Mathematical analysis and dynamical systems : modeling Highland malaria in western Kenya

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Dedication

I dedicate this Thesis to my children :

– Elijah Mbugua
– Favour Lilly Wamuca and
– Victor Mwaniki

For the suffering you endured during my long and repeated absence. May you find consolation and comfort enough to ease the grieve it has caused you.

Abstract

The objective of this thesis is to model highland malaria in Western Kenya using dynamical systems. Two mathematical models are formumated, one, on differentiated susceptibility and differentiated infectivity in a metapopulation setting, two, a saturated vector feeding rate model with disease induced deaths and varying host and vector populations.
In the first model, we consider the different ecosystems identified as malaria hotspots in the Western Kenya highlands and consider the ecosystems as different patches. The population in each patch is classified as, either, child (age 0-5 years), or, adult (over (years of age). Our results are compared with some published results in [149].

The model will aid in examining the role of ecosystem heterogeneity and age structure to the persistent malaria epidemics in the highlands. We formulate the differentiated susceptibility and infectivity model that extend to multiple patches the well known epidemiological models in one patch.

Classifying the hot spots as n patches, we give its mathematical analysis using the theory of triangular system, monotone dynamical systems or anti-monotone non-linear dynamical systems, and Lyapunov-Lasalle invariance principle techniques. Key to our analysis is the definition of a reproductive number, $\mathcal{R}_0$, (the number of new infections caused by one individual in an otherwise fully susceptible population throughout the duration of the infectious period). The existence and stability of disease-free and endemic equilibrium is established with a prove that the disease free state of the systems is globally asymptotically stable when the basic reproduction number $\mathcal{R}_0$ is less than or equal to the unity, and when $\mathcal{R}_0$ is greater than one an endemic equilibrium is established which is locally and globally asymptotically stable. The model shows that the age structuring reduces the magitude of infection. Using relevant data we did some simulation, to demonstrate the role played by metapopulation and age structuring on the incidence and $\mathcal{R}_0$.

In the second part we formulate a model for malaria with saturation on the vector feeding rates that lead to a nonlinear incidence. The vector feeding rate is assumed, as in the predator prey models, to rise linearly as a function of the host-vector ratio until it reaches a threshold Q_v, after which the vector feeds freely at its desired rate. The two populations (host and vector) are variable and drive malaria transmission, such that when the vectors are fewer than hosts, the rate of feeding is determined by the vectors feeding desire, whereas, when the hosts are more than the vectors, the feeding rate is limited by host availability, other feeding sources may have to be sought by the vector. Malaria induced deaths are introduced in the host population, while the vector is assumed to survive with the parasite till its death. We prove that the DFE equilibrium is locally and globally asymptotically stable, if $\mathcal{R}_0 < 1$, and when $\mathcal{R}_0 > 1$, an endemic equilibrium emerges, which is unique, locally and globally asymptotically stable. The role of the saturated mosquito feeding rate is explored with simulation showing the crucial role it plays especially on the basic reproduction number.

Key Words : Modeling, Metapopulation, Differentiated infectivity and Susceptibility, Monotone Dynamical Systems, Lyapunov methods, Basic Reproduction Number, Global stability, Saturation, Malaria, Numerical Simulation.

Resume

L'objectif de cette thèse est de modéliser la transmission du paludisme dans la région montagneuse de l'Ouest du Kenya, en se servant des outils de systèmes dynamiques. Nous considérons deux modèles mathématiques. Le premier prend en compte une susceptibilité et une infectivité différentielle dans les métapopulations, et le second un taux de saturation des repas sanguins dans la population des moustiques.

Dans le premier modèle, nous considérons plusieurs écosystèmes identifiés comme zones sensibles dans la région montagneuse de l'Ouest du Kenya. Dans ce modèle, ces zones sensibles sont considérées comme nos différents patchs. Les populations de chaque patch sont divisées en deux : les enfants (0 à 5 ans), et les adultes (dont l'âge est supérieur à 5 ans). Les résultats obtenus sont comparés avec ceux obtenus dans [149]. Le modèle nous permet d'évaluer le rôle de l'hétérogénéité de l'écosystème et la persistance de l'épidémie dans la région, due à la structuration d'âge. Nous prenons en compte la susceptibilité et l'infectivité différentielle afin d'étendre le modèle d'un patch en un modèle à plusieurs patchs.

Après avoir subdivisé la région en n zones sensibles, nous faisons une analyse mathématique du modèle obtenu. Pour effectuer cette analyse, nous utilisons la théorie des systèmes triangulaires, des systèmes dynamiques monotones, des systèmes dynamiques non linéaires anti-monotones et le principe d'invariance de LaSalle. Un des éléments très utilisés dans notre analyse qui est un concept clé en épidémiologie, est le taux de reproduction de base, très souvent noté $\mathcal{R}_0$. Cette quantité, sans dimension, est le nombre moyen de cas secondaires, engendré par un individu infectieux typique durant sa période d'infectiosité, quand il est introduit dans une population constituée entièrement de susceptibles. L'existence et la stabilité du point d'équilibre sans maladie (DFE) sont établies et nous prouvons que le DFE est globalement asymptotiquement stable lorsque $\mathcal{R}_0 \leq 1$. Lorsque $\mathcal{R}_0 > 1$, le modèle admet un point d'équilibre endémique qui est globalement asymptotiquement stable. L'analyse de notre modèle montre que la structuration d'âge réduit l'ampleur de l'infection. En utilisant les données relevées, nous faisons quelques simulations numériques afin montrer l'impact de la métapopulation et de la structuration d'âge sur le taux de reproduction de base.

Dans la seconde partie, nous formulons un modèle de paludisme avec saturation du taux d'alimentation des moustiques qui nous conduit à une incidence non linéaire. Nous démontrons que le DFE est globalement asymptotiquement stable si $\mathcal{R}_0 < 1$. Lorsque $\mathcal{R}_0 > 1$, il existe un unique point d'équilibre endémique qui est globalement asymptotiquement stable. Des simulations numériques sont faites afin d'illustrer l'impact de la saturation du taux d'alimentation sur le taux de reproduction de base.

Mots clés : Modélisation, métapopulation, susceptibilité et infectivité différentielle, systèmes dynamiques monotones, méthode de Lyapunov, taux de reproduction de base, stabilité globale, saturation, paludisme, simulations numériques.

Introduction

Contents

0.0.1 Highland Malaria

Malaria is a protozoan disease caused by a parasite transmitted by a female anopheles mosquito, as it seeks a blood meal for its egg development. The disease is common in the East African region, Kenya included. Malaria is one of the leading causes of morbidity and mortality in Kenya and it kills an estimated 34,000 children under five in Kenya every year. 77% of Kenya's population lives in areas where the disease is transmitted. The disease is responsible for 30% of all out-patient visits (requiring more than eight million out-patient treatments at health facilities each year) and 15% of all hospital admissions. About 3.5 million children are at risk of infection and developing severe malaria. Pregnant women also face high risks. There are approximately 1.1 million pregnancies per year in malaria endemic areas. During pregnancy, malaria can cause miscarriages and anemia. Each year, an estimated 6,000 pregnant women suffer from malaria-associated anemia, and 4,000 babies are born with low birth weight as a result of maternal anemia. Economically, it is estimated that 170 million working days in Kenya are lost each year because of malaria illness.

Malaria did not exist in the Western Kenya highlands until the second decade of the 20th century, so the highlands were regarded as safe havens from the surrounding malarious areas of Uganda and Kenya [102, 72]. After the first World War, malaria was prevalent in the communities inhabiting the highlands. This was as a result of wide-scale population settlement resulting from the completion of the railway line from Kenyan coast via the highlands to Lake Victoria. This also facilitated the gradual spread of infective mosquitoes into the highlands from the low-lying hyperendemic-disease areas [44]. The development of tea estates and agriculture in the highlands, with the concomitant clearing of the forests, provided suitable mosquito breeding grounds. Finally, importation of infected laborers completed the conditions necessary for malaria transmission [99].

This resulted to frequent malaria epidemics, with some authors labeling the resurgent epidemics

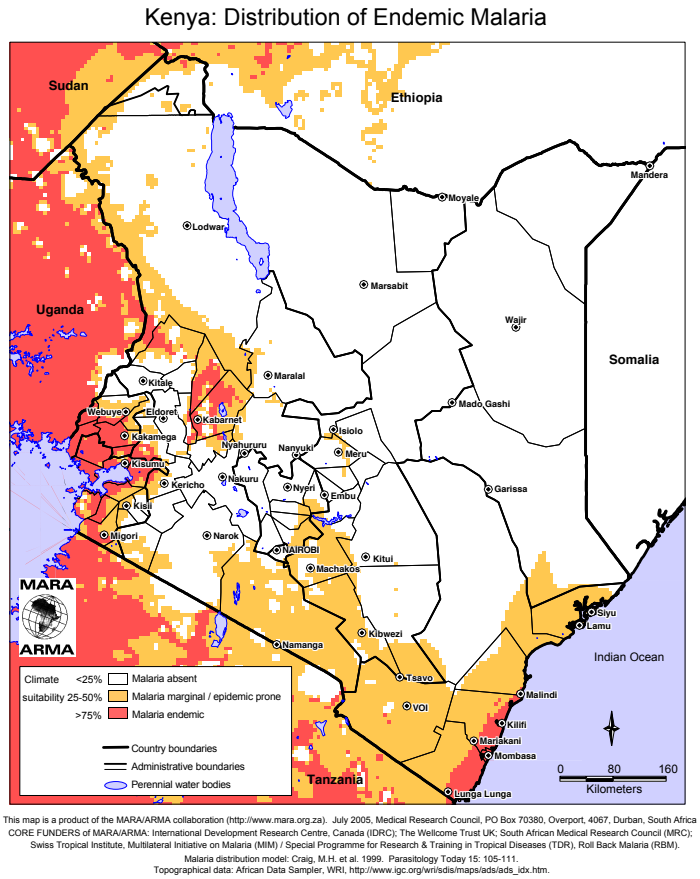

Figure 1 – The Distribution of Malaria in Kenya (MARA/ARMA)

as 'Highland malaria', because they viewed it as a new typology variant, demanding special attention in the new global commitment to Roll Back Malaria [153]. 'Highland' malaria therefore, either is a new phenomena or a reemergence of a previous prevailing epidemiology [129].

Highland malaria in Western Kenya is characterized by unstable and high transmission variability which results in epidemics during periods of suitable climatic conditions. The sensitivity of a site to malaria epidemics depends on the level of immunity of the human population. The epidemics in the highlands have continued to wreck havoc on the public health of the inhabitants, resulting in high morbidity and mortality especially in children under five years [129]. Malaria kills approximately 26,000 children per year in Kenya and about 170 million working days (an average of 5.5 working days per person) are lost due to malaria per year. Malaria accounts for 30 percent of all outpatient attendance and 19 percent of all admissions to Kenyan health facilities (Kenya Ministry of Health 2001c). Since the early 1980s, there have been massive percentage increases in P. falciparum burden at African highland locations [56]. The epidemics varies seasonally and spatially with many studies being carried out to ascertain the drivers of

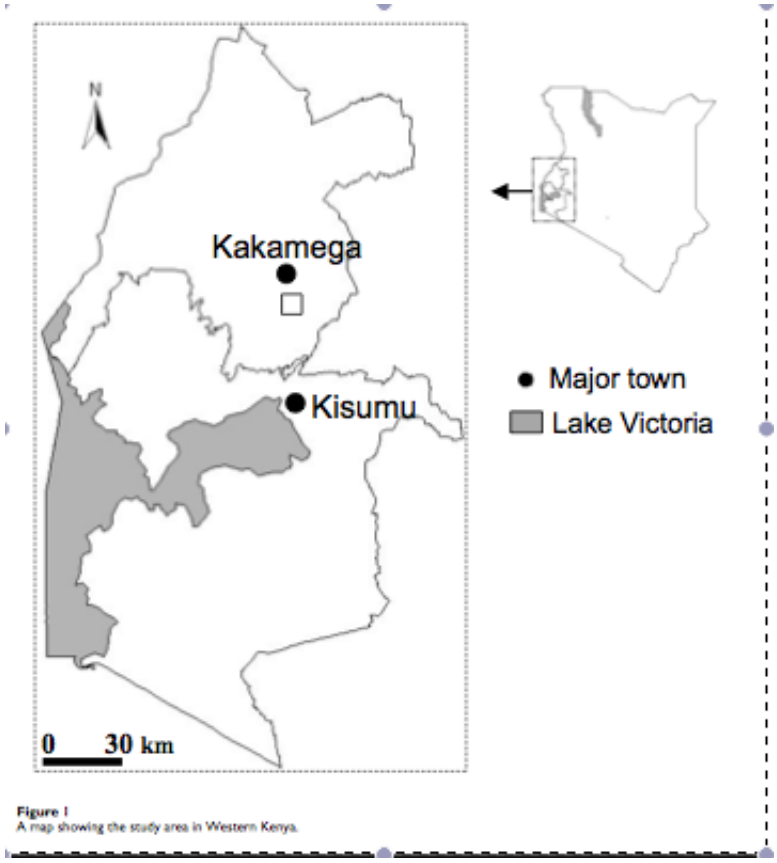

Figure 2 – The malaria endemic Western Kenya Highlands. The areas affected by epidemics are 1500-2500 meters above sea level [49]

such variations. Among the factors considered as key drivers of the resurgent epidemics that characterise the highlands include but are not limited to :

- Climate Variation.
  Climate variation plays an important role in initiating malaria epidemics in the Western Kenya highlands. The developmental rates and survivorship of the malaria parasite and the malaria vector is highly temperature dependent, while rainfall influences the availability of breeding places, hence their demography. Small changes in temperature could therefore provide transiently suitable conditions for unstable transmission within populations that have acquired little functional immunity. Studies on climatic variations and malaria epidemics in Western Kenya show that, there is a high spatial variation in the sensitivity to malaria outpatient number to climate fluctuations in the highlands [154]. The contribution of climate variation to reemergence of malaria epidemics has been controversial, and a good conclusion is that other factors together with climate change are more plausible explanations for the malaria resurgences

- Drug Resistance
  During the past two decades, Chloroquine (CQ) resistance has spread geographically, in-

creased in prevalence within its range, and intensified in its severity of clinical failure [137, 152]. CQ resistance has been identified as an important factor in the malaria resurgence on the Kericho tea estates [45]. How much effect this one has on the magnitude of the epidemics is a point of discussion, this is because drug resistance can only aggravate malaria induced morbidity and mortality not initiating an epidemic. Again, drug resistance cannot explain the sporadic malaria epidemics in the Kenyan highlands in the 1920s and 1950s, when the problem of drug resistance was insignificant [48].

– Land Use Changes.
The increasing human populations in the East African highlands puts a lot pressure on the sensitive ecosystem [96]. There is an increase in changing human activities such as deforestation and swamp cultivation for subsistence agriculture, growing cash crops, and firewood acquisition that have characterized the region. Reports indicate that there is an 8% reduction in forest coverage in the East African highlands in one decade [5]. The changes in land use, especially deforestation in the highlands, have significantly changed the microclimatic conditions of mosquito breeding sites that have significantly had effects on the life history traits of the vectors.
Deforestation is said to have enhanced vectorial capacity by 10.6% and 29% in the dry and rainy seasons in the highlands, respectively, thereby resulting in high indoor temperatures. This causes faster blood meal digestion, thereby shortening the length of the gonotrophic cycle of mosquitoes. Reduced gonotrophic cycle length would cause mosquitoes to feed more often and lay eggs more frequently in a deforested area. [5].

– Population Growth and Health Service Provision
An important factor to consider in the escalating malaria incidence in Western Kenya is population growth. Of vital consideration is the relationship between the percentage population growth rate in the districts served by each health facility and the percentage rises in malaria cases. Over the last 3 decades, sub-Saharan Africa including the highlands, has seen a high rate of increase in population size, resulting from high fertility rates and increasing child survival with annual growth rates averaged 3.9%. This implies that, holding the incidence of malaria constant, the disease would be expected to have doubled over approximately an 18-year period. Clearly, without a concomitant investment in essential clinical services, beds, staff, and supporting infrastructure, the changing requirements for clinical management will have been perceived by most district-level public health officials as a crisis [55].

Defining true epidemics is difficult [129]. For most public health workers, epidemics represent exacerbations of disease out of proportion to the normal level to which that facility is subject ; these increases overwhelm the facilitys ability to cope. Therefore, a slow but pervasive epidemic of clinical malaria may have emerged in the highlands, where lack of investment in the physical capacity to manage an increasing population has resulted inevitably in more malaria cases that require a basic clinical service.

– Immunity.
Due endemicity of malaria in Africa, people are infected so frequently that after a long time, they develop a degree of acquired immunity, making them asymptomatic carriers of infection [15]. The people who use mosquito nets in the night are not generally infected by

the disease since the small number of bites they receive when they are outside the nets are not sufficient to cause the disease, but rather, the small exposure to infection gives them immunity. The low level exposure to infection however, is important as it acts as vaccination and develops immunity against the disease [80]. Those who acquire the immunity are however susceptible to reinfections because the immune protection may wane over time (temporary immunity) or may not be fully protective (partial immunity) [139].

Studies in Western Kenya indicate that in areas of unstable transmission in the highlands, the prevalence of circumsprozoite protein (CSP) is about 13% in adults over 40 years of age whereas in the stable transmission lowlands, approximately 65% of children are antibody positive [6]. This shows that the human population in the highlands has fewer people with immunity and this renders them vulnerable to severe forms of malaria during epidemics [149]. Since the risk of an epidemic is closely related to the level of immunity of the human population, the final outcome of the epidemic will be closely linked by the proportion of people who may not have had exposure to the disease and who have no immunity to malaria.

– Ecosystem heterogeneity.
A study [149] on the different ecosystems in the Western Kenya highlands identify three major characteristics. The plateaus, V-shaped valleys and U-shaped valleys. The V-shaped valleys have steep hillsides and narrow valleys that allow fast flow of the rivers, while the U-shaped valleys have flat bottomed valleys with slow moving rivers.

Figure 3 – A picture of an U-shaped Valley [149]

The Studies carried out in the different highland ecosystems show that transmission is heterogeneous in the three types of ecosystem, with the annual entomological inoculation rates (EIR) ranging from 0.4-1.1 and 16.6 infectious bites per person for the V-shaped and U-shaped valleys, respectively [62]. Along the flat valley bottoms, there are suitable surfaces providing more ideal breeding sites of malaria vectors than the narrow valleys [61].
The V-shaped ecosystems have very low malaria prevalence and few individuals with an

Figure 4 – A picture of a V-shaped Valley [149]

immune response to malaria antigens. Provided evidence show that there is an 8.5- fold and a 2-fold greater parasite and antibody prevalence respectively, in the U-shaped compared to the V-shaped valleys. This makes the V-shaped valleys epidemic hotspot as the inhabitants are exposed to a higher risk of severe forms of malaria during periods that support hyper-transmission of the parasites.

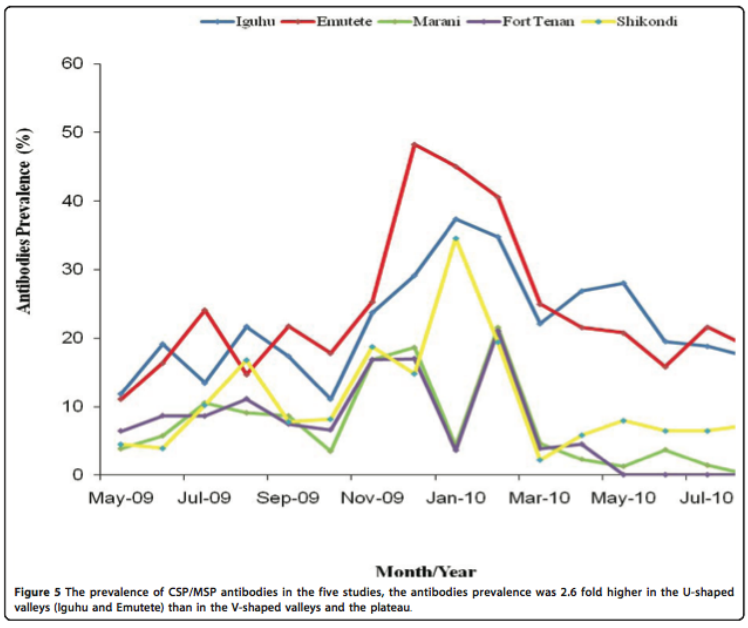

Figure 5 – The antibodies prevalence for the U-shaped and the V-shaped valleys [149]

The plateau‘s antibody and parasite prevalence was similar to that of the V-shaped valleys. Although climatic variability drives malaria epidemics in Western Kenya highlands the terrain characteristics can modify the level of malaria transmission and the rate of immunity development.

It is our aim in this thesis to formulate a mathematical model that captures the heterogenity in the terraine characteristic and the infection dynamics of this very important disease in the economy Kenya.

0.0.2 Mathematical Modeling

Mathematical models have become important tools in analyzing the spread and control of infectious diseases. The model formulation process clarifies assumptions, variables, and parameters ; moreover, models provide conceptual results such as thresholds, basic reproduction numbers, contact numbers, and replacement numbers. Understanding the transmission characteristics of infectious diseases in communities, regions, and countries can lead to better approaches to decreasing the transmission of these diseases.

Mathematical modeling arises from the idea that infectious disease spread and transmission dynamics follows laws that can be formulated in mathematical language. It begun with Daniel Bernoulli in 1766 when he modeled the effects of smallpox variolation (a precursor of vaccination) on life expectancy [31]. In the beginning of that century there was much discussion about why an epidemic ended before all susceptible were infected with hypotheses about changing virulence of the pathogen during the epidemic. Sir Ronald Ross, who received the Nobel prize in 1902 for elucidating the life cycle of the malaria parasite, used mathematical modeling to investigate the effectiveness of various intervention strategies for malaria [121]. Kermack and McKendrick described the dynamics of disease transmission in terms of a system of differential equations in [77, 78, 79]. They were the first to use the so-called basic reproduction number, a threshold that determine if a disease dies out or spreads in a susceptible population. Literature review in [19, 34, 36, 58] show the rapid growth of epidemiology modeling towards the end of the twentieth century as mathematical modeling became more popular to aid in public health policy making.

Many mathematical models describing the dynamics of AIDS pandemic have been used to predict the course of the epidemic and identifying the most effective prevention strategies. The need for evaluating intervention strategies for newly emerging and re-emerging pathogens has revealed real impact of mathematical modeling on public health.

There are two types of mathematical models, deterministic and stochastic. The deterministic models are transmission models using ordinary differential equations to describe the process, whereas stochastic models use statistical mechanisms to describe the transmission of infection between two individuals. The rigorous mathematical analyses of the processes contribute to the understanding of disease transmission in much detail. Therefore, developing a mathematical model helps address the essential processes involved in shaping the epidemiology of an infectious disease and reveals the parameters that are most important and crucial for control and data collection. Mathematical modeling is then also integrative in combining knowledge from very different disciplines like microbiology, social sciences, and clinical sciences [85].

Of special interest in this thesis is metapopulation models, which refer to many small and extinction-prone local populations connected via migration in fragmented environment. Metapopulation theory is based on the Levin‘s multi groups model [20]. The population is subdivided into a finite number of discrete subpopulation called patches that are assumed to be homoge-

neous and well mixed. Then each patch in the population is subdivided into compartments corresponding to different epidemiological status. This leads to multi-patch, multi-compartmental systems. There are three possible formulations. The first assumes that an individual in a patch of infection can infect a susceptible individual in the other patch. This approach assumes that there is a short distance between patches, but individuals (human or mosquito) do not migrate between patches (they can make brief visits sufficient for transmission). This assumption leads to a series of models that has been studied in [60, 65, 90]. The legendary model of Lajmanovich and Yorke [90] is a key example of such models.

The second formulation considers the mobility of individuals between patches with two forms of movement : Migration, that is change of respective patch residence. The situation is that of a digraph or directed movement graph. For the short visits, the individuals visits a number of patches but returns to his patch of residence. The "Mover -Stayer " movement is covered in the mode of Satttenspiel and Dietz [126]. Here, the formulation takes care of the degree of patches connectivity. Recently there has been an increasing interest in this type of models [12, 10, 14, 29, 43, 73, 147, 148].

The third formulation is more recent and takes into account the network structure of the metapopulations, that is those patches that (local populations) are locally connected. This formulation takes into account the degree of connectivity (number of links between a patch and its immediate neighbours) of a patch and model the mobility of individuals in terms of diffusion between discrete patches. This is a statistical approach where the system states depends on the local population densities of the metapopulation network. The leads to a situation of a non-oriented graph connectivity. [123, 124, 27, 3, 4]. The rest of the thesis is arranged as follows.

In part 1,we construct and analyze mathematically an age structured model for highland malaria in Western Kenya, with differentiated patch susceptibility and infectivity and human migration between patches. We show that there is a threshold below which the disease vanishes and above which the disease is persistent in the metapopulation. It is applied to two sites in Western Kenya that have been identified as 'malaria hotspots' in literature cited above. This part contributes significantly mathematics as the rigorous analysis of these types of models or metapopulation are rather rare

In the second part, we formulate a model for the dynamics of vector feeding habits with saturation and varying host and vector population. We establish mathematically the existence of a disease free equilibrium where the disease dies out and an endemic equilibrium, where the disease persists in the population using $\mathcal{R}_0$ as a threshold.The local and endemic equilibrium are proved to be locally and globally asymptotically stable. The analysis on the role of saturation in biting rate is also done to show that it plays a key role in infection and also incidence of malaria.

CHAPITRE 1

Some Epidemiological Models

Contents

1.1 The First Model : D.Bernoulli

The main objective of Bernoulli was to calculate the gain in life expectancy at birth if smallpox were to be eliminated as a cause of death. Smallpox is endemic, a potentially lethal infectious disease and a scourge that is dreaded and feared. It kills one in every five adults, (nearly one in three patients). When it is not fatal, it often leaves a trail of destroyed lives. Effective treatment for smallpox has remained elusive. In the eleventh century, the Chinese practiced variolation, which is a form of inoculation, where infectious material from smallpox cases was transferred into the skin of susceptibles with the intention to induce lifelong immunity by a mild infection with a low case fatality. The result was, however risky, because the mortality rate could rise by 1 to 2%. In 1721 this method was introduced from Turkey into England by the wife of the English Ambassador to Constantinople, Lady Mary Wortley Montague.

Smallpox was fortunately eradicated by the first human voluntary control. Its official "disappearance" dates back to 1977 (when the last case of smallpox was reported). This was made possible by the combined efforts of smallpox vaccination and screening program led by WHO in 1967. Bernoulli demonstrated before the Academy of Sciences that, despite the dangers it presented in the fight against smallpox, the generalization of variolation imported from the East, would increase the life expectancy from 26 years and 7 months to 29 years and 9 months. His

reasoning cannot be refuted, his calculations has passed the test of time, and he was persuaded that his model was good. It suffices then for his critics to learn what a mathematical model is. We give the details in the next section of the steps he followed to build his model.

D. Bernoulli assumed the following

- The probability that an individual is infected by smallpox for the first time dies is p and the individual survives is $1-p$ and this probability is independent of the individuals age.
- q is the probability that an individual is infected in the year and it is independent of his age. (ie the probability that an individual is infected during small time interval dx between age x and age $x+dx$ is $q.dx$)
- when an individual survives after being infected with smallpox, he is immune for the rest of his life.

Let $m(x)$ be the natural mortality at age x, then the probability that an individual dies in a small time interval dx between age x and age $x+dx$ is $m(x).dx$. Considering a group of P_0 individuals born in the same year we have :

- $S(x)$ the number of individuals who are still alive at age x without having been infected (and therefore are more likely to be)
- $R(x)$ the number of immune individuals who are still alive at age x.
- $P(x) = S(x) + R(x)$ the total number of individuals who are still alive at age x.

When births correspond to $x = 0$, $S(0) = P(0) = P_0$ while between age x and age $x+dx$ (dx is infinitely small), an uninfected individual has a probability $q.\,dx$ of catching smallpox and a probability $m(x).dx$ of dying from another cause. So the variation in the number of individuals who are not yet infected is $d\,S(x) = -q\,S(x).\,dx - m(x)\,S(x).\,dx$, then we have the differential equation,

$$\frac{dS}{dx} = -q\,S(x) - m(x)\,S(x). \tag{1.1}$$

During the same small time interval, the number of individuals who die of smallpox is $p\,q\,S(x)\,dx$ and the number of individuals who survive and become is $(1-p)\,q\,S(x)\,dx$. In addition, there are $m(x)\,R(x)$ already immune individuals who suffer natural death, leading to a second differential equation

$$\frac{dR}{dx} = q\,(1-p)\,S(x) - m(x)\,R(x). \tag{1.2}$$

Summing the above two equations we obtain

$$\frac{dP}{dx} = -p\,q\,S(x) - m(x)\,P(x). \tag{1.3}$$

From equations 1.1 and 1.3, Bernoulli showed that the fraction of individuals at age x who are at still at risk of contracting smallpox is

$$\frac{S(x)}{P(x)} = \frac{1}{(1-p)\,e^{qx} + p}. \tag{1.4}$$

Analysis of the model

Bernoulli eliminated $m(x)$ between the equations 1.1 and 1.3 by expressing $m(x)$ as

$$-m(x) = q + \frac{1}{S}\frac{dS}{dx} = p\,q\frac{S}{P} + \frac{1}{P}\frac{dP}{dx}$$

to get the following expression

$$\frac{1}{P}\frac{dP}{dx} - \frac{S}{P^2}\frac{dP}{dx} = -q\,\frac{S}{P} + p\,q\,(\frac{S}{P})^2$$

where the right hand side is the derivative of $f(x) = S(x)$, and it is the proportion of infected individuals are who survives to age x. Therefore

$$\frac{df}{dx} = -q\,f + p\,q\,f^2. \tag{1.5}$$

The solution of this type of equation ca be found courtesy of Jacques Bernoulli. Let $g(x) = \frac{1}{f(x)}$, we see that $dg/dx = d\,g - p\,q$ and that $g(0) = 1/f(0) = 1$. We then set $h(x) = g(x) - p$, so that $dh/dx = q\,h$. So $h(x) = h(0)\,e^{qx} = (1-p)\,e^{qx}$. Finally, $g(x) = (1-p)\,e^{qx} + p$ and $f(x) = 1/g(x)$.

To illustrate his theory, Bernoulli uses the mortality table by Halley (1656 - 1742) built for the city of Breslau (1693). This table lists the number of survivors at the beginning of the year $x(x = 1, 2, \ldots)$ of a cohort of 1238 individuals born in year 0. Bernoulli however, believed like most of his contemporaries, that the numbers given by Halley are for the survivors reaching age x, that is $P(x)$ in the model. Because of this little confusion (Halley's article is indeed not very explicit), Bernoulli replaces the numbers 1238 by 1300 to obtain a realistic mortality for the first year of life.

Parameter values chosen by Bernoulli are

- The probability of dying from smallpox $p = \frac{1}{8}$
- The annual probability of catching smallpox $q = \frac{1}{8}$. This probability can be estimated directly, Bernoulli then chooses q so that the total death toll of a smallpox represents $\frac{1}{13}$of all deaths, which corresponds to the proportion found in many cities in Europe.

With the formula 1.4 and data values of $P(x)$ from the table of Halley we can calculate the number of individuals $S(x)$ who are still alive at age x without being infected. Then determine easily the number of individuals who had smallpox and survived to age x :$R(x) = P(x) - S(x)$. Finally, we determine for each age x, the number of deaths due to smallpox between age x and age $x + 1$. In theory, it is should be given by the integral $p\,q\,\int_x^{x+1} S(t)\,dt$ but the formula $p\,q(S(x) + S(x+1))/2$ is a good approximation (Trapezium Rule). In total, he deduced that out of the 1300 newborns, 101 are destined to die of smallpox, which is 1/13 as he had calculated.

Bernoulli then considers a harmless way in which the whole population would be inoculated from small pox at birth. Smallpox would be eradicated and the question is, what the gain would be in life expectancy. Thus, starting from the same number P_0 at birth and noting $P^*(x)$ the number of individuals surviving at age x in the absence of smallpox, we have,

$$\frac{dP^*}{dx} = -m(x)\,P^* \tag{1.6}$$

Using equation 1.3, Bernoulli found showed that

$$P^*(x) = \frac{P(x)}{1 - p + p\,P^* e^{-qx}}. \tag{1.7}$$

In particular the $P(x)/P^*(x)t \to 1-p$ for large values of x. One way to compare $P(x)$ and $P^*(x)$ is to estimate the life expectancy at birth, whose theoretical, expression is

$$EP = \frac{1}{P_0}\int_0^\infty P(x)\,dx$$

with smallpox, and a similar expression with $P^*(x)$ instead of $P(x)$ in the absence of smallpox. Bernoulli used the approximation expression $(P(0)+P(1)+P(2)+\ldots)/P0$ which is similar to the one given by the trapezium rule. He finally found that life expectancy E with smallpox is 26 years and 7 months. Without smallpox, the life expectancy $E^* =$ is 29 years and 8 months.

Inoculation at birth would save more than 3 years of life expectancy. Of course, inoculation with a little virulent strain of smallpox, is not completely without risk. If p' is the probability of dying from smallpox during inoculation ($p' < p$), while life expectancy in the case where all children are inoculated at birth becomes $(1-p')E^*$. This remains greater than the natural life expectancy E, if $p < 1 - E/E^*$, about 11%. Although there was no precise data available at the time, Bernoulli estimated the risk p, to be in fact less than 1%.

1.2 An SIR Deterministic Model :Kermack and MC Kendrick

W.O. Kermack and AG Mc Kendrick formulated a simple model of directly transmitted diseases at the beginning of the twentieth century. They tested their model with real data of the spread of plague in Bombay between 1905 and 1906. They divided the population into three compartments, S, for susceptible, I for infected the and R for removed, the model contains only two parameters : β the infection rate and γ the rate of recovery, whose values of are determined from the observed data. The size of the total population is assumed to be constant :

$$N = S(t) + I(t) + R(t)$$

Their model can be described by the following set of differential equations

$$\begin{cases} S'(t) = -\beta I(t)\,S(t) \\ I'(t) = \beta(t)\,S(t) - \gamma\,I(t) \\ R'(t) = \gamma\,I(t) \end{cases} \tag{1.8}$$

The general hypothesis adopted is that in the time interval dt, a fixed proportion of subjects no longer be considered as "infected". This applies to the proportion of individuals removed from the infection process because either they are immune, isolated, or dead. This proportion represented by the parameter γ may be zero and the model reduces to an SI model. It may also be equal to 1, in which case all infected are removed from the infection process during the time interval dt. Generally, the recovery rate γ takes an intermediate value.

Analysis of the model

The previous model is referred to as a general deterministic model, and its study led to establishment of the "threshold theorem". System 1.8 together with the initial condition $S(0) = S_0$, $I(0) = I_0$, and $R(0) = 0$ such that $I_0(0)$ and $S_0 = N$ is well posed. Here after we consider a susceptible population in which a small number of infectives is introduced. We show that the positive cone,

$$\mathbb{R}^3_+ = \{(S,I,R) \in \mathbb{R}^3_+ \;\mid\; S \geq 0,\; I \geq 0,\; R \geq 0\}$$

is positively invariant for system 1.8. As $N = \ constant = S(t)+I(t)+R(t)$, the study of system 1.8 is reduced to the study of

$$\begin{aligned} S'(t) &= -\beta I(t)\, S(t) \\ I'(t) &= \beta I(t)\, S(t) - \gamma\, I(t) \end{aligned} \tag{1.9}$$

Consider the following set

$$\triangle = \{(0 \leq S \leq N, 0 \leq I \leq N) \ \mid \ 0 \leq S + I \leq N\}$$

Dividing the second equation of 1.9 by $\gamma I(t)$, we have

$$\left\{ \ \frac{I'(t)}{\gamma I(t)} = \frac{\beta S(t)}{\gamma} - 1 \right. \tag{1.10}$$

Then, for $\frac{\beta\, S(t)}{\gamma} > 1$ each in infective individual infects more than one susceptible, and the disease will spread to an increasing number of individuals. So it will reduce the number of susceptible, $S(t)$ are such that $\frac{\beta\, S(t)}{\gamma} < 1$. The ratio $\frac{\beta}{\gamma}$ can then be interpreted as the number of sufficient contacts to transmit the disease in an infectives entire life of infectiousness.

By multiplying by the fraction of susceptible individuals at each instant, we get the total number of new cases infected by a single infectious individual. Equation 1.10 therefore highlights the importance of initial conditions in the general model, since $\frac{\beta\, S_0}{\gamma} > 1$, there is likely to be an epidemic, on the contrary, $\frac{\beta\, S_0}{\gamma} < 1$, only a few individuals will be infected before the epidemic dies out.

Let $\mathcal{R}_0 = \frac{\beta\, N}{\gamma}$. This threshold $\mathcal{R}_0$ is called the basic reproductive rate, it refers to the number of secondary cases produced by an average infectious individual during the entire period of his infectivity in a population that is entirely susceptible.

In case $\mathcal{R}_0 > 1$, although the system 1.8 can be solved explicitly, we have the following properties

1. S and I have the limits at $+\infty$. In effect, we know that $S'(t) = -\beta I(t)\, S(t) < 0$ so S is a decreasing function, again $S(t) \geq 0$, or $S(\infty) \geq 0$. In a similar reasoning in R, which is decreasing and bounded, we obtain $R(\infty) \geq 0$ and we deduce the result $I(\infty) = N - S(\infty) - R(\infty)$
2. If $S_0 > 0$ and $I_0 > 0$, then $0 < S(\infty) < S_0$ and $I(\infty) = 0$. Consequently, suppose that $S_0 > 0\ I_0 > 0$ and $R_0 = 0$ (without loss of generality, otherwise just set $N = N - R_0$. On one hand, for all $t > 0,\ S(t) > 0,\ I(t) > 0,\ R(t) > 0$ and

$$\frac{dS}{dR} = -\frac{\beta}{\gamma}\, S$$

or

$$S(R) = S_0\, e^{-\frac{\beta}{\gamma} R} \geq S_0\, e - \frac{\beta}{\gamma} N > 0$$

So $0 < S(\infty) < S_0$. on the other hand, $\lim\limits_{t\to\infty} S'(t) = -\beta S(\infty) I(\infty)$ exists. Furthermore, $\lim\limits_{t\to\infty} S'(t) = 0$. Otherwise if $\lim\limits_{t\to\infty} S'(t) = \alpha < 0$, then there exists a $T > 0$ such that for all $t > T,\ S'(t) < \frac{\alpha}{2}$, and therefore,

$$S(t) < S_0 + \frac{\alpha}{2} < 0 \quad for \quad t > -\frac{2S_0}{\alpha}.$$

This would contradict the fact that $S(t) > 0$ for all $t > 0$. So $S(\infty)I(\infty) = 0$ and when $S(\infty) > 0$, then $I(\infty) = 0$

3. The final size of the epidemic is given by $R(\infty) = N - S(\infty)$
4. We have $\frac{dI}{dS} = -1 + \frac{\gamma}{\beta S}$, and by integration we obtain,

$$I = -S + \frac{\gamma}{\beta} lnS + C$$

where C is a constant. Or

$$I + S - \frac{\gamma}{\beta} lnS = C = N - \frac{\gamma}{\beta} lnN.$$

The maximum size of the epidemic, i.e. I_{max} is given by

$$I_{max} = -\frac{\gamma}{\beta} + \frac{\gamma}{\beta} ln\frac{\gamma}{\beta} = N - \frac{\gamma}{\beta} lnN$$

since $S = \frac{\gamma}{\beta}$ in I_{max}

1.3 Transmission of DHF in an Age Structured Population

Pongpunsum studied an SIR model to describe the transmission of Dengue Hemorrhagic Fever (DHF). They divided the human population into two separate groups, viz ; an adult class and juvenile class with a differentiated transmission in the two age classes. The structure in age was motivated by DHF case in Thailand where most cases occur in children less than 15 years old.

The infection occurs to both classes but the rate for adults is assumed to be less than that of the children. Since most adults are exposed to DHF infection and develop immunity, many are not aware and they are referred to as the silent population. For the infected children, the antibodies will develop and they become adults with immunity. This means that the adults class composes of the silent population, those who are known to have been infected and those who have never had an infection. All the adults however are represented by S_A.

The grouping together solves the puzzle of identifying from which group an individual comes from. Such that the transmission from an infectious mosquito is the average of the transmission rates to the different subclasses. The dynamics of the SIR model with age structure is given by

$$\begin{cases} \frac{dS'_J}{dt} = \lambda' - \frac{b\,\beta_J}{N_T+m}\, S'_J\, I'_v - (\mu_h + \delta)\, S'_J \\ \\ \frac{dR'_J}{dt} = r\, I'_J - (\mu_h + \delta)\, R'_J \\ \\ \frac{dI'_J}{dt} = \frac{b\,\beta_J}{N_T+m} S'_J I'_v - (\mu_h + \delta + r)\, I'_J \\ \\ \frac{dS'_A}{dt} = \delta\,(S'_J + I'_J + R'_J) - \epsilon\,\beta_J \frac{b}{N_T+m}\, S'_A\, I'_v - \mu_h\, S'_J \\ \\ \frac{dR'_A}{dt} = r\, I'_A - \mu_h\, R'_A \\ and \\ \frac{dI'_A}{dt} = \epsilon\,\beta_J \frac{b}{N_T+m}\, S'_A\, I'_v - (\mu_h + r)\, I'_A \end{cases} \tag{1.11}$$

where $S'_{J(A)}$, $I'_{J(A)}$, *and* $R'_{J(A)}$ are the susceptible juveniles (adults), infected juveniles (adults),and recovered juveniles(adults), respectively ; N_T, the total population which is a constant ; m, the number of other animals the mosquito can bite ; b, the average number of bites a mosquito takes per day ; λ, the birth rate ; μ_h, the death rate similar for all categories) ; δ, the rate at which the juveniles pass into adulthood, and r is the rate at which the infected juvenile recover. I'_v is the number of infected mosquitoes ; β_J, the probability of the virus surviving in the juvenile after being bitten by an infected mosquito, and $\epsilon\beta_J$ is the probability of the virus surviving in a susceptible adult after an infectious bite. ϵ is the ratio between the probability than an adult becomes infected and the probability that a juvenile becomes infected by an infectious mosquito bite. It is assumed to be less than one.

The juvenile population dynamics is given by the equation

$$\frac{dN_J}{dt} = \lambda\, N_T - (\mu_h + \delta) N_J, \tag{1.12}$$

which was obtained by adding the first three equations of 1.11

The dynamics of the vectors is described by

$$\begin{cases} \frac{dS'_v}{dt} = A - \frac{b\,\beta_v}{N_T+m} S'_v\,(I'_J + I'_A) - \mu_h + S'_v \\ and \\ \frac{dI'_v}{dt} = \frac{b\beta_v}{N_T+m} S'_v\,(I'_J + I'_A) - \mu_h\, I'_v \end{cases} \tag{1.13}$$

where S'_v and I'_v is the number of susceptible and infected mosquitoes respectively ; μ_v, the death rate of the mosquitoes ; A, the mosquito carrying capacity of the environment and β_v is the probability that a dengue virus transmitted to the mosquito from an infected human, from a juvenile or an adult is infectious.
The vector population dynamics is given by

$$\frac{dS'_v + I'_v}{dt} = A - \mu_v\, N_v, \tag{1.14}$$

They normalized the parameters and eliminated the equations for R_J, R_A, and S_v to study the following set of equations

$$\begin{cases} \frac{dS_J}{dt} = (\mu_h + \delta)(1 - S_J) - \gamma_h S_J I_v \\ \frac{dI_J}{dt} = \gamma_h S_J I_v - (\mu_h + \delta + r) I_J \\ \frac{dS_A}{dt} = \mu_h - \epsilon \gamma_h S_A I_v - \mu_h S_A \\ \frac{dI_A}{dt} = \epsilon \gamma_h S_A I_v - (\mu_h + r) I_A \\ \frac{dI_v}{dt} = \gamma_{vJ}(1 - I_v) I_J + \gamma_{vA}(1 - I_v) I_A - \mu_v I_v \end{cases} \tag{1.15}$$

where

$$\gamma_h = \frac{b\,\beta_J(A/\mu_v)}{N_T + m}, \tag{1.16}$$

and

$$\gamma_{vJ} = \frac{b\,\beta_v\,N_{J(A)}}{N_T + m}. \tag{1.17}$$

By setting the RHS of equation 1.15 to zero, they established that a disease free equilibrium $E_0 = (1, 0, 1, 0, 0)$ and an endemic equilibrium $E_1 = (S_J^*, I_J^*, S_A^*, I_A^*, I_v^*)$ exists. Using linearization method they calculated the value of $\mathcal{R}_0$, and showed using Routh-Hurwiz criteria that the disease free equilibrium is locally asymptotically stable when $\mathcal{R}_0 \leq 1$.

The endemic equilibrium analysis was not easy and further simplifications were made. Looking at the data from Bangkok, it was clear that adults have only a small or no chance of becoming sick with the disease. So they set ϵ to zero and since the adults have developed immunity to the DHF, the two categories I_A' and R_A' would cease to exist. Now in the absence of adults and simplifications as explained above they studied an easier system. This enabled them to study the stability of the endemic equilibrium using linearization.

The endemic equilibrium is shown by simulation to be a stable spiral state. The periods of fluctuations in the number of individuals in each class became much shorter in the absence of any age structure. But the spiraling in, is much more severe in the absence of the age structure and the conclusion was that the age structure appears to calm down the fluctuations.

The model is a one patch model and quite different from malaria which attacks both the children and the adults albeit with differentiated magnitude.

1.4 Differential Susceptibility and Infectivity by Hyman

Hyman et al [69], formulated a differential susceptibility and infectivity model for disease transmission. They divided the susceptibles into n groups based on their susceptibilities, and the infectives are divided into m groups according to their infectivities. Using the standard and bilinear incidence for different diseases, they defined explicit formulas for the reproductive number for each subgroup.

The reproductive number for the entire population is a weighted average of the reproductive numbers for the subgroups. They showed that the infection-free equilibrium is globally stable

as the reproductive number is less than one for the models with the bilinear incidence or with the standard incidence but no disease-induced death. They then showed that if the reproductive number is greater than one, there exists a unique endemic equilibrium for these models. Numerical examples are provided to demonstrate that the unique endemic equilibrium is asymptotically stable if it exists. Here is a brief review of the model;

They considered the spread of a disease in a randomly mixing population that approaches a steady state S^0 if there is no disease infection. They assumed that infected individuals become fully immune or are removed from the susceptible population after they recover from the infection thus studying an SIR model.

The susceptibles who are assumed to have differential susceptibilities are divided into n groups $S_1, S_2, \ldots, S_n$. The individuals in each group have homogeneuos susceptibilities but the susceptibilities of individuals from different groups are distinct. The susceptibles are distributed into the n susceptible subgroups based on their inherent susceptibility, in such a way that the input flow into S_i is $p_i \mu S^0$ with $\sum_{i=1}^{n} p_i = 1$. The infectives are divided into m groups, $I_1, I_2, \ldots, I_m$, such that upon infection, a susceptible individual in group S_i enters group I_j with the probability q_{ij} and stays in this group until becoming recovered or removed, where $\sum_{i=1}^{n} q_{ij} = 1$ for $i - 1, 2, \ldots, n$. From this definition the transmission dynamics of infection are governed by the differential equations;

$$\dot{S}_i = \mu\,(p_i\,S^0 - S_i) - \lambda_i\,S_i, \qquad i = 1, \ldots, n \tag{1.18}$$

$$\dot{I}_j = \sum_{i=1}^{n} q_{ij}\,S_i - (\mu + \nu_j)\,I_j \qquad j = 1, \ldots, m \tag{1.19}$$

$$\dot{R} = \sum_{j=1}^{m} \nu_j\,I_j - (\mu + \delta)\,R \tag{1.20}$$

μ is the natural death rate in the absence of infection, ν_j is the recovery rate for infectives in group I_j, and δ is the death rate of the recovered or removed individuals.
The Basic reproduction number is defined as the dorminant eigenvalue of the Jacobian matrix at the disease free equilibrium as follows;
For the bilinear incidence we have;

$$\mathrm{R}_0 = \sum_{i=1}^{n} p_i\,c_o\,S^0\,\alpha_i \sum_{j=1}^{m} \frac{q_{ij}\,\beta_j}{\mu + \nu_j} \tag{1.21}$$

For the standard incidence it is defined as

$$\mathrm{R}_0 = \sum_{i=1}^{n} p_i\,r\,\alpha_i \sum_{j=1}^{m} \frac{q_{ij}\,\beta_j}{\mu + \nu_j} \tag{1.22}$$

They defined the reproductive number of infection in the susceptible group S_i from all infectives for the standard and bilinear incidence model to be

$$\mathrm{R}_{0i} = c\,(S^0)\beta_i\,\tau_i.$$

Where

$$\tau_i := \sum_{j=1}^{m} \frac{q_{ij}}{\mu + \nu_j}$$

defines the mean duration of infection from all infectives to susceptibles in group S_i and

$$\beta_i := \alpha_i \frac{1}{\tau_i} \sum_{j=1}^{m} \frac{q_{ij}\,\beta_j}{\mu + \nu_j}$$

is the mean transmissiom probability from all infectives to susceptibles in group S_i.
Then the reproductive number for the entire population can be expressed as the weighted average of the group reproductive numbers such that

$$\mathrm{R}_0 = \sum_{i=1}^{n} p_i\,\mathrm{R}_{0i}.$$

Hyman et al, proved that the disease free equilibrium is globally stable when $\mathrm{R}_0 < 1$ and unstable otherwise. When $\mathrm{R}_0 > 1$ its shown that there exists an endemic equilibrium and solutions approach this equilibrium asymptotically. They did not proceed to consider the differential susceptibility and infectivity for spatial population in their research.

1.5 A model for Disease transmission in a Metapopulation by J.Arino

Arino et al [11], formulated a model that incorporates the movement of individuals over a range of spatial scale. They investigated the behavior of the system for a case in which the spatial component consist of a ring of patches and the disease is transmitted between different species in multiple patches. A formula for R_0 is provided and a stability analysis for the disease free equilibrium.

They formulated model that involves s species and n spatial patches and they proceeded as follows
Let N_{ip} be the population number of species $i = 1, 2, \ldots, n$ in patch $p = 1, 2, \ldots, n$. For species i the rate of travel or migration from patch q to patch p is denoted by $m_{ipq} \geq 0$. These rates form a non negative matrix $\hat{M}_i = [m_{ipq}]$ with $m_{ipp} = 0$. They excluded demography and the rate of change of N_{ip} is given by

$$\dot{N}_{ip} = \sum_{q=1}^{n} m_{ipp}\,N_{iq} - \Gamma_{ip}\,N_{ip} \tag{1.23}$$

where $\Gamma_{ip} = \sum_{q=1}^{n} m_{iqp}$. Setting $N_i = [N_{i1}, N_{i2}, \ldots, N_{in}]^T$, where superscript T denotes transpose, gives the travel equation

$$\dot{N}_i = M_i\,N_i \tag{1.24}$$

with the mobility matrix $M_i = \hat{M}_i - D_i$. Where D_i is a diagonal matrix with Γ_{ip} as the (p, p) entry.

From the sign pattern of M_i and the fact that each column sum is 0, it follows that $(-M)$ is a singular M- matrix ([42] Th. 5 :11). The non-zero entries of M_i specify the arcs of a directed graph for travel connections between patches (as vertices). Arino assumed that from each patch

p, to patch q there exists a path in the directed graph so that M_i is irreducible.
For each of the n, patches they formulated a general SEIRS compartmental epidemic model for a disease that confers temporary immunity with $S_{ip}, E_{ip}, I_{ip}, R_{ip}$ denoting the Susceptibles, Latent, Infected (Infectious), and Recovered individuals of species i in patch p at time t,respectively. Therefore

$$N_{ip} = S_{ip} + E_{ip} + I_{ip} + R_{ip}.$$

The new borns from species i in patch p enter the susceptible class with the birth term $d_{ip}N_{ip}$. The transmission term between the species is a standard incidence is $\beta_{ijp} \geq 0$ and defines the average number of adequate contacts per unit time in patch p, between susceptible of species i and infectives of species j. Assuming that the rates of travel are independent of disease status and neglecting disease related deaths, they derived the following system of $4sn$ equations for species $i = 1, 2, \ldots, s$ in patch $p = 1, 2, \ldots, n$

$$\dot{S}_{ip} = d_{ip}\,(N_{ip} - S_{ip}) + V_{ip}\,R_{ip} - \sum_{j=1}^{s} \beta_{ij}\,S_{ip}\,\frac{I_{ip}}{N_{ip}} + \sum_{q=1}^{n} m_{ipq}S_{iq} - \Gamma_{ip}\,S_{ip} \tag{1.25}$$

$$\dot{E}_{ip} = \sum_{j=1}^{s} \beta_{ij}\,S_{ip}\frac{I_{ip}}{N_{ip}} - (d_{ip} + \varepsilon_{ip}) + \sum_{q=1}^{n} m_{ipq}E_{iq} - \Gamma_{ip}\,E_{ip} \tag{1.26}$$

$$\dot{I}_{ip} = \varepsilon_{ip}\,E_{ip} - (dip + \gamma_{ip})\,I_{ip} + \sum_{q=1}^{n} m_{ipq}\,E_{iq} - \Gamma_{ip}\,I_{ip} \tag{1.27}$$

$$\dot{R}_{ip} = \gamma_{ip}\,I_{ip} - (d_{ip} + \nu_{ip})\,R_{ip} + \sum_{q=1}^{n} m_{ipq}R_{iq} - \gamma_{ip}\,R_{ip} \tag{1.28}$$

To study the stability of this system they proceeded as follows;

Let

$$F = \begin{bmatrix} 0 & G \\ 0 & 0 \end{bmatrix},$$

where $G = \oplus_{k=1}^{n} G_k$, *and* $\oplus$ denotes direct sum.

$$V = \begin{bmatrix} A & 0 \\ -C & B \end{bmatrix},$$

with

$$A = \begin{bmatrix} A_{11} & \ldots & A_{1n} \\ \ldots & \ldots & \ldots \\ A_{n1} & \ldots & A_{nn} \end{bmatrix},$$

and

$$B = \begin{bmatrix} B_{11} & \ldots & B_{1n} \\ \ldots & \ldots & \ldots \\ B_{n1} & \ldots & B_{nn} \end{bmatrix},$$

and

$$C = \oplus_{k=1}^{n} C_k$$

Here G_k, A_{jk}, B_{jk}, C_k are s x s matrices with A_{jk}, B_{jk}, C_k diagonal. Matrix G_k has (i,j) entry equal to $\beta_{ijk}\frac{N^*_{ik}}{N^*_{jk}}$, the (i,i) entry A_{kk} is equal to $d_{ik}+\varepsilon_{ik}+\sum_{l=1}^{n} m_{ilk}$, whereas for $j=k$ the (i,i) entry of A_{jk} is $-m_{ijk}$.

Matrix B is the same as A but with ε_{ik} replaced by γ_{ik}. Finally C_k has (i,i) entry equal to ε_{ik}.
From the sign pattern and the fact that they are diagonally dorminant by columns, A and B are non singular M- matrices [2], thus A^{-1} and B^{-1} are non negative. Using the result in [141], a formula was obtained for the basic reproduction number $\mathcal{R}_0$ and the following stability result.

Theorem 1.1. For the model 1.25 with s species and n patches $\mathcal{R}_0 = \rho(GB^{-1}CA^{-1})$, Where ρ denotes the spectral radius. If $\mathcal{R}_0 \leq 1$, then the disease free equilibrium is globally asymptotically stable, and if $\mathcal{R}_0 > 1$, then the disease free equilibrium is unstable.

In this study metapopulation and its dynamical effect on disease transmission has been done but the study did not consider differential susceptibility and differential infectivity in the patches.

1.6 Ross Model

Ronald Ross modeled the transmission of malaria and identified the basic reproduction number as a threshold for the invasion and persistence of infection. The basic reproduction number which defines the number of secondary infections resulting from one infectious individual in an entirely susceptible population, determines if the disease will invade the population (if it is greater than 1) or die out (if it is less than 1).

The Ross model divides the entire population as either susceptible or infected (hence infectious). Assuming a constant host population H, he defines I_h as the number of hosts that are infectious, thus there are $H - I_h$ susceptible hosts. Using proportions, he used $\frac{I_h}{H}$ and $\frac{H-I_h}{H}$ to define the fraction of infectious and susceptible hosts respectively. The total vector population is similarly defined with V, the total and vector population, and I_v, the number of infectious vectors, such that $S_v = V - I_v$.

According to Ross, an infection only occurs if a susceptible host is bitten by an infectious vector. The rate at which vectors bite is independent of the number of hosts available since it is clear that each vector needs a certain number of blood meals per unit time. Assuming that the hosts are readily available when the vector needs a blood meal, the biting rate will be proportional to the number of vectors and not the number of hosts.

The man biting rate of vectors is taken to be a, and the proportion of infectious bites to a host, b_1. Once infected the host will remain infectious for a period $\frac{1}{\gamma}$ and then recover to join again the susceptible class. The probability that a susceptible vector gets infected when it bites an infected host is defined as b_2. It is assumed that once a mosquito is infected, it remains so for its entire life, which is assumed to be $\frac{1}{\mu}$ time units.
This leads to the pair of equations

$$\begin{cases} \dot{I}_h = b_1\, a\, \frac{(H-I_h)}{H} I_v - (\gamma)\, I_h \\ \dot{I}_v = b_2\, a\, (V - I_v)\, \frac{I_h}{H} - \mu\, I_v \end{cases} \tag{1.29}$$

He found out that the basic reproductive ratio $\mathcal{R}_0$ is a threshold that determines if the malaria will persist or die out. Precisely if

$$\mathcal{R}_0^2 = \frac{a^2\, b_1\, b_2\, V}{\gamma\, \mu\, H} \leq 1,$$

Malaria will disappear in the long run
and if

$$\mathcal{R}_0^2 = \frac{a^2\, b_1\, b_2\, V}{\gamma\, \mu\, H} > 1,$$

Malaria will settle to an endemic equilibrium where both the infectious host and infectious vector populations will be positive.

The square on $\mathcal{R}_0$ comes from the fact that two generations are needed for transmission of malaria to take place, first from an infectious host to a susceptible mosquito and then from an infectious mosquito to a susceptible host. The square on the biting rate a, results from the two cycles of biting necessary for an infection to occur. The expression of basic reproduction number shows that it is directly proportional to the vector population and inversely proportional to the host population. The threshold $\mathcal{R}_0^2 = 1$ determines if the disease will break out or die out.

1.7 Global analysis of a vector-host epidemic model with nonlinear incidences by Li-Ming Cai et. al.

Ming proposed an epidemic model with nonlinear incidences that describe the dynamics of diseases spread by vectors (mosquitoes) with a constant human and vector populations. Basing their formulating on the Ross-Macdolnald model, they included a Holling Type 2 saturation in the vector populations, which is divided into susceptible and infected vectors.

The dynamics of the human host is described by an SIR mode, that is, susceptible, infected and removed compartments. They considered transmission of a vector borne disease where the transmission is affected by the host behaviour and therefore assumed that the number of infective vectors is proportional to those of the infective human hosts. The result of preventive behaviour in hosts may also limit further transmission of the disease. Another factor that affects transmission is immunity which they argue enhances transmission. From these facts, they assumed that the infection force of the host population saturates with the infected vectors. The following three hypothesis guides the dynamics of their model.

(H_1) : For host population, the total population under consideration is divided into three classes : $S_H(t)$, $I_H(t)$, and $R_H(t)$, the susceptible, infected and recovered respectively at time t. $N_H(t) = S_H(t) + I_H(t) + R_H(t)$ is the total number of the human population and μK is the recruitment rate of the newborns into the susceptible population. μ, γ_0, γ_1 represents the natural death rate, recovery rate and rate of human treatment respectively.

(H_2) : For the vector population, $S_v(t)$, $I_v(t)$, is the number of susceptible and infective vectors respectively, at time t. The recovery class of mosquitoes is omitted since mosquitoes do

not recover from parasite infection. The total vector population thus, is given by $N_v(t) = S_v(t) + I_v(t)$. The rate of recruitment for the vector is the constant rate Λ and the total deaths in mosquitos occur at a rate $mN_v(t)$, where m is the per capita mortality. The differential equation governing the dynamics of the vector population is

$$N_v'(t) = \Lambda - mN_v(t).$$

As $t \to \infty$ the solution N_v approach Λ/m.

(H_3) : Let β_1 be the transmission rate from vector to human and β_2, the transmission form human to vector. Then considering the saturation in the force of infection the incidence terms for the host and vector populations are given respectively by

$$\frac{\beta_1 S_H I_v}{1+\alpha_1 I_v}, \qquad \frac{\beta_2 S_v I_H}{1+\alpha_2 I_v},$$

where $\alpha_1,\ \alpha_2$ determine the level at which the force of infection saturates.

The dynamics of the vector host epidemics is described by the following equations

$$\begin{aligned}
S_H' &= \mu K - \tfrac{\beta_1 S_H I_v}{1+\alpha_1 I_v} - \mu S_H \\
I_H' &= \tfrac{\beta_1 S_H I_v}{1+\alpha_1 I_v} - (\mu+\gamma) I_H, \\
R_H' &= \gamma I_H - \mu R_H, \\
S_v' &= \Lambda - \tfrac{\beta_2 S_v I_H}{1+\alpha_2 I_v} - m S_v \\
I_v' &= \tfrac{\beta_2 S_v I_H}{1+\alpha_2 I_v} - m I_v
\end{aligned} \tag{1.30}$$

where $\gamma = \gamma_0 + \gamma_1$. Since $N_v \to \Lambda/m$, then we can assume $S_v = \Lambda/m - I_v$; The system is feasible in the regionR_+^5, the positive orthant of R^5. Since R_H and S_v can be determined from the total population, the dynamics of model 1.30 is determined by the three dimension nonlinear system

$$\begin{aligned}
S_H' &= \mu K - \tfrac{\beta_1 S_H I_v}{1+\alpha_1 I_v} - \mu S_H \\
I_H' &= \tfrac{\beta_1 S_H I_v}{1+\alpha_1 I_v} - \omega I_H, \\
I_v' &= \tfrac{\beta_2 S_v I_H}{1+\alpha_2 I_v}(\Lambda/m - I_v) - m I_v
\end{aligned} \tag{1.31}$$

where $\omega = \mu + \gamma$. For the system 1.31, the region

$$\Omega = \{(S_H; I_H, I_v) \in R_+^3 \ \ 0 \le S_H + I_H \le K, \ \ 0 \le I_v \le \Lambda/m\}$$

The basic reproduction number for the system was calculated to be

$$\mathcal{R}_0 = \frac{\beta_1\, \beta_2\, K \Lambda}{m^2\, \omega}$$

where and they proved that in the absence of the disease all solutions tend to the disease free equilibrium E_0, when $\mathcal{R}_0 \le 1$. When the $\mathcal{R}_0 > 1$, E_0 becomes unstable and an endemic

equilibrium emerges in Ω. Linearising the system at the endemic equilibrium and using the second additive matrix result, they established the local and global stability of system 1.12. Finally they simulated the model and demonstrated some analytical results and explored the significance of the nonlinear incidence. These results showed that even though the stability results do not depend directly on the parameters $\alpha_1,\ \alpha_2$, a decrease in these two parameters produces an increase in the number of secondary infections. They confirmed therefore that the parameters $\alpha_1,\ \alpha_2$ which are varying, control the magnitude of the infective individuals.

1.8 Ross-Macdonald Model in a Patchy environment by Auger et. al.

Auger et al [14], modified Ross-Macdonald model and subdivided the populations into n patches with susceptible/infectious humans and vectors residing in the patches. They assumed that some patches can be vector free, the hosts can migrate between the patches but not the vectors, and that the susceptible and infectious individuals have the same dispersal rate.

Basing their equations on the Ross-macdonald models, they came up with a set of equations describing their new model. They computed the basic reproduction ratio R_0 and proved that when $\mathrm{R}_0 \leq 1$, the disease free equilibrium is globally asymptotically stable, and when $\mathrm{R}_0 > 1$, there exists and endemic equilibrium, which is also globally asymptotically stable on the biological domain minus the disease free equilibrium. Here is a brief description of their model : The transfer rate from patch i to patch j, for $i \neq j$, is denoted by $m_{ij} \geq 0$. The total host population on patch i is denoted N_i. For $i = 1, 2, \ldots, n$, the dynamics is given by

$$\dot{N}_i = \sum_{j=1^n, j\neq i} m_{ij} N_j - N_i \sum_{j=1, j\neq i^n} m_{ij}.$$

This system can be written as

$$\dot{N} = MN \tag{1.32}$$

They used the following notations

- $I_{h,i}$ is the infectious host population on patch i
- p is the number of patches harboring vectors, $I_{v,i}$, V_i are, respectively, the infectious vector population and constant vector population on patch i. If $i > p$ there is no vector on patch i, i.e., V_i=0
- a is the man biting rate of vectors
- b_1 is the proportion of infectious bites on hosts that produce a patent infection.
- b_2 is the proportion of infectious bites by susceptible vectors on infectious hosts that produce a patent infection.
- μ is the per capita rate of vector mortality.
- γ is the per capita rate of host recovery from infection.

Auger et al numbered the patches such that only the first p patches, $1 \leq p \leq n$, are infested by the vectors. On the patches i for $i > p$, $V_i = 0$, hence $I_{v,i} = 0$
For patches such that $i \leq p$, i.e., where vectors are present, we have

$$\dot{I}_{h,i} = b_1\, a\, I_{v,i}\frac{N_i - I_{h,i}}{N_i} - \gamma\, I_{h,i} + \sum_{j=i,j\neq i}^{n} m_{ij}\, I_{h,j} - I_{h,i}(\sum_{j=i,j\neq i}^{n} m_{ij}) \tag{1.33}$$

$$\dot{I}_{v,i} = b_2\, a\,(V_i - I_{v,i})\frac{I_{h,i}}{N_i} - \mu\, I_{v,i} \tag{1.34}$$

For $i > p$, there are no vectors on patch i and the equation for the infectious hosts has only the recovery and migration terms. The equation governing the evolution of $I_{h,i}$ is the following

$$\dot{I}_{h,i} = -\gamma\, I_{h,i} + \sum_{j=i,j\neq i}^{n} m_{ij} I_{h,j} - I_{h,i}(\sum_{j=i,j\neq i}^{n} m_{ij}) \tag{1.35}$$

They used some notations and conventions to represent the whole system as

$$\dot{N} = M\, N \tag{1.36}$$

$$\tag{1.37}$$

$$\dot{I}_h = \beta_1\, \mathrm{d}iag(N)^{-1}\, \mathrm{d}iag\,(N - I_h)\, I_v - \gamma\, I_h + M I_h \tag{1.38}$$

$$\tag{1.39}$$

$$\pi\, \dot{I}_v = \beta_2\, \mathrm{d}iag(\pi N)^{-1}\, \mathrm{d}iag\,(\pi\,(V - I_v))\pi\, I_h - \mu\, \pi\, I_v \tag{1.40}$$

where $\mathrm{d}iag(X, p, q)$ denotes, the $p \times q$ matrix diagonal matrix whose diagonal is given by the components of X and the other terms are zero for $X \in \mathcal{R}^p$ or $X \in \mathcal{R}^q$

Using the concept of Metzler matrices and with further simplification of the system they showed that the origin is the disease free equilibrium and computed the basic reproduction number as

$$\mathcal{R}_0^2 = \frac{\beta_1\, \beta_2}{\mu}\rho(-\mathrm{d}iag\,(\pi\, \mathrm{m})\, Z),$$

where $Z = (D - \gamma I)^{-1}(1 : p, 1 : p)$, i.e., the sub-matrix of the p first rows and p first columns of $D - \gamma I)^{-1}$. It was proved that the disease free equilibrium is globally asymptotically stable.

The stability analysis of the endemic equilibria was done using the theory of irreducible monotonic systems, Lyapunov functions and the La Salle invariance principle. They proved that the endemic equilibrium is locally and also globally asymptotically stable. In this study the researchers concentrated on metapopulation of malaria and the dynamics of transmission when the human host migrates. However they did not consider, differentiated susceptibility and infectivity which are important factors in malaria transmission, that we cannot afford to ignore especially in a patchy environment.

CHAPITRE 2

A Differentiated Susceptibility and Infectivity Age Structured Malaria model

Contents

Introduction

2.1 An SIS malaria model in a patchy environment

2.2 Introduction

Malaria is caused by a parasite of a genus plasmodium, that is transmitted by the female anopheles mosquito as it sucks blood from human hosts for its egg development.
In Kenya, malaria is the leading cause of morbidity and mortality. It is estimated that it accounts for 30% of all outpatient attendance and 19% of all admissions to health facilities. The infection ranges from intense in the lowland to endemic in the highlands causing havoc to the public health system especially during periods of suitable climatic conditions. About 20% of all deaths in children under five are as a result of malaria infection (MOH 2006). Although the disease is found in most parts of the country, the lake stable and coastal region plus the highland epidemic-prone districts have risks of over 20% and 19% respectively, with an estimated population of 19 million people (or 49% of the total Kenyan population).
The Western Kenya highlands bares the greatest blunt of the disease with some areas suffering as high as 70% infection rates. Entomological studies in different highland ecosystems indicate that transmission is heterogeneous. The terrain characteristics and topography which processes rain, results to big differences in epidemic magnitudes. A result identified three hydrological systems including the V-shaped valleys, the U-shaped valleys and the plateaus.
The types of valleys determine drainage quality, the rainfall threshold and consequently vector

breeding. The U-shaped valleys are broad shaped and have slow moving rivers or streams with poor drainage. This favors mosquito population growth resulting in high malaria infection rates and incidence.

The V-shaped valleys have narrow bottoms with fast flowing rivers or streams with good drainage, this makes it hard for mosquito to find suitable breeding sites and thus lower their population growth. The plateaus are flat, though they have good drainage, and their ecosystem behaves like the V-shaped valleys unless there are large water bodies like dams. This implies that the terrain characteristics can modify the level of malaria transmission and the rate of development of immunity as the risk of an epidemic is closely related to the level of immunity of the human population [149].
The V-shaped and the U-shaped valleys are located in different geographical locations, thus clearly separated, and are apart, so in this case the 'spatialization' is discontinuous. Then the natural tool for modeling in this case is metapopulation.

In Kenya malaria is labeled as a 'travelling disease'. Report from Kibera's Ushirika clinic in Nairobi, where malaria is the main disease treated daily, estimates that 80% percent of the people treated for malaria had travelled out of Nairobi. This implies they got infected and returned, with symptoms only appearing once they are back in the estate. The neighbouring estate is inhabited by people who live near Lake Victoria, where the disease is widespread. By being less exposed to malaria, many loose the semi-immunity they used to have. This is why they contract it easily when travelling upcountry, (http://www.irinnews.org/Report/73501/KENYA-Climate-change-and-malaria-in-Nairobi). This brings the disease to the city which has been free of malaria. Then metapopulation models with migration between the patches suits the 'highland malaria' dynamics in Kenya. Understanding human movement will facilitate the identification of individuals and key zones in malaria transmission and may guide intervention measures, monitoring and improve the intervention programs.

Result from literature also confirms that children between 1 and 5 years represent a very significant source of mosquito infections compared to adults [49] and they are not also bitten in same way as adults [109, 130]. Moreover it is well observed that there is a differentiation in these two age groups as most deaths occur in infants and parasitemia levels of infected individuals decrease with age [139]. This naturally constricts us to differentiated susceptibility and infectivity models.
With the predicted climate change [105], the epidemics may become more frequent and severe posing a serious threat on the already strained public health system. Furthermore, due to the large areas affected by epidemic malaria, it may not be affordable to spray every house with indoor residual insecticides [149]. A model that would lead to a better understanding of transmission and risk of severe disease comes in handy at this time.

Mathematical modeling plays a major role in understanding infectious disease dynamics as it describes the complex disease transmission processes. It also provides insights into the disease dynamics during the rigorous analysis process. The first malaria model was formulated by Sir. Ronald Ross in 1911 [121]. Since then, modeling of vector borne disease has grown in leaps and bounds as shown in reviews [19, 34, 36, 58]. Hyman [69] et al. formulated a general differential susceptibility and differential infectivity model for a disease transmission. They proved that the disease free equilibrium is globally stable when $\mathcal{R}_0 \leq 1$ and unstable otherwise. When $\mathcal{R}_0 > 1$

they show that there exists an endemic equilibrium and solutions approach this equilibrium asymptotically. The model can only be used for directly transmitted disease. Pongsumpun [119] formulated a model to study the influence of age structure in an SIS model for Dengue Hemorrhagic Fever (DHF) and showed that age structure reduces the periods of oscillation on the susceptible and infected human population and the infected mosquito population. It also tightens the spiraling into the endemic equilibrium state. The difference with our intended model is the metapopulation setting, the differentiated patch and age susceptibility and infectivity, not forgeting the disease malaria.
Auger et.al. [14] modified Ross model to n patches. A thorough analysis on the local and global stability of the disease free and the endemic equilibrium is done using $\mathcal{R}_0$. The model however assumed that the susceptibility and infectivity is similar in all the patches, an important difference that we wish to model considering the heterogenity in the ecosystem of Western Kenyan Highlands.
Motivated by the work of [14] and [119], we formulate an age structured malaria model with susceptibility and infectivity of an individual depending on their age and residence patch. We shall then compare our results with the current findings.

The region is subdivided into homogenous patches and the population in the patches is further subdivided into children, ages 1-5, and adults, over 5 years of age. The susceptibility of the two age groups is differentiated to depend on the patch where the individual resides. The two age groups are allowed to migrate between the patches, making short visits to return to their residences later.

We assume that the rate of migration does not depend on the epidemiological status and age of the human host, that is, that the infected or uninfected children move with the same migration rate with the infected or uninfected adults. We also assume that mosquitoes do not migrate.
In Section 2, we formulate a mathematical model describing the dynamics of a two class age structure of the human population occupying the patches with migration rates between the patches similar for the two classes. In Section 3,the system is reduced to a more compact form for ease of analysis. In Section 4, we describe the basic properties of the model. In Section 5, we study the stability of the model. An example of the model in two patches is presented in Section 6 and numerical analysis is done in Section 7.

2.3 The model

Let S_{hi}^C (S_{hi}^A), denote the susceptible children (adults) in patch i respectively, while I_{hi}^C (I_{hi}^A) denotes the susceptible children (adults) respectively. The vector population is likewise identified by S_{vi} and I_{vi} for the susceptible and infective vectors respectively. The total human population which is assumed to be constant, is given by the sum of all host in all the patches as $N = S_h + N_h$. So that $N_i = N_i^C + N_i^A$ denotes the total host population in patch i. The total vector populations is given by the sum of all vectors in all the patches as $V = S_v + I_v$ and $V_i = S_i + I_i$ is the total vector population in patch i. Migration of hosts is allowed in and out of the patch with an assumption that those who visit return to their resident patches (i.e. they make short visits sufficient for transmission to take place). We assume a uniform migration rate $m_{ij} \geq 0,\ i = 1..n$ denoting proportion of individuals from patch j to patch i. The flow of individuals into the different compartments is represented in Diagram 2.1 shown below

The total host population on patch i is defined as $N_i = N_i^C + N_i^A$ and its dynamics is given

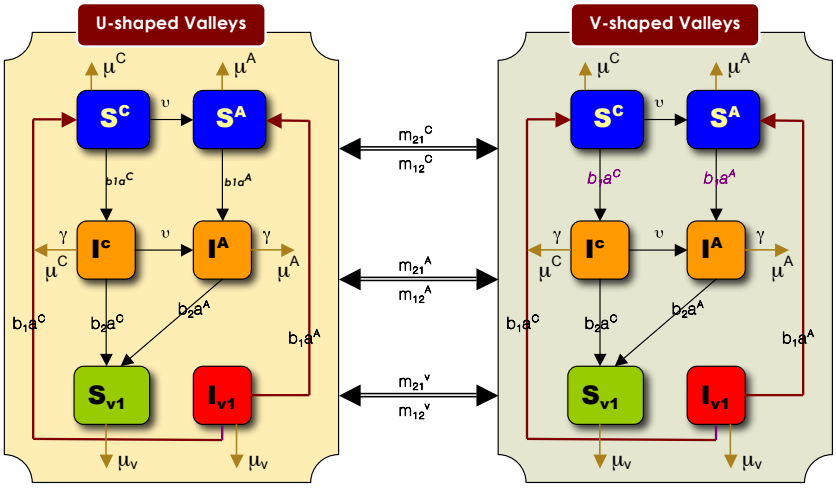

Figure 2.1 – Transfer Diagram for the different epidemiological groups in different patches

by $\dot{N}_i = \dot{N}_i^C + \dot{N}_i^A$, and

$$\dot{N}_i^C = \sum_{j=1, j\neq i}^{n} m_{ij}^C N_j^C - \sum_{j=1, j\neq i}^{n} m_{ji}^C N_i^C$$

$$\dot{N}_i^A = \sum_{j=1, j\neq i}^{n} m_{ij}^A N_j^A - \sum_{j=1, j\neq i}^{n} m_{ji}^A N_i^A$$

where $\sum_{j=1,j\neq i}^{n} N_j$ is the total number of residents of patch i at time t [10].

We define the vector of $\mathbb{R}_+^n$, N^C, N^A and N^v whose components are respectively N_i^C, N_i^A and N_i^v.

If we define the matrix M^C by

$$M_{i,j}^C = \begin{cases} m_{ij}^C \text{ if } i \neq j \\ \\ m_{ii}^C = -\sum_{j=1, j\neq i}^{n} m_{ji}^C \text{ otherwise} \end{cases}$$

and the matrix M^A analogously, the preceding equations are

$$\hat{E}\dot{N}^C = M^C N^C \quad \dot{N}^A = M^A N^A$$

We can also assume that there is some migration for the mosquitoes, at least for some nearby patches. Then in the same way we introduce

$$\hat{E}\dot{N}^v = M^v N^v$$

If all the patches are sufficiently distant from each others, then no migration of mosquitoes occurs then $\mathcal{M}^v = 0$

Therefore the dynamics of the total host and vector population on patch i is be defined by

$$\dot{N}_i^{\triangle} = \mathcal{M}\, N_i^{\triangle} \tag{2.1}$$

where $N^{\triangle}$ is the vector defined by

$$\hat{E}N^{\triangle} = \begin{bmatrix} N^C \\ N^A \\ N^v \end{bmatrix}$$

and the matrix $\mathcal{M}$ is the diagonal block matrix

$$\hat{E}\mathcal{M} = \begin{bmatrix} M^C & 0 & 0 \\ 0 & M^A & 0 \\ 0 & 0 & M^v \end{bmatrix}$$

Our migration equation becomes

$$\dot{N} = \mathcal{M}\, N. \tag{2.2}$$

The following are the notations used in the model :

- Λ_i is the recruitment of new born children in patch i.
- $S_{h,i}$, $I_{h,i}$ is the susceptible, respectively infectious host population on patch i
- $S_{v,i}$, $I_{v,i}$ is the susceptible, respectively infectious vector population on patch i.
- a_i is the man biting rate of vectors in patch i.
- b_1 is the proportion of infectious bites on host that produce a patent infection
- b_2 is the proportion of bites by susceptible vectors on infected host that produce a patent infection
- $\mu_{h,i}^C(\mu_{h,i}^A)$ is the per capita rate of children (adult) mortality in patch i.
- ν is the rate children translate to adults. Then $\frac{1}{\nu}$ is the mean duration of childhood.
- $\mu_{v,i}$ is the per capita rate of vector mortality.
- γ_i^C is the per capita rate of child recovery from infection, and $\frac{1}{\gamma_i^C}$ is the childs' mean duration in the infectious compartment in patch i. A similar definition holds for the adult recovery, γ_i^A .

The total host and vector population in all the patches is constant. We assume that the parameters a_i is dependent on the host age group in the patches. We also assume that recovery rate γ_i does not depend on age [139] but on how quickly the host receives treatment and their history of malaria infection. This clearly depends on the nature of the health system in the patch i.
We consider age structured system where children translate to adults at a rate ν.

For the patches $i = 1, \ldots, n$ we have the $6\,n$ equations

$$
\begin{aligned}
\dot{S}^C_{h,i} &= \Lambda_i - b_1 a^C_i \tfrac{S^C_{h,i}}{N_i} I_{v,i} + \gamma^C_i\, I^C_{h,i} - (\mu^C_i + \nu) S^C_{h,i} + \sum_{j=1, j\neq i}^{n} m^C_{ij} S^C_{h,j} - S^C_{h,i} \sum_{j=1, j\neq i}^{n} m^C_{ji} \\
\dot{S}^A_{h,i} &= \nu S^C_{h,i} - b_1 a^A_i \tfrac{S^A_{h,i}}{N_i} I_{v,i} + \gamma^A_i\, I^A_{h,i} - \mu^A_i S^A_{h,i} + \sum_{j=1, j\neq i}^{n} m^A_{ij} S^A_{h,j} - S^A_{h,i} \sum_{j=1, j\neq i}^{n} m^A_{ji} \\
\dot{I}^C_{h,i} &= b_1 a^C_i \tfrac{S^C_{h,i}}{N_i} I_{v,i} - (\gamma^C_i + \mu^C_i + \nu) I^C_{h,i} + \sum_{j=1, j\neq i}^{n} m^C_{ij} I^C_{h,j} - I^C_{h,i} \sum_{j=1, j\neq i}^{n} m^C_{ji} \\
\dot{I}^A_{h,i} &= b_1 a^A_i \tfrac{S^A_{h,i}}{N_i} I_{v,i} + \nu I^C_{h,i} - (\gamma^A_i + \mu^A_i) I^A_{h,i} + \sum_{j=1, j\neq i}^{n} m^A_{ij} I^A_{h,j} - I^A_{h,i} \sum_{j=1, j\neq i}^{n} m^A_{ji} \\
\dot{S}_{v,i} &= \Lambda_v - \tfrac{S_{h,i}}{N_i}(b_2 a^C_i I^C_{h,i} + b_2 a^A_i I^A_{h,i}) - \mu_{v,i} S_{v,i} + \sum_{j=1, j\neq i}^{n} m^v_{ij} S^v_{v,j} - S_{v,i} \sum_{j=1, j\neq i}^{n} m^v_{ji} \\
\dot{I}_{v,i} &= \tfrac{S_{h,i}}{N_i}(b_2 a^C_i I^C_{h,i} + b_2 a^A_i I^A_{h,i}) - \mu_v\, I_{v,i} + \sum_{j=1, j\neq i}^{n} m^v_{ij} I^v_{v,j} - I_{v,i} \sum_{j=1, j\neq i}^{n} m^v_{ji}
\end{aligned}
\tag{2.3}
$$

The term Λ_i represents the recruitment of newborns into the susceptible children's class. $b_1 a^C_i I_{v,i} \frac{(S^C_{h,i})}{N_i}$ in the first equation represents the differentiated infection of susceptible children by infectious mosquitoes using frequency dependent transmission and a non constant host population in patch i. The term $-\gamma_i I^C_{h,i}(-\gamma_i I^A_{h,i})$ defines the recovery of infected child (adult) respectively, μ^C_i is the per capita death rate of children in patch i, ν is the rate children pass into adulthood, and the last term defines host migration. For the second and third equations the terms are defined similarly for Adults. The fifth equation for infectious vectors has the first term corresponding to the infection of susceptible mosquitoes by infected Children and infected Adults, while the last term $-\mu_i I_{v,i}$ caters for vector mortality.

We will assume in the sequel that $\nu < \gamma^A_i$ for any index i
The rationale for this assumption is that the rate of recovering, for an adult or a child, is considerably greater than the mean sojourn time in the compartment of childhood. Actually $\nu \approx \dfrac{1}{5 \times 365}\, j^{-1}$ and $\gamma^A_i \approx \dfrac{1}{2 \times 30}\, j^{-1}$
The complete system is given by equations and (2.3).

2.4 Reduced System

It turns out that system given by equations (2.3) can be rewritten in a triangular form so we need the following theorem to reduce such a system and thus study a smaller system.

Theorem 2.1 (Vidyasagar). Consider the following $\mathcal{C}^1$ system :

$$
\begin{cases}
\dot{x} = f(x) \qquad x \in \mathbb{R}^n, y \in \mathbb{R}^m \\
\dot{y} = g(x, y) \\
\textit{with an equilibrium point,} \quad (x^*, y^*) i.e \\
f(x^*) = 0 \ \textit{and} \ g(x^*, y^*) = 0
\end{cases}
\tag{2.4}
$$

If x^* is globally asymptotically stable (GAS) in $\mathbb{R}^n$ for the system $\dot{x} = f(x)$, and if y^* is GAS in $\mathbb{R}^n$, for the system $\dot{y} = g(x^*, y)$, then (x^*, y^*) is (locally) asymptotically stable for (2.4). Moreover if all the trajectories of (2.4) are forward bounded, then (x^*, y^*) is a GAS for (2.4). To apply the above Vidyasagar theorem we would need to prove the stability analysis of first equation, then we would only have to test the stability of the infection equation.

From equation (2.3) if we add equation (i) and equation (iii) together we get

$$\dot{N}_i^C = \Lambda_{h,i} - (\mu_{h,i}^C + \nu)N_i^C + \sum_{j=1, j\neq i}^{n} m_{ij}^C N_j^C - \sum_{j=1, j\neq i}^{n} m_{ji}^C N_i^C$$

Which gives

$$\hat{E}\dot{N}^C = \Lambda + (-\mathrm{diag}(\mu_h^C + \nu\, 1) + M^C)\, N^C.$$

We note that the matrix $[-\mathrm{diag}(\mu_h^C + \nu\, 1) + M^C] \geq 0$, is a Metzler matrix.

For a matrix M the stability modulus, that we will denote $s(M)$, is the largest real part of the elements of the spectrum $Spec(M)$ of M

$$s(M) = \max_{\lambda \in \mathrm{Spec}(M)} Re(\lambda).$$

We have now

$$\hat{E}1^T\, [-\mathrm{diag}(\mu_h^C + \nu\, 1) + M^C] = -(\mu_h^C + \nu)^T \ll 0.$$

This proves ([?, 131]) that the stability modulus of M^C satisfies

$$\hat{E}s\left(-\mathrm{diag}(\mu_h^C + \nu\, 1) + M^C\right) < 0,$$

implying that this Metzler matrix is non singular, which in turn implies that the opposite its inverse is nonnegative [?, 131] .

Therefore the equilibrium of this linear system is given by

$$\hat{E}\bar{N}^C = -[-\mathrm{diag}(\mu_h^C + \nu\, 1) + M^C]^{-1}\, \Lambda_h > 0,$$

and is globally asymptotically stable.

A similar result is obtained for the adult population with an equilibrium denoted by $\bar{N}^A$

$$\bar{N}^A = -\nu\, \left(-\mathrm{diag}(\mu^A) + M^A\right)^{-1}\, \bar{N}^C > 0,$$

and for the mosquito population with an equilibrium denoted by $\bar{V}$.

$$\bar{V} = (-\mathrm{diag}(\mu_v) + M^v)^{-1}\, \Lambda_v.$$

Reduction process

We will now gives different expressions for the equation of our system. Depending on the case at hand we will use the most convenient form to give the properties of this system and the corresponding proofs.
We can rewrite system (2.3) in $\mathbb{R}_+^{6n}$, with a immediate variable change

$$\begin{cases} \dot{N}^C = \Lambda + (-\text{diag}(\mu_h^C + \nu\, 1) + M^C)\, N^C \\ \dot{N}^A = \nu N^C + (-\text{diag}(\mu_h^A) + M^A)\, N^A \\ \dot{N}_v = \Lambda_v + (-\text{diag}(\mu_v) + M^v)\, N^v \\ \dot{I}_{h,i}^C = \beta_1^C\, I_{v,i} \dfrac{(N_i^C - I_{h,i}^C)}{N_i} - (\gamma^C + \mu_h^C + \nu\, 1)\, I_{h,i}^C + \displaystyle\sum_{j=1, j\neq i}^{n} m_{ij}^C\, I_{h,j}^C - I_{h,i}^C \sum_{j=1, j\neq i}^{n} m_{ji}^C \\ \dot{I}_{h,i}^A = \beta_1^A I_{v,i} \dfrac{(N_i^A - I_{h,i}^A)}{N_i} + \nu I_{h,i}^A - (\gamma^A + \mu_i^A) I_{h,i}^A + \displaystyle\sum_{j=1, j\neq i}^{n} m_{ij}^A\, I_{h,j}^A - I_{h,i}^A \sum_{j=1, j\neq i}^{n} m_{ji}^A \\ \dot{I}_{v,i} = \dfrac{(N^v - I_{v,i})}{N_i} (\beta_2^C I_{h,i}^C + \beta_2^A I_{h,i}^A) - \mu_v I_{v,i} + \displaystyle\sum_{j=1, j\neq i}^{n} m_{ij}^v\, I_{v,j} - I_{v,i} \sum_{j=1, j\neq i}^{n} m_{ji}^v \end{cases} \tag{2.5}$$

This system is clearly triangular if we consider the first variables (N^C, N^A, N^v). By application of Theorem 2.1, the stability analysis of (2.5) is now reduced to the stability analysis of the system

$$\begin{cases} \dot{I}_{h,i}^C = \beta_1^C I_{v,i} \dfrac{(\bar{N}_i^C - I_{h,i}^C)}{\bar{N}_i} - (\gamma^C + \mu_h^C + \nu\, 1) I_{h,i}^C + \displaystyle\sum_{j=1, j\neq i}^{n} m_{ij}^C\, I_{h,j}^C - I_{h,i}^C \sum_{j=1, j\neq i}^{n} m_{ji}^C \\ \dot{I}_{h,i}^A = \beta_1^A\, I_{v,i}\, \dfrac{(\bar{N}_i^A - I_{h,i}^A)}{\bar{N}_i} + \nu I_{h,i}^C - (\gamma^A + \mu_i^A)\, I_{h,i}^A + \displaystyle\sum_{j=1, j\neq i}^{n} m_{ij}^A\, I_{h,j}^A - I_{h,i}^A \sum_{j=1, j\neq i}^{n} m_{ji}^A \\ \dot{I}_{v,i} = \dfrac{(\bar{V}_i - I_{v,i})}{\bar{N}_i} (\beta_2^C I_{h,i}^C + \beta_2^A I_{h,i}^A) - \mu_v\, I_{v,i} + \displaystyle\sum_{j=1, j\neq i}^{n} m_{ij}^v\, I_{v,j} - I_{v,i} \sum_{j=1, j\neq i}^{n} m_{ji}^v \end{cases} \tag{2.6}$$

We set

$$\begin{aligned} \bar{N} &= \bar{N}^C + \bar{N}^A \\ I_h^C &= (I_{h,1}^C, I_{h,2}^C, \ldots, I_{h,n}^C)^T \\ I_h^A &= (I_{h,1}^A, I_{h,2}^A, \ldots, I_{h,n}^A)^T \\ I_v &= (I_{v,1}, I_{v,2}, \ldots, I_{v,n})^T \end{aligned}$$

Then equation (2.6) can be written, in a vectorialized way, as

$$\begin{cases} \dot{I}_h^C = \text{diag}(\beta_1^C)\text{diag}(\bar{N})^{-1}\text{diag}(\bar{N}^C - I_h^C)I_v - \text{diag}(\gamma^C + \mu_h^C + \nu\,1)\,I_h^C + M^C\,I_h^C \\ \dot{I}_h^A = \text{diag}(\beta_1^A)\text{diag}(\bar{N})^{-1}\text{diag}(\bar{N}^A - I_h^A)I_v + \nu I_h^C - \text{diag}(\gamma^A + \mu_h^A)I_h^A + M^A I_h^A \\ \dot{I}_v = [\text{diag}(\beta_2^C I_h^C) + \text{diag}(\beta_2^A I_h^A)]\text{diag}(\bar{N})^{-1}(\bar{V}_i - I_{v,i}) - \text{diag}(\mu_v)\,I_v + M^v\,I_v \end{cases} \tag{2.7}$$

For another variable change, we set

$$\begin{aligned} x &= \text{diag}(\bar{N}^C)^{-1} I_h^C \\ y &= \text{diag}(\bar{N}^A)^{-1} I_h^A \\ z &= \text{diag}(\bar{V})^{-1} I_v. \end{aligned}$$

Rewriting system (2.7) in terms of x, y and z, we have

$$\begin{cases} \dot{x} = \text{diag}(\beta_1^C)\text{diag}(\bar{N})^{-1}\text{diag}(\bar{V})\text{diag}(1-x)z - \text{diag}(\gamma^C + \mu_h^C + \nu\,1)\,x + \tilde{M}^C x \\ \dot{y} = \text{diag}(\beta_1^A)\text{diag}(\bar{N})^{-1}\text{diag}(\bar{V})\text{diag}(1-y)z - \text{diag}(\gamma^A + \mu_h^A)\,y + \nu x + \tilde{M}^A y \\ \dot{z} = \text{diag}(\bar{N})^{-1}\ \left[\text{diag}(\beta_2^C)\text{diag}(\bar{N}^C)\text{diag}(x) + \text{diag}(\beta_2^A)\text{diag}(\bar{N}^A)\text{diag}(y)\right](1-z) - \text{diag}(\mu_v)\,z + \tilde{M}^v\,z, \end{cases} \tag{2.8}$$

where we define the matrices

$$\begin{aligned} \tilde{M}^C &= \text{diag}(\bar{N}^C)^{-1}\,M^C\,\text{diag}(\bar{N}^C), \\ \tilde{M}^A &= \text{diag}(\bar{N}^A)^{-1}\,M^A\,\text{diag}(\bar{N}^A), \\ \tilde{M}^v &= \text{diag}(\bar{N}^v)^{-1}\,M^v\,\text{diag}(\bar{N}^v). \end{aligned}$$

Finally, we will make a final "vectorization" of the system

$$\hat{E}\mathcal{A} = \begin{bmatrix} \text{diag}(\beta_1^C)\,\text{diag}(\bar{N})^{-1}\,\text{diag}(\bar{V}) & 0 & 0 \\ 0 & \text{diag}(\beta_1^A)\,\text{diag}(\bar{N})^{-1}\,\text{diag}(\bar{V}) & 0 \\ 0 & 0 & \text{diag}(\bar{N})^{-1} \end{bmatrix},$$

$$\mathcal{B} = \begin{bmatrix} 0 & 0 & I_n \\ 0 & 0 & I_n \\ \text{diag}(\beta_2^C)\text{diag}(\bar{N}^C) & \text{diag}(\beta_2^A)\text{diag}(\bar{N}^A) & 0 \end{bmatrix}$$

Ê

$$\mathcal{C} = \begin{bmatrix} \mathrm{diag}(\gamma^C + \nu\,1 + \mu_h^C) & 0 & 0 \\ -\nu I_n & \mathrm{diag}(\gamma^A + \mu_h^A) & 0 \\ 0 & 0 & \mathrm{diag}(\mu_v) \end{bmatrix}$$

Ê

$$\tilde{\mathcal{M}} = \begin{bmatrix} \tilde{M}^C & 0 & 0 \\ 0 & \tilde{M}^A & 0 \\ 0 & 0 & \tilde{M}^v \end{bmatrix}$$

Ê
We observe that $\tilde{\mathcal{M}} = \Delta^{-1}\,\mathcal{M}\,\Delta$ where Δ is the diagonal matrix

$$\Delta = \begin{bmatrix} \mathrm{diag}(\bar{N}^C) & 0 & 0 \\ 0 & \mathrm{diag}(\bar{N}^A) & 0 \\ 0 & 0 & \mathrm{diag}(\bar{N}^v) \end{bmatrix}$$

Ê
$\mathcal{A}$ and $\mathcal{B}$ are nonnegative matrices and we claim that $-\mathcal{C} + \tilde{\mathcal{M}}$ is a stable Meztler matrix.

Indeed the stability modulus of $-\mathcal{C}$ is negative and

$$s(-\mathcal{C}) = -\min(\gamma^C + \nu\,1 + \mu_h^C, \gamma^A + \mu_h^A, \mu_v) < 0$$

where the minimum is taken over the components of the 3 positive vectors.
We have

$$-\mathcal{C} + \tilde{\mathcal{M}} \leq -s(\mathcal{C})\,I_{3n} + \tilde{\mathcal{M}}$$

Since the matrices involved are Metzler matrices, this implies the following inequality for the corresponding stability modulus

$$s\left(-\mathcal{C} + \tilde{\mathcal{M}}\right) \leq -s(\mathcal{C})\,I_{3n} + s(\tilde{\mathcal{M}}) = -s(\mathcal{C}) < 0$$

The relation $s(\tilde{\mathcal{M}})$ follows from $s(\tilde{\mathcal{M}}) = s(\mathcal{M})$ and from $1^T\,\mathcal{M} = 0$ which implies by Perron-Frobenius that $s(\mathcal{M}) = 0$.

Using the preceding matrices and the vector $X = (x, y, z)$ we rewrite equation (2.8) in a compact form as

$$\dot{X} = \mathcal{A}\,\mathrm{diag}(1 - X)\,\mathcal{B}\,X + (-\mathcal{C} + \tilde{\mathcal{M}})\,X \tag{2.9}$$

This system evolves on the unit cube of $\mathbb{R}^{3n}$.

2.5 Basic properties of the model

For any index i we shall use the classical notations : $x < y$ if $x \leq y$ and $x_i \leq y_i$ for some i and we write $x_i \ll y_i$ if $x_i < y_i$ for all i.

Proposition 1 (Positively invariant set).
The unit cube

$$\mathfrak{K} = \{(x, y, z) \in \mathbb{R}^{3n} \ \mid \ 0 \leq x \leq 1; \quad 0 \leq y \leq 1, \quad 0 \leq z \leq 1\}.$$

is positively invariant for system (2.8).

Proof
To show the invariance of the unit cube $\mathfrak{K}$, under the flow of the system (2.8), it suffices to show that each of the faces of the cube cannot be crossed.

On the patch i we have

$$\hat{E}\dot{x}_i = \beta_1^C \frac{\bar{V}_i}{\bar{N}_i} z_i (1 - x_i) - (\gamma_i^C + \mu_{h,i}^C + \nu) x_i + \sum_{j=1, j\neq i}^{n} m_{ij}^C \frac{\bar{N}_j^C}{\bar{N}_i^C} x_j - x_i \sum_{j=1, j\neq i}^{n} m_{ji}^C$$

Ê

If $x_i = 0$

$$\dot{x}_i = \beta_1^C \frac{\bar{V}_i}{\bar{N}_i} z_i + \sum_{j=1, j\neq i}^{n} m_{ij}^C \frac{\bar{N}_j^C}{\bar{N}_i^C} x_j \geq 0.$$

implying that $x = 0$ cannot be crossed from positive to negative.

If $x_i = 1$, then for $j \neq i$ we have $x_j = 0$, since the entire population is 1. Then

$$\dot{x}_i = -(\gamma_i^C + \mu_{h,i}^C + \nu) - \sum_{j=1, j\neq i}^{n} m_{ji} < 0.$$

The equation for y_i in patch i is

$$\hat{E}\dot{y}_i = \beta_1^A \frac{\bar{V}_i}{\bar{N}_i} z_i (1 - y_i) - (\gamma_i^A + \mu_{h,i}^A) y_i + \sum_{j=1, j\neq i}^{n} m_{ij} \frac{N_j^A}{N_i^A} y_j - y_i \sum_{j=1, j\neq i}^{n} m_{ji}$$

Ê
If $y_i = 0$ then

$$\dot{y}_i = \beta_1^A \frac{\bar{V}_i}{\bar{N}_i} z_i + \sum_{j=1, j\neq i}^{n} m_{ij} \frac{N_j^A}{N_i^A} y_j \geq 0.$$

if $y_i = 1$ we have again $y_j = 0$ for any $j \neq i$ and

$$\hat{E}\hat{E}\dot{y}_i = -(\gamma_i^A + \mu_{h,i}^A) - \sum_{j=1, j\neq i}^{n} m_{ji} < 0$$

Finally the equation for z_i in patch i is given by

$$\hat{E}\dot{z}_i = \beta_2^C \frac{\bar{N}_i^C}{\bar{N}_i} x_i (1 - z_i) + \beta_2^A \frac{\bar{N}_i^A}{\bar{N}_i} y_i (1 - z_i) - \mu_{v,i} z_i + \sum_{j=1, j\neq i}^{n} m_{ij}^v \frac{\bar{V}_j}{\bar{V}_i} z_j - z_i \sum_{j=1, j\neq i}^{n} m_{ji}^v$$

Ê

If $z_i = 0$, then for any i,

$$\dot{z}_i = \beta_2^C \frac{\bar{N}_i^C}{\bar{N}_i} x_i + \beta_2^A \frac{\bar{N}_i^A}{\bar{N}_i} y_i + \sum_{j=1, j\neq i}^{n} m_{ij}^v \frac{\bar{V}_j}{\bar{V}_i} z_j \geq 0,$$

and if $z_i = 1$ then for any $j \neq i$, $z_j = 0$ since the whole population is 1 and thus

$$\dot{z}_i = -\beta_2^C \frac{\bar{N}_i^C}{\bar{N}_i} x_i - \beta_2^A \frac{\bar{N}_i^A}{\bar{N}_i} y_i - \sum_{j=1, j\neq i}^{n} m_{ji}^v < 0$$

proposition is proved.

Proposition 2.
If the matrix $M^C + M^A + M^v$ is irreducible, then the system (2.9) is strongly monotone in the interior of the positively invariant set $[0, 1]^{3n}$

Proof
We utilise the theory of monotone dynamical systems introduced by [63, 65, 64], developed further in [63] and applied in [14].
System (2.9) is monotone if its Jacobian is a Metzler matrix on the unit cube. The Jacobian of system (2.9) is given by

$$\hat{E}J(X) = \mathcal{A}\,\mathrm{diag}(1 - X)\,\mathcal{B} + (-\mathcal{C} + \tilde{\mathcal{M}}) - \mathcal{A}\,\mathrm{diag}(\mathcal{B}X)$$

The Jacobian $J(X)$ is clearly a Metzler matrix since $0 \leq X \leq 1$, which implies that the system is cooperative in the unit cube.
Next, we show that the Jacobian $J(X)$ is an irreducible matrix in the set $[0, 1]^{3n}$. This will imply strong monotonicity of the system in the interior of the unit cube. In this set the diagonal terms of $\mathrm{diag}(1 - X)$ are positive, the same property is satisfied for $\mathcal{A}$, then the connectivity of the associated graph of $\mathcal{A}\,\mathrm{diag}(1 - X)\,\mathcal{B}$ is reduced to consider the connectivity of $\mathcal{B}$.
It is well known that a matrix is irreducible if its associated graph is strongly connected. Then only the off diagonal terms are concerned. Then it is sufficient to prove that the matrix

$$\hat{E}\mathcal{A}\,\mathrm{diag}(1 - X)\,\mathcal{B} + (-\mathcal{C} + \tilde{\mathcal{M}})$$

Ê

is irreducible. For the associated graph we distinguishes three categories of vertices : the vertices corresponding to the x_i (children vertices), y_i (adults vertices), z_i (mosquitoes vertices). Considering the matrix $\mathcal{B}$ it is clear that a vertex x_i is connected to the vertices of the same patch i, i.e, y_i and z_i. In other words on the three vertices of patch i are contained in a strongly connected component. The vertices from a patch is a subgraph and we can use the contraction of each (x_i, y_i, z_i) in the general digraph to obtain a new digraph wich represents movements between the patches. To prove the strong connectedness it is sufficient to prove that this contracted digraph is strongly connected.

To the matrix $\tilde{\mathcal{M}}^{\mathcal{C}}$ correspond a digraph between the patches. This graph is equivalent to the associated digraph of $\mathcal{M}^{C}$. Since M^{C}, M^{A} and M^{v} are Metzler matrices, we can consider the matrix $M^{C}+M^{A}+M^{v}$ and its corresponding multigraph on the graph of patches. This oriented multigraph represents actually the circulation of malaria parasites between the patches. Malaria parasites can be transported either by child, adults or mosquitoes.
Since we have assumed that the matrix, our graph is strongly connected, consequently the Jacobian is irreducible. We note that we are in a context of multiple species (i.e., childs, adults and mosquitoes) in a metapopulation model as conceptualized in [?].
Our assumption simply means that the circulation of paras

CHAPITRE 3

Stability Analysis

Contents

3.1 Basic Reproduction Number, $\mathcal{R}_0$

Using the classical framework defined in [32],[141], we define

$$\mathcal{F} = \begin{bmatrix} \operatorname{diag}(\beta_1^C)\operatorname{diag}(\bar{N})^{-1}\operatorname{diag}(\bar{N}^v)\operatorname{diag}(1-x)\,z \\ \operatorname{diag}(\beta_1^A)\operatorname{diag}(\bar{N})^{-1}\operatorname{diag}(\bar{N}^v)\operatorname{diag}(1-y)\,z \\ (\operatorname{diag}(\beta_2^C)\operatorname{diag}(\bar{N}^C)\operatorname{diag}(\bar{N})^{-1}\operatorname{diag}(x) + \operatorname{diag}(\beta_2^A)\operatorname{diag}(\bar{N}^A)\operatorname{diag}(\bar{N})^{-1}\operatorname{diag}(y))\operatorname{diag}(1-z) \end{bmatrix}$$

the appearance of new infections in infectious compartments and by

$$\mathcal{V} = \begin{bmatrix} -(\gamma^C + \tilde{\mu}_h^C)\,x + M^C\,x \\ -(\gamma^A + \mu_h^A)\,y + \nu x + M^A\,y \\ -\mu_v\,z + M^v\,z \end{bmatrix}$$

the transfer into the compartments by all other means. The Jacobian F of $\mathcal{F}$ is given by

$$\mathrm{F} = \begin{bmatrix} -\mathrm{diag}(\beta_1^C)\,\mathrm{diag}(\bar{N})^{-1}\,\mathrm{diag}(\bar{N}^v)\,\mathrm{diag}(z) & 0 & \mathrm{diag}(\beta_1^C)\,\mathrm{diag}(\bar{N})^{-1}\,\mathrm{diag}(\bar{N}^v)\,\mathrm{diag}(1-x) \\ 0 & -\mathrm{diag}(\beta_1^A)\,\mathrm{diag}(\bar{N})^{-1}\,\mathrm{diag}(\bar{N}^v)\,\mathrm{diag}(z) & \mathrm{diag}(\beta_1^A)\,\mathrm{diag}(\bar{N})^{-1}\,\mathrm{diag}(\bar{N}^v)\,\mathrm{diag}(1-y) \\ \mathrm{diag}(\beta_2^C)\,\mathrm{diag}(\bar{N}^C)\,\mathrm{diag}(\bar{N})^{-1}(1-z) & \mathrm{diag}(\beta_2^A\,\mathrm{diag}(\bar{N}^A)\,\mathrm{diag}(\bar{N})^{-1}(1-z) & 0 \end{bmatrix}$$

When there is no infection (at the origin) is the Jacobian F of $\mathcal{F}$ is given by

$$\mathrm{F(0,0,0)} = \begin{bmatrix} 0 & 0 & \mathrm{diag}(\beta_1^C)\,\mathrm{diag}(\bar{N})^{-1}\,\mathrm{diag}(\bar{V}) \\ 0 & 0 & \mathrm{diag}(\beta_1^A)\,\mathrm{diag}(\bar{N})^{-1}\,\mathrm{diag}(\bar{V}) \\ \mathrm{diag}(\beta_2^C)\,\mathrm{diag}(\bar{N}^C)\,\mathrm{diag}(\bar{N})^{-1} & \mathrm{diag}(\beta_2^A)\,\mathrm{diag}(\bar{N}^A)\,\mathrm{diag}(\bar{N})^{-1} & 0 \end{bmatrix}.$$

The Jacobian V of $\mathcal{V}$ is given by

$$\mathrm{V} = \begin{bmatrix} -(\gamma^C + \tilde{\mu}_h^C) + M^C & 0 & 0 \\ \nu & -(\gamma^A + \mu_h^A) + M^A & 0 \\ 0 & 0 & -\mu_v + M^v \end{bmatrix}$$

The matrix

$$\mathrm{V}^{-1} = \begin{bmatrix} (-(\gamma^C + \tilde{\mu}_h^C) + M^C)^{-1} & 0 & 0 \\ -\frac{\nu}{((\gamma^C+\tilde{\mu}_h^C)+M^C)((\gamma^A+\mu_h^A)+M^A)} & (-(\gamma^A + \mu_h^A) + M^A)^{-1} & 0 \\ 0 & 0 & (-\mu_v + M^v)^{-1} \end{bmatrix}$$

The basic reproduction number is defined in [141] as

$\mathcal{R}_0 = \rho(FV^{-1}) = \rho(V^{-1}F)$.

Now we are using Metzler instead of M-matrices so we use our $\mathcal{R}_0$ is defined by

$\mathcal{R}_0 = \rho(-FV^{-1})$.

$$-FV^{-1} = \begin{bmatrix} 0 & 0 & \mathrm{diag}(\beta_1^C)\,\mathrm{diag}(\bar{N})^{-1}\,\mathrm{diag}(\bar{N}^v)(-\mu I_{n\times n})^{-1} \\ 0 & 0 & \mathrm{diag}(\beta_1^A)\,\mathrm{diag}(\bar{N})^{-1}\,\mathrm{diag}(\bar{N}^v)(-\mu I_{n\times n})^{-1} \\ \eta & \mathrm{diag}(\beta_2^A\,\mathrm{diag}(\bar{N}^A)\,\mathrm{diag}(\bar{N})^{-1}((\gamma_i^A + \mu_h^A) - M^A)^{-1} & 0 \end{bmatrix}$$

where

$$\eta = \frac{\mathrm{diag}(\beta_2^C)\,\mathrm{diag}(\bar{N}^C)\,\mathrm{diag}(\bar{N})^{-1}}{(-(\gamma^C+\tilde{\mu}_h^C)+M^C)} - \frac{\nu\mathrm{diag}(\beta_2^A)\,\mathrm{diag}(\bar{N}^A)\,\mathrm{diag}(\bar{N})^{-1}}{(-(\gamma^C+\tilde{\mu}_h^C)+M^C)(-(\gamma^A+\mu_h^A)+M^A)}$$

We have

$$\mathcal{R}_0^2 = \frac{\operatorname{diag}(\beta_1^C)\operatorname{diag}(\beta_2^C)\operatorname{diag}(\bar{N}^C)\operatorname{diag}(\bar{N})^{-2})\operatorname{diag}(\bar{N}^v)}{(\mu_v - M^v)(\gamma^C + \tilde{\mu}_h^C - M^C)}$$

$$+\frac{\nu\operatorname{diag}(\beta_1^C)\operatorname{diag}(\beta_1^A)\operatorname{diag}(\bar{N}^A)\operatorname{diag}(\bar{N})^{-2}\operatorname{diag}(\bar{N}^v)}{(\mu_v + M^v)(\gamma^C + \tilde{\mu}_h^C - M^C)(\gamma^A + \mu_h^A - M^A)}$$

$$+\frac{\operatorname{diag}(\beta_1^A)\operatorname{diag}(\beta_2^A)\operatorname{diag}(\bar{N}^A)\operatorname{diag}(\bar{N})^{-2})\operatorname{diag}(\bar{N}^v)}{(\mu_v - M^v)(\gamma^A + \mu_h^A - M^A)}$$

When $\mathcal{R}_0 < 1$, the DFE is locally asymptotically stable, and if $\mathcal{R}_0 > 1$ the DFE is unstable, see [141, 32].

3.2 Main Result

In this section establish global stability of the DFE and a global stability result for $\mathcal{R}_0 > 1$. We have the following theorem

Theorem 3.1. If $\mathcal{R}_0 \leq 1$, then system (2.9) is globally asymptotically stable at the origin. If $\mathcal{R}_0 > 1$, then there exists a unique endemic equilibrium E^*, which is globally asymptotically stable on $\mathfrak{K} \in [0,1]^{3n}$.

Proof
We recall system (2.9).

$$\dot{X} = \mathcal{A}\operatorname{diag}(1-X)\mathcal{B}X + [-\mathcal{C} + \mathcal{M}]X$$

The Jacobian at the origin will be given by

$$J(X) = \mathcal{A}\mathcal{B}\operatorname{diag}(1-X) + \mathcal{B}(-AX) + [-\mathcal{C} + \mathcal{M}]$$

or

$$J(0) = \mathcal{A}\mathcal{B} + [-\mathcal{C} + \mathcal{M}]$$

that is

$$J = \mathcal{A}\mathcal{B} + [-\mathcal{C} + \mathcal{M}].$$

To prove the proposition above we assume that $\rho(\mathcal{A}\mathcal{B} + [-\mathcal{C} + \mathcal{M}]^{-1}) \leq 1$.

Since $[-\mathcal{C} + \mathcal{M}]$ is a metzler matrix which is invertible and $\mathcal{A} \geq 0$, this is a regular splitting of J [144]. We know from [71, 141, 143] that

$$\mathcal{R}_0 \leq 1 \quad \Longleftrightarrow \quad \rho(-\mathcal{A}\mathcal{B}[-\mathcal{C} + \mathcal{M}]^{-1}) \leq 0.$$

From the preceeding section we proved that the Jacoban J is an irreducible metzler martrix. So there exists a positive vector $\mathbf{c} \gg 0$, such that

$$\mathbf{c}^t(\mathcal{A}\mathcal{B} + \mathcal{C}) = \alpha(J)\,\mathbf{c}^t \leq 0.$$

To prove the global stability of the DFE we consider the Lyapunov function

$$L(X) = \langle \mathbf{c} \mid X \rangle,$$

where $\langle \mid \rangle$, denotes the inner product. From the definition of $\mathbf{c} \gg 0$, this function is actually positive definite in the nonnegative orthant. We compute the derivative of L along the trajectories of 2.9 and find that it is equivalent to

$$\begin{aligned}
\dot{L}(X) &= \langle \mathbf{c} \mid (\mathcal{A}\,\mathrm{diag}(1-X)\,\mathcal{B} + [-\mathcal{C} + \mathcal{M}])\,X \rangle \\
&\leq \langle \mathbf{c} \mid \mathcal{A}\,\mathcal{B} + [-\mathcal{C} + \mathcal{M}] \rangle \\
&= \langle (\mathcal{A}\,\mathcal{B} + [-\mathcal{C} + \mathcal{M}])^t\,\mathbf{c} \mid X \rangle \qquad (3.1) \\
&= \langle \alpha(J)\,\mathbf{c} \mid X \rangle \\
&= \alpha(J) \langle \mathbf{c} \mid X \rangle.
\end{aligned}$$

Since $\alpha(J) \leq 0$ the derivative is negative.
We now consider the case when $\mathcal{R}_0 < 1$. Computing the derivative along the trajectories of 2.9, we have

$$\dot{L}(X) = \langle \mathbf{c} \mid (\mathcal{A}\,\mathcal{B} + [-\mathcal{C} + \mathcal{M}])\,X \rangle = \alpha(\mathcal{A}\,\mathcal{B} + [-\mathcal{C} + \mathcal{M}]) \langle \mathbf{c} \mid X \rangle.$$

Since we know that $\mathcal{R}_0 < 1$ implies $\alpha(J) < 0$ the derivative is again negative definite. This proves the asymptotic stability of the DFE.

When $\mathcal{R}_0 = 1$, we have

$$\begin{aligned}
\dot{L}(X) &= \langle \mathbf{c} \mid \mathcal{A}\,\mathrm{diag}(1-X)\,\mathcal{B}\,X + [-\mathcal{C} + \mathcal{M}]\,X \rangle, \\
&= \langle \mathbf{c} \mid (\mathcal{A}\mathcal{B} + [-\mathcal{C} + \mathcal{M}])\,X - \mathcal{A}\,\mathrm{diag}(X)\,\mathcal{B}\,X \rangle,
\end{aligned}$$

but we are in the case when $\mathcal{R}_0 = 1 \quad \Rightarrow \quad \alpha\,(\mathcal{A}\,\mathcal{B} + [-\mathcal{C} + \mathcal{M}]) = 0$, therefore,

$$\dot{L}(X) = -\langle \mathbf{c} \mid \mathcal{A}\mathrm{diag}(X)\,\mathcal{B}\,X \rangle.$$

Since $\mathbf{c} \gg 0$ for $\dot{L}$ to be zero, then $\mathcal{A}\,\mathrm{diag}(X)\,\mathcal{B}X$ must be equal to zero. Now we show that the largest invariant set $\mathfrak{L} \in \mathfrak{E}$ is reduced to the origin.
This set is defined by

$$\mathfrak{E} = \{X \in [0,1]^{3n} \mid \dot{L}(X) = 0\}.$$

The expression $\mathrm{diag}(X)\,\mathcal{B}\,X = 0$ defines points equivalent to $x_i\,y_i = 0$, $x_i\,z_i = 0$ and $y_i\,z_i = 0$, $i = 1, \ldots, n$. We also recall that our system is irreducible, and so there exists at least a point in $\mathfrak{L}$ such that $x_i = 0$ *or* $y_i = 0$ *or* $z_i = 0$ $i = 1, \ldots, n$.

From the system 2.9,

If $x_i = 0$, then for

$$\dot{x}_i = \mathrm{diag}(\beta_1^C)\,\mathrm{diag}(\bar{N})^{-1}\,\mathrm{diag}(\bar{N}^v)\,\mathrm{diag}(z) + \sum_{j \neq i} m_{ij}^C\,x_j = 0.$$

This shows that $z_i = 0$, and all the $x_j = 0$ for which $m_{ij} \neq 0$, i.e.. all x_j connected to x_i are equal to zero.

Using the irreducibility hypothesis, we can argue that all the x_i and x_j are equal to zero.

Next, if $y_i = 0$, then

$$\dot{y}_i = \operatorname{diag}(\beta_1^A)\operatorname{diag}(\bar{N})^{-1}\operatorname{diag}(\bar{N}^v)\operatorname{diag}(z) + \sum_{j\neq i} m_{ij}\, y_j = 0 \quad \Rightarrow\ z_i = y_j = 0$$

and all the $y_j = 0$ for which $m_{ij} \neq 0$, i.e.. all y_j connected to y_i are equal to zero.

And, if $z_i = 0$, then

$$\dot{z}_i = \operatorname{diag}(\beta_2^C)\operatorname{diag}(\bar{N}^C)\operatorname{diag}(\bar{N})^{-1}\operatorname{diag}(x) + \operatorname{diag}(\beta_2^A\operatorname{diag}(\bar{N}^A)\operatorname{diag}(\bar{N})^{-1}\operatorname{diag}(y) + \sum_{j\neq i} m_{ij}\, z_j = 0$$

$$\Rightarrow \quad x_i = y_i = z_j = 0.$$

and all the $z_j = 0$ for which $m_{ij}^v \neq 0$, i.e.. all z_j connected to z_i are equal to zero. The invariance of $\mathfrak{L}$ shows that $x_i = 0$ and therefore for all cases of x, y and z, the set $\mathfrak{L}$ is reduced to the origin. The global stability of the DFE is concluded from LaSalle's Invariance Principle [91]. To prove the second part of our theorem, we need the following theorem according to Hirsch [63].

Theorem 3.2. Let F be a C^1 vector field in $\mathbb{R}^n$, whose flow ϕ preserves $\mathbb{R}^n_+$ for $t \geq 0$ and is strongly monotone in $\mathbb{R}^n_+$. Assume that the origin is an equilibrium and that all trajectories in $\mathbb{R}^n_+$ are bounded. Suppose the matrix-valued map $DF : \mathbb{R}^n_+ \to \mathbb{R}^n_+ \times \mathbb{R}^n_+$ is strictly anti monotone, in the sense that,

$$if\ x < y,\ then\ \ DF(x) > DF(y),$$

then either all the trajectories in $\mathbb{R}^n_+ \backslash \{0\}$ tend to the origin, or else there is a unique equilibrium $p \in\ Int\ \mathbb{R}^n_+$ $(p \gg 0)$ and all the trajectories in $\mathbb{R}^n_+$ tend to p.

For our case we shall consider the positively invariant unit cube $\mathfrak{K} \in \mathbb{R}^{3n}$. We recall the Jacobian of system 2.9, with the Jacobian

$$D(X) = -\mathcal{A}\mathcal{B}X + \mathcal{A}\operatorname{diag}(1 - X)\mathcal{B} + [-\mathcal{C} + \mathcal{M}],$$

The Jacobian is clearly an irreducible metzler matrix therefore its right to conclude that the flow of system 2.9 is monotone in $\mathfrak{K}$.

The matrix valued map $DX(x, y, z)$ is a decreasing function of (x, y, z) since $\mathcal{B}$ is nonzero with nonegative rows. This proves that the Jacobian is strictly antimonotone. That is ;

If we take any $X_1 < X_2 \in X$ then $D(X_1) > DX_2)$ therefore the anti monotone criteria is met.

We have already proved that that the DFE is unstable when $\mathcal{R}_0 > 1$, then from theorem 5.3, there exists an endemic equilibrium $E^* \gg 0$ in the interior of $\mathfrak{K}$ and all trajectories in $\mathbb{R}^{3n}$ tend to this equilibrium. This equilibrium satisfies the equation

$$\mathcal{A}\,\mathrm{diag}(1-E^*)\,\mathcal{B}\,E^* + [-\mathcal{C}+\mathcal{M}]\,E^* = 0.$$

The Jacobian at the endemic equilibrium satisfies

$$D(E^*)E^* = (-\mathcal{A}\,\mathcal{B}\,E^* + \mathcal{A}\,\mathrm{diag}(1-E^*)\,\mathcal{B} + [-\mathcal{C}+\mathcal{M}])E^* \;=\; -\mathcal{A}\,\mathcal{B}\,E^* < 0.$$

Since $\mathcal{A}$ is a stable Metzler matrix and $\mathcal{B}$ is nonnegative this expression implies that the matrix is stable, hence the stability modulus $s(DX(E^*)) < 0$, [2] (critelion I_{28} of Theorem 6.2.3). Consequently the endemic equilibrium, E^* is locally asymptotically stable. The global stability is a result of theorem 5.3, and this concludes our proof.

3.3 An Example in Two Patches

In this section we give a result to the case of two patches. We shall use the structure defined in Subsection 3.1.

$$\mathcal{F} = \begin{bmatrix} \beta_1^C\, I_{v,1}\, \frac{(N_1^C - I_{h,1}^C)}{N_1} \\ \beta_1^C\, I_{v,2}\, \frac{(N_2^C - I_{h,2}^C)}{N_2} \\ \beta_1^A\, I_{v,1}\, \frac{(N_1^A - I_{h,1}^A)}{N_1} \\ \beta_1^A\, I_{v,2}\, \frac{(N_2^A - I_{h,2}^A)}{N_2} \\ \frac{(N_1^v - I_{v,1})}{N_1}\,(\beta_2^C I_{h,1}^C + \beta_2^A\, I_{h,1}^A) \\ \frac{(N_2^v - I_{v,2})}{N_2}(\beta_2^C I_{h,2}^C + \beta_2^A\, I_{h,2}^A) \end{bmatrix},\quad \mathcal{V} = \begin{bmatrix} (-\gamma_1^C + \mu_1^C + \nu)\, I_{h,1}^C + m_{12}\, I_{h,2}^C - m_{21}\, I_{h,1}^C \\ (-\gamma_2^C + \mu_2^C + \nu)\, I_{h,2}^C + m_{21}\, I_{h,1}^C - m_{12}\, I_{h,2}^C \\ (-\gamma_1^A + \mu_1^A)\, I_{h,1}^A + \nu\, I_{h,1}^C + m_{12}\, I_{h,2}^A - m_{21}\, I_{h,1}^A \\ (-\gamma_2^A + \mu_2^A)\, I_{h,2}^A + \nu\, I_{h,2}^C + m_{21}\, I_{h,1}^A - m_{12}\, I_{h,2}^A \\ -\mu_v\, I_{v,1} + m_{12}^v\, I_{v,2} - m_{21}^v\, I_{v,1} \\ -\mu_v\, I_{v,2} + m_{21}^v\, I_{v,1} - m_{12}^v\, I_{v,2} \end{bmatrix}.$$

The derivative $F = D(\mathcal{F})$ of $\mathcal{F}$ is given by

$$F(0,0,0) = \begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\beta_1^C\, N_1^C}{N_1} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_1^C\, N_2^C}{N_2} \\ 0 & 0 & 0 & 0 & \frac{\beta_1^A\, N_1^A}{N_1} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_1^A\, N_2^A}{N_2} \\ \frac{\beta_2^C\, N_1^v}{N_1} & 0 & \frac{\beta_2^A\, N_1^v}{N_1} & 0 & 0 & 0 \\ 0 & \frac{\beta_2^C\, N_2^v}{N_2} & 0 & \frac{\beta_2^A\, N_2^v}{N_2} & 0 & 0 \end{bmatrix},$$

while the derivative $V = D(\mathcal{V})$ of $\mathcal{V}$ at the origin is given by $V(0,0,0)$

$$= \begin{bmatrix} -(\gamma_1^C + \mu_1^C + \nu + m_{21}) & m_{12} & 0 & 0 & 0 & 0 \\ m_{21} & -(\gamma_2^C + \mu_2^C + \nu + m_{12}) & 0 & 0 & 0 & 0 \\ \nu & 0 & -(\gamma_1^A + \mu_1^A + m_{21}) & 0 & 0 & 0 \\ 0 & \nu & 0 & -(\gamma_2^A + \mu_2^A + m_{12}) & 0 & 0 \\ 0 & 0 & 0 & 0 & -(\mu_v + m_{21}^v) & 0 \\ 0 & 0 & 0 & 0 & 0 & -(\mu_v + m_{12}^v) \end{bmatrix}$$

The basic reproduction number is given by $\rho(-FV^{-1})$ From our example and at the DFE, this matrix is defined by FV^{-1} which has the values

$$\begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\beta_1^C N_1^C}{\mu_v N_1} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_1^C N_2^C}{\mu_v N_2} \\ 0 & 0 & 0 & 0 & \frac{\beta_1^A N_1^A}{\mu_v N_1} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_1^A N_2^A}{\mu_v N_2} \\ \frac{N_1^C \bar{\gamma}_2^C}{N_1 D}(\beta_2^C + \frac{\beta_2^A}{\bar{\gamma}_1^A}) & \frac{m_{21} N_1^v}{N_1 D}(\beta_2^C + \frac{\nu \beta_2^A}{\bar{\gamma}_1^A}) & \frac{\beta_2^A N_1^v}{\bar{\gamma}_1^A N_1 D} & 0 & 0 & 0 \\ \frac{N_1^v m_{21}}{N_2 D}(\beta_2^C + \frac{\nu \beta_2^A}{\gamma_2^A}) & \frac{N_2^v \bar{\gamma}_1^C}{N_2 D}(\beta_2^C + \frac{\beta_2^A}{\bar{\gamma}_2^A}) & 0 & \frac{\beta_2^A N_2^v}{\bar{\gamma}_2^A N_2} & 0 & 0 \end{bmatrix}$$

assuming that

$$D = (\gamma_1^C + \mu_1^C + \nu + m_{21})(\gamma_2^C + \mu_2^C + \nu + m_{12}) - m_{12}m_{21}) = \bar{\gamma}_1^C \bar{\gamma}_2^C - m_{12}\, m_{21},$$

and

$$\bar{\gamma}_1^C = (\gamma_1^C + \mu_1^C + \nu + m_{21}), \quad \bar{\gamma}_2^C = (\gamma_2^C + \mu_2^C + \nu + m_{12})$$

and

$$\bar{\gamma}_1^A = (\gamma_1^A + \mu_1^A + \nu + m_{21}), \quad \bar{\gamma}_2^A = (\gamma_2^A + \mu_1^A + \nu + m_{12})$$

To get the basic reproduction number we need to solve $det|\lambda I - J| = 0$ which is a 6×6 matrix. Rewriting the matrix in the form

$$\Theta = \begin{bmatrix} 0I_4 & B \\ A & 0I_2 \end{bmatrix}.$$

The determinant of Θ is given by

$$det(\Theta - \lambda I_6) = \begin{vmatrix} -\lambda I_4 & B \\ A & -\lambda I_2 \end{vmatrix} = \lambda^4 \begin{vmatrix} I_4 & -\frac{1}{\lambda}B \\ A & -\lambda I_2 \end{vmatrix},$$

$$= \lambda^4 \left| \begin{bmatrix} I_4 & 0 \\ A & I_2 \end{bmatrix} \begin{bmatrix} I_4 & -\frac{1}{\lambda}B \\ 0 & -\lambda I_2 + \frac{1}{\lambda}AB \end{bmatrix} \right|.$$

Using the properties of determinants we have

$$det(\Theta - \lambda I_6) = \lambda^4 det(-\lambda I_2 + \frac{1}{\lambda}AB) = \lambda^2 det(AB - \lambda^2 I_2) = 0.$$

We see after some calculation, that

$$\mathcal{R}_0^2 = \frac{a_0 + \sqrt{a_0^2 - 4a_1}}{2}$$

where

$$a_0 = (A_{11}B_{11} + A_{13}B_{31} + A_{22}B_{22} + A_{24}B_{42})$$

$$a_1 = [(A_{11}B_{11} + A_{13}B_{31})(A_{22}B_{22} + A_{24}B_{42})] - [(A_{21}B_{11} + A_{23}B_{31})(A_{12}B_{22} + A_{14}B_{42})]$$

3.4 Simulation

In this section we obtain two baseline values for two sites in each ecosystem namely, the U-shaped valleys and V-shaped valleys. We also describe our reasons for using these values and the references, where available. We estimate parameter values from published studies and country-wide data. For migration rates, we pick realistically feasible values from literature. Umutete and Iguhu are two patches representing the U-shaped valleys, and, Marani and Fort Tenan for the V-shaped valleys. From the study on the different ecosystems, the plateaus and the U-shaped valleys ecosystem have the characteristic, such that the results for the V-shaped valleys apply to the plateau ecosystem. Some suitable references for our values are [25, 149, 111, 47, 140].

3.4.1 Parameter values

b_1 : For the proportion of infectious bites on susceptible hosts we shall use the value 0.011 for the U-shaped and the and 0.08 for the V-shaped valley ecosystem .

b_2 : The proportion of infectious bites on susceptible mosquitoes, is different for the two ecosystems due to acquired or partial immunity so we assume that it is five times higher in the V-shaped valleys (0.24) than the higher in the U-shaped valleys (0.048).

a_h^C : The man biting rate for the children is assume to be 0.52 in the U-shaped valleys and 0.42 in the V-shaped valleys. We have assumed that the rate is higher due to the high mosquito population in the U-shaped valleys.

a_h^A The biting rate for the adults is less than that of the children and we shall use the value 0.15 for the adults the U-shaped valleys and 0.12 in the V-shaped valleys.

$\gamma_i^C = \gamma_i^A$: Since the rate of recovery depends on how fast diagnosis is done and the effectiveness of treatment in patch i we assume here the same value for the two ecosystems at 0.33 or

30 days period of infectiousness.

ν : The rate children become adults is not easy to determine, but since the two ecosystems have similar economic status, we shall use the value 0.00283 as used in literature.

μ_1^C : The natural death rate for children under five death for the U-shaped valleys is estimated at 7.9% in Kenya by Unicef. This figure may include disease related deaths but the data is not elaborate. In this case we have assumed that this high rate is for the U-shaped valleys and 5.9% for the V-shaped valleys which may be suffering fewer deaths due to malaria.

$\mu_1^A = \mu_2^A$: The per capita death rate for adults is assumed to be the same for the two ecosystem. We use the death rate for the country (Kenya) which is estimated at 3.5%.

μ_v : The per capita mosquito death rate is estimated at 0.033 from literature.

Λ_h : This is the recruitment by birth to the susceptible human compartment, we in the V-shaped valleys (0.07) is assumed to be less than the rate in the U-shaped valleys (0.13).

Data for N_1, N_2, and N_v was not exactly available so we decided to use random values with the total population being 10000 people so that we have 5000 people on each patch (3500 children and 1500 adults for each ecosystem). The mosquito population likewise was estimated to be 20000 mosquitoes in the U-shaped valleys and 1500 mosquitoes in the V-shaped valleys.
The summary of the parameter values described above is is given in table 3.1 below.

Table 3.1 – parameter values and ranges for system 2.3

Parameter	U-Shaped Valleys	V-shaped Valleys	Dimension
a^C	0.52	0.42	day^{-1}
a^A	0.15	0.12	day^{-1}
b_1	0.011	0.08	day^{-1}
b_2	0.048	0.24	day^{-1}
μ_h^C	0.079	0.059	day^{-1}
μ_h^A	0.033	0.033	day^{-1}
μ_v	0.033	0.033	day^{-1}
ν_h^A	0.000283	0.000283	day^{-1}
m_{12}^C	0.08	0.08	day^{-1}
m_{21}^C	0.08	0.08	day^{-1}
m_{12}^A	0.5	0.5	day^{-1}
m_{21}^A	0.5	0.5	day^{-1}
$\gamma_1^C(\gamma_1^A)$	0.0035	0.0035	day^{-1}
$\gamma_2^C(\gamma_2^A)$	0.0035	0.0035	day^{-1}
Λ_h	0.04	0.04	day^{-1}
Λ_v	0.13	0.07	day^{-1}

3.5 Numerical simulation

In this section, we calculate the reproductive number, $\mathcal{R}_0$ for model 2.3 for the parameter values given in table 3.1.

3.5.1 The U-shaped Valley Sites : Iguhu and Umutete, $\mathcal{R}_0 = 5.36$

We show a numerical simulation of the malaria model 2.3 in the figures below using the parameter values given in Table 3.1 When the age structuring is ignored the dynamics of the host

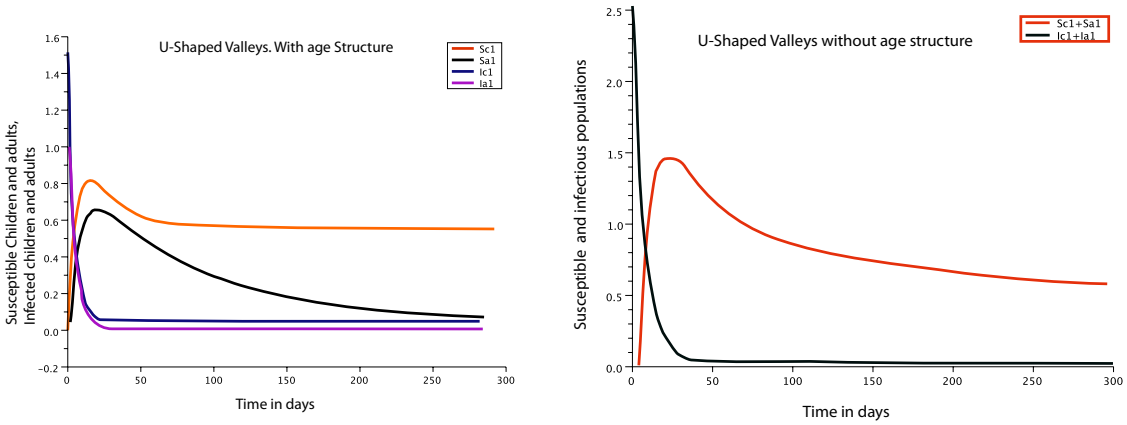

Figure 3.1 – A numerical simulation of model 2.3 using parameter values defined in Table 3.1 for the U-shaped valleys system. The age structure in the populations is clearly shown. In this case $\mathcal{R}_0 = 5.36$

population in the U-shaped valleys is represented by Figure 3.2. The disease in the age structured model fades out faster than the unstructured. The steady states also settle to the endemic equilibrium faster in the age structured model. If there is no spatialization the values for the U-shaped valleys for both ecosystems has host population variation represented in Figure 3.3. The interaction between the patches raises infection rate, so that the disease persists in the total population, while it fades out fast when the patches are isolated.

3.5.2 The V-shaped Valley Sites : Fort Tenan and Marani, $\mathcal{R}_0 = 1.67$

When the age structuring is ignored the variation of the host population in the V-shaped valleys is represented by Figure 3.5.

3.5.3 Conclusion

We have presented in this paper, an analysis of an age structured metapopulation model, by extending the Ross-Maddonald model. We assumed that, for malaria, age structuring is important

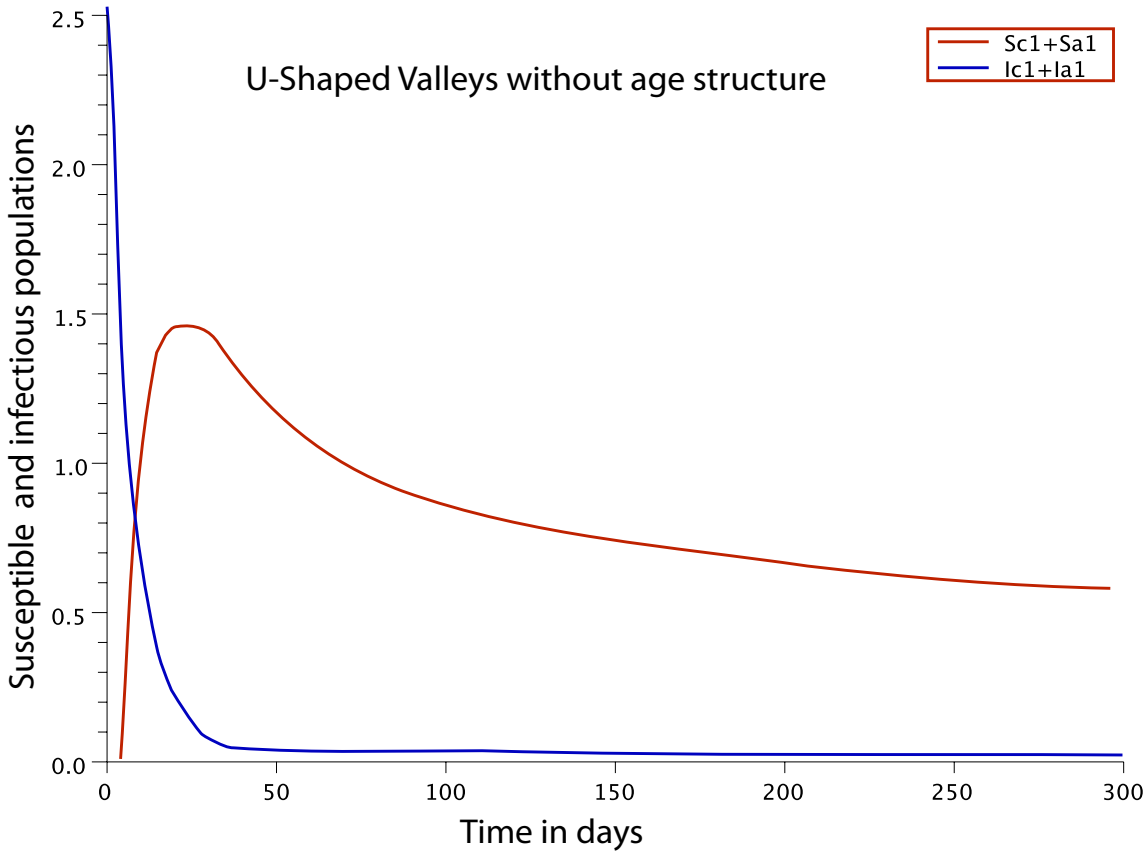

Figure 3.2 – A numerical simulation of model 2.3 using parameter values defined in Table 3.1 for the U-shaped valleys ecosystem. A case where there is no age structure in the population. In this case $\mathcal{R}_0 = 5.36$

as the severity of the disease, its infectivity and susceptibility is age specific. We have assumed that the two age groups migrate to neighboring patches and that their epidemiological characteristics are ecosystem dependent. We assumed that vectors do not migrate, and the migration parameters for hosts are constant, similar and independent of the compartment. The same result can be easily extended to the case where vectors migrate to explore the migration model for both populations since the villages are not very far apart.

A formular for $\mathcal{R}_0$ is obtained, which although complex due to the infinite number of patches, can be used to explore the effects of the parameters on the model. This formula will allow theoretical exploration of the options and efficiency of targeted public health intervention policies. The example in the two ecosystems simplifies the expression for $\mathcal{R}_0$, which we used to do the simulation with some realistic data.

This model can be extended to increase applicability in real situations. The two populations which we assumed to be constant can be varied and some disease induced deaths be included. The acquired immunity can also be included to show the dynamics. Treatment and vaccinated classes can also be incorporated in the force of infection.

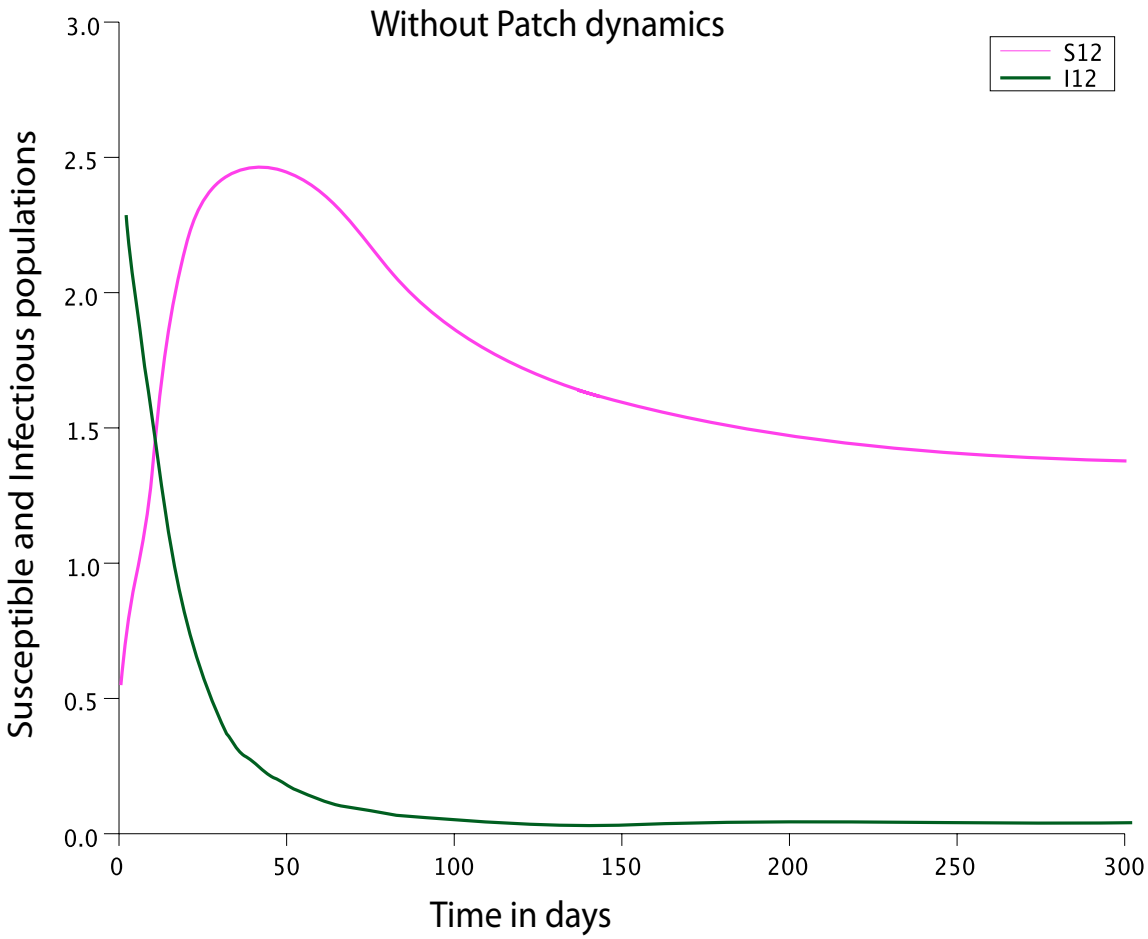

Figure 3.3 – A numerical simulation of model 2.3 using parameter values defined in Table 3.1 for the U-shaped valleys ecosystem. The is no age structure and the two ecosystems are treated as one U-shaped valley ecosystem

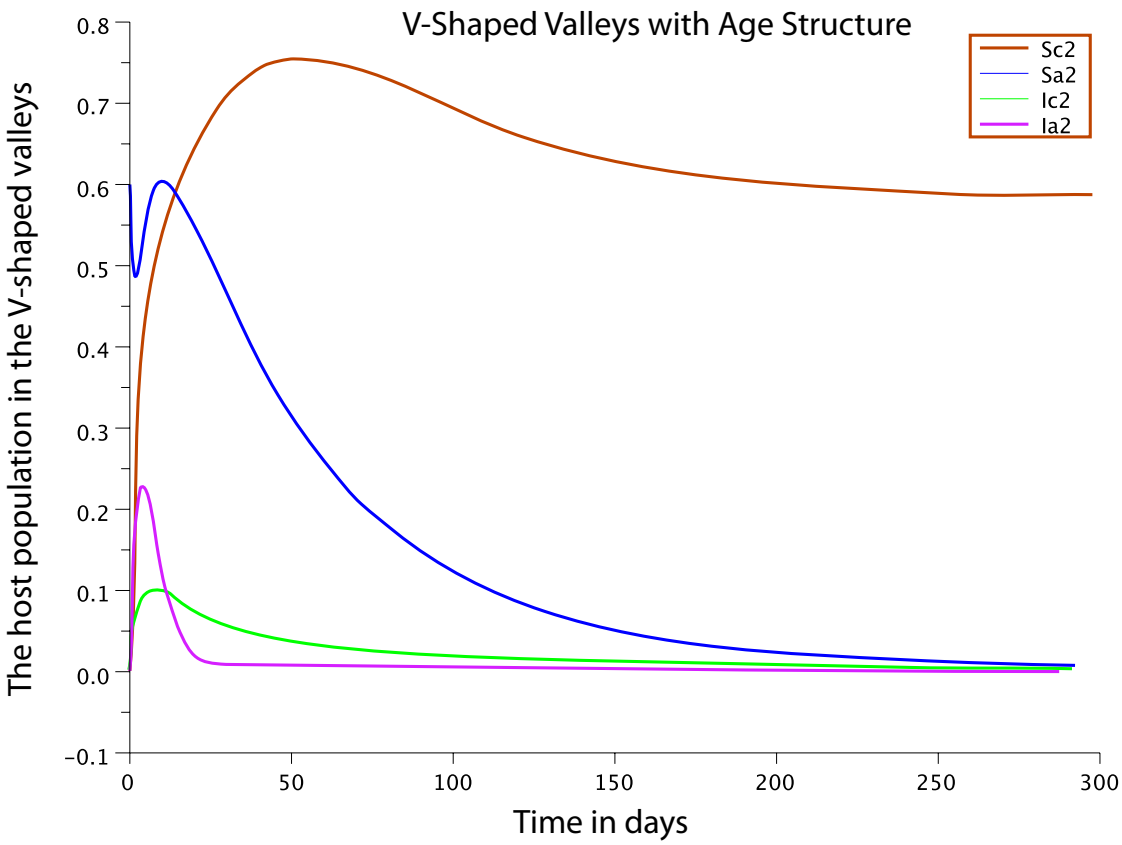

Figure 3.4 – A numerical simulation of model 2.3 using parameter values defined in Table 3.1 for the V-shaped valleys ecosystem with age structure. In this case $\mathcal{R}_0 = 1.67$

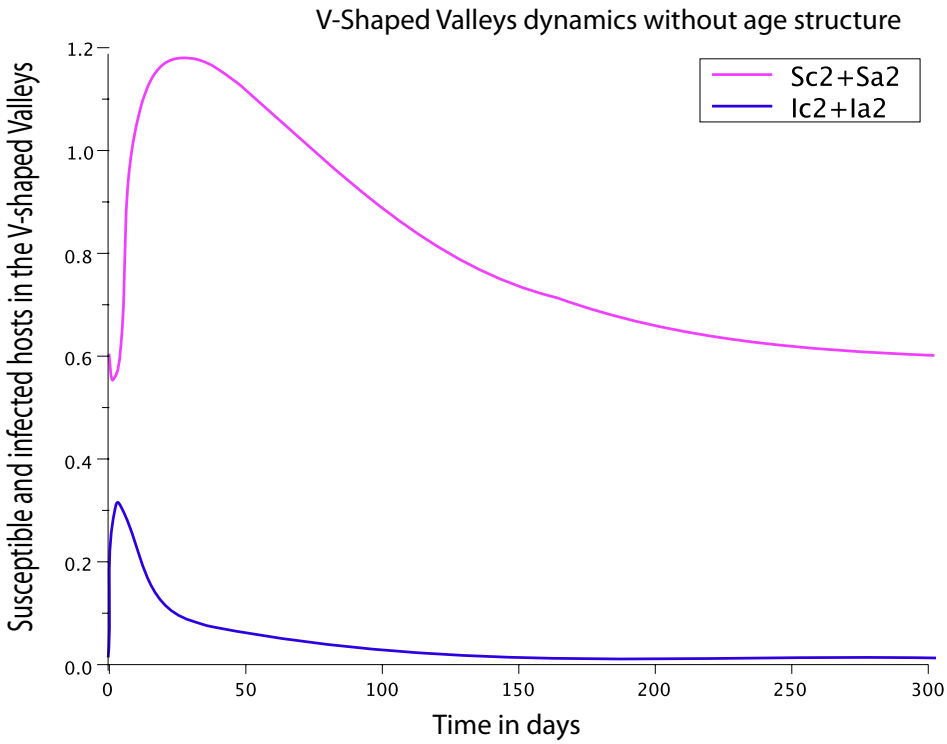

Figure 3.5 – A numerical simulation of model 2.3 using parameter values defined in Table 3.1 for the V-shaped valleys ecosystem. The is no age structures in the populations. In this case $\mathcal{R}_0 = 1.67$

The important of age structure in the dynamics of malaria can not be overemphasized as most malaria induced deaths occur in infants and the average parasitemia levels of infected individuals decreases with age. The acquired immune response also changes with age.
Adding age structure allows age specific control strategies that have greater impact in reducing disease incidence.

Metapopulation modeling on the other hand is an important feature in the dynamics of malaria. If the disease is controlled in one patch below the threshold size, there is possibility of a reintroduction from other patches, thus there is need to understand spatial heterogenity for effective and thorough control strategies. On the other hand, migration may effectively raise the level of infection. In such a case the disease will disappear in isolated patches, but will persist in the total population.

Further studies may include the probability of increased/decreased travel risk to and from the endemic region.

Our attempt towards the search for a practical solution on elimination and control of highland malaria in Western Kenya, is only but a small step in the right direction.

CHAPITRE 4

Dynamics of Vector-Host feeding Contact Rate with Saturation in malaria

Contents

4.1 Introduction

Malaria is an infectious disease caused by a parasite of the genus, Plasmodium. It is transmitted between human hosts by female anopheles mosquitoes as they seek blood meal for their eggs development. When a mosquito bites an infected person, a small amount of blood is taken in which contains microscopic malaria parasites. When the mosquito takes its next blood meal, these parasites mix with the mosquito saliva and are injected into the person being bitten and the transmission process is perpetuated.

Malaria constitutes a big health problem especially within sub-saharan Africa and Asia. World Malaria Report 2011, estimates that it causes between 250-260 million infections and more than a million deaths (mostly among children in Africa), annually. In Kenya, reports show that despite the many control strategies to eliminate malaria, it has re-emerged and increased in incidence. The disease continues to wreck havoc on millions especially from the poor countries [129].

Vector abundance in Western Kenya is driven by temperature variation, ecosystem characteristics and human activities. The population varies depending on the site, the season and the species of the vector. Some sites in Western Kenya has 12.7 fold indoor resting densities during he long rainy season (March-June) and 23.3 fold during the dry season (January-March) [110]. This implies that the vector populations is never constant as assumed in many models. On the other hand host population changes due seasons and economic activities, natural deaths and death due to diseases like malaria and migration to urban centers and other regions for greener pastures. For our model to capture the reality of the epidemics in Western Kenya highlands, we assume that the host and mosquito populations change with time.

Most malaria models assume a constant human biting rates in their models, which means that hosts are freely available whenever a mosquito wants to bite, but in practice, this is more of a simplifying assumption. Research shows that for small host population, this rate is proportional to the host population size, and for large host population, it is constant [52, 66]. The feeding cycle of a mosquito involves, host-seeking, feeding, resting, site-seeking, oviposition and host seeking resumes [83, 113]. The probability of finding a host and successfully obtaining a blood meal depends on many factors. Among them is human avoidance and defensive behaviour [39, 97].

If the mosquito survives this process, and has a successful blood meal, it rests, finds a larval habitat, oviposit and continue host seeking. Since this process drives malaria transmission, it is necessary to address the specific form of the mosquito-human contact process. Arditi [75], argues that the rates of (successful predation) contact between a predator and a prey is most properly a function of the ratios of their proportions. This would fit into malaria mosquito which inhabit homesteads and other areas where human hosts are available, like farms and urban areas [133]. It is also clear that this contact rate does not increase without bound, as the predator -prey ratio increases, this is because once a mosquito is fed, it rests before ovipositing, to resume host seeking and biting again [106].

When the predator-prey ratio value is low, the contact rate will be limited by the predators ability to find the prey, on the other hand if the ratio is high, the contact rate is limited by the predators satiation (desired predation rate) [66, 75]. For malaria, the contact rate takes a similar course where the mosquito bites will increase as a function of host-vector ratio until the ratio reaches a critical level [89].

Saturation models are also not lacking in literature. A cholera model with saturation in the incidence was proposed by Capasso [24] . They argue that when there is a real threat to infection people become cautious and take preventive measures which controls further infection. Heesterbeek [57] formulated a saturated individual contact rate in relationships such as courting and marriage, where they assume that the population mixes randomly. Zu and Ma [120] analyzed a SEIR epidemic model whose latent period is described by delay and included a saturated incidence rate. Zhang and Ma [70] studied a SEIR model with saturation in contact rates and did a thorough analysis of its global dynamics.

In 2010, ming and Li [23] formulated vector borne disease model, where they argue that increasing the density of the susceptible hosts with respect to infected ones leads to Holling type II saturation on the force of infection of host. In this model the biting rate of vectors and both populations are assumed to be constant. Further the model neglects disease related deaths a very crucial factor in malaria infection.

A model by [40] on dengue with variable human population is formulated and analyzed for both local and global dynamics. Ngwa et at [112] analyzed the stability of a malaria model, with disease deaths, recovery and variable host and vector populations. However they assumed that the biting rate of vectors is constant hence their infection term is the one described in [121]. Realising then the need to predict the dynamics and transmission of malaria with great precision, we are motivated to engage in this study, as we pay particular attention to saturation in mosquito feeding habits and the varying host and vector populations.
The rest of the paper is subdivided as follows ; Section two covers vector-host contact with satu-

ration. In section three, the saturated contact process model is formulated. Section 4 is dedicated to the existence of equilibiria, while section 5 studies the stability of the Disease Free and the Endemic equilibrium. Finally in section six we give some results on numerical simulation.

4.2 Vector-Host Contact

Vector-host contact results from the need for mosquitoes to obtain a blood meal for their eggs development. A given vector's biting rate is limited by both host population density and its own feeding frequency [87]. Therefore the per vector biting rate should increase as a function of the host ratio until the ratio reaches a critical level, which we denote Q_v, above which, biting rate saturates and the average vector can feed at its preferred rate b_v (contacts per vector per time). Below this threshold, the relative scarcity of hosts constrains the rate at which a vector can feed on the given type of hosts (it must seek other sources).
We assume that an average host can receive bites at a maximum rate b_h beyond which it successfully defends itself against the vector (including leaving the place altogether) [89]. Then this threshold density ratio is given by

$$Q_v = \frac{b_v}{b_h}.$$

We shall assume a saturated contact process as used in [86, 88] with the so-called Holling Type 1 form. Under this assumption, the per-vector contact rate can be described as a function of the host-vector density ratio $z = \frac{N_h}{N_v}$ as

$$f(z) = b_v \min\{z/Q_v, 1\}.$$

When $z > Q_v$ (many host per vector) the rate completely saturates at the maximum desired biting rate $f(z) = b_v$, while for $z < Q_v$ (ie. few hosts per vector) $f(z) = b_v \frac{z}{Q_v}$, and the rate rises linearly with the host-vector ratio. The later is our interest in this study since the saturated contact process $f(z) = b_v$ has been used in the classical Ross model for malaria [121]. Substituting $z = \frac{N_h}{N_v}$ in the function $f(z)$ and multiply by N_v, we obtain the total biting rate which is

$$b_v\, min(N_h, \frac{N_v}{Q_v}).$$

which can be rewritten in the form

$$\min\{b_h\, N_h, b_v\, N_v\}.$$

We note that for the current host density the maximum number of vectors that can effectively bite hosts at one given time is $\frac{N_v}{Q_v}$. Therefore the parameter Q_v is an important determinant in our of model. It determines which of the two population densities is driving the biting contact rate.
To examine the rate of appearance of new malaria infections from the rate of mosquito feeding contacts, we have to take into account the probability of infection resulting from an effective contact where one party (host or vector) is infected with malaria parasite and the other is not. Let π_h be the probability that such a contact between an infected vector and an uninfected host results in infecting the host, π_v as the proportion of blood meal contacts between infected hosts and uninfected vectors which result in an infected vector. Further if S_h, I_h are the susceptible and infectious hosts respectively and S_v, I_v are the susceptible and infectious vectors respectively, the new infections will be given as defined in [89].

– For the Hosts

$$b_h\, N_h\, \frac{S_h}{N_h}\frac{I_v}{N_v}.\,\pi_h = \pi_h\, b_h\, S_h \frac{I_v}{N_v}$$

– For the Vectors

$$b_h\, N_h \frac{S_v}{N_v}\frac{I_h}{N_h}.\,\pi_v = \frac{\pi_v\, b_v}{Q_v}\, I_h \frac{S_v}{N_v},$$

since $b_h = \frac{b_v}{Q_v}$

In many malaria models, saturation has been assumed to be constant [14, 121, 138]. Here we consider the density dependent biting rate, and the populations ratio plays a vital role in the transmission. If the vectors-host ratio is low, the bites are few and hence the probability of transmission reduces too. As the ratio increases the infection will rise as a function of the ratio until it reaches the threshold and it becomes a constant. We wish to model this change in biting rate as the vector-host ratio changes and study its effect on the basic reproduction ratio.

4.3 The Model Equations

The model we derive here is mathematically equivalent to the classical Ross model [121]. The saturation in contact processes will address how the infection rates depend on this ratio. We assume that mosquito has a variable population growth such that birth $\Lambda_v > \mu_v$. For the human population, we assume a density dependent mortality rate, such that the total population vary with time and is modified by a logistic equation that include disease induced deaths.

A description of the variables and parameters used in the model follows in tables 5.1 and 4.2 respectively.

Table 4.1 – Variables used in the model related to infection contact process

Variable	Definition	Units
S_h	Susceptible Host Population Density	Hosts
S_v	Susceptible Vector Population Density	Vectors
I_h	Infectious Host Population Density	Hosts
I_v	Infectious Vector Population Density	Vectors
N_h	Total Host Population Density (constant)	Hosts
N_v	Total Vector Population Density (variable)	vectors/time

The dynamics of our model will be governed by the following set of equations :

$$\begin{cases} \dot{S}_h = \Lambda_h - \pi_h\, b_h\, S_h \frac{I_v}{N_v} + \gamma_h\, I_h - \mu_h\, S_h, \\ \\ \dot{I}_h = \pi_h\, b_h\, S_h\, \frac{I_v}{N_v} - (\mu_h + \gamma_h + \nu_h)\, I_h, \\ \\ \dot{S}_v = \Lambda_v - \frac{\pi_v\, b_v}{Q_v}\, I_h \frac{S_v}{N_v} - \mu_v\, S_v, \\ \\ \dot{I}_v = \frac{\pi_v\, b_v}{Q_v}\, I_h \frac{S_v}{N_v} - \mu_v\, I_v. \\ and \\ \dot{N}_h = \Lambda_h - \mu_h\, N_h - \alpha_h I_h \quad \dot{N}_v = \Lambda_v - \mu_v\, N_v. \end{cases} \tag{4.1}$$

Table 4.2 – Parameters used in the model related to infection contact process

Parameter	Definition	Units
Λ_h, Λ_v	Hosts, Vectors density dependent birth rate	host, vector/unit time
π_h	probability of host infection per contact	host/vec/ time
π_v	probability of vector infection per contact	vec/host/ time
γ_h	Hosts rate of recovery	host/unit time
Q_v	vector-host ratio above which per-vector biting saturates	vec/host
b_h	host irritability biting threshold	bites/host/time
b_v	preferred (max.) vector feeding rate	bites/vec/ time
α_h,	disease dependent death rate	host/time

The term Λ_h in the susceptible hosts compartment corresponds to a constant recruitment of susceptible hosts by natural birth. The transmission term $-\pi_h\, b_h\, S_h \frac{I_v}{N_v}$ corresponds to frequency dependent infection of susceptible hosts by infectious mosquitoes, on infection they move to the infectious compartment. The infected hosts who recover $\gamma_h\, I_h$ become susceptible again as malaria has no permanent immunity. The last terms $-\mu_h\, S_h,\ -\mu_h\, I_h$ represents per capita deaths of the susceptible, infected hosts respectively. In the susceptible mosquito vectors,Λ_v represent the recruitment of susceptible mosquitoes by birth. The term $\frac{\pi_v\, b_v}{Q_v}\, S_h \frac{I_v}{N_v}$ corresponds to the transmission of malaria to an susceptible mosquito by and infected host. Both the susceptible and infectious mosquitoes are subject to natural deaths as defined in the terms $-\mu_v\, S_v,\ -\mu_v\, I_v$ respectively. Infective period of mosquitoes ends with their death due to their relatively short life-cycle so we do not have recovery or immune term in the vector equations [16, 68].

All the parameters in the model are non negative and the model equations are well posed. For initial values $(S_h, I_h, S_v, I_v, N_h, N_v)$ in $\mathbb{R}^6_+$, the solutions exist and remains in the region for all $t \geq 0$.
In the absence of disease the host population dynamics is given by $\dot{N}_h = \Lambda_h - \mu_h N_h$. In this kind of demographic structure, the total human and mosquito population size $N_h(t)$ approaches a carrying capacity $\frac{\Lambda_h}{\mu_h}$ for any non zero initial population size.
The mosquito population $N_v(t)$ also approaches a carrying capacity $\frac{\Lambda_v}{\mu_v}$. For ease of studying the system, we let setting $\beta_h = \pi_h b_h$, $K = (\mu_h + \gamma_h + \nu_h)$ and $\beta_v = \frac{\pi_v b_v}{Q_v}$, and the equation now takes the form

$$\begin{cases} \dot{S}_h = \Lambda_h - \beta_h\, S_h\, \frac{I_v}{N_v} + \gamma_h\, I_h - \mu_h\, S_h, \\ \\ \dot{I}_h = \beta_h\, S_h \frac{I_v}{N_v} - K\, I_h, \\ \\ \dot{S}_v = \Lambda_v - \beta_v I_h \frac{S_v}{N_v} - \mu_v\, S_v, \\ \\ \dot{I}_v = \beta_v\, I_h\, \frac{S_v}{N_v} - \mu_v\, I_v. \\ and \\ \dot{N}_h = \Lambda_h - \mu_h\, N_h - \alpha_h I_h \quad \dot{N}_v = \Lambda_v - \mu_v\, N_v. \end{cases} \tag{4.2}$$

Using the relation $S_h = N_h - I_h$, and $S_v = N_v - I_v$, we will now study the system

$$\begin{cases} \dot{I}_h = \beta_h \left(N_h - I_h\right) \frac{I_v}{N_v} - K\, I_h, \\ \dot{I}_v = \beta_v\, I_h\, \frac{N_v - I_v}{N_v} - \mu_v\, I_v. \\ \dot{N}_h = \Lambda_h - \mu_h\, N_h - \nu_h\, I_h \\ \dot{N}_v = \Lambda_v - \mu_v\, N_v. \end{cases} \tag{4.3}$$

which is defined in feasible region (ie. where the model makes biological sense)

$$\Gamma = \{(I_h, I_v, N_h, N_v) \in \mathbb{R}^4_+ \ : 0 \leq I_h \leq 1,\ 0 \leq I_v \leq 1, N_h \geq 0, N_v \geq 0\}$$

where $\mathbb{R}^4_+$ denotes the non-negative cone of $\mathbb{R}^4$ including its lower dimensional faces. It is clear that Γ is positively invariant with respect to (4.3). We denote the boundary and the interior of Γ by $\partial\Gamma$and $\overset{\circ}{\Gamma}$ respectively.

CHAPITRE 5

Stability Analysis :Saturation

Contents

5.1 Local Stability of the DFE

In the absence of infection, the model has a constant solution, P_0, also referred to as the Disease Free equilibrium (DFE) which is defined by $P_0 = (0, 0, \frac{\Lambda_h}{\mu_h}, \frac{\Lambda_v}{\mu_v})$.
To establish the stability of this equilibrium, the Jacobian of 4.3 is computed at the DFE. The stability of P_0 is determined by the signs of the eigenvalues of this jacobian. If the real parts of the eigenvalues are all negative, then, the equilibrium P_0 is locally asymptotically stable. The Jacobian of system 4.3 is given by

$$J_P = \begin{bmatrix} -\beta_h \frac{I_v}{N_v} - K & \beta_h \frac{(N_h - I_h)}{N_v} & \beta_h \frac{I_v}{N_v} & \beta_h (N_h - I_h) \frac{I_h}{N_v} \\ \beta_v \frac{(N_v - I_v)}{N_v} & -\beta_v \frac{I_h}{N_v} - \mu_v & 0 & -\beta_v \frac{(N_v - I_v)}{N_v^2} I_h \\ -\nu_h & 0 & -\mu_h & 0 \\ 0 & 0 & 0 & -\mu_v \end{bmatrix}$$

The Jacobian at the DFE is given by the matrix

$$J_{P^0} = \begin{bmatrix} -K & \beta_h \frac{\Lambda_h \mu_v}{\Lambda_v \mu_h} & 0 & 0 \\ \beta_v & -\mu_v & 0 & 0 \\ 0 & 0 & -\mu_h & 0 \\ 0 & 0 & 0 & -\mu_v \end{bmatrix}$$

We note that there is only one non zero element int the third and the fourth rows, and both elements are negative, we can the determine if the eigenvalues of this J_{P^0} have negative real parts by getting the eigenvalues of the the block matrix

$$J_{01} = \begin{bmatrix} -K & \beta_h \frac{\Lambda_h \mu_v}{\Lambda_v \mu_h} \\ \beta_v & -\mu_v \end{bmatrix}$$

The characteristic equation is given by

$$\lambda^2 + \lambda(K + \mu_v) + K\mu_v(1 - \tilde{\mathcal{R}}_0)$$

whose eigenvalues are purely negative if and only if $\tilde{\mathcal{R}}_0 < 1$, where

$$\tilde{\mathcal{R}}_0 = \mathcal{R}_0^2 = \frac{\beta_h \, \beta_v \, \Lambda_h}{\mu_h \, \Lambda_v \, K} = \frac{b_h \, \pi_h \, b_v \, \pi_v \, \Lambda_h}{\Lambda_v \, \mu_h \, Q_v \, (\gamma_h + \mu_h + \nu_h)}$$

hence we have established the following proposition :

Proposition 3. The DFE P_0 is locally asymptotically stable if $\tilde{\mathcal{R}}_0 \leq 1$ and unstable if $\tilde{\mathcal{R}}_0 > 1$.

$\tilde{\mathcal{R}}_0$ is referred to as the basic reproduction number. It is defined as the number of secondary infectious cases resulting from one infectious individual introduced into an entirely susceptible population in his entire life of infectiousness [?]. The quantity $\tilde{\mathcal{R}}_0$ is important in the study of infectious diseases as it is the threshold that determines if the disease dies out or it persists in the population. When $\tilde{\mathcal{R}}_0 \leq 1$, then the DFE is locally stable.

Proposition 4. If $N_v = 0$ the model has only the disease free equilibrium $P_0 : (0, 0, \frac{\Lambda_h}{\mu_h}, \frac{\Lambda_v}{\mu_v})$ as a constant solution.

Proof
If $N_v = 0$, then the only possible nonnegative constant solution for the system is P_0. The characteristic shows clearly that the DFE will always exist, and when $\tilde{\mathcal{R}}_0 > 1$ an endemic equilibrium where the disease persists in the populations is established. The steady state solution for which the total vector and human populations are both zero is not realistic since there is nothing to prove. In the presence of the disease, without disease deaths both populations are equal to $(N_h, N_v) = (\frac{\Lambda_h}{\mu_h}, \frac{\Lambda_v}{\mu_v})$. With the progress of the disease, the total host population size will be determined by the magnitude of ν_h, and a new equilibrium for the host will be established.

This equilibrium is given by

$$N_h^* = \frac{\Lambda_h - \nu_h I_h^*}{\mu_h}.$$

Its important to note that if the disease deaths are high enough then the value of N_h^* would be negative and the equilibrium would cease to exist.
We also note that since infection is determined by the ratios of the total human and host populations, the parameter Q_v, plays an important role in the overall model and especially $\tilde{\mathcal{R}}_0$.

5.2 Global stability of the Disease Free Equilibrium

Theorem 5.1. The disease-free equilibrium $P_0 = (0, 0, \frac{\Lambda_h}{\mu_h}, \frac{\Lambda_v}{\mu_v})$ of ?? is globally asymptotically stable in Γ if $\tilde{\mathcal{R}}_0 \leq 1$ and it is unstable if $\tilde{\mathcal{R}}_0 > 1$.

Proof
Consider the Lyapunov function

$$\mathcal{L} = \beta_v \, I_h + K I_v.$$

The derivative of $\mathcal{L}$ along the trajectories of 4.3 is given by

$$\begin{cases} \dot{\mathcal{L}} = \beta_v \, \dot{I}_v + K \, \dot{I}_v] \\ \quad = \beta_v \, [\beta_h \, (N_h - I_h) \, \frac{I_v}{N_v} - K \, I_h] + K \, [\beta_v \, I_h \, \frac{(N_v - I_v)}{N_v} - \mu_v \, I_v] \\ \quad = \beta_v \beta_h \, I_v - \beta_v \, \beta_h \, I_h \, \frac{I_v}{N_v} - \beta_v \, K \, I_h + K \, \beta_v \, I_h - K \, \beta_v \, I_h \frac{I_v}{N_v} - K \, \mu_v \, I_v \\ \quad = [\beta_v \, \beta_h - K \, \mu_v] \, I_v - \beta_v \, I_h (\beta_h - K) \, \frac{I_v}{N_v} \\ \quad = K \, \mu_v \, [\tilde{\mathcal{R}}_0 - 1] \, I_v - \beta_v \, I_h (\beta_h - K) \, \frac{I_v}{N_v} \\ \quad \leq K \, \mu_v \, I_v [\tilde{\mathcal{R}}_0 - 1] \\ \quad \leq 0, \quad if \ and \ only \ if \ \ \tilde{\mathcal{R}}_0 \leq 1 \end{cases} \tag{5.1}$$

From the Lyapunov-Lasalle theorem [54], we know that all paths in Γ approach the largest positively invariant subset of the set E where $\dot{V} = 0$. The set E is defined when $I_h = 0$ and $I_v = 0$. On the boundary of Γ where $I_h = I_v = 0$ we have

$$\dot{N_h} = \Lambda_h - \mu_h \, N_h$$

which implies

$$N_h = \frac{\Lambda_h}{\mu_h} + [N(0) - \frac{\Lambda_h}{\mu_h}] \, e^{-t}$$

so that as t tends to ∞, N_h tends to $\frac{\Lambda_h}{\mu_h}$. Similarly as t tends to ∞, N_v tends to $\frac{\Lambda_v}{\mu_v}$.
Therefore all the solution paths in Γ approach the disease free equilibrium P_0.

This means that when $\tilde{\mathcal{R}}_0 \leq 1$, the infected host and vector subpopulations vanishes over time and the disease dies out [70]. In the next section we show that the disease persists when $\tilde{\mathcal{R}}_0 > 1$.

5.3 Existence and stability of the Endemic Equilibrium (EE)

Theorem 5.2. If $\tilde{\mathcal{R}}_0 \leq 1$, then all the trajectories of 4.3 tend to the disease-free equilibrium, which is globally asymptotically stable on the positive orthant. If $\tilde{\mathcal{R}}_0 > 1$, then there exists a unique endemic equilibrium $(I_h^*, I_v^*) \gg 0$, and all the trajectories of the positive orthant, minus the origin, tend to this equilibrium which is GAS on the unit cube minus the origin.

Proof
As our model focuses on saturation in the vector feeding habits, and this saturation depends in the ratio of the densities of the two population, then we know that these densities drive the infection dynamics. From the total human population equation

$$\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - \nu I_h,$$

we get the solution

$$N_h(t) = \frac{\Lambda_h - \nu_h}{\mu_h I_h} + N_h(0)\, e^{-\mu_h t}$$

and similarly

$$N_v(t) = \frac{\Lambda_v}{\mu_v} + N_v(0)\, e^{-\mu_v t}$$

Since $N_h(t) \to \frac{\Lambda_h}{\nu_h + \mu_h I_h}$, as $t \to +\infty$ and $N_v(t) \to \frac{\Lambda_v}{\mu_v}$, as $t \to +\infty$ we can substitute for N_h and N_v into the first and the second equations of system 4.3 to get the following two dimensional asymptotically autonomous differential equation

$$\begin{cases} \frac{dI_h}{dt} = \frac{\beta_h \mu_v}{\Lambda_v \mu_h}[\Lambda_h - (\nu_h + \mu_h) I_h] I_v - K I_h, \\ \\ \frac{dI_v}{dt} = \frac{\beta_v}{\Lambda_v}(\Lambda_v - \mu_v I_v) I_h - \mu_v I_v \end{cases} \tag{5.2}$$

Which is positively invariant in the region

$$\mathcal{K} = \{I_h, I_v \in \mathbb{R}^2_+ \;\; ; \;\; 0 \leq I_h \leq \frac{\Lambda_h}{\mu_v}, \;\; 0 \leq I_h \leq \frac{\Lambda_v}{\mu_v + \nu_h}\}$$

Ensuing next us an application of the theory of monotone and strongly monotone dynamical systems, that was developed by Hirsch in a series of papers. If we show that the Jacobian of system is a metzler matrix then it is a prove that the dynamical system is monotonic.
We need the following theorem according to Hirsch [63],

Theorem 5.3. Let F be a C^1 vector field in $\mathbb{R}^n$, whose flow ϕ preserves $\mathbb{R}^n_+$ for $t \geq 0$ and is strongly monotone in $\mathbb{R}^n_+$. Assume that the origin is an equilibrium and that all trajectories in $\mathbb{R}^n_+$ are bounded. Suppose the matrix-valued map $DF : \mathbb{R}^n_+ \to \mathbb{R}^n_+ \times \mathbb{R}^n_+$ is strictly antimonotone, in the sense that,

$$if \; x < y, \; then \;\; DF(x) > DF(y),$$

then either all the trajectories in $\mathbb{R}^n_+ \backslash \{0\}$ tend to the origin, or else there is a unique equilibrium $p \in \; Int \; \mathbb{R}^n_+ \; (p \gg 0)$ and all the trajectories in $\mathbb{R}^n_+$ tend to p.

We rewrite system 5.2 in the form $\dot{X} = A(X)X$, where $X = (I_h, I_v)$, and then show that it is cooperative and strongly monotonic. The system will take the form

$$\dot{Z} = \begin{pmatrix} I_h \\ I_v \end{pmatrix} = \begin{bmatrix} -K & a[\Lambda_h - (\mu_h + \nu_h) I_h] \\ b[\Lambda_v - \mu_v I_v] & -\mu_v \end{bmatrix} \begin{bmatrix} I_h \\ I_v \end{bmatrix} \tag{5.3}$$

where $a = \frac{\beta_v \mu_v}{\Lambda_h \mu_h}$ and $b = \frac{\beta_v}{\mu_v}$. The Jacobian of the system is given by

$$J = \begin{bmatrix} -K - a(\mu_h + \nu_h) I_v & a[\Lambda_h - (\mu_h + \nu_h) I_h] \\ b(\Lambda_v - \mu_v I_v) & -\mu_v - b\mu_v I_h \end{bmatrix}$$

We see that A is a metzler matrix. We need to show that it is irreducible hence strongly monotonic. To prove irreducibility of a Metzler matrix it is enough to show that the directed graph associated with J is strongly connected [2]. We name the vertices of the associated graph m_{12}, m_{21}. If $I_h \ll \frac{\Lambda_h}{\mu_h + \nu_h}$, then the element $m_{12} = [\Lambda_h - (\mu_h + \nu_h)] > 0$ which means that there is a path connecting m_{12} to m_{21}. Again if $I_h \ll \frac{\Lambda_v}{\mu_v}$, the element $m_{21} = b(\Lambda_v - \mu_v I_v) > 0$. This proves strong monotonicity on the flow of the system in the positive orthant except on the faces not $I_h \ll \frac{\Lambda_h}{\mu_h + \nu_h}$ and not $I_h \ll \frac{\Lambda_v}{\mu_v}$. Any trajectory with an initial point outside these faces, will leave the face.

Since our Jacobian is irreducible, the system is cooperative and therefore strongly monotonic.
Now we show that the trajectories are bounded.

When $I_h = 0$, we have

$$\dot{I}_h = a\Lambda_h I_v \geq 0,$$

when $I_h = 0$, we have

$$\dot{I}_v = a\Lambda_v I_h \geq 0,$$

when $I_h = \frac{\Lambda_h}{(\mu_h + \nu_h)}$, we have

$$\dot{I}_h = -\frac{K\Lambda_h}{(\mu_h + \nu_h)} < 0,$$

when $I_v = \frac{\Lambda_v}{(\mu_v)}$, we have

$$\dot{I}_v = -\Lambda_v < 0,$$

This clearly shows that no trajectory can leave the region $\mathcal{K}$, hence all the trajectories are bounded.
From theorem 5.3 and the fact that $\tilde{\mathcal{R}}_0 > 1$, we conclude that the trajectories of system 5.2 converge to an equilibrium $\bar{P}$ as $t \to \infty$. We s also deduce that $\bar{P} = (\bar{I}_h, \bar{I}_v) \gg 0$ from the fact that the system is strongly monotonic.

Lastly we recall the Jacobian of our system

$$J = \begin{bmatrix} -K - a\left(\mu_h + \nu_h\right) I_v & a\left[\Lambda_h - \left(\mu_h + \nu_h\right) I_h\right] \\ \\ b\left(\Lambda_v - \mu_v\, I_v\right) & -\mu_v - b\mu_v\, I_h \end{bmatrix},$$

if we take $I_{h1} < I_{h2} \in I_h$ and $I_{v1} < I_{v2} \in I_v$ then we see clearly that $J(I_{h1}, I_{v1}) > J(I_{h2}, I_{v2})$. Thus our system satifies the antimonotone criteria. Since we have already shown that the DFE P^0 is unstable when $\tilde{\mathcal{R}}_0 > 1$,there exists therefore, an endemic equilibrium $\bar{P} \gg 0$ in the interior of $\mathcal{K}$ and all the trajectories in $\mathbb{R}^2$ tend to this equilibrium. This equilibrium satisfies $\dot{X} = A(\bar{P})\bar{P} = 0$, that is

$$\begin{bmatrix} -K & a\left[\Lambda_h - \left(\mu_h + \nu_h\right) \bar{I}_h\right] \\ \\ -b\left[\Lambda_v - \mu_v\, \bar{I}_v)\right] & -\mu_v \end{bmatrix} \begin{bmatrix} \bar{I}_h \\ \\ \bar{I}_v \end{bmatrix} = \begin{bmatrix} 0 \\ \\ 0 \end{bmatrix}$$

The Jacobian above at the Endemic equilibrium is given by

$$J = \begin{bmatrix} -K - a\left(\mu_h + \nu_h\right) \bar{I}_v & a\left[\Lambda_h - \left(\mu_h + \nu_h\right) \bar{I}_h\right] \\ \\ b\left(\Lambda_v - \mu_v \bar{I}_v\right) & -\mu_v - b\,\mu_v\, \bar{I}_h \end{bmatrix}$$

and $J(\bar{P})\bar{P}$ is given by

$$\begin{bmatrix} -K & a\left[\Lambda_h - \left(\mu_h + \nu_h\right) \bar{I}_h\right] \\ \\ -b\left[\Lambda_v - \mu_v\, \bar{I}_v)\right] & -\mu_v \end{bmatrix} \begin{bmatrix} \bar{I}_h \\ \\ \bar{I}_v \end{bmatrix} + \begin{bmatrix} -(\mu_h + \nu_h)\bar{I}_v\bar{I}_h & 0 \\ \\ 0 & -b\mu_v\bar{I}_v\bar{I}_h \end{bmatrix}.$$

But since $A(\bar{P})\bar{P} = 0$, we notice that

$$J(\bar{P})\bar{P} = \begin{bmatrix} -(\mu_h + \nu_h)\bar{I}_v\bar{I}_h & 0 \\ \\ 0 & -b\mu_v\bar{I}_v\bar{I}_h \end{bmatrix} < 0.$$

This implies that the stability modulus $\alpha(J(\bar{P})) < 0$, [2], which implies therefore that the endemic equilibrium $\bar{P}$ is locally asymptotically stable. The uniqueness and global stability is a direct result of theorem 5.3. □

5.4 Conclusion and discussion

In this study, we developed a vector feeding habits saturation model for the spread of malaria with disease induced deaths and varying human and host populations. We have shown that the two populations drive the entire infection process through the parameter Q_v, which plays a vital role in the basic reproduction number. Mathematical analysis was done to establish that in the absence of the disease, a disease free equilibrium will always exist if $\tilde{\mathcal{R}}_0 \leq 1$. In the presence of the disease, that is when $\tilde{\mathcal{R}}_0 > 1$, an endemic equilibrium is established with the infectious populations greater than zero.

Table 5.1 – Parameters used in the model related to infection contact process

Parameter	Value	Dimension
Λ_h	0.04	unit time
Λ_v	0.13	unit time
π_h	0.22	unit time
π_v	0.48	unit time
γ_h	0.33	unit time
b_h	0.21	unit time
b_v	0.43	unit time
α_h,	0.0329	unit time
μ_h	0.033	unit time
μ_v	0.033	unit time

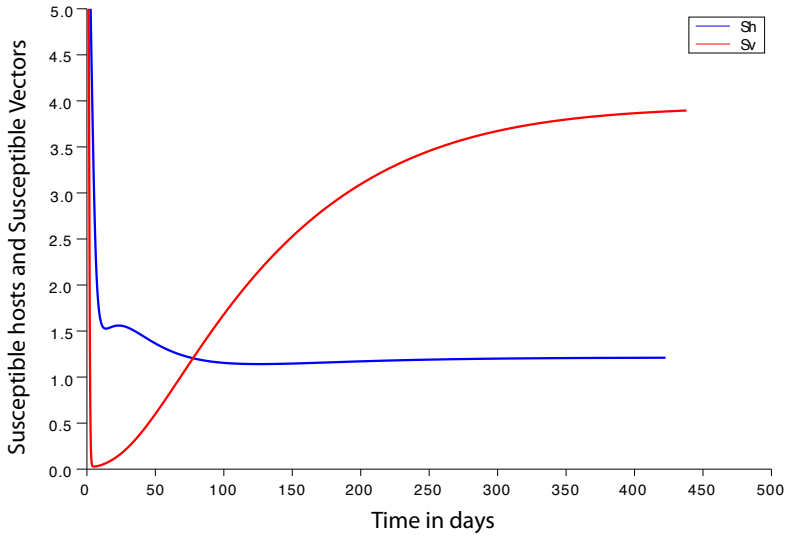

Figure 5.1 – Variation of susceptible host and vector populations at the Disease Free equilibrium. $Q_v = 0.3$ and $\tilde{\mathcal{R}}_0 = 0.718 < 1$

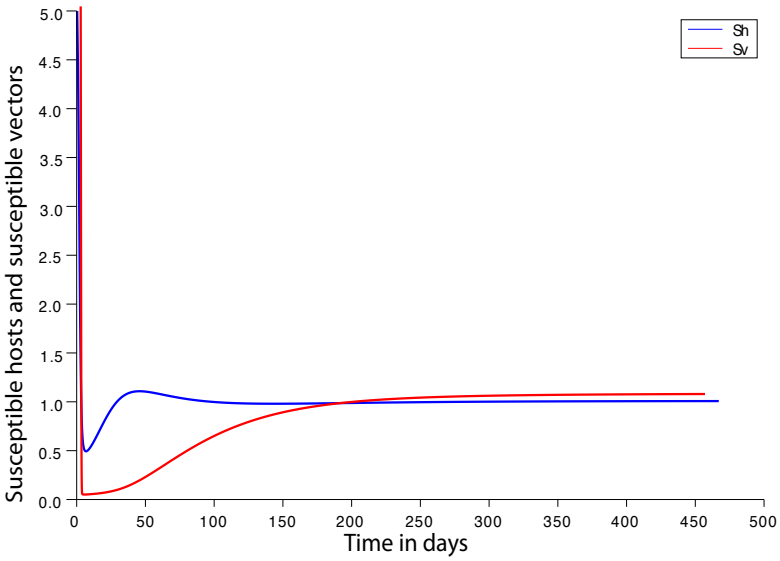

Figure 5.2 – Variation of susceptible host and vector populations at the Endemic equilibrium. $Q_v = 0.09$ and $\tilde{\mathcal{R}}_0 = 2.495 > 1$

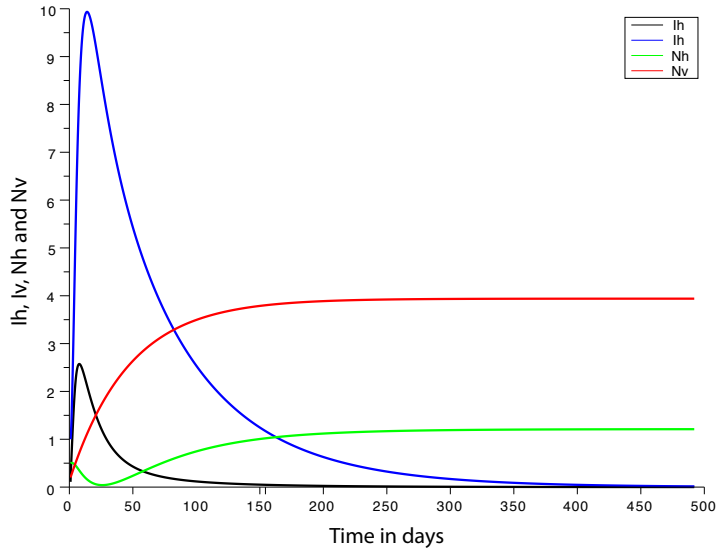

Figure 5.3 – Variation of Infected Host, Infected Vector, Total Host and Total Vector populations at the Disease Free equilibrium. $Q_v = 0.3$ and $\tilde{\mathcal{R}}_0 = 0.718 < 1$

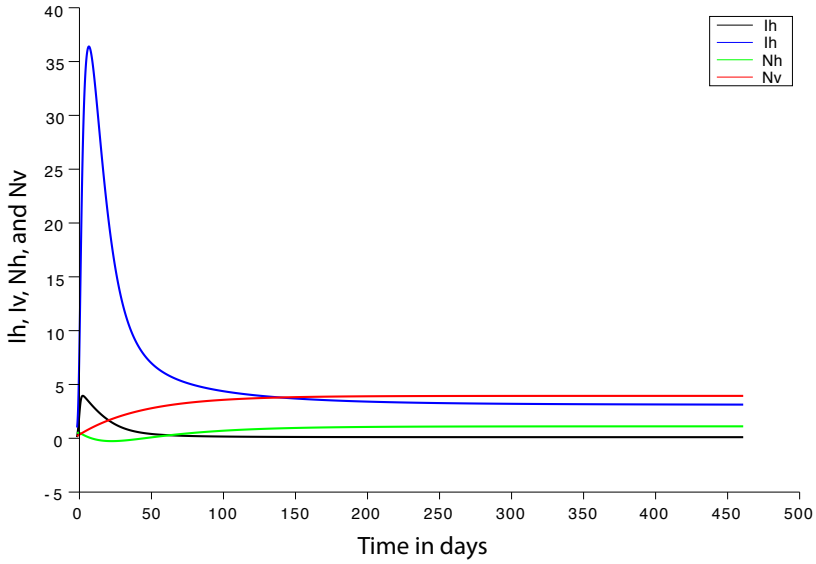

Figure 5.4 – Variation of Infected Host, Infected Vector, Total Host and Total Vector populations at the Endemic Equilibrium. $Q_v = 0.09$ and $\tilde{\mathcal{R}}_0 = 2.495 > 1$

Using the values in Table 5.1 we simulate system 4.1, and show the dynamics of various populations in the figures below.
We observe from Figure 5.3 and Figure 5.4 and that a decrease in Q_v increases $\tilde{\mathcal{R}}_0$ and vice versa. That is when the human population is very low, mosquitoes will turn to other bloodmeal source, and malaria transmission goes down. Then Q_v controls the magnitude of malaria transmission. This implies that the best methods of controlling malaria in the highlands should target the adult mosquito, its biting habits and alternative sources of blood meals. Our results are consistent with results in literature that, $\tilde{\mathcal{R}}_0$ is a threshold that completely determines the global dynamics of disease transmission [104]

CHAPITRE 6

Conclusion and Perspective

We formulated and studied two models for highland malaria transmission in Western Kenya. Some basic models in disease dynamics and epidemiology useful to this thesis have been reviewed.
Our first interest was modeling the discontious spatialization, exhibited by the different terrain ecosystems. Considering the importance of the individual's age in the malaria infection and transmission, we grouped the metapopulation in each patch as children (0-5 years) and adults (over 5 years). With a set of differential equations the dynamics of malaria transmission in children and adults in n different patches was described by a system of first order, ordinary equations.
A qualitative analysis was done for the age structured-metapopulation model by applying dynamical systems theory. A threshold $\mathcal{R}_0$ was computed, which completely determines if the disease dies out or persists in the population. We prove that, if $\mathcal{R}_0 \leq 1$, the disease free equilibrium is globally stable, and, if $\mathcal{R}_0 > 1$, the endemic equilibrium is unique and globally asymptotically stable. An example of the model on two patches is given. We also provide some numerical study applied to four sites in Western Kenya grouped as U-shaped and V-shaped valley ecosystems. The simulation was done with data from Western Kenya where available and also from published literature. Different scenarios were analysed and model validated to highlight the importance of metapopulation and age structuring which are often neglected in many malaria models.

In the second model, we studied the dynamics of malaria transmission in the highlands, with disease induced deaths and varying vector and human populations, and saturation in the vector feeding rate. In this model the biting rate is density dependent, and the two population densities ratio plays a vital role in the transmission. We assume that if the host-vector ratio is low, the bites are few and therefore the probability of transmission reduces too. We introduce a threshold ratio Q_v, such that, as the ratio increases the biting rate, will rise as a function of the density ratio until it reaches this threshold and it becomes a constant. Q_v is an important parameter in our model as it determines which of the two population densities is driving the biting rate hence malaria transmission.
We assume that the vector and the human population vary with time since malaria causes deaths, hence can have profound effects on the population size. A qualitative study of this model has been done and a basic reproduction number calculated. As in the previous case, the existence of

equilibrium solutions and their stability depends on the basic reproductive number, $\mathcal{R}_0$ which in turn depends on Q_v. When $\mathcal{R}_0 \leq 1$, we proved that the disease free equilibrium is locally and globally asymptotically stable, and if $\mathcal{R}_0 > 1$, there exists an unique endemic equilibrium that is locally and globally asymptotically stable. The model was validated with some realistic data to show the populations and the role of Q_v on the basic reproduction number, $\mathcal{R}_0$.

ANNEXE A

Mathematical Tools

Contents

Mathematical modeling of infectious diseases is done by analysing the dynamical systems developed during model formulation. The systems may be ordinary, partial or difference differential equations, which may be linear or nonlinear. In this thesis we have dealt with nonlinear ordinary differential equations and hereby give some definitions and classical results from dynamical systems theory .

A.1 Preliminaries and Notation

Ordered vector space $\mathbb{R}^n$

We use the standard notation $x \in \mathbb{R}^n$ to define a vector and x_i to denote the i^{th} vector component in $\mathbb{R}^n$. The vector space $\mathbb{R}^n$ is said to be ordered if, when $x \geq y$ the inequality $x_i \geq y_i$ also holds. On the positive orthant the inequality $x \geq y$ is equivalent to $x - y \in \mathbb{R}^n$ and in particular

$$x \geq 0 \quad \Leftrightarrow \quad \text{for every index} i, \quad x_i \geq 0.$$

We write $x > 0$, when $x \geq 0$ and $x \neq 0$, and write $x \gg 0$, if x is in the interior of $\mathbb{R}^n_+$ such that

$$x \gg 0 \quad \Leftrightarrow \quad \text{for every index} i, \quad x_i > 0.$$

The same notation is used for matrices and we define a matrix $A(n, n, \mathbb{R}^{n^2})$ as an $n \times n$ matrix in $\mathbb{R}^{n^2}$. The notation $A \geq B$ holds if for the pair of indices (i, j) we have $a_{ij} \geq b_{ij}$ and $A > B$ holds if $A \gg B$.
For the ordered vector space $\mathbb{R}^n$, we define a closed interval

$$[a, b] = \{x \in \mathbb{R}^n \mid a \leq x \leq b\} = [a_1, b_1] \times \ldots, \times, [a_n, b_n].$$

This notation can also be used on the open interval

$$]]a, b[[= \{x \in \mathbb{R}^n \mid a \ll x \ll b\} =]a_1, b_1[\times, \ldots, \times]a_n, b_n[.$$

If E and F are subsets of $\mathbb{R}^n$, we have the classical definition

$$\mathbb{R}_+ E = \{\lambda\, x \mid \lambda \in \mathbb{R}_+ \quad x \in E\}$$

and

$$E + F = \{x + y \mid x \in E \quad y \in F\}.$$

A scalar product of two vectors is denoted by $\langle x \mid y \rangle$. If M is a matrix and M^T its transpose, we can define the vectors on $\mathbb{R}^n$ and the $n \times 1$ column vectors and express the scalar product as $\langle x \mid y \rangle = x^T y$. We denote by e_i the canonical basis of $\mathbb{R}^n$.

Definition A.1 (Autonomous Systems). Let Ω be a subset of $\mathbb{R}^n$. Consider the autonomous differential equation defined by :

$$\dot{x} = X(x) \qquad x \in \Omega \tag{A.1}$$

Suppose that $X : \Omega \subset \mathbb{R}^n \to \mathbb{R}^n$ is continuous and satisfies the conditions as a solution of A.1, is unique and continously depend on the initial conditions. The stationary or equilibrium points of the system A.1 are the points $x_0 \in \Omega$ satisfying $X(x_0) = 0$. For each $x \in \Omega$, we denote by $X_t(x)$ the solution of the system A.1 satisfying $X_0(x) = x$. We suppose that X satisfies the conditions that $X_t(x)$ is continuous in (t, x).

A.2 Stability

A system which lacks stability would be a poor model for reality as reality is always a perturbation of what we think it is. So some kind of stability is needed in modeling. Two kinds of stability are of great importance in application of differential equations : stability respecting perturbation of initial values for a fixed equation and stability respecting perturbations of the equation itself. In the first case we say the system is 'persistent' and second case 'robust'. We say that an equilibrium point is locally stable if all solutions which start near $\bar{x}$ (meaning that the initial conditions are in the neighborhood of $\bar{x}$) remain near $\bar{x}$ for all future time.

A.2.1 Stability : Basic definition

Consider system A.1.

Definition A.2 (Equilibrium point). A point $\bar{x} \in \mathbb{R}^n$ is an equilibrium point of the system A.1 if $f(\bar{x}, t) = 0$.

Definition A.3 (Lyapunov stability). Let $\bar{x} \in \omega$ be an equilibrium point. System A.1 is stable (we say also Lyapunov stable) at $\bar{x}$ or $\bar{x}$ is a stable equilibrium position for A.1, if for each $\epsilon > 0$ there exists a positive real number δ such that for each x with $|x - \bar{x}| < \delta$, the solution $X(t(x))$ is defined for all $t \geq 0$ and satisfies $|X(t(x)) - \bar{x}| < \epsilon$ for all $t > 0$. When A.1 is not Lyapunov stable at $\bar{x}$, we say that it is unstable at $\bar{x}$.

Definition A.4 (Attractivity). The steady state $\bar{x}$ is said to be attractive (We say also that A.1 is attractive at $\bar{x}$) if there exists a neighborhood $U \in \Omega$ of $\bar{x}$ in such a way that for any initial condition x belonging to U, the corresponding solution $X(t(x))$ of A.1 is defined for all $t \geq 0$ and tends to $\bar{x}$ as t tends to infinity, i.e., $\lim_{t \to +\infty} Xt(x) = \bar{x}$.

Definition A.5 (Asymptotic stability). We say that $\bar{x}$ is stable if solutions starting "close" to it at a given time, remain close to it for all future times. It is said to be asymptotically stable if nearby solutions actually converge to $\bar{x}$ at $t \to \infty$. That means it is lyapunov stable and attractive.

Definition A.6 (Exponential stability). The system A.1 is exponentially stable (respectively globally exponentially stable) at $\bar{x}$, if there exist two positive constants K and λ such that $|X(x) - \bar{x}| < \epsilon < K |x - \bar{x}| \epsilon^{-\lambda t}$ for all x in a neighborhood of $\bar{x}$ (respectively for all $x \in \Omega$) and all positive time t.

Definition A.7 (Attractor). This refers to a compact, nonempty set K which attracts some neighborhood N of itself. It is assumed that K is invariant, that is, it contains the orbits of all its equilibrium points. The neighbourhood N can always be chosen to be invariant also by simply replacing it with the union of all its points. The largest of such N, ie. the set of all points attracted to K is called the basin of K. An attractor enjoys some kind of stability. Any trajectory starting near it may wonder away, but eventually returns to approach it asymptotically.

Definition A.8 (Global stability). We say an equilibrium point $\bar{x}$ is globally stable if it is stable for all initial conditions $x_0 \in \mathbb{R}^n$

A.2.2 Dynamical Properties

Definition A.9 (Invariant set). Given the dynamical system $\dot{x} = f(x)$ and a trajectory $s(t, x_0)$ where x_0 is the initial point. Let

$$\mathcal{O} \triangleq \{x \in \mathbb{R}^n \mid \phi(x) = 0\}$$

where ϕ is a real valued function. Then the set $\mathcal{O}$ is said to be positively invariant if $x_0 \in \mathcal{O}$ implies that $x(t, x_0) \in \mathcal{O}$, for all $t \geq 0$. This means that once a trajectory of the system enters $\mathcal{O}$, it will not leave it again.

Definition A.10 (Orbit). The orbit $\gamma^+(x_0)$ is called a positive orbit if for all x_0 in the set

$$\{x(t, x_0) \mid t \geq 0\},$$

the orbit is defined by :

$$\gamma(x_0) = \{x(t, x_0) \mid t \in \mathbb{R}\}.$$

The set is positively invariant if $\gamma^+(M) \subset M$, and invariant if it contains the orbits of each of its points.

Note : In the study of dynamical systems, a limit set is the state a dynamical system reaches after an infinite amount of time has passed, by either going forward or backwards in time. Limit sets are important because they can be used to understand the long term behavior of a dynamical system.

Definition A.11 (ω-Limit point). A point p is called an ω-limit point of $X_t(x)$ if there exists a sequence $t_n \in \mathbb{R}$ such that

$$\lim_{n\to+\infty} t_n = +\infty \quad and \quad \lim_{n\to+\infty} x_{t_n}(x) = p$$

The set of all ω-limit point is the ω-limit set of x and is denoted by $\omega(x)$. This means that the sequence t_n tends to $+\infty$ as n tends to infinity and the flow through x tends to p as n tend to $+\infty$

Theorem A.1. If the positive orbit $\gamma^+(x_0)$ is bounded then the set of points ω-limit points, $\omega(\gamma)$ is non empty, compact, connected and invariant.

Theorem A.2 (Poincare-Bendixon). Consider the equation $\dot{x} = f(x)$ in $\mathbb{R}^2$. Suppose that γ^+ is a bounded positive orbit and $\omega(\gamma^+)$ does not contain equilibrium points. Then $\omega(\gamma^+)$ is a periodic orbit. If $\omega(\gamma^+) \neq \gamma^+$ this periodic orbit is called a limit cycle.

Definition A.12. For the $\mathcal{C}^1$ autonomous system $\dot{x} = f(x)$ and an equilibrium point x_0, the linearised system in x_0 is defined by the linear system

$$\dot{x} = Df(x_0)x,$$

where $Df(x_0)$ is the derivative of f at x_0.

Theorem A.3 (Poincare-Lyapunov). Consider the $\mathcal{C}^1$ system $\dot{x} = f(x)$ and an equilibrium point x_0.

1. If $Df(x_0)$ has the real parts of all its eigenvalues negative, then x_0 is asymptotically stable.
2. If $Df(x_0)$ has (at least) one of its eigenvalues with a positive real part,then x_0 is unstable.

A.3 Monotone systems

Consider the system A.1 where X is $\mathcal{C}^1$ and Ω is an open set in $\mathbb{R}^n$.

- X is said to be of type K in Ω if for each i ; $X_i(a) \leq X_i(b)$ for any two points a and b in Ω satisfying $a_k \leq b_k$ and $a_i = b_i, \quad (i \neq k \ \ and \ \ i,k = 1,2,\ldots,n)$;
- We say that Ω is $p-convex$ if $tx + (1-t)y \in \Omega$, for all $t \in [0,1]$ whenever $x,\ y \in \Omega$ and $x \leq y$;
- The system A.1 is said to be a cooperative system if Ω is $P-convex$ and

$$\frac{\partial X_i(x)}{\partial x_j} \geq 0, \quad i \neq j,\ x \in \Omega$$

- We say that system A.1 is a competitive system if Ω is $P-convex$ and

$$\frac{\partial X_i(x)}{\partial x_j} \leq 0, \quad i \neq j,\ x \in \Omega$$

A.3.1 Monotone Dynamical System

Consider a dynamical system with a flow $\phi_t : x \to \phi_t(x)$. This dynamical system is said to be monotone if it is defined on an ordered metric space with the following property ;

$$t \geq 0,\ x \leq y \ \Rightarrow \quad \phi_t(x) \leq \phi_t(y)$$

It is said to be strongly monotone if

$$t \geq 0,\ x < y \ \Rightarrow \quad \phi_t(x) \ll \phi_t(y)$$

We say that the system is anti-monotone if

$$t \geq 0,\ x \leq y \ \Rightarrow \quad DX(x) > DX(y),\ and$$

It is strictly anti-monotone if

$$t \geq 0,\ x < y \ \Rightarrow \quad DX(x) > DX(y).$$

A.3.2 Triangular System

A triangular system is precisely an $\mathbb{R}^n \times \mathbb{R}^m$ system of the form

$$\begin{cases} \dot{x}_1 = f_1(x_1) \\ \dot{x}_2 = f_2(x_1, x_2) \end{cases} \tag{A.2}$$

where f_1 is a map from $\mathbb{R}^n$ to $\mathbb{R}^n$ and f_2 from $\mathbb{R}^n$ to $\mathbb{R}^m$. We suppose that the conditions for existence and uniqueness of solutions are satisfied, (eg. f_1 *and* $f_2$are $\mathcal{C}^1$). The trajectories of the system have the same projection on $\mathbb{R}^n \times \{0\}$ and hence the name triangular. In fact the Jacobian of this system is a lower triangular block, and it is also said to be hierachical. We will deduce a stability result from Vidyasagar Theorem [146]. The version presented here is independent and much simpler than the general case given by Vidyasagar.

Theorem A.4 (Vidyasagar). Consider the following $\mathcal{C}^1$ system :

$$\begin{cases} \dot{x}_1 = f_1(x_1) \\ \dot{x}_2 = f_2(x_1, x_2) \end{cases} \tag{A.3}$$

If the origin of $\mathbb{R}^n$ is globally asymptotically stable (GAS) for the system $\dot{x}_1 = f_1(x_1)$ in $\mathbb{R}^n$ and the origin of $\mathbb{R}^m$ is GAS for $\dot{x}_2 = f_x(0, x_2)$ on $\mathbb{R}^n$, then the origin of $\mathbb{R}^n \times \mathbb{R}^m$ is asymptotically stable. Furthermore if all the trajectories are bounded, then the origin is GAS for A.3 on $\mathbb{R}^n \times \mathbb{R}^m$.

Proof of Stability
Let the following be a neighborhood of the the origin

$$B(0, \varepsilon) = \{(x_1, x_2) \mid \|x_2\| \leq \varepsilon\}.$$

Since the equilibrium points of the isolated $\mathcal{C}^1$ system are GAS, we can apply the inverse Lyapunov theorem. There exists positive definite $\mathcal{C}^1$ functions $V_1(x_1)$ *and* $V_2(x_2)$ such that

$$\dot{V}_1 = \langle \nabla V_1(x_1) \mid f_1(x_1) \rangle \leq 0, \qquad \dot{V}_2 = \langle \nabla V_2(x_2) \mid f_2(0, x_2) \rangle \leq 0$$

The functions $\dot{V}_1$ and $\dot{V}_2$ are negative definite on $B(0,\varepsilon)$ for ε sufficiently small since f_1 and V_1 are $\mathcal{C}^1$. Let

$$L = \max_{(x_1,x_2)\in B(0,\varepsilon)} \frac{\partial f_1}{\partial x_2}(x_1,x_2)$$

$$M = \max_{(x_1,x_2)\in B(0,\varepsilon)} \nabla V_2(x_2)$$

Since V_2 is a Lyapunov function, we can choose $\delta_1 < \frac{\varepsilon}{2}$ sufficiently small such that

$$\max_{\|x_2\|\leq\delta_1} \nabla V_2(x_2) < \min_{\frac{\varepsilon}{2}\leq\|x_2\|\leq\varepsilon} \nabla V_2(x_2)$$

$$\dot{V}_2(x_2) = \langle \nabla V_2(x_2) \mid f_2(x_1,x_2)\rangle = \langle \nabla V_2(x_2) \mid f_2(0,x_2)\rangle + \langle \nabla V_2(x_2) \mid f_2(x_1,x_2) - f_2(0,x_2)\rangle$$

From Taylors formular we have the following relation

$$f_2(x_1,x_2) - f(0,x_2) = \int_0^1 \frac{\partial f_2}{\partial x_1}(x_1,x_2)\, x_1\, dt$$

and on $B(0,\varepsilon)$ we have

$$\|f_2(x_1,x_2) - f_2(0,x_2)\| \leq \|x_1\|$$

and the Cauchy Schwarz gives

$$\dot{V}_2(x_2) \leq \langle \nabla V_2(x_2) \mid f_2(0,x_2)\rangle + L\,M\|x_1\| \tag{A.4}$$

Since the function $\langle \nabla V_2(x_2) \mid f_2(0,x_2)\rangle$ is negative, we can define a function φ by

$$\varphi(c) = \min_{c\leq\|x_2\|\leq\varepsilon} -\langle \nabla V_2(x_2) \mid f_2(0,x_2)\rangle$$

This function φ, defined on $\mathbb{R}$, is continous, decreasing and tend to 0 as $c \to 0$. We show that $\varphi(c) > 0$ for all $c > 0$.
Since the system $\dot{x_1} = f_1(x_1)$ is asymptotically stable, we can choose $\delta_2 \leq \delta_1$ such that for all initial conditions satisfying $\|x_1(0)\| \leq \delta_2$, and $t \geq 0$, we have the inequality $\|x_1(t)\| \leq \frac{\varphi(c)}{L\,M}$. Moreover if we have $\|x_1\| \leq \delta_2$ and $\|x_2\| \geq \delta_1$, with the inequality A.4, we deduce the relation

$$\langle \nabla V_2(x_2) \mid f_2(0,x2)\rangle + L\,M\|x_1\| < 0 \tag{A.5}$$

We define $0 < \delta_3 < \delta_2$ so that

$$\max_{\|x_1\|\leq\delta_3} V_1(x_1) < \min_{\delta_2\leq\|x_1\|\leq\varepsilon} V_1(x_1)$$

Consider the open set $\mathcal{U}$ defined by

$$\mathcal{U} = \{(x_1,x_2) \mid \|x_1\| \leq \delta_2, \quad \|x_2\| \leq \delta_3\}.$$

If $x_1(0) \leq \delta_3$, since V_1 is decreasing, the preceding inequality implies that $\|x_1(t)\| \leq \delta_2$ (all the trajectory are inside the sphere of radius δ_2 in $\mathbb{R}^n$).
For $x_2(0) \leq \delta_3$, we have

$$\max_{\|x_2\| \leq \delta_3} V_2(x_2) \leq \max \|x_2\| \leq \delta_1 V_2(x_2) < \min_{\frac{\varepsilon}{2} \leq \|x_2\| \leq \varepsilon} V_2(x_2).$$

The trajectory $(x_1(0), x_2(0))$ satisfy $\|x_2(t)\| \leq \delta_1$ which implies

$$V_2(x_2) \leq \min_{\delta_1 \leq \|x_2\| \leq \varepsilon} V_2(x_2).$$

Consequently, we have $\|x_2\| \leq \delta_2$. This leads to the inequality $\|x_2(t)\| \geq \delta_1$, and from the inequality A.5, we have $\dot{V}_2 \leq 0$.
Since V_2 is decreasing on the trajectories contained in the ring $\|x_1\| \leq \delta_2$, $\|x_2\| \leq \frac{\varepsilon}{2}$, we note that a trajectory cannot reach the sphere of radius $\frac{\varepsilon}{2} \in \mathbb{R}^m$. This shows that $\|x_1(t)\| \leq \delta_2 \leq \varepsilon$ and $\|x_2(t)\| \leq \frac{\varepsilon}{2}$, which completes the prove of stability.

We will now show the local attractivity by the Lasalle invariance principle of Lasalle.
Since the origin is stable, there exists a compact set X neighborhood U of the origin which is positively invariant. This restricts us to the invariant set U.
Consider the Lyapunov-Lasalle function V_1. By the hypothesis

$$\dot{V}_1 = \langle \nabla V_1(x_1) \mid f_1(x_1) \rangle \leq 0.$$

Let

$$E = \{(x_1, x_2) \in \mathcal{U} \mid \dot{V}_1(x) = 0\}$$

We also consider the largest invariant set E . This is evidently the set $\{0\} \times \mathbb{R}^m \cup \mathcal{U}$. By hypothesis the system $\dot{x}_2 = f_2(0, x_2)$ is globally asymptotically stable in $\{0\} \times \mathbb{R}^m$. This implies that any negative trajectory of the system $\mathcal{U} \backslash \{0\}$ exit $\mathcal{U}$. In effect if that is not the case, then there exists a trajectory $\gamma \in \mathcal{U}$. Then the set of α-limit points of γ are invariant. By the asymptotic stability and invariance, this point contains the origin. This means that the trajectory starting close to the origin remain close to it. The fact that this trajectory is invariant contradicts the stability so the property stated is true. This means that the largest invariant set containing E is reduced to the origin. Which shows that $\mathcal{U}$ is attractive.

If a trajectory is relatively compact, then the ω-limit points are in $\{0\} \times \mathbb{R}^m$. In effect, for $t_n \to \infty$, we have $x_1(t_n) \to 0$. If all the trajectories are compact, then the ω-limit points are in $\{0\} \times \mathbb{R}^m$. By the asymptotic stability of $\{0\} \times \mathbb{R}^m$, the origin is an ω-limit. All trajectories gets as close as possible to the origin. Due to stability they are attracted to the open set $\mathcal{U}$ defined above, otherwise they approach the origin asymptotically.

A.3.3 Lyapunov Methods

The Lyapunov function plays a major role in the study of dynamical systems' stability. We dedicate this section to some results due to Lyapunov. Let $V : \Omega \subset \mathbb{R}^n \to \mathbb{R}$ be a continous function.

Definition A.13. We have the following definitions

1. The function V is said to be positive definite if $V(x) = 0$ and $V(x) > 0$ in a neighborhood Ω_0 of x_0 for all $x \neq x_0$ in the neighborhood.
2. The function V is said to be negative definite if $-V$ is positive definite.
3. The function V is said to be semi-positive if $V(x_0) = 0$ and $V(x) \geq 0$ in a neighborhood Ω of x_0

Theorem A.5 (Lyapunov Theorem). Let V be a function

- If a function V is positive definite and $\dot{V}$ is negative semi-definite in Ω, then the equilibrium point x_0 is stable for the system A.1.
- If the function V is positive definite and $\dot{V}$ is negative definite in Ω, then the equilibrium point X_0 is asymptotically stable for the system A.1

This theorem implies that to show that an equilibrium point x_0 is stable, it is sufficient to a find a Lyapunov function for the point. Moreover, to use the original Lyapunov theorem to show the asymptotic stability of a given system, we must determine a function V whose derivative is positive definite and the derivative $\dot{V}$ is negative definite. In a general case, this is not straightforward. The condition on the derivative $\dot{V}$ can be relaxed by using the LaSalle Invariance principle introduced in the next section.

A.3.4 LaSalle Invariance Principle

Theorem A.6 (LaSalle Invariance Principle [91, 92]). Let $\Omega \subset \mathbb{R}^n$ be a compact set that is positively invariant with respect to the system A.1. Let $V : \Omega \to \mathbb{R}$ be continously differentiable such that $\dot{V}(x) \leq 0$ in Ω. Let E be the set of all points in Ω where $\dot{V}(x) = 0$. Let L be the largest invariant set in E. Then every solution starting in Ω approaches L as $t \to \infty$

This theorem is a very important tool for systems analysis, and is different from Lyapunov, as it does not require V to be positive definite and $\dot{V}$ to be negative definite. However, it only provides information on the attractiveness of the considered system at the equilibrium x_0. For example, it can be used to prove that the solutions tend toward an equilibrium point when the set L is reduced to that equilibrium point. It does not indicate whether this equilibrium is stable or not. When one wants to establish asymptotic stability of an equilibrium $x_0 \in \Omega$, we use the following corollary which is a consequence of the LaSalle invariance principle.

Corollary A.1 (LaSalle,[92]). Consider the compact set $\Omega \in \mathbb{R}n$ with $x_0 \in \Omega$. Let $V : \mathbb{U} \to \mathbb{R}$ be a continously differentiable positive definite function such that $\dot{V} \leq 0$ in $\mathbb{U}$. Let $E = \{x \in \mathbb{U} \mid \dot{V} = 0\}$. Assume that the largest positively invariant set contained in E is reduced to the point x_0. Then x_0 is an asymptotically stable equilibrium point for the system A.1. If these conditions are satisfied for $\mathbb{U} = \Omega$, if in addition V is in Ω ie. $\lim V(x) = +\infty$ when $d(x, \frac{\partial}{\partial x}\Omega) + \|x\| \to +\infty$, then all trajectories are bounded for $t \geq 0$ and x_0 is a globally stable equilibrium point for the system A.1.

Corollary A.2. Under the assumptions of the previous theorem, if the set L is reduced to the point $x_0 \in \Omega$, then x_0 is a globally stable equilibrium point for the system A.1 defined on Ω

A.4 Matrices

Definition A.14 (Stability Modulus, Spectral radius). Let A be a square matrix, we denote by $spec(A)$ all the eigenvalues of A. The stability modulus of A is the number defined by

$$\alpha(A) = \max\{Re(\lambda); \lambda \in \ Spec(A)\}.$$

The matrix A is said to be stable if $\alpha(A) < 0$.
The spectral radius is the real number $\rho(A)$ defined by

$$\rho(A) = \max_{\lambda \in Spec(A)} |\,\lambda|.$$

We say that a matrix A is stable if its eigenvalues have strictly negative real parts. Such a matrix is also said to be Hurwiz.

Theorem A.7. Let $A \in \mathcal{M}_n(\mathbb{R})$. The spectrum of A is contained in the union of disks whose centers are the diagonal coefficients a_{ii} of the matrix A and radii are the respective sums of the absolute values of the remaining coefficients in the row.
In other words for each index i, $\ 1 \leq i \leq n$, if we set $r_i = \sum_{j=1, j\neq i}^{n} |a_{ij}|$, then

$$Spec(A) \ \subset \cup_{i=1}^{n} B\,(a_{ii}, r_i)$$

Lemma 1. Let $A \in \mathcal{M}_n(\mathbb{R})$ be a square matrix. If A is a singular matrix, then there exists an index i_0 such that

$$|\,a_{i_0\,i_0}\,| \ \leq \ \sum_{j=1, j\neq i} |\,a_{i_o j}\,|.$$

In other words, the term $a_{i_0\,i_0}$ dominates the column i_0.

Proof
Let n be an arbitrary integer. Assume that A is a singular matrix. Then, the matrix A will be the linear map of $\mathbb{R}^n$ to itself, or its corresponding matrix. Since A is singular, $Ker(A) \neq \{0\}$; Let $x = (x_1, x_2, \ldots, x_n)^T \in Ker(A)$; Let i_0 be an index of the component x such that x_{i_0} achieves the maximum of x (that is to say $|x| = \max_{1 \leq i \leq n} |\,x_i\,| \ = \ \|x\|_\infty$

$$Ax \ = \ 0 \ \ \Rightarrow (Ax)_{i_0} \ = \sum_{j=1}^{n} a_{i_0}\, x_j = 0$$

$$\Rightarrow -a_{i_0\,i_0}\, x_{i_0} = \sum_{j=1, j\neq i}^{n} a_{i_0 j}\, x_j = 0$$

$$\Rightarrow |a_{i_0\,i_0}||x_{i_0}| \ \leq \ \sum_{j=1, j\neq i}^{n} |\,a_{i_0 j}|\,|x_j| \ = 0$$

$$\leq \sum_{j=1, j\neq i}^{n} |\,a_{i_0 j}|\,|x_j| \ = \ 0.$$

Since $x_{i_0} \neq 0$, it follows that

$$| a_{i_0\, i_0} | \leq \sum_{j=1, j\neq i}^{n} | a_{i_0 j} |$$

which ends the proof of the lemma. The following is a better consequence of the theorem and the preceding lemma ;

Corollary A.3. Let $A \in \mathcal{M}_n(\mathbb{R})$ be a square matrix. If A is a singular matrix, then there exists an index i_0 such that

$$|a_{i_0 i_0}| \leq \sum_{j=1, j\neq i}^{} |a_{i_0 j}|.$$

In other words, the term $a_{i_0 i_0}$ dominates the column i_0. The proof of this corollary is identical to that of the previous lemma, however we replace the matrix A by its transpose A^T which has the same properties as the matrix A.

Proof of theorem A.7 Let $A \in \mathcal{M}_n(\mathbb{R})$; then for all $\lambda \in SpecA$, $(A - \lambda I)$ is a singular matrix. The previous lemma implies that for all $\lambda \in SpecA$, there exists $i_\lambda \in \mathbb{N}$, $1 \leq i_\lambda \leq n$ such that

$$|a_{i_\lambda i_\lambda}| \leq \sum_{j=1, j\neq i_\lambda}^{n} |a_{i_\lambda}|$$

If we set $r_i \sum_{j=1, j\neq i_\lambda}^{n} |a_{i_\lambda}|$; the previous inequalities are equivalent to ; for all $\lambda \in Spec(A)$, there exists $i_\lambda \in \mathbb{N}$, $1 \leq i_\lambda \leq n$ such that $B(a_{i_\lambda}, r_{i_\lambda})$. If we consider the balls $B(a_{ii}, r_i)$ for all i, $1 \leq i \leq n$, it follows that any $\lambda \in Spec(A)$ is inside on of them. So we can say that $\lambda \in \cup_{i=0}^{n}(B(a_{ii}, r_i)$. This completes the prove.

Corollary A.4. Let $A = (a_{ij}) \in \mathcal{M}_n(\mathbb{R})$ be a square matrix. The spectrum of the matrix A is contained in the union of the disks whose centers are the diagonal coefficients a_{ii} diagonal of the matrix A and whose radii are are the sums of the absolute values of the off-diagonal coefficients of the corresponding columns. In other words, for all i, $1 \leq i \leq n$, if we set $r_i = \sum_{j=1, j\neq i}^{n} |a_{i_{ji}}|$, then

$$Spec(A) \subset \cup_{i=1}^{n} B(a_{ii}, r_i)$$

Proof
This is a consequence of Theorem A.7 and Corollary A.3. In effect A is strictly diagonally dominant, then for all i such that $1 \leq i \leq n$, we have $|a_{ii}| > r_i (r_i = \sum_{j=1, j\neq i}^{n} |a_{i_{ji}}|$, for the respective columns, or $r_i = \sum_{j=1, j\neq i}^{n} |a_{i_{ij}}|$ for the respective row). So none of the balls $B(a_{ii}, n)$ contains the origin of $\mathbb{C}$. Therefore no eigenvalue of A can be zero.

Definition A.15. We have the following definitions

- A matrix $A = (a_{ij}) \in \mathcal{M}_n(\mathbb{R})$ is a strictly column diagonally dominant if for all i such that $1 \leq i \leq n$, we have

$$|a_{ii}| > \sum_{j=1, j\neq i}^{n} |a_{i_{ji}}|$$

– A matrix $A = (a_{ij}) \in \mathcal{M}_n(\mathbb{R})$ is a strictly row diagonally dominant if for all i such that $1 \leq i \leq n$, we have

$$|a_{ii}| > \sum_{j=1, j\neq i}^{n} |a_{i_{ij}}|$$

– We say that a matrix is strictly column (respectively row) diagonally dominant if the above inequalities strictly hold.

Corollary A.5. If a matrix A is strictly diagonally dominant, then it is invertible.

This is an immediate consequence of A.7 (Proof by contradiction).

Definition A.16. Let $A = (a_{ij}) \in \mathcal{M}_n(\mathbb{R})$ be a square matrix. We say that the matrix A is reducible, if there exists a permutation matrix P such that

$$P^T AP = \begin{bmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{bmatrix} \tag{A.6}$$

The matrix A is said to be irreducible if and only if it is not reducible.

A.4.1 Metzler Matrices

Definition A.17. We say that $A = (a_{ij}) \in \mathcal{M}_n(\mathbb{R})$ is a metzler matrix if all the off-diagonal entries are positive. That is, $a_{ij} \geq 0$ for all i and j with $i \neq j$.

The following theorem due to Frobenius will be very useful for studying the stability of our models.

Theorem A.8 (Perron-Frobenius Theorem, [63]). If $A = (a_{ij}) \in \mathcal{M}_n(\mathbb{R})$ is a non negative matrix ;

– Then the spectral radius $\rho(A)$ is an eigenvalue of A and there is a corresponding vector $v > 0$
– If in addition the matrix A is irreducible, then $\rho(A) > 0$ and $v \gg 0$; moreover, $\rho(A)$ has algebraic multiplicity 1 and and if $u > 0$ is an eigenvector of A, then there exists $s > 0$ such that $u = s\, v$.
– If $B > A$, then $\rho(B) > \rho(A)$.
– Finally, if $A \gg 0$, then $|\lambda| < \rho(A)$ for all other eigenvalues λ of A.

Corollary A.6. Let $A = (a_{ij}) \in \mathcal{M}_n(\mathbb{R})$ be a Metzler matrix.

– The stability modulus $\alpha(A)$ is an eigenvalue of A and there exists a vector $v > 0$ such that $Av = \alpha(A)v$. Moreover $Re(\lambda) < \alpha(A)$ for all $\lambda \in Spec(A) - \{\alpha(A)\}$.
– If in addition A is irreducible, then
  1. $\alpha(A)$ is a simple eigenvalue ;
  2. $v \gg 0$ and all other positive eigenvectors of A are multiples of v ;
  3. If B satisfies $B > A$, then $\alpha(B) > \alpha(A)$;
  4. If $\alpha(A) < 0$, then $-A^{-1} \gg 0$.

Proof
Let $C \geq 0$ large enough such that $A + CI \geq 0$. Hence applying the Perron-Frobenius theorem defined above on $A + CI$ implies that $C \geq 0$. In particular, the spectral radius $\rho(A + CI) > 0$. We note that $Spec(A + CI) = C + Spec(A)$; which implies that

$$\alpha(A + CI) = \rho(A + CI) = C + \alpha(A)$$

and consequently, $\alpha(A)$ is an eigenvalue of A. If A is irreducible, $A + CI$ is also irreducible. The theorem of Perron-Frobenius theorem applied to A implies properties $1, 2, 3$. Moreoveras $-a^{-1} = \int_0^\infty e^{tA} dt \gg 0$, (4) is satisfied. The following theorem is important to study the stability of equilibrium points and the construction of Lyapunov functions.

Theorem A.9 (Metzler Stable Matrices). Let $A = (a_{ij}) \in \mathcal{M}_n(\mathbb{R})$ be a Metzler matrix, the following statements are equivalent :

- The Matrix A is Metzler stable,
- The Matrix A is invertible and $-A^{-1} \geq 0$,
- If $b \gg 0$, then the equation $Ax + b = 0$ has a solution $x \gg 0$,
- There exists a vector $c > 0$, such that $Ac \ll 0$,
- There exists a vector $c \gg 0$, such that $Ac \ll 0$

The proof given here is an adaptation of a similar proof given in [2].
Proof :
1) $\Rightarrow$ 2)

The matrix A is stable, invertible and $\alpha(A) < 0$; there exists a scalar k such that for all

$$x_0 \in \mathbb{R}_n, \ \|e^{tA} x_0\| \leq K e^{\alpha(A) t} \| x_0\|.$$

We deduce that the integral $\int_0^\infty e^{tA} x_0 \, dt$ is normally convergent for all x_0, therefore the matrix $\int_0^\infty e^{tA} dt$ is absolutely convergent In effect the function $t \in \mathbb{R}_+ \to e^{tA} \in \mathcal{M}_n(\mathbb{R})$ is in $L^1(0, \infty)$ and

$$B = \int_0^\infty e^{tA} dt = -A^{-1}$$

We will determine the sign of each of the coefficients of the matrix $B = (b_{ij})$; For this we consider the canonical base (e_i) in $\mathbb{R}^n$; we note that ;

$$b_{ij} = \langle B e_j, e_i \rangle = (Be_j)_i = \langle \int_0^\infty e^{tA} dt \ e_j, \ e_i \rangle$$

$$= \int_0^\infty \langle e^{tA}, \ e_i \rangle \, dt$$

$$= \int_0^\infty (e^{tA} ej)_i \, dt \geq 0$$

Hence the matrix $-A^{-1} = B \geq 0$.

2) $\Rightarrow$ 3)

Let b be a vector such that $b \gg 0$, and $x = -A^{-1} b$; then $x \gg 0$ is a product of two positive matrices. The matrix $A x + b = 0$

3) $\Rightarrow$ 4)

Let $b \gg 0$ be a vector in $\mathbb{R}^n_+$; Let $c = -A^{-1} b$; it is clear that $AC = -b \ll 0$.

4) $\Rightarrow$ 5)

Perturbing property (4) a little, we set $\varepsilon > 0$ and $c_1 = c + \varepsilon \sum_{i=1}^{n} e_i \gg 0$.
So $A\,c_1 = A\,c + \varepsilon \sum_{i=1}^{n} A\,e_i$. By continuity we can choose $\varepsilon > 0$ sufficiently small such that $A\,c_1 \ll 0$.

5) $\Rightarrow$ 1)

Consider the differential equation $\dot{x} = A^T x$ in the positive orthant. We choose a function

$$V(x) = \langle c, x \rangle.$$

From the hypothesis $c \gg 0$, V is positive definite in $\mathbb{R}^n_+$ and so

$$\dot{V}(x) = \langle c, A\,x \rangle = \langle A^T c, x \rangle.$$

$\dot{V}(x) = 0$, if and only if $x = 0$. The Lyapunov theorem proves that the matrix A^T is asymptotically stable, hence A is stable since A and A^T have the same eigenvalues. This completes the prove of the theorem.

Theorem A.10. Let $A = (a_{ij}) \in \mathcal{M}_n(\mathbb{R})$ be a Metzler matrix.

1. The stability modulus $\alpha(A)$ of A is an eigenvalue of A with an associated positive eigenvector $v \in \mathbb{R}^n_+$ such that $v \neq 0$ and $Av = \alpha(A)v$;
2. If in addition the matrix A is irreducible, then $\alpha(A)$ is a simple eigenvalue of the matrix A to which a positive eigenvector is associated. That is to say, there exists $v \in \mathbb{R}^n_+$ such that $v \gg 0$ and $Av = \alpha(A)v$.

Proof
Let $m = min\{\min_{1 \leq i \leq n} a_{ii}, 0\}$ then $A - mI \geq 0$. Applying the Perron-Frobenius theorem on the matrix $A - mI$ it follows that there exist

$$v \in \mathbb{R}^n_+; (A - mI)v = \rho(A - mI)v$$

or there exists $v \in \mathbb{R}^n_+$ such that

$$Av = (\rho(A - mI) + m)v$$

the vector v is an eigenvector of the matrix A associated with the eigenvalue $\rho(A - mI) + m$.

We note that for a square matrix B we have

$$Spec(B + kI) = k + Spec(B)$$

or $\rho(A - mI)) = \max_{\lambda \in Spec(A - mI)} Re(\lambda)$ or

$$(\rho(A - mI) + m) = \max_{\lambda \in Spec(A - mI + mI)} Re(\lambda) = \max_{\lambda \in Spec(A)} Re(\lambda) = \alpha(A).$$

So v is an eigenvector of A associated with the eigenvalue

$$\alpha(A) = \rho(A - mI) + m \in \mathbb{R}.$$

Although this proof can be found in [125], we have given the complete proof because the theorem is very crucial in this thesis.

A.4.2 Characteristics of Metzler stable matrices

Let M be a metzler matrix of the form

$$M = \begin{pmatrix} A & B \\ C & D \end{pmatrix}$$

M is stable if and only if A and $D - CA^{-1}B$ are stable.

Proof
We first prove the necessary condition. Since any principal sub-matrix of a Metzler stable matrix is still a Metzler stable matrix, (see [144]), then A and D are Metzler stable. As A is Metzler stable, there exists a vector $c = (c_1, c_2) \gg 0$, such that $Mc \ll 0$ (condition I_{28} of theorem 2.3 [2]). This means that

$$Ac_1 + Bc_2 \ll 0,$$

$$Cc_1 + Dc_2 \ll 0.$$

Since A is Metzler stable, $-A^{-1} \geq 0$ and C is positive. Multiplying $Ac_1 + Bc_2 \ll 0$ by $-CA^{-1}$, we obtain $-CC_1 - CA^{-1}Bc_2 \ll 0$ and consequently $(D - CA^{-1}B)c_2 \ll 0$. This proves, from I_{28} that $(D - CA^{-1}B)$ is Metzler stable. This is a necessary condition.

We now prove the sufficient condition.

Since A and $(D - CA^{-1}B)$ are Metzler stable, there exists a vector $c_2 \ll 0$ such that

$$(D - CA^{-1}B)c_2 \ll 0.$$

So we now have $c_3 = -A^{-1}Bc_2$, since A is Metzler stable, we have $-A^{-1} \geq 0$. AS B is positive and $c_2 \gg 0$, we deduce that $c_3 \gg 0$ and the inequalities

$$Cc_3 + Dc_2 \ll 0, \quad Ac_3 + Bc_2 \ll 0.$$

A is Metzler stable, so there exists a vector $v \gg 0$ such that $Av \ll 0$ (see theorem A.9). Now we choose $c_1 = c_3 + \varepsilon v \gg 0$, for $\varepsilon > 0$. We have

$$Cc_1 + Dc_2 = Cc_3 + Dc_2 + \varepsilon Cv.$$

One can choose $\varepsilon > 0$ sufficiently small so that $Cc_1 + Dc_2 \ll 0$. Now,

$$Ac_1 + Bc_2 = Ac_2 + \varepsilon Av \ll 0.$$

So we find that $c = (c_1, c_2) \gg 0$ such that $Mc \ll 0$. which proves that M is Metzler stable (see theorem A.9). This proves the sufficient condition. In the following result we will show that the stability modulus is an increasing function of Metzler matrices.

Theorem A.11 (Monotonicity and Stability Modulus).

1. If there exist $v \gg 0$ such that $Av \leq \beta v$, then $\alpha(A) \leq \beta$.
2. If in addition, A is irreducible then $v > 0$ and $Av < \beta v$ leading to $\alpha(A) < \beta$. Infact we must have $v \gg 0$.
3. If there exists $v > 0$ such that $sv \leq Av$, then $s \leq \alpha(A)$.
4. If in addition A is irreducible, then $s < Av$ implies $s < \alpha(A)$

A.4.3 Irreducible Metzler Matrices

In this section we will characterize a dynamical property of irreducible Metzler matrices. A Metzler matrix is invariant on the positive orthant. First, we prove a result on the irreducibility. The definition of irreducibility for Metzler matrices is equivalent to following property,

Proposition 5 (Irreducible Metzler Matrices). A Metzler matrix A is irreducible if and only if, for any vector $x > 0$ belonging to a face F of $\mathbb{R}^n_+$, where F is defined by :

$$F = \{x \geq 0 \mid \exists I \in I,\ \langle e_i \mid x \rangle = 0\}$$

there exists and index i such that $\langle e_i \mid x \rangle = 0$ and $\langle e_i \mid Ax \rangle > 0$.

Proof
From theorem A.12, the irreducibility of a matrix depends only on its off-diagonal terms. We can always replace A with $A + \lambda I$ for λ sufficiently large. The irreducibility condition is equivalent to the proposition condition. If there exists i such that $\langle e_i \mid x \rangle = 0$ and $\langle e_i \mid Ax \rangle > 0$, then this is equivalent to $\langle e_i \mid x \rangle = 0$ and $\langle e_i \mid (A+\lambda I)x \rangle > 0$. Without loss of generality we will therefore assume that $A \geq 0$.

The sufficient condition.
As a consequence, we suppose that for all i such that $\langle e_i \mid x \rangle = 0$, we have $\langle e_i \mid Ax \rangle > 0$. Let $F_x = \mathbb{R}^+[0, x]$ be the face generated by x. Since $A \geq 0$, we have $AF_x = \mathbb{R}^+[0, Ax]$. The face F_x is characterized by the set of indices I. Now we have $F_x = \{x \geq 0 \mid \langle e_i \mid x \rangle = 0\}$. For these indices we have $\langle e_i \mid x \rangle = 0$. As a result $AF_x \subset F_x$ and the matrix A is not irreducible.

The necessary condition.
If A is reducible, there there exists a face denoted by F_x, such that, $AF_x \subset F_x$. For any index such that $\langle e_i \mid x \rangle = 0$ we have $\langle e_i \mid Ax \rangle = 0$.

Definition A.18. A directed graph $\mathcal{G} = (X, U)$ is a pair consisting of a set $X = \{x_1, \ldots, x_n\}$ and a set U of $X \times X$. The elements of X are called nodes or vertices of the graph. An element $(x, y) \in U$ is called an arc, x is the origin and y is the endpoint. A directed graph (resp. undirected) is a set of vertices with directed arcs (resp. undirected) linking the vertices.

Definition A.19. A path is a sequence of arcs $(u_1, \ldots, u_p)$ such that each arc u_i has the endpoint which is the origin of u_{i+1}. It is said that the path joins the origin u_1 with the end u_p. A graph is strongly connected if every pair of distinct vertices is joined by a path.

Any square matrix is associated with a directed graph.

Definition A.20. Consider a square matrix $A = (a_{ij})$. Consider also the graph with n vertices given by set $X = \{x_1, \ldots, x_n\}$. There is a path joining a vertex i to vertex j if $a_{ji} \neq 0$. Conversely, to a directed graph we associate a square matrix $n \times n$, where $a_{ij} = 1$ if there is an arc that connects i and j and $a_{ij} = 0$, otherwise.

We can charaterize an irreducible matrix elegantly by the properties of the associated directed graph.

Theorem A.12. A matrix A is irreducible if and only if its graph $\mathcal{G}(A)$ is strongly connected.

Proof : The necessary condition.
Suppose the matrix A is irreducible. Let i be a vertex, we define I as the set of vertices different from i that can be reached from i. In the set I for all vertices $j \neq i$ there exists an arc joining j *to* i. The set I is non empty. In effect, if we consider the set, J, Indeed, and if we consider the set J, the complementary of the singleton $\{i\}$, as A is irreducible there exists $k \notin J$ and $j \in J$ such that $a_{jk} \neq 0$. But given the definition of J, this means that there exists $j \neq i$ such that $a_{ji} \neq 0$. In other words there is an arc from i to j.

Suppose by contradiction that $I \neq \{1, \ldots, n\}$. By irreducibility of A, there exists $j \in I$ and $k \notin I$ such that $a_{kj} \neq 0$. That is there is an arc from i to k. But as $j \in I$, it is accessible from i, so k is accessible from i. This is a contradiction.

Sufficient condition.
Assume by contradiction that the graph is strongly connected and the associated matrix A is reducible. Then there exists a subset of indices I, such that if J is its complement, then $a_{ji} = 0$ for all $i \in I$ and $j \in J$. We choose an index $i \in I$ and an index $j \in J$. This is always possible since I ia a proper subset. Then there exists an arc joining i to j. Let there the set of indices $\{k_1, \ldots, k_p\}$ be such that the following coefficients are non-zero

$$a_{j,k_1}; a_{k_1,k_2}, \ldots, a_{k_p,i}.$$

From the assumptions on i and j, it follows that $a_{k_p,i} \neq 0,\ k_p \notin J$ or $k_p \in J$. But if $k_p \in I$ the same reasoning applied on a_{k_p,k_p} prove that $k_{p-1} \in I$. reasoning by induction shows that $j \in I$ which is a contradiction.

Proposition 6. A is an irreducible Metzler matrix then each trajectory of the system $\dot{x} = Ax$ are and will remain on one face. Precisely, A is an irreducible matrix, if and only if for any $t > 0$, we have $e^{tA} \gg 0$

Proof
We assume that it is not true. Then there exists a $t > 0$ such that $e^{tA} \in \partial\mathcal{R}_+^{n^2}$. But for all s such that $0 \leq s \leq t$ we have $e^{(t-s)A}e^{tA}$. The matrix $e^{(t-s)A}$ is positive because (A is Metzler) and it is invertible. consequently if $e^{sA} \gg 0$ this implies $e^{tA} \gg 0$. We now show that e^{sA} is not strongly positive for all $o \leq s \leq t$. There exists $x > 0$ belonging to the boundary of the orthant, such that $e^{tA}x$ belongs to the boundary of the orthant. From the previous proposition, there is an index i such that $\langle e_i \mid e^{tA}x\rangle = 0$ and $\langle e_i \mid Ae^{tA}x\rangle > 0$.

The function $\varphi(s) = \langle e_i \mid e^{tA}x\rangle$ is positive for all s. It vanishes at $t = s$. This is a minimum, thus the derivative vanishes at t. Now

$$\dot{\varphi}(t) = \langle e_i \mid e^{tA}x\rangle > 0.$$

This is a contradiction. Conversely, if A is reducible, then A can be expressed as :

$$P^T A P = \begin{bmatrix} A_1 & A_2 \\ 0 & A_4 \end{bmatrix},$$

or as

$$P^T e^{tA} P = \begin{bmatrix} e^{tA_1} & M(t) \\ 0 & e^{tA_4} \end{bmatrix}$$

The matrix e^{tA} is reducible and positive, and there exists a vector $x > 0$ on the boundary such that $e^{tA}x$ is on the boundary of the orthant. This means that we cannot verify that $e^{tA} \gg 0$.

A.4.4 Regular Splitting of a Metzler matrix

We present and prove a result of Varga [144], which is applied in the formula for calculating the basic reproduction number, $\mathcal{R}_0$.

Definition A.21. Let a Metzler matrix A be invertible. A regular decomposition is a decomposition of the form

$$A = F + V$$

where $F \geq 0$ and V is a Metzler stable matrix.

The following theorem is proved in [144], but given its importance int this thesis, we also present the proof here.

Theorem A.13. Let A be an invertible Metzler matrix. For a regular decomposition of A of the form $A = F + V$, the following two assertions are equivalent.

1. A is a stable matrix
2. $\rho(-FV^{-1}) < 1$

Proof
Suppose A is a Metzler matrix, then from theorem A.9, we have $-A^{-1} \geq 0$.
The matrix $V = A - F$ and A are invertible so we can write

$$-FV^{-1} = -F(A-F)^{-1} = -FA^{-1}(I - FA^{-1})^{-1}$$

We let $G = -FV^{-1}$ be a a positive matrix. To get the spectral radius using the Perron-Frobenius theorem, it is sufficient to restrict ourselves to the positive eigenvectors. So let $v > 0$ be an eigenvector of G corresponding to an eigenvalue $\lambda \geq 0$, so that $Gv = \lambda v$. Now,

$$-FV^{-1}v = G(I-G)^{-1}v = \frac{\lambda}{1-\lambda}v$$

The matrix $-FV^{-1}$ is positive. Conversely, let $\mu \geq 0$ be an eigenvalue corresponding to an eigenvector $v > 0$. Then $G(I-G)^{-1}v = \mu v$. The matrix G and $(I-G)^{-1}$ commute, and we deduce that $Gv = \mu(I+G)v$. This necessarily implies that $\mu \neq 1$ and v is an eigenvector of G corresponding to the eigenvalue $\frac{\mu}{1+\mu}$.
The function defined by $x \to \frac{x}{1+x}$ in $[0,1] \in \mathbb{R}^+$ is a bijection between the eigenvalues of $G = -FA^{-1}$ and those of $-FV^{-1}$. This is a monotonic function. Consequently we have

$$\rho(-FV^{-1}) = \frac{\rho(G)}{1+\rho(G)} < 1.$$

Conversely, assume $\rho(-FV^{-1}) < 1$. Then the matrix $I - FV^{-1}$ is invertible and in addition a Metzler matrix. Since $\rho(-FV^{-1})$, we have $\alpha(-I - FV^{-1}) < 1$. This is a Metzler stable matrix. Its inverse if positive and therefore

$$-A^{-1} = (-I - FV^{-1})^{-1}V^{-1} \geq 0.$$

We see from theorem A.9 that A is a Metzler stable matrix, and this completes the proof.

A.5 Calculation of Basic Reproduction Number

To calculate basic reproduction number we demonstrate here the method developed by van den Driessche and Watmough [141]. In the formular, $\mathcal{R}_0$ is defined as the spectral radius of Next Generation Operator. The determination of the operation involves the distribution into two compartments, the compartment of infected (latent, infectious ...) and the compartment of uninfected individuals.

This technique was developed first by Diekmann and Heesterbeek in [32] and later developed by van den Driessche and Watmough in [141] for finite dimensional systems.
Consider an epidemiological model with no classes or with homogeneous compartments. The vector x represents the state of the system and x_j is the number (or concentration) of individuals in compartment j. The compartments are sorted in such a way that the first k compartments are free of infection (susceptibles) while the others are the infected compartments (latents, infected.).

Set the vector $x = x_j,\ j = 1, \ldots, n$ where x_j is the number of individuals in compartment j.
Let $\mathcal{F}_j(x)$ be the rate of appearance of new infections in compartment i, $\mathcal{V}_i^+(x)$ be the rate of transfer of individuals into compartment i by all other means, and $\mathcal{V}_j^-(x)$, the rate of transfer of individuals out of compartment j. The dynamics of the compartment is defined by

$$\dot{x}_j = \mathcal{F}_j(x) + \mathcal{V}_j^+(x) - \mathcal{V}_j^-(x)$$

It is assumed that each function is continuously differentiable at least twice in each variable. If we put $\mathcal{V}_j(x) = \mathcal{V}_j(x)^+ - \mathcal{V}_j(x)^-$ the previous system becomes

$$\dot{x}_j = \mathcal{F}_j(x) + \mathcal{V}_j(x).$$

If x_0 is the disease free state of the system, and the infected compartments are empty. This equilibrium is called the Disease Free Equilibrium, ie $j > k,\ (x_0)_j = 0$. For biological reasons we have the following hypothesis :

1. $x \geq 0,\ \mathcal{F}_j(x) \geq 0,\ \mathcal{V}_j^+(x) \geq 0, \mathcal{V}_j^-(x) \geq 0$. Since each function represents a directed transfer of individuals, they are all non-negative. If a compartment is empty, then there can be no transfer of individuals out of the compartment by death, infection, nor any other means. Therefore,
2. If $x_i = 0$ then $\mathcal{V}_j^-(x) = 0$. In particular, we if set $X_s = \{x \geq 0; x_j = 0, i = 1, \ldots, n\}$ and if $x \in X_s$, then $\mathcal{V}_j^-(x) = 0$. In other words, there can be no transfer from an empty compartment.
3. If $j \leq k$ then $\mathcal{F}_j(x) = 0$. That is, there is no immigration of infectives from the uninfected compartment.

4. If x_0 is the disease free state then $\mathcal{F}_j(x_0) = 0$ and for $j \geq k$, $\mathcal{V}_j^+(x_0) = 0$. If the population remains near the DFE ie. if the there is no disease, then introduction of a few infected individual will not result in an epidemic.

We now estimate the average number of new infections resulting from introduction of a typical individual near the DFE. To determine the fate of a typical infective individual introduced into the population, we consider the dynamics of the linearized system with reinfection blocked. That is the system

$$\dot{x} = D\mathcal{V}(x_0)(x - x_0) = D\mathcal{V}^+(x_0)(x - x_0) - D\mathcal{V}^-(x_0)(x - x_0).$$

The following result is the precise structure of the linearised system $DX(x_0)$ near the disease free equilibrium x_0.

Lemma 2. If x_0 is a DFE, then the matrices $D\mathcal{F}(x_0)$ and $D\mathcal{V}(x_0)$ are decomposed in blocks

$$D\mathcal{F}(x_0) = \begin{bmatrix} 0 & 0 \\ 0 & F \end{bmatrix}, \qquad D\mathcal{V}(x_0) = \begin{bmatrix} J_1 & J_2 \\ 0 & V \end{bmatrix}$$

$F \geq 0$ *and* V is a Metzler stable matrix.

The matrix ${}_FV^{-1}$ is called the Second Generation Matrix. A complete prove of this theorem is done in [141].

Definition A.22 (Basic Reproduction Number, $\mathcal{R}_0$). The basic reproduction number, $\mathcal{R}_0$ is the spectral radius of the second generation matrix, namely

$$\mathcal{R}_0 = \rho(-FV^{-1})$$

The following interpretation is given for the matrix $-FV^{-1}$:
Consider an infected individual introduced into compartment $k > m$ to a population without disease. The entry (i, k) of the matrix $-V^{-1}$ is the average length of time this individual spends in compartment j during its lifetime, assuming that the population remains near the DFE and re-infection is blocked. The (i, j) entry of F is the rate at which infected individuals in compartment j produce new infections in compartment i. Hence, the (i, k) entry of the product FV^{-1} is the expected number of new infections in compartment i produced by the infected individual originally introduced into compartment k. The spectral radius of the matrix $-FV^{-1}$ is the basic reproduction number. That is

$$\mathcal{R}_0 = \rho(-FV^{-1})$$

.

ANNEXE B

Biology of mosquito and malaria parasite

Contents

In this appendix, we describe the history and biology of malaria and the malaria transmitting mosquito. The word, malaria, is derived from the Italian phrase, 'mal-aria', meaning bad air. Malaria infection is caused by a protozoan parasite of the genus Plasmodium four species of which infect human beings, the most common being Plasmodium vivax and most deadly being Plasmodium falciparum. The Anopheles mosquito serves as Plasmodium 's delivery system, or vector. Only female mosquitoes can transmit it since males don't take blood meals.

B.0.1 The parasites life cycle.

The malaria parasite exhibits a complex life cycle involving the mosquito and a human host. Infection begins when the female Anophele mosquito bites an infected human and injects saliva with sporozoites into the human blood stream. Sporozoites are carried by the circulatory system to the liver and invade a variety of liver cells. The sporoziotes replicate to produce merozoites which are released into the bloodstream. Merozoites invade erythrocytes and enlarge to produce trophozoites. The trophozoites subdivide and mature to become schizonts, which are released following a rupture of the infected erythrocyte. Invasion of erythrocytes reinitiates another round of the blood-stage replicative cycle, usually referred to as the assexual cycle.
Sometimes, instead of the asexual replicative cycle, the parasite can differentiate into sexual forms known as macro- or microgametocytes. Ingestion of gametocytes by the mosquito vector induces gametogenesis (i.e., the production of gametes). Microgametes then fertilize the macrogamete to produce a zygote which develops into a motile ookinete. The ookinet will penetrates the gut wall cells and develops into an oocyst. The oocyst mature and releases the sporozoites which migrate to and invade the salivary glands. This completes the life cycle of the parasite cycle. The incubation period (time from infection to development of the disease) is usually about 10 to 15 days.

B.0.2 Mosquitoes Life cycle

The Anopheles has four stages in their life cycle : egg, larva, pupa, and adult. The first three stages last 5-14 days depending on the species and the ambient temperature. The adult females lives for about 1-2 weeks in nature.

Eggs : An anopheles mosquito lays between 50-200 eggs per oviposition directly on water. The eggs have floats on either side to help them float till they hatch within 2-3 days, in ambient temperature.

Larvae : Mosquito larvae have a well-developed head with mouth brushes used for feeding, a large thorax, and a segmented abdomen.They breathe through spiracles located on the abdomen and therefore must come to the surface frequently. Larvae spend most of their time feeding on algae, bacteria, and other microorganisms in the surface microlayer. They dive below the surface only when disturbed. They develop through 4 stages, or instars, after which they metamorphose into pupae. At the end of each instar, the larvae molt, shedding their exoskeleton, or skin, to allow for further growth. The larvae prefer clean, unpolluted water and many species prefer habitats with vegetation. Some breed in open, sun-lit pools while others are found only in shaded breeding sites in forests.

Pupae : The pupa is comma-shaped when viewed from the side. The head and thorax are merged into a cephalothorax with the abdomen curving around underneath.They usually come to the surface frequently to breathe, through a pair of respiratory trumpets on the thorax. After a few days the pupa, splits and the adult mosquito emerges. The duration from egg to adult varies considerably among species and is strongly influenced by ambient temperature. Mosquitoes can develop from egg to adult in as little as 5 days but usually take 10-14 days in tropical conditions.

Adults : Anopheles mosquitoes can be distinguished from other mosquitoes by the palps, which are as long as the proboscis, and by the presence of discrete blocks of black and white scales on the wings. Adult Anopheles can also be identified by their typical resting position : males and females rest with their abdomens sticking up in the air rather than parallel to the surface on which they are resting. Mosquitoes can develop from egg to adult in as little as 5 days but usually take 10-14 days in tropical conditions.
Some Anopheles mosquitoes prefer to bite humans and others prefer animals, usually referred to as anthropophilic and zoophilic respectively. The anthrophilic are more likely to spread malaria because they bite humans more often. Most Anopheles are active at dusk and dawn (crepuscular) while others are nocturnal (active mostly at night). Some anophelines prefer to feed/rest indoors (endophagic / endophilic), while others feed/rest outdoors (exophagic / exophilic). When feeding, the female mosquito first injects some saliva into the host to prevent clotting, allowing the malaria parasite to enter the human host.

Some Anopheles species are poor vectors of malaria, because the parasites do not develop well (or at all) within them. These refractory strains have an immune response that encapsulates and kills the parasites after they have invaded the mosquito's stomach wall. It is hoped that some day, genetically modified mosquitoes that are refractory to malaria can replace wild mosquitoes, thereby limiting or eliminating malaria transmission. Once larvae emerge to become adults, the rate at which they feed on man is dependent upon the ambient temperature.

At 17^0C the female mosquitoes feed on humans every 4 days while at 25^0C they take blood meals from humans every 2 days. Rainfall increases the breeding habitats for mosquitoes leading to increased population sizes and the rate of malaria transmission. The rate of the parasite development in the female mosquito has an exponential relationship to temperature. Thus a very small increase in external temperature will reduce the time it takes for the parasite to mature several fold. In Western Kenya a 0.5^0C increase in temperature since the 1970's can explain the eight-fold increase in malaria cases (http ://www.ipsnews.net/news).

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