

# Modelling Malaria and Sickle Cell Gene.

by

Juliet Nakakawa

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Supervisor: Dr. Rachid Ouifki (SACEMA)

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## Declaration

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## Abstract

The high sickle cell gene frequency has been hypothesised to be related to the protective advantage against malaria disease among heterozygous individuals. In this thesis, we study the interaction between the dynamics of malaria and sickle cell gene. The main aim is to investigate the impact of malaria treatment on the frequency of sickle cell gene. For this, we develop a mathematical model that describes the interactions between malaria and sickle cell gene under malaria treatment. The model includes both homozygous for the normal gene (AA) and heterozygous for sickle cell gene (AS) and assumes that AS individuals are not treated since they do not show clinical symptoms. We first analyse the model without malaria treatment, using singular perturbation techniques, basing on the fact that epidemiological and demographical dynamics occur on two different time scales (fast and slow dynamics). Our analysis on the fast time scale shows that high sickle cell gene frequency leads to high endemic levels for longer duration of parasitemia among heterozygous individuals. However, if the duration of parasitemia is reduced then high sickle cell gene frequency is associated with low endemic levels. We also note that on the slow time scale, the invasion ability of sickle cell gene is dependent on the malaria epidemiological parameters. The invasion coefficient given as the difference in the weighted death rates of AA and AS individuals is used as a measure to determine the establishment of sickle cell gene in the population. Results show that, the gene may establish itself if the weighted death rate of AA individuals is greater than that of AS individuals otherwise it fails. We note that, high mortality of AA individuals leads to establishment of sickle cell gene in the population. Then we analysed the model with treatment, our results indicate that the frequency of sickle cell gene decreases with an increase in the recovery rate of AA individuals. We thus conclude that eradication of malaria disease will lead to a reduction in sickle cell gene frequency.

## Opsomming

Daar word veronderstel dat die hoë sekelsel geenfrekwensie onder heterosigotiese individue verwant is aan die beskermende voordeel teen malaria siekte. In hierdie verhandeling ondersoek ons die wisselwerking tussen die dinamika van malaria en die sekelsel geen. Die hoofdoel is om die invloed van malaria behandeling op die frekwensie van die sekelsel geen te ondersoek. Hiervoor het ons 'n wiskundige model ontwikkel, wat die wisselwerking tussen die dinamika van malaria en die sekelsel geen met malaria behandeling, beskryf. Die model sluit beide homosigotiese vir die normale geen (AA) en heterosigotiese vir die sekelsel geen (AS) in, en neem aan dat AS individue nie behandel is nie omdat hulle nie die eerste kliniese simptome getoon het nie. Ons ontleed eers die model sonder malaria behandeling, deur gebruik te maak van enkelvoudige pertubasie tegnieke, wat gegrond is op die feit dat epidemiologiese en demografiese dinamika plaasvind op twee verskillende tydskaal (vinnige en stadige dinamika). Ons ontleding op die vinnige tydskaal dui dat hoë sekelsel geenfrekwensie onder heterosigotiese individue lei tot hoë endemiese vlakke vir 'n langer duur van parasitemie. Nietemin, as die duur van parasitemie afneem, dan word hoë sekelsel geenfrekwensie verbind met lae endemiese vlakke. Ons neem ook waar dat op die stadige skaal die indringingsvermoë van die sekelsel afhanklik is van malaria se epidemiologiese parameters. Die indringingskoëffisiënt wat bereken word as die verskil van die geweegde sterftekoerse van AA en AS individue, word gebruik as 'n maatstaf om die vestiging van die sekelsel geen in die bevolking te bepaal. Resultate toon dat die geen homself kan vestig as die geweegde sterftekoerse van AA individue groter is as dié van die AS individue, andersins misluk dit. Ons let op dat hoë mortaliteit van AA individue lei tot die vestiging van die sekelsel geen in die bevolking. Daarna het ons die model wat behandeling insluit ge-analiseer en ons resultate toon dat die frekwensie van die sekelsel geen afneem met 'n toename in die herstelkoerse van AA individue. Ons kom dus tot die gevolgtrekking dat die uitwissing van malaria siekte sal lei tot die afname in sekelsel geenfrekwensie.

## Dedication

*I dedicate this thesis to my late Dad, Charles Male Busuulwa, to my beloved mother, Mrs. Rosemary Nandyose Busuulwa for being my strength and encouragement and to my siblings Charles, Caroline, Grace, Philip and Alex. I love you all.*

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# Chapter 1

## Introduction

### 1.1 Background: About malaria

Malaria comes from an Italian word mal'aria meaning “ bad air ”. It is an infectious disease that is caused by a parasite of the genus *plasmodium* from the protozoa group. It is transmitted from one person to another through bites of infected female anopheles mosquitoes (malaria-vectors). There are four different species of parasite leading to malaria disease among humans. These include; plasmodium falciparum, plasmodium vivax, plasmodium malarie and plasmodium ovale. The fact that the parasite constantly changes its immune make up, the four species remain a threat to mankind even with the current advances in medicine. With this looming, it is no wonder that no malaria vaccine has been discovered so far. Of the four species, plasmodium falciparum is the most common and widely spread fatal species especially in Africa. Its ability to attack all red blood cells both old and young causing them to clamp together thereby blocking vessels in vital organs and enlargement of the spleen makes it a common species [14]. Plasmodium vivax causes clinical malaria but it is not as fatal as plasmodium falciparum. Plasmodium malarie and plasmodium ovale also cause clinical malaria but not as frequently as the other two and can stay in the body for a long period of time.

The high spread of malaria has been attributed to;

- Mosquito resistance to the usual insecticide sprays.

- The economic status and control operations of a particular setting.
- The resistance of some parasite strains to commonly used anti-malaria drugs like chloroquine, quinine e.t.c.
- The population's low awareness of the disease and preventative measures.

However, eradication programmes that are based on vector control and anti-malaria drugs have successfully eradicated malaria from Europe, Asia and North America [46]. In the tropics and sub-tropic regions, malaria has remained prevalent. This is because the tropics and sub-tropic regions have favourable climatic conditions allowing continuous breeding and survival of the mosquitoes. Temperatures between  $22^{\circ}\text{C}$  and  $32^{\circ}\text{C}$  are suitable for vector survival hence high transmission while temperatures below  $18^{\circ}\text{C}$  hinder mosquito survival [35].

About 40% of the world's population live in malaria endemic areas [13]. In 2009, WHO<sup>1</sup> reported that, about 250 million malaria cases and one million deaths are experienced annually [2]. These were noted to occur mainly among pregnant women and children below five years. It is estimated that every 45 seconds, a child dies of malaria which accounts for about 20% of all childhood deaths [3].

### 1.1.1 The plasmodium life cycle

The plasmodium parasite has part of its life cycle in the mosquito (vector) and the other part in the human (host). It starts its life cycle in the mosquito where it inhabits the salivary gland of the female anopheles mosquito as sporozoites. When a healthy individual is bitten by such a mosquito, the sporozoites are transmitted into the human body through the blood stream. They are then carried by the circulatory system to the liver in about 30 minutes. In the liver cells, the parasite transforms into feeding trophozoites that undergo asexual reproduction (schizogony) giving rise to thousands of merozoites in about two weeks.

The merozoites then infect the red blood cells within 48 hours. The merozoites differentiate further in the cytoplasm to form enlarged round shaped trophozoites. These also undergo

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<sup>1</sup>World Health Organisation

asexual reproduction producing thousands of merozoites just as in the liver. When the infected red blood cells burst, they release these merozoites thereby infecting the remaining healthy red blood cells. Infected red blood cells circulate to other body organs such as the brain, heart and liver hence causing damage.

The cycle of the plasmodium parasite continues as some merozoites differentiate into male and female gametocytes that are later taken up by the mosquito on the next meal bite. The gametocytes undergo gametogenesis in the body of the mosquito to form male and female gametes. The male gametes divide giving rise to flagellated microgametes that later fertilize the female gametes to form a zygote. The zygote develops into ookinete<sup>2</sup> that passes through the epithelium of the midgut and develops into oocyst on the exterior wall of the midgut. The oocyst matures to form an enlarged structure and after several divisions ruptures and releases hundreds of sporozoites that are then taken to the salivary gland of the mosquito [18] ( Figure 1.1). The cycle is repeated as the sporozoites are injected into the human body on the next meal bite.

The incubation period of the malaria parasite is about 7–30 days before symptoms such as fever, shivering, severe pain in the joints, vomiting, headaches among others can manifest. Symptoms like very high body temperature, drowsiness, convulsions and coma indicate severe cases and can lead to death if not attended to and treated in time.

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<sup>2</sup>the fertilized form of the malarial parasite in a mosquito's body



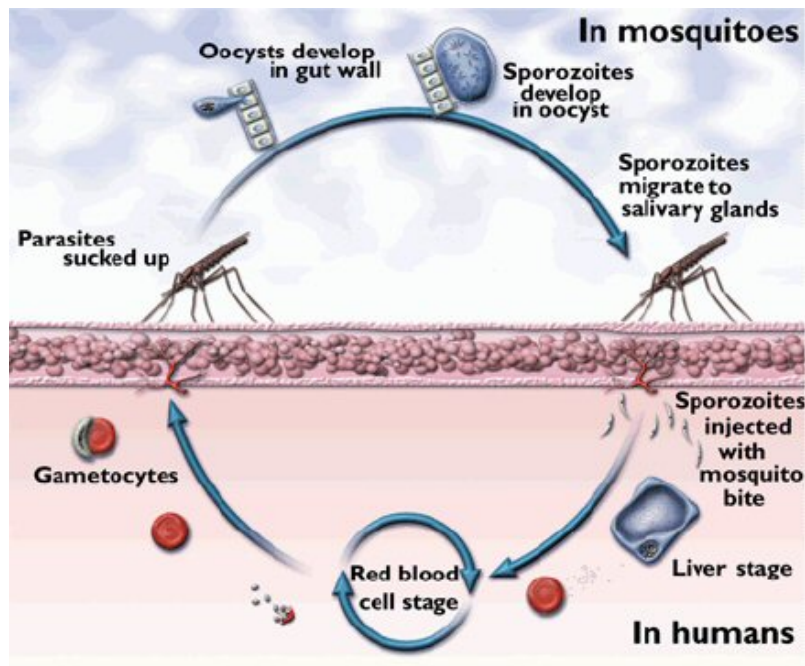


Figure. 1.1. *Malaria parasite life cycle* [1].

### 1.1.2 Malaria treatment and control

Malaria is treated using medications such as chloroquine, sulfadoxine-pyrimethamine (Fansidar), mefloquine (Lariam) and quinine after a laboratory test confirming the existence of the parasite. However, severe cases may require hospitalization where special treatments like intravenous fluids, blood transfusion, kidney diagnosis and oxygen therapy may be administered. Sometimes proper diagnosis is not done either due to ignorance or poverty and people resort to self medication. This has led to the high spread of drug resistant malaria. For example, chloroquine which was the most commonly used effective drug has been replaced by other drugs due the parasite's resistance towards it. Depending on the parasite species or severity of malaria diagnosed, many lives can be saved if proper treatment is administered in time.

Besides treatment, other control strategies for malaria have been adopted. For instance, the use of Dichloro-Diphenyl Trichloroethane (DDT) on mosquitoes which was invented during World War II in the fight against malaria, administering of anti-malaria drugs to people travelling to malaria endemic areas and the use of mosquito treated nets especially

for children and pregnant women [29, 35].

In spite of all these control measures in place, malaria has remained prevalent in most African countries. This has been attributed to the favourable temperature, parasite resistance to anti-malaria drugs and mosquito resistance to insecticides such as DDT. However, the presence of the recessive sickle cell gene in heterozygous form also plays a part.

## 1.2 The S-gene

S-gene stands for the sickle cell gene. It is an inherited genetic disorder that is characterized by the red blood cell assuming an abnormal, rigid and sickle shape (Figure 1.2). Sickling of the red blood cells occurs as a result of the non synonymous substitution of the sixth amino acid glutamic acid with valine in the  $\beta$ - chain of the haemoglobin. This is due to the mutation of a single nucleotide from GAG to GTG codon which causes the change in the haemoglobin gene and function [17].

Sickled red blood cell have reduced oxygen carrying capacity and usually get stuck in small blood vessels causing organ damage. They are continuously destroyed by the spleen in about 10 – 20 days as compared to 120 days for normal red blood cells. The bone marrow fails to produce new cells fast enough to replace the destroyed sickled cells which causes more complications among people having it.

Every individual has two copies of haemoglobin inherited one from the father and the other from the mother. If both copies are normal, then he/she is said to be homozygous for HbAA (AA genotype). If a child inherits the two copies of mutated gene, he/she is said to be homozygous for HbSS (SS genotype). Such individuals have sickle cell anaemia and usually die before reaching adulthood. When a single mutated gene is inherited, the individual is heterozygous for HbAS (AS genotype). Heterozygous for HbAS individuals are characterized by the sickle cell trait and are referred to as sickle cell carriers. Sickle cell carriers are less affected by sickle cell anaemia complications as the normal haemoglobin can still supply oxygen to vital body organs [4].

There is a 50% chance that parents with the sickle cell trait will pass on the same trait (AS) to their child, a 25% chance that their child will have both copies of normal haemoglobin (AA) and a 25% chance that the child will have the two mutated genes (SS).

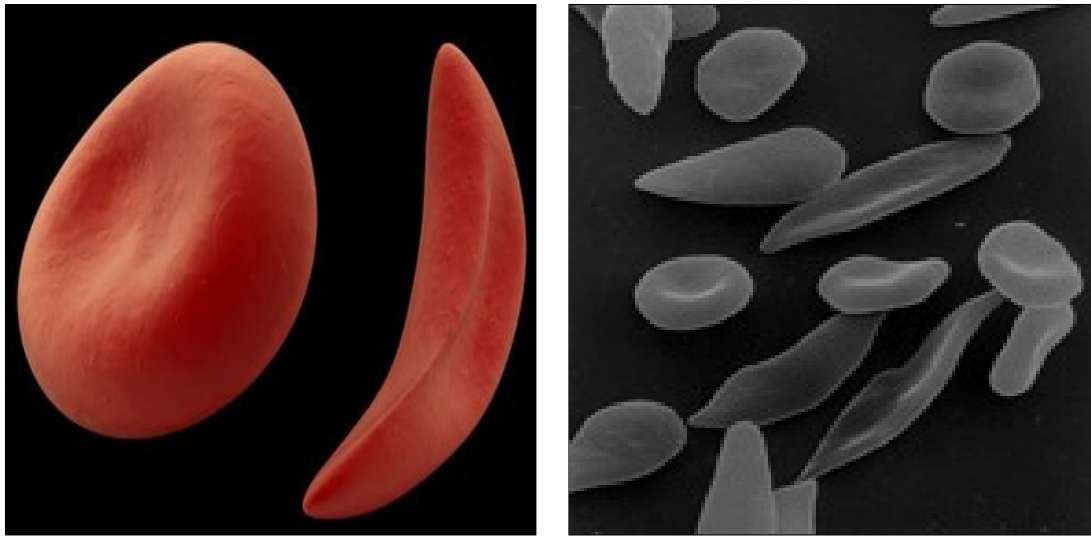


Figure. 1.2. *Normal and abnormal sickled red blood cells.* [5]

Sickle cell anaemia symptoms vary from mild to severe cases that may require hospitalisation. It is always present at birth though many infants may not show symptoms until after four months. Symptoms and signs relating to sickle cell anaemia include, tiredness, irritability, dizziness, difficulty in breathing, fast heart rate, pale skin color, slow growth, coldness in hands and feet among others. These also relate to other complications due to blockage of blood vessels like stroke, eye problems, leg ulcers e.t.c. Sickle cell anaemia can only be cured through bone marrow transplant. However, it is not easy to find a matching donor, very risky, expensive and only a few experts can handle it. Management of the sickle cell anaemia problem is by blood transfusion, malaria chemoprophylaxis and use of hydroxyurea drug. Hydroxyurea drug has been shown to decrease the severity of attacks but the long term use of it may be harmful.

Sickle cell disease is common among people originating from sub-Saharan Africa, western hemisphere and Mediterranean countries [4]. In United States, with an estimated population of 270 million people, about 1000 babies are born with sickle cell disease every year. On the contrary, in Nigeria with an estimated population of 90 million, 45,000 – 90,000 babies are born with sickle cell disease every year [6]. The gene frequency ranges between 10% to 40% across equatorial Africa, <1% in South Africa and 1-2% along the North African coast [42]. The variation in the sickle cell gene frequency does not only vary across countries but also among regions in the same country. For example, in the

eastern part of Uganda, sickle cell trait prevalence in 2010 was 17.5% compared to 13.3% and 3% in the western and south western part of the country respectively [38]. Figure 1.3 shows the percentage of sickle cell gene frequency among heterozygous individuals for some African countries. [42]. We notice that sickle cell gene frequency is high in malaria

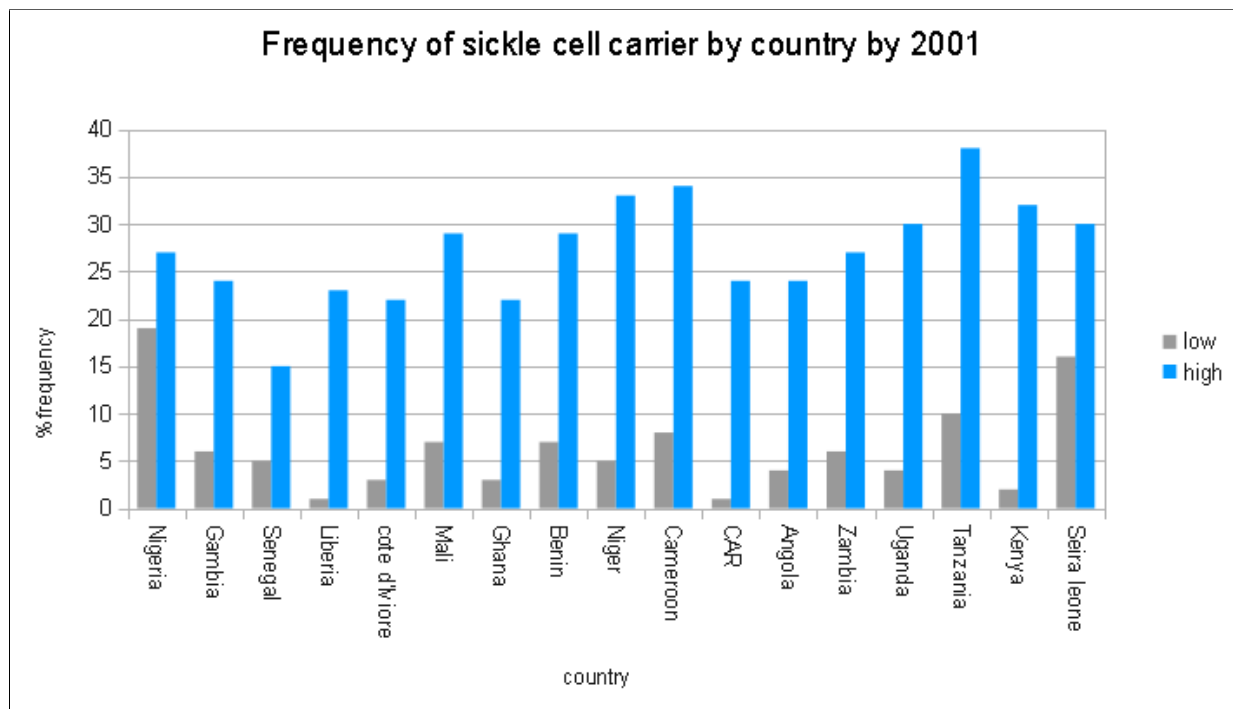


Figure. 1.3. *Sickle cell frequency distribution for some African countries* [42, 49]

endemic countries. This gets one wondering how the gene is maintained in the population at such high frequency in spite of the constant elimination of the gene through death from anaemia [8]. The next section explains why sickle cell gene has been maintained at such high frequency in African countries.

### 1.3 Malaria and S-gene

The S-gene is believed to provide protection against the deadly malaria falciparum disease [27]. Unlike AS genotype individuals, those without the gene are at risk of dying from malaria during their early age. Death of AA genotype individuals results into removal

of the A allele<sup>3</sup> from the pool. Additionally, AS genotype individuals do not suffer from anaemia and have less chances of developing clinical malaria. Therefore, they are able to survive in malaria endemic regions thereby passing on their genetic make up to the next generation. When these people with sickle cell trait procreate, both the gene for normal haemoglobin and that for sickle haemoglobin are maintained in the population.

AS individuals are protected from malaria because;

- Sickled red blood cells have very low oxygen tension failing the parasite to survive.
- The sickled shape of the red blood cell leads to nutrients leakage like potassium needed for the parasite's survival.
- Sickled red blood cells are continuously destroyed by the spleen within 10 – 20 days together with the parasites.

It should be noted that, individual response to malaria parasite is also influenced by other heritable haematological and immunological traits like sickle-haemoglobin C disease (HbSC), sickle beta-zero-thalassaemia (HbS/ $\beta^0$ ) and sickle beta-plus-thalassaemia (HbS/ $\beta^+$ ) [20]. Therefore the actual protection is likely to be polygenic but we consider it to be due to the presence of sickle cell trait for this study.

## 1.4 Motivation

Malaria is one of the most deadliest diseases in Africa especially among young children and pregnant women. Many advances have been made towards the fight against malaria such as the use of treated mosquito nets, administering of anti-malaria drugs and the use of insecticide spray on mosquitoes. Various studies including mathematical modelling of malaria and its control have been conducted by many researchers, some of them are, Ross-Macdonald [43], Ngwa and Shu [37], Dietz et al. [16], Chitnis [12, 13], Chiyaka et al. [14] among others. Surveys on malaria and sickle cell gene have confirmed the common hypothesis that sickle cell gene provides protection against malaria falciparum

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<sup>3</sup>One of the given pair of genes

if it exists in heterozygous form [7, 8]. They have shown that sickle cell carriers are less likely to develop clinical malaria compared to their counterparts. However, they inhabit the parasite leading to high endemic levels and high S-gene frequency. The high frequency leads to high mortality as result of inheriting two copies of the gene. Bone marrow transplant is the only cure but it is hard to get a matching donor, risky, expensive and few experts can handle it. It is thus important that alternative strategies are sought one of them being the use of mathematical models to give insights into what interventions could be used to control the gene frequency in malaria endemic areas. With these facts, we are motivated to study mathematical models to understand the dynamics of malaria and sickle cell gene and the impact of malaria treatment as a control measure for malaria on the frequency of the S-gene.

### 1.4.1 Aim and objectives.

The main aim of our study is to investigate the impact of malaria treatment among AA genotype individuals on sickle cell gene frequency. Specific objectives include;

- Review the model developed by Feng et al. [20].
- Extend the model by Feng et al. to include malaria treatment among AA genotype individuals.
- Investigate mathematically and numerically how the treatment rate affects the frequency of sickle cell gene.

## 1.5 Thesis outline

Having given the biological background and the motivation for our study in Chapter 1, the rest of the thesis is organised as follows:

In Chapter 2, we present some of the mathematical models on malaria and sickle cell gene that we have identified from literature.

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In Chapter 3, we have the mathematical tools that are used to address our problem. These tools include the mathematical model formulation and analysis of the local behaviour of a system of ordinary differential equations. Furthermore, we consider the use of singular perturbation techniques to analyse models with different time scales (perturbed systems).

Chapter 4 introduces the model without malaria treatment which we analyse on two time scales, that is fast and slow dynamics. We carry out the analysis on the fast time scale which involves malaria dynamics alone. We also investigate the impact of sickle cell gene frequency on malaria prevalence. Analysis of the slow dynamics for sickle cell gene is carried out and we investigate the impact of malaria parameters on sickle cell gene frequency.

In Chapter 5, we extend the model in Chapter 4 to include malaria treatment of AA genotype individuals. Mathematical analysis which includes determining equilibrium points and their stability is done. We investigate how treatment affects the frequency of the sickle cell gene. We also carry out numerical simulation to confirm the mathematical results.

In Chapter 6, we give the conclusions, recommendations drawn from our project, its limitations and future work.

# Chapter 2

## Literature Review

In this chapter, we review some of the work done on malaria and sickle cell disease. A good number of researchers have invested their skills and resources in understanding the dynamics of malaria transmission and control. However, little research has been conducted for sickle cell gene and its impact on malaria prevalence. Nevertheless, we present some of the work below.

### 2.1 Malaria models

Malaria modelling started as early as 1911 by Ross Ronald. Ross who demonstrated that malaria is transmitted by female anopheles mosquitoes developed a mathematical model for malaria transmission with emphasises that “ mathematical methods of treatment are really nothing but the application of careful reasoning to the problems at issue ” [36, 43]. He developed a simple *SIS* model ( susceptible - infected - susceptible ) with the assumption that at any time, the total population can be divided into distinct compartments. His model was extended by Ronald MacDonald hence the Ross-MacDonald model [13]. In the Ross-MacDonald model, two populations, that is, host (human) and vector (mosquitoes) were considered and modelled by a system of differential equations;

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



where  $x$  is the proportion of infected humans and  $y$  is the proportion of infected female anopheles mosquitoes. The number of bites of humans by a single mosquito per day is  $a$ ,  $r$  is the recovery rate of humans,  $b$  is the probability of transmission of infection by an infected mosquito to a susceptible person per bite and  $\mu$  is the mosquito death rate.  $N$  is the total size of human population and  $M$  is the total size of the mosquito population.

More work was done by Aron and May as cited by Chitnis [13] who described the properties of the model including the determination of the basic reproductive number  $R_0$  as

$$R_0 = \frac{Ma^2b}{N\mu r}.$$

The basic reproductive number was given as a product of the number of humans that one infectious mosquito infects throughout its infectious period and the number of mosquitoes that one infectious human infects throughout his infectious period [13]. This was used as a measure of the transmission intensity and prevalence of the disease. With this work, they came to a concrete conclusion that "...in order to counteract malaria anywhere, we need to reduce the number of infections below a certain value (reproductive number)..." [36, 44]. Furthermore, programmes that integrate vector eradication, drug treatment and personal protection were more likely to succeed than the use of only one intervention [36]. They noted that temporary interventions can lead to temporary reduction in prevalence. The model also predicts that when the basic reproductive number becomes very large, then virtually everyone in the population would be infected and no one will be susceptible [29].

Ngwa [37] developed an SEIR mathematical model considering only a single immune class. Chitnis [13] extended Ngwa's model and included the immigration and emigration of the susceptible population. He considered two base line parameters for endemic areas to carry out mathematical analysis and numerical simulation of his model. Determination of the important parameters for the spread of malaria was conducted using sensitivity analysis [13, 12]. The baseline set of parameters were used to compute the sensitivity indices for the reproduction number  $R_0$  and the endemic equilibrium. He noted that the most important parameters to target for malaria control included the biting rate, transmission probabilities and the mosquito birth rate.

For almost all parameters, the sign of the sensitivity indices of  $R_0$  agreed with the intuitive expectation except for the case of mosquito birth rate where  $R_0$  decreases with an increase

in the birth rate. This is due to the fact that mosquito death rate is density dependent. As the birth rate increases, the number of mosquitoes increases and the death rate also increases since the environment can only accommodate a given number. Hence few infections and a reduction in the reproduction number  $R_0$  [13]. Chitnis recommended the use of insecticide treated nets and prompt diagnosis and treatment as the most effective methods for malaria control.

Dietz [16], Yang [51], Aron [10] Koella and Anita [30] looked at different models on super-infection, acquired immunity obtained through continuous reinfection and also the human resistance to malaria treatment drugs. Chiyaka et al. [14] considered a model that incorporated the delay in both disease latency and immunity.

## 2.2 Sickle cell – Malaria models

Literature on sickle cell models alone is not common but its selective advantage towards malaria disease has been brought to attention by many researchers. As noted by most of them, in the absence of malaria disease, the gene is disadvantaged and its frequency declines in the whole population.

In 1910, Herrick made the first description of sickle cell disease in a Caribbean man of African origin. Then Archibald described the first case of the disease in 1926 as reviewed by T.R. Jones [27]. Jones examined the prediction of sickle cell gene frequency and its selective advantage towards heterozygous individuals in malaria endemic areas. He investigated what can be deduced about malaria transmission from the analysis of the distribution of the sickle cell gene. He noted that the inheritance of the gene followed an autonomous recessive pattern<sup>1</sup>. He used Hardy-Weinberg law to predict the expected gene frequency at equilibrium when the frequency of the parental population is known. In order to use Hardy-Weinberg law [27], he assumed that the population was isolated (no emigration and immigration), infinitely large so that mating was random, meiosis was normal and no mutation from one allele to another occurred.

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<sup>1</sup>mutation occurs in both copies of the gene

Hardy-Weinberg law is given by

$$p^2 + q^2 + 2pq = 1$$

with  $p$  and  $q$  as the proportionals of A and S alleles in the parental pool respectively. The frequency of the dominant homozygous genotype is given as  $p^2$ , heterozygous genotype as  $2pq$  and that of the recessive genotype given by  $q^2$ . Using Hardy-Weinberg's law, the distribution of the expected genotype at equilibrium could be calculated from the expected gene frequencies. He noted that if we know the gene frequency then the number of malaria deaths will be in the same proportions as the frequency of the A-gene to S-gene. Furthermore, the proportion of sickle cell gene in the population is proportional to the malaria transmission density. Therefore, any effort to eradicate malaria will result in reduction of the sickle cell allele after many generations since the gene will cease to provide selective advantage but become disadvantaged in the population.

Allison [8], noted that individuals with sickle cell trait suffer from malaria less often and less severely compared to those without the trait. Therefore in malaria endemic areas, children without the S-gene are eliminated before acquiring solid immunity. To justify these remarks, Alison carried out two different studies. One was conducted among a group of 30 adult men of which 50% had the sickle cell trait. He infected them, with plasmodium falciparum and followed the development of parasitemia<sup>2</sup> for 32 days. After this period, it was noted that 2 out of the 15 adults with the sickle cell trait developed parasitemia compared to 14 out 15 of those without the trait. He therefore concluded that sickle cell trait was associated with protection from parasitemia [8, 27].

In the same paper, he conducted a study to record the malaria incidence among a group of 290 Ganda children around Kampala aged between 5 months and 5 years. He obtained the results shown below.

Table. 2.1. *Malaria incidence among the Ganda children* [8]

	With parasitaemia	Without parasitaemia	Total
Sicklers (HbAS)	12 (27.0%)	31(72.1%)	43
Non-sicklers (HbAA)	113(45.7%)	134(53.3%)	247

It was noted that, the incidence of parasitaemia was lower in sicklers compared to non-

<sup>2</sup>Presence of malaria parasite in the body

sicklers. These two groups were further tested for plasmodium malaria and plasmodium falciparum and it was found that sickle cell trait provided protection for only plasmodium falciparum and not other species.

Michael and colleagues [7] carried out a study to investigate the protective effect of sickle cell gene against malaria morbidity and mortality in Kenya. HbAS results were found to be significantly associated with the reduction in all cause morbidity during 2 to 16 months of age. However when compared with HbAA genotype, there was no significant reduction in morbidity among children of the same age. The reduced risk of morbidity among children between 2–16 months was attributed to sickle cell gene. Children below two months have got immunity from their mothers while those of more than 16 months have gained solid immunity. The reduction in morbidity against malaria was about 60% for those between 2–16 months which was provided by the recessive gene.

Feng and colleagues [18, 20] considered a mathematical model to analyse the dynamics of malaria disease and sickle cell evolution and how malaria parameters affect the establishments of the gene in a fully susceptible population. To the best of our knowledge, this is the only model that incorporated the dynamics of malaria and genetic make up of individuals. More information on this model is given in Chapter 4.

## 2.3 Summary

We have reviewed some of the work done on malaria modelling which included models for malaria transmission dynamics, immunity and treatment as conducted by different researchers. Furthermore, we have reviewed studies conducted on malaria parasitemia and sickle cell gene frequency. We noted that AS individuals are less likely to be affected by malaria parasites than AA individuals. This background gives the basis for our study.

# Chapter 3

## Mathematical Modelling

### 3.1 Basic concepts

Mathematical models have played an important role in dealing with the spread and control of infectious diseases. They are based on the assumptions made about the variables, parameters and functions describing the relationship between parameters and variables. The modelling process is a series of steps taken to convert ideas first to a conceptual model and then into a quantitative model. A conceptual model represents our ideas about what is happening in the real world and is usually represented with the diagram showing the flow of activities between and within the system. From these, mathematical equations are formulated to describe the processes that occur. The equations are then studied mathematically and numerically using computer simulations.

Formulated models are very useful experimental tools for building and testing hypotheses, assessing quantitative conjectures, estimating parameters from data, determining sensitivity to parameter changes and answering specific questions. They provide a good insight of the real world scenarios and more so for the infectious diseases in the human population where experiments are unethical, expensive and almost impossible. There are various types of models such as stochastic, deterministic, discrete, continuous and so on. Some of which are described below.

- **Stochastic and deterministic:** Stochastic models are characterized by uncertainty

whereby things happen by chance. In this case, random probability distributions are assigned to parameters and variables so that results obtained change depending on the distribution taken. On the other hand, deterministic models have got no component of uncertainty i.e. no parameter or state variable is characterized by a probability distribution. They use a single estimate for a particular variable. For these models, starting with a fixed initial condition will always yield the same results.

- **Static and dynamic:** Static models are independent of time, such as equilibrium or steady states. Dynamic models on the contrary change with time and are usually formulated as difference or differential equations.
- **Discrete and continuous:** Discrete models are characterized with discrete time step and formed as difference equations while continuous models are characterized with continuous time and are formulated as differential equations.

We note that despite the differences in these models, they can all be used to study similar scenarios and give results in the same range. In this chapter, we introduce the concept of deterministic models with continuous time step.

Consider time to be the independent variable and  $x_1, x_2, \dots, x_n$  as the dependent variables for a particular conceptual model, then the system of differential equations can be formulated as,

$$\frac{d}{dt} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ \vdots \\ x_n \end{pmatrix} = \begin{pmatrix} f_1(x_1, x_2, \dots, x_n) \\ f_2(x_1, x_2, \dots, x_n) \\ f_3(x_1, x_2, \dots, x_n) \\ \vdots \\ f_n(x_1, x_2, \dots, x_n) \end{pmatrix}. \quad (3.1)$$

In general, the system can be formulated as;

$$\frac{d}{dt} X(t) = f(X(t)). \quad (3.2)$$

Such a system is considered to be autonomous since it does not depend on the independent variable. Although system (3.1) seems to consider first order derivatives, higher orders can also be used to describe biological phenomena. However we restrict our study to first order derivatives. In order to capture the biological picture of the real world, all initial conditions

must be non-negative.

Using the fundamental theorem of existence and uniqueness of initial valued problems, the solution to (3.1) exists and is unique if  $f_i$  is continuous and differentiable [39]. To examine the local behaviour of system (3.1), we determine the equilibrium points by setting the right hand side to zero. We then compute the Jacobian matrix evaluated at those equilibrium points.

Suppose  $x^* = (x_1^*, x_2^* \dots x_n^*)$  is any arbitrary equilibrium point of (3.1) so that  $f(x^*) = 0$ , then the Jacobian matrix evaluated at  $x^*$  is given by;

$$\mathbf{J} = \begin{pmatrix} \frac{\partial}{\partial x_1} f_1(x^*) & \frac{\partial}{\partial x_2} f_1(x^*) & \dots & \frac{\partial}{\partial x_n} f_1(x^*) \\ \frac{\partial}{\partial x_1} f_2(x^*) & \frac{\partial}{\partial x_2} f_2(x^*) & \dots & \frac{\partial}{\partial x_n} f_2(x^*) \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial}{\partial x_1} f_n(x^*) & \frac{\partial}{\partial x_2} f_n(x^*) & \dots & \frac{\partial}{\partial x_n} f_n(x^*) \end{pmatrix}. \quad (3.3)$$

When all the eigenvalues of  $\mathbf{J}$  have negative real parts, then, locally  $(x_1(t), x_2(t)) \dots x_n(t) \rightarrow x^*$  as  $t \rightarrow +\infty$  and the equilibrium point  $x^*$  is said to be locally asymptotically stable. This implies that all solutions with initial condition starting close to  $x^*$  will always tend to  $x^*$  as  $t \rightarrow +\infty$ . On the contrary, if at least one of the eigenvalues has a positive real part, the equilibrium point is unstable. This concept is widely applied to dynamical systems describing the dynamics of infectious diseases to predict the extinction or persistence of an infection in a given population.

## 3.2 Singular perturbation theory

Most dynamical systems consider the occurrence of activities in the system to be on the same time scale yet this is not always the case in the real world. For instance malaria and sickle cell gene dynamics, the demographic events occur on a much slower time scale compared to the transmission event of malaria. Therefore to analyse such systems, it is important that we rescale the parameters such that there is consistence in their variation. By re-writing the system with the rescaled parameters, we have a rescaled system referred to as a singular perturbed system. Singular perturbation systems are systems that

can not be approximated by setting the rescaling parameter to zero. They are analysed using techniques that aim at investigating whether the structure of the unperturbed system is preserved after perturbation. In order to attain a clear understanding of singular perturbation techniques, we need to define some important terminology.

- **Invariant set**

An invariant set is a set that remains unchanged when transformations of a certain kind are applied to it. The equilibrium point is an example of an invariant set. If we consider an autonomous system (3.1), then a set  $S \subset \mathbb{R}^n$  is invariant with respect to the system if for every trajectory  $x$ ,

$$x(t) \in S \Rightarrow x(\tau) \in S \text{ for all } \begin{cases} \tau \geq t \text{ (positively invariant) or} \\ \tau \leq t \text{ (negatively invariant).} \end{cases}$$

In other words, the trajectory  $x$  will always stay in  $S$  provided it starts close to  $S$  or move away from  $S$  for negative invariance. An invariant set  $V$  is said to be locally invariant with respect to an open set  $W$  under the system (3.1) if  $V$  is a subset of  $W$  and if any trajectory leaving  $V$  simultaneously leaves  $W$  [28].

- **Stable, Unstable and Centre manifold**

Consider a system of differential equations (3.1) whose Jacobian matrix evaluated at its equilibrium point  $x^*$  has eigenvalues with positive or negative real parts. Such an equilibrium point is referred to as a hyperbolic equilibrium point otherwise its non hyperbolic. Let  $v^1, \dots, v^{n-k}$  denote the eigenvectors corresponding to the eigenvalues with positive real parts and  $v^{n-k+1}, \dots, v^n$  denote the eigenvectors whose eigenvalues have negative real parts. Then the linear subspaces of  $\mathbb{R}^n$  defined as

$$\begin{aligned} E^s &= \text{span}\{v^{n-k+1}, \dots, v^n\}, \\ E^u &= \text{span}\{v^1, \dots, v^{n-k}\} \end{aligned} \tag{3.4}$$

are referred to as stable and unstable subspaces of the linearised system respectively. The stable and unstable manifold Theorems given in 3.2.1 asserts that in a neighbourhood of the equilibrium point, there exist a differentiable  $k$ - dimensional surface tangent to  $E^s$  and a differentiable  $n - k$ - dimensional surface tangent to  $E^u$  with



properties that orbits of points on those surfaces approach the equilibrium point asymptotically in positive and negative time respectively [50]. These surfaces are referred to as stable and unstable local manifolds respectively of the equilibrium point. If the linearised system has eigenvalues with zero real parts, then such a subspace is referred to as a centre subspace and the corresponding surface is called the center manifold.

**Theorem 3.2.1** (Stable and unstable theorem). [39, 40]

Let  $E$  be an open subset of  $\mathbb{R}^n$  containing the origin, let  $f \in C^1(E)$  and  $\phi(t)$  the flow of the non-linear system (3.1). Suppose  $f(0) = 0$  and  $Df(0)$  has  $k$  eigenvalues with negative real parts and  $n - k$  eigenvalues with positive real part. Then there exist a  $k$ -dimensional differentiable stable manifold  $S$  tangent to the stable subspace  $E^s$  of the linear system at 0 such that for all  $t \geq 0$   $\phi_t(S) \subset S$  and for all  $x_0 \in S$

$$\lim_{t \rightarrow \infty} \phi_t(x_0) = 0$$

and there exist an  $n - k$  dimensional differentiable unstable manifold  $U$  tangent to the unstable subspace  $E^u$  such that for all  $t \leq 0$ ,  $\phi_t(U) \subset U$  and for all  $x_0 \in U$

$$\lim_{t \rightarrow -\infty} \phi_t(x_0) = 0.$$

Furthermore,  $S$  and  $U$  have the same dimension as  $E^s$  and  $E^u$

Note:  $Df$  represents the Jacobian matrix of the system.

Kaper [28], demonstrates the application of singular perturbation techniques to differential equations. The aim is to identify dynamical structures such as invariant sets, phase space and manifolds of the singular perturbation problem near a point (local) or on a larger domain (global) [21]. Singular perturbation problems are characterized by two time scales i.e.  $t$  fast time scale and  $\tau$  slow time scale which are related such that  $\tau = \epsilon t$ . Here  $\epsilon$  is a parameter that measures the separation of the two time scales. For easy reference we describe this approach below.

Consider a singularly perturbed ordinary differential system of equations;

$$\begin{aligned} \frac{du}{dt} &= f(u, v, \epsilon), \\ \frac{dv}{dt} &= \epsilon g(u, v, \epsilon), \end{aligned} \tag{3.5}$$

with  $f$  and  $g$  sufficiently smooth vector functions in  $u, v$ . Then  $u$  is the fast variable and  $v$  is the slow variable. By changing the variable such that  $\tau = \epsilon t$ , the reformed system (3.5) is given by;

$$\begin{aligned}\epsilon \frac{du}{d\tau} &= f(u, v, \epsilon), \\ \frac{dv}{d\tau} &= g(u, v, \epsilon).\end{aligned}\tag{3.6}$$

Note that the two systems (3.5) and (3.6) are the same provided  $\epsilon \neq 0$ . Setting  $\epsilon = 0$ , we obtained the reduced fast and slow systems of (3.5) and (3.6) as;

$$\begin{aligned}\frac{du}{dt} &= f(u, v, 0), \\ \frac{dv}{dt} &= 0,\end{aligned}\tag{3.7}$$

and

$$\begin{aligned}0 &= f(u, v, 0), \\ \frac{dv}{d\tau} &= g(u, v, 0),\end{aligned}\tag{3.8}$$

respectively.

When  $\epsilon$  is sufficiently small, the system is singular and the singularities on the slow time scale appear as manifolds (center manifold) of the equilibrium points of the fast dynamics [21]. The reduced systems (3.7) and (3.8) represent the unperturbed systems that can be analysed using the techniques described in Section 3.1.

From the second equation of (3.7),  $v$  is considered to be a parameter and the stability of the first equation can be used to describe the dynamics of the reduced system on the fast time-scale. Fenichel [21] illustrates that if the equilibrium point is hyperbolic, then it corresponds with a nearby hyperbolic invariant manifold called the *slow manifold* [48]. Therefore we have the normally hyperbolic stable and unstable manifold<sup>1</sup>  $M_0^s$  and  $M_0^u$  which by Fenichel's second theorem persists<sup>2</sup> for small non- zero  $\epsilon$  as  $M_\epsilon^s$  and  $M_\epsilon^u$  with the slow flow on it [21].

<sup>1</sup>manifolds that agree with the hypothesis of the stable and unstable manifold theorem

<sup>2</sup>A manifold persists if for small non zero  $\epsilon$  there exists  $\epsilon_0$  such that the construction is valid for any  $0 < \epsilon < \epsilon_0$  [25]. Such persistent manifold are labelled slow manifolds.

**Theorem 3.2.2** (Fenichel's second theorem). [21] Suppose  $M_0 \in \{f(u, v, 0) = 0\}$  is compact possibly bounded and normally hyperbolic, and suppose  $f$  and  $g$  are sufficiently smooth<sup>3</sup>, then for  $\epsilon > 0$  and sufficiently small, there exist manifolds  $W^u(M_\epsilon)$  and  $W^s(M_\epsilon)$  that are  $o(\epsilon)$  close and diffeomorphic<sup>4</sup> to  $W^u(M_0)$  and  $W^s(M_0)$  respectively invariant under the flow of system 3.5.

### 3.2.1 Implications of Fenichel's second theorem

- i. Hyperbolic fixed points of the differential equation persist under small perturbations together with their stable and unstable manifolds.
- ii. The manifolds  $W^u(M_\epsilon)$  and  $W^s(M_\epsilon)$  are still stable and unstable respectively but in a different sense since  $M_\epsilon$  is no-longer a set of fixed points but has a property that solutions in  $W^u(M_\epsilon)$  decay to  $M_\epsilon$  at an exponential rate in backward time and solutions in  $W^s(M_\epsilon)$  decay exponentially to  $M_\epsilon$  in forward time.
- iii. Local invariance in this case implies that the solutions only decay to  $M_\epsilon$  as long as they stay in the neighbourhood of the compact possibly bounded  $M_\epsilon$ .

## 3.3 Summary

In this chapter, we have presented the basic concepts relevant to mathematical modelling. We have discussed the techniques used to analyse a deterministic model which included the linearisation of the model system and stability analysis of the equilibrium point. We have also described singular perturbation techniques for perturbed systems of equations. We intend to use these techniques to analyse the model in Chapter 4 considering the fact that malaria parameters occur on a much faster time scale than demographic parameters. Other methods we intend to use include numerical simulations obtained by writing computer codes in Python and Matlab programming languages.

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<sup>3</sup>at least  $C^1$  in  $u, v$  and  $\epsilon$  [25]

<sup>4</sup> A mapping  $f : X \rightarrow Y$  of a subset of two euclidean spaces is called a  $C^r$  diffeomorphism if its one to one and onto and if the  $f^{-1} = Y \rightarrow X$  is also  $C^r$  [50].

# Chapter 4

## Model Without Treatment

### 4.1 Introduction

In this chapter, we adopt the model by Feng and colleagues [18, 20] to describe the dynamics of malaria disease and sickle cell gene. Our main aim is to get a clear understanding on how malaria parameters influence the dynamics of sickle cell gene among heterozygous individuals and how sickle cell gene frequency affects the dynamics of malaria. This model will later be extended to include malaria treatment of AA genotype individuals.

### 4.2 Model formulation

The model described below is the classical Ross-MacDonald model including the relevant genotype structure of the human population, that is AA and AS genotype. Let  $S_1$  and  $S_2$  be the population densities of uninfected AA and AS individuals respectively, and let  $I_1$  and  $I_2$  be the densities for the infected individuals of AA and AS genotype. We do not consider SS genotype individuals on assumption that, due to the high mortality rate in countries with high malaria transmission, they do not reach reproductive maturity. However, a complex model including these individuals could be formulated and analysed though it will be difficult to interpret the threshold conditions. Given the total human

population,  $N_h = S_1 + S_2 + I_1 + I_2$ , the proportion of AS and AA individuals is given by

$$w = \frac{S_2 + I_2}{N_h} \quad \text{and} \quad (1 - w) = \frac{S_1 + I_1}{N_h} \quad \text{respectively.}$$

The frequency of the S-gene is then given by  $q = \frac{w}{2}$  and consequently that of the A-gene is given by  $p = 1 - q$ . Let  $m$  be the proportion of mosquitoes carrying the plasmodium parasite ( $I_m/N_m$ ) with  $I_m$  as the number of infected mosquitoes and  $N_m$  the total number of mosquitoes.

Individuals are recruited in the respective susceptible classes,  $S_1$  and  $S_2$  by birth. When a mosquito carrying plasmodium parasite bites a susceptible human, there is a risk that the parasite will be passed on to the human and the person will move to the respective infected class  $I_1$  or  $I_2$ . The probability that an individual of genotype AA acquires parasitemia<sup>1</sup> per bite,  $\theta_1$ , is taken to be greater than that of AS individuals,  $\theta_2$ . i.e  $\theta_1 > \theta_2$ . Infected individuals from  $I_i$ , ( $i = 1, 2$ ), either recover spontaneously and join the susceptible population again at a rate  $\gamma_i$  (with  $\gamma_1 < \gamma_2$ ) or die at a rate  $\alpha_i$  (with  $\alpha_1 > \alpha_2$ ). The biting rate per human per mosquito is taken to be  $a$ . The mortality rate of humans of genotype AA,  $\mu_1$ , is assumed to be equal to natural mortality, while that of individuals of genotype AS is given by  $\mu_2 = \mu_1 + \nu$ , where  $\nu$  is the extra mortality due to S-gene complications.

A mosquito biting an infected individual of either genotype AA or AS acquires plasmodium with a probability  $\phi_i$  (with  $\phi_1 > \phi_2$ ). The average life span of mosquitoes is taken to be  $1/\delta$  and we assume that there is no mortality due to the presence of the parasite.

In addition to the above assumptions, we consider the ratio of the total number of mosquitoes to humans ( $N_m/N_h$ ) to be a constant  $c$ . Secondly, the fractions of the new born individuals of the two genotypes AA and AS are given by  $P_1$  and  $P_2$  respectively where,

$$P_1 = p^2 \quad p \text{ is the frequency of the A-gene,}$$

$$P_2 = 2pq \quad q \text{ is the frequency of the S-gene.}$$

Figure 4.1 illustrates the dynamics of the model showing the in-flow and out-flow of individuals of both genotypes in each compartment.

<sup>1</sup>The presence of a parasite in the blood

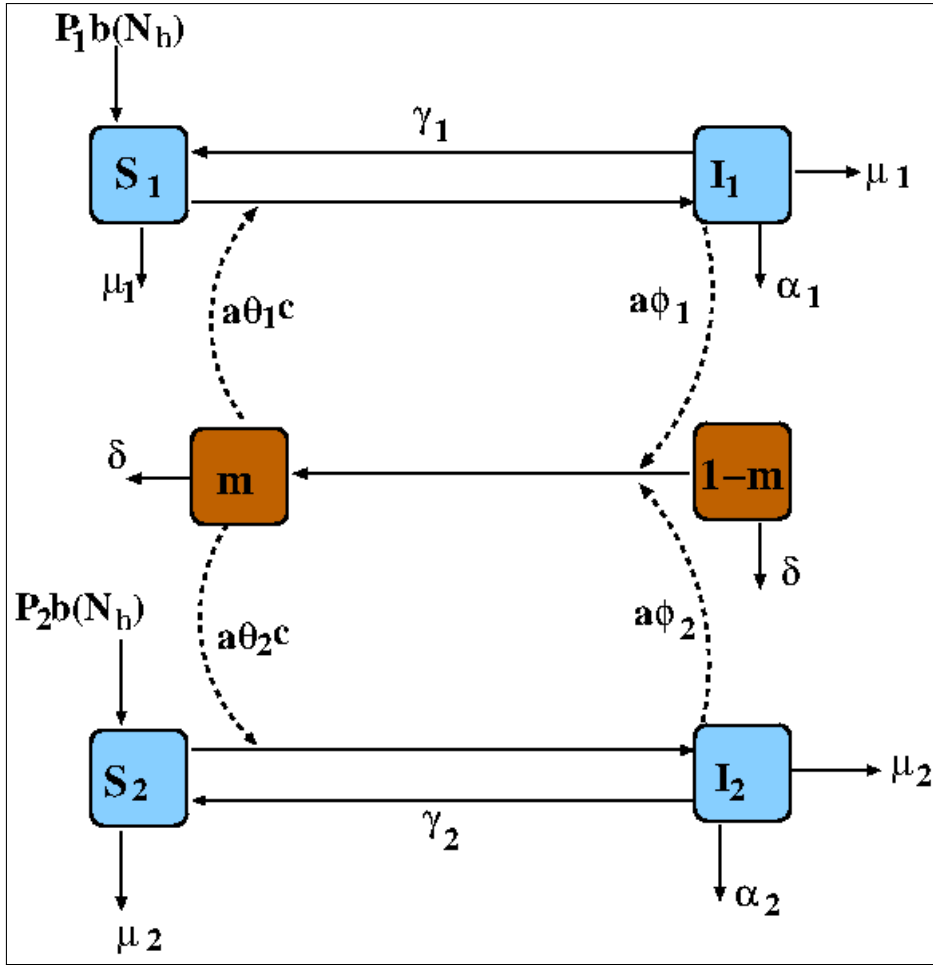


Figure. 4.1. Schematic diagram illustrating the dynamics of malaria and S-gene.

We formulate the model mathematically as a system of coupled ordinary differential equations given in (4.1)

$$\begin{aligned}
 \frac{dS_1}{dt} &= P_1 b(N_h) N_h - \mu_1 S_1 - \lambda_{h_1} S_1 + \gamma_1 I_1, \\
 \frac{dS_2}{dt} &= P_2 b(N_h) N_h - \mu_2 S_2 - \lambda_{h_2} S_2 + \gamma_2 I_2, \\
 \frac{dI_1}{dt} &= \lambda_{h_1} S_1 - (\mu_1 + \gamma_1 + \alpha_1) I_1, \\
 \frac{dI_2}{dt} &= \lambda_{h_2} S_2 - (\mu_2 + \gamma_2 + \alpha_2) I_2, \\
 \frac{dm}{dt} &= (1 - m) (\lambda_{m_1} + \lambda_{m_2}) - \delta m,
 \end{aligned} \tag{4.1}$$

where  $b(N_h)$  is the density dependent per capita birth rate given by  $b(N_h) = b(1 - N_h/K)$  with  $b$  the maximum birth rate constant when the population size is small and  $K$  is approximately the density dependent reduction in the birth rate (carrying capacity).  $m$  is the proportion of mosquitoes with plasmodium. The force of infection of humans of genotype  $i$  by mosquitoes ( $\lambda_{h_i}$ ) is given

$$\lambda_{h_i} = amc\theta_i = a\theta_i \frac{I_m}{N_h}$$

and the force of infection of mosquitoes by humans of genotype  $i$  is also given by

$$\lambda_{m_i} = a\phi_i \frac{I_i}{N_h} \quad \text{for } i = 1, 2.$$

The other parameters are described in Table 4.1 below.

Table. 4.1. *Parameters and their description for the model*

Name	Description
$i = 1$	Individuals with AA genotype.
$i = 2$	Individuals with AS genotype.
$S_i$	Number of uninfected individuals of genotype $i$ .
$I_i$	Number of infected individuals of genotype $i$ .
$m$	Proportion of mosquitoes with plasmodium parasite.
$a$	Biting rate per human per mosquito.
$N_h$	Total human population.
$\theta_i$	Probability that an individual of type $i$ acquires plasmodium per bite, $\theta_1 > \theta_2$ .
$\phi_i$	Probability that a mosquito acquires plasmodium from biting an infected individual of genotype $i$ , $\phi_1 > \phi_2$ .
$\delta$	Mortality rate of mosquitoes.
$c$	Ratio of mosquitoes to human.
$\mu_1$	Human natural mortality rate.
$\nu$	Extra mortality due to sickle cell gene complications.
$\alpha_i$	Malaria-induced mortality rate for genotype $i$ , $\alpha_1 > \alpha_2$ .
$q$	Frequency of the S-gene.
$\gamma_i$	Recovery rate from malaria for genotype $i$ . $\gamma_1 < \gamma_2$ .
$b(N_h)$	Per capita birth rate of humans.
$w$	Fraction of AS individuals.
$P_1$	Fraction of the total birth of individuals of genotype AA, $1 - w + \frac{w^2}{4}$ .
$P_2$	Fraction of the total birth of individuals of genotype AS, $w(1 - \frac{w}{2})$ .

### 4.3 Model analysis

The model for malaria and sickle cell gene described by system (4.1) is analysed in a biologically feasible region. Thus, the following theorem holds.

**Theorem 4.3.1.** *Suppose  $S_1(0), S_2(0), I_1(0), I_2(0)$  are non negative initial conditions, then  $S_1(t), S_2(t), I_1(t), I_2(t)$  are also non negative for  $t > 0$ . Moreover,*

$$\limsup_{t \rightarrow \infty} N_h(t) \leq K.$$

Furthermore, if in addition

$$N_h(0) \leq K, \quad \text{then} \quad N_h(t) \leq K.$$

In particular, the region  $\mathbf{D}$  with

$$\mathbf{D} = \{(S_1, S_2, I_1, I_2) \in \mathbb{R}^4 : S_1 + S_2 + I_1 + I_2 \leq K \quad \text{and} \quad 0 < m < 1\}$$

is positively invariant.

*Proof.* Suppose  $(S_1(0), S_2(0), I_1(0), I_2(0))$  is a set of non negative initial conditions and that the maximum interval of existence of the corresponding solution is  $[0, t_{max}]$ .

Let,

$$t_1 = \sup\{0 < t < t_{max} : S_1, S_2, I_1, I_2 \quad \text{are positive for} \quad [0, t]\}.$$

Since  $S_1(0), S_2(0), I_1(0), I_2(0)$  are non negative, then  $t \geq 0$ . If  $t_1 < t_{max}$ , then by the variation of constant formulae, we obtain from the first equation of (4.1)

$$S_1(t_1) = U(t_1, 0)S_1(0) + \int_0^{t_1} U(t_1, \xi)(P_1 b(N_h)N_h + \gamma_1 I_1)(\xi) d\xi \quad (4.2)$$

where

$$U(t, \xi) = e^{-\int_{\xi}^t (\lambda_{h_1} + \mu_1)(s) ds}.$$

Clearly  $S_1(t_1) > 0$ . We can show in the similar way that all the other variables are positive at  $t_1$ . This contradicts the fact that at  $t_1$  at least one of the variables is equal to zero. Thus  $t_1 = t_{max}$ .

Moreover,

$$\frac{dN_h}{dt} = P_1 b(N_h)N_h + P_2 b(N_N)N_h - \mu_1(S_1 + I_1) - \mu_2(S_2 + I_2) - \alpha_1 I_1 - \alpha_2 I_2.$$



Since all the variables are positive for  $t < t_{max}$ , we obtain

$$\frac{dN_h}{dt} \leq b(P_1 + P_2)N_h \left(1 - \frac{N_h}{K}\right).$$

Thus,

$$N_h(t) \leq \frac{KN_h(0)e^{b(P_1+P_2)t}}{K + N_h(0)(e^{b(P_1+P_2)t} - 1)}.$$

Moreover, if  $N_h(0) \leq K$  then  $N_h(t) \leq K$  for all  $t < t_{max}$ . Therefore  $t_{max} = \infty$ . These results establishes the invariance property of **D**. Therefore the system of equations (4.1) is biologically feasible in region **D**.

□

Using proportions;

$$x_i = \frac{S_i}{N_h}, \quad y_i = \frac{I_i}{N_h}, \quad i = 1, 2 \quad \text{and} \quad x_1 + x_2 + y_1 + y_2 = 1, \quad (4.3)$$

we obtain;

$$\begin{aligned} \dot{y}_1 &= \beta_1 m(1 - y_1 - w) - (\mu_1 + \gamma_1 + \alpha_1)y_1 - \frac{\dot{N}_h}{N_h}y_1, \\ \dot{y}_2 &= \beta_2 m(w - y_2) - (\mu_2 + \gamma_2 + \alpha_2)y_2 - y_2 \frac{\dot{N}_h}{N_h}, \\ \dot{m} &= (1 - m)(\rho_1 y_1 + \rho_2 y_2) - \delta m, \\ \dot{w} &= P_2 b(N_h) - \mu_2 w - \alpha_2 y_2 - w \frac{\dot{N}_h}{N_h}, \\ \dot{N}_h &= N_h((P_1 + P_2)b(N_h) - \mu_1(1 - w) - \mu_2 w - \alpha_1 y_1 - \alpha_2 y_2), \end{aligned} \quad (4.4)$$

where  $\beta_i = a\theta_i c$  and  $\rho_i = a\phi_i$ . The notation “ $\dot{\cdot}$ ” hereafter represents the derivative with respect to time  $t$ .

In order to proceed with the mathematical analysis of the model equations, we note that malaria and genetic changes occur on different time scales, therefore the parameters vary across many orders of magnitude. The malaria parameters ( $\rho_i$ ,  $\beta_i$  and  $\delta$ ) occur on a much faster time scale i.e. on the order 1/days while the genetic and demographic parameters ( $\mu_1$ ,  $b$ ,  $\alpha_i$ ) occur on a slower time scale i.e. on the order 1/decades. Therefore though we have a coupled system of equations describing the dynamics of malaria and genetic

changes, we can not ignore the differences in the time scales. We rescale the demographic and genetic parameters so that  $\hat{\mu}_i = \mu_i/\epsilon$ ,  $\hat{b} = b/\epsilon$  and  $\hat{\alpha}_i = \alpha_i/\epsilon$  with  $0 < \epsilon \ll 1$  as the scaling factor and  $\hat{\mu}_i, \hat{b}, \hat{\alpha}_i$  as the new scaled parameters. Then system (4.4) can be formulated as;

$$\begin{aligned}
 \dot{y}_1 &= \beta_1 m(1 - y_1 - w) - (\epsilon \hat{\mu}_1 + \gamma_1 + \epsilon \hat{\alpha}_1) y_1 - \frac{\dot{N}_h}{N_h} y_1, \\
 \dot{y}_2 &= \beta_2 m(w - y_2) - (\epsilon \hat{\mu}_2 + \gamma_2 + \epsilon \hat{\alpha}_2) y_2 - y_2 \frac{\dot{N}_h}{N_h}, \\
 \dot{m} &= (1 - m)(\rho_1 y_1 + \rho_2 y_2) - \delta m, \\
 \dot{w} &= P_2 \epsilon \hat{b}(N_h) - \epsilon \hat{\mu}_2 w - \epsilon \hat{\alpha}_2 y_2 - w \frac{\dot{N}_h}{N_h}, \\
 \dot{N}_h &= N_h \left( (P_1 + P_2) \epsilon \hat{b}(N_h) - \epsilon \hat{\mu}_1 (1 - w) - \epsilon \hat{\mu}_2 w - \epsilon \hat{\alpha}_1 y_1 - \epsilon \hat{\alpha}_2 y_2 \right).
 \end{aligned} \tag{4.5}$$

System (4.5) has a similar format as system (3.5) in Chapter 3. Therefore system (4.5) is a singular perturbation problem that we analyse using the method described in Chapter 3. By rescaling the independent variable  $t$  such that  $t = \tau/\epsilon$ , system (4.5) can be written on the slow time-scale as;

$$\begin{aligned}
 \epsilon y'_1 &= \beta_1 m(1 - y_1 - w) - (\epsilon \hat{\mu}_1 + \gamma_1 + \epsilon \hat{\alpha}_1) y_1 - \epsilon y_1 \frac{N'_h}{N_h}, \\
 \epsilon y'_2 &= \beta_2 m(w - y_2) - (\epsilon \hat{\mu}_2 + \gamma_2 + \epsilon \hat{\alpha}_2) y_2 - \epsilon y_2 \frac{N'_h}{N_h}, \\
 \epsilon m' &= (1 - m)(\rho_1 y_1 + \rho_2 y_2) - \delta m, \\
 w' &= P_2 \hat{b}(N_h) - \hat{\mu}_2 w - \hat{\alpha}_2 y_2 - w \frac{N'_h}{N_h}, \\
 N'_h &= N_h \left( (P_1 + P_2) \hat{b}(N_h) - \hat{\mu}_1 (1 - w) - \hat{\mu}_2 w - \hat{\alpha}_1 y_1 - \hat{\alpha}_2 y_2 \right),
 \end{aligned} \tag{4.6}$$

where “ $\prime$ ” is the derivative with respect to  $\tau$ . Thus the malaria variables  $y_1, y_2$  and  $m$  are considered as the fast variables whereas the measure of the abundance of S-gene,  $w$ , and the total human population,  $N_h$ , are the slow variables. In the next section we carry out the analysis on the fast time scale.

## 4.4 Fast dynamics of malaria

In this section, we carry out the analysis on the fast time scale using singular perturbation techniques. Setting  $\epsilon = 0$ , the reduced system on the fast time scale represents the dynamics of malaria only. Moreover, the variable corresponding to the frequency of sickle cell gene,  $w$ , is then considered as a constant parameter. System (4.5) thus reduces to;

$$\begin{aligned} \dot{y}_1 &= \beta_1 m(1 - y_1 - w) - \gamma_1 y_1, \\ \dot{y}_2 &= \beta_2 m(w - y_2) - \gamma_2 y_2, \\ \dot{m} &= (1 - m)(\rho_1 y_1 + \rho_2 y_2) - \delta m. \end{aligned} \quad (4.7)$$

### 4.4.1 Existence of equilibrium points

Let  $E^* = (y_1^*, y_2^*, m^*)$  represent any arbitrary equilibrium point of system (4.7) obtained by setting the right hand side to zero;

$$\begin{aligned} \beta_1 m^*(1 - y_1^* - w) - \gamma_1 y_1^* &= 0, \\ \beta_2 m^*(w - y_2^*) - \gamma_2 y_2^* &= 0, \\ (1 - m^*)(\rho_1 y_1^* + \rho_2 y_2^*) - \delta m^* &= 0. \end{aligned} \quad (4.8)$$

In the absence of malaria disease, we have  $E_0 = (0, 0, 0)$  as an equilibrium point referred to as the disease free equilibrium point.

### 4.4.2 Basic reproduction number, $R_0$

The basic reproduction number denoted as  $R_0$ , is a threshold value that is often used in mathematical models to measure the spread of a disease. It is defined as the number of new infections in humans that arise as a result of a single infected individual being introduced in a fully susceptible population. When  $R_0 < 1$ , it implies that on average an infectious individual infects less than one person throughout his/her infectious period and in this case the disease is wiped out. On the other hand, when  $R_0 > 1$ , then on average every infectious individual infects more than one individual during his/her infectious period and the disease

persists in the population. P.van den Driessche and J. Watmough [47] described the next generation method used to compute the basic reproduction number. Given as system,

$$\begin{aligned} \frac{dX}{dt} &= f(X), \\ &= \mathcal{F}(\mathcal{X}) + \mathcal{V}(\mathcal{X}), \\ &= \mathcal{F}(\mathcal{X}) - (\mathcal{V}^+(\mathcal{X}) - \mathcal{V}^-(\mathcal{X})), \end{aligned}$$

where  $\mathcal{F}(\mathcal{X})$  is the rate at which new infections appear in each compartment,  $\mathcal{V}^+(\mathcal{X})$  is the rate of transfer into each compartment and  $\mathcal{V}^-(\mathcal{X})$  is the rate of transfer out of each compartment. Applying this to system (4.7), we have,

$$\mathcal{F} = \begin{bmatrix} \beta_1 m(1-w-y_1) \\ \beta_2 m(w-y_2) \\ (1-m)(\rho_1 y_1 + \rho_2 y_2) \end{bmatrix} \quad \text{and} \quad \mathcal{V} = \begin{bmatrix} \gamma_1 y_1 \\ \gamma_2 y_2 \\ \delta m \end{bmatrix}.$$

We evaluate the Jacobian matrices for  $\mathcal{F}$  and  $\mathcal{V}$  at disease free equilibrium such that;

$$\mathbf{F} = D\mathcal{F}|_{\mathbb{E}(0,0,0)} = \begin{bmatrix} 0 & 0 & \beta_1(1-w) \\ 0 & 0 & \beta_2 w \\ \rho_1 & \rho_2 & 0 \end{bmatrix} \quad \text{and} \quad \mathbf{V} = D\mathcal{V}|_{\mathbb{E}(0,0,0)} = \begin{bmatrix} \gamma_1 & 0 & 0 \\ 0 & \gamma_2 & 0 \\ 0 & 0 & \delta \end{bmatrix}.$$

The reproduction number  $\mathbf{R}_0$  is given as the dominant positive eigenvalue of the next generation matrix

$$\mathbf{FV}^{-1} = \begin{bmatrix} 0 & 0 & \frac{\beta_1(1-w)}{\delta} \\ 0 & 0 & \frac{\beta_2 w}{\delta} \\ \frac{\rho_1}{\gamma_1} & \frac{\rho_2}{\gamma_2} & 0 \end{bmatrix}. \quad (4.9)$$

The eigenvalues of (4.9) are,

$$\lambda = 0, \quad \lambda = \pm \sqrt{\frac{\beta_1 \rho_1}{\gamma_1 \delta} (1-w) + \frac{\beta_2 \rho_2}{\gamma_2 \delta} w}.$$

Thus;

$$\tilde{\mathbf{R}}_0 = \sqrt{\frac{\beta_1 \rho_1}{\gamma_1 \delta} (1-w) + \frac{\beta_2 \rho_2}{\gamma_2 \delta} w} = \sqrt{\mathbf{R}_0}. \quad (4.10)$$

The original definition of  $R_0$  gives the number of humans that one infected human infects through out his or her infectious period when introduced in a fully susceptible population. However, the reproduction number given in (4.10) obtained from the next generation operator gives the number of infected human (mosquito) that an infected mosquito (human) infects throughout out the infectious period when introduced to a fully susceptible human (mosquito) population [11, 12, 47]. Thus, the basic reproduction number as per the original definition is given by;

$$R_0 = \frac{\beta_1 \rho_1}{\gamma_1 \delta} (1 - w) + \frac{\beta_2 \rho_2}{\gamma_2 \delta} w.$$

$R_0$  can be written as

$$R_0 = R_1(1 - w) + R_2 w,$$

where

$$R_i = \frac{\beta_i \rho_i}{\gamma_i \delta} \quad \text{for } i = 1, 2$$

is the reproduction number when the population consists of entirely individuals of genotype  $i$ . The threshold value  $R_0$  is a very important parameter for explaining disease outbreak and determining control strategies to encounter the problem. Furthermore, the stability of the equilibria can be analysed based on  $R_0$ .

### 4.4.3 Local stability of disease free equilibrium (DFE)

The local stability of the DFE is determined by the eigenvalues of the Jacobian matrix of system (4.7) evaluated at DFE.

$$\mathbf{J}|_{E_0} = \begin{pmatrix} -\gamma_1 & 0 & \beta_1(1 - w) \\ 0 & -\gamma_2 & \beta_2 w \\ \rho_1 & \rho_2 & -\delta \end{pmatrix}. \quad (4.11)$$

That is, the roots of

$$\lambda^3 + r_2 \lambda^2 + r_1 \lambda + r_0, \quad (4.12)$$

with

$$r_2 = \delta + \gamma_1 + \gamma_2, \quad r_1 = \delta\gamma_1(1 - R_1) + \delta\gamma_2(1 - R_2) \quad \text{and} \quad r_0 = \delta\gamma_1\gamma_2(1 - R_0).$$

Routh-Hurwitz stability criterion suggests that if  $r_0, r_1, r_2 > 0$  and  $r_2r_1 > r_0$  then all the eigenvalues are negative [24].

- If  $R_0 < 1$ , then  $r_0, r_1, r_2 > 0$  and  $r_2r_1 - r_0 > 0$ , thus DFE is locally asymptotically stable.
- When  $R_0 > 1$ ,  $r_0 < 0$ , then atleast one root of equation (4.12) is positive thus the DFE is unstable.

#### 4.4.4 Endemic equilibrium point (EE)

Solving (4.8), we obtain

$$\begin{aligned} y_1^* &= \frac{\beta_1 m^*(1-w)}{\beta_1 m^* + \gamma_1}, \\ &= \frac{T_{h_1} m^*(1-w)}{T_{h_1} m^* + 1} \quad \text{where} \quad T_{h_1} = \frac{\beta_1}{\gamma_1}. \end{aligned} \quad (4.13)$$

Similarly from the second equation of (4.8),

$$\begin{aligned} y_2^* &= \frac{\beta_2 m^* w}{\beta_2 m^* + \gamma_2}, \\ &= \frac{T_{h_2} m^* w}{T_{h_2} m^* + 1} \quad \text{where} \quad T_{h_2} = \frac{\beta_2}{\gamma_2}. \end{aligned} \quad (4.14)$$

Substituting equations (4.13) and (4.14) in the third equation (4.8) and simplifying we obtain  $m^*$  as a solution to the quadratic equation

$$k_0 m^{*2} + k_1 m^* + k_2 = 0, \quad (4.15)$$

where,

$$\begin{aligned} k_0 &= T_{h_1}T_{h_2} + R_1T_{h_2}(1-w) + R_2T_{h_1}w > 0, \\ k_1 &= T_{h_1}(1-wR_2) + T_{h_2}(1-(1-w)R_1) + R_0, \\ k_2 &= 1 - R_0. \end{aligned}$$

We determine the conditions for which positive roots of equation (4.15) exist. We consider the following,

- When  $R_0 < 1$ ,  $k_2 > 0$  and  $k_1 > 0$ , then (4.15) has no positive root. Therefore, no endemic equilibria exist when  $R_0 < 1$ .
- If  $R_0 > 1$ , then  $k_2 < 0$ .

Let  $f(m^*) = k_0m^{*2} + k_1m^* + k_2$ , then

$$\begin{aligned} f(0) &= k_2 < 0, \\ f(1) &= k_0 + k_1 + k_2, \\ &= T_{h_1}T_{h_2} + T_{h_1} + T_{h_2} + 1, \\ &> 0. \end{aligned}$$

The intermediate value theorem guarantees the existence of one root in the interval  $(0,1)$  of equation (4.15). The other root is negative since the product of roots is  $k_2/k_0 < 0$ . Therefore, when  $R_0 > 1$ , system (4.7) has one unique endemic equilibrium point.

#### 4.4.5 Local stability of EE

The Jacobian matrix of system (4.7) is used to determine the local stability of the endemic equilibrium point  $E^*$ . Thus

$$\mathbf{J}|_{E^*(y_1^*, y_2^*, m^*)} = \begin{bmatrix} -(\beta_1 m^* + \gamma_1) & 0 & \beta_1(1-w-y_1^*) \\ 0 & -(\beta_2 m^* + \gamma_2) & \beta_2(w-y_2^*) \\ \rho_1(1-m^*) & \rho_2(1-m^*) & -(\rho_1 y_1^* + \rho_2 y_2^* + \delta) \end{bmatrix}.$$

The above matrix  $\mathbf{J}$  can be written as

$$\mathbf{J} = H - D$$

where,

$$H = \begin{bmatrix} 0 & 0 & \beta_1(1 - w - y_1^*) \\ 0 & 0 & \beta_2(w - y_2^*) \\ \rho_1(1 - m^*) & \rho_2(1 - m^*) & 0 \end{bmatrix}$$

and

$$D = \begin{bmatrix} (\beta_1 m^* + \gamma_1) & 0 & 0 \\ 0 & (\beta_2 m^* + \gamma_2) & 0 \\ 0 & 0 & (\rho_1 y_1^* + \rho_2 y_2^* + \delta) \end{bmatrix}.$$

We note that  $H$  is a positive matrix since  $1 - w - y_1^* = x_1^* > 0$  and  $0 < m^* < 1$ . Also  $D$  is a diagonal matrix therefore non-singular.

Then the eigenvalues of  $\mathbf{J}$  have negative real parts if the spectral radius of  $HD^{-1}$  is less than one [47]. We have

$$HD^{-1} = \begin{bmatrix} 0 & 0 & \frac{\beta_1(1-w-y_1^*)}{\rho_1 y_1^* + \rho_2 y_2^* + \delta} \\ 0 & 0 & \frac{\beta_2(w-y_2^*)}{\rho_1 y_1^* + \rho_2 y_2^* + \delta} \\ \frac{\rho_1(1-m^*)}{\beta_1 m^* + \gamma_1} & \frac{\rho_2(1-m^*)}{\beta_2 m^* + \gamma_2} & 0 \end{bmatrix}.$$

with eigenvalues,

$$\lambda_0 = 0,$$

$$\lambda_1 = -\sqrt{\left(\frac{\beta_1(1-w-y_1^*)}{(\rho_1 y_1^* + \rho_2 y_2^* + \delta)}\right) \left(\frac{\rho_1(1-m^*)}{(\beta_1 m^* + \gamma_1)}\right) + \left(\frac{\beta_2(w-y_2^*)}{(\rho_1 y_1^* + \rho_2 y_2^* + \delta)}\right) \left(\frac{\rho_2(1-m^*)}{(\beta_2 m^* + \gamma_2)}\right)},$$

$$\lambda_2 = \sqrt{\left(\frac{\beta_1(1-w-y_1^*)}{(\rho_1 y_1^* + \rho_2 y_2^* + \delta)}\right) \left(\frac{\rho_1(1-m^*)}{(\beta_1 m^* + \gamma_1)}\right) + \left(\frac{\beta_2(w-y_2^*)}{(\rho_1 y_1^* + \rho_2 y_2^* + \delta)}\right) \left(\frac{\rho_2(1-m^*)}{(\beta_2 m^* + \gamma_2)}\right)}.$$



From system (4.8), we have,

$$m^* = \frac{\rho_1 y_1^* + \rho_2 y_2^*}{\rho_1 y_1^* + \rho_2 y_2^* + \delta} = \frac{\gamma_1 y_1^*}{\beta_1(1 - w - y_1^*)} = \frac{\gamma_2 y_2^*}{\beta_2(w - y_2^*)}$$

and using  $\gamma_i < \gamma_i + \beta_i m^*$  for  $i = 1, 2$ ,

$$\begin{aligned} \lambda_2^2 &= \left( \frac{\beta_1(1 - w - y_1^*)}{(\rho_1 y_1^* + \rho_2 y_2^* + \delta)} \right) \left( \frac{\rho_1(1 - m^*)}{(\beta_1 m^* + \gamma_1)} \right) + \left( \frac{\beta_2(w - y_2^*)}{(\rho_1 y_1^* + \rho_2 y_2^* + \delta)} \right) \left( \frac{\rho_2(1 - m^*)}{(\beta_2 m^* + \gamma_2)} \right), \\ &< \left( \frac{\gamma_1 y_1^*}{\rho_1 y_1^* + \rho_2 y_2^*} \right) \frac{\rho_1(1 - m^*)}{\gamma_1} + \left( \frac{\gamma_2 y_2^*}{\rho_1 y_1^* + \rho_2 y_2^*} \right) \frac{\rho_2(1 - m^*)}{\gamma_2}, \\ &= 1 - m^* < 1. \end{aligned}$$

This implies that the dominant eigenvalue of  $HD^{-1} < 1$  and therefore all the eigenvalues of  $\mathbf{J}$  have negative real parts implying that the unique endemic equilibrium point  $E^* = (y_1^*, y_2^*, m^*)$  is locally asymptotically stable. The results of the fast dynamics are summarized in the following theorem,

**Theorem 4.4.1.** *For the system of equations (4.7) of the fast dynamics,*

- (i) *If  $R_0 < 1$ , the disease free equilibrium  $E_0$  is locally asymptotically stable and endemic equilibrium  $E^*$  is not biologically feasible.*
- (ii) *If  $R_0 > 1$ , then  $E_0$  is unstable and the  $E^*$  is locally asymptotically stable.*

## 4.5 Estimation of parameter values

Here, we present the parameter values that are used for our numerical simulations. Estimation of the parameters for both genotype is not trivial since most of the malaria models in literature do not consider the genetic make up of individuals. Most of the parameters used in this model are obtained from [18, 19, 20]. Other parameters used for numerical simulations are either assumed or obtained from other malaria models from literature as explained below.

- **Demographic parameters**

Demographic parameters vary from one setting to another. We consider a birth rate,  $b$ , of 0.00004 per day obtained from [18, 19, 20]. We assume that the recruitment by birth of both AA and AS individuals depends on the frequency of the sickle cell gene of the parental pool.

The human mortality rate,  $\mu_1$ , was estimated to be 0.00004 per day which corresponds to 65 years of life expectancy [20, 34]. The extra mortality rate due to sickle cell complications,  $\nu$ , was estimated to be 0.00002 [20]. This implies that the total mortality rate for the AS individuals was taken to be 0.00006 per day which corresponds to their life expectancy of 45 years.

The malaria induced mortality rate,  $\alpha_i, i = 1, 2$ , is estimated to be 0.0005 [20, 37]. This rate is varied depending on whether the individual has AA or AS genotype.

- **Transmission parameters**

The mosquito biting rate,  $a$ , was taken to be 0.2 in [34] and between 1 and 2 in [19]. Feng et al. [20] estimated the probability of mosquito transmission of plasmodium parasite to humans,  $\theta_i, i = 1, 2$ , to be between 0.01 to 0.09. Other malaria models considered this value to be 0.833 [11, 15, 32, 34]. The human to mosquito transmission probability,  $\phi_i$ , is estimated to range between 0.01 to 0.09 [15, 34]. This variation in these probabilities is due to the different settings taken and also the distribution of the sickle cell gene frequency.

- **Mosquito parameters**

The mosquito survival period is about 10 – 25 days. We note that mosquitoes are not affected by the malaria parasite. Therefore, on average the estimated mortality rate of mosquitoes,  $\delta$ , is 0.07 which corresponds to an average of 15 days of life expectancy [34].

- **Recovery parameters**

The spontaneous recovery rate of AA individuals,  $\gamma_1$ , is estimated to be 0.033 which corresponds to 33 days of infection [41]. It is assumed that it takes a maximum of 33 days to clear the parasite from body by the immune system. On the other hand, the recovery rate for the AS individuals,  $\gamma_2$ , is assumed to be 0.066 which is twice that of

AA individuals. This is because the parasite is continuously destroyed together with sickled red blood cells by the spleen in a period of 10 – 20 days compared 120 days for the normal red blood cells. This gives an advantage to the AS individuals since it takes a shorter period to clear the parasite from their body as compared to their counterparts of AA genotype. Depending on the individuals immune system, these values can vary between 0 – 0.2.

## 4.6 Numerical simulation of fast dynamics

In this section, we carry out numerical simulation of the model given in system (4.7). The Euler and 4<sup>th</sup> order Runge Kutta methods are the common numerical techniques used for solving ordinary differential systems of equations. However, convergence and stability of results obtained by applying these techniques is only guaranteed for small time step size ( $< 0.1$ ). For any arbitrary step size, the two techniques may fail or diverge. On addition, the two schemes do not necessarily preserve positivity of the solution which is a basic property as far as biological systems are concerned. The non-standard finite difference method is a technique that has been proved to preserve both positivity and stability of the equilibrium point. It is developed from the forward finite difference method but with a denominator function and has been used by various researchers including Ibijola et al. [26], Lubuma and Patidar [33], and Anguelov et al. [9]. Here, we restrict ourselves to the 4<sup>th</sup> order Runge Kutta scheme in Matlab and *odesolver packages* in Python with small step size for our numerical simulations. The choice of the parameters used in this model are as per the explanation given in Section 4.5 but mostly obtained from [19, 18, 20] (Table 4.2). Simulations carried out in this section explain the dynamics of malaria disease among individuals of AA and AS genotypes.

Table 4.2. *Parameter values used for the model given in (4.7) obtained from [20]*

Parameter	Parameter value (per day)
$a$	1
$b$	0.00004
$\theta_1$	0.05
$\theta_2$	0.06
$\phi_1$	0.05
$\phi_2$	0.09
$\gamma_1$	0.05
$\gamma_2$	0.05, 0.09
$\alpha_1$	0.0001
$\alpha_2$	0.00005
$\delta$	0.07
$\mu_1$	0.00003
$\nu$	0.00002
$\epsilon$	$10^{-5}$
$c$	4
$K$	10000
$w$	0.1, 0.7

Figure 4.2 and Figure 4.3 show the change in the proportions of infected AS, AA individuals and mosquitoes with plasmodium for  $R_0$  less than one while Figure 4.4 and Figure 4.5 indicate the change when  $R_0$  is greater than one. We note that when  $R_0 < 1$ , both the human and mosquito infected proportions go to zero. On the other hand, when  $R_0 > 1$ , then the proportion of infected humans and mosquitoes stabilize at the endemic equilibrium  $E^* = (0.187, 0.303, 0.344)$  given  $w = 0.7$ . This is in agreement with the local stability of the disease free and endemic equilibrium points as stated in Theorem 4.4.1. Furthermore, Figure 4.6 and Figure 4.7 demonstrates that irrespective of the initial conditions, the disease will always persist in the population for  $R_0 > 1$ . This agrees with the global stability results of the endemic equilibrium point.

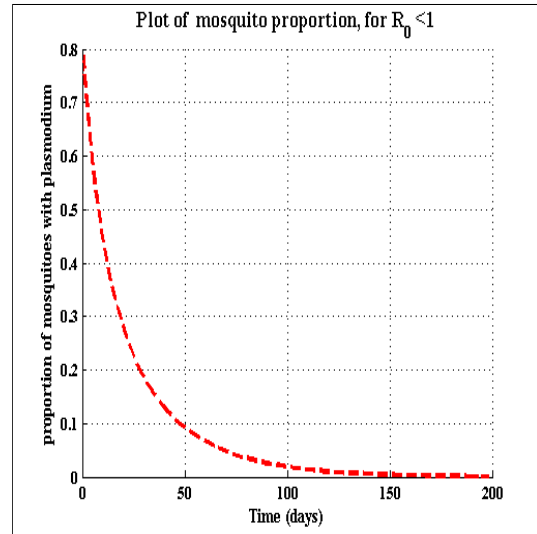
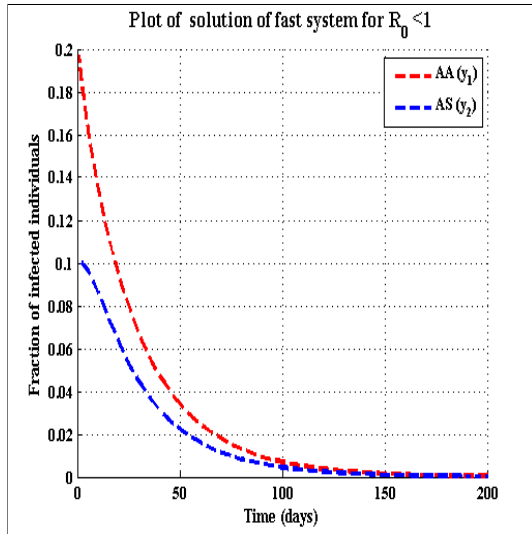


Figure. 4.2. Illustrates a decrease in the proportion of infected individuals with time,  $R_0 < 1$

Figure. 4.3. Illustrates a decrease in the proportion of mosquitoes carrying plasmodium parasite with time,  $R_0 < 1$

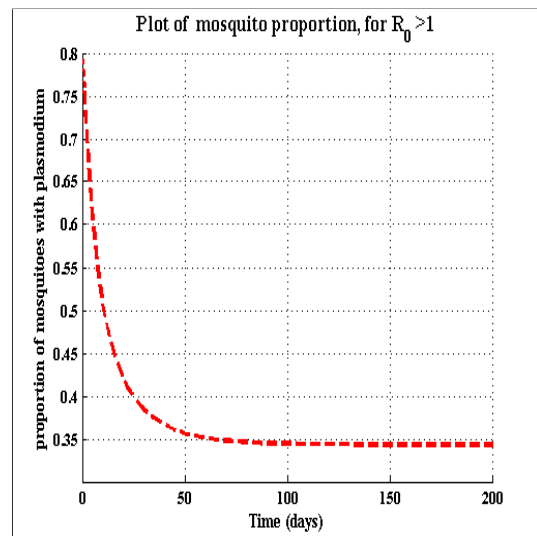
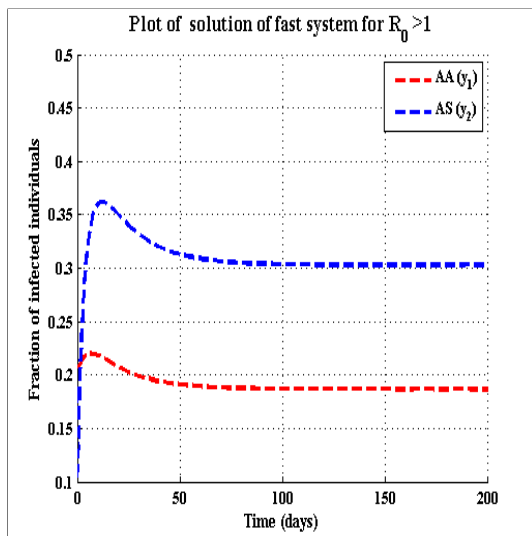


Figure. 4.4. Illustrates how the proportion of infected AA and AS individuals change with time,  $R_0 > 1$

Figure. 4.5. Demonstrates how the proportion of mosquitoes with plasmodium parasite change with time,  $R_0 > 1$

### 4.6.1 Impact of S-gene frequency on malaria prevalence

In this subsection, we investigate the impact of S-gene frequency on malaria prevalence. We consider two cases, when the recovery rate of AS individuals is small i.e.  $\gamma_2 = 0.055$

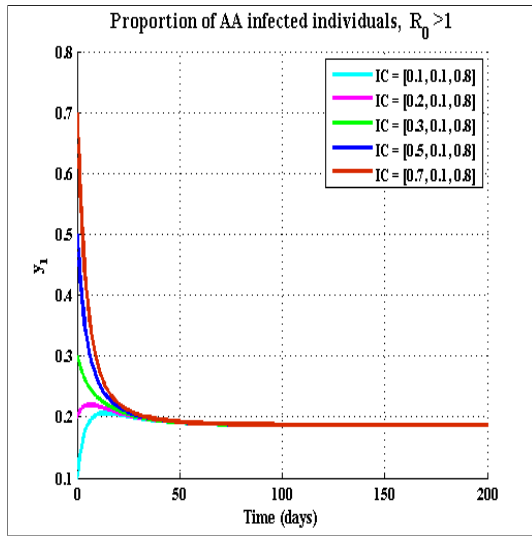


Figure. 4.6. Shows the behaviour of the proportion of infected AA individuals for  $R_0 > 1$  given different initial conditions

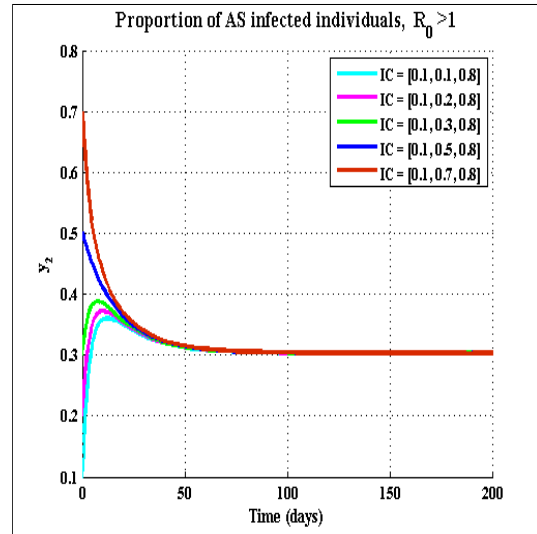


Figure. 4.7. Demonstrates the behaviour of the proportion of infected AS individuals for  $R_0 > 1$  given different initial conditions

and when  $\gamma_2 = 0.09$ . We observe the change in the malaria prevalence as we increase the frequency of S-gene. Figure 4.8 shows that malaria prevalence increases with increase in S-gene frequency for small values of  $\gamma_2$ . This implies that for smaller values of  $\gamma_2$ , higher S-gene frequency leads to higher malaria endemic levels at equilibrium. This is expected especially in cases where AS individuals rarely show clinical symptoms but still inhabit the parasite and transmit it. On the other hand, increasing the recovery rate with  $\gamma_2 = 0.09$ , Figure 4.9 shows that at equilibrium, malaria prevalence decreases with increase in S-gene frequency. This is also illustrated in Figure 4.10. where the reproduction number  $R_0$  increases with increase in frequency for smaller values of  $\gamma_2$  and decreases with sickle cell gene frequency for higher values of  $\gamma_2$ . Therefore, increasing the duration of parasitemia for AS individuals (reducing  $\gamma_2$ ) leads to higher malaria prevalence thus increased selection for the S-gene.

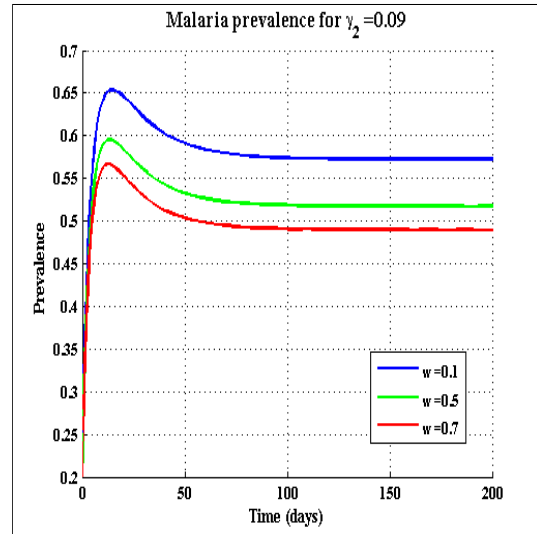
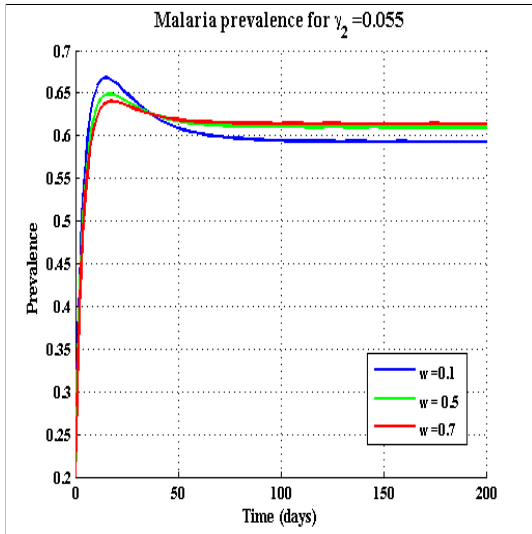


Figure 4.8. Plot showing the change in malaria prevalence with time for different values of the sickle cell gene frequency, recovery rate,  $\gamma_2 = 0.055$

Figure 4.9. Plot showing the change in malaria prevalence with time for different values of the sickle cell gene frequency,  $\gamma_2 = 0.09$

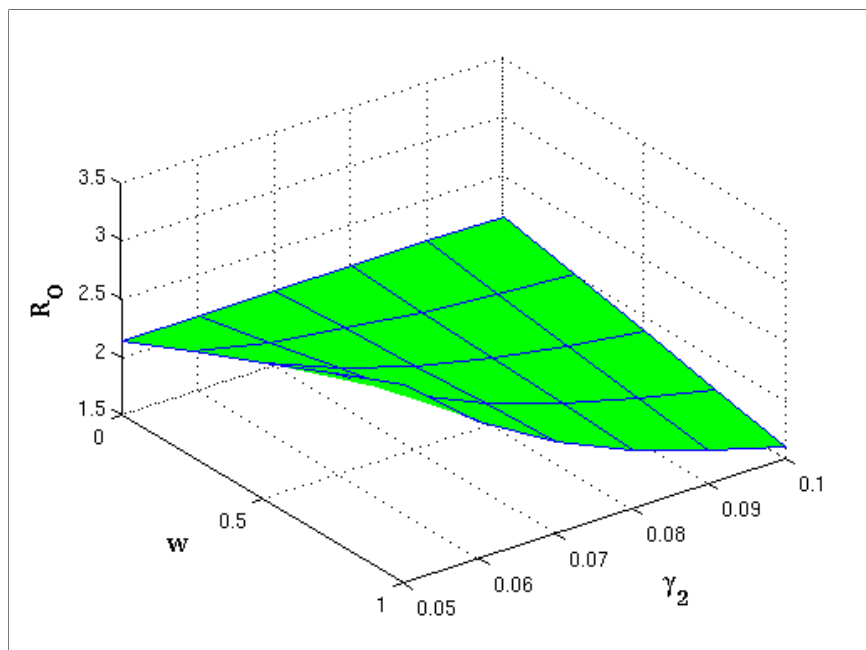


Figure 4.10. Plot of variation of the reproduction number with recovery rate  $\gamma_2$  and S-gene frequency  $w$

## 4.7 Sensitivity analysis

In this section, we carry out sensitivity analysis of the reproduction number in order to determine the important parameters that can be targeted so as to bring the reproduction value below one. Sensitivity analysis is commonly used to determine the robustness of the model predictions to parameter values [12]. One way of studying the sensitivity of the model's parameters is to calculate the sensitivity index which is the measure of the relative change in the parameter value to a given outcome (variable).

**Definition 4.7.1.** [12] *The normalised forward sensitivity index of a variable  $u$  that differentially depends on the parameter  $p$  can be defined as;*

$$\mathbf{X}_p^u = \frac{\partial u}{\partial p} \frac{p}{u} \quad (4.16)$$

### 4.7.1 Sensitivity indices for reproduction number

Using parameters in Table 4.2 and Definition 4.7.1, we compute the indices for the reproduction number given above. For example, for the malaria infection rate of humans of AA genotype  $\beta_1$ , we have

$$\mathbf{X}_{\beta_1}^{R_0} = \frac{\beta_1 \rho_1 \gamma_2 (1-w) w}{\beta_1 \rho_1 \gamma_2 (1-w) + \beta_2 \rho_2 \gamma_1}.$$

In the same way the sensitivity indices of the other parameters used in the model for the fast dynamics are computed and their values given in Table 4.3. We consider two cases, when S-gene frequency is small ( $w = 0.1$ ) and when  $w = 0.7$  to compare our results. Figure 4.11 and Figure 4.12 give the graphic representation of these values.

The sign of the sensitivity index gives the behaviour of the reproduction number with an increase or decrease in that parameter value. The (+) shows that the reproduction number is an increasing function of the parameter implying that an increase in the parameter value leads to an increase in the reproduction number. The (-) shows that the reproduction number is a decreasing function of that parameter implying that an increase in the parameter value leads to a decrease in the reproduction number. For the sensitivity analysis done, we discover that when  $w = 0.1$ , the reproduction number is most sensitive to the infection rates and the recovery rate of AA individuals i.e  $\beta_1$ ,  $\rho_1$  and  $\gamma_1$ . It shows that an increase in the infection rate leads to an increase in the reproduction number while an



increase in the recovery rate leads to a decrease in the reproduction number. This agrees with intuitive reasoning since we expect a high transmission rate if the infection rate is increased and a longer period of infectiousness with a reduced recovery rate. We also note that increasing the mortality rate of mosquitoes with plasmodium by 10% decreases the reproduction number by 10%.

When the frequency of the S-gene is high i.e  $w = 0.7$ , the basic reproduction number is sensitive to the recovery rate of AS individuals. An increase in the recovery rate by 10% decreases the reproduction number by 6.604% (see Table 4.3 and Figure 4.12). This concurs with the numerical results obtained above whereby reduction in duration of parasetaemia leads to reduction in the reproduction number. We also note that the reproduction number is as equally sensitive to infection rate of the mosquitoes by individuals of each genotype as to the infection rate of individuals by the mosquitoes.

Table. 4.3. *Sensitivity indices for  $R_0$  given  $w = 0.1$  and  $w = 0.7$*

Parameter	Parameter Value	$w = 0.1$	$w = 0.7$
$\beta_1$	0.24	+0.9153	+0.3396
$\beta_2$	0.2	+0.0325	+0.0487
$\gamma_1$	0.05	-0.7627	-0.2830
$\gamma_2$	0.09	-0.0847	-0.6604
$\delta$	0.07	-1	-1
$\rho_1$	0.05	+0.9153	+0.3396
$\rho_2$	0.09	+0.0325	+0.0487

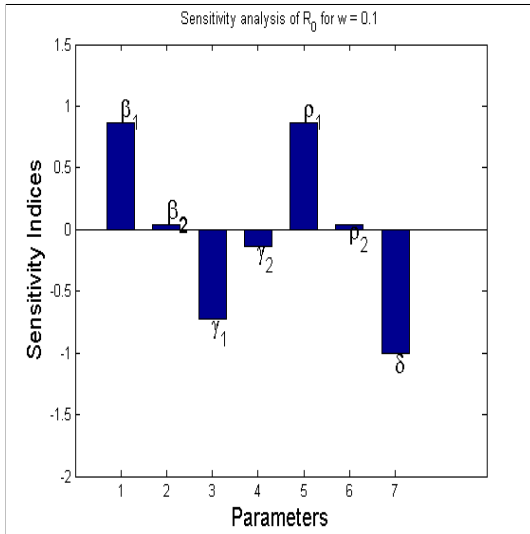


Figure 4.11. *Sensitivity indices for  $R_0$  given  $w = 0.1$*

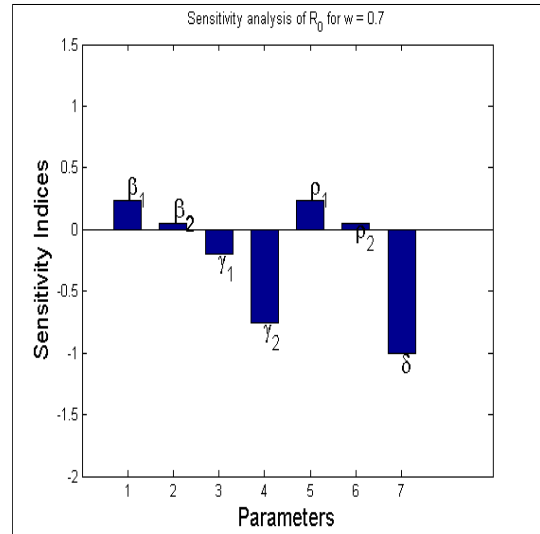


Figure 4.12. *Sensitivity indices for  $R_0$  given  $w = 0.7$*

## 4.8 Slow dynamics

In this section, we study the dynamics of malaria and sickle cell gene in the limit as  $\epsilon \rightarrow 0$  where the fast system is singular and the singularities appear as manifolds on the slow system (Chapter 3). In this case, the set of equilibria of the fast system gives a two dimension slow manifold which is normally hyperbolically stable. i.e

$$M^0 = \{(y_1, y_2, m, w, N_h) : y_1 = y_1^*(w, N_h), y_2 = y_2^*(w, N_h), m = m^*(w, N_h)\}$$

with  $y_1^*, y_2^*$  given by equations (4.13) and (4.14) respectively. Fenichel's second theorem, Theorem 3.2.2 guarantees the persistence of this manifold for small non zero  $\epsilon$  as

$$M^\epsilon = \{(y_1, y_2, m, w, N_h) : y_1 = y_1^\epsilon, y_2 = y_2^\epsilon, m = m^\epsilon\}.$$

The stable manifold  $M^\epsilon$  has a property that for the initial condition close to it, the solution will always decay towards  $M^0$  for  $t > 0$ . Singular perturbation techniques thus allow us to study system (4.6) as the following reduced system;

$$\begin{aligned}\frac{dw}{d\tau} &= ((1-w)P_2 - wP_1)\hat{b}(N_h) + (\hat{\mu}_1 - \hat{\mu}_2)w(1-w) + \hat{\alpha}_1wy_1^* - \hat{\alpha}_2(1-w)y_2^*, \\ \frac{dN_h}{d\tau} &= N_h \left( (P_1 + P_2)\hat{b}(N_h) - \hat{\mu}_1(1-w) - \hat{\mu}_2w - \hat{\alpha}_1y_1^* - \hat{\alpha}_2y_2^* \right).\end{aligned}\quad (4.17)$$

This gives the differential system that describes the evolution of the slow variable when constrained on the fast system for  $\epsilon = 0$ . Therefore on the slow manifold, we have smooth functions

$$y_1^\epsilon = y_1^* + o(\epsilon), \quad y_2^\epsilon = y_2^* + o(\epsilon) \quad \text{and} \quad m^\epsilon = m^* + o(\epsilon).$$

The manifold  $M^\epsilon$  is diffeomorphic to  $M^0$ , normally hyperbolically stable and invariant with respect to both equations (4.5) and (4.6) for  $\epsilon > 0$ .  $M^\epsilon$  admits asymptotic phase such that;

$$\begin{aligned}y_1 &= y_1^\epsilon(w, N_h) + Y_1(t), \\ y_2 &= y_2^\epsilon(w, N_h) + Y_2(t), \\ m &= m^\epsilon(w, N_h) + M(t),\end{aligned}\quad (4.18)$$

with  $w$  and  $N_h$  being solutions of the reduced system (4.17) and  $Y_1(t), Y_2(t), M(t)$  are exponential decay functions with exponents in the scale of upper bound of eigenvalues of the linearised system (4.7) about the equilibrium point  $(y_1^*, y_2^*, m^*)$  [18, 25]. Thus, if we can describe the dynamics of system (4.17) using bifurcation parameters, we get a clear understanding of this system on the manifold hence for the full system (4.6). Analysis of both systems (4.7) and (4.17) explains the dynamics of malaria and sickle cell gene.

### 4.8.1 Dynamics on the slow manifold

Recall that when  $R_0 > 1$ , the unique positive solution of equation (4.15) is given by,

$$m^* = \frac{-k_1 + \sqrt{\Delta}}{2k_0},$$

where,

$$\begin{aligned}\Delta &= k_1^2 - 4k_0k_2, \\ &= a_0w^2 + 2a_1w + a_2,\end{aligned}\tag{4.19}$$

with,

$$\begin{aligned}a_0 &= (R_1(1 + T_{h2}) - R_2(1 + T_{h1}))^2, \\ a_1 &= -(1 + T_{h2})^2R_1 + (1 + T_{h2})(T_{h2} - T_{h1} + R_2(1 + T_{h1}))R_1 - R_2(1 + T_{h1})(T_{h1} - T_{h2}), \\ a_2 &= (T_{h1} - T_{h2} + (1 + T_{h2})R_1)^2.\end{aligned}\tag{4.20}$$

Then the unique endemic equilibrium point of system (4.7) is given by;

$$y_1^* = \frac{-k_1 + \sqrt{\Delta}}{-(k_1 - u_1k_0) + \sqrt{\Delta}}(1 - w),\tag{4.21}$$

$$y_2^* = \frac{-k_1 + \sqrt{\Delta}}{-(k_1 - u_2k_0) + \sqrt{\Delta}}w,\tag{4.22}$$

$$m^* = \frac{-k_1 + \sqrt{\Delta}}{2k_0},\tag{4.23}$$

where  $u_i = 2/T_{h_i}$  for  $i = 1, 2$ .

We also recall that,  $q = w/2$ ,  $p = 1 - w/2$  and  $P_1 = p^2$ ,  $P_2 = 2pq$ , then

$$P_1 + P_2 = 1 - \frac{w^2}{4} \quad \text{and} \quad (1 - w)P_2 - wP_1 = -\frac{w^2}{2} \left[ 1 - \frac{w}{2} \right].$$

The reduced system (4.17) can be re-written as;

$$w' = w \left( -\frac{1}{2}\hat{b}w \left( 1 - \frac{w}{2} \right) \left( 1 - \frac{N_h}{K} \right) + g_1(w) \right),\tag{4.24}$$

$$N_h' = N_h \left( \hat{b} \left( 1 - \frac{w^2}{4} \right) \left( 1 - \frac{N_h}{K} \right) - g_2(w) \right),\tag{4.25}$$

where

$$g_1(w) = (1 - w)(\tilde{\alpha}_1L_1(w) - \tilde{\alpha}_2L_2(w)),\tag{4.26}$$

$$g_2(w) = \tilde{\alpha}_1L_1(w)(1 - w) + \tilde{\alpha}_2L_2(w)w,\tag{4.27}$$

with  $\tilde{\alpha}_i = \hat{\alpha}_i + \hat{\mu}_i > 0$  for  $i = 1, 2$  and

$$L_i(w) = \frac{-(k_1 - v_i k_0) + \sqrt{\Delta}}{-(k_1 - u_i k_0) + \sqrt{\Delta}} \quad (4.28)$$

with

$$v_i = \frac{\hat{\mu}_i}{\tilde{\alpha}_i} u_i = \frac{\hat{\mu}_i}{\hat{\alpha}_i + \hat{\mu}_i} u_i < u_i.$$

We can re-write equation (4.28) by rationalising and simplifying as;

$$\begin{aligned} L_1(w) &= 1 - M_1 \left( C_{11} + \frac{C_{12} + \sqrt{\Delta}}{1 - w} \right), \\ L_2(w) &= 1 - M_2 \left( C_{21} + \frac{C_{22} - \sqrt{\Delta}}{w} \right), \end{aligned} \quad (4.29)$$

where

$$\begin{aligned} M_i &= \frac{\hat{\alpha}_i T_{h_i}}{2R_i \tilde{\alpha}_i (T_{h_1} - T_{h_2})(1 + T_{h_i})}, \\ C_{11} &= (-1 + T_{h_2} - 2T_{h_1})R_1 + (1 + T_{h_1})R_2, \\ C_{12} &= T_{h_1} - T_{h_2} - R_2(1 + T_{h_1}), \\ C_{21} &= (1 - T_{h_1} + 2T_{h_2})R_2 - (1 + T_{h_2})R_1, \\ C_{22} &= T_{h_1} - T_{h_2} + R_1(1 + T_{h_2}). \end{aligned}$$

Moreover with  $m^* > 0$ , the following proposition can be stated;

**Proposition 4.8.1.** *For  $i = 1, 2$ ,  $L_i(w)$  are smooth functions such that*

$$0 < L_i(w) < 1.$$

Using equations (4.26) and (4.27), we can re-write equation (4.24) as;

$$\begin{aligned} w' &= wq_1(w)(N_h - H_1(w)), \\ N_h' &= -N_hq_2(w)(N_h - H_2(w)), \end{aligned} \quad (4.30)$$

where

$$\begin{aligned} q_1(w) &= \frac{\hat{b}}{2K}w \left(1 - \frac{w}{2}\right), & q_2(w) &= \frac{\hat{b}}{K} \left(1 - \frac{w^2}{4}\right), \\ H_1(w) &= K - \frac{g_1(w)}{q_1(w)} \quad \text{and} \quad H_2(w) = K - \frac{g_2(w)}{q_2(w)}. \end{aligned} \quad (4.31)$$

Analysis of the slow system (4.30) is not a trivial task due to the complexity of functions  $g_i(w)$  and  $H_i(w)$ . In order to proceed with the analysis, we note that system (4.30) is in a biologically feasible region with the following property;

**Proposition 4.8.2.** [18] *With respect to system (4.30), the closed rectangle*

$$\mathbf{D} := \{(w, N_h) | 0 \leq w \leq 1, 0 \leq N_h \leq K\}$$

*is invariant and attracting.*

## 4.8.2 Existence of equilibrium points

The equilibrium points for the slow system (4.30) are obtained by setting the right hand side to zero. Thus, we have the trivial equilibrium point  $E_0 = (0, 0)$ , boundary equilibrium on the  $N_h$  - axis  $\tilde{E} = (0, \tilde{N}_h)$  where  $\tilde{N}_h = H_2(0)$  and the boundary equilibrium on the  $w$ -axis has the form  $\hat{E} = (\hat{w}, 0)$  where  $\hat{w}$  is a solution of  $H_1(w) = 0$  with  $\hat{w} \in (0, 1)$ . The intersection of  $N_h = H_1(w)$  and  $N_h = H_2(w)$  gives the interior equilibrium  $E^* = (w^*, N_h^*)$  with  $w^* \in (0, 1)$ .

The most crucial parameters to describe the dynamics on the slow time scale are scaled per-capita birth rate  $\hat{b}$  and the weighted death rates  $\sigma_i = \tilde{\alpha}_i L_i(0)$ ,  $i = 1, 2$  where,

$$\begin{aligned} \sigma_1 &= \tilde{\alpha}_1 L_1(0) = \hat{\mu}_1 + \frac{T_{h_1}(R_1 - 1)}{(1 + T_{h_1})R_1} \hat{\alpha}_1, \\ \sigma_2 &= \tilde{\alpha}_2 L_2(0) = \hat{\mu}_2 + \frac{T_{h_1}(R_1 - 1)}{(1 + T_{h_2})R_1 + T_{h_1} - T_{h_2}} \hat{\alpha}_2. \end{aligned} \quad (4.32)$$

We use these parameters as bifurcation parameters to analyse the existence and stability of the equilibria points. By fixing  $\hat{b} > 0$  and varying  $\sigma_1$  and  $\sigma_2$ , the stability for any arbitrary equilibrium point  $E = (w, N_h)$  is determined by the eigenvalues of the Jacobian matrix  $\mathbf{J}$

for system (4.30);

$$\mathbf{J}(E) = \begin{pmatrix} (q_1 + wq_1')(N_h - H_1) - wq_1H_1' & wq_1 \\ -N_hq_2'(N_h - H_2) + N_hq_2H_2' & -q_2(N_h - H_2) - q_2N_h \end{pmatrix}. \quad (4.33)$$

The notation “ $\prime$ ” denotes the derivative with respect to  $w$ .

### Trivial equilibrium $E_0$

First we consider the trivial equilibrium point  $E_0$  such that;

$$\mathbf{J}(E_0) = \begin{pmatrix} \sigma_1 - \sigma_2 & 0 \\ 0 & \hat{b} - \sigma_1 \end{pmatrix}. \quad (4.34)$$

The eigenvalues  $\sigma_1 - \sigma_2$  and  $\hat{b} - \sigma_1$  give the stability of  $E_0$ . This can be summarised in the following proposition.

- Proposition 4.8.3.** *i). If  $\sigma_1 > \sigma_2$  and  $\hat{b} < \sigma_1$  or  $\sigma_1 < \sigma_2$  and  $\hat{b} > \sigma_1$ , then  $E_0$  is a hyperbolic saddle point.*
- ii). If  $\sigma_1 > \sigma_2$  and  $\hat{b} > \sigma_1$ , then  $E_0$  is a repelling node.*
- iii). If  $\sigma_1 < \sigma_2$  and  $\hat{b} < \sigma_1$ , then  $E_0$  is an attracting node.*
- iv). If  $\sigma_1 = \sigma_2$  and  $\sigma_1 = \hat{b}$ , then  $E_0$  is a degenerate<sup>2</sup> equilibrium with at least two co-dimension but if  $\sigma_1 = \sigma_2$  and  $\sigma_1 \neq \hat{b}$  or  $\sigma_1 \neq \sigma_2$  and  $\sigma_1 = \hat{b}$  then it is a saddle node<sup>3</sup>*

The above analysis indicates the trivial case where the frequency of the S-gene is zero when the population is zero. This implies that the entire population can be wiped out provided the weighted death rate of AS individuals is greater than that of AA individuals and the per-capita birth rate.

<sup>2</sup>Degenerate node if the two eigenvalues are identical

<sup>3</sup>A saddle node occurs when the critical equilibrium has one zero eigenvalue. The other describes the stability of the saddle node

### The $N_h$ - axis equilibrium point

The equilibrium point on the  $N_h$  - axis is given by  $\tilde{E} = (0, \tilde{N}_h)$  where

$$\tilde{N}_h = H_2(0) = \frac{K}{\hat{b}}(\hat{b} - \sigma_1)$$

which is positive if  $\hat{b} > \sigma_1$ . Therefore

$$\mathbf{J}(\tilde{E}) = \begin{pmatrix} \sigma_1 - \sigma_2 & 0 \\ -\frac{K}{\hat{b}}(\hat{b} - \sigma_1) & \sigma_1 - \hat{b} \end{pmatrix}. \quad (4.35)$$

**Proposition 4.8.4.** *i). The equilibrium point  $\tilde{E}$  is only feasible provided  $\sigma_1 < \hat{b}$*

*ii). If  $\sigma_1 < \hat{b}$  and  $\sigma_1 < \sigma_2$ , then  $\tilde{E}$  is an attracting node.*

*iii). If  $\sigma_1 < \hat{b}$  and  $\sigma_1 > \sigma_2$ , then  $\tilde{E}$  is a saddle point.*

*iv). We note that if  $\sigma_1$  increases and crosses  $\sigma_1 = \sigma_2$ , then  $\tilde{E}$  coalesces with one interior equilibrium point to form an attracting saddle node.*

*v). If  $\sigma_1 = \hat{b}$ , then the equilibrium point  $\tilde{E}$  coalesces with the trivial equilibrium point at the origin. This becomes an attracting saddle node if  $\sigma_2 > \hat{b}$ , a repelling saddle node if  $\sigma_2 < \hat{b}$  and a degenerate node if  $\sigma_2 = \hat{b}$ .*

From the above proposition, we note that the S-gene frequency will tend to zero provided the weighted death rate of AS individual is greater than that of AA individuals but less than the per-capita birth rate. In this case the population will be composed of entirely AA individuals.

### Equilibrium on the $w$ -axis

The equilibrium points on the  $w$ -axis are given by the solution set of  $H_1(w) = 0$  for  $w \in (0, 1)$ . This can be written as

$$\phi(w) = g_1(w) - \frac{\hat{b}}{2}w\left(1 - \frac{w}{2}\right) = 0. \quad (4.36)$$



After some tedious calculations we obtain;

$$\sqrt{\Delta} = \frac{h_1}{h_0}, \quad (4.37)$$

where

$$\begin{aligned} h_1 &= \frac{\hat{b}}{4}w^3 - w^2 \left( \tilde{\alpha}_1 - \tilde{\alpha}_2 - M_1C_{11}\tilde{\alpha}_1 + \tilde{\alpha}_2C_{21}M_2 + \frac{\hat{b}}{2} \right), \\ &\quad + w(\tilde{\alpha}_1 - \tilde{\alpha}_2 - \tilde{\alpha}_1M_1(C_{11} + C_{12}) + \tilde{\alpha}_2M_2(C_{21} - C_{22})) + \tilde{\alpha}_2M_2C_{22}, \\ h_0 &= \tilde{\alpha}_1M_1w + \tilde{\alpha}_2M_2(1 - w), \end{aligned}$$

and  $\Delta$  is given by equation (4.19).

Let  $G_1(w) = \sqrt{\Delta}$  and  $G_2(w) = \frac{h_1}{h_0}$ , we have

$$\frac{d^2G_1}{dw} = \frac{(a_0a_2 - a_1^2)}{\Delta\sqrt{\Delta}}, \quad (4.38)$$

then using the idea of convexity analysis, we note that  $G_1$  is concave or convex if  $a_0a_2 - a_1^2 \neq 0$ . Then  $G_1$  has at most two roots. However, we can not conclusively determine the number of roots of equation (4.36) in this case.

If  $a_0a_2 - a_1^2 = 0$ , then  $a_2 = \frac{a_1^2}{a_0}$ . From equation (4.19), we obtain

$$\Delta = a_0 \left( w + \frac{a_1}{a_0} \right)^2.$$

Thus equation (4.37) has at most three roots. Also, if we re-write  $G_2$  such that,

$$G_2 = f_2(w) + \frac{p_0}{\tilde{\alpha}_2M_2 + w(\tilde{\alpha}_1M_1 - \tilde{\alpha}_2M_2)}, \quad (4.39)$$

where  $f_2(w)$  is a quadratic function of  $w$  and  $p_0$  is a constant.

The second derivative of (4.39) equated to zero is equivalent to,

$$(\tilde{\alpha}_2M_2 + w(\tilde{\alpha}_1M_1 - \tilde{\alpha}_2M_2))^3 = p_1 \quad (4.40)$$

which admits at most one root in  $(0,1)$ . Therefore there are at most three equilibria on the  $w$ -axis. However, we recall that  $w = 0$  gives the trivial equilibrium, this implies that equation (4.30) has at most two equilibria for  $w \in (0, 1)$ . From equation (4.36), we note

that  $\phi(0) = g_1(0) = \sigma_1 - \sigma_2$  and  $\phi(1) = -\hat{b}/4 < 0$ . We summarize these results in the proposition below.

**Proposition 4.8.5.** *i). If  $\sigma_1 > \sigma_2$ , then  $\phi(0) > 0$  and  $\phi(1) < 0$ . The intermediate value theorem guarantees that equation (4.36) has at least one positive root ( $\hat{w}_0$ ) in interval  $(0,1)$  such that  $\phi(\hat{w}_0) = 0$ . But since  $\phi(w) = 0$  has at most two roots, then there is a unique root  $\hat{w}_0$  in  $(0,1)$ .*

*ii). If  $\sigma_1 < \sigma_2$ , then  $\phi(0) < 0$  and  $\phi(1) < 0$ . This implies that (4.36) has zero or two positive roots in the interval  $(0,1)$ . Suppose equation (4.36) has two positive roots  $\hat{w}_{01}, \hat{w}_{02}$  and that  $\hat{w}_{01} < \hat{w}_{02}$ , then  $\phi'(\hat{w}_{01}) > 0$  and  $\phi'(\hat{w}_{02}) < 0$ . Also if  $\hat{w}_{01} = \hat{w}_{02} = \hat{w}_0$ , then  $\phi'(\hat{w}_0) = 0$ .*

*iii). If  $\sigma_1 = \sigma_2$ , then  $\phi(0) = 0$  and  $\phi(1) < 0$  indicating that (4.36) has zero or one unique root in the interval  $(0,1)$ .*

Then the Jacobian matrix evaluated at the boundary equilibrium point  $\hat{E} = (\hat{w}, 0)$  simplifies to;

$$\mathbf{J}(E) = \begin{pmatrix} -\frac{\hat{b}}{4}\hat{w}^2 + g_1(\hat{w}) + \hat{w}g_1'(\hat{w}) & wq_1(\hat{w}) \\ 0 & -q_2(\hat{w})H_2(\hat{w}) \end{pmatrix}. \quad (4.41)$$

The eigenvalues of this matrix are used to determine the stability of the equilibria points on the  $w$ -axis. Using the parameter values given Table 4.2, we show the intersection of the two curves  $g_1(w)$  and  $\hat{b}/2w(1 - w/2)$  in Figure 4.13 and Figure 4.14 which concurs with our analytical results.

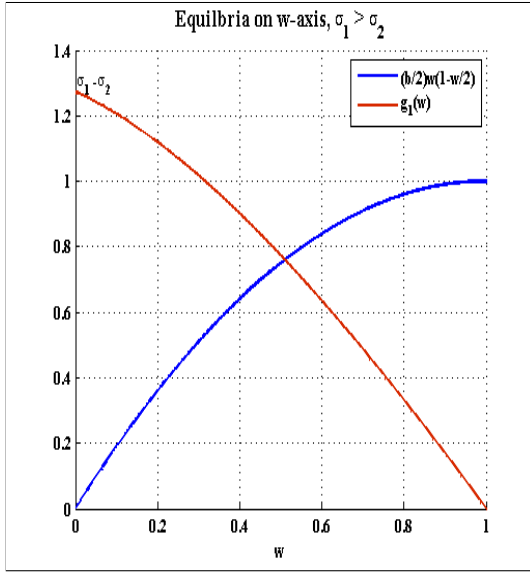


Figure 4.13. shows the equilibria on the  $w$ -axis for  $\sigma_1 > \sigma_2$

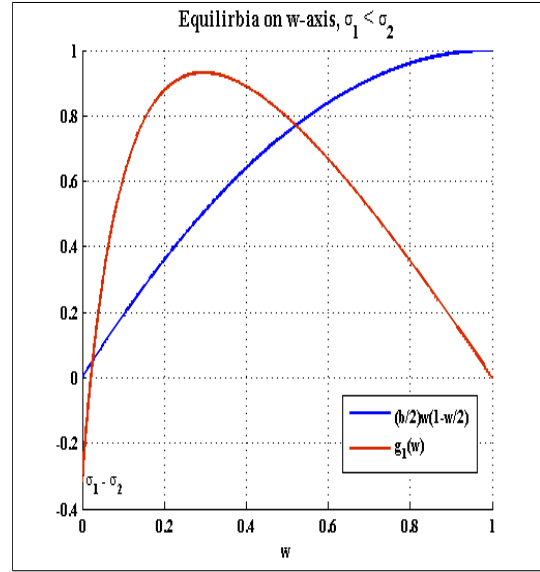


Figure 4.14. Demonstrates the equilibria on the  $w$ -axis for  $\sigma_1 < \sigma_2$

### The interior equilibria

The positive interior equilibrium point  $E^* = (w^*, N_h^*)$  of equation (4.30) is given by the intersection of  $H_1(w)$  and  $H_2(w)$ . By equating the two functions and simplifying, we obtain the  $w$ -coordinate  $w^*$  in the interval  $(0,1)$  as the root to the following equation;

$$H(w) = -\left(1 + \frac{w}{2}\right)g_1(w) + \frac{w}{2}g_2(w). \quad (4.42)$$

By substituting  $w^*$  in either  $H_1(w)$  or  $H_2(w)$ , we obtain the  $N_h$ -coordinate hence the interior equilibrium point. Just as we did in the previous section, we can write  $H(w) = 0$  as;  $P_1(w) = P_2(w)$  where

$$P_1(w) = \sqrt{\Delta}, \quad P_2(w) = \frac{h_{21}}{h_{20}}$$

and

$$\begin{aligned} h_{21} &= [2\hat{\alpha}_1(1 - M_1C_{11}) - \hat{\alpha}_2(1 - M_2C_{21})]w^2, \\ &\quad + [2\hat{\alpha}_2(1 - M_2C_{21}) - 2\hat{\alpha}_1(1 - M_1(C_{11} + C_{12})) + \hat{\alpha}_2M_2C_{22}]w - 2\hat{\alpha}_2M_2C_{22}, \\ h_{20} &= (\hat{\alpha}_2M_2 - 2\hat{\alpha}_1M_1)w + 2\hat{\alpha}_2M_2. \end{aligned}$$

From equation (4.38), we note the  $P_1(w)$  is concave or convex if  $a_0a_2 - a_1^2 \neq 0$ . If  $a_0a_2 - a_1^2 = 0$  then (4.42) has at most two roots. Also,

$$P_2(w) = f(w) + \frac{d_0}{(\hat{\alpha}_2M_2 - 2\hat{\alpha}_1M_1)w + 2\hat{\alpha}_2M_2},$$

where  $f(w)$  is a linear function and  $d_0$  is a constant. Thus  $H(w)$  has at most two roots in the interval  $(0,1)$ . From equation (4.42), it is shown that  $H(0) = \sigma_2 - \sigma_1$  and  $H(1) = \tilde{\alpha}L_2(1) > 0$  from proposition 4.8.1. Thus, the roots of equation (4.42) depend on whether  $\sigma_2 - \sigma_1$  is positive or negative. We consider the following cases

- If  $\sigma_1 > \sigma_2$ , then  $H(0) < 0$  and  $H(1) > 0$ . This implies that  $H(w)$  has at least one root in the interval  $(0,1)$ . But since  $H(w)$  has at most two roots, then  $H_1(w)$  and  $H_2(w)$  have a unique intersection point thus a unique equilibrium point  $(w^*, H_1(w^*))$ . The interior equilibrium point remains in  $\mathbf{D}$  provided  $\sigma_1 < \hat{b}$  for a fixed  $\sigma_2 \in (0, \hat{b})$ . However, if  $\sigma_1$  increases such that  $\sigma_1 > \hat{b}$ , then the interior equilibrium point  $(w^*, H_1(w^*))$  coincides with the unique equilibrium on the  $w$ -axis  $\tilde{E} = (\tilde{w}, 0)$ .
- If  $\sigma_1 < \sigma_2$ , then  $H(0) > 0$  and  $H(1) > 0$  thus,  $H(w)$  has either zero or two roots in the interval  $(0,1)$ . Therefore  $H_1(w)$  and  $H_2(w)$  have two points of intersection  $w_1^*, w_2^*$ . Then the two interior equilibria are  $(w_1^*, H(w_1^*))$  and  $(w_2^*, H(w_2^*))$ . If  $w_1^* < w_2^*$ , then  $H'(w_1^*) < 0$  and  $H'(w_2^*) > 0$ . Moreover if  $w_1^* = w_2^* = w^*$ , then  $H'(w^*) = 0$  agreeing to a unique equilibrium. We note that this is only true if  $\sigma_1 < \hat{b}$ . However if  $\sigma_1$  increases such that  $\sigma_1 > \hat{b}$ , then the only equilibrium point that exist will be the trivial equilibrium.
- If  $\sigma_1 = \sigma_2$ , then  $H(0) = 0$  and  $H(1) > 0$  this implies that there exists zero or one equilibrium point depending on the sign of  $H'(0)$ . If  $H'(0) < 0$ , then there is no interior equilibrium but if  $H'(0) > 0$ , then an interior equilibrium point say

$(w^*, H(w^*))$  exists. If  $H'(0) = 0$ , then the existing equilibrium coincides with the trivial equilibrium point.

These results are summarised in the Table 4.4.

Table. 4.4. *Interior equilibria points*

Condition	Number of roots
$\sigma_1 > \sigma_2$ and $\sigma_1 < \hat{b}$	One unique interior equilibrium point.
$\sigma_1 > \sigma_2$ and $\sigma_1 > \hat{b}$	Interior equilibrium coincides with the w-axis equilibrium $\tilde{E} = (\tilde{w}, 0)$ .
$\sigma_1 < \sigma_2$ and $\sigma_1 < \hat{b}$	Two interior equilibria point exist with $w_1^* < w_2^*$ such that $H'(w_1^*) < 0$ and $H'(w_2^*) > 0$ .
$\sigma_1 < \sigma_2$ and $\sigma_1 > \hat{b}$	The two interior equilibria combine and coincide with the trivial equilibrium point.
$\sigma_1 = \sigma_2$	Zero or one interior equilibrium point exist.

Furthermore, for the interior equilibrium point  $E^* = (w^*, N_h^*)$ ,  $N_h^* = H_1(w^*) = H_2(w^*) = 0$  and  $H_2(w^*) > 0$ . The Jacobian matrix evaluated at  $E^*$  reduces to;

$$\mathbf{J}(E^*) = \begin{pmatrix} -w^*q_1(w^*)H_1'(w^*) & w^*q_1(w^*) \\ q_2(w^*)H_2(w^*)H_2'(w^*) & -q_2(w^*)H_2(w^*) \end{pmatrix}. \quad (4.43)$$

We note that;

$$\begin{aligned} \text{Det}(\mathbf{J}(E^*)) &= w^*q_1(w^*)q_2(w^*)H_2(w^*)(H_1'(w^*) - H_2'(w^*)), \\ &= w^*q_1(w^*)q_2(w^*)H_2(w^*)H'(w^*). \\ \text{Trace}(\mathbf{J}(E^*)) &= -(w^*q_1(w^*)H_1'(w^*) + q_2(w^*)H_2(w^*)). \end{aligned}$$

From this, we have the determinant negative provided  $H'(w^*) < 0$ . Thus, the interior equilibrium point is a hyperbolic saddle point. If  $H'(w^*) > 0$ , then all the eigenvalues are negative and the equilibrium point is stable. We illustrate the intersection of the interior equilibrium points for  $\sigma_1 < \sigma_2$  and  $\sigma_1 > \sigma_2$  in Figure 4.15 and Figure 4.16.

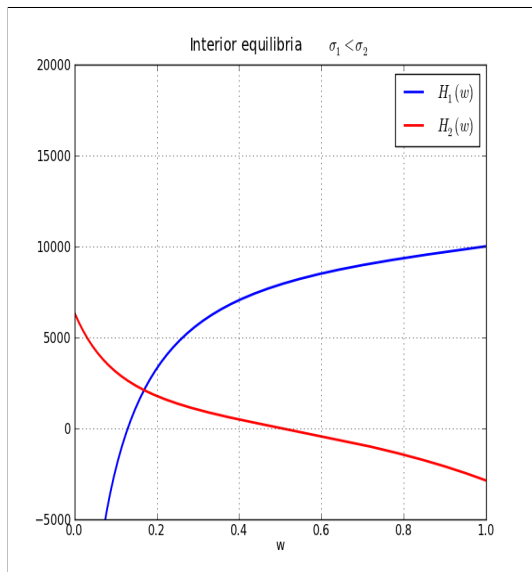


Figure 4.15. Demonstrates the interior equilibria points as the intersection of  $H_1(w)$  and  $H_2(w)$  for  $\sigma_1 > \sigma_2$

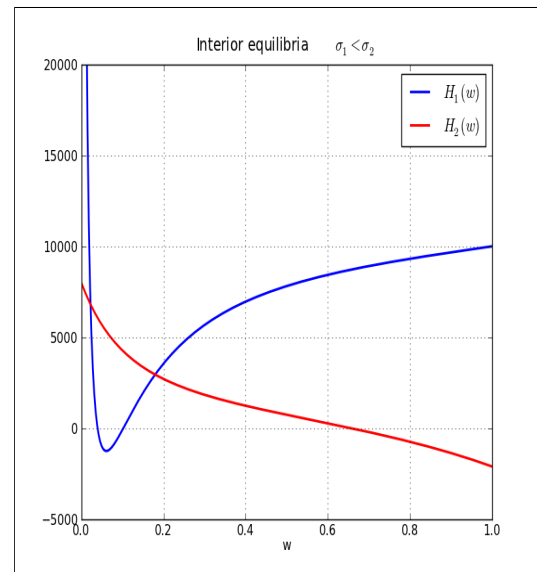


Figure 4.16. Shows the interior equilibria points as the intersection of  $H_1(w)$  and  $H_2(w)$  for  $\sigma_1 < \sigma_2$

## 4.9 Numerical results of slow dynamics

In this section, we present the numerical results for the slow dynamics to support our analytic results obtained in the previous section and explain other findings. As discussed earlier, the existence and stability of these equilibrium points depend on the bifurcation parameters,  $\sigma_1, \sigma_2$  and  $\hat{b}$ . By changing the parameter values given in Table 4.2 obtained from [18, 19, 20] and using *odesolver package* in Python programming language, we obtain the phase portraits illustrating the stability of these equilibria points.

Figure 4.17 explains the trivial equilibrium point. As noted earlier, this equilibrium point exists and is an attracting node provided the per-capital birth rate is less than the weighted death rates of AA and AS individuals. This implies that the human population declines and eventually will be wiped out if more deaths occur compared to births. Numerical results obtained concur with our analytical results.

Figure 4.18 demonstrates the behaviour of the equilibrium point on the  $w$ -axis. We note that, with different initial conditions, we have a stable and attracting equilibrium on the  $w$ -axis as the total population decreases. This occurs when the weighted death rate of

AA individuals is greater than the weighted death rate of AS individuals and the per-capita birth rate, that is ( $\sigma_1 > \sigma_2$  and  $\sigma_1 > \hat{b}$ ). It implies that, as the population of AA individuals decreases due to the high death rates, the S-gene frequency establishes itself. However, since the birth rate is also small to balance the death rates, eventually the total population goes to extinction as the S-gene frequency reaches maximum value.

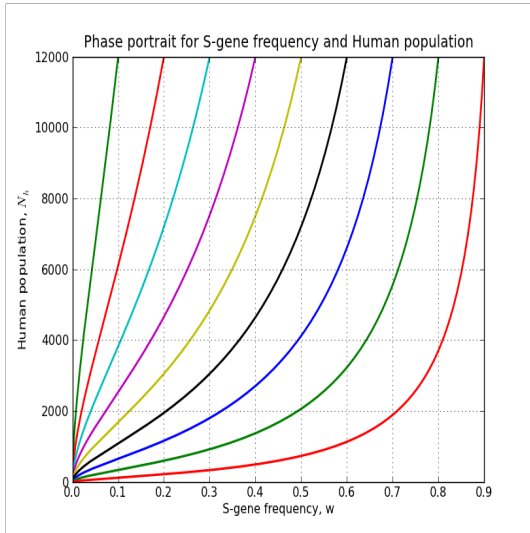


Figure. 4.17. Phase portrait for the slow system given ( $\sigma_1 < \sigma_2$  and  $\sigma_1 > \hat{b}$ )

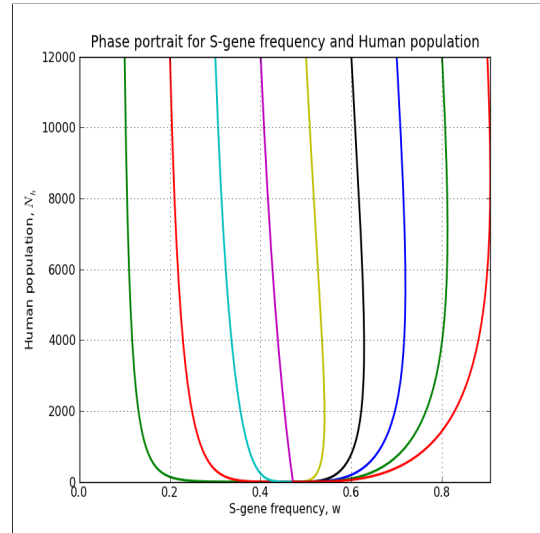


Figure. 4.18. Phase plot for the slow system given ( $\sigma_1 > \sigma_2$  and  $\sigma_1 > \hat{b}$ )

Figure 4.19 and Figure 4.20, illustrate the interior equilibria points which exist for  $\sigma_1 < \sigma_2$  and  $\sigma_1 < \hat{b}$  or  $\sigma_2 < \sigma_1$  and  $\sigma_2 < \hat{b}$ . These equilibria demonstrate the persistence of S-gene in the population which is also in agreement with our analytical results. It implies that as long as the birth rate is big enough to balance the death rate of AA and AS individuals, we will always have sickle cell anaemia people in the population.

Figure 4.21 and Figure 4.22, illustrate the equilibrium point on the  $N_h$  - axis where the entire population is S-gene free. In this case the population will be composed of only AA individuals. This implies that we only need to reduce the death rates of AA individuals as compared to AS individuals or if the death rate of AS individuals is greater than that of AA individuals, then the birth rate should be greater than the death rate of AA individuals.

Basing on both our analytic and numerical results, we note that the dynamics on the slow time scale are highly influenced by the weighted death rates and per -capita birth rate.

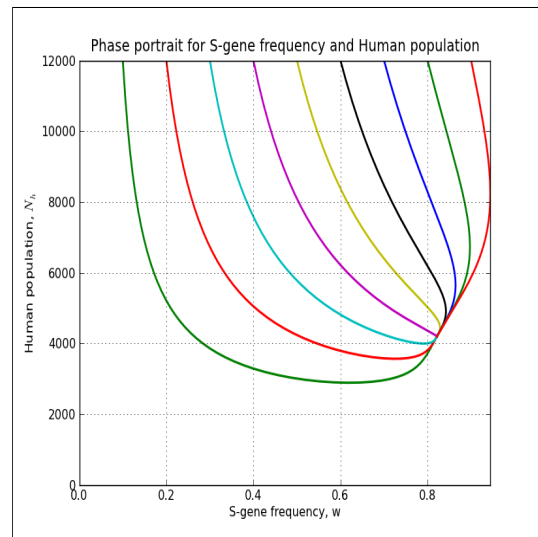
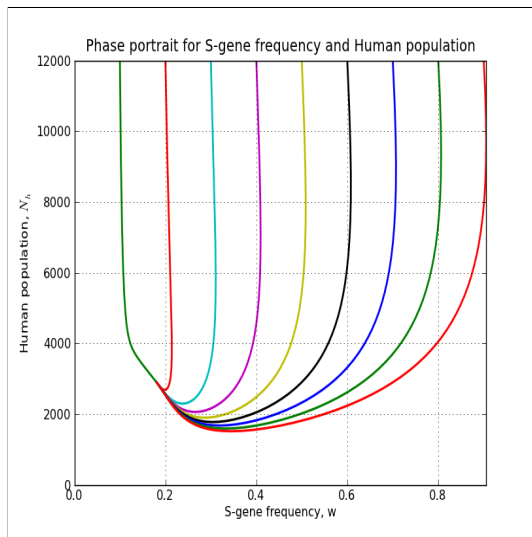


Figure. 4.19. *Phase diagram for the slow system given  $(\sigma_1 < \sigma_2$  and  $\sigma_1 < \hat{b})$*

Figure. 4.20. *Phase portrait for the slow system given  $(\sigma_2 < \sigma_1$  and  $\sigma_2 < \hat{b})$*

Moreover these rates are dependent on the epidemiological parameters such as  $\beta_i, \gamma_i, \rho_i$  for  $i = 1, 2$ . Our analysis of both the fast and slow system thus explains the interaction of malaria and sickle cell gene in the population. In the next subsection, we investigate how these epidemiological parameters influence the extinction or establishment of S-gene in a population.



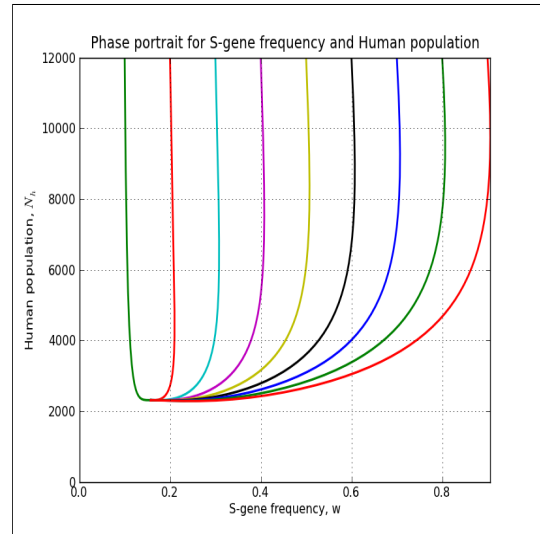
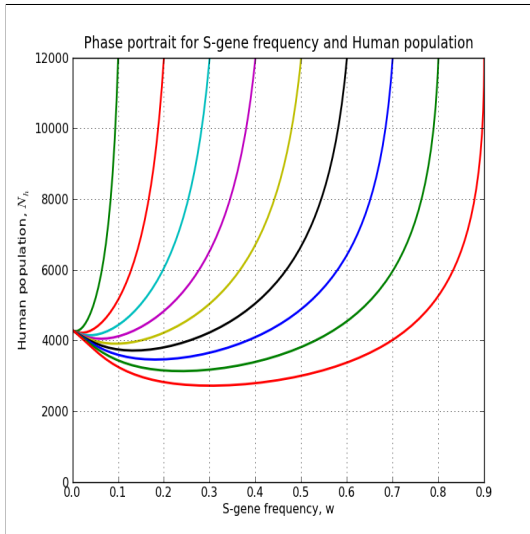


Figure. 4.21. Phase portrait for the slow system given  $(\sigma_1 < \sigma_2 \text{ and } \sigma_2 < \hat{b})$

Figure. 4.22. Phase diagram for the slow system given  $(\sigma_2 < \sigma_1 \text{ and } \sigma_1 < \hat{b})$

### 4.9.1 Impact of malaria parameters on S-gene frequency

In order to examine the impact of epidemiological parameters on the frequency of sickle cell gene, we use a quantity  $\mathbf{F}$  that gives the fitness of the S-gene whereby;

$$\mathbf{F} = \left( \frac{1}{w} \frac{dw}{d\tau} \right) \Big|_{w=0}$$

If  $w$  is the abundance of the S-gene, then  $\mathbf{F}$  will represent the per-capita growth rate of the S-gene when the gene is initially introduced into the population. Thus  $\mathbf{F}$  describes the invasion ability of the S-gene [20]. The interpretation of the fitness coefficient  $\mathbf{F}$  can be related to the reproduction number of the infectious disease whereby the S-gene can establish itself or not depending on this value.

From equations (4.24) and (4.28), we have;

$$\begin{aligned}
 \left. \frac{1}{w} \frac{dw}{d\tau} \right|_{w=0} &= \tilde{\alpha}_1 L_1(0) - \tilde{\alpha}_2 L_2(0), \\
 &= \hat{\mu}_1 - \hat{\mu}_2 + \hat{\alpha}_1 \left( \frac{T_{h_1}(R_1 - 1)}{R_1(1 + T_{h_1})} \right) - \hat{\alpha}_2 \left( \frac{T_{h_2}(R_1 - 1)}{T_{h_1} + R_1(1 + T_{h_2}) - T_{h_2}} \right), \\
 &= \hat{\mu}_1 + \hat{\alpha}_1 W_1 - (\hat{\mu}_2 + \hat{\alpha}_2 W_2),
 \end{aligned} \tag{4.44}$$

where

$$W_1 = \frac{T_{h_1}(R_1 - 1)}{R_1(1 + T_{h_1})} \text{ and } W_2 = \frac{T_{h_2}(R_1 - 1)}{T_{h_1} + R_1(1 + T_{h_2}) - T_{h_2}}.$$

Then  $\mathbf{F} = \sigma_1 - \sigma_2$  where  $\sigma_i = \hat{\mu}_i + W_i \hat{\alpha}_i$ .

$\sigma_i$  gives the total per-capita death rate of type  $i$  individuals that is weighted by  $W_i$  which depends on the malaria epidemiological parameter. This suggests that the establishment of the S-gene that is initially introduced in a population depends on whether the fitness is positive or negative. i.e.  $\sigma_1 < \sigma_2$  or  $\sigma_1 > \sigma_2$ .

If the fitness coefficient is negative i.e.  $\sigma_1 < \sigma_2$ , then it indicates that the selection for the S-gene is weak and it cannot establish itself. Relating our result here and those obtained from the model, Figure 4.17 and Figure 4.21 of our analysis depicts these findings whereby the entire population can be wiped out if  $\sigma_2 > \hat{b}$  or composed of only AA genotype individual if  $\sigma_2 < \hat{b}$ .

Contrary to the above, when the fitness coefficient is positive i.e.  $\sigma_1 > \sigma_2$ , then there is a strong selection for the S-gene and in this case it gets established in the population. As depicted from our model in Figures 4.18 and 4.22, the entire population can be wiped out in this case as the S-gene frequency attains the maximum value i.e. if  $\sigma_1 > \hat{b}$  or persist if  $\sigma_1 < \hat{b}$ .

Let  $R_0 = \frac{\sigma_1}{\sigma_2}$ , this value describes the invasion ability of sickle cell gene in the same way the basic reproduction number determines the invasion of the infectious disease. Note that if  $R_0 < 1$  i.e.  $\sigma_1 < \sigma_2$  then the gene fails to establish it self but if  $R_0 > 1$  i.e.  $\sigma_1 > \sigma_2$ , then persistence of the gene in the population is observed.

We proceed to determine how the fitness coefficient is influenced by the epidemiological parameters;

Recall  $\hat{\mu}_1 - \hat{\mu}_2 = -\hat{\nu}$ , thus;

$$\mathbf{F} = -\hat{\nu} + \frac{\hat{\alpha}_1 T_{h_1} (R_1 - 1)}{(1 + T_{h_1}) R_1} - \frac{\hat{\alpha}_2 T_{h_2} (R_1 - 1)}{(1 + T_{h_2}) R_1 + T_{h_1} - T_{h_2}}$$

where

$$R_i = T_{h_i} T_{v_i} \quad i = 1, 2$$

$T_{h_i}$  involves only parameters that are related to the malaria infection of genotype  $i$  individual by mosquitoes and  $T_{v_i}$  involves parameters that are related to mosquito infection by humans of genotype  $i$ . In Figure 4.23, we note that the fitness of the S-gene does not change much with  $T_{h_2}$  for a given value of  $T_{h_1}$ . This implies that any change in malaria transmission rate  $\theta_2$  or in the recovery rate  $\gamma_2$  will not cause a greater change in the fitness of the S-gene. On the other hand, for a given value of  $T_{h_2}$  an increase in the transmission rate of AA genotype individuals or a decrease in the recovery rate increases the fitness coefficient. This explains the high percentages of sickle cell gene frequency in malaria endemic areas.

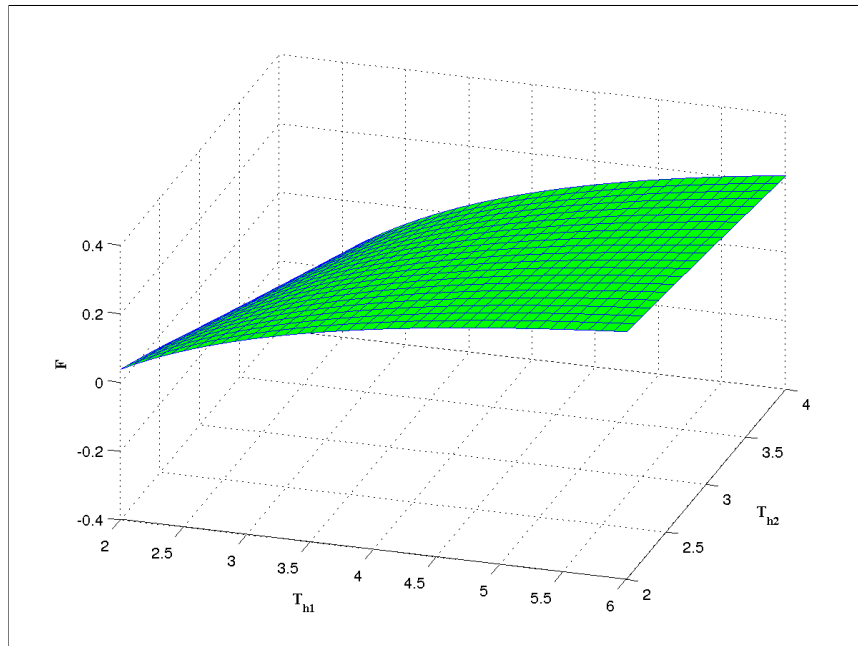


Figure. 4.23. *Fitness of S-gene with transmission parameters*

## 4.10 Summary

In this chapter, we have analysed the model developed by Feng et al. [18, 19, 20] for the interaction between malaria and sickle cell gene. We considered malaria epidemiological parameters and demographic/genetic parameters to occur on two different time scales that is 1/days and 1/decades respectively. This was done using singular perturbation techniques discussed in Chapter 3.

On the fast time scale, we carried out both analytical and numerical simulations to investigate how malaria dynamics change with time. We considered the measure of the S-gene frequency  $w$  as a constant. The basic reproduction number of the reduced system was computed. Our results indicated that the basic reproduction number is composed of two terms that is,  $R_i$ , for  $i = 1, 2$  where  $R_i$  represents the basic reproduction number if the population is composed of individuals of only genotype  $i$ . Furthermore, we checked for the existence and stability of the equilibrium points. We found that the disease free equilibrium point exists and is locally asymptotically stable only if  $R_0 < 1$  and unstable otherwise. On the other hand, the endemic equilibrium was found to be unique and locally asymptotically stable for  $R_0 > 1$ . Our numerical simulations confirmed the analytic results obtained.

We further investigated how the sickle cell gene frequency affects the epidemiological measure i.e. reproduction number. Our findings showed that higher sickle cell gene frequency lead to high malaria endemic levels for low values of the recovery rate of AS individuals,  $\gamma_2$ , and to low endemic levels for higher values of  $\gamma_2$ . In addition, using sensitivity analysis of the basic reproduction number to the parameter values given in Table 4.2, we observed that the most important parameters were transmission parameters of malaria parasite from and to humans, the recovery rates of both AA and AS individuals as well as the mosquito death rate. In all this analysis, we note that the recovery rate of both AA and AS individuals has a great influence on the maintenance of the S-gene in the population.

On the slow time scale, we described the evolution of the slow variable on the manifold (slow manifold). We carried out both analytical and numerical simulations to investigate the existence and stability of equilibrium points on the manifold. In our analysis, we discovered that the most important and crucial parameters to describe the dynamics on the slow time scale were the weighted death rates of both AA and AS individuals and the per-capita birth rate. We examined all the possible equilibria and their stability using

these parameters. Furthermore, we investigated the impact of epidemiological parameters on the sickle cell gene frequency. The fitness coefficient obtained as the difference between the weighted death rates  $\sigma_1$  and  $\sigma_2$  was used as a measure to determine the influence of the malaria epidemiological parameters on the invasion of the S-gene. Our findings indicated that the gene may or may not establish itself depending on whether this coefficient is positive or negative. In addition, we discovered that the gene's ability to invade is more dependent on the transmission parameters of AA than for AS individuals. In conclusion, our analysis of both the fast and slow dynamics give a clear understanding of malaria and sickle cell gene which other epidemiological models without genetic structure ignore or genetic models without malaria epidemiology can not explain.

Furthermore, given that the recovery rate of AA and AS individuals have a great influence on the maintenance of sickle cell gene in the population, it would be good venture for us to investigate how malaria treatment of AA individuals affect the frequency of sickle cell gene. This is done in the next chapter with the assumption that AS individuals are less likely to develop clinical malaria therefore no drugs are administered to them.

# Chapter 5

## Model With Treatment

### 5.1 Introduction

Malaria treatment involves the use of drugs such as quinine, chloroquine, sulfadoxine-pyrimethamine (Fansidar), mefloquine (Lariam) as well as hospitalization for the severe cases. Administering of malaria drugs leads to a reduction in the malaria induced mortality rate.

Our analysis in Chapter 4 suggests that sickle cell gene will always persist with high frequency provided the mortality rate of AA individuals is greater than that of AS individuals. As a result, we extend the model discussed in Chapter 4 to include malaria treatment for AA genotype individuals. We do not consider treatment of AS individuals because they are less likely to develop clinical symptoms [8]. Our main objective is to investigate the impact of malaria treatment on the frequency of S-gene. Thus, we modified the model described in Chapter 4 as follows.

- We add an extra compartment ( $R$ ) for the recovered individuals of AA genotype. Infected AA individuals from  $I_1$  recover due to treatment at a rate  $\eta$  and move to compartment  $R$ . Recovered individuals have partial immunity but still inhabit some parasite in their blood stream and can be passed on to the mosquitoes though with a reduced probability [13, 15]. Immunity is lost at a rate  $k$  and individuals become susceptible again as shown in Figure 5.1. However, new infections boosts the immune system thereby development of solid immunity [29, 30].

- For simplicity, we assume the probability of transmission from mosquitoes to humans of genotype  $i$  to be the same in malaria endemic areas ( $\theta_1 = \theta_2 = \theta$ ). Thus, the force of infection of mosquitoes to humans is given by

$$\lambda_h = a\theta \frac{I_m}{N_h}.$$

Additionally, the probability of transmission from humans of genotype  $i$  to mosquitoes is also considered to be the same ( $\phi_1 = \phi_2 = \phi$ ). Then the force of infection of humans to mosquitoes is given by

$$\lambda_m = a\phi \left( \frac{I_1 + I_2 + \varepsilon R}{N_h} \right)$$

where  $\varepsilon$  is reduced transmission factor of recovered individuals ( $0 < \varepsilon < 1$ ).

- In the previous model we considered a logistic birth rate but in the modified model we take the recruitment rate by birth of both AA and AS individuals to be constants  $\Lambda_1$  and  $\Lambda_2$  for simplicity.
- The malaria induced mortality rate of AS individuals is not considered in this model for simplicity. We assume that in extreme cases, AS individuals do not die from malaria since they are less likely to develop clinical symptoms. Thus, malaria induced mortality rate of AA individuals is given by  $\alpha_1 = \alpha$ .
- Two compartments for the mosquito dynamics are considered, that is  $S_m$  and  $I_m$  for the susceptible and infected mosquitoes respectively. In the previous model, we considered a constant ratio of mosquito to human population  $c$ . However, due to the high migration of people to urban areas thus creating habitats for mosquitoes makes such an assumption to be unrealistic. This implies that mosquitoes are recruited at different rates. Thus, the ratio of mosquitoes to human vary causing a change in the transmission dynamics.

Let the recruitment rate of mosquitoes into  $S_m$  by birth be a constant  $\Lambda_m$ .

Having made the above changes in the model described in Chapter 4, the following diagram shows the in flow and out flow of individuals for each compartment.

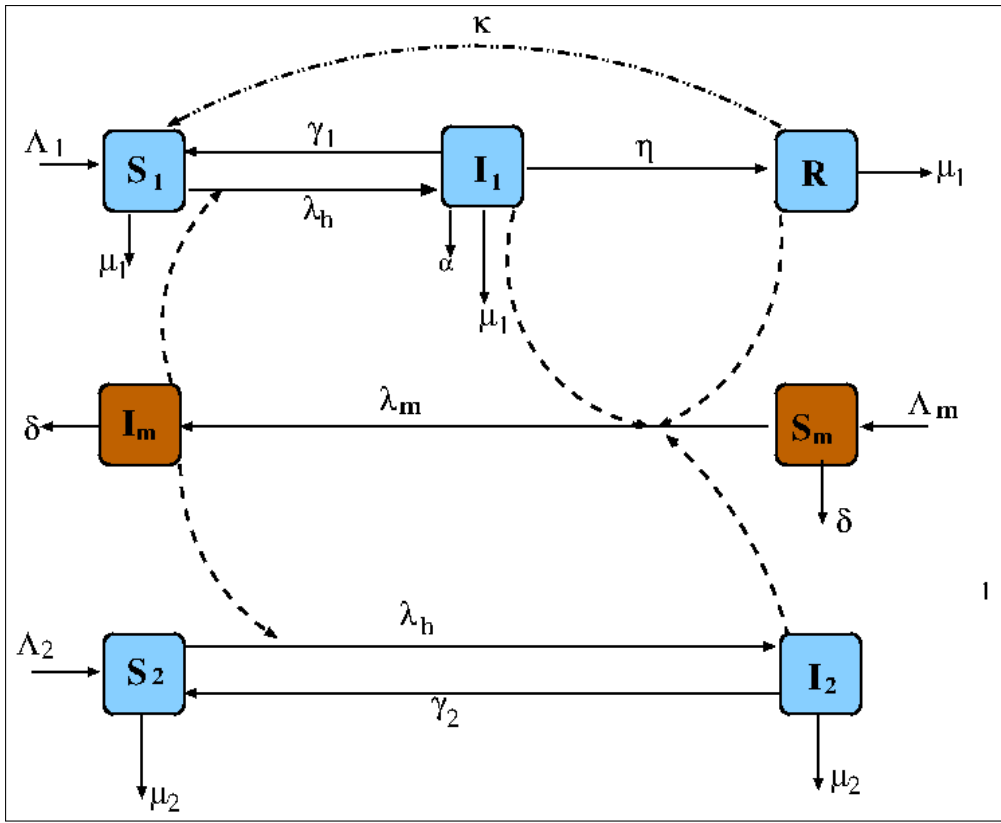


Figure. 5.1. Schematic diagram for malaria and sickle cell gene with malaria treatment

### 5.1.1 Model equations

The conceptual model described by the schematic diagram in Figure 5.1 with above assumptions can be formulated as a system of ordinary differential equations for humans and mosquitoes respectively as;

$$\dot{S}_1 = \Lambda_1 - \lambda_h S_1 + \gamma_1 I_1 + kR - \mu_1 S_1, \quad (5.1)$$

$$\dot{S}_2 = \Lambda_2 - \lambda_h S_2 + \gamma_2 I_2 - \mu_2 S_2, \quad (5.2)$$

$$\dot{I}_1 = \lambda_h S_1 - (\alpha + \gamma_1 + \mu_1 + \eta) I_1, \quad (5.3)$$

$$\dot{I}_2 = \lambda_h S_2 - (\gamma_2 + \mu_2) I_2, \quad (5.4)$$

$$\dot{R} = \eta I_1 - (\mu_1 + k) R, \quad (5.5)$$



and

$$\dot{S}_m = \Lambda_m - \lambda_m S_m - \delta S_m, \quad (5.6)$$

$$\dot{I}_m = \lambda_m S_m - \delta I_m, \quad (5.7)$$

with

$$\lambda_h = a\theta \frac{I_m}{N_h}, \quad \lambda_m = a\phi \left( \frac{I_1 + I_2 + \varepsilon R}{N_h} \right) \quad \text{and} \quad \mu_2 = \mu_1 + \nu.$$

Then,

$$\dot{N}_h = \Lambda_1 + \Lambda_2 - \mu_1 N_h - \nu(S_2 + I_2) - \alpha I_1, \quad (5.8)$$

$$\dot{N}_m = \Lambda_m - \delta N_m, \quad (5.9)$$

where  $N_h(t) = S_1(t) + S_2(t) + I_1(t) + I_2(t) + R(t)$  and  $N_m(t) = S_m(t) + I_m(t)$  whenever  $N_h(0) = S_1(0) + S_2(0) + I_1(0) + I_2(0) + R(0)$  and  $N_m(0) = S_m(0) + I_m(0)$ .

## 5.2 Model analysis

In this section we study the quantitative behaviour of the model. This involves linearisation of the model system to determine the stability of the equilibrium points. In the model described in Chapter 4, we considered two time scales to analyse it. However, in modified model we ignore the differences in time scales for simplicity.

The state variables used in the model with non-negative initial values are analysed in a biologically feasible region. Theorem 5.2.1 gives this property.

**Theorem 5.2.1.** *Suppose  $S_1(0), S_2(0), I_1(0), I_2(0), R(0), S_m(0)$  and  $I_m(0)$  are all non-negative values, then  $S_1(t), S_2(t), I_1(t), I_2(t), R(t), I_m(t), S_m(t)$  are also non-negative for  $t > 0$  moreover ,*

$$\limsup_{t \rightarrow \infty} N_h(t) \leq \frac{\Lambda_1 + \Lambda_2}{\mu_1} \quad \text{and} \quad \limsup_{t \rightarrow \infty} N_m(t) \leq \frac{\Lambda_m}{\delta}.$$

Furthermore, if in addition

$$N_h(0) \leq \frac{\Lambda_1 + \Lambda_2}{\mu_1}, \quad N_m(0) \leq \frac{\Lambda_m}{\delta},$$

then

$$N_h(t) \leq \frac{\Lambda_1 + \Lambda_2}{\mu_1}, \quad N_m(t) \leq \frac{\Lambda_m}{\delta}.$$

In particular, the region  $\Delta = \Delta_h \times \Delta_m$  with

$$\begin{aligned} \Delta_h &= \{(S_1, S_2, I_1, I_2, R) \in \mathbf{R}_+^5 : S_1 + S_2 + I_1 + I_2 + R \leq \frac{\Lambda_1 + \Lambda_2}{\mu_1}\}, \\ \Delta_m &= \{(S_m + I_m) \in \mathbf{R}_+^2 : S_m + I_m \leq \frac{\Lambda_m}{\delta}\}, \end{aligned} \quad (5.10)$$

is positively invariant.

Theorem 5.2.1 is proved in the similar way as Theorem 4.3.1 in Chapter 4.

### 5.2.1 Existence and stability of equilibrium points

In this subsection, we determine equilibrium points of the model by setting the right hand side of equations (5.1) – (5.7) to zero. When all the infectious classes equal to zero, we obtain the disease free equilibrium point,

$$E_0 = \left( \frac{\Lambda_1}{\mu_1}, \frac{\Lambda_2}{\mu_2}, 0, 0, 0, \frac{\Lambda_m}{\delta}, 0 \right),$$

otherwise we have endemic equilibrium points.

### 5.2.2 The basic reproduction number with treatment, $R_T$

The existence and stability of the equilibrium points depend on the basic reproduction number,  $R_T$ , which is obtained by the next generation matrix as described by P. van den Driessche and J. Watmough [47]. We consider the reduced system for infectious classes i.e.  $I_1, I_2, R, I_m$  as;

$$\begin{aligned}
 \dot{I}_1 &= \lambda_h S_1 - (\alpha + \gamma_1 + \mu_1 + \eta)I_1, \\
 \dot{I}_2 &= \lambda_h S_2 - (\gamma_2 + \mu_2)I_2, \\
 \dot{R} &= \eta I_1 - (\mu_1 + k)R, \\
 \dot{I}_m &= \lambda_m S_m - \delta I_m.
 \end{aligned} \tag{5.11}$$

Separating (5.11), into matrix of new infections,  $\mathcal{F}$ , and transition matrix,  $\mathcal{V}$ , we have

$$\mathcal{F} = \begin{pmatrix} \lambda_h S_1 \\ \lambda_h S_2 \\ 0 \\ \lambda_m S_m \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} (\gamma_1 + \alpha + \mu_1 + \eta)I_1 \\ (\gamma_2 + \mu_2)I_2 \\ (\mu_1 + k)R - \eta I_1 \\ \delta I_m \end{pmatrix}.$$

Then we determine the Jacobian matrix of  $\mathcal{F}$  and  $\mathcal{V}$  evaluated at DFE  $E_0$ . Thus

$$\mathbf{F} = D\mathcal{F}|_{E_0} = \begin{pmatrix} 0 & 0 & 0 & \frac{a\theta\Lambda_1}{\mu_1 N_h^*} \\ 0 & 0 & 0 & \frac{a\theta\Lambda_2}{\mu_2 N_h^*} \\ 0 & 0 & 0 & 0 \\ \frac{a\phi\Lambda_m}{\delta N_h^*} & \frac{a\phi\Lambda_m}{\delta N_h^*} & \frac{a\varepsilon\phi\Lambda_m}{\delta N_h^*} & 0 \end{pmatrix},$$

$$\mathbf{V} = D\mathcal{V}|_{E_0} = \begin{pmatrix} (\gamma_1 + \mu_1 + \eta + \alpha) & 0 & 0 & 0 \\ 0 & \gamma_2 + \mu_2 & 0 & 0 \\ -\eta & 0 & \mu_1 + k & 0 \\ 0 & 0 & 0 & \delta \end{pmatrix}.$$

Let

$$q_1 = \alpha + \mu_1 + \eta + \gamma_1, \quad q_2 = \mu_2 + \gamma_2, \quad q_3 = k + \mu_1.$$

Note: In the absence of disease,  $N_h^* = \frac{\Lambda_1\mu_2 + \Lambda_2\mu_1}{\mu_1\mu_2}$ .

Then the spectral radius (dominant eigenvalue) of the next generation matrix ( $\mathbf{FV}^{-1}$ ) gives the reproduction number  $R_T$ .

Thus

$$\tilde{R}_T = \sqrt{\frac{a^2\theta\phi\Lambda_m\mu_2^2\mu_1^2}{\delta^2(\Lambda_1\mu_2 + \Lambda_2\mu_1)^2} \left[ \frac{(q_3 + \varepsilon\eta)\Lambda_1}{\mu_1q_1q_3} + \frac{\Lambda_2}{\mu_2q_2} \right]} = \sqrt{R_T}$$

gives the number of humans (mosquitoes) that one infectious mosquito (human) infects through out the infectious period when introduced in a fully susceptible human (mosquito) population. The basic reproduction number as per the original definition is given as;

$$R_T = \frac{a^2\theta\phi\Lambda_m\mu_2^2\mu_1^2}{\delta^2(\Lambda_1\mu_2 + \Lambda_2\mu_1)^2} \left[ \frac{(q_3 + \varepsilon\eta)\Lambda_1}{\mu_1q_1q_3} + \frac{\Lambda_2}{\mu_2q_2} \right],$$

Note that  $R_T$  can be given as;

$$R_T = R_{T1} + R_{T2}$$

where,

$$R_{T1} = \frac{a^2\theta\phi\Lambda_m\mu_2^2\mu_1^2}{\delta^2(\Lambda_1\mu_2 + \Lambda_2\mu_1)^2} \frac{(q_3 + \varepsilon\eta)\Lambda_1}{\mu_1q_1q_3},$$

$$R_{T2} = \frac{a^2\theta\phi\Lambda_m\mu_2^2\mu_1^2}{\delta^2(\Lambda_1\mu_2 + \Lambda_2\mu_1)^2} \frac{\Lambda_2}{\mu_2q_2}.$$

$R_{T1}$  and  $R_{T2}$  are referred to as the basic reproduction numbers if the population composed of only AA and AS individuals respectively.

### 5.2.3 Local stability of the DFE

Using the stability analysis techniques discussed in Chapter 3, the stability of the DFE is obtained by the eigenvalues of the Jacobian matrix of the linearised system of (5.1) – (5.7)

evaluated at  $E_0$ . Thus;

$$\mathbf{J}|_{E_0} = \begin{pmatrix} -\mu_1 & 0 & \gamma_1 & 0 & k & 0 & -\frac{a\theta\Lambda_1}{\mu_1 N_h^*} \\ 0 & -\mu_2 & 0 & \gamma_2 & 0 & 0 & -\frac{a\theta\Lambda_2}{\mu_2 N_h^*} \\ 0 & 0 & -q_1 & 0 & 0 & 0 & \frac{a\theta\Lambda_1}{\mu_1 N_h^*} \\ 0 & 0 & 0 & -q_2 & 0 & 0 & \frac{a\theta\Lambda_2}{\mu_2 N_h^*} \\ 0 & 0 & \eta & 0 & -q_3 & 0 & 0 \\ 0 & 0 & -\frac{a\phi\Lambda_m}{\delta N_h^*} & -\frac{a\phi\Lambda_2}{\delta N_h^*} & -\frac{a\varepsilon\phi\Lambda_m}{\delta N_h^*} & -\delta & 0 \\ 0 & 0 & \frac{a\phi\Lambda_m}{\delta N_h^*} & \frac{a\phi\Lambda_2}{\delta N_h^*} & \frac{a\varepsilon\phi\Lambda_m}{\delta N_h^*} & 0 & -\delta \end{pmatrix}. \quad (5.12)$$

Then the characteristic polynomial of (5.12) equated to zero gives the following eigenvalues;

$$\lambda = -\mu_1, \quad \lambda = -\mu_2, \quad \lambda = -\delta,$$

and the zeros of

$$c_4\lambda^4 + c_3\lambda^3 + c_2\lambda^2 + c_1\lambda + c_0 = 0, \quad (5.13)$$

where,

$$c_4 = \delta\mu_1\mu_2(N_h^*)^2,$$

$$c_3 = \delta\mu_1(N_h^*)^2\mu_2(q_1 + q_2q_3 + \delta),$$

$$c_2 = \delta^2(N_h^*)^2\mu_1\mu_2[q_1(1 - R_{T1}) + q_2(1 - R_{T2})] + \delta\mu_1(N_h^*)^2\mu_2(q_3\delta + q_1q_2 + q_1q_3 + q_2q_3) + \frac{a^2\theta\phi\varepsilon\eta\Lambda_1\Lambda_m}{q_3},$$

$$c_1 = \delta^2(N_h^*)^2\mu_1\mu_2[q_1q_3(1 - R_{T1}) + q_2q_3(1 - R_{T2}) + q_1q_2(1 - R_T) + q_1q_2q_3] + \frac{a^2\varepsilon\theta\phi\Lambda_1\Lambda_m\eta\mu_2q_2}{q_3},$$

$$c_0 = \delta^2(N_h^*)^2\mu_1\mu_2q_2q_3(1 - R_T).$$

We use Descartes' rule of signs given by Theorem 5.2.2 to determine the number of positive and negative roots of (5.13).

**Theorem 5.2.2.** [45] *Let  $P(X)$  be a polynomial with real coefficients.*

- i. *The number of positive roots of  $P$  is at most the number of sign changes of the coefficients of  $P(X)$ .*
- ii. *The number of negative roots of  $P$  is at most the number of sign changes of the coefficients of the polynomial  $P(-X)$ .*

Applying Theorem 5.2.2 to equation (5.13), we have,

- If  $R_T < 1$ , all the coefficients of (5.13) are positive hence no positive root. Thus all the eigenvalues are negative. This implies that the DFE is locally asymptotically stable.
- $R_T > 1$ ,  $c_0 < 0$  and Descartes' rule of sign guarantees at least one positive root of (5.13). Thus one positive eigenvalue implying DFE is unstable.

These results are be summarised by Theorem 5.2.3;

**Theorem 5.2.3.** *Disease free equilibrium is locally asymptotically stable if  $R_T < 1$  and unstable otherwise.*

### 5.2.4 Existence and stability of endemic equilibrium points

Let  $E^* = (S_1^*, S_2^*, I_1^*, I_2^*, R^*, S_m^*, I_m^*)$  represent any arbitrary equilibrium point of the model and let

$$\lambda_h^* = \frac{a\theta}{N_h^{**}} I_m^* \quad \text{and} \quad \lambda_m^* = \frac{a\phi}{N_h^{**}} (I_1^* + I_2^* + \varepsilon R^*) \quad (5.14)$$

represent the forces of infection at equilibrium for the human and mosquito population respectively.  $E^*$  is obtained by setting the right hand side of equations (5.1) –(5.7) to zero.

We have,

$$\begin{aligned} S_1^* &= \frac{\Lambda_1 q_1 q_3}{\lambda_h^* ((\mu_1 + \alpha) q_3 + \mu_1 \eta) + \mu_1 q_1 q_3}, \\ S_2^* &= \frac{\Lambda_2 q_2}{\mu_2 (\lambda_h^* + q_2)}, \\ I_1^* &= \frac{\Lambda_1 q_3 \lambda_h^*}{\lambda_h^* ((\mu_1 + \alpha) q_3 + \mu_1 \eta) + \mu_1 q_1 q_3}, \\ I_2^* &= \frac{\Lambda_2 \lambda_h^*}{\mu_2 (\lambda_h^* + q_2)}, \\ R^* &= \frac{\Lambda_1 \lambda_h^* \eta}{\lambda_h^* ((\mu_1 + \alpha) q_3 + \mu_1 \eta) + \mu_1 q_1 q_3}, \\ S_m^* &= \frac{\Lambda_m}{\lambda_m^* + \delta}, \\ I_m^* &= \frac{\Lambda_m \lambda_m^*}{\delta (\lambda_m^* + \delta)}. \end{aligned} \quad (5.15)$$

Substituting (5.15) in (5.14) gives,

$$\lambda_h^* = a\theta \frac{\Lambda_m \lambda_m^*}{N_h^{**} \delta (\lambda_m^* + \delta)}, \quad (5.16)$$

$$\lambda_m^* = a\phi \frac{\lambda_h^*}{N_h^{**}} \left( \frac{\Lambda_1 (q_3 + \varepsilon \eta)}{((\mu_1 + \alpha) q_3 + \mu_1 \eta) \lambda_h^* + \mu_1 q_1 q_3} + \frac{\Lambda_2}{\mu_2 (\lambda_h^* + q_2)} \right), \quad (5.17)$$

with

$$N_h^{**} = \frac{\Lambda_1 (q_1 q_3 + \lambda_h^* q_1 + \eta \lambda_h^*)}{((\mu_1 + \alpha) q_3 + \mu_1 \eta) \lambda_h^* + \mu_1 q_1 q_3} + \frac{\Lambda_2}{\mu_2},$$

and  $q_1 = (\mu_1 + \gamma_1 + \eta + \alpha)$ ,  $q_2 = (\mu_1 + \nu + \gamma_2)$ ,  $q_3 = \mu_1 + k$ .

Substituting equation (5.17) in equation (5.16) and simplifying we obtain,

$$\lambda_h^*(b_0(\lambda_h^*)^2 + b_1\lambda_h^* + b_2) = 0, \quad (5.18)$$

where,

$$b_0 = \delta N_h^{**}(\mu_2(\delta N_h(\mu_1\eta + (\alpha + \mu_1)q_3) + a\phi(\varepsilon\eta + q_3)\Lambda_1) + a\phi(\mu_1\eta + (\mu_1 + \alpha)q_3)\Lambda_2),$$

$$b_1 = a\phi\delta N_h^{**}(q_2\mu_2\Lambda_1(\varepsilon\eta + q_3) + \mu_1q_1q_3\Lambda_2) + \delta^2(N_h^{**})^2q_1q_3\mu_2\mu_1(1 - R_{T1}) \\ + \delta^2(N_h^{**})^2q_2\mu_2(\mu_1\eta + (\mu_1 + \alpha)q_3)(1 - R_{T2}),$$

$$b_2 = \delta^2\mu_1(N_h^{**})^2q_1q_2q_3\mu_2(1 - R_T).$$

We consider the following,

- i. When  $R_T < 1$ , then  $b_2 > 0$  and  $b_1 > 0$ , then equation (5.18) has no positive roots.
- ii. When  $R_T = 1$ ,  $b_2 = 0$  and  $b_1 > 0$ . Since  $b_0 > 0$ , then there is one negative root hence no endemic equilibrium point.
- iii. When  $R_T > 1$ , then  $b_2 < 0$  and  $\Delta = b_1^2 - 4b_0b_2 > 0$ . Then equation (5.18) has two real roots, since the product is given by  $b_2/b_0 < 0$ , then one of them is negative and the other is positive.

We proceed to determine the endemic equilibrium point when  $R_T > 1$  by substituting for  $N_h^{**}$  in equation (5.18). We have

$$\lambda_h^*(a_3(\lambda_h^*)^3 + a_2(\lambda_h^*)^2 + a_1\lambda_h^* + a_0) = 0 \quad (5.19)$$



where,

$$a_3 = \delta[(\eta + q_3)\mu_2\Lambda_1 + y\Lambda_2][(\eta(\delta + a\varepsilon\phi) + (\delta + a\phi)q_3)\mu_2\Lambda_1 + (\delta + a\phi)y\Lambda_2] > 0,$$

$$\begin{aligned} a_2 = & \delta[(\eta + q_3)\mu_2\Lambda_1 + y\Lambda_2][(\eta(\delta + a\varepsilon\phi) + (\delta + a\phi)q_3)\mu_2\Lambda_1 + (\delta + a\phi)y\Lambda_2] \\ & + \delta q_1 q_3 ((\eta(2\delta + a\varepsilon\phi) + (2\delta + a\phi)q_3)\mu_2^2\Lambda_1^2 + (\mu_1\eta(4\delta + a\phi(2 + \varepsilon))) \\ & + (2\alpha\delta + a\alpha\phi + 4\delta\mu_1 + 3a\phi\mu_1)q_3)\mu_2\Lambda_1\Lambda_2 + 2(\delta + a\lambda)\mu_1y\Lambda_2^2) \\ & - a^2\theta\phi\mu_1\mu_2[(\varepsilon\eta + q_3)\mu_2\Lambda_1 + y\Lambda_2]\Lambda_m, \end{aligned}$$

$$\begin{aligned} a_1 = & \delta^2 q_1^2 q_3^2 (\mu_2\Lambda_1 + \mu_1\Lambda_2)^2 \left( 1 - \frac{1}{q_1 q_3} (R_{T1}(1 + yq_2\mu_1) + \frac{2yq_2 R_{T2}}{q_1 q_3}) \right) \\ & + \delta q_1 q_3 [2y\Lambda_2 + (\mu_2\Lambda_1 + \mu_1\Lambda_2)[q_2(\eta(2\delta + a\varepsilon\phi) + q_3(a\phi + 2\delta\mu_2\Lambda_1))] + a\phi\mu_1 q_1 q_3 \Lambda_2], \end{aligned}$$

$$a_0 = \delta^2 q_1^2 q_2^2 q_3^2 (\mu_2\Lambda_1 + \mu_1\Lambda_2)^2 [1 - R_T] < 0$$

$$\text{with } y = \mu_1\eta + (\alpha + \mu_1)q_3.$$

Then  $\lambda_h^* = 0$  corresponds to the disease free equilibrium point and the cubic polynomial gives the value of  $\lambda_h^*$  for which the endemic equilibrium point exists. Using Descartes rule of signs, we find that equation (5.19) has at most three positive roots for  $R_T > 1$ . The roots depend on the discriminant,  $\Delta$  given by;

$$\Delta = 18a_3a_2a_1a_0 - 4a_2^3a_0 + a_2^2a_1^2 - 4a_3a_1^3 - 27a_3a_0^2. \quad (5.20)$$

But we know from equation (5.18) that equation (5.19) has only one positive root when  $R_T > 1$  and no positive root when  $R_T \leq 1$ . In this case necessarily  $\Delta < 0$  and

$$\lambda_h^* = \frac{1}{3a_3} \sqrt[3]{\frac{1}{2} \left[ \sqrt{(2a_2^3 - 9a_3a_2a_1 + 27a_3^2a_0)^2 - 4(a_2^2 - 3a_3a_1)^3} - (2a_2^3 - 9a_3a_2a_1 + 27a_3^2a_0) \right]}. \quad (5.21)$$

The other two roots are complex. In Figure 5.2 we illustrate that the model exhibits transcritical bifurcation whereby the endemic equilibrium point only exists for  $R_T > 1$  and is stable.

When  $\lambda_h^*$  is substituted back in equation (5.15) we obtain the endemic equilibrium point

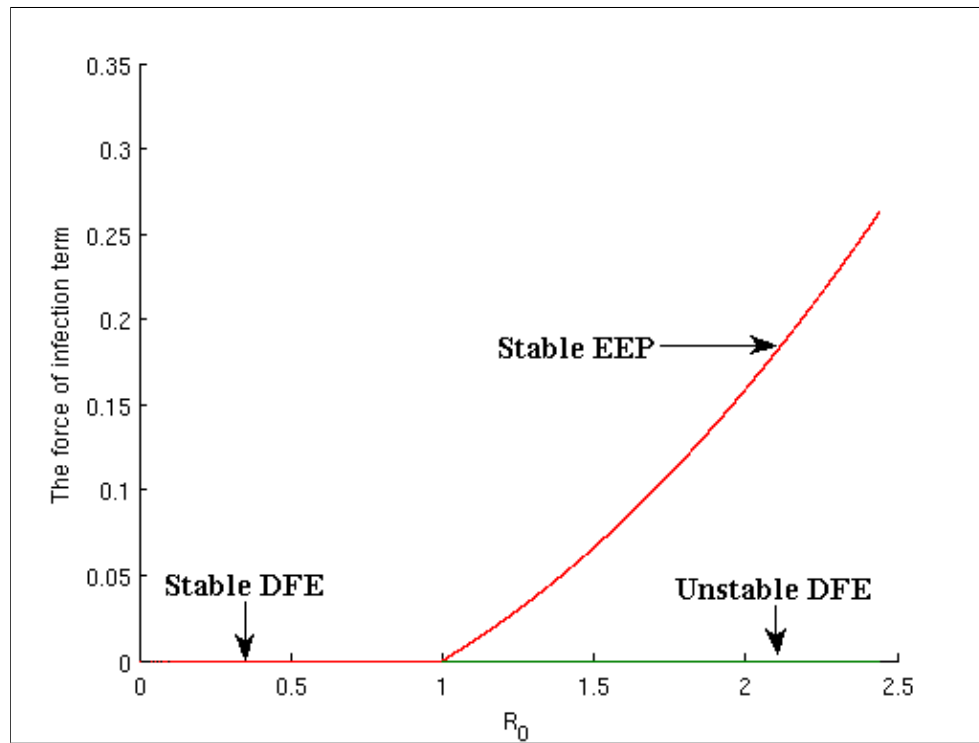


Figure 5.2. Bifurcation diagram for system (5.1) – (5.7) as a function of the reproduction number

$E^*$ . The existence of the endemic equilibrium is summarised in the theorem below.

**Theorem 5.2.4.** *A unique endemic equilibrium point exist if  $R_T > 1$  and no biologically feasible equilibrium exists for  $R_T < 1$*

### 5.3 Numerical results

In this section, we carry out numerical simulations to confirm our analytical results and other findings as regards to this model. In addition to the parameter values given in Section 4.5 in Chapter 4, other parameters used are described below;

- **Recruitment parameters**

Richard Gammon [22], estimated the current birth rate to be 0.05 per year. Then the birth rate per day is estimated as  $0.05/365$ . We assume this rate to be the same for both AA and AS individuals more so in malaria endemic areas. This is multiplied

by the total population to give the recruitment rate,  $\Lambda_1$ , into the human population. The female anopheles mosquitoes are continuously recruited by birth. It is estimated that 500 mosquitoes are produced every day [31]. Thus, the recruitment rate,  $\Lambda_m = 500$  per day.

- **Transmission parameters**

In addition to the transmission parameters described in Section 4.5 in Chapter 4, we assume that recovered individuals transmit the parasite at a reduced rate. we consider the reduced transmission factor,  $\varepsilon$ , to be 0.5.

- **Treatment parameters**

The recovery rate,  $\eta$ , due to treatment vary depending on how quickly the infected person receives treatment and the kind of treatment given to him/her. It can take 3 to 14 days to clear the parasite which corresponds to 0.014 and 0.333 recovery rates respectively. we use an estimated value of 0.2 which corresponds to 5 days [15, 41]. Malaria treatment does not provide permanent immunity therefore recovered individuals tend to lose their immunity in a period of 0 to 2 years. We estimate the rate,  $k$ , at which immunity is lost to be  $1/(2 \times 365)$  [34].

The chosen parameter values and their references are given in Table 5.1.

Table. 5.1. *Parameter values used in the model*

Parameter	Description	Value	Reference
$a$	Biting rate	0.2	[34, 15]
$\Lambda_1$	Recruitment rate	0.2	estimated
$\Lambda_m$	Mosquito recruitment rate	500	[31]
$\alpha$	Malaria induced death rate	0.0005	[37]
$\gamma_1$	Recovery rate of AA individuals	0.033	[41, 32]
$\gamma_2$	Recovery rate of AS individuals	0.066	Assumed
$\mu_1$	Human natural mortality rate	0.00004	[34, 20, 15]
$\nu$	Sickle cell related death rate	0.00002	[20]
$\varepsilon$	Reduced transmission factor	0.5	Assumed
$\phi$	Probability of human to mosquito transmission	0.09	[34, 15]
$\theta$	Probability of mosquito to human transmission	0.833	[34, 15, 11, 32]
$\eta$	Recovery rate due to treatment	0.2	[15, 41]
$\delta$	Mosquito mortality rate	1/15	[34]
$k$	Rate at which immunity is lost	$1/(2 \times 365)$	[34, 15]

Using parameter values in Table 5.1 and *odesolver packages* in Python programming language, we investigate how the populations of susceptible, infectious and recovered, for both AA and AS groups change over time when the reproduction number is less or greater than unity. In order to simulate these results, we choose the following initial conditions,  $S_1(0) = 500, S_2(0) = 500, I_1(0) = 100, I_2(0) = 100, R(0) = 1, S_m(0) = 950, I_m(0) = 50$ . We assume the same recruitment rate of AA and AS individuals.

We illustrate with the following numerical simulations that indeed the analysed model has locally asymptotically stable equilibria points whenever the initial conditions are in the feasible region. The prevalence defined as the proportion of infected individuals in the population at a given time is also simulated to show the spread or extinction of the disease.

Figure 5.3 illustrates how total prevalence changes with time for  $R_T < 1$ . We observe that malaria prevalence goes to zero for  $R_T < 1$ . Epidemiologically, our results agree with the universal understanding of the reproduction number whereby the disease is wiped out whenever  $R_T$  is less than unity. Moreover, our analytical results given in Theorem 5.2.3 concur these results.

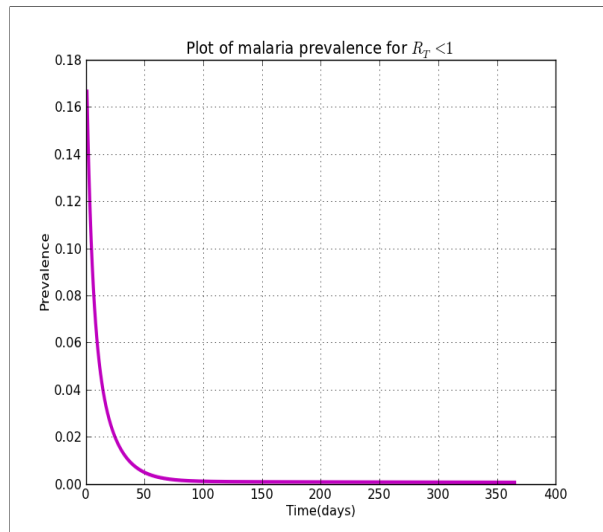


Figure. 5.3. Shows the malaria prevalence for values in Table 5.1 given  $R_T < 1$ .

The dynamics of malaria disease with  $R_T < 1$  are given in Figure 5.4. We observe that the infected populations converge to zero as the susceptible populations increase for both humans and mosquitoes.

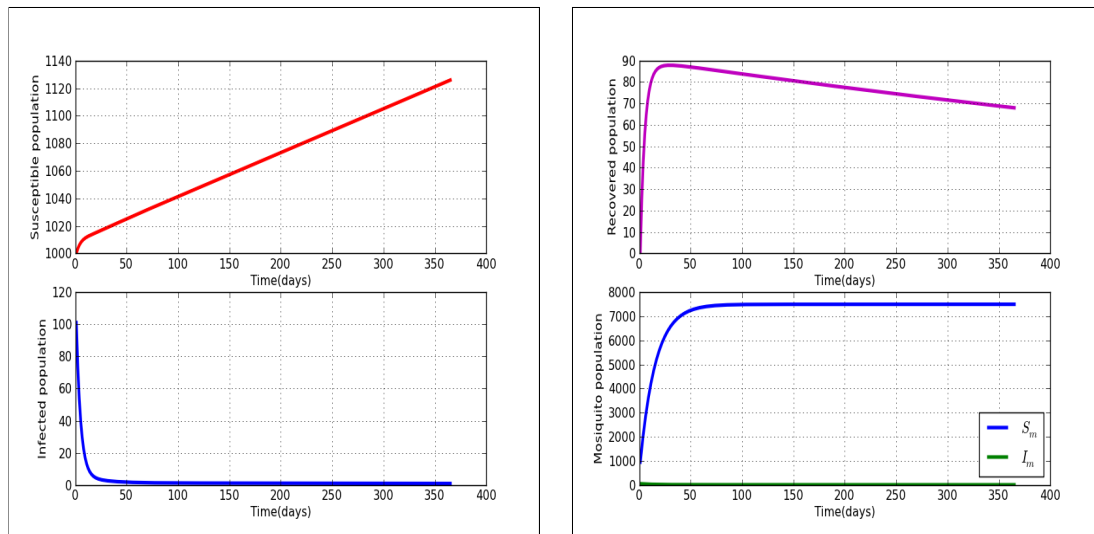


Figure. 5.4. *Illustrates the dynamics of malaria disease for  $R_T = 0.30$*

When  $R_T > 1$ , Figure 5.5 illustrates that, malaria prevalence increases with time but later stabilizes when the dynamics are at equilibrium. This describes the disease persistence equilibrium point obtained in subsection 5.2.4. This also is in agreement with the epidemiological interpretation of  $R_T$ .

Figure 5.6 shows how the dynamics of malaria vary for both AA and AS genotype.

In Figure 5.7, we observe that the susceptible human population decreases as the infected population increases. However, due to treatment, we have an increase in the recovered population.

The high prevalence of malaria in the population for  $R_T > 1$  is attributed towards the infected AS individuals. In our model, we considered treatment of AA individuals only because we assume that they are the only ones who show clinical symptoms and AS individuals do not show clinical symptoms. But although AS individuals rarely show symptoms, long duration of parasitemia leads to high endemic levels hence high prevalence.

In Figure 5.8, the graph shows malaria prevalence of AA individuals taken independently. We note that the prevalence increases and then declines. The decline in prevalence among AA individuals is a result of malaria treatment as transmission will be reduced in this population. On the other hand, Figure 5.9, illustrate malaria prevalence among AS genotype individuals. We observe that the prevalence increases to high values. This is due to the fact that AS individuals are not treated therefore in an isolated population of such individuals

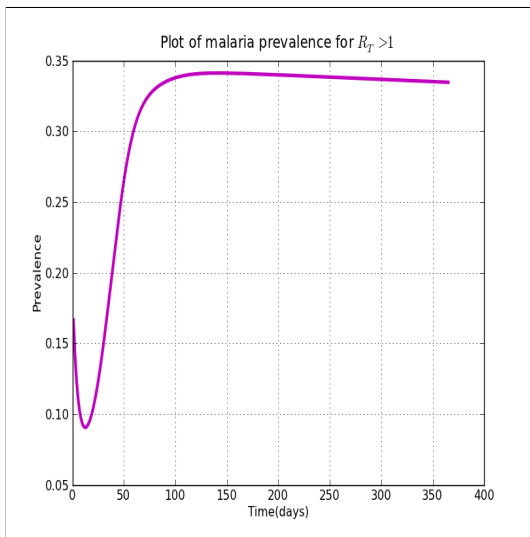


Figure. 5.5. *Demonstrates malaria prevalence for  $R_T = 3.14$*

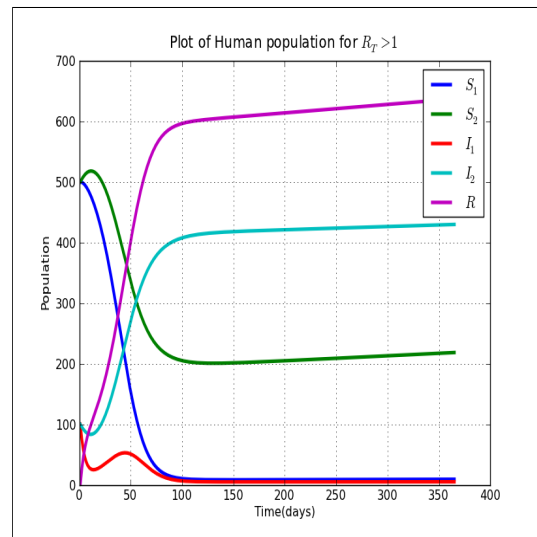


Figure. 5.6. *Shows human population dynamics for  $R_T = 3.14$*

the prevalence increases. This explains why treatment of only individuals showing clinical symptoms is bound to fail in the fight for malaria eradication.

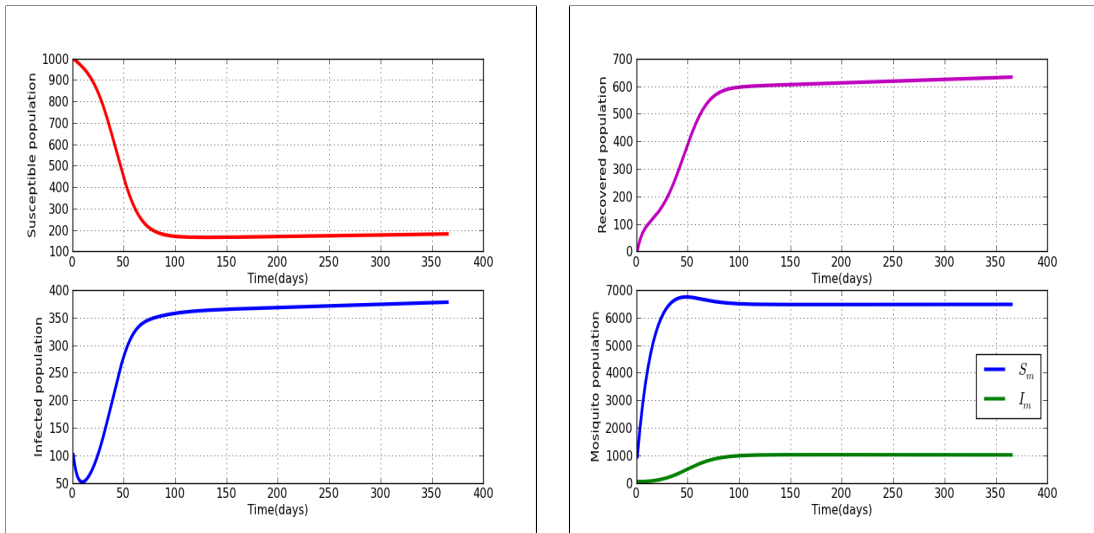


Figure. 5.7. Illustrates the dynamics of malaria disease for  $R_T = 3.14$

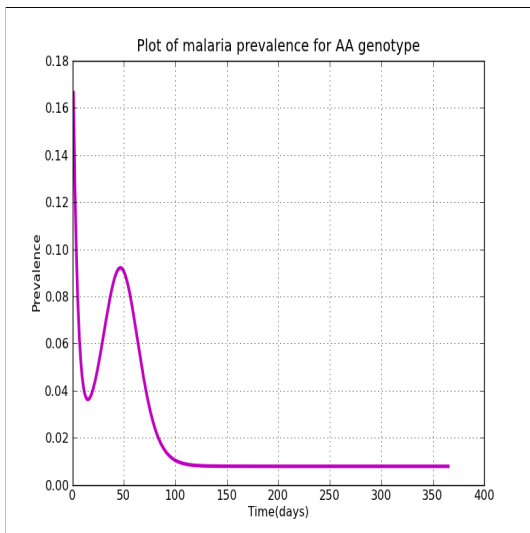


Figure. 5.8. Demonstrates malaria prevalence for AA genotype individuals,  $R_T = 3.13$

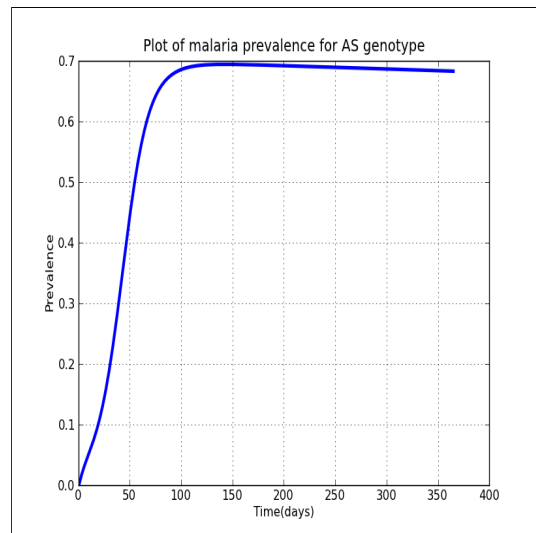


Figure. 5.9. Illustrates malaria prevalence for AS genotype individuals,  $R_T = 3.13$

### 5.3.1 Impact of recovery rate on S-gene frequency

In this subsection, we investigate the impact of the recovery rate on the frequency of S-gene. Much as treatment does not directly affect the frequency of the gene, it leads to an increase in AA genotype group which in return affects the emergence of new AS individuals. We note that, AS individuals have a single copy of the S-gene, thus the frequency of the gene is given as half the proportion of AS individuals in the population. The frequency of S-gene,  $q$  in the population is given by;

$$q = \frac{S_2 + I_2}{2N_h}. \quad (5.22)$$

To investigate how  $q$  changes with the recovery rate  $\eta$ , we determine the derivative of  $q$  with respect to  $\eta$ . If the derivative for a given value of  $\eta$  is positive, then the frequency is an increasing function of  $\eta$  and if its negative, then  $q$  is a decreasing function of  $\eta$ . However, since we can not explicitly solve system (5.1 – 5.7) to obtain the expression for  $q$ , we use the equilibrium point given in equation (5.15) to examine how the frequency changes with  $\eta$  at equilibrium. Thus;

$$q^* = \frac{S_2^* + I_2^*}{2N_h^{**}}. \quad (5.23)$$

Figure 5.10 shows that, at equilibrium the the sickle cell gene frequency decreases as the recovery rate of AA individual increases. If we consider the recovery rate to take values between 0 – 0.4, it shows that individuals take at least three days to recover. On average, infected individuals take atleast 5 days to recover from the infection. This implies that with a recovery rate of 0.4, either strong medication should be administered or combined therapy where more than one drugs should be given. Therefore, with effective treatment of AA population a reduction in the emergence of new AS individuals in a long run will be observed.

In Figure 5.11, we observe that even though malaria may persist in the population, that is increase in reproduction number, the frequency declines because of the effective treatment. When we plot the frequency at equilibrium with the number of AS infected individuals (Figure 5.12), it is shown that the frequency declines as AS infected population reduces. This implies that much as AS individuals do not show symptoms, they indirectly contribute toward the high mortality rate of AA genotype individuals. We know that malaria mortality



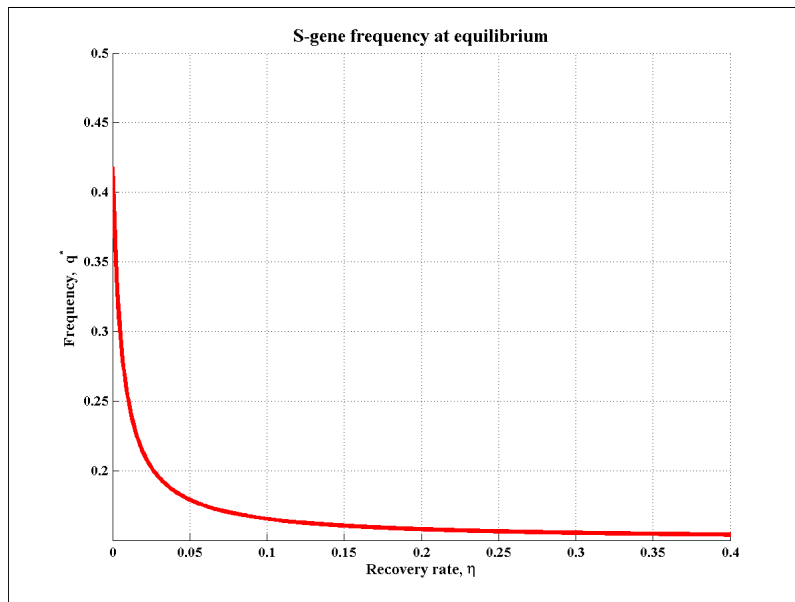


Figure. 5.10. *Demonstrates the decrease in sickle cell gene frequency as the recovery rate,  $\eta$  increases at equilibrium.*

is high among children below 5 years and pregnant women, Brian Greenwood [23] in his study suggested that chemoprophylaxis is an effective way of preventing morbidity and mortality among these vulnerable groups. He suggested the use of intermittent preventive methods where anti-malaria drugs are given to infants, children and pregnant mothers in consistent intervals. If chemoprophylaxis is administered to all infants irrespective of their genotype status and infectious status, then we would not only control the spread of malaria but also reduce the frequency of sickle cell gene in the entire population. However this is bound to increase spread of drug-resistance malaria in low endemic areas though its has little impact in high endemic areas [41].

Figure 5.13, shows that the frequency of sickle cell gene decreases as time increases for different recovery rates,  $\eta$ . We observe a bigger decline when the recovery rate is 0.4 compared to 0.1. This implies that the effectiveness of malaria treatment will influence the frequency of sickle cell gene. As explained earlier, even though malaria treatment does not directly affect the frequency of sickle cell gene, it leads to a reduction in mortality of AA individuals.

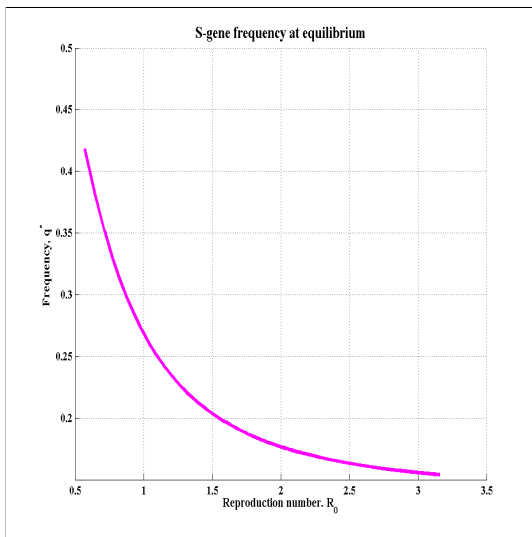


Figure. 5.11. Demonstrates the decrease in sickle cell gene frequency at equilibrium with change in reproduction number,  $R_T$

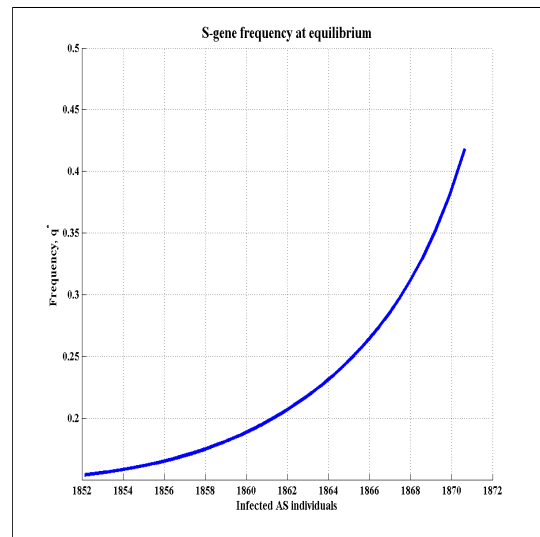


Figure. 5.12. Demonstrates the decline in sickle cell gene frequency at equilibrium with a decrease in the number of infected AS individuals

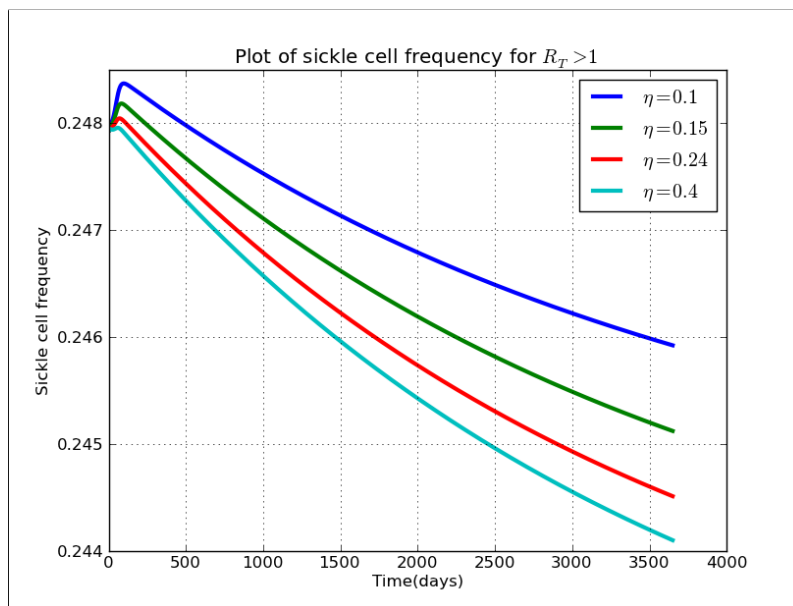


Figure. 5.13. Shows the decrease in sickle cell gene frequency with time as we increase the recovery rate.

## 5.4 Summary

In this chapter, we analysed a 7-dimensional ordinary differential system of equations showing the dynamics of malaria and sickle cell gene for two genotypes. The system is composed of 5 - variables for the humans and 2-variables for the mosquitoes. We demonstrated that the model is epidemiologically feasible and mathematically well posed in a specific domain. From the model, we were able to determine the basic reproduction number which was given as a sum of two terms, that is AA and AS reproduction numbers  $R_{T1}$  and  $R_{T2}$  respectively. Furthermore, we studied the existence of the disease free and the unique endemic equilibrium points. Our analysis showed that for  $R_T < 1$ , the disease free equilibrium is locally asymptotically stable and unstable otherwise. Moreover, the unique endemic equilibrium point only exists for  $R_T > 1$  thus transcritical bifurcation.

We also carried out numerical simulations to verify our analytical results and to investigate the impact of malaria treatment of AA individuals on the frequency of the S-gene. Results showed that, the frequency declines with increase in the recovery rate due to treatment upto a certain level. This implies that treatment of a single group will not lead sickle cell eradication but will only reduce its frequency.

# Chapter 6

## Conclusion and Recommendations

### 6.1 Conclusion

In this thesis, we investigated the impact of malaria treatment of AA genotype individuals on the frequency of sickle cell gene using mathematical models. We first started by reviewing the model by Feng et al. [20] to understand the impact of sickle cell gene on malaria dynamics and how the malaria epidemiological parameters affect the maintenance of S-gene. We used singular perturbation techniques to analyse this model with an argument that malaria dynamics occur on a much faster time scale compared to the sickle cell dynamics. Therefore, we considered two time scales (fast and slow time scale).

On the fast time scale, the dynamics discussed correspond to malaria disease only. We determined the basic reproduction number and noted that it constitutes two terms  $R_1$  and  $R_2$  with  $R_1$  and  $R_2$  being the basic reproduction numbers when the population is composed of AA and AS individuals respectively. Both our analytical and numerical results indicated that, when  $R_0 < 1$ , then malaria is wiped out in both populations. This is in agreement with the previous work done on malaria models. When  $R_0 > 1$ , our model suggested that a unique endemic equilibrium point exists which is locally asymptotically stable. Furthermore, we investigated how the frequency of the S-gene affects the dynamics of malaria. We were able to conclude that higher frequency of sickle cell gene leads to high malaria endemic levels for small recovery rate values for AS individuals. On the other hand, reduced level of endemicity was observed for high recovery rate values in areas with

high sickle cell gene frequency. This was also confirmed by the numerical results of the reproduction number as we change the frequency of the gene and the recovery rate of AS individuals. Thus, a single copy of sickle cell gene is only advantageous to the population in malaria endemic areas provided the parasite is cleared quickly from the blood stream of those individuals otherwise it leads to high malaria endemic levels.

We also carried out sensitivity analysis of the basic reproduction number. All the sensitivity indices obtained agreed with the intuitive expectations. Moreover, we noted that the basic reproduction number was most sensitive to the infection rates and the recovery rate of AS individuals in areas with high sickle cell gene frequency. The basic reproduction number was also observed to be sensitive to the mosquito death rate. Therefore, for malaria encounter in both populations, these parameters should be targeted so as to bring the reproduction number to value below unity.

Singular perturbation techniques suggest that the locally asymptotically hyperbolic equilibrium point of the fast time scale appears as a normally hyperbolic manifold on the slow time scale. This is in the sense that when we start in the neighbourhood of equilibrium set, the solution will always decay towards the manifold. The evolution of the slow variables on the slow time scale was studied on this manifold. We noted that the dynamics of the slow variable i.e the abundance of the S-gene ( $w$ ) and the human population ( $N_h$ ) are well explained by the per-capita birth rate and the weighted (maximum per-capita ) death rates of AA and AS individuals. These parameters were the most crucial ones to describe the existence and stability of the equilibria points on the slow time scale.

We used the fitness coefficient as a measure for the invasion ability of the S-gene when initially introduced in a population. This was given as the difference between the weighted death rate of AA and AS individuals. Both our mathematical and numerical results indicated that, the gene may establish itself if the death rate of AA individuals is greater than that of AS individuals. Moreover, if the per-capita birth rate is greater than both the weighted death rate of AA and AS individuals, the gene will always be maintained in the population and if it is less than both the weighted death rates, then eventually the entire population will be wiped out. The fitness coefficient was noted to be composed of mainly malaria parameters. This explains why in malaria endemic areas, the frequency of the gene is high compared to areas where malaria has been eradicated.

We extended this model by adding another compartment for the recovered AA individuals in order to investigate the impact of malaria treatment on sickle cell gene frequency. In the extended model, we assumed that AS individuals do not show clinical symptoms for malaria therefore do not need treatment. We carried out mathematical analysis of the model which included determining of the basic reproduction number and the equilibria points. We noted that the disease free equilibrium point is locally asymptotically stable for  $R_T < 1$  and unstable otherwise.

In addition, the model exhibits transcritical bifurcation whereby a unique endemic equilibrium point exists for  $R_T > 1$ . The stability of the endemic equilibrium point was only determined numerically due to the complexity of its form. In order to investigate the impact of malaria treatment of AA individuals on the sickle cell gene frequency, we evaluated the gene frequency at equilibrium and used the parameters values given in Table 5.1 to carry out the numerical results. Our results indicated that, the frequency declined with an increase in the recovery rate. We noted that sickle cell gene frequency could only reduce to a certain value no matter the increase in the recovery rate. We also noted that if the number of infected AS individuals is reduced, then the frequency also reduces. This is not surprising since even though AS individuals do not show malaria symptom they still transmit the parasite. Therefore, we conclude that, malaria treatment of a single group will to some extent lead to the reduction in the sickle cell gene frequency.

## 6.2 Recommendations

Basing on the results obtained from both models, we recommend the following.

- Administering of drugs to both AA and AS individuals irrespective of whether symptoms show or not. Brian Greenwood [23] suggested the use of intermittent preventative programmes whereby malaria drugs are given to all individuals in intervals irrespective of their infection status as one way to control malaria morbidity and mortality. This has been noticed to be effective among pregnant women. If this is extended for young children that have not yet developed solid immunity, it would reduce on malaria transmission and mortality, hence reducing new AS individuals. However, implementation of this programme might lead to high spread of drug re-

sistance in low malaria endemic areas. Therefore, it would require invention of new drugs or combination therapy.

- Combined strategies such as the use of mosquito treated nets, treatment and use of insecticides for mosquitoes will greatly lead to malaria eradication and reduction in the frequency of the S-gene.

### 6.3 Limitations and future work

In this thesis, we did not considered all the possible dynamics of malaria and sickle cell gene in order to reduce on the complexity of the model. For instance, we did not include the exposed classes for both human and mosquitoes. We assumed that the time since infection and onset of the disease is too small and can be ignored which is not entirely true.

Due to the fact that malaria models in literature did not consider genetic make up of individuals, obtaining of parameter values was also a limitation to our study.

We could not obtain data in order to validate our models. Therefore, for future work, we suggest the following.

- A model explaining the full dynamics of malaria and sickle cell gene should be formulated. i.e SEIR model for both genotypes.
- A model with treatment of AS individuals should be formulated and a measure for cost effectiveness of this intervention be investigated.
- Use of data to validate the model.

## References

- [1] Malaria parasite life cycle. <http://post.queensu.ca/forsdyke/pfalcip01.htm>, 14 October 2011.
- [2] Malaria facts. <http://www.who.int/features/factfiles/malaria/en/>, 2009.
- [3] Malaria statistics. <http://www.who.int/mediacentre/factsheets/fs094/en/index.html>, 2010. Malaria Statistics.
- [4] Data and statistics. <http://www.cdc.gov/NCBDDD/sicklecell/data.html>, 2011.
- [5] Sickle cell disease. <http://en.wikipedia.org/wiki/Sickle-cell-disease>, 2011.
- [6] Sickle cell disease national statistics. <http://wandefightsforsicklecellanemia.com/DataStats.html>, 2011.
- [7] M. Aidoo, D.J. Terlouw, M.S. Kolczak, P.D. McElroy, F.O. Kuile, S. Kariuki, B.L. Nahlen, A.A. Lal, and V. Udhayakumar. Protective effects of the sickle cell gene against malaria morbidity and mortality. *Lancet*, 359:3111–3112, 2002.
- [8] A.C. Allison. Protection afforded by sickle- cell trait against subtertian malarial infection. *Medical Journal*, -:290–294, 1954.
- [9] R. Anguelov, J.M.-S. Lubuma, and M. Shillor. Dynamically consistent nonstandard finite difference schemes for continuous dynamical systems. *Discrete and Continuous Dynamical Systems*, 61:34–43, 2009.
- [10] J.L. Aron. Mathematical modeling of immunity to malaria. *Mathematical Biosciences*, 90:385–396, 1988.



- 
- [11] N. Chitnis, J.M. Chusing, and J.M. Hynam. Bifurcation analysis of a mathematical model for malaria transmission. *Journal of Applied Mathematics*, 67:24–45, 2006.
- [12] N. Chitnis, J.M. Hyman, and J.M. Chusing. Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model. *Bulletin of Mathematical Biology*, 70:1272–1296, 2008.
- [13] N. R. Chitnis. *Using mathematical models in controlling the spread of malaria*. PhD thesis, The University Of Arizona, 2005.
- [14] C. Chiyaka, W. Garira, and S. Dube. Transmission model of endemic human malaria in a partially immune population. *Mathematical and Computer Modelling*, 46(5-6):806–822, 2007.
- [15] C. Chiyaka, J.M. Tchuente, W. Garira, and S. Dube. A mathematical analysis of the effects of control strategies on the transmission dynamics of malaria. *Applied Mathematics and Computation*, 195:641–662, 2008.
- [16] K. Dietz, L. Molineaux, and A. Thomas. A malaria model tested in the african savannah. *Bulletin World Health Organisation*, 50:347–357, 1974.
- [17] S. Diop, F. Soudre, M. Seck, Y.B. Gueye, T.N. Dieye, A.O. Toure Fall, A. Sall, D. Thiam, and L. Diakhate. Sickle-cell disease and malaria: evaluation of seasonal intermittent preventive treatment with sulfadoxine-pyrimethamine in senegalese patients- a randomized placebo-controlled trial. *Annals of Hematology*, 90:23–27, 2011.
- [18] Z. Feng, D.L. Smith, F.E. McKenzie, and S.A. Levin. Fast and slow dynamics of malaria and the s-gene frequency. *Journal of Dynamics and Differential Equations.*, 16:869–896, 2004.
- [19] Z. Feng, Y. Yi, and H. Zhu. Malaria epidemics and sickle-cell gene dynamics, 2002.
- [20] Z. Feng, Y. Yi, and H. Zhu. Coupling ecology and evolution: malaria and the S-gene across time scales. *Mathematical Bioscience.*, 189:1–19, 2004.
- [21] N. Fenichel. Geometric singular perturbation theory for ordinary differential equations. *Journal of Differential Equations*, 31:53–98, 1979.

- [22] R. Gammon. Estimate the steady birth rate of humans on earth. 2007.
- [23] B. Greenwood. Anti-malarial drugs and the prevention of malaria in the population of malaria endemic areas. *Malaria Journal*, 9:1–7, 2010.
- [24] W.S. Harwin. Routh - hurwitz stability criterion. March. 2007.
- [25] G. Hek. Geometric singular perturbation theory in biological practice. *Journal of Mathematical Biology*, 60:347–386, 2008.
- [26] E.A. Ibijola, R.B. Ogunrinde, and O.A. Ade-Ibijola. On the theory and applications of new nonstandard finite difference methods for the solution of initial value problems in ordinary differential equations. *Advances in Natural and Applied Sciences*, 2(3):214 – 224, 2008.
- [27] T.R. Jones. Quantitative aspects of the relationship between the sickle-cell gene and malaria. *Parasitology Today*, 13:107–111, 1997.
- [28] T.J. Kaper. An introduction to geometric methods and dynamical system theory for singular perturbation problems. *Proceedings of Symposia in Applied Mathematics*, 56:85–131, 1999.
- [29] J.C. Koella. Review on the use of mathematical models of malaria transmission. *Acta Tropica*, 49:1–25, 1991.
- [30] J.C. Koella and R. Anita. Epidemiological models for the spread of anti-malarial resistance. *Malaria Journal*, 2:1–11, 2003.
- [31] A.A. Lashari and G. Zaman. Global dynamics of vector-borne diseases with horizontal transmission in host population. *Computers and Mathematical Applications*, 61:745–754, 2011.
- [32] J. Leander and P. Johansson. Mathematical modeling of malaria. -:1–36, 2010.
- [33] J.M.-S Lubuma and K.C. Patidar. Uniformly convergent nonstandard finite difference methods for self-adjoint singular perturbation problems. *Journal of Computational and Applied Mathematics*, 191:229–238, 2006.

- 
- [34] O.D. Makinde and K.O. Okosun. Impact of chemotherapy on optimal control of malaria disease with infected immigrants. *Biosystems*, 104:32–41, 2011.
- [35] T. Marijani. Modelling drug resistance in malaria. Master's thesis, Stellenbosch University, 2009.
- [36] F.E. Mckenzie and E.M. Samba. The role of mathematical modeling in evidence-based malaria control. *American Journal of Tropical Medicine and Hygiene*, 71:94–96, 2004.
- [37] G.A. Ngwa and W.S. Shu. A mathematical model for endemic malaria with variable human and mosquito populations. 1999.
- [38] A.L. Okwi, W.Byarugaba, C.M. Ndugwa, A. Parkes, M. Ociado, and J.K. Tumwine. An up-date on the prevalence of sickle cell trait in eastern and western uganda. *BMC Blood Disorder*, 10:1–6, 2010.
- [39] L. Perko. *Differential Equations and Dynamical Systems*. Springer, 2000.
- [40] E.K. Phongi. Centre manifold theorem with application in population modelling. Master's thesis, University of Kwazulu Natal, 2009. Masters Dissertation.
- [41] W.O. Prudhomme, D.L. Smith, and F.E. McKenzie. Potential impact of intermittent preventive treatment on spread of drug resistant malaria. *Plos Medicine*, 3:663–642, 2006.
- [42] I. Roberts and M. Montalembert. Sickle cell disease as a paradigm of immigration hematology: New challenges for hematologists in europe. *The Hematology Journal*, 92:865–871, 2007.
- [43] R. Ross. *The Prevention of malaria*. John Murray, 1911.
- [44] R.Ross. *Studies on Malaria*. John Murray, 1928.
- [45] C. Smorynski. *History of Mathematics: A suplement*. Springer, 2000.
- [46] J. Tumwiine, J.Y.T. Mugisha, and L.S. Luboobi. A mathematical model for the dynamics of malaria in a human host and mosquito vector with temporary immunity. *Applied Mathematics and Computation*, 189:1953–1965, 2007.

- 
- [47] P. van den Driessche and J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Bioscience*, pages 1–21, 2005.
- [48] F. Verhulst. Periodic solutions and slow manifolds. *International Journal of Bifurcation and Chaos*, 17:2533–2540, 2007.
- [49] D.J. Weatherall and J.B. Clegg. Inherited haemoglobin disorders: An increasing global health problem. *Bulletin World Health Organisation*, 79:704 – 712, 2001.
- [50] S. Wiggins. *Normally Hyperbolic Invariant Manifolds in Dynamical Systems*. Springer-Verlag, 1994.
- [51] H.M. Yang. Malaria transmission model for different levels of acquired immunity and temperature dependent parameters (vector). *Rev. Saude Publica*, 34:223–231, 2000.