameter m. If the host birth rate is less than the natural death rate the host population is decreasing on the curve of endemic equilibria and as m is increasing the situation becomes more endemics. Then there is no equilibrium for the NDM−model. If the host birth rate is in an interval a little above the natural death rate there is a saddle endemic equilibrium for the NDM−model with a one dimensional unstable manifold well approximated by the curve of endemic equilibria for the simplified NDM−model. On one side of the saddle the host population decreases and the situation becomes more endemic. On the other side the host population increases and in long term the situation becomes disease-free. There are found analytical expressions for the endemic equilibrium for the simplified NDM−model and the saddle point of the NDM−model and they are proved to be unique. The other results are mainly based on numerical experiments.

The modified NDM−model is a modification of the NDM−model where latency is added to the mosquito population and the host population is assumed constant.

The main result for the modified NDM−model is that disease−free equilibrium is a global attractor for the bifurcation parameter $Bm < 1$ and there is a unique endemic equilibrium which is a global attractor for $Bm > 1$. For $Bm = 1$ there is a transcritical bifurcation giving the endemic equilibrium. Analytical expressions for the endemic equilibrium are obtained and the uniqueness is proved. Other results are mainly numerical. Anyhow there is also shown that the clinically infectious population obtains a maximum for a certain m after which it decreases for increasing rate m between the mosquito and the host populations and it is shown that the re−infectious population increases with m. Analytical expressions both for the maximal clinically infectious and for the m where the

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maximum is attained are obtained. The maximum depends only on the ratios between the recovering parameters and the rate of loss of immunity and a parameter for the incidence to re−infectious class. It does not depend on other incidence parameters or the mortality rates.

A new version of periodicity is introduced in malaria modelling using the seasonal birth rates of the mosquito. The mosquito population is assumed to oscillate with a period of one year, since the birth rates are different in dry, heavy rain and light rain seasons. We incorporated this seasonal birth rate into the Ross model and the modified NDM−model to obtain periodic versions of these models.

The main results introducing periodicity are that in the high endemic cases the endemicity can vary considerable if the mosquito populations have big variations like 10−20 times more in wet seasons than in dry. For low endemicity the variations are less also relatively. The periodic models have a global periodic attractor in the endemic case which occurs through a bifurcation exactly at same time as in the non-periodic case if the value of m for the periodic systems is taking as the average over one year. In the disease−free case the disease−free equilibrium is a global attractor. The average infectious population in the periodic models can differ from the constant value given by corresponding non−periodic system where the ratio m is taken as the average mosquito population for the corresponding periodic system.

Discussion

The uniqueness of the endemic equilibrium is common for most models with linear incidence rates as, for instance, except NDM−model, Ross and Ngwa models. In these models the endemic equilibrium is also a global attractor. In the case of non-linear incidence it is usual to have more than one endemic equilibrium. This can also happen in the model of Chitnis with more complicated

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and realistic incidence. In most models the endemic equilibrium arises through a transcritical bifurcation like in the NDM−model. In models with non−linear incidence saddle−node bifurcations are usual and it can happen in some models of Chitnis.

There is a slow motion when the host population varies is also observed in other models except, for instance, in Chitnis model where the immigration is considered strong. If the motion cannot be divided into slow and fast motions the simplification with constant host population does not give a good approximation. Some models like Ngwa and Chitnis have a stable equilibrium instead of the saddle equilibrium of the NDM−model as they consider stabilizing factors of host populations.

For other systems (like Chitnis (2005) and Ngwa and Shu (2000)), there might be a stable endemic equilibrium on the slow motion curve attracting all solutions. Whether this endemic equilibrium can be reached in realistic time, depends on the concrete parameter values and the initial conditions. In Chitnis (2005), there is sometimes the possibility for more than one endemic equilibrium.

The main difference between the NDM−model and other malaria is that, the maximal clinical infection is always less than the corresponding infectious classes in the other models.

The ratio $K = \frac{\beta_H \beta_M m}{\gamma \mu_M}$ is an important approximative bifurcation parameter, so that there is a transcritical bifurcation for the simplified system at $K = 1$ and endemic solution exists only for $K > 1$. The proportion of susceptible population is approximately $1/K$. This quantity K can be a very good candidate for some type of basic reproductive number R_0.

Experiments show that by varying different parameters and initial conditions for the first three years, the simplified NDM−model approximates well, to the main NDM−model with a relative error of less than two percent. This

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situation occurs if the simplified model has an endemic equilibrium with a size not too small (i.e., the value of K is not too near to the bifurcation value) and in addition the sizes of some of the populations are not less than one percent of the total population.

Experiments also show that in the long term the dynamics of main NDM−model follows the curve C_e which has a saddle point on it as describe above.

We have more detailed examined typical high endemic situation. For instance, analysing the Ross model incorporated with the seasonal mosquito birth rate, we had the estimates for host and vector infection in an endemic situation as follows: The minimum relative infectious host population is 0.84 and attained June, the maximum relative infectious host is 0.97 and attained in October/November, the minimum relative infectious vector is 0.40 and attained in June and the maximum relative infectious vector is 0.54 and attained in December/January. The other estimates includes: the maximum increase in infectious host, 1.6, occurring in July, maximum increase in infectious vector, 57.1, occurring in August and the mean relative infectious host is 0.92.

Comparing Ross model and the periodic model, we establish the following estimates: the Ross model predicted a relative infectious host population at endemic as 0.94 and the periodic model reports a mean relative infectious host population as 0.92.

Two types of comparison were made for the modified NDM−model and the periodic model: comparing the estimates of malaria infection when the amplitude of mosquito population which is determined by minimal mosquito birth rate (b_{min}) is varied and also comparing the estimates of malaria infection when mosquito to human ratio is varied for a given amplitude of mosquito population.

In the first comparison, three quantities were estimated (i.e., infectious, re−infectious and recovery) for both models and the average estimates from modified model compared with the mean estimates by the periodic model. The

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following were the simulation results:

1. The difference between the average infection estimated by modified NDM −model and mean infection estimated by the periodic model when the cycle starts with low mosquito birth rate is about 2%, and can make a tremendous impact on malaria control strategies. On the other hand, when the cycle starts with very small amplitude of mosquito population (high mosquito birth rate like $b_{min} = 0.049999$ which is close to the mortality rate which is 0.05), then we have both the modified NDM−model's average infection and the periodic model's mean infection estimating the same amount of human malaria infection.

2. The average re−infection estimated by the modified NDM−model is equal to the mean re−infection estimated by the periodic model for whatever mosquito birth rate considered and

3. The difference between the average recovery estimated by modified NDM −model and mean recovery estimated by the periodic model when the cycle starts with low mosquito birth rate is about 16%, and can make a tremendous impact on malaria control strategies. On the other hand, when the cycle starts with very small amplitude of mosquito population (high mosquito birth rate like $b_{min} = 0.049999$, which is close to the mortality rate), then we have both the modified NDM−model's average recovery and the periodic model's mean recovery estimating the same amount of human malaria recovery.

In the second comparison, the estimation of malaria infection and recovery shows similar trends. We observe that both have their maximal, minimal, mean and average estimates attaining their maximum maximum within $0 < m < 15$ and there after decreases as m increases for any amplitude of mosquito population. However, they also show that for high amplitude of mosquito population the

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maximal and minimal estimates differ significantly from the average estimates, and the mean estimates of the periodic model slightly differ from the average estimates. For low amplitude of mosquito population, both the maximal and minimal closely estimate the average and the mean estimates is almost same as the average.

The re−infectious estimates shows a continuous increase in re−infection as m increases for any amplitude of mosquito population, but it however, presents similar behaviour to infection and recovery estimates. Thus, it shows that for high amplitude of mosquito population, the maximal and minimal estimates differ significantly from the average estimates, and the mean estimates of the periodic model slightly differ from the average estimates. For low amplitude of mosquito population both the maximal and minimal closely estimate the average and the mean estimates is almost same as the average.

In the middle of heavy rain season, the severe infectious host population can be much greater than possibly at endemic equilibrium, for the non-periodic system with the same parameters except birth rate of mosquitoes and for any density of mosquitoes. This is a consequence of low re-infectious population. The incidence of the infectious host populations (amount of new clinical cases for a period) can also be calculated and for high endemic situation as in the Figures presented, the incidence is considerable higher in the middle of the rain season as observed in many places in practice. Anyhow for low endemicity, this is not the case which might give reasons for further modifications of the model.

Conclusion

Most mathematical models of malaria can be divided into two classes. Those simplified, assuming total host and vector population constant, and those allowing at least the host population to change. In general, the change in the size of the total host populations are slow compared with the other developments

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and then the system can be very well approximated by a simplified system. An exception is when the migration factor is greater as in Chitnis et al. (2006) and Chitnis et al. (2008), and then affecting essentially the dynamics for some initial conditions.

In models with constant populations, we have at least one equilibrium that is the disease-free situation. Disease-free equilibrium points are steady state solutions where there is no infection in either the human or mosquito populations.

In most models for some parameter ranges we also have endemic equilibria, where the disease persists in the population (all state variables are positive). In some models (and this is usual in models with non-linear incidence terms) we can have more than one endemic equilibrium.

Usually, the endemic equilibrium appears at a transcritical bifurcation at the disease-free equilibrium. This is the case for the simplified Ross and NDM−model and main Ngwa and Shu (2000) model and usually also for the Chitnis et al. (2006) model. There is also a possibility for saddle-node bifurcations where two endemic equilibria arise suddenly, one stable and the other of a saddle type. This can happen in the Chitnis et al. (2006) model and is usually in models with non-linear incidence. In Chitnis et al. (2006), this sometimes happens on the slow motion curve but never for the scaled versions. In the NDM−model, the existence of a real endemic equilibria depend approximately on the value of a bifurcation parameter K of four essential parameters (contact rate between susceptible humans and infectious mosquitoes, contact rate between susceptible mosquitoes and infectious humans, rate of recovery from clinical infection and mortality rate of mosquitoes) and the ratio between mosquitos and the host populations. This is also usual for many other models.

In all our models endemic equilibrium can be calculated analytically and uniqueness proved for the ranges of parameter values of interest. The global stability of the endemic equilibrium can numerically be proved. In addition, the en-

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demic equilibrium for the non-periodic system of the modified NDM−model can be calculated analytically and an expression for the maximal clinically infectious host population can be obtained. This maximum, depends only on parameter c and ratios $\frac{\gamma}{\omega}$ and $\frac{\gamma}{\alpha}$ between recovering parameters and the parameter of loss of immunity. It does not depend on the incidence parameters nor on the mortality rate of mosquitoes. For increasing recovery γ the maximum is decreasing.

Both systems have a bifurcation from disease-free situation at $Bm = 1$ and this is the only bifurcation observed. In the case of non-linear incidence functions or when the parameters are outside our ranges, there can be other bifurcations. In the case of non-linear incidence function, disease-free for one case does not imply disease-free for the other. For examples of other types of bifurcations which can occur in case of non-linear incidence function we refer to (Akoto et al., 2012).

The variation in host population does not have a great effect on the dynamics of the NDM model but the latency of mosquito population is known to be serious it is natural to modify the model by assuming host population constant and introducing a latency class. Introducing periodicity makes a lot of knew mathematical problems but is very important why it is natural to study this effect.

The obtained maximum for the clinically infectious when the ratio m varies can be of great importance as elimination of mosquitos have a positive effect only if the mosquito population is small.

The effect of periodicity is similar in our cases to that observed for Ross model in May and Anderson except that we do some more detailed examinations and consider periodicity in a more complicated model. The incidence of the disease for high endemic parameters follow known statistics in Ghana with highest incidence during the later heavy rain period. Anyhow for lower endemicity this coincidence is not observed giving need for possible further modifications of

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model.

For future research it is important to study more detailed the outcome of periodic models and models with non−linear incidence. Also it is important to get mathematical proofs for the global stability of attractors.

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APPENDIX: SOME BIOLOGICAL AND MEDICAL BACKGROUND OF MALARIA

Brief History of Malaria

The history of malaria dates back so many years ago, and indeed there is evidence of how prehistoric man was being affected. Hippocrates was among the first people to detect malaria in the fifth century BC. He did not only identify clinical details, but was able to established the association between the disease and various environmental and seasonal factors. He particularly noted a connection with stagnant water, which today we now recognize as breeding habitat of the mosquito (Web Site, 2004). Later, an accurate description of the disease was given by Celsus round about AD 30. Recurrent epidemics continued right on through the Middle Ages, especially in Europe (Cunha & Cunha, 2008). These were widely referred to in the seventeenth and eighteenth centuries as the "ague". The Italian term *mal'aria* "bad air", appeared in the eighteenth century, reflecting the common belief that the foul air arising from marshes was somehow involved in causing the disease. The French word *paludisme*, also indicating the association between the disease and swamps, was only introduced much later in the 1880's.

There is no clear documentation to what extent a general awareness of the connection between certain fevers an marshy localities directly encouraged the draining of swamps, as already practiced by the Greeks and Romans as early as the sixth century BC, it may be that, natural trends in economic and social development automatically led to a certain degree of disease limitation and control, for example, through the elimination of marshes and swamps in an attempt to improve the neatness of the surroundings of a settlements. Ross (1909), however, certainly believed that "The ancients knew that drainage reduces malaria" and he also considered that a wide variety of preventive measures had been followed

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since the earliest times, but unconsciously.

The earliest and the biggest success in systematically combating malaria came with discovery, at the beginning of the seventeenth century, of the use by Peruvian Indians of the bark of a certain tree. This was later named *Cinchona* and quinine was eventually isolated from it (Remedy, 2013). In the second half of the nineteenth century a substantial progress was made in the advances in bacteriology. When Laveran the first to see and describe malarial parasites in human red blood cells in 1880, for which he received a Nobel Prize in 1907. However, Manson had already shown in 1877 that a certain species of mosquito could act as a vector for human filaria, and he suggested in 1894 that malaria might be transmitted to humans by mosquitoes. Three years later, in 1897, Ronald Ross found a form of the malarial parasite in the body of a mosquito that had previously fed on an infected malaria patient. In 1898 Ross saw sporozoites in the salivary gland of a mosquito, and then established experimentally the complete cycle for bird malaria. In the same year, Grassi, Bignami and Bastianelli in Italy described the cycle for human malaria transmitted by anopheline mosquitoes. This was confirmed by Ross the following year, and in 1902 he was awarded a Nobel Prize for his substantial contributions in elucidating the whole complex cycle of human malaria (Cox, 2010).

These discoveries had an immediate impact on public health control and various anti-mosquito measures, such as the use of oil or Paris Green as larvicides were already being taken in 1899 by Ross in Sierra Leone. Gorgas and Le Prince in Cuba and again by the latter in the Panama Canal zone from 1904 to 1914. This kind of work has been greatly explained in the present century, although of course there have been many further advances in malaria parasitology as a whole (Marshall, 1913).

The development of a series of efficient synthetic drugs against the malaria parasite, stimulated by shortages of quinine During World War I there was a

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shortage of quinine and stimulated a series of efficient synthesis of drugs against the malaria parasite. This began in 1924 with Schulemann's discovery of pamaquine and this was followed by mepacrine in 1930, chloroquine in 1934, etc. These successes were beginning to be threatened by 1961, when reports started to come in from Latin America and South-east Asia of strains of plasmodium falciparum that were resistant to chloroquine. This has stimulated the search for new therapeutic drugs and because the malaria parasite has developed resistance to all the above drugs in different parts of the world. In response to this, WHO recommended artemisinin combination therapy in recent years (Hobbs & Duffy, 2011).

According to Hemingway and Ranson (2000) the direct insecticidal action against mosquitoes became possible in 1935 with the application of pyrethrum sprays to kill adult mosquitoes in South Africa, India, etc., while around 1939 the insecticidal action of DDT was first discovered. A number of other useful insecticides have been developed, but their utility is now being eroded by the gradual appearance in recent years of insecticide resistance in many important species of anopheline mosquitoes.

Trigg and Kondrachine (1998) indicated that further progress has been made through the institutions of internationally promoted activities. Thus, the World Health Assembly adopted the concept of malaria eradication in 1955, followed by global campaign two years later. For 15 years good results were obtained in Europe and North America and in parts of Asia, USSR and Australia. Success in tropical countries was more limited. And in 1969 the World Health Organization revised its strategy to include a more multidisciplinary range of approaches, including a greater recognition of the importance of general health service, further efforts to find new insecticides and new ant-malarial drugs, improved forms of surveillance, etc.

Unfortunately, new difficulties have recently arisen in several tropical coun-

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tries with malaria again being on the increase. Drug resistance, insecticide resistance and increased contact-rates due to the rising volume of international travel, are amongst the factors thought to be responsible. New approaches are therefore required to deal with a very serious and widespread disease threat which is in many ways more complex than it used to be. It seems probable that new quantitative methodologies, specially designed to handle the complex and interlocking systems of relevant factors, will have to be developed and applied if public health authorities are to bring malaria finally under control in large areas of the developing world.

Malaria remains one of the major tropical health challenges. It is estimated to be endemic in 107 countries worldwide and in continents except Europe and North America. Although in the 1950s it was found in about 140 countries, malaria is seen as a risk to over 2.4 billion people globally today. It affects an estimated 700 million people directly and results in about 200 million deaths annually. Ninety per cent of all morbidities and mortalities are found in Africa south of the Sahara. Between 1999 and 2004 malaria affected between 1.1 million and 1.3 million people in Africa south of the Sahara. In 2004 alone, the World Health Organization (WHO) estimated malaria incidence to be between 350 million and 500 million cases (Malaria, Organization, & UNICEF, 2005).

Since the end of the last millennium, governments of malaria endemic countries have identified malaria as a high priority disease and there is a growing commitment to its control. International concern has resulted in the WHO's establishment of the Roll-Back Malaria (RBM) programme. RBM consists of a worldwide partnership in which all stake holders contribute skills and resources to maximize the impact of malaria control. Its major objective is to significantly reduce the burden of malaria through interventions adapted to local needs. Key among the interventions of WHO-RBM antimalarial treatment, possession and use of insecticide treated bed nets and the use of intermittent preventive treat-

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ment among pregnant women, indoor and outdoor residual spraying as well as thermal fogging. In addition, all of the 191 member states of the United Nations pledged to achieve certain development targets by the year 2015. These goals, together with their specific tasks, are dubbed the Millennium Development Goals (MDG) (UnitedNations, 2000). The sixth goal stresses the need to halt and reverse the spread of malaria. The objective is to reduce its incidence by fifty percent by 2015. Beside, the Ghana Poverty Reduction Strategy Paper I also emphasizes the governments determination to reduce the impact of malaria among its population.

Recent reports indicate significant decreases in malaria incidence. For instance, the World Malaria Report 2012 indicates that, there were about 219 million cases of malaria in 2010 and an estimated 660000 deaths. Africa is the most affected continent: about ninety percent of all malaria deaths occur there. Between 2000 and 2010, malaria mortality rates fell by 26% around the world. In the WHO African Region the decrease was 33%. During this period, an estimated 1.1 million malaria deaths were averted globally, primarily as a result of a scale-up of interventions (Malaria, Organization, & UNICEF, 2012).

Malaria is hyper endemic in all parts of the country. Ghanas entire population of 24 million is at risk of malaria, although transmission rates are lower in the urban areas. Transmission occurs year-round with seasonal variations during the rainy season. According to Ghana Health Service (GHS) health facility data, malaria is the number one cause of morbidity, accounting for about 38% of all outpatient illnesses, 36% of all admissions, and 33% of all deaths in children under five years. Between 3.1 and 3.5 million cases of clinical malaria are reported in public health facilities each year, of which 900,000 cases are in children under five years. An estimated 14,000 deaths in children under five were attributable to malaria in 2008. The verbal autopsy component of the 2008 DHS household survey found that malaria accounted for 43% of all deaths in children aged 29

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days to 5 years, and that roughly half of deaths in children under five occurred at home.

Ghana can be stratified into three malaria epidemiologic zones: the northern savannah; the tropical rainforest; and the coastal savannah and mangrove swamps. The major vectors are Anopheles gambiae and An. funestus. Characteristically, these species bite late in the night, are indoor resting, and are commonly found in the rural and peri-urban areas where socio-economic activities lead to the creation of breeding sites. Anopheles melas is found in the mangrove swamps of the southwest and An. arabiensis in savannah areas of northern Ghana. Northern Ghana experiences pronounced seasonal variations with a prolonged dry season from September to April. The normal duration of the intense malaria transmission season in the northern part of the country is about seven months beginning in April/May and lasting through to September. There are no areas of epidemic malaria in Ghana (Organization, 2010).

The Life Cycles of the Malaria Parasite and the Mosquito

In this section, we consider a brief details about malaria parasites and mosquitoes, and their life cycles.

The malaria parasite

The parasite that causes malaria is of the genus Plasmodium. There are four species that affect humans are: P. falciparum, P. vivax, P. malariae and P. ovale. We note that, the first two parasite are common in the tropical and temperate areas respectively, whilst are virtually absent. There are other species of Plasmodium that cause malaria in other animals.

Life cycle of parasite

The species of Plasmodium that infect humans have three main life stages: two of which require a human host (in the liver and blood) and one requiring

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a mosquito host. Figure 72 shows the life cycle of the malaria parasite. When

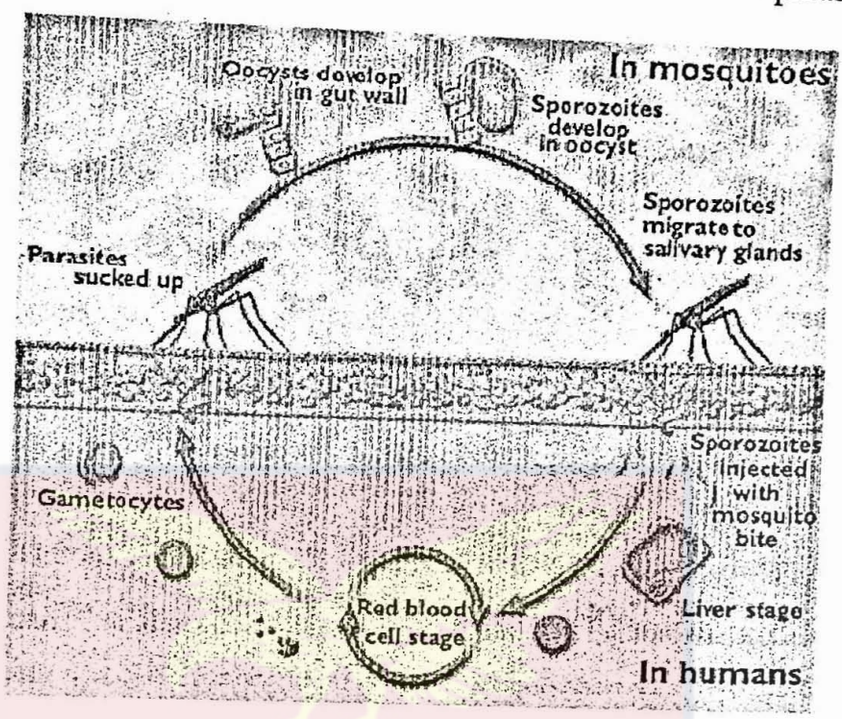


Figure 72: **Life cycle of malaria parasite**

an infectious mosquito bites a human, the parasite, in the form of sporozoites in the saliva of the mosquito, enters the human. The sporozoites then migrate to the liver, invading the hepatic cells. In 5-15 days, the sporozoites develop into schizonts. The schizonts contain thousands of "daughter" merozoite cells. The merozoites invade erythrocytes (red blood cells) and mature into schizonts, rupturing the erythrocytes and releasing more merozoites. It usually takes about 48 hours for the merozoites to reproduce more merozoites for P. falciparum, P. vivax and P. ovale; and about 3 days for P. malariae. These merozoites go on to invade more erythrocytes and the cycle continues (until treatment or death). Some merozoites differentiate into sexual forms, known as gametocytes. These gametocytes then enter a feeding mosquito where they fuse to form a zygote. The zygote matures into an ookinete which penetrates the stomach wall. The ookinete develops into an oocyst which, in a week or more, releases over 10,000 sporozoites. These sporozoites then migrate to the salivary glands. When the mosquito bites again, the sporozoites in the saliva enter a new human host and

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the cycle continues. It takes about 7-21 days for the gametocytes to form new sporozoites in the mosquito. This incubation time can vary greatly depending on the environmental temperature, humidity and the species of Plasmodium. The optimal environmental conditions for sporozoite development are temperatures between 20°C and 30°C; and relative humidity greater than 60%. P. falciparum cannot develop if the ambient temperature is below 15°C: largely the reason why the parasite is not prevalent in temperate zones.

The mosquito

There are about 3500 species of mosquito worldwide, of which 430 are in the genus Anopheles. Of these 430, only 3040 species of Anopheles are capable of transmitting malaria (they are suitable for the development of the parasite). The Anopheles mosquitoes are found worldwide, with the exception of Antarctica and some islands in the Pacific Ocean. The Anopheles mosquitoes are easy to recognize because of their characteristic stance: they rest with their head down and their abdomen sticking out, while other mosquitoes usually rest with their body parallel to the resting surface.

Life cycle of mosquito

The life cycle of the mosquito can be divided into four main stages, i.e. eggs to larvae to pupae and then to adult mosquito. The mosquito eggs usually hatch into larvae in two to three days, although this process is temperature-dependent and can take up to two to three weeks in cold weather. The eggs are not resistant to drying and require water for successful hatching. The larvae require water and prefer clean unpolluted water. They have to frequently rise to the water surface to breathe. They feed on algae, bacteria and other microorganisms. The pupae also require water and need to resurface frequently to breath. The adult males usually feed on nectar and other sources of sugar. Their average lifespan is about a week. Both males and females are sexually active a few days after emerging from the pupal state. At dusk, both male and female

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mosquitoes fly into the swarm to mate. The adult female also feeds on nectar and other sources of sugar, but requires a blood meal for the protein needed to produce eggs. After the blood meal, the female usually rests until the eggs develop. This process too is temperature-dependent and usually takes two to three days in tropical conditions. Once it has laid the eggs, the female will mate again and look for another blood meal. The adult female mosquito can live up to a month (longer in captivity) but has an expected lifetime of 12 weeks in nature. The lifespan of the mosquito also depends on temperature and humidity, among other factors.The transition from egg to adult usually occurs in 10-14 days in tropical conditions, but can take as little as 5 days or up to a month. The development time for mosquitoes depends on the environmental conditions and on the species of mosquito, with warmer temperatures promoting quicker development.

Malaria Disease

Malaria is a parasitic disease. This means that it is caused by a parasite, a tiny organism that lives in or on other organisms called a host. This parasite is from the genus Plasmodium and the host is a female mosquito of the Anopheles genus. The parasite is transferred to a susceptible human when he or she is bitten by an infectious mosquito. It can, however, be directly transmitted from human to human through blood transfusions, needle sharing and vertically from mother to child, but the incidence of direct human to human transmission is significantly lower than that from through mosquitoes. In section we will discuss the symptoms and treatment of malaria as a disease.

Signs and symptoms

The symptoms of Malaria can vary greatly, from no symptoms at all or mild to extremely serious and may even result in death. Malaria is often divided into two different categories. The first category is called the uncomplicated category and the other is complicated category. Depending on the type of parasite

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the incubation period can range anywhere from seven to thirty days (the time it takes for the sporozoites from a new mosquito bite to travel to the liver and develop into merozoites in the blood stream). In extreme cases, some types of malaria can delay onset of symptoms for up to a year.

Uncomplicated malaria

The general attack of malaria usually continues six to ten hours. There are three phases to this and these usually return every two to three days, depending upon the type of parasite.

1. The cold stage (shivering, feeling cold).
2. The hot stage (vomiting, fever, headache; convulsions in children).
3. The Sweating stage (sweating, normal temperature, sleepiness).

However, more often the patient usually has the following signs and symptoms:

Chills

Fever

Nausea and vomiting

Headache

General discomfort

Body aches

In some patients, one may observe enlarged spleen, fever, perspiration, general weakness. If a patient is infected with P. Falciparum, they may develop symptoms such as enlarged Liver, mild jaundice, and increase respiratory rate.

Complicated or severe malaria

This category of malaria occurs when P. falciparum infections are complicated by severe or multiple organ failure. This usually occurs in people with little or no immunity and must be treated as a medical emergency. Some of the symptoms of severe malaria are:

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1. Cerebral malaria (characterized by abnormal behavior, impaired consciousness or coma).
2. Severe anaemia caused by hemolysis (destruction of red blood cells).
3. Hemoglobinuria (hemoglobin in the urine) due to hemolysis.
4. Pulmonary edema (fluid build-up in the lungs) and Acute Respiratory Distress Syndrome (ARDS).
5. Thrombocytopenia (decrease in blood platelets) and abnormalities in blood coagulation and
6. Cardiovascular collapse and shock.

Malaria relapse

Malaria relapses are also known to happen, even months and years after the first attack. This is due to P. vivax and P.ovale Sporozoites having dormant stages that have been known to reactivate long after the disease has been cured. It is also possible to not show the first symptoms of malaria until many years have passed since the infectious bite.

People infected with P. falciparum and P. malariae can also show symptoms of malaria some period of time after termination of treatment. This, however, is due to surviving parasites in the bloodstream and is known as recrudescence.

Clinical markers for diagnosis

1. Polymerase Chain Reaction (PCR) For identification of malaria parasites in blood, Polymerase Chain Reaction (PCR) is now a common and often vital technique, which amplifies a minute amount of DNA of the parasite across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence. Due to absence of parasite in susceptible (S) and recovered (R) classes PCR indicates negativity whereas for exposed (E) and infected classes (I) PCR shows positivity.

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2. Sero-conversion (Sc) To determine antibody positivity as a result of infection or immunization, the clinical technique Serology is used. The development of detectable specific antibodies to microorganisms in the blood serum (Sero-conversion) is a reliable indicator for different infectious diseases including malaria. Before Sero-conversion, the blood test shows Sero-negativity for the antibody (in susceptible and exposed classes); after Sero-conversion it shows Sero-positivity for the antibody (in infected and recovered classes).

3. Cellular immunity (C).

Parasite infection lead to development of specific memory immune cells (T-cells and/or B-cells), which is detected positive through clinical diagnostic of cellular immunity (C) in the recovered class.

Treatment of Malaria Disease

Laboratory tests should be performed and diagnosis of Malaria Disease should be confirmed before any treatment is started. Not doing this should be reserved only for special cases, limiting it to those situations where clear suspicion of a very extreme case is determined and lack of facilities necessitates doing so. Treatment is determined by three specifications:

1. The species of infecting parasite - This is for three different reasons.
   a. P. falciparum causes a severe and quickly progressing illness or death, while the other three species rarely are this severe.
   b. P. vivax and P. ovale demand treatment for forms that remain dormant and can induce repeat infections.
   c. P. falciparum and P. vivax are known for different resistance levels in different geographic areas where infections occur. For P. Falciparum rapid beginning of treatment is extremely necessary.

2. The physical state of the infected person.

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3. The resistance level of the parasites determined by the place the person was when infected.

In addition, other things to remember about the drug treatment, is to consider other ailments the patient has,pregnancy, drug allergies and sensitivities.

Drugs

The usual medications for malaria are:

Chloroquine

Sulfadoxine-pyrimethamine

Mefloquine

Atovaquone-proguanil

Quinine

Doxycycline

Artemisinin derivatives.

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