Immune Response in the Study of Infectious Diseases (Co-Infection) in an Endemic Region

by

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ABSTRACT

Diseases have been part of human life for generations and evolve within the population, sometimes dying out while other times becoming endemic or the cause of recurrent outbreaks. The long term influence of a disease stems from different dynamics within or between pathogen-host, that have been analyzed and studied by many researchers using mathematical models. Co-infection with different pathogens is common, yet little is known about how infection with one pathogen affects the host's immunological response to another. Moreover, no work has been found in the literature that considers the variability of the host immune health or that examines a disease at the population level and its corresponding interconnectedness with the host immune system.

Knowing that the spread of the disease in the population starts at the individual level, this thesis explores how variability in immune system response within an endemic environment affects an individual's vulnerability, and how prone it is to co-infections. Immunology-based models of Malaria and Tuberculosis (TB) are constructed by extending and modifying existing mathematical models in the literature. The two are then combined to give a single nine-variable model of co-infection with Malaria and TB. Because these models are difficult to gain any insight analytically due to the large number of parameters, a phenomenological model of co-infection is proposed with subsystems corresponding to the individual immunology-based model of a single infection. Within this phenomenological model, the variability of the host immune health is also incorporated through three different pathogen response curves using nonlinear bounded Michaelis-Menten functions that describe the level or state of immune system (healthy, moderate and severely compromised).

The immunology-based models of Malaria and TB give numerical results that agree with the biological observations. The Malaria–TB co-infection model gives reason-

able results and these suggest that the order in which the two diseases are introduced have an impact on the behavior of both. The subsystems of the phenomenological models that correspond to a single infection (either of Malaria or TB) mimic much of the observed behavior of the immunology-based counterpart and can demonstrate different behavior depending on the chosen pathogen response curve. In addition, varying some of the parameters and initial conditions in the phenomenological model yields a range of topologically different mathematical behaviors, which suggests that this behavior may be able to be observed in the immunology-based models as well.

The phenomenological models clearly replicate the qualitative behavior of primary and secondary infection as well as co-infection. The mathematical solutions of the models correspond to the fundamental states described by immunologists: virgin state, immune state and tolerance state. The phenomenological model of co-infection also demonstrates a range of parameter values and initial conditions in which the introduction of a second disease causes both diseases to grow without bound even though those same parameters and initial conditions did not yield unbounded growth in the corresponding subsystems. This results applies to all three states of the host immune system. In terms of the immunology-based system, this would suggest the following: there may be parameter values and initial conditions in which a person can clear Malaria or TB (separately) from their system but in which the presence of both can result in the person dying of one of the diseases.

Finally, this thesis studies links between epidemiology (population level) and immunology in an effort to assess the impact of pathogen's spread within the population on the immune response of individuals. Models of Malaria and TB are proposed that incorporate the immune system of the host into a mathematical model of an epidemic at the population level.

To my father who should have lived to see this,

my wife who got me through it,

and Amandine, Yeleen and Susuni

who inspired me every single moment of the way.

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Chapter 1

OVERVIEW OF MATHEMATICAL MODELING AND IMMUNOLOGY

1.1 Thesis Overview

Before we start to develop any aspect of the thesis, we want to highlight to originality of our research work. To date and to our knowledge there are no mathematical models that include in the modeling process the variability of the immune system response. Using the basic principal of linear and nonlinear dynamical system, mathematical biology and population dynamic, we introduce an immunological model of the interaction between immune system and pathogen(s); with explicit consideration of the nonlinear bounded Michaelis-Menten functions to describe the state of the health of the host. With this function we can have an infinite states as the Hill coefficients varied. In the thesis for simplicity we only consider three states (health, moderately compromised and severely compromised) of the immune system.

The thesis is organized into two main parts. In the first part, we discuss some basic background informations on epidemiology and immunology (Chapter 1) and then we propose a co-infection model of Malaria and TB based on the immunology of each disease (Chapter 2). This yields a complicated model, which we then use to create a phenomenological model that captures much of the biology and allows for us to better understand the mechanisms of co-infection. The phenomenological model is discussed in full mathematical detail by considering three subsystems of it that allow us to characterize the full system. The phenomenological model is proposed at the end of Chapter 2 and then fully justified and analyzed in Chapters 3-5. At the end of Chapter 5, we compare the immunology-based Malaria–TB co-infection model with the corresponding phenomenological model. In the second part of the thesis, we propose a method (in Chapter 6) by which we can link

the individual immune system (immunology) to the overall population (epidemiology). Finally, we propose specific epidemiological models of Malaria and TB by incorporating this new technique.

1.2 Introduction.

Epidemiology and immunology have been around for centuries. The earliest known notion of immunity dates back to the plague of Athens in 430 B. C., where Thucydides noted that people who had recovered from a previous bout of the disease could nurse the sick without contracting the illness a second time [105], and epidemiology back to Hippocrates (460 BC - 370 BC) who is the first person known to have examined the relationships between the occurrence of disease and environmental influences. Despite these first discoveries, many aspects of immunity were not explored in any great detail until toward the end of eighteen century by Pierre-Louis Moreau de Maupertuis, Louis Pasteur, etc. Additionally, there had been no attempt in understanding the immune system dynamic until the nineteenth century with the rapid developments of immunology or cellular immunology by Elie Metchnikoff [47], who was recognized by the award of a Nobel Prize in 1908. A similar situation holds for epidemiology. The standard mathematical methods were introduced into epidemiology by Ross (1911) [100], McKendrick (1912) [79], and Martini (1928) [75] with the modeling of malaria which today is one of the deadly infectious diseases in Sub Sahara Africa transmission. After this first wave of publication, Kermack and McKendrick published a series of papers on deterministic models for the spread of infectious diseases [65–67; 78]. These papers, later extended in a number of publications by Bailey (1979) [10], Hethcote and Yorke (1984) [52; 54] , Dietz and Hadeler (1988) [36], and Anderson and May (1991) [3; 4; 76], provide and shed an important light on problems of theoretical investigation of the evolution of infectious diseases.

The paper published in 1927 by Kermack and McKendrick, develops the SIR (Susceptible-Infected-Removed) epidemic model that incorporates variable periods of infectivity; that is, the infection rate depends on the duration in the infected state; and the infection only happens one time in the life span of the host individual. If the infectivity is assumed to be constant, the SIR model reduces to a well known ordinary differential equation model [2]. There have also been studies on variable infectivity [4; 58; 72; 108]. In "The Legacy of Kermack and McKendrick" by Diekmann *et al.* [35], the basic assumptions of the model formulation are

1. a single infection triggers an autonomous process within the host;
2. the disease results in either complete immunity or death;
3. contacts are according to the law of mass action;
4. all individuals are equally susceptible;
5. the population is *closed*;
6. the population size is large enough to warrant a deterministic description.

These above assumptions, when focusing on the immune system response, may not be sufficient. During the past decades, the SIR and SEIR (susceptible-exposed-infective-removed) epidemic models have been extended to various epidemic demographic situations, see for example [4; 7; 16; 21; 23–27; 45; 51–53; 108].

The mathematical epidemiological models examine the population of individual people and describe the spread of the disease due to "interactions" or "contacts" between susceptible and infectious. The Law of Mass Action addresses processes which occur simultaneously, and it is widely accepted idea that the rate of contact between two groups in a population is proportional to the size of each of the groups

concerned [107]. The simplest transmission model assumes homogeneous mixing, that is, each individual has an equal chance of coming in contact with another individual in the population. Sometimes, one can have a slightly more realistic transmission assumption, e.g. proportionate mixing, where the rate at which individuals make such random contacts depends on the class to which they belong. Even though different approaches may be used to define the interactions for transmission rates, the parameters of mathematical epidemiology models are considered as statistical means from a sample of the overall population. As with most models that use ordinary differential equations, this is usually a reasonable first assumption.

Tremendous progress has been made on numerous communicable diseases that have plagued our societies since the beginning of humanity and continue to globally affect the overall health and social well-being of many individuals [57] in under-developed countries. Our understanding in recent years of infectious-disease epidemiology and control has greatly increased through mathematical modeling, which now plays a key role in policy making, emergency planning and risk assessment, control program evaluation, etc.

Mathematical models in epidemiology help to understand a vast array of diseases, including smallpox, measles, malaria, tuberculosis, HIV and countless others [7; 15; 16; 21; 23–27; 39; 40; 45; 51–53; 108]. As part of theoretical epidemiology, the epidemiological modeling can use dynamical systems to characterize and explain epidemic patterns. Most models have adopted one of two methodologies. The first is a phenomenological approach. The second approach is the construction of explicit deterministic or stochastic models of the demography which generates pathogen distributions. In the classic theory of infectious diseases the key concept is the so called basic reproductive rate R, which allows one to specify the minimum intervention effort to make the disease-free-equilibrium stable. It is usually interpreted as the number of secondary cases that one case could produce if the total

population were susceptible. With R, we can accurately describe conditions on the parameters for when a disease will remain endemic in the population.

Parallel to all these approaches, we can add another layer of complexity to the models described above when host immune response is included. Immunological models are often considered to be either too simplistic or too complex. This area recently received considerable theoretical attention, particularly in the derivation of immuno-epidemiological models [50; 117; 118]. Because of the complexity and the diversity of the immune system, there is general limited acceptance of the models by immunologist.

Within the population, there are many different pathogens in circulation and any assumptions about how they interact can profoundly affect the outcome of any study. In the presence of two or more infectious diseases, any formulation of a mathematical model should identify the entire infection history of the individual and its immunological status with respect to the various pathogens/strains. Such general models can be difficult to study due to the large number of degrees of freedom resulting in the difficulty of both parametrization (setting of parameters) and analysis. Some parameters (e.g., contact rate) depend on interactions within the population while other parameters, e.g., recovery rate or rate of infection, depend on the individual that has been exposed to or is fighting/recovering from the disease (both of which depend heavily on the person's immune system and their body's ability to get rid of the disease). Hence, detailed immunological studies are required to clarify some of the typical behavior. With the advances in science, technology and computing, more molecular and immunological data is now available and we face the challenge to integrate this knowledge with the epidemiology and the evolutionary disease models that we know so far. However, when considering all this information, we notice that very little work has been done to try to tie together epidemiological modeling with immunological modeling, that is, to use knowledge

of one's immune system response to rewrite the relevant terms in the traditional epidemiological models as functions of the immune system. This is particularly important if, when focusing on the immune system, we realize that the body, in a geographically endemic region of disease is not able to respond as quickly to a disease if there is already another one present. In this latter situation, the measured value of the relevant parameters may be consequently, unfairly skewed.

The focus here is to understand the role of host immune response in determining patterns of infection when considering the degree to which the individual is immune compromised, if it can be clearly identified. We specifically study how the interaction between pathogen and (compromised) host immune system can affect the variability in the influence of the infection rates observed at the population level. Understanding the state of individual immune system within the population can help to evaluate the evolution of disease in the population. However, it is equally important to understand how the dynamic of the population can thus help to predict the average state of an individual immune system. This work begins to examine the immune system response when the host is invaded by one pathogen or two pathogens (co-infections) in an endemic region and what effect is seen by incorporating this in the overall population dynamics.

1.3 Basic understanding of the immune response

In order to describe the immune system response to any infectious disease, we need to know the characteristics of the immune system itself. The function of the immune system is to protect our body from infections and illnesses. The immune system works to identify pathogens and tumor cells that could cause diseases and to eliminate them from our system. The immune system is like a community or team that is comprised of many different cells that work together to keep us healthy. Many of these cell types have specialized functions and ways of communicating

with each other. The immune system is composed of many interdependent cell types that collectively protect the body from foreign organisms (parasites). All cells of the immune system are initially produced from the bone marrow.

Right after birth, the newborn's immune system is functionally naive and enters a state of differentiation and reorganization [89]. A number of critical maturation and activation events occur before any immune system cells (T cells, B cells, NK cells, etc.) acquire specific effector functions. At birth, the bone marrow and thymus are fully colonized with hemopoietic stem cells that gradually mature into various different lineages of immune cells (lymphoid, karyocyte or granulocyte lineage); see Figure 1.1 for the key stages in stem cell differentiation [43].

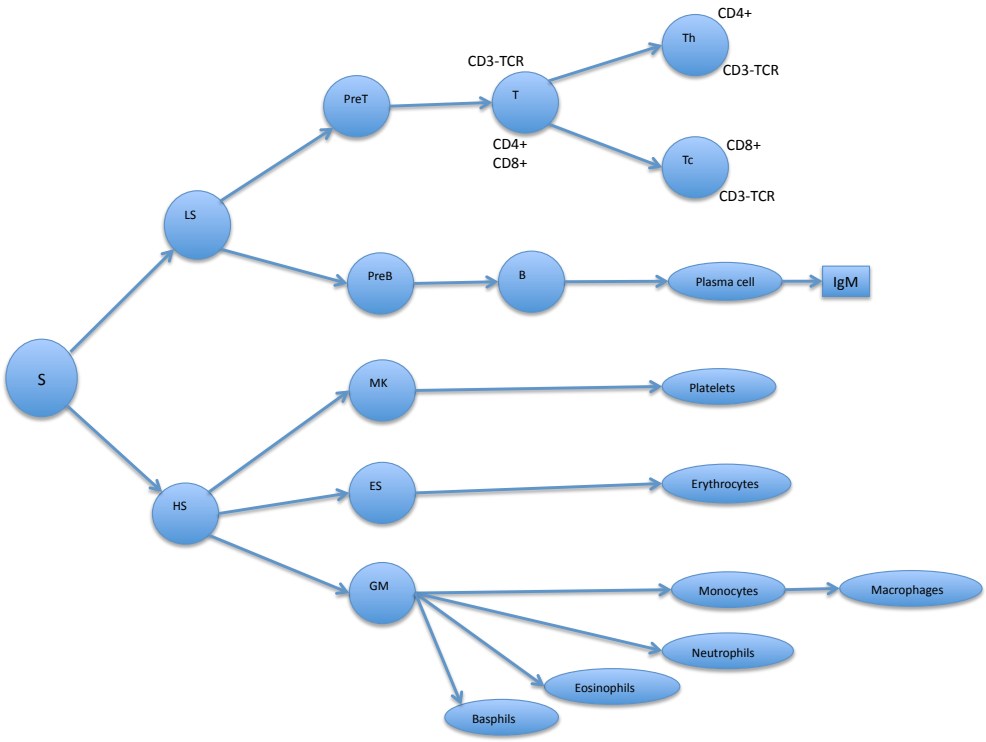


Figure 1.1: Key stages of stem cell differentiation. Abbreviations used: S = stem cell; LS= lymphoid stem cell; HS= hemopoietic stem cell; MK= megakaryocyte; ES=erythroid stem cell; GM= granulocyte-monocyte precursor; T= T lymphocyte; B= B lymphocyte; Th= T helper cell; Tc= T cytotoxic cell; TCR= T cell receptor; CD= cluster of differentiation marker [43].

Throughout growth, the total cellularity of the spleen and lymph nodes increases dramatically as immune cells begin to migrate from primary immune organs to establish residence in secondary immune organs. And it is within the secondary immune organs that some of them (T and B lymphocytes) develop memory for specific antigens or pathogens. Immunological memory is clearly an important topic in any consideration of the interaction between host and pathogen both at the individual and at the population levels [4]. It is not uncommon for people to be concurrently infected with more than one infectious disease. The immune system is designed to fight infection by making proteins called antibodies; a different antibody is produced for each different infection, and each type of antibody attacks only its particular virus or bacterium.

The immune system is divided into two functionally distinct parts: one part which is innate (nonadaptive), and the other part which is acquired (adaptive). Innate immunity (non-adaptive) refers to immune elements which are non-specific, whereas acquired (adaptive) immunity refers to immune elements which are specific.

The response of the adaptive immune system of vertebrates [111] is a function of exposure to past infectious disease. An immune response can have several different effects on future exposures: immunity for identical or nearly identical diseases, some amount of cross-reactive protection for similar diseases, no effect for unrelated diseases, and in exceptional cases an increased vulnerability.

The adaptive immune system derives the ability to respond to new infections through a diverse population of cells, each having a distinct set of chemicals to which it can respond [92; 93; 103]. The mechanisms that generate this diversity also generate cells that will respond inappropriately to inert environmental chemicals (allergens), or even the body's own chemicals, thereby causing autoimmune disease. There are two types of specific immunity: Humoral (antibody) Mediated Immunity (HMI) and Cell Mediated Immunity (CMI).

HMI involves the production of antibody molecules in response to an antigen and is mediated by B cells. The B cell is a type of white blood cell and, specifically, a type of lymphocyte. Many B cells mature into what are called plasma cells that produce antibodies (proteins) necessary to fight off infections while other B cells mature into memory B cells. The B cells become transformed into antibody-secreting plasma cells which produce immunoglobulins (antibodies) when a foreign antigen (parasite) triggers the immune response [109]. Antibodies circulate in the blood and lymph streams and attach to foreign antigens to mark them for destruction by other immune cells such as scavenging cells which include neutrophil and macrophages.

CMI involves the production of cytotoxic T cells, T helper cells, activated macrophages, activated natural killer cells, and cytokines in response to an antigen and is mediated by T cells. T cells are usually divided into two major sub-populations — the T helper cells also called CD4+ T cells (Cluster of Differentiation Antigen No.4 Positive T cells) and Cytotoxic T cells (CD8+ T-cells). The T helper cell is further divided into Th1 and Th2 depending on their lymphokines profiles [63]. The T helper cells stimulate B cells to divide repeatedly and form a clone. Most cells of the clone differentiate into plasma cells which synthesize and secret antibodies; other cells of the clone become memory B cells. The memory B cells remain in circulation after plasma cells have died. On secondary infection by the same antigen, memory B cells detect the antigen quickly and respond more intensively. They develop into plasma cells much more rapidly than the original or naive B cells and proceed to secrete their immunoglobulins. This second response is much quicker than the first, and often prevents symptoms of the disease from occurring.

The T helper cells also can activate other T cells and immune system scavenger cells. The Cytotoxic T cells grow and divide into mature CD8+ T cells and memory CD8+ T cells when activated by parasites. Mature CD8+ cells attack and destroy infected cells and parasites. Memory CD8+ cells function like memory B cells;

they persist, multiply and mature if they are re-exposed to the same antigen. For the immune response to be active, the host has to be exposed to foreign pathogens that in certain circumstances provoke an infectious disease. Antibodies, cytokines, natural killer cells, and T cells are essential components of a normal immune response. Indeed, in most infections cytotoxic T lymphocytes play a critical role in host system defense [13; 81; 86].

1.4 Basic understanding of infectious diseases

Infectious diseases are part of the human condition and evolution. Infectious diseases, also known as communicable diseases [56], or transmissible diseases comprise clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence and growth of pathogenic biological agents in an individual host organism [83]. Broadly speaking for any infectious diseases the immune system regards all micro organisms not belonging to the individual host as "non-self" and reacts against them. Especially, the immune system response discriminates between self and non-self agents within the body and remove the non-self elements [92; 93; 103]. Infectious diseases have also been shown to directly trigger certain autoimmune diseases [9].

Although, diseases can spread directly or indirectly, the transmission of a pathogen can occur in various ways including physical contact, contaminated food, body fluids, objects, airborne inhalation, or through vector organisms. Most of the epidemic infections are caused by micro organisms such as viruses, bacteria and protozoa.

Bacteria are among the oldest living organisms on Earth, and they are very small and can only be seen through a microscope. Bacteria are commonly found in the ground, water and in other living organisms. Infectious agents are easily spread by oral means, fecal matter, water, air or food. While some types of bacteria can cause diseases and become harmful to the environment, animals

and humans, others offer benefits that we likely could not live without [83]. For example, many bacteria that are beneficial to humans live in the digestive system of the human body. They compete with the harmful bacteria and also help in certain body functions. Also beneficial to humans are the anaerobic bacteria used in fermentation of vinegar, antibiotic drugs, the aging process of cheese, etc. In humans, certain harmful bacteria can cause tetanus, pneumonia, syphilis, tuberculosis and other illnesses. As long as the host is not infected with antibiotic resistant bacteria, they can be treated with antibiotics, which kill bacteria or at least hamper their growth. Antiseptics, sterilization and disinfectants can help prevent contamination and the risk of infection from bacteria.

Virus can be defined as a submicroscopic parasite that can infect and often lead to a serious or deadly disease. A virus consists of a core of RNA or DNA, generally surrounded by a protein, lipid or glycoprotein coat, or some combination of the three, allowing it to initially 'trick' the body into thinking that it belongs. No virus can replicate without the help of a host cell. Some of the most common or best known viruses include the human immunodeficiency virus (HIV), which is the virus that causes AIDS, the herpes simplex virus (which causes cold sores), smallpox, multiple sclerosis, and the human papilloma virus (now believed to be a leading cause of cervical cancer in adult women). The common human cold is also caused by a virus. Viruses can be spread in many ways. Viruses in animals can be carried by blood-sucking insects known as vectors sometimes through coughing and sneezing (influenza), by the fecal-oral route entering the body in food or water (norovirus and rotavirus), and through sexual contact and by exposure to infected blood (HIV).

Parasite is an organism that obtains nourishment and shelter from another organism. Parasites can cause harm or disease to their host. They are gen-

erally much smaller than their hosts and cannot live independently. Parasitic diseases include infections by protozoa (e.g., malaria by plasmodium), helminths (schistosomiasis), and arthropods.

Co-infection with different microorganisms is common, yet little is known about how infection with one affects the host's response to another. For example, TB and HIV can be a lethal combination: HIV weakens the immune system and promotes the progression of recent exposure to TB and latent tuberculosis infection to active TB disease [68]. Co-infection can also complicate treatment. For example, people with liver damage due to chronic hepatitis are more likely to experience hepatotoxicity (liver toxicity) related to anti-HIV drugs [104].

We cannot start to comprehensively model the dynamic of interaction with the human host as it is not only complex but much remains unknown. With the advances in diverse fields related to systems biology, recent studies have taken a more global approach to defining the host immune response to bacilli. Previous mathematical models have been developed to consider the Mtb and parasite *P. falciparum* dynamics in the human host. For example, looking at TB cases, mathematical models consider macrophage dynamics with partial differential equation (PDE) models of tumor biology [87; 88]; ODE models of bacilli infection [46; 74; 116], phagocytosis and in the immune response to an unspecified disease or infection [12; 95]. All these models consist of equations governing the temporal dynamics of the *P. falciparum*, alveolar macrophages, neutrophils, extracellular and intracellular bacteria, T cells and cytokines. We have not been able to find any models of co-infection with diseases caused by parasite and bacteria respectively.

Here in this chapter we described the most useful definition about pathogens, infection diseases, and immune system functionality, that will help throughout our

research for the understanding and elaboration of the diverse biologically relevant assumptions we will be using.

Chapter 2

WITHIN HOST DYNAMICAL IMMUNE RESPONSE TO CO-INFECTION WITH MALARIA AND TUBERCULOSIS

To elaborate and explore different hypotheses, we need to give a clear understanding of the different elements or pathogens causing the different diseases, their evolution and interaction. The ultimate goal is to use the assumptions and definitions in the beginning of this chapter to derive realistic models for Malaria, Tuberculosis and ultimately co-infection with both.

2.1 Malaria and the immune response

Parasitic infections present a major cause of disease and morbidity in Africa. Malaria is one of the most dangerous human infections and is caused by one of the four protozoan parasites of the genus plasmodium: *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale*. Of these, *P falciparum* is of greatest risk to non-immune humans and inflicts the largest burden. Early treatment of Malaria will shorten its duration, prevent complications and avoid a majority of deaths [30]. It is estimated that 40% of the world's population is at risk of Malaria, and about 90% of the populations infected with Malaria live in sub-Sahara Africa [48]. Malaria is a major cause of morbidity and mortality. It ranks alongside acute respiratory infections, measles and diarrheal diseases as a major cause of mortality worldwide. Unlike other acute diseases which produce life-long resistance to reinfection, Malaria only elicits partial immunity after several years of continuous exposure during which time recurring infections and illness occur which could be fatal, especially in children. This immunity is only partially effective unless reinforced through frequent reinfection.

Malaria is transmitted by the female mosquito (genus anopheles) to the human host. According to Aron and May (1982), the biology of the four species of plasmodium is generally the same and consists of two distinct phases; sexual and asexual. The asexual phase consists of sporozoites, merozoites and trophozoites. The sexual phase consists of gametocytes. Infection of the human host begins with the bite of a female anopheline mosquito vector, and the injection of sporozoites into the blood stream. The infectious sporozoites enter the liver parenchyma cells. Here, they replicate, giving rise to the merozoite form at about the time the human host natural defense begin to attack the infected cells. After an incubation period of about 7 days which is not accompanied by illness, about 30,000 merozoites are released from each infected liver cell into the blood stream.

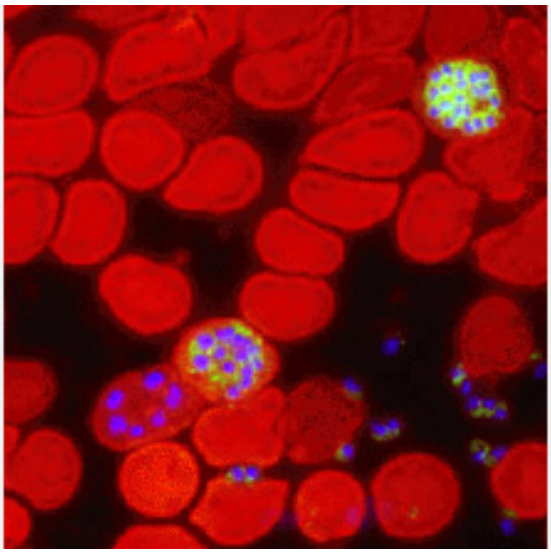


Figure 2.1: Malaria parasites inside: red blood cells infected with malaria parasites (cell nucleus in blue). See Section 2.1. [Credit: Biomedical Primate Research Centre, Netherlands]

The merozoites attack and invade the red blood cells (erythrocytes) (Fig. 2.1) where upon they change into the trophozoite form. *P. falciparum*, in particular, attacks all ages of erythrocytes. This form undergoes asexual division and in approximately 48 hours (depending on species) the infected erythrocyte ruptures releasing about

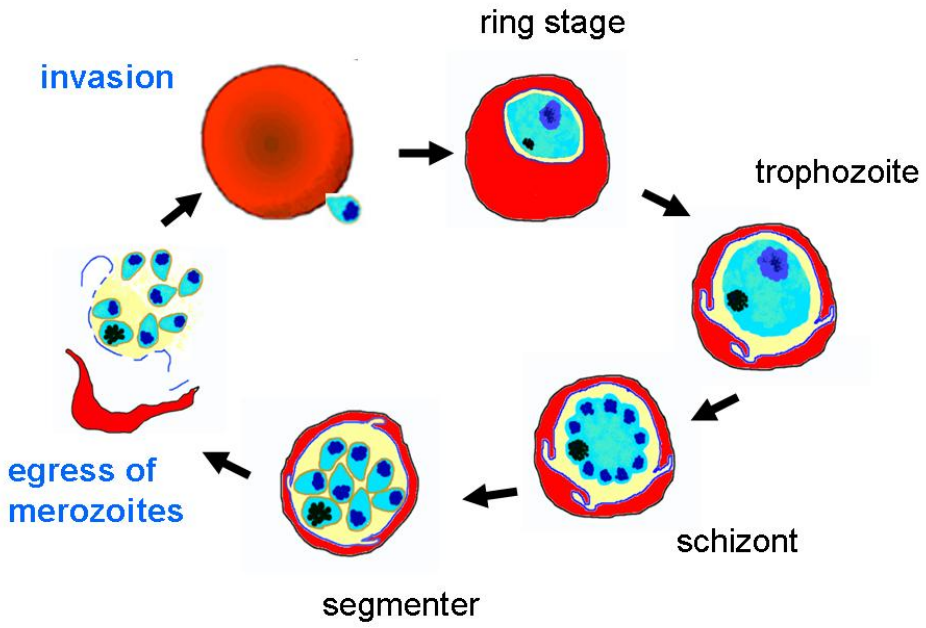


Figure 2.2: The process of red blood cell invasion and the egress of the parasites from the host cell. See Section 2.1.

8 - 32 merozoites [49] which invade other erythrocytes (see erythrocytic cycle, Figure 2.2).This process is responsible for the clinical symptoms of the disease. The erythrocytic cycle usually continues until controlled by the immune system response or chemotherapy or until the patient dies (in the case of *P. falciparum*). Some merozoites differentiate into the sexual forms of the parasites called gametocytes (microgamete and macrogamete). Gametocytes are transmitted to a mosquito during the blood meal of an infected person. The female gametes are fertilized and develop into oocysts on the walls of the mosquito gut. Each oocyst gives rise to about 1000 immature sporozoites [49] which migrate to the mosquito salivary gland and mature to repeat the cycle.

Variables definition and immune response model for Malaria

We consider the following variables and parameters in Table 2.1 that will be used to construct our ODE model describing the immune response to Malaria.

Table 2.1: Brief description of state variables for Malaria within host; see Model (2.1.1).

Variables	Description
X	Concentration of uninfected RBC
Y	Concentration of infected RBC
F	*P. falciparum* malaria parasite load (merozoites)
T	Concentration of T cells
s_R	Recruitment rate of red blood cell
d_R	Natural death rate of naive RBC
β	Infection rate of naive RBC
d_I	Death rate of infected RBC
k_2	Rate immune effectors clear *P. falciparum*
α	Maturation rate of infected RBC
k_1	Rate immune effectors (T cells) clear infected RBC
p	Carrying capacity of infected RBC
d_F	Natural death rate of *P. falciparum*
s_T	Recruitment rate of T cells
d_T	Natural death rate of T cells
c_1	Half-saturation constant for infected RBC
a_2	Immunostimulation strength for *P. falciparum*
a_1	Immunostimulation strength for infected RBC
a_3	Immunostimulation strength for immune effector
b	Half-saturation constant for immune effector

Erythrocyte red blood cell (RBC) dynamics. At a given time t, the naive or healthy erythrocytes $X(t)$ are assumed to be produced from the source (bone marrow, known as 'hematopoietic stem cell') at a constant recruitment rate s_R, and die naturally at a per capita rate d_R. During the infection, on contact with merozoites parasite $F(t)$, erythrocytes get infected at a constant rate β and become the infected $Y(t)$ using the law of mass action. Infected erythrocytes

die rapidly at the constant per capita death rate d_I, or mature at rate α. At maturation, given an average of intracellular carrying capacity p, new merozoites , $p\alpha Y$, burst from the host cell to invade new erythrocytes, beginning another round of infection [8]. At the same time the infected RBCs activate the immune response, they are also being killed at the net rate $k_1 \frac{Y}{c_1+Y} T$, where k_3 is the successful removal rate of infected RBCs by the immune effector and c_1 is the half saturation constant for the infected cells in parallel to $k_1 YT$ used in [80] when assumed that the immune response functions are unbounded.

T cells. They are recruited for the source at a constant rate s_T and their proliferation is induced by the infection at rate a_1 and the presence of the merozoites at the rate a_2. They die at the per-capita rate d_T. Without loss of generality, the T cells, as immune effector agents, will be stimulated by the parasites (immunostimulation factor) which is follow by the additional processes of autocatalytic and/or cooperative reinforcement through the function $g(T)$ where a_3 is the immunostimulation strength for immune effector and b the half-saturation constant for immune effector. The T cells can also clear, respectively, the merozoites and infected erythrocytes at constant rates k_2 and k_1.

Merozoites. With a finite lifetime, *P. falciparum* parasites die at rate d_F. Mature infected erythrocytes $Y(t)$ produce $p\alpha Y$ merozoites per unit of time by lysin, which can again infect the naive erythrocytes (see Figure 2.2).

Within host model for malaria

Based on all the assumptions, we propose a simple immunological model for Malaria:

$$\begin{aligned}
\frac{dX}{dt} &= s_R - d_R X - \beta XF, \\
\frac{dY}{dt} &= \beta XF - d_I Y - k_1 \frac{Y}{c_1 + Y} T, \\
\frac{dF}{dt} &= p\alpha Y - \beta XF - d_F F - k_2 \frac{F}{c_2 + F} T, \\
\frac{dT}{dt} &= s_T - d_T T + a_2 \frac{F}{c_2 + F} T + a_1 \frac{Y}{c_1 + Y} T + a_3 \frac{T^2}{b + T^2}.
\end{aligned} \tag{2.1.1}$$

Analysis of the model

The domain $\mathscr{D}$ is valid epidemiologically because the populations X, Y, F and T are all nonnegative. We denote points in $\mathscr{D}$ by $x = (X, Y, F, T)$. The nonnegative orthant $\mathbb{R}^4_+ = \{x \in \mathbb{R}^4 | x \geq 0\}$ is called a positively invariant region if for any trajectory that starts in the nonnegative quadrant remains in the same quadrant forever. It can be shown using standard techniques described in [106; 107] that if initial conditions are specified for each of the states variables at time $t = 0$, then there exists a unique solution satisfying these initial conditions for all time $t \geq 0$. We need to show that solutions of the model are nonnegative with an initial condition $X(0), Y(0), F(0)$ and $T(0) \geq 0$.

Lemma 1. *The closed positive orthant is positively invariant for the Model (2.1.1).*

Proof. Since $Y = 0$ and $F = 0$ are invariant planes for the model, we only need to prove that $X(t) \geq 0$, and $T(t) \geq 0$ for $t \geq 0$ if the initial conditions are in the positive octant. Assume there exists $t_1 > 0$ such that $X(t_1) = 0$, $T(t_1) = 0$, and $0 < t_1 < t$. Then

$$\frac{dX(t_1)}{dt} = s_R > 0, \qquad \text{and} \qquad \frac{dT(t_1)}{dt} = s_T > 0,$$

which imply that $X(t) \geq 0$ and $T(t) \geq 0$ for $t \geq t_1$. Thus, $X(t) \geq 0$, and $T(t) \geq 0$ for all $t \geq 0$. □

Local stability

Let $P = (X^*, Y^*, F^*, T^*)$ be steady state. Whether the human host is infected or not, there are always RBCs (erythrocytes) and T cells in the human body. This implies simply that there is no trivial equilibrium i.e., we cannot have $(X^*, Y^*, F^*, T^*) = (0,0,0,0)$. Setting the right hand sides of Equations (2.1.1) to zero gives the following equilibrium solutions:

At the disease-free-equilibrium, $F^* = 0$, we have $Y^* = 0$, $X^* = \frac{s_T}{d_T}$ and

$$s_T + a_3 \frac{T^2}{b + T^2} - d_T T = 0. \tag{2.1.2}$$

Solving Equation (2.1.2) for nonnegative real solutions T^*, implies that the disease-free-equilibrium (DFE) exists and is $(\frac{s_T}{d_T}, 0, 0, T^*)$.

If one varies the parameters of Equation (2.1.2) within a positive domain of the parameters values, the long-term behavior may change since we can have one or three DFE using the "Descartes' Rule of Signs;" the "Sturm chain or sequence method" (cf. Beaumont and Pierce, 1963) provides more precise conditions for the number of steady states. The appearance or disappearance of equilibria produce topological changes in the system and are examples of bifurcations.

The Jacobian (J) evaluated at the DFE gives

$$J = \begin{bmatrix} -d_R & 0 & -\beta X^* & 0 \\ 0 & -d_I - \frac{k_1}{c_1} T^* & \beta X^* & 0 \\ 0 & p\alpha & -\beta X^* - d_F - \frac{k_2}{c_2} T^* & 0 \\ 0 & -\frac{a_1}{c_1} T^* & -\frac{a_2}{c_2} T^* & 2\frac{a_3 b T^*}{\left(b + T^{*2}\right)^2} - d_T \end{bmatrix}.$$

Simulation

It is almost impossible to find explicitly the solutions of Equations (2.1.1), and since the parameters that govern the rates and behavior of interactions in the model may change from individual to individual and over time, we then simulate the model by solving the differential equations using an appropriate numerical method. We discuss below the results of the computational experiments within an individual; see Figures 2.3 - 2.4.

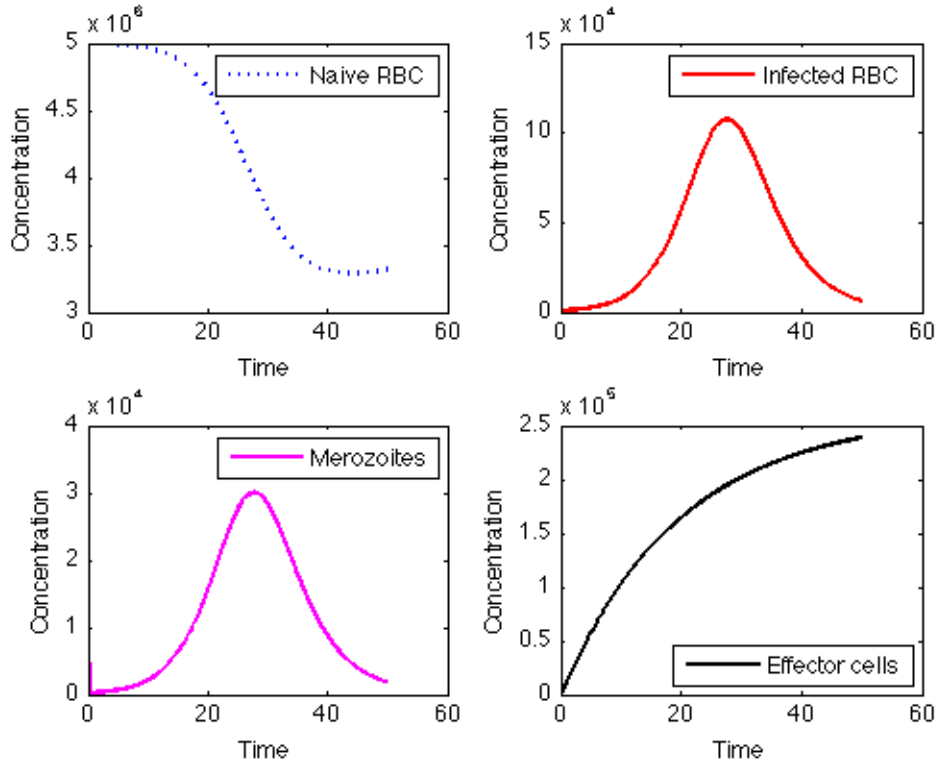


Figure 2.3: Time series of parasite *P. falciparum*, red blood cells, and the immune effector at the beginning of the interaction within host. Next figure (Figure 2.4) captures the long-term behavior.

Through this simple mathematical model, we can understand the dynamics of the parasite and the immune effector (T). Depending on the initial conditions, specifi-

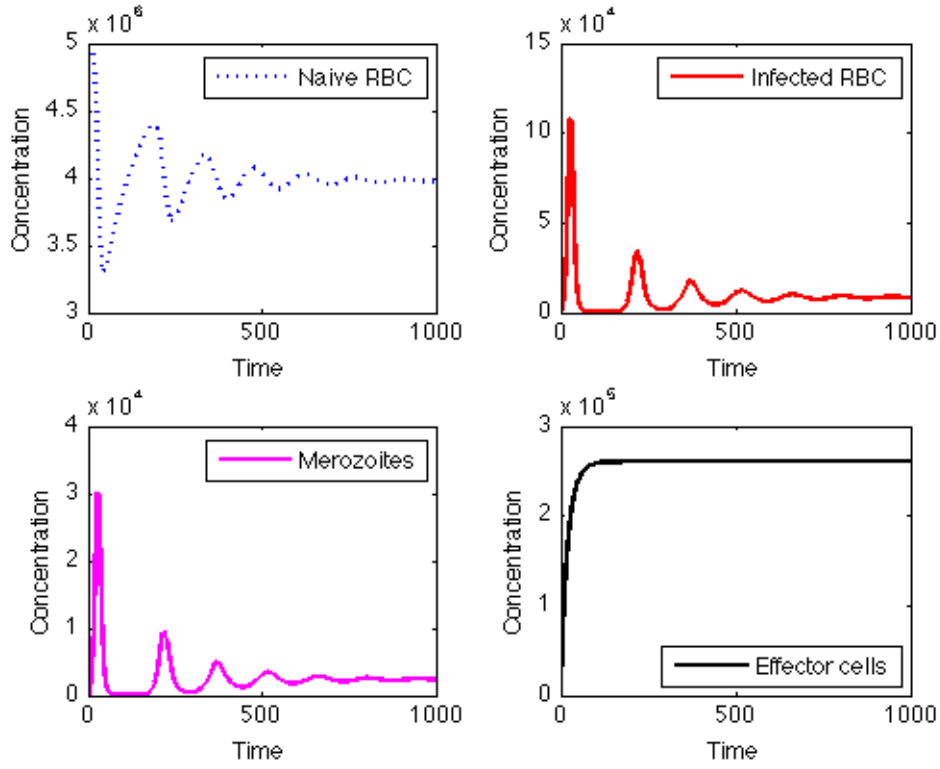


Figure 2.4: Time series of parasite *P. falciparum*, red blood cells, and the immune effector which reach a steady state; see Figure 2.3 for the transient solution up to $t = 50$.

cally the initial amount of merozoites releases in the blood stream, we see the rise of the infected red blood cells with a slow decrease of the naive RBC. Following the activation of the naive immune effector cells, we see a decline of the parasite and the infected RBC, respectively. This type of behavior can be observed in the initial stages of Malaria. In an endemic region, a prolonged exposure of the host to a parasite due to a constant presence of mosquitos can lead to a tolerant immunological state of the individual immune system.

2.2 Tuberculosis within the individual

Tuberculosis (TB) has been a leading cause of death in the world for centuries. During the period after the second world war, because of the medical im-

provement for treatment and hygiene practices, the number of cases steadily declined in the world to a level that could be controlled [41; 42]. However, in one third of the world, TB still is a big threat and much of the population harbors the latent form of tuberculosis infection [82]. Today, within the pathogen-induced diseases worldwide, TB counts more that 1.5 million deaths [31].

During its latency period, the bacteria causing TB, Mycobacterium tuberculosis (Mtb), is postulated to exist in a dormant state where the host can effectively contain the pathogen.

Mtb is an obligatory aerobic-intracellular pathogen, which has a predilection for the lung tissues rich in oxygen supply [97]. The tubercle bacilli enter the host via the respiratory route. In certain situations, the bacilli spread from the site of the infection in the lung to other parts of the body through the lymphatics or blood.

In the lung, the alveolar macrophages represent the first line of immune defense in the host-pathogen relationship with the phagocytosis of mycobacterium tuberculosis. This first line of defense is followed by the cell-mediated immunity with an influx of lymphocytes (T cells) and activated macrophages/monocytes into the lesion resulting in granuloma formation (Figure 2.5). One of three things may happen to the bacilli. They may remain forever within the granuloma causing no/little harm, get activated later, or may get discharged into the airways after an enormous increase in number, necrosis of bronchi and cavitation [97]. At the site of bacilli multiplication, neutrophils (monocytes) are the first cells to arrive followed by natural killer (NK) cells, a type of lymphocyte (a white blood cell), T cells, γ/δ cells and α/β cells. It has been noticed that a significant reduction in NK activity is associated with multi-drug-resistant TB (MDR-TB) [14]. The tuberculous granuloma contain T cells (both $CD4^+$ and $CD8^+$) that contain the infection within the granuloma and prevent reactivation. T cell ($CD4^+$) depletion causes a rapid activation of the infection. In humans, the pathogenesis of HIV infection which causes the loss

of $CD4^+$ T cells greatly increases susceptibility to both acute and re-activated TB [98].

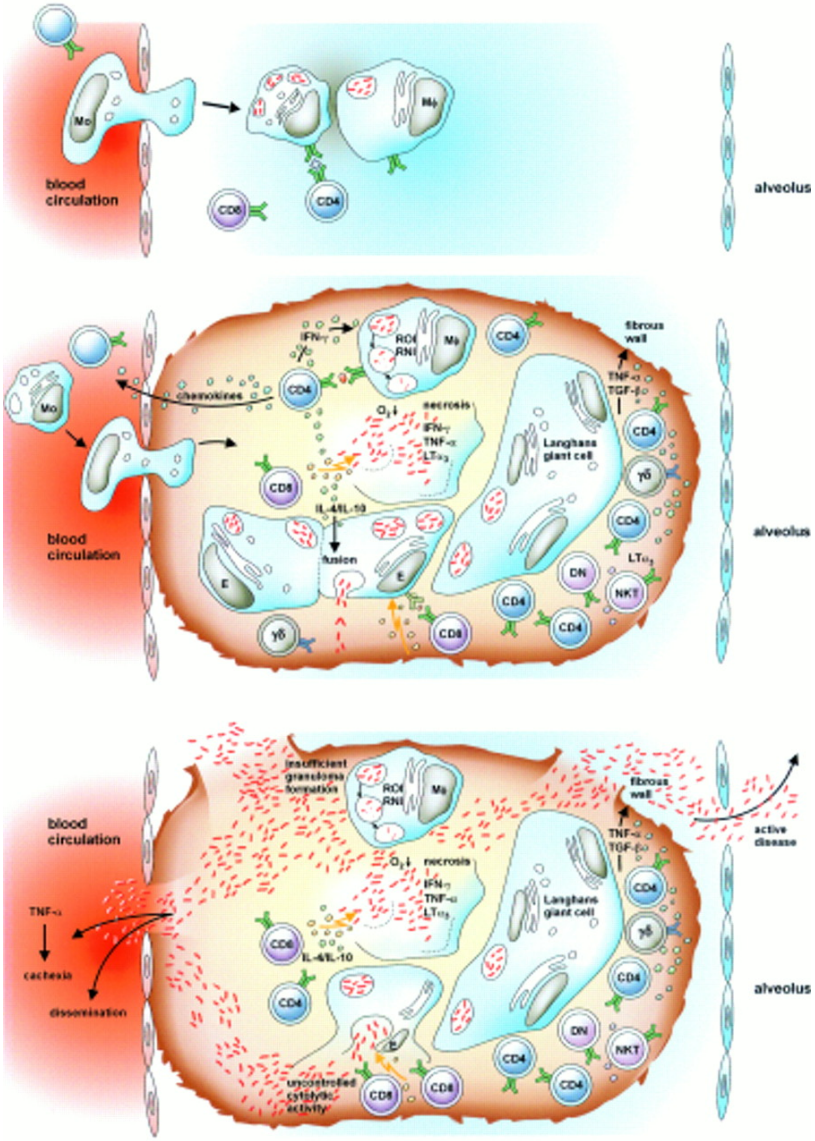


Figure 2.5: The formation of granuloma [64]. See section 2.2.

In spite of this persistence over many centuries, TB can be controlled. Treatment of TB is well known and developed in the case of non-resistant strains. To treat active TB, it is necessary to take several antibiotics at the same time. If not treated properly, TB can be fatal. The common regime of treatment is the combination of isoniazid, rifampicin and pyrazinamide for two months followed by isoniazid and

rifampicin for at least four to seven months, if the organism is known to be sensitive, until all the bacteria have been completely cleared [69; 99].

The different system models of Wigginton and Kirschner [116] on TB and host immune response, Perelson on the dynamic of T cells [91], Artavanis-Tsokonas on Malaria and immunopathology [8], Mackinnon [73], serve as background models for the immune response in the environment of co-infection of TB and Malaria. In regions endemic with malaria and TB such as sub-Sahara Africa, it will be interesting to track the progression of both diseases in the human host and the outcome of the interactions and respective impact of the pathogens. And to investigate the possibility of repeated malaria infection promoting an active TB within the individual host.

Variables definition and immune response model for Tuberculosis

We have the following variables and parameters in Table 2.2 that will be used in our ODE model:

Macrophage dynamics. The rate of change of the macrophages, especially the resting or naive monocytes, includes the recruitment term (s_M) from the source and undergo a natural death term ($\mu_M M_R$). This is natural assuming that the macrophages have a finite life span, and in the absence of infection the monocytes undergo a renewed process or constant turnover to maintain an equilibrium. In the close proximity of infection, the naive monocytes are infected at the maximum rate of β, which depends on the extracellular bacterial load. Here we use the sigmoidal saturation function based on a form of the Hill equation [68]. The infected macrophages can be cleared by maturation at rate α, where given the intracellular carrying capacity they burst, or the im-

Table 2.2: Brief description of state variables for TB within host; see Model (2.2.1).

Variables	Description
T	Concentration of T cells
M_R	Resting Macrophages
M_I	Infected Macrophages by Mtb
B_I	Intracellular Bacteria (TB)
B_E	Extracellular Bacteria (TB)
α	Rate of busting of chronically infected macrophages
s_T	Recruitment rate of T cells
d_T	Natural death rate of T cells
s_M	Recruitment rate of macrophages
β	Resting macrophages infection rate
μ_R	Natural death rate of resting macrophages
μ_I	Natural death rate of infected macrophages
γ_M	Rate immune effectors (T cells) clear infected macrophages
γ_B	Rate immune effectors (T cells) clear extracellular bacteria
α_I	Intracellular bacterial growth rate
N	Carrying capacity of infected macrophages
α_E	Extracellular bacterial growth rate
k_4	Extracellular bacterial rate of phagocytosis
c_0	Half-saturation constant for extracellular bacteria
c_1	Half-saturation constant for infected macrophages
a_2	Immunostimulation strength for extracellular bacteria
a_1	Immunostimulation strength for infected macrophages
a_3	Immunostimulation strength for immune effector
b	Half-saturation constant for immune effector

mune response through the T cells, or by natural death at the constant rate μ_I.

Bacteria. The interactions and growth of Mtb are described by extracellular and intracellular bacteria. Extracellular bacteria (B_E) grow at a maximum rate α_E and are killed by macrophages at rate k_4. The intracellular grow within the macrophages at a maximum rate of α_I with Hill kinetics accounting for the carrying capacity [68]. They become extracellular when the host macrophage bursts when it becomes chronically infected at an assumed threshold of half of the carrying capacity N.

T cells. They are recruited for the source at a constant rate s_T and their proliferation is induced by the infected macrophages at rate a_1 and extracellular bacteria at the rate a_2. They have a finite lifetime and die at rate d_T. Without loss of generality, the T cells, as immune effector agents, will be stimulated by the bacteria (immunostimulation factor) which is followed by the additional processes of autocatalytic and/or cooperative reinforcement through the function $g(T)$ where a_3 is the immunostimulation strength for immune effector and b the half-saturation constant for immune effector. The T cells can also clear infected macrophages at a constant rates γ.

Within host model for TB

Based on all the assumptions, we propose a simple basic immunological model for TB:

$$\begin{aligned}
\frac{dM_R}{dt} &= s_M - \beta M_R\left(\frac{B_E}{B_E+c_0}\right) - \mu_R M_R - k_4 M_R B_E,\\
\frac{dM_I}{dt} &= \beta M_R\left(\frac{B_E}{B_E+c_0}\right) - \mu_I M_I - \alpha M_I\left(\frac{B_I^2}{B_I^2+(NM_I)^2}\right) - \gamma_M M_I T,\\
\frac{dB_E}{dt} &= \alpha_E B_E - k_4 M_R B_E + \alpha N M_I\left(\frac{B_I^2}{B_I^2+(NM_I)^2}\right) - \gamma_B B_E T\\
&\quad -\beta\left(\frac{N}{2}\right) M_R\left(\frac{B_E}{B_E+c_0}\right) + \gamma_M N M_I T + \mu_I B_I, \qquad (2.2.1)\\
\frac{dB_I}{dt} &= \alpha_I B_I\left(1-\frac{B_I^2}{B_I^2+(NM_I)^2}\right) - \alpha N M_I\left(\frac{B_I^2}{B_I^2+(NM_I)^2}\right)\\
&\quad +\beta\left(\frac{N}{2}\right) M_R\left(\frac{B_E}{B_E+c_0}\right) - \gamma_M N M_I T - \mu_I B_I\\
\frac{dT}{dt} &= s_T - d_T T - \gamma M_I T - \gamma_B B_E T + a_2\frac{B_E}{c_0+B_E}T + a_1\frac{M_I}{c_4+M_I}T + a_3\frac{T^2}{b+T^2}.
\end{aligned}$$

Analysis of the model

The domain $\mathscr{D}$ is valid epidemiologically because the populations M_R, M_I, B_E, B_I and T are all nonnegative. We denote points in $\mathscr{D}$ by $x = (M_R, M_I, B_E, B_I, T)$. The nonnegative orthant $\mathbb{R}^5_+ = \{x \in \mathbb{R}^5 | x \geq 0\}$ is called a positively invariant region if

for any trajectory that starts in the nonnegative orthant remains in the same orthant forever. Parallel to the Malaria model, we can use standard techniques described in [106; 107]: if initial conditions are specified for each of the states variables at time $t = 0$, then there exists a unique solution satisfying these initial conditions for all time $t \geq 0$. We need to show that solutions of the model are nonnegative with an initial condition $M_R(0), M_I(0), B_E(0), B_I(0)$ and $T(0) \geq 0$.

Lemma 2. *The closed positive orthant is positively invariant for the Model (2.2.1).*

Proof. Since $M_I = 0, B_E = 0$ and $B_I = 0$ are invariant planes for the model, we only need to prove that $M_R(t) \geq 0$, and $T(t) \geq 0$ for $t \geq 0$ if the initial conditions are in the positive orthant. Assume there exists $t_1 > 0$ such that $M_R(t_1) = 0$, $T(t_1) = 0$, and $0 < t_1 < t$. Then

$$\frac{dM_R(t_1)}{dt} = s_M > 0, \qquad \text{and} \qquad \frac{dT(t_1)}{dt} = s_T > 0,$$

which imply that $M_R(t) \geq 0$ and $T(t) \geq 0$ for $t \geq t_1$. Thus, $M_R(t) \geq 0$, and $T(t) \geq 0$ for all $t \geq 0$. □

Local stability

Let $P = (M_R^*, M_I^*, B_E^*, B_I^*, T^*)$ be steady state. Whether the human host is infected or not, there are always macrophages and T cells in the human body. This implies simply that we cannot have $(M_R^*, M_I^*, B_E^*, B_I^*, T^*) = (0,0,0,0,0)$, i.e., that there is no trivial equilibrium. Setting the right hand sides of Equations (2.2.1) to zero gives the following equilibrium solutions:

At the disease-free-equilibrium, $B_E^* = 0$, we have $M_I^* = 0, B_I^* = 0, M_R^* = s_M/\mu_R$ and

$$s_T + a_3 \frac{T^2}{b + T^2} - d_T T = 0. \tag{2.2.2}$$

Solving Equation (2.2.2) for positive real solutions T^*, implies that the disease-free-equilibrium (DFE) exists and is $(\frac{s_M}{\mu_R}, 0, 0, 0, T^*)$. We can try to complete the

analytical analysis of Equations (2.2.1), but it will be too involved and complicated, and since we are mostly interested in the phenomenological behavior, we instead simulate the model by solving the differential equations using an appropriate numerical method. We discuss below the results of these computational experiments within an individual.

Simulation

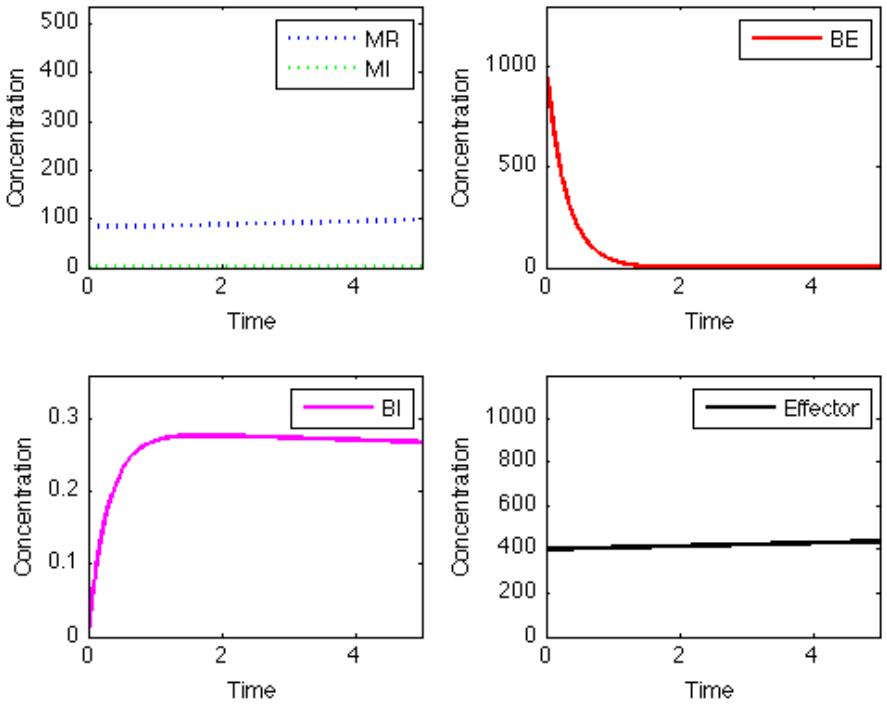


Figure 2.6: The TB infection time series for Model (2.2.1). The transient solutions of the concentrations of macrophages, bacteria and effector, M_R, M_I, B_E, B_I and effector (T) the beginning are shown; see Figure 2.7 for the long-term behavior. Observe the increase of intracellular bacteria while the concentration of extracellular bacteria decreases.

For the parameters found in the literature [68; 74; 116], we see from the simulation (Figures 2.6-2.7) that at the initial stages, the extracellular bacteria give rise to intra-

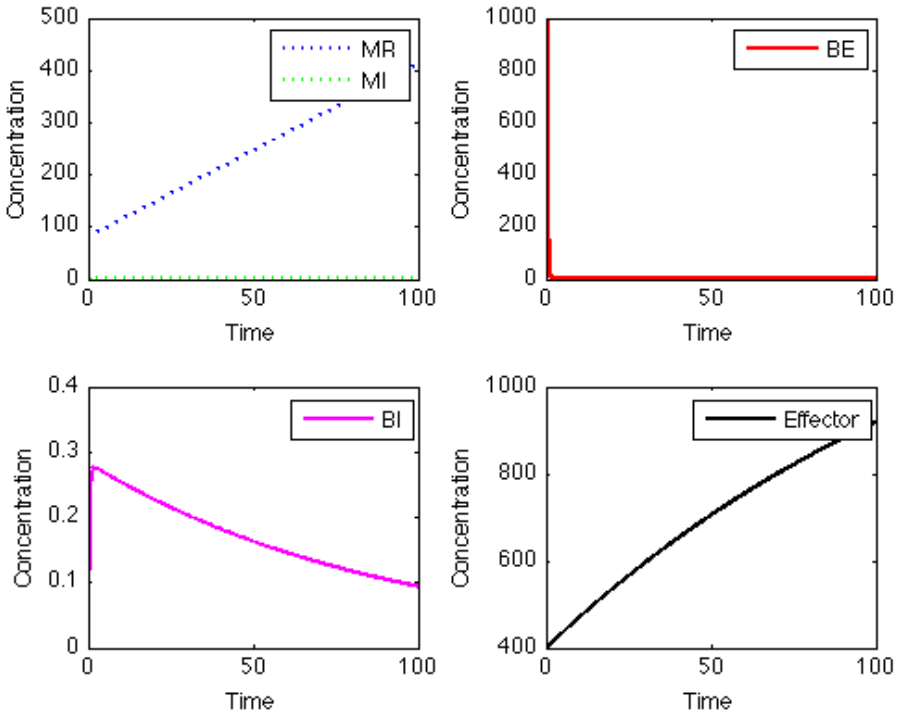


Figure 2.7: Time series of Model (2.2.1) showing the long-term behavior of the concentration of macrophages, bacteria and effector, M_R, M_I, B_E, B_I and effector (T). Figure 2.6 shows the initial transient solutions up to $t = 5$.

cellular bacteria that ultimately reach the carrying capacity before the extracellular bacteria die off. The effector population also reaches a carrying capacity locally around the granuloma which contains a small population of extracellular bacteria and infected macrophages, as can be seen from the Figure 2.7 in which the final time is 100. This type of behavior can be observed in the initial stages of TB.

2.3 Co-infection with Malaria and TB within the individual

The human immune system has two main responses to the introduction of foreign antigen into the body: a cellular-mediated response and a humoral response (antibodies). Both TB and Malaria primarily affect a cellular-mediated immune response for which we gave a brief description in the previous sections. In this

section we focus mainly on the effect that TB or Malaria has on each other but also comment on how the model may explain the activation of latent TB.

We consider the following variables and parameters in Table 2.4 that we will be used to construct our ODE model describing the immune response to Malaria an TB co-infection. Based on the assumptions from the previous sections, we propose

Table 2.3: Brief description of state variables for Model (2.3.1); cf. Models (2.1.1) and (2.2.1) with respective Tables 2.1 and 2.2 with $u \neq v$.

Variables	Description
X	Concentration of uninfected RBC
Y	Concentration of infected RBC
F	*P. falciparum* malaria parasite load
T	Concentration of T cells
M_R	Resting Macrophages
M_I	Infected Macrophages by Mtb
B_I	Intracellular Bacteria (TB)
B_E	Extracellular Bacteria (TB)

a simple immunological model for TB and Malaria co-infection that combines the

Table 2.4: Parameters - symbols and descriptions. Brief description of parameters for Model (2.3.1); cf. Models (2.1.1) and (2.2.1) with respective Tables 2.1 and 2.2 with $u \neq v$.

Symbol	Explanation
s_R	Recruitment rate of red blood cell
d_R	Natural death rate of naive RBC
β	Infection rate of naive RBC
d_I	Death rate of infected RBC
k_1	Rate immune effectors C clear *P. falciparum*
α_1	Maturation rate of infected RBC
k_2	Rate immune effectors (T cells) clear infected RBC
p	Carrying capacity of infected RBC
d_F	Natural death rate of *P. falciparum*
s_T	Recruitment rate of T cells
d_T	Natural death rate of T cells
γ_M	Rate immune effectors (T cells) clear infected macrophages
λ_M	Half-saturation constant for infected macrophages
α_2	Rate of busting of chronically infected macrophages
s_M	Recruitment rate of macrophages
k_3	Infection rate of resting macrophages
μ_R	Natural death rate of resting macrophages
μ_I	Natural death rate of infected macrophages
α_I	Intracellular bacterial growth rate
N	Carrying capacity of infected macrophages
α_E	Extracellular bacterial growth rate
k_4	Extracellular bacterial rate of phagocytosis
γ_B	Rate immune effectors (T cells) clear extracellular bacteria
$c_0 = \lambda_B$	Half-saturation constant for extracellular bacteria
c_1	Half-saturation constant for *P. falciparum*
c_3	Half-saturation constant for infected RBC
c_4	Half-saturation constant for infected macrophages
a_1	Immuno-stimulation strength for *P. falciparum*
a_2	Immuno-stimulation strength for extracellular bacteria
a_3	Immuno-stimulation strength for infected RBC
a_4	Immuno-stimulation strength for infected macrophages
a_5	Immuno-stimulation strength for immune effector
b	Half-saturation constant for immune effector

Models (2.1.1) and (2.2.1) where $u = v = 1$ in those models:

$$
\begin{aligned}
\frac{dX}{dt} &= s_R - d_R X - \beta X F, \\
\frac{dY}{dt} &= \beta X F - d_I Y - k_2 \frac{Y}{c_3 + Y} T, \\
\frac{dF}{dt} &= p\alpha_1 Y - \beta X F - d_F F - k_1 \frac{F}{c_1 + F} T, \\
\frac{dT}{dt} &= s_T - d_T T - k_1 F T + k_2 Y T + a_1 \frac{F^u}{c_1 + F^v} T + a_3 \frac{Y^u}{c_3 + Y^v} T \\
&\quad + a_2 \frac{B_E^u}{c_0 + B_E^v} T + a_4 \frac{M_I^u}{c_4 + M_I^v} T + a_5 \frac{T^2}{b + T^2} \\
&\quad - k_1 \frac{F}{c_1 + F} T - k_2 \frac{Y}{c_3 + Y} T - \gamma_B \frac{B_E}{\lambda_B + B_E} T - \gamma_M \frac{M_I}{\lambda_M + M_I} T, \qquad (2.3.1) \\
\frac{dM_R}{dt} &= s_M - k_3 M_R \left(\frac{B_E}{B_E + c_0} \right) - \mu_R M_R, \\
\frac{dM_I}{dt} &= k_3 M_R \left(\frac{B_E}{B_E + c_0} \right) - \mu_I M_I - \alpha_2 M_I \left(\frac{B_I^2}{B_I^2 + (N M_I)^2} \right) - \gamma_M \frac{M_I}{\lambda_M + M_I} T, \\
\frac{dB_E}{dt} &= \alpha_E B_E + \alpha_2 N M_I \left(\frac{B_I^2}{B_I^2 + (N M_I)^2} \right) - k_4 M_R B_E \\
&\quad - k_3 \left(\frac{N}{2} \right) M_R \left(\frac{B_E}{B_E + c_0} \right) + \mu_I B_E - \gamma_B \frac{B_E}{\lambda_B + B_E} T + \gamma_M N \frac{M_I}{\lambda_M + M_I} T, \\
\frac{dB_I}{dt} &= \alpha_I B_I \left(1 - \frac{B_I^2}{B_I^2 + (N M_I)^2} \right) - \alpha_2 N M_I \left(\frac{B_I^2}{B_I^2 + (N M_I)^2} \right) - \mu_I B_E \\
&\quad + k_3 \left(\frac{N}{2} \right) M_R \left(\frac{B_E}{B_E + c_0} \right) - \gamma_M N \frac{M_I}{\lambda_M + M_I} T.
\end{aligned}
$$

2.4 Analysis of the model

The domain $\mathscr{D}$ is valid epidemiologically because the populations X, Y, F, T, M_R, M_I, B_E, and B_I are all nonnegative. We let $x = (X, Y, F, T, M_R, M_I, B_E, B_I)$ denote the points in $\mathscr{D}$. The nonnegative orthant $\mathbb{R}^8_+ = \{x \in \mathbb{R}^8 | x \geq 0\}$ is called a positively invariant region if for any trajectory that starts in the nonnegative quadrant remains in the same orthant forever. By the same token, we can shown that if initial conditions are specified for each of the states variables at time $t = 0$, then there exists a unique solution satisfying these initial conditions for all time $t \geq 0$. We need to show that solutions of the model are nonnegative with an initial condition $X(0), Y(0), F(0), T(0), M_R(0), M_I(0), B_E(0)$ and $B_I(0) \geq 0$.

Lemma 3. *The closed positive orthant is positively invariant for the Model (2.3.1).*

Proof. Since $Y = 0$, $F = 0$, $M_I = 0$, $B_E = 0$, and $B_I = 0$ are invariant planes for the model, we only need to prove that $X(t) \geq 0$, $T(t) \geq 0$, and $M_R(t) \geq 0$ for $t \geq 0$ if the initial conditions are in the positive orthant.

Assume there exists $t_1 > 0$ such that $X(t_1) = 0$, $T(t_1) = 0$, and $M_R(t_1) = 0$, and $0 < t_1 < t$. Then

$$\frac{dX(t_1)}{dt} = s_R > 0, \qquad \frac{dT(t_1)}{dt} = s_T > 0, \quad \text{and } \frac{dM_R(t_1)}{dt} = s_M > 0,$$

which imply that $X(t) \geq 0$, $T(t) \geq 0$, and $M_R(t) \geq 0$ for $t \geq t_1$. Thus, $X(t) \geq 0$, $T(t) \geq 0$, and $M_R(t) \geq 0$ for all $t \geq 0$. □

Equilibria and reproductive number

Let $P = (X^*, Y^*, F^*, T^*, M_R^*, M_I^*, B_E^*, B_I^*)$ be steady state. Whether the human host is infected or not, there are always RBCs (erythrocytes) and T cells in the human body. This implies simply that there is no trivial equilibrium i.e. we cannot have $(X^*, Y^*, F^*, T^*, M_R^*, M_I^*, B_E^*, B_I^*) = (0,0,0,0,0,0,0,0)$.

Existence of the disease-free equilibrium point

Disease-free equilibrium points are steady state solutions where there is no disease. This is the state in which an individual has no parasites (*P. falciparum*) or bacteria (*Mtb*) in the body. Thus, we take $Y^* = F^* = M_I^* = B_E^* = B_I^* = 0$. From Equations (2.3.1) we get $X^* = X_0 = \frac{s_R}{d_R}$, where X_0 is the equilibrium density of all ages of erythrocytes in absence of pathogens; $M_R^* = M_0 = \frac{s_M}{\mu_{M_R}}$ the equilibrium density of macrophages; and for the T cells, T_0, will depend on average degree of stimulation of leukocyte and no matter what, the number of T cells in human body remains bounded, and the dynamics of (2.3.1) reduce to examine the dynamic of

$$s_T + a_5 \frac{T^2}{b + T^2} - d_T T = 0. \tag{2.4.1}$$

By solving Equation (2.4.1) in the appropriate domain for the positive solution that represents the biologically relevant steady state of the system, the pathogen-free equilibrium (PFE) is given by

$$P_0 = \left(\frac{s_R}{d_R}, 0, 0, T^*, \frac{s_M}{\mu_R}, 0, 0, 0 \right).$$

It can easily be shown that the PFE is unstable. Finding the rest of the steady states of Model (2.3.1) analytically is very complicated and involved; therefore we use numerical simulation for understanding the dynamics of the TB and Malaria co-infection and interaction on the immune response.

2.5 Results of simulation

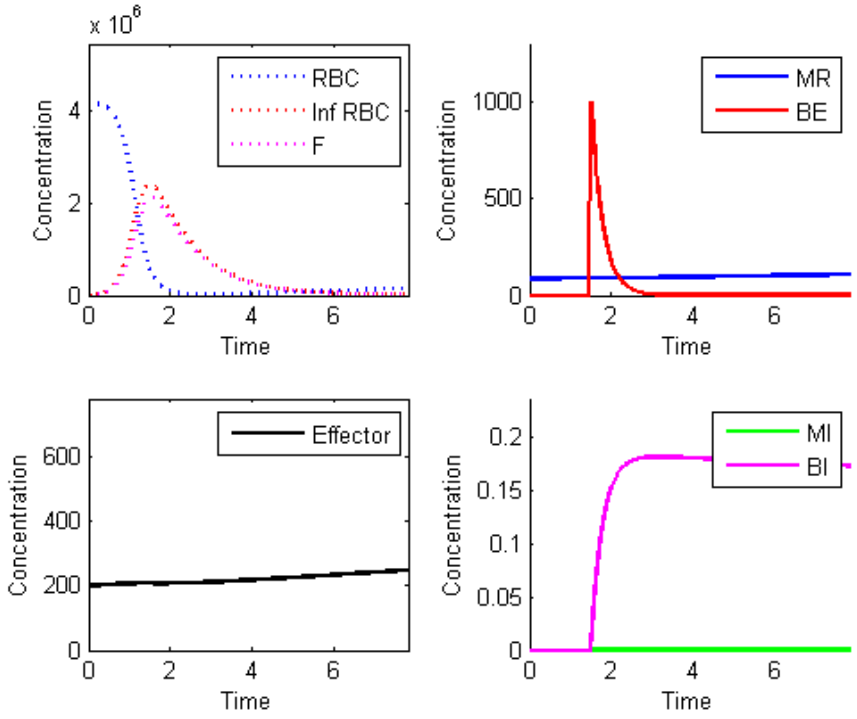


Figure 2.8: Co-infection Model (2.3.1) with Malaria introduced first, then TB at $t = 1.5$ with $t_f = 6$ and $u = v = 1$.

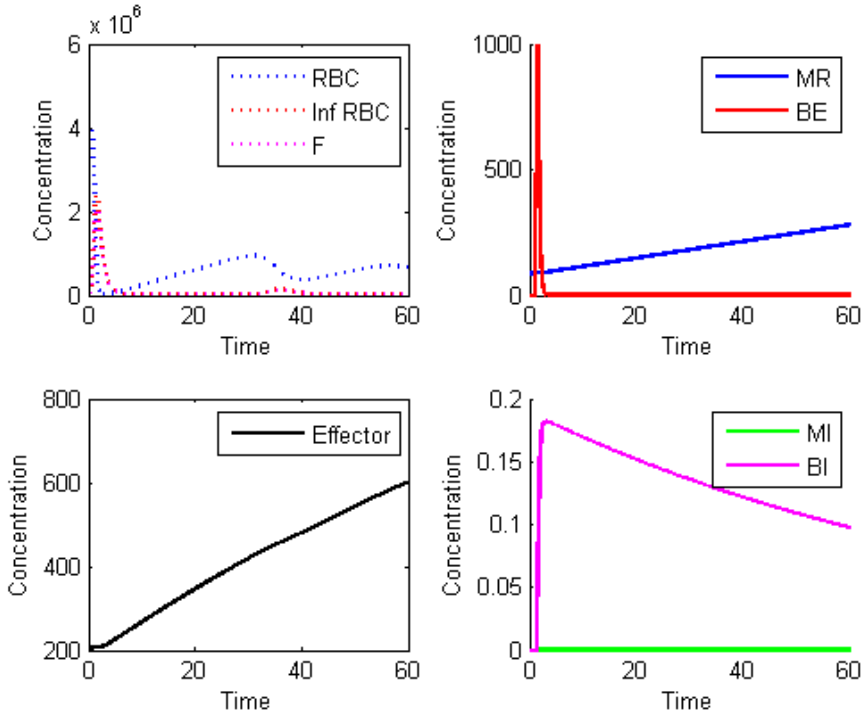


Figure 2.9: Co-infection Model (2.3.1) with Malaria introduced first, then TB at $t = 1.5$ with $t_f = 60$ and $u = v = 1$.

One numerical observation we make before moving on is that an increase in the death rate from $d = .007$ to $d = .03$ has a noticeable impact on the effector levels as they drop when Malaria is introduced. This drop can be exaggerated significantly by changing the initial conditions of the various quantities. Thus even changing one parameter may have significant influence on the transient and/or long-term behavior of the system.

Since we have only been able to explore the dynamics of the Malaria, TB and co-infection Malaria–TB models through numerical simulation, we want to simplify the different models with appropriate caricatures (phenomenological models) to focus on the relevant mechanisms and central components of a single pathogen or two pathogens together with the effector cell (T cells). In all situations, we first make sure that the system is well-posed and makes immunological sense in the absence

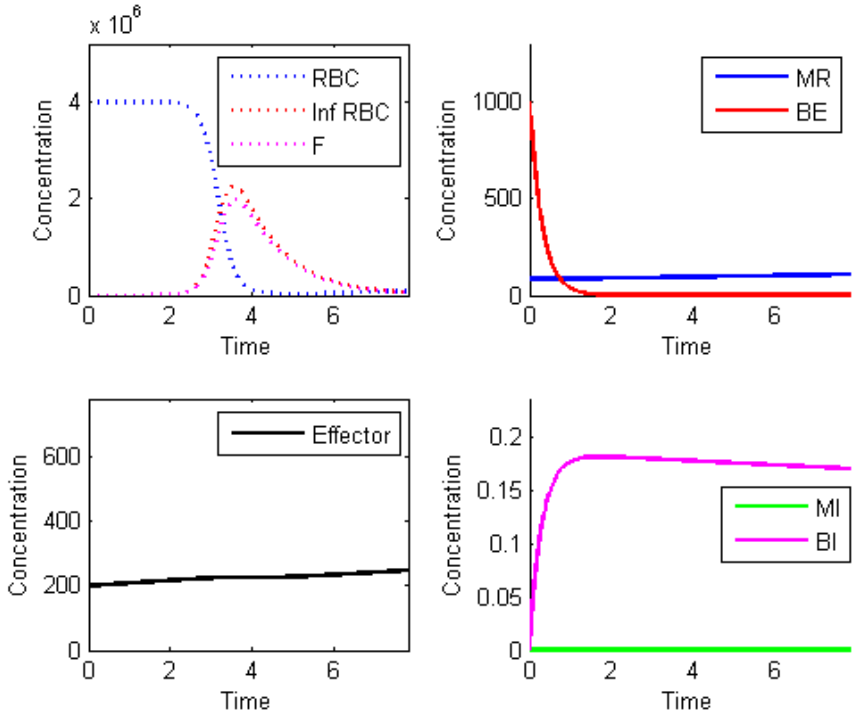


Figure 2.10: Co-infection Model (2.3.1) with TB introduced first, then Malaria at $t = 1.5$ with $t_f = 6$ and $u = v = 1$.

of pathogen(s), namely the pathogen(s) free steady-state. Next, we expect that each pathogen should be able to sustain its own infection. Furthermore, throughout the caricature/phenomenological models we want to include the degree of healthiness of the individual using the Michaelis-Menten function with specific Hill coefficients. We consider the different possible responses of the immune system stages with respect to the pathogens, namely healthy immune, moderately compromised immune and severely compromised systems.

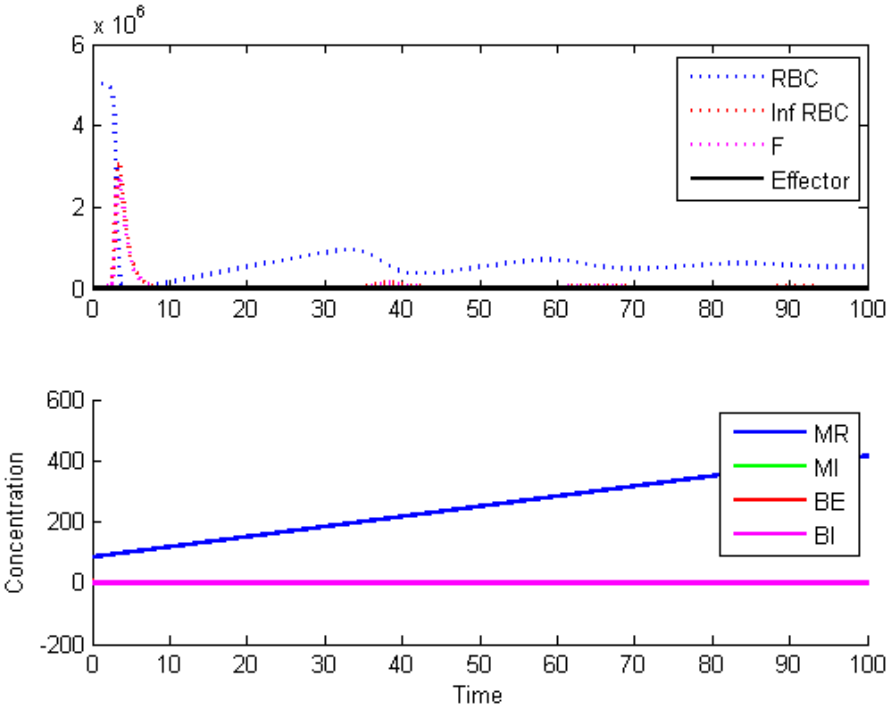


Figure 2.11: Co-infection Model (2.3.1) with TB introduced first, then Malaria at $t = 1.5$ with $t_f = 60$ and $u = v = 1$.

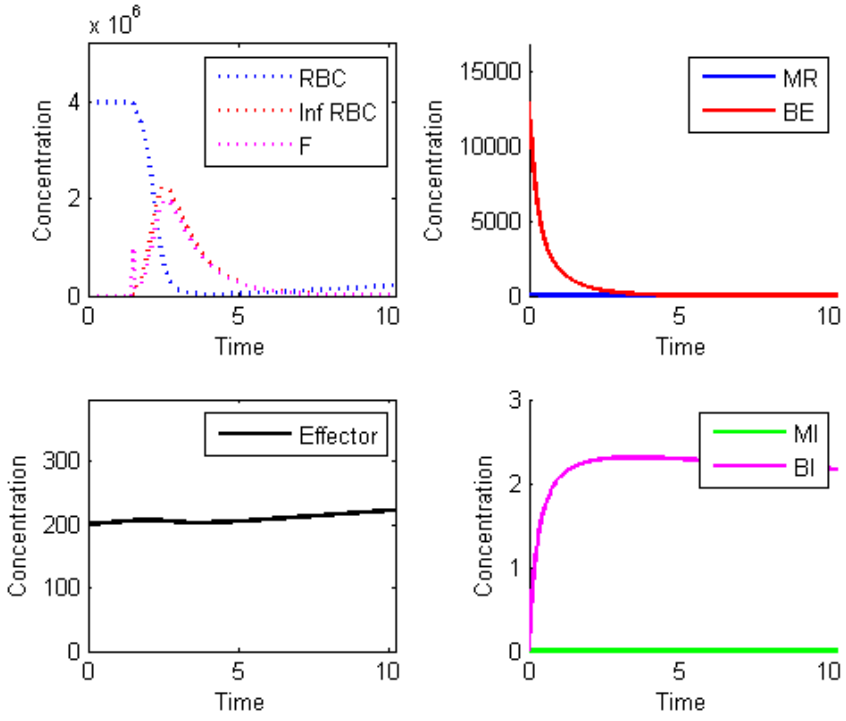


Figure 2.12: Co-infection Model (2.3.1) with TB introduced first, then Malaria at $t = 1.5$ with $t_f = 6$. The natural death rate of effectors is increased here compared with the previous figures, from $d = .007$ to $d = .03$. This gives a noticeable drop of the effector levels when Malaria is introduced.

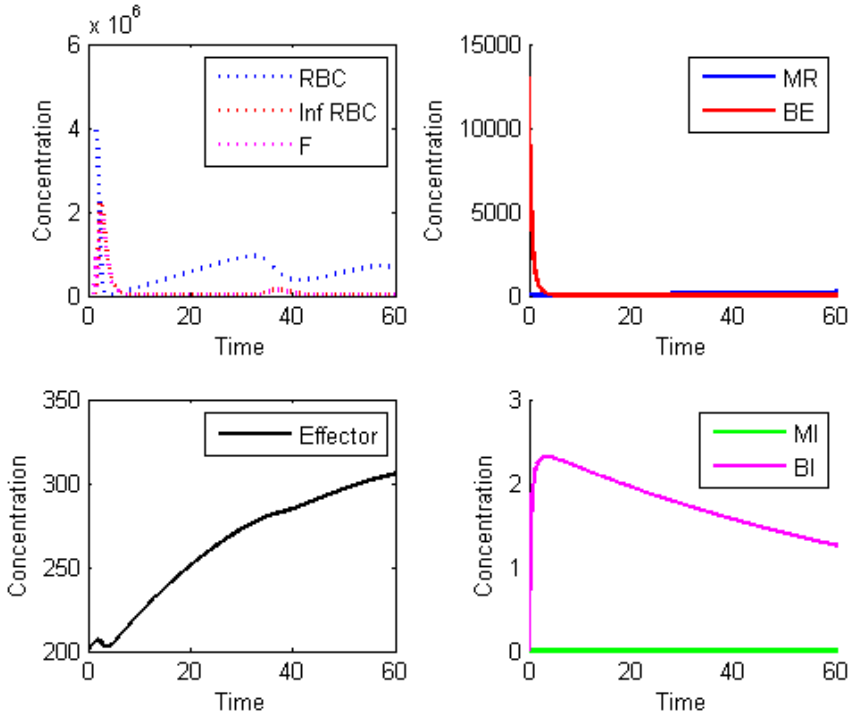


Figure 2.13: Co-infection Model (2.3.1) with TB introduced first, then malaria at $t = 1.5$ with $t_f = 60$. The natural death rate of effectors is increased here compared with the previous figures, from $d = .007$ to $d = .03$. This gives a noticeable drop of the effector levels when Malaria is introduced.

2.6 A Phenomenological Approach

It is difficult to gain insight into the mechanisms that affect the long term behavior of the co-infection Model (2.3.1). While we could perform a sensitivity analysis in an effort to find key parameters, we instead choose to take a phenomenological approach. We consider both Malaria and TB as generic "pathogens" and do not focus on their biological intricacies. Instead, as we describe in detail in the next chapter, we consider each pathogen to have a natural birth rate and death rate and a removal rate by the effectors (usually T-cells). The equation describing the effectors is based on the biology of the T-cells as stated in the malaria and TB models, which we will again elaborate on in the next chapter, and involves stimulation of the effector in the presence of the pathogen as well as when more effectors are present together with a constant recruitment rate, natural death rate, and removal rate upon engagement with a pathogen. Thus, our first phenomenological model takes the form

$$\begin{aligned} \frac{dP_1}{dt} &= rP_1 - kP_1E \\ \frac{dP_2}{dt} &= \rho P_2 - \kappa P_2E \\ \frac{dE}{dt} &= e + f(P_1)E + f(P_2)E + s\frac{E^2}{b+E^2} - dE - (kP_1 + \kappa P_2)E, \end{aligned} \tag{2.6.1}$$

where

$$f(P_i) = p_i\frac{P_i}{a_i + P_i}, \qquad i = 1,2,$$

describes the stimulation of the effector population by the pathogen. The variables and parameters are given in Table 2.5,

Such a phenomenological model may give us insight into the mechanisms that govern the long term behavior of solutions in the co-infection Model (2.3.1). However, in order to fully utilize the mathematical tools that will help us gain this insight we will consider some generalizations of this model. We first will generalize the

Table 2.5: States Variables for phenomenological Models (2.6.1) and (2.6.4).

Symbol	Definition
P_1	First pathogen (target cell) population
P_2	Second pathogen (target cel) population
E_1	Inactivated effector population
E, E_2	Immune competence, (activated) effectors agent population
α	Natural growth rate of naive effector
e	Recruitment rate of naive immune effector
K	Carrying capacity of naive effector
c, c_1	Activation rate of naive immune effector by pathogen 1
c_2	Activation rate of naive immune effector by pathogen 2
d	Natural per capita death rate
r	Within host growth rate of pathogen 1
ρ	Within host growth rate of pathogen 2
k	Clearance rate of pathogen 1 by immune effector agent
κ	Clearance rate of pathogen 2 by immune effector agent
p	Immunostimulation strength for pathogen 1
π	Immunostimulation strength for pathogen 2
s	Immunostimulation strength for immune effector
a, a_1	Half-saturation constant for pathogen 1
a_2	Half-saturation constant for pathogen 2
b	Half-saturation constant for immune effector

stimulation function, $f(P_i)$, currently given as $p_i \frac{P_i}{a_i+P_i} E$. We will do this by considering various responses based on what we will characterize as the health of a person's immune system. This can be done by considering the stimulation function as a specific example of a Hill function and we will consider three variations of the $f(P_i)$:

$$\begin{aligned} p_i \frac{P_i^2}{a_i + P_i^2} &: \quad \text{healthy immune system} \\ p_i \frac{P_i^3}{a_i + P_i^3} &: \quad \text{moderately compromise immune system} \\ p_i \frac{P_i^3}{a_i + P_i^4} &: \quad \text{severely compromised system.} \end{aligned} \tag{2.6.2}$$

In Appendix A, we discuss various Hill functions for a simpler one-pathogen version of Model (2.6.1) that doesn't multiply the stimulation function by the effector

(as is required by the immunology). This mathematically simpler but immunologically incorrect model was proposed by Mayer in 1995 and is presented in the appendix for completeness.

Another generalization of Model (2.6.1) with (2.6.2) that can easily be considered is the effect of considering activation in the effector equation, which we again fully justify in a later chapter. Model (2.6.1) gives a constant recruitment e into the effector equation. However, a more accurate biological model would consider two levels of effectors: inactivated (E_1) and activated (E_2). In this case we can write two effector equations:

$$\begin{aligned} \frac{dE_1}{dt} &= e + \alpha E_1\left(1-\frac{E_1}{K}\right) - (c_1P_1 + c_2P_2)E_1 \\ \frac{dE_2}{dt} &= (c_1P_1 + c_2P_2)E_1 + (f(P_1) + f(P_2))E_2 + g(E_2) - (kP_1 + \kappa P_2)E_2 - dE_2; \end{aligned} \tag{2.6.3}$$

see Table 2.5 for the definitions of state variables and parameters. Incorporating the two stages of effectors can occur in any of the models. Thus our most general phenomenological model consists of

$$\begin{aligned} \frac{dP_1}{dt} &= rP_1 - kP_1E, \\ \frac{dP_2}{dt} &= \rho P_2 - \kappa P_2E, \\ \frac{dE_1}{dt} &= e + \alpha E_1\left(1-\frac{E_1}{K}\right) - (c_1P_1 + c_2P_2)E_1, \\ \frac{dE_2}{dt} &= (c_1P_1 + c_2P_2)E_1 + (f(P_1) + f(P_2))E_2 + g(E_2) - (kP_1 + \kappa P_2)E_2 - dE_2, \end{aligned} \tag{2.6.4}$$

with the $f(P_i)$ given in equations (2.6.2). We will ultimately compare the long-term behavior of (2.6.4) with its fully-biologically based counterpart, Model (2.3.1).

However, in order to mathematically obtain insight into (2.6.4), we first consider three subsystems contained within it.

Chapter 3: subsystem containing one pathogen, one stage of effector; the predictions of this phenomenological model will be compared with both the malaria

Model (2.1.1) and TB Model (2.2.1).

Chapter 4: subsystem containing one pathogen, two stages of effector; the predictions of this phenomenological model will again be compared with the malaria Model (2.1.1) and TB Model (2.2.1) and we additionally comment on the incorporation of the inactivated class of effectors into the behavior of the overall model.

Chapter 5: subsystem containing two pathogens and one stage of effector; subsystem containing two pathogens and two stages of effectors; the prediction of these phenomenological models will be compared with the numerical results of the co-infection Model (2.3.1).

Chapter 3

PHENOMENOLOGICAL SUBSYSTEM: SINGLE-PATHOGEN, SINGLE-STAGE EFFECTOR MATHEMATICAL MODELS OF IMMUNE RESPONSE

3.1 Introduction

During an epidemic outbreak in a population, one can control the spread of the disease when we understand the mode of transmission of the pathogen between the individuals. Observing that the individual is the epicenter of the population, we can even better control the dynamic of any infectious diseases at the population level if we fully understand and can begin to control what is going on with the pathogens within the individual. Understanding the dynamic of the pathogen within the individual can help to isolate the different groups within the population and implement measures to facilitate a speedy recovery of the individual. At the human level, the dynamics of the immune response have a very high degree of complexity. Therefore it is quite challenging to develop any realistic and complete mathematical model to capture every situation of the host defense. The immune system is a masterwork that effectively prevents our body from being overtaken by scavenging germs every day. Without an effective immune system, we would develop all sorts of infections from bacteria, viruses, protozoa, parasites and fungi. A pathogen proliferates in a habitat (e.g., host tissue, internal organ) in which it is normally limited by physical and chemical barriers (e.g., phagocytic in Figure 3.1, macrophage and others cells of the immune system). Evolution occurs in both the microbial invaders population and the host immune system. The immune system is an ideal example for the study of complex systems. It offers adaptation and evolution on observable time scales and offers testable hypotheses. In response to diseases the immune system is adapting to its environment.

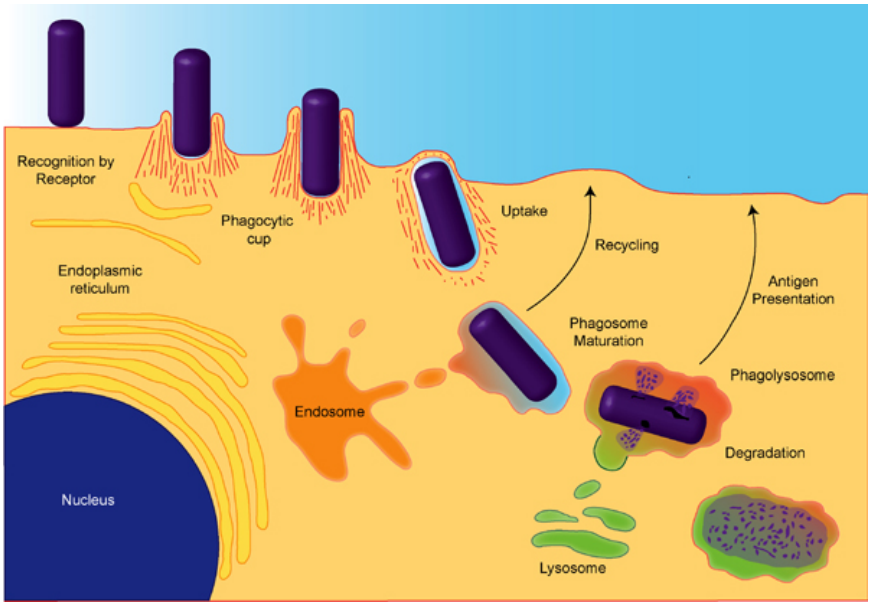


Figure 3.1: The formation of the phagocytic cup - the foreign pathogen is degraded. See Section 2.2.

Nowadays, with the advances in science and technology, it is important to understand how the immune system impacts the infectivity or recovery from diseases; this is the "avant-garde" of the future development of treatment. For example, it has been demonstrated and we now better understand that there is a firm link between the immune system and cancer, and that by properly stimulating the immune system, certain forms of cancers can be treated [96]. This is the underlying concept of the new principle of "Immune Therapy". There has been much interest in mathematical modeling of the immune response during an epidemic and the dynamics of targets or pathogens (virus, bacteria, etc.) [62; 71; 90; 102; 113–115; 120]. Much of the mathematical modeling consists of systems of differential equations. The differential equation lets us describe how a physical system changes in time. Formulating the dynamics of a system in terms of rules for how they change rather than their specific behavior allows a single equation to describe many different types of phenomena. The differences between these phenomena arise from varying initial conditions and choices of parameters. Newton's single differential equation for

projectile motion describes both how an object falls to the ground and the orbital motion of satellites, the differences in behavior coming from the initial positions and momenta of these objects.

Motivated by the approach taken in [34], our focus is to examine the variability of the immune competence E, based on more realistic and reasonable biological assumptions, with a mathematical model. We modify and extend a mathematical model from the literature [77], so that it additionally accounts for the differentiation and maturation of immune competence cells, and for the formation of immune memory after infection. The immune effector or competence can be defined as the elimination capacity of the immune system with respect to that special pathogen or "non-self" micro-organism within the host. Our ultimate goal is to study and understand the effect of individual immune responses on the outcome of the outbreak or an epidemic at the population level. Our models can capture many essential features of the immune system that are able to produce a variety of immune responses, many of which we observed experimentally or clinically [11; 32; 59; 61; 101].

3.2 Phenomenological Model formulation

In constructing our phenomenological models, the populations of interest are represented by P and E. Table 2.5 gives the definitions and symbols of the populations and parameters that we will use. Note that in all our models, as in Segel and Pereleson [103], lymphocytes (memory, naive and effector cells) are not specifically T or B cells, but a generalization having properties common to both types.

In the development of our models, we take into account some specific biological assumptions that are based on a generally accepted understanding of immune system function [60], and that we seen in our immunology-based models of Malaria and TB, Models (2.1.1) and (2.2.1). In the host, the targets have an innate net growth rate constant r (nonnegative) and the elimination as a result of the interaction with

the immune effector E is assumed to be proportional to the concentration of the target and the immune effector with non-negative constant k using the law of mass-action. Here, taking into consideration the different hypotheses for this first (naive) model we consider the temporal change of the pathogenic infectious agent population size P to be determined by the difference between their reproduction r_1P and their elimination by the immune effector kPE and the natural death within the host d_1P. We can establish the following equation for the dynamics of pathogens:

$$\frac{dP}{dt} = r_1P - kPE - d_1P.$$

For simplicity, the dynamics of the pathogen population in our model can be reduced by setting $r = r_1 - d_1$. Therefore, the pathogen equation yields

$$\frac{dP}{dt} = rP - kPE.$$

Also we assume that rates of infection are small enough that the immune system completely eliminates one pathogen, and relaxes to the uninfected state long before the next infection occurs. For the immune competence E, we assume it to be constituted by a minimum of four different factors that were all seen in the Malaria Model (2.1.1) and TB Model (2.2.1): the innate recruitment rate for reproduction e; the natural death of the immune effectors dE and removal due to the pathogens eradication k_iP_iE; the presence of the targets in the host trigger the immune response, which is the immunostimulation factor or the speed of activation of the immune effector also defined as the speed of activation $f(P_i)E$ with $i = \{1,2\}$; followed by the additional strength of the immune activation processes by autocatalytic and/or cooperative reinforcement $g(E)$ [77]. Throughout these processes, the nonspecific and antigen-specific immune responses are activated, which lead to increases in the immune competence, E. All the parameters are positive. Note that, unlike the Mayer model (see Appendix A), we multiply the activation function $f(P)$ by the factor E because this immune effector response requires cell interactions with the

target cells [60]. In our model, $t = 0$ marks the time when the pathogen is mixed into the lymph and begins to stimulate an immune response. This represents how once a small amount of the pathogen bypasses the physical barriers of the innate immune system it will proliferate until it finds its way into the blood and then lymph nodes, at which point the immune response is triggered. Taking into account the cell proliferation and saturation within the host, the appropriate way of defining the functions $f(P_i)$ and $g(E)$ is with the nonlinear bounded Michaelis-Menten functions. This attempt was first used by Agur *et al.* [1] in 1988, Anite *et al.* [6] in 1994 and later properly formulated by De Boer and Perelson [33] in 1995.

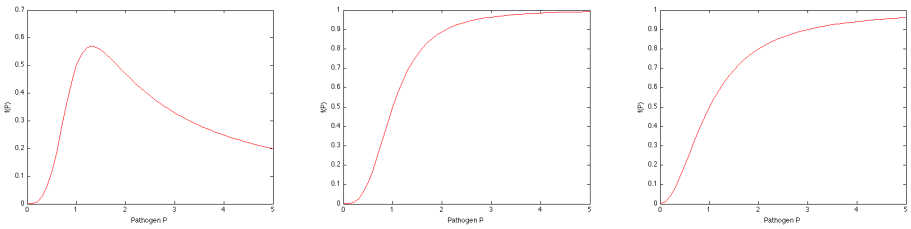
Using the list of the assumptions from above and substituting specific mathematical forms for each of the descriptions yield a system of two coupled differential equations, in which each equation gives the rate of change of a particular cell population described in Table 2.5. The model is given by following system, cf. (2.6.1) with (2.6.2) and $P_2 = 0$:

$$\begin{aligned} \frac{dP}{dt} &= rP - kPE \\ \frac{dE}{dt} &= e + f(P)E + g(E) - dE - kPE \end{aligned} \tag{3.2.1}$$

where $f(P)$ and $g(E)$ are defined as in Mayer's model (see Appendix A):

$$f(P) = p\frac{P^u}{m^v + P^v} \qquad \text{with } P \geq 0, \quad u \leq v \text{ and} \qquad g(E) = s\frac{E^n}{c^n + E^n}.$$

In general, depending on the integer exponent there exist three qualitatively different shapes of the stimulation function $f(P_i)$ as illustrated by Figure 3.2. On the other hand, the qualitative shape of $g(E)$ is like Figure 3.2(c) for $n > 1$. All these functions are bounded taking into account the fact that the population is limited and cannot grow unbounded. We note that the Malaria Model (2.1.1) and TB Model (2.2.1), as currently formulated, correspond to the specific case of $u = v = 1$.



(a) $1 \leq u < v$. Severely immune compromised.

(b) $2 \leq u = v$. Moderately immune compromised.

(c) $1 < u \leq v$. Healthy immune.

Figure 3.2: Graph of stimulation function $f(P)$. Whenever $v > 1$ we have a small delayed response (Allee effect) as the immune system mounts its response. In (a), the immune system initially responds in the normal way for small P levels but it cannot continue and decreases its response for larger P values. In (b) and (c) the immune response increases with pathogen levels but reaches a saturation level. Although the qualitative shape of (b) and (c) are similar, we assume that both the saturation levels and immune response are less in the moderate immune compromised versus the healthy individual.

For the purpose of our work and for simplification, we will assume some specification about the function $f(P)$ which will clearly correspond to the qualitative representation of the immune response to pathogen invasion in the three situations on which we would like to focus. In the line of development, we will consider only the following three scenarios of the immune system response:

- Immune non-compromised (healthy immune system): $u = v = 2$.
- Immune moderately compromised: $u = v = 3$,
- Immune severely compromised: $u = 3$ and $v = 4$.

with a specific parameter value within the parameters domain see Figures 3.3 - 3.5. For each of the scenarios, the parameters will take the respective values:

- immune non-compromised (healthy): $u = v = 2$; $p = 1$ and $a = 0.85$.
- immune moderately compromised: $u = v = 3$; $p = 0.75$ and $a = 0.50$

- immune severely compromised: $u = 3$ and $v = 4$; $p = 1$ and $a = 1.20$

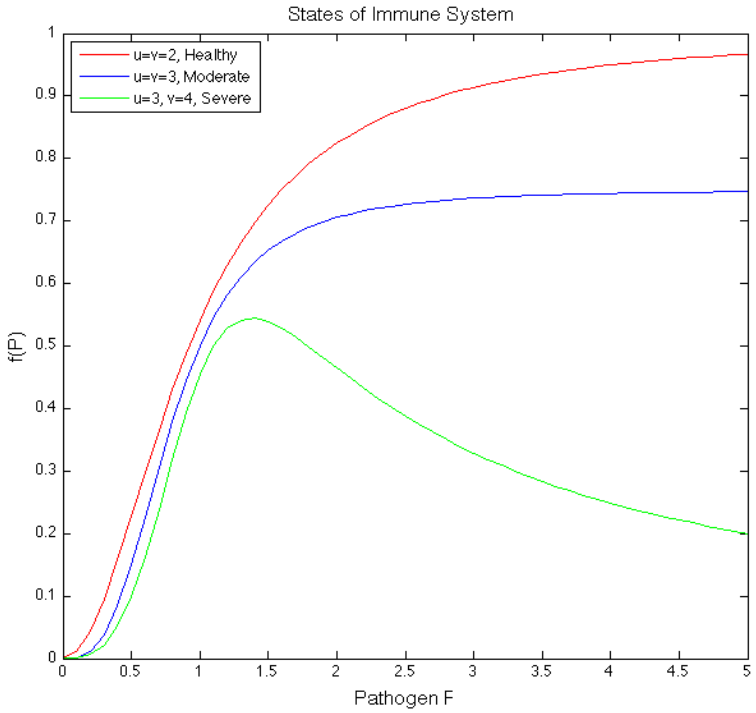


Figure 3.3: Three functions that describe the state of the immune system response to pathogen invasion.

Thus we model the immune response under the following conditions:

- For simplification, we consider every model with:

$$n = 2; \quad m^v = a; \quad \text{and} \quad c^n = b;$$

- Using a Michaelis-Menten saturation function, the qualitative behavior of $f(P)$ allows us to qualify the state of the immune system. Throughout our work, we will focus on three scenarios:

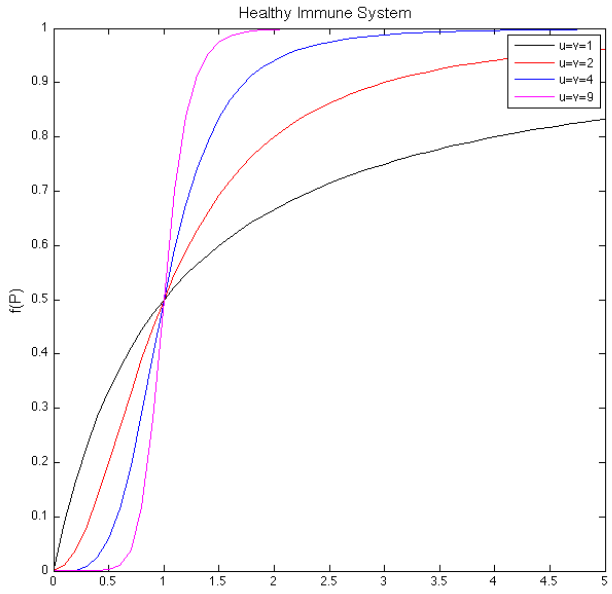


Figure 3.4: Dynamic of pathogens for different degrees of healthy immune or moderately compromised individuals. As n increases the response to the pathogen increases rapidly to reach saturation.

The first scenario where the host immune system is healthy yields the following system of equations:

$$\begin{aligned} \frac{dP}{dt} &= rP - kPE \\ \frac{dE}{dt} &= e + p\frac{P^2}{a+P^2}E + s\frac{E^2}{b+E^2} - dE - kPE. \end{aligned} \tag{3.2.2}$$

For the second scenario, the immune system is moderately compromised, and the equations are the following:

$$\begin{aligned} \frac{dP}{dt} &= rP - kPE \\ \frac{dE}{dt} &= e + p\frac{P^3}{a+P^3}E + s\frac{E^2}{b+E^2} - dE - kPE. \end{aligned} \tag{3.2.3}$$

The third scenario yields:

$$\begin{aligned} \frac{dP}{dt} &= rP - kPE \\ \frac{dE}{dt} &= e + p\frac{P^3}{a+P^4}E + s\frac{E^2}{b+E^2} - dE - kPE. \end{aligned} \tag{3.2.4}$$

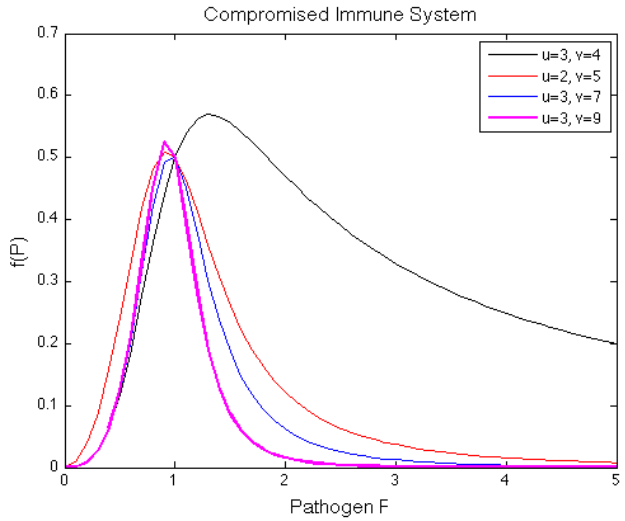


Figure 3.5: Dynamic of response to pathogen for different degrees of compromised immune systems. As $u < v$ and $v - u$ both increase, the response increases rapidly and soon after starts to decline. The higher the value of $v - u$, the more compromised the host is.

These three phenomenological Models (3.2.2)-(3.2.4) are caricatures of the Malaria Model (2.1.1) and TB Model (2.2.1) with the health of the host additionally incorporated via the different $f(P_i)$ stimulation functions.

3.3 Existence of solutions

Due to the biological meaning of the different variables P and E, we have to restrict the domain to the nonnegative quadrant $\mathbb{R}^2_+$ where the populations P and E are all nonnegative. This restriction will be applicable to each model. The domain is called a positively invariant region if any trajectory that starts in the nonnegative quadrant remains in the same quadrant forever. It can be shown using standard techniques described in [106; 107] that if initial conditions are specified for each of the state variables at time $t = 0$, then there exists a unique solution satisfying these initial conditions for all time $t \geq 0$.

Proposition 4. *The closed positive quadrant $\mathbb{R}^2_+$ is positively invariant for the Models (3.2.2) - (3.2.4).*

Proof. The proof is similar in all three scenarios. Here using the first scenario model, we need to show that the solutions for the Model (3.2.2) are nonnegative given an initial condition $P(0) \geq 0$ and $E(0) \geq 0$. For $P = 0$, we have an invariant line for the system of Equations (3.2.2), and thus we only need to prove that $E(t) \geq 0$, for $t \geq 0$ if the initial conditions are in the positive quadrant.

Assume there exists $t_1 > 0$ such that $E(t_1) > 0$. Then

$$\frac{dE(t_1)}{dt} \approx e > 0$$

which implies that $E(t) \geq 0$, for $t \geq t_1$. Therefore, $E(t) \geq 0$ for all $t \geq 0$. □

3.4 Analysis of equilibria

We shall first determine the equilibrium solutions of Models (3.2.2)-(3.2.4) and then investigate the type(s) of possible bifurcations from the equilibria. The equilibria are defined when we equate the right hand sides of every equation of the system to zero and solve for the state variables. We study the stability of the fixed

points by analyzing the distribution of the eigenvalues of the linearized system. Due to the nonlinearity of the system, it may not be possible to express the fixed points in closed form.

Pathogen-free-equilibrium

In the absence of targets cells, $P = 0$, all the systems (3.2.2) - (3.2.4) yield

$$e + s\frac{E^2}{b+E^2} - dE = 0. \tag{3.4.1}$$

Solving Equation (3.4.1) for positive real solutions E^*, for the fixed points of the systems (3.2.2) - (3.2.4), we have to solve the following polynomial of degree three for E:

$$dE^3 - (e+s)E^2 + dbE - eb = 0.$$

With all the parameters positive, using "Descartes' Rule of Signs" there are three or one positive roots. This implies that the pathogen-free-equilibrium (PFE) exists and is $(0, E^*)$.

If one varies the parameters of Equation (3.4.1) within a positive domain of the parameters values, the long-term behavior may change since we can have one or three DFE using the "Descartes' Rule of Signs;" "Sturm chain or sequence method" (cf. Beaumont and Pierce, 1963) provides more precise conditions for the number of steady states. The appearance or disappearance of equilibria produce topological changes in the system and are examples of bifurcations.

The Jacobian (J), evaluated at the critical points, $(0, E^*)$ is:

$$J = \begin{bmatrix} r - kE^* & 0 \\ h(E^*) & 2\frac{sbE^*}{\left(b+E^{*2}\right)^2} - d \end{bmatrix},$$

where

$$h(E) = \frac{\partial}{\partial P}\left(\frac{dE}{dt}\right).$$

Depending on the values assigned to u and v, $h(E)$ will have different expressions. The Jacobian matrix can be simplified to

$$J = \begin{bmatrix} r - kE^* & 0 \\ -kE^* & 2\frac{sbE^*}{\left(b+E^{*2}\right)^2} - d \end{bmatrix},$$

which is an upper triangular matrix whose eigenvalues can easily be identified:

$$\lambda_1 = r - kE^*$$
$$\lambda_2 = 2\frac{sbE^*}{\left(b+E^{*2}\right)^2} - d.$$

In the case that the immune system has never encountered a specific pathogen, $E = 0$ as memory cells, we have

Proposition 5. *Consider the Systems (3.2.2) - (3.2.4) with $e = 0$ and all other parameters positive. The pathogen-free-equilibrium $(0,0)$ is unstable.*

Although mathematically convenient, requiring $e = 0$ goes against one of our key modeling assumptions; it is more realistic to have $e > 0$.

In the case the pathogen has been presented to the immune system and has been cleared out, $E > 0$, we have

Proposition 6. *Consider the Systems (3.2.2) - (3.2.4) with all parameters positive. For $E^* > r/k$ and $2\frac{sbE^*}{\left(b+E^{*2}\right)^2} < d$ the pathogen-free-equilibrium $(0,E^*)$ is stable otherwise it is unstable.*

Endemic equilibrium

The different values assigned to u and v will play a major role in the existence of endemic equilibria, (P^*,E^*) when $P^*,E^* > 0$. In all the three scenarios, solving the right-hand side of the first equations in Models (3.2.2) - (3.2.4) for $P(t) > 0$, the

first equation yields always to

$$E^* = \frac{r}{k}.$$

When we substitute $E^* = \frac{r}{k}$ in the second equation, we solve for P^*. Depending on the different scenarios, we reach the following equations where, for all positive parameters, let

$$A = e + s\frac{E^2}{b+E^2} - dE.$$

- For $u = v = 2$, we have

$$-rkP^3 + (kA + pr)P^2 - rkaP + aAk = 0. \tag{3.4.2}$$

  1. $A < 0$ and $kA + pr < 0 \Rightarrow$ zero positive roots
  2. $A < 0$ and $kA + pr > 0 \Rightarrow$ zero or two positive roots
  3. $A > 0 \Rightarrow$ one or three positive roots

  Using the "Descartes rule of Signs" for Eq. (3.4.2), we can say that it is possible we have three, two, one or zero real positive roots as biologically relevant solutions. Thus, we can have zero, one, two or three endemic equilibri(um/a).

- For $u = v = 3$, we have

$$-rkP^4 + (Ak + pr)P^3 - rkaP + aAk = 0 \tag{3.4.3}$$

  1. $A < 0$ and $kA + pr < 0 \Rightarrow$ one positive root
  2. $A < 0$ and $kA + pr > 0 \Rightarrow$ zero or two positive roots
  3. $A > 0 \Rightarrow$ one or three positive roots

  Using the "Descartes rule of Signs" for Eq. (3.4.3), we can see that we can have three, two, one or zero real positive roots as biologically relevant solutions. Thus, we can have zero, one, two or three endemic equilibri(um/a).

- For $u = 3$ and $v = 4$, we have

$$-rkP^5 + AkP^4 + prP^3 - rkaP + aAk = 0. \tag{3.4.4}$$

1. $A < 0 \Rightarrow$ zero or two positive roots
2. $A > 0 \Rightarrow$ one or three positive roots

By the same token, with the "Descartes rule of Signs" for Eq. (3.4.4), we conclude that there may exist zero, one, two or three real positive roots. Thus, we can have zero, one, two, or three endemic equilibri(um/a).

3.5 Simulations and discussion

Of course, the time series of the targets/pathogens P and the immune effector E are determined as the solutions of the differential equations, which depend on the initial conditions. We present some numerical simulations using the parameters values in Table 3.1 to illustrate the behavior of the interaction immune effector-pathogen as an explicit function of time.

Table 3.1: Parameters for Figures 3.6 and 3.7, which give some numerical solutions of Model (3.2.2).

r	k	p	a	s	b	d	e
2.3	2	1	.85	2.5	1	1	2

In the presence of a single target invading the host without trying to solve for solutions that depend on the initial condition, we can use phase plane analysis to analyze the Models (3.2.2) - (3.2.4). When moving along the trajectories the system finally converges toward the immune state where only "memory cells" exist, no targets, as we can see in Figure 3.7. As the pathogen load decreases, the activation of the antibody (immune competence) will cease and the population of antibodies will decrease to a minimum load of memory cells, near the time of complete

antigen inactivation, that can be present in the host as along as he lives. Here, the model predicts that the target cells can be completely cleared from the host by its immunocompetent cells.

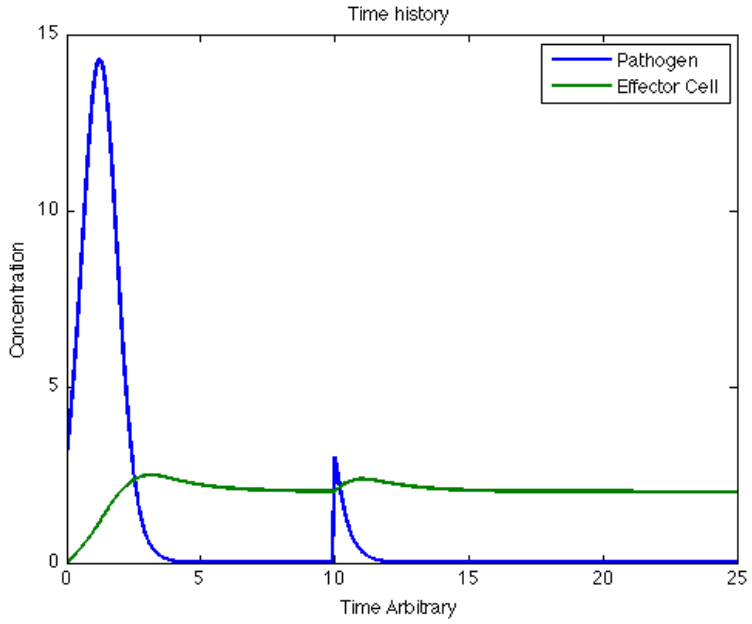
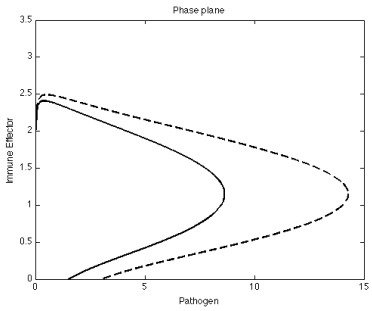
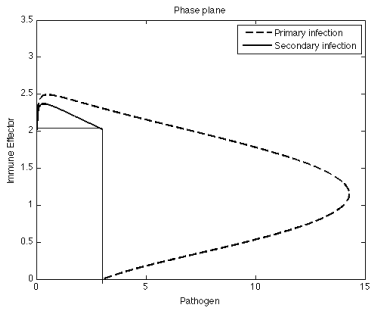


Figure 3.6: Primary and secondary response of the immune competence to a same pathogen infection. Note that the response of the immune system is quicker for the second exposure to the pathogen, which is expected given that memory cells are now present. The qualitative behaviors are the same in all three scenarios depending on the pathogen virulence, except for the time it takes to clear the pathogens decreases from severe compromise down to health immune system. Scenario (3.2.2) presented in this picture; however, (3.2.3) and (3.2.4) have the same qualitative behavior. Values of parameters for computation: $[r,k,p,a,s,b,d,e] = [2.3,2,1,.85,2.5,1,1,2]$.

Due to the complexity and high non-linearity of each system we are not able to find an explicit solution for the endemic equilibrium. Since we are mostly interested in the qualitative behavior, in the following section we provide some simulations to illustrate the dynamics. Before doing so, we consider possible bifurcations that may occur in our system. Each of the two dimensional systems that we have, (3.2.2)-(3.2.4), is different from the others only in the expression governing the response



(a) Two differently infections trajectories.



(b) Primary and one secondary response to a same pathogen.

Figure 3.7: Phase plane of a single type of pathogen and immune effector agent. Again note that the response of the immune system is quicker for the second exposure to the pathogen, which is expected given that memory cells are now present. Scenario (3.2.2) presented in these pictures; however, (3.2.3) and (3.2.4) have the same qualitative behavior. Values of parameters for computation: $[r,k,p,a,s,b,d,e] = [2.3,2,1,.85,2.5,1,1,2]$.

curves

$$f(P) = \frac{pP^u}{a+P^v}.$$

where we consider a healthy immune system as $u = v = 2, a = .85, p = 1$, a moderately immune compromised system as $u = v = 3, a = .5, p = .75$, and a severely immune compromised system as $u = 3, v = 4, a = 1.2, p = 1$. We consider what happens to the stability of the equilibria as we change some of the parameters.

In each of the three scenarios, we look for Hopf bifurcations of the various pathogen-free equilibrium and the endemic equilibria. If we let J^* represent the Jacobian matrix evaluated at the given equilibrium, the conditions for a Hopf bifurcation are found by substituting $\lambda = i\omega$ into the characteristic equation $\det(J^*) = 0$, equating real and imaginary parts to zero and eliminating ω from the equation. The resulting equation gives curves along which Hopf bifurcations potentially occur. However, performing this procedure does not yield any bifurcation for $\omega > 0$. Thus we can conclude that the system does not undergo any Hopf bifurcations for any choices of parameter values.

The other basic type of bifurcation that we can have is a $\lambda = 0$ bifurcation, such as transcritical, saddle node, or pitchfork bifurcations. We go to the original system to calculate the Jacobian and corresponding characteristic equation. As we vary d, we observe $\lambda = 0$ bifurcations for the given scenarios, which are given below.

Healthy immune response

Fix parameter values $k = .135, a = .85, \alpha = 2.95, K = 250, c = .88, e = 4, s = 0.0007, b = 1, p = 1, r = 2.75$ in Model (3.2.2). As we increase d, we can go from having

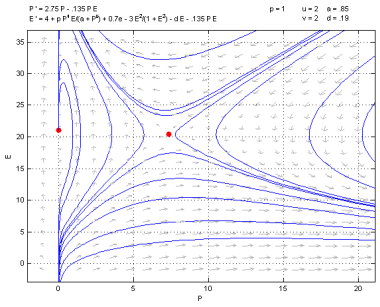
- one endemic equilibrium (E_1^*) and one pathogen-free equilibria (E^*); E_1^* is a saddle and is biologically relevant; E^* is stable; for the given parameters this situation will hold when $d < 0.192509928950910$ (approximately); "Descartes rule of Signs" predicts 3 or 1 positive endemic equilibria ($A > 0,\ kA + pr > 0$ in (3.4.2));

- three endemic equilibria (E_1^*, E_2^*, E_3^*) with one pathogen-free equilibria (E^*); E^* remains stable and $E_1{}^*$ remains a biologically relevant saddle; equilbria E_2^*, E_3^* were born in a saddlenode bifurcation with E_2^* a saddle, E_3^* a stable spiral, and E_3^* "slightly above" E_2^* in the phase plane; for the given parameters this situation will hold when $0.192509928950910 < d < 0.1963979174$ (approximately); "Descartes rule of Signs" predicts 3 or 1 positive endemic equilibria ($A > 0,\ kA + pr > 0$ in (3.4.2));

- two endemic equilibria (E_1^*, E_2^*, E_3^*) with one pathogen-free equilibria (E^*); E_2^* and E^* underwent a transcritical bifurcation with E_2^* no longer biologically relevant (but mathematically stable) and E^* now a saddle; equilbria E_3^* is still a stable spiral and E_1^* a saddle; for the given parameters this situation will hold when $0.1963979174 < d < 0.751421838984983$ (approxi-

mately); "Descartes rule of Signs" predicts 2 or 0 positive endemic equilibria ($A < 0,\ kA + pr > 0$ in (3.4.2));

- one endemic equilibrium (E_2^*) remains not biologically relevant (but stable) and one pathogen-free equilibria (E^*) remains a saddle; E_1^* and E_3^* underwent a saddlenode bifurcation and no longer exist mathematically; for the given parameters this situation will hold when $0.751421838984983 < d$ (approximately); "Descartes rule of Signs" predicts 2 or 0 positive endemic equilibria ($A < 0,\ kA + pr > 0$ in (3.4.2));



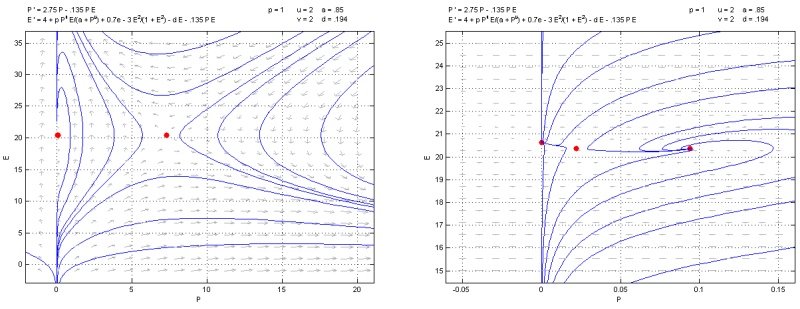
(a)

Figure 3.8: Phase plane portrait for healthy immune response before it undergoes a saddle-node bifurcation. For this figure, we have $d < 0.192509928950910$.

Moderately compromised immune response

Fix parameter values $k = .135, a = .85, \alpha = 2.95, K = 250, c = .88, e = 4, s = 0.0007, b = 1, p = 1, r = 2.75$ in Model (3.2.3). As we increase d, we can go from having

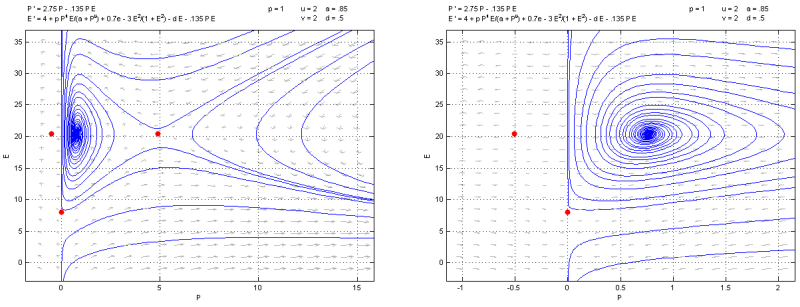
- one endemic equilibrium (E_1^*) and one pathogen-free equilibria (E^*); E_1^* is a saddle and is biologically relevant; E^* is stable; for the given parameters this situation will hold when $d < 0.178717215$ (approximately); "Descartes rule of Signs" predicts 3 or 1 positive endemic equilibria ($A > 0,\ kA + pr > 0$ in (3.4.3));



(a)

(b) The right picture is a "blow up" of the left.

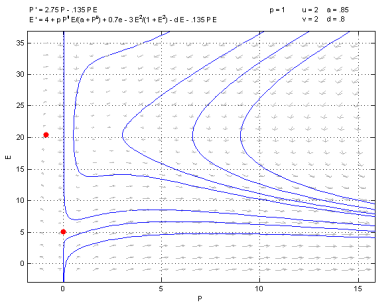
Figure 3.9: Phase plane portrait for healthy immune response after it has undergone a saddle-node bifurcation. The new endemic equilibria that appeared are located very near the pathogen-free point, as can be seen in (b). We have $0.192509928950910 < d < 0.1963979174$.



(a)

(b) The right picture is a "blow up" of the left.

Figure 3.10: Phase plane portrait for healthy immune response. The system has undergone a transcritical bifurcation with only two endemic equilibria now biologically relevant. This holds for $0.1963979174 < d < 0.751421838984983$.



(a)

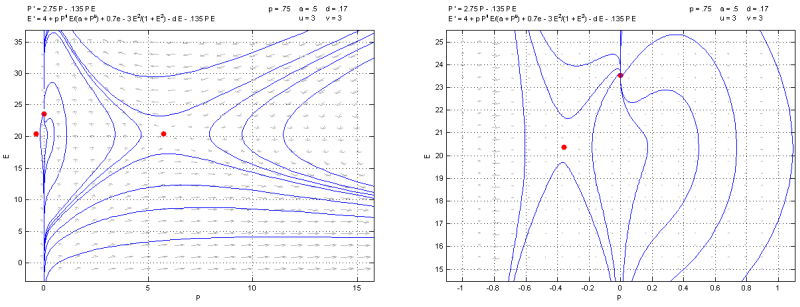
Figure 3.11: Phase plane portrait for healthy immune response, after having undergone another saddle-node bifurcation. We have $0.751421838984983 < d$.

- three biologically relevant endemic equilibrium (E_1^*, E_2^*, E_3^*) and one pathogen-free equilibria (E^*); E^* is stable; E_1^* is a saddle and is biologically relevant; E_2^* is a saddle and is "below" the stable spiral E_3^* in the phase plane; for the given parameters this situation will hold when $0.178717215 < d < 0.180726721966789$ (approximately); "Descartes rule of Signs" predicts 3 or 1 positive endemic equilibria ($A > 0,\ kA + pr > 0$ in (3.4.3));

- two biologically relevant endemic equilibria (E_1^*, E_3^*) with one pathogen-free equilibria (E^*); E_2^* and E^* underwent a transcritical bifurcation with E_2^* no longer biologically relevant (but mathematically stable) and E^* now a saddle; equilbria E_3^* is still a stable spiral and E_1^* a saddle; for the given parameters this situation will hold when $0.180726721966789 < d < 0.8307$ (approximately); "Descartes rule of Signs" predicts 2 or 0 positive endemic equilibria ($A < 0,\ kA + pr > 0$ in (3.4.3));

- one endemic equilibrium (E_2^*) remains not biologically relevant (but stable) and one pathogen-free equilibria (E^*) remains a saddle; E_1^* and E_3^* underwent a saddlenode bifurcation and no longer exist mathematically; for the given parameters this situation will hold when $0.8307 < d$ (approximately);

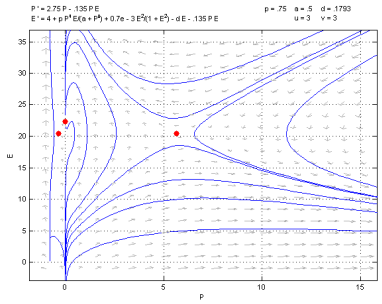
"Descartes rule of Signs" predicts 2 or 0 positive endemic equilibria ($A < 0$, $kA + pr > 0$ in (3.4.3));



(a)

(b) The right picture is a "blow up" of the left.

Figure 3.12: Phase plane portrait for a moderately compromised immune response before it undergoes a transcritical bifurcation. This picture is valid for $d < 0.180726721966789$.

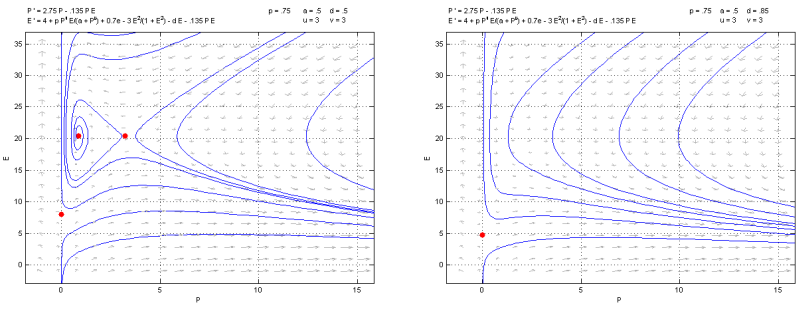


(a)

Figure 3.13: Phase plane portrait for a moderately compromised immune response after having undergone a transcritical bifurcation. This picture is valid for $0.180726721966789 < d < 0.8307$.

Severely compromised immune response

Fix parameter values $k = .135, a = .85, \alpha = 2.95, K = 250, c = .88, e = 4, s = 0.0007, b = 1, p = 1, r = 2.75$ in Model (3.2.4). As we increase d, we can go from having



(a) (b)

Figure 3.14: Phase plane portrait for a moderately compromised immune response after having undergone another saddlenode bifurcation. This qualitative behavior holds for $0.8307 < d$.

- one endemic equilibrium (E_1^*) and one pathogen-free equilibria (E^*); E_1^* is a saddle and is biologically relevant; E^* is stable; for the given parameters this situation will hold when $d < .175458204034150$ (approximately); "Descartes rule of Signs" predicts 3 or 1 positive endemic equilibria ($A > 0$ in (3.4.4));

- three endemic equilibria (E_1^*, E_2^*, E_3^*) with one pathogen-free equilibria (E^*); E^* remains stable and ${E_1}^*$ remains a biologically relevant saddle; equilbria E_2^*, E_3^* were born in a saddle-node bifurcation with E_2^* a saddle, E_3^* a stable spiral, and E_3^* "slightly above" E_2^* in the phase plane; for the given parameters this situation will hold when $0.17878084 < d < .1963979174$ (approximately); "Descartes rule of Signs" predicts 3 or 1 positive endemic equilibria ($A > 0$ in (3.4.4));

- two biologically relevant endemic equilibria (E_1^*, E_3^*) with one pathogen-free equilibria (E^*); E_2^* and E^* underwent a transcritical bifurcation with E_2^* no longer biologically relevant (but mathematically stable) and E^* now a saddle; equilbria E_3^* is still a stable spiral and E_1^* a saddle; for the given parameters this situation will hold when $.1963979174 < d$ (approximately); "Descartes rule of Signs" predicts 2 or 0 positive endemic equilibria ($A < 0$ in (3.4.4));

- one endemic equilibrium (E_2^*) remains not biologically relevant (but stable) and one pathogen-free equilibria (E^*) remains a saddle; E_1^* and E_3^* underwent a saddlenode bifurcation and no longer exist mathematically; for the given parameters this situation will hold when $0.62647 < d$ (approximately); "Descartes rule of Signs" predicts 2 or 0 positive endemic equilibria ($A < 0$ in (3.4.4));

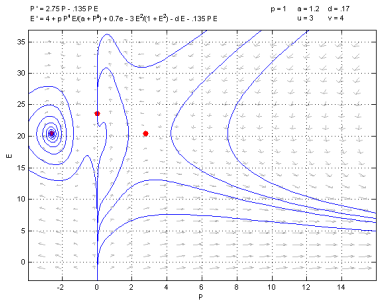


Figure 3.15: Phase plane portrait for a severely compromised immune response that has undergone a saddle-node bifurcation. The necessary condition for this picture is $0.17878084 < d < .1963979174$ and we have the existence of two biologically relevant fixed points.

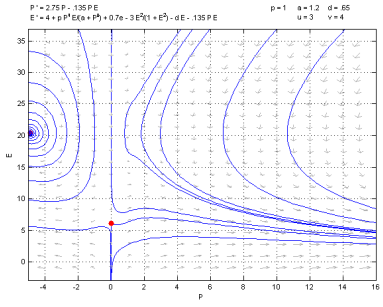


Figure 3.16: Phase plane portrait for a severely compromised immune response after having undergone another saddle-node bifurcation, leaving no biologically relevant endemic equilibria. This hold when $0.62647 < d$. The sequence of figures is qualitatively the same as in the healthy and moderately compromised immune systems.

Comparison of single-pathogen, single-stage effector with Malaria Model (2.1.1) and TB Model (2.2.1)

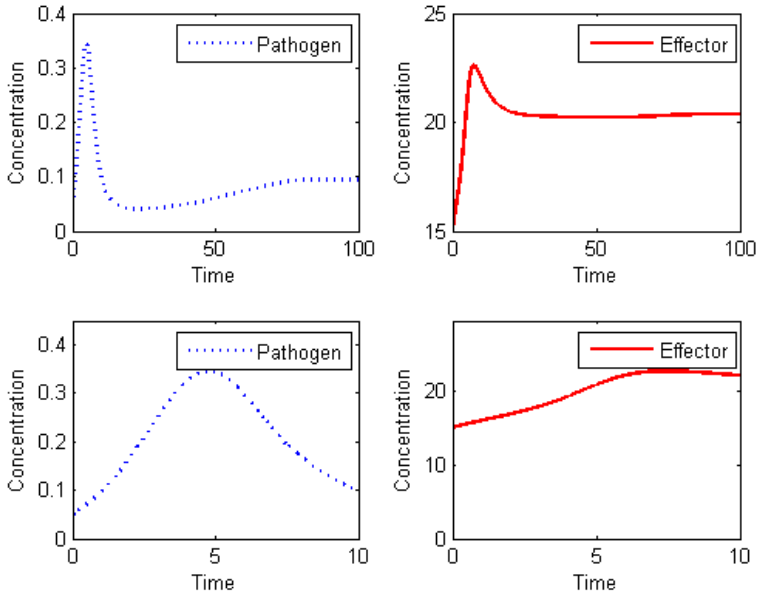


Figure 3.17: Time series of pathogen and activated immunocompetent cells concentration in the host for healthy individual and $IC = (.05, 15)$. (a) Transient behavior; (b) Transient dynamics at the beginning of infection. The qualitative behavior of the moderately and severely compromised immune system is the same for the given choice of parameters.

While we have been able to gain tremendous insight into the behavior of our phenomenological Models (3.2.2)-(3.2.4), our ultimate goal is to compare these with the immunology-based Malaria Model (2.1.1) and TB Model (2.2.1).

In the case of the Malaria model, Figure 3.17 illustrates the same qualitative behavior of the pathogen as the immune system gets the pathogen (Malaria) under control but does not completely eliminate it from the body. Thus our phenomenological models capture a key feature of the actual immunology-based model. Another key

feature of the immunology-based Malaria Model (2.1.1) is that the effector population monotonically increases to its steady-state value. In our 2-dimensional phenomenological Models (3.2.2)-(3.2.4), we are not able to observe this behavior in the effector as a spiral that gives the correct pathogen behavior also requires oscillatory behavior of the effector. In order to mathematically observe oscillatory behavior in one variable and monotonic behavior in a second variable, we would need a third variable to be present. Thus, when we examine the next subsystem of the general phenomenological Model (2.6.4) that includes two classes of effectors (inactivated and activated) we may be able to mimic the behavior of the true system.

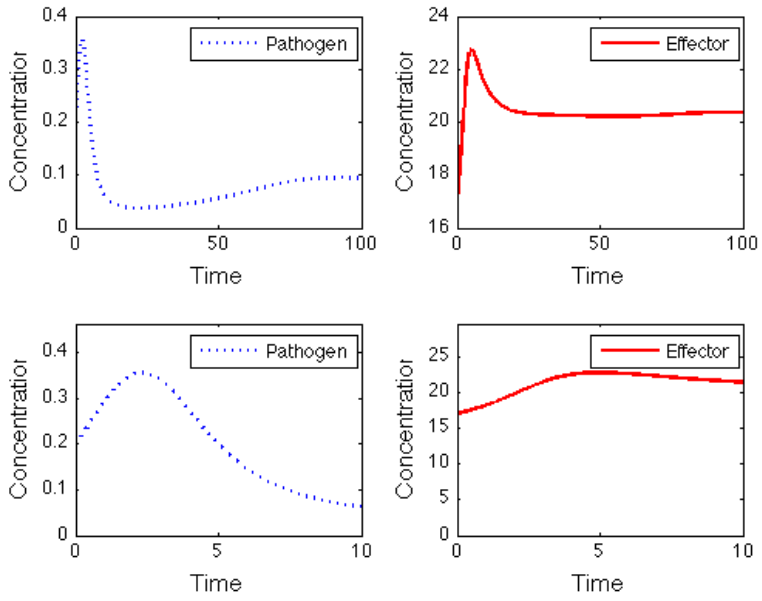


Figure 3.18: Time series of pathogen and activated immunocompetent cells concentration in the host for healthy individual and $IC = (.02, 17)$. (a) Transient behavior; (b) Transient dynamics at the beginning of infection. The qualitative behavior of the moderately and severely compromised immune system is the same for the given choice of parameters.

In the case of the TB model, Figure 3.18, we can choose initial conditions that give behavior close to that observed for BI and E. The immunology-based TB model appears to have a very weak oscillatory behavior in the BI equation and monotonic

behavior in the E equation. The phenomenological models again correctly mimic the behavior of the immunology-based TB model in the pathogen (BI) variable but not the effector variable since it predicts small oscillations as it approaches steady-state (and this is not observed in the immunological Model (2.2.1). As with the malaria Model, considering the next subsystem of the general phenomenological Model (2.6.4) that would include two classes of effectors (activated and inactivated) we may be able to mimic the behavior of the true system. In both models, as future research, we intend to investigate whether varying the parameter d in the Malaria and TB models can yield the qualitatively observed behavior (bifurcations) of the phenomenological models. However, even without having such a numerical bifurcation analysis of the immunological models, we are able to conclude that the first subsystem of the phenomenological model helps us better understand the potential mechanisms underlying the behavior of the true models.

3.6 Conclusion

The immune response in the presence of one pathogen has been analyzed with a simplistic mathematical model based on assumptions that we defined earlier. The model predicts the increase of memory cell formation with the decrease in time to response during the second infection with the same pathogen in all the scenarios. At the same time one can notice the decrease in the time of infection from the severely compromised to healthy immune systems. Even though there are no experimental data to support the classification of the immune system state using the Hill function with anything other that $u = v = 1$, we can see how the degree of the saturation function can affect the dynamics of the immune system.

To our knowledge, there is no mathematical models of the immune system response that can be compared to our phenomenological model for one stage of the effector maturation and that take into consideration the state of the individual health.

The selected models capture a key feature of the actual immunology-based model, monotonically increasing of the effector population to get the pathogen under control before reaches its steady state. Under certain conditions, these models illustrate the qualitative behavior of the Malaria model.

General speaking, with the complexity of the immune response, we cannot pretend to include all the aspects of the immune system and its interaction with the foreign agents in a simple mathematical model. But still, the model presented herein is among the simplest phenomenological models to describe the pathogen–immune system interaction. In the next chapter, we incorporate additional realistic assumptions into the modeling such as the maturation of the immune effector cells, which then gives extensions of Equations (3.2.2) - (3.2.4).

Chapter 4

PHENOMENOLOGICAL SUBSYSTEM: SINGLE PATHOGEN, TWO STAGE EFFECTOR MATHEMATICAL MODELS OF IMMUNE RESPONSE

4.1 Introduction

A healthy immune system aims to create a state of immunity against many pathogens or invaders. To reach this state it is essential to be marked by a specific non-self agent (bacteria, viruses, immunization, etc.). The agent or pathogen that enters the host is recognized by the immune system and consequently causes a specific reaction. The immune response is a specific process resulting from the confrontation of organism(host) with an antigen, and immunity is the result of successful course of the immune response. In our initial Models, (3.2.2) - (3.2.4), one cannot observe the stages of the immune system from inactivated to activated effector. Thus our extension of (3.2.2) - (3.2.4), which is also the justification of Equation (2.6.3), will now account for the activation of immune competence cells and for the formation of immune memory after infection. Although occurring on a vastly different time scale and only in a developing immune system, we can also think of the two stages of effectors as naive and mature. It has been noted that the foreign pathogen provoking the response is also called the antigen and the immune response itself is characterized by the production and the maturation of antibodies, which are antigen specific, and that the bindings to the antigen (foreign pathogen) hasten its destruction and elimination from the host.

In the development of our models, we take into account some specific biological assumptions that are based on a generally accepted understanding of the immune system function [60]:

1. The mature immune effector cells can kill the target cells and be killed. Note that the binding reaction between the pathogen and the immunocompetence cells is not always one to one.

2. The immune effector cells or agents have a finite lifetime.

3. As part of innate immunity, the effectors are always present and active in the host where they are recruited.

4. All foreign or invader cells have the potential to activate and stimulate the immune effectors by increasing metabolic activity; this reaction induces the precursor cells for increased proliferation or differentiation. Note that the level of immune competence depends on both the number of target cells present as well as the host individual immune effector agents.

The binding of an antibody to a pathogen facilitates its removal and is carried out by specialized immune competence cells (phagocytes or macrophages). In certain circumstances, pathogen binding and detachment occurs without damaging the immunocompetence cells. The surface of the immune cell is covered with identical receptors. The activation and the eradication can occur on a one-to-one basis or when a sufficiently many receptors of the immune effector cell are bound to pathogens. For simplicity, we assume that each unit of pathogen has a single site of binding to immune effector cell, and similarly each immune effector cell can bind only a single pathogen. In fact pathogens (bacteria, viruses) or cells have many binding sites for antibody, and some of the immune effector cells have two or more sites for pathogens binding. It may be interesting to consider binding site rather that cells or molecules as fundamental unit.

When we consider a child vs. an adult or the environment of the host exposed to multiple pathogens, we know that there is a difference in the immune response [38; 94]; the competition of two pathogens or a pathogen with multiple strains may

weaken the immune system as well. Also, when we look at, for example, the T cell maturation, activation and differentiation one can see some specifications. It will be very difficult to incorporate in a mathematical model all these specifications which increase the complexity of the analysis. Here are some of the requirements:

- During the recirculation, the naive T cells circulate from the blood to lymph node back to the blood every 12 to 24 hours.
- Naive T cell: Cells never meet antigens before and can only be activated by dendritic cells.
- Effector cells: Short lived cells with special functions such as cytokine secretion and B cell help and cytotoxic killing activity. Effector cells are divided from naive or memory cells after antigen activation Th1, Th2 subsets.
- Memory cells: Long lived resting cells that are derived from naive and effector cells. They respond faster and stronger to a subsequent challenge with the same antigen.
- $CD_4^+CD_{25}^+$ regulatory T cells: Cells that can inhibit the proliferation of other T cells population.

We thus group the effector cells into two basic categories: naive vs. mature. Figure 4.1 shows this specific breakdown.

Table 2.5 gives the definitions and symbols of the populations of interest. Recall that in our model, as in Segel and Pereleson [103], the variables (memory, naive and effector cells) are not specifically T or B cells, but a generalization with properties common to both types.

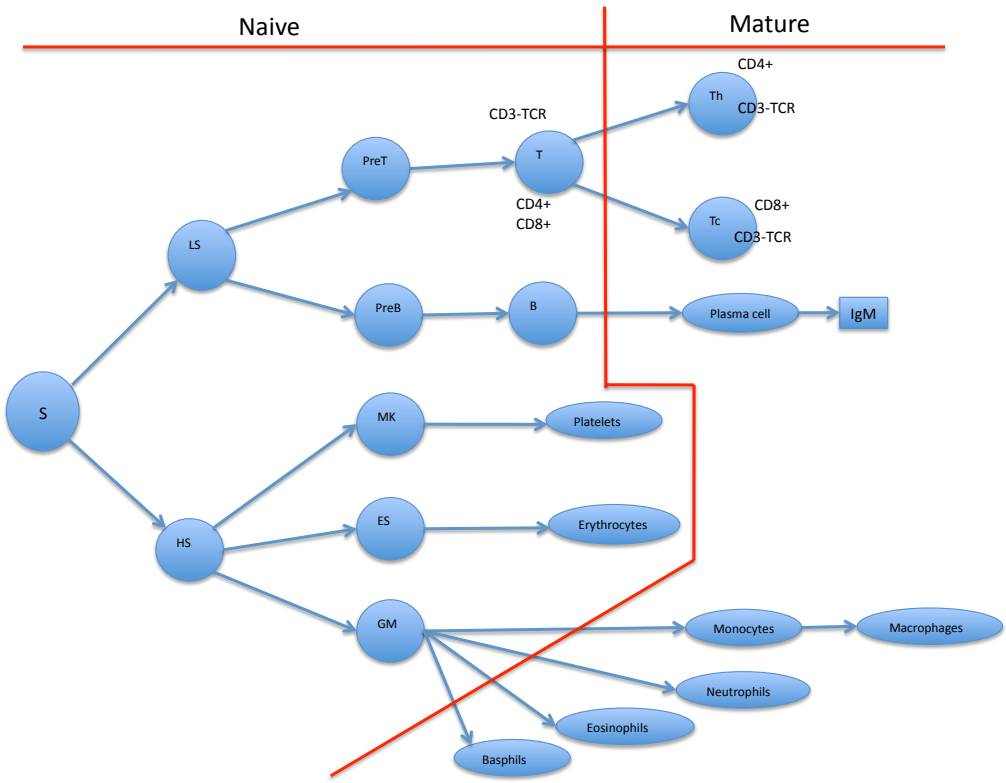


Figure 4.1: Key stages of stem cell differentiation grouped into two basic categories: naive vs. mature.

4.2 Model formulation

Based on all the previous assumptions and hypotheses, we thus consider our next subsystem of the general phenomenological Model (2.6.4) by considering a single pathogen but now with two stages of effectors. To account for the two-stage activation–inactivation or the alternative interpretation as chronological stages, growth or maturation of the immune effector agents, we consider the following phenomenological model for the immune response:

$$\begin{aligned} \frac{dP}{dt} &= rP - kPE_2 \\ \frac{dE_1}{dt} &= e + \alpha E_1\left(1 - \frac{E_1}{K}\right) - cPE_1 \\ \frac{dE_2}{dt} &= cPE_1 + f(P)E_2 + g(E_2) - kPE_2 - dE_2, \end{aligned} \tag{4.2.1}$$

with $f(P) = p\frac{P^u}{a+P^v}$ and $g(E_2) = s\frac{E_2^2}{b+E_2^2}$, where u and v are positive integers as defined in Chapter 2. In our model, $t = 0$ marks the time when the pathogen is mixed into the lymph and begins to stimulate an immune response. We do not consider how a small amount of pathogen can bypass the physical barriers of the innate immune system and proliferate until it finds its way into the blood and then lymph nodes, at which point the immune response is triggered. Let us note that within the host the homeostatic mechanisms keep the total number of cells relatively constant and controlled. Homeostatic regulation in the immune system refers to the mechanisms that control the number of cells in the system. Without homeostatic regulation cells would either experience unconstrained growth (cancer), or decay to extinction.

This model differs from the basic model (System (3.2.1)) because it also takes into account two stages of the effector immune competence as shown in Figure 4.1. The parameter r is the per capita growth rate of the pathogen P in the host and k is the positive rate of elimination of the antigen by the immune competence through one to one binding. The maximum growth rate of the naive immune effector E_1 is α with K its carrying capacity, and c the rate of maturation of the immune effector in presence of the pathogen. With respect to this current approach, we will again consider the previous three scenarios, namely

- Immune non-compromised, $u = v = 2, \Rightarrow f(P) = p\frac{P^2}{a+P^2}$.
- Immune moderately compromised, $u = v = 3, \Rightarrow f(P) = p\frac{P^3}{a+P^3}$.
- Immune severely compromised, $u = 3$ and $v = 4, \Rightarrow f(P) = p\frac{P^3}{a+P^4}$.

With this approach of separating the immune competence into naive and mature immune agents, we can identify two time scales:

1. the fast time scale occurs with the maturation and the differentiation of the immune effector cells from the stem cell of the bone marrow (or equivalently, the inactivated effector cells)

2. the slow time is associated with the activation, metabolic reaction of the immune competence agents and their proliferation and influx into the spleen.

This motivates the application of quasi-steady state approximation to the equation involving the fast time scale, (i.e. $\frac{dE_1}{dt} \approx 0$) which yields the following relation with regard to every scenario:

$$E_1 \approx \frac{K}{2\alpha}\left(\alpha - c\bar{P} + \sqrt{(\alpha - c\bar{P})^2 + 4e\alpha/K}\right),$$

where $\bar{P}$ is the pathogen load when we consider the quasi-steady state. For simplicity, the Model (4.2.1) can be reduced to a two dimensional system of equations when we substitute $E_1 \approx \frac{K}{2\alpha}\left(\alpha - c\bar{P} + \sqrt{(\alpha - c\bar{P})^2 + 4e\alpha/K}\right)$ into the mature immune effector cells equation. The subsystem yields

$$\begin{aligned} \frac{dP}{dt} &= rP - kPE_2 \qquad (4.2.2) \\ \frac{dE_2}{dt} &= cP\frac{K}{2\alpha}\left(\alpha - c\bar{P} + \sqrt{(\alpha - c\bar{P})^2 + 4e\alpha/K}\right) + f(P)E_2 \\ &\quad + s\frac{E_2^2}{b + E_2^2} - kPE_2 - dE_2. \end{aligned}$$

4.3 Existence of steady state

The precise values of the steady states of the Model (4.2.2), can be determined analytically if we are lucky. Setting the right-hand sides of each equation in (4.2.2) to zero with the assumption that the naive immune competence has a fast

time scale, meaning E_1 reaches a quasi-steady state yields:

$$\begin{aligned} 0 &= rP - kPE_2 \qquad (4.3.1)\\ 0 &= cP\frac{K}{2\alpha}\left(\alpha - c\bar{P} + \sqrt{(\alpha - c\bar{P})^2 + 4e\alpha/K}\right) + f(P)E_2 \\ &\quad + s\frac{E_2^2}{b+E_2^2} - kPE_2 - dE_2, \end{aligned}$$

with $f(P)$ different due to the change of u and v values as previously mentioned.

Pathogen-free steady state

In the absence of a pathogen, $P = 0$ at all time, all the scenarios we consider yield to the same expression:

$$0 = s\frac{E_2^2}{b+E_2^2} - dE_2.$$

Here one can have two different possibilities when solving for E_2:

If a specific pathogen has never been presented to the immune system for the isolated host, the system (4.2.2) with the initial conditions $P(0) = E_2(0) = 0$ has the unique solution $(P^*, E_2^*) = (0,0)$ or for the complete Model (4.2.1)

$$(P^*, E_1^*, E_2^*) = \left(0, \frac{K}{2\alpha}\left(\alpha + \sqrt{\alpha^2 + 4e\alpha/K}\right), 0\right)$$

for all times.

In the case that the host been in contact with the pathogen, the system has to be solved with non-zero initial conditions for the mature immune competence and it has an equilibrium:

$$\begin{aligned} (P^*, E_2^*) &= \left(0, \frac{s}{2d}\right) \text{ for } s^2 = 4bd^2, \\ (P^*, E_2^*) &= \left(0, \frac{s + \sqrt{s^2 - 4bd^2}}{2d}\right) \text{ for } s^2 > 4bd^2. \end{aligned}$$

We discuss its stability in the next section.

Endemic steady state

In the presence of pathogen $P(t) > 0$, and considering that E_1 is in the quasi-steady state, the system is solved with non-zero initial conditions. For

$$0 = e + \alpha E_1 \left(1 - \frac{E_1}{K}\right) - cPE_1,$$

we obtain

$$E_1^* = \frac{K}{2\alpha}\left(\alpha - c\bar{P} + \sqrt{(\alpha - c\bar{P})^2 + 4e\alpha/K}\right), \text{ with } \bar{P} > 0.$$

Substituting $E_2 = \frac{r}{k}$ and E_1^* in the following equation

$$0 = cPE_1 + f(P)E_2 + s\frac{E_2^2}{b + E_2^2} - dE_2 - kPE_2 \tag{4.3.2}$$

yields a different order of polynomial in P based on the values assigned to u and v. This can be rearranged and possibly solved analytically for the positive roots.

If we consider the first scenario, for example, Eq.(4.3.2) becomes

$$0 = cPE_1 + p\frac{P^2}{a + P^2}E_2 + s\frac{E_2^2}{b + E_2^2} - dE_2 - kPE_2.$$

Thus, the positive roots of this polynomial

$$cP\frac{K}{2\alpha}\left(\alpha - cP + \sqrt{(\alpha - cP)^2 + 4e\alpha/K}\right) + p\frac{P^2}{a + P^2}\frac{r}{k} + s\frac{(\frac{r}{k})^2}{b + (\frac{r}{k})^2} - d\frac{r}{k} - rP = 0 \tag{4.3.3}$$

give the possible endemic steady state(s) that we are going to observe. Hence, the positive endemic equilibrium is

$$\left(\bar{P}, \frac{r}{k}\right),$$

where $\bar{P}$ takes the values of the positive roots of (4.3.3).

4.4 Stability analysis of the steady states

To analyze the local stability of the equilibrium points of the Model (4.2.2) we will refer to the Jacobian matrix linearization around the steady state. The Jacobian of the model is

$$J = \begin{bmatrix} r - kE_2 & -kP \\ \Omega & f(P) + 2\frac{sbE_2}{(b+E_2^2)^2} - d - kP \end{bmatrix},$$

where

$$\Omega = \frac{\partial}{\partial P}\left(\frac{dE_2}{dt}\right).$$

Pathogen-free steady state

The Jacobian evaluated at the pathogen-free-equilibrium will be very similar in all scenarios. For the immune system that has never encountered a specific pathogen, we have

Proposition 7. *For all positive parameters, the pathogen-free-equilibrium* $(0,0)$ *is unstable at all times t.*

Proof. We know that the PFE is $(0,\bar{E_1},0)$. The Jacobian around the PFE is

$$J_{(0,\bar{E_1},0)} = \begin{bmatrix} r & 0 & 0 \\ -c\bar{E_1} & \alpha - 2\frac{\alpha\bar{E_1}}{K} & 0 \\ c\bar{E_1} & 0 & -d \end{bmatrix},$$

with $\bar{E_1} = \frac{K}{2\alpha}\left(\alpha + \sqrt{\alpha^2 + 4e\alpha/K}\right)$. The eigenvalues are r, $\alpha - 2\frac{\alpha\bar{E_1}}{K}$ and $-d$.

We have

$$\begin{aligned} \lambda_2 = \alpha - 2\frac{\alpha\bar{E_1}}{K} &= \alpha - 2\frac{\alpha}{K}\frac{K}{2\alpha}\left(\alpha + \sqrt{\alpha^2 + 4e\alpha/K}\right) \\ &= -\sqrt{\alpha^2 + 4e\alpha/K} \\ &< 0. \end{aligned}$$

Since all the parameters are positive,

$$\lambda_1 > 0, \quad \lambda_2 < 0, \quad \lambda_3 < 0.$$

Hence the PFE $\left(0, \frac{K}{2\alpha}\left(\alpha + \sqrt{\alpha^2 + 4e\alpha/K}\right), 0\right)$ is unstable. □

In the case that pathogen has been presented to the immune system and has been cleared out, we have

Proposition 8. *At the pathogen-free-equilibrium* $\left(0, \frac{1}{2d}(s + \sqrt{s^2 - 4bd^2})\right)$*:*

1. *For* $s^2 - 4bd^2 = 0$*, if* $r - \frac{ks}{2d} < 0$*, then the pathogen-free-equilibrium* $\left(0, \frac{s}{2d}\right)$ *is stable otherwise it is saddle.*

2. *For* $s^2 - 4bd^2 > 0$*, if* $r - \frac{ks}{2d} < 0$*, then the pathogen-free-equilibrium* $\left(0, \frac{1}{2d}\left(s + \sqrt{s^2 - 4bd^2}\right)\right)$ *is stable otherwise it is a saddle.*

Endemic steady state stability

Since it is very difficult to get a reasonable expression for the endemic equilibria, here we shall use phase portraits in the $P - E_2$ plane to illustrate the qualitative behavior that may happen depending on the scenario.

To determine stability of the various endemic equilibria and the possible bifurcations that they may undergo, we go back to the original system (4.2.1). As mentioned earlier, we consider the three scenarios of the healthy, moderately immune-compromised, and severely immune-compromised individuals. In each of the three scenarios, we look for Hopf bifurcations of the various pathogen-free equilibrium and the endemic equilibria. As before, we let J^* represent the Jacobian matrix evaluated at the given equilibrium, substitute $\lambda = i\omega$ into the characteristic equation, equate real and imaginary parts to zero, and eliminate ω from the equation. We do not obtain any bifurcation for $\omega > 0$. Thus we can conclude that the system does not undergo any Hopf bifurcations for any choices of parameter values.

However, we do have $\lambda = 0$ bifurcation (transcritical and saddlenode) and we go to the original system to calculate show this.

Healthy immune response

Fix parameter values $k = .135, a = .85, \alpha = 2.95, K = 250, c = .88, e = 4, s = 0.0007, b = 1, p = 1, r = 2.75$ in Model (4.2.1). As we increase d, we can go from having

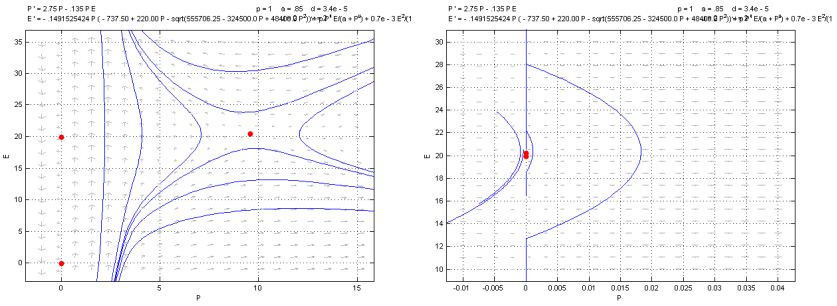
- one endemic equilibrium (E^{1*}) and three pathogen-free equilibria (${E_0}^*$, ${E_1}^*$, ${E_2}^*$); E^{1*} is a saddle and is biologically relevant; ${E_0}^*$ is stable, while both ${E_1}^*$ and ${E_2}^*$ are saddles; another endemic equilibrium (E^{2*}) is not biologically relevant but gets nearer to E_0^*; for the given parameters this situation will hold when $d < 0.0000342810092997205$ (approximately);

- two endemic equilibria (E^{1*}, E^{2*}) with three pathogen-free equilibria (${E_0}^*$, ${E_1}^*$, ${E_2}^*$); pathogen-free equilibria ${E_1}^*$, ${E_2}^*$ do not change stability; E^{1*} also remains unchanged as a biologically relevant saddle; equilbria ${E_0}^*$ and E^{2*} changed stability in transcritical bifurcation with ${E_0}^*$ now unstable and E^{2*} biologically relevant and stable; for the given parameters this situation will hold when $0.0000342810092997205 < d < 0.0003500$ (approximately);

- two endemic equilibria (E^{1*}, E^{2*}) with one pathogen-free equilibria (${E_1}^*$); ${E_0}^*$ and ${E_2}^*$ underwent a saddlenode bifurcation; ${E_1}^*$ is still a saddle; equilbria E^{1*} and E^{2*} do not change stability and remain a saddle and a stable spiral, respectively; for the given parameters this situation will hold when $0.0003500 < d < 9.79200204375484$ (approximately);

- there is only one pathogen-free equilibria (${E_1}^*$) that is a saddle; E^{1*} and E^{2*} underwent a saddlenode bifurcation and no longer exist mathematically; for

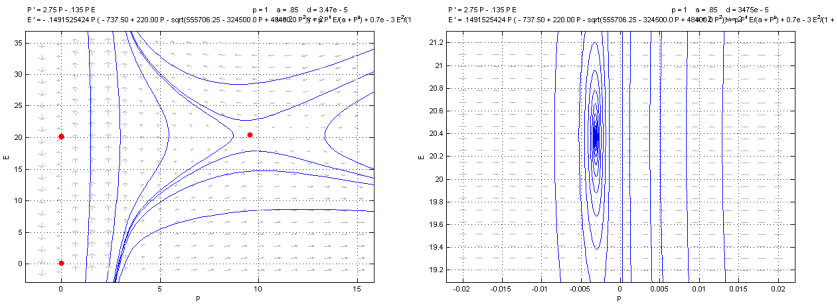
the given parameters this situation will hold when $9.79200204375484 < d$ (approximately);



(a) Three biologically relevant fixed points.

(b) The right picture is a "blow up" of the left.

Figure 4.2: Phase plane portrait for a healthy immune response before it undergoes a transcritical bifurcation. The necessary condition for this picture is $d < 0.0000342810092997205$.



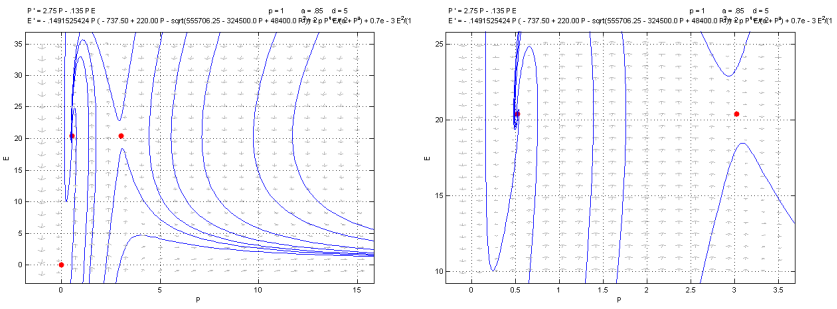
(a)

(b) The right picture is a "blow up" of the left.

Figure 4.3: Phase plane portrait for a healthy immune response after having undergone a transcritical bifurcation. The necessary condition for qualitatively behavior to hold is $0.0000342810092997205 < d < 0.0003500$.

Moderately compromised immune response

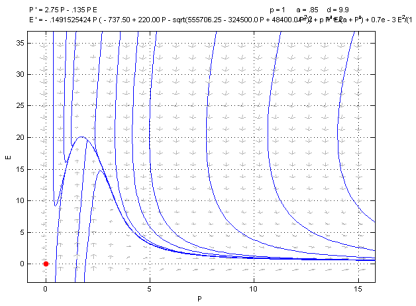
Fix parameter values $k = .135$, $a = .5$, $\alpha = 2.95$, $K = 250$, $c = .88$, $e = 4$, $s = 0.0007$, $b = 1$, $p = .75$, $r = 2.75$ in Model (4.2.1). As we increase d, we can go from having



(a) Three fixed points.

(b) The right picture is a "blow up" of the left.

Figure 4.4: Phase plane portrait for a healthy immune response after having undergone a saddle node bifurcation that destroyed two pathogen-free equilibria. This picture is valid for $0.0003500 < d < 9.79200204375484$.



(a) Only one fixed point exists.

Figure 4.5: Phase plane portrait for a healthy immune response after the endemic equilibria undergo a saddlenode bifurcation, leaving only a pathogen-free equilibria as a saddle. This picture holds for $9.79200204375484 < d$.

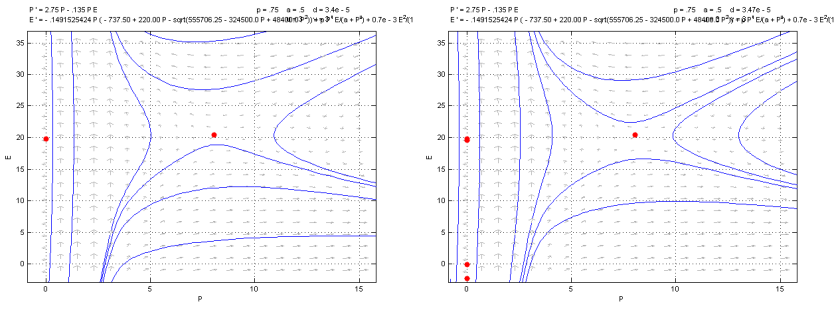
- one endemic equilibrium (E^{1*}) and three pathogen-free equilibria ($E_0{}^*$, $E_1{}^*$, $E_2{}^*$); E^{1*} is a saddle and is biologically relevant; $E_0{}^*$ is stable, while both $E_1{}^*$ and $E_2{}^*$ are saddles; another endemic equilibrium (E^{2*}) is not biologically relevant but gets nearer to $E_0{}^*$; for the given parameters this situation will hold when $d < 0.0000342810219339179$ (approximately);

- two endemic equilibria (E^{1*}, E^{2*}) with three pathogen-free equilibria ($E_0{}^*$, $E_1{}^*$, $E_2{}^*$); pathogen-free equilibria $E_1{}^*$, $E_2{}^*$ do not change stability; E^{1*} also remains unchanged as a biologically relevant saddle; equilbria $E_0{}^*$ and E^{2*}

changed stability in a transcritical bifurcation with ${E_0}^*$ now unstable and E^{2*} biologically relevant and stable; for the given parameters this situation will hold when $0.0000342810219339179 < d < 0.0003500$ (approximately);

- two endemic equilibria (E^{1*}, E^{2*}) with one pathogen-free equilibria $({E_1}^*)$; ${E_0}^*$ and ${E_2}^*$ underwent a saddlenode bifurcation; ${E_1}^*$ is still a saddle; equilbria E^{1*} and E^{2*} do not change stability and remain a saddle and a stable spiral, respectively; for the given parameters this situation will hold when $0.0003500 < d < 9.872106885$ (approximately);

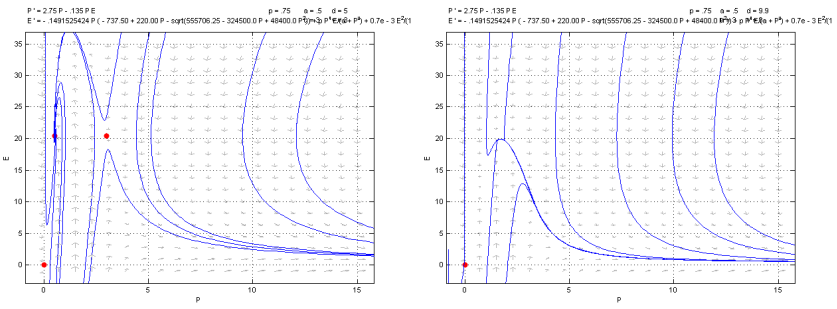
- there is only one pathogen-free equilibria $({E_1}^*)$ that is a saddle; E^{1*} and E^{2*} underwent a saddlenode bifurcation and no longer exist mathematically; for the given parameters this situation will hold when $9.872106885 < d$ (approximately);



(a) On two fixed points.

(b) Three biologically relevant equilibria.

Figure 4.6: Phase plane portrait for a moderately compromised immune response before it undergoes a trancritical bifurcation. This picture holds for $d < 0.0000342810219339179$.



(a) Existence of three equilibria (b) Only one fixed point.

Figure 4.7: Phase plane portrait for a moderately compromised immune response underwent a saddlenode bifurcation of pathogen-free equilibria. This picture is valid for $0.0003500 < d < 9.79200204375484$. The sequence of bifurcations observed in the healthy individual is also observed here and thus only two phase plane pictures are presented.

Severely compromised immune response

Fix parameter values $k = .135, a = 1.2, \alpha = 2.95, K = 250, c = .88, e = 4, s = 0.0007, b = 1, p = 1, r = 2.75$ in Model (4.2.1). As we increase d, we can go from having

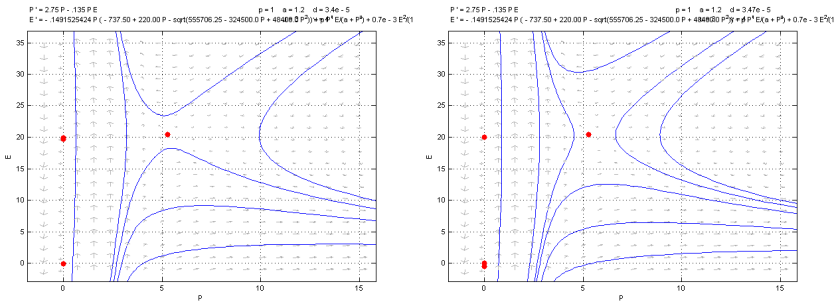
- one endemic equilibrium (E^{1*}) and three pathogen-free equilibria ($E_0{}^*$, $E_1{}^*$, $E_2{}^*$); E^{1*} is a saddle and is biologically relevant; $E_0{}^*$ is stable, while both $E_1{}^*$ and $E_2{}^*$ are saddles; another endemic equilibrium (E^{2*}) is not biologically relevant but gets nearer to $E_0{}^*$; for the given parameters this situation will hold when $d < 0.0000342810219339179$ (approximately);

- two endemic equilibria (E^{1*}, E^{2*}) with three pathogen-free equilibria ($E_0{}^*$, $E_1{}^*$, $E_2{}^*$); pathogen-free equilibria $E_1{}^*$, $E_2{}^*$ do not change stability; E^{1*} also remains unchanged as a biologically relevant saddle; equilbria $E_0{}^*$ and E^{2*} changed stability in a transcritical bifurcation with $E_0{}^*$ now unstable and E^{2*}

biologically relevant and stable; for the given parameters this situation will hold when $0.0000342810219339179 < d < 0.0003500$ (approximately);

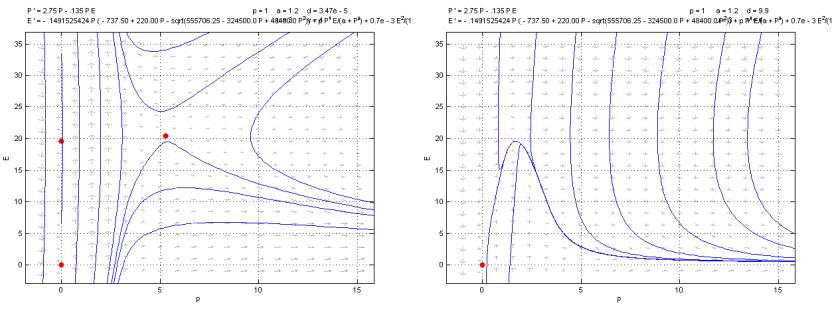
- two endemic equilibria (E^{1*}, E^{2*}) with one pathogen-free equilibria $({E_1}^*)$; ${E_0}^*$ and ${E_2}^*$ underwent a saddlenode bifurcation; ${E_1}^*$ is still a saddle; equilbria E^{1*} and E^{2*} do not change stability and remain a saddle and a stable spiral, respectively; for the given parameters this situation will hold when $0.0003500 < d < 9.8722068853$ (approximately);

- there is only one pathogen-free equilibria $({E_1}^*)$ that is a saddle; E^{1*} and E^{2*} underwent a saddlenode bifurcation and no longer exist mathematically; for the given parameters this situation will hold when $9.8722068853 < d$ (approximately);



(a) (b)

Figure 4.8: Phase plane portrait for a severely compromised immune response before it undergoes a transcritical bifurcation. This picture is valid for $d < 0.0000342810219339179$.



(a) (b)

Figure 4.9: Phase plane portrait for a severely compromised immune response after having undergone a saddlenode bifurcation. This behavior holds for $0.0000342810219339179 < d < 0.0003500$. The sequence of bifurcations observed in the healthy and moderately compromised individuals is also observed here and thus only two phase plane pictures are presented.

4.5 Simulation and comparison of single-pathogen, two-stage effector phenomenological model with Malaria Model (2.1.1) and TB Model (2.2.1)

For the qualitative behavior and the understanding of different processes, we use the following parameter values and the respective values for a and p

Table 4.1: Parameters value for Figures in 4.10 - 4.12.

r	k	e	α	c	s	b	d	K
2.5	0.0075	1	2.95	0.88	0.37	4	0.089	250

- In immune non-compromised (healthy), $f(P) = \frac{P^2}{.85+P^2}$.
- In immune moderately compromised, $f(P) = \frac{.75P^3}{.5+P^3}$.
- In immune severely compromised, $f(P) = \frac{P^3}{1.20+P^4}$.

It has been seen that our model for the competition between the pathogen and the host immune response (antibody) admit a rich variety of solutions depending on the

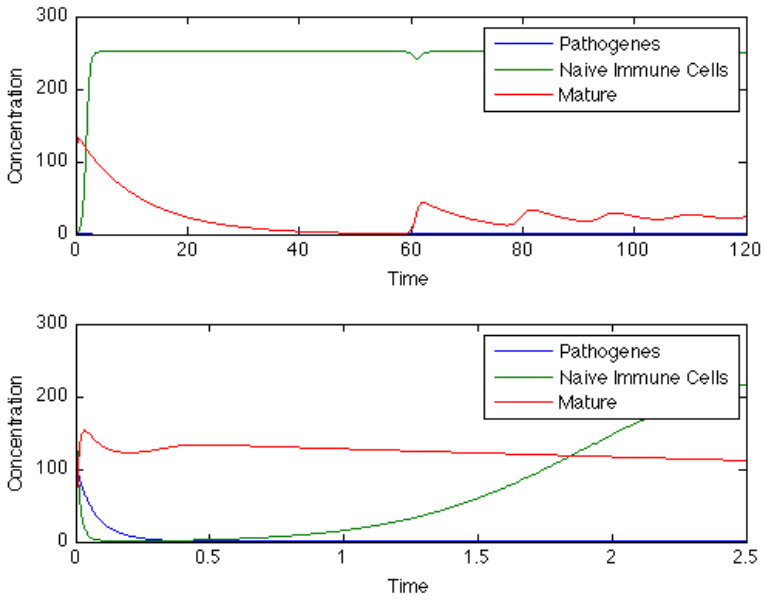


Figure 4.10: Time series of pathogen, naive and mature immunocompetent cells concentration in the host for healthy individual and $IC = (75, 165, 0)$. (a) Transient behavior; (b) Transient dynamics at the beginning of infection.

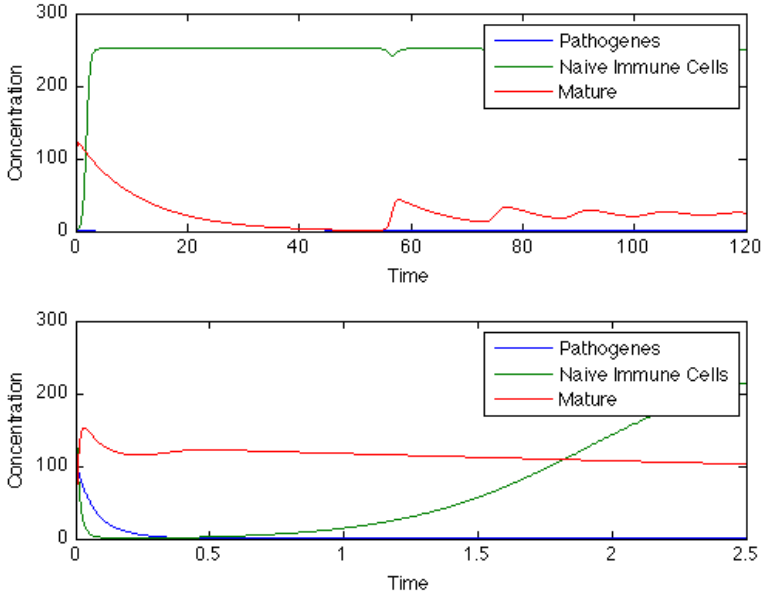


Figure 4.11: Time series of pathogen, naive and mature immunocompetent cells concentration in the host for a moderately immune compromised individual.

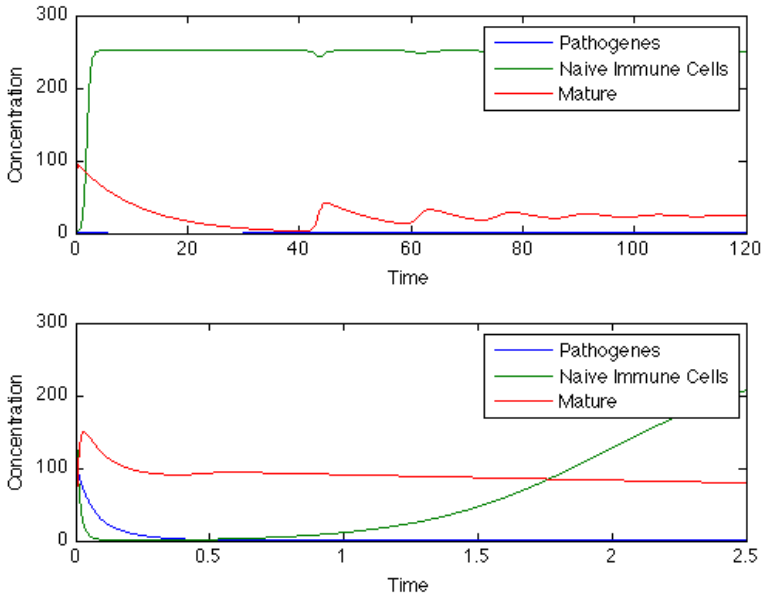


Figure 4.12: Time series of pathogen, naive and mature immunocompetent cells concentration in the host for a severely immune compromised individual.

model parameters. Based on the assumptions, the simulation of the model shows that the pathogens cannot be completely cleared from the host (example of diseases). Also the mature immune cells and memory cells cannot grow without bound within the host.

While we have been able to gain tremendous insight into the behavior of our phenomenological single-pathogen two-stage effector Model (4.2.1) our ultimate goal is to again compare these with the immunology-based Malaria Model (2.1.1) and TB Model (2.2.1).

As seen in Figures 4.13 and 4.14, the slow time scale of the phenomenological models considered in this chapter can display the same qualitative behavior as the Malaria Model (2.1.1) and TB Model (2.2.1) for certain parameter values and initial conditions when considering the pathogen. However, the problem in the previous chapter (with only one-class of effector) is the same that is encountered here when

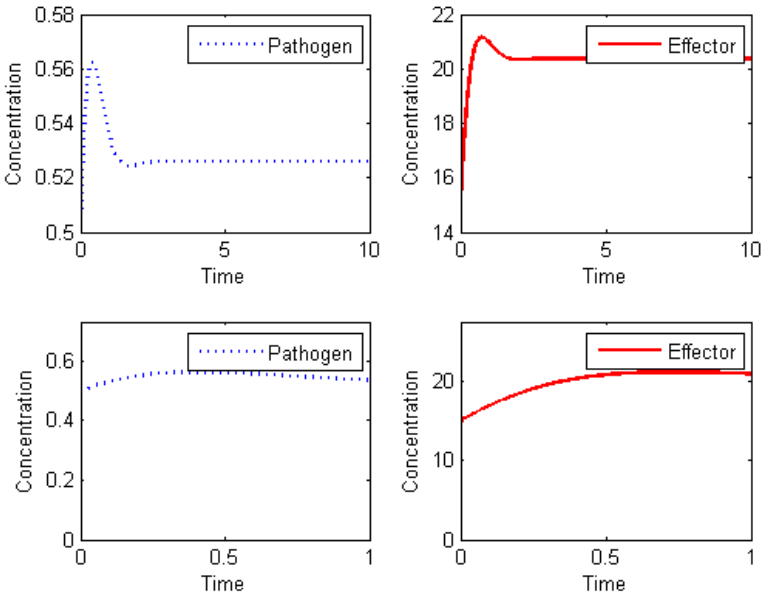


Figure 4.13: Time series of pathogen and activated immunocompetent cells concentration in the host for healthy individual in the slow time scale, Model (4.2.1).

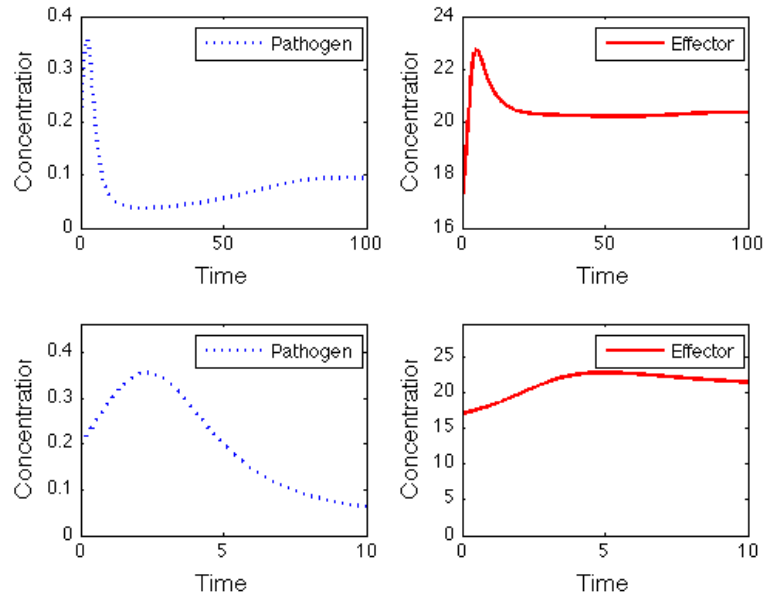


Figure 4.14: Time series of pathogen and activated immunocompetent cells concentration in the host for healthy individual in the slow time scale, Model (4.2.1).

we only consider the slow time scale of the phenomenological models. Thus in order to investigate whether we have better qualitative agreement by considering two stages of effectors, we consider the full 3-dimensional system as we did in the bifurcation analysis (but not in the phase plane pictures).

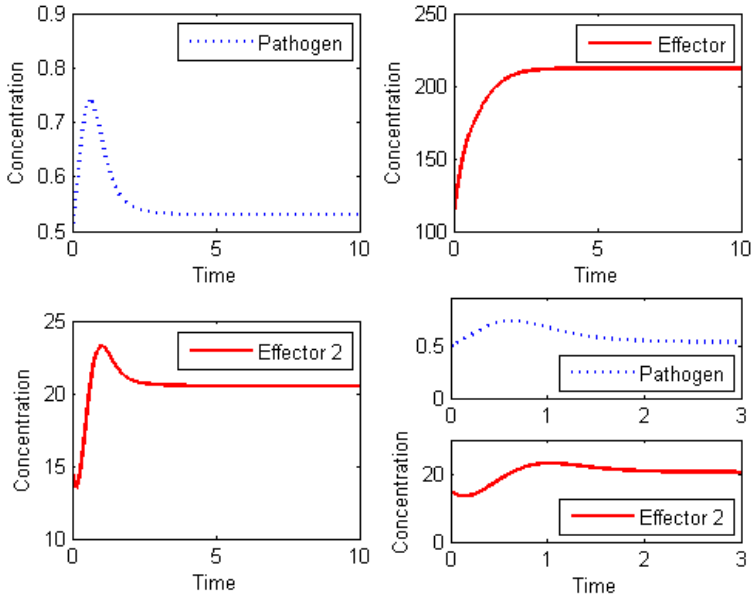


Figure 4.15: Time series of pathogen, inactivated (naive) and activated immunocompetent cells concentration in the host for healthy individual in the 3-dimensional Model (4.2.1). Observe that we now have oscillation of the pathogen and monotonic behavior of one of the effector classes.

In the case of both Malaria and TB immunological model, Figure 4.15 illustrates the same qualitative behavior of a pathogen concentration oscillating as it approaches its non-zero steady-state value while the inactivated (naive) effector class monotonically approaches its non-zero steady-state value; the activated class of effectors is predicted to oscillate as it goes to its non-zero steady-state value. Thus the current two-stage effector phenomenological model, in addition to incorporating some of the important results of the simpler one-stage version, captures another observed feature of the Malaria and TB immunological models. This shows the importance

of including this if we intend to capture as much of the observed realistic behavior as possible.

4.6 Discussion and conclusion

The immune response in the presence of one pathogen has been analyzed with two phenomenological models that had single-stage and two-stage classes of effectors. Among other things, the models also predict the increase in the formation of memory cells. Also from Figure 4.10, 4.11 and 4.12 we can see the decrease in time to response during the second infection with the same pathogen.

As the pathogen load decreases, the maturation and stimulation of the antibody (mature immune competence) will cease and the population of antibodies will decrease to a minimum load of memory cells, near the time of complete antigen inactivation, which will be present within the host as along as he lives. When we keep all the parameters identical except p and a, we have a similar qualitative behavior. Beside the reduction of the region of attraction of the immune effectors there is little observed difference between moderately and severely immune compromised versus healthy.

One thing we have with the two-stage phenomenological model but not with the single-stage version, is the variation in the formation of the memory cells in the host. There is less formation of memory cells in the healthy host compared to the host with compromised immune response. The length of infection by a pathogen can change from finite to infinite, persistent or chronic in an endemic environment. In addition, instead of an infection by a single antigen having a single viral load peak, it can have multiple peaks or can rebound if the host is not isolated. The decrease of the time of infection is not necessarily related to a large immune competence production. Within the scenario of healthy host, we can reach the eradication

of pathogens from the host in a short period of time without the accumulation of a high concentration of specialized immune effectors.

The different steady state solutions of the one-stage and two-stage phenomenological models can describe various immunologist classification of stages of infection by the pathogen: "virgin state," is the stage where the host has never been invaded by a specific target and completely free from infection; "immune state" is the state where the host achieves the control of the pathogens and the formation of memory cells for the future; and "state of tolerance." For the latter of these, we recall that one of the defining features of the immune system is its ability to distinguish self from non-self; that is, it must be capable of mounting a reaction against any foreign antigen (pathogen) but not respond to substances normally present in the organism itself. This essentially describes the phenomenon of natural tolerance.

We see that whether the immune system is compromised or not, when the pathogen and effector levels are located outside of the region of attraction, the recovery of the host from the infection can only be achieved through therapeutic treatment, which allows the immune system to bring the pathogen invasion under control.

As we introduce a new immunological mathematical model with two stages of maturation of the effector cells and the variability of the individual state, we can identify and qualitatively assess the dynamics of the interaction between the immune system and one pathogen, that was not noticeable with the one stage maturation model. Through these phenomenological models, we can highlight the importance of the state of the health of the individuals.

The previous chapters give us some understanding and insight of the immune system response during a single pathogen invasion. In general the immune response as it relates to host-pathogen interaction is always specific and our phenomenological

models allowed us to get away from some of this specificity while still capturing much of the qualitative behavior.

Comparative tables of the two approach of modeling one pathogen interacts with the immune response:

Table 4.2: Healthy immune state, comparison of result from Chapters 3 and 4. E^* is pathogen-free equil.; E_i^* and E_i^{j*} are endemic equil.

Single stage immune response	
	P, E_2
$d < .1925$	E^* stable E_1^* saddle,
$.1925 < d < .19639$	E^* stable E_1^* saddle, E_2^* saddle, E_3^* stable
$.19639 < d < .7514$	E^* saddle E_1^* saddle, E_2^* stable
$.7514 < d$	E^* saddle

Two stage immune response	
	P, E_1, E_2
$d < .000034$	E^{1*} saddle, E_0^* stable, E_1^* saddle, E_2^* saddle
$.000034 < d < .00035$	E^{1*} saddle, E^{2*} stable E_0^* saddle, E_1^* saddle, E_2^* saddle
$.00035 < d < 9.79$	E^{1*} saddle, E^{2*} stable E_1^* saddle
$9.79 < d$	E_1^* saddle

Table 4.3: Moderately compromised immune state, comparison of result from Chapters 3 and 4. E^* is pathogen-free equil.; E_i^* and E^{j*} are endemic equil.

Single stage immune response	
	P, E_2
$d < .1807$	E^* stable E_1^* saddle, E_2^* saddle, E_3^* stable
$.1807 < d < .8307$	E^* saddle E_1^* saddle, E_3^* stable
$.8307 < d$	E^* saddle
Two stage immune response	
	P, E_1, E_2
$d < .000034$	E^{1*} saddle E_0^* stable , E_1^* saddle, E_2^* saddle
$.000034 < d < .00035$	E^{1*} saddle, E^{2*} stable E_0^* saddle, E_1^* saddle, E_2^* saddle
$.00035 < d < 9.8721$	E^{1*} saddle, E^{2*} stable E_1^* saddle
$9.8721 < d$	E_1^* saddle

Table 4.4: Severely compromised immune state, comparison of result from Chapters 3 and 4. E^* is pathogen-free equil.; E_i^{j*} and E^{j*} are endemic equil.

Single stage immune response	
	P, E_2
$d < .1754$	E^{1*} saddle, E^* stable
$.1754 < d < .19639$	E^* stable E_1^* saddle, E_2^* saddle, E_3^* stable
$.19639 < d < .62647$	E^* saddle E_1^* saddle, E_3^* stable
$.62647 < d$	E^* saddle
Two stage immune response	
	P, E_1, E_2
$d < .000034$	E^{1*} saddle E_0^* stable, E_1^* saddle, E_2^* saddle
$.000034 < d < .00035$	E^{1*} saddle, E^{2*} stable E_0^* saddle, E_1^* saddle, E_2^* saddle
$.00035 < d < 9.8722$	E^{1*} saddle, E^{2*} stable E_1^* saddle
$9.8722 < d$	E_1^* saddle

Chapter 5

FULL PHENOMENOLOGICAL MODEL

In Chapters 3 and 4, we analyzed the two subsystems of the phenomenological Model (2.6.4) to help us gain insight into the dynamics of the interaction between pathogen and immune effector. We first considered a single-pathogen one-stage effector model and then a single-pathogen two-stage effector model and compared the qualitative behavior of both with their immunology-based Malaria Model (2.1.1) and TB Model (2.2.1). In this chapter, we focus on the impact of a second disease on the individual with a one-stage effector and two-stage effector phenomenological models that account for co-infection. These qualitative results are then compared to the immunology-based Malaria–TB co-infection Model (2.3.1).

5.1 Within host single stage immunological model with co-infection

Model formulation

In considering a second pathogen, we assume that each pathogen is sufficiently different, as in the Malaria–TB co-infection Model (2.3.1), so that each requires a different metabolic immuno-stimulation strength on the immune competence agents. For simplicity, we consider that both pathogens have the same virulence, which depending of the circumstances can have different interpretation. Casadevall and Pirofski produce a mini review on the basic concept of virulence [20]. But here, by virulence of pathogen, we mean the response of the immune system to the pathogen is the same in each scenario, which will show on the immunostimulation of the pathogen for the pathogen and the half saturation constant. With state variables and parameters defined as in Table 2.5 and the two pathogens having characteristics described above, the two-pathogen one-stage effector model

is given by the following system:

$$\begin{aligned} \frac{dP_1}{dt} &= rP_1 - kP_1E \\ \frac{dP_2}{dt} &= \rho P_2 - \kappa P_2E \\ \frac{dE}{dt} &= e + f(P_1)E + f(P_2)E + g(E) - dE - kP_1E - \kappa P_2E \end{aligned} \tag{5.1.1}$$

In this model, we consider

$$f(P_1) = p\frac{P_1^u}{a_1 + P_1^v};\ f(P_2) = \pi\frac{P_2^u}{a_2 + P_2^v};\ \text{and}\ g(E) = s\frac{E^2}{b + E^2}$$

with $f(P_i),\ i = 1,2$, defined as before:

- Immune non-compromised, $u = v = 2, \Rightarrow f(P_i) = p\frac{P_i^2}{a_i + P_i^2}$;
- Immune moderately compromised, $u = v = 3, \Rightarrow f(P_i) = p\frac{P_i^3}{a_i + P_i^3}$;
- Immune severely compromised, $u = 3$ and $v = 4, \Rightarrow f(P_i) = p\frac{P_i^3}{a_i + P_i^4}$.

For simplicity, we model the immune response under co-infection with the virulence being the same, i.e., where $p = \pi$ and $a_1 = a_2$.

Existence of solutions

Due to the biological meaning of the different variables P_1, P_2 and E in any proposed scenario depending on the values of u and v, we have to restrict the domain to the nonnegative octant $\mathbb{R}^3_+$ where the populations P_1, P_2 and E are all nonnegative. We again state that the domain is called a positively invariant region if any trajectory that starts in the nonnegative octant remains in the same octant forever and it can be shown using standard techniques described in [106; 107] that if initial conditions are specified for each of the states variables at time $t = 0$, then there exists a unique solution satisfying these initial conditions for all time $t \geq 0$.

Lemma 9. *The closed positive octant $\mathbb{R}^3_+$ is positively invariant for the Model (5.1.1).*

Proof. We need to show that the solutions for the Model (5.1.1) are nonnegative given an initial condition $P_1(0) \geq 0$, $P_2(0) \geq 0$ and $E(0) \geq 0$. For $P_1 = 0$ and $P_2 = 0$, we have two invariant planes for the system of equations (5.1.1), we only need to prove that $E(t) \geq 0$, for $t \geq 0$ if the initial conditions are in the positive octant.

Assume there exists $t_1 > 0$ such that $E(t_1) > 0$. Then

$$\frac{dE(t_1)}{dt} = e > 0$$

which implies that $E(t) \geq 0$, for $t \geq t_1$. Therefore, $E(t) \geq 0$ for all $t \geq 0$. □

Local stability and possible bifurcations

When we consider any of the three scenarios of healthy, moderately compromised or severely compromised immune systems, due to the nonlinearity of the system it may not be possible to express the fixed points in closed form. In the absence of targets cells, $P_1 = P_2 = 0$, the System (5.1.1) yields

$$e + s\frac{E^2}{b+E^2} - dE = 0. \tag{5.1.2}$$

Solving Equation (5.1.2) in the domain and obtaining a positive real solution, implies that the disease-free-equilibrium (DFE) exists and is $(0,0,E^*)$ with $E^* > 0$. The stability analysis of the DFE is identical to the single-pathogen models and we refer the reader to Section 3.4.

The Jacobian (J) evaluated at the critical points, $(0,0,E^*)$, for the first scenario simplifies to

$$J = \begin{bmatrix} r - kE^* & 0 & 0 \\ 0 & \rho - \kappa E^* & 0 \\ -kE^* & -\kappa E^* & 2\frac{sbE^*}{\left(b+E^{*2}\right)^2} - d \end{bmatrix}.$$

In the presence of a single target invading the host (i.e., $P_1 = 0$ or $P_2 = 0$), we can refer to Section 3.4 for the dynamics of the steady state. Because of the complexity of the model to the dynamics of the system, we can use also phase space analysis and simulation for the qualitatively different behaviors in each scenario.

Numerical simulations and discussion

The time courses of the targets P_1 and P_2, and the immune effector E are determined as the solutions of the differential equations, which depend on the initial conditions. Because of the high non-linearity of Model (5.1.1), we present some numerical simulations using the parameters values in Table 5.1.

Table 5.1: Parameters values for Figures 5.1 - 5.2.

r	k	ρ	κ	s	b	d	e
2.3	1.5	2.4	1.71	2.5	1	.75	5

Table 5.2: Parameter values associated with immune system state.

Immune system state	u	v	$p = \pi$	$a_1 = a_2$
Healthy	2	2	1	.85
Moderately compromised	3	3	.75	.50
Severely compromised	3	4	1	1.20

For the simulations, we assume that the pathogens invade the host at different time. We are not suggesting that the event of two pathogens invading the immune system at exactly the same time is impossible but we consider the probability of such an event occurring to be negligible.

In each of the three scenarios, we look for Hopf bifurcations of the various pathogen-free equilibrium and the endemic equilibria, and we can conclude that the system does not undergo any Hopf bifurcations for any choices of parameter values.

The other basic type of bifurcation that we can have is a $\lambda = 0$ bifurcation, such as transcritical, saddle node, or pitchfork bifurcations. We go to the original system to calculate the Jacobian and corresponding characteristic equation. As we vary d, we observe $\lambda = 0$ bifurcations for the given scenarios, which are given below.

Healthy immune response

Fix parameter values $k = .135$, $\kappa = .135$, $a = .85$, $\alpha = 2.95$, $K = 250$, $c = .88$, $e = 4$, $s = 0.0007$, $b = 1$, $p = 1$, $r = 2.77$, $\rho = 2.75$ in Model (5.1.1). As we increase d, we can go from having

- two endemic equilibria (E_1^{1*}, E_2^{1*}) and one pathogen-free equilibria (E_0^*); E_1^{1*}, E_2^{1*} are a saddle and are biological relevant; E_0^* is stable; for the given parameters this situation will hold when $d < 0.195$ (approximately)

- four endemic equilibria $(E_1^{1*}, E_1^{2*}, E_2^{1*}, E_2^{2*},)$ with one pathogen-free equilibria (E_0^*); E_0^* now saddle and ${E_1}^1*$, ${E_2}^1*$ remain biologically relevant saddle; equilbria ${E_1}^2*$, E_2^{2*} were born in a saddle node bifurcation with ${E_2}^2*$ a saddle and E_1^{2*} a stable spiral; for the given parameters this situation will hold when $0.195 < d < 0.755$ (approximately);

Moderately compromised immune response

Fix parameter values $k = .135$, $\kappa = .135$, $a = .5$, $\alpha = 2.95$, $K = 250$, $c = .88$, $e = 4$, $s = 0.0007$, $b = 1$, $p = .75$, $r = 2.77$, $\rho = 2.75$ in Model (5.1.1). As we increase d, we can go from having

- two endemic equilibria (E_1^{1*}, E_2^{1*}) and one pathogen-free equilibria (E_0^*); E_1^{1*}, E_2^{1*} are a saddle and are biological relevant; E_0^* is stable; for the given parameters this situation will hold when $d < 0.175$ (approximately)

- four endemic equilibria ($E_1^{1*}, E_1^{2*}, E_1^{3*}, E_2^{1*}$) with one pathogen-free equilibria (E_0^*); E_0^* remains stable and E_2^{1*} a saddle; equilbria ${E_1}^2*, {E_1}^3*$ were born in a saddle node bifurcation with E_1^{2*} a stable spiral and E_1^{3*} a saddle; for the given parameters this situation will hold when $0.175 < d < 0.185$ (approximately);

- six endemic equilibria ($E_1^{1*}, E_1^{2*}, E_1^{3*}, E_2^{1*}, E_2^{2*}, E_2^{3*}$) with one pathogen-free equilibria (E_0^*); E_0^*, E_1^{2*} remain stable and ${E_1}^1*, {E_1}^3*$ remain biologically relevant saddle; equilbria E_2^{2*}, E_2^{3*} were born in a saddle node bifurcation with ${E_2}^2*, {E_2}^3*$ a saddle; for the given parameters this situation will hold when $0.185 < d < 0.195$ (approximately);

- four endemic equilibria ($E_1^{1*}, E_1^{2*}, E_2^{1*}, E_2^{2*}$) with one pathogen-free equilibria (E_0^*); E_1^{3*} and $E_2 3^*$ underwent a transcritical bifurcation and are no longer biologically relevant (but mathematically stable) and E_0^* now a saddle; equilbria E_1^{2*} is still a stable spiral and $E_1^{1*}, E_2^{1*}, E_2^{2*}$ a saddle; for the given parameters this situation will hold when $0.195 < d < 0.645$ (approximately);

- one endemic equilibrium (E_2^{1*}) remains not biologically relevant (but stable) and one pathogen-free equilibria (E_0^*) remains a saddle; E_1^{2*} and E_1^{2*} underwent a saddle node bifurcation and no longer exist mathematically; for the given parameters this situation will hold when $0.645 < d$ (approximately);

Severely compromised immune response

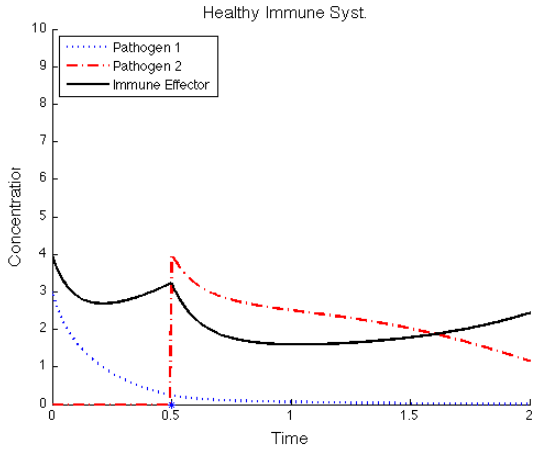
Fix parameter values $k = .135$, $\kappa = .135$, $a = 1.2$, $\alpha = 2.95$, $K = 250$, $c = .88$, $e = 4$, $s = 0.0007$, $b = 1$, $p = 1$, $r = 2.77$, $\rho = 2.75$ in Model (5.1.1). As we increase d, we can go from having

- two endemic equilibria (E_1^{1*}, E_2^{1*}) and one pathogen-free equilibria (E_0^*); E_1^{1*}, E_2^{1*} are a saddle and are biological relevant; E_0^* is stable; for the given parameters this situation will hold when $d < 0.175$ (approximately)

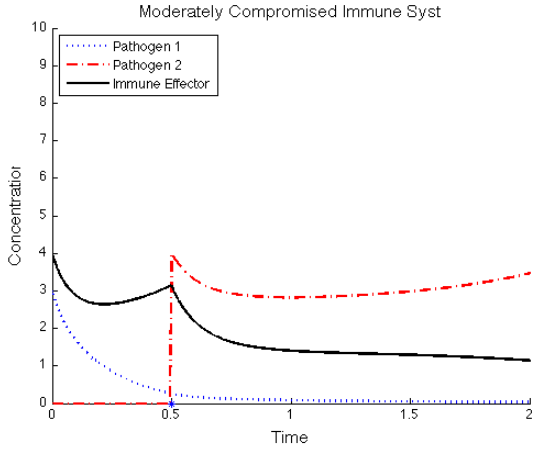
- six endemic equilibria ($E_1^{1*}, E_1^{2*}, E_1^{3*}, E_2^{1*}, E_2^{2*}, E_2^{3*}$) with one pathogen-free equilibria (E_0^*); E_0^* remains stable; equilbria ${E_1}^2*, {E_1}^3*$ were born in a saddle node bifurcation with E_1^{2*} a stable spiral and E_1^{3*} a saddle, and equilbria E_2^{2*}, E_2^{3*} were born in a saddle node bifurcation with ${E_2}^2*, {E_2}^3*$ a saddle; for the given parameters this situation will hold when $0.175 < d < 0.185$ (approximately);

- four endemic equilibria ($E_1^{1*}, E_1^{2*}, E_2^{1*}, E_2^{2*}$) with one pathogen-free equilibria (E_0^*); E_0^* is now saddle with $E_1^{1*}, E_2^{1*}, E_2^{2*}$ and E_1^{2*} remains stable spiral; equilbria ${E_1}^3*, {E_2}^3*$ underwent a transcritical bifurcation and are no longer biological relevant; for the given parameters this situation will hold when $0.185 < d < 0.565$ (approximately);

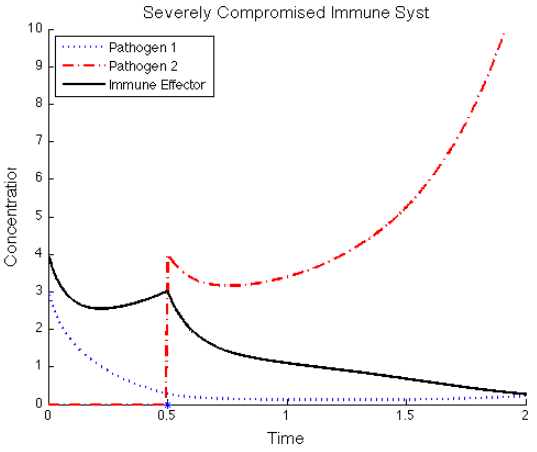
- one endemic equilibrium (E_1^{2*}) remains not biologically relevant (but stable) and one pathogen-free equilibria $(E)^*$) remains a saddle; E_1^{1*}, E_2^{1*} and E_2^{2*} underwent a saddlenode bifurcation and no longer exist mathematically; for the given parameters this situation will hold when $0.565 < d$ (approximately);



(a)

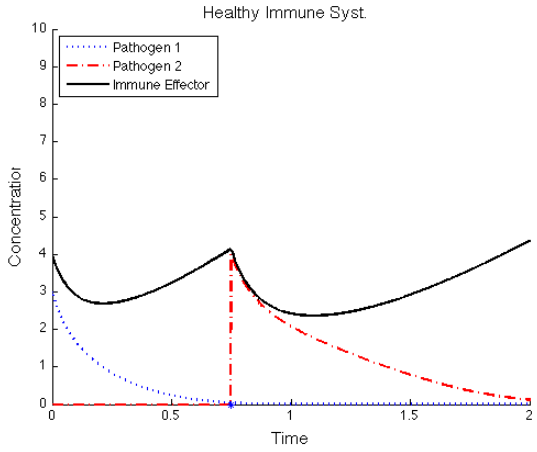


(b)

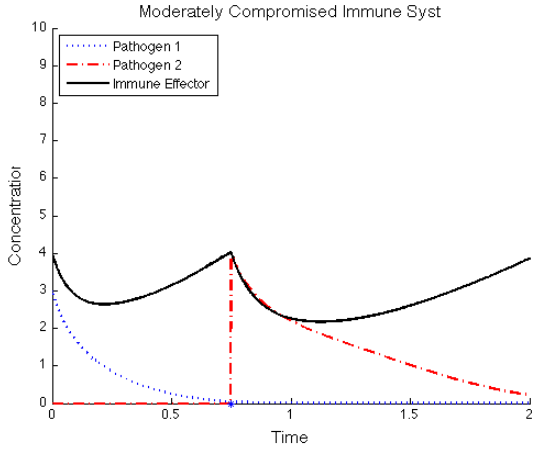


(c)

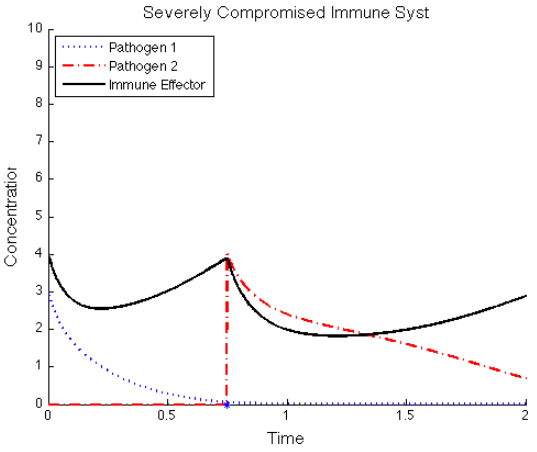
Figure 5.1: Time series of different agents for the same set of initial conditions. (a) healthy immune system, (b) moderately immune compromised and (c) severely immune compromised. Only the healthy immune system succeeded in controlling both pathogens.



(a)



(b)



(c)

Figure 5.2: Time series of different agents for the same set of initial conditions but a later invasion time of pathogen 2 when compared to Figure 5.1. (a) healthy immune system, (b) moderately immune compromised and (c) severely immune compromised. In all three scenarios, both pathogens are kept under control.

Discussion of numerical results for two-pathogen one-stage effector phenomenological model

We observed the following different qualitative behaviors in our model:

- parameter values and initial conditions exist so that a healthy individual immune system can keep both pathogens under control if the second pathogen is introduced at time $t > t_{crit}$ but will succumb to the second pathogen if it is introduced at time $t < t_{crit}$; this also holds for both moderately and severely compromised immune systems; see Figures 5.1 - 5.2 for examples with moderately and severely compromised individuals;

- parameter values and initial conditions exist so that a healthy individual immune system can keep both pathogens under control but the moderately compromised and severely compromised individuals cannot keep the second pathogen under control; see Figure 5.1;

- parameter values and initial conditions exist so that both healthy individual and moderately compromised immune systems can keep both pathogens under control but the severely compromised individuals cannot keep the second pathogen under control

The time it takes to clear both pathogens is very different in the scenario of the severely immune compromised system compared to the moderately compromised and healthy immune systems, where under the same conditions (same parameters values and initial conditions) it takes approximately the same duration to clear the host of both pathogens for the latter two; see Figure 5.2. In the scenario where the immune system is severely compromised, the time the second pathogen invades the

host compared to the first pathogen invasion dramatically affects the dynamics of the immune response under the same assumption.

It is important to note that the same pathogen, (under certain conditions), can be deadly if it invades the host at an earlier stage, this situation can also occur when there exist some environment factors that can affect the immune system such as malnutrition or lack of hygiene, especially in an endemic region. The severely compromised immune system response is not always deadly for the host. The host can still clear both pathogens if the second pathogen invasion occurs after a certain time $t + \tau$ with t the time of the initial invasion by any first pathogen. There may exist some factors that, to be realistic, will change the outcome of the immune system such as the specificity of immune cells (T cells, B cells, NK cells, etc.) and also their stages of differentiation and maturation, knowing that all rise from the stem cells. However, our two-pathogen one-stage phenomenological model suggests that the health of the individual and the time of invasion of the second pathogen may play large roles in determining the long term behavior of the two pathogens within their host. This is significant as we were not able to observe this behavior in the Malaria–TB co-infection Model (2.3.1) but this may very well be due to our inability to correctly be in the appropriate parameter regimes (expected, given that we have 33 parameters), even though many of the parameters had realistic ranges based on the literature. As with the single-pathogen models, we also performed a numerical table of bifurcations based on varying d and we present this after discussion of the full phenomenological model.

5.2 Phenomenological model (2.6.4): Co-invasion of pathogens with two-stage effectors

Model

We are finally ready to consider the two-pathogen two-stage effector phenomenological model that provides us with a caricature of the Malaria–TB co-infection Model (2.3.1). We use our knowledge of its subsystems in order to complete our analysis. Thus we consider Model (2.6.4):

$$\begin{aligned}
\frac{dP_1}{dt} &= rP_1 - kP_1E_2 \\
\frac{dP_2}{dt} &= \rho P_2 - \kappa P_2E_2 \\
\frac{dE_1}{dt} &= e + \alpha E_1\left(1 - \frac{E_1}{K}\right) - (c_1P_1 + c_2P_2)E_1 \\
\frac{dE_2}{dt} &= (c_1P_1 + c_2P_2)E_1 + (f(P_1) + f(P_2))E_2 + g(E_2) - (kP_1 + \kappa P_2)E_2 - dE_2,
\end{aligned}$$

with $f(P_i)$ defined previously in Section 5.1 and state variables and parameters again given in Table 2.5.

Analysis of the model

The domain $\mathscr{D}$ is valid epidemiologically because the populations P_1, P_2, E_1 and E_2 are all nonnegative. We denote points in $\mathscr{D}$ by $x = (P_1, P_2, E_1, E_2)$. The nonnegative orthant $\mathbb{R}^4_+ = \{x \in \mathbb{R}^4 | x \geq 0\}$ is called a positively invariant region. With an initial condition $X(0), Y(0), F(0),$ and $T(0) \geq 0$ we can show that the first orthant is positively invariant.

Lemma 10. *The closed positive orthant is positively invariant for the Model (2.6.4).*

The proof is fairly easy and similar to one in the previous chapters.

In the same line of development compared to the previous sections and chapters, we will consider the three scenarios of the immune system response: healthy, mod-

erately compromised and severely compromised immune systems.Parallel to the previous chapter, for the steady state analyses of the disease-free and one pathogen equilibrium for each of the scenarios we refer to Sections 4.3 - 4.4. For the dynamics of two pathogens within the host, we provide a numerical simulation and bifurcation analysis (varying d) to understand the qualitative behavior.

Numerical simulations and conclusions

Let us recall that the active immune effector is composed of the memory cell resulting from the immune response to both pathogens. The three types of immune systems considered are as before; see Table B.3. The parameter values used in the simulation are given in Table 5.3, with the initial conditions the same in Figures 5.3 - 5.5.

Table 5.3: Parameter values for Figures 5.3 - 5.5

r	k	ρ	κ	e	α	K	c_1	c_2	s	b
2.77	0.75	2.75	1.45	1	2.95	250	1.88	2.68	.0007	1

To determine stability of the various endemic equilibria and the possible bifurcations that they may undergo, we go back to the original system (2.6.4). As mentioned earlier, we consider the three scenarios of the healthy, moderately immune-compromised, and severely immune-compromised individuals. In each of the three scenarios, we look for Hopf bifurcations of the various pathogen-free equilibrium and the endemic equilibria. As before, we can conclude that the system does not undergo any Hopf bifurcations for any choices of parameter values.

However, we do have $\lambda = 0$ bifurcation (transcritical and saddlenode) and we go to the original system to calculate show this.

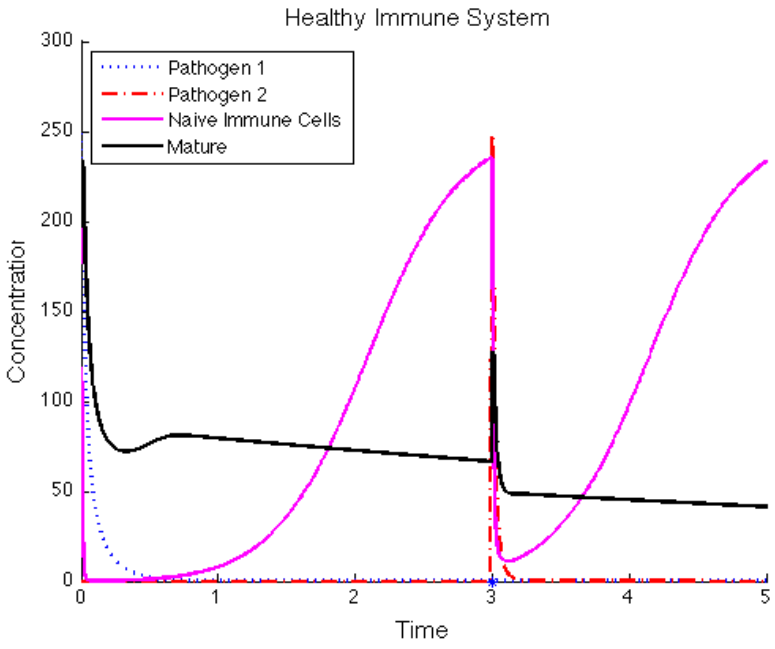


Figure 5.3: The time series plot of pathogens and immune effectors concentration in a co-infection environment for a healthy immune system. Both pathogens are kept under control.

Healthy immune response

Fix parameter values $k = .135$, $\kappa = .135$, $a = .85$, $\alpha = 2.95$, $K = 250$, $c_1 = .88$, $c_2 = .88$, $e = 4$, $s = 0.0007$, $b = 1$, $p = 1$, $r = 2.77$, $\rho = 2.75$ in Model (2.6.4). As we increase d, we can go from having

- four endemic equilibria (E_1^{1*}, E_1^{2*}, E_2^{1*}, E_2^{2*}) with one pathogen-free equilibria (E_0^*); E_0^* is saddle and E_1^{1*} a stable; equilbria E_1^{2*}, E_2^{1*} and E_2^{2*} a saddle; for the given parameters this situation will hold when $d < 9.725$ (approximately);

- two endemic equilibria (E_2^{1*}, E_2^{2*}) with one pathogen-free equilibria (E_0^*); E_0^* is saddle; equilbria E_2^{1*} and E_2^{2*} remain a saddle and E_1^{1*}, E_1^{2*} changed stabil-

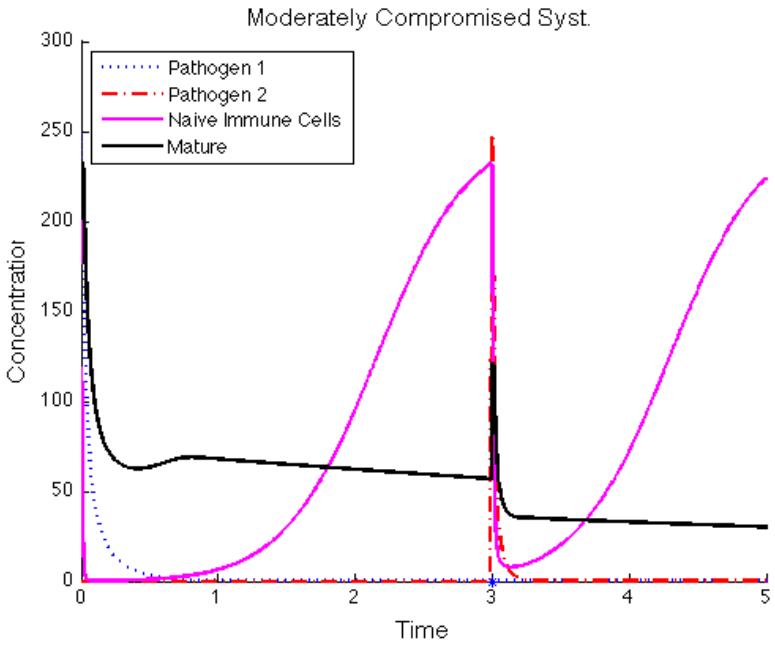


Figure 5.4: The time series plot of pathogens and immune effectors concentration in a co-infection environment of a moderately compromised system. As with Figure 5.3, both pathogens are kept under control although the level of mature (activated) effectors is lower when the second pathogen is introduced (compared with the healthy system).

ity in transcritical but no longer biological relevant; for the given parameters this situation will hold when $9.725 < d < 9.795$ (approximately);

- there is only one pathogen-free equilibria ($E_0{}^*$) that is a saddle; E_2^{1*} and E_2^{2*} underwent a saddlenode bifurcation and no longer exist mathematically; for the given parameters this situation will hold when $9.795 < d$ (approximately);

Moderately compromised immune response

Fix parameter values $k = .135$, $\kappa = .135$, $a = .5$, $\alpha = 2.95$, $K = 250$, $c_1 = .88$, $c_2 = .88$, $e = 4$, $s = 0.0007$, $b = 1$, $p = .75$, $r = 2.77$, $\rho = 2.75$ in Model (2.6.4). As we increase d, we can go from having

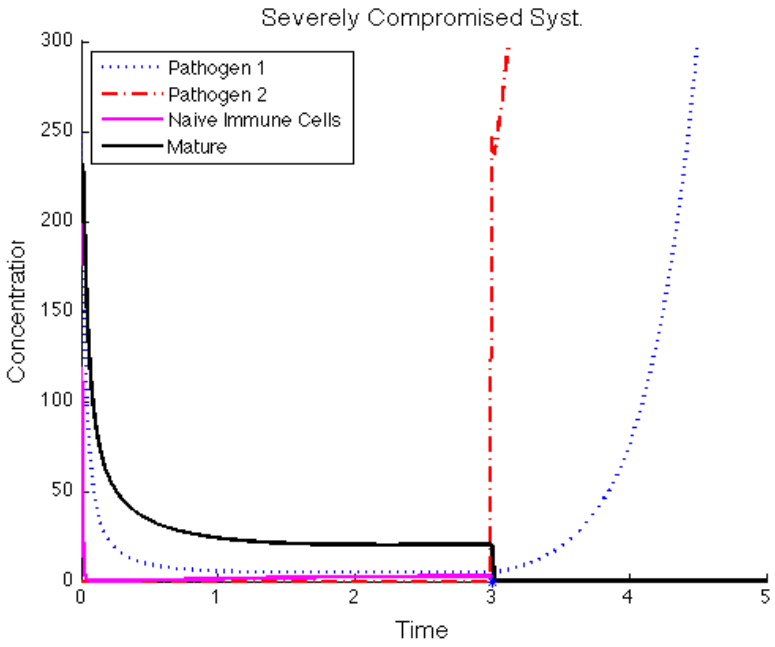


Figure 5.5: The time series plot of pathogens and immune effectors concentration in a co-infection environment of a severely compromised system. As the pathogen 2 invades, the immune response decreases considerably and both pathogens take over the host; at the time of the invasion by the second pathogen, the mature (activated) effector population is lower than in the healthy or moderately compromised systems.

- four endemic equilibria (E_1^{1*}, E_1^{2*}, E_2^{1*}, E_2^{2*}) with one pathogen-free equilibria (E_0^*); E_0^* is saddle and E_1^{1*} a stable; equilbria E_1^{2*}, E_2^{1*} and E_2^{2*} a saddle; for the given parameters this situation will hold when $d < 9.635$ (approximately);

- two endemic equilibria (E_2^{1*}, E_2^{2*}) with one pathogen-free equilibria (E_0^*); E_0^* is saddle; equilbria E_2^{1*} and E_2^{2*} remain a saddle and E_1^{1*}, E_1^{2*} changed stability in transcritical but no longer biological relevant; for the given parameters this situation will hold when $9.635 < d < 9.695$ (approximately);

- there is only one pathogen-free equilibria ($E_0{}^*$) that is a saddle; E_2^{1*} and E_2^{2*} underwent a saddlenode bifurcation and no longer exist mathematically; for the given parameters this situation will hold when $9.695 < d$ (approximately);

Severely compromised immune response

Fix parameter values $k = .135$, $\kappa = .135$, $a = 1.2$, $\alpha = 2.95$, $K = 250$, $c_1 = .88$, $c_2 = .88$, $e = 4$, $s = 0.0007$, $b = 1$, $p = 1$, $r = 2.77$, $\rho = 2.75$ in Model (2.6.4). As we increase d, we can go from having

- four endemic equilibria (E_1^{1*}, E_1^{2*}, E_2^{1*}, E_2^{2*}) with one pathogen-free equilibria (E_0^*); E_0^* is saddle and E_1^{1*} a stable; equilbria E_1^{2*}, E_2^{1*} and E_2^{2*} a saddle; for the given parameters this situation will hold when $d < 9.465$ (approximately);

- two endemic equilibria (E_2^{1*}, E_2^{2*}) with one pathogen-free equilibria (E_0^*); E_0^* is saddle; equilbria E_2^{1*} and E_2^{2*} remain a saddle and E_1^{1*}, E_1^{2*} changed stability in transcritical but no longer biological relevant; for the given parameters this situation will hold when $9.465 < d < 9.535$ (approximately);

- there is only one pathogen-free equilibria ($E_0{}^*$) that is a saddle; E_2^{1*} and E_2^{2*} underwent a saddlenode bifurcation and no longer exist mathematically; for the given parameters this situation will hold when $9.535 < d$ (approximately);

Conclusion

In comparing Figures 5.1 - 5.2 (two-pathogen, one-stage effector) and Figures 5.3 - 5.5 (two-pathogen, two-stage effector) with their immunology-based counterpart in Figures 2.8 - 2.13, we see some key similarities in qualitative results: we can choose parameter values and initial conditions of the Malaria–TB Model (2.3.1) that

- gives monotone behavior of the effector class and one pathogen while it gives oscillatory behavior in the other pathogen; this can be mimicked in the phenomenological model only when considering the full two-stage model;

- gives monotone behavior of the effector class while it gives oscillatory behavior in both pathogens; this can be mimicked in the phenomenological model when considering the full two-stage model or the simpler one-stage effector model;

- causes a significant decrease in the effector population when the Malaria pathogen is introduced although the body is able to ultimately keep both pathogens under control; this is mimicked in both one-stage and two-stage phenomenological model for appropriate choices of parameters and initial conditions; for the Malaria Model (2.1.1) and TB Model (2.2.1) with parameters as presented in Chapter 2, this would be the "expected" result

One of the significant predictions of the two-pathogen phenomenological models (both one-stage and two-stage effector) is that we can find parameters and initial conditions in each of the respective immune systems in which the introduction of the second pathogen causes one or both pathogens to overrun the body. Numerical "guessing" of parameters and initial conditions failed to give a comparable outcome in the Malaria–TB Model (2.3.1) and it seems that the reason was the current TB parameters don't cause a decrease in the effector population.

The models described here provide a rigorous means of thinking about and describing the immune system response and its interaction with different pathogens. The state of the immune system (compromised or healthy) of the host before the invasion of the pathogen(s), is very critical in defining what approach to adopt or implement to keep the infection (single or co-infection) under control mostly in endemic regions where the prevalence may be high. Even though there are likely more

types of dynamic behavior occurring in other domains of the parameters, we have only considered a small domain of parameters to stay consistent with the relative individual immune system, meaning each host is different and responds differently in each environment. To be able to test these models we will have to be specific (i.e., depict a single disease and identify the immune cells that interact the most with this pathogen).

Looking critically at the contents of the above chapters, we can identify various improvements that can be addressed. In relation to chapters 3 and 4 the following aspects are worth examining and analyzing in more detail:

- differentiate more immune system states or levels to categorize the variation from healthy system to a severely compromised one.
- introduce a realistic time delay between the introduction of the infection and the different reactions occurring through the interaction of the pathogen - host immune system.
- consider specific memory cells in identifying the targeted area of the immune system.
- identify more realistic experiments which can provide quantitative measurement that are directly relevant to a specific infection of pathogen and the immune dynamic within a given host.

With a very simplistic phenomenological co-infection models caricature based on the nonlinear mathematical models of Malaria, TB, and their co-infection, we observe the same findings as in the single pathogen models. Also, we can highlight the importance of the host state and the critical time of invasion of the second pathogen in accessing the qualitative behavior of the immune system throughout the infections.

With the advances in science, technology and computing, more immunological data have become available and we face the challenge to integrate this knowledge with the epidemiology and the evolutionary disease models that we know so far. The biggest challenge may be knowing how to incorporate the vast amounts of data at hand, which consists of transferring all the above ideas into an effective, realistic and not too complex mathematical model with properly identified parameters to truly appreciate the reality and the wonder of the immune system.

Comparative tables of the two approach of modeling the co-infection and the immune response:

Table 5.4: Healthy immune state. Comparison of results from Sections 5.1 and 5.2. E_0^* is pathogen-free equil.; E_i^{j*} is endemic equil.

Single stage immune response.	
	P_1, P_2, E_2
$d < .195$	E_0^* stable E_1^{1*} saddle E_2^{1*} saddle
$.195 < d < .755$	E_0^* saddle E_1^{1*} saddle, E_1^{2*} stable E_2^{1*} saddle, E_2^{2*} stable
$.755 < d$	E_0^* saddle
Two stage immune response	
	P_1, P_2, E_1, E_2
$d < 9.725$	E_0^* saddle E_1^{1*} stable, E_1^{2*} saddle E_2^{1*} saddle, E_2^{2*} saddle
$9.725 < d < 9.795$	E_0^* saddle E_2^{1*} saddle, E_2^{2*} saddle
$9.795 < d$	E_0^* saddle

Table 5.5: Moderately compromised immune state. Comparison of results from Sections 5.1 and 5.2. E_0^* is pathogen-free equil.; E_i^{j*} is endemic equil.

Single stage immune response.	
	P_1, P_2, E_2
$d < .175$	E_0^* stable E_1^{1*} saddle E_2^{1*} saddle,
$.175 < d < .185$	E_0^* stable E_1^{1*} saddle, E_1^{2*} stable, E_1^{3*} saddle E_2^{1*} saddle,
$.185 < d < .195$	E_0^* stable E_1^{1*} saddle, E_1^{2*} stable, E_1^{3*} saddle E_2^{1*} saddle, E_2^{2*} saddle, E_2^{3*} saddle
$.195 < d < .645$	E_0^* saddle E_1^{1*} saddle, E_1^{2*} stable, E_2^{1*} saddle, E_2^{2*} saddle,
$.645 < d$	E^* saddle

Two stage immune response	
	P_1, P_2, E_1, E_2
$d < 9.635$	E_0^* saddle E_1^{1*} stable, E_1^{2*} saddle E_2^{1*} saddle, E_2^{2*} saddle
$9.635 < d < 9.695$	E_0^* saddle E_2^{1*} saddle, E_2^{2*} saddle
$9.695 < d$	E_0^* saddle

Table 5.6: Severely compromised immune state. Comparison of results from Sections 5.1 and 5.2. E_0^* is pathogen-free equil.; E_i^{j*} is endemic equil.

Single stage immune response.	
	P_1, P_2, E_2
$d < .175$	E_0^* stable E_1^{1*} saddle E_2^{1*} saddle,
$.175 < d < .185$	E_0^* stable E_1^{1*} saddle, E_1^{2*} stable , E_1^{3*} saddle E_2^{1*} saddle, E_2^{2*} saddle, E_2^{3*} saddle
$.185 < d < .565$	E_0^* saddle E_1^{1*} saddle, E_1^{2*} stable E_2^{1*} saddle, E_2^{2*} saddle
$.565 < d$	E_0^* saddle

Two stage immune response	
	P_1, P_2, E_1, E_2
$d < 9.465$	E_0^* saddle E_1^{1*} saddle, E_1^{2*} stable E_2^{1*} saddle, E_2^{2*} saddle
$9.645 < d < 9.535$	E_0^* saddle E_2^{1*} saddle, E_2^{2*} saddle
$9.535 < d$	E_0^* saddle

Chapter 6

IMMUNO - EPIDEMIOLOGY

6.1 Bridge between immunology and epidemiology

Introduction and preliminaries

An integro-differential (difference) equation is an equation which involves both integrals (sum) and the derivatives of the functions. As is typical with differential equations, obtaining a closed form solution can be difficult. Nevertheless, in some situations integro-differential equations can be solved using the Laplace transform for integrals and derivatives.

Integro-differential equations can be used to model many situations in science and engineering. For example, one can encounter a particularly rich source in electric-circuit analysis. Integro-differential (difference) equations are widely used in mathematical biology, especially theoretical ecology, to model the dispersal and growth of populations. The following intgro-differential equations are given, investigated and analyzed thoroughly among others, by MacDonald with the model for the parasite population growth (MacDonald, 1978); Volterra for predator-prey models (Volterra, 1928), Kendal (1957,1965) and Mollison (1972); Medlock & Kot (2003); Allen & Ernest (2002) with an integro-difference equation.

Reducible systems - Linear chain trick

Frague [44] observed that the integro-differential equation

$$\dot{x} = H(x,t) + \int_{-\infty}^{t} K(t-\tau)F(x(\tau))d\tau$$

with initial condition $x(t) = \phi(t),\ -\infty < t < 0$, is equivalent to a differential equation system with initial condition if and only if the kernel K (that satisfies a differential equation with constant coefficients) is a linear combination of functions

$$e^{at}, te^{at}, \ldots, t^m e^{at},\ \ a \in \mathbb{C}$$

where K is a non-negative, continuous function.

In the following, we assume that every kernel K is a normalized convex combination of functions $K_m(t)$ with

$$K_m(t) = \frac{a^m}{(m-1)!} t^{m-1} e^{-at}, \qquad m \in \mathbb{N},\ a \in \mathbb{C}.$$

The first derivative of K_m is given by

$$\frac{d}{dt} K_m(t) = a\big(K_{m-1}(t) - K_m(t)\big), \quad \text{with } F_0(t) = 0.$$

Alternatively, we can introduce new variables x_m as

$$\begin{aligned} x_0(t) &= x(t), && (6.1.1)\\ x_m(t) &= \int_{-\infty}^{t} K_m(t-\tau) x(\tau) d\tau, \qquad m \in \mathbb{N}. && (6.1.2) \end{aligned}$$

Differentiating Equation (6.1.2) under the integral sign, it follows for the integro-differential equation that these new variables satisfy

$$\begin{aligned} \dot{x}_0(t) &= H(x,t) - x_m(t), && (6.1.3)\\ \dot{x}_m(t) &= a\big(x_{m-1}(t) - x_m(t)\big), \qquad m \in \mathbb{N}, && (6.1.4) \end{aligned}$$

since we have

$$K_m(0) = 0; \qquad K_1(0) = a; \qquad K_m(\infty) = 0.$$

Hypothesis

We consider our previously analyzed two-pathogen one-stage effector phenomenological model as a caricature of the immunology-based co-infection model at the individual level:

$$\begin{aligned} \frac{dP_1}{dt} &= rP_1 - kP_1E,\\ \frac{dP_2}{dt} &= \rho P_2 - \kappa P_2 E, && (6.1.5)\\ \frac{dE}{dt} &= e + f(P_1)E + f(P_2)E + g(E) - dE - (kP_1 + \kappa P_2)E. \end{aligned}$$

If one takes the equation of E, we rewrite it and approximate the increase of the immune competence by stimulation (activation), $f(P_1)E$ and $f(P_2)E$, by a function of $I_j,\ j=1,2$, where I is traditional epidemiological state variable describing the population of the infectious individual. In other words we say that

$$f(P_1)E+f(P_2)E=\vartheta(I_1,I_2,E,t)$$

where $\vartheta(I_1,I_2,E,t)$ can be some simple kernel function, for example,

$$\vartheta(I_1,I_2,E,t)=\theta E\int_{-\infty}^{t}(I_1+I_2)(\tau)e^{-\sigma(t-\tau)}\,d\tau.$$

In the population, the presence of an infectious disease results from the presence of at least one infected individual or infected vector from whom the pathogens can spread. Thus $I_j, j=1,2$, represents the population of the infected class that will spread the pathogens and $\vartheta(I_1,I_2,E,t)$ represents the stimulation of the immune effector agents due to the presence of pathogens through the infectious class of host or vector. Thus we can write

$$\begin{aligned}\frac{dE}{dt} &= e+f(P_1)E+f(P_2)E+g(E)-dE-(kP_1+\kappa P_2)E\\ &= e+\theta E\int_{-\infty}^{t}(I_1+I_2)(\tau)e^{-\sigma(t-\tau)}\,d\tau+g(E)-dE-(kP_1+\kappa P_2)E,\end{aligned}$$

where θ, σ are arbitrary. This will allow us to explicitly incorporate immune competence into our problem.

Let us assume that this is possible, so we can have

$$\frac{dE}{dt}=e+\theta E\int_{-\infty}^{t}(I_1+I_2)(\tau)e^{-\sigma(t-\tau)}\,d\tau+s\frac{E^2}{b+E^2}-dE-(kP_1+\kappa P_2)E. \quad (6.1.6)$$

In Equation (6.1.6), the immune competence activation is approximated, using an integro-differential equation, by

$$H(t)=\theta E\int_{-\infty}^{t}(I_1+I_2)(\tau)e^{-\sigma(t-\tau)}\,d\tau. \quad (6.1.7)$$

Here we can use the linear chain method for the nonlinear integro-differential introduced in the previous Section 6.1, to write the system of ordinary differential equations

$$\begin{aligned}
\frac{d}{dt}E &= e+H(t)+g(E)-dE-(kP_1+\kappa P_2)E, && (6.1.8)\\
\frac{d}{dt}H &= \theta\sigma E\left((I_1+I_2)(t)-\int_{-\infty}^{t}(I_1+I_2)(\tau)e^{-\sigma(t-\tau)}\,d\tau\right). && (6.1.9)
\end{aligned}$$

This system is equivalent to

$$\begin{aligned}
\frac{d}{dt}E &= e+H(t)+g(E)-dE-(kP_1+\kappa P_2)E, && (6.1.10)\\
\frac{d}{dt}H &= \sigma\left(\theta E\left[(I_1+I_2)(t)-\int_{-\infty}^{t}(I_1+I_2)(\tau)e^{-\sigma(t-\tau)}\,d\tau\right]\right), && (6.1.11)
\end{aligned}$$

which can be simplified to

$$\begin{aligned}
\frac{d}{dt}E &= e+H(t)+g(E)-dE-(kP_1+\kappa P_2)E, && (6.1.12)\\
\frac{d}{dt}H &= \theta\sigma E\big((I_1+I_2)(t)\big)-\sigma H.
\end{aligned}$$

Incorporating these last Equations (6.1.12) into our two-pathogen one-stage effector phenomenological model gives a model that encompasses both the immunological and epidemiological effects on the individual:

$$\begin{aligned}
\frac{dP_1}{dt} &= rP_1-kP_1E,\\
\frac{dP_2}{dt} &= \rho P_2-\kappa P_2E, && (6.1.13)\\
\frac{dE}{dt} &= e+H(t)+g(E)-dE+g(E)-dE-(kP_1+\kappa P_2)E,\\
\frac{dH}{dt} &= \theta\sigma E\big((I_1+I_2)(t)\big)-\sigma H.
\end{aligned}$$

In the remainder of this chapter we propose various immuno-epidemiology models that incorporate this new approach into a traditional epidemiological model.

6.2 Immuno-epidemiology example 1 - Malaria

Introduction

Many models have been developed to explore the dynamic of Malaria within the population [28; 30; 37; 70; 85]. We now consider an extension of the Malaria model that now explicitly includes the population of humans in relation to Malaria. We briefly derive the mathematical model of Malaria which incorporates compartments for the mosquitos and human population. We introduce a Malaria model that crosses epidemiology and immunology. We are well aware of the interaction of diseases in the population and the immune response of the host, which sometimes can be intricate and complex.

Our approach is to develop a mathematical model and analyze the dynamics of Malaria with loss of immunity in the population of humans by taking into consideration the "competence" of the immune response of the individual. Furthermore, the immune competence can affect the infection rate and the recovery rate of the host within the population.

Model

Before deriving the mathematical model, we define the following variables and parameters; see Table 6.1. The host and vector populations are divided into classes containing susceptible, asymptomatic, and infectious individuals. At time t, there are S_v, S_h susceptible mosquitos and human, A_h asymptomatic humans, and I_v, I_h infectious vector and humans where $N_v = S_v + I_v$ and $N_h = S_h + A_h + I_h$ are the total population of the mosquitos and humans, respectively, in the specific environment. We assume in the model no vertical transmission i.e., all newborns are susceptible in both populations with $\Lambda_v > 0$ and $\Lambda_h > 0$ as the constant recruitment rates for vectors and humans, respectively. All individuals have a limited lifespan

Table 6.1: State variables.

State variables	
Variable	Explanation
S_v	Susceptible vector population
I_v	Infected vector population
S_h	Susceptible human population
A_h	Asymptomatic human population
I_h	Infectious human population
Symbol	Description
Λ_v	Recruitment rate for the vector
β_v	Rate of infection of vector by biting infected human
μ_v	Vector natural death rate
Λ_h	Recruitment rate of human population
β_h	Rate of infection of human
μ_h	Natural death rate for human
δ_h	Recovery rate
q	Proportion of asymptomatic
γ_h	Rate of progression from asymptomatic to infectious
d_h	Death rate due to infection

in both populations and experience natural per capita death rates positive $\mu_v > 0$ and $\mu_h > 0$ for mosquitos and humans, respectively. The effective contact leading to infection of susceptible individuals in the population is considered β_v and β_h, respectively for the vectors and the host. Based on the competence of the immune response, a proportion, $1-q$ with $q \in [0,1]$, of the susceptible class will become infectious while q will be asymptomatic. As discussed in previous chapters, the immune reaction is additionally strengthened by autocatalytic and/or competitive reinforcement of immune activation processes. In other words, competence immune effector cells can proliferate and/or stimulate themselves or precursor cells for increasing proliferation or differentiation.

In the human population, an asymptomatic individual becomes infectious at the per capita rate constant γ_h, and infectious individual recovers at rate δ_h. At the same time, an infectious individual can die from the disease at a constant rate d_h.

We can now write the equations of the model describing the Malaria dynamics using the standard mass action laws:

$$\frac{dS_v}{dt} = \Lambda_v - \beta_v S_v \frac{I_h}{N_h} - \mu_v S_v, \tag{6.2.1}$$

$$\frac{dI_v}{dt} = \beta_v S_v \frac{I_h}{N_h} - \mu_v I_v, \tag{6.2.2}$$

$$\frac{dS_h}{dt} = \Lambda_h - \beta_h S_h \frac{I_v}{N_v} - \mu_h S_h + \delta_h I_h, \tag{6.2.3}$$

$$\frac{dA_h}{dt} = q\beta_h S_h \frac{I_v}{N_v} - (\mu_h + \gamma_h) A_h, \tag{6.2.4}$$

$$\frac{dI_h}{dt} = (1-q)\beta_h S_h \frac{I_v}{N_v} + \gamma_h A_h - (\mu_h + d_h + \delta_h) I_h. \tag{6.2.5}$$

By adding up Equations (6.2.1)-(6.2.2) and (6.2.3)-(6.2.5), we get the equations for the vector and human total population, respectively:

$$\frac{dN_v}{dt} = \Lambda_v - \mu_v N_v, \qquad \frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - d_h I_h$$

where all the parameters are assumed to be positive. All these equations are valid as long as $N_v > 0$ and $N_h > 0$. It can easily be shown that if the initial conditions are defined for all the states variables at $t = 0$, then there exists a unique solution satisfying the initial conditions for all $t \geq 0$. For nonnegative initial values, the model is well posed with $N_v \leq \frac{\Lambda_v}{\mu_v}$ and $N_h \leq \frac{\Lambda_h}{\mu_h}$.

For mathematical simplicity, we make the change of variables

$$s_v = \frac{S_v}{N_v},\ i_v = \frac{I_v}{N_v},\ s_h = \frac{S_h}{N_h},\ a_h = \frac{A_h}{N_h},\ i_h = \frac{I_h}{N_h},$$

so that the respective total populations become

$$s_v + i_v = 1 \text{ and } s_h + a_h + i_h = 1.$$

If we introduce the following variables

$$L_v = \frac{\Lambda_v}{N_v},\ L_h = \frac{\Lambda_h}{N_h},$$

then the system (6.2.1 - 6.2.5) becomes

$$\frac{di_v}{dt} = \beta_v(1-i_v)i_h - L_v i_v, \tag{6.2.6}$$

$$\frac{da_h}{dt} = q\beta_h(1-a_h-i_h)i_v - (\gamma_h + L_h)a_h + d_h i_h a_h, \tag{6.2.7}$$

$$\frac{di_h}{dt} = (1-q)\beta_h(1-a_h-i_h)i_v + \gamma_h a_h - (d_h + \delta_h + L_h)i_h + d_h i_h^2. \tag{6.2.8}$$

This new Model (6.2.6) - (6.2.8) is given in terms of proportions and has corresponding initial conditions in $\Omega = \Omega_1 + \Omega_2$, where

$$\Omega_1 = \{(i_v, a_h, i_h) \in [0,1]^3 | 0 \leq i_v < 1, 0 \leq a_h + i_h \leq 0\},$$

and

$$\Omega_2 = \left\{ (N_v, N_h) \in R^2 \middle| 0 < N_v \leq \frac{\Lambda_v}{\mu_v}, 0 < N_h \leq \frac{\Lambda_h}{\mu_h} \right\}.$$

If we denote points in Ω by $x = (i_v, a_h, i_h, N_v, N_h)^t$, then we re-write System (6.2.6) - (6.2.8) in the considered form

$$\frac{dx_j}{dt} = f_j(x), \qquad j = 1,2,3 \tag{6.2.9}$$

where we develop results that will guarantee the global well posedness of the model.

The small variation we intend to include with the analysis of the model, is to investigate the impact of the spread of diseases in the population on the individual immune system response and if possible the dependence of β_h and δ_h on the immune competence of the individuals within the population of interest. From here, we can rewrite the Model (6.2.6) - (6.2.8) by including the immune competence effector using the approach developed earlier. With only one pathogen in consideration for Malaria

(*P. falciparum*), our model will become

$$\frac{di_v}{dt} = \beta_v(1-i_v)i_h - L_v i_v, \tag{6.2.10}$$

$$\frac{da_h}{dt} = q\beta_h(1-a_h-i_h)i_v - (\gamma_h+L_h)a_h + d_h i_h a_h, \tag{6.2.11}$$

$$\frac{di_h}{dt} = (1-q)\beta_h(1-a_h-i_h)i_v + \gamma_h a_h - (d_h+\delta_h+L_h)i_h + d_h i_h^2, \tag{6.2.12}$$

$$\frac{dE}{dt} = e + H + s\frac{E^2}{b+E^2} - dE, \tag{6.2.13}$$

$$\frac{dH}{dt} = \sigma\theta E i_v - \sigma H. \tag{6.2.14}$$

Existence of steady state solutions

Here, we explore the dynamics of the model and present some results concerning the existence of equilibria. Considering the two populations, there is no solution for the model in which all variables are 0. For the DFE, we have $I_v = A_h = I_h = H = 0$, and from Equations (6.2.1) and (6.2.3) we have $S_v^* = \Lambda_v/\mu_v$, $S_h^* = \Lambda_h/\mu_h$ and $E^* = \bar{E}$. Hence the disease-free equilibrium is

$$DFE_0 = \left(\frac{\Lambda_v}{\mu_v}, 0, \frac{\Lambda_h}{\mu_h}, 0, 0, \bar{E}, 0\right).$$

As it is customary in epidemiological models, the basic reproductive number, which give the number of secondary cases following the introduction of a single infected individual into a fully susceptible population, allows us to summarize the transmission and the dynamics of a disease. We leave for future research the completion of the analysis of this model to see if understanding the dynamics at the population level could give some insight on the immunology of the individual.

6.3 Immuno-epidemiology example 2 - Tuberculosis

Introduction

Tuberculosis (TB) in all its forms (pneumonia, bones, meningitis, etc.) can be traced to the beginning of mankind and saw a surge with the industrial development.

In the early history, TB was a fatal disease and had been a leading cause of human death. Today it still claims more that 1.3 million deaths within in one third of the world population. The world becomes aware of the pathogen causing TB after the brilliant scientific discovery of Robert Koch of the *Micobacterium tuberculosis bacillus* (Mtb). Mtb is an obligatory aerobic-intracellular pathogen, which has a predilection for the lung tissues rich in oxygen supply [97]. The tubercle bacilli enter the host via the respiratory route. In certain situations, the bacilli spread from the cite of infection in the lung to other parts of the body through the lymphatics or blood. Most infected individuals remain latent for a long period of time and sometimes for their entire lives. During the latency period, Mtb is postulated to exist in a dormant state where the host can effectively contain the pathogen. However, the risk of developing active TB increases with the presence of any impairment of the immune system [41; 69].

TB can be controlled and treatment of TB is well known and developed in the case of non-resistant strains. To treat active TB, it is necessary to take several antibiotics at the same time. If not treated properly, TB disease can be fatal. The common regime of treatment is the combination of isoniazid, rifampicin and pyrazinamide for two months followed by isoniazid and rifampicin for a further and at least four to seven months, if the organism is known to be sensitive, until all the bacteria have been completely cleared (WHO, 2009 *Global Tuberculosis Control*).

Many contributions [7; 22; 25; 26; 45; 46; 110; 116] in the fields of science, mathematics, epidemiology, etc. have helped in the understanding of the dynamics of TB within the humans population and also at the individual level.

Model

As is typically done in epidemic models, the population of humans of interest is divided into groups or subpopulations - S Susceptible, L Exposed or Latent, and I

Table 6.2: State variables and parameters.

State variable	
Symbol	Explanation
S	Susceptible
L	Latent/Exposed
I	Infectious
Parameters	
Symbol	Description
Λ	Recruitment rate
β	Rate of infection
μ	Natural death rate
p	Degree/level of re-infection
γ	Progression rate from latent to infectious
δ	Rate of recovery
d	Disease induced death rate

Infectious with $N = S+L+I$ to be the total population. We consider the population to be closed and the transmission of TB to be governed by homogeneous mixing. The susceptible individuals can become infected but not infectious and move to the latent class at the rate $\beta SI/N$. The exposed class of individuals can develop active TB and become infectious. The progression rate from latent class to active TB (the infectious class) is given by γL. Within the population when considering the continuous exposure of individuals, latently-infected individuals can still be re-infected through additional contact with the infectious class. The exogenous re-infection is given by $p\beta L\frac{I}{N}$. Individuals in the infectious class can lose being infectious and move to the exposed compartment. All individuals have a limited lifespan and die at the per capita rate μ. We note that the meaning or interpretation of some of the parameters may vary, (β for example, is considered as the likelihood of transmission or the force of infection). The simplest dynamic model of TB can

be written as,

$$\frac{dS}{dt} = \Lambda - \beta S\frac{I}{N} - \mu S, \tag{6.3.1}$$

$$\frac{dL}{dt} = \beta S\frac{I}{N} - p\beta L\frac{I}{N} - (\mu+\gamma)L + \delta I, \tag{6.3.2}$$

$$\frac{dI}{dt} = p\beta L\frac{I}{N} + \gamma L - \delta I - (\mu+d)I. \tag{6.3.3}$$

The basic reproductive number, that is the number of secondary infections generated by an actively infectious individual in a population of susceptibles, is given by

$$\mathscr{R}_0 = \left(\frac{\beta}{\mu+\delta+d}\right)\left(\frac{\gamma}{\mu+\gamma}\right).$$

$\mathscr{R}_0$ is obtained by the product $\beta/(\mu+\delta+d)$, that is the average number of susceptible infected by one infectious individual during his/her effective infectious period and $\gamma/(\mu+\gamma)$ which represents the fraction of the population which survives the exposed/latent period.

It can be shown for Equations (6.3.1) - (6.3.3) that the first octant in the state space is positively invariant. The total population is given by

$$\frac{dN}{dt} = \Lambda - \mu N - dI.$$

Since $N'(t) < 0$ for $N > \Lambda/\mu$, we can reduce the state space to a positively invariant subset of $\mathbb{R}^3_+$ represented by

$$\Omega = \left\{(S,L,I)|S,L,I \geq 0, S+L+I \leq \frac{\Lambda}{\mu}\right\}.$$

Here also, we can rewrite the TB model by including the immune competence effector using the approach developed earlier. The model becomes:

$$\frac{dS}{dt} = \Lambda - \beta S\frac{I}{N} - \mu S, \tag{6.3.4}$$

$$\frac{dL}{dt} = \beta S\frac{I}{N} - p\beta L\frac{I}{N} - (\mu+\gamma)L + \delta I, \tag{6.3.5}$$

$$\frac{dI}{dt} = p\beta L\frac{I}{N} + \gamma L - \delta I - (\mu+d)I, \tag{6.3.6}$$

$$\frac{dE}{dt} = e + H + s\frac{E^2}{b+E^2} - dE, \tag{6.3.7}$$

$$\frac{dH}{dt} = \sigma\theta EI - \sigma H. \tag{6.3.8}$$

Parallel to Equations (6.2.10) - (6.2.14), any insight on the dynamics of the immune system of the host based on the disease dynamics in the population will come from a complete analysis of Equations (6.3.4) - (6.3.8). As with the Malaria immuno-epidemiology model, we leave this analysis for future research.

6.4 Conclusion

While the earlier chapters of this thesis addressed various aspects of co-infection at the immunological level, this chapter proposes a novel method for bridging the currently distinct approaches to an epidemic of immunology versus epidemiology. Using the integro-differential equation method, we were able to derive a set of equations that related the class of infectious individuals at the population level to the immune effector at the individual level. Knowing that our phenomenological models from earlier chapters capture many key features of a true immunology-based model, we have hope that further analysis of this approach may yield significant contributions to our understanding of disease and its spread through the population, whether in the specific cases of the Malaria Model (6.2.10) - (6.2.14), TB Model (6.3.4) - (6.3.8), or other similar model formulation.

Chapter 7

SUMMARY

The object of this thesis is to model the interaction of the immune system response with two pathogens (co-infection), namely the *P falciparum* parasite for Malaria and the *Mycobacterium tuberculosis* (Mtb) for TB. One thing that became clear very early in the thesis is the complexity of the immune system. Every aspect of the immune system that one tries to include in any mathematical model adds another layer of complexity to the model. Coupled with the complexity of the immune response, we cannot pretend to include every aspect of the immune system and its interaction with the foreign agents in our "simple" mathematical model of co-infection (2.3.1), which consisted of 8 state variables and 33 parameters. One of the key approaches to this thesis was to propose and analyze a phenomenological model that captured much of the qualitative behavior of the original immunology-based model. The phenomenological Model (2.6.4) and its various subsystems are among the first mathematical models to mimic the interaction of the pathogen with the immune effectors.

Through the nonlinear mathematical models of Malaria, TB and their co-infection, we introduce new mathematical models of the immune response in order to identify and qualitatively assess the phenomenological time evolution of the distribution of the interacting populations. These new mathematical models greatly simplify the complex dynamics of the immune response and include several assumptions about the known biology. The findings suggest the importance of incorporating the state of the health of the individual in the mathematical modeling of the immune response with respect to the location (endemic regions).

One important contribution was in describing the processes occurring during the activation of the naive immune effector cells (T cells), which gave rise to our two-

stage models. Through simple biological and immunological assumptions, these processes were transcribed into mathematical models using differential equations. Due to the complexity of the model and because of the high nonlinearity of the system, we could not proceed too far with the analytical analysis and had to resort to numerical simulation to understand the temporal dynamics of the pathogens and the target cells.

In the first part of the thesis, we focused on the formulation of our full Malaria–TB co-infection model and the corresponding phenomenological models (and its subsystems) of pathogen(s) interacting with the immune system. For the immune system, for simplicity, we considered one-stage and two-stage activation of the immune effector in which we incorporated the state of the individual health, namely healthy, moderately compromised and severely compromised immune systems, using the Michaelis-Menten modal function with specific Hill coefficients. With these phenomenological models, we proved the well posedness of the system and the existence of steady states. When we considered the equilibria, we do not have Hopf bifurcations but only saddle node and transcritical bifurcations, which also can describe the various immunologist classifications of the immune system state after infection by pathogen: "naive state," "immune state," and the "state of tolerance."

Bolstered by the success of the single-pathogen phenomenological models, we then considered the two-pathogen phenomenological that we considered our caricature of the fully immunology-based Malaria-TB Model (2.3.1). We examined the within host dynamics of the phenomenological model using mathematical analysis and numerical simulation. In particular, the co-infection phenomenological models did not exhibit any Hopf bifurcations. The steady states only underwent saddle node and transcritical bifurcations. Depending on the state of the individual health, the invasion of the second pathogen can prove deadly for the individual in an endemic region. We did not observe this equivalent qualitative behavior in the case of the

co-infection Malaria–TB model, where it was difficult to do anything other than "guess" how we might change a set of realistically-based parameters in order to see such behavior and observe the impact of both diseases on the immune system. Although we obtained qualitative agreement with the Malaria Model (2.1.1) and TB Model (2.2.1), it would remain to be seen if this agreement would hold if we considered different stages of Malaria or TB infection such as asymptomatic Malaria or latent TB.

In the second part of the thesis, we laid out a potential implication of our research about understanding the level or state of compromised immune system and the impact on the population. We proposed a method by which we can link the immunology and the epidemiology using the integro-differential equation with the linear chain trick based on the observation of Fragueb [44]. With this approach we proposed a simple immuno-epidemiology model for the specific cases of Malaria and TB that will be analyzed for future work. This future analysis would need to discuss the possibility of defining and understanding the overlapping time scales of the diseases in the population and the pathogen within the individual. The progress in immuno-epidemiology is controlled by the development of rigorous methods that are capable of using the large data at hand and systematically analyzing complex mathematical or statistical models including more realistic descriptions of the immune system or the development of immunity. Here, we face the challenge of time scales, since developed models require an explicit within-host dynamics, where epidemiological dynamics (slow or fast) overlap these within-host dynamics.

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APPENDIX A

MAYER MODEL

In 1995, Mayer *et al.* [77] proposed a very simple model of the typical immune response, which is capable of describing a variety of possible situations. The model consists of two ordinary differential equations (ODE) describing the evolution of a pathogen (target cell) population P (e.g., viruses, bacteria, fungi, protozoa) in interaction with the relevant host immunocompetent's agents denoted E (e.g., leukocyte, macrophages):

$$\begin{aligned} \frac{dP}{dt} &= rP - kPE \\ \frac{dE}{dt} &= f(P) + g(E) - dE \end{aligned} \tag{A.0.1}$$

with

$$f(P) = p\frac{P^u}{m^v + P^v}, \text{ and } g(E) = s\frac{E^n}{c^n + E^n},$$

where $P \geq 0$, $E \geq 0$ and p, s, m and c are positive constants, and n, u and v are positive integer parameters.

In the model, it is assumed that before any stimulation, there is already a certain population of immunocompetent cells and also that a lot of basic immunology principles have been neglected. The rich variety of qualitatively different solutions of the model is due to the highly nonlinear terms in the equations, $f(P)$ and $g(E)$ which describe the production rates of E, and to the nonlinear interaction term. However, since the model consists of only two ODEs it has only regular solutions, such as fixed points, periodic orbits and asymptotic orbits.

There is one important aspect of the immune response that cannot be ignored and which is not the focus of our study, but it is worth mentioning: time delays. As we can see in [33], antigenic stimulation may need a period of time τ to react that may depend on the pathogen population at the time of infection or invasion $t - \tau$.

Using Mayer's model and under certain assumptions of retarded immune response, Burić *et al.* [17], and Yu *et al.* [119] studied the effect of time delay of the immune response. With the same approach but considering slightly different models, Nelson *et al.* [84], Canabarro *et al.* [19], and Wang *et al.* [112] also investigated immune response and time delay. Burić *et al.*, in particular, discussed and extended the Mayer model by replacing certain constant parameters with the parameters that are periodically dependent on time [18].

APPENDIX B

VARIABLES AND PARAMETERS

The parameters and variables of all our models are, in theory, all able to be estimated with experimental data for a specific disease. For our analysis, we have assumed arbitrary parameters due to the generality of the models with values in a range that we consider to be biologically realistic.

Table B.1: Variables description and units

Variables	Unit	Description
P	$cells\,ml^{-1}$	Population of pathogen
E	$cells\,ml^{-1}$	Population of immune effector (e.g., leukocyte, macrophages)

Table B.2: Summary of parameters units

Parameters	Unit	Description
r	day^{-1}	Rate of pathogen proliferation
k	$ml\,cell^{-1}day^{-1}$	Removal rate by immune system
e	$cells\,day^{-1}$	Rate of recruitment of immune effector
α	day^{-1}	Rate of naive immune effector proliferation
K	$cells$	Carrying capacity of naive cells
c	$ml\,cell^{-1}day^{-1}$	Maturation/activation rate of immune effector
d	day^{-1}	Death rate of cells
p	$ml\,cell^{-1}day^{-1}$	Stimulation rate of immune system by pathogen
a	$ml\,cell^{-1}$	Half saturation constant for pathogen
s	$ml\,cell^{-1}day^{-1}$	Proliferation rate of mature immune effector
b	$ml\,cell^{-1}$	Half saturation constant for mature immune effector

Table B.3: Parameters for Malaria model within the host from [5; 29; 55].

Parameter	Value	Description
s_R	4.15×10^4	Rate of prodoction of RBC
d_R	8.3×10^{-3}	Death rate of RBC
d_I	1.0	Rate of decay of infected RBC
d_F	48	Death rate of malaria parasites
d_T	0.007	Death rate effector cell
β	2×10^{-6}	Rate of infection of RBC
α	1.2	Rate of maturation of infectious RBC
k_1	10^{-8}	Removal rate of infected RBC
p	36	Rate of production of parasites
k_2	10^{-8}	Removal rate of merozoides
s_T	10	Recruitment rate of immune effector
a_1	2.5×10^{-5}	Rate of stimulation by infected RBC
a_2	4.69×10^{-5}	Rate of stimulation by parasites
a_3	1.43	Stimulation strength of effector cells
c_1	5×10^{-4}	Half saturation of infectious RBC
c_2	6.67×10^{-4}	Half saturation of parasite
b	10^3	Half saturation of immune effector