Mathematical Modelling of Malaria Transmission and Pathogenesis

by

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DEDICATION

I wish to dedicate this thesis, to my father (Chief Bernard Okrinya of Blessed memory) who apart from initiating my early education gave me a positive direction to life, to the Petroleum Technology Development Fund (PTDF) Nigeria for funding this project and to Senator Clever Ikisikpo, without whom this thesis would not exist. May God receive the Glory.

ACKNOWLEDGEMENT

CONTENTS

ABSTRACT

In this thesis we will consider two mathematical models on malaria transmission and pathogenesis. The transmission model is a human-mosquito interaction model that describes the development of malaria in a human population. It accounts for the various phases of the disease in humans and mosquitoes, together with treatment of both sick and partially immune humans. The partially immune humans (termed asymptomatic) have recovered from the worst of the symptoms, but can still transmit the disease. We will present a mathematical model consisting of a system of ordinary differential equations that describes the evolution of humans and mosquitoes in a range of malarial states.

A new feature, in what turns out to be a key class, is the consideration of reinfected asymptomatic humans. The analysis will include establishment of the basic reproduction number, R_0, and asymptotic analysis to draw out the major timescale of events in the process of malaria becoming non-endemic to endemic in a region following introduction of a few infected mosquitoes. We will study the model to ascertain possible time scale in which intervention programmes may yield better results. We will also show through our analysis of the model some evidence of disease control and possible eradication.

The model on malaria pathogenesis describes the evolution of the disease in the human

host. We model the effect of immune response on the interaction between malaria parasites and erythrocytes with a system of delay differential equations in which there is time lag between the advent of malaria merozoites in the blood and the training of adaptive immune cells. We will study the model to ascertain whether or not a single successful bite of an infected mosquito would result in death in the absence of innate and adaptive immune response.

Stability analysis will be carried out on the parasite free state in both the immune and non immune cases. We will also do numerical simulations on the model to track the development of adaptive immunity and use asymptotic methods, assuming a small delay to study the evolution of the disease in a naive individual following the injection of small amount of merozoites into the blood stream. The effect of different levels of innate immune response to the pathogenesis of the disease will be considered in the simulations to elicit a possible immune level that can serve as a guide to producing a vaccine with high efficacy level.

CHAPTER 1

INTRODUCTION

1.1. The biology of malaria

Malaria is one of the most fatal diseases in the world. The symptoms that characterised malaria may have been observed as far back as the prehistoric period [89], through the classical era but it was not until the European renaissance period that the name malaria was derived from the Medieval Italian word, *mal aria* meaning "bad air", thinking that the foul vapours emanating from the stagnate water and swamps was the cause of fever, a major symptom of the disease.

A brief historical overview of the disease shows that some descriptions of what seemed to be the disease symptoms are given in the historical records of some early civilisations. The Chinese record, *Huangdi Neijing* describes the disease as repeated fever paroxysm that causes enlargement of the spleen with the potential of generating an epidemic. Ateminisinin combination treatment, a front line drug adopted by the World Health Organisation for the treatment of malaria came from a Chinese plant, *Qing-hao*. This was discovered about 2300 years ago when it was first used to treat acute intermittent fever episodes. An account of

the disease is also given in the ancient Egyptian medical *Papyri*. For instance, the ancient Hindus of India ascribe the disease to the bite of a certain insect. Ancient Greeks, including Homer, Empedocles and Hippocrates also referred to the disease as having characteristics of intermittent fever causing enlarged spleens seen in people living in marshy places. It is believed by some researchers that malaria must have been responsible for the fall of the Roman Empire following an archaeological discovery of the presence of malaria in the bones of a Roman child who died 1500 years ago. The cause of malaria was not known from the down of history until later part of the 19th century when Charles Laveran discovered the malaria parasite in human blood in Africa. Few years later, Giovanni Grassi and Raimondo Filetti used the word plasmodium to name the malaria parasite and in 1897, Ronald Ross demonstrated that plasmodium parasite can be transmitted from infected human to mosquitoes.

The aim of this chapter is to provide the reader with some of the biological and historical background of malaria in an attempt to create an insight to the problem that forms the basis of this study. Malaria is an infectious disease with characteristic symptoms of recurrent episodes of chills, fever, sweating, and anaemia mostly prevalent in tropical climatic regions caused by the parasitic infection of red blood cells by a protozoan of the genus Plasmodium, which is transmitted from human to human by the bite of an infected female anopheles mosquito [3], which requires a blood meal to nurture its eggs. Plasmodium parasites that cause diseases in humans are basically of four species namely, *plasmodium falciparum*, *plasmodium vivax*, *plasmodium ovale* and *plasmodium malariae*. *Falciparum* malaria caused by *plasmodium falciparum* is far more severe than other types of malaria, which is being described as the most deadly of all types [48]. The parasite undergoes a series of changes as part of its complex life cycle.

WHO revealed that malaria kills at least one million people annually in sub-Saharan Africa

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[116] with the potential to significantly increase in response to climate change (due to the role of temperature and rainfall in the population dynamics of its mosquito vector) [63, 122]. Since malaria increases morbidity and mortality, it continues to inflict major public health and socio-economic burdens in developing countries, which in Africa, slows economic growth by up to 1.3 percent each year [115].

Most researches conducted in malaria epidemiology border around disease transmission, parasite interaction with the human host as well as the mosquito vector. These have resulted in the generation and advancement of various intervention strategies aimed at control, elimination and total eradication of the disease. Although Malaria elimination has already been achieved in most of Europe, North America, Australia, North Africa and the Caribbean, and parts of South America, Asia and Southern Africa [119], the disease still remains endemic especially, in the tropical and sub tropical regions of the world. Tremendous contributions are being made by the World Health Organisation with the aim of eradicating the disease worldwide. This led to the initiation of the Roll-Back Malaria Programme saddled with responsibilities bordering on two key areas of prevention and treatment. However, this eradication initiative has been met with some intervening factors reducing it to mere disease control characterised by high mortality of children and pregnant women, the most vulnerable group.

The way to disease eradication appears to be far fetched since there is evidence of rapid re-establishment of the disease in areas where it has been eliminated due to mosquitoes and parasites that are resistant to chemicals to which they were previously susceptible [18, 121]. Other challenges include, use of adulterated drugs instead of the recommended ones, single dosage medication or 'quick treatment' without complete clearance of parasites, the paradox of partial immunity or asymptomatic parasite carriage. The issue of asymptomatic parasite carriage is crucial in the the transmission and pathogenesis of malaria. Intermittent Preventive

Treatment (ITP) is part of the public health programme instituted by the WHO with the aim of treating and clearing existing malaria parasites and preventing new infections in children and pregnant women. Due to ongoing debates on whether or not asymptomatic carriers should be treated, an increased knowledge on the asymptomatic carriage of malaria parasites is needed to assess the risk-benefit ratio of Intermittent Preventive Treatment [117].

Due to a research carried out on the prevalence of asymptomatic carriage of *P. falciparum* in sub-saharan Africa, Ogutu et al. [85] maintains that a large proportion of *P. falciparum* infections are asymptomatic or sub-clinical and microscopy-detected levels of asymptomatic carriage as high as 39% on children under 10 years old have been reported. Based on this they presented a hypothesis that "if a significant reduction of the malaria parasite pool could be obtained through treatment of asymptomatic carriers, over a period of time, a reduction in disease transmission could be obtained across the entire endemic population, even in areas of high transmission". Without testing the hypothesis, the paper highlights some of the implications including the benefits and challenges associated with the treatment of asymptomatic carriers. Therefore, it becomes imperative to understand their role in perpetuating an endemic malaria, for which mathematical modelling can play a key role.

In this thesis, we present a mathematical modelling framework to explicate the dangers of partial immunity necessitated by 'quick treatment' through intake of single dosage of malaria medicine leading to inappropriate clearance of parasites in mostly malaria endemic regions. The discovery of malaria vaccine would be a sure way to disease eradication. Thus, concerted efforts are required to create adequate understanding of the pathogenesis of the disease in the human host. The blood stage parasite is the main cause of disease pathology and to date, efforts to generate an effective blood stage vaccine have not been successful on the ground that clinical immunity is slow to develop and short lived and one reason for this is the

extensive antigenic diversity found in plasmodium parasite leading to a poor understanding of protective host immune responses [25]. We also present a mathematical model to describe the key processes involved in the interaction of blood stage parasites (merozoites), healthy erythrocytes and the human immune system. In the remaining subsections we shall discuss the structure of the thesis, the life history of the malaria parasite and intervention strategies.

1.1.1. The structure of the thesis

This thesis is made up of 6 chapters. In chapter 1 we present the introduction to our work in which some relevant biological issues leading to the work are discussed. In chapter 2, we present a review of some infectious disease models including mathematical models in malaria epidemiology to prepare the background to the transmission model. We present the derivation and analysis of the transmission model in chapter 3 and round up the chapter with a brief discussion of the numerical simulations and asymptotic analysis. In chapter 4 we discuss the immune system in relation to malaria infection and a brief review of some relevant mathematical models as this will create an enabling environment in the derivation and analysis of the in-host model in chapter five. This is followed by an overall conclusion and suggestions for future work in chapter 6.

1.2. Life cycle of malaria parasite

In this section we present the life cycle of the plasmodium parasite. Understanding the various stages in which the parasite exists will provide some useful information to the reader by creating an understanding of the modelling methodology that we have used in this thesis. The malaria parasite has a complicated life cycle involving a mosquito and a human, which can be identified in three phases namely the sporozoite phase, merozoite or erythrocytic phase and gametocyte phase. The merozoite phase starts and ends within the human host whereas
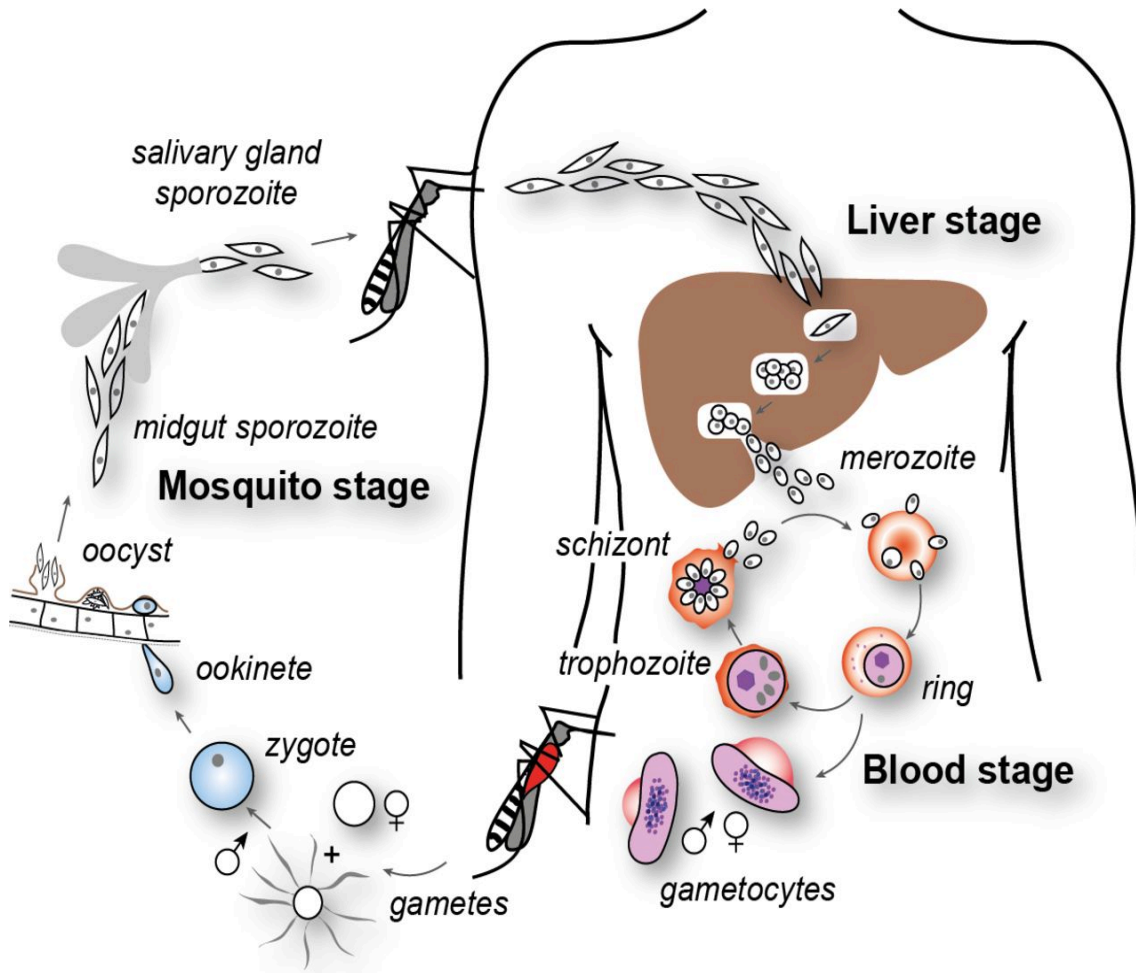
Figure 1.1: A figure describing the life cycle of *P. falciparum*, the most deadly of all Plasmodium species. Other species have a similar life cycle. However, time of development from one stage to another varies. Following infection from a mosquito bite, the parasite in the form of sporozoites evade the immune system and evade the liver where they undergo asexual reproduction. A large number of Merozoites, which are products of the asexual reproduction are released into the blood steam. Each merozoite invades a red blood cell and reproduces asexually. After approximately 48 hours the erythrocyte ruptures and quickly invades a fresh erythrocyte to renew the cycle. Some merozoites differentiate into male and female gametes that are later picked up by a feeding mosquito. Sexual reproduction occurs in the stomach of the mosquito and in addition to some form of asexual replication, sporozoites are released to complete the cycle. This picture is reproduced, with kind permission, from Alan F. Cowman [25].

the parasite in the first and third stages need both the mosquito and human environments to strive. The female anopheles mosquito requires blood meal to nurture its eggs and during the process of blood feeding it injects the malaria parasite in form of sporozoites that preoccupy its salivary glands into the body of its human host at the site of bite. These sporozoites are conveyed via the circulatory system to the liver after evading innate immune cells, in which they invade hepatic cells.

Each of these sporozoites penetrates a liver cell using it to reproduce asexually through

a process often referred to as exoerythrocytic schizogony culminating in the production of merozoites, which are released into the bloodstream. During the process of schizogony an infected hepatic cell or red blood cell passes through four metamorphic stages namely young ring, old ring, young trophozoite and old trophozoite to become a schizont. However, this process may vary depending on the plasmodium species. For instance, for some malaria parasites such as *Plasmodium vivax* and *Plasmodium ovale*, the development of certain trophozoites is arrested at earlier stages to form some temporarily dormant cells termed *hypnozoites*, which may reactivate after some weeks, months, or years being responsible for relapses of the disease [27]. Once these merozoites are released into the blood stream, each starts another round of asexual replication using a red blood cell and after approximately 48 hours, except *Plasmodium malariae* that maintains a 72 hour cycle, each surviving merozoite from any of the other three species produces a second generation of merozoites. Immediately after the erythrocyte invasion, the *Plasmodium falciparum* parasite has the appearance of a 'ring' and after about 12 hours it gradually adopts a more solid appearance known as a 'young trophozoite', which continues to grow after 24 hours to become a schizont or segmenta and after about 12 hours later ruptures to release daughter parasites that infect other erythrocytes [45]. The production of second and subsequent generations of merozoites increases the level of parasitemia creating intermittent fever paroxysms and other disease symptoms due to inflammations from continuous rupturing of infected erythrocytes. *Plasmodium falciparum* merozoites attack all red blood cells, not just the young or old cells, as do other types and a patient with this type of malaria can die within hours of the first symptoms [71]. Prolonged fever destroys so many red blood cells causing blockage of the blood vessels in vital organs (especially the kidneys), which in some cases culminates in the enlargement of the spleen [7]. When malaria infection is left untreated for a long time, it can lead to many complications including severe anaemia.

There may be brain damage, leading to coma and convulsions. The kidneys and liver may also fail [35].

An infected red blood cell committed to a further generation of merozoites, passes through a period of schizogony as illustrated in Figure 3.3, with permission from [25]. The period starts from an immature ring stage, through trophozoite stage to a mature schizont, and eventually bursts to release merozoites. As an alternative to continuous merozoite replication cycles, some of these merozoites differentiate into sexual forms of the parasite called gametocyte. These gametocytes, made up of the male form (microgametocytes) and the female form (macrogametocytes) are later picked up by a female anopheles mosquito during blood feeding. Fertilization occurs in the stomach of the mosquito as a microgamete becomes flagellated and penetrates a macrogamete to form a zygote. The zygote developed into a motile form oockinete and penetrates the midgut wall of the mosquito for further development into an asexual form, oocyst. After rounds of multiple replication the oocyst ruptures to release sporozoites, which migrate to the salivary gland of the mosquito waiting to be injected into the skin of the human host.

1.3. Intervention strategies and immunity to malaria

The global struggle to combat malaria is being led by the world Health Orgaisation (WHO). It has been a joint effort by local, national and international governments including some non governmental organisations. There is no vaccination yet for the disease but certain measures are being taken to control it. These control measures are being taken under a Global Partnership programme called Roll Back Malaria (RBM), targeted at reducing the burden of the disease, in particular for the most vulnerable, namely children and pregnant women. In order to throw more light on our research we will have a brief survey of the main control strategies that have been so far adopted in the fight against the disease. The control

measures include

- Intermitent preventive treatment (IPT) especially, for pregnant women during antinatal and infants irrespective of disease symptoms.

- The use of Insecticide-treated bed nets (ITN)

- Prompt and effective management of the disease through testing, treating and tracking (T3) of every malaria case using antimalarial drug combination (eg. Ateminisinin combination treatments).

- Reducing mosquito population through the destruction of breeding sites or killing of the larva stage at breeding sites that cannot be destroyed.

- Use of indoor residual spaying (IRS) in killing infected mosquitoes resting indoors after feeding and susceptible mosquitoes that may be hiding indoor waiting to feed on humans.

- Introduction of insecticide-treated livestock in treating castles in areas where mosquitoes feed on domestic animals

- Introduction of genetically modified mosquitoes that would produce single sex young ones. Although this has not been implemented but researches are ongoing in this area.

- Administration of transmission blocking drugs like gametocydal drugs to reduce the transition of merozoites to gametocytes.

These control measures have not been able to produce the desired results as they are bound to face some challenges. For instance one of the greatest challenges in the fight against malaria is drug resistance which has been on the increase. Similarly, the benefits of intermittent preventive treatment may not be certain since, the effects of repeated treatments on the development of immunity are the major challenges of intermittent preventive treatment (IPT)[117]. The

treatment policies are designed to reduce morbidity and mortality by ensuring that rapid and complete cure of every malaria case is achieved so that fatal and severe disease situations including cases of chronic anaemia are prevented. Another important objective of effective treatment is to reduce the human reservoir of infection so that disease transmission can be minimised.

The World Health Organisation aims at tackling malaria at the community level so as to reduce the intensity of malaria transmission at the local level by protecting people against infective mosquito bites reducing the density of mosquitoes as well as their life span. The application of indoor and outdoor residual spraying, clearing of home surroundings, good drainage systems, use of treated bed nets, among others are geared towards achieving these objectives. For instance one of the greatest challenges in the fight against malaria is drug resistance which has been on the increase. Mono-therapies have been identified as contributing immensely to drug resistance and the recommended use of Ateminisinin combination treatments is a measure to cub this form of drug resistance. This is an indication that single dose treatments do not always result in complete parasite clearance. Thus, in addition to creating drug resistance, mono therapy makes the patient temporarily asymptomatic.

Based on the problem we have described so far our objective is to derive a mathematical model that can specifically characterise the dynamics of the disease in endemic regions with special interest in its transmission and control. We will employ relevant techniques with the aid of relevant data characterising intensive malaria transmission to analyse the model with the aim of determining possibilities of elimination of the disease. In the next chapter we will discuss some important infectious disease models and their relevance to malaria epidemiology.

CHAPTER 2

MODELLING BACKGROUND

2.1. Infectious disease models

Since malaria is an infectious disease, its models may share in common some characteristic features of other infectious disease models. Any investigation of such a model must take into consideration the mode of infection or transmission, that is whether the disease is contagious or vector transmitted. This however, would be one of the determining factors as to whether an epidemic would prevail or the disease is habitually prevalent in the population. A particular disease could be an epidemic, pandemic or endemic. Contagious diseases sometimes turn out to be epidemic especially, when new cases in a particular human population within a particular period exceed peoples expectations based on recent experience. Often, an epidemic can be pandemic in that it spreads and affects a very high proportion of the population across a large region within a continent or between continents. On the other hand, an infectious disease is said to be endemic if it is persistently prevalent in a population. Most of the infectious disease models reviewed focus on explicating the dynamics of the disease by investigating its incidence and prevalence through some basic assumptions relating the affected population,

the status and spread of the disease, and the mode of recovery. These models are the well known compartmental models SI, SIS, SIR, SEIR and SEIRS, S=Susceptible, I=Infectious, E=incubating, R=Recovered [17, 50, 68]. However, Hethcote [50], discusses two additional models, MSEIR and MSEIRS where M represents child immunity transferred by a mother in form of antibodies through the placenta. Hence a newborn may have temporary passive immunity to an infection and after the antibodies disappear from the body the infant moves to the S class.

The SI model describes a simple epidemic in which a susceptible population is exposed to infection. The basic foundation of this model can be found in the following assumptions.

- The disease is contagious and can only be transmitted from human to human.

- The rate that susceptible people and infected people interact is proportional to both the number of susceptible people and the number of infected people with the rate of proportionality expressed by a contagion parameter.

- A susceptible who gets infected becomes infectious immediately and remains so indefinitely without recovery.

- The duration of the epidemic is relatively short, therefore, the population is always constant and closed meaning that there are no births and deaths.

The SI model constructed on the basis of the foregoing assumptions is a coupled system of two ordinary differential equations. The rate of change of the susceptible population with respect to time would be decreasing and that of the infective would be increasing at a rate proportional to the contagion parameter or precisely, the infectious contact rate. The implication of this is that, if a susceptible population is exposed to an infectious disease with some proportion of the population being infected then the disease would spread exponentially to engulf the

entire population. The SI epidemic model does not describe an epidemic realistically since an infective may die or recover and if in some diseases there is no immunity, then the recovered becomes susceptible again. The SIS model describes a disease scenario where infected people have the tendency of recovering from the disease without gaining immunity. Thus, infected people become susceptible again immediately after recovery. It might be appropriate for some sexually transmitted diseases like gonorrhoea because after recovery, the host is once again susceptible to infection [17]. The SIR model describes an infectious disease in which some infected people recover from the disease and after acquiring immunity cannot be susceptible again. This model unlike the SI and SIS models may have some practical implications. For instance it may be suitable for the transmission of a flu epidemic since once a person has had a particular strain of flu, his immune system prevents him from being reinfected with that strain. The classical SIR model is of the form

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

where β is the contagion parameter and α, the recovery rate assumed to be proportional to the number of infected people. The system is nonlinear and cannot be solved explicitly, although implicit solutions can be found. In addition to determining equilibrium and stability of the model, we can obtain by analytical means the final state of the epidemic. We note that this form of the SIR model does not involve demography but inclusion of some host demographic factors like birth and death may alter its dynamics by permitting the disease to persist in the population in a long term. Despite its limitations as entrenched in the assumptions characterising the SIR model, it is the basis for more involved deterministic models in epidemiology. The SEIR model is an improvement on the SIR in most disease case

where incubation is relevant. It involves recovery and immunity without the possibility of contacting the disease again but differ slightly from the SIR model in that the later, once being infected, passes through an incubation period E before showing disease symptoms. The SEIRS models describe the dynamics of endemic diseases where individuals who contact the disease progress through a period of incubation before showing disease symptoms and becoming infectious and after recovery from the disease may gain partial immunity and later become susceptible after loss of immunity. Although, early transmission models in malaria epidemiology seem to have taken the shape of the SIR model, the SEIRS model appears to portray a better representation of the dynamics involved. Malaria transmission is a cyclic relationship between an infectious human population and a susceptible mosquito population on one hand and an infectious mosquito population and a susceptible human population in the other hand. Various mathematical models have been constructed to help understand the dynamics of malaria. We present a review of some of these models in the next section that are closely related to the work in this thesis.

2.2. A survey of mathematical models in malaria epidemiology

2.2.1. Transmission models

Sir Ronald Ross was the first to construct a mathematical model for malaria [96]. He used two equations, one representing the rate of change of infected humans with time and the other that of infected mosquitoes. One important outcome of the analysis of his model is that of threshold density of the *Anopheles* mosquito, which according to him, "to counter malaria anywhere we need not banish *Anopheles* there entirely but we need only to reduce their number below a certain figure". Based on this, Kermack and McKendrick published a classic paper in 1927 that discovered a threshold condition for the spread of a disease and gave a means of predicting the ultimate size of an epidemic [17]. In 1957, MacDonald made

further extensions on the work on the malaria model of Ross [65].

In a systematic historical review of mathematical models in epidemiology, Smith et al. [103] avers that several mathematicians and scientists contributed to the Ross-Macdonald model for a period of 70 years. The model plays a crucial role in the development of malaria transmission model and was first written by Aron and May in 1982 as

$$\frac{dx}{dt} = mabz(1-x) - rx, \tag{2.2.1}$$

$$\frac{dz}{dt} = ax(1-z) - gz, \tag{2.2.2}$$

where x and z are fractions of infectious humans and adult females mosquitoes respectively. The parameter a represents the number of bites a single female mosquito gives to humans and b is the probability that a single bite transmits infection to the human. The average number of female mosquitoes is represented by m. The mortality rates of humans and adult female mosquitoes are gz and rx respectively. This model has been extensively discussed in Chitnis [21]. Its assumptions are based on a simplified process-based description of the pathogen life cycle [103], as represented by the biology in section 1.2. These are described by the following four events.

- Mosquito transmits pathogen to susceptible human during blood feeding.

- Pathogen infects human and multiplies to a high density.

- Susceptible mosquito ingests pathogen during blood feeding.

- Pathogen develops in the mosquito and migrates to the salivary gland ready to be injected into a susceptible human.

Further work done on the Ross-Macdonald model by Bailey in 1982, led to the general theory that describes malaria transmission in form of the classical $SIR\text{-}SI$ model and since then

considerable modifications have been made in the quest for a model that will better describe the mosquito-human interaction process and pathogen transmission.

A more sophisticated model that incorporates acquired immunity in malaria was constructed by Dietz et al. [30], which gave a more realistic description of malaria epidemiology at the Garki area in Nigeria, given entomological input and provided conditional inputs and comparative forecasts for several specific intervention.

Many malaria models involving immunity have been reviewed in [20, 22, 81]. The models proposed by Anderson and May [5] and Aron and May [9] use the assumption that acquired immunity does not depend on duration of exposure. While the models of Aron [7, 8] and Bailey [12] are based on the assumption that immunity is boosted by additional infections. A more comprehensive mathematical model typical of a characteristic endemic malaria is the one proposed by Ngwa and Shu [82]. A malaria model with periodic mosquito birth and death rates was proposed in [29]. The paper considers a novel situation where the birth and death rates of mosquitoes and human death rate are periodic. Although the model does not include incubating classes of both human and mosquitoes but they established a basic reproduction number such that the disease will only prevail if this number was greater than unity, otherwise the disease will die out. Another model involving the effects of seasonality and immigrations of infected humans was proposed in [76]. The results show that the strength of seasonality increases the number of infections and it is not possible to achieve a disease free equilibrium in the presence of infective immigrants, signifying that the disease cannot be completely eradicated if there is constant inflow of infected immigrants. Most prominent in the models discussed so far is the concept of the basic reproduction number. The basic reproduction number of an infectious disease is a very important concept in epidemiology. This important quantity provides the key to transmission dynamics, indicating the ease by

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which major epidemics may be prevented and prospects for the eradication of an infection [95]. The symbol R_0 is often used to represent it. If a single infectious case is introduced in a population of susceptibles and assuming the population evolves in a continuum sense, it is expected to generate a chain of subsequent infections for the disease to fully register itself (endemic) or die out eventually. The expected number of secondary cases that would arise from the introduction of a single primary case into a fully susceptible population is referred to as the basic reproduction number of the disease. R_0 is a threshold parameter which determines whether or not an infectious disease will be endemic, such that

- if $R_0 < 1$ each successive infection generation is smaller than its predecessor, and the infection cannot persist

- if $R_0 > 1$ successive infection generations are larger than their predecessors, and the number of cases in the population will initially increase, not necessarily indefinitely, but the disease remains endemic.

The method of analytical solutions to these models have always been that of defining a domain where the model is mathematically and epidemiologically well-posed, proving the existence and stability of a disease-free equilibrium point, defining the basic reproduction number and describing the existence and stability of the endemic equilibrium points.

2.2.2. Summary from the survey

We have presented a review of some of the known models found to be relevant to our work. To the best of our knowledge, none of the transition models considers the assumption that immune humans being bitten by infectious mosquitoes may be constantly incubating and there is the possibility of some immune humans falling sick immediately after loss of immunity. We incorporate into our model some of the features found in the $SEIRS$ model of Ngwa and

Shu [82]. In the next chapter we will present and analyse the proposed model of malaria transmission.

CHAPTER 3

TRANSMISSION MODEL

In this chapter we derive and study an epidemiological model of malaria. This model extends that of Ngwa and Shu [82] to take into account the various phases of the disease in humans and mosquitoes. The partially immune humans (termed asymptomatic) have recovered from the worst of the symptoms, but can still transmit the disease. A new feature, in what turns out to be a key class, is the consideration of re-infected asymptomatic humans leading to an additional incubating class. We first derive the model, then we undertake stability analysis to establish a basic reproduction number and finally employ a time scale analysis to gain insight into how an epidemic evolves from a small outbreak from a disease free population. The modelling is relevant for a 0.5 year timescale in which the population is not expected to change too much in the absence of malaria. The modelling also takes into account a routine treatment administered to symptomatic individuals. In addition, we consider a putative treatment for post symptomatic humans, to limit the capacity for asymptomatic human carriers of the disease.

3.1. Derivation of the model

A population of humans in a region is susceptible to malaria infection if the environmental conditions in that region favour the breeding of the anopheles mosquitos. We recall from Section 1.2, that once an infectious female anopheles mosquito injects malaria parasites into a human at the site of bite, these parasites undergo some developmental stages within the host. These stages partition the host into a waiting state to disease manifestation, or disease state or non-disease state in the presence of parasites. In order to set the necessary framework for the proposed model, we divide the human population into compartments of susceptible, latent, latent asymptomatic, symptomatic and asymptomatic carriers, and that of mosquitoes into susceptible, latent and infectious compartments. State variables in the model are given in Table 3.1 and the movement between compartments is summarised in Figure 3.1, the individual pathways to be discussed below.

State variable	Description
N	Total human population
C	Susceptible human population
L	Incubating human population
L_A	Number of latent asymptomatic infectious humans
S	Number of symptomatic infectious humans
A	Number of asymptomatic infectious humans
M	Total mosquito (female anopheles) population
X	Number of susceptible mosquitoes
Y	Number of incubating (latent) mosquitoes
Z	Number of infectious mosquitoes

Table 3.1: The state variables in the model   .

The total population of humans and (female) mosquitoes are simply the sum of their

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respective state variables, i.e.

$$N = C + L + L_A + S + A,$$

$$M = X + Y + Z.$$

We use C to represent the set of susceptible humans who initially do not have malaria parasites but have natural nonspecific immunity, whilst L represents the collection of humans who have received infectious bites and are within the liver and early erythrocyte stage infection (humans will remain in this state, untreated, for about 15 days). The S class involves those in the erythrocyte stage that have developed both disease symptoms and gametocytes. Unlike those in the L class, symptomatic infectious humans require treatment as those in the L class do not know they are infected. Individuals reach a partially immune or asymptomatic status A when they no longer have symptoms of the disease that would warrant clinical attention but are still infectious to mosquitoes, which may be caused by improper treatment or reinfection (individuals in this class can remain so for a mean time of around 165 days, provided they
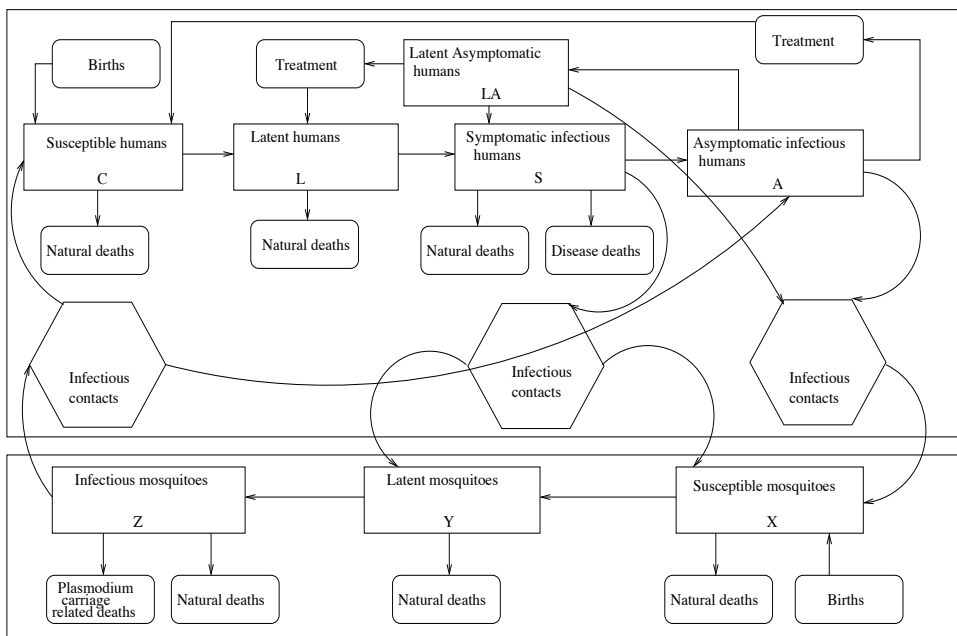
Figure 3.1: Schematic representation of mosquito human interraction model. The rectangle indicates the state variables, the ovals are actions within humans and mosquitoes and the hexagon indicates action between species.

are not infected again). We use L_A for individuals in the A class being bitten by infectious mosquitoes. Since they carry both gametocytes and asexual parasites, loss of immunity may cause their immediate transition into the S class instead of the C class. A mosquito is said to be in the Y class as soon as it ingests gametocytes from an infectious human until the time (about 12 days) before sporozoites migrate to the salivary gland when the mosquito becomes infectious and proceed to the Z class. The L_A, S and A classes are infectious to X while the Z class infects C and A.

What is most fascinating about an infectious disease model is its suitability for disease control, or ideally the eradication of infection. The practical use of such models must rely heavily on the realism put into the model. As usual, this does not mean inclusion of all possible effects, but rather the incorporation in the model mechanisms, in as simple a way as possible, that appear to be the major components [77]. The model explains the dynamics of both human and mosquito populations as they progress from susceptible noninfectious states to infectious states. Malaria is transmitted when a susceptible human is bitten by an infected Anopheline mosquito. The rate at which a susceptible person becomes infected is a function of contact rate with infective mosquitoes and level of host susceptibility [90]. We assume that mosquito biting vectors are equally susceptible and human infectiousness to mosquitoes is determined solely by the gametocyte density or the density of infection in the human host [55].

Susceptible humans get infected at rate $\beta_h e Z \frac{C}{N}$ where eZ is the rate at which infected mosquitoes bite (constant e being the biting rate per human per unit time), $\frac{C}{N}$ is the probability that the human bitten is susceptible and β_h is the number of human infections per bite. Likewise the rate of reinfection of an asymptomatic individual is $\beta_h e Z \frac{A}{N}$. The rate at which uninfected mosquitoes obtain the plasmodium parasite from human carriers is

$e\left(\beta_s S + \beta_a A + \beta_a L_A\right)\dfrac{X}{N}$, noting that humans in class L are in the incubating stage of infection and are not infectious to mosquitoes. Susceptible mosquitoes are recruited into the mosquito population through a constant birth rate λ_m. Assuming that each mosquito has the same biting behaviour, there will be a total of eM bites by mosquitoes on humans. But only $\dfrac{C}{N}$ of these bites will be made on susceptible humans. The probability that a bite is made by an infectious mosquito is $\dfrac{Z}{M}$. It is important to note here that the parameter β_h assumes that not all bites by an infectious mosquito on a susceptible human can lead to infection. The parameter $\beta_h \in [0,1]$ is the proportion of bites by an infectious mosquito that passes on the infection, where $\beta_h = 1$ means all bites transmits the disease. However, $\beta_h = 0.086$ in data, so there is only a 10% chance of an infected mosquito to pass on its infection. The cross infection rate $\beta_h e \dfrac{Z}{N}$ between the human and mosquito populations depends on the average number of mosquito bites per unit time and the transmission probability normalised by the human population [15, 120]. We also assume that the recruitment of humans into the susceptible population occurs at a constant per capita birth rate λ_h and apart from asymptomatic individuals no human in the latent and symptomatic infectious classes would be affected by a bite from an infectious mosquito. This assumption becomes necessary since we are primarily concerned about how infectious bites from mosquitoes can lead to the disease. Those in the L class are already in the process of transition into the S class who are entitled to treatment. Incubating humans become infectious after a mean latency time $\dfrac{1}{\eta_h}$.

All human classes "die naturally" at per capita rate μ_h while some individuals in the S class die at an additional rate $\alpha_h S$ from the disease. The survivors receive treatment and either recover with complete clearance of parasites to join the susceptible class at a rate $r_s S$ (individuals undergo a 14-day treatment), or only recover from symptoms (after a 3-day monotherapy) without parasite clearance to join the A class at a rate $r_a S$.

The post symptomatic class, A still carry merozoites and produce gametocytes, so can infect biting mosquitoes. A human can be in this state for several weeks or months and hence play an important part in sustaining an epidemic, noting that symptomatic individuals are in this state for 3-14 days [19, 34, 38]. It seems that if there exists some treatment to target post infected humans, then the pool of people who infect mosquitoes will be reduced. We then consider in our model a putative treatment which removes individuals from the A and L_A class down to C and L respectively. The effect of the treatment parameter, $\phi\theta_h$ (ϕ are being treated) in R_0 will be an important part of the analysis.

Susceptible mosquitoes get infected through infectious contacts with infectious humans at a rate $e\left(\beta_s S + \beta_a A + \beta_a L_A\right)\frac{X}{N}$ and proceed to the incubating compartment. Although there are some conflicting findings on whether or not the plasmodium parasite reduces the life span of infectious mosquitoes, direct laboratory results of [40, 52, 58, 59] suggest that the malaria parasite reduces mosquito survival. Since mosquitoes do not recover from infection it follows that the infectiousness of mosquitoes end in their death [15, 82]. We assume that mosquitoes in the incubating class die naturally at a rate $\mu_m Y$ and the rest get infectious at a rate $\eta_m Y$ to join the infectious compartment which they remain until their death either naturally, or through the carriage of infectious parasites in their body [76] at a rate $\alpha_m Z$.

Using the above assumptions, then the system of equations for the human classes are

$$\frac{dC}{dt} = \lambda_h N + r_s S + l_a A - \beta_h e\frac{Z}{N}C - \mu_h C + \phi\theta_h A, \qquad (3.1.1)$$

$$\frac{dL}{dt} = \beta_h e\frac{Z}{N}C - \eta_h L - \mu_h L + \phi\theta_h L_A, \qquad (3.1.2)$$

$$\frac{dL_A}{dt} = \beta_h e\frac{Z}{N}A - \eta_h L_A - \mu_h L_A - \phi\theta_h L_A, \qquad (3.1.3)$$

$$\frac{dS}{dt} = \eta_h L + \eta_h L_A - \alpha_h S - r_s S - r_a S - \mu_h S, \qquad (3.1.4)$$

$$\frac{dA}{dt} = r_a S - \beta_h e\frac{Z}{N}A - l_a A - \mu_h A - \phi\theta_h A, \qquad (3.1.5)$$

and for the mosquito classes are

$$\frac{dX}{dt} = \lambda_m M - \beta_s e \frac{S}{N} X - \beta_a e \frac{A}{N} X - \beta_a e \frac{L_A}{N} X - \mu_m X, \tag{3.1.6}$$

$$\frac{dY}{dt} = \beta_s e \frac{S}{N} X + \beta_a e \frac{A}{N} X + \beta_a e \frac{L_A}{N} X - \eta_m Y - \mu_m Y, \tag{3.1.7}$$

$$\frac{dZ}{dt} = \eta_m Y - \alpha_m Z - \mu_m Z, \tag{3.1.8}$$

and the total populations are

$$\frac{dN}{dt} = \lambda_h N - \alpha_h S - \mu_h N, \tag{3.1.9}$$

$$\frac{dM}{dt} = \lambda_m M - \alpha_m Z - \mu_m M, \tag{3.1.10}$$

where $(3.1.9)$ is derived from adding $(3.1.1)-(3.1.5)$ and $(3.1.10)$ is the sum of $(3.1.6)-(3.1.8)$. To close this system we need a set of initial conditions for each of the state variables. A suitable set depends on the context of the study. In section 3.7 we will consider the evolution of the disease in a disease free human population with a small number of infected mosquitoes. Nevertheless, we impose

$$t = 0, \quad N = N_0, \quad M = M_0$$

as initial population values for humans and mosquitoes.

3.2. Parameter values

All the model parameters are listed in Table 3.2 together with values taken from various sources. We note that these parameters are from *P. falciparum* malaria, the most deadly parasite, predominant in Sub-saharan Africa. Some of the data are experimentally measured and some are values assumed in models. However, we have made some assumptions on parameters that do not seem to have well defined values. In [21, 82] for instance, β_a was considered to be of lower value than β_s as they arbitrarily assume in their model that the probability of transmission of infection from recovered or partially immune humans to susceptible mosquitoes is

Symbol	Description	Value		Unit	Source
λ_h	Per capita human birth rate	0.000104	●	day^{-1}	[92]
e	Average number of bites each mosquito gives to humans per unit time	0.44	●	day^{-1}	[73]
l_a	Rate of immunity loss by asymptomatic infectious humans	0.006061	●	day^{-1}	[1]
e	Average number of bites each mosquito gives to humans per unit time	0.44	●	day^{-1}	[73]
β_h	The probability that a bite by an infectious mosquito infects a susceptible human	0.086	*	dimensionless	[80]
μ_h	Per capita human death rate	0.0000356	●	day^{-1}	[92]
η_h	Transition rate of incubating humans into symptomatic infectious class per unit time	0.0670.13	*	day^{-1}	[37, 66]
α_h	Per capita death rate of humans due to disease influence	0.0006061		day^{-1}	assumed
r_s	Drug recovery rate of symptomatic infectious humans per unit time	0.07	●	day^{-1}	[38]
r_a	Transition rate of symptomatic infectious humans to asymptomatic infectious class per unit time	0.33	●	day^{-1}	calculated by using data from [19, 34] and [16]
λ_m	Per capita mosquito birth rate	0.13	*	day^{-1}	[21]
μ_m	Per capita mosquito death rate	0.125	●	day^{-1}	[43]
η_m	Transition rate of incubating mosquitoes into the infectious class per unit time	0.0830.13	*	day^{-1}	[5]
β_s	The probability that a susceptible mosquito gets infected after biting a symptomatic infectious human	0.1	●	dimensionless	[44]
β_a	The probability that a bite by a susceptible mosquito on an asymptomatic infectious human transfers the infection to the mosquito	0.53	●	dimensionless	[44]
α_m	Per capita death rate of mosquitoes due to gametocyte carriage per unit time	0.03152		day^{-1}	assumed
θ_h	Recovery rate of asymptomatic infectious humans due to treatment per unit time			day^{-1}	
ϕ	Fraction of post malaria treatment			dimensionless	

Table 3.2: Model parameters and their dimensions. Values marked with asterisk (∗) are assumed values in other mathematical models and those marked with bullet (•) are obtained from experimental sources.

one tenth the probability of transmission from infectious humans to susceptible mosquitoes. But in this model we obtain the values of β_a and β_s based on the experimental findings of [44] which reveals that asymptomatic humans are rather far more infectious than those in the disease class. Although the mechanism of immunity to malaria is not well understood, Ngwa and Shu [82] avers that a smaller proportion of humans recover from malaria without gaining immunity.

3.3. Nondimensionalisation

Since the variables N and M are the sum of the relevant compartment values, it is convenient to re-express the compartment values as population fractions using

$$\hat{C} = \frac{C}{N}, \quad \hat{L} = \frac{L}{N}, \quad \hat{L}_A = \frac{L_A}{N}, \quad \hat{S} = \frac{S}{N}, \quad \hat{A} = \frac{A}{N}, \quad \hat{X} = \frac{X}{M}, \quad \hat{Y} = \frac{Y}{M}, \quad \hat{Z} = \frac{Z}{M},$$

so that

$$\hat{C} + \hat{L} + \hat{L}_A + \hat{S} + \hat{A} \;=\; 1, \tag{3.3.1}$$

$$\hat{X} + \hat{Y} + \hat{Z} \;=\; 1. \tag{3.3.2}$$

The time derivatives for the variables will become, using variable C as an example

$$\frac{dN\hat{C}}{dt} = N\frac{d\hat{C}}{dt} + \hat{C}\frac{dN}{dt} = N\frac{d\hat{C}}{dt} + (\lambda_h - \alpha_h\hat{S} - \mu_h)N\hat{C},$$

There are a number of time scales in the system, mosquito life cycle (weeks), incubation and symptom (weeks), population turnover (tens of years), asymptomatic clearance (~ 6 months), and the most suitable choice for the scaling depends on the context. We are focusing on an endemic area and year time scale, in which the total population change is negligible in the absence of the disease, hence we scale time with the asymptomatic susceptible transmission parameter l_a, and write

$$t = \frac{\hat{t}}{\hat{l}_a}$$

so that $\hat{t} = 1$ is about 165 days. Recalling that M_0 and N_0 are the initial populations of humans and mosquitoes respectively, we write

$$N = N_0 \hat{N}, M = M_0 \hat{M}$$

and define the following dimensionless parameters:

$$\beta = \frac{\beta_h e M_0}{l_a N_0}, \ b = \frac{\beta_s e}{l_a}, \ d = \frac{\beta_a e}{l_a}, \ \eta = \frac{\eta_h}{l_a}, \ \mu = \frac{\mu_h}{l_a}, \ \lambda = \frac{\lambda_h}{l_a}, \ \alpha = \frac{\alpha_h}{l_a},$$

$$\gamma = \frac{r_s}{l_a}, \ \rho = \frac{r_a}{l_a}, \ \theta = \frac{\phi \theta_h}{l_a}, \ f = \frac{\eta_m}{l_a}, \ q = \frac{\lambda_m}{l_a}, \ g = \frac{\mu_m}{l_a}, \ h = \frac{\alpha_m}{l_a},$$

and by substituting these new parameters into $(3.1.1)-(3.1.10)$ and dropping the hats for clarity we get

$$\frac{dC}{dt} = \lambda + \gamma S + A - \beta Z C \frac{M}{N} - \lambda C + \alpha C S + \theta A, \qquad (3.3.3)$$

$$\frac{dL}{dt} = \beta Z C \frac{M}{N} - \eta L - \lambda L + \alpha L S + \theta L_A, \qquad (3.3.4)$$

$$\frac{dL_A}{dt} = \beta Z A \frac{M}{N} - \eta L_A - \lambda L_A + \alpha L_A S - \theta L_A, \qquad (3.3.5)$$

$$\frac{dS}{dt} = \eta L + \eta L_A - (\alpha + \gamma + \rho + \lambda) S + \alpha S^2, \qquad (3.3.6)$$

$$\frac{dA}{dt} = \rho S - A - \beta Z A \frac{M}{N} - \lambda A + \alpha A S - \theta A, \qquad (3.3.7)$$

$$\frac{dX}{dt} = q(1 - X) - bSX - dAX - dL_A X + hXZ, \qquad (3.3.8)$$

$$\frac{dY}{dt} = bSX + dAX + dL_A X - (f + q) Y + hYZ, \qquad (3.3.9)$$

$$\frac{dZ}{dt} = fY - (h + q) Z + hZ^2, \qquad (3.3.10)$$

$$\frac{dN}{dt} = -\alpha SN + (\lambda - \mu) N, \qquad (3.3.11)$$

$$\frac{dM}{dt} = -hZM + (q - g) M. \qquad (3.3.12)$$

In solving the problem we can use (3.3.1) and (3.3.2) to reduce the number of ODEs. We solve the system together with (3.3.1) and (3.3.2).

Dimensional form	Nondimensional parameter	Value	Value in terms of ϵ
$\frac{\beta_h e M_0}{l_a N_0}$	β	62.43	$O(\frac{1}{\epsilon^2})$
$\frac{\eta_h}{l_a}$	η	11.1	$\frac{1}{\epsilon}$
$\frac{\mu_h}{l_a}$	μ	0.0056	$O(\epsilon^2)$
$\frac{\lambda_h}{l_a}$	λ	0.017	$O(\epsilon^2)$
$\frac{\alpha_h}{l_a}$	α	0.01	$O(\epsilon^2)$
$\frac{r_s}{l_a}$	γ	11.5	$O(\frac{1}{\epsilon})$
$\frac{r_a}{l_a}$	ρ	54.45	$O(\frac{1}{\epsilon^2})$
$\frac{\beta_s e}{l_a}$	b	7.2	$O(\frac{1}{\epsilon})$
$\frac{\beta_a e}{l_a}$	d	38.2	$O(\frac{1}{\epsilon})$
$\frac{\eta_m}{l_a}$	f	14	$O(\frac{1}{\epsilon})$
$\frac{\lambda_m}{l_a}$	q	21.45	$O(\frac{1}{\epsilon})$
$\frac{\mu_m}{l_a}$	g	20.62	$O(\frac{1}{\epsilon})$
$\frac{\alpha_m}{l_a}$	h	1.45	$O(1)$
$\frac{\phi\theta_h}{l_a}$	θ		

Table 3.3: List of dimensionless parameters and their definitions in terms of the original parameters, the dimensional values. In the final column we express the size of the parameter in terms of the small parameter $\epsilon = \eta^{-1} \approx 0.09$, this being relevant for section 3.7.

The dimensionless parameter values are shown in Table 3.3 and the parameters in relation to the small parameter ϵ $(= \eta^{-1})$ are also included. We note from the rescalings that the population of humans, N_0, and mosquitoes, M_0, need not be presented but only $\frac{M_0}{N_0}$. We do not have data for malaria vectors/human populations, but we assume that the initial female mosquito population M_0 is ten times that of humans N_0 due to the claim that in an endemic area of dengue fever the ratio of female *Aedes aegypti* (the main vector of the virus) population to human population is 10 : 1 [10]. Though the main vector in our case is the female Anopheles mosquito, we expect that in an endemic malaria region, the distribution of female *An. gambiae* mosquito will be well compared with that of *Aedes aegypti*. But the rescalings are such that $\frac{M_0}{N_0}$ only affects the parameter β. By definition, ϵ is the ratio of η_h and l_a (i.e. the proportion of time for the latency period compared to the mean asymptomatic state

timescale) and $\epsilon \ll 1$, means that asymptomatic humans remain infectious for a longer time compared to the latency period of humans. Analysing the model using ϵ as a small parameter provides a convenient basis for the application of asymptotic methods in understanding the effect of partial immunity on the spread of malaria.

3.4. Establishing the basic reproduction number of the transition model

The application of approaches like the traditional or intuitive method used in [5, 82] or the next generation matrix method used in [21, 20] may be used in the determination of the basic reproduction number, R_0. Here we use the next generation operator approach, which approximates the number of secondary infections due to one infected individual and express R_0 in the traditional form as suggested by van den Driessche and Watmough [31]. As usual we consider a small perturbation of the disease free state ($C = 1, X = 1, L = L_A = S = A = X = Y = Z = 0$) and assume that growth and decay is much faster than population change, i.e. $M = N = 1$, we consider the linearised system expressed in the form

$$R' = FR - VR, \tag{3.4.1}$$

where, $R' = \dfrac{dR}{dt}$ and

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & \beta \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & d & b & d & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} a_1 & -\theta & 0 & 0 & 0 & 0 \\ 0 & a_0 & 0 & 0 & 0 & 0 \\ -\eta & -\eta & a_2 & 0 & 0 & 0 \\ 0 & 0 & -\rho & a_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & a_4 & 0 \\ 0 & 0 & 0 & 0 & -f & a_5 \end{bmatrix}, \quad R = \begin{bmatrix} L \\ L_A \\ S \\ A \\ Y \\ Z \end{bmatrix};$$

here, FR represents the emergence of new infections, VR the transition of these infections between compartments and R the "reservoir of infection". The constants $a_i's$ are expressed in terms of the model parameters as follows:

$$a_1 = \eta + \lambda, \quad a_0 = \eta + \lambda + \theta, \quad a_2 = \alpha + \gamma + \rho + \lambda, \tag{3.4.2}$$

$$a_3 = 1 + \lambda + \theta, \quad a_4 = f + q, \quad a_5 = h + q.$$

This method assumes that there is a non-negative matrix $G = FV^{-1}$ that guarantees a unique, positive and real eigenvalue strictly greater than all others. Computing the inverse of V yields

$$G = \frac{1}{b_0} \begin{bmatrix} 0 & 0 & 0 & 0 & \beta b_{11} & \beta b_{12} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ f_1 & f_2 & f_3 & f_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \tag{3.4.3}$$

where,

$$b_0 = a_0 a_1 a_2 a_3 a_4 a_5, \ b_{11} = f a_0 a_1 a_2 a_3, \ b_{12} = a_0 a_1 a_2 a_3 a_4, \ f_1 = b b_2 + d b_3, f_2 = d b_4 + b b_5 + d b_6,$$

$$f_3 = b b_7 + d b_8, \ f_4 = d b_9, b_2 = \eta a_0 a_3 a_4 a_5, \ b_3 = \eta \rho a_0 a_4 a_5, \ b_4 = a_1 a_2 a_3 a_4 a_5, b_5 = \eta a_1 a_3 a_4 a_5,$$

$$b_6 = \eta \rho a_1 a_4 a_5, \ b_7 = a_0 a_1 a_3 a_4 a_5, \ b_8 = \rho a_0 a_1 a_4 a_5, \ b_9 = a_0 a_1 a_2 a_4 a_5.$$

The characteristic equation of (3.4.3) in terms of the eigenvalue, σ, shows that four of the eigenvalues vanish leaving the expression

$$\sigma^2 = \frac{\beta \left(b b_2 + d b_3 \right) b_{11}}{b_0^2}, \tag{3.4.4}$$

which expressed in terms of the model parameters gives

$$\sigma^2 = \frac{\beta \eta f \left(b \left(1 + \lambda + \theta \right) + \rho d \right)}{\left(\eta + \lambda \right) \left(\alpha + \gamma + \rho + \lambda \right) \left(1 + \lambda + \theta \right) \left(f + q \right) \left(h + q \right)}. \tag{3.4.5}$$

Although the next generation matrix demands that $R_0 = \sigma$ is the basic reproduction number, in practice σ^2 is often taken as R_0 (indeed this was the assumption used in the original work applying this method). We note from the numerator of (3.4) that the basic reproduction number is proportional to the square of mosquito biting rate (e^2) as expected.

3.5. Steady state solution and model analysis

Consider the domain

$$\Gamma \in \mathbb{R}^{10} = \{C, L, L_A, S, A, X, Y, Z, N, M : C \geq 0, L \geq 0, L_A \geq 0, S \geq 0, A \geq 0,$$

$$X \geq 0, Y \geq 0, Z \geq 0, N > 0, M \geq 0, C + L + L_A + S + A = 1, X + Y + Z = 1\}, \quad (3.5.1)$$

and suppose at $t = 0$ all variables are non-negative, then $C(0) + L(0) + L_A(0) + S(0) + A(0) = 1$ and $X(0) + Y(0) + Z(0) = 1$. If $C = 0$, and all other variables are in Γ, then $\frac{dC}{dt} \geq 0$. This is also the case for all other variables in $(3.3.3)-(3.3.10)$. If $N = 0$, then $\frac{dN}{dt} = 0$ and $M = 0$ implies $\frac{dM}{dt} = 0$. But if $N > 0$ and $M > 0$, assuming $\lambda > \mu$ and $q > g$ i.e. $\lambda_h > \mu_h$ and $\lambda_m > \mu_m$, then with appropriate initial conditions, $\frac{dN}{dt} > 0$ and $\frac{dM}{dt} > 0$ for all values of $t > 0$. We note that the right-hand side of $(3.3.3)-(3.3.12)$ is continuous with continuous partial derivatives, so solutions exist and are unique. The model is therefore mathematically and epidemiologically well posed with solutions in Γ for all $t \in [0, \infty)$. The disease free state $(C, L, L_A, S, A, X, Y, Z) = (1, 0, 0, 0, 0, 1, 0, 0)$ is locally and globally asymptotically stable when $R_0 < 1$ and unstable for $R_0 > 1$, where

$$R_0 = \frac{\beta \eta f \{b(1 + \lambda + \theta) + \rho d\}}{(\eta + \lambda)(\alpha + \gamma + \rho + \lambda)(1 + \lambda + \theta)(f + q)(h + q)}, \quad (3.5.2)$$

is the expected number of secondary infection cases that would arise from the introduction of a single primary case into a fully susceptible population. We note that $R_0 = 1$ is a bifurcation surface in which the system changes its stability status, but we will only show proof of stability for the disease free state. Since $R_0 \gg 1$ using Table 3.3 and the infectiousness of asymptomatic humans to mosquitoes is significantly large, a good target for treatment is to reduce the infectivity of asymptomatic humans (reduce d) and that of symptomatic humans (reduce b) by increasing the treatment parameters θ and γ. An important task is to determine an amount of treatment that can bring R_0 to a safe level. For instance, for R_0 to be brought

down to unity, we will expect, θ to be

$$\theta_c = \frac{(\eta + \lambda)(\alpha + \gamma + \rho + \lambda)(f + q)(h + q)(1 + \lambda) - \beta \eta f \{b(1 + \lambda) + \rho d\}}{\beta \eta f b - (\eta + \lambda)(\alpha + \gamma + \rho + \lambda)(f + q)(h + q)}, \tag{3.5.3}$$

in terms of the parameters.

3.6. Stability analysis of the transition model

Here we derive sufficient conditions for global stability of the disease free state from all initial conditions $\in \Gamma$. The Jacobian matrix obtained by linearising system $(3.3.3) - (3.3.10)$ about the disease free equilibrium point, $(C, L, L_A, S, A, X, Y, Z) = (1, 0, 0, 0, 0, 1, 0, 0)$ is

$$J_{df} = \begin{bmatrix} -\lambda & 0 & 0 & a_6 & 1+\theta & 0 & 0 & -\beta \\ 0 & -a_1 & \theta & 0 & 0 & 0 & 0 & \beta \\ 0 & 0 & -a_0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \eta & \eta & -a_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \rho & -a_3 & 0 & 0 & 0 \\ 0 & 0 & -d & -b & -d & -q & 0 & h \\ 0 & 0 & d & b & d & 0 & -a_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & f & -a_5 \end{bmatrix} \tag{3.6.1}$$

with the $a_i's$ as defined above and $a_6 = \alpha + \gamma$. Its characteristic polynomial equation with eigenvalues (κ) is

$$(\kappa + \lambda)(\kappa + a_0)(\kappa + q)(\kappa^5 + H_1 \kappa^4 + H_2 \kappa^3 + H_3 \kappa^2 + H_4 \kappa + H_5) = 0, \tag{3.6.2}$$

where

$$H_1 = a_1 + a_2 + a_3 + a_4 + a_5$$

$$H_2 = a_2 a_5 + a_3 a_4 + a_4 a_5 + a_1 a_2 + a_1 a_3 + a_1 a_4 + a_3 a_5 + a_2 a_3 + a_2 a_4 + a_1 a_5,$$

$$H_3 = a_1 a_2 a_3 + a_1 a_2 a_4 + a_2 a_3 a_4 + a_2 a_3 a_5 + a_2 a_4 a_5 + a_3 a_4 a_5 + a_1 a_4 a_5 + a_1 a_2 a_5 + a_1 a_3 a_4 + a_1 a_3 a_5,$$

$$H_4 = a_1 a_2 a_4 a_5 + a_1 a_3 a_4 a_5 + a_2 a_3 a_4 a_5 + a_1 a_2 a_3 a_4 + a_1 a_2 a_3 a_5 - \beta \eta f b,$$

$$H_5 = a_1 a_2 a_3 a_4 a_5 - \beta \eta f (b a_3 + \rho d).$$

We note the linear factorisation $=$ (3.6.2) clearly yields negative real eigenvalues, however, from the quintic equation, no such deduction can immediately be made.

Lemma 3.6.1. *The disease-free equilibrium is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. From the definition of a_i in (3.4.2), R_0 is given by

$$R_0 = \frac{\beta \eta f (ba_3 + \rho d)}{a_1 a_2 a_3 a_4 a_5}.$$

If $R_0 < 1$, then

$$a_1 a_2 a_3 a_4 a_5 > \beta \eta f (ba_3 + \rho d).$$

The the coefficients of the quintic polynomial of (3.6.2) are all positive and non zero; so by the Descartes' rule of signs there are no positive real eigenvalues, this means there are 1, 3 or 5 negative real eigenvalues with the remaining being complex conjugate pairs. We need to show that Routh Hurwitz stability conditions for a fifth order polynomial as stated in [2] and given in this case by

$$H_1 H_2 H_3 > H_3^2 + H_1^2 H_4,$$

$$\left(H_1 H_4 - H_5 \right) \left(H_1 H_2 H_3 - H_3^2 - H_1^2 H_4 \right) > H_5 \left(H_1 H_2 - H_3 \right)^2 + H_1 H_5^2$$

are both satisfied. By letting $F = H_1 H_2 H_3 - H_3^2 - H_1^2 H_4$ we express the above conditions as $F > 0$ implies $Q > 0$ where,

$$Q = (H_1 H_4 - H_5) F - H_5 \left(H_1 H_2 - H_3 \right)^2 - H_1 H_5^2.$$

We need to express Q as a finite sum of positive terms involving the model parameters. Using Maple to undertake the tedious algebra, we are able to show that F and Q_1 are sums of positive terms and

$$Q = Q_1 + \left\{ (a_3^2 D_1 + a_1 D_2 + D_3 + D_4 + D_5 + D_6)(C_1 + E_2) + \right. \tag{3.6.3}$$

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$$a_1^2(D_7 + D_8) + a_1 D_9 + D_{10})\}(C_1 - E_2) + \{a_3^2 E_2 + C_2(b_4 + E_1)\}(b_4 - E_1) (3.6.4)$$

Expressions for the constants, $C_i's$, $D_i's$, $E_i's$ and b_4 are given in Appendix A.1. The Maple input file used in obtaining the results is not included in the Appendix due to its size but can be made available on request.

Since $b_4 > E_1$ and $C_1 > E_2$, it follows that $Q > 0$. Thus, the disease-free equilibrium is locally and asymptotically stable if $R_0 < 1$. The coefficients H_1, H_2, H_3 are positive and we observe that if $R_0 > 1$, $a_1 a_2 a_3 a_4 a_5 < \beta \eta f \rho d + \beta \eta f b a_3$ wherein H_5 is negative. Therefore the sequence of coefficients, 1, H_1, H_2, H_3, H_4, H_5 has only one sign change irrespective of the sign of H_4. By using Descartes' rule of sign there must exist at least one positive real eigenvalue, we conclude that the disease free state is unstable if $R_0 > 1$. $\qquad \square$

When $R_0 = 1$, $a_1 a_2 a_3 a_4 a_5 = \beta \eta f \rho d + \beta \eta f b a_3$ and 3.6.2 has one zero eigenvalue, which shows that $R_0 = 1$ is a bifurcation surface in $(\beta, \eta, f, \rho, d, b, \lambda, \theta, \gamma, \alpha, q, h)$ parameter space.

Lemma 3.6.2. *The disease-free equilibrium is globally asymptotically stable in Γ if*

$$\frac{\eta \beta}{\eta + \lambda} \leq (h + q), \quad \frac{fb}{f + q} \leq \gamma + \lambda \text{ and } \frac{fd}{f + q} \leq \frac{\lambda(\eta + \theta + \lambda)}{\eta + \lambda}.$$

Proof. Consider the function $\phi : \{(C, L_A, S, A, X, Y, Z) \in \Gamma : C, X > 0\} \to \mathbb{R}$, where

$$\phi = \frac{\eta}{\eta + \lambda}(1 - C) + \frac{\lambda}{\eta + \lambda}(L_A + S + A) + \frac{f}{f + q}(1 - X) + \frac{q}{f + q}Z. \qquad (3.6.5)$$

We note that $\phi \geq 0$ and is continuously differentiable on the interior of Γ. We shall show that the disease free equilibrium is a global minimum of ϕ on Γ if (3.6.7) holds. The derivative of ϕ computed along solutions of the system is

$$\begin{aligned}
\frac{d\phi}{dt} &= (\frac{\eta \beta}{\eta + \lambda} - q)Z + \{\frac{fb}{f + q} - (\gamma + \lambda)\}S + \{\frac{fd}{f + q} - (1 + \theta + \lambda)\}A \\
&\quad + \{\frac{fd}{f + q} - \frac{\lambda(\eta + \theta + \lambda)}{\eta + \lambda}\}L_A - \frac{\eta \beta}{\eta + \lambda}(L_A + S + A)ZS
\end{aligned}$$

$$-\alpha\left(C + \frac{\lambda}{\eta+\lambda}L\right) - \frac{1}{f+q}\left\{fbS + fd(A + L_A + qhZ)\right\}YS$$

$$-\frac{1}{f+q}(fbS + fdA + fdL_A + qhX)Z. \tag{3.6.6}$$

We can see clearly that $\dfrac{d\phi}{dt} \leq 0$ whenever

$$\frac{\eta\beta}{\eta+\lambda} \leq (h+q), \quad \frac{fb}{f+q} \leq \gamma+\lambda, \quad \frac{fd}{f+q} \leq \frac{\lambda(\eta+\theta+\lambda)}{\eta+\lambda}. \tag{3.6.7}$$

In fact, for $(L_A, S, A, Y, Z) = (0,0,0,0,0)$, $\dfrac{d\phi}{dt} \leq 0$ and (L_A, S, A, Y, Z) is the largest positively

invariance subset in the interior of Γ and by LaSalle's invariant principle [60], $(L_A, S, A, Y, Z) \to$

$(0,0,0,0,0)$ as $t \to \infty$, while $(C, X) \to (1, 1)$ on the boundary of Γ. Some calculations given

in Appendix A.2, using the inequalities in (3.6.7) show that the basic reproduction number

is less than unity. The disease free state is globally stable if (3.6.7) are true, noting (3.6.7)

$\Rightarrow R_0 < 1$. $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\square$

3.7. Time scale analysis

In this section we present the time scale analysis of the model. Asymptotic analysis on the

M and N equations show that M changes on the time scale $t = O(\epsilon)$, while N changes on

$t = O(\frac{1}{\epsilon^2})$. Thus we assume $\frac{M}{N}$ to be constant over the time scale of our analysis. By letting

$\theta = 0$, we present the time scale analysis of the dimensionless system

$$\epsilon^2 \frac{dC}{dt} = \epsilon^4\hat{\lambda} + \epsilon\hat{\gamma}S + \epsilon^2 A - \hat{\beta}ZC - \epsilon^4\hat{\lambda}C + \epsilon^4\hat{\alpha}CS, \tag{3.7.1}$$

$$\epsilon^2 \frac{dL}{dt} = \hat{\beta}ZC - \epsilon\hat{\eta}L - \epsilon^4\hat{\lambda}L + \epsilon^4\hat{\alpha}LS, \tag{3.7.2}$$

$$\epsilon^2 \frac{dL_A}{dt} = \hat{\beta}ZA - \epsilon\hat{\eta}L_A - \epsilon^4\hat{\lambda}L_A + \epsilon^4\hat{\alpha}L_A S, \tag{3.7.3}$$

$$\epsilon^2 \frac{dS}{dt} = \epsilon\hat{\eta}L + \epsilon\hat{\eta}L_A - \left(\hat{\rho} + \epsilon\hat{\gamma} + \epsilon^4\hat{\alpha} + \epsilon^4\hat{\lambda}\right)S + \epsilon^4\hat{\alpha}S^2, \tag{3.7.4}$$

$$\epsilon^2 \frac{dA}{dt} = \hat{\rho}S - \left(\epsilon^2 + \epsilon^4\hat{\lambda}\right)A - \hat{\beta}ZA + \epsilon^4\hat{\alpha}AS, \tag{3.7.5}$$

$$\epsilon \frac{dX}{dt} = \hat{q}(1 - X) - \hat{b}SX - \hat{d}AX - \hat{d}L_A X + \epsilon\hat{h}XZ, \tag{3.7.6}$$

$$\epsilon \frac{dY}{dt} = \hat{b}SX + \hat{d}AX + \hat{d}L_A X - \left(\hat{f} + \hat{q}\right)Y + \epsilon\hat{h}YZ, \tag{3.7.7}$$

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$$\epsilon \frac{dZ}{dt} = \hat{f}Y - \left(\epsilon\hat{h} + \hat{q}\right)Z + \epsilon\hat{h}Z^2, \tag{3.7.8}$$

subject to

$$C(0) = 1, \quad L(0) = 0, \quad L_A(0) = 0, \quad S(0) = 0, \quad A(0) = 0,$$

$$Y(0) = y_0, \quad X(0) = 1 - y_0, \quad Z(0) = 0.$$

The definitions of the parameters with hats are given as

$$\beta = \frac{1}{\epsilon^2}\hat{\beta}, \quad \eta = \frac{1}{\epsilon}\hat{\eta}, \quad \mu = \epsilon^2\hat{\mu}, \quad \lambda = \epsilon^2\hat{\lambda}, \quad \alpha = \epsilon^2\hat{\alpha}, \quad \gamma = \frac{1}{\epsilon}\hat{\gamma}, \quad \rho = \frac{1}{\epsilon^2}\hat{\rho}, \tag{3.7.9}$$

$$b = \frac{1}{\epsilon}\hat{b}, \quad d = \frac{1}{\epsilon}\hat{d}, \quad f = \frac{1}{\epsilon}\hat{f}, \quad g = \frac{1}{\epsilon}\hat{g}, \quad h = \hat{h}. \quad q = \frac{1}{\epsilon}\hat{q},$$

where we have assumed for simplicity all parameters to be equal (not proportional) to the powers of ϵ as indicated in Table 3.3. We will carry out the analysis in the limit, $\epsilon \to 0$, $y_0 \to 0$ and $y_0 \ll \epsilon$. We note $R_0 \sim \frac{1}{\epsilon}$ in this limit so endemic outbreak is guaranteed. The time scale analysis reveals the endemic equilibrium for the human population as

$$C \sim \epsilon^2 \frac{\hat{\gamma}\hat{\eta}\left(\hat{q} + \hat{d}\right)\left(\hat{q} + \hat{f}\right)}{\hat{\rho}\hat{\beta}\hat{f}\hat{d}},$$

$$L_A \sim 1,$$

$$S \sim \epsilon\frac{\hat{\eta}}{\hat{\rho}},$$

$$A \sim \epsilon\frac{\hat{\eta}\left(\hat{q} + \hat{d}\right)\left(\hat{q} + \hat{f}\right)}{\hat{\beta}\hat{f}\hat{d}},$$

$$L \sim \epsilon\frac{\hat{\gamma}}{\hat{\rho}},$$

and for mosquitoes

$$X \sim \frac{\hat{q}}{\hat{q} + \hat{d}},$$

$$Y \sim \frac{\hat{d}\hat{q}}{\left(\hat{q} + \hat{d}\right)\left(\hat{q} + \hat{f}\right)},$$

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$$Z \sim \frac{\hat{f}\hat{d}}{\left(\hat{q}+\hat{d}\right)\left(\hat{q}+\hat{f}\right)}.$$

Details of the analysis are presented below in which there is evolution from an introduction of infected mosquitoes (population fraction $y(0) = y_0$) to an uninfected area.

The left-hand side of equations $(3.7.1)-(3.7.8)$ seem to provide an initial guess of two time scales (i.e $t = O(\epsilon^2)$ and $t = O(\epsilon)$) but quite interestingly it happens to be a multi-scale problem. The method we use is that of formal asymptotics, namely singular perturbation methods whose application to problems in mathematical biology and classical mechanics is well established. The report does not include all the technical details involved as we are only interested in the leading-order behaviour of the system. There are a number of timescales but the six main timescales as predicted by the model are

$t = O(\epsilon^2)$, $\approx$ **1-3 days:** A small amount of infected mosquitoes introduced into the system become infectious after passing through the incubation period. Susceptible humans bitten by these mosquitoes get infected. The early infection registers itself in the human compartments. However the effect of this early infection remains unnoticeable ($O(\epsilon y_0)$) in the latent asymptomatic class. The amount of susceptible mosquitoes increases linearly due to natural birth.

$t = O(\epsilon^{\frac{4}{3}})$, $\approx$ **7-8 days:** In this time scale susceptible mosquitoes get infected by biting asymptomatic infectious humans. The amount of mosquitoes converting to the infectious class is also balanced by the amount of mosquitoes becoming infected by biting people in the asymptomatic infectious class. This behaviour is expected because individuals with clinical malaria have low level of gametocytes. Thus the early infection of susceptible mosquitoes is likely to come through contact with asymptomatic infectious humans since they have high gametocyte density. Infected humans are still "negligible",

$O(\epsilon^{1/3}y_0)$.

$t = O(\epsilon^{\frac{5}{4}})$, $\approx$ 9-10 days: As more mosquitoes get infected through contact with asymptomatic infectious humans, the amount of susceptible mosquitoes reaches its maximum and starts decreasing. Whereas the feedback from infectious humans offsets the linear growth effect of the initial small amount of infected mosquitoes introduced, eventually causing the amount of latent mosquitoes to grow exponentially. Human infected = $O(\epsilon^{-1/2}y_0)$.

$t = \epsilon^{\frac{5}{4}} \ln(\epsilon^{1/2}/y_0)/K_0 + O(\epsilon^{\frac{5}{4}})$, $K_0 = (\hat{\beta}\hat{\eta}\hat{f}\hat{d})^{\frac{1}{4}}$, $\approx$ 2 weeks: Asymptomatic humans become infected with new asexual parasites due to contact with infectious mosquitoes. The amount of sick people converting to asymptomatic status is being balanced by the amount of asymptomatic humans converting to the latent asymptomatic class due to a boost in their partial immunity level. Thus , more mosquitoes become infected and the overall flow of infection culminates in a fast transition of susceptible humans into the latent class.

$t = O(\epsilon)$, $\approx$ 2-3 weeks: Disease has become noticeable with infected humans = $O(1)$. Latent asymptomatic humans are still infectious to mosquitoes as C, S and A adjust to their equilibrium values. L decays exponentially.

$t = \epsilon \ln(1/\epsilon)/\hat{\eta} + O(\epsilon)$, $\approx$ 2 months: In this time scale all the human compartments equilibriate, notably $C = O(\epsilon^2)$, and latent individuals are becoming symptomatic and converting to L_A rapidly. While the mosquito compartments adjust to assume their equilibrium state.

3.7.1. $t = O(\epsilon^2)$

Using "^" to denote the variables in this time scale we write

$$t = \epsilon^2 \hat{t},$$

and with appropriate balancing of terms in each of the equations exploring the idea that out of a small amount y_0 of infected mosquitoes introduced into the population only a smaller proportion ϵy_0 becomes infectious, we seek leading order solution of the form,

$$C \sim 1 + \epsilon y_0 \hat{C}_1, \quad L \sim \epsilon y_0 \hat{L}_0, \quad L_A \sim \epsilon^3 y_0^2 \hat{L}_{A_0}, \quad S \sim \epsilon^2 y_0 \hat{S}_0,$$

$$A \sim \epsilon^2 y_0 \hat{A}_0, \quad X \sim 1 - y_0 + \epsilon y_0 \hat{X}_1, \quad Y \sim y_0 + \epsilon y_0 \hat{Y}_1, \quad Z \sim \epsilon y_0 \hat{Z}_0.$$

On substitution of these rescalings into (3.7.1)-(3.7.8), we obtain the leading order system

$$\frac{d\hat{C}_1}{d\hat{t}} = -\hat{\beta}\hat{Z}_0, \quad \frac{d\hat{L}_0}{d\hat{t}} = \hat{\beta}\hat{Z}_0, \quad \frac{d\hat{L}_{A_0}}{d\hat{t}} = \hat{\beta}\hat{A}_0\hat{Z}_0, \qquad (3.7.10)$$

$$\frac{d\hat{S}_0}{d\hat{t}} = \hat{\eta}\hat{L}_0 - \hat{\rho}\hat{S}_0, \quad \frac{d\hat{A}_0}{d\hat{t}} = \hat{\rho}S_0, \quad \frac{d\hat{X}_1}{d\hat{t}} = \hat{q}, \qquad (3.7.11)$$

$$\frac{d\hat{Y}_1}{d\hat{t}} = -\left(\hat{f} + \hat{q}\right), \quad \frac{d\hat{Z}_0}{d\hat{t}} = \hat{f}, \qquad (3.7.12)$$

recalling $y_0 \ll \epsilon \ll 1$, satisfying the initial conditions

$$\hat{C}_1(0) = 0, \quad \hat{L}_0(0) = 0, \quad \hat{L}_{A_0}(0) = 0, \quad \hat{S}_0(0) = 0,$$

$$\hat{A}_0(0) = 0, \quad \hat{Y}_1(0) = 0, \quad \hat{X}_1(0) = 0, \quad \hat{Z}_0(0) = 0.$$

By doing direct integration we get the following leading order solutions

$$\hat{C}_1 \sim -\frac{1}{2}\hat{\beta}\hat{f}\hat{t}^2, \quad \hat{L}_0 \sim \frac{1}{2}\hat{\beta}\hat{f}\hat{t}^2, \quad \hat{L}_{A_0} \sim \frac{1}{30}\hat{\beta}^2\hat{\eta}\hat{f}^2\hat{t}^5, \quad \hat{S}_0 \sim \frac{\hat{\beta}\hat{\eta}\hat{f}}{2\hat{\rho}}\hat{t}^2,$$

$$\hat{A}_0 \sim \frac{1}{6}\hat{\beta}\hat{\eta}\hat{f}\hat{t}^3, \quad \hat{X}_1 \sim \hat{q}\hat{t}, \quad \hat{Y}_1 \sim (-\hat{f} - \hat{q})\hat{t}, \quad \hat{Z}_0 \sim \hat{f}\hat{t}.$$

We observe that susceptible humans (C) and latent mosquitoes (Y) are decaying linearly in time from their initial values due to latent mosquitoes converting to the infectious class and

susceptible humans becoming infected as a consequence of infectious contact with mosquitoes in the Z class. With $\hat{A}_0 = O(t^3)$ there is a balance shift in (3.7.7), when $\hat{A}_0 = O(\epsilon^{-2})$ i.e. at a timescale $t = O(\epsilon^{-\frac{2}{3}})$, as susceptible mosquitoes become infected by biting asymptomatic humans. It is interesting to note that L and S equilibrate such that $\dfrac{S}{L} \sim \dfrac{\epsilon\eta}{\rho}$ in this time scale and remain so as we will see in all the following timescales.

3.7.2. $t = O(\epsilon^{4/3})$

Denoting variables with over-bars in this time scale we write

$$t = \epsilon^{4/3}\bar{t},$$

and obtain the variable rescalings

$$C \;\sim\; 1 + \epsilon^{-1/3}y_0\bar{C}_1, \quad L \sim \epsilon^{-1/3}y_0\bar{L}_0, \quad L_A \sim \epsilon^{-1/3}y_0^2\bar{L}_{A_0}, \quad S \sim \epsilon^{2/3}y_0\bar{S}_0,$$

$$A \;\sim\; y_0\bar{A}_0, \quad X \sim 1 - y_0 + \epsilon^{1/3}y_0\bar{X}_1, \quad Y \sim y_0 + \epsilon^{1/3}y_0\bar{Y}_1, \quad Z \sim \epsilon^{1/3}y_0\bar{Z}_0.$$

On substitution of these rescalings into (3.7.1)−(3.7.8), and considering the leading order terms we found that all the other equations remain the same as (3.7.10)−(3.7.12) in the previous time scale but the X and the Y equations both have an additional term, $\hat{d}\bar{A}_0$, given by

$$\frac{d\bar{X}_1}{d\bar{t}} = \hat{q} - \hat{d}\bar{A}_0, \quad \frac{d\bar{Y}_1}{d\bar{t}} = \hat{d}\bar{A}_0 - \left(\hat{f} + \hat{q}\right),$$

marking the advent of feedback of infection from asymptomatic individuals to susceptible mosquitoes due to the initial small amount of infected mosquitoes introduced into the totally susceptible human population. This creates a balancing effect between the amount of mosquitoes converting to the infectious class and the amount becoming infected by biting people in the asymptomatic infectious class. We use the initial conditions

$$\bar{C}_1(0) \;=\; 0, \quad \bar{L}_0(0) = 0, \quad \bar{L}_{A_0}(0) = 0, \quad \bar{S}_0(0) = 0,$$

$$\bar{A}_0(0) \;=\; 0, \bar{Y}_1(0) = 0, \quad \bar{X}_1(0) = 0, \quad \bar{Z}_0(0) = 0,$$

to obtain the following solutions.

$$\bar{C}_1 \;\sim\; -\frac{1}{2}\hat{\beta}\hat{f}\bar{t}^2, \quad \bar{L}_0 \sim \frac{1}{2}\hat{\beta}\hat{f}\bar{t}^2, \quad \hat{L}_{A_0} \sim \frac{1}{30}\hat{\beta}^2\hat{\eta}\hat{f}^2\bar{t}^5, \quad \bar{S}_0 \sim \frac{\hat{\beta}\hat{\eta}\hat{f}}{2\hat{\rho}}\bar{t}^2,$$

$$\bar{A}_0 \;\sim\; \frac{1}{6}\hat{\beta}\hat{\eta}\hat{f}\bar{t}^3, \quad \bar{X}_1 \sim -\frac{1}{24}\hat{\beta}\hat{\eta}\hat{f}\hat{d}\bar{t}^4, \quad \bar{Y}_1 \sim \frac{1}{24}\hat{\beta}\hat{\eta}\hat{f}\hat{d}\bar{t}^4, \quad \bar{Z}_0 \sim \hat{f}\bar{t}.$$

The only notable difference between these and the earlier time scale is in X and Y with an accelerated rate of mosquito infection from asymptomatic infectious humans. The implication of this is that the flow of the solution may change direction especially when the amount of mosquitoes getting infected becomes more than the inflow of new born mosquitoes. This happens at the point of breakdown

$$\bar{t} = O(\epsilon^{-1/12}),$$

where $\bar{Y}_1$ becomes $O(y_0)$. The dynamics of the system in the next time scale is a consequence of the change in the order of $\bar{Y}_1$.

3.7.3. $t = O(\epsilon^{5/4})$

We use " $\sim$ " to denote variables in this time scale where,

$$t = \epsilon^{5/4}\tilde{t},$$

and the appropriate rescalings of the variables are

$$C \;\sim\; 1+\epsilon^{-1/2}y_0\tilde{C}_1, \quad L \sim \epsilon^{-1/2}y_0\tilde{L}_0, \quad L_A \sim \epsilon^{-3/4}y_0^2\tilde{L}_{A_0}, \quad S \sim \epsilon^{1/2}y_0\tilde{S}_0,$$

$$A \;\sim\; \epsilon^{-1/4}y_0\tilde{A}_0, \quad X \sim 1+y_0\tilde{X}_1, \quad Y \sim y_0\tilde{Y}_1, \quad Z \sim \epsilon^{1/4}y_0\tilde{Z}_0.$$

On substitution of these into (3.7.1)−(3.7.8) we find (at leading order) that the equations representing the human compartments are unchanged, but due to the dominant contribution

of asymptomatic infectious humans on the infection of mosquitoes, the rate of change of $\tilde{Y}_1$ and $\tilde{X}_1$ are proportional to the amount of asymptomatic humans with that of $\tilde{Z}_0$ proportional to $\tilde{Y}_1$. The system in full is

$$
\begin{aligned}
\frac{d\tilde{C}_1}{d\tilde{t}} &= -\hat{\beta}\tilde{Z}_0, \quad \frac{d\tilde{L}_0}{d\tilde{t}} = \hat{\beta}\tilde{Z}_0, \quad \frac{d\tilde{L}_{A_0}}{d\tilde{t}} = \hat{\beta}\tilde{A}_0\tilde{Z}_0, \quad \hat{\eta}\tilde{L}_0 = \hat{\rho}\tilde{S}_0, \\
\frac{d\tilde{A}_0}{d\tilde{t}} &= \hat{\rho}\tilde{S}_0, \quad \frac{d\tilde{X}_1}{d\tilde{t}} = -\hat{d}\tilde{A}_0, \quad \frac{d\tilde{Y}_1}{d\tilde{t}} = \hat{d}\tilde{A}_0, \quad \frac{d\tilde{Z}_0}{d\tilde{t}} = \hat{f}\tilde{Y}_1.
\end{aligned}
$$

Through successive differentiation of $\dfrac{d\tilde{Z}_0}{d\tilde{t}}$ we find that $\dfrac{d^4\tilde{Z}_0}{d\tilde{t}^4} = K\tilde{Z}_0$, and by matching with the solution of section 3.7.2 as $\bar{t} \to \infty$ we have as initial conditions

$$
\begin{aligned}
\tilde{C}_1(0) &= \tilde{L}_0(0) = \tilde{L}_{A_0}(0) = \tilde{S}_0(0) = \tilde{A}_0(0) = \tilde{Z}_0(0) = 0, \quad \tilde{X}_1(0) = -1, \\
\tilde{Y}_1(0) &= 1, \quad \frac{d\tilde{Z}_0}{d\tilde{t}}(0) = \hat{f}, \quad \frac{d^2\tilde{Z}_0}{d\tilde{t}^2}(0) = 0, \quad \frac{d^3\tilde{Z}_0}{d\tilde{t}^3}(0) = 0, \quad \tilde{Z}_0(0) = 0,
\end{aligned}
$$

where $K = \hat{\beta}\hat{\eta}\hat{f}\hat{d}$. The large time solution of the system given by

$$
\begin{aligned}
\tilde{C}_1 &\sim -\frac{\hat{\beta}\hat{f}}{4K^{1/2}}e^{K^{1/4}\tilde{t}}, \quad \tilde{L}_0 \sim \frac{\hat{\beta}\hat{f}}{4K^{1/2}}e^{K^{1/4}\tilde{t}}, \quad L_{A_0} \sim \frac{\hat{\beta}\hat{f}}{32\hat{d}K^{1/4}}e^{2K^{1/4}\tilde{t}}, \quad \tilde{S}_0 \sim \frac{\hat{\beta}\hat{\eta}\hat{f}}{4\hat{\rho}K^{1/2}}e^{K^{1/4}\tilde{t}}, \\
\tilde{A}_0 &\sim \frac{\hat{\beta}\hat{\eta}\hat{f}}{4K^{3/4}}e^{K^{1/4}\tilde{t}}, \quad \tilde{X}_1 \sim -\frac{1}{4}e^{K^{1/4}\tilde{t}}, \quad \tilde{Y}_1 \sim \frac{1}{4}e^{K^{1/4}\tilde{t}}, \quad \tilde{Z}_0 \sim \frac{\hat{f}}{4K^{1/4}}e^{K^{1/4}\tilde{t}},
\end{aligned}
$$

shows that both the mosquito and human compartments are growing exponentially. For $K_0 = K^{\frac{1}{4}}$, the approximations for this timescale become poor when $\tilde{C}_1 = O(e^{K_0\tilde{t}}) = O(\epsilon^{1/2}/y_0)$, i.e. $\tilde{t} = \ln(\epsilon^{1/2}/y_0)/K_0$ when asymptomatic humans become infected with new asexual parasites due to contact with infectious mosquitoes.

3.7.4. $t = \epsilon^{\frac{5}{4}}\ln(\epsilon^{1/2}/y_0)/K_0 + O(\epsilon^{\frac{5}{4}})$

In order to describe events captured on this time scale we translate in time from the former time scale and write

$$
t = \epsilon^{\frac{5}{4}}\ln(\epsilon^{1/2}/y_0)/K_0 + \epsilon^{\frac{5}{4}}\check{t},
$$

where "˘" is the symbol for variable representation. The initial small amount of infection has been totally distributed and whose effect has developed into the beginnings of a full blown

epidemic with C and L becoming $O(1)$ and no dependence on y_0, to leading order as we can see in the following rescalings

$$C \sim \check{C}_0, \quad L \sim \check{L}_0, \quad L_A \sim \epsilon^{1/4}\check{L}_{A_0}, \quad S \sim \epsilon\check{S}_0, \quad A \sim \epsilon^{1/4}\check{A}_0,$$

$$X \sim 1 + \epsilon^{1/2}\check{X}_1, \quad Y \sim \epsilon^{1/2}\check{Y}_1, \quad Z \sim \epsilon^{3/4}\check{Z}_0.$$

Following the usual substitution procedure we find that at leading order, some equations remain the same as in the preceding time scale whereas the C, L, A, X and Y equations are now being expressed as

$$\frac{d\check{C}_0}{d\check{t}} = -\hat{\beta}\check{C}_0\check{Z}_0, \quad \frac{d\check{L}_0}{d\check{t}} = \hat{\beta}\check{C}\check{Z}_0, \quad \frac{d\check{L}_{A_0}}{d\check{t}} = \hat{\beta}\check{Z}_0 A_0, \tag{3.7.13}$$

$$S_0 = \frac{\hat{\eta}}{\hat{\rho}}\check{L}_0, \quad \frac{d\check{A}_0}{d\check{t}} = \hat{\rho}S_0 - \hat{\beta}\check{Z}_0\check{A}_0, \quad \frac{d\check{X}_1}{d\check{t}} = -\hat{d}\check{A}_0 - \hat{d}\check{L}_{A_0}, \tag{3.7.14}$$

$$\frac{d\check{Y}_1}{d\check{t}} = \hat{d}\check{A}_0 + \hat{d}\check{L}_{A_0}, \quad \frac{d\check{Z}_0}{d\check{t}} = \hat{f}\check{Y}_1$$

where by matching with the long time solution of section 3.7.3

$$\check{t} \to -\infty,$$

$$\check{C}_0 \to 1^-, \quad \check{L}_0 \to 0^+, \quad \check{L}_{A_0} \to 0^+, \quad \check{S}_0 \to 0^+, \quad \check{A}_0 \to 0^+, \quad \check{X}_1 \to 0^+, \quad \check{Y}_1 \to 0^+, \quad \check{Z}_0 \to 0^+,$$

the situation where asymptomatic humans become infected with new asexual parasites due to their contact with infectious mosquitoes, which eventually reduces the size of A as asymptomatic humans leave for the L_A class. Consequently, more susceptible mosquitoes get infected as latent asymptomatic humans transfer infection. In order to obtain a solution of the system, we note

$$\frac{d\check{C}_0}{d\check{t}} + \frac{d\check{L}_0}{d\check{t}} = 0, \quad \frac{d(\check{L}_{A_0} + \check{A}_0)}{d\check{t}} = \hat{\eta}\check{L}_0, \quad \frac{d^3\check{Z}_0}{d\check{t}^3} = \hat{\eta}\hat{f}\hat{d}\check{L}_0.$$

The first equation yeilds, $\check{C}_0 + \check{L}_0 = 1$. Substituting this into the differential equation for $\check{C}_0$, leads to the fourth-order nonlinear ode, which is the main equation that drives the dynamics

of the system on this time scale given by

$$\frac{d^4 \check{F}}{d\check{t}^4} = -K \left(1 - e^{\check{F}} \right)$$

where, K is as defined above and $\check{F} = \ln(\check{C}_0)$. This equation does not seem to have an analytical solution but we can extract some key information by investigating its behaviour. It is straightforward to show that $F = 0 (\check{C}_0 = 1)$ is an unstable steady state. Considering $g(F) = -K \left(1 - e^{\check{F}} \right)$, $F = 0 \Rightarrow g = 0$, $F < 0 \Rightarrow g < 0$ and $F > 0 \Rightarrow g > 0$. Thus, $F = 0$ is unstable. By matching we have $F \to 0^-$, or $\check{C}_0 \to 1^-$, as $\check{t} \to -\infty$ hence $\dfrac{d\check{F}}{d\check{t}} < 0$ as $\check{t}$ increases, i.e. a non-negligible amount of humans are becoming infected. For large, negative $\check{F}$ we have

$$\frac{d^4 \check{F}}{d\check{t}^4} \sim -K,$$

as the homogenous ODE whose general solution is,

$$\check{F} = -\frac{1}{24} K \check{t}^4 + \frac{1}{6} \alpha_1 \check{t}^3 + \frac{1}{2} \alpha_2 \check{t}^2 + \alpha_3 \check{t} + \alpha_4,$$

as $\check{t} \to +\infty$, where $\alpha_1, \alpha_2, \alpha_3$ and α_4 are unresolved constants depending on solution as $\check{t} \to -\infty$. The solutions for the susceptible and latent human compartments are

$$\check{C}_0 \sim B_0 \exp\left(\frac{a_1}{6} \check{t}^3 + \frac{a_2}{2} \check{t}^2 + a_3 \check{t} \right) e^{-\frac{K}{24} \check{t}^4}, \quad \check{L}_0 \sim 1 - B_0 \exp\left(\frac{a_1}{6} \check{t}^3 + \frac{a_2}{2} \check{t}^2 + a_3 \check{t} \right) e^{-\frac{K}{24} \check{t}^4},$$

indicating a very rapid exchange from the C to the L class describe how the force of infection generated by infectious mosquitoes, Z drastically reduces the size of C and increases that of L. As $\check{C}_0 \to 0$ and by applying dominant balancing of terms we obtain large time behaviour of other variables as

$$\hat{L}_{A_0} \sim \hat{\eta} \check{t}, \quad \check{S}_0 \sim \frac{\hat{\eta}}{\hat{\rho}}, \quad \check{A}_0 \sim \frac{6\hat{\eta}}{k} \check{t}^{-3}, \check{X}_1 \sim -\frac{1}{2} \hat{d} \hat{\eta} \check{t}^2, \quad \check{Y}_1 \sim \frac{1}{2} \hat{d} \hat{\eta} \check{t}^2, \quad \check{Z}_0 \sim \frac{k}{6\hat{\beta}} \check{t}^3.$$

as $\check{t} \to \infty$. Due to the rapid drop in the C class, there are series of minor transition timescales in which $C = O(1)$ falls to $C = O(\epsilon^2)$, in several very small timescale stages. We shall omit

the details and move on to the next major rebalance of the system, at $\check{t} = O(\epsilon^{-\frac{1}{4}})$, where the infected mosquito classes become non-negligible and the latent classes dominate the human population.

3.7.5. $t = O(\epsilon)$

We use the symbol " $\star$ " to denote variables on this time scale. By expressing time as

$$t = \epsilon t^\star,$$

we state the rescalings of the variables as follows:

$$C \sim \epsilon^2 C_0^\star, \quad L \sim L_0^\star, \quad L_A \sim L_{A0}^\star, \quad S \sim \epsilon S_0^\star, \quad A \sim \epsilon A_0^\star, \quad X \sim X_0^\star, \quad Y \sim Y_0^\star, \quad Z \sim Z_0^\star,$$

noting that susceptible class is now $O(\epsilon^2)$ and that most of human population are in the latent classes. On substitution of these into the full system as usual, yields a situation where some of the variables have assumed quasi-steady states, i.e. they are expressed in terms of the other variables, especially,

$$C_0^\star = \frac{\hat{\gamma}}{\hat{\rho}} A_0^\star, \quad S_0^\star = \frac{\hat{\eta}}{\hat{\rho}} \left(L_0^\star + L_{A0}^\star \right), \quad A_0^\star = \frac{\hat{\rho} S_0^\star}{\hat{\beta} Z_0^\star}.$$

The remaining variables are described by the system

$$\frac{dL_0^\star}{dt^\star} = -\eta L_0^\star, \quad \frac{dL_{A0}^\star}{dt^\star} = \eta L_0^\star, \quad \frac{dX_0^\star}{dt^\star} = \hat{q} - \left(\hat{q} + \hat{d} L_{A0}^\star \right) X_0^\star,$$

$$\frac{dY_0^\star}{dt^\star} = \hat{d} L_{A0}^\star X_0^\star - (\hat{f} + \hat{q}) Y_0^\star, \quad \frac{dZ_0^\star}{dt^\star} = \hat{f} Y_0^\star - \hat{q} Z_0^\star$$

subject to

$$L_0^\star(0) = 1, \quad L_{A0}^\star(0) = 0, \quad Y_0^\star(0) = 0, \quad X_0^\star(0) = 1, \quad Z_0^\star(0) = 0.$$

The straightforward solutions are

$$L_0^\star \sim e^{-\eta t^\star}, \quad L_{A0}^\star \sim 1 - e^{-\eta t^\star},$$

and consequently, $S_0^\star = \dfrac{\hat{\eta}}{\hat{\rho}}$. We cannot solve for the other variables, but it is useful to note that the leading behaviour as $t^\star \to \infty$, are the steady states

$$C_0^\star \sim \epsilon^2 \frac{\hat{\gamma}\hat{\eta}\left(\hat{q}+\hat{d}\right)\left(\hat{q}+\hat{f}\right)}{\hat{\rho}\hat{\beta}\hat{f}\hat{d}}, \quad A_0^\star \sim \epsilon \frac{\hat{\eta}\left(\hat{q}+\hat{d}\right)\left(\hat{q}+\hat{f}\right)}{\hat{\beta}\hat{f}\hat{d}},$$

$$X_0^\star \sim \frac{\hat{q}}{\hat{q}+\hat{d}}, \quad Y_0^\star \sim \frac{\hat{d}\hat{q}}{\left(\hat{q}+\hat{d}\right)\left(\hat{q}+\hat{f}\right)}, \quad Z_0^\star \sim \frac{\hat{f}\hat{d}}{\left(\hat{q}+\hat{d}\right)\left(\hat{q}+\hat{f}\right)}.$$

We note that while other variables are in their steady states, the amount of latent humans decays rapidly causing the amount of latent asymptomatic humans to grow due to massive inflow of asymptomatic humans being infected with asexual parasites. Although not apparent from the solutions we can show that approximation to L will no longer be $O(1)$ when

$$t^\star = \frac{1}{\hat{\eta}} \ln\left(1/\epsilon\right) + O(1)$$

which leads us to the final time scale.

3.7.6. $t = \epsilon \ln(1/\epsilon)/\hat{\eta} + O(\epsilon)$

Variables on this time scale are described using " ´ " so that;

$$t = \frac{\epsilon}{\hat{\eta}} \ln(1/\epsilon) + \epsilon\acute{t}$$

and

$$C \sim \epsilon^2 \acute{C}_0, \quad L \sim \epsilon \acute{L}_0, \quad L_A \sim 1, \quad S \sim \epsilon \acute{S}_0, \quad A \sim \epsilon \acute{A}_0, \quad X \sim \acute{X}_0, \quad Y \sim \acute{Y}_0, \quad Z \sim \acute{Z}_0.$$

On substitution of these into $(3.7.1)-(3.7.8)$ we find that the variables in their steady states remain unchanged and $L_A \sim 1$. Only $\acute{L}$ is evolving at leading order according to,

$$\frac{d\acute{L}_0}{d\acute{t}} = \frac{\hat{\gamma}\hat{\eta}}{\hat{\rho}} - \hat{\eta}\acute{L}_0.$$

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Figure 3.2 shows that the rapid drop of susceptible humans as shown in the fourth timescale of the analysis follows immediately after a sharp increase in the number of infectious mosquitoes. The fraction of Latent humans, L increases as C drops. The number
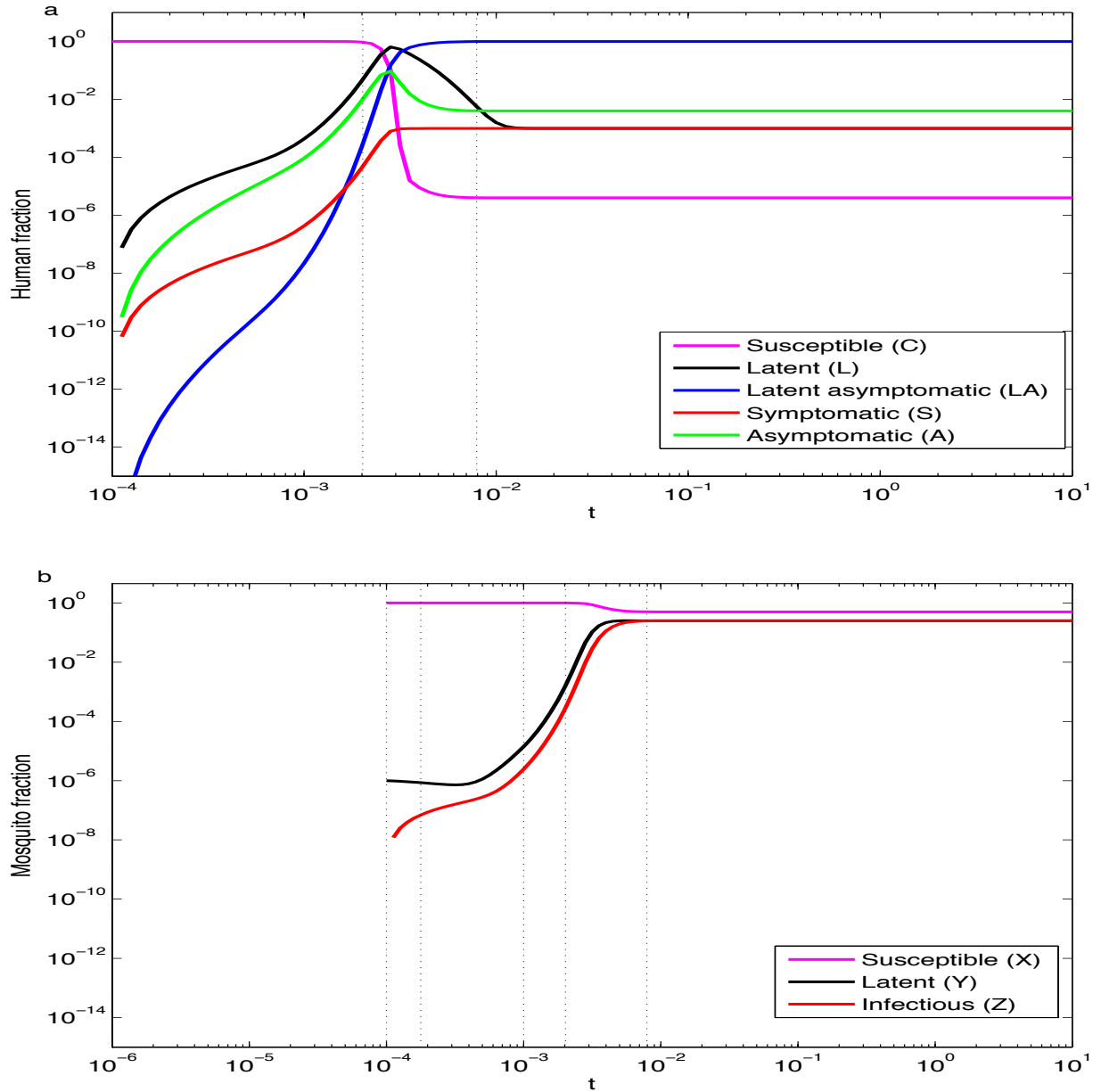
Figure 3.2: Solutions of dimensionless system (3.7.1)-(3.7.8) using $\epsilon = 0.001$ and all other dimensionless parameters set to unity. The top graph represents the various compartments in the human population and the bottom graph shows the fractions of mosquito population. Note the time axes are the log_{10} values for time and that the human and mosquito fractions are also been logged. The vertical dotted lines indicate different timescales, marking conspicuous events. The six timescales are $t = \epsilon^2$, $t = O(\epsilon^{\frac{4}{3}})$, $t = O(\epsilon^{\frac{5}{4}})$, $t = \epsilon^{\frac{5}{4}} \ln(\epsilon^{1/2}/y_0)/K + O(\epsilon^{\frac{5}{4}})$, $t = O(\epsilon)$ and $t = \epsilon \, ln(1/\epsilon)/\hat{\eta} + O(\epsilon)$. We only present the fourth and the sixth timescales for the human population whilst the third timescale is omitted from the mosquito classes.

of latent asymptomatic humans had been of low order from the beginning of the analysis and L had always dominated the infection classes. But immediately after the disease fully established itself, we observe that in the fifth timescale, L is no longer $O(1)$ as L_A grows to overtake L, which culminates in the final state of the disease showing about 90% of the human population in the Latent asymptomatic class as predicted by the analysis. Different stages of events in the mosquito population as predicted by the analysis are also well represented by the simulations.

By matching with the previous timescale we have $\acute{L}_0 \sim e^{-\eta \acute{t}}$ as $\acute{t} \to -\infty$, hence the solution

$$\acute{L}_0 = \frac{\hat{\gamma}}{\hat{\rho}} - e^{-\hat{\eta}\acute{t}},$$

which decays to $\dfrac{\hat{\gamma}}{\hat{\rho}}$ as $\acute{t} \to \infty$. Thus we reach the complete equilibrium state at leading order, namely

$$C \sim \epsilon^2 \frac{\hat{\gamma}\hat{\eta}\left(\hat{q}+\hat{d}\right)\left(\hat{q}+\hat{f}\right)}{\hat{\rho}\hat{\beta}\hat{f}\hat{d}}, \ L \sim \epsilon\frac{\hat{\gamma}}{\hat{\rho}}, \ L_A \sim 1, \ S \sim \epsilon\frac{\hat{\eta}}{\hat{\rho}}, A \sim \epsilon\frac{\hat{\eta}\left(\hat{q}+\hat{d}\right)\left(\hat{q}+\hat{f}\right)}{\hat{\beta}\hat{f}\hat{d}},$$

$$X \sim \frac{\hat{q}}{\hat{q}+\hat{d}}, \ Y \sim \frac{\hat{d}\hat{q}}{\left(\hat{q}+\hat{d}\right)\left(\hat{q}+\hat{f}\right)}, \ Z \sim \frac{\hat{f}\hat{d}}{\left(\hat{q}+\hat{d}\right)\left(\hat{q}+\hat{f}\right)}.$$

3.7.7. Conclusion from the analysis

Through our timescale analysis we have provided insight into the transmission of the disease as shown by the numerical simulations. Six main time scales as predicted by the model are used with appropriate rescalings to explicate the dynamics of the disease in relation to events as they evolve from early incidence to endemic state. There are important concluding remarks about the spread of the disease:

- Throughout the analysis, S has been proportional to L showing that the level of the disease depends very much on non-immune individuals becoming infected. We also find

that C remained at $O(1)$ from the first timescale until the fourth time scale,

$$\mathbf{t} = \epsilon^{\frac{5}{4}} \, \ln(\epsilon^{1/2}/\mathbf{y_0})/\mathbf{K_0} + \mathbf{O}(\epsilon^{\frac{5}{4}}),$$

when it suddenly dropped to $O(\epsilon^2)$, which suggests that intervention programs may yield better results if implemented before this time scale, preferably by the time $\mathbf{t} = \mathbf{O}(\epsilon^{\frac{5}{4}})$, during which the feedback from infectious humans offsets the linear growth effect of the initial small amount of infected mosquitoes. This equates to about 2-3 weeks from the initial infection.

- The contribution of asymptomatic infectious humans has a significant effect on the dynamics of the disease. This becomes evident in the time scale $t = O(\epsilon^{4/3})$ and influences the mode of infection throughout the period of analysis. This is due to our choice of the values of the model parameters, which we have assumed that asymptomatic humans are far more infectious than symptomatic humans. We recall that disease symptoms are associated with the erythroctye cycle, a period characterised by incursion and invasion of the red blood cells by asexual parasites.

- The noticeable build-up of latent asymptomatic humans at steady state is a clear characteristic of the dynamics of malaria in an endemic region. This portends a dangerous scenario and creates adverse effect on public policies aimed at control or eradication of the disease. It appears adults get partial immunity at the expense of children and women (who may likely loose immunity) during pregnancy. The condition $\epsilon \ll 1$, or precisely $l_a \ll \eta_h$, on which our analysis is based, represents a situation where humans spend a very long time in the asymptomatic class potentially, but they get infected almost immediately harbouring infection without remarkable symptom of the disease and from known results, this is reinforced through continuous infection as shown in our

analysis.

- In order to use our model to achieve effective control or eradication of the disease we will perform some more simulations in the future to ascertain if it is worth considering an option of reducing the time humans spend in the asymptomatic class through treatment so that we can recommend and promote the simple slogan, check your 'Malaria Infection Status' (MIS) and get treated. Another option is to ascertain whether or not prompt treatment of sick people would guarantee a disease free state by considering γ as a treatment parameter.

- The scenario in which the analysis is based has $R_0 > 1$ so an endemic situation is guaranteed. It is intresting to note that the dominant human class is the L_A class who are both latent and infectious to mosquitoes. This class is absent in all other models to our knowledge, yet, this model suggests, it is by far the most important class in sustaining the disease. Throughout this analysis, $S = O(\epsilon)$ which means that the amount of death due to the disease is negligibly small, and, together with a negligible natural birth and death rate, $N \approx 1$ throughout this analysis. The scalings for mosquitoes suggest that death by the disease is negligible compared to natural death, and hence $\frac{dM}{dt} \sim (\hat{q} - \hat{g})M/\epsilon$ so that M will change in a $t = O(\epsilon)$ timescale. In reality there will be limitation to population growth, but is not expected that the main conclusion of the analysis are not too affected by this.

3.8. Numerical Simulations

In section 3.6 we analysed the transition model by adducing sufficient conditions to show that the diseases free state is locally and asymptotically stable if $R_0 < 1$ and unstable for $R_0 > 1$. We also conducted a timescale analysis in section 3.7 to study the evolution of the

disease based on $R_0 > 1$ to demonstrate the existence of an endemic state. In this section we will use numerical simulations to verify the results of our analysis. We will also demonstrate numerically that the endemic state is globally and asymptotically stable if $R_0 > 1$ using a set of initial conditions described in Γ defined by (3.5.1).

Due to the findings in the asymptotic analysis, we assume that $\frac{M}{N}$ is constant throughout the simulations. The numerical solution is obtained by using MATLAB's ode45, a variable order Runge-Kutta method with a relative tolerance of 10^{-7} and absolute tolerance of 10^{-6}. The parameters used for the simulations as defined in Table 3.3 are $\beta = 62.43$, $\eta = 11.1$ (i.e. $\epsilon = 0.09$), $\mu = 0.0056$, $\lambda = 0.017$, $\alpha = 0.01$, $\gamma = 11.5$, $\rho = 54.45$, $\theta = 0$, $b = 7.2$, $d = 38.2$, $f = 14$, $g = 21.12$, $h = 1.45$, $q = 21.45$. At time $t = 0$ we have the following initial conditions in the proportions: $C = 1$, $L = 0$, $L_A = 0$, $S = 0$, $A = 0$, $X = 0.9999$, $Y = y_0 = 0.0001$, $Z = 0$, $N = 1$, $M = 1$. This is a situation where the entire susceptible human population is exposed to a small fraction of infected mosquitoes. The program was run in MATLAB with different sets of initial conditions, a check was also conducted using MAPLE's ode45 in all cases and the qualitative form of the steady state solutions were the same, although the system gets to a steady state faster as y_0 increases. In Figure 3.3a,c, the proportion of susceptible human population drops. This is more pronounced in Figure 3.3a, in which we have used $\theta = 0$ to represent non-treatment of asymptomatic humans leading to more infection of susceptible humans. The latent human fraction peaks and later drops to a steady state. There is a high proportion of latent asymptomatic humans showing that asymptomatic state is being preserved in continuous infection. In Figure 3.3b, more than half of the mosquito population are infected indicating high level of disease prevalence. However a smaller proportion of mosquitoes become infected when $\theta = 20$ as shown in Figure 3.3d. In Figure 3.4a,b, the population of humans and mosquitoes are gradually increasing. Figure

3.4c,d,e,f show the effect of different values of y_0 on the various fractions of human population. We investigate each of the human sub-populations as y_0 varies from 0.00001 to 0.1 and the results show that there is a unique steady state for each human compartment irrespective of the value of y_0 except that it takes a longer time to reach the steady state with a smaller y_0. We note that the delay increases linearly as y_0 decreases exponentially as predicted by the
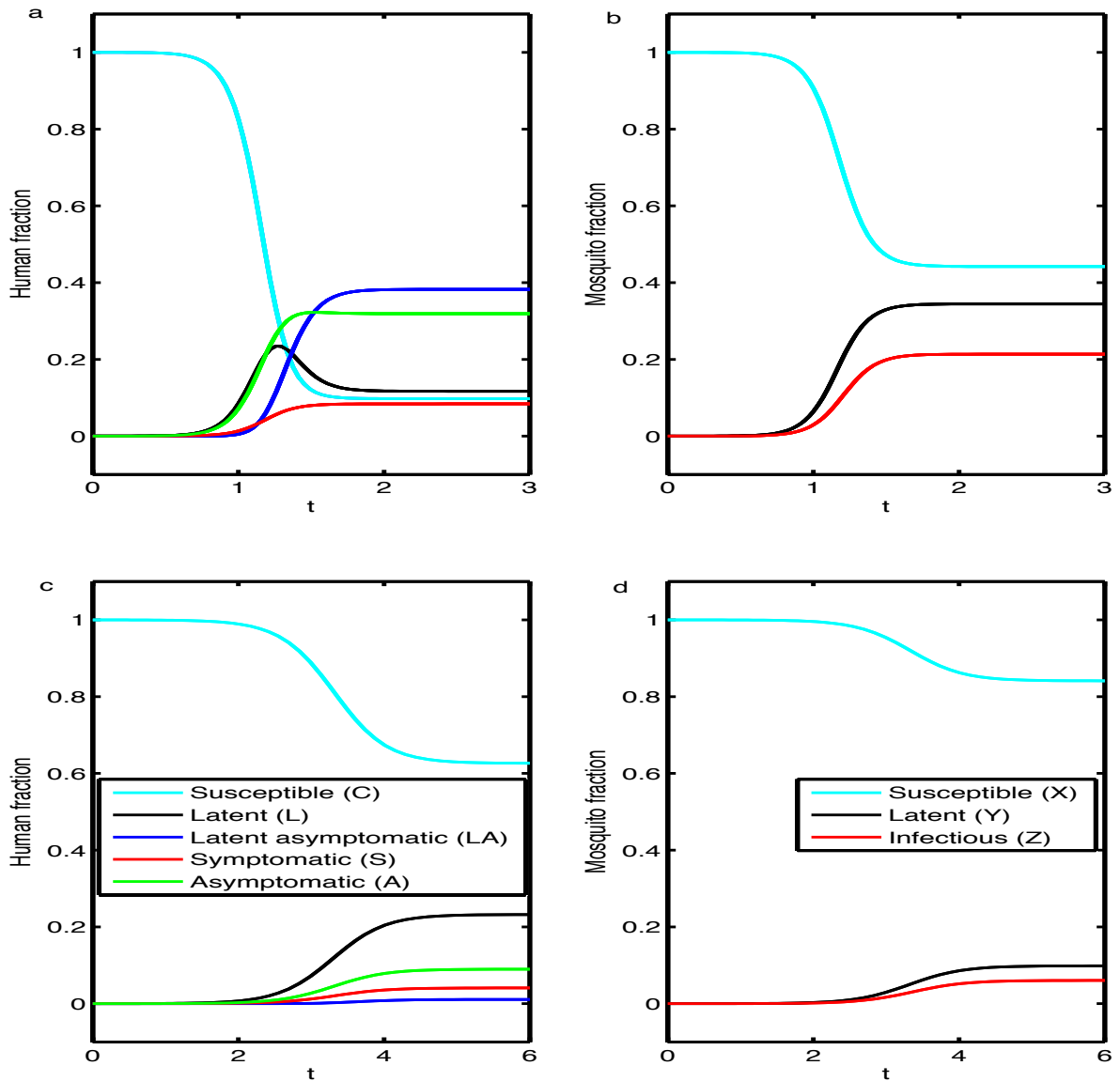
Figure 3.3: Results showing the effect of the initial infected mosquito population on evolution of endemic infection where $t = 1$, represents 165 days in real time. The initial conditions used are $C = 1$, $L = 0$, $L_A = 0$, $S = 0$, $A = 0$, $X = 0.9999$, $Y = 0.0001$, $Z = 0$, $N = 1$, $M = 1$ and the parameter values are given in Table 3.3. In Figure 3.3c,d, there is some level of post disease treatment ($\theta = 20$), whilst we have used $\theta = 0$ in Figure 3.3a,b to explicate the dynamics of endemic malaria in which asymptomatic humans are not treated

analysis of section 3.7.4

The results demonstrate the typical behaviour of rapid infection of susceptible individuals
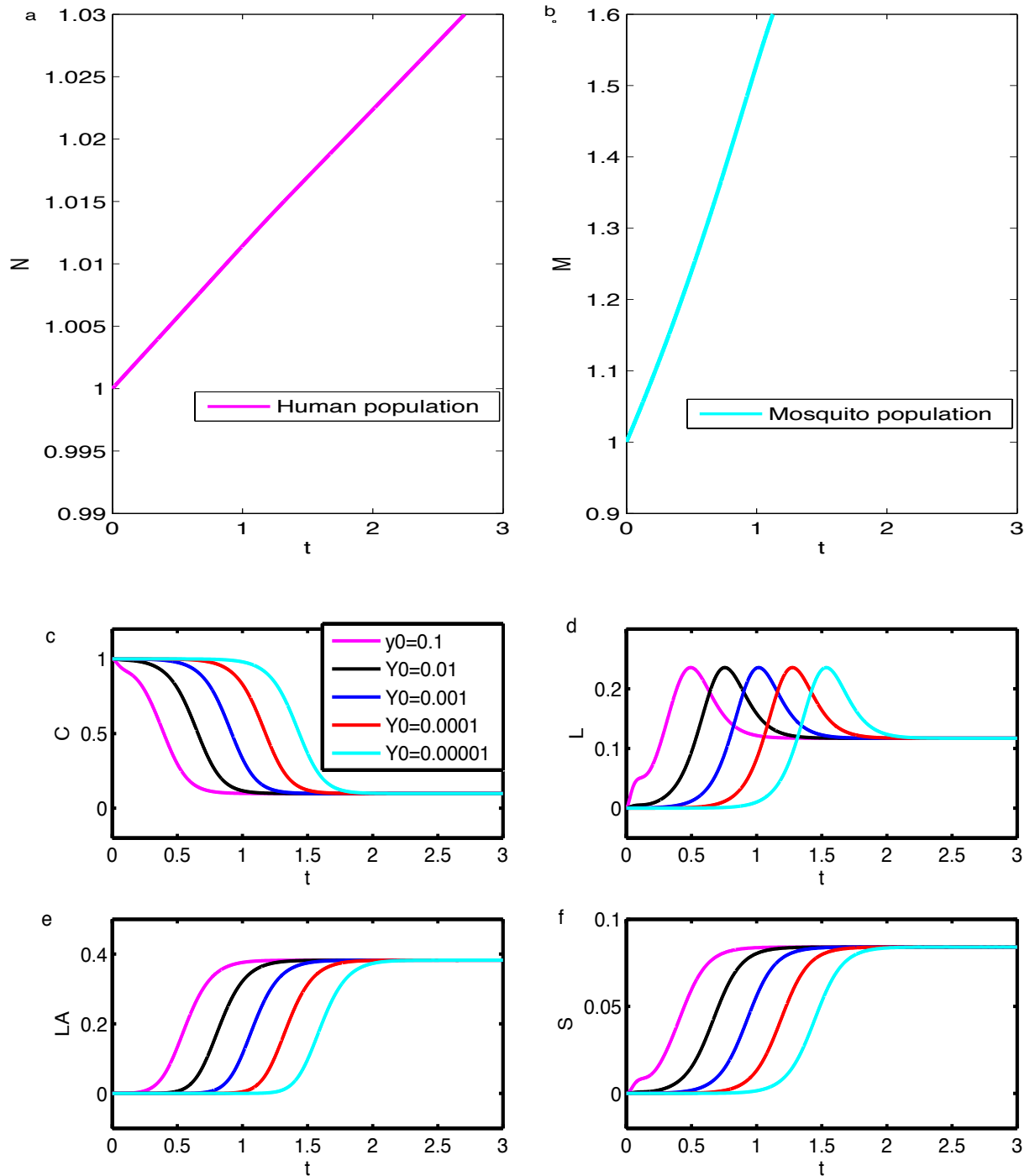
Figure 3.4: Results showing the human and mosquito populations (Figure 3.4a,b) and the effect of introducing different amount of infected mosquitoes on the various fractions of human population (Figure 3.4c,d,e,f). The values used for the simulations are the same as those in (Figure 3.3c,d) except that for Figure 3.4a,b we used $g = 21.02$ and for (Figure 3.4c,d,e,f) we have used the initial conditions, $C = 1, L = 0, LA = 0, S = 0, A = 0, X = 1 - y_0, Y = y_0, Z = 0, N = 1, M = 1$ with different values of y_0 as shown in the graphs.
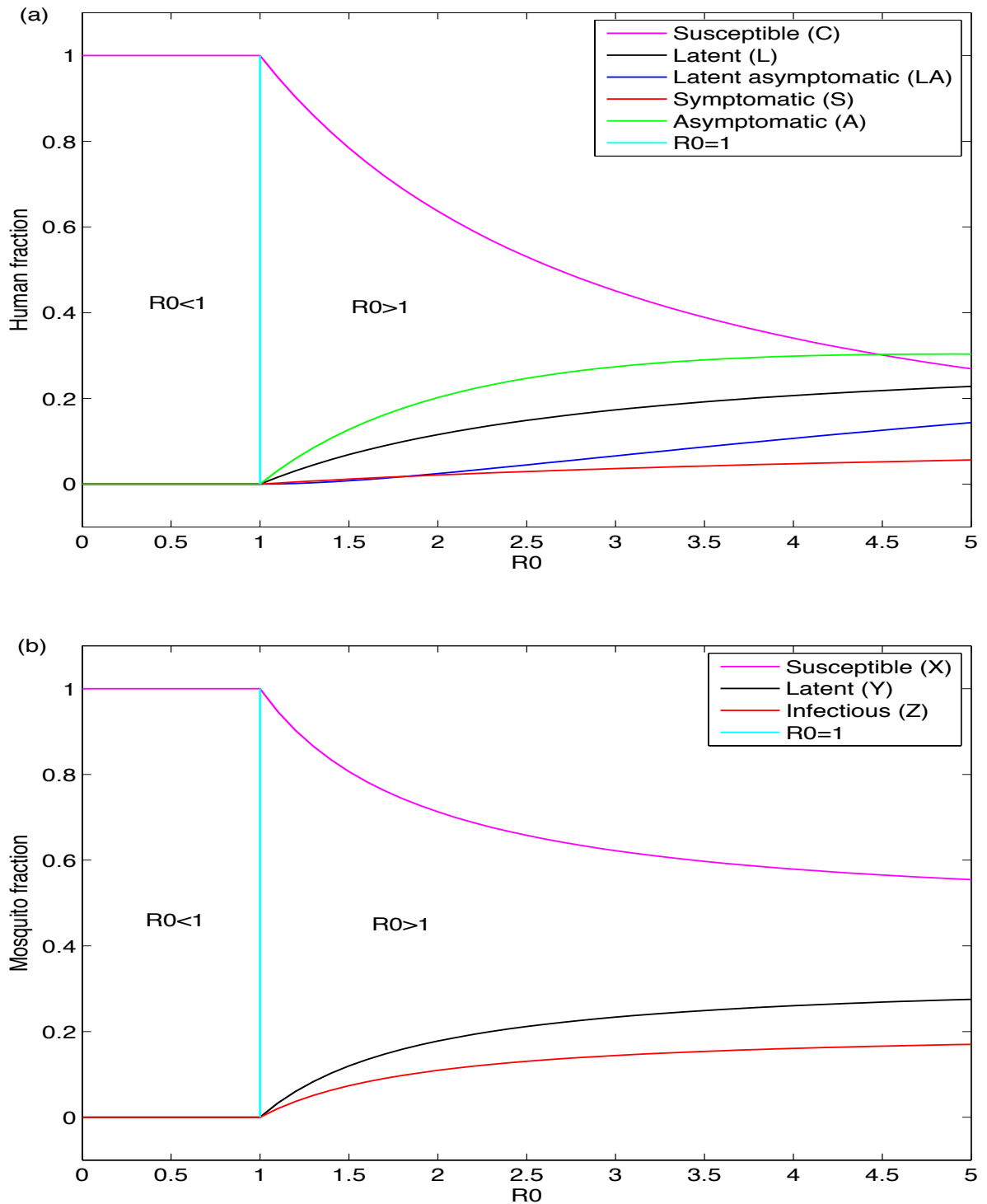
Figure 3.5: Results showing the disease free state when $R_0 < 1$ and the endemic state for $R_0 > 1$ by varying the value of R_0 from 0 to 5. The parameter values used to obtain these results are given in Table 3.3 except $\theta = 4.13$. We used the parameter, β to change R_0 where $R_0 = 5$ corresponds to $\beta = 9.35$.
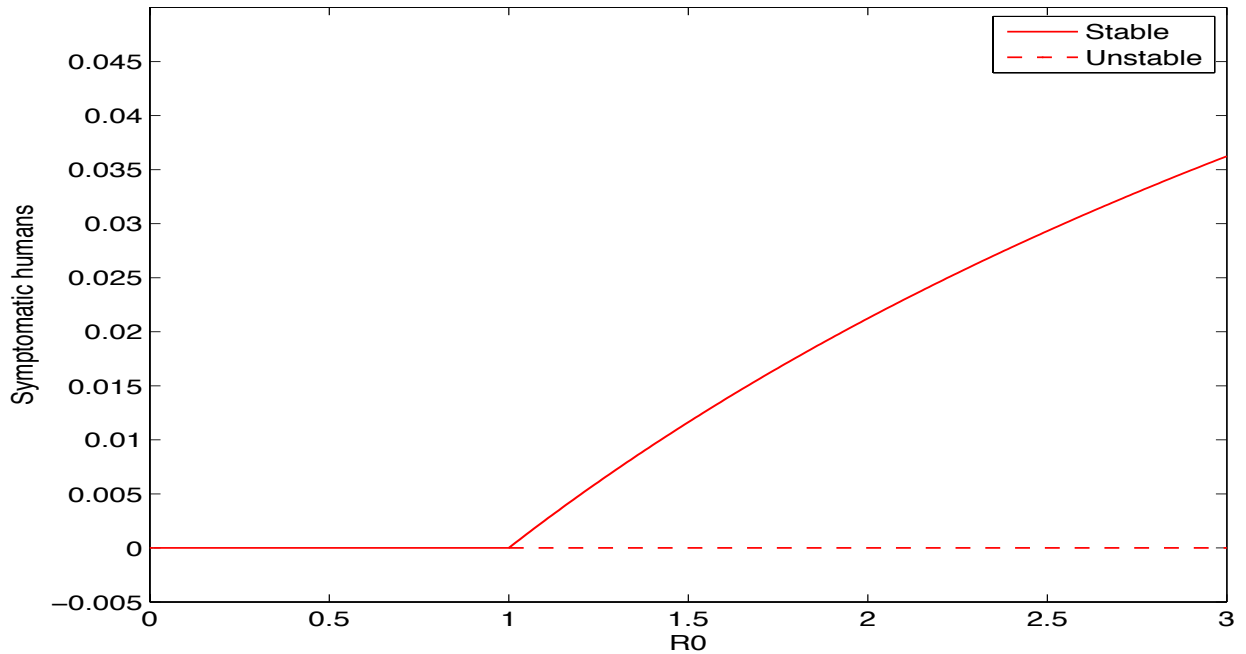
Figure 3.6: Basic reproduction number (R_0) bifurcation diagram. The curve shows a transcrital bifurcation obtained by drawing the steady states of symptomatic humans against different values of R_0 ranging from 0 to 3. Parameter values are the same as those in Figure 3.5

in a malaria endemic region. Figure 3.5a, b shows the relationship between the basic reproduction number and the disease profile as it affects both mosquito and human populations. The disease establishes itself for values of $R_0 > 1$ and dies out if $R_0 < 1$. The values of R_0 were obtained by varying β and $R_0 = 1$ corresponds to $\beta = 1.87$. Figure 3.6 is a bifurcation diagram showing a switch from a disease free state to an endemic state. The result is obtained by drawing the steady states of symptomatic humans against different values of R_0.

Each curve in Figure 3.7a represents the effect of θ on S for a given γ. The red curve in particular shows that for a certain level of symptomatic treatment, $\gamma = 60$ it requires a post disease treatment, $\theta = 21$ to drive the disease to extinction. Treatment of both symptomatic and asymptomatic humans can easily lead to a disease free state. Figure 3.7b gives the variation of the amount of symptomatic humans as γ gradually increases from zero in the absence of post disease treatment.

In order to demonstrate the impact of the basic reproduction number on the dynamics of the system, we plot the steady states of the various human and mosquito compartments against the basic reproduction number (R_0). Figures 3.5a,b show the disease free state when R_0 is less than unity and for $R_0 > 1$ the disease invades both the human and mosquito populations. The plot shows a transcritical bifurcation in the vicinity of $R_0 = 1$, as is expected from the analysis. Although some uncertainty still surrounds our quest on whether or not the disease invades at $R_0 = 1$ the disease free state is stable for values of $R_0 < 1$, but becomes unstable when $R_0 > 1$ whereas, the endemic state becomes stable as expected.

The disease free state assumes that the entire mosquito and human populations are free from the disease. Any simulation leading to $S = 0$, by varying the model parameters will not be valid if it does not target $C = 1$ and $X = 1$. Hence we also demonstrate the effect of θ and γ on C and X in Figure 3.8. The results show that as $S \to 0$, there is the indication
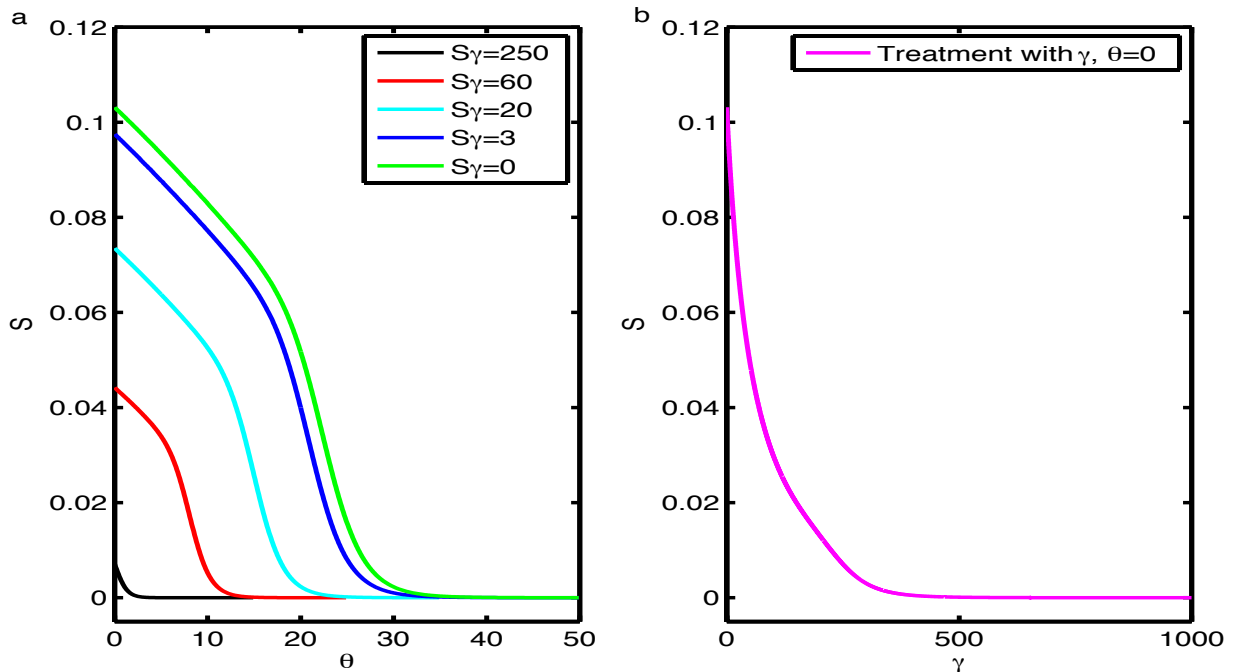
Figure 3.7: Plot of symptomatic humans against drug strength showing impact of clinical and post disease treatment on malaria control. In Figure 3.7b, $\theta = 0$, Whilst each curve in Figure 3.7a represents a plot of symptomatic humans with a given level of treatment against different values of θ. Initial conditions and parameter values are the same as those in Figure 3.3

that with various combinations of symptomatic and asymptomatic treatment, humans and mosquitoes will likely become free from the disease.

3.9. Discussion

Our model describes a typical situation of an endemic malaria. This is supported by the value of R_0 for $\theta = 0$, given as 33.4, obtained from data using (3.5.2). There is a high proportion of latent asymptomatic humans since they require a longer time to loose infection before experiencing disease symptoms. The numerical solution (Figure 3.3) shows that about 90% of the entire population will be engulfed by the disease within a period of one year out of which about 8% will be sick and would require medical attention in the hospital resulting in loss of man-hours. Although those mostly affected by the disease are usually children and pregnant women [83], the economic cost of the disease to households and government is
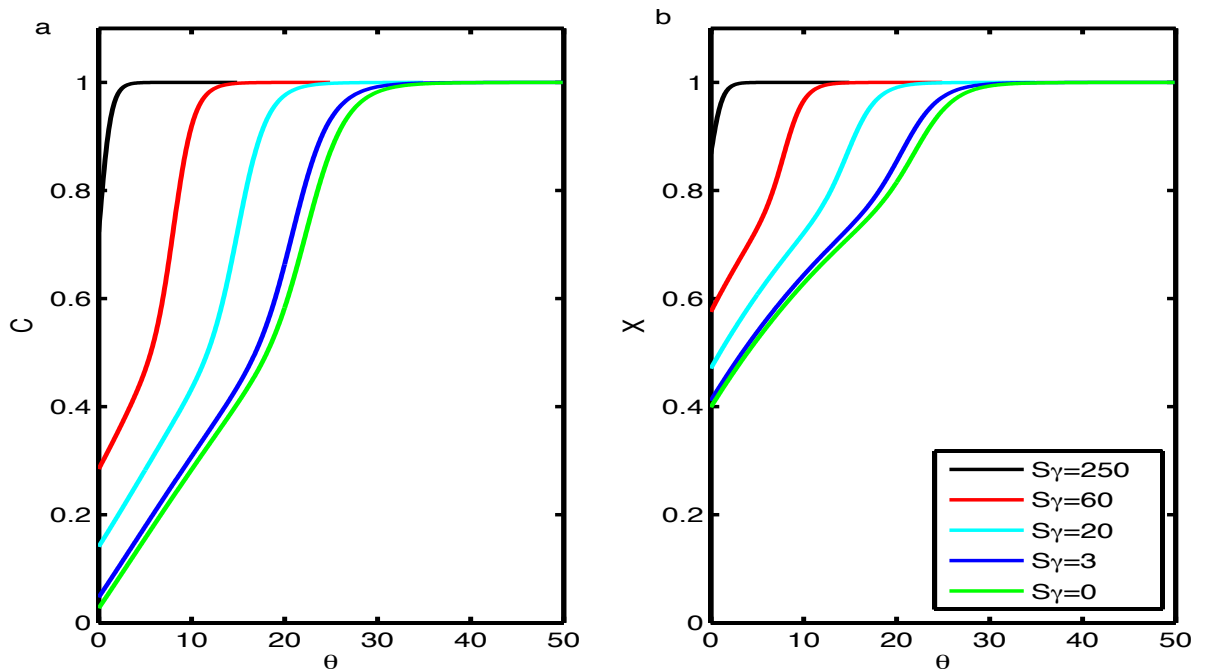
Figure 3.8: Plot of susceptible humans and mosquitoes against drug strength. Parameter values and initial conditions are the same as those in Figure 3.7. The disease dies out for different combined values of γ and θ.

enormous. The results also show that about 38% of the population would be carrying a greater number of gametocytes without showing symptoms of the disease within the period whilst approximately 32% of the population is asymptomatic and equally harbouring some levels of asexual parasites due to their being infected from infectious mosquitoes despite their partial immunity. We assume an equal transmission rate η_h into the symptomatic compartment for both latent and latent asymptomatic classes but the latter keeps on building up instead of flowing into the symptomatic class. Although, the asymptotic analysis shows approximately 90% of humans in the Latent asymptomatic class, this does not in any way show that the results are not correct. The reason for this disparity is that the analysis is based on the assumption that $\epsilon \ll 1$ and we have presented a simulation in this regard in section 3.7.6 that agrees well with the results of the analysis.

The model prediction seems plausible since immunity to malaria has always been associated with continuous exposure to infection. In particular, [91] has shown that the rate of development of clinical immunity to malaria correlates with the length of infection and that asymptomatic status is reached sooner when the infections are longer. Although we expect this behaviour since latent asymptomatic individuals have partial immunity and are not expected to show disease symptoms until they loose immunity, it rather portends a dangerous scenario which could pose serious threats to the control of the disease especially if there happens to be a sudden upsurge of the disease in the population if more of these individuals loose immunity within a short interval of time. This is expected since, asymptomatic carriage may represent a mode of entry to symptomatic malaria especially in young children [101] and in regions of high malaria transmission, every member of the community might be chronically infected and as such there could be a high prevalence of sub-clinical malaria [109]

A good mathematical model of epidemiology(apart from being mathematically tractable)

can be assessed on its application to disease control. We consider γ as a treatment parameter due to the results of our time scale analysis. The non-dimensional parameter, γ is the ratio of r_h and l_a where r_h is the recovery rate of symptomatic humans due to treatment and l_a is the loss of asymptomatic infection or simply, the recovery rate of asymptomatic humans. The duration of untreated or inadequately treated *P. falciparum* infection ranges from 197 to 480 days [36] and due to epidemiological observation of populations under treatment, the average duration of infection reduces from 270 days to 14 days [38]. From results obtained by Tumwiine et al. [111], early, prompt and proper treatment of symptomatic humans reduces the duration of infection to as low as 3 days.

In order to determine the effect of γ we consider an ideal situation where the duration of infection can be reduced to zero through effective administration of treatment to symptomatic infectious human on the first day of the observation of the disease symptoms such that the gametocytes are destroyed or made inactive to the extent that they would not infect suscepti-ble mosquitoes, i.e, $r_h \in [0, \infty)$. We deduce that increasing the duration of partial immunity increases R_0. Acquisition of partial immunity is beneficial to the individual who has it but could be detrimental to the entire population because it increases the reservoir of infection. A strict suggestion by [22] demands that in order to bring a disease under control in a population of varying size, we need to reduce the reservoir of infection to zero with increasing time. We note that a faster way of reducing R_0 is by reducing β, η or f. The only way of reducing η is by increasing l_a, the rate of immunity loss or the duration of asymptomatic infection. We de-duce that reducing the duration of asymptomatic infection reduces R_0, which agrees with the findings of [22]. We also introduce a post disease parameter $\theta \in [0, \infty)$ aimed at reducing the time partially immune humans spend in the asymptomatic and latent asymptomatic classes.

An asymptotic analysis on the model with the treatment parameters shows that for $\theta = 0$,

the model can only predict a disease free state when γ is of $O(\epsilon^{-3})$. In order to assess treatment success we consider the distinguished limit case

$$\gamma = \frac{\gamma_0}{\epsilon}, \ \epsilon \to 0, \ \gamma \to \infty \tag{3.9.1}$$

with an assumption that for successful treatment to take place, $S \sim O(small)$, $C \sim 1 + O(small)$ and $X \sim 1 + O(small)$. The results suggest that treatment of symptomatic humans alone cannot lead to the eradication of malaria but could only help in the management and control of the disease. We deduce from our analysis that at leading order

$$R_0 = \frac{1}{\gamma_0} \frac{\hat{\beta}\hat{f}\hat{\rho}\hat{d}}{\hat{q}(\hat{f} + \hat{q})}, \tag{3.9.2}$$

where $\gamma_0 = O(\epsilon^2)$ compares well with the one obtained using the next generation matrix. We also consider the cases $\gamma = 0$ with treatment of asymptomatic humans and treatment of both sick and partially immune individuals. The results show that there is the possibility of eradicating the disease by treating both symptomatic and asymptomatic infectious humans. The key information we derive from the treatment analysis is that if for instance, a particular drug of reasonable efficacy administered on sick people requires $O(\epsilon^{-3})$ to bring the disease under control, then less effort of $O(\epsilon^{-1})$ is required to achieve the same objective when combined with asymptomatic treatment effort of $O(\epsilon^{-1})$.

Malaria transmission is a cyclic process of parasite transfer between human and mosquito populations. While there is the likelihood of humans avoiding the irritating bites from mosquitos, there seems to be a natural or ecological demand from the female anopheles mosquito to feed on humans in order to reproduce. Although the origin of the parasite is yet to be known, considering the process in one direction, it seems the mosquito deposits young parasites during blood meal and later comes back to ingest the matured form of the parasite and provide a conducive environment for its reproduction, since it lacks the ability

to reproduce sexually in the human host. The parasite spends a longer time in the human host than in the vector and its within-host occupation apart from causing disease pathology and mortality, also sets the pace for transmission to another host. If the host has a hash environment inimical to the survival of the parasite then disease morbidity, mortality and transmission will be greatly reduced. The immune system plays a great role in defending the host's system against foreign pathogens. In the next chapter we will study the human immune system and its mechanism in relation to malaria pathogenesis.

CHAPTER 4

PATHOGENESIS OF MALARIA

4.1. In-host pathogenesis

In a single bite an estimated average of 15 sporozoites are injected into the human body by a feeding mosquito infected with *plasmodium falciparum* [97]. A sporozoite travels in the blood stream to the liver where it invades hepatic cells, matures into schizonts and produces 30000 to 40000 merozoites within 6 days [87]. Each merozoite tries to invade a red blood cell where it reproduces asexually, and after approximately 48 hours the erythrocyte ruptures, releasing a number of merozoites to renew the cycle. Some merozoites differentiate into gametocytes which are later picked up by a female anopheles mosquito during her blood meal. The interaction between merozoites and red blood cells is well represented in the malaria parasite life cycle diagram (bottom-right) in section 1.2.

Malaria infection in humans by Plasmodium species is associated with a reduction in haemoglobin levels, frequently leading to anaemia [72]. This happens especially when the destruction of red blood cells is followed by a decreased production of red blood cells from the bone marrow. During the pre-antibiotic era for treating neurosyphilis, patients were

treated with malariotherapy, in which they were inoculated with the asexual form of the malaria parasite in order to raise their body temperature. Data from such patients will help to explain the interaction between merozoites and red blood cells during a malaria episode.

Patient data

Here, we present data of two previously uninfected neurosyphilis patients undergoing malaria therapy inoculated with two different strains of *P. falciparum* malaria parasites, namely *El Limon* and *McLendon strains*. These data were extracted from Jakeman et al. [54] and
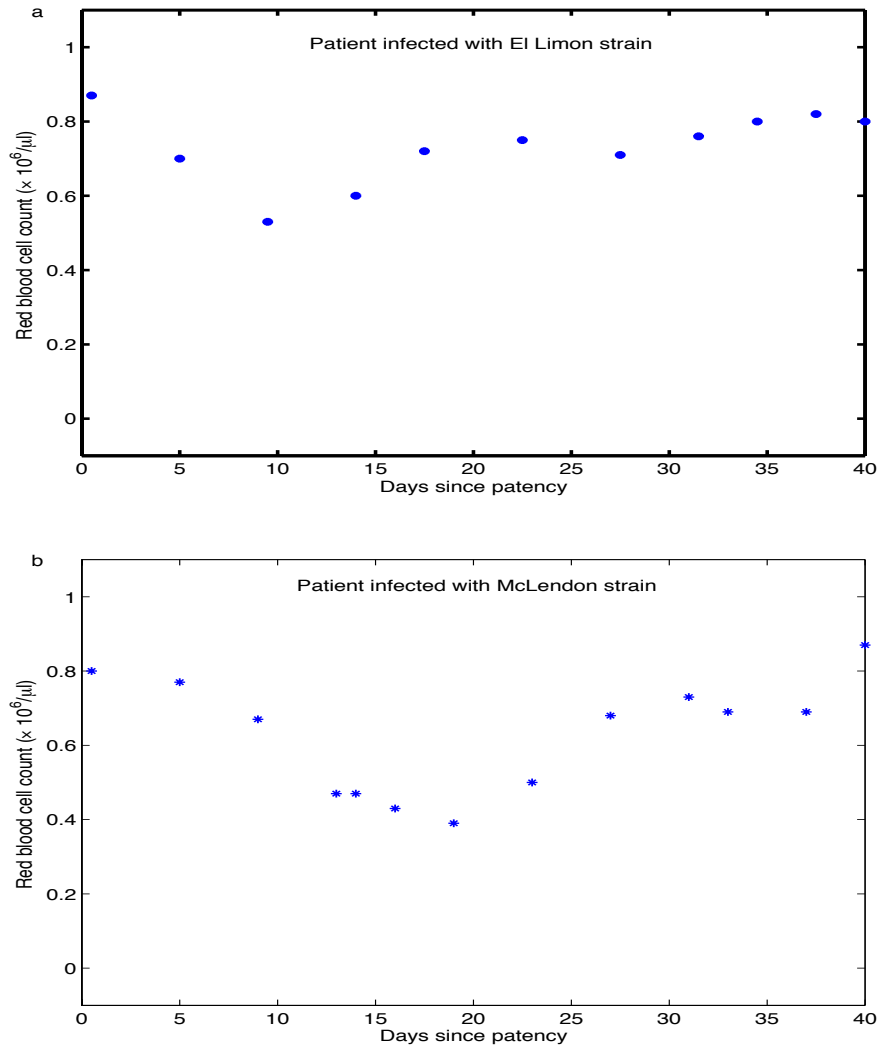
Figure 4.1: Malaria data of neurosiphilis patients inoculated with *El Limon* and *McLendon* strains of *Plasmodium falciprum* malaria parasite marked as patient $S1301$ and $S1288$ respectively in [54].

are part of the data set obtained from the South Carolina and Milledgeville State hospitals. Haemoglobin values were converted to red blood cell counts using 5×10^6 erythrocytes/μl in a person with $15 g/dl$ haemoglobin. The data demonstrate how red blood cell count drops and peaks in both patients during the period of the disease. Since these individuals had no previous malaria at the time of inoculation, we assume they did not have malaria specific immune cells prior to inoculation apart from the normal level of innate immune cells.

The evolution of malaria parasites like any other pathogen can instigate an immune response in the host and depending on the effectiveness of the immune system the parasites are either eliminated with little or no trace of disease symptoms or the parasites establish themselves with life threatening symptoms if left untreated.

4.2. The immune system

Malaria is caused by the interaction between the plasmodium parasite and red blood cells in the human host. The immune system is known to be the defender of the body against antigenic substances. It exhibits a complex system of specialised network of cells, organs and tissues in which their molecular and cellular interactions generate protection against foreign invaders. The entire process of immunity consists of the innate and adaptive immune responses. The former is nonspecific as to the type of infection and is ready to be mobilised as a first line of action against the invading organism without recourse to previous infection, whereas the latter, which takes some time to develop displays some immunological memory by reacting more rapidly on subsequent exposure to the same pathogen.

All cells of the immune system are produced in the bone marrow and they include myeloid (neutrophils, basophils, eosinpophils, macrophages and dendritic cells) and lymphoid (B lymphocyte, T lymphocyte and Natural Killer) cells [69]. The significance of these two varieties of immune cells is that myeloid induces red blood cells and platelets in addition to controlling

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the innate immune mechanism. Whilst lymphoid, comprising T cells, B cells and natural killer(NK) cells plays a crucial role in adaptive immune response. T cells produced in the bone marrow undergo a process of maturation in the thymus differentiating into naive $CD8^+$ cells and $CD4^+$ T helper cells($Th1$ and $Th2$). These helper cells later prime $CD8^+$ cells to kill pathogens directly by cytotoxicity and indirectly by inducing B cells to produce antigen specific antibodies.

The immune response to malaria is greatly determined by the activities of antigen presenting cells ($APCs$), namely dendritic cells(DCs), macrophages and B lymphocytes. $APCs$ capture and process antigens for presentation to T cells ($CD4^+$ and $CD8^+$ T cells). During phagocytosis, bacteria are usually altered through a process called opsonization, such that they are more readily and more efficiently engulfed. Although macrophages contribute immensely to opsonisation and phagocytosis of malaria pathogens it is still unclear as to how tissue macrophages interact with blood stage merozoites. Due to the inherent connectivity of the organs of the immune system with one another and with other organs and tissues by the network of lymphatic vessels, it becomes possible for lymphocytes to travel through blood vessels and cells through the lymphatic vessels thereby, creating an exchange of fluid and cells through blood and lymphatic vessels, enabling the lymphatic system to track evading pathogens. There are likely two possibilities in which tissue macrophages can encounter blood stage merozoites. The lymph node could be a meeting point since antibodies are known to mill around a lymph node waiting for a macrophage to bring an antigen [79], or a macrophage stationed in the tissue might catch a merozoite or infected erythrocyte since these could be found in the blood transported to the tissues. Furthermore, given that the erythrocyte stages of plasmodium circulates in the blood and do not enter tissues, the most likely location for such innate mechanism to take place is the spleen [104]. Figure 4.2 illustrates the working of

the immune system starting from antigen presentation by the innate immune cells to the development of specific immune response. With the aid of toll-like receptors ($TLRs$) expressed on their membrane, dendritic cells recognise and capture malaria parasites and infected red blood cells most likely at the Marginal Zone for presentation to $CD4^+$ and $CD8^+$ T cells. Initial preparations involves coating the pathogens with antigens especially in association with MHC class II and other costimulatory molecules for proper recognition by the T cells. This initiates differentiation of $CD4^+$ T cells into helper cells, namely T helper $1(Th1)$ and T helper 2 ($Th2$) cells and Regulatory T cells (T_{reg}). Mature dendritic cells produce IL-12 inducing
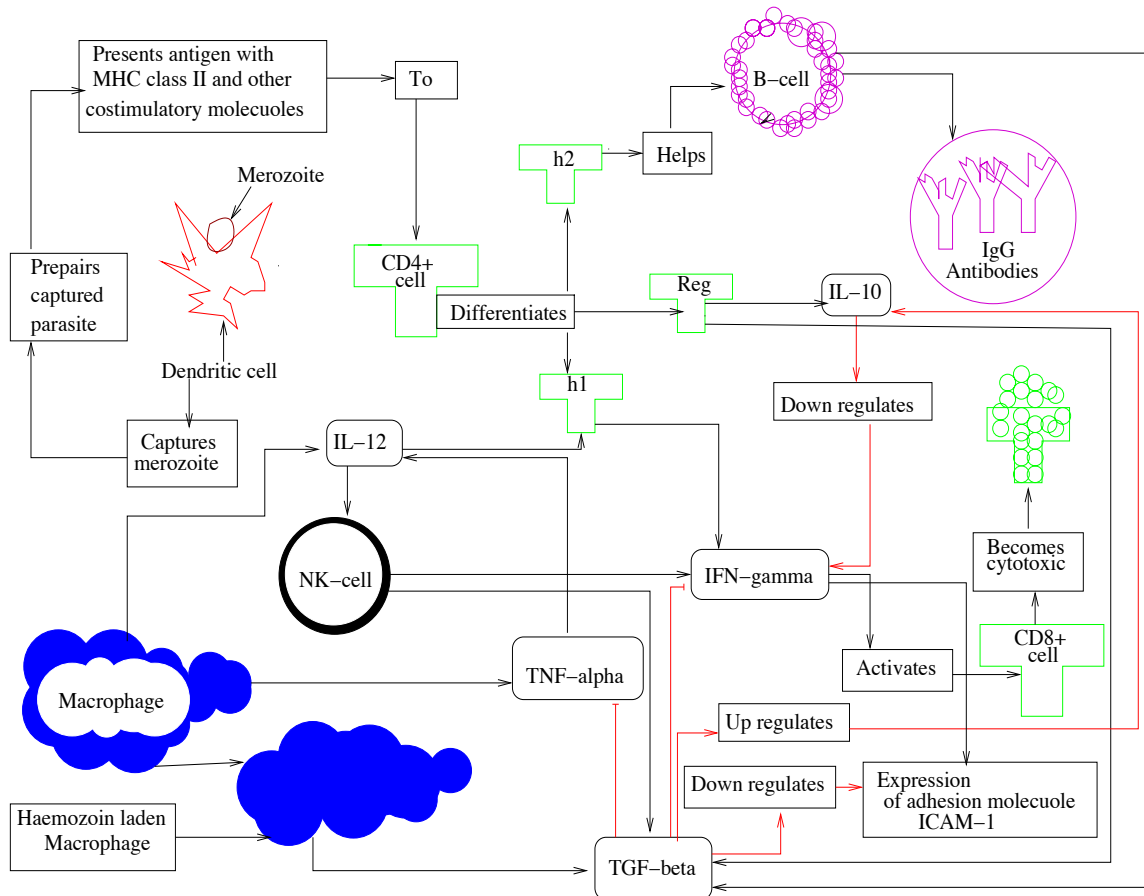
Figure 4.2: Pathway diagram of immune response in relation to malaria infection. Dendritic cells capture parasites and present antigens to naive $CD4^+$ T cells. These cells differentiates into regulatory cells and $Th1$ and $Th2$ helper cells. The $Th2$ cells help B cells to produce IgG malaria specific antibodies. The $Th2$ cells produce Interferon gamma which activates $CD8^+$ T cells to kill parasites. Natural killer cells and macrophages also produce interferon gamma directly or indirectly. In a situation of severe pathology, the partway diagram illustrates inhibition of interferon gamma and other stimulatory molecules to reduce disease severity.

$Th1$ cell to produce inflammatory cytokine Interferon gamma (IFN-γ), which makes $CD8^+$ T cells to become cytotoxic, hence having the capacity to phagocytose. $Th2$ cells help B cells to differentiate into plasma cells and secret antibodies. IL-12 activates natural Killer (NK) cells, which further enhances the production of (IFN-γ). Macrophages activated by (IFN-γ) produce inflammatory cytokines such as Tumour Necrosis Factor$-\alpha$ (TNF-α), IL-1, IL-6. In the majority of patients with severe and uncomplicated malaria, TNF-α and IL-1 regulate intercellular adhesion molecule 1 ($ICAM$-1) [88], which in addition to $CD36$, bind infected erythrocytes [88, 13]. We note that binding of uninfected red blood cells is also possible. The binding of uninfected and parasite infected erythrocytes to endothelial cells through $CD36$ has been examined in vitro by [75] with the binding of parasite infected erythrocytes being significantly higher than that of uninfected erythrocytes, which may have been bound inadvertently since uninfected erythrocyte binding is independent of IFN-γ. Through phagocytosis, macrophages and dendritic cells become heavily loaded with indigestive particles, haemozoin due to uptake of haemoglobin, retarding their functional capacity as antigen-presenting cells and resulting in a situation where large amounts of pro-inflammatory cytokines, precisely (IFN-γ) and (TNF-α).

The pathogenic manifestations of malaria are mainly due to these pro-inflammatory cytokines released by macrophages in response to malaria parasites and their products [102]. However, these unpleasant inflammatory responses do not continue indefinitely as they are often regulated by some immunosuppressive anti-inflammatory cytokines. For instance, the immunomodulatory cytokines IL-10 and Transforming growth factor β (TGF-β) play a key role in limiting the pathology of malaria [86]. High ratios of IFN-γ, TNF-α and IL-12 to TGF-β, or IL-10 are associated with decreased risk of malaria infection but increased risk of clinical disease in those who do become infected [33]. TGF-α particularly plays an important

role in controlling the transition between proinflammatory and anti-inflammatory responses during the acute and resolving phases of the disease by mediating through a dose-depended effect, the activation of macrophages, inhibiting both IFN-γ and TNF-α production, while at the same time upregulating IL-10 and downregulating the expression of adhesion molecules [78]. The immune system plays a key role in disease pathogenesis in the human host. Many epidemiological modellers have used mathematical models to describe in-host interaction of blood stage malaria parasites with red blood cells and the immune system. We present a brief review of some of these models in the next section.

4.2.1. Review of within host models

We learnt from the life history of the malaria parasite that the female anopheles mosquito deposits sporozoites, the assexual form of the parasite into the human system and later picks up gametocyte, the sexual form of the parasite from the human blood. Out of the three phases of the malaria parasite development, it is only the sporozoite formation phase that takes place inside the mosquito. The other two phases namely, the merozoite and the gametocyte formation stages occur in the human host. The blood stage merozoite replication process is the main cause of malaria morbidity and mortality. Like most, all other infectious diseases, malaria infection triggers both the innate and adaptive immune responses [11]. Thus, understanding the dynamics of the parasite in the human host is crucial to the quest for malaria elimination and eradication.

The first model describing malaria parasite interaction with the human host seems to be that of Anderson et al. [4] where they used several mathematical models to examine nonlinear dynamical phenomena in host parasite interaction. One of these models was used to investigate the effects of immunological responses that target different stages in a parasite life cycle. In a more detailed consideration, they made particular reference to the malaria

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parasite life cycle in which their findings suggest that the effectiveness of a given immunological response is inversely proportional to the life expectancy of the target stage of the parasite development cycle.

In a related work, a single strain mathematical model was proposed by Hetzel and Anderson [51] to investigate blood-stage malaria infection. The model is a slight modification of that of Anderson et al. [4] in which an additional loss term was included based on the assumption that merozoites are equally likely to be absorbed into already infected erythrocytes. In analysing the model they consider the parasite and host red blood cell population dynamics in the absence of immunity. They find that certain conditions determined by the model parameters will favour persistent invasion of red blood cells by parasites, leading to the identification of some important parameters like the rates of merozoite production and death and those of erythrocyte production, death and invasion. Numerical results show oscillatory behaviour in which they aver that the basic force behind the rise and fall in parasitaemia in the model without immunity is the density of susceptible erythrocytes, suggesting that availability of red blood cells is crucial in the determination of the initial pattern of infection during malaria. On analysing the model with simple immune response, they find that the destruction of infected red blood cells by immune cells is much more effective in controlling parasite density than the destruction of merozoites by immune cells.

Considering antigenic variation and multiple strain biology, Anderson [6] presented a mathematical framework to interpret the interaction between parasite population growth and the host immune system with special attention to the effect of antigenic variation and parasite evolution in response to immunological attack through the use of a chemotherapeutic agents. The concept of multiple strain presence in the parasite population was integrated in a simple mathematical model and the results show a build-up of non-specific immunological responses

leading to reduction of total parasite abundance. Prior to this reduction, the periods of the oscillations in the abundances of each strain are set by the proliferation rate of each parasite strain and the magnitude of the specific immunological responses induced death rate of the parasites.

Since 1988, when the first work on within-host modelling was initiated, a considerable work has been done in this area and a review of some of them is given by Molineaux and Dietz [74]. Most of the works range from modelling the dynamics of the densities of healthy erythrocytes, infected erythrocites and free merozoites without the immune system to those involving immune effectors. Prominent in the characteristics of the results is the periodicity and synchronisation of events during parasite invasion of red blood cells. For instance, Hoshen et al. [53] used an in-host mathematical model with and without immune response to study the blood stage development of *P. falciparum* asexual parasite and they find that synchronicity of the infection followed by periodic symptoms seems to be an inherent feature of infection, irrespective of the duration of merozoite released from the liver. It will, therefore, cause fever and other uncomfortable symptoms as known in malaria patients. They also simulate the effects of an induced host immune response and show how the level of immunity affects the development of the disease. Using an age-structured model, Rouzine and McKenzie [98] also show that Periodic fever experienced by the host during malaria attack is due to synchronisation between the replication cycles of parasites in red blood cells initiated by innate immune responses. Although the mechanism of synchronisation is yet to be well understood, periodic oscillations characterising intra-host models with immunity has been widely reported.

During malaria infection interaction between red blood cells, merozoites and the immune effectors lead to erythrocyte destruction. Thus anaemia appears to be an inevitable consequence of malaria infection. Gravenor et al. [46], proposed an in-host model with immune

response aimed at regulating malaria parasitemia. They fitted their model to data from Kitchen [57] representing percentage of uninfected erythrocytes over 4 weeks of an artificially induced infection in a malaria therapy patient. In a concluding remark they state that the interaction between parasites and erythrocytes when combined with immune mechanisms indicates that in the long term, parasite replication at low parasite densities can contribute significantly to the high degree of anaemia observed in natural infection. However, Jakeman et al. [54] contend that it is the destruction of uninfected red blood cells that primarily results in anaemia in non-immune patients. They fitted their discrete model result to parasitemia and anaemia data from neurosiphilis patients undergoing malaria therapy and find that for each red blood cell that is observed to become parasitised, an additional 8.5 red blood cells are destroyed through phagocytosis of erythrocytes bound to merozoites.

However in a new treatment model of within host dynamics proposed by Chiyaka et al. [23], non-oscillatory solutions are observed. Their model is aimed at correcting two key areas they identified as lacking in previous models. That is, inability to show the effect of immune effectors on merozoite invasion of red blood cells including suppression of parasite production by antibodies and the inability to account for the accelerated supply rate of red blood cell from the bone marrow during a malaria infection and the loss of infected erythrocytes. The model is a system of five ordinary differential equations in which the contributions of red blood cells, infected red blood cells, merozoites, B cells and antibodies are well represented. In analysing the model, they derived the basic reproduction number for parasite invasion in the presence or absence of immune response and a critical drug efficacy that is required for parasite clearance in case the immune system fails to clear the parasites. The numerical results show that without treatment, the most effective role the immune system plays to clear parasite is its ability in inhibiting parasite growth in erythrocytes. Increasing the death rate

of infected red blood cells is more effective than the death rate of merozoites by immune cells.

This model appears to improve on previous models by integrating some of the known biology. However, it does not account for the natural death rate of infected red blood cells that may occur within the period of schizogony, but rather considers the bursting rate as the death rate, a trend that has followed other previous in-host models. This gives an incorrect expression for the basic reproduction number as expressed in their work. Although, their basic reproduction number contains the infected red blood cell death rate constant, it can be shown through the same method they have used that this constant will vanish when determining the largest eigenvalue of the matrix describing the secondary infections arising from the initial infection. A later work by Tuwiine et. al [112] improved on this limitation, but omitted some important aspect of the biology since other parts of the model replicate the structure of previous in-host models. Another in-host model with immune response describing the dynamics of malaria infection was proposed by Li et al. [61] in which they generalise the ideas in some known models including those in Anderson [6] and Chiyaka et al. [23]. A more general class of within host malaria model has been given by Tewa et al. [107] in which they carry out local and global stability analysis on the disease free equilibrium.

4.2.2. Summary from the survey

In-host malaria models describe the interaction of host red blood cells with blood stage parasites. Throughout our survey, we find that none of the in-host models show explicitly the effect of innate immune response on the pathology of the disease or account for the natural death rate of infected red blood cells during the period of schizogony.

In the next chapter, we present the derivation, and analysis of an in-host model. We will model the post-liver stage of malaria development and immune response with time delay between first contact of innate immune cells and antigen presenting cells, and the emergence

of trained adaptive immune cells aimed at describing the interaction between red blood cells in a naive human host after a single infectious mosquito bite. Some of the features of the model proposed in Chiyaka et al. [23] will be adopted and we show explicitly, the activities of innate immune cells in respect of antigen presentation, describing their role in activating specific immune response. For mathematical tractability we will be making considerable simplifications, however the separate and common role of innate and adaptive response will be preserved.

CHAPTER 5

DESCRIPTION AND ANALYSIS OF WITHIN-HOST MATHEMATICAL MODELS

5.1. Model development

In the previous chapter, the human pathogenesis and immune response was discussed. In this chapter we derive and study a mathematical model that describes the infiltration of red blood cells by merozoites and the immune activity that aims to interfere and destroy the infection. The health of the infected individual is dependent on the red blood cell count of the host, denoted as density X. We assume that a population of merozoites, of density M, are introduced at $t = 0$ say, representing release from the liver. Red blood cells infected by merozoites react with healthy cells to move to an infected state, (density Y). The maturation of infected red blood cells results in the production of subsequent generations of merozoites with some differentiating into gametocytes being the asexual form of the parasites. We use G to represent the concentration of gametocytes.

The working of the immune system in response to the plasmodium parasite ensures several immune cells working in unison to protect the host against severe pathology. Due to

mathematical tractability and simplicity, coupled with a reasonable consideration of biological relevance, we use one variable P to represent the blood-borne phagocytic innate immune cell density (NK cells, macrophages and dendritic cells) that also serve as antigen presenting cells. Antibodies are produced in large amount by B cells induced through T cells activation in response to signals from P, and since antibody-mediated immunity is more effective than cell-mediated immunity [28], we denote the activities of antibodies, trained T cells and B cells by the variable A designating it as concentration of adaptive immune cells. Although It is quite unusual, but for the purpose of this work we will also be referring to A as concentration of antibodies. Cytokine output by adaptive immune cells is assumed to be rapid, and in quasi-equilibrium with immune cell density. The state variables and their descriptions are summarised in Table 5.1

State variable	Description
X	Concentration of red blood cells
Y	Concentration of infected red blood cells
M	Concentration of merozoites
G	Concentration of gametocytes
P	Concentration of innate immune cells
A	Concentration of antibodies

Table 5.1: The state variables in the model   .

Merozoites infect red blood cells on contact but the presence of antibodies restricts this process. Adopting a single mass action kinetic form for the interaction between merozoites and blood cells, we assume infection rate is given by $\beta_x X M/(1 + c_0 A)$, where β_x and c_0 are constants. The factor $1/(1 + c_0 A)$ is the role of antibodies in blocking invasion and c_0, the efficiency of antibodies in reducing erythrocytic invasion. Since red blood cells develop continuously from stem cells in the bone marrow through reticuloctyes to mature in about

7 days and live a total of about 120 days [93], we assume a rate of recruitment, λ_x, of fresh erythrocytes from the bone marrow and a natural death rate, $\mu_x X$. Combining these assumptions, we have for infected red blood cells

$$\frac{dX}{dt} = \lambda_x - \frac{\beta_x X M}{1 + c_0 A} - \mu_x X. \tag{5.1.1}$$

The removal of Infected red blood cells through phagocytosis by the innate immune cells occurs on contact, and is enhanced by the presence of antibodies [123]. A single expression to describe this process is $k_y P Y (1 + k_a A)$, where k_y and k_a are constants. We assume that during the $2-$day period of parasitised erythrocyte schizogony, which occurs in 5 stages, first and subsequent generation infected red blood cells die at rates $\mu_n Y$ [14], or survive to experience a per capita death rate μ_y due to parasite induced rupture. Combining these assumptions gives

$$\frac{dY}{dt} = \frac{\beta_x X M}{1 + c_0 A} - (\mu_y + \mu_n) Y - k_y P Y (1 + k_a A), \tag{5.1.2}$$

where the source term assumes that there is no loss of blood cells on infection.

The rupturing of an infected red blood cell produces an average of r merozoites such that the net rate of merozoites production is $r \mu_y Y (1 - \theta)/(1 + c_1 A)$, where θ is the fraction of merozoites committed to gametocytogenesis, r is the the number of merozoites per bursting schizont and c_1 is the efficiency of antibodies in blocking the release of new merozoites. Gametocytes and merozoites die naturally at rates $\mu_g G$ and $\mu_m M$ or are killed by innate and adaptive immune cells. Merozoites last only about 30 minutes if they fail to infect red blood cells [70]. Whilst the lifespan of gametocyte is about 16 days [49]. As with infected red blood cells, the immune system will attack merozoites directly on encounter, this too being enhanced by antibodies presence. Unlike [23] that considers antibodies that block invasion only, we assume that antibodies assist phagocytic cells in killing merozoites [67] and also inhibit gametocyte development in the human host by binding to young gametocytes during

their developmental stages [108]. An antibody binding to the surface of a merozoite, could neutralise parasites, or lead to Fc-dependent mechanisms of parasite killing by macrophages [67, 100]. The rate of merozoites and gametocytes killing through binding are expressed as $k_m k_b PAM$ and $k_g k_c PAG$ in (5.1.3) and (5.1.4) respectively with rate constants k_m and k_g. Hence,

$$\frac{dM}{dt} = \frac{r\mu_y (1-\theta) Y}{1+c_1 A} - \frac{\beta_x MX}{1+c_0 A} - \mu_m M - k_m PM (1+k_b A), \qquad (5.1.3)$$

$$\frac{dG}{dt} = \frac{r\mu_y \theta Y}{1+c_1 A} - \mu_g G - k_g PG (1+k_c A). \qquad (5.1.4)$$

It is assumed that immune cells are partly supplied from stem cells in the bone marrow at a constant net rate b_m and partly stimulated by the presence of infected red blood cells and merozoites [23] at a constant per capita rate. We assume that immune cells die at a rate $\mu_p P$. The induced rate of innate immune cell production by parasites presence is represented by $\eta_1(Y + \phi M)$ where ϕ is some constant indicating the phagocyte growth differences between merozoites and infected red blood cells. The production of malaria specific antibodies is most likely associated with the presence of sporozoites or merozoites and their ability to infect host cells triggering immune response. Antibodies A are recruited at rates proportional to merozoites and parasites presence at a rate $\eta_2\{Y(t - d_1) + g_2 M(t - d_1)\}$ with a constant, g_2, representing adaptive immune cell production difference between merozoites and parasitized red blood cells, and a time delay, d_1, being the lag between the time of contact of parasites and antigen presenting cells and the time when adaptive cells are produced. The terms $P(k_y Y + k_m M)$ and $A(\eta_3 Y + \eta_4 M)$ describe the deterioration rates of innate immune cells and antibodies, respectively, due to their interaction with the parasites. We assume that antibodies die at a rate $\mu_t(A_0 - A)$, where, A_0 is some non-zero starting density and assuming the number of memory cells does not change much over the course of a single malaria cycle, then the number of memory cells decline as the merozoites are removed. Combining these

assumptions we have for the innate immune cells and antibodies

$$\frac{dP}{dt} = b_m + \eta_1\left(Y + \phi M\right) - \mu_p P - P\left(k_d Y + k_n M\right), \tag{5.1.5}$$

$$\frac{dA}{dt} = \eta_2\{Y(t - d_1) + g_2 M(t - d_1)\} + \mu_a\left(A_0 - A\right) - A\left(\eta_3 Y + \eta_4 M\right). \tag{5.1.6}$$

5.1.1. Initial and history conditions

Our primary aim is to study infection in a previously uninfected human caused by a single mosquito infectious bite. Thus the initial condition for X is the concentration of red blood cells describing the healthy state of the individual. This is represented by the healthy steady state rate, λ_x/μ_x. Similarly, we will use the immune cell steady state b_m/μ_p as the initial density of innate immune cells in the individual. We recall from 4.1 that a successful infectious bite of a mosquito can produce an average of 525000 merozoites giving the initial concentration of merozoites released into the blood stream as 0.105 cells/μl. The concentration of infected red blood cells as well as that of gametocytes is zero at the release of hepatic merozoite since it is the blood stage merozoites that penetrate red blood cells and eventually convert to gametocytes.

As mentioned in the equation describing the concentration of antibodies we want to emphasize that the choice of A_0 as a non-zero initial density of antibodies is important in that instead of restricting the model to only a single contact it makes provision for subsequent contacts which will lead to accumulated immunity from previous infections. For first contact, $A_0 = 0$ and since the number of memory cells does not change much over the course of a single infection, then $A \to 0$ as the parasites are cleared. However, if a second infection is initiated before antibodies completely decline to zero, after the first set of parasites have been removed, then $A \to A_0$ indicates some additional amount of immunity after one infection.

Hence, we will study the system subject to the initial conditions

$$X(0) \;=\; \lambda_x/\mu_x, \;\; Y(0) = 0, \;\; M(0) = 0.105, \;\; G(0) = 0, \;\; P(0) = \beta_m/\mu_p, \;\; A(0) = 0$$

In a delay differential equation, the time derivative at the current time depends on the solution and possibly its derivative at previous times. The derivative in (5.1.6) depends on the solution at the previous time $t - d_1$, it is necessary to provide an initial history function to specify the value of the solution before time $t = 0$. Hence we state the following history condition.

$$X(t) \;=\; \lambda_x/\mu_x, \;\; Y(t) = 0, \;\; M(t) = 0, \;\; G(t) = 0, \;\; P(t) = \beta_m/\mu_p, \;\; A(0) = 0, \;\; \forall t < 0.$$

The model has lots of parameters and we need to determine their values in order to carry out a proper study of the dynamics. However, we will first derive the dimensionless form of the model in the next section as this will provide a basis for determining the dimensional parameter values.

5.2. Nondimensionalisation

The dynamics in this system works on a number of time scales, e.g. natural red blood cell turnover (~ 120 days), blood infiltrated merozoite maturation in blood cells (~ 2 days), non-infiltrated merozoite survival (~ 30 minutes), adaptive immune response (~ 2 days), etc. We scale time with the maturation of merozoites and write

$$t = \frac{\hat{t}}{\mu_y},$$

where, more precisely, $\dfrac{1}{\mu_y}$ is the duration of schizogony leading to cell induced death of infected red blood cells and subsequent release of new generation merozoites. The dimensionless time, $\hat{t} = 1$ represents a time scale of about 2 days, which is a relatively longer time compared with the longevity of merozoites and their invasion capacity. The choice of this scaling will enable us to study the system in relation to the replication rate of blood stage parasites. We

normalise the red blood cell variable using the healthy steady state rate, λ_x/μ_x. We also rescale the infected red blood cell, merozoite and gametocyte using the same parameter, so, it is easier to ascertain directly the ratio between blood cells and merozoites. We rescale the innate immune density with the healthy state b_m/μ_p and antibodies with activation level $1/c_0$. We thus make the following scalings,

$$X = \frac{\lambda_x}{\mu_x}\hat{X}, \; Y = \frac{\lambda_x}{\mu_x}\hat{Y}, \; M = \frac{\lambda_x}{\mu_x}\hat{M}, \; G = \frac{\lambda_x}{\mu_x}\hat{G}, \; P = \frac{b_m}{\mu_p}\hat{P}, \; A = \frac{1}{c_0}\hat{A}.$$

We define the following non-dimensional parameters

$$
\begin{aligned}
\sigma &= \frac{\mu_x}{\mu_y}, \; \beta = \frac{\beta_x\lambda_x}{\mu_x\mu_y}, \; \mu = \frac{\mu_n}{\mu_y}, \; d = \frac{\mu_m}{\mu_y}, \; k_1 = \frac{k_a}{c_0}, \; k_2 = \frac{k_b}{c_0}, \; k_3 = \frac{k_c}{c_0}, \; k = \frac{k_y b_m}{\mu_p\mu_y}, \\
e &= \frac{\mu_g}{\mu_y}, \; b = \frac{\mu_p}{\mu_y}, \; \alpha = \frac{k_m b_m}{\mu_p\mu_y}, \; f = \frac{k_g b_m}{\mu_p\mu_y}, \; \omega = \frac{\lambda_x\mu_p\eta_1}{b_m\mu_x\mu_y}, \; h_1 = \frac{\eta_3\lambda_x}{\mu_x\mu_y}, \; h_2 = \frac{\eta_4\lambda_x}{\mu_x\mu_y}, \\
\phi_0 &= c_0 A_0, \; g_1 = \frac{\eta_2 c_0\lambda_x}{\mu_x\mu_y}, \; g_3 = \frac{\mu_a}{\mu_y}, \; k_4 = \frac{k_d\lambda_x}{\mu_x\mu_y}, \; k_5 = \frac{k_n\lambda_x}{\mu_x\mu_y}, \; \tau = d_1\mu_y, \; k_6 = \frac{c_1}{c_0}.
\end{aligned}
$$

which leads to the dimensionless form of the system

$$\frac{dX}{dt} = \sigma(1-X) - \frac{\beta XM}{1+A}, \tag{5.2.1}$$

$$\frac{dY}{dt} = \frac{\beta XM}{1+A} - (1+\mu)Y - kPY(1+k_1 A), \tag{5.2.2}$$

$$\frac{dM}{dt} = \frac{r(1-\theta)Y}{1+k_6 A} - \frac{\beta MX}{1+A} - dM - \alpha PM(1+k_2 A), \tag{5.2.3}$$

$$\frac{dG}{dt} = \frac{r\theta Y}{1+k_6 A} - eG - fPG(1+k_3 A). \tag{5.2.4}$$

$$\frac{dP}{dt} = b(1-P) + \omega(Y+\phi M) - P(k_4 Y + k_5 M), \tag{5.2.5}$$

$$\frac{dA}{dt} = g_1\{Y(t-\tau) + g_2 M(t-\tau)\} + g_3(\phi_0 - A) - A(h_1 Y + h_2 M). \tag{5.2.6}$$

subject to the following history and initial conditions

$$(X(t), Y(t), M(t), G(t), P(t), A(t)) = \begin{cases} (1,0,0,0,1,0) & \text{for } t < 0, \\ (1,0,1.05\times 10^{-7},0,1,0) & \text{for } t = 0. \end{cases} \tag{5.2.7}$$

We note that (5.2.4) is redundant since it is decoupled from the other equations. However, we include it in order to determine the concentration of gametocytes in a single malaria cycle.

We solve the system using the dimensionless parameter values shown in Table 5.2, where parameter values are expressed in terms of a small parameter, ϵ to enable the application of asymptotic analysis in describing timescales of events in the human host as parasites interact with red blood cells. We define ϵ as the ratio of μ_n and μ_m so that $\epsilon \ll 1$ describes a situation where the death rate of merozoites is large compared to the death rate of infected red blood cells making merozoite survival a direct consequence of parasite replication and disease pathology. Following our remarks in the last part of section 5.1.1, we will now discuss the estimation of the model parameter values in the next section.

5.3. Parameter values

The definitions of the various dimensionless and dimensional parameters are given in Table 5.2 and Table 5.3 respectively. The values of the parameters used for the simulations are derived from different sources including experimental data, estimates from other mathematical models and estimates from our model. Parameter values obtained from experimental sources or other mathematical models are indicated in Table 5.3 using asterisk or bullet with a description provided at the bottom. The choices of the remaining parameter values are made based on fitting the model to the malaria data of neurosiphilis patients in section 4.1.

Firstly we determine the dimensionless parameter values in the third column of Table 5.2 by fitting the model equations (5.2.1)−(5.2.6) to the malaria data of the patient infected with the *El Limon* strain. The solution is obtained using *dde*23, a MATLAB routine solver, with the initial and history conditions stated in (5.2.7). We show results in Figure 5.1 whilst details of the solver will be provided in section 5.8. The choice of parameter values is motivated by the qualitative behaviour of the solution. We note that there is evidence of secondary outbreak of the disease as shown in Figure 5.2. However, we have used a continuum approximation such that we ignore the concentration of merozoites when it is reasonably small, i.e. if $M < M_{min}$,

then $M \equiv 0, Y \equiv 0$ so, $dX/dt = \sigma(1-X)$. We consider sensible time scales for these processes, which will be discussed later in section 5.7, and we will only focus on the case where $M < M_{min}$ in section 5.7.6. Secondly we determine the values of the remaining dimensional parameters in Table 5.3 using the combinations of parameters expressed in the first column of Table 5.2

Dimensional form	Nondimensional parameter	Value	Value in terms of ϵ
$\frac{\mu_x}{\mu_y}$	σ	0.02	ϵ
$\frac{\beta_x \lambda_x}{\mu_x \mu_y}$	β	49	$O(\frac{1}{\epsilon})$
$\frac{\mu_n}{\mu_y}$	μ	0.11	$O(1)$
$\frac{\mu_m}{\mu_y}$	d	96	$O(\frac{1}{\epsilon})$
$\frac{k_a}{c_0}$	k_1	2.3	$O(1)$
$\frac{k_b}{c_0}$	k_2	20	$O(1)$
$\frac{k_c}{c_0}$	k_3	2.1	$O(1)$
$\frac{c_1}{c_0}$	k_6	15.2	$O(1)$
$\frac{k_y b_m}{\mu_p \mu_y}$	k	0.23	$O(1)$
$\frac{\mu_g}{\mu_y}$	e	0.034	$O(\epsilon)$
$\frac{\mu_p}{\mu_y}$	b	0.6	$O(1)$
$\frac{k_m b_m}{\mu_p \mu_y}$	α	30	$O(\frac{1}{\epsilon})$
$\frac{k_g b_m}{\mu_p \mu_y}$	f	0.35	$O(1)$
$\frac{\lambda_x \mu_p \eta_1}{b_m \mu_x \mu_y}$	ω	10	$O(1)$
$\frac{\eta_3 \lambda_x}{\mu_x \mu_y}$	h_1	0.45	$O(1)$
$\frac{\eta_4 \lambda_x}{\mu_x \mu_y}$	h_2	0.34	$O(1)$
$\frac{\eta_2 c_0 \lambda_x}{\mu_x \mu_y}$	g_1	1.8	$O(1)$
$\frac{\mu_a}{\mu_y}$	g_3	0.6	$O(1)$
$\frac{k_d \lambda_x}{\mu_x \mu_y}$	k_4	0.028	$O(\epsilon)$
$\frac{k_n \lambda_x}{\mu_x \mu_y}$	k_5	0.031	$O(\epsilon)$
r	r	16	$O(1)$
θ	θ	0.0064	$O(\epsilon)$
ϕ	ϕ	2	$O(1)$
g_2	g_2	1.86	$O(1)$
m_0	m_0	0.000000105	$O(\epsilon^2)$

Table 5.2: Dimensionless parameter values of Inhost model defined in terms of the small parameter $\epsilon = \frac{\mu_n}{\mu_m} \approx 0.001$, this being relevant for section 5.7.

Symbol	Description	Value	Unit	Source
λ_x	Rate at which red blood cells are recruited	4.15×10^4 *	$cells/\mu l/day$	[61, 4]
β_x	Rate constant describing infection rate of red blood cells	4.9×10^{-6} ●	$\mu l/cell/day$	estimated
μ_x	Natural per capita death rate of red blood cells	0.0083 ●	day^{-1}	[4]
μ_n	Natural death rate of infected red blood cells	0.055	day^{-1}	estimated
μ_y	Conversion rate of infected erythrocytes to merozoites	0.5 ●	day^{-1}	[51, 4]
r	Number of merozoites released per bursting schizont	16 ●	$dimensionless$	[51]
μ_m	Death rate of merozoites	48 ●	day^{-1}	[70, 61]
θ	Fraction of merozoites converting to gametocytes	6.4×10^{-3}	$dimensionless$	[106]
μ_g	Natural per capita death rate of Gametocytes	0.02	day^{-1}	estimated
c_0	Efficiency of antibodies in blocking merozoite invasion	0.6 *	$cell/mol$	[23]
c_1	Efficiency of antibodies in blocking merozoite release	1.12	$cell/mol$	estimated
k_a	Antibodies induced Fc-dependent killing rate of infected red blood cells	1.38	$cell/mol$	estimated
k_b	Antibodies induced Fc-dependent killing rate of merozoites	12	$cell/mol$	estimated
k_c	Antibodies induced Fc-dependent killing rate of gametocytes	1.26	$cell/mol$	estimated
k_y	Elimination rate of infected red blood cells by innate immune cells	0.9 *	$\mu ll/cell/day$	[23]
k_m	Elimination rate of merozoites by innate immune cells	1.18×10^2	$\mu l/cell/day$	estimated
k_g	Elimination rate of gametocytes by innate immune cells	1.4	$\mu l/cell/day$	estimated
b_m	Supply rate of immune cells from stem cells	0.038	$cell/\mu l/day$	estimated
η_1	Parasite induced innate immune cell production rate	1.3×10^{-7}	day^{-1}	estimated
η_2	Parasite induced specific immune cell production rate	3×10^{-7}	$mol\mu l/cell^2/day$	estimated
ϕ	Phagocyte growth difference between merozoites and infected red blood cells	2	$dimensionless$	estimated
g_2	antibodies production difference between merozoites and infected red blood cells	0.85	$dimensionless$	estimated
k_d	Deterioration rate of innate immune cells due to infected erythrocytes killing	2.8×10^{-9}	$\mu l/cell/day$	estimated
k_n	Deterioration rate of innate immune cells due to interaction with merozoites	3.1×10^{-9}	$\mu l/cell/day$	estimated
η_3	Deterioration rate of antibodies due to interaction with infected red blood cells	4.5×10^{-8}	$\mu l/cell/day$	estimated
η_4	Deterioration rate of antibodies due to interaction with merozoites	3.4×10^{-8}	$\mu l/cell/day$	estimated
μ_p	Death rate of innate immune cells	0.3	day^{-1}	estimated
A_0	Starting density of antibodies	0	$mol/cell$	estimated
μ_a	Death rate of antibodies	0.3	day^{-1}	estimated

Table 5.3: Inhost model parameters and their units. Values marked with asterisk (*) are estimates from other mathematical models and those marked with bullet (●) are obtained from experimental sources.
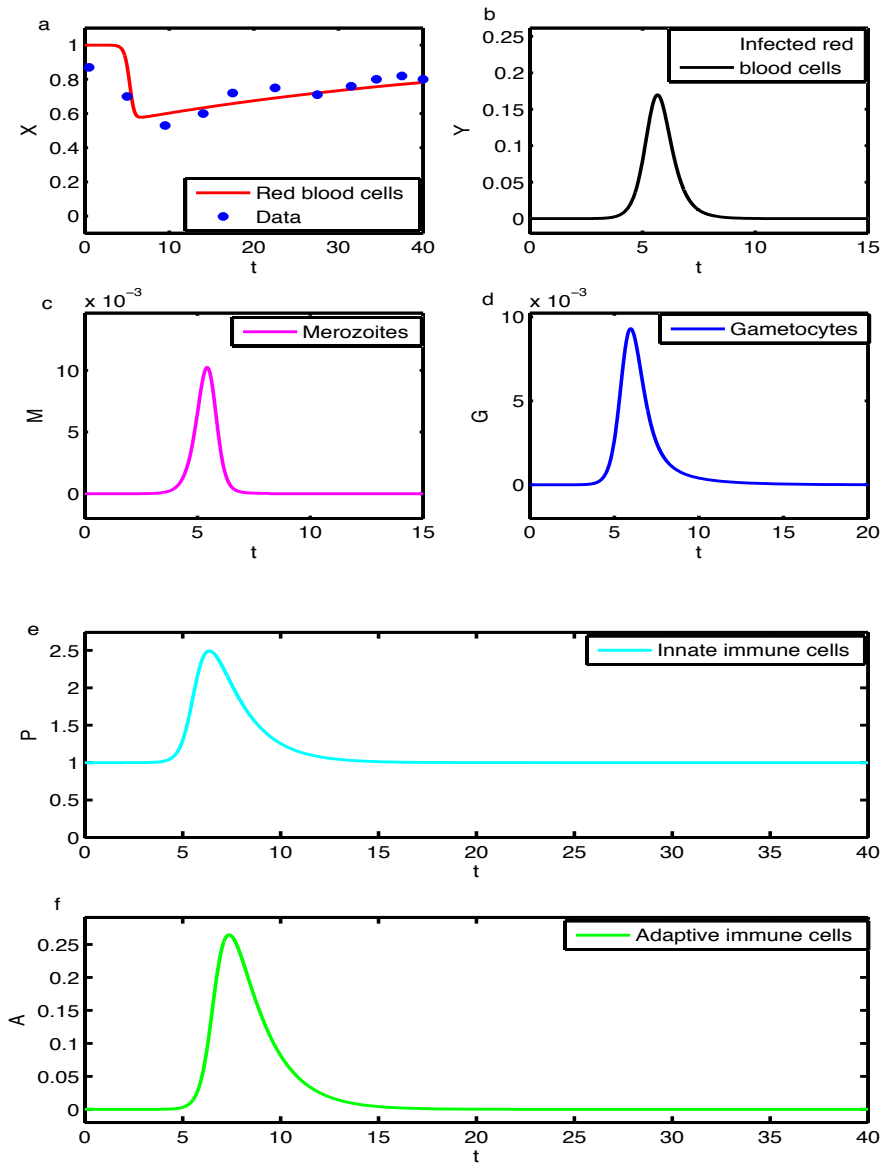
Figure 5.1: Results showing pathogenesis of malaria in the human host in which initially introduced merozoites invade red blood cells to reproduce and in the process form sexual parasites. Innate immune cells proliferate as they respond to pathogens. This culminates in the production of specific immune response that leads to parasite clearance. We note that $t = 1$, represents 2 days in real time corresponding to the the period of each erythrocytic schizogony. The initial conditions used are as stated above whereas the parameter values are $\sigma = 0.02$, $\beta = 49$, $\mu = 0.11$, $d = 96$, $k_1 = 2.3$, $k_2 = 20$, $k_3 = 2.1$, $k_6 = 15.2$, $k = 0.23$, $e = 0.034$, $b = 0.6$, $\alpha = 30$, $f = 0.35$, $\omega = 10$, $h_1 = 0.45$, $h_2 = 0.34$, $g_1 = 1.8$, $g_3 = 0.6$, $k_4 = 0.028$, $k_5 = 0.031$, $r = 16$, $\theta = 0.0064$, $\phi = 2$, $\phi_0 = 0$, $g_2 = 1.86$. The data represent those of a malaria patient infected with *El Limon* strain marked as patient $S1301$ in [54]

In Figure 5.1, the concentration of infected red blood cells drops to its minimum level due to invasion by merozoites and starts growing at the time of recovery when the immune system gains control. The minimum level of X, 0.55 occurs around $t = 5.4$. At the beginning of infection, the red blood cells seem to maintain their normal level until perhaps the
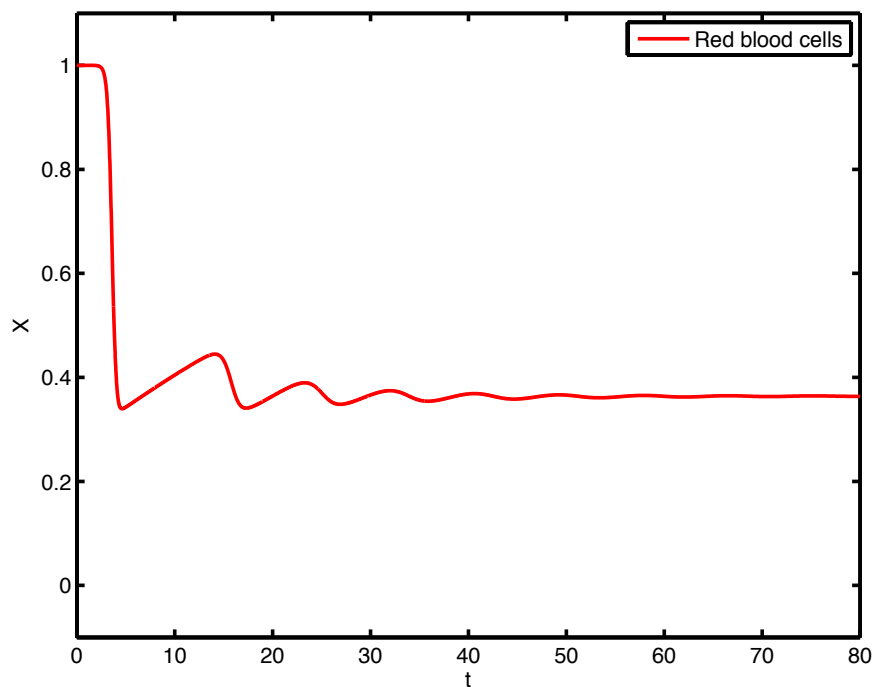
Figure 5.2: Results showing secondary outbreak of the disease. The concentration of red blood cells drops after the initial attack and recovery is initiated as immune response gains control. However, the immune cells relax after the concentration of merozoites drops creationg room for merozoites growth and re-invasion of the red blood cells. The initial conditions and the parameter values are the same as those in Figure 5.1

concentration of merozoites is large enough to offset the erythropoietic

function of red blood cells. In Figure 5.1b, c, d, the concentrations of infected red blood cells, merozoites and gametocytes peak, round about the same period when X drops to its minimum with M and Y having similar shapes an indication of some form of proportionality. This is an expected behaviour since a merozoite convert to an infected red blood cell on successfully penetrating a red blood cell. Although the peak value of M is less than that of Y, it may not be unconnected with the high death rate of merozoites.

Figure 5.1e describes how innate immune cells respond to the presence of malaria pathogens by proliferating to a peak value and finally tail off. At the initial stage of infection, P maintained its normal level and shortly after concentrations of parasites attain their maximum levels by dragging the concentration of red blood cells to its minimum, P grows to its peak.

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This facilitates rapid production of specific immune cells as shown in Figure 5.1f. Although not very clear from the graph, quite a negligible amount of A emerge after the time lag $t = 1$ during which innate immune cells initiates the training of naive T cells and B cells. The peak of innate immune cells marks a massive destruction of gametocytes, merozoites and infected red blood cells and as M and Y die out there is no more feed back from Y to G. Hence, the concentration of gametocytes decays and since there is no more infection to boost the production of antibodies, A dies out whilst P returns to its normal level.

In Figure 5.3 we show the effect of ϕ_0 on the dynamics of the disease. Up to now we have shown only the first contact case of $\phi_0 = 0$. After each contact the value of ϕ_0 in the context of the model will increment upwards a small amount, $\Delta\phi_0$ say, though we have assumed that $\Delta\phi_0 \ll 1$ in the analysis. The graph shows increasing ϕ_0, and hence the readiness of the
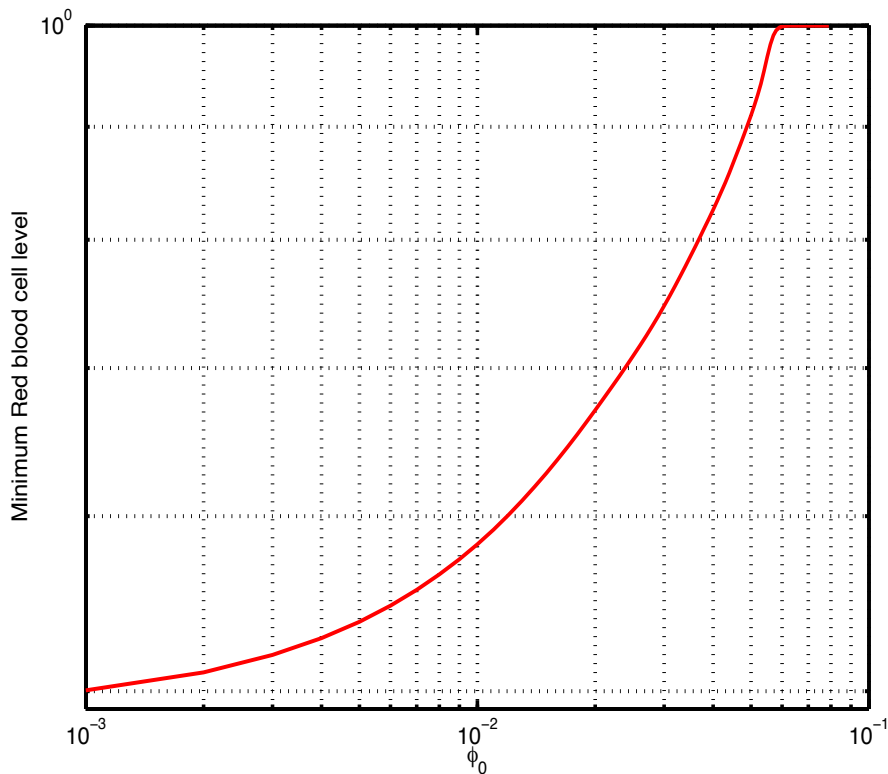

Figure 5.3: Results showing the effect of changing ϕ_0 on minimum level of red blood cells. The initial conditions and parameter values used are the same as those in Figure 5.1 except that $\phi_0 = 0$ was varied from 0 to 0.08 at interval of 0.001

innate immune response to respond, the amount of damage caused to red blood cells decreases until $\phi_0 \geq 0.071$ when the immune system is completely effective and interestingly, $\phi_0 = 0.71$ corresponds to $R_0 = 1$.

5.4. Existence and uniqueness of solution

The rescaling means that the uninfected state has $X = 1$, $P = 1$ and all other variables being zero. We note that since $\omega > k_4$ and $\omega\phi > k_5$ then $P \geq 1$. The scaling on Y and M being the same as that of X means that the RHSs are continuous. The solution of $(5.2.1)-(5.2.6)$ belongs to the set Ω, where Ω is defined on the set

$$\Omega = \{X, Y, M, G, P, A : 0 \leq X \leq 1, 0 \leq Y \leq 1, 0 \leq M \leq 1, 0 \leq G \leq 1, P \geq 1, A \geq 0\}.$$

It is straightforward to deduce positivity, as in each case $dZ/dt \geq 0$ when $Z = 0$, where $Z \in S = \{X, Y, M, G, P, A\}$ and all variables in S/Z are non-negative. We can easily show from (5.2.1) that $0 \leq X \leq 1$. Assuming there are times t_1 and t_2 such that $X(t_1) < 0$ and $X(t_2) > 1$. If we start with initial conditions, $X(0) > 0$, $M(0) > 0$ and $A(0) > 0$, then the trajectories of $X(t)$ for $0 < t < t_1, t_2$ will either tend towards 0, 1 or oscillate between 0 and 1. Suppose $X(t) = 0$, then $dX/dt > 0$ meaning $X(t)$ is increasing and cannot cross the line $X = 0$. Similarly, $X(t) = 1$ implies $dX/dt < 0$ and $X(t)$ cannot cross the line $X = 1$. Both cases contradict our initial assumptions $X(t_1) < 0$ and $X(t_2) > 1$ and we conclude that $0 \leq X(t) \leq 1$. *Theorem A* in (Driver, 1977, P259) states that a system

$$\frac{d\mathbf{X}}{dt} = \mathbf{F}\left(t, \mathbf{X}, \mathbf{X}\left(t - \tau_1\right), ..., \mathbf{X}\left(t - \tau_j\right)\right), \tag{5.4.1}$$

subject to the history condition

$$\mathbf{X}(t) = \mathbf{X}_0(t), \text{ for } - \max_{i=1,..,j}\left(\tau_i\right) \leq t \leq 0,$$

where $\mathbf{F}$ and $\mathbf{X}_0$ are Lipschitz continuous and the positivity condition

$$\frac{\partial \mathbf{F}_i}{\partial \mathbf{X}_i} \geq 0, \text{ when } X_i = 0 \text{ and } X_k \geq 0 \text{ for } k \neq i, \text{ holds,} \qquad (5.4.2)$$

then there exists a solution and it is unique. Although the theorem is hinged on "local Lipschitz" conditions, it suffices for uniqueness and F is locally Lipschitzian if it has first partial derivatives with respect to all the $X_i's$ [32]. In our case, $j = 1$, the history condition in 5.2.7 is continuous and F is the right hand side of system $(5.2.1)-(5.2.6)$. Certainly F is continuous, and so too are the partial derivatives. The system meets the criteria of this theorem, hence there exists a solution and it is unique.

5.5. The basic reproduction number

Using the same next generation matrix as in our previous analysis in Chapter 3, we consider the system

$$R'_h = F_h R_h - V_h R_h, \qquad (5.5.1)$$

where,

$$F_h = \begin{bmatrix} 0 & q_6 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad V_h = \begin{bmatrix} q_1 & 0 & 0 \\ -q_2 & q_3 & 0 \\ -q_4 & 0 & q_5 \end{bmatrix}, \quad R_h = \begin{bmatrix} Y \\ M \\ G \end{bmatrix}.$$

It can be shown that the linearisation of $(5.2.1)-(5.2.6)$ at the disease-free equilibrium is a two dimensional system without delay, which justifies the use of the next generation matrix approach. We note that whenever a merozoite penetrates a healthy red blood cell, a new infection or precisely, a new infected red blood cell emerges. The matrix $F_h R_h$ describes the emergence of these new infections. Every surviving infected red blood cell undergoes a process of schizogony or transition back to the merozoite compartment or differentiates into gametocytes. These pathogenic processes together with the immune response is represented

by $V_h R_h$ where R_h denotes the erythrocytic stages of the plasmodium life cycle. The constants $q_i's$ are expressed in terms of the model parameters as follows:

$$q_1 = 1 + \mu + k(1 + k_1\phi_0), \quad q_2 = \frac{r(1 - \theta)}{1 + k_6\phi_0}, \quad q_3 = \frac{\beta}{1 + \phi_0} + d + \alpha(1 + k_2\phi_0),$$

$$q_4 = \frac{r\theta}{1 + k_6\phi_0}, \quad q_5 = e + f(1 + k_3\phi_0), \quad q_6 = \frac{\beta}{1 + \phi_0}.$$

The non-negative matrix $G_h = F_h V_h^{-1}$ is expressed in the form

$$G_h = \begin{bmatrix} q_7 & q_8 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \tag{5.5.2}$$

where,

$$q_7 = \frac{q_2 q_6}{q_1 q_3}, \quad q_8 = \frac{q_6}{q_3}.$$

The square of the largest eigenvalue of G_h gives the inhost basic reproduction number

$$R_{01} = \frac{\beta r(1 - \theta)}{(1 + k_6\phi_0)(kk_1\phi_0 + 1 + \mu + k)(\alpha k_2\phi_0^2 + \alpha k_2\phi_0 + \alpha\phi_0 + d\phi_0 + \beta + d + \alpha)}, \tag{5.5.3}$$

which approximates the number of secondary red blood cell infections due to one hepatic merozoite released into the blood stream of a disease free human. Although the largest eigenvalue of G_h is $R_{01}^{1/2}$ the square root arises on the ground that it takes two generations for infected hosts to produce new infected hosts [31]. But in practise, the square root is left off the reproduction number.

We recall that one of the objectives of this work is to investigate whether or not a naive individual who contacts malaria through a single infectious bite will survive without treatment. The innate immune response and the development of adaptive immunity to contain the disease is imperative. Thus we will present three forms (R_{01}, R_{02} and R_{03}) of the basic reproduction number. The form presented in (5.5.3) contains ϕ_0, an initial amount of antibodies. This represents a situation in which an individual has a second or subsequent

contact after going through the first malaria episode and the time interval between contacts is short enough to guarantee the existence of some antibodies before the next contact. For first malaria infection, $\phi_0 = 0$ and the basic reproduction number will be

$$R_{02} = \frac{\beta r (1 - \theta)}{(1 + \mu + k)(\beta + d + \alpha)}. \tag{5.5.4}$$

A mere view of R_{02} suggests that the contribution of immunity to the control of infection is dominated by the innate immunity parameters k and α since the adaptive immunity profile parameters k_1, k_2, k_6 and ϕ_0 are absent. However, we note that $\phi_0 = 0$ is only an initial state of the level of specific immune cells in an individual without malaria antibodies at the time of infectious contact with a mosquito and as we can see clearly from (5.5.3), $\phi_0 = 0$ nullifies the specific contributions of k_1, k_2 and k_6 to the clearance of parasites but during infection some amount of antibodies are created and these parameters will become effective. The ability of innate immune cells in training naive T cells and B cells to create antibodies and complement the activities of phagocytic and natural killer cells, depends on the efficiencies of k and α. However, this may vary from human to human but lacking in HIV/AIDS patients. We can easily show that in the worst scenario where both innate and specific immune responses are absent, the basic reproduction number is

$$R_{03} = \frac{\beta r (1 - \theta)}{(1 + \mu)(\beta + d)}. \tag{5.5.5}$$

5.6. Steady state solution and stability analysis

It is worth noting that using the values in Table 5.2, $R_{03} \approx 3$. Since β is significantly smaller than d, then viable therapeutic strategies targeting merozoite invasion of red blood cells (reducing β) and enhancing merozoite death (increasing d) could potentially be effective.

This assumes that the values are reliable.

Our preliminary investigation centres on analysing the model, $(5.2.1)-(5.2.6)$ to ascertain whether a naive individual without immune response can survive a single infectious mosquito bite with the aim of determining the total number of gametocytes produced at the end of the infection or at death. The disease-free equilibrium point of system $(5.2.1)-(5.2.6)$ is $(X, Y, M, G, P, A) = (1, 0, 0, 0, 1, \phi_0)$. We commence the stability analysis by assuming a little perturbation away from the disease-free state. For instance, if we let for $t \geq 0$

$$X = 1 + \varepsilon \rho_1 e^{\lambda t}, \ Y = \varepsilon \rho_2 e^{\lambda t}, \ M = \varepsilon \rho_3 e^{\lambda t},$$

$$G = \varepsilon \rho_4 e^{\lambda t}, \ P = 1 + \varepsilon \rho_5 e^{\lambda t}, \ A = \phi_0 + \varepsilon \rho_6 e^{\lambda t},$$

where the $p_i s$ are constants and ε is a small parameter given the size of the perturbation, and $(X, Y, M, G, P, A) = (1, 0, 0, 0, 1, 0)$ for $t < 0$. The task is to find the eigenvalues, $\lambda = \lambda_i, i = 1, ..., 6$, such that $(\rho_1, \rho_2, \rho_3, \rho_4, \rho_5, \rho_6) \neq (0, 0, 0, 0, 0, 0)$.

By substituting the perturbations of X, Y, M, G, P and A in system $(5.2.1)-(5.2.6)$, which after rearranging and ignoring terms of $O(\varepsilon^2)$ leads to

$$
\begin{bmatrix}
r_1 & 0 & \beta & 0 & 0 & 0 \\
0 & r_2 & -\beta & 0 & 0 & 0 \\
0 & -r_4 & r_3 & 0 & 0 & 0 \\
0 & -r_6 & 0 & r_5 & 0 & 0 \\
0 & r_7 & r_8 & 0 & r_9 & 0 \\
0 & r_{10} & r_{11} & 0 & 0 & r_{12}
\end{bmatrix}
\begin{bmatrix}
\rho_1 \\
\rho_2 \\
\rho_3 \\
\rho_4 \\
\rho_5 \\
\rho_6
\end{bmatrix}
=
\begin{bmatrix}
0 \\
0 \\
0 \\
0 \\
0 \\
0
\end{bmatrix}
$$

where the $r_i s$ are expressed as

$$r_1 = (\phi_0 + 1)(\lambda + \sigma), \quad r_2 = (\phi_0 + 1)(kk_1\phi_0 + k + \lambda + \mu + 1),$$

$$r_3 = \alpha k_2 \phi_0^2 + \alpha k_2 \phi_0 + \alpha \phi_0 + d\phi_0 + \lambda \phi_0 + \beta + d + \alpha + \lambda,$$

$$r_4 = r(1 - \theta)(\phi_0 + 1), \quad r_5 = (k_6\phi_0 + 1)(fk_3\phi_0 + e + f + \lambda), \tag{5.6.1}$$

$$r_6 = r\theta, \quad r_7 = k_4 - \omega, \quad r_8 = k_5 - \omega\phi, \quad r_9 = b + \lambda,$$

$$r_{10} = e^{\lambda\tau}h_1\phi_0 - g_1, \quad r_{11} = e^{\lambda\tau}h_2\phi_0 - g_1 g_2, \quad r_{12} = e^{\lambda\tau}(g_3 + \lambda).$$

Since $(\rho_1, \rho_2, \rho_3, \rho_4, \rho_5, \rho_6) \neq (0, 0, 0, 0, 0, 0)$, the determinant of the coefficient matrix must be zero. Thus the eigenvalues satisfy the characteristic equation

$$r_1 r_{12} r_9 r_5 (r_2 r_3 - \beta r_4) = 0. \tag{5.6.2}$$

We observe that four of the eigenvalues are trivially negative and the remaining two are expressed in the following equation.

$$\lambda^2 + \left(r_{13} + \frac{r_{14}}{\phi_0 + 1}\right)\lambda + \frac{r_{13}r_{14}}{\phi_0 + 1}\left(1 - \frac{\beta r(1 - \theta)}{(k_6\phi_0 + 1)r_{13}r_{14}}\right) = 0. \tag{5.6.3}$$

where, r_{13}, r_{14} are defined as

$$r_{13} = kk_1\phi_0 + k + \mu + 1, \ r_{14} = \alpha k_2 \phi_0^2 + \alpha k_2 \phi_0 + \alpha\phi_0 + d\phi_0 + \beta + d + \alpha,$$

and the ratio in the second bracket is an expression for R_{01} in 5.5.3.

$$Sum\ of\ roots = -\left(r_{13} + \frac{r_{14}}{\phi_0 + 1}\right)\ and\ Product\ of\ roots = \frac{r_{13}r_{14}}{\phi_0 + 1}(1 - R_{01}).$$

Since all the parameters are positive, there will be at most one positive root if $R_{01} > 1$. Thus the disease free state is locally asymptotically stable if $R_{01} < 1$ and unstable for $R_{01} > 1$. We note that the delay term in (5.2.6) for dA/dt makes no contribution to this analysis.

5.7. Asymptotic analysis of in-host model

In this section, we will present the timescale analysis of the in-host model, which we have used to describe the progression of the disease from the release of merozoites from a rupturing hepatic schizont into the blood stream to the time of parasite clearance assuming a single infectious mosquito bite. The analysis shows that following a single infectious bite of a

mosquito, blood stage parasites proliferate causing a reduction in red blood cell level and depending on the intervention and efficiency of the immune response, parasites will be cleared. We have assumed that $\epsilon \ll 1$ and all parameters are equal to the fractional powers of ϵ as given in Table 5.2. It is a common practice in timescale analysis to use different notations in describing variables in different timescales but due to the numerous time scales involved in this analysis and for the sake of brevity, we have resorted to using an "over-bar" for each time scale noting that the solutions and discussions only apply to the particular time scale being considered. There are 7 major timescales as predicted by our model describing the trend of events on malaria pathogenesis in the human host. These include:

$t = O(\epsilon)$ **:** Initial concentration of merozoites decays as meroziotes infect red blood cells initiating the processes involved in the training of T cells and B cells with no significant effect on the order of X and P. Due to short term viability, meroziotes that could not penetrate red blood cells die out.

$t = \frac{\epsilon}{b_0} \ln\left(\frac{1}{\epsilon}\right) + O(\epsilon)(b_0 = \hat{\beta} + \hat{d} + \hat{\alpha})$ **:** In this timescale, the fast decaying density of merozoites drops by an order of magnitude due to infiltration into red blood cells.

$t = O(1)$ **:** A non-negligible amount of infected red blood cells convert to merozoites causing M and Y to equilibriate. Immature gametocytes emerge in low concentration as infected red blood cells mature to release subsequent generation merozoites some of which are committed to gametocytogenesis

$t = \tau + O(\epsilon)$ **:** This timescale marks the emergence of an initially negligible concentration of specific immune response in the form of trained T cells, B cells and antibodies after the initial lag time of antigen presentation.

$t = \tau + O(1)$ **:** increased density of parasites and infected red blood cells in this timescale

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stimulates more production of trained T cells and B cells. Break down in this timescale occurs when the concentration of infected red blood cells become $O(1)$, a period preceding the development of innate immune response capable of reducing the level of infection.

$t = \tau + \frac{2}{R} \ln(\frac{1}{\epsilon}) + O(1) \left(R = \frac{\hat{\beta}\hat{r}}{\hat{\beta}+\hat{d}+\hat{\alpha}} - (1 + \hat{\mu} + \hat{k}) \right)$ **:** This is the major timescale that describes the in-host dynamics. Infected red blood cell density, X decreases to its minimum. The immune system gains control as parasite levels peak and after reducing Y, M and G to negligible levels, P and A return to their normal states.

$t = O\left(\epsilon^{-1}\right)$ **:** In this time scale, red blood cells recover and return to normal level.

In this analysis, we will consider a case of first malaria infection caused by a single mosquito bite in which we have assumed $\phi_0 = 0$, signifying absence of initial concentration of malaria specific immune cells. Using the size of parameters indicated in Table 5.2 in terms of ϵ we rescale the parameters as follows.

$$
\begin{aligned}
\sigma &= \epsilon\hat{\sigma}, \;\; \beta = \frac{1}{\epsilon}\hat{\beta}, \;\; \mu = \hat{\mu}, \;\; d = \frac{1}{\epsilon}\hat{d}, \;\; k_1 = \hat{k}_1, \;\; k_2 = \hat{k}_2, \;\; k_3 = \hat{k}_3, \\
k_6 &= \hat{k}_6, \;\; k = \hat{k}, \;\; e = \epsilon\hat{e}, \;\; b = \hat{b}, \;\; \alpha = \frac{1}{\epsilon}\hat{\alpha}, \;\; f = \hat{f}, \;\; \omega = \hat{\omega}, \quad\quad (5.7.1) \\
h_1 &= \hat{h}_1, \;\; h_2 = \hat{h}_2, \;\; g_1 = \hat{g}_1, \;\; g_3 = \hat{g}_3, \;\; k_4 = \epsilon\hat{k}_4, \;\; k_5 = \epsilon\hat{k}_5, \\
r &= \hat{r}, \;\; \theta = \epsilon\hat{\theta}, \;\; \phi = \hat{\phi}, \;\; g_2 = \hat{g}_2, \;\; m_0 = \epsilon^2\hat{m}_0,
\end{aligned}
$$

where the quantities with hats are assumed $O(1)$ in size. These rescalings lead to the following system

$$
\epsilon\frac{dX}{dt} = \epsilon^2\hat{\sigma}\left(1 - X\right) - \frac{\hat{\beta}XM}{1+A}, \quad\quad (5.7.2)
$$

$$
\epsilon\frac{dY}{dt} = \frac{\hat{\beta}XM}{1+A} - \epsilon\left(1 + \hat{\mu}\right)Y - \epsilon\hat{k}PY(1 + \hat{k}_1 A), \quad\quad (5.7.3)
$$

$$
\epsilon\frac{dM}{dt} = \epsilon\frac{\hat{r}\left(1 - \epsilon\hat{\theta}\right)Y}{1+k_6 A} - \frac{\hat{\beta}XM}{1+A} - \hat{d}M - \hat{\alpha}PM\left(1 + \hat{k}_2 A\right), \quad\quad (5.7.4)
$$

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$$\frac{dG}{dt} = \epsilon\frac{\hat{r}\hat{\theta}Y}{1 + k_6 A} - \epsilon\hat{e}G - \hat{f}PG(1 + \hat{k}_3 A). \tag{5.7.5}$$

$$\frac{dP}{dt} = \hat{b}(1 - P) + \hat{\omega}\left(Y + \hat{\phi}M\right) - \epsilon P\left(\hat{k}_4 Y + \hat{k}_5 M\right), \tag{5.7.6}$$

$$\frac{dA}{dt} = \hat{g}_1 Y\left(t - \tau\right) + \hat{g}_1 \hat{g}_2 M\left(t - \tau\right) - \hat{g}_3 A - \hat{h}_1 AY - \hat{h}_2 AM, \tag{5.7.7}$$

subject to

$$t = 0, \ X = 1, \ Y = 0, \ M = \epsilon^2 \hat{m}_0, \ G = 0, \ P = 1, \ A = 0,$$

$$t < 0, \ X = 1, \ Y = 0, \ M = 0, \ G = 0, \ P = 1, \ A = 0.$$

We summarise the analysis for each timescale with full details in Appendix C.1.

5.7.1. $t = O(\epsilon)$

We scale time using

$$t = \epsilon\bar{t}$$

and relevant scalings for the dependent variables are

$$X \sim \bar{X}, \ Y \sim \epsilon^2 \bar{Y}, \ M \sim \epsilon^2 \bar{M}, \ G \sim \epsilon^4 \bar{G}, \ P \sim \bar{P}, \ A = 0. \tag{5.7.8}$$

To leading order we obtain

$$\frac{d\bar{X}}{d\bar{t}} \sim 0, \quad \frac{d\bar{Y}}{d\bar{t}} \sim \hat{\beta}\bar{M}, \quad \frac{d\bar{M}}{d\bar{t}} \sim -\left(\hat{d} + \hat{\beta} + \hat{\alpha}\right)\bar{M}, \quad \frac{d\bar{G}}{d\bar{t}} \sim r\theta\bar{Y}, \quad \frac{d\bar{P}}{d\bar{t}} \sim 0, \tag{5.7.9}$$

describing the initial state of the disease. These are subject to

$$\bar{t} = 0, \ \bar{X} = 1, \ \bar{Y} = 0, \ \bar{M} = \hat{m}_0, \ \bar{G} = 0, \ \bar{P} = 1, \ \bar{A} = 0.$$

Solving this system leads to the leading order solution

$$\bar{X} \sim 1, \quad \bar{P} \sim 1, \quad \bar{Y} \sim \frac{\hat{\beta}\hat{m}_0}{b_0}\left(1 - e^{-b_0\bar{t}}\right), \quad \bar{M} \sim \hat{m}_0 e^{-b_0\bar{t}},$$

$$\bar{G} \sim \frac{\hat{r}\hat{\theta}\hat{\beta}\hat{m}_0}{b_0}\bar{t} - \frac{\hat{r}\hat{\theta}\hat{\beta}\hat{m}_0}{b_0^2}\left(1 - e^{-b_0\bar{t}}\right), \quad \bar{A} = 0, \tag{5.7.10}$$

where

$$b_0 = \hat{\beta} + \hat{d} + \hat{\alpha}.$$

We observe that the initial concentration of merozoites released from hepatic schizont is decaying as meroziotes infect red blood cells. However, this does not have any significant effect on the order of X and P. The contact between innate immune cells and merozoites initiates the processes involved in the training of T cells and B cells, and due to the short term viability of merozoites the parasites that could not penetrate red blood cells die out. A rebalance of the system occurs when $\bar{M} = O(\epsilon)$, i.e. on a time scale of $\bar{t} = \dfrac{1}{b_0} \ln \left(\dfrac{1}{\epsilon} \right) + O(1)$.

5.7.2. $t = \frac{\epsilon}{b_0} \ln(\frac{1}{\epsilon}) + O(\epsilon)$

In order to describe events in this time scale, we write

$$t = \frac{\epsilon}{b_0} \ln \left(\frac{1}{\epsilon} \right) + \epsilon \bar{t}$$

and rescale the dependent variables as

$$X \sim \bar{X}, \;\; Y \sim \epsilon^2 \bar{Y}, \;\; M \sim \epsilon^3 \bar{M}, \;\; G \sim \epsilon^4 \frac{\hat{r}\hat{\theta}\hat{\beta}}{b_0^2} \ln \left(\frac{1}{\epsilon} \right) + \epsilon^4 \bar{G}, \;\; P \sim \bar{P}, \;\; A = 0.$$

Substituting these into the non dimensional system gives the leading order system

$$\frac{d\bar{X}}{d\bar{t}} \sim 0, \;\; \frac{d\bar{Y}}{d\bar{t}} \sim 0, \;\; \frac{d\bar{M}}{d\bar{t}} \sim \frac{\hat{\beta} r m_0}{b_0} - b_0 \bar{M}, \;\; \frac{d\bar{G}}{d\bar{t}} \sim \frac{\hat{r}\hat{\theta}\hat{\beta} \hat{m}_0}{b_0}, \;\; \frac{d\bar{P}}{d\bar{t}} \sim 0, \qquad (5.7.11)$$

subject to, by matching with $t = O(\epsilon)$ timescale solution

$$\bar{X} \sim 1, \;\; \bar{Y} \sim \frac{\hat{\beta}\hat{m}_0}{b_0}, \;\; \bar{M} \sim \hat{m}_0 e^{-b_0\bar{t}}, \;\; \bar{G} \sim \frac{\hat{r}\hat{\theta}\hat{\beta}\hat{m}_0}{b_0}\bar{t}, \;\; \bar{P} \sim 1, \qquad (5.7.12)$$

as $t \to -\infty$, to leading order. The solutions are

$$\bar{X} \sim 1, \;\; \bar{Y} \sim \frac{\hat{\beta}\hat{m}_0}{b_0}, \;\; \bar{M} \sim \frac{\hat{\beta}\hat{m}_0}{b_0^2} + \hat{m}_0 e^{-b_0\bar{t}}, \;\; \bar{G} \sim \frac{\hat{r}\hat{\theta}\hat{\beta}\hat{m}_0}{b_0}\bar{t} - \frac{\hat{r}\hat{\theta}\hat{\beta}\hat{m}_0}{b_0^2}, \;\; \bar{P} \sim 1, \;\; \bar{A} = 0,$$

The merozoites that have successfully penetrated red blood cells are undergoing the first round of erythrocytic schizogony. We note this is an artefact of the continuum assumption

and the time scale of $t = \frac{\epsilon}{b_0} \ln \left(\frac{1}{\epsilon} \right)$ (about 2 hours) is too short for the likely release of new merozoites. However, the contribution at this stage is negligible at leading order so we argue that is sound to this order. Concentrations of red blood cells and innate immune cells still remain at normal levels whilst gametocytes and adaptive immune cells are yet to emerge. There is a rebalance in the system in the gametocyte equation at $t = O \left(\frac{1}{\epsilon} \right)$.

5.7.3. $t = O(1), t < \tau$

In this timescale, we scale time as

$$t = \bar{t}.$$

The scalings of the variables are

$$X \sim \bar{X}, \quad Y \sim \epsilon^2 \bar{Y}, \quad M \sim \epsilon^3 \bar{M}, \quad G \sim \epsilon^3 \bar{G}, \quad P \sim \bar{P}, \quad A = 0.$$

Following our usual substitution of the rescalings into $(5.7.2)-(5.7.7)$, we found that other equations are similar to those in the preceding time scale except

$$\frac{d\bar{Y}}{d\bar{t}} \sim \left(\frac{\beta r}{b_0} - (1 + \mu + k) \right) \bar{Y}, \quad \bar{M} \sim \frac{\hat{r}\bar{Y}}{b_0}, \quad \frac{d\bar{G}}{d\bar{t}} \sim \hat{r}\hat{\theta}\bar{Y} - \hat{f}\bar{G}, \quad \frac{d\bar{P}}{d\bar{t}} \sim \hat{b}(1 - \bar{P}),$$

subject to, by matching,

$$\bar{Y} = \frac{\hat{\beta}\hat{m}_0}{b_0}, \quad \bar{M} = \frac{\hat{\beta}\hat{r}\hat{m}_0}{b_0^2}, \quad \bar{P} = 1, \quad \bar{G} = 0, \text{ at } \bar{t} = 0.$$

Solving the system yields

$$\bar{X} \sim 1, \quad \bar{P} \sim 1, \quad \bar{Y} \sim \frac{\hat{\beta}m_0}{b_0} e^{+R\bar{t}}, \quad \bar{M} \sim \frac{\hat{r}\hat{\beta}m_0}{b_0^2} e^{+R\bar{t}}, \quad \bar{A} = 0,$$

$$\bar{G} = \frac{\hat{r}\hat{\theta}\hat{\beta}m_0}{\left(\hat{f} + R\right) b_0} e^{+R\bar{t}}, \quad R = a_0 \left(R_c - 1 \right),$$

where

$$R = a_0(R_c - 1),$$

and where $a_0 = 1 + \hat{\mu} + \hat{k}$, and in particular,

$$R_c = \frac{\hat{\beta}\hat{r}}{a_0 b_0} = \frac{\hat{\beta}\hat{r}}{(1 + \hat{\mu} + \hat{k})(\hat{\beta} + \hat{d} + \hat{\alpha})},$$

is the leading order basic reproduction number approximating that of the system for $\theta \ll 1$, is a necessary and sufficient condition for the disease to die out. We observe that $R_c < 1$ means $R < 0$ so that merozoites and infected red blood cells decay to zero, such that Y never exceeds $O(\epsilon^2)$; this is to be expected on $(\bar{M}, \bar{Y}) = (0, 0)$ as a steady state when $R_c < 1$. However, if $R_c > 1$, $\bar{M}$ and $\bar{Y}$ grow exponentially indicating the disease is beginning to establish itself as the first set of merozoites start producing subsequent merozoites and immature gametocytes. The results suggest that chemotherapy may yield optimum result if implemented in this time scale to keep the basic reproduction number less than unity as it would help to eliminate second generation merozoites during their release. In the case of $R_c < 1$ the disease will die off without impacting significantly on red blood cells (presumably there will be no symptoms), we will then not discuss this case further and concentrate on $R_c > 1$. The adaptive immune system begins to activate at $t = \tau$, indicating the next time scale.

5.7.4. $t = \tau + O(\epsilon), R_c > 1$

This time scale corresponds to the initial $t = O(\epsilon)$ time scale of merozoite emergence from the liver, and the initial phase of merozoite presentation to naive T and B cells by dendritic cells. After a delay of $t = \tau$, the adaptive immune response and, consequently, antibody production is starting. For this timescale we write

$$t = \tau + \epsilon\bar{t}.$$

Due to this being a rapid time scale the variables X, Y, M, G and P are "frozen" at leading order, namely

$$X \sim \bar{X}, \quad Y \sim \epsilon^2 \bar{Y}, \quad M \sim \epsilon^2 \bar{M}, \quad G \sim \epsilon^4 \bar{G}, \quad P \sim \bar{P}. \tag{5.7.13}$$

Since $Y(t - \tau) = O(\epsilon^2)$ and $M(t - \tau) = O(\epsilon^2)$ then

$$A = \epsilon^3 \bar{A}.$$

and substituting the $t = O(\epsilon)$ solution for Y and M yields

$$\frac{d\bar{A}}{d\bar{t}} = \hat{g}_1 \frac{\hat{\beta}\hat{m}_0}{b_0} \left(1 - e^{-b_0 \hat{t}}\right) + \hat{g}_1 \hat{g}_2 m_0 e^{-b_0 \bar{t}},$$

subject to $\bar{A}(0) = 0$, which has the solution

$$\bar{A} = \frac{\hat{g}_1 \hat{\beta}\hat{m}_0}{b_0}\{\bar{t} + \hat{g}2 - 1 + (1 - \hat{g}_1)e^{-b_0\bar{t}}\}.$$

We observe that in large time A will grow linearly. As indicated by the first two timescales, the output of antibodies/T cells is through infected red blood cell stimulation as merozoites momentarily decline at $\frac{\epsilon}{b_0} \ln \left(\frac{1}{\epsilon}\right) + O(\epsilon)$ timescale. The next balance shift at leading order occurs at $\bar{t} = O\left(\frac{1}{\epsilon}\right)$, i.e. $\bar{A} = O\left(\frac{1}{\epsilon}\right)$.

5.7.5. $t = \tau + O(1), R_c > 1$

In this timescale we scale time as

$$t = \tau + \bar{t}.$$

The scalings of other variables are given as

$$X \sim \bar{X}, \quad Y \sim \epsilon^2 \bar{Y}, \quad M \sim \epsilon^3 \bar{M}, \quad G \sim \epsilon^3 \bar{G}, \quad P \sim \bar{P}, \quad A \sim \epsilon^2 \bar{A}.$$

Substituting these rescalings into (5.7.2)−(5.7.7) yields a system in which X and P still maintain their normal levels. Other variables are expressed by the following equations

$$\frac{d\bar{Y}}{d\bar{t}} = \hat{\beta}\bar{M} - \left(1 + \hat{\mu} + \hat{k}\right)\bar{Y}, \quad \bar{M} = \frac{\hat{r}\bar{Y}}{\left(\hat{d} + \hat{\beta} + \hat{\alpha}\right)},$$

$$\frac{d\bar{G}}{d\bar{t}} = \hat{r}\hat{\theta}\bar{Y} - \hat{f}\bar{G}, \quad \frac{d\bar{P}}{d\bar{t}} = \hat{b}(1 - \bar{P}), \quad \frac{d\bar{A}}{d\bar{t}} = \hat{g}_1\bar{Y}(t - \tau) - \hat{g}_3\bar{A},$$

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subject to

$$\bar{Y}(0) \sim \frac{\hat{\beta}\hat{m}_0}{b_0}, \quad \bar{G}(0) \sim 0, \quad \bar{P}(0) = 1, \quad \bar{A}(0) \sim 0, \quad \text{by matching.}$$

The solutions are

$$\bar{Y} \sim \frac{\hat{\beta}\hat{m}_0}{b_0}e^{R\bar{t}}, \quad \bar{A} \sim \frac{\hat{g}_1\hat{\beta}\hat{m}_0}{b_0(g_3+R)}e^{R(t-\tau)}, \quad \bar{G} \sim \frac{\hat{r}\hat{\theta}\hat{\beta}\hat{m}_0}{b_0(\hat{f}+R)}e^{R\bar{t}}, \quad \bar{M} \sim \frac{\hat{\beta}\hat{m}_0 e^{R\bar{t}}}{b_0^2}, \quad P \sim 1.$$

The solution indicates that densities of the various parasite stages are growing exponentially and there is possibility of full blown malaria with consequences of anaemia. There is also rapid production of antibodies, however their contribution to controlling the disease is still negligible. There is a shift in balance in the system at leading order when the infected cells $\bar{Y} = O(1)$, corresponding to a time scale $\frac{2}{R}\ln\left(\frac{1}{\epsilon}\right) + O(1)$

5.7.6. $t = \tau + \frac{2}{R}\ln(\frac{1}{\epsilon}) + O(1), R > 0$

This is a significant timescale in which the effect of malaria reaches its peak and the adaptive immune response begins to take effect. We translate in time from the previous time scale and write

$$t = \tau + \frac{2}{R}\ln(\frac{1}{\epsilon}) + \bar{t},$$

though we note here that formerly the τ term is superfluous, however, since the large term is logarithmic, in practise τ will not be that much smaller. The variable rescalings in this time scale are

$$X \sim \bar{X}, \quad Y \sim \bar{Y}, \quad M \sim \epsilon\bar{M}, \quad G \sim \epsilon\bar{G}, \quad P \sim \bar{P}, \quad A \sim \bar{A},$$

subject to

$$\bar{X} \sim 1, \quad \bar{Y} \sim \frac{\hat{\beta}m_0}{b_0}e^{R\bar{t}}, \quad \bar{M} \sim \frac{\hat{\beta}m_0 e^{R\bar{t}}}{b_0^2}, \quad \bar{G} \sim \frac{\hat{r}\hat{\theta}\hat{\beta}m_0}{b_0(\hat{f}+R)}e^{R\bar{t}}, \quad \bar{P} \sim 1, \quad \bar{A} \sim \frac{\hat{g}_1\hat{\beta}m_0}{b_0(\hat{g}_3+R)}e^{-R\tau}e^{R\bar{t}},$$

as $\bar{t} \to \infty$, from matching. On substitution of these variables into $(5.7.2)-(5.7.7)$ followed by appropriate balancing of terms we have the following leading order system,

$$\frac{d\bar{X}}{d\bar{t}} = -\frac{\hat{\beta}\bar{X}\bar{M}}{1+\bar{A}}, \tag{5.7.14}$$

$$\frac{d\bar{Y}}{d\bar{t}} = \frac{\hat{\beta}\bar{X}\bar{M}}{1+\bar{A}} - (1+\hat{\mu})\bar{Y} - \hat{k}\bar{P}\bar{Y}\left(1+\hat{k}_1\hat{A}\right), \tag{5.7.15}$$

$$\bar{M} = \frac{\hat{r}\bar{Y}}{\hat{\beta}\bar{X} + \left(\hat{\alpha}\bar{P}+\hat{d}\right)(1+k_6\bar{A}) + \hat{\alpha}\hat{k}_2\bar{P}\bar{A}(1+\bar{A})}, \tag{5.7.16}$$

$$\frac{d\bar{G}}{d\bar{t}} = \frac{\hat{r}\hat{\theta}\bar{Y}}{1+k_6\bar{A}} - \hat{f}\bar{P}\bar{G} - \hat{f}\hat{k}_3\bar{P}\bar{G}\bar{A}, \tag{5.7.17}$$

$$\frac{d\bar{P}}{d\bar{t}} = \hat{b}(1-\bar{P}) + \hat{\omega}\bar{Y}, \tag{5.7.18}$$

$$\frac{d\bar{A}}{d\bar{t}} = \hat{g}_1\bar{Y}(t-\tau) - \hat{h}_1\bar{A}\bar{Y} - \hat{g}_3\bar{A}. \tag{5.7.19}$$

This system is considerably more difficult than those in the previous timescales, and full solutions cannot be found. A key observation of the equation is that $\dfrac{d\bar{X}}{d\bar{t}} < 0$, so there will be a noticeable decline in red blood cells. Furthermore, $\dfrac{d\bar{P}}{d\bar{t}} > 0$ so innate cells are increasing and inflammatory response is expected. We thus expect, it is this timescale in which the malaria symptoms will be experienced.

Numerical simulations suggest that $\bar{Y} \to 0$ as $\bar{t} \to \infty$ and $\bar{X} \to X_\infty > 0$. We derive lower and upper bounds for X_∞ in the following section, and in particular, $X_\infty = O(1)$. We present a numerical solution to demonstrate this behaviour.

5.7.6.1. Numerical simulations

The numerical simulations describing events in this timescale are presented in Figure 5.4a, b,c,d and Figure 5.5a, b. The results suggest rapid exponential decay in Y and M after attaining their maximum levels whilst Red blood cell density, X decays to its minimum level. Gametocytes, innate immune cells and antibodies are also decaying after an initial peak.

5.7.6.2. Lower bound

The leading order system appears not to have a closed form solution but considering a worse scenario characterising absence of adaptive immune response with the following assumptions

$$\omega \ll 1, \quad b \ll \omega, \quad g_1 \ll 1, \quad h_1 \ll 1, \quad \bar{A} = O\left(max(\hat{g}_1, \hat{h}_1)\right), \quad \frac{d\bar{P}}{d\bar{t}} = O\left(\omega\right),$$

then $\bar{P} \sim 1$ and we obtain the first two equations of the SIR model

$$\frac{d\bar{X}}{d\bar{t}} = -\frac{\hat{\beta}\hat{r}\bar{X}\bar{Y}}{\hat{\beta}\bar{X} + \hat{\alpha} + \hat{d}},$$

$$\frac{d\bar{Y}}{d\bar{t}} = \left(\frac{\hat{\beta}\hat{r}\bar{X}}{\hat{\beta}\bar{X} + \hat{\alpha} + \hat{d}} - a_0\right)\bar{Y},$$

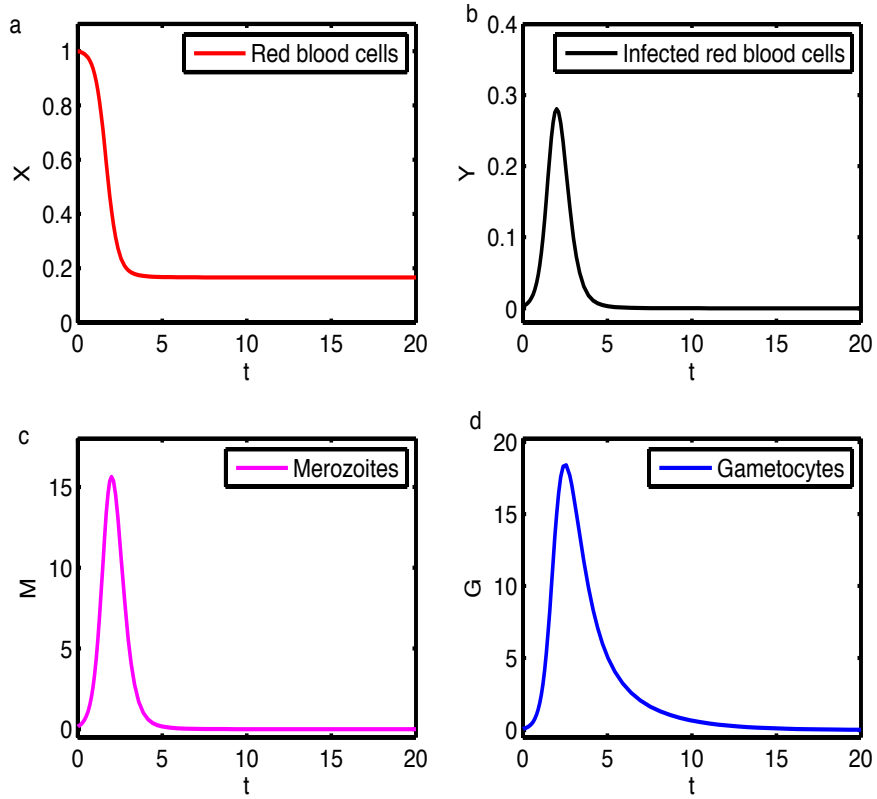Figure 5.4: Result showing the behaviour of X, Y, M and G. The variable X decays while Y, M and G initially grow but later decay. The initial conditions are $X = 1$, $Y = Rt + \ln(\hat{\beta}m_0/b_0)$, $G = \hat{r}\hat{\theta}\hat{\beta}m_0 \exp(R\bar{t})/\left(\hat{f}b_0 + Rb_0\right)$, $P = 1$, $A = g_1\beta m_0 \exp\left(R(t-\tau)\right)/(\hat{g}_3 b_0 + Rb_0)$, with the parameter values $\hat{\sigma} = 20$, $\hat{\beta} = 0.049$, $\hat{\mu} = 0.11$, $\hat{d} = 0.096$, $\hat{r} = 16$, $\hat{\theta} = 6.4$, $\hat{e} = 34$, $\hat{f} = 0.35$, $\hat{\phi} = 2$, $\hat{\alpha} = 0.03$, $\hat{k} = 0.28$, $\hat{k}_1 = 2.3$, $\hat{k}_2 = 0.038$, $\hat{k}_3 = 2.1$, $\hat{k}_4 = 28$, $\hat{k}_5 = 31$, $\hat{k}_6 = 15.2$, $\hat{b} = 0.6$, $\hat{\omega} = 10$, $\hat{\phi}_0 = 0$, $\hat{g}_1 = 1.8$, $\hat{g}_2 = 1.86$, $\hat{g}_3 = 0.6$, $\hat{h}_1 = 0.45$, $\hat{h}_2 = 0.34$, $\hat{m}_0 = 0.0105$.
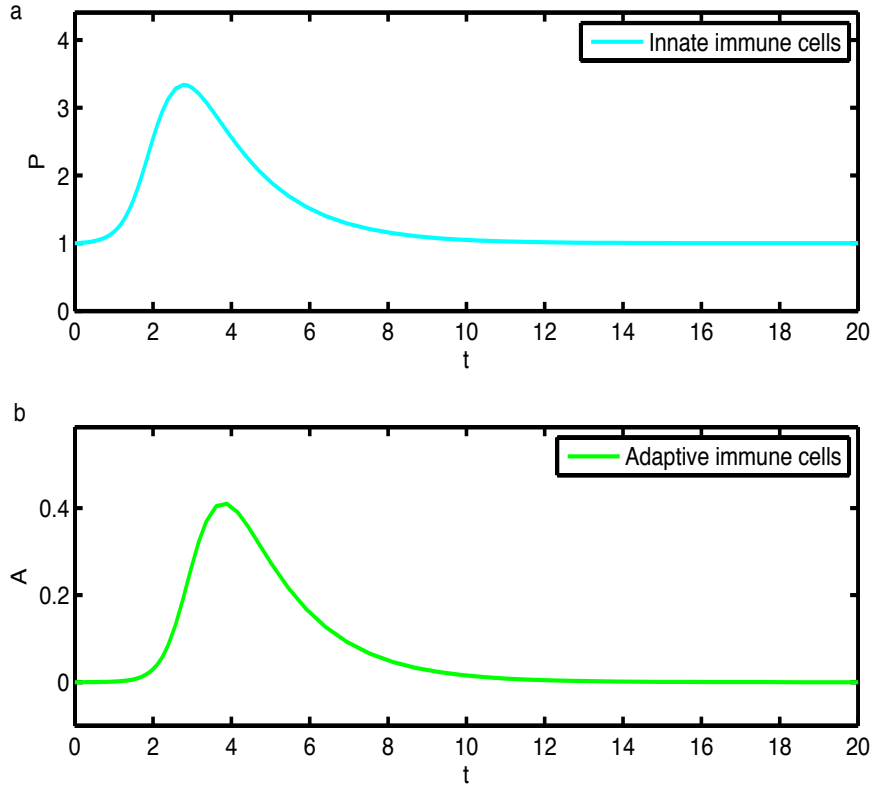
Figure 5.5: Result showing the behaviour of P and A. The variables P and A decay after an initial growth. Parameter values and initial conditions are the same as those in Figure 5.4.

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This is a special form of the classic SIR model where the infection rate is bounded by healthy red blood cells. The term $a_0 \bar{Y}$ describes the rate at which infected red blood cells are removed through natural deaths and immune response. The first approximation to the system in this time scale is obtained by analysing the the ordinary differential equation

$$\frac{d\bar{Y}}{d\bar{X}} = -\left(1 - \frac{a_0}{\hat{r}}\right) + \frac{a_0\left(\hat{\alpha} + \hat{d}\right)}{\hat{\beta}\hat{r}\bar{X}},$$

describing the rate of change of concentration of infected red blood cells with respect to the concentration of healthy red blood cells. The solution of the equation is given by

$$\bar{Y} - \bar{Y}_0 = \left(1 - \frac{a_0}{\hat{r}}\right)\left(1 - \bar{X}\right) + \frac{a_0\left(\hat{\alpha} + \hat{d}\right)}{\hat{\beta}\hat{r}}\ln\left(\bar{X}\right),$$

since $\bar{Y} \to 0$ and $\bar{X} \to 1$ as $\bar{t} \to -\infty$. As with SIR model, $\bar{Y}_0 \to 0$ as $\bar{t} \to -\infty$, then we can deduce $\bar{X} \to X_\infty$, where

$$\left(1 - \frac{a_0}{\hat{r}}\right)(1 - X_\infty) + \frac{a_0\left(\hat{\alpha} + \hat{d}\right)}{\hat{\beta}\hat{r}} \ln\left(X_\infty\right) \approx 0. \qquad (5.7.20)$$

This is the first approximation to X, a long term behaviour of the concentration of red blood cells guaranteeing possible recovery from the disease, a case where $R_c < 1$. By definition, a requirement for primary invasion is that the basic reproduction number must exceed unity [51]. Considering the case of a large $R_c > 1$, then $X_\infty \ll 1$ and (5.7.20) reduces to

$$\frac{a_0\left(\hat{\alpha} + \hat{d}\right)}{\hat{\beta}\hat{r}} \ln\left(X_\infty\right) \approx -\left(1 - \frac{a_0}{\hat{r}}\right),$$

with solution

$$X_\infty^{SIR} \approx \exp\left(-\frac{\hat{\beta}(\hat{r} - a_0)}{a_0(\hat{\alpha} + \hat{d})}\right).$$

An improved approximation to X_∞ may be obtained by considering the contribution of innate immune cells (P), to the dynamics of the disease. Assuming, $g_1 \ll 1$, $b \ll 1$ and $A \ll 1$, then we analyse the system

$$\frac{d\bar{X}}{d\bar{t}} = -\frac{\hat{\beta}\hat{r}\bar{X}\bar{Y}}{\hat{\beta}\bar{X} + \hat{\alpha}\bar{P} + \hat{d}}, \qquad (5.7.21)$$

$$\frac{d\bar{Y}}{d\bar{t}} = \left(\frac{\hat{\beta}\hat{r}\bar{X}}{\hat{\beta}\bar{X} + \hat{\alpha}\bar{P} + \hat{d}} - (1 + \hat{\mu} + \hat{k}\bar{P})\right)\bar{Y}, \qquad (5.7.22)$$

$$\frac{d\bar{P}}{d\bar{t}} = \hat{\omega}\bar{Y}. \qquad (5.7.23)$$

We consider as a first case, the equation

$$\frac{d\bar{P}}{d\bar{X}} = -\frac{\hat{\omega}}{\hat{r}} - \frac{\hat{\alpha}\hat{\omega}}{\hat{\beta}\hat{r}}\frac{\bar{P}}{\bar{X}} - \frac{\hat{\omega}\hat{d}}{\hat{\beta}\hat{r}\bar{X}}. \qquad (5.7.24)$$

Multiplying through by $\bar{X}^{\frac{\hat{\alpha}\hat{\omega}}{\hat{\beta}\hat{r}}}$ $\left(\text{assumming } \frac{\hat{\alpha}\hat{\omega}}{\hat{\beta}\hat{r}} \neq 1\right)$, we get

$$\frac{d}{d\bar{X}}\left(\bar{P}\bar{X}^{\frac{\hat{\alpha}\hat{\omega}}{\hat{\beta}\hat{r}}}\right) = -\frac{\hat{\omega}}{\hat{r}}X^{\frac{\hat{\alpha}\hat{\omega}}{\hat{\beta}\hat{r}}} - \frac{\hat{\omega}\hat{d}}{\hat{\beta}\hat{r}}\bar{X}^{\frac{\hat{\alpha}\hat{\omega}}{\hat{\beta}\hat{r}} - 1}$$

By integrating and matching the solution with that of the previous timescale ($P = 1, X = 1$ as $\bar{t} \to -\infty$), we have

$$P = \left(1 + \frac{\hat{\omega}\hat{\beta}}{\hat{\alpha}\hat{\omega} + \hat{\beta}\hat{r}} + \frac{\hat{d}}{\hat{\alpha}}\right)\bar{X}^{-\frac{\hat{\alpha}\hat{\omega}}{\hat{\beta}\hat{r}}} - \frac{\hat{\omega}\hat{\beta}}{\hat{\alpha}\hat{\omega} + \hat{\beta}\hat{r}}\bar{X} - \frac{\hat{d}}{\hat{\alpha}} \tag{5.7.25}$$

describing P in terms of X. Also, by considering the second case we integrate the equation

$$\frac{d\bar{Y}}{d\hat{t}} = -\frac{d\bar{X}}{d\hat{t}} - \frac{(1 + \hat{\mu})}{\hat{\omega}}\frac{d\bar{P}}{d\hat{t}} - \frac{\hat{k}}{2\hat{\omega}}\frac{d\bar{P}^2}{d\hat{t}}$$

to get

$$\bar{Y} = 1 - \bar{X} + \frac{(1 + \hat{\mu})}{\hat{\omega}}(1 - \bar{P}) + \frac{\hat{k}}{2\hat{\omega}}(1 - P^2).$$

We have as $\bar{t} \to \infty$,

$$0 = 1 - \bar{X}_\infty + \frac{(1 + \hat{\mu})}{\hat{\omega}}(1 - \bar{P}_\infty) + \frac{\hat{k}}{2\hat{\omega}}(1 - P_\infty^2), \tag{5.7.26}$$

and by substituting (5.7.25) in (5.7.26) we have

$$f(\bar{X}_\infty) = 0,$$

where

$$f(\bar{X}) = 1 - \bar{X} + \frac{(1 + \hat{\mu})}{\hat{\omega}}(1 - \bar{P}(\bar{X}) + \frac{\hat{k}}{2\hat{\omega}}(1 - P(\bar{X})^2), \tag{5.7.27}$$

and as $\hat{\omega} \to \infty$, $f(\bar{X}) \to 1 - \bar{X}$. By considering real solution for P_∞ in (5.7.26) we obtain the expression,

$$\bar{X}_\infty^{XYP} \leq \frac{(1 + \hat{\mu})^2}{2\hat{\omega}\hat{k}} + \frac{(1 + \hat{\mu})}{\hat{\omega}} + \frac{\hat{k}}{2\hat{\omega}} + 1. \tag{5.7.28}$$

We expect $X_\infty^{XYP} > X_\infty^{SIR}$, signifying a reduction of red blood cell invasion by merozoites due to innate immune cell activation. Thus

$$\exp\left(-\frac{\hat{\beta}(\hat{r} - a_0)}{a_0(\hat{\alpha} + \hat{d})}\right) \leq \bar{X}_\infty \leq \frac{(1 + \hat{\mu})^2}{2\hat{\omega}\hat{k}} + \frac{(1 + \hat{\mu})}{\hat{\omega}} + \frac{\hat{k}}{2\hat{\omega}} + 1.$$

We note from section 5.3 that we only consider first outbreak and hence as $Y \to \epsilon$ we assume that infection is finished. In Figure 5.4 and Figure 5.5 infected red blood cells, merozoites and

gametocytes die out whilst innate immune cells and antibodies return to their normal state, after clearing the infection. The remaining equation describes the recovery of uninfected red blood cells at time $\bar{t} = O\left(\frac{1}{\epsilon}\right)$.

5.7.7. $t = O\left(\epsilon^{-1}\right)$

In this timescale, red blood cells return to normal level. The scalings are

$$t = \frac{1}{\epsilon}\bar{t}, \quad X \sim \bar{X}.$$

On substitution of these into (5.7.2), we obtain the leading order equation

$$\frac{d\bar{X}}{d\bar{t}} = \hat{\sigma}\left(1 - \bar{X}\right).$$

The initial condition $\bar{X}(0) = X_\infty$ solves the equation to give

$$\bar{X} \sim 1 - \left(1 - X_\infty\right)e^{-\hat{\sigma}\hat{t}},$$

and as $\hat{t} \to \infty$, $X \sim 1$ as expected.

5.7.7.1. Comparing asymptotic solutions with numerical solution

In this section we compare the solution of the full system with the asymptotic approximation. Figure 5.6a, b, c, d gives approximations for red blood cells, infected red blood cells merozoites and gametocytes whilst the approximations for innate immune cells and antibodies are given in Figure 5.7a, b. The minimum of x and the peaks of Y, G, P and A appear reasonable. The choice of the comparison parameters, σ, b and g_3, does not need the implementation of the continuum approximation assumption. The reduced system is a reasonable approximation of the biology described by the full system and we note from 5.7.18 and 5.7.19 that what drives the immune system is mainly infected red blood cells. Parameters for comparison are $\hat{\sigma}$, b and g_3. For $\hat{\sigma} = 30$, recovery is noticeably moderate t. Also, $\hat{b} = \hat{g}_3 = 0.1$, so P and A relax slowly leading to a negligible bounce back of Y and M in $t \in [0, 40]$
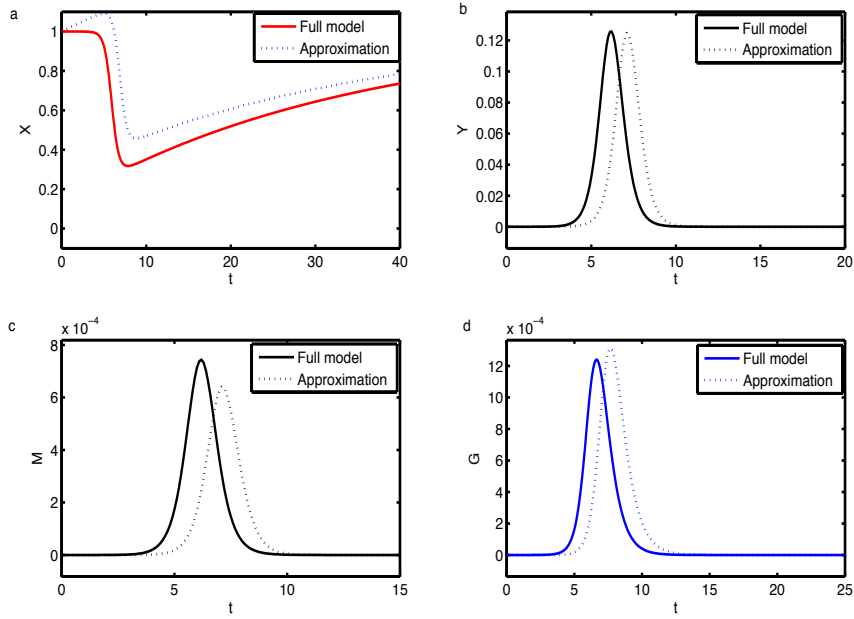
Figure 5.6: Results showing the numerical solutions of the full system and approximations from the asymptotic analysis. Solid lines represent the full model whilst dotted lines are used for the approximations. We used the same initial conditions as those in Figure 5.4 and parameter values are $\epsilon = 0.001$, $\hat{\sigma} = 30$, $b = 0.1$, $g_3 = 0.1$ with every other dimensionless parameter set to unity.

5.7.8. Conclusion from this analysis

In this section we have used asymptotic analysis to describe the interaction of the malaria parasite, human erythrocytes and the immune cells. The analysis explains a situation in which a individual who contacts malaria for the first time through a single infectious bite of a mosquito progresses with the disease from the initial release of erythrocytic merozoites into the blood stream. There are seven major time scales predicted by the model in which following a single infectious mosquito bite, blood stage parasites proliferate causing a reduction in red blood cell level and depending on the effectiveness of the immune system, both sexual and asexual parasites are eliminated. We note the following concluding remarks from the analysis about the progression of the disease in the human host:
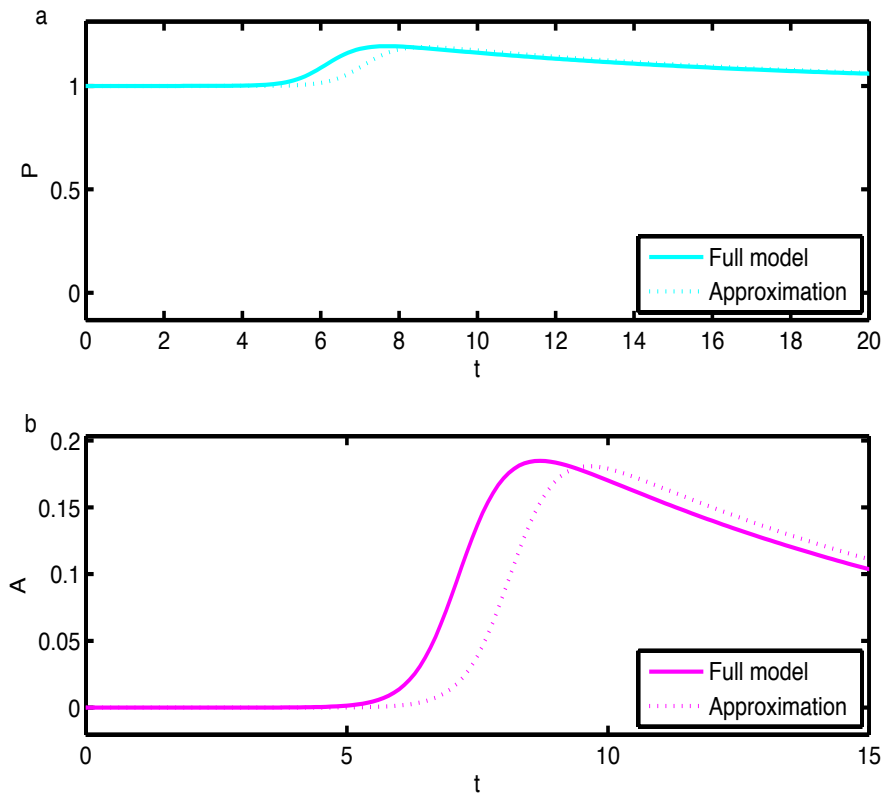
Figure 5.7: Results comparing numerical solutions and asymptotic approximations of P and A. Initial conditions and parameter values are the same as those in Figure 5.6

- Upon release from the liver, initial population of merozoites decline rapidly as they invade red blood cells. However it has negligible impact on the red blood cells and innate immune system, as X and P remained at their normal concentrations from the first time scale until the sixth time scale, i.e. approximately 5 days; a period within which the concentration of merozoites is not large enough to cause a significant reduction in red blood cell level.

- Although the activities of antigen presentation and phagocytosis leading to the training of naive B cells and T cells were initiated in the early time scales, it was not until the time scale, $t > \tau$ that specific immune response emerged into the system. It appears the initial stimulation comes from immune cell interaction with merozoites only. However

this stimulation has an additional boost as shown in the analysis when innate immune cells started interacting with infected red blood cells generated by subsequent generation merozoites leading to substantial increase in A.

- Throughout the analysis, we have demonstrated that the development of specific immunity depends on the presence of malaria parasites. The concentration of red blood cells drops to its minimum as evident in time scale

$$t = \tau + \frac{2}{R} \ln \left(\frac{1}{\epsilon} \right) + O(1). \tag{5.7.29}$$

Events in this timescale demonstrate that it is infected red blood cells that contribute most to the development of adaptive immune response. It is during this timescale when the adaptive and innate immune response takes control of the infection and eventually drives down merozoite level as infected red blood cells are being removed.

- One important result from our analysis in $t = O(1)$ time scale is that the parasite will invade if the leading order basic reproduction number is greater than unity, which suggest that chemotherapy may yield optimum result if implemented in this time scale to keep the basic reproduction number less than unity as it would help to eliminate second generation merozoites during their release. We expect perpetual presence of parasite in the human host as in the case of the endemic state of the transmission model but it is quite interesting from our findings that emergence of the immune profile, which may be individual specific, will lead to parasite clearance.

- We note that if we allowed secondary outbreak in section 5.7.6, then after first outbreak as $Y \to O(\epsilon)$, P and A relax to pre-illness levels which can then allow $Y \to O(1)$ and cause a secondary outbreak ultimately leading to a steady state where $1 - X = O(1)$. Other factors absent in the model may become important in these circumstances.

5.8. Numerical simulations of in-host model

In this section we present more numerical simulations of our model to corroborate the findings in the asymptotic analysis. We will also make reference to some of the simulations presented in section 5.3. The system under consideration is that of delay differential equations in which there is a single constant delay, τ in the A equation that expresses the time lag before the emergence of adaptive immune response. The numerical routine solver, MATLAB dde23, which we have used here, deals with the solution of delay differential equations with constant delays. Note in some cases some of the variables are presented in a logged axis. The dimensionless parameters used for the simulations are defined in Table 5.2 and the initial conditions are $X = 1$, $Y = 0$, $M = 0.000000105$, $G = 0$, $P = 1$, $A = 0$. These conditions describe a situation where a naive human, i.e. $A(0) = \phi_0$, where $\phi_0 = 0$, is exposed to malaria infection for the first time in which hepatic merozoites from a single infectious bite of a mosquito are released into the blood stream to undergo the first phase of erythrocytic schizogony. An individual having normal concentration of red blood cells ($X = 1$) and normal concentration of innate immune cells($P = 1$) is infected with an initial concentration of merozoites ($M = 0.000000105$ representing 35000 merozoites [87]). The program was run in MATLAB using a relative and absolute tolerance of 10^{-7} with a delay of two days. The history conditions are the same as the initial conditions for $t \geq 0$, but if $t < 0$, except that we set M to zero.

In Figure 5.8, merozoites invade red blood cells and immune cells respond by attacking and eliminating pathogens, leading to red blood cell recovery and subsequent drop down of immune cells. Although different sets of parameter values are used, the form of the solution is similar to the one in Figure 5.1. However, the minimum red blood cell levels and the times it takes to reach such levels in both cases are different. This is expected because different
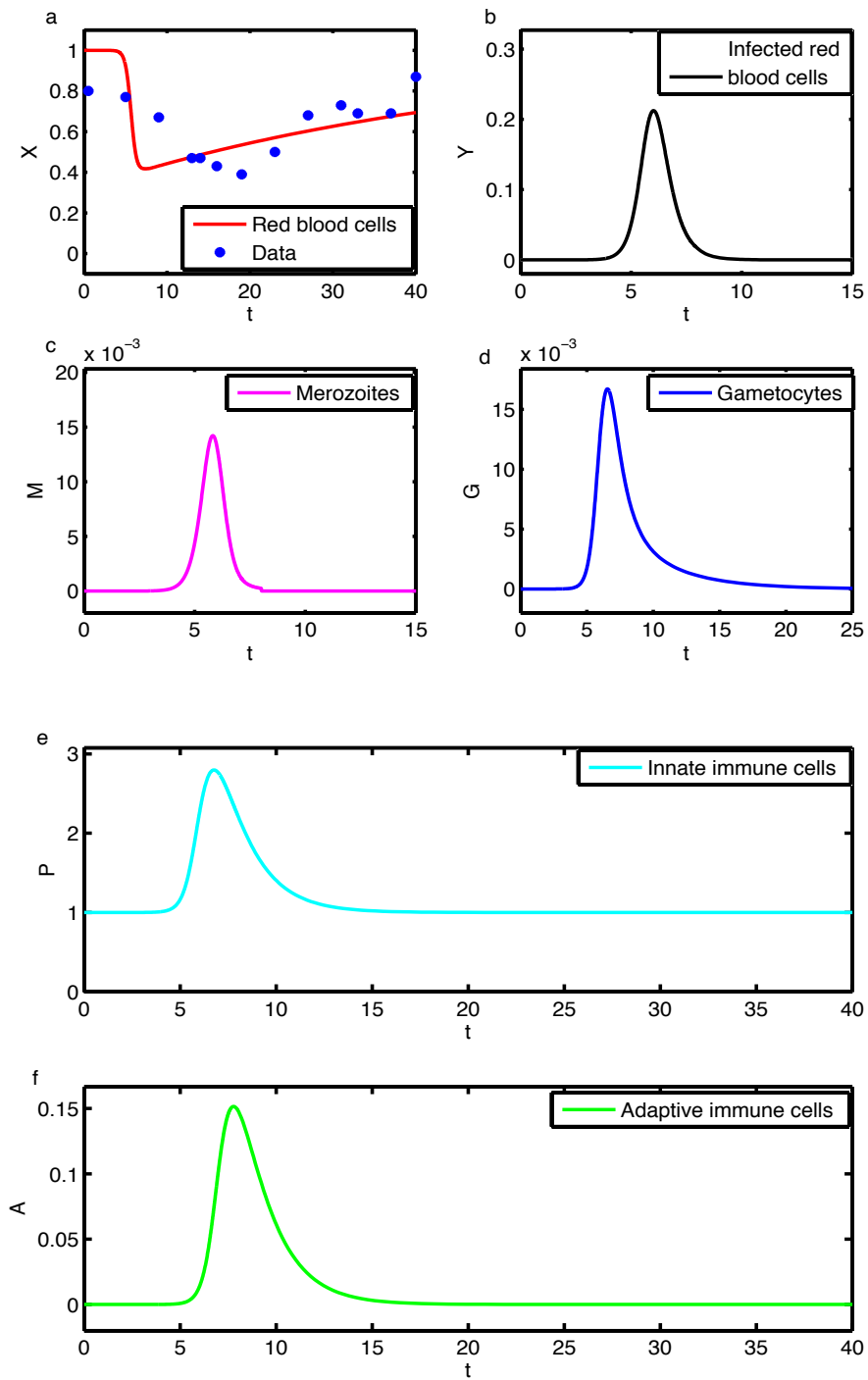
Figure 5.8: Results showing model fitting to data. The blue dots are data of the McLendon strain malaria infected patient in Figure 4.1b with $t = 1$, representing 2 days in real time corresponding to the the period of each erythrocytic schizogony. The initial and history conditions used are stated in section 5.2.7 and our choice of parameter values are the same as those in Figure 5.1 except $k_2 = 28$, $k_6 = 4.2$, $k = 0.13$, $e = 0.0012$, $\alpha = 35$, $f = 0.25$, $\omega = 9$, $h_1 = 0.45$, $h_2 = 0.34$, $g_1 = 0.8$, $g_2 = 1.26$.

Figure 5.9: Results showing the effect of immune response on the pathogenesis of malaria. The red curve represents concentration of red blood cells when the individual has both innate and adaptive 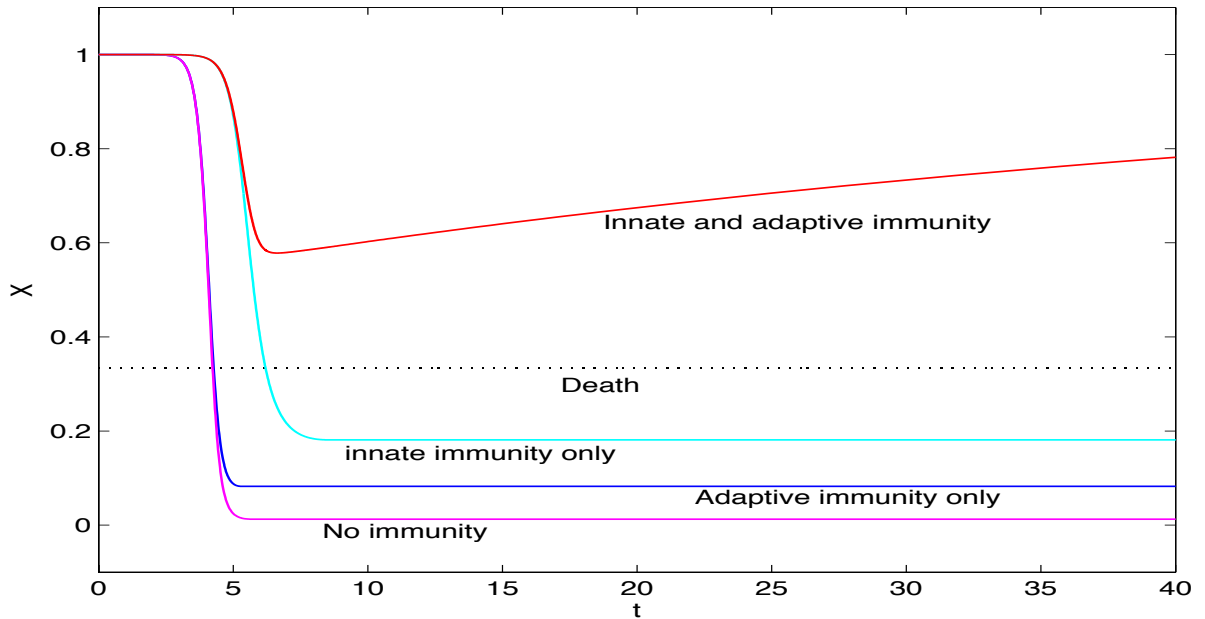immune response. The curves with the cyan and blue colours indicate red blood cell concentrations due to innate immunity only and adaptive immunity only, respectively. The initial conditions and parameter values used are the same as those in Figure 5.1. Death is assumed to occur at red blood cell levels below the dotted horizontal line and red blood cell level reduces to as low as the magenta curve in the absence of immunity.

individuals respond differently to disease pathology and may have different immune response statuses due to several individual specific factors. For instance, a good feeding habit of an individual can promote a strong immune system that can even reduce the infection rate of red blood cells.

The blue dots in Figure 5.8a represent data on the concentration of red blood cells of a malaria patient infected with a different (*McLendon*) strain from that of Figure 5.1a. These data were extracted from Jakeman [54] and are part of the data set obtained from the South Carolina and Milledgeville State hospitals in which previously uninfected neurosyphilis patients were inoculated with P. *falciparum* malaria parasites as a means of malaria therapy for neurosyphilis. In Figure 5.9 we demonstrate the effect of different immune profiles on disease pathology using a death threshold defined by a third of the normal red blood cell level. The
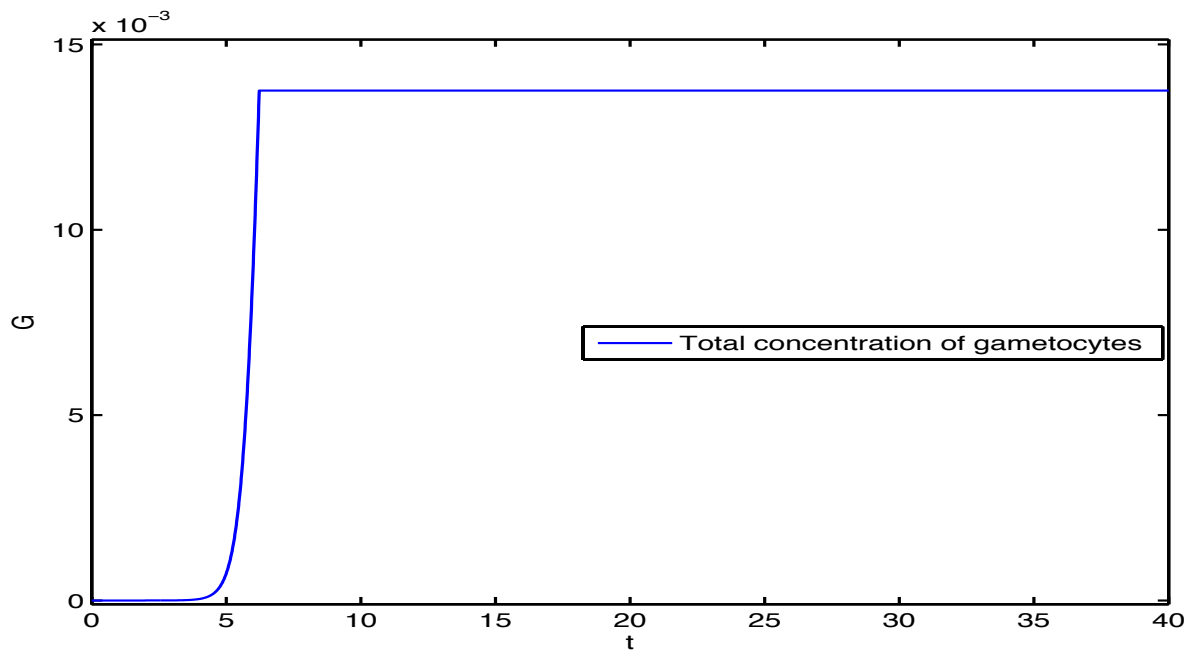
Figure 5.10: Results showing total concentration of gametocyte at any point in time as the disease progresses until death at $t = 6.2$. The initial conditions and parameter values used are the same as those in Figure 5.9.

results suggest with both innate and adaptive immune response the minimum level of red blood cell tend to be above the threshold level. But in the absence of one or both of the immune types the minimum blood level will be below the threshold. As the disease progresses, gametocytes are produced from infected red blood cells. The rate of production is higher in the absence of immunity. Figure 5.10 shows the total amount of gametocyte produced at any point in time from the start of the disease until death.

5.8.1. Discussion

We formulated a mathematical model for the in-host dynamics of malaria parasites focusing on the erythrocytic blood-stage asexual parasite and gametocyte formation. This is of importance as it is this stage in which clinical symptoms and mortality is relevant, as well as the stage by which humans can transmit the disease to the mosquito vector. At the beginning of first contact with the malaria parasite, innate immune cells first swing into action

through antigen presentation mechanism leading to the training of naive T cells and B cells and subsequent production of antibodies. This informed us of the inclusion of the delay parameter τ that provides for the time lag between contact and emergence of specific immune response. Throughout our simulations we assumed a delay of 2 days, which seems realistic as it is within the range of specific immune cells development for other infectious diseases. In our numerical simulations we have been able to demonstrate some of the dynamic processes, describing in-host interaction of the malaria parasite with red blood cells and host immunity. A major feature in this interaction is the depletion or reduction of the concentration of red blood cells eventually resulting to anaemia. Although several factors may seem to influence the development of anaemia, the primary influence appears to be parasite density especially, maintenance of high or moderately high density [57].

After the release of merozoites into the blood stream from the liver, there is rapid invasion by parasites but this does not immediately cause the concentration of red blood cells to fall. This could be partly due to recruitment of red blood cells and the intervention of innate immune cells providing a first line of defence to thwart the growth of parasites. During malaria infection like in many other infections, the innate immune system plays a dual role. On one hand it acts as a first line of defence to limit rapid parasite growth and to initiate an adaptive immune response and avoid re-infections [62], and on the other hand, its excessive activation can drive over-production of pro-inflamatory cytokines leading to inflammation and pathology [105]. Another reason could be that since there are only 1.05×10^{-7} of them at $t = 0$, immune response is low key until M and Y have reached sufficient levels.

We note that our model is a continuum model and does not guarantee complete clearance of parasites. It is constructed in such a way that the presence of malaria pathogens stimulates the innate immune response to activate the adaptive immune responses. Thus a rise in parasite

level will be followed by a corresponding rise in the concentration of both humoral and T cell and B cell mediated immune response. We observed that the parasite invades red blood cells, causing a fall in the concentration of uninfected red blood cells and a corresponding rise in the concentrations of infected red blood cells, merozoites and gametocytes. Consequently, the concentrations of both the innate and adaptive immune cells rise to force down the concentrations of merozoites, infected red blood cells and gametocytes to a negligible level incapable of invading, leading to red blood cell recovery and eventual return of the immune cells to their normal levels.

Considering the case of the patient infected with McLendon strain, we determine from the numerical solution an estimate of the total amount of gametocytes at death as $6.9 \times 10^4 cells/\mu l$. For survival purposes, it is not in the interest for malaria plasmodium to kill the human host, as this would deny a mosquito's access to gametocytes; in order to maximise mosquito uptake of gametocyte it is best for the host to survive the disease, producing gametocytes for as long as possible. Our primary aim of this model is to investigate whether or not parasites deposited in the human host through a single infectious bite could lead to death. It is actually a difficult thing to determine at what stage death would occur during malaria attack, but since red blood cell concentration is crucial in the survival of the human host, we assume that death occurs when the concentration of red blood cells has dropped to its fatal level, specifically, around third of the normal blood level. Using this definition, our results show that a non-immune deficiency human, though depending on the values of the model parameters which are individual specific may likely survive a single bite malaria infection. This is illustrated in Figure 5.1a and Figure 5.8a where we have fitted the model to neurosyphilis data extracted from [54], part of the data set obtained from the South Carolina and Milledgeville State hospitals in which previously uninfected neurosyphilis patients

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were inoculated with *P. falciparum* malaria parasites as a means of malaria therapy for neurosyphilis. In both cases the minimum level of red blood cells is a little above the estimated fatal level.

The behaviour of the solution follows the pattern described in Kitchen, [57], in which he avers that in the naturally evolving disease, the greatest loss of erythrocyte occurs during that period subsequent to attainment of the maximum parasite density and prior to the appearance of definite evidence that the host defence mechanism has gained control over the situation. In a related development, he asserts that if a moderate parasite density is maintained for a period of three or four weeks in *P. falciparum* or *P. vivax* attack then this might reduce the initial normal level of red blood cells to $1.5 \times 10^6 cells/\mu l$ or less. Although our numerical result in Figure 5.1a shows that it takes 14 days after the realease of merozoites into the blood stream for the blood level to drop to its minimum of $2.7 \times 10^6 cells/\mu l$, we note that the likely time duration from the period of infectious bite to attainment of minimum blood level is about 3 weeks since it takes about 6 days from the time of bite to the release of merozoites. In dimensional terms, the concentration of merozoites reached its maximum of $5.5 \times 10^5 cells/\mu l$, two days prior to the attainment of the minimum level of red blood cells, whilst maximum concentration of adaptive immune cells or evidence of sufficient immune defence was attained three days after.

We seek an understanding of the effect of immune response on the control of parasitemia and also the role innate immune response play in protecting the individual against malaria in first infection. By switching off the specific immune response mechanism we find that an individual without adaptive immunity is likely to die after 18 days of infectious bite. This is shown in Figure 5.9 in which the the horizontal line intersects with the red blood cell curve at $(6.2, 0.3)$ where we have assumed death to occur when the individual attains

a fatal haemoglobin or red blood cell level. We find from the simulations that the initial level of adaptive immune cells or antibodies, ϕ_0, plays a crucial role in the elimination of parasites. This explains how continuous malaria contacts especially in endemic areas can lead to acquisition of partial immunity. Increasing ϕ_0 reduces the rate at which red blood cells are invaded thus improving the minimum level. Figure 5.3 shows a plot of ϕ_0 against various minimum levels of red blood cells. An important aspect of this result is that given a particular concentration of antibodies, we can determine the strength of parasite invasion of red blood cells noting that the strength of invasion is determined by the extent to which the parasite can reduce the red blood cell level.

An optimum concentration of antibodies is one that will be capable of protecting the individual from invasion. We find from the simulations that by boosting the specific immune response up to a concentration of 0.071 in dimensionless form will prevent the parasite from invading, thus ensuring parasite/disease free situation. A mathematical model structured to create a good understanding of the immune effector mechanisms of parasite regulation, control and elimination will facilitate the production of a malaria vaccine of relatively high efficacy.

The global effort in malaria control especially, the contributions of the World Health Organisation is commendable in many areas including that of vaccine production. Following the emergence of RTS, S, the only malaria vaccine that has entered the phase 3 trial, there are indications of some rising hope that a malaria vaccine will soon be in use. It is a pre-erythrocytic vaccine aimed at stopping the release of merozoites from the liver into the blood stream. Although some successes have been recorded in terms of severe disease reduction in young children within the age group of 6-12 weeks and older children of the age range 5-17 months, the drug is still within an efficacy level of about 36.6%-50% [99] including the tendency of the individual becoming reinfected. Thus, more work is required to identify the

optimum vaccination age and dosing schedule for RTS, S, more immediate issues are to define an acceptable level of protection and determine the true rate at which vaccine efficacy declines below this level, as this will help determine the optimal boosting strategy [94].

The significance of ϕ_0 in our model as it relates to subsequent contacts seems to provide an insight into a boosting strategy in which the immune system can be conditioned to a level that the individual will be capable of avoiding reinfection.

CHAPTER 6

CONCLUSION

6.1. Concluding remarks

Malaria is an infectious disease with a dangerous global burden in which the quest for regional elimination and entire global eradication cannot be over emphasized. In this work we have constructed and analysed two mathematical models describing two major areas involving the transmission of the disease between human and mosquito populations, and its dynamics as the parasites within the human host interact with red blood cells and the immune system. Our transmission model describes human-mosquito interaction on malaria epidemiology. Susceptible and asymptomatic humans get infected when they are bitten by an infectious mosquito. They then progress through the latent, symptomatic and asymptomatic classes, before re-entering the susceptible class. Susceptible mosquitoes can become infected when they bite symptomatic, asymptomatic or latent asymptomatic humans, and once infected they move through the latent and infectious mosquito classes. We used both numerical simulations and analytical methods to obtain solutions to the system. The numerical results show the model can predict an endemic malaria situation but for some values of the model parameters a

disease free state can be realised.

Single dose malaria drugs do not completely clear parasites but temporarily create asymptomatic malaria and this has not been considered in previous models. Another area of novelty is the second class of incubating humans resulting from the reinfection of asymptomatic humans. We have proposed and analysed a new transmission model incorporating these ideas. The methods of analysis employed in previous malaria models have mainly focused on stability analysis. In our case we have used in addition, asymptotic analysis to track the dynamics of disease transmission starting from an initial introduction of a small amount of infected mosquitos into a malaria free human population. Through our asymptotic analysis we have provided insight into the transmission of the disease as shown by the numerical simulations. There are important remarks about the transmission of the disease, which we have highlighted.

The noticeable build-up of latent asymptomatic humans at steady state confirms previous experimental results that asymptomatic status is maintained through continuous infection. This is a clear characteristic of the dynamics of malaria in an endemic region. It portends a dangerous scenario and creates adverse effect on public policies aimed at control or eradication of the disease. Although Ross [96] posits that to remove malaria in a region, the number of mosquitos needs to be reduced below a particular threshold, Ngwa et al. [82] contend that this approach would only be a temporary measure, especially in a malaria endemic region claiming that the disease will resurface as the mosquito population recovers. However, our findings suggest that Ngwa's claim may hold in a situation of high proportion of asymptomatic carriers. But if they are treated then the disease will not resurface despite recovery of the mosquito population. If the attainment of asymptomatic status is an advantage then it appears adults are gaining at the expense of children and women (who may likely loose immunity during pregnancy). This gain may not be sustained for a long time as the analysis demonstrates that

asymptomatic individuals will rapidly become latent when the epidemic takes hold.

During the treatment analysis we considered options of transmitting treated latent asymptomatic humans to either the susceptible or latent class but the basic reproduction number remains unchanged in both cases. This suggests that partially immune individuals may be treated by gametocyte destroying drugs only, or by drugs that act on both asexual parasites and gametocytes. We recall from our previous discussion in chapter 2 that the basic reproduction number R_0 plays a crucial role in disease dynamics. It is a threshold value that determines whether or not a disease will fully establish itself. Comparing the R_0 of our transmission model with that obtained in [29], we found that there are additional parameters in our R_0, namely η, α, ρ, f, h, d, which is due to the additional classes found in our model. When the putative drug parameter, $\theta \neq 0$, the term $1 + \lambda + \theta$ replaces $1 + \lambda$ and taking the limit as $\theta \to \infty$ does not drive R_0 to 0 but only reduces it to less than unity depending on the values of the model parameters. This suggest that treating only asymptomatic individuals, apart from being a mere epidemiological paradox would not guarantee disease eradication except it is done with some form of vector control keeping the parameter β at a reasonable level.

Our result is a deterministic approach to the hypothesis given in [85]. Past and present policies of the WHO for the elimination and eradication of malaria have been geared towards vector control and treatment of symptomatic humans and despite the huge amount of money spent there are still reports of greater part of the world population affected by the disease. The recent Global Malaria Programme's new initiative, T3, urges malaria-endemic countries to ensure that every suspected malaria case is tested, that every confirmed case is treated with a quality-assured antimalarial medicine, and that the disease is tracked through timely and accurate surveillance systems to guide policy and operational decisions [118].

Our results suggest that testing, treating and tracking of suspected symptomatic cases without considering the asymptomatic group that forms a greater part of the reservoir of infection will thwart the global effort on the elimination and eradication of malaria. Although the issue of treating asymptomatic humans may be difficult to control in that it would take a lot of sensitisation and enlightenment campaigns to be able to persuade people who are not having the symptoms of a disease to take treatment. However, we suggest that 'Check Your Malaria Status' (CYMS) be introduced along side T3.

In this work, we have also proposed and analysed a within-host malaria model in which the interaction between parasites, red blood cells and the immune system are well represented based on a simplified form of the known biology. The novelty in the model comprises inclusion of terms describing the mechanism of antigen presentation of innate immune cells at the start of infection in preparation to triggerring adaptive immune response after a time delay and an Fc-dependent mechanism of parasite killing. We used the model to study the dynamics of disease pathology, parasite evolution from the young asexual erythrocyte stage to the mature sexual exo-erythrocytic stage in a naive host. Both numerical simulations and asymptotic analysis were employed in our study and the numerical results show that a naive human that cannot develop specific immunity to malaria may not be able to survive a single mosquito bite but in the presence of adaptive immunity there is possibility of parasite clearance even though some levels of anaemia could be experienced.

6.1.1. Limitations of the models

Models are generally simplifications of reality and therefore subject to limitations. For instance in an attempt to construct models to curb the shortcomings of previous models, we end up having models with other limitations. Our in-host model does not account for the accelerated production of red blood cells during malaria infection and the additional killing

of erythrocytes by phagocytosis of nonviable merozoites attached to them. This is considered in the model of Chiyaka et al. [23] by including additional two terms. The exclusion in our model is based on the assumption that the two terms might cancel out. But in a situation where the net contributions of these terms is large it may affect the results. The issue of parasite clearance is another limitation. Another factor we have not considered in our model is the inhibition of immune cell growth. Inhibitory cytokines reduce the secretion of IL-10, a major cytokine that induces B cell proliferation and immunoglobulin production [67], thereby reducing the production of antibodies. Our model is a continuum model and we find out from the simulations that the immune system drives the concentration of parasite to a very low level which we assumed to be negligible in terms of number of parasites present in the blood stream. Similarly, during the asymptotic analysis, gametocytes are seen to emerge in the third time scale, less than two days after infection and before the end of the first cycle of schizogony, which may not be a good representation of reality. However, since $\epsilon = 0.001$, the density of gametocytes, being $O(\epsilon^4)$ is assumed to be zero. It was not until the sixth time scale when a non negligible amount of $O(\epsilon)$ was produced.

6.1.2. Suggestion for future work.

The two models we have developed in this study are aimed at describing the dynamics of malaria transmission and pathogenesis with the aim of assessing possible elimination strategies. The models can be relevant in areas where malaria has been persistently prevalent and regions that have achieved malaria elimination. However, the models are mere simplifications of reality and some modifications are required for improvement, which will provide directions for further studies. The following areas are included for consideration.

- Numerical simulations of the transmission model suggest that combined treatment of both symptomatic and asymptomatic individuals will lead to malaria elimination. We

propose pilot studies in malaria endemic regions using this model as a theoretical frame-
work.

- Environmental factors favourable to mosquito breeding also contribute to the pattern of disease transmission. These factors may vary seasonally within a region or between regions. We propose a model modification that will incorporate temperature and rainfall so as to ensure regional specific results.

- An asymptotic expansion of R_0 shows that the putative drug, θ, used for the treatment of asymptomatic humans is not as effective as γ, the full treatment parameter. Whilst in the numerical simulations, θ appears to be much more effective in killing off the disease. The mechanism for this behaviour is not yet known, and hence the need for further investigation.

- Antibodies production: Though it is assumed that the production of antibodies comes from activation of naive T cells and B cells through interaction between innate immune cells and pathogens, it is not fully represented in the in-host model. The delay term appears to cover this limitation but in strict sense we do not expect antibodies production whenever innate immune cells are absent. Thus we propose a modification in which the antibodies equation is multiplied by $P - 1$.

- Subsequent contact: The in-host model is studied by assuming only a first contact in the analysis whereas results from our simulations indicate a good prospect of reducing disease pathology on consideration of boosting the immune response, and hence we propose inclusion of subsequent contact in future work on the model.

- During malaria infection certain mechanisms operate to inhibit the production of an-tibodies especially when the effect of proinflamatory activities is high and phagocytic

cells become heavily laden with haemozoin particles. Regulatory T cells produce inhibitory cytokines to reduce the secretion of IL-10, a major cytokine that induces B cell proliferation and immunoglobulin production[67]. Consideration of this may create a major extension of the model as it will require two additional equations for T cells and B cells.

- Through the asymptotic analysis of the in-host model we found that the immune system is mostly driven by infected red blood cells. Further investigation is recommended to ascertain the validity of this result. The genetic constituent of red blood cells as different from that of merozoite should be determined. This may create an insight into manufacturing a vaccine that will boost the immune system to the extent of stopping merozoite invasion of red blood cells.

This list is not exhaustive and it has not in any way invalidated the results of our work but we hope that these suggestions will help to extend the frontier of knowledge and create a better direction in the quest for malaria eradication.

APPENDIX A

APPENDIX

A.1. Expressions for important constants in the stability analysis of transition model

$$b_4 = a_1a_2a_3a_4a_5, \; C_1 = a_1a_2a_4a_5, \; C_2 = a_1 + a_2 + a_3 + a_4 + a_5,$$

$$C_3 = a_1a_5^2\{a_5(4a_2^2 + 5a_2a_4) + 4a_2^3 + 8a_2^2a_4 + 8a_2a_4^2\},$$

$$C_4 = a_1\{a_5(5a_2^3a_4 + 8a_2^2a_4^2 + 5a_2a_4^3) + 4a_2^3a_4^2 + 4a_2^2a_4^3 + a_2a_4^4\},$$

$$C_5 = a_1a_5\{a_5^3(a_2 + a_4) + 4a_4^2a_5^2 + 4a_4^3a_5 + a_4^4 + 2a_2^3a_5^2 + 4a_5(a_2^4 + 5a_2^2a_4^3)\},$$

$$C_6 = a_2a_4(a_2^2a_4 + a_2^2a_5 + 2a_2a_4^2 + 5a_2a_4a_5 + a_4^3 + 5a_4^2a_5),$$

$$C_7 = a_1a_5^3\{a_5(a_2^2 + a_2a_4 + a_4^2) + 5a_2^2a_4 + 5a_2a_4^2 + 2a_4^3\},$$

$$C_8 = a_1a_5^2(8a_2^2a_4^2 + 5a_2a_4^3 + a_4^4) + a_1a_2a_4^4a_5 + a_2^4a4^2a_5,$$

$$C_9 = a_5^3\{a_5(a_2^2a_4 + a_2a_4^2) + 2a_2^3a_4 + 4a_2^2a_4^2 + 2a_2a_4^3\},$$

$$C_{10} = a_5\{a_5(a_2^4a_4 + 4a_2^3a_4^2 + 4a_2^2a_4^3 + a_2a_4^4) + 2a_2^3a_4^3 + a_2^2a_4^4\},$$

$$D_1 = a_3 + 2(a_1 + a_2 + a_4 + a_5), \; D_2 = a_1(a_1 + 3a_2 + 2a_3 + 3a_4 + 3a_5) + 3a_2^2 + 4a_2a_3,$$

$$D_3 = a_1(6a_2a_4 + 6a_2a_5 + 4a_3a_4 + 4a_3a_5 + 3a_4^2), \; D_4 = 6a_1a_4a_5 + 3a_1a_5^2 + a_2^3 + 2a_2^2a_3 + 3a_2^2a_4,$$

$$D_5 = a_4(a_4^2 + 3a_2a_4 + 3a_4a_5 + 2a_3a_4 + 3a_5^2 + 4a_3a_5 + 6a_2a_5,$$

$$D_6 = 4a_2a_3a_4 + a_5^3 + 2a_3a_5^2 + 3a_2a_5^2 + 3a_2^2a_5 + 4a_2a_3a_5,$$

$$D_7 = C_1^2(a_2a_4 + a_5^4)(a_2 + a_4) + C_1^2a_5(a_2^2 + a_2a_4 + a_4^2) + C_8,$$

$$D_8 = 2C_1a_2a_4a_5^4(a_2 + a_4) + C_1a_2a_4a_5^3(5a_2a_4 + 4a_2^2 + 4a_4^2) + C_3,$$

$$D_9 = a_2^2a_4^2(a_4 + a_2)^2 + a_1a_4^2a_5(8a_2^2 + 5a_2a_4 + a_4^2) + C_4 + C_5,$$

$$D_{10} = a_2^2C_1 + C_6C_7, \; D_{11} = a_2a_4a_5(a_4^3 + 2a_4^2a_5 + a_4a_5^2 + 4a_2a_4a_5 + a_2a_5^2),$$

$$E_1 = \beta\eta f\rho d, \; E_2 = \beta\eta fb.$$

A.2. Demonstrating the effect of inequalities obtained in 3.6.7 on R_0

$$R_0 = \frac{\beta\eta f\{b(1 + \lambda + \theta) + \rho d\}}{(\eta + \lambda)(\alpha + \gamma + \rho + \lambda)(1 + \lambda + \theta)(f + q)(h + q)}. \tag{A.2.1}$$

$$\frac{\eta\beta}{\eta + \lambda} \leq q, \tag{A.2.2}$$

$$\frac{fb}{f + q} \leq \gamma + \lambda, \tag{A.2.3}$$

$$\frac{fd}{f + q} \leq \frac{\lambda(\eta + \theta + \lambda)}{\eta + \lambda}. \tag{A.2.4}$$

We show that if (A.2.2)−(A.2.4) hold, then $R_0 \leq 1$.

$$\textit{Numerator of (A.2.1)} = \beta\eta f\{b(1 + \lambda + \theta) + \rho d\}.$$

$$\textit{Numerator of (A.2.1)} = \beta\eta\{fb(1 + \lambda + \theta) + f\rho d\}. \tag{A.2.5}$$

$$\textit{Denominator of (A.2.1)} = (\eta + \lambda)(h + q)\{(\lambda + \gamma)(f + q)(1 + \lambda + \theta)$$
$$+ (\alpha + \rho)(1 + \lambda + \theta)(f + q)\},$$

$$\textit{Denominator of (A.2.1)} = (\eta + \lambda)(h + q)\{(\lambda + \gamma)(1 + \lambda + \theta)(f + q) \tag{A.2.6}$$
$$+ \{\rho(1 + \lambda + \theta)(f + q) + \alpha(1 + \lambda + \theta)(f + q)\}\}$$

Comparing (A.2.5) and (A.2.6) we observe from (A.2.2) that

$$\beta\eta \leq (\eta + \lambda)q \leq (\eta + \lambda)(h + q), \tag{A.2.7}$$

and from (A.2.3) that

$$fb \leq (\gamma + \lambda)(f + q), \tag{A.2.8}$$

and hence

$$fb(1 + \theta + \lambda) \leq (\gamma + \lambda)(f + q)(1 + \theta + \lambda). \tag{A.2.9}$$

Also, from (A.2.4),

$$fd \leq \frac{(f + q)\lambda(\eta + \lambda + \theta)}{\eta + \lambda} \Rightarrow fd \leq (f+q)(1+\lambda+\theta), \text{ since } 1+\theta+\lambda > \frac{\lambda(\eta + \lambda + \theta)}{\eta + \lambda}. \tag{A.2.10}$$

Thus, the numerator of (A.2.1) is less than the denominator, meaning, $R_0 < 1$.

APPENDIX B

APPENDIX

B.1. Time-scale analysis (transition model)

By letting $\theta = 0$, we present the time scale analysis of the dimensionless system

$$\epsilon^2 \frac{dC}{dt} = \epsilon^4 \hat{\lambda} + \epsilon \hat{\gamma} S + \epsilon^2 A - \hat{\beta} ZC - \epsilon^4 \hat{\lambda} C + \epsilon^4 \hat{\alpha} CS, \tag{B.1.1}$$

$$\epsilon^2 \frac{dL}{dt} = \hat{\beta} ZC - \epsilon \hat{\eta} L - \epsilon^4 \hat{\lambda} L + \epsilon^4 \hat{\alpha} LS, \tag{B.1.2}$$

$$\epsilon^2 \frac{dL_A}{dt} = \hat{\beta} ZA - \epsilon \hat{\eta} L_A - \epsilon^4 \hat{\lambda} L_A + \epsilon^4 \hat{\alpha} L_A S, \tag{B.1.3}$$

$$\epsilon^2 \frac{dS}{dt} = \epsilon \hat{\eta} L + \epsilon \hat{\eta} L_A - \left(\hat{\rho} + \epsilon \hat{\gamma} + \epsilon^4 \hat{\alpha} + \epsilon^4 \hat{\lambda} \right) S + \epsilon^4 \hat{\alpha} S^2, \tag{B.1.4}$$

$$\epsilon^2 \frac{dA}{dt} = \hat{\rho} S - \left(\epsilon^2 + \epsilon^4 \hat{\lambda} \right) A - \hat{\beta} ZA + \epsilon^4 \hat{\alpha} AS, \tag{B.1.5}$$

$$\epsilon \frac{dX}{dt} = \hat{q} (1 - X) - \hat{b} SX - \hat{d} AX - \hat{d} L_A X + \epsilon \hat{h} XZ, \tag{B.1.6}$$

$$\epsilon \frac{dY}{dt} = \hat{b} SX + \hat{d} AX + \hat{d} L_A X - \left(\hat{f} + \hat{q} \right) Y + \epsilon \hat{h} YZ, \tag{B.1.7}$$

$$\epsilon \frac{dZ}{dt} = \hat{f} Y - \left(\epsilon \hat{h} + \hat{q} \right) Z + \epsilon \hat{h} Z^2, \tag{B.1.8}$$

subject to

$$C(0) = 1, \quad L(0) = 0, \quad L_A(0) = 0, \quad S(0) = 0, \quad A(0) = 0,$$

$$Y(0) = y_0, \quad X(0) = 1 - y_0, \quad Z(0) = 0, \quad \epsilon \ll 1, \quad y_0 \ll \epsilon,$$

in which all parameters are expressed in terms of their size as a power of ϵ indicated in table 3.3, namely

$$
\begin{aligned}
\beta &= \frac{1}{\epsilon^2}\hat{\beta}, \ \eta = \frac{1}{\epsilon}\hat{\eta}, \ \mu = \epsilon^2\hat{\mu}, \ \lambda = \epsilon^2\hat{\lambda}, \ \alpha = \epsilon^2\hat{\alpha}, \ \gamma = \frac{1}{\epsilon}\hat{\gamma}, \ \rho = \frac{1}{\epsilon^2}\hat{\rho}, \quad \text{(B.1.9)} \\
b &= \frac{1}{\epsilon}\hat{b}, \ d = \frac{1}{\epsilon}\hat{d}, \ f = \frac{1}{\epsilon}\hat{f}, \ g = \frac{1}{\epsilon}\hat{g}, \ h = \hat{h}, \ q = \frac{1}{\epsilon}\hat{q}.
\end{aligned}
$$

We analyse this system for the case of newly introduced infected mosquitoes to a previously uninfected region.

B.1.1. Time scale 1: $t = O(\epsilon^2)$

- Scalings: $t = \epsilon^2\hat{t}$,

$$
\begin{aligned}
C &\sim 1 + \epsilon y_0 \hat{C}_1, \quad L \sim \epsilon y_0 \hat{L}_0, \quad L_A \sim \epsilon^3 y_0^2 \hat{L}_{A_0}, \quad S \sim \epsilon^2 y_0 \hat{S}_0, \\
A &\sim \epsilon^2 y_0 \hat{A}_0, \quad X \sim 1 - y_0 + \epsilon y_0 \hat{X}_1, \quad Y \sim y_0 + \epsilon y_0 \hat{Y}_1, \quad Z \sim \epsilon y_0 \hat{Z}_0.
\end{aligned}
$$

Substituting these scalings into the dimensionless system leads to the following

- Equations

$$
\begin{aligned}
\frac{d\hat{C}_1}{d\hat{t}} &= -\hat{\beta}\hat{Z}_0(1 + \epsilon y_0\hat{C}_1) + \epsilon^2(\hat{\gamma}\hat{S}_0 + \hat{A}_0) - \epsilon^4\hat{\lambda}\hat{C}_1 + \epsilon^5\hat{\alpha}(1 + \epsilon y_0\hat{C}_1)\hat{S}_0, \\
\frac{d\hat{L}_0}{d\hat{t}} &= \hat{\beta}\hat{Z}_0(1 + \epsilon y_0\hat{C}_1) - \epsilon\hat{\eta}\hat{L}_0 - \epsilon^4\hat{\lambda}\hat{L}_0 + \epsilon^6 y_0\hat{\alpha}\hat{L}_0\hat{S}_0, \\
\frac{d\hat{L}_{A_0}}{d\hat{t}} &= \hat{\beta}\hat{A}_0\hat{Z}_0 - \epsilon\hat{\eta}\hat{L}_{A_0} - \epsilon^4\hat{\lambda}\hat{L}_{A_0} + \epsilon^6 y_0\hat{\alpha}\hat{L}_{A_0}\hat{S}_0, \\
\frac{d\hat{S}_0}{d\hat{t}} &= \hat{\eta}L_0 - \hat{\rho}\hat{S}_0 + \epsilon^2 y_0\hat{\eta}\hat{L}_{A_0} - (\epsilon\hat{\gamma} + \epsilon^4\hat{\alpha} + \epsilon^4\hat{\lambda})\hat{S}_0 + \epsilon^6 y_0\hat{\alpha}\hat{S}_0^2, \\
\frac{d\hat{A}_0}{d\hat{t}} &= \hat{\rho}S_0 - (\epsilon^2 + \epsilon^4\hat{\lambda})\hat{A}_0 - \epsilon y_0\hat{\beta}\hat{Z}_0\hat{A}_0 + \epsilon^6 y_0\hat{\alpha}\hat{A}_0\hat{S}_0, \\
\frac{d\hat{X}_1}{d\hat{t}} &= \hat{q}(1 - \epsilon\hat{X}_1) - \epsilon^2\hat{b}\hat{S}_0(1 - y_0 + \epsilon y_0 X_1) - \epsilon^2\hat{d}\hat{A}_0(1 - y_0 + \epsilon y_0\hat{X}_1) \\
&\quad + \ \epsilon^2\hat{h}(1 - y_0 + \epsilon y_0\hat{X}_1)\hat{Z}_0) - \epsilon^3 y_0\hat{d}\hat{L}_{A_0}(1 - y_0 + \epsilon y_0\hat{X}_1), \\
\frac{d\bar{Y}_1}{d\hat{t}} &= -\left(\hat{f} + \hat{q}\right)(1 + \epsilon\hat{Y}_1) + \epsilon^2\hat{b}\hat{S}_0(1 - y_0 + \epsilon y_0 X_1) + \epsilon^2\hat{d}\hat{A}_0(1 - y_0 + \epsilon y_0 X_1)
\end{aligned}
$$

$$+ \quad \epsilon^2 \hat{h}(1 - y_0 + \epsilon y_0 \hat{Y}_1)\hat{Z}_0) + \epsilon^3 y_0 \hat{d}\hat{L}_{A_0}(1 - y_0 + \epsilon y_0 \hat{X}_1),$$

$$\frac{d\hat{Z}_0}{d\hat{t}} = \hat{f}(1 + \epsilon Y_1) - \epsilon(\hat{q} + \epsilon\hat{h})\hat{Z}_0 + \epsilon^3 y_0 \hat{h}\hat{Z}_0^2,$$

— The system changes balance at $\hat{t} = O(\epsilon^{-2/3})$. This happens in the Y equation as the lower order term $\epsilon^2 \hat{d}\hat{A}_0$ catches up with the $O(1)$ term $\hat{f} + \hat{q}$. We observe from the solution in this timescale that $\hat{A}_0 = O(t^3)$. Thus $\epsilon^2 \hat{t}^3 = O(1)$ implies $\hat{t} = O(\epsilon^{-\frac{2}{3}})$. We note that $y_0 \ll \epsilon$ and $\hat{t} = O(\epsilon^{-\frac{2}{3}})$ is the smallest time in which the asymptotic expansion will no longer be valid.

B.1.2. Time scale 2: $t = O(\epsilon^{4/3})$

- Scalings: $t = \epsilon^{4/3}\bar{t}$,

$$C \sim 1 + \epsilon^{-1/3} y_0 \bar{C}_1, \quad L \sim \epsilon^{-1/3} y_0 \bar{L}_0, \quad L_A \sim \epsilon^{-1/3} y_0^2 \bar{L}_{A_0},$$

$$S \sim \epsilon^{2/3} y_0 \bar{S}_0, \quad A \sim y_0 \bar{A}_0, \quad X \sim 1 - y_0 + \epsilon^{1/3} y_0 \bar{X}_1,$$

$$Y \sim y_0 + \epsilon^{1/3} y_0 \bar{Y}_1, \quad Z \sim \epsilon^{1/3} y_0 \bar{Z}_0.$$

On substitution of these scalings into the dimensionless system we have

- Equations

$$\frac{d\bar{C}_1}{d\bar{t}} = -\hat{\beta}\bar{Z}_0(1 + \epsilon^{-\frac{1}{3}}y_0\bar{C}_1) + \epsilon^{\frac{4}{3}}(\hat{\gamma}\bar{S}_0 + \epsilon^{\frac{1}{3}}\bar{A}_0) - \epsilon^4\hat{\lambda}\bar{C}_1) + \epsilon^{\frac{13}{3}}\hat{\alpha}(1 + \epsilon^{-\frac{1}{3}}y_0\bar{C}_1)\bar{S}_0,$$

$$\frac{d\bar{L}_0}{d\bar{t}} = \hat{\beta}\bar{Z}_0(1 + \epsilon^{-\frac{1}{3}}y_0\bar{C}_1) - \epsilon^{\frac{1}{3}}\hat{\eta}\bar{L}_0 - \epsilon^{\frac{10}{3}}\hat{\lambda}\bar{L}_0 + \epsilon^4 y_0\hat{\alpha}\bar{L}_0\bar{S}_0,$$

$$\frac{d\bar{L}_{A_0}}{d\bar{t}} = \hat{\beta}\bar{A}_0\bar{Z}_0 - \epsilon^{\frac{1}{3}}\hat{\eta}\bar{L}_{A_0} - \epsilon^{\frac{10}{3}}\hat{\lambda}\bar{L}_{A_0} + \epsilon^4 y_0\hat{\alpha}\bar{L}_{A_0}\bar{S}_0,$$

$$\epsilon^{\frac{2}{3}}\frac{d\bar{S}_0}{d\bar{t}} = \hat{\eta}\bar{L}_0 - \hat{\rho}\bar{S}_0 + y_0\hat{\eta}\bar{L}_{A_0} - (\epsilon\hat{\gamma} + \epsilon^4\hat{\alpha} + \epsilon^4\hat{\lambda})\bar{S}_0 + \epsilon^{-\frac{14}{3}}y_0\hat{\alpha}\bar{S}_0^2,$$

$$\frac{d\bar{A}_0}{d\bar{t}} = \hat{\rho}\bar{S}_0 - \frac{y_0}{\epsilon^{\frac{1}{3}}}\hat{\beta}\bar{Z}_0\bar{A}_0 - (\epsilon^{\frac{4}{3}} + \epsilon^{\frac{10}{3}}\hat{\lambda})\bar{A}_0 + \epsilon^4 y_0\hat{\alpha}\bar{A}_0\bar{S}_0,$$

$$\frac{d\bar{X}_1}{d\bar{t}} = \hat{q}(1 - \epsilon^{\frac{1}{3}}\bar{X}_1) - \hat{d}\bar{A}_0(1 - y_0 + \epsilon^{\frac{1}{3}}y_0\bar{X}_1) - \epsilon^{\frac{2}{3}}\hat{b}\bar{S}_0(1 - y_0 + \epsilon^{\frac{1}{3}}y_0\bar{X}_1)$$

$$- \frac{y_0}{\epsilon^{\frac{1}{3}}}\hat{d}\bar{L}_{A_0}(1 - y_0 + \epsilon^{\frac{1}{3}}y_0 X_1) + \epsilon^{\frac{4}{3}}\hat{h}(1 - y_0 + \epsilon^{\frac{1}{3}}y_0\bar{X}_1)\bar{Z}_0,$$

$$\frac{d\bar{Y}_1}{d\bar{t}} = -\left(\hat{f}+\hat{q}\right)(1+\epsilon^{\frac{1}{3}}\bar{Y}_1) + \hat{d}\bar{A}_0(1-y_0+\epsilon^{\frac{1}{3}}y_0\bar{X}_1) + \epsilon^{\frac{2}{3}}\hat{b}\bar{S}_0(1-y_0+\epsilon^{\frac{1}{3}}y_0\bar{X}_1)$$

$$+ \ \frac{y_0}{\epsilon^{\frac{1}{3}}}\hat{d}\bar{L}_{A_0}(1-y_0+\epsilon^{\frac{1}{3}}y_0\bar{X}_1) + \epsilon^{\frac{4}{3}}y_0\hat{h}(1+\epsilon^{\frac{1}{3}}\bar{Y}_1)\bar{Z}_0,$$

$$\frac{d\bar{Z}_0}{d\bar{t}} = \hat{f}(1+\epsilon^{\frac{1}{3}}\bar{Y}_1) - \epsilon^{\frac{1}{3}}(\epsilon\hat{h}+\hat{q})\bar{Z}_0 + \epsilon^{\frac{5}{3}}y_0\hat{h}\bar{Z}_0^2,$$

— Solutions in this timescale suggest that $X_1 = O(\bar{t}^4)$ and the approximations become poor when the second term $\epsilon^{\frac{1}{3}}\bar{t}^4$ becomes $O(1)$, i.e. $\bar{t}^4 = O(\epsilon^{-\frac{1}{3}})$. This leads to a break down in the X equation when $\bar{t} = O(\epsilon^{-1/12})$.

<div align="center">

B.1.3. Time scale 3: $t = O(\epsilon^{5/4})$

</div>

- Scalings: $t = \epsilon^{5/4}\tilde{t}$,

$$C \ \sim \ 1+\epsilon^{-1/2}y_0\tilde{C}_1, \quad L \sim \epsilon^{-1/2}y_0\tilde{L}_0, \quad L_A \sim \epsilon^{-3/4}y_0^2\tilde{L}_{A_0},$$

$$S \ \sim \ \epsilon^{1/2}y_0\tilde{S}_0, \quad A \sim \epsilon^{-1/4}y_0\tilde{A}_0, \quad X \sim 1+y_0\tilde{X}_1,$$

$$Y \ \sim \ y_0\tilde{Y}_1, \quad Z \sim \epsilon^{1/4}y_0\tilde{Z}_0.$$

By substituting the scalings into the dimensionless system and carrying out some simplifications we get the following

- Equations

$$\frac{d\tilde{C}_1}{d\tilde{t}} = -\hat{\beta}\tilde{Z}_0(1+\epsilon^{-\frac{1}{2}}y_0\tilde{C}_1) + \epsilon^{\frac{3}{2}}(\tilde{A}_0+\epsilon^{\frac{1}{4}}\hat{\gamma}\tilde{S}_0) - \epsilon^{\frac{13}{4}}\hat{\lambda}\tilde{C}_1 + \epsilon^{\frac{9}{2}}\hat{\alpha}(1+\epsilon^{-\frac{1}{2}}y_0\tilde{C}_1)\tilde{S}_0,$$

$$\frac{d\tilde{L}_0}{d\tilde{t}} = \hat{\beta}\tilde{Z}_0(1+\epsilon^{-\frac{1}{2}}y_0\tilde{C}_1) - \epsilon^{\frac{1}{2}}\hat{\eta}\tilde{L}_0 - \epsilon^{\frac{10}{4}}\hat{\lambda}\tilde{L}_0 + \epsilon^{\frac{15}{4}}y_0\hat{\alpha}\tilde{L}_0\tilde{S}_0,$$

$$\frac{d\tilde{L}_{A_0}}{d\tilde{t}} = \hat{\beta}\tilde{A}_0\tilde{Z}_0 - \epsilon^{\frac{1}{4}}\hat{\eta}\tilde{L}_{A_0} - \epsilon^{\frac{13}{4}}\hat{\lambda}\tilde{L}_{A_0} + \epsilon^{\frac{15}{4}}y_0\hat{\alpha}\tilde{L}_{A_0}\tilde{S}_0,$$

$$\epsilon^{\frac{1}{2}}\frac{d\tilde{S}_0}{d\tilde{t}} = \hat{\eta}\tilde{L}_0 - \hat{\rho}\tilde{S}_0 + \frac{y_0}{\epsilon^{\frac{1}{4}}}\hat{\eta}\tilde{L}_{A_0} - (\epsilon\hat{\gamma}+\epsilon^4\hat{\alpha}+\epsilon^4\hat{\lambda})\tilde{S}_0 + \epsilon^4 y_0\hat{\alpha}\tilde{S}_0^2,$$

$$\frac{d\tilde{A}_0}{d\tilde{t}} = \hat{\rho}\tilde{S}_0 - \frac{y_0}{\epsilon^{\frac{1}{3}}}\hat{\beta}\tilde{Z}_0\tilde{A}_0 - (\epsilon^{\frac{5}{4}}+\epsilon^{\frac{13}{4}}\hat{\lambda})\tilde{A}_0 + \epsilon^{\frac{15}{4}}y_0\hat{\alpha}\tilde{A}_0\tilde{S}_0,$$

$$\frac{d\tilde{X}_1}{d\tilde{t}} = -\hat{d}\tilde{A}_0(1+y_0\tilde{X}_1) - \epsilon^{\frac{1}{4}}\hat{q}\tilde{X}_1 - \epsilon^{\frac{3}{4}}\hat{b}\tilde{S}_0(1+y_0\tilde{X}_1) - \epsilon^{\frac{1}{2}}y_0\hat{d}\tilde{L}_{A_0}(1+y_0\tilde{X}_1)$$

$$+ \ \epsilon^{\frac{3}{2}}\hat{h}(1+y_0\tilde{X}_1)\tilde{Z}_0,$$

<div align="center">133</div>

$$\frac{d\tilde{Y}_1}{d\tilde{t}} = \hat{d}\tilde{A}_0(1 + y_0\tilde{X}_1) - \epsilon^{\frac{1}{4}}(\hat{f} + \hat{q})\tilde{Y}_1 + \epsilon^{\frac{3}{4}}\hat{b}\tilde{S}_0(1 + y_0\tilde{X}_1) + \epsilon^{\frac{1}{2}}y_0\hat{d}\tilde{L}_{A_0}(1 + y_0\tilde{X}_1)$$

$$+ \epsilon^{\frac{3}{2}}y_0\hat{h}\tilde{Y}_1\tilde{Z}_0,$$

$$\frac{d\tilde{Z}_0}{d\tilde{t}} = \hat{f}\tilde{Y}_1 - \epsilon^{\frac{1}{4}}(\hat{q} + \epsilon\hat{h})\tilde{Z}_0 + \epsilon^{\frac{3}{2}}y_0\hat{h}\tilde{Z}_0^2,$$

— The governing equation of the system is $\dfrac{d^4\tilde{Z}_0}{d\tilde{t}^4} = K\tilde{Z}_0$, obtained by successive differentiation of $\dfrac{d\tilde{Z}_0}{d\tilde{t}}$, where $K = \hat{\beta}\hat{\eta}\hat{f}\hat{d}$ and For $K_0 = K^{\frac{1}{4}}$, change in balance occurs in the C solution when $\tilde{t} = \ln(\epsilon^{1/2}/y_0)/K_0$.

B.1.4. Time scale 4: $t = \epsilon^{\frac{5}{4}}\ln(\epsilon^{1/2}/y_0)/K + O(\epsilon^{\frac{5}{4}})$

- Scalings: $t = \epsilon^{\frac{5}{4}}\ln(\epsilon^{1/2}/y_0)/K + \epsilon^{\frac{5}{4}}\check{t},$

$$C \sim \check{C}_0, \quad L \sim \check{L}_0, \quad L_A \sim \epsilon^{1/4}\check{L}_{A_0}, \quad S \sim \epsilon\check{S}_0, \quad A \sim \epsilon^{1/4}\check{A}_0,$$

$$X \sim 1 + \epsilon^{1/2}\check{X}_1, \quad Y \sim \epsilon^{1/2}\check{Y}_1, \quad Z \sim \epsilon^{3/4}\check{Z}_0.$$

- Equations

$$\frac{d\check{C}_0}{d\check{t}} = -\hat{\beta}\check{C}_0\check{Z}_0 + \epsilon^{\frac{3}{2}}(\check{A}_0 + \epsilon^{\frac{1}{4}}\hat{\gamma}\check{S}_0) - \epsilon^{\frac{13}{4}}\hat{\lambda}(1 - \check{C}_0) + \epsilon^{\frac{17}{4}}\hat{\alpha}\check{C}_0\check{S}_0,$$

$$\frac{d\check{L}_0}{d\check{t}} = \hat{\beta}\check{C}_0\check{Z}_0 - \epsilon^{\frac{1}{4}}\hat{\eta}\check{L} - \epsilon^{\frac{13}{4}}\hat{\lambda}\check{L}_0 + \epsilon^{\frac{17}{4}}\hat{\alpha}\check{L}_0\check{S}_0,$$

$$\frac{d\check{L}_{A_0}}{d\check{t}} = \hat{\beta}\check{A}_0\check{Z}_0 - \epsilon^{\frac{1}{4}}\hat{\eta}\check{L}_{A_0} - \epsilon^{\frac{13}{4}}\hat{\lambda}\check{L}_{A_0} + \epsilon^{\frac{17}{4}}y_0\hat{\alpha}\check{L}_{A_0}\check{S}_0,$$

$$\epsilon^{\frac{3}{4}}\frac{d\check{S}_0}{d\check{t}} = \hat{\eta}\check{L}_0 - \hat{\rho}\check{S}_0 + \epsilon^{\frac{1}{4}}\hat{\eta}\check{L}_{A_0} - (\epsilon\hat{\gamma} + \epsilon^4\hat{\alpha} + \epsilon^4\hat{\lambda})\check{S}_0 + \epsilon^5\hat{\alpha}\check{S}_0^2,$$

$$\frac{d\check{A}_0}{d\check{t}} = \hat{\rho}\check{S}_0 - \hat{\beta}\check{Z}_0\check{A}_0 - (\epsilon^{\frac{5}{4}} + \epsilon^{\frac{13}{4}}\hat{\lambda})\check{A}_0 + \epsilon^{\frac{17}{4}}\hat{\alpha}\check{A}_0\check{S}_0,$$

$$\frac{d\check{X}_1}{d\check{t}} = -\hat{d}\check{A}_0(1 + \epsilon^{\frac{1}{2}}\check{X}_1) - \hat{d}\check{L}_{A_0}(1 + \epsilon^{\frac{1}{2}}\check{X}_1) - \epsilon^{\frac{1}{2}}\hat{q}\check{X}_1 - \epsilon^{\frac{3}{4}}\hat{b}\check{S}_0(1 + \epsilon^{\frac{1}{2}}\check{X}_1)$$

$$+ \epsilon^{\frac{3}{2}}\hat{h}(1 + \epsilon^{\frac{1}{2}}\check{X}_1)\check{Z}_0,$$

$$\frac{d\check{Y}_1}{d\check{t}} = \hat{d}\check{A}_0(1 + \epsilon^{\frac{1}{2}}\check{X}_1) + \hat{d}\check{L}_{A_0}(1 + \epsilon^{\frac{1}{2}}\check{X}_1) + \epsilon^{\frac{3}{4}}\hat{b}\check{S}_0(1 + \epsilon^{\frac{1}{2}}\check{X}_1) - \epsilon^{\frac{1}{2}}(\hat{f} + \hat{q})\check{Y}_1$$

$$+ \epsilon^2\hat{h}\check{Y}_1\check{Z}_0,$$

$$\frac{d\check{Z}_0}{d\check{t}} = \hat{f}\check{Y}_1 - \epsilon^{\frac{1}{4}}(\hat{q} + \epsilon\hat{h})\check{Z}_0 + \epsilon^2\hat{h}\check{Z}_0^2.$$

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— Some simplification leads to the following fourth order nonlinear ordinary differential equation that determines the dynamics of the system

$$\frac{d^4 \check{F}}{d\check{t}^4} = -K\left(1 - e^{\check{F}}\right),$$

$$\check{F} = \ln(\check{C}_0).$$

— Major break down of the solutions occur in the X equation where the X_1 term becomes $O(1)$, i.e when $\check{t} = O\left(\epsilon^{-1/4}\right)$.

B.1.5. Time scale 5: $t = O(\epsilon)$

- Scalings: $t = \epsilon t^\star$,

$$C \sim \epsilon^2 C_0^\star,\ L \sim L_0^\star,\ L_A \sim L_{A_0}^\star,\ S \sim \epsilon S_0^\star,$$

$$A \sim \epsilon A_0^\star,\ X \sim X_0^\star,\ Y \sim Y_0^\star,\ Z \sim Z_0^\star.$$

Substituting these scalings into the dimensionless system leads to

- Equations

$$\epsilon \frac{dC_0^\star}{dt^\star} = -\hat{\beta} C_0^\star Z_0^\star + \hat{\gamma} S_0^\star + \epsilon A_0^\star - \epsilon^2 \hat{\lambda}(1 - \epsilon^2 C_0^\star) + \epsilon^4 \hat{\alpha} C_0^\star S_0^\star,$$

$$\frac{dL_0^\star}{dt^\star} = -\hat{\eta} L_0^\star + \epsilon \hat{\beta} Z_0^\star C_0^\star - \epsilon^3 \hat{\lambda} L_0^\star + \epsilon^4 \hat{\alpha} L_0^\star S_0^\star,$$

$$\frac{dL_{A_0}^\star}{dt^\star} = \hat{\beta} Z_0^\star A_0^\star - \hat{\eta} L_{A_0}^\star - \epsilon^3 \hat{\lambda} L_{A_0}^\star + \epsilon^4 \hat{\alpha} L_{A_0}^\star S_0^\star,$$

$$\epsilon \frac{dS_0^\star}{dt^\star} = \hat{\eta}(L_0^\star + L_{A_0}{}^\star) - \hat{\rho} S_0^\star - (\epsilon \hat{\gamma} + \epsilon^4 \hat{\alpha} + \epsilon^4 \hat{\lambda}) S_0^\star + \epsilon^5 \hat{\alpha} S_0^{2\star},$$

$$\epsilon \frac{dA_0^\star}{dt^\star} = \hat{\rho} S_0^\star - \hat{\beta} Z_0^\star A_0^\star - (\epsilon^2 + \epsilon^4 \hat{\lambda}) A_0^\star + \epsilon^4 \hat{\alpha} A_0^\star S_0^\star,$$

$$\frac{dX_0^\star}{dt^\star} = \hat{q}(1 - X_0^\star) - \hat{d} L_{A_0}^\star X_0^\star - \epsilon(\hat{b} S_0^\star X_0^\star + \hat{d} A_0^\star X_0^\star - \hat{h} X_0^\star Z_0^\star),$$

$$\frac{dY_0^\star}{dt^\star} = +\hat{d} L_{A_0}^\star X_0^\star - (\hat{f} + \hat{q}) Y_0^\star + \epsilon(\hat{b} S_0^\star X_0^\star + \hat{d} A_0^\star X_0^\star - \hat{h} Y_0^\star Z_0^\star),$$

$$\frac{dZ_0^\star}{dt^\star} = \hat{f} Y_0^\star - \hat{q} Z_0^\star - \epsilon \hat{h}(1 - Z_0^{\star 2}).$$

— Approximation to L will no longer be $O(1)$ when $t = \ln\left(1/\epsilon\right)/\eta$.

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B.1.6. Time scale 6: $t = \epsilon \ln(1/\epsilon)/\eta + O(\epsilon)$

- Scalings: $\epsilon \ln(1/\epsilon)/\eta + \epsilon\acute{t}$,

$$C \sim \epsilon^2 \acute{C}_0, \quad L \sim \epsilon \acute{L}_0, \quad L_A \sim 1, S \sim \epsilon \acute{S}_0,$$

$$A \sim \epsilon \acute{A}_0, \quad X \sim \acute{X}_0, \quad Y \sim \acute{Y}_0, \quad Z \sim \acute{Z}_0.$$

On substitution of these into the dimensionless system we obtain the following

- Equations

$$\epsilon \frac{d\acute{C}_0}{d\acute{t}} = -\hat{\beta}\acute{C}_0\acute{Z}_0 + \hat{\gamma}\acute{S}_0 + \epsilon\acute{A}_0 - \epsilon^2\hat{\lambda}(1 - \epsilon^2\acute{C}_0) + \epsilon^4\hat{\alpha}\acute{C}_0\acute{S}_0,$$

$$\frac{d\acute{L}_0}{d\acute{t}} = -\hat{\eta}\acute{L}_0 + \hat{\beta}\acute{Z}_0\acute{C}_0 - \epsilon^3\hat{\lambda}\acute{L}_0 + \epsilon^4\hat{\alpha}\acute{L}_0\acute{S}_0,$$

$$\frac{d\acute{L}_{A_0}}{d\acute{t}} = \hat{\beta}\acute{Z}_0\acute{A}_0 - \hat{\eta}\acute{L}_{A_0} - \epsilon^3\hat{\lambda}\acute{L}_{A_0} + \epsilon^4\hat{\alpha}\acute{L}_{A_0}\acute{S}_0,$$

$$\epsilon \frac{d\acute{S}_0}{d\acute{t}} = \hat{\eta}\acute{L}_{A_0} - \hat{\rho}\acute{S}_0 + \epsilon\hat{\eta}\acute{L}_0 - (\epsilon\hat{\gamma} + \epsilon^4\hat{\alpha} + \epsilon^4\hat{\lambda})\acute{S}_0 + \epsilon^5\hat{\alpha}\acute{S}_0^2,$$

$$\epsilon \frac{d\acute{A}_0}{d\acute{t}} = \hat{\rho}\acute{S}_0 - \hat{\beta}\acute{Z}_0\acute{A}_0 - (\epsilon^2 + \epsilon^4\hat{\lambda})\acute{A}_0 + \epsilon^4\hat{\alpha}\acute{A}_0\acute{S}_0,$$

$$\frac{d\acute{X}_0}{d\acute{t}} = \hat{q}(1 - \acute{X}_0) - \hat{d}\acute{L}_{A_0}\acute{X}_0 - \epsilon(\hat{b}\acute{S}_0\acute{X}_0 + \hat{d}\acute{A}\acute{X}_0 - \hat{h}\acute{X}_0\acute{Z}_0),$$

$$\frac{d\acute{Y}_0}{d\acute{t}} = \hat{d}\acute{L}_{A_0}\acute{X}_0 - (\hat{f} + \hat{q})\acute{Y}_0 + \epsilon(\hat{b}\acute{S}_0\acute{X}_0 + \hat{d}\acute{A}_0\acute{X}_0 - \hat{h}\acute{Y}_0\acute{Z}_0),$$

$$\frac{d\acute{Z}_0}{d\acute{t}} = \hat{f}\acute{Y}_0 - \hat{q}\acute{Z}_0 - \epsilon\hat{h}(1 - \acute{Z}_0^2).$$

— Other variables maintain their steady status and $L_{A_0} \sim 1$,

— and the only remaining equation is

$$\frac{d\acute{L}_0}{d\acute{t}} = \frac{\hat{\gamma}\hat{\eta}}{\hat{\rho}} - \hat{\eta}\acute{L}_0.$$

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APPENDIX C

APPENDIX

C.1. Asymptotic analysis (in-host model)

For the Inhost dynamics we seek asymptotic analysis of The dimensionless system

$$\epsilon \frac{dX}{dt} = \epsilon^2 \hat{\sigma} (1 - X) - \frac{\hat{\beta} X M}{1 + A}, \tag{C.1.1}$$

$$\epsilon \frac{dY}{dt} = \frac{\hat{\beta} X M}{1 + A} - \epsilon (1 + \hat{\mu}) Y - \epsilon \hat{k} P Y (1 + \hat{k}_1 A), \tag{C.1.2}$$

$$\epsilon \frac{dM}{dt} = \epsilon \frac{\hat{r} \left(1 - \epsilon \hat{\theta} \right) Y}{1 + k_6 A} - \frac{\hat{\beta} X M}{1 + A} - \hat{d} M - \hat{\alpha} P M \left(1 + \hat{k}_2 A \right), \tag{C.1.3}$$

$$\frac{dG}{dt} = \epsilon \frac{\hat{r} \hat{\theta} Y}{1 + k_6 A} - \epsilon \hat{e} G - \hat{f} P G (1 + \hat{k}_3 A). \tag{C.1.4}$$

$$\frac{dP}{dt} = \hat{b}(1 - P) + \hat{\omega} \left(Y + \hat{\phi} M \right) - \epsilon P \left(\hat{k}_4 Y + \hat{k}_5 M \right), \tag{C.1.5}$$

$$\frac{dA}{dt} = \hat{g}_1 Y (t - \tau) + \hat{g}_1 \hat{g}_2 M (t - \tau) - \hat{g}_3 A - \hat{h}_1 AY - \hat{h}_2 AM, \tag{C.1.6}$$

subject to

$$t = 0, \ X = 1, \ Y = 0, \ M = \epsilon^2 \hat{m}_0, \ G = 0, \ P = 1, \ A = 0,$$

$$t < 0, \ X = 1, \ Y = 0, \ M = 0, \ G = 0, \ P = 1, \ A = 0.$$

We want our readers to note that for the purpose of brevity, we have used an "over-bar"

to identify the rescaled variables in each time scale instead of the usual practice of different

variables for different timescales.

C.1.1. Time scale 1: $t = O(\epsilon)$

- Scalings: $t = \epsilon \bar{t}$,

$$X \sim \bar{X}, \quad Y \sim \epsilon^2 \bar{Y}, \quad M \sim \epsilon^2 \bar{M}, \quad G \sim \epsilon^4 \bar{G}, \quad P \sim \bar{P}, \quad A = 0$$

Substituting these into the dimensionless system leads to

- Equations

$$
\begin{aligned}
\frac{d\bar{X}}{d\bar{t}} &= \epsilon^2 \hat{\sigma} \left(1 - \bar{X}\right) - \epsilon^2 \hat{\beta} \bar{X} \bar{M}, \\
\frac{d\bar{Y}}{d\bar{t}} &= \hat{\beta} \bar{X} \bar{M} - \epsilon \left(1 + \hat{\mu}\right) \bar{Y} - \epsilon \hat{k} \bar{P} \bar{Y}, \\
\frac{d\bar{M}}{d\bar{t}} &= \left(\hat{d} + \hat{\beta} + \hat{\alpha} \bar{P}\right) \bar{M} + \epsilon \hat{r} \bar{Y} - \epsilon^2 r \hat{\theta} \bar{Y}, \\
\frac{d\bar{G}}{d\bar{t}} &= \hat{r} \hat{\theta} \bar{Y} - \epsilon \hat{f} \bar{P} \bar{G} - \epsilon^2 \hat{e} \bar{G}, \\
\frac{d\bar{P}}{d\bar{t}} &= \epsilon \hat{b} \left(1 - \bar{P}\right) + \epsilon^3 \hat{\omega} \left(\bar{Y} + \hat{\phi} \bar{M}\right) - \epsilon^3 \hat{k}_4 \bar{P} \bar{Y} - \epsilon^3 \hat{k}_5 \bar{P} \bar{M},
\end{aligned}
$$

- There is a change in balance when $\bar{M} = O(\epsilon)$. i.e at $\bar{t} = \frac{1}{b_0} \ln(\frac{1}{\epsilon}) + O(1)$

C.1.2. Time scale 2: $t = \frac{\epsilon}{b_0} \ln(\frac{1}{\epsilon}) + O(\epsilon)$

- Scalings: $t = \dfrac{\epsilon}{b_0} \ln(\dfrac{1}{\epsilon}) + \epsilon \bar{t}$,

$$X \sim \bar{X}, \quad Y \sim \epsilon^2 \bar{Y}, \quad M \sim \epsilon^3 \bar{M}, \quad G \sim \epsilon^4 \frac{\hat{r} \hat{\theta} \hat{\beta}}{b_0^2} \ln\left(\frac{1}{\epsilon}\right) + \epsilon^4 \bar{G}, \quad P \sim \bar{P}, \quad A = 0$$

On substitution of these into (C.1.1)-(C.1.6) we have the following

- Equations

$$
\begin{aligned}
\frac{d\bar{X}}{d\bar{t}} &= \epsilon^2 \hat{\sigma} \left(1 - \bar{X}\right) - \epsilon^3 \hat{\beta} \bar{X} \bar{M}, \\
\frac{d\bar{Y}}{d\bar{t}} &= \epsilon \hat{\beta} \bar{X} \bar{M} - \epsilon \left(1 + \hat{\mu}\right) \bar{Y} - \epsilon \hat{k} \bar{P} \bar{Y},
\end{aligned}
$$

$$\frac{d\bar{M}}{d\bar{t}} = \hat{r}\bar{Y} + \left(\hat{d} + \hat{\beta} + \hat{\alpha}\bar{P}\right)\bar{M} - \epsilon r\hat{\theta}\bar{Y},$$

$$\frac{d\bar{G}}{d\bar{t}} = \hat{r}\hat{\theta}\bar{Y} - \epsilon\hat{f}\bar{P}\bar{G} - \epsilon^2\hat{e}\bar{G},$$

$$\frac{d\bar{P}}{d\bar{t}} = \epsilon\hat{b}\left(1 - \bar{P}\right) + \epsilon^3\hat{\omega}Y + \epsilon^4\left(\hat{\omega}\hat{\phi}M - \hat{k}_4\bar{P}\bar{Y}\right) - \epsilon^5\hat{k}_5\bar{P}\bar{Y},$$

- The Solution breaks down at $\bar{t} = O(1/\epsilon)$

C.1.3. Time scale 3: $t = O(1), t < \tau$

- Scalings: $t = \bar{t}$,

$$X \sim \bar{X}, \quad Y \sim \epsilon^2\bar{Y}, \quad M \sim \epsilon^3\bar{M}, \quad G \sim \epsilon^3\bar{G}, \quad P \sim \bar{P}, \quad A = 0$$

Substituting these scalings into the dimensionless system yeilds

- Equations

$$\frac{d\bar{X}}{d\bar{t}} = \epsilon\hat{\sigma}\left(1 - \hat{X}\right) - \epsilon^2\hat{\beta}\bar{X}\bar{M},$$

$$\frac{d\bar{Y}}{d\bar{t}} = \hat{\beta}\bar{X}\bar{M} - \left(1 + \hat{\mu}\right)\bar{Y} - \epsilon\hat{k}\bar{P}\bar{Y},$$

$$\epsilon\frac{d\bar{M}}{d\bar{t}} = \hat{r}\bar{Y} - \left(\hat{d} + \hat{\beta} + \hat{\alpha}\bar{P}\right)\bar{M} - \epsilon r\hat{\theta}\bar{Y},$$

$$\frac{d\hat{G}}{d\hat{t}} = \hat{r}\hat{\theta}Y - \hat{f}\bar{P}\bar{G} - \epsilon\hat{e}\bar{G},$$

$$\frac{d\bar{P}}{d\bar{t}} = \hat{b}\left(1 - \bar{P}\right) + \epsilon^2\left(\hat{\omega} - \hat{k}_4\bar{P}\right)\bar{Y} + \epsilon^3\left(\hat{\omega}\hat{\phi} - \hat{k}_5\bar{P}\right)\bar{M},$$

C.1.4. Time scale 4: $t = \tau + O(\epsilon), R_c > 1$

- Scalings: $t = \tau + \epsilon\bar{t}$,

— In this time scale, all other variables become frozen but

$$A \sim \epsilon^3\bar{A}$$

By substituting this together with the scalings of Y and M for the first time scale into (C.1.6)

we have the

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- Equation

$$\frac{d\bar{A}}{d\bar{t}} = \hat{g}_1 \bar{Y}\left(t - \tau\right) + \hat{g}_1 \hat{g}_2 \bar{M}\left(t - \tau\right) - \epsilon \hat{g}_3 A - \epsilon^3 \hat{h}_1 \bar{A}\bar{Y} - \epsilon^3 \hat{h}_2 \bar{A}\bar{M}.$$

- The solution to this equation breaks down at $\hat{t} = \frac{\ln(\frac{1}{\epsilon})}{b_0} + O(1)$

C.1.5. Time scale 5: $t = \tau + O(1), R_c > 1$

- Scalings: $t = \tau + \bar{t}$,

$$X \sim \bar{X}, \quad Y \sim \epsilon^2 \bar{Y}, \quad M \sim \epsilon^3 \bar{M},$$

$$G \sim \epsilon^3 \bar{G}, \quad P \sim \bar{P}, \quad A \sim \epsilon^2 \bar{A},$$

Substituting these scalings into the dimensionless system leads to the following

- Equations

$$\begin{aligned}
\frac{d\bar{X}}{d\bar{t}} &= \epsilon \hat{\sigma}\left(1 - \hat{X}\right) - \epsilon^2 \hat{\beta} \bar{X}\bar{M}, \\
\frac{d\bar{Y}}{d\bar{t}} &= \hat{\beta} \bar{X}\bar{M} - (1 + \hat{\mu}) \bar{Y} - \hat{k} \bar{P}\bar{Y}, \\
\epsilon \frac{d\bar{M}}{d\bar{t}} &= \hat{r} \bar{Y} + \left(\hat{d} + \hat{\beta} + \hat{\alpha} \bar{P}\right) \bar{M} - r\hat{\theta} \bar{Y}, \\
\frac{d\hat{G}}{d\hat{t}} &= \hat{r}\hat{\theta} Y - \hat{f} \hat{P} G - \epsilon \hat{e} \hat{G}, \\
\frac{d\hat{P}}{d\hat{t}} &= \hat{b}\left(1 - \bar{P}\right) + \epsilon^2 \left(\hat{\omega} - \hat{k}_4 \bar{P}\right) \bar{Y} + \epsilon^3 \left(\hat{\omega}\hat{\phi} - \hat{k}_5 \bar{P}\right) \bar{M}, \\
\frac{d\bar{A}}{d\bar{t}} &= \hat{g}_1 \bar{Y}\left(t - \tau\right) - g_3 \bar{A} + \epsilon \hat{g}_1 \hat{g}_2 \bar{M}\left(t - \tau\right) - \epsilon^2 \hat{h}_1 \bar{A}\bar{Y} - \epsilon^3 \hat{h}_2 \bar{A}\bar{M}..
\end{aligned}$$

- The approximations will become poor in the P equation, when $Y = O(1/\epsilon^2)$, i.e. $t = \frac{\frac{2}{R} \ln(\frac{1}{\epsilon})}{b_0} + O(1)$.

C.1.6. Time scale 6: $t = \tau + \frac{2}{R} \ln(\frac{1}{\epsilon}) + O(1), R > 0$

- Scalings: $t = \tau + \frac{2}{R} \ln(\frac{1}{\epsilon}) + \bar{t}$,

$$X \sim \bar{X}, \quad Y \sim \bar{Y}, \quad M \sim \epsilon \bar{M},$$

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$$G \quad \sim \quad \epsilon \bar{G}, \quad P \sim \bar{P}, \quad A \sim \bar{A},$$

- Equations

$$\frac{d\bar{X}}{d\bar{t}} = -\frac{\hat{\beta}\bar{X}\bar{M}}{1+\bar{A}} - \epsilon\hat{\sigma}(1-\bar{X}), \tag{C.1.7}$$

$$\frac{d\bar{Y}}{d\bar{t}} = \frac{\hat{\beta}\bar{X}\bar{M}}{1+\bar{A}} - (1+\hat{\mu})\bar{Y} - \hat{k}\bar{P}\bar{Y}\left(1+\hat{k}_1\bar{A}\right), \tag{C.1.8}$$

$$\epsilon\frac{dM}{dt} = \frac{\hat{r}\bar{Y}}{1+k_6\bar{A}} - \frac{\hat{\beta}\bar{X}\bar{M}}{1+\bar{A}} - \hat{d}\bar{M} - \hat{\alpha}\bar{P}\bar{M}(1+\hat{k}_2\bar{A}) - \frac{\epsilon\hat{\theta}Y}{1+k_6A}, \tag{C.1.9}$$

$$\frac{d\bar{G}}{d\bar{t}} = \frac{\hat{r}\hat{\theta}\bar{Y}}{1+k_6\bar{A}} - \hat{f}\bar{P}\bar{G}(1+\hat{k}_3\bar{A}) - \epsilon\hat{e}\bar{G}, \tag{C.1.10}$$

$$\cdot\frac{d\bar{P}}{d\bar{t}} = \hat{b}(1-\bar{P}) + \hat{\omega}\bar{Y} + \epsilon(\hat{\omega}\hat{\phi}\bar{M} - \hat{k}_4\bar{P}\bar{Y}) - \epsilon^2\hat{k}_5\bar{P}\bar{M}, \tag{C.1.11}$$

$$\frac{d\bar{A}}{d\bar{t}} = \hat{g}_1\bar{Y}\left(t-\tau\right) - \hat{h}_1\bar{A}\bar{Y} - g_3\bar{A} + \epsilon(\hat{g}_1\hat{g}_2\bar{M}(t-\tau) - \hat{h}_2\bar{A}\bar{M}).. \tag{C.1.12}$$

- The system does not seem to have a closed form solution but we have made some important approximations for the variables in this time scale in which details are given in section 5.7.6 of the main text. Numerical solution in this timescale shows that Y, M, G and A are exponentially small and $P \sim 1$.

- The X equation changes balance at the commencement of recovery when $t = O(1/\epsilon)$

C.1.7. Time scale 7: $t = O\left(\epsilon^{-1}\right)$

- Scalings: $t = \frac{1}{\epsilon}\hat{t}$,

$$X \sim \bar{X},$$

Substituting these into (C.1.1) we get,

- Equation

$$\frac{d\bar{X}}{d\bar{t}} = \hat{\sigma}\left(1-\bar{X}\right),$$

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