Mathematical modelling of mosquito dispersal for malaria vector control

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von Prof. Dr. Thomas Smith, and Prof. Dr. Azra Ghani.

Basel, den 26.März 2013

Prof. Dr. Jörg Schibler
Dekan

To my parents Magoke Mashauri
and Lutambi Kahema

Summary

In malaria endemic regions, dispersal of mosquitoes from one location to another searching for resources for their survival and reproduction is a fundamental biological process that operates at multiple temporal and spatial scales. This dispersal behaviour is an important factor that causes uneven distribution of malaria vectors causing heterogeneous transmission. Although mosquito dependence in a heterogeneous environment has several implications for malaria vector control and in public health in general, its inclusion in mathematical models of malaria transmission and control has received limited attention.

Most models of malaria transmission and control explain relationships between the number of mosquitoes and malaria transmission in humans while assuming enclosed systems of mosquitoes in which spatial dynamics and movements are not taken into account. These models have limited ability to assess and quantify the distribution of risks and interventions at local scales. Therefore, in order to overcome this limitation, mathematical models that consider the interaction between dispersal behaviour, population dynamics, environmental heterogeneity, and age structures of the mosquito are needed for designing, planning, and management of the control strategies at local scales.

Advances in malaria modelling have recently begun to incorporate spatial heterogeneity and highlight the need for more spatial explicit models that include all the vital components of ecological interactions.

In response to this need, this thesis develops a spatial mathematical model that captures mosquito dispersal and includes all of the above characteristics to achieve a broader and deeper understanding of mosquito foraging behaviour, population dynamics, and its interactions with environmental heterogeneity, distribution of malaria risk, and vector control interventions. The model is applied to assess the impact of dispersal and heterogeneous distribution of mosquito resources on the spatial distribution, dynamics, and persistence of mosquito populations, to estimate the distance travelled by mosquitoes, and to evaluate and assess the impact of spatial distribution of vector control interventions on effectiveness of interventions under mosquitoes' natural dispersal behaviour.

Chapter 2 develops a spatial mathematical model of mosquito dispersal in heterogeneous environments with a framework that is simple to allow investigation of aspects that affects malaria transmission. The model incorporates age distribution in form of the aquatic and adult stages of the mosquito life cycle and further divides the adult mosquito population into three stages of the mosquitoes searching for hosts, those resting, and those searching for oviposition sites. These three adult stages provide an opportunity to study the life style of the adult mosquito, and also offer a direct opportunity to assess the impact of interventions targeting different adult states such as insecticide treated bednets (ITNs), indoor residual spraying (IRS), and spatial repellents that reduce contacts between host seeking mosquitoes and human hosts. The spatial characteristics of the model are based on discretization of space into discrete patches. Host and oviposition site searching mosquitoes disperse to the nearest neighbours across the spatial platform where hosts and breeding sites are distributed.

In the same Chapter, the model is applied to investigate the effect of heterogeneous distribution of resources used by mosquitoes, estimate the dispersal distance, and to assess the impact of spatial repellents on the dispersal distance. Results revealed that due to dispersal, the distribution of mosquitoes highly depend on the distribution of hosts and breeding sites and the random distribution of spatial repellents reduces the distance travelled by mosquitoes; offering a promising vector control strategy for malaria. In addition, analysis indicated that when only a single patch is considered, and movement ignored, the recruitment parameter and parameters related to the larval and host seeking stages of the mosquito strongly determine mosquito population persistence and extinction.

Chapter 3 extends the model developed in Chapter 2 to include vector control interventions. As vector control intervention deployment plans need to consider the spatial distribution of intervention packages, the model extension developed in this chapter is used to examine the effect of spatial arrangement of vector control interventions on their effectiveness. Application of the model to IRS, larvicide, and ITNs showed that randomly distributing these interventions will in general be more effective than clustering them on side of an area.

Mosquito dispersal and the different patterns of heterogeneity have different effects on population distribution and dynamics of mosquitoes, and thus, that of malaria. Models that incorporate dispersal when integrated with environmental heterogeneity allow predictions to capture ecological behaviour of mosquitoes, the main source of variations in malaria risk at local spatial scales, providing information needed for determining risk areas for malaria vector control purposes.

Zusammenfassung

Das Flugverhalten von Moskitos bei der Nahrungssuche und Fortpflanzung und die damit verbundene Verbreitung dieser Malaria-Überträger ist ein wichtiger biologischer Prozess in malariaendemischen Gebieten. Dieser Prozess erstreckt sich über mehrere zeitliche und örtliche Grössenordnungen, und erzeugt Heterogenität in der Verbreitung der Moskitovektoren und damit in der Malariaübertragung. Obwohl ein besseres Verständnis dieser Prozesse für die Planung von Malaria-Kontrollprogrammen bedeutsam ist, gab es bisher nur wenige mathematische Modelle zur Studie der Malaria Übertragung und Kontrolle, welche diesem Umstand Rechnung tragen.

Die meisten mathematische Modelle zum Studium der Malaria-Übertragung und -Kontrolle basieren auf der vereinfachenden Annahme eines geschlossenen Systems ohne räumliche Struktur. Solche Modelle können nur beschränkt Aussagen über die kleinräumige Malaria-Verbreitung und den Einfluss von Kontrollmassnahmen darauf machen. Für die bessere Planung von Massnahmen auf kleinem Raum braucht es deshalb verfeinerte Modelle, welche das Zusammenspiel zwischen dem Flugverhalten, der Populationsdynamik, der Umweltheterogenität und der Altersstruktur der

Moskitopopulation berücksichtigen. Neuere Malariamodelle, welche räumliche Heterogenität berücksichtigen, zeigen die Notwendigkeit von räumlich expliziten Modellen unter Berücksichtigung aller essentiellen ökologische Interaktionen auf.

Im Rahmen dieser Dissertation werden neue mathematische Modelle entwickelt, welche diesen Ansprüchen gerecht werden, und damit zu einem besseren Verständnis des Zusammenhangs zwischen dem Moskito Verhalten, der Populationsdynamik, der Umweltheterogeneität, der Verteilung des Risikos der Malaria und Vektorkontroll-Massnahmen beitragen. Das Modell wird angewendet, um den Einfluss einer heterogenen Verteilung der für Moskitos relevanten Resourcen auf die räumliche Verteilung, die Dynamik, und die Persistenz von Moskito-Populationen zu untersuchen. Ausserdem werden mittels Modell Schätzungen der von Moskitos zurückgelegten Wege erstellt und die daraus resultierenden Konsquenzen für die Effektivität von Kontroll-Massnahmen vorhergesagt.

In Kapitel 2 wird ein räumliches Modell des Moskito-Flugverhaltens entwickelt. Das Modell beinhaltet die Altersstruktur in Form der aquatischen und adulten Stadien des Moskito-Lebenszyklus, und unterteilt das Adultstadium weiter in nach Blutwirten suchende, ruhende und nach Eiablageplätzen suchende Moskitos. Die Unterteilung in drei Adultstadien ermöglicht das Studium des Lebenszyklus der Adulten, und gleichzeitig die Voraussage der Auswirkungen verschiedener Kontrollstrategien wie imprägnierte Moskitonetze, Insektizide, und räumliche Moskitoschutzmittel. Die räumliche Struktur im Modell wird durch eine Aufteilung des Raumes in diskrete Patches erreicht. Moskitos auf der Suche nach Blutwirten oder Eiablageplätzen wandern dabei über benachbarte Patches durch den Raum.

Kapitel 2 beschreibt die Anwendung des Modells zur Untersuchung der Auswirkungen einer heterogenen Verteilung von Resourcen und der Anwendung von räumlichen Insektenschutzmittel auf die Flugdistanz der Moskitos. Dabei zeigt sich, dass die Verteilung der Moskitos im Raum

aufgrund des modellierten Suchverhaltens massgeblich von der Verteilung der Blutwirte und der Eiablageplätze bestimmt wird. Eine zufällige Verteilung der räumlichen Insektenschutzmittel verringert die durchschnittliche Flugdistanz und stellt damit eine vielversprechende Kontroll-Massnahme dar. Weitere Analysen der Vorraussagen zeigen ausserdem, dass bei Bercksichtigung eines einzelnen Patches unter Vernachlässigung der Moskito-Bewegungen die Persistenz der Population in erster Linie vom Rekrutierungs-Parameter und von Parametern im Zusammenhang mit den Larven- und Wirt-suchenden Stadien bestimmt wird.

In Kapitel 3 wird das Modell aus Kapitel 2 erweitert, um die Simulation von Vektorkontroll-Massnahmen zu ermöglichen. Da Vektorkontroll-Massnahmen der räumlichen Struktur berücksichtigen sollten, wird mittels der Modell-Erweiterung die Effektivität verschiedener Strategien zur räumlichen Anordnung von Kontroll-Massnahmen eruiert. Die Anwendung des Modells auf Insektizide, imprägnierte Moskitonetze und Larvizide zeigt, dass die zufällige Verteilung der Massnahme im Allgemeinen effizienter ist als eine geklumpte Verteilung.

Das Flugverhalten von Moskitos und unterschiedliche Heterogenitätsmuster haben verschiedene Auswirkungen auf die Populations-Verteilung und die Dynamik der Moskitos, und somit auf die Malaria. Mathematische Modelle, welche die Umweltheterogenitt und das Flugverhalten der Moskitos beinhalten, erlauben Voraussagen unter Berücksichtigung der Verhaltensökologie der Moskitos, der Hauptursache der Variation des Malaria-Risikos auf engem Raum. Damit können sie eine wichtige Rolle bei der Planung von Vektorkontroll-Interventionen spielen.

Acknowledgements

Contents

List of Figures

List of Tables

CHAPTER 1

Introduction

Malaria is a vector-borne disease transmitted by *Anopheles* mosquitoes. The disease is transmitted between humans through bites of infectious mosquitoes. It is estimated that more than 3 billion people live in malarious areas (Figures 1.1), most of whom live in sub-Saharan Africa (WHO, 2011). Most individuals in this region are infected by *Plasmodium falciparum* parasite which is the most prevalent and prominent malaria parasite in sub-Sahara Africa (Gething et al., 2011a). This parasite is not only associated with severe malaria but also is life threatening, causing high morbidity and mortality rates in the region. The World Health Organization (WHO) estimates that in 2010, more than 200 million malaria cases occurred worldwide (WHO, 2012). Of the $660,000$ malaria deaths that occurred in 2010 around the world, 91% were in Africa and 86% were children under the age of five years (WHO, 2012). Malaria also causes serious adverse effects in pregnant women such as miscarriage, low birth weight, and anaemia and has been a source of poverty in many families as the costs linked to the disease are high (White et al., 2011).
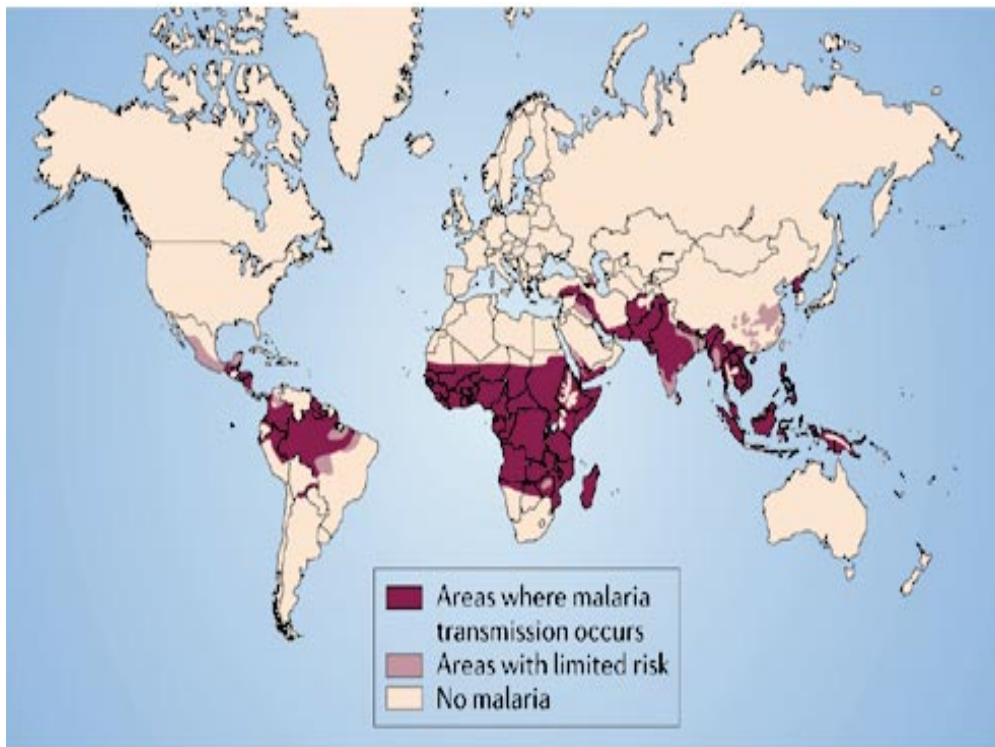
Figure 1.1: Distribution of malaria risk (Source:(Bell et al., 2006)).

Despite the growing international pressure and efforts to provide treatment, develop vaccines, and implement vector control, malaria continues to remain a major problem in the world. Due to this trend, it is unlikely that the set targets for reducing the global burden of malaria will be met. Therefore, countries where malaria is prevalent need to examine in depth the vectors that are responsible for transmitting the disease, and what sort of behaviour, and dynamics these vectors follow. There is also a need to understand in detail the natural cause of the continuous transmission, and to design better control strategies for vector management at local level.

1.1   Vectors and their distribution

The life of a mosquito is divided into four main stages (Figure 1.2). The first stage is the egg stage, where eggs are laid on standing water by adult females. The development process of eggs is temperature dependent and eggs are likely to survive low temperatures. The second stage is the larval stage. In this stage,

larvae progress through several stages of growth. Their survival depends on climatic conditions and rely very much on standing water providing food in form of organic matters. After the second stage, larvae develop into pupae, the third aquatic stage. It is from this stage mosquitoes emerge as adults. In the fourth stage, emerging adult mosquitoes fly in space, then mate; an action which takes place roughly one day after becoming adults. Female mosquitoes start seeking for a blood meal. After a feed, the mosquitoes rest, and later oviposit their eggs, all of which account for different distribution patterns.
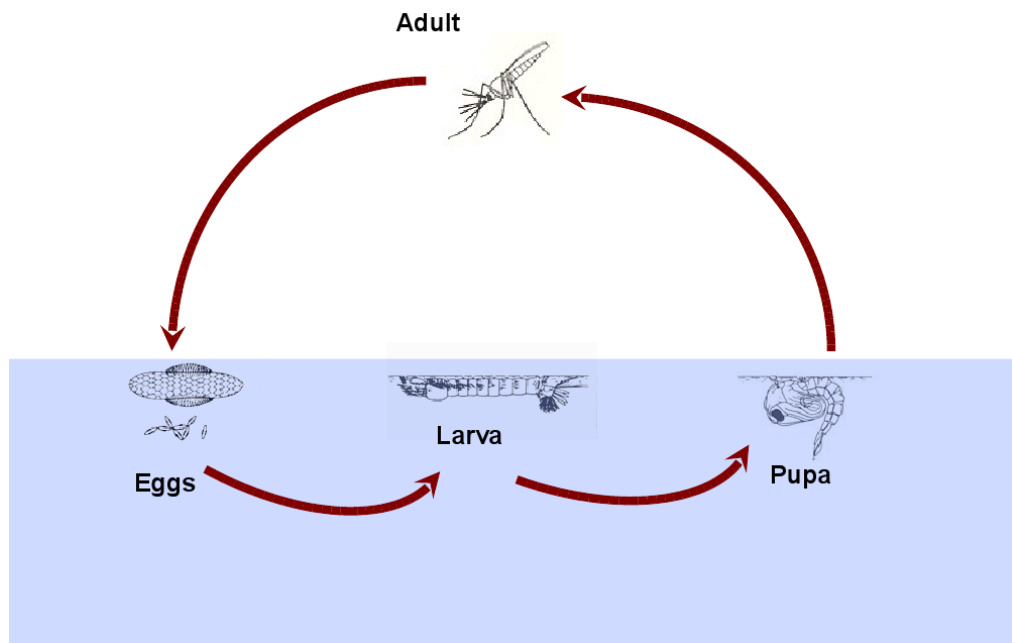
Figure 1.2: An illustration of the mosquito life cycle (individual parts of the diagram obtained from Centers for Disease Control and Prevention (CDC) (CDC, 2013)).

Mosquito distribution differs in time and space due to seasonal variations and environmental heterogeneity. In areas with favourable environmental factors such as temperature, rainfall and humidity, malaria transmission distribution is highly related to the mosquitoes abundance. In parts where temperature is not a limiting factor, malaria transmission is highly seasonal. Global maps on the distribution of malaria vectors highlight the present spatial variability of mosquito species across different regions (see for example Figure 1.3). In

Africa, for example, *An. gambiae*, *An. arabiensis* and *An. funestus* are prevalent vectors that are responsible for malaria transmission. In Asia and other regions, multiple species co-exists. These differences in species across regions are mainly due to differences in climatic and environmental conditions (Sinka et al., 2012). These conditions are critical for sustaining the production of resources needed by mosquitoes for survival and reproduction.
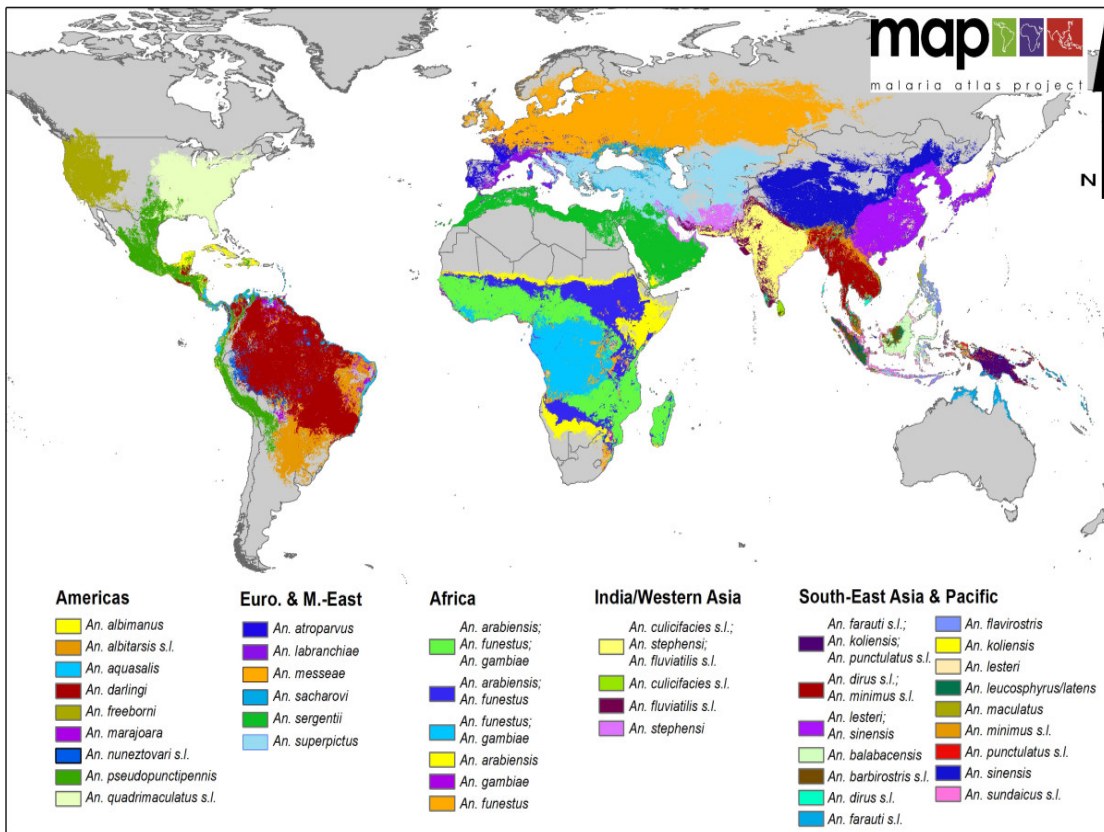
Figure 1.3: Distribution of predominant malaria vectors in 2012 (Source:(Sinka et al., 2012)).

Since mosquitoes need a variety of resources in to survive and reproduce, the distribution of these resources in space affect their distribution (Sinka et al., 2012) and rate of dispersal. This effect contributes to variation in local densities (Cano et al., 2006; Li et al., 2008; Minakawa et al., 2002; Smith et al., 2004), human exposure to vectors, and our ability to control disease transmission.

1.2   Vector control

Vector control has been an important part of the global malaria control strategy with several interventions targeting at reducing the contact between humans and vectors. The reduction of human-vector contacts reduces the population density of vectors and hence, malaria transmission. Several vector control intervention programs have been implemented and have proved to be effective in providing protection to humans. It is over a decade now since the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), and the World Bank launched the Roll Back Malaria Global Partnership (RBM) programme for increased efforts to fight against malaria. In 2000, the African summit set vector control scaling up coverage in sub-Saharan Africa as a priority, and the political will to combat malaria has been increasing (Sambo et al., 2011). Since then, numerous control activities have been implemented.

Source reduction and management remain effective strategies for malaria vector control (Gu et al., 2006). Habitat identification for management has been an ongoing activity in African urban settings as part of the vector control activities. Larval habitats are mapped to understand the spatial distribution of malaria vectors. It has been hard to clearly identify the ecological characterization of the mosquitoes (Sattler et al., 2005) as human activities and urbanization have been sources of the growing presence of stagnant water bodies which are potential sources of malaria (Sattler et al., 2005). Apart from source reduction, routine application of larvicide have been extensively used in some African countries (Geissbuhler et al., 2009). Studies show that larviciding suppresses the number of malaria transmitting mosquitoes in malarious places (Fillinger and Lindsay, 2006; Kroeger et al., 1995; Majambere et al., 2007, 2010; Mwangangi et al., 2011). However, larval control can only be effective if larval habitats are limited and well defined.

Interventions such as insecticide treated nets (ITNs) or long-lasting insecticide treated nets (LLINs), and Insecticide residual spray (IRS) have been widely

used as means for adult vector control (WHO, 2012). ITNs prevent access of host seeking malaria vectors to people, thus providing personal protection against malaria to the individuals using ITNs (Lengeler, 2004; Takken, 2002; WHO, 2007). ITNs also give an extended effect to non-users (Hawley et al., 2003) mainly due to their killing effects which reduce mosquito longevity. Even if not killing directly, repellents (de Zulueta and Cullen, 1963) increase the duration of host seeking, and hence associated mortality and providing a community effect. In addition, IRS primarily kill resting adult mosquitoes, providing protection against diseases (WHO, 2006) with minimal direct personal protection against mosquito bites.

Universal coverage of these vector control interventions among risk groups has been recommended (RBM, 2008). Currently, LLINs are distributed through different distribution programs, some of which are subsidized to reach the majority of people. Although there has been some increase in malaria control funding since 2006 (Pigott et al., 2012), the World Malaria Report 2012 shows the existence of variations of donor funds over time for scaling up of vector control activities in malaria endemic countries (WHO, 2012). Sustainability of universal coverage is unlikely because of the limited life time of the nets and repeated mass distribution of the nets is necessary to sustain high coverage. However, if funds are stopped, there is a risk of malaria resurgence as high coverage of these interventions will no longer be sustained by poor countries and a shifting pattern from universal coverage to low coverage levels is possible. This shifting pattern of coverage guarantees heterogeneous distribution of interventions and of mosquitoes among places; calling for more behavioural studies that consider different aspects of vectors affecting their spatial distribution at local levels.

1.3   Mosquito dispersal

Mosquito dispersal[1] is a fundamental biological process that operates at multiple temporal and spatial scales, making it an important factor that causes uneven distribution of malaria vectors in local settings. Dispersal may lead to temporary extinction in local settings without driving the population of the whole region to extinction and this is achieved if the population in one or more locations goes to zero. Re-colonization is also possible and can be achieved subsequently through dispersal from other locations.
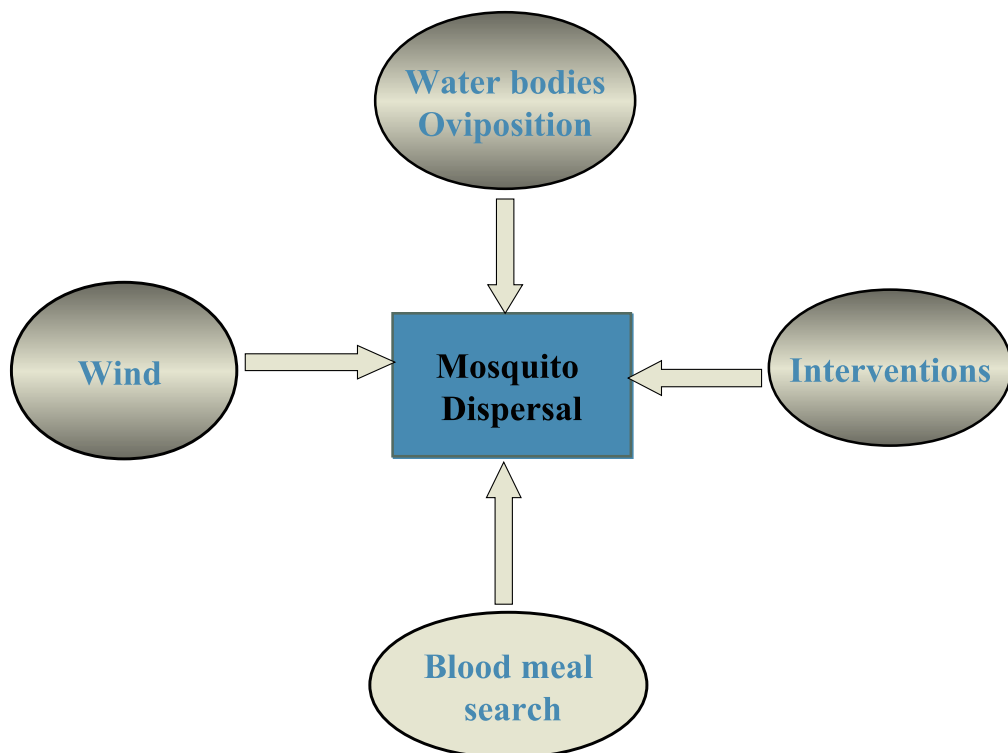
Figure 1.4: Factors affecting dispersal

Studies indicate that the existence of olfactory, visual, and thermal cues play an important role in modifying mosquito flying behaviour (Becker et al., 2010; Takken and Knols, 1999). Several experiments have been performed to understand mosquito dispersal (Gillies, 1961; Gillies and Wilkes, 1978, 1981) and factors such as those shown in Figure 1.4 affect mosquito dispersal at local level. Experiments from capture-mark-recapture methods have shown that

[1]Mosquito dispersal is the movement of mosquitoes from one location to another.

mosquito dispersal distance is short and variable if driven by search for food, sheltering, and egg laying (Service, 1997). These short distances are for a few hundred meters although longer flights of 1 km may be necessary if hosts and oviposition sites are widely separated. The searching strategy may depend on whether mosquitoes rely on information from neighbouring areas or from places that are far apart from their present locations. The later can be incrementally achieved by movements made to neighbouring locations. The dispersal can be random or unidirectional if facilitated by environmental factors such as wind (Service, 1997). Sometimes, long dispersal is likely to be facilitated by human travel.

Dispersal is also affected by vector control interventions. Interventions such as source reduction or environmental management create distances between breeding sites, affecting their spatial distribution. Several studies have shown that there is an association between distance to potential mosquito breeding sites and the variability in the *Anopheline* density (Cano et al., 2006) and that availability of hosts and the distribution of larval habitats has an influence on malaria vector abundance (Li et al., 2008; Minakawa et al., 2002; Smith et al., 2004). Some interventions divert mosquitoes without killing them (e.g. cream, lotion, soap, and gel, insect proofing of houses, sprays, coils, and local herbs) (Moore et al., 2007; Pates and Curtis, 2005; Rowland et al., 2004) resulting into local dispersal; others change mosquito densities (e.g. insecticide treated bed-nets) by reducing mosquito population and hence change patterns of mosquito variations among different places. This relationship has a potential effect on the spatial distribution of mosquitoes, and thus of malaria morbidity and mortality.

Mosquito dispersal is directly linked to the population density of mosquitoes, and is the driving force of heterogeneous transmission in local settings (Figure 1.5). Dispersal and its interaction with other factors such as population density, interventions, and transmission is complex and has several implications
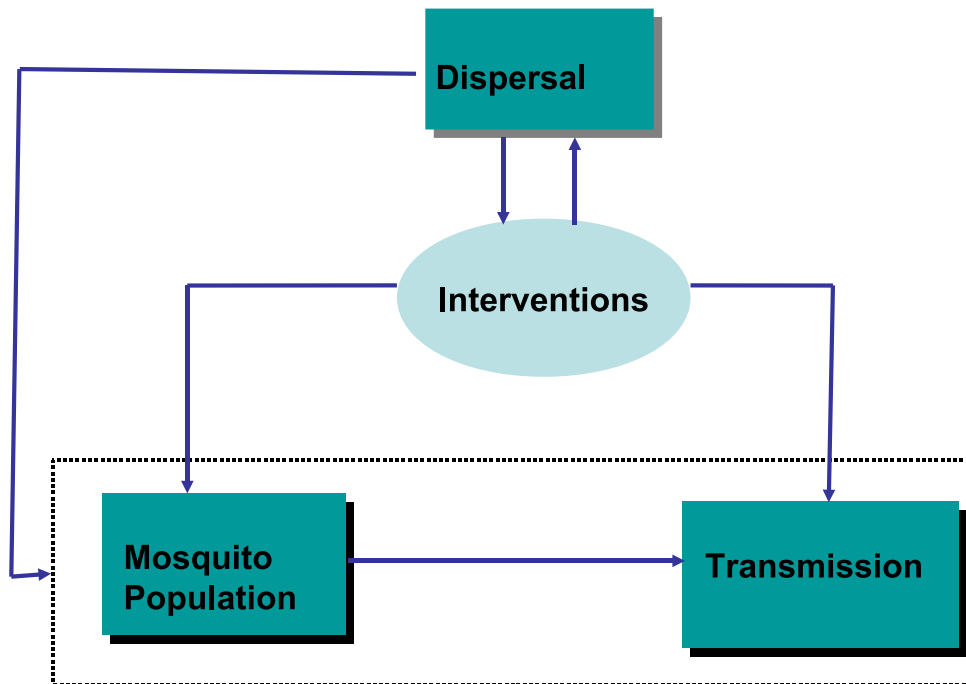
Figure 1.5: Interaction of dispersal with population, interventions, and malaria transmission

in public health. The effect of dispersal on interventions is two fold. Interventions may appear less effective when evaluated because of mosquito movement between areas under interventions and those not under interventions (Killeen et al., 2003) or may appear beneficial due to the community effects catalysed by dispersal. The interaction between a heterogeneous environment and movement behaviour of malaria vectors is challenging, requiring different techniques to combat the disease.

1.4   Models of malaria and vector control

Several studies have demonstrated that remote sensing and geographical information systems (GIS) are powerful tools for understanding mosquito distribution (Hay et al., 2004, 2009; Sinka et al., 2012) and are suitable for understanding the link between seasonal variations and environmental factors to malaria transmission indicators at large spatial scales. However, these tools

remain reliable only at global spatial scales. At local scales, mathematical models provide an alternative way of assessing and quantifying the distribution of risks or assessing interventions. They can also explain the complex dynamics of local populations and dispersal patterns exhibited by mosquitoes. They are also useful tools for capturing spatial characteristics for assisting decisions on mosquito surveillance and malaria prevention (Li et al., 2008). In these models, groups or spatially distributed populations can be linked together across a set of spatial locations.

The concept of modelling mosquito dispersal was highlighted a century ago by Ronald Ross (Ross, 1905). In his model, Ross described distribution of the mosquitoes by distance moved and concluded that mosquitoes movement follows a "centripetal law of random wandering" in which the number of dispersing mosquitoes is high in the vicinity and low far away from their original location. This law is conserved even in situations where the distribution of resources such as hosts and breeding sites is heterogeneous.

Although Ross's idea of modelling mosquito dispersal is an important aspect for improving scientific experiments (Ross, 1905), modelling studies has rarely considered it. Other mathematical models of Ronald Ross (Ross, 1915), have long been used to explain relationships between the number of mosquitoes and malaria transmission in humans. The extension of Ross model to include different factors has been carried out by several authors (Mandal et al., 2011) and has continued to contribute to the theoretical basis of malaria control. However, these model extensions have always assumed closed systems of mosquitoes in which spatial dynamics and movements are not taken into account. This assumption has enabled many intuitive analyses but has considerable consequences for implementing better strategies for control and evaluation of control interventions in field settings.

A deterministic model studied by Smith et al. (Smith et al., 2004) incorporated the spatial heterogeneity context of the dynamic process of mosquitoes. The findings show a link between human distribution and larval habitats, with

mosquito distribution following a similar pattern to that of humans. Spatial models have also been used to evaluate the impact of source reduction programmes on vectors and malaria transmission and highlighted the importance of considering the relationship between resource-seeking behaviours of mosquitoes and malaria transmission (Gu and Novak, 2009a). Although others have focused on the distribution of malaria based on mosquito oviposition behaviour without including mosquito dispersal explicitly (Menach et al., 2005), spatial aspect of mosquitoes have been modelled in terms of migration between patches in a hypothetical landscape. Findings of (Menach et al., 2005) indicate the likelihood of mosquitoes aggregating around places with water, and thus, determining the distribution of malaria. Likewise, models of spatial dynamics have shown that the use of insecticides on adult stage as opposed to aquatic stages as a control strategy significantly reduce mosquitoes (Takahashi et al., 2005). These modelling studies indicate the need for more explicit models that include vital components of ecological interactions. In order to overcome this need, mathematical models that consider the interaction between dispersal behaviour, population dynamics, environmental heterogeneity, and age distribution of the mosquito are needed for designing, planning, and management of the control strategies at local scales.

1.5   Objectives

The primary objective of this thesis is to develop a spatial mathematical model that captures mosquito dispersal to achieve a broader understanding of mosquito foraging behaviour and its interactions with environmental heterogeneity and vector control interventions. The specific objectives are as follows:

- To develop a simple model without dispersal that include aquatic and adults stages of the mosquito to determine stages that are important for targeted malaria vector control.

- To develop a comprehensive mathematical model and a spatial framework that captures mosquito dispersal behaviour in a heterogeneous environment as factors that affect the distribution of mosquitoes in a spatial environment.

- To incorporate and determine the effect of spatial heterogeneity on mosquito populations.

- To evaluate and determine the effect of spatial distribution of malaria vector control interventions on effectiveness of interventions under mosquitoes' natural dispersal behaviour.

1.6   Outline

Chapter 2 develops a mathematical model and a framework for modelling environmental heterogeneity and mosquito movement. A simple model of mosquito population dynamics is developed for a single patch and used to determine stages of the mosquito life cycle that significantly affect mosquito population. Embedding the model into a spatial context, the landscape is divided into discrete locations called patches. These patches are assumed to be connected by migration of mosquitoes which move between patches as they search for oviposition sites and blood meals. Local dispersal is modelled by assuming that dispersing adults move from their current locations enter nearest neighbouring locations and long-range dispersal is achieved through repeated movements. The model is based on ordinary differential equations and is replicated across a landscape, a multi-patch system that represents a two-dimensional space. The model is applied to investigate the impact of dispersal and heterogeneous distribution of resources on the distribution and dynamics of mosquito populations, estimate mosquito dispersal distances, and to evaluate the effect of spatial repellents as a vector control strategy.

Chapter 3 extends the model developed in chapter 2 by modelling vector control. As vector control intervention deployment plans need to consider the

spatial distribution of intervention packages, the model extension developed in this chapter is used to examine how spatial arrangements of vector control interventions are likely to affect their effectiveness. As part of model application, insecticide residual spraying (IRS), larvicide, and insecticide treated bed-nets (ITNs) are evaluated.

Chapter 4 summarizes, discusses, and concludes the modelling work presented in the thesis and suggests directions for future work.

Mathematical modelling of mosquito dispersal in a heterogeneous environment

Authors: Angelina M. Lutambi, Melissa A. Penny, Thomas Smith, and Nakul Chitnis

2.1 Abstract

Mosquito dispersal is a key behavioural factor that affects the persistence and resurgence of several vector-borne diseases. Spatial heterogeneity of mosquito resources, such as hosts and breeding sites, affects mosquito dispersal behaviour and consequently affects mosquito population structures, human exposure to vectors, and the ability to control disease transmission. In this paper, we develop and simulate a discrete-space continuous-time mathematical model to investigate the impact of dispersal and heterogeneous distribution of resources

on the distribution and dynamics of mosquito populations. We build an ordinary differential equation model of the mosquito life cycle and replicate it across a hexagonal grid (multi-patch system) that represents two-dimensional space. We use the model to estimate mosquito dispersal distances and to evaluate the effect of spatial repellents as a vector control strategy. We find evidence of association between heterogeneity, dispersal, spatial distribution of resources, and mosquito population dynamics. Random distribution of repellents reduces the distance moved by mosquitoes, offering a promising strategy for disease control.

2.2   Introduction

Mosquitoes transmit malaria, dengue, yellow fever, filariasis, and several other important diseases. Malaria, in particular, shows considerable spatial variation predominantly determined by climatic variation (Hay et al., 2009), intervention coverage, and human movement (Martens and Hall, 2000; Service, 1997; Stoddard et al., 2009; Tatem et al., 2006). At local scales (i.e. from 100 m to 1 km), mosquito behaviour and ecology play an important role in determining the distribution of transmission (Menach et al., 2005). Like other animals, mosquitoes can move in any direction, motivated by resource availability and other drivers of dispersal, but can only travel over limited distances. Control interventions should consider locality and mosquitoes' ability to move, to achieve a high level of effectiveness in reducing the mosquito population.

The impact of vector dispersal in the spread and control of diseases was first highlighted a century ago by Ronald Ross (Ross, 1905), but has received limited attention within the public health community. Ross stipulated that mosquito density within any area is always a function of four variables, which include the reproduction rate, mortality rate, immigration, and emigration rates. A study by Manga et al. (Manga et al., 1993) also showed that the spatial variation in the distribution of resources used by mosquitoes affects their reproduction and their rate of dispersal. This in turn contributes to variation in

densities (Cano et al., 2006; Gu and Novak, 2009a; Li et al., 2008; Smith et al., 2004), human exposure to vectors, and the ability to control disease transmission (Service, 1997). The effects of resource availability on transmission can be surprising. For instance, even the presence of non-productive larval habitats may affect biting densities (Menach et al., 2005). However, conducting experimental studies of mosquito dispersal (Gillies, 1961; Gillies and Wilkes, 1978, 1981; Midega et al., 2007) are challenging.

Mathematical models play an important role in understanding and providing solutions to phenomena which are difficult to measure in the field, but few models have incorporated dispersal or heterogeneity when modelling resource availability (Depinay et al., 2004; Menach et al., 2005; Nourridine et al., 2011; Otero et al., 2008; Smith et al., 2004; Yakob and Yan, 2010) or varied the usual assumption of a closed vector population (Ngwa, 2006; Otero et al., 2006; White et al., 2011). Others have sub-divided the adult stage of the mosquitoes into different stages (Ngwa, 2006; Otero et al., 2006; Saul, 2003). To investigate the effects of dispersal and heterogeneity, a model should incorporate features of the mosquito life cycle, the feeding cycle, spatial heterogeneity in mosquito resources, and dispersal.

Spatial models have commonly used the diffusion approach, which considers space as a continuous variable. Despite the existence of diffusion models, which account for heterogeneity (Raffy and Tran, 2005; Tran and Raffy, 2006), it is difficult to explicitly incorporate the various factors that affect movement. For example, in areas where resources are located in patches or discrete locations, mosquito dispersal is more conveniently modelled using a metapopulation approach, in which the population is divided into discrete patches. In each patch, the population is sub-divided into subgroups, corresponding to different states, leading to a multi-patch, multi-compartment system.

Several models using diffusion approaches (Dumont, Y; Dumont,Y and Dufourd, C) have incorporated heterogeneity and have shown that the environment has a strong influence on the distribution of disease vectors. However,

none of them have included the aquatic stages of the mosquitoes or have provided a general and simple framework for modelling arbitrary spatial patterns of mosquito control interventions. A model framework that includes the aquatic stages and that partitions space into discrete locations allows us to capture the various forms of spatial heterogeneity that exist in our environment.

In this paper, a mathematical model, that includes all of the above features is developed and simulated to investigate the impact of dispersal and heterogeneous distribution of mosquito resources, such as hosts and breeding sites, on the spatial distribution, dynamics, and persistence of mosquito populations. The distance a mosquito can travel from its place of emergence or food source is a critical factor for vector control interventions, thus the model is used to project likely dispersal distances and considers how these might be changed by vector control interventions.

In the following sections, we develop and analyze a model for mosquito population dynamics that does not consider movement of mosquitoes. We then develop a meta-population model for mosquito movements with discrete space in hexagonal patches and compare it to a continuous space model. We then combine the two models and run simulations of a spatially explicit model of the full mosquito life cycle to determine the effect of repellents.

2.3 Description of the basic model: mosquito dynamics without dispersal

Mosquito life begins with eggs, which hatch into larvae under suitable conditions. The larvae develop into pupae that mature and emerge into adults (see Figure 2.1). Female mosquitoes then feed on human or animal blood to provide protein for their eggs. After biting, female mosquitoes rest while their eggs develop. Once eggs are fully developed, the females oviposit and then proceed to find another blood meal thus completing the mosquito feeding cycle (Chitnis et al., 2008a).
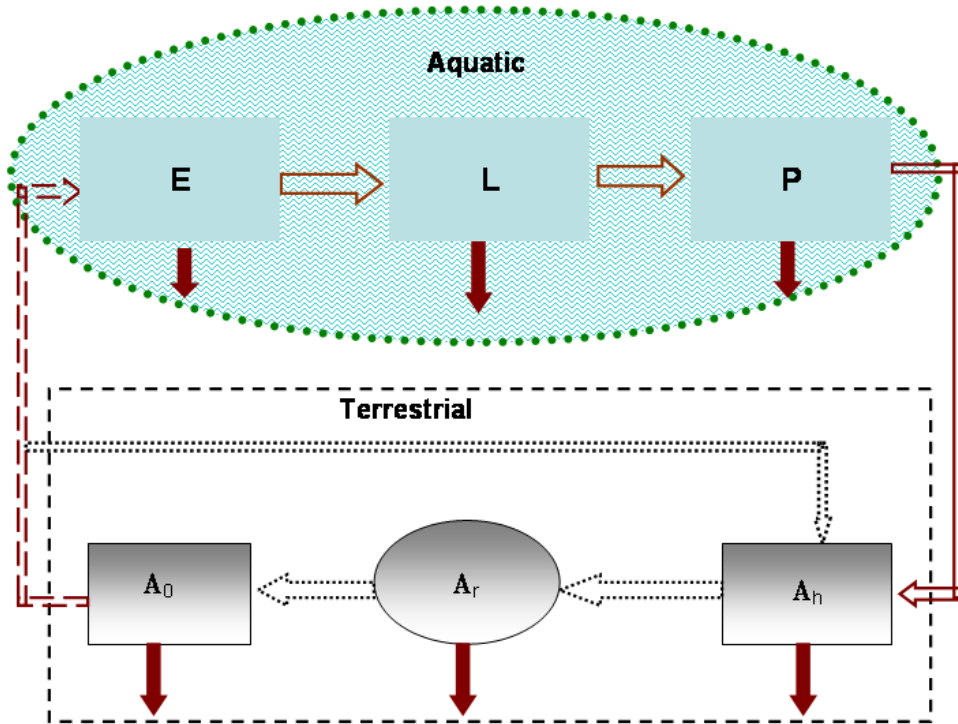
Figure 2.1: Schematic representation of *Anopheles* mosquito life cycle and feeding cycle. Model states are Eggs(E), Larvae(L), Pupae(P), host seeking adults(A_h), resting adults(A_r), and oviposition site searching adults(A_o).

Ignoring the effects of hibernation and breaks in the reproductive cycle, and assuming that eggs deposited at breeding sites proceed through development immediately (Service, 2004), we consider six compartments of the mosquito life cycle: eggs (E), larval (L), pupal (P), host seeking adults (A_h), resting adults (A_r), and oviposition site seeking adults (A_o) (Figure 2.1). In contrast to other models (Li, 2011), we distinguish all of these stages because interventions may be applied to any one (or more) of them. Since only female mosquitoes are involved in the transmission of vector-borne diseases, this model ignores males. The six subgroups have different mortality and progression rates. Each subgroup is affected by three processes: increase due to recruitment, decrease due to mortality, and development or progression of survivors into the next state. The parameter b is the average number of female eggs laid during an oviposition and ρ_{A_o} (day^{-1}) is the rate at which new eggs are oviposited (i.e. reproduction rate). Exit from the egg stage is either due to mortality, μ_E (day^{-1}), or hatching into larvae, ρ_E (day^{-1}). In the larval stage, individuals exit by

death or progress to pupal stage at a rate, ρ_L (day^{-1}). Assuming a stable environment, inter-competition for food and other resources for larvae may occur, leading to density-dependent mortality, $\mu_{L_2}L^2$ (day^{-1} mosquitoes^{-1}) or natural death at an intrinsic rate, μ_{L_1} (day^{-1}). Pupae die at a rate, μ_P (day^{-1}) and survivors progress and emerge as adults at rate ρ_P(day^{-1}). In the adult stage, host seeking mosquitoes die at a rate μ_{A_h} (day^{-1}). Those surviving this stage, and if they are successful in feeding, enter the resting stage at a rate ρ_{A_h} (day^{-1}). In the resting stage, mosquitoes die at a rate, μ_{A_r} (day^{-1}). Survivors progress to the oviposition site searching stage at a rate ρ_{A_r} (day^{-1}). Oviposition site searchers die at rate μ_{A_o} (day^{-1}) and after laying eggs return to the host seeking stage. These processes account for the dynamics of each subgroup over time. Although mosquitoes might require more than one blood meal to produce eggs (Beier, 1996), this model assumes the simple case where only one blood meal is enough for eggs to mature. Throughout this work, we use the words oviposition sites and breeding sites interchangeably.

From the description above, we develop the following system of differential equations to describe mosquito dynamics without movement:

$$
\begin{aligned}
\frac{dE}{dt} &= b\rho_{A_o}A_o - (\mu_E + \rho_E)\,E, \\
\frac{dL}{dt} &= \rho_E E - (\mu_{L_1} + \mu_{L_2}L + \rho_L)\,L, \\
\frac{dP}{dt} &= \rho_L L - (\mu_P + \rho_P)\,P \\
\frac{dA_h}{dt} &= \rho_P P + \rho_{A_o}A_o - (\mu_{A_h} + \rho_{A_h})\,A_h, \\
\frac{dA_r}{dt} &= \rho_{A_h}A_h - (\mu_{A_r} + \rho_{A_r})\,A_r, \\
\frac{dA_o}{dt} &= \rho_{A_r}A_r - (\mu_{A_o} + \rho_{A_o})\,A_o,
\end{aligned}
\tag{2.1}
$$

with initial conditions $E(0)$, $L(0)$, $P(0)$, $A_h(0)$, $A_r(0)$, and $A_o(0)$. Mosquito survival in each stage and the progression period from one stage to the next are assumed to be exponentially distributed. The definitions of state variables and the associated parameters are given in Tables 2.1 and 2.2 respectively.

Since the system in Eq. (2.1) monitors populations in each stage of mosquito

Table 2.1: State variable definitions

Variable	Description
E	density of eggs
L	density of larvae
P	density of pupae
A_h	density of mosquitoes searching for hosts
A_r	density of resting mosquitoes
A_o	density of mosquitoes searching for oviposition sites

development and because all model parameters (Table 2.2) are positive, there exists a region $\mathbb{D}$ such that

$$
\mathbb{D} = \left\{ \begin{pmatrix} E \\ L \\ P \\ A_h \\ A_r \\ A_o \end{pmatrix} \in \mathbb{R}^6 \;\middle|\; \begin{array}{l} E \geq 0, \\ L \geq 0, \\ P \geq 0, \\ A_h \geq 0, \\ A_r \geq 0, \\ A_o \geq 0 \end{array} \right\}, \tag{2.2}
$$

where the model is mathematically and biologically meaningful and all solutions of the system (2.1) with non-negative initial data will remain non-negative in the feasible region $\mathbb{D}$ for all time $t \geq 0$. We use the notation X' to represent $\frac{dX}{dt}$ here and denote the boundary of $\mathbb{D}$ by $\partial\mathbb{D}$.

Table 2.2: Description and values of parameters of the model. All parameters are positive and time is measured in days. For the model with dispersal, these parameters are patch dependent

Parameter	Description	Units	Baseline	Range	Source
b	number of female eggs laid per oviposition	-	100	$50 - 300$	(Service, 2004)
ρ_E	egg hatching rate into larvae	day^{-1}	0.50	$0.33 - 1.0$	(Service, 2004; Yaro et al., 2006)
ρ_L	rate at which larvae develop into pupae	day^{-1}	0.14	$0.08 - 0.17$	(Service, 2004; Gething et al., 2011b)
ρ_P	rate at which pupae develop into adult/emergence rate	day^{-1}	0.50	$0.33 - 1.0$	(Service, 2004; Holsetein, 1954)
μ_E	egg mortality rate	day^{-1}	0.56	$0.32 - 0.80$	(Okogun, 2005)
μ_{L_1}	density-independent larvae mortality rate	day^{-1}	0.44	$0.30 - 0.58$	(Okogun, 2005)
μ_{L_2}	density-dependent larvae mortality rate	day^{-1} mosq^{-1}	0.05	$0.0 - 1.0$	Variable
μ_P	pupae mortality rate	day^{-1}	0.37	$0.22 - 0.52$	(Okogun, 2005)
ρ_{A_h}	rate at which host seeking mosquitoes enter the resting state	day^{-1}	0.46	$0.322 - 0.598$	(Chitnis et al., 2008b), Estimated
ρ_{A_r}	rate at which resting mosquitoes enter oviposition site searching state	day^{-1}	0.43	$0.30 - 0.56$	(Chitnis et al., 2008b)
ρ_{A_o}	oviposition rate	day^{-1}	3.0	$3.0 - 4.0$	(Chitnis et al., 2008b)
μ_{A_h}	mortality rate of mosquitoes of searching for hosts	day^{-1}	0.18	$0.125 - 0.233$	(Chitnis et al., 2008b), Estimated
μ_{A_r}	mortality rate of resting mosquitoes	day^{-1}	0.0043	$0.0034 - 0.01$	(Chitnis et al., 2008b)
μ_{A_o}	mortality rate of mosquitoes searching for oviposition sites	day^{-1}	0.41	$0.41 - 0.56$	(Chitnis et al., 2008b)

Theorem 2.3.1. *If the initial conditions of system* (2.1) *lie in region* $\mathbb{D}$, *then there exists a unique solution for* (2.1), $E(t)$, $L(t)$, $P(t)$, $A_h(t)$, $A_r(t)$, *and* $A_o(t)$ *that remains in* $\mathbb{D}$ *for all time* $t \geq 0$.

Proof. The right hand side of the system (2.1) is continuous with continuous partial derivatives in $\mathbb{D}$, therefore (2.1) has a unique solution that exists for all time. It remains to be shown that $\mathbb{D}$ is forward-invariant. We see from system (2.1) that if $E = 0$, then $E' = b\rho_{A_o}A_o \geq 0$; if $L = 0$, then $L' \geq 0$; if $P = 0$, then $P' \geq 0$; if $A_h = 0$, then $A'_h \geq 0$; if $A_r = 0$, then $A'_r \geq 0$; and if $A_o = 0$, then $A'_o \geq 0$. Therefore all solutions of the system of equations (Eq. (2.1)) are contained in the region $\mathbb{D}$. $\square$

2.4 Analytical results of the basic model without mosquito dispersal

2.4.1 Existence of Equilibrium points

This section presents existence and stability results of the model (Eq. (2.1)) of the steady states. An equilibrium point of a given a system of equations ($\dot{\mathbf{X}}(t)$) (where $\mathbf{X}$ is a vector composed by state variables) is a steady state solution, where $\mathbf{X}(t) = \mathbf{X}^*$ for all t.

Proposition 2.4.1. *The model in* (2.1) *has exactly one equilibrium point on* $\partial\mathbb{D}$ *given by* $P_0 = (0, 0, 0, 0, 0, 0)$. *We label* P_0 *the mosquito-free equilibrium point.*

Proof. Substituting P_o into the right hand side of (2.1) shows that all derivatives are zero so P_o is an equilibrium point of (2.1). Setting any of E, L, P, A_h, A_r, or A_o equal to zero, we see that all other remaining state variables must also be equal to zero for the system to be at equilibrium. Therefore, P_o is the only equilibrium point on $\partial\mathbb{D}$. $\square$

Similar to White et al. (White et al., 2011), we define the population reproduction number, R_0, as the expected number of female mosquitoes produced by a single female mosquito in her life time in the absence of density-dependence.

In (van den Driessche and Watmough, 2002), a method for computing the reproduction number for epidemic models was developed. However, it can equivalently be used in ecological models where new births are treated as new infections. We determine the mosquito population reproduction number for model (2.1) using the next-generation technique (van den Driessche and Watmough, 2002).

Defining x as a set of all state variables (E, L, P, A_h, A_r, A_o) in the model, then $x = (x_1, x_2, ..., x_i)^T$ for $i = 1, 2, ..., 6$. The system in (2.1) can be written in the form of $\frac{dx_i}{dt} = F_i(x) - V_i(x)$, where F_i is the rate of new recruitment (birth of eggs) in a compartment, $V_i = V_i^- - V_i^+$, with V_i^+ being the rate of transfer of mosquitoes into a compartment and V_i^- is the rate of transfer of mosquitoes out of the compartment. For this model, F, and V are given by:

$$F = \begin{bmatrix} b\rho_{A_o} A_o \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \text{ and } V = \begin{bmatrix} (\mu_E + \rho_E)E \\ (\mu_{L_1} + \rho_L)L + \mu_{L_2}L^2 - \rho_E E \\ (\mu_P + \rho_P)P - \rho_L L \\ (\mu_{A_h} + \rho_{A_h})A_h - \rho_P P - \rho_{A_o} A_o \\ (\mu_{A_r} + \rho_{A_r})A_r - \rho_{A_h} A_h \\ (\mu_{A_o} + \rho_{A_o})A_o - \rho_{A_r} A_r \end{bmatrix}. \text{ To obtain the}$$

next generation operator, $\mathbf{F}\mathbf{V}^{-1}$, we calculate $\mathbf{F_{ij}} = \left.\frac{\partial F_i}{\partial x_j}\right|_{P_0}$ and $\mathbf{V_{ij}} = \left.\frac{\partial V_i}{\partial x_j}\right|_{P_0}$ to obtain

$$\mathbf{F} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & b\rho_{A_o} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \tag{2.3}$$

and

$$
\mathbf{V} =
\begin{bmatrix}
(\mu_E + \rho_E) & 0 & 0 & 0 & 0 & 0 \\
-\rho_E & (\mu_{L_1} + \rho_L) & 0 & 0 & 0 & 0 \\
0 & -\rho_L & (\mu_P + \rho_P) & 0 & 0 & 0 \\
0 & 0 & -\rho_P & (\mu_{A_h} + \rho_{A_h}) & 0 & -\rho_{A_o} \\
0 & 0 & 0 & -\rho_{A_h} & (\mu_{A_r} + \rho_{A_r}) & 0 \\
0 & 0 & 0 & 0 & -\rho_{A_r} & (\mu_{A_r} + \rho_{A_r})
\end{bmatrix}
\tag{2.4}
$$

The population reproduction number, R_0, is the spectral radius of the next generation operator, $\rho(\mathbf{F}\mathbf{V}^{-1})$. This value is given by

$$
R_o = \frac{b \prod\limits_{j} \left(\dfrac{\rho_j}{\mu_j + \rho_j} \right)}{1 - \prod\limits_{A_i} \left(\dfrac{\rho_{A_i}}{\mu_{A_i} + \rho_{A_i}} \right)}.
\tag{2.5}
$$

where $j = E, L, P, A_h, A_r, A_o$ and $i = h, r$, and o. $\frac{\rho_j}{\mu_j + \rho_j}$ is the probability that a mosquito in stage j will survive to the next stage. The value $\prod\limits_{A_i} \left(\frac{\rho_{A_i}}{\mu_{A_i} + \rho_{A_i}} \right) \in (0,1)$ for all i is the probability that an adult mosquito survives the feeding cycle. Although density-dependent mortality of larvae affects mosquito population, R_0 does not depend on density-dependent mortality of larvae.

Theorem 2.4.2. *The system of equations* (2.1) *has a persistent positive equilibrium*

solution $Pe = (E^*, L^*, P^*, A_h^*, A_r^*, A_o^*)$, *with its components given by*

$$
\begin{aligned}
E^* &= \frac{b\rho_{A_o} A_o^*}{\mu_E + \rho_E}, \\
L^* &= \frac{(\mu_{L_1} + \rho_L)(R_o - 1)}{\mu_{L_2}}, \\
P^* &= \frac{\rho_L L^*}{\mu_P + \rho_P}, \\
A_h^* &= \frac{\rho_P P^* R_0}{(\mu_{A_h} + \rho_{A_h}) B_1}, \\
A_r^* &= \frac{\rho_{A_h} A_h^*}{\mu_{A_r} + \rho_{A_r}}, \\
A_o^* &= \frac{\rho_{A_r} A_r^*}{\mu_{A_o} + \rho_{A_o}},
\end{aligned}
\tag{2.6}
$$

with R_0 given in Eq.(2.5) and $B_1 = b \prod_j \left(\dfrac{\rho_j}{\mu_j + \rho_j} \right)$ for $j = E, L, P, A_h, A_r, A_o$, which exist in the interior of $\mathbb{D}$ if $R_0 > 1$.

Proof. Substituting $P_e = (E^*, L^*, P^*, A_h^*, A_r^*, A_o^*)$ into (2.1) shows that P_e is an equilibrium point of (2.1). If $R_o > 1$, we see that all components P_e are positive. Thus, P_e exist in the interior of $\mathbb{D}$ if $R_o > 1$. $\square$

2.4.2   Stability of the equilibrium points

Theorem 2.4.3. *The mosquito-free equilibrium is locally asymptotically stable when $R_o < 1$ and unstable otherwise.*

Proof. Let the new births in the ecological model (2.1) be equivalent to new infections in the epidemic models studied in van den Driessche and Watmough (van den Driessche and Watmough, 2002). The matrices $F(x), V(x)^+$, and $V(x)^-$ satisfy the assumptions $A(1) - A(5)$ (van den Driessche and Watmough, 2002). Thus, this theorem is a straightforward application of Theorem 2 given in (van den Driessche and Watmough, 2002). $\square$

Theorem 2.4.4. *The persistent equilibrium is locally asymptotically stable whenever $R_o > 1$ and unstable when $R_o < 1$. When $R_o = 1$, $P_e = P_o$*

Proof. Let J_{P_e} be the Jacobian matrix of system (2.1) at the mosquito persistent

equilibrium given by

$$
J_{P_e} =
\begin{bmatrix}
-(\mu_E + \rho_E) & 0 & 0 & 0 & 0 & b\rho_{A_o} \\
\rho_E & -A_1 & 0 & 0 & 0 & 0 \\
0 & \rho_L & -(\mu_P + \rho_P) & 0 & 0 & 0 \\
0 & 0 & \rho_P & -(\mu_{A_h} + \rho_{A_h}) & 0 & \rho_{A_o} \\
0 & 0 & 0 & \rho_{A_h} & -(\mu_{A_r} + \rho_{A_r}) & 0 \\
0 & 0 & 0 & 0 & \rho_{A_r} & -A_2)
\end{bmatrix}
\tag{2.7}
$$

where $A_1 = (\mu_{L_1} + \rho_L) - \Phi$, $A_2 = (\mu_{A_r} + \rho_{A_r}$, and $\Phi = 2(\mu_{L_1} + \rho_L)(R_o - 1)$. To obtain the eigenvalues of J_{P_e}, we solve $\det(J_{P_e} - \lambda I) = 0$. We use the concept of block matrices to compute this determinant. Let $J = J_{P_e} - \lambda I$ be a block matrix given by

$$
J =
\begin{bmatrix}
A & B \\
C & D
\end{bmatrix}
\tag{2.8}
$$

with the following components:

$$
A =
\begin{pmatrix}
-(\mu_E + \rho_E) - \lambda & 0 & 0 \\
\rho_E & -(\mu_{L_1} + \rho_L) - \Phi - \lambda & 0 \\
0 & \rho_L & -(\mu_P + \rho_P) - \lambda
\end{pmatrix},
$$

$$
B =
\begin{pmatrix}
0 & 0 & b\rho_{A_o} \\
0 & 0 & 0 \\
0 & 0 & 0
\end{pmatrix}, C =
\begin{pmatrix}
0 & 0 & \rho_P \\
0 & 0 & 0 \\
0 & 0 & 0
\end{pmatrix}, \text{ and}
$$

$$
D =
\begin{pmatrix}
-(\mu_{A_h} + \rho_{A_h}) - \lambda & 0 & \rho_{A_0} \\
\rho_{A_h} & -(\mu_{A_r} + \rho_{A_r}) - \lambda & 0 \\
0 & \rho_{A_r} & -(\mu_{A_0} + \rho_{A_0}) - \lambda
\end{pmatrix}. \text{ It follows}
$$

from the concepts of block matrices that $\det(J) = \det(AD - BC)$. But in this case, BC is a zero matrix leading to $\det(J_{P_e} - \lambda I) = \det(J) = \det(AD) = 0$. By solving the equation, we obtain three of the eigenvalues given by $\lambda_1 =$

$-(\mu_E + \rho_E)$, $\lambda_2 = -(\mu_{L_1} + \rho_L) - \Phi$, and $\lambda_3 = -(\mu_P + \rho_P)$. When $R_o > 1$, $\lambda_2 < 0$, which forms the necessary condition for a stable equilibrium point. When $R_o < 1$, $\lambda_2 > 0$, P_e is unstable. The remaining three eigenvalues are given by the roots of the following equation:

$$a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{2.9}$$

where

$$
\begin{aligned}
a_0 &= 1, \\
a_1 &= (\mu_{A_h} + \rho_{A_h}) + (\mu_{A_r} + \rho_{A_r}) + (\mu_{A_o} + \rho_{A_o}), \\
a_2 &= (\mu_{A_h} + \rho_{A_h})(\mu_{A_r} + \rho_{A_r}) + (\mu_{A_h} + \rho_{A_h})(\mu_{A_o} + \rho_{A_o}) + (\mu_{A_r} + \rho_{A_r})(\mu_{A_o} + \rho_{A_o}), \\
a_3 &= (\mu_{A_h} + \rho_{A_h})(\mu_{A_r} + \rho_{A_r})(\mu_{A_o} + \rho_{A_o}) - \rho_{A_h}\rho_{A_r}\rho_{A_o} \\
&= (\mu_{A_h} + \rho_{A_h})(\mu_{A_r} + \rho_{A_r})(\mu_{A_o} + \rho_{A_o})\left(\frac{B_1}{R_o}\right),
\end{aligned}
\tag{2.10}
$$

where $B_1 = b\prod_j\left(\dfrac{\rho_j}{\mu_j + \rho_j}\right)$ for $j = E, L, P, A_h, A_r, A_o$. It remains to be shown that when $R_o > 1$, the eigenvalues have negative real parts. The roots of the polynomial in Eq.(2.9) are difficult to calculate explicitly, but it is clear from (2.9) that $a_0 > 0$, $a_1 > 0$, $a_2 > 0$, and $a_3 > 0$ always. By the Routh-Hurwitz criteria (Meinsma, 1995) we need to show that $a_1a_2 - a_3 > 0$ for all roots of Eq.(2.9) to have negative real parts.

$$
\begin{aligned}
a_1 a_2 - a_3 &= \left[(\mu_{A_h} + \rho_{A_h}) + (\mu_{A_r} + \rho_{A_r}) + (\mu_{A_o} + \rho_{A_o})\right]\left[(\mu_{A_h} + \rho_{A_h})(\mu_{A_r} + \rho_{A_r})\right. \\
&\quad + (\mu_{A_h} + \rho_{A_h})(\mu_{A_o} + \rho_{A_o}) + (\mu_{A_r} + \rho_{A_r})(\mu_{A_o} + \rho_{A_o})\right] \\
&\quad - (\mu_{A_h} + \rho_{A_h})(\mu_{A_r} + \rho_{A_r})(\mu_{A_o} + \rho_{A_o}) - \rho_{A_h}\rho_{A_r}\rho_{A_o} \\
&= (\mu_{A_h} + \rho_{A_h})^2[(\mu_{A_r} + \rho_{A_r}) + (\mu_{A_o} + \rho_{A_o})] \\
&\quad + (\mu_{A_r} + \rho_{A_r})^2[(\mu_{A_h} + \rho_{A_h}) + (\mu_{A_o} + \rho_{A_o})] \\
&\quad + (\mu_{A_o} + \rho_{A_o})^2[(\mu_{A_h} + \rho_{A_h}) + (\mu_{A_r} + \rho_{A_r})] \\
&\quad + 2(\mu_{A_h} + \rho_{A_h})(\mu_{A_r} + \rho_{A_r})(\mu_{A_o} + \rho_{A_o}) - \rho_{A_h}\rho_{A_r}\rho_{A_o} \\
&= (\mu_{A_h} + \rho_{A_h})^2[(\mu_{A_r} + \rho_{A_r}) + (\mu_{A_o} + \rho_{A_o})] \\
&\quad + (\mu_{A_r} + \rho_{A_r})^2[(\mu_{A_h} + \rho_{A_h}) + (\mu_{A_o} + \rho_{A_o})] \\
&\quad + (\mu_{A_o} + \rho_{A_o})^2[(\mu_{A_h} + \rho_{A_h}) + (\mu_{A_r} + \rho_{A_r})] \\
&\quad + (\mu_{A_h} + \rho_{A_h})(\mu_{A_r} + \rho_{A_r})(\mu_{A_o} + \rho_{A_o})\left[1 + \frac{B_1}{R_o}\right].
\end{aligned}
\tag{2.11}
$$

From (2.11) we see that $a_1 a_2 - a_3 > 0$ for all values of R_o. Thus, the roots of (2.9) have negative real parts. Therefore, when $R_o > 1$, the six eigenvalues have negative real parts and the persistent equilibrium point is locally asymptotically stable. Where, as when $R_o < 1$, $\lambda_2 > 0$. The persistent equilibrium point is unstable. Substituting $R_o = 1$ in (2.6) shows that at $R_o = 1$, $P_e = P_o$. $\square$

2.4.3   Sensitivity Analysis of R_0

Sensitivity analysis determines the effects of parameters on model outcomes (Cariboni et al., 2007). To carry out local sensitivity analysis, we use a simple approach to compute the sensitivity index, which is a partial derivative of the output variable with respect to the input parameters (Cariboni et al., 2007; Chitnis et al., 2008a).

For the base reproduction number, R_0, and p_i, an input parameter, the sensitivity index can be computed as $\partial R_0 / \partial p_i$. The normalized sensitivity index, $\Omega_{p_i}^{R_0}$, of R_o, with respect to parameter p_i at a fixed value, p^0 (Cariboni et al., 2007;

Chitnis et al., 2008a) is

$$\Omega_{p_i}^{R_0} = \frac{\partial R_0}{\partial p_i} \times \frac{p_i}{R_0}\bigg|_{p_i=p^0}. \tag{2.12}$$

Using the parameter values presented in Table 2.2, we compute the sensitivity indices using Eq. (2.12). In figure 2.2A we show the impact of each parameter on the reproduction number. The number of female eggs laid per oviposition, b, is the most important parameter in the model ($\Omega_b^{R_o} = 1.00$), indicating a maximum impact on model outcomes. Increasing or decreasing b by 10%, for example, can increase or decrease R_o by 10%. The parameters with the next highest sensitivity indices are ρ_L and μ_{L_1}. If the development rate from larval to pupae stage (ρ_L) is increased, we observe a decreased risk of dying of larvae (μ_{L_1}) and vice versa. A 10% increase (or decrease) in ρ_L, for example, increases (or decreases) R_o by 7.6%, while a similar increase (or decrease) of μ_{L_1} in R_o decreases (or increases) R_o by 7.6%. Other important parameters with higher indices are ρ_{A_h} and μ_{A_h}. Similar to ρ_L and μ_{L_1}, these parameters indicate an equal but opposite impact on R_o. Increasing ρ_{A_h} can lead to an increase in R_o. Increasing μ_{A_h}, however would decrease R_o.

Local sensitivity analysis shows the effect of one parameter while all others are kept constant. Global sensitivity analysis estimates the effect of one parameter on the output, while allowing all other parameters to vary, enabling the identification of interactions (Cariboni et al., 2007). Here, we used SaSAT software (Hoare et al., 2008) to carry out the global sensitivity analysis of the mosquito population reproduction number. The Latin Hypercube Sampling Method (LHS), a type of stratified Monte Carlo sampling (Blower and Dowlatabadi, 1994), was used to sample the input parameters using the parameter value ranges provided in Table 2.2. Due to the absence of data on the distribution function of the parameters used in our model, a uniform distribution for all input parameters was chosen. The sets of input parameter values sampled using the LHS method were used to run 5000 simulations. To identify input parameters with the greatest influence on R_o, we computed the Partial Rank
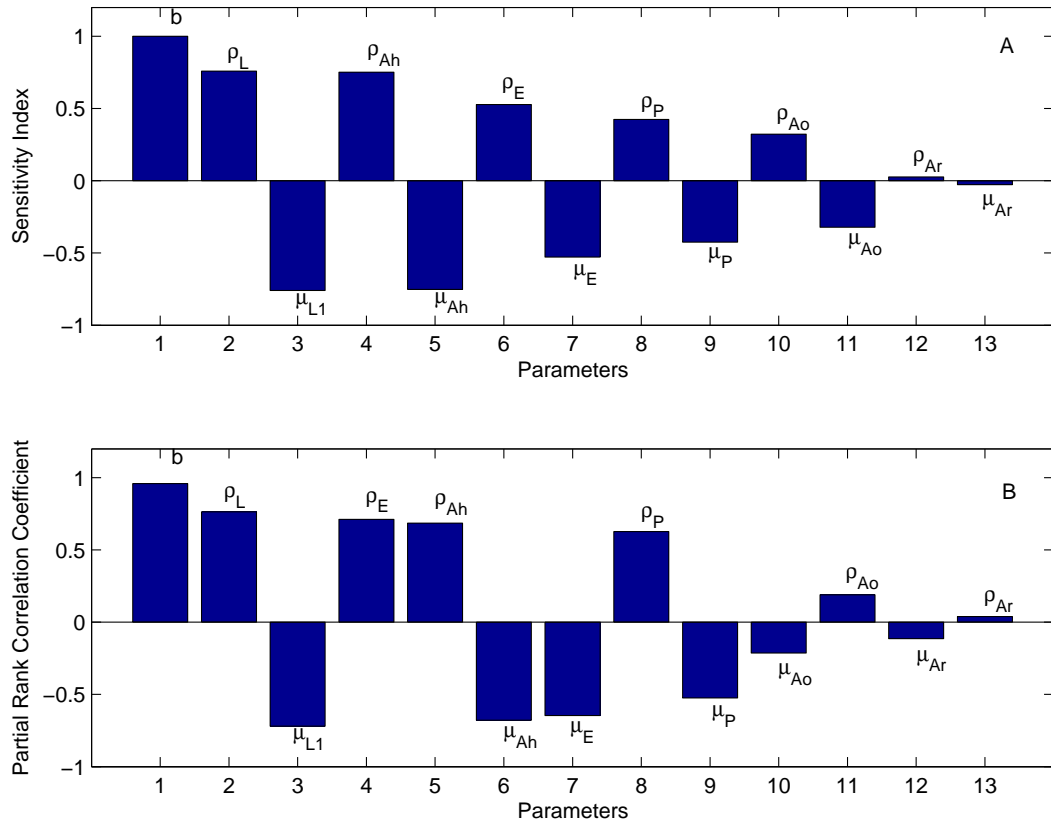
Figure 2.2: Sensitivity Analysis of R_o. A: Local sensitivity analysis. Normalized sensitivity indices of R_0 to parameters evaluated at the baseline parameter values given in Table 2.2. B: Global sensitivity analysis. Partial Rank correlation coefficients showing the ranking of parameter influence on R_0.

Correlation Coefficients between the input parameters and our output variable using the SaSAT software.

In figure 2.2B, we present the results of the partial rank correlation coefficients for each of the parameters. Again, results show that birth parameter, b, has the highest influence on the mosquito population reproduction number. Next to b are the parameters associated with the larvae stage, followed by the egg development rate and the parameters related to the host seeking stage. Parameters related to the resting stage of the mosquitoes show the lowest influence on R_o.

In general, we find that mortality rates are negatively correlated to the population reproduction number, while development rates are positively correlated. Because the population reproduction number gives information on the stability of the equilibrium point and the persistence of the mosquito population,

increasing parameters that are positively correlated to the reproduction number would result in the persistence of the mosquito population.

2.5 Modelling movement

2.5.1 Continuous space model

Traditional methods of modelling diffusion have involved the use of the heat equation in which the domain is assumed to be continuous. If we assume that the movement of individual mosquitoes is similar to that of Brownian motion, then we can define the rate of change of mosquito density at time t at location (x, y), $M(x, y, t)$ as

$$\frac{\partial M(x, y, t)}{\partial t} = D^* \nabla^2 M(x, y, t) \tag{2.13}$$

where $(x, y) \in \mathbb{R}^2$, ∇ represents the partial derivative in 2-dimensional space and $\nabla^2 M = \partial^2 M / \partial x^2 + \partial^2 M / \partial y^2$, and D^* is the diffusion coefficient (metres^2 time^{-1}). We assume that the initial conditions are given by $M(x, y, 0) = K\delta(x, y)$, where $\delta(x, y)$ is the 2-dimension Dirac delta function, $\delta(x, y) = 0$ for $x^2 + y^2 \neq 0$ and $\int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \delta(x, y) dx dy = 1$. Therefore, $\int_{-\infty}^{\infty} \int_{-\infty}^{\infty} M(x, y, 0) dx dy = K$ represents an initial condition of K mosquitoes released at the origin. The standard solution to the heat equation (2.13) is given by:

$$M(x, y, t) = \frac{K}{4\pi D^* t} \exp\left[-\frac{(x^2 + y^2)}{4D^* t}\right] \tag{2.14}$$

for $t > 0$ and $(x, y) \in \mathbb{R}^2$. We convert our solution to polar coordinates with

$$x = r \cos\theta \text{ and } y = r \sin\theta, \text{ implying that } r = \sqrt{x^2 + y^2} \text{ and } dxdy = rdrd\theta \tag{2.15}$$

Using (2.14) and (2.15) we obtain

$$M(r, \theta, t) = \frac{K}{4\pi D^* t} \exp\left[-\frac{r^2}{4D^* t}\right] \tag{2.16}$$

for $r \geq 0$ is the radial distance measured from centre. The mosquito density at a given distance, r from the centre is obtained from $\bar{M}(r, t) = \int_0^{2\pi} M(r, \theta, t) r d\theta$, which gives

$$\bar{M}(r, t) = \frac{Kr}{2D^* t} \exp\left[-\frac{r^2}{4D^* t}\right]. \tag{2.17}$$

Although partial differential equations (PDEs) are a good way of modelling dispersal (Dumont, Y; Dumont,Y and Dufourd, C), their analysis is usually limited to numerical simulations when modelling environmental heterogeneity. Discrete approaches offer a better and simpler way of modelling heterogeneity (Arino et al., 2005, 2007; Jin and Wang, 2005), specifically when resources such as hosts and breeding sites are variable across regions. In the next section, we develop a mosquito dispersal model which considers discrete space and describes how we model heterogeneity in resources and its influence on mosquito dispersal.

2.5.2 Discrete space model spatial structure

We let Ξ be the set of all patches and ξ be any patch in Ξ. We construct the model by dividing 2-dimensional space into a set of discrete hexagonal patches (Figure 2.3). We label the hexagonal grid with a coordinate system, (i, j), where $1 \leq i \leq n$ and $1 \leq j \leq m$ represent the locations of the centre of the patches and $i, j \in \mathbb{N}$.

We define the neighbourhood, $N(i, j)$, (figure 2.3) of an index patch as an ordered set of six patches given by

$$N(i, j) = \{(i, j + 1), (i, j - 1), (i + 1, j), (i - 1, j), (i - 1, j + 1), (i - 1, j - 1)\} \tag{2.18}$$
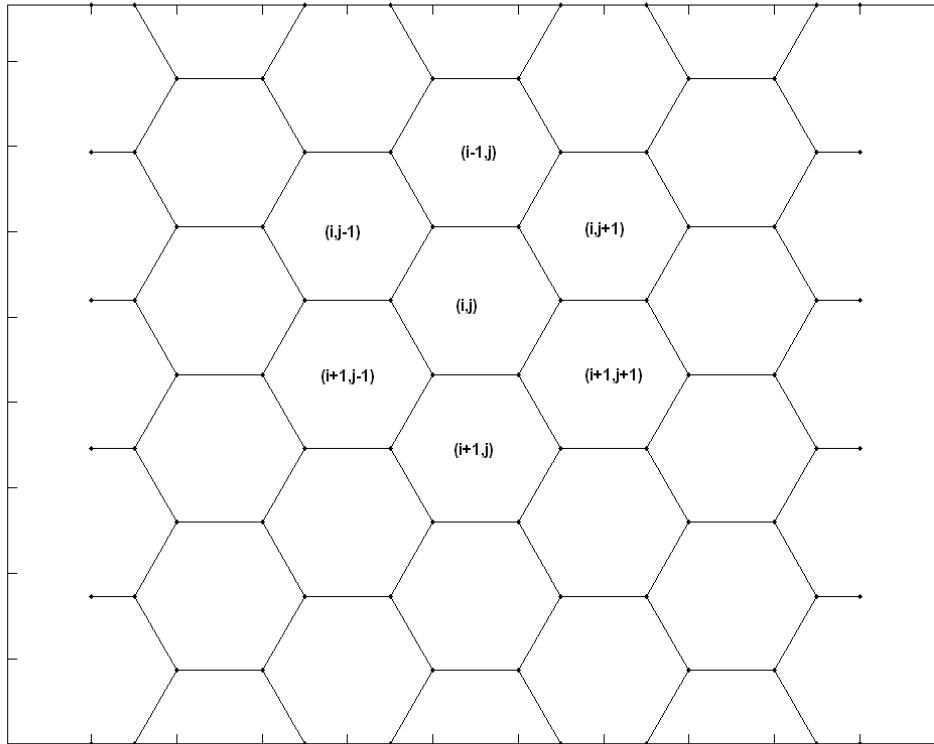
Figure 2.3: A Schematic representation of a landscape division into hexagonal patches. Model equations (Eq. (2.36) apply in each patch.

when j is even or

$$N(i,j) = \{(i,j+1), (i,j-1), (i+1,j-1), (i-1,j), (i+1,j+1), (i+1,j)\} \tag{2.19}$$

when j is odd. We assume periodic boundary conditions so that patch $(i,0) = (i,m)$ and $(0,j) = (n,j)$.

2.5.3   Dispersal in a homogeneous landscape

Mosquitoes disperse while searching for hosts or oviposition sites, causing a link between patches. A given fraction of adults searching for hosts and a fraction of adults searching for oviposition sites leave their original or current patches of residence, while others stay behind. We assume that dispersing

adults move from their current patch to enter any of the other six nearest neighbouring patches (Figure 2.3) and that long-range dispersal is achieved through a repeated single patch movement. That is, patch jumping is precluded.

Mosquitoes can detect host odour (Knols and Meijerink, 1997; Mwandawiro et al., 2000), but it is unclear whether they have the learning capacity they would need to enable them to return to particular hosts or breeding sites (Alonso and Schuck-Paim, 2006). We make the simplifying assumption that mosquitoes do not preferentially return to their previous locations, so that movement is a Markov process. In the case where all patches have similar characteristics (i.e. a homogeneous landscape), the mosquitoes disperse equally to each of the six neighbouring patches surrounding the current position (Figure 2.3) and the dispersal parameter is the same for all patches. If we let $D > 0$ (per time) be the rate at which mosquitoes move from one patch to a neighbouring patch, we can compute its value from:

$$D = \frac{D^*}{A} \tag{2.20}$$

where D^* is the diffusion coefficient in the absence of all other factors affecting flight. The area A (in metres^2) of a hexagon is given by:

$$A = \frac{\sqrt{3}L^2}{2}, \tag{2.21}$$

with L (in metres) being the patch size defined as the measurement from the centre of one patch to the centre of the neighbouring patch.

We let $M_{(i,j)}$ be the number of free flying mosquitoes in patch (i, j). We let mosquitoes move from patch (i, j) (a source or index patch) to a neighbouring patch $\xi \in N(i, j)$. We define the movement rate from patch (i, j) to a neighbouring patch ξ to be $D_{(i,j)/\xi}$ and the movement rate from the neighbouring patch to the index patch to be $D_{\xi/(i,j)}$. For a homogeneous environment,

$D_{(i,j)/\xi} = D_{\xi/(i,j)} = D$. Assuming that mosquitoes do not reproduce or die during dispersal, the dynamics of free-flying mosquitoes in any patch (i, j) can be represented as

$$\frac{dM_{(i,j)}}{dt} = \sum_{\xi \in N(i,j)} DM_\xi - \sum_{\xi \in N(i,j)} DM_{(i,j)} \tag{2.22}$$

with initial conditions $M_{(i,j)}(0)$. The first term represents mosquitoes moving into the patch and the second term represents mosquitoes moving out of a patch. The movement model in (2.22) is biologically and mathematically meaningful in the domain $\Omega = M_{(i,j)} \in \mathbb{R}^{nm}$, such that $M_{(i,j)} \geq 0$.

Theorem 2.5.1. *If initial conditions lie in region Ω, the movement equation (2.22) has a unique solution that exists and remains in Ω for all time $t \geq 0$.*

Proof. The right hand side of Eq. (2.22) is continuous with a continuous partial derivative in region Ω and therefore (2.22) has a unique solution. We then show that Ω is forward-invariant. If $M_{(i,j)} = 0$, then $M'_{(i,j)} = \sum_{\xi \in N(i,j)} DM_\xi \geq 0$ for all (i, j). Thus, the solution to Eq. (2.22) is enclosed in Ω and a unique solution exists for all t. $\square$

2.5.4 Dispersal in a heterogeneous landscape

Differences in the distribution of resources creates heterogeneity on the grid, since patches may have different degrees of attractiveness to mosquitoes. In this section, we describe how heterogeneity and differences in patch attractiveness to mosquitoes during movement is incorporated.

Dispersal with heterogeneity in host availability

The number of hosts is allowed to differ between patches across the grid, introducing heterogeneity. Because of the neighbour to neighbour dispersal nature of this model, movement of mosquitoes from one patch to other patches is only

affected by the patches bordering each neighbourhood. We therefore calculate and use the proportion of hosts in each set of seven patches relative to each other, using the number of hosts on the particular patch and on its six neighbours. However, we assume that host distribution across patches is constant over time.

We recall that Ξ is a set of patches on the grid, ξ is any patch in Ξ, and $N(i, j)$ is a set of neighbours given by (2.18) and (2.19) of an index patch (i, j). We also let $c_{i,j}$ be a set of seven patches sharing boundaries, that is, patch (i, j) and its 6 neighbours. $c_{i',j'}$ is a set of seven patches sharing boundaries made up of patch ξ' and its six neighbours, of which one is patch (i, j). For easy reference, we use the following notations:

- H^{ξ} is the population of hosts in patch ξ

- H_T^{ij} is the total population of hosts in $c_{i,j}$

- $H^{\xi'}$ is the population of hosts in patch ξ'

- $H_T^{i'j'}$ is the total population of hosts in $c_{i',j'}$

- $\bar{H}_{\xi}^{ij}$ is the proportion of hosts in patch $\xi \in c_{i,j}$ out of all hosts in $c_{i,j}$

- $\bar{H}_{\xi'}^{ij}$ is the proportion of hosts in patch $\xi' \in c_{i,j}$ out of all hosts in $c_{i,j}$

- $\bar{H}_{\xi}^{i'j'}$ is the proportion of hosts in patch $\xi \in c_{i',j'}$ out of all hosts in $c_{i',j'}$

- $\bar{H}_{\xi'}^{i'j'}$ is the proportion of hosts in patch $\xi' \in c_{i',j'}$ out of all hosts in $c_{i',j'}$

We calculate the total number of hosts over these seven patches sharing boundaries from

$$H_T^{ij} = \sum_{\xi \in c_{i,j}} H^{\xi}, \tag{2.23}$$

and the proportion of hosts in each $\xi \in c_{i,j}$ from

$$\bar{H}_{\xi}^{ij} = \frac{H^{\xi}}{H_T^{ij}} \tag{2.24}$$

with

$$\sum_{\xi \in c_{i,j}} \bar{H}^{ij}_{\xi} = 1 \qquad (2.25)$$
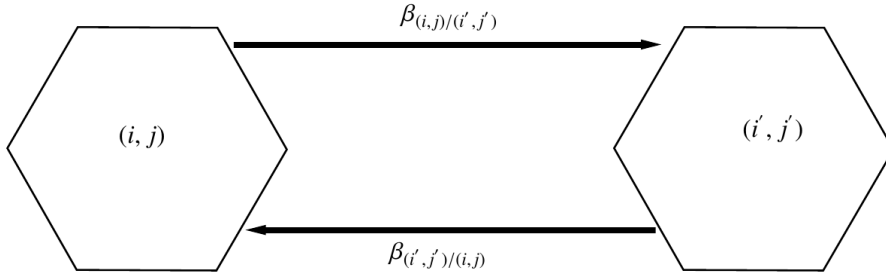
Figure 2.4: Diagrammatic representation of mosquito movement between an index patch (source patch (i, j)) and a neighbouring patch $((i', j') = \xi' \in N(i, j))$ where $N(i, j)$ is defined by Eqs. (2.18) and (2.19).

Mosquitoes are attracted to odours released by hosts (Costantini et al., 1998; Knols and Meijerink, 1997; Mwandawiro et al., 2000; Takken and Knols, 1999). This leads to mosquitoes being less likely to leave the patch if their current patch is a home to many hosts and likely to move out of the patch if there are few hosts. To mimic this phenomenon, we use a decreasing exponential function to model the movement rate. If (i, j) is a source patch and its neighbours (Figure 2.4), and if we take into account the availability of hosts in each of the patches contained in $c_{i,j}$, we can define the movement out of a patch i, j to a neighbour patch ξ' as

$$\beta^{H}_{(i,j)/\xi'} = D e^{-\lambda\left(\bar{H}^{ij}_{\xi} - \bar{H}^{ij}_{\xi'}\right)}. \qquad (2.26)$$

Here, λ is a constant parameter for the decay function and $\bar{H}^{ij}_{\xi'}$ is the proportion of hosts in patch ξ' contained in $c_{i,j}$, which is obtained from

$$\bar{H}^{ij}_{\xi'} = \frac{H^{\xi'}}{H^{ij}_{T}}. \qquad (2.27)$$

The function in Eq. (2.26) (its behaviour is shown in Figure 2.5) represents

different possible characteristics of two patches sharing boundaries as follows:

- If $\bar{H}^{ij}_{\xi} > \bar{H}^{ij}_{\xi'}$, then $0 < \beta^{H}_{(i,j)/\xi'} < D$. This condition establishes that the source patch (i,j) contains more hosts compared to patch ξ'. The patch is therefore more attractive to mosquitoes compared to its neighbour and will tend to retain mosquitoes; few mosquitoes will tend to move away from it.

- If $\bar{H}^{ij}_{\xi} = \bar{H}^{ij}_{\xi'}$, then $\beta^{H}_{(i,j)/\xi'} = D$. This implies that the two patches have equal attractiveness to mosquitoes.

- If $\bar{H}^{ij}_{\xi} < \bar{H}^{ij}_{\xi'}$, then $\beta^{H}_{(i,j)/\xi'} > D$. Here, patch (i,j) is less attractive to mosquitoes because it has fewer hosts compared to patch ξ'. The dispersal rate out of the patch is high as more mosquitoes will migrate out to patches that are more attractive.
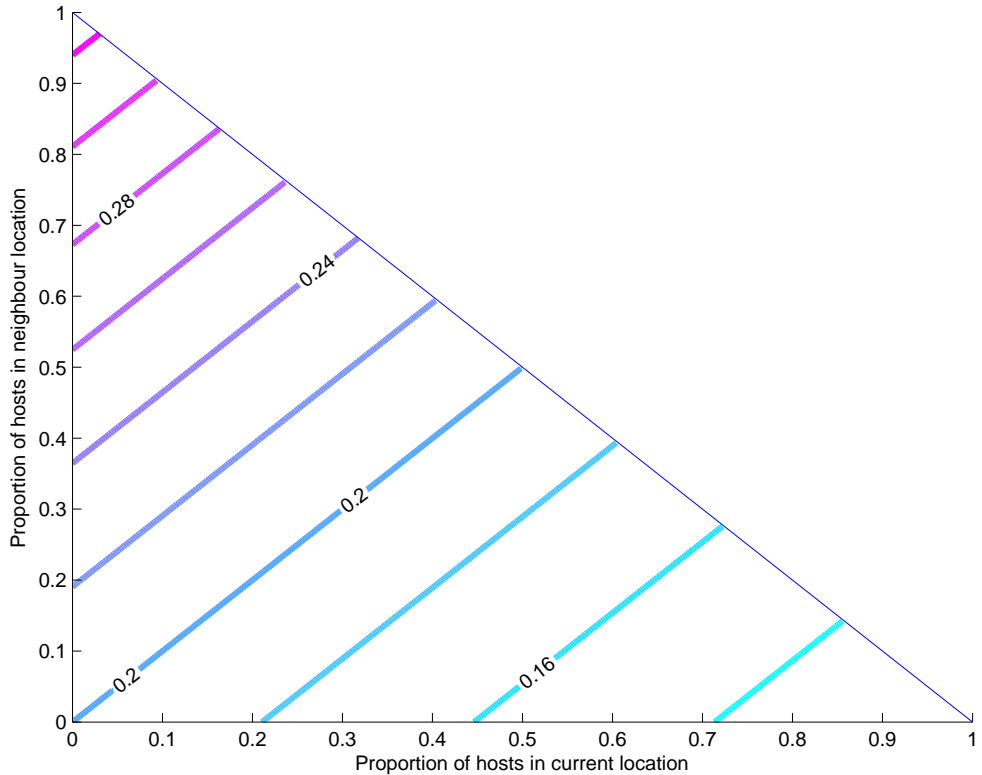
Figure 2.5: Behaviour of the dispersal function in Eq. (2.26) at $D = 0.2$, $\lambda = 0.5$, and $\bar{H} \in [0, 1]$.

Similarly, the movement of mosquitoes from patch ξ' to patch (i,j) (Figure 2.4), where both ξ' and (i,j) are contained in $c_{i,j}$, is modelled. In this respect, $H^{i'j'}_{T}$ is

calculated using a different set of neighbouring patches, $c_{i',j'}$. In other words, it is the total number of hosts in ξ' and its six neighbours, of which one of them is patch (i,j). We calculate it using

$$H_T^{i'j'} = \sum_{\xi \in c_{i',j'}} H^\xi. \tag{2.28}$$

Therefore, we model the movement rate from any neighbouring patch ξ' into patch (i,j) (as shown in Figure 2.4) using

$$\beta_{\xi'/(i,j)}^H = D e^{-\lambda\left(\bar{H}_{\xi'}^{i'j'} - \bar{H}_\xi^{i'j'}\right)} \tag{2.29}$$

where

$$\bar{H}_\xi^{i'j'} = \frac{H^\xi}{H_T^{i'j'}}, \tag{2.30}$$

and

$$\bar{H}_{\xi'}^{i'j'} = \frac{H^{\xi'}}{H_T^{i'j'}}. \tag{2.31}$$

In general, the movement rate from patches with relatively low attraction is higher compared to patches with higher attraction and vice versa. To summarise, we re-write the general movement model presented in Eq. (2.22) as

$$\frac{dA_{h(i,j)}}{dt} = \left(\sum_{\xi' \in N(i,j)} \beta_{\xi'/(i,j)}^H A_{h\xi'}\right) - \left(\sum_{\xi' \in N(i,j)} \beta_{(i,j)/\xi'}^H\right) A_{h(i,j)}, \tag{2.32}$$

to describe the dynamics of host seeking mosquitoes in the absence of new recruitment and deaths in any of the patches. Here, the dispersal rate takes into account the dependence of dispersal on hosts availability.

Dispersal with heterogeneity in oviposition site availability

Another form of heterogeneity is imposed by the availability of oviposition sites in an area. Mosquitoes searching for breeding sites for egg laying are attracted by the availability of breeding sites (Minakawa et al., 2002). We incorporate this in a manner similar to that for hosts.

If $B_{c_{i,j}}$ is the number of oviposition sites in a patch and $\bar{B}_{c_{i,j}}$ is the proportion of oviposition sites in a patch relative to its neighbours, the movement rate out of the index patch (i, j) is expressed as

$$\beta^B_{(i,j)/\xi'} = De^{-\lambda\left(\bar{B}^{ij}_\xi - \bar{B}^{ij}_{\xi'}\right)} \tag{2.33}$$

and the movement rate into the patch from neighbouring patches:

$$\beta^B_{\xi'/(i,j)} = De^{-\lambda\left(\bar{B}^{i'j'}_{\xi'} - \bar{B}^{i'j'}_\xi\right)} \tag{2.34}$$

Similarly, the movement rate of mosquitoes from a patch is higher if there are few breeding sites (B) in the patch. We represent the movement of mosquitoes searching for oviposition sites in the following equation

$$\frac{dA_{o(i,j)}}{dt} = \left(\sum_{\xi' \in N(i,j)} \beta^B_{\xi'/(i,j)} A_{o\xi'}\right) - \left(\sum_{\xi' \in N(i,j)} \beta^B_{(i,j)/\xi'}\right) A_{o(i,j)}. \tag{2.35}$$

Since the density of breeding sites is affected by seasonal variations, as temporal sites are created due to rainfall for example, their distribution changes over time. However, in this model, for simplicity, we consider only permanent breeding sites. So the initial distribution of breeding sites does not change over time.

2.5.5   Full dispersal model equations

In section 2.3, we studied the dynamics of mosquito populations in each stage of the mosquito life cycle within a single patch. We extend this model to incorporate dispersal processes. If we allow host seeking and oviposition site searching mosquitoes to move between patches, then we can combine the system of equations in Eq. (2.1) for patch (i, j) and the movement terms in Eq.(2.32) and (2.35) to form the following system of equations:

$$
\begin{aligned}
\frac{dE_{(i,j)}}{dt} &= b_{(i,j)}\psi^B_{(i,j)}\rho_{A_o(i,j)}A_{o(i,j)} - \left(\mu_{E(i,j)} + \rho_{E(i,j)}\right)E_{(i,j)} \\
\frac{dL_{(i,j)}}{dt} &= \rho_{E(i,j)}E_{(i,j)} - \left(\mu_{L_1(i,j)} + \mu_{L_2(i,j)}L_{(i,j)} + \rho_{L(i,j)}\right)L_{(i,j)} \\
\frac{dP_{(i,j)}}{dt} &= \rho_{L(i,j)}L_{(i,j)} - \left(\mu_{P(i,j)} + \rho_{P(i,j)}\right)P_{(i,j)} \\
\frac{dA_{h(i,j)}}{dt} &= \rho_{P(i,j)}P_{(i,j)} + \psi^B_{(i,j)}\rho_{A_o(i,j)}A_{o(i,j)} - \left(\mu_{A_{h(i,j)}} + \psi^H_{(i,j)}\rho_{A_{h(i,j)}}\right)A_{h(i,j)} \\
&\quad - \left(\sum_{\xi' \in N(i,j)} \beta^H_{(i,j)/\xi'}\right)A_{h(i,j)} + \left(\sum_{\xi' \in N(i,j)} \beta^H_{\xi'/(i,j)}A_{h\xi'}\right) \qquad (2.36) \\
\frac{dA_{r(i,j)}}{dt} &= \psi^H_{(i,j)}\rho_{A_{h(i,j)}}A_{h(i,j)} - \left(\mu_{A_{r(i,j)}} + \rho_{A_{r(i,j)}}\right)A_{r(i,j)} \\
\frac{dA_{o(i,j)}}{dt} &= \rho_{A_{r(i,j)}}A_{r(i,j)} - \left(\mu_{A_{o(i,j)}} + \psi^B_{(i,j)}\rho_{A_{o(i,j)}}\right)A_{o(i,j)} \\
&\quad - \left(\sum_{\xi' \in N(i,j)} \beta^B_{(i,j)/\xi'}\right)A_{o(i,j)} + \left(\sum_{\xi' \in N(i,j)} \beta^B_{\xi'/(i,j)}A_{o\xi'}\right)
\end{aligned}
$$

with initial conditions $E_{(i,j)}, L_{(i,j)}, P_{(i,j)}, A_{h(i,j)}, A_{r(i,j)}, A_{o(i,j)} \geq 0$ at time $t = 0$. Here, H and B represents hosts and breeding sites respectively. The state variables and some of the parameters carry the same meaning as in system (2.1) (see Tables 2.1 and 2.2). The individual equations in system (2.36) describe the evolution of eggs, larvae, pupae, host seeking, resting, and oviposition site searching mosquitoes in patch (i, j).

The progression from the oviposition site searching state, A_o, to the host seeking state, A_h. is possible if and only if oviposition site searching mosquitoes have laid eggs. We introduce a parameter $\psi^B_{(i,j)}$ defined by:

$$\psi^B_{(i,j)} = \begin{cases} 1 & \text{if } B_{(i,j)} > 0 \\ 0 & \text{if } B_{(i,j)} = 0, \end{cases} \tag{2.37}$$

to control this process, since laying eggs in a patch is possible only if the particular patch contains at least one breeding site. In patches where $B_{(i,j)} = 0$, the initial conditions for $E_{(i,j)}$, $L_{(i,j)}$, and $P_{(i,j)}$ are 0. Similarly, the progression from host seeking to the resting stage is possible if there are hosts in the patch (Killeen et al., 2001). As such, we define

$$\psi^H_{(i,j)} = \begin{cases} 1 & \text{if } H_{(i,j)} > 0 \\ 0 & \text{if } H_{(i,j)} = 0. \end{cases} \tag{2.38}$$

Patches without hosts have initial conditions $A_{r(i,j)} = 0$. All other parameters are patch dependent and their definitions are summarized in Tables 2.2 and 2.3.

The total number of mosquitoes in each stage at time t over all patches on the grid is given by the sum over all locations Ξ. That is

$$S(t) = \left(\sum_{\xi \in \Xi} S_\xi(t) \right) \tag{2.39}$$

with $S(t)$ representing the stage specific total number of mosquitoes ($E(t)$, $L(t)$, $P(t)$, $A_h(t)$, $A_r(t)$, and $A_o(t)$). The solutions of Eq. (2.36) remain non-negative in the region

$$\Gamma = \left\{ \begin{pmatrix} E_{(i,j)} \\ L_{(i,j)} \\ P_{(i,j)} \\ A_{h(i,j)} \\ A_{r(i,j)} \\ A_{o(i,j)} \end{pmatrix} \in \mathbb{R}^{6nm} \left| \begin{array}{l} E_{(i,j)} \geq 0, \\ L_{(i,j)} \geq 0, \\ P_{(i,j)} \geq 0, \\ A_{h(i,j)} \geq 0, \\ A_{r(i,j)} \geq 0, \\ A_{o(i,j)} \geq 0 \end{array} \right. \right\}, \tag{2.40}$$

because movement always stops when there are no mosquitoes in a patch. The model is therefore mathematically and biologically well posed.

Table 2.3: Description of parameters and variables specific to the dispersal model

Parameter	Description	Units
H	number of hosts	hosts
B	number of breeding sites	breeding sites
β^H	dispersal rate of host seeking mosquitoes	per time
β^B	dispersal rate of mosquitoes searching for breeding sites	per time
β^{H*}	dispersal rate of mosquitoes in the presence of repellents	per time
L	patch size	metres
D	rate of movement	per time
λ	a constant parameter for the decay function	dimensionless
$D*$	diffusion coefficient	metres^{2}time^{-1}
p	repellents blocked ability of mosquitoes to enter a patch	dimensionless
ϕ^H	a fraction measuring the strength of a repellent in in patch i, j	unitless

Theorem 2.5.2. *Assuming that initial conditions lie in Γ, the system of equations for the mosquito population dynamics for all patches* (2.36) *has a unique solution that exists and remains in Γ for all time $t \geq 0$.*

Proof. The right hand side of system (2.36) is continuous with continuous partial derivatives in region Γ. Thus, there exists a unique solution for (2.36). We show that region Γ is forward-invariant. From system (2.36) we see that if $E_{(i,j)} = 0$, then $E'_{(i,j)} = b_{(i,j)}\psi^B_{(i,j)}\rho_{A_o(i,j)}A_{o(i,j)} \geq 0$; if $L_{(i,j)} = 0$, then $L'_{(i,j)} = \rho_{E(i,j)}E_{(i,j)} \geq 0$; if $P_{(i,j)} = 0$, then $P'_{(i,j)} = \rho_{L(i,j)}L_{(i,j)} \geq 0$; if $A_{h(i,j)} = 0$,

then $A'_{h(i,j)} = \rho_{P(i,j)}P_{(i,j)} + \psi^B_{(i,j)}\rho_{A_o(i,j)}A_{o(i,j)} + \left(\sum\limits_{\xi' \in N(i,j)} \beta^H_{\xi'/(i,j)}A_{h\xi'} \right) \geq 0$; if

$A_{r(i,j)} = 0$, then $A'_{r(i,j)} = \psi^H_{(i,j)}\rho_{A_h(i,j)}A_{h(i,j)} \geq 0$; and if $A_{o(i,j)} = 0$, then $A'_{o(i,j)} =$

$\rho_{A_r(i,j)}A_{r(i,j)} + \left(\sum\limits_{\xi' \in N(i,j)} \beta^B_{\xi'/(i,j)}A_{o\xi'} \right) \geq 0$. Therefore, all solutions of the system

of equations in (2.36) are contained in the region Ξ and a unique solution exists for all t. $\square$

System (2.36) is at an equilibrium if the right hand side is zero at all time t.

Patch (i, j) is at a mosquito-free equilibrium if $E_{(i,j)} = L_{(i,j)} = P_{(i,j)} = A_{h(i,j)} = A_{r(i,j)} = A_{o(i,j)} = 0$. However, given the complexity of the model, we do not show its stability or show the existence of other invariant subsets and only run numerical simulations of this model.

2.6 Numerical simulations

The model without dispersal (Eq. (2.1)) and the model with dispersal (Eq. (2.36)) are both simulated using Matlab 7.10.0(R2010a) student version (MAT-LAB, 2010) and the *ode45* solver for solving differential equations is used. The 25 by 21 grid (see sketch in Figure 2.3) is used as a platform to simulate movement of mosquitoes between hexagonal patches. To ensure that boundary conditions do not influence results, periodic boundary conditions are used. This implies a torus topology for the landscape, where edge patches are such that their nearest neighbours on the outside are patches on the opposing edges.

For model simulation and investigation, we use data on stage specific mortality and development rates from the literature (see appendix 2.9), summarised in Table 2.2. For mosquito dispersal, some studies show that mosquitoes can move up to $800\,$m a day (Gillies, 1961). Field studies on mark release recapture experiments of *Anopheles gambiae* also show that daily flight range from 200 to $400\,$m (Midega et al., 2007). These results indicate that mosquito dispersal distance is variable. Due to these variations, in section 2.7.1 we use our model platform (section 2.5) and the movement rate D (Eq. (2.20)) to produce distributions of dispersed mosquitoes by distance travelled in a day. However, for numerical illustration of the model with dispersal, we set the distance from the centre of one patch to the centre of the neighbouring patch, L, to $50\,$m.

We run simulations with total numbers of 2700 eggs, 1900 larvae, 2000 pupae, 2400 host seeking adults, 1800 resting adults, and 1200 oviposition site seeking adults, initially distributed across the grid (Figure 2.7). The distribution is based on the whether a patch contains breeding sites or hosts. Five scenarios are set up to simulate the effect of different kinds of heterogeneity (Figure 2.6).
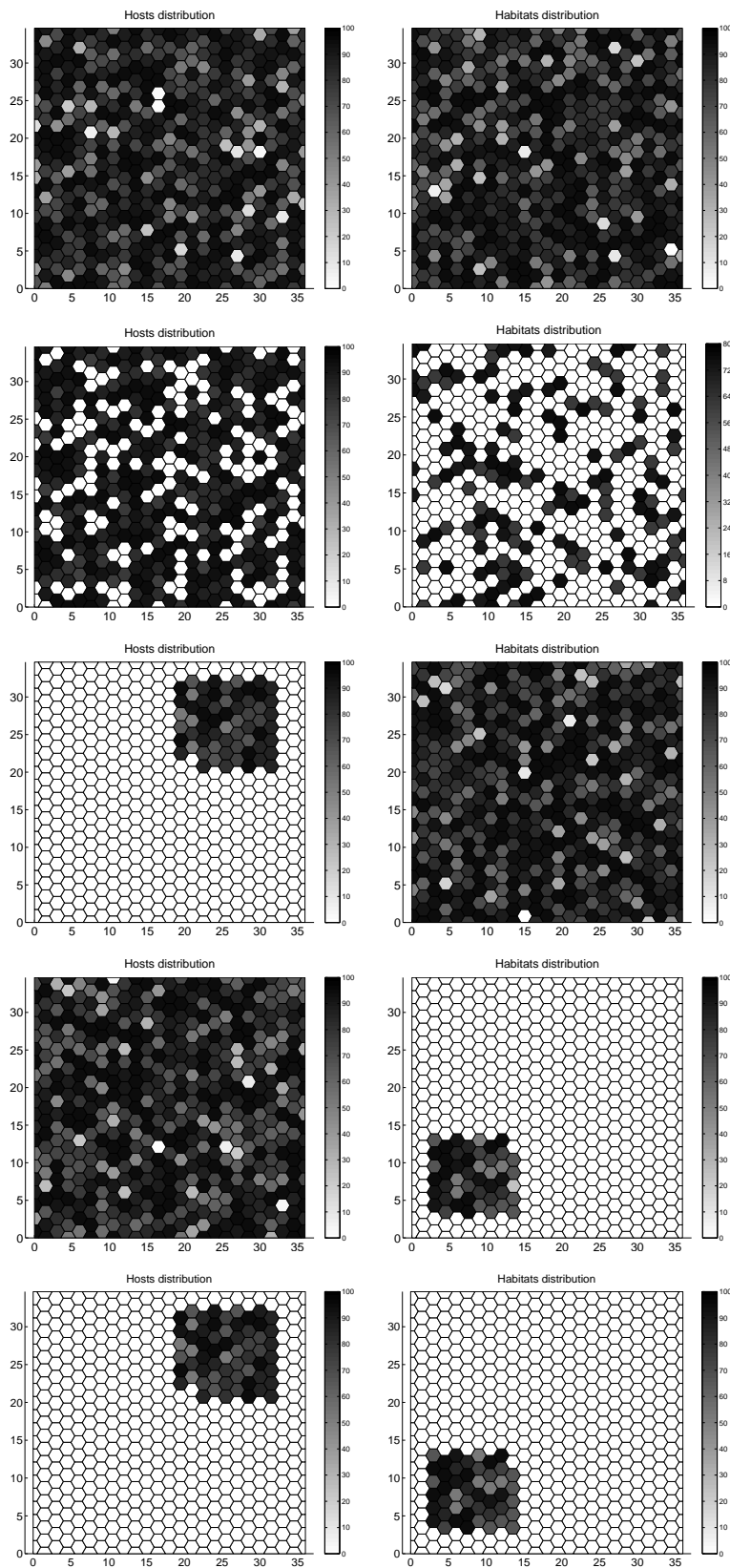
Figure 2.6: Spatial arrangements of hosts and breeding sites on the grid showing the set up of scenarios. Scenario 1 (first row): all patches contain hosts and breeding sites. Scenario 2 (second row): random distribution of hosts and breeding sites. Scenario 3(third row): all patches contain breeding sites but hosts on one side of the grid. Scenario 4 (fourth row): all patches contain hosts but breeding sites are on one side of the grid. Scenario 5 (fifth row): clusters of hosts and breeding sites are far apart from each other.

In the first scenario, all patches contain hosts and breeding sites; the second scenario simulates the case when hosts and breeding sites are randomly distributed on the grid. In the third scenario, all patches contain breeding sites and hosts are only on one side of the grid; while in the fourth scenario, hosts are present in all patches, with breeding sites being on one side of the grid. In scenario five, hosts and breeding sites are placed in clusters that are far apart from each other. Simulations are continued for each scenario until the total mosquito population over the entire grid for each of the stages and their spatial distribution reaches an equilibrium. The final time of analysis for the simulations for all results presented in this work is 250 days, except where stated otherwise.

2.7 Model application, comparisons, and results

2.7.1 Dispersal distances

In this section, we use the dispersal model to estimate the distance travelled by an average mosquito. The evolution of equation (2.22) is simulated on a homogeneous grid with uniform attractiveness to mosquitoes. The system is initialized with all mosquitoes placed at a single source patch. We then calculate the total number of mosquitoes per patch and per neighbourhood, the average density of mosquitoes per patch, and the average of the dispersal distance after time 1.

We let $M_n(t)$ be the average density of mosquitoes in a patch at time t, where n measures the distance from the source patch. Here, n is $0, 1, 2, ..., m$, with $n = 0$ being the source patch, $n = 1$ being the nearest neighbouring patches (first ring of patches), $n = 2$ being the second ring of patches, $n = 3$ being the third ring of patches, and so on (see Figure 2.8). The total number of patches in each of the rings is given by

$$N_n = \begin{cases} 6n & \text{for } n \geq 1 \\ 1 & \text{for } n = 0. \end{cases} \tag{2.41}$$
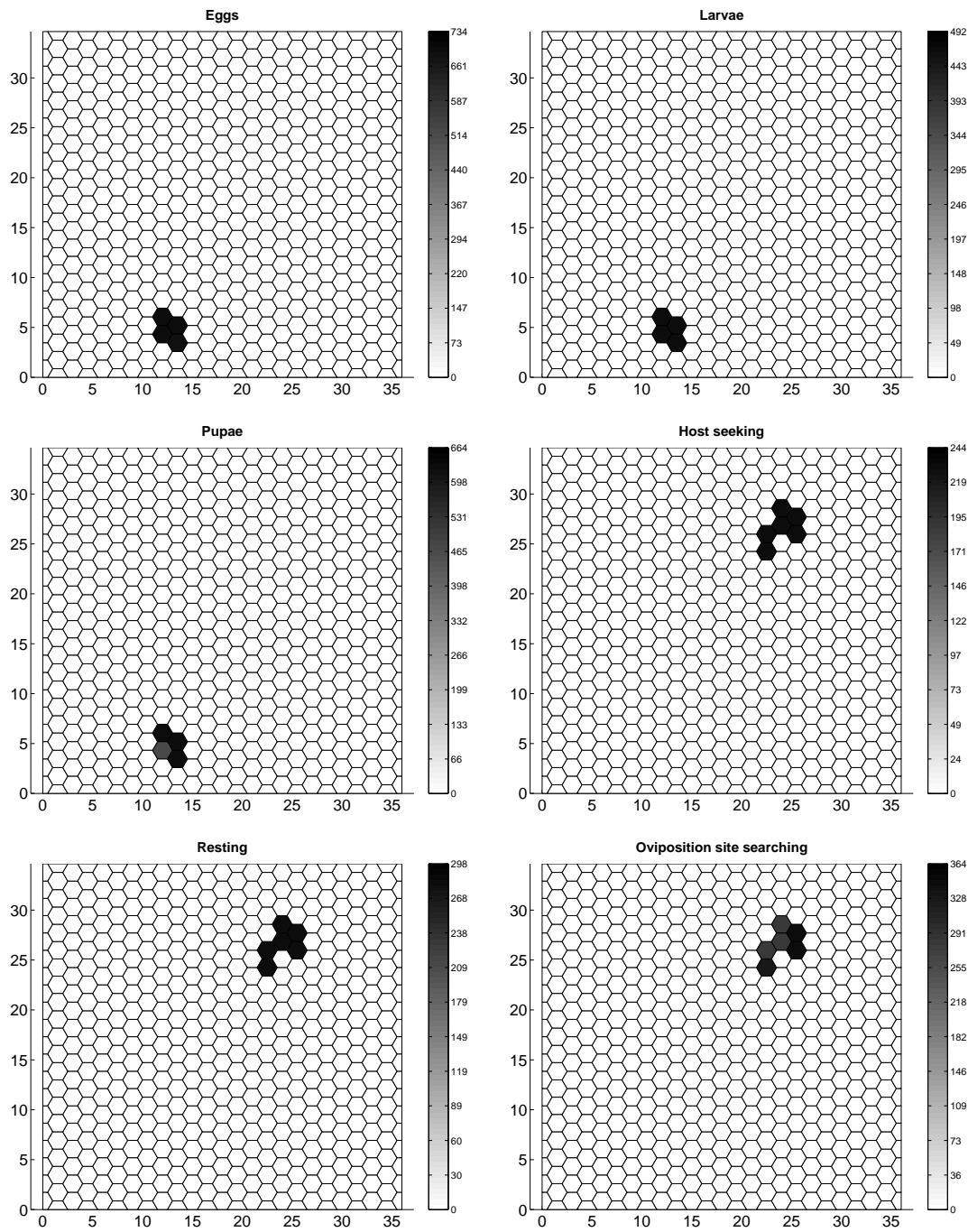
Figure 2.7: Spatial population distribution of initial conditions by stage. The distribution of initial conditions is common to all scenarios (figure 2.6) for comparative purposes.

The total number of mosquitoes that reached ring n after time t, $P_n(t)$ is

$$P_n(t) = \sum_{k=1}^{N_n} C_k(t), \tag{2.42}$$

where C_k is the number of mosquitoes in patch k contained in n. From equation (2.42), we obtain the mosquito frequency by distance travelled from the source patch for a particular time t. We present the results in figure 2.9A for $t = 1$ day and different values of D.
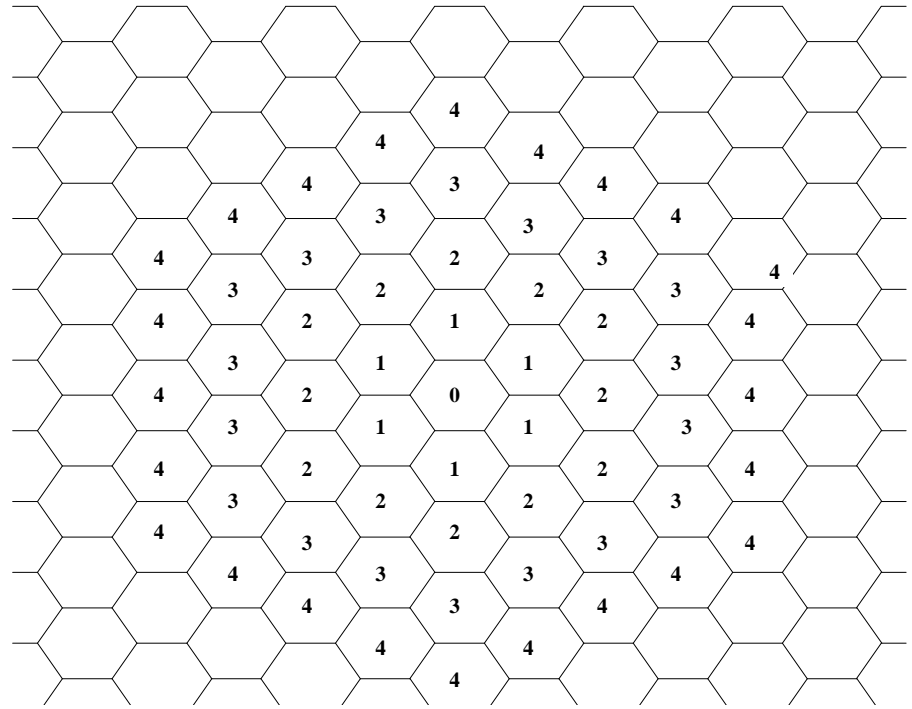
Figure 2.8: Sketch diagram showing how the distance from the source patch was obtained. Each ring of neighbours to source patch, $n = 0, 1, 2, ..., m$ can be multiplied by patch size to obtain the distance.

The average density of mosquitoes per patch, after time t has elapsed, is obtained from:

$$M_n(t) = \frac{P_n(t)}{N_n},$$
(2.43)

which gives the average density distribution presented in figure 2.9B when $t = 1$ day.

We let S_1 be the initial number of mosquitoes released from the source patch and the weighted average distance travelled by one mosquito at time t, $W_d(t)$, is

$$W_d(t) = \left(\frac{\sum_{n=0}^{m} n P_n(t)}{S_1} \right) \times L \tag{2.44}$$

where L is the patch size. We calculate the weighted average of the dispersal distance travelled by a mosquito in one day, $W_d(1)$.

In Figure 2.9A we present the results of the frequency distribution of mosquitoes dispersed in a day by distance from source at different values of the diffusion parameter. As expected, increasing values of D results in mosquitoes moving faster and reaching larger distances. Figure 2.9B shows the average density of mosquitoes per patch by distance moved in a day. After one day, most mosquitoes have moved, but the source still contains the highest density.

From simulations, the weighted mean distance travelled by each mosquito per day (as calculated from Eq. (2.44)) is estimated to be $43, 79$, and 103 m when $L = 50$ m and mosquitoes are allowed to move at a rate, D, of $0.2, 0.5$, and 0.8, respectively.

2.7.2 Comparison between discrete and continuous space form of the models

The nearest neighbours movement approach has been shown to relate closely to diffusion models (Arino et al., 2007; Keeling and Rohani, 2008). To evaluate the effects of using discrete space, we compare the behaviour of the discrete space movement model (Eq. (2.22)) under homogeneous conditions to that of the model that uses the diffusion approach (Eq. (2.13)). By comparing the behaviour of the two approaches, we calculate how far a mosquito can travel in a day (and time is set to 1 day in the simulations for both models).

Figure 2.10 presents the results of the discrete (Eq. (2.22)) and continuous forms (Eq. (2.17)) of the model. The scenario we compare to the diffusion model is such that all patches contain mosquito resources, creating uniformity in attractiveness to mosquitoes between patches. The probability of a
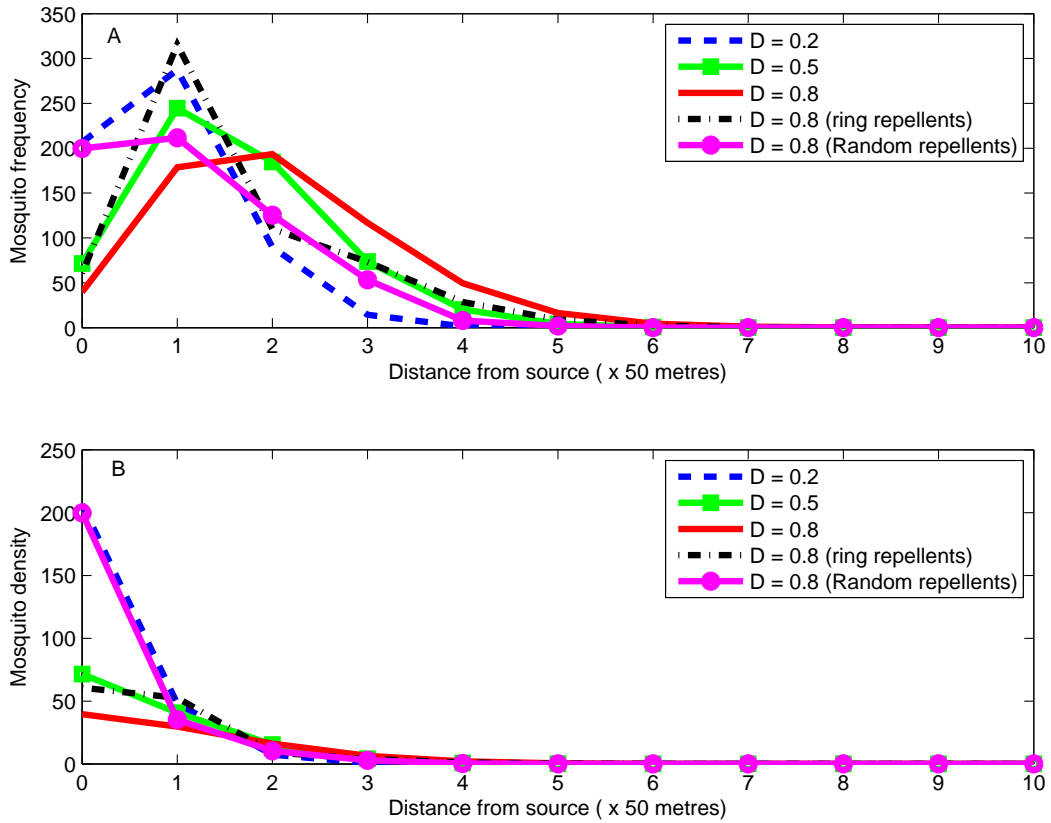
Figure 2.9: Distribution of mosquitoes as a function of the distance from center. A: Frequency distributions of mosquitoes by the distance moved from mosquito source (source patch with $n = 0$) in a day (Eq. (2.42) in Section 2.7.1). B: Average density of mosquitoes per patch (Eq. (2.43)). A total number of 600 (i.e. $S_1 = 600$) mosquitoes were initially placed in one patch and simulated at different values of D and different distributions of repellents for one day with $\lambda = 0.5$.

mosquito moving in any direction is therefore the same. The two models produce slightly different results. However, the distributions show similar properties in terms of the modelled mosquito trajectories between the discrete space and the continuous space models. Both models show peaks in mosquito density near the point of release. The continuous model shows a higher peak and a higher rate of decrease compared to the discrete model.

2.7.3 Spatial repellents

Spatial repellents can have different effects on mosquito dispersal, and hence population dynamics, in different areas. These repellents can be non-physical
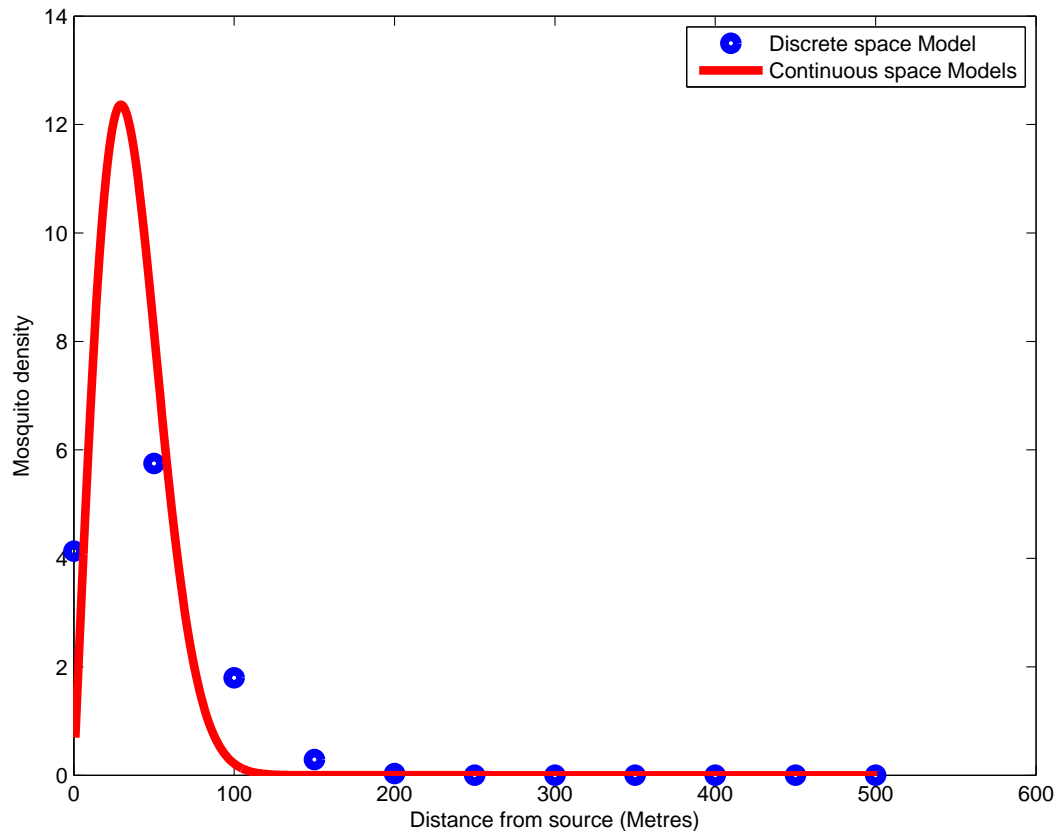
Figure 2.10: Comparison between the discrete space (Eq. (2.32)) and continuous space (Eq. (2.17)) (obtained from Eq. (2.13)) models. A total number of 600 mosquitoes initially placed at the source patch during the simulation of the discrete space model (with $\lambda = 0.5$) were also used in the continuous space version of the model (i.e $K = 600$). Mosquitoes were allowed to move at the same rate (i.e. $D = 0.2$) for both forms of the model and time was set to 1 day.

barriers, such as the treatment perimeters with insecticides to protect populations from mosquito bites (Britch et al., 2009) by reducing the number of biting mosquitoes moving into the area (Britch et al., 2010).

We use the dispersal model developed in this paper to evaluate the effect of including patches with spatial repellents on the distance travelled by mosquitoes. We include a multiplicative factor $\phi_{(i,j)} = 1 - p_{(i,j)}$, where $p_{(i,j)} \in [0,1]$ to account for the effect of spatial repellents on flying mosquitoes in some patches. The parameter p can be interpreted as the blocked ability of mosquitoes to enter into a patch. When $p_{(i,j)} = 1$, the barrier in the patch acts as an obstacle which completely blocks movement and when $p_{(i,j)} = 0$, movement is not impeded. For host seeking mosquitoes, the dispersal rates from the source patch

become:

$$\beta^{H*}_{(i,j)/\xi'} = \phi_{\xi'}\beta^{H}_{(i,j)/\xi'} \qquad (2.45)$$

and the dispersal rate into the patch changes to

$$\beta^{H*}_{\xi'/(i,j)} = \phi_{(i,j)}\beta^{H}_{\xi'/(i,j)}. \qquad (2.46)$$

We note that in this way of modelling spatial repellents, emerging adults are not chased away by the repellents unless they have entered the host seeking stage.

We set up two scenarios to simulate the effect of repellents, with $p_{(i,j)} = 0.8$. In the first scenario, we place repellents in the second ring to source (i.e $n = 2$) to form a regular ring distribution. In the second scenario, we randomly distribute repellents over the patches across the landscape. Results from these two scenarios were compared with results produced under homogeneous conditions (without repellents in any of the patches).

The presence of repellents in patches placed at $n = 2$ creates a barrier to mosquitoes (Figure 2.9A). Most mosquitoes move away from the source and cluster in the first neighbourhood ($n = 1$). Few mosquitoes are observed in the second neighbourhood. The density of mosquitoes for $n > 2$ are lower, compared to the scenario when there are no repellents. At larger distances from the source patch, the presence of repellents in patches near the source did not show any impact on mosquito dispersal.

The density of mosquitoes in the source patch is found to be higher when D is 0.8, with repellents placed in a ring of patches, than at $D = 0.2$ with no repellents. From $n = 1$ to $n = 2$, there is no major difference between the two scenarios. For $n > 2$, mosquito density is smaller when D is set to 0.2, compared to when repellents are placed in a ring distribution. In this case, the repellent does not have a strong impact on the movement of mosquitoes and

therefore the value of the movement rate has a substantial role in controlling movement to other patches. When there are patches with repellents, the average number of mosquitoes dispersed per patch (Figure 2.9B) does not differ much from a scenario where the are no repellents. On the other hand, a small difference is observed for $n < 2$.

A random distribution of repellents results in mosquitoes clustering in the source patch and in the nearest neighbourhoods. Fewer mosquitoes are observed clustering in the patches far from the source patch compared to a situation when there are no repellents.

In the presence of spatial repellents, with $D = 0.8$, the weighted mean distance moved is estimated to be 78 m when repellents are placed at $n = 2$ and 55 m when repellents are randomly distributed across the landscape.

2.7.4   Impact of heterogeneity on spatial distribution

Figure 2.11 shows the effect of heterogeneity on the spatial distribution of larvae, host seeking, and oviposition site searching mosquitoes when the system is at equilibrium. The population distribution is highly dependent on the distribution of both hosts and breeding sites. As expected, when all patches on the grid have both hosts and breeding sites, the entire grid become densely populated. Host seeking mosquitoes show a pronounced spread across the grid when hosts and breeding sites are randomly distributed, compared to mosquitoes searching for oviposition sites. When breeding sites are placed in all patches and hosts are clustered on one part of the grid, host seeking mosquitoes spread over a larger area, compared to a scenario where hosts are present in all patches and breeding sites are clustered on one side of the grid.
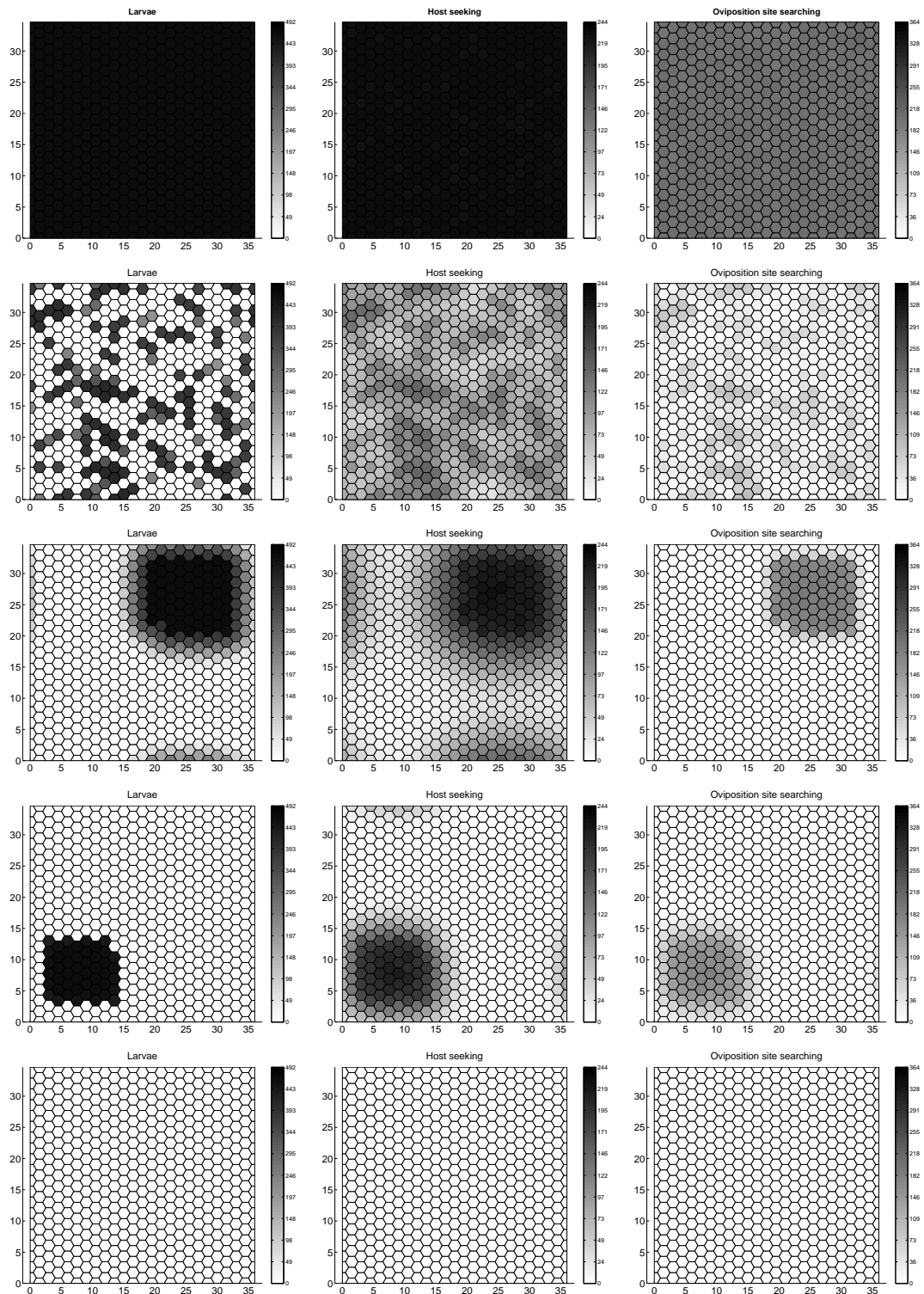
Figure 2.11: Spatial population distribution of mosquitoes by scenario (Figure 2.6) and stage. Scenario 1 (first row): all patches contain hosts and breeding sites. Scenario 2 (second row): random distribution of hosts and breeding sites. Scenario 3(third row): all patches contain breeding sites but hosts are on one side of the grid. Scenario 4 (fourth row): all patches contain hosts but breeding sites are on one side of the grid. Scenario 5 (fifth row): clusters of hosts and breeding sites are far apart from each other. These results are a snapshot taken at day 250 when the whole system is at an equilibrium.

2.7.5   Impact of dispersal on population distribution

Mosquito dispersal becomes more important when the distribution of hosts and breeding sites on the grid is heterogeneous (Figure 2.11). Clustering of host seeking mosquitoes towards patches containing both hosts and breeding sites is observed. However, when hosts and breeding sites are located in separate parts of the grid, the population dies out within a few days (given the assumed initial densities of mosquitoes for these simulations).

2.7.6   Impact of heterogeneity on the dynamics of the total population

Figure 2.12 presents the dynamics of the total population (Eg. (2.39)) over all patches on the grid. Heterogeneous distributions of breeding sites and hosts, to a large extent, reduces the population at equilibrium. When clusters of breeding sites and hosts are placed far from each other, mosquitoes become unable to reproduce as distances required to travel is increased. Hence, population extinction is possible.

2.7.7   Impact of dispersal and heterogeneity on population dynamics

To evaluate the impact of dispersal and heterogeneity on population dynamics, we carried out numerical simulations using models both without (system (2.1)) and with dispersal (system (2.36)). While maintaining the same set up of multiple sources of mosquitoes (Figure 2.7) for comparison purposes, we computed the average number of mosquitoes at equilibrium across all patches on the grid for the dispersal model. The two models show slightly different equilibrium values (Figure 2.13) (i.e (7339, 577, 93, 194, 206, 26) for the model without dispersal and $(7197, 564, 91, 190, 202, 25)$ for the dispersal model when all patches have hosts and breeding sites). For randomly distributed mosquito resources, the average equilibrium value across all patches on the grid was
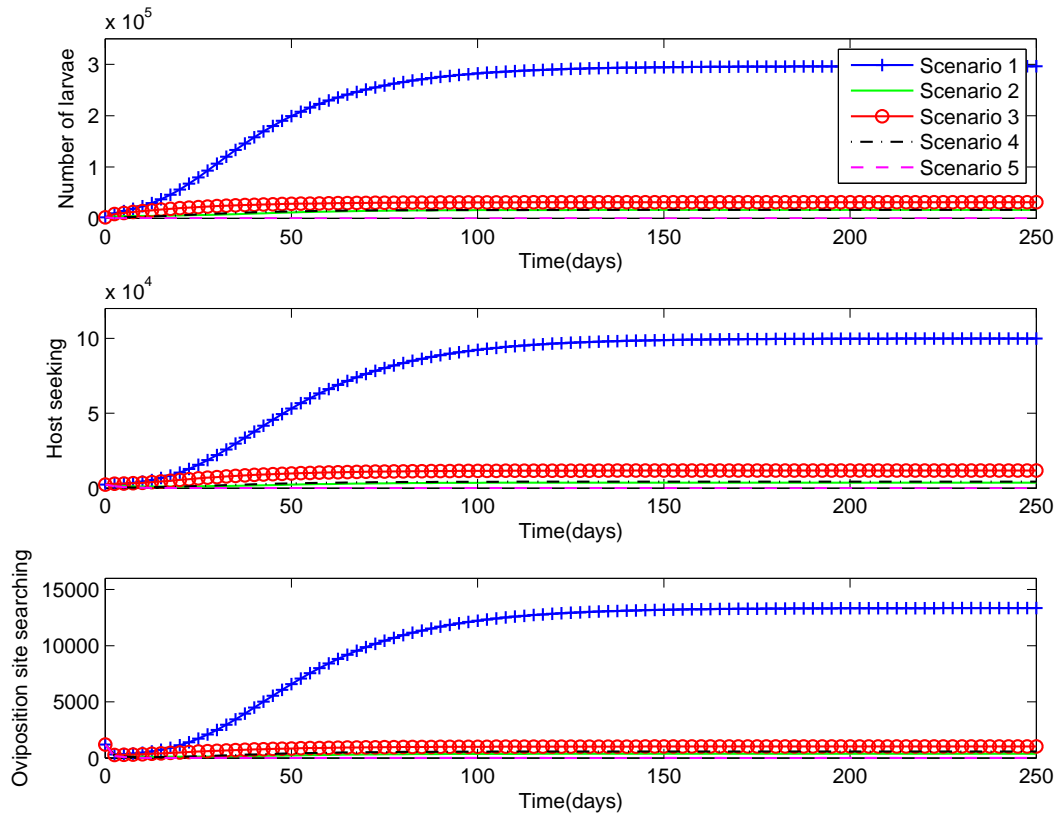
Figure 2.12: Population dynamics of mosquitoes across the grid by scenario and stage. Scenario 1: Both hosts and breeding sites were present in all patches. Scenario 2: Both hosts and breeding sites were randomly distributed across the grid. Scenario 3: Breeding sites were placed in all patches, hosts were clustered on one part of the grid. Scenario 4: Hosts were placed in all patches, but breeding sites were placed on one part of the grid. Scenario 5: Both hosts and breeding sites were placed on one part of the grid, far from each other. Figure 2.6 shows the set up of the scenarios.

$(118, 31, 5, 7, 6, 1)$. This corresponds to an equilibrium population, measured as number of mosquitoes per km^2, as $(33.2, 2.6, 0.4, 0.9, 0.9, 0.1) \times 10^5$ when hosts and breeding sites were present in all patches and approximately $(54.374, 14.380, 2.314, 3.257, 2.630, 0.333) \times 10^3$ when resources are randomly distributed across the grid.

2.8 Discussion

Mathematical models for evaluating the impact of the transmission of vector borne diseases do not consider effects on vector mobility, despite evidence
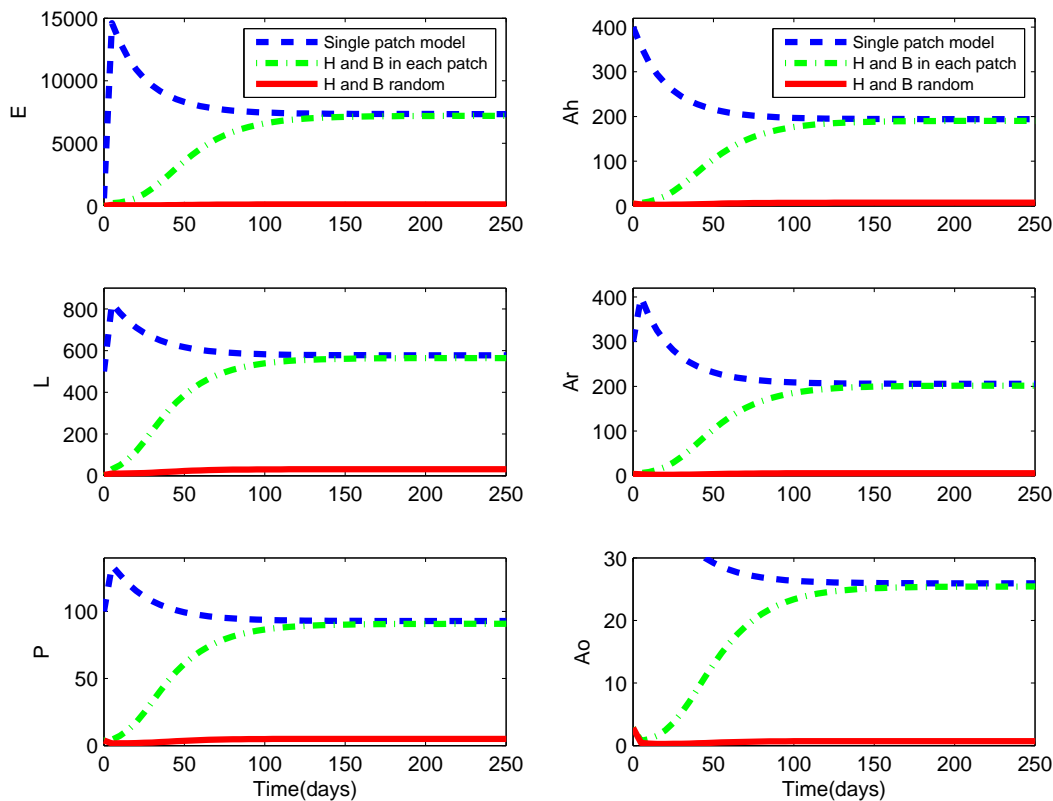
Figure 2.13: A comparison of time series plots between the model without (system (2.1)) and with dispersal((2.36)) was simulated under parameter values given in Table 2.2. For the model with dispersal, the average number of mosquitoes across all patches on the grid are plotted. Two scenarios were simulated for the dispersal model: hosts and breeding breeding sites randomly distributed across the landscape (H and B random), and hosts and breeding breeding sites present in all patches (H and B in each patch).

that the relative locations of mosquito breeding sites and of human hosts profoundly affect transmission of both malaria (Clarke et al., 2002; Smith et al., 2002) and the dengue virus (Jeefoo et al., 2011; Vazquez-Prokopec et al., 2010). One reason for this is that, whereas spatial variation in biting rates is relatively easy to study, rates of movement of mosquitoes can only be studied using challenging mark-recapture techniques, which provide sparse data. Consequently, there is little evidence of the impact of heterogeneity in the distribution of resources used by mosquitoes on the mosquito population size and its spatial distribution. The likely impact of interventions that may affect mosquito movement is thus even less well understood.

Our compartment model of the life cycle and feeding cycle of mosquitoes incorporates spatial heterogeneity both in densities of breeding sites and of human hosts. It also incorporates mosquito movement and can be used to predict the effects of interventions targeting different stages of the mosquito life cycle. We consider effects on population size, on the spatial distribution of mosquitoes, and on how far individual mosquitoes move. We use the example of spatial repellents to illustrate how these parameters can be affected by a relatively simple intervention.

In a homogeneous environment, the model without dispersal indicates that there is a linear relationship between population reproduction numbers and both age-stage specific survival and developmental rates of mosquitoes. This leads to straightforward relationships between the size of the mosquito population, developmental rates from larvae to pupae, and mortality rates of larvae. However, when there are heterogeneities in resource availability, these linear relationships are disturbed, and have far-reaching the effects on spatial distribution and population dynamics of mosquitoes (Vinatier et al., 2011). If breeding sites are eliminated from the neighbourhoods of hosts or are not available in most patches, mosquitoes searching for breeding sites are forced to move longer distances in search of oviposition sites, prolonging the feeding cycle (Chitnis et al., 2008b; Menach et al., 2007) and increasing mortality during searching (Saul, 2003). In general, environmental heterogeneity forces mosquitoes to move longer distances and increases their mortality (Saul, 2003). In our models, we could eliminate mosquito populations by separating breeding sites and hosts.

From the host's perspective, living in proximity to mosquito breeding sites increases exposure to mosquito bites and potentially also to disease. Because the vector-host ratio is higher around breeding sites (Menach et al., 2005), selectively eliminating breeding sites in areas of human habitation can prevent mosquitoes from using human hosts for blood meals (Gu and Novak, 2009a). Similarly, a possible intervention strategy is to deploy interventions such as spatial repellents or bed nets around breeding sites. However, our simulations

suggest that such a ring strategy for repellent deployment is advantageous only if mosquito sources are few, clearly defined, and known. In situations where mosquito sources and households are scattered throughout the area, this strategy will not be feasible. However, even random deployment of repellents reduces the distance moved by mosquitoes, making it more difficult for them to complete their life cycle, and hence has beneficial effects.

Spatial heterogeneity in resource availability can thus, on its own, have complex effects on mosquito populations. Even relatively simple interventions, such as spatial repellents, can be deployed in a variety of ways in such environments. We have only just begun to use our model to explore the implications of the resulting multiplicity of combinations of environments with intervention strategies. Analysing of the spatial effects of more complex interventions, such as insecticide treated mosquito nets, which have simultaneous killing and repellent effects, will bring further challenges.

Like any model, ours has limitations. Effects of wind, which can either facilitate or prevent movement (Bowen, 1991; Cummins et al., 2012; Knols and Meijerink, 1997; Raffy and Tran, 2005; Smallegange et al., 2005), were not incorporated. We chose to use a discrete hexagonal patches as a representation of space, rather than using a continuous space model (Raffy and Tran, 2005), (Tran and Raffy, 2006) because this makes it easier to model arbitrary spatial distributions of resources. At the same time, this constrained the modelled mosquito movements to follow a limited set of trajectories. We do not know what trajectories mosquitoes adopt in reality and strategies such as Levy flight (Reynolds and Frye, 2007) may well be used to optimize foraging efficiency. An alternative approach to our discrete space model is to use a PDE model for mosquito dispersal, for example that of Raffy and Tran (Raffy and Tran, 2005; Tran and Raffy, 2006). Here attractiveness is represented via chemotaxis or an advection term, taking into account blood meals, breeding sites, wind, etc. The advantage of the discrete space model proposed in this paper is that one can easily assess vector control strategies, as the discrete space enables easy representation of interventions that cover sets of households or villages.

The differences in the peaks and rates of decrease in mosquito distributions by distances travelled indicate that the choice of the exponential movement rate in the discrete model does not force the results to be the same as those produced by the continuous space approach. However, we could show that although there are differences, mosquito distributions by distances moved have similar properties (both models show peaks in mosquito density in the regions close to the origin and are zero far away from the release point) to those predicted by a continuous space diffusion model (O'Sullivan and Perry, 2009), and suggest that our results are broadly applicable no matter what foraging strategies mosquitoes may adopt.

We could also show that the various factors taken into account by the model play an important role in the spatial distribution of mosquitoes. The model could show realistic behaviours in simple theoretical situations on an artificial landscape. Our model, together with field data, could be used to determine areas of high transmission within local settings, evaluate the community effect of interventions, and aid in developing possible and efficient vector control strategies, which can optimize the allocation of scarce resources.

2.9   Appendix: Data for model parameters

Data for parameterizing the model was obtained from literature. There is variability in the available data as study designs and conditions under which studies were carried out vary from one place to another. A single value was chosen from a range of values as baseline and used for the numerical simulation of the model.

The development of mosquitoes in their early stages is a nonlinear process that depends on water temperature (Holsetein, 1954; Otero et al., 2006; Depinay et al., 2004). However, for simplicity, we assume that the mean development time for each stage is constant over time.

For *Anopheles gambiae*, the duration of egg development (from oviposition to

hatching into a larva) $(1/\rho_E)$ is about 2 days in field environments (Service, 2004). Under laboratory conditions and tropical areas this period extends to 3 days (Holsetein, 1954; Yaro et al., 2006), and (Service, 2004). In a study by (Service, 2004), the larval period for mosquitoes of the *Anopheles* genus is found to be 7 days. Other studies have shown that the larval stage may last $(1/\rho_L)$ between 6 to 10 days in field environments or 11 to 13 days in laboratory conditions (Holsetein, 1954) or last between 7 to 15 days in temperate and tropical areas (Bayoh and Lindsay, 2003; Kirby and Lindsay, 2009; Gething et al., 2011b). It has also been found that the pupal period $(1/\rho_P)$ lasts for $1 - 2$ days in field environments but under laboratory conditions the pupal period lasts for about 2 days (Holsetein, 1954). In tropical regions the pupal stage for *Anopheles* genus last between 2 to 3 days (Service, 2004).

We used mean mortality rates of 0.56 ± 0.28 for eggs, 0.51 ± 0.14 for larvae instars I and II, 0.37 ± 0.14 for larvae instars III and IV, and 0.37 ± 0.15 for pupae (Okogun, 2005). The average of the two categories of larvae for the density independent mortality of larvae, $\mu_{L_1} = 0.44 \pm 0.14$. Larval mortality can be resolved into natural mortality rates, μ_{L_1} and density dependent mortality of larvae, μ_{L_2}. For our simulations, we allow μ_{L_2} to take any value between 0 and 1.

Since the model details the adult mosquito life cycle via the mosquito feeding cycle, we derive the estimates of most of the parameters from studies on the mosquito feeding cycle. The time spent while searching for hosts $(1/\rho_{A_h})$ can be estimated. From (Chitnis et al., 2008b), we can calculate $\rho_{A_h} = 0.46$. Once mosquitoes survive the host seeking stage and have successfully fed, mosquitoes rest for food digestion and egg maturation. Using $1/\rho_{A_r} = 2.33$ days (Chitnis et al., 2008b), which is $\rho_{A_r} = 0.43$ per day, we can calculate the value of μ_{A_r} as 0.0043 given that the probability of surviving while resting is $1 - \mu_{A_r}/(\mu_{A_r} - \rho_{A_r}) = \rho_{A_r}/(\mu_{A_r} + \rho_{A_r}) = 0.99$ (Chitnis et al., 2008b). If mosquitoes spend $1/\rho_{A_o} = 0.33$ days ovipositing, then $\rho_{A_o} = 3$ per day. The corresponding probability of surviving the oviposition site searching stage $1 - \mu_{A_o}/(\mu_{A_o} + \rho_{A_o}) = \rho_{A_o}/(\mu_{A_o} + \rho_{A_o})$ is 0.88 (Chitnis et al., 2008b). From this probability, we

obtain $\mu_{A_o} = 0.41$ per day. From (Chitnis et al., 2008b) we see that the probability of surviving the feeding cycle is $p_f = 0.623$. From our model, this probability can be calculated from $\left(\rho_{A_h}/(\mu_{A_h} + \rho_{A_h})\right)\left(\rho_{A_r}/(\mu_{A_r} + \rho_{A_r})\right)\left(\rho_{A_o}/(\mu_{A_o} + \rho_{A_o})\right)$. Substituting the values for the survival probabilities of the oviposition site search and resting given above in this section, we obtain $\rho_{A_h}/(\mu_{A_h} + \rho_{A_h}) = 0.72$ as the probability of surviving during the host searching. Thus, we obtain $\mu_{A_h} = 0.18$ (Table 2.2).

Clustering of vector control interventions has important consequences for their effectiveness

Authors: Angelina M. Lutambi, Nakul Chitnis, Olivier J.T. Briët, Thomas Smith, and Melissa A. Penny

3.1 Abstract

Vector control interventions have resulted in considerable reductions in malaria morbidity and mortality. When universal coverage cannot be achieved for financial or logistical reasons, the spatial arrangement of vector control is potentially important for optimizing benefits. Here we show, via the use of mathematical models, that spatial clustering of vector control influences mosquito density and dispersal patterns and thus has consequences for the effectiveness of an intervention package. When hosts and breeding sites are distributed

homogeneously over a landscape, we find that at medium to high coverage levels of both larvicidal and adultcidal interventions, it is more effective to spatially spread these interventions than to cluster them. In the case of limited resources, high spatial clustering of larviciding is more effective compared to random distribution. It is often stated that locally high coverage is needed to achieve a community effect of insecticide treated nets (ITNs) or indoor residual spraying (IRS). However we find that, if the coverage of ITNs or IRS are insufficient to achieve universal coverage and there is no targeting of high risk areas, the overall effects on mosquito densities are much greater if they are distributed in an unclustered way, rather than clustered in specific localities. Interventions are often delivered preferentially to accessible areas, and such clustered, possibly inequitable distributions are likely to be the cheapest, but our model results show this may well be inefficient.

3.2   Background

Efforts to reduce malaria transmission have lead to the development of efficient vector control interventions, particularly deployment of insecticide treated nets[1] (ITNs), indoor residual spraying (IRS), and larviciding (Bayoh et al., 2010; Kroeger et al., 1995; Lengeler, 2004; Muturi et al., 2008; WHO, 2004). These interventions are currently widely used in malaria endemic countries especially those in sub-Saharan Africa (WHO, 2011) and have lead to substantial reduction in malaria morbidity and mortality. Nevertheless, malaria continues to claim hundreds of thousands of lives every year (WHO, 2011), thus necessitating a continued control effort to fight the disease. While over \$2 billion are invested each year in procuring and distributing vector control interventions (RBM, 2013) for malaria control , this funding is insufficient to achieve universal coverage (RBM, 2013) and it is not clear if this will be sustained given

---

[1]includes two categories (WHO, 2007): The first category consist of conventional nets treated with a WHO recommended insecticide. Net re-treatment is repeated after every three washes. The second category consists of long-lasting insecticidal nets (LLINs). These are factory-treated nets made of fibres that incorporate insecticides or have a wash resistant coating containing insecticide.

current economic constraints.

Mosquito flight from one place to another (Gillies, 1961; Gillies and Wilkes, 1978, 1981; Service, 1997) is motivated by several factors including wind, odour, blood and nectar sources, availability of breeding sites, mating, etc (Edman et al., 1998; Cummins et al., 2012). These factors and mosquito movements influence the spatial distribution of mosquitoes, and thus, that of malaria. The probability that a mosquito will encounter areas that are under a particular vector control intervention is dependent on the spatial arrangement of an intervention. Consequently, the spatial arrangement of the intervention will affect the effectiveness of an intervention in controlling malaria. When financial resources are insufficient, or due to geographic limitations, it may be difficult to achieve universal coverage where a whole community is covered by an intervention. Thus, an understanding of how the degree of spatial clustering of these interventions affects effectiveness is needed for planning optimal benefits of interventions.

While the World Health Organization (WHO) strategy on vector management provides information on improving the efficacy, cost-effectiveness, ecological soundness and sustainability of vector control (WHO, 2004), there is limited relevant information on the influence of spatial distribution of these interventions on effectiveness. Approaches coupling both theory and empirical evidence are needed to evaluate and measure effectiveness of interventions at different degrees of spatial distribution for each level of intervention coverage. Despite the importance of these approaches, their development and integration in vector control programmes has been receiving inadequate attention.

Mathematical models play an important role in assessing interventions (McKenzie and Samba, 2004). Many studies evaluate intervention effectiveness (Chitnis et al., 2010; Eckhoff, 2011; Griffin et al., 2010; Gu and Novak, 2009a; Gu et al., 2006; Menach et al., 2007; White et al., 2011; Worrall et al., 2007; Yakob and Yan, 2009, 2010), depending on intervention coverage (Chitnis et al., 2010;

White et al., 2011; Worrall et al., 2007; Yakob and Yan, 2009) and the significance of distribution of mosquito resources for malaria transmission (Gu et al., 2006; Yakob and Yan, 2010). Some studies consider spatial and network models (Gu and Novak, 2009a; Gu et al., 2006; Gu and Novak, 2009b; Yakob and Yan, 2010) while others consider spatial distributions of mosquito populations (Nourridine et al., 2011; Otero et al., 2008). These models allow the evaluation of interventions by coverage or by any combination of intervention packages (Gu and Novak, 2009a).

In contrast to these studies, this paper focuses on the spatial distribution of interventions rather than on heterogeneity in distribution of resources for mosquitoes. Using insights from a recent study on mosquito movements (Lutambi et al., 2013), a spatial model of vector population dynamics and interventions is used to assess the impact of spatial distribution of vector control interventions on reducing the population of biting mosquitoes. The effects are explored at different coverage levels to provide theoretical evidence on the existence of variability in intervention effectiveness, depending on their spatial distribution.

3.3 Methods

A discrete-space continuous-time mathematical model of mosquito population dynamics and dispersal (Lutambi et al., 2013) was extended to incorporate IRS, larviciding, and ITN interventions. The model includes six stages of the mosquito life and feeding cycle: three juvenile stages (egg (E), larval (L), pupal (P)) and three adult stages (host seeking (A_h), resting (A_r), and oviposition site searching (A_o)). The population dynamics of mosquitoes in each stage are described by ordinary differential equations. The discrete space used in the model is a grid made up of hexagons called patches that allows any representation of spatial distribution of hosts and breeding sites and mosquito movement (dispersal) between patches. Dispersal of adult mosquitoes searching for hosts or breeding sites is restricted to the nearest six neighbours.

3.3.1   Model equations with interventions

As described in more details in (Lutambi et al., 2013), the population dynamics of mosquitoes are governed by the recruitment of new mosquitoes through the average number of eggs laid per oviposition, b, the development/progression rate from one stage to the next, ρ, the stage specific mortality, μ, the movement rates of host seeking, β^H, and oviposition site searching mosquitoes, β^B. The dynamics of each stage of the life cycle in patch (i,j) with interventions and movement are described using ordinary differential equations:

$$
\begin{aligned}
\frac{dE_{(i,j)}}{dt} &= b_{(i,j)}\rho_{A_o(i,j)}A_{o(i,j)} - \left(\mu_{E(i,j)} + \rho_{E(i,j)}\right)E_{(i,j)}, \\
\frac{dL_{(i,j)}}{dt} &= \rho_{E(i,j)}E_{(i,j)} - \left(\mu_{L_1(i,j)} + \rho_{L(i,j)}\right)L_{(i,j)} - \mu_{L_2(i,j)}L_{(i,j)}^2, \\
\frac{dP_{(i,j)}}{dt} &= (1 - \varepsilon_{\mathrm{LV}})\rho_{L(i,j)}L_{(i,j)} - \left(\mu_{P(i,j)} + \rho_{P(i,j)}\right)P_{(i,j)}, \\
\frac{dA_{h(i,j)}}{dt} &= \rho_{P(i,j)}P_{(i,j)} + \rho_{A_o(i,j)}A_{o(i,j)} - \left(\mu_{A_{h(i,j)}} + \rho_{A_{h(i,j)}}\right)A_{h(i,j)} \\
&\quad - \gamma_{\mathrm{ITN(i,j)}}\mu_{A_{h(i,j)}}A_{h(i,j)} - \Psi_{\mathrm{out}}^H A_{h(i,j)} + \Psi_{\mathrm{in}}^H A_{h\xi'}, \\
\frac{dA_{r(i,j)}}{dt} &= \rho_{A_{h(i,j)}}A_{h(i,j)} - \left(\mu_{A_{r(i,j)}} + \rho_{A_{r(i,j)}}\right)A_{r(i,j)} - \gamma_{\mathrm{IRS(i,j)}}\mu_{A_{r(i,j)}}A_{r(i,j)}, \\
\frac{dA_{o(i,j)}}{dt} &= \rho_{A_{r(i,j)}}A_{r(i,j)} - \left(\mu_{A_{o(i,j)}} + \rho_{A_{o(i,j)}}\right)A_{o(i,j)} - \Psi_{\mathrm{out}}^B A_{o(i,j)} + \Psi_{\mathrm{in}}^B A_{o\xi'}.
\end{aligned}
$$

The terms $\gamma_{\mathrm{IRS}(i,j)}\mu_{A_{r(i,j)}}A_{r(i,j)}$ and $\gamma_{\mathrm{ITN}(i,j)}\mu_{A_{h(i,j)}}A_{h(i,j)}$ are additional mortality terms due to IRS and ITNs respectively and described in section 3.3.2. The term $(1 - \varepsilon_{\mathrm{LV}})\rho_{L(i,j)}L_{(i,j)}$ represents the reduced number of larvae developing to pupae from untreated breeding sites, where $\varepsilon_{\mathrm{LV}}$ represents the proportion of breeding sites in a given patch covered by larvaciding (see section 3.3.3). Parameters $\Psi_{out}^H = \sum\limits_{\xi' \in N(i,j)} \beta_{(i,j)/\xi'}^H$ and $\Psi_{in}^H = \sum\limits_{\xi' \in N(i,j)} \beta_{\xi'/(i,j)}^H$ represent dispersal out and into patch i,j for host seeking adults respectively, and $N(i,j)$ is a set of six nearest neighbours to patch (i,j) and $\xi' \in N(i,j)$ (Lutambi et al., 2013). Similarly, $\Psi_{\mathrm{out}}^B = \sum\limits_{\xi' \in N(i,j)} \beta_{(i,j)/\xi'}^B$ and $\Psi_{\mathrm{in}}^B = \sum\limits_{\xi' \in N(i,j)} \beta_{\xi'/(i,j)}^B$ represent dispersal

out and into patch i, j for oviposition site searching adults. Details of calculation of β are provided in (Lutambi et al., 2013). H and B represent hosts and breeding sites respectively. The remaining parameter definitions and their corresponding values are summarized in Table 3.2.

3.3.2   Modelling of the killing effects of ITNs and IRS

ITNs kill and prevent access to people for host seeking malaria vectors, thus providing personal protection against malaria to the individuals using them (Takken, 2002; WHO, 2007). ITNs also provide community protection to non-users (Hawley et al., 2003) due to their killing effects which reduce mosquito longevity. Even if not killing directly, repellent or deterrent effects (de Zulueta and Cullen, 1963) increase the duration of host seeking and mosquito mortality during host seeking. Here, ITNs deployed in a patch are assumed to kill mosquitoes directly and repel mosquitoes seeking blood meals, hence affecting the density of host seeking adults in that patch. The killing effect of ITNs in the host seeking stage is modelled as additional mortality to normal mortality associated with host seeking process in the absence of ITNs.

IRS is the application of insecticides on the indoor walls and roofs of houses primarily to kill resting adult mosquitoes. IRS reduces malaria transmission by reducing the vector's life span and population density of vectors (WHO, 2006), but provides little direct personal protection against bites. Although some ingredients used in IRS may repel mosquitoes, this study considers only those without repellency. Therefore, only the direct killing effect to resting adult mosquitoes is considered.

For ITNs, we let γ_{ITN} be the model parameter for additional mortality of host seeking adults and for IRS, we let γ_{IRS} be the model parameter for additional mortality of resting adults. To compare interventions, γ_{ITN} and γ_{IRS} are expressed as functions of intervention efficacy where efficacy is defined as the ability of an intervention to reduce mosquito survival proportionally. For ITNs or IRS, efficacy, ε_{I}, (where I represents ITNs or IRS) is given by

$$\varepsilon_{\mathrm{I}} = \frac{S_0 - S_{\mathrm{I}}}{S_0}. \tag{3.1}$$

Here S_0 represents the survival probability of mosquitoes in the absence of an intervention in a given mosquito stage given by

$$S_0 = \frac{\rho_s}{\mu_s + \rho_s}, \tag{3.2}$$

and S_{I} represents the survival probability of mosquitoes in the presence of interventions in a given stage given by

$$S_{\mathrm{I}} = \frac{\rho_s}{\mu_T + \rho_s}. \tag{3.3}$$

In equations (3.2) and (3.3), ρ_s is the development rate of a mosquito from stage s to the next stage, and μ_s (per unit time) is the natural mortality rate of a mosquito in stage s in the absence of an intervention. μ_T (per unit time) is the total mortality rates of mosquitoes in stage s in the presence of interventions expressed by:

$$\mu_T = \mu_s + \mu_s \gamma_{\mathrm{I}}. \tag{3.4}$$

Here, γ_{I} (unitless) is a multiplicative factor associated with the effect of intervention I (ITN or IRS). The term $\mu_s \gamma_{\mathrm{I}}$ represents additional mortality of intervention, I. In order to obtain the expression for γ_{I}, we substitute equations (3.2), (3.3), and (3.4) into (3.1) to obtain

$$\gamma_{\mathrm{I}} = \frac{\varepsilon_{\mathrm{I}}(\rho_s + \mu_s)}{\mu_s(1 - \varepsilon_{\mathrm{I}})}. \tag{3.5}$$

Using the stage specific parameter values for ρ_s, and μ_s (given in Table 3.2), with $\varepsilon_{\mathrm{I}} \in [0, 1]$, the relationship between γ_{I} and ε_{I} is shown in Figure 3.1. As would be expected model intervention parameters γ_{I} increase with increasing efficacy of ITNs or IRS, with IRS showing higher values of γ_{I} compared to ITNs given our model parameter values in Table 3.2.
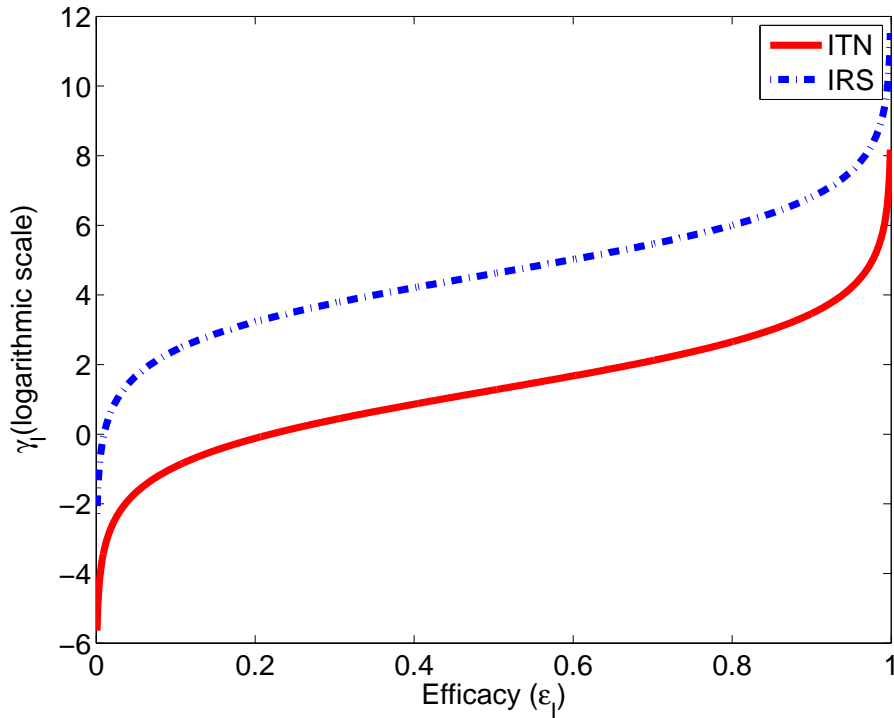
Figure 3.1: Relationship between ITN and IRS intervention parameters to efficacy (Equation 3.5).

3.3.3   Modelling the effect of larviciding

Larviciding is the application of insecticides to mosquito breeding sites targeting the larval stages of the mosquitoes. Studies show that larviciding kills all larvae in treated breeding sites (Fillinger and Lindsay, 2006; Majambere et al., 2007; Mwangangi et al., 2011) and has proved to be important in suppressing the number of malaria transmitting mosquitoes in certain areas (Fillinger and Lindsay, 2006; Kroeger et al., 1995; Majambere et al., 2007, 2010; Mwangangi et al., 2011). However, where breeding sites are scattered, field studies show that it is difficult to find and treat the majority of productive breeding sites (Killeen et al., 2006). The effect of larvaciding in the model is to reduce the development of larvae into pupae and thus include a parameter representing the proportion of breeding sites identified and treated within patch (i, j), as $\epsilon_{\mathrm{LV}}(i, j)$. The proportion $(1 - \epsilon_{\mathrm{LV}}(i, j))$ represents the untreated breeding sites, where larvae develop into pupae.

3.3.4   ITN repellency

The repellent effect of ITNs reduces the availability of hosts within a particular patch. We assume that hosts covered by ITNs are protected and some mosquitoes are repelled during the host seeking process. In the dispersal model, the attractive effect of hosts affects the dispersal rate of mosquitoes (Lutambi et al., 2013). Consequently, simulations of the repellent effect are performed by considering that only unprotected hosts are attracting mosquitoes in a particular patch (appendix 3.6).

3.3.5   Spatial clustering

Ecological models have been developed and used to study effects of landscape spatial heterogeneity on population dynamics (Hiebeler, 1997, 2000; Okuyama, 2008) with increasing interest in the field of epidemiology (Hiebeler, 2005). Some models have been used to investigate spatial clustering effects in ecology (Hiebeler, 2005; Lee et al., 2007; Su et al., 2009; Thomson and Ellner, 2003; Tsonis et al., 2008; Westerberg et al., 2005). To our knowledge, such methods have not been used by the malaria community to investigate clustering of vector control interventions. The degree of clustering, as used in this study, is a measure of the extent to which areas under interventions on a landscape are aggregated together. This degree varies from 0 (if the spatial distribution of interventions is random) to 1 (if the spatial distribution of interventions is highly concentrated on a certain portion of the landscape, or highly grouped together).

To evaluate the effect of spatial clustering of interventions using the model, we distributed interventions on the spatial grid (Lutambi et al., 2013). The spatial distribution of interventions was varied according to the degree of spatial clustering chosen. These spatial clusters used for distributing interventions were created using the pair approximation method (Hiebeler, 1997, 2000). Two pair states were used: intervention and non-intervention states. These two states

were assigned after defining a coverage area (that is proportion of patches assumed to be under interventions). Following Hiebeler (Hiebeler, 2000), the degree of clustering, q_{00} was defined as the probability that a randomly chosen neighbour to a patch with intervention also contains the intervention. Spatial clusters of varying degrees on the model grid were created in Matlab using the steps detailed by Hiebeler (Hiebeler, 2000). Several configurations of spatial clusters were created from different initial random distributions of the intervention states to account for stochasticity of the method. Figure 3.2 illustrates one such cluster configuration produced at different degrees of clustering, q_{00}, when intervention coverage is 50% over the entire grid.

For the vector control investigations, cluster configurations were created at $10\%, 30\%, 50\%$, and 70% coverage levels, with the degree of spatial clustering, q_{00} ranging from 0 to 1 at an interval of 0.1. However, it is only possible to create spatial clusters when $q_{00} \geq 2-(1/p_0)$ (Hiebeler, 2000) (where p_0 represent intervention coverage). This was due to the fact that when an intervention coverage is high, it is likely that neighbours of patches under intervention, are also under intervention. This implies a lower bound on q_{00} for high coverage.

3.3.6   Model parameterizations and assumptions

Parameter values on stage specific mortality, and development rates used to simulate the model are similar to those used in (Lutambi et al., 2013) (also presented in Table 3.2). Various experimental studies show that ITN killing efficacy is variable (Chouaibou et al., 2006; Oxborough et al., 2008) as it depends on local entomological and epidemiological conditions (Smith et al., 2009). For the parameter values of interventions, we make the assumption that ITNs and IRS are 80% efficacious so that $\varepsilon_{\mathrm{ITN}}$ and $\varepsilon_{\mathrm{IRS}}$ were fixed at 0.8.

Since the aim is to show the general trend of effects of clustering on effectiveness, and for comparing interventions on a fair basis, this study uses a the average repellent effect of 80% ($Z = 80\%$) for an ITN in all simulations. A patch coverage level (percent of resources to mosquitoes (in this case hosts)
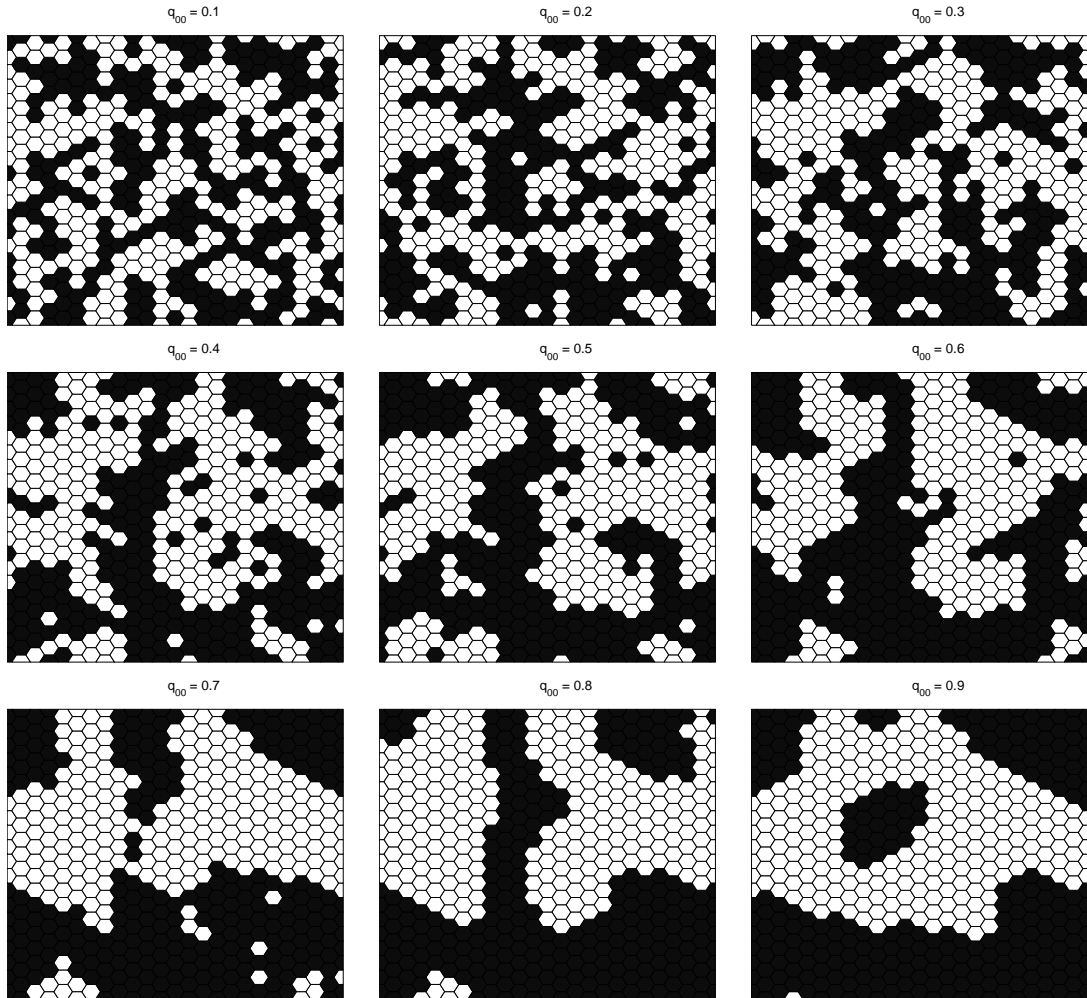
Figure 3.2: An example of spatial clusters generated at different degrees of clustering (q_{00}) with a coverage of $p_0 = 0.5$ for the desired states (white) for interventions deployment and undesired states (black). Clustering increases with increasing q_{00}.

covered within a patch) of 80% ($Pc = 80\%$) was also used.

When a larvicide is applied to a breeding site, all larvae experience an increased mortality. Field studies show that larviciding is likely to kill all larvae when applied to a breeding site (Fillinger and Lindsay, 2006; Majambere et al., 2007; Mwangangi et al., 2011). However, not all breeding sites can be identified for larvicidal treatment. Here, $80\%(\epsilon_{LV} = 0.8)$ of the breeding sites inside a patch are assumed to be identified and treated with larvicide. Thus, leaving 20% of breeding sites within a patch without larvicide, allowing larvae develop into pupae. We also make the assumption that larvae are distributed uniformly across breeding sites.

A 25 by 21 grid was used as a hypothetical representation of a landscape. The distance from the centres of neighbouring patches was assumed to be 50 m (Lutambi et al., 2013). At the edges of the grid, periodic boundary conditions were used. This assumes the area being modelled is comparable to its neighbourhood. For simplicity, simulations were performed with all patches on the grid containing breeding sites and hosts. The dispersal related parameters for host seeking (β^H) and oviposition site searching (β^B) mosquitoes depend on the availability of hosts and breeding sites respectively. Similar to (Lutambi et al., 2013), the diffusion rate, $D = 0.2$ per day was used in all simulations.

3.3.7 Simulations

Simulations were carried out in Matlab 7.10.0 (R2010a). The adaptive step size Runge-Kutta method of fourth and fifth order (*ode45*) was used to solve the system of ordinary differential equations (Eqn. (3.1)). Simulations were performed at intervention coverage levels of 0% coverage (no intervention), $10\%, 30\%, 50\%$, and 70%. The 0% level scenario was included to compute intervention effectiveness (Equation 3.7).

For each scenario a representative total population of 2700 eggs, 1900 larvae, 2000 pupae, 2400 host seeking mosquitoes, 1800 resting, and 1200 oviposition site searching mosquitoes were initially distributed across the grid. We numerically tested that there exists only one equilibrium point given different initial conditions for both the non-intervention and intervention scenarios. Simulations were run until the system (3.1) was at equilibrium. The resulting equilibrium values were recorded and used to evaluate intervention effectiveness.

3.3.8 Measuring intervention effectiveness

We define intervention effectiveness as the reduction in the total equilibrium population of host seeking mosquitoes, over all patches on the grid. In malaria transmission control, the number of potentially infective mosquitoes should be

reduced. Thus, only host seeking adults, which transmit malaria, are considered. From the model, the equilibrium total number of host seeking mosquitoes is calculated over the entire grid as

$$A_h^* = \sum_{\xi \in \Xi} A_{h\xi}^*,$$

(3.6)

where $A_{h\xi}$ is the equilibrium number of adult host seeking mosquitoes in patch ξ and Ξ is the set of all patches on the entire grid. In this context, we calculate intervention effectiveness, ϵ_{int}, as the proportionate reduction of an equilibrium population of host seeking mosquitoes, namely

$$\epsilon_{\text{int}} = 1 - \frac{A_h^{*(\text{int})}}{A_h^*},$$

(3.7)

where A_h^* is the equilibrium population of host seeking mosquitoes in the absence of interventions, and $A_h^{*(\text{int})}$ is the equilibrium population of host seeking mosquitoes in the presence of an intervention.

3.3.9 Statistical analysis of the relationship between intervention spatial clustering and effectiveness

Simulation results for each coverage level (Figures 3.3 and 3.4) were further analysed using statistical methods. The aim was to quantify the relationships between effectiveness and the degree of spatial clustering of an intervention. Since the effectiveness is measured as the proportionate reduction in host seeking mosquitoes, its range lies within 0 and 1. Thus, robust generalized linear models with a logit link (Papke and Wooldridge, 1996) were used.

3.4   Results

The effectiveness of IRS, larviciding, and ITNs is related to the degree of spatial clustering of interventions and coverage levels (Figure 3.3). When the spatial

coverage of larviciding and IRS is 10% (Figure 3.3A), simulation results indicate that these interventions are more effective when highly clustered, compared to low clustering (Table 3.1). However, at 30% coverage, high clustering of IRS appears to be no longer more effective than low clustering. For larviciding, at 30% spatial coverage level, larviciding is more effective when highly clustered compared to when lowly clustered. For ITNs distributed at low coverages of 10% to 30% (Figure 3.3A-B), the intervention is more effective with a low degree of spatial clustering compared to with a high degree of spatial clustering (ITN effectiveness is negatively correlated to the degree of spatial clustering).
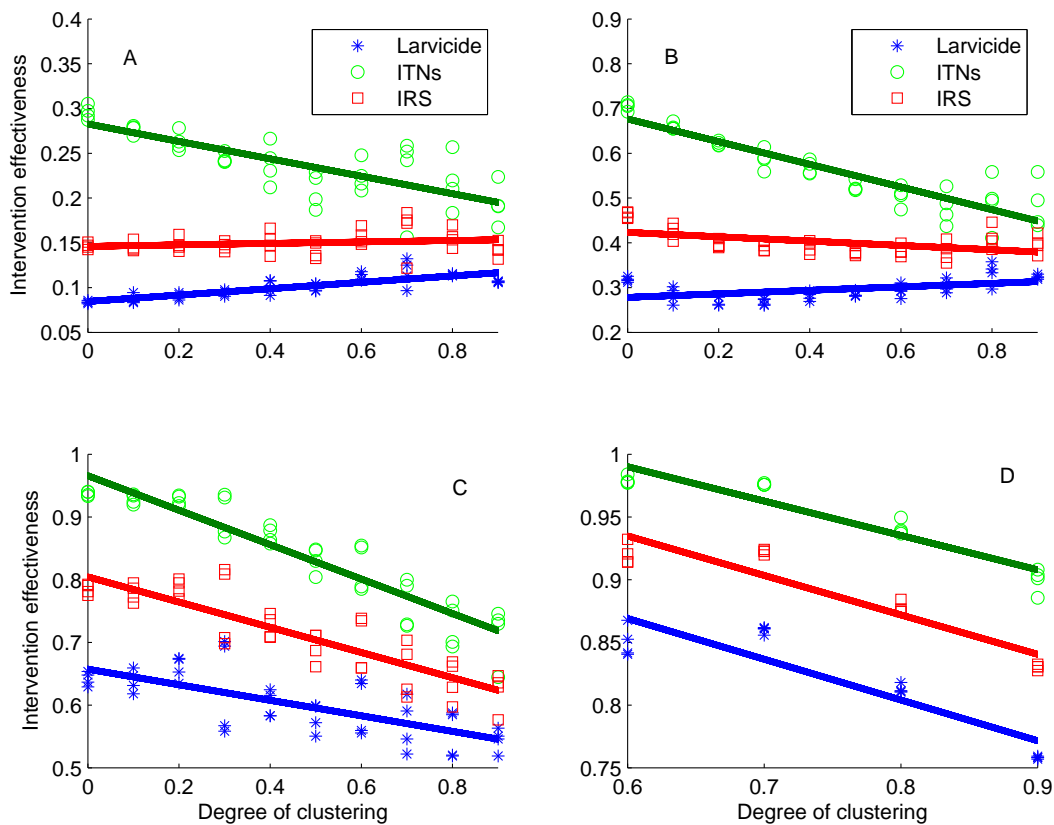
Figure 3.3: Intervention effectiveness by degree of spatial clustering of ITNs, IRS, and larviciding at different coverage levels. The symbols represent simulated intervention effectiveness data from different configurations of intervention distribution to account for stochastic variations and the lines are the result of a linear fit. Effectiveness is measured as the proportionate reduction of the equilibrium population of host seeking mosquitoes. Mosquito resources were homogeneously distributed across the grid. Coverage levels A: 10%, B: 30%, C: 50%, and D: 70%. Axes are not the same and do not start at zero.

At a moderate intervention coverage level of 50% (Figure 3.3C), there is no added benefits of highly clustering compared to low clustering of IRS and larviciding, while distributing ITNs widely was more beneficial than clustering. At intervention coverage level of 70% (Figure 3.3D), distributing interventions widely and randomly is more effective than clustering for any of the interventions.

When interventions are combined (Figure 3.4), effectiveness decreases with increasing degree of spatial clustering. However, the combination of IRS and larviciding was not associated with the degree of spatial clustering when coverage was less then 30%.
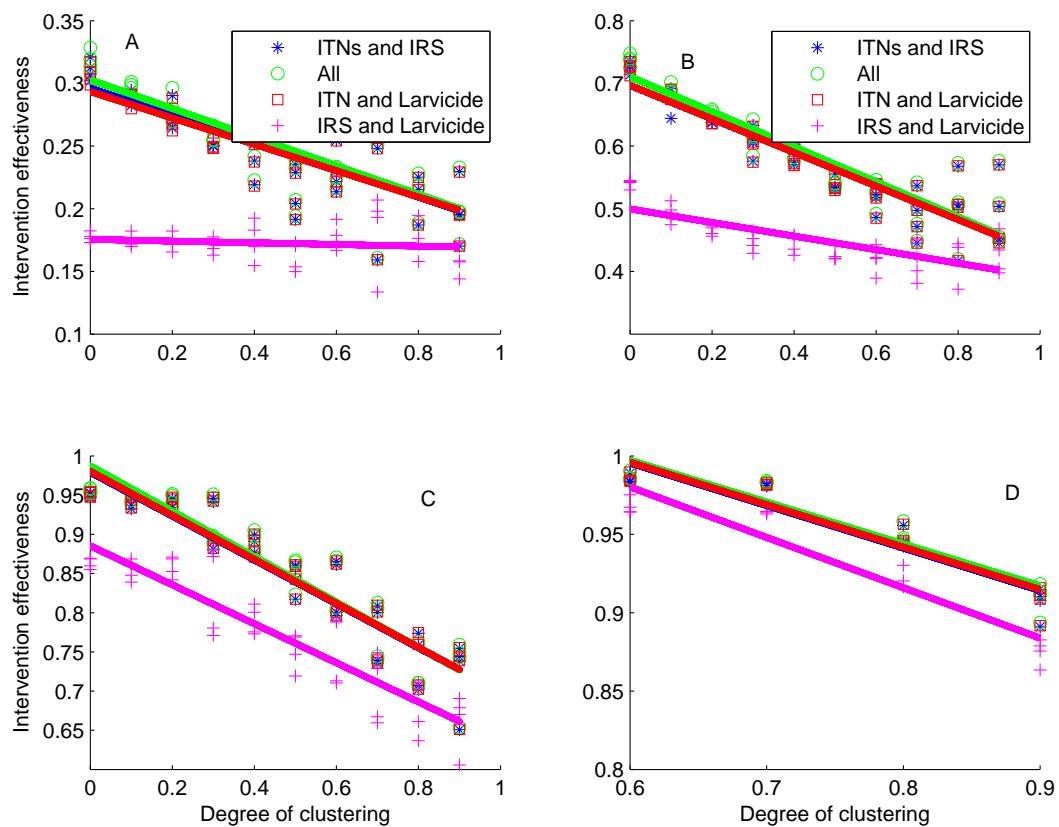
Figure 3.4: Effect of spatial clustering of interventions by coverage levels for combined interventions. The symbols represent simulated intervention effectiveness from different realizations depicting initial distribution of interventions before the process of clustering was undertaken to account for stochastic variations and the lines are the result of a linear fit. Mosquito resources were homogeneously distributed over the grid. Coverage levels A: 10%, B: 30%, C: 50%, and D: 70%. Axes are not the same and do not start at zero.

Effectiveness of an intervention at zero clustering is highest for ITNs and lowest for larviciding (given our parameter values) when interventions are singly deployed (Table 3.1). Effectiveness at zero clustering is highest when all interventions are combined together, but the additional effect over ITNs alone is small. The combination of IRS and larviciding had the lowest effectiveness at zero clustering, irrespective of the coverage level.

The predicted effectiveness varies strongly with coverage level, degree of spatial clustering, and intervention or combination of interventions. At low coverage, effectiveness increases with clustering for the less effective interventions, in particular larviciding (Table 3.1) and decreases with clustering for the more effective interventions, in particular ITNs (Figure 3.3A and B and Table 3.1). At moderate and high coverage levels, effectiveness decreases with clustering with similar slopes for different intervention (Figure 3.3D and (Figure 3.4C).

At lower spatial coverage levels of single interventions, the difference in effectiveness between one intervention and another decreases with increasing value of the degree of spatial clustering. This difference remains almost constant at high coverage levels (Figure 3.3). For combined interventions and at all coverage levels, there is almost no difference in effectiveness for all combinations of interventions that included ITNs (Figure 3.4). The effectiveness of a combination of IRS and larviciding is consistently lower across all coverage levels. In addition, the difference in effectiveness between a combination of IRS and larviciding and other combinations is always high. However, at lower coverage levels, this difference decreased with increasing degree of spatial clustering (Figure 3.4A and B).

Table 3.1: Association between intervention effectiveness and the degree of spatial clustering of interventions by coverage levels. β_1 is an estimate (gradient) of the effect of the degree of spatial clustering of an intervention and β_0 is an intercept measuring the effectiveness of the intervention at zero clustering. The higher β_0, the higher the the effectiveness at zero clustering. Figures in parenthesis are standard error.

Coverage	10%	30%	50%	70%
Effectiveness at zero clustering (β_0)(logit transformed) [a]				
Larvicide	-2.37 (0.02)	-0.95 (0.04)	0.65 (0.04)	2.29 (0.24)
ITNs	-0.92 (0.02)	0.73 (0.04)	2.80 (0.06)	6.56 (0.41)
IRS	-1.77(0.02)	-0.31 (0.03)	1.38 (0.04)	3.49 (0.28)
IRS and larviciding	-1.55 (0.02)	0.00 (0.04)	1.93 (0.05)	6.21 (0.38)
ITNs and IRS	-0.86 (0.02)	0.82 (0.04)	3.01 (0.07)	7.41 (0.45)
ITNs and larviciding	-0.87 (0.02)	0.82 (0.04)	3.03 (0.07)	7.51 (0.45)
All	-0.82 (0.02)	0.88 (0.04)	3.14 (0.07)	7.78 (0.46)
Effect of clustering (β_1) on the effectiveness (logit scale)				
Larviciding	0.39 (0.04)[b]	0.19 (0.07)[b]	-0.52 (0.06)	-1.09 (0.32)
ITNs	-0.54 (0.07)	-1.04 (0.10)	-2.20 (0.12)	-4.75 (0.50)
IRS	0.06 (0.05)[b]	-0.20 (0.07)	-0.99 (0.07)	-1.95 (0.36)
IRS and larviciding	-0.05 (0.05)	-0.43 (0.08)	-1.46 (0.09)	-4.73 (0.49)
ITNs and IRS	-0.59 (0.07)	-1.11 (0.10)	-2.42 (0.13)	-5.64 (0.54)
ITNs and larviciding	-0.57 (0.07)	-1.11 (0.10)	-2.44(0.13)	-5.75 (0.54)
All	-0.61 (0.07)	-1.17 (0.10)	-2.5(0.14)	-6.02 (0.55)

[a] $\beta_0 = \ln(\frac{p_0}{1-p_0})$, where p_0 is the actual effectiveness
[b] Positive relationship, implying a benefit of clustering the intervention

3.5 Discussion

In this study, an existing mathematical model of mosquito dispersal (Lutambi et al., 2013) was extended to include vector control interventions. This model was combined with an approach for modelling spatially heterogeneous landscapes (Hiebeler, 2000) to assess the effects of spatial clustering of vector control interventions on their effectiveness at various levels of spatial coverage and intervention combinations. As in another study White et al. (2011), the reduction in the overall vector population density was used as an indicator of the population-wide effect of interventions. The results have important implications for deployment strategies in situations where universal coverage is not achievable.

Our model indicates that, with a single intervention of either larviciding or IRS in an environment where breeding sites and hosts are homogeneously distributed and spatial coverage of the intervention is low (i.e. few patches are covered), there is a small increase in effectiveness when deployment is highly spatially clustered compared to widely distributed in space. However, with high spatial coverage, it is more effective to distribute these interventions randomly in an unclustered manner. ITNs were less effective at a higher degree of clustering than at a lower degree of clustering for any spatial coverage level.

At a spatial coverage of less than 50%, if larviciding is highly clustered, then treated areas become almost mosquito free. However, if larviciding is not clustered, mosquitoes that breed in neighbouring patches can still feed in areas that have been larvicided. If coverage is moderate to high (50% or larger), larviciding is more effective when randomly distributed and unclustered, because a greater proportion of the remaining adult mosquitoes is likely to encounter the intervention when ovipositing. When larviciding is clustered, most of the ovipositing occurs in non-larvicided areas because adult mosquitoes are rare in larvicided areas. When larviciding is widespread and unclustered, a proportion of adult mosquitoes emerging in non-larvicided patches will migrate to, feed and oviposit in larvicided breeding sites.

With adulticidal interventions, especially ITNs, the benefits of distributing the intervention widely and unclustered are greater, because the mosquitoes need to avoid intervention patches each gonotrophic cycle if they are to survive. Where adulticidal interventions are clustered, mosquitoes emerging in locations remote from the intervention area are unlikely to be killed, whereas when interventions are non-clustered, a mosquito will encounter them sooner or later. Consequently, at any spatial coverage level, average biting densities are reduced more by deploying ITNs in an unclustered manner than by clustering them. It also follows that widespread distribution of adulticidal interventions will reduce the number of old (potentially disease-transmitting) mosquitoes even more than it will reduce average densities. This finding, that the overall effect in the reduction of mosquito numbers is much greater if the intervention is spatially non-clustered and widely distributed, especially when coverage is moderate and insufficient to achieve universal coverage, contradicts the notion that a locally high coverage is needed to achieve a community effect of ITNs or IRS for reduction in disease.

While non-clustered deployment of most intervention packages is generally most effective, this may be expensive to achieve since it requires delivery even to remote locations. Interventions are more cheaply delivered to more accessible areas, resulting often in clustered (and sometimes inequitable) distributions. To investigate how delivery costs affect cost-effectiveness, there is a need for modelling of different distribution schemes (for example for ITNs or IRS) of interventions given a fixed budget in various settings with different degrees of clustering, coverage levels and accessibility.

In the cases of larviciding and IRS, these results lead to the practical question of how to decide whether or not a program is likely to achieve a level of effectiveness where clustering should be avoided. This is not simply a question of the efficacy of the intervention, because the different vector control interventions act in different ways. So the efficacy, defined as the effect on the target stage of

the vector as a proportion of the theoretical maximum effect, translates differently into effectiveness defined on some common metric of levels of transmission, disease control, or, in this paper, densities of host seeking mosquitoes. We have assumed 80% efficacious interventions throughout, and our results are consistent with other modelling work suggesting that at constant efficacy, ITNs have the highest impact on biting densities of mosquitoes (Chitnis et al., 2010; White et al., 2011) and in our simulations any combination of interventions which includes ITNs is also highly effective at all levels of coverage and across all spatial clusters. However, the efficacy that can be achieved in practice is very different for the different interventions.

The total area modelled in this study was limited to one square kilometre. The patch size, with patch centroids 50 m apart, determined in (Lutambi et al., 2013), and used in this work, was based on flight distances of mosquitoes and numerical ease. The diffusion coefficient of dispersal scales with patch size and as a result the equilibrium results presented in this study also scale with increasing patch size or increasing number of patches (and total area modelled). The current results are indicative of the effect of applying interventions within a small village, with a small number of dwellings or breeding sites per patch, but should also be broadly applicable to smaller patches corresponding to single individuals or breeding sites. We would not necessarily expect the same results to hold with very large patches, e.g. corresponding to whole villages where patch size might be comparable to the flight range of the mosquitoes and where other factors such as spatial variation within patches might be relevant.

Modelling and simulation provides a much easier approach to investigate these issues than field studies do, but inevitably requires making simplifying assumptions. This analysis focuses on general principles and intervention effectiveness on downstream outcomes such as morbidity and mortality (Lengeler, 2004) (which would require more complicated models), was not assessed. The simulations assumed homogeneous distributions of both human hosts and

breeding sites, and the cues that these resources provide that influence movement of mosquitoes cancel each other out, therefore movement was not influenced by the availability of these resources (Killeen et al., 2001). Further investigations need to incorporate scenarios in which mosquito resources such as breeding sites and hosts are heterogeneously distributed. In such scenarios, knowledge about hotspots will allow targeted (and therefore likely spatially clustered) deployment of interventions and this may well be more cost-effective than non-clustered deployment. In other words, in scenarios with spatially heterogeneous resources for mosquitoes, the cost of knowledge about where these are may well compensate for potential gains in effectiveness. However, in the absence of knowledge about spatial location of resources for mosquitoes (even for scenarios with heterogeneous resources) non-clustered distribution may be most cost-effective.

Results from this study provide evidence that the effectiveness of an intervention can be highly dependent on its spatial distribution. Given logistical and financial constraints, vector control plans should consider the spatial arrangement of any intervention package to ensure effectiveness is maximized, and in the case of high achievable coverage, in the absence of information that allows targeting, that the distribution is as equitable and as evenly spatially spread as possible as this will maximise benefits.

3.6   Appendix: Modelling ITN repellency

In addition to the killing effect of ITNs that directly affects the density of host seeking adults, the pyrethroid insecticide used to treat nets has a repellent effect acting as a chemical barrier that irritates mosquitoes as they come close to the nets. Repellency of nets reduces the availability of blood meals to mosquitoes, increases host searching time, and subsequently prolongs the mosquito gonotrophic cycle duration which in turn impacts mosquito population size. Doing so, the repellent effect of ITNs acts on host seeking mosquitoes. All hosts covered by ITNs are therefore protected to degree Z as mosquitoes

are repelled during the host seeking process. We model the repellency effect of ITNs as follows:

Let Pc be the proportion of hosts within a patch who are covered by ITNs (patch coverage), and Z be the repellent effect of ITNs. If $H_{(i,j)}$ is the number of hosts in patch (i,j), and $I_{(i,j)} = H_{(i,j)}Pc_{(i,j)}Z$ is the number of protected hosts in patch (i,j), then the number of unprotected hosts ($U_{(i,j)}$) in that particular patch is given by

$$U_{(i,j)} = H_{(i,j)} - I_{(i,j)} = H_{(i,j)}\left(1 - Pc_{(i,j)}Z\right). \tag{3.8}$$

If the patch does not have ITNs ($Pc_{(i,j)} = 0$), then $U_{(i,j)} = H_{(i,j)}$.

Since the repellent effect of ITNs affects host seeking mosquitoes, their dispersal rate into patches containing ITNs is affected. This effect is included by assuming that ITN repellency reduces hosts availability to mosquitoes in a given patch so that attractiveness of the patch to hosts seeking mosquitoes is reduced. The dispersal rate, $\beta^H_{\xi'/(i,j)}$, detailed in (Lutambi et al., 2013) was modified by replacing the number of hosts present in a patch by those who are not protected by ITNs in the particular patch as:

$$\beta^H_{\xi'/(i,j)} = De^{-\lambda\left(\bar{U}^{ij}_{\xi'} - \bar{U}^{ij}_{\xi}\right)} \tag{3.9}$$

where $\bar{U}^{ij}_{\xi'}$ is the proportion of unprotected hosts available in patch ξ' contained in $c_{i,j}$ given by $\bar{U}^{ij}_{\xi'} = U^{\xi'}/H^{ij}_u$, and H_u is the total number of unprotected hosts in $c_{i,j}$. Here, $c_{i,j}$ is a set of seven neighboring patches.

Table 3.2: Summary of parameter values used in model simulations (details in (Lutambi et al., 2013)).

Parameter	Description	Units	Baseline	Source
b	number of female eggs laid per oviposition mosquitoes	-	100	(Service, 2004)
ρ_E	egg hatching rate into larvae	day^{-1}	0.50	(Service, 2004; Holsetein, 1954; Yaro et al., 2006)
ρ_L	rate at which larvae develop into pupae	day^{-1}	0.14	(Bayoh and Lindsay, 2003; Gething et al., 2011b)
ρ_P	rate at which pupae develop into adult	day^{-1}	0.50	(Service, 2004; Holsetein, 1954)
μ_E	egg mortality rate	day^{-1}	0.56	(Okogun, 2005)
μ_{L_1}	density-independent larvae mortality rate	day^{-1}	0.44	(Okogun, 2005)
μ_{L_2}	density-dependent larvae mortality rate	day^{-1} mosq.$^{-1}$	0.05	
μ_P	pupae mortality rate	day^{-1}	0.37	(Okogun, 2005)
ρ_{A_h}	rate at which host seeking mosquitoes enter the resting state	day^{-1}	0.46	(Chitnis et al., 2008b; Lutambi et al., 2013)
ρ_{A_r}	rate at which resting mosquitoes enter oviposition searching state	day^{-1}	0.43	(Chitnis et al., 2008b)
ρ_{A_o}	oviposition rate	day^{-1}	3.0	(Chitnis et al., 2008b)
μ_{A_h}	mortality rate of mosquitoes of searching for hosts	day^{-1}	0.18	(Chitnis et al., 2008b; Lutambi et al., 2013)
μ_{A_r}	mortality rate of resting mosquitoes	day^{-1}	0.0043	(Chitnis et al., 2008b)
μ_{A_o}	mortality rate of mosquitoes searching for oviposition sites	day^{-1}	0.41	(Chitnis et al., 2008b)

CHAPTER 4

Discussion

The interaction between a heterogeneous environment and ecological behaviour of malaria vectors requires novel modelling approaches that can investigate these complex relationships. This thesis contributes o this investigation by developing a mathematical model for local mosquito dispersal to understand vector ecological behaviours, distribution of mosquitoes, and their interactions with malaria vector control interventions. This model sets up a framework for use in understanding, assessing, and evaluating the malaria intervention programs. The model was simulated and applied to explain some properties of heterogeneity, and to answer specific questions concerning current malaria vector control interventions.

This chapter gives an overview of the model developed and its extensions, summarizes the results obtained from applying the model, discusses contributions and implications, provides directions for future work, and highlights the conclusions.

4.1   Model overview

The model developed in this thesis categorizes the life of a mosquito into six stages; namely, egg, larva, pupa, host seeking, resting, and oviposition site searching adults. It consists of three main components (Chapter 2) . The first component is the continuous time model based on ordinary differential equations that describe the population dynamics of mosquitoes in each stage. The dynamics are driven by the birth, mortality, and development rates from one stage to another. The second component of the model involves the inclusion of the spatial characteristics. The space is discretised into discrete locations to form a spatial grid made by hexagonal patches. The third component of the model involves modelling dispersal of adult mosquitoes which move from one patch to another across the spatial grid in search of hosts and breeding sites.

The model incorporates two key features: spatial heterogeneity and mosquito dispersal. Spatial heterogeneity was included by allowing hosts and breeding sites (resources) to differ between patches across the spatial grid (Chapter 2). Mosquito dispersal was modelled using the nearest neighbour approach where dispersal of adult mosquitoes searching for hosts or breeding sites is restricted to the nearest six neighbouring patches. Because of the neighbour to neighbour dispersal nature, dispersal of mosquitoes from one patch to other patches is only affected by the patches bordering each neighbourhood. In this case, the number of resources used by mosquitoes available in the neighbour locations influence movement of mosquitoes present in a certain location. Therefore, all nearest neighbours of each patch on the spatial grid were identified and the number of resources counted. The proportion of available resources in each patch relative to each neighbourhood was computed and used as input values in the dispersal rate of mosquitoes.

In order to incorporate the effects of spatial repellents, two approaches have been developed as extensions to the model. Chapter 2 presents the first approach to modelling the effects of spatial repellents. This approach includes those repellents which act on the whole area where they are applied to protect

all individuals living in the area by creating a mosquito free space (Achee et al., 2012; Grieco et al., 2007) or those which act as non physical treatment barriers (Britch et al., 2009). The second modelling approach of repellents is presented in Chapter 3. This approach includes those repellents which protect only individuals using them, for example ITNs. They reduce the number of potential hosts available to mosquitoes in the area or location of application, leaving non-users under risk of contacting the disease (Achee et al., 2012). These approaches can have similar functions if the repellents provide full protection to all individuals in a given location by either driving all mosquitoes away or blocking them from entering. However, in situations where mosquitoes have insecticide resistance, these approaches function differently, providing an alternative to situations of reduced effects.

Another extension to the model was made in order to incorporate parameters for vector control interventions (Chapter 3). Interventions such as larvicide, ITNs, and IRS were included in equations describing the dynamics of larvae, host seeking, and resting stages respectively as additional mortality due to interventions. These interventions were spatially distributed on the spatial grid depending on coverage level based on spatial cluster configurations generated using available numerical algorithms (Hiebeler, 1997, 2000).

4.2 Summary of results

Investigations of the effects of heterogeneity showed that mosquito dispersal is highly unstable as it is dependent on the availability of resources used by mosquitoes. If hosts and breeding sites are separated and the distance between them is large, then mosquitoes can be eliminated without requiring an intervention. Because mosquitoes are forced to move longer distances searching for hosts and breeding sites, the feeding cycle is prolonged (Chitnis et al., 2008b; Menach et al., 2007) and mortality is increased (Saul, 2003). From the host point of view, living near by mosquito breeding sites increases exposure

to mosquito bites and potentially to the disease. Because the vector-host ratio is higher around breeding sites, removing breeding sites in areas of human habitation can prevent mosquitoes from using human hosts for blood meals, hence preventing disease transmission.

Results of spatial distribution of interventions show that when randomly distributed, interventions would maximize the community effect of an intervention. This is because distributing interventions widely reduces the distance from locations under interventions and those without interventions. In so doing, the effects of an intervention are maximized. A study by (Gimnig et al., 2003) shows that interventions such as ITNs confer community effects to neighbouring villages which are not under interventions. These villages benefit from interventions deployed in neighbouring villages. Although these benefits may vary, places that are close to intervention areas get more protection compare to those that are far away. Mosquito dispersal is another factor that causes community effect. Dispersal of mosquitoes leading to exchange of vectors between neighbouring places can have a negative effect when an intervention is evaluated (Killeen et al., 2003). This is because the effect of an intervention is shared between places. In so doing some areas receive an indirect benefit of an intervention delivered within their proximity (Gimnig et al., 2003). Although community effect of an intervention might be seen as due to the overall reduction of mosquito density (Gimnig et al., 2003), this thesis have indicated that mosquito dispersal is another factor that causes community effect. Even interventions like larviciding which targets the aquatic stage of the mosquitoes could still show that randomly distributing them is beneficial. This is because in the presence of dispersal, the likelihood that gravid mosquitoes lay eggs in breeding sites under larvicide is high.

Current vector control programs target at host seeking, resting, and larva stages (WHO, 2012). When these intervention programs are compared, several studies show that interventions targeting the host seeking stage of the mosquito such as ITNs/LLINs are the most effective interventions (White et al., 2011). Furthermore, current evidence indicates that IRS targeting resting mosquitoes

is more effective than larvicide which targets at larvae (White et al., 2011). The concept is that adult stages are involved directly in the transmission process than larvae and the impact of adultciding is highly non-linear because of the relationship of vectorial capacity with adult survival (Macdonald, 1956).

Treatment barriers such as spatial repellents are of great importance in malaria vector control (de Zulueta and Cullen, 1963). Using the model, the effects of spatial repellents on the distance travelled by mosquitoes under the natural phenomenon of dispersal were investigated. It was found that distributing repellents encircling a cluster of households in the region is an advantageous strategy only if mosquito sources are few, clearly defined, and known. If not, then, distributing repellents randomly has an advantage as it reduces the distance moved by mosquitoes by make it difficult for mosquitoes to complete their life cycle.

4.3   Contributions

The model has several contributions to science and to public health. The coupling of the compartments of each mosquito stage and the spatial grid of the model makes it comprehensive but simple model that explicitly captures mosquito behavioural and ecological features that are often neglected.

The model incorporates both the aquatic and adult stages of the mosquito life cycle and further divides the adult mosquito population into three classes of the mosquitoes searching for hosts, those resting, and those searching for oviposition sites. These three classes provide an opportunity to study the life style of the adult mosquito, and also offer direct opportunity to assess the impact of interventions specifically targeting a certain state to reduces contacts between mosquitoes and human hosts. For example, larvicide, ITNs, and IRS were directly incorporated in the larval, host seeking, and resting stage respectively. The inclusion of the oviposition site searching stage can be used to assess the impact of the transfer of insecticides by oviposition site searching mosquitoes from treated rested walls to breeding sites (Devine et al., 2009).

The advantage of the discrete space model developed in this work is that one can easily assess vector control strategies, because the discrete space enables easy representation of interventions that cover sets of households or villages. The model, together with field data, can be used to determine areas of high transmission within local settings, evaluate the community effect of interventions, and assist to develop possible and efficient vector control strategies, which can optimize the allocation of scarce resources.

In situations where countries approach malaria elimination, transmission hotspots normally appear to maintain transmission, especially during high transmission seasons (Bousema et al., 2012). These hotspots are a collection or a cluster of households. When full coverage of these clusters is not possible, the model presented in this thesis suggests better ways of distributing interventions, even at very low coverage levels. Because of mobility behaviour of mosquitoes, the transmission hotspot buffers can extend to areas that are no longer involved in transmission. In a situation like this one, the model can be used to define buffer zones of possible transmission, for targeted interventions.

This work provide means for measuring numbers moving from one hut to another based on treatment schemes. For example, by considering only host seeking mosquitoes, parameter values for the dispersal of host seeking mosquitoes can be determined in the presence and absence of interventions. With the growing need to understand the interaction between repellent effect and the contact insecticide properties, the model may be able to make use of the estimates of diversion/killing rates, and can be linked to data from experimental hut trials, including mark-recapture studies on mosquito movement.

In practice, optimal deployment strategies need to identify the type of settings suitable for a particular intervention, to identify the kind of delivery modes to be considered, how to best integrate specific interventions with the health system. In addition, the model can help understand whether or not high coverage is important especially when countries are economically constrained. The model can be used in the field to determine locations in villages where the

mosquito population is likely to be older and hence contains more infectious vectors, or peripheral areas where the population of mosquitoes is likely to be more newly emerged mosquitoes.

4.4   Implications

Based on the results, the model will stimulate dialogue and future modelling directions in response to the results generated by this study and field research for valuable resource management and rational decisions about strategies for local malaria control. The translation of the knowledge gained from models to the field will improve our understanding of ecological processes such as dispersal and interactions among populations.

Methodologically, malaria elimination plans are confronted by the difficulty of how best interventions should be distributed in cases where full coverage is not possible. The WHO provides guidelines of vector management (WHO, 2004), however, until now, effective ways of distributing vector control interventions are not known. This study, through simulations, provides a solution to how interventions should be distributed when coverage is not 100%. This work is a first attempt to assess the effect of spatial distribution of interventions when the mosquitoes' natural behaviour of dispersal is included. Thus, this study has served a useful purpose as a guide for understanding the interplay between spatial distribution of interventions and effectiveness. It could also serve as a prototype for future modelling work, planning, implementation, and management of vector control for reducing malaria transmission in endemic places.

Mathematical analysis is an essential tool for assessing the true impact of each parameter and to provide evidence for interventions that aim at reducing mosquito abundance. Results from analysis that host seeking mosquitoes are important for control agree with the current focus of vector control interventions where interventions like ITNs targeting host seeking mosquitoes have reduced the malaria burden in most endemic countries (WHO, 2012). In addition, results

of intervention effectiveness from this study highlights the significance of targeting host seeking mosquitoes. This evidence has important implications for the vector management and for understanding the role of each stage in sustaining the mosquito population.

The findings concerning different impacts of heterogeneity have important implications for the development of control strategies. In addition, the model can be used to explore the implications of the resulting multiplicity of combinations of different environments with intervention strategies in understanding malaria epidemiology and control. The knowledge gained from the model allow informed decisions on designing the most effective intervention strategies in the area. At local level, transmission appears to be shaped by the availability of resources (Smith et al., 2004) because mosquito movement between places is often related to the distribution of resources. Thus, routine movement play a key role in spread diseases at local spatial scales. This finding has important implications for malaria prevention, challenging the appropriateness of current approaches to vector control. The argument is that assessment of current approaches and sampling methods used in vector control should consider vector dispersal. This will lead to improvements in preventing transmission.

4.5 Limitations and Future work

The model developed in this thesis has some limitations but also is capable of accommodating further extensions which could improve its performance qualities to enable further investigations.

From the mathematical point of view, the dispersal model could be analysed further to gain mathematical insight. Since all patches become connected during dispersal, computing the mosquito reproduction number for the whole domain would help understand the effects of dispersal on the overall total population of mosquitoes and its implication on the maintaining disease risk.

The development times of each stage of the mosquito, particularly the aquatic

stages highly dependent on the environmental conditions. Since the model structured the mosquito into its life stages, incorporating environmental and seasonal effects such as rainfall, temperature is possible (Depinay et al., 2004; Lunde et al., 2013; Otero et al., 2006; Stoddard et al., 2012). These environment-dependent parameters include the mosquito recruitment or birth rate, the mosquito mortality rates, and the development rates. The seasonal effects could be modelled by making some of these parameters periodic functions of time. However, these environmental effects have implications on the analytical results of the model. Analysing periodical models with changes in the mosquito population reproductive number and steady states is complex but could provide more information on the spatial distribution of mosquitoes over time and its implications on the distribution of vector control interventions.

The assumption of constant number of hosts in each patch allowed a straight-forward assessment of the effects of host availability on mosquito distribution. However, in real situations, human hosts move from one place to another. Studies idicate that human movement is an important factor in resurgence of vector-borne diseases such as malaria and dengue (Adams and Kapan, 2009; Cosner et al., 2009; Stoddard et al., 2009; Tatem et al., 2009). Local human movement between houses affect the local distribution of disease (Stoddard et al., 2012) as human movement changes the distribution of human hosts, hence affecting the dispersal rate of host seeking mosquitoes. This has implications on the malaria transmission and could affect the performance of vector control interventions and the effectiveness of the distribution strategies of these interventions. A further extension to the model would be to combine both local movement of hosts and vector dispersal. This would help to understand the distribution of risks and to determine which among the two factors have the most significant effect in sustaining malaria transmission in local settings.

The presence of wind facilitates dispersal if the movement of the mosquito is in the same direction as that of the wind. In some cases, especially when wind speed is high, the mosquito can be blown away from its original direction. This

could affect the distribution of mosquitoes and has implications on the distribution of malaria risk. An extension to the model to incorporate wind effects on mosquito dispersal could help to understand non-behavioural influences.

Studies suggest that host odour attracts host-seeking mosquitoes (Knols and Meijerink, 1997; Mukabana et al., 2002) which are due to the differences in the make-up of body emanations, and olfactory signals in particular (Okumu et al., 2010). This is another factor to include in the model. However, the challenge would be to link host odour influence on dispersal with the effect of wind. Including the influence of host odour raises another important factor, the differential attractiveness (Costantini et al., 1998; Knols et al., 1995; Mukabana et al., 2002) and the emission of different levels of carbon-dioxide (CO_2) by different hosts. It is known from the model that there is a direct relationship between the host density within a patch and the number of mosquitoes in that particular patch. An additional extension to include variability in attractiveness to mosquitoes (Takken and Verhulst, 2013) could help identify the factors that influence dispersal more strongly. Thus, providing an understanding of the main factors that influence the spatial distribution of vectors and hence malaria risk.

In the field, the model could be validated by applying it to an area which is endemic to malaria. Using data from mark-recapture studies, parameter values specific to particular locations could be used as input values in the model, and simulations of the effects of host and breeding sites distribution on the distribution of mosquitoes could be made with and without interventions.

4.6   Conclusions

This thesis has presented a mathematical model with the life cycle and feeding cycle model where the adult host-seeking and oviposition site-seeking mosquitoes move between patches. The model developed in this work can be used to assign different levels of attractiveness to the patches depending on their properties. This work has shown the applicability of the model developed and

the results have refined our knowledge of how distribution of interventions can affect their effectiveness. This model can serve as a groundwork for future studies aiming at exploring the relationship between heterogeneity and malaria risks and the effectiveness of interventions.

Mosquito dispersal and the different patterns of heterogeneity have various effects on mosquito population distributions, and thus, that of malaria. Counterintuitive findings include the observation that random distribution of spatial repellents reduces the distance moved by mosquitoes. It might also be expected that models that incorporate dispersal when integrated with environmental heterogeneity could be used to predict the high-risk areas for targeting malaria vector control, however we find that random distribution of malaria vector control interventions such as ITNs, IRS, and larviciding will in general be more effective than clustering them.

Crucial to assessing disease transmission spatial variations, this work shows that alongside patterns of heterogeneity, mosquito dispersal should be considered when designing intervention strategies. The spatial grid is a realistic representation of spatial variations and thus, offering a promising way of quantifying variability of mosquito densities in different local settings of environmental heterogeneity. The predictions made by model presented in this thesis can be intuitively understood and the relative risk between various areas can easily be conveyed to policy and decision makers. This thesis provides another considerable step towards the techniques and knowledge required for more effective strategies in the management of vector borne diseases. Moreover it has a potential for continued research into dispersal models across heterogeneous environments by providing a simple framework that researchers can use for further investigations.

Taken together, spatially-explicit dispersal models integrated with environmental heterogeneity allow predictions to capture ecological behaviour of mosquitoes,

the main source of variations in malaria risk at local spatial scales. These predictions vary in space but provide more information than predictions of models that assume enclosed systems without taking into account the underlying heterogeneity of the landscape. Such predictions can assist not only in determining risk areas for targeted control, but also in determining optimal strategies for deploying interventions to assist achieving malaria elimination goals.

Throughout this thesis, the importance of models that incorporate dispersal and environmental heterogeneity, and the variations in intervention distribution was shown. This model and the results emerging from its application are essential for implementation of better malaria vector control programs. Together with field data, this model could help determine better ways of spatially distributing interventions in local settings to optimize the allocation of scarce resources available especially when country economies do not allow high coverage levels.

Bibliography

Achee, N. L., Bangs, M. J., Farlow, R., Killeen, G. F., Lindsay, S., Logan, J. G., Moore, S. J., Rowland, M., Sweeney, K., Torr, S. J., Zwiebel, L. J., and Grieco, J. P. (2012). Spatial repellents: from discovery and development to evidence-based validation. *Malaria Journal*, 11:164.

Adams, B. and Kapan, D. D. (2009). Man bites mosquito: Understanding the contribution of human movement to vector-borne disease dynamics. *PLoS ONE*, 4(8).

Alonso, W. J. and Schuck-Paim, C. (2006). The 'ghosts' that pester studies on learning in mosquitoes: guidelines to chase them off. *Medical and Veterinary Entomology*, 20(2):157 – 165.

Arino, J., Davis, J. R., Hartley, D., Jordan, R., Miller, J. M., and van den Driessche, P. (2005). A multi-species epidemic model with spatial dynamics. *Mathematical Medicine and Biology*, 22(2):129–142.

Arino, J., Jordan, R., and van den Driessche, P. (2007). Quarantine in a multi-species epidemic model with spatial dynamics. *Mathematical Biosciences*, 206(1):46–60.

Bayoh, M. N. and Lindsay, S. W. (2003). Effect of Temperature on the development of the aquatic stages of *Anopheles gambiae sensu stricto* (Diptera: Culicidae). *Bulletin of Entomological Research*, 93(5):375 – 381.

Bayoh, M. N., Mathias, D. K., Odiere, M. R., Mutuku, F. M., Kamau, L., Gimnig, J. E., Vulule, J. M., Hawley, W. A., Hamel, M. J., and Walker, E. D. (2010). *Anopheles gambiae*: historical population decline associated with regional distribution of insecticide-treated bed nets in western Nyanza province, Kenya. *Malaria Journal*, 9(62).

Becker, N., Petric, D., Zgomba, M., Boase, C., Dahl, C., Madon, M., and Kaiser, A. (2010). *Mosquitoes and Their Control.* Springer, Second edition.

Beier, J. C. (1996). Frequent blood-feeding and restrictive sugar-feeding behavior enhance the malaria vector potential of *Anopheles gambiae sl* and *An. funestus* (Diptera: Culicidae) in western Kenya. *Journal of Medical Entomology*, 33(4).

Bell, D., Wongsrichanalai, C., and Barnwell, J. W. (2006). Ensuring quality and access for malaria diagnosis: how can it be achieved? *Nature Reviews Microbiology*, 4:S7 – S20.

Blower, S. M. and Dowlatabadi, H. (1994). Sensitivity and Uncertainty Analysis of complex models of Disease Transmission: an HIV model, as an Example. *International Statistical Review*, 62(2):229–243.

Bousema, T., Griffin, J. T., Sauerwein, R. W., Smith, D. L., Churcher, T. S., Takken, W., Ghani, A., Drakeley, C., and Gosling, R. (2012). Hitting hotspots: Spatial targeting of malaria for control and elimination. *PLoS Medicine*, 9(1).

Bowen, M. F. (1991). The sensory physiology of host-seeking behavior in mosquitoes. *Annual Review of Entomology*, 36.

Britch, S. C., Linthicum, K. J., Wynn, W. W., Walker, T. W., Farooq, M., Smith, V. L., Robinson, C. A., Lothrop, B. B., Snelling, M., Gutierrez, A., and Lothrop, H. D. (2009). Evaluation of barrier treatments on native vegetation in a southern California desert habitat. *J Am Mosq Control Assoc.*, 25(2).

Britch, S. C., Linthicum, K. J., Wynn, W. W., Walker, T. W., Farooq, M., Smith, V. L., Robinson, C. A., Lothrop, B. B., Snelling, M., Gutierrez, A., and Lothrop, H. D. (2010). Residual mosquito barrier treatments on U.S. military camouflage netting in a southern California desert environment. *Mil Med*, 75(8).

Cano, J., Descalzo, M. A., Moreno, M., Nzambo, Z. S., Bobuakasi, L., Buatiche, J. N., Ondo, M., Micha, F., and Benito, A. (2006). Spatial variability in the

density, distribution and vectorial capacity of anopheline species in a high transmission village (Equatorial Guinea). *Malaria Journal*, 5(21).

Cariboni, J., Gatelli, D., Liska, R., and Saltelli, A. (2007). The role of sensitivity analysis in ecological modelling. *Ecological modelling*, 203(1-2):167–182.

CDC (2013). *Anopheles* mosquitoes. Center for Disease Control (CDC) http://www.cdc.gov/malaria/about/biology/mosquitoes/index.html.

Chitnis, N., Hyman, J. M., and Cushing, J. M. (2008a). Determining Important Parameters in the spread of Malaria through the Sensitivity analysis of a mathematical model. *Bulletin of Mathematical Biology*, 70(5).

Chitnis, N., Schapira, A., Smith, T., and Steketee, R. (2010). Comparing the effectiveness of malaria vector-control interventions through a mathematical model. *The American Journal of Tropical Medicine and Hygiene*, 83(2).

Chitnis, N., Smith, T., and Steketee, R. (2008b). A mathematical model for the dynamics of malaria in mosquitoes feeding on a heterogeneous host population. *Journal of Biological Dynamics*, 2(3).

Chouaibou, M., Simard, F., Chandre, F., Etang, J., Darriet, F., and Hougard, J.-M. (2006). Efficacy of bifenthrin-impregnated bednets against *Anopheles funestus* and pyrethroid-resistant *Anopheles gambiae* in North Cameroon. *Malaria Journal*, 5:77.

Clarke, S. E., Bogh, C., Brown, R. C., Walraven, G. E., Thomas, C. J., and Lindsay, S. W. (2002). Risk of malaria attacks in Gambian children is greater away from malaria vector breeding sites. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 96:499 – 506.

Cosner, C., Beier, J. C., Cantrell, R. S., Impoinvil, D., Kapitanski, L., Potts, M. D., Troyo, A., and Ruan, S. (2009). The effects of human movement on the persistence of vector-borne diseases. *Journal of Theoretical Biology*, 258(4):550 – 560.

Costantini, C., Sagnon, N. F., della Torre, A., Diallo, M., Brady, J., Gibson, G., and Coluzzi, M. (1998). Odor-mediated host preferences of west african mosquitoes, with particular reference to malaria vectors. *The American Journal of Tropical Medicine and Hygene*, 1(58):56–63.

Cummins, B., Cortez, R., Foppa, I. M., Walbeck, J., and Hyman, J. M. (2012). A Spatial Model of Mosquito Host-Seeking Behavior. *PLoS Computational Biology*, 8(5).

de Zulueta, J. and Cullen, J. R. (1963). Deterrent effect of insecticides on malaria vectors. *Nature*, 200.

Depinay, J. O., Mbogo, C., Killeen, G., Knols, B., Beier, J., Carlson, J., Dushoff, J., Billingsley, P., Mwambi, H., Githure, J., Toure, A. M., and McKenzie, F. E. (2004). A simulation model of African *Anopheles* ecology and population dynamics for the analysis of malaria transmission. *Malaria Journal*, 3:29.

Devine, G. J., Perea, E. Z., Killeen, G. F., Stancil, J. D., Clark, S. J., and Morrison, A. C. (2009). Using adult mosquitoes to transfer insecticides to *Aedes aegypti* larval habitats. *PNAS*, Early Edition.

Dumont, Y (2011). *Modeling mosquito distribution. Impact of the vegetation*, volume Volume A of *Proceedings of the international Conference of Numerical Analysis and Applied mathematics, Haldiki, Greece*. Haldiki: American Institute of Physics, AIP conference proceedings.

Dumont,Y and Dufourd, C (2011). *Spatio-temporal modelling of mosquito distribution*. AIP conference proceedings.

Eckhoff, P. A. (2011). A malaria transmission-directed model of mosquito life cycle and ecology. *Malaria Journal*, 303:10.

Edman, J., Scott, T., Costero, A., Morrison, A., Harrington, L., and Clark, G. (1998). *Aedes aegypti* (diptera culicidae) movement influenced by availability of oviposition sites. *Journal of Medical Entomology*, 35(4):578 – 583.

Fillinger, U. and Lindsay, S. W. (2006). Suppression of exposure to malaria vectors by an order of magnitude using microbial larvicides in rural Kenya. *Tropical Medicine and International Health*, 11(11).

Geissbuhler, Y., Kannady, K., Chaki, P., Emidi, B., Govella, N., Mayagaya, V., Kiama, K., Mtasiwa, D., Mshinda, M., Lindsay, S. W., Tanner, M., Fillinger, U., Caldas de Castro, M., and Killeen, G. F. (2009). Microbial Larvicide Application by a Large-Scale, Community-Based Program Reduces Malaria Infection Prevalence in Urban Dar es Salaam, Tanzania. *PLoS ONE*, 4(3).

Gething, P. W., Patil, A. P., Smith, D. L., Guerra, C. A., Elyazar, I. R., Johnston, G. L., Tatem, A. J., and Hay, S. I. (2011a). A new world malaria map: *Plasmodium falciparum* endemicity in 2010. *Malaria Journal*, 10:378.

Gething, P. W., Van Boeckel, T. P., Smith, D. L., Guerra, C. A., Patil, A. P., Snow, R. W., and Hay, S. I. (2011b). Modelling the global constraints of temperature

on transmission of *Plasmodium falciparum* and *P. vivax*. *Parasites and Vectors*, 92:2.

Gillies, M. T. (1961). Studies on the dispersion and survival of *Anopheles Gambiae Giles* in East Africa, by means of marking and release experiments. *Bulletin of Entomological Research*, 52:99–127.

Gillies, M. T. and Wilkes, T. J. (1978). The effect of high fences on the dispersal of some West African mosquitoes (Diptera: Culicidae). *Bulletin of Entomological Research*, 68:401 – 408.

Gillies, M. T. and Wilkes, T. J. (1981). Field experiments with a wind tunnel on the flight speed of some West African mosquitoes (Diptera: Culicidae). *Bulletin of Entomological Research*, 71:65 – 70.

Gimnig, J., Kolczak, M., Hightower, A., Vulule, J., Schoute, E., Kamau, L., Phillips-Howard, P., ter Kuile, F., Nahlen, B., and Hawley, W. (2003). Effect of permethrin-treated bed nets on the spatial distribution of malaria vectors in western Kenya. *The American Journal of Tropical Medicine and Hygiene*, 68(4 Suppl):115–20.

Grieco, J. P., Achee, N. L., Chareonviriyaphap, T., Suwonkerd, W., Chauhan, K., Sardelis, M. R., and Roberts, D. R. (2007). A new classification system for the actions of IRS chemicals traditionally used for malaria control. *PLoS ONE*, 2(8).

Griffin, J., Hollingsworth, T., Okell, L., Churcher, T., White, M., Hinsley, W., Bousema, T., Drakeley, C. J., Ferguson, N. M., Basanez, M.-G., and Ghani, A. C. (2010). Reducing *Plasmodium falciparum* malaria transmission in Africa: A model-based evaluation of intervention strategies. *PLoS Medicine*, 7(8).

Gu, W. and Novak, R. J. (2009a). Agent-based modelling of mosquito foraging behaviour for malaria control. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 103(11):1105 – 1112.

Gu, W. and Novak, R. J. (2009b). Predicting the impact of insecticide-treated bed nets on malaria transmission: the devil is in the detail. *Malaria Journal*, 256:8.

Gu, W., Regens, J. L., Beier, J. C., and Novak, R. J. (2006). Source reduction of mosquito larval habitats has unexpected consequences on malaria transmission. *PNAS*, 103(46).

Hawley, W., Phillips-Howard, P., ter Kuile, F., Terlouw, D., Vulule, J., Ombok, M., Nahlen, B., Gimnig, J., Kariuki, S., Kolczak, M., and Hightower, A. (2003). Community-wide effects of permethrin-treated bed nets on child mortality and malaria morbidity in western Kenya. *The American Journal of Tropical Medicine and Hygiene*, 68(4 Suppl):121 – 7.

Hay, S. I., Guerra, C. A., Gething, P. W., Patil, A. P., Tatem, A. J., Noor, A. M., Kabaria, C. W., Manh, B. H., Elyazar, I. R. F., Brooker, S., Smith, D. L., Moyeed, R. A., and Snow, R. W. (2009). A World Malaria map: Plasmodium falciparum endemicity in 2007. *PLoS Med*, 6(3).

Hay, S. I., Guerra, C. A., Tatem, A. J., Noor, A. M., and Snow, R. W. (2004). The global distribution and population at risk of malaria: past, present, and future. *The Lancet Infectious Diseases*, 4(6):327 – 336.

Hiebeler, D. (1997). Stochastic spatial models: From simulations to mean field and local structure approximations. *Journal of Theoretical Biology*, 187.

Hiebeler, D. (2000). Populations on fragmented landscapes with spatially structured heterogeneities: Landscape generation and local dispersal. *Ecology*, 81(6).

Hiebeler, D. (2005). A cellular automaton SIS epidemiological model with spatially clustered recoveries. In Sunderam, V. S., van Albada, G. D., Sloot, P. M. A., and Dongarra, J., editors, *International Conference on Computational Science (2)*, number 3515 in Lecture Notes in Computer Science, pages 360–367. Springer.

Hoare, A., Regan, D. G., and Wilson, D. P. (2008). Sampling and sensitivity analyses tools (SaSAT) for computational modelling. *Theoretical Biology and Medical Modelling*, 5(4).

Holsetein, M. H. (1954). Biology of *Anopheles Gambiae*: research in French West Africa. Monograph series number 9, World Health Organization, Palais des Nations, Geneva.

Jeefoo, P., Tripathi, N. K., and Souris, M. (2011). Spatio-temporal diffusion pattern and hotspot detection of dengue in chachoengsao province, thailand. *Int J Environ Res Public Health*, 8:51 – 74.

Jin, Y. and Wang, W. (2005). The effect of population dispersal on the spread of a diasese. *Journal of Mathematical Analysis and Applications*, 308:343–364.

Keeling, M. J. and Rohani, P. (2008). *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press.

Killeen, G., Tanner, M., Mukabana, W., Kalongolela, M., Kannady, K., Lindsay, S., Fillinger, U., and de Castro, M. (2006). Habitat targeting for controlling aquatic stages of malaria vectors in Africa. *The American Journal of Tropical Medicine and Hygiene*, 74(4).

Killeen, G. F., Knols, B. G. J., and Gu, W. (2003). Taking malaria transmission out of the bottle: implications of mosquito dispersal for vector control interventions. *THE LANCET Infectious Diseases*, 3.

Killeen, G. F., McKenzie, F. E., Foy, B. D., Bogh, C., and Beier, J. C. (2001). The availability of potential hosts as a determinant of feeding behaviours and malaria transmission by African mosquito populations. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 95(5).

Kirby, M. J. and Lindsay, S. W. (2009). Effect of temperature and inter-specific competition on the development and survival of *Anopheles gambiae sensu stricto* and *An. arabiensis* larvae. *Acta Tropica*, 109(2).

Knols, B., de Jong, R., and Takken, W. (1995). Differential attractiveness of isolated humans to mosquitoes in Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 89(6):604 – 6.

Knols, B. G. J. and Meijerink, J. (1997). Odors influence mosquito behavior. *Science and Medicine*, 4(5):56–63.

Kroeger, A., Horstick, O., Riedl, C., Kaiser, A., and Becker, N. (1995). The potential for malaria control with the biological larvicide Bacillus thuringiensis israelensis (Bti) in Peru and Ecuador. *Acta Tropica*, 60.

Lee, S.-H., Su, N.-Y., and Bardunias, P. (2007). Exploring landscape structure effect on termite territory size using a model approach. *BioSystems*, 90.

Lengeler, C. (2004). Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database of Systematic Reviews*, (2).

Li, J. (2011). Malaria model with stage structured mosquitoes. *Mathematical Biosciences and Engineering*, 8(3):753–768.

Li, L., Bian, L., and Yan, G. (2008). A study of the distribution and abundance of the adult malaria vector in western kenya highlands. *International Journal of Health Geographics*, 7(50).

Lunde, T. M., Korecha, D., Loha, E., Sorteberg, A., and Lindtjrn, B. (2013). A dynamic model of some malaria-transmitting anopheline mosquitoes of the afrotropical region. I. model description and sensitivity analysis. *Malaria Journal*, 12:28.

Lutambi, A., Penny, M., Smith, T., and Chitnis, N. (2013). Mathematical modelling of mosquito dispersal in a heterogeneous environment. *Mathematical Biosciences*, 241(2):198 –216.

Macdonald, G. (1956). Theory of the eradication of malaria. *Bulletin of the World Health Organization*, 15(3-5):369 – 387.

Majambere, S., Lindsay, S. W., Green, C., Kandeh, B., and Fillinger, U. (2007). Microbial larvicides for malaria control in The Gambia. *Malaria Journal*, 6:76.

Majambere, S., Pinder, M., Fillinger, U., Ameh, D., Conway, D., Green, C., Jeffries, D., Jawara, M., Milligan, P., Hutchinson, R., and Lindsay, S. W. (2010). Is mosquito larval source management appropriate for reducing malaria in areas of extensive flooding in The Gambia? A cross-over intervention trial. *The American Journal of Tropical Medicine and Hygiene*, 82(2).

Mandal, S., Sarkar, R. R., and Sinha, S. (2011). Mathematical models of malaria - a review. *Malaria Journal*, 10:202.

Manga, L., Fondjo, E., Carnevale, P., and Robert, V. (1993). Importance of low dispersion of *Anopheles gambiae* (diptera: Culicidae) on malaria transmission in hilly towns in south Cameroon. *Journal Medical Entomology*, 5(30):936–8.

Martens, P. and Hall, L. (2000). Malaria on the move: human population movement and malaria transmission. *Emerging Infectious Diseases*, 6(2):103 – 109.

MATLAB (2010). *MATLAB version 7.10.0 (R2010a)*. The MathWorks Inc., Natick, Massachusetts.

McKenzie, F. E. and Samba, E. M. (2004). The role of mathematical modeling in evidence-based malaria control. *The American Journal of Tropical Medicine and Hygiene*, 71(Suppl 2):94 – 96.

Meinsma, G. (1995). Elementary proof of the Routh-Hurwitz test. *Systems and Control Letters*, 25:237–242.

Menach, L. A., McKenzie, F. E., Flahault, A., and Smith, D. L. (2005). The unexpected importance of mosquito oviposition behaviour for malaria: non-productive larval habitats can be sources for malaria transmission. *Malaria Journal*, 4(23).

Menach, L. A., Takala, S., McKenzie, F. E., and Andre, P. (2007). An elaborated feeding cycle model for reductions in vectorial capacity of night-biting mosquitoes by insecticide-treated nets. *Malaria Journal*, 6:10.

Midega, J. T., Mbogo, C. M., Mwambi, H., Wilson, M. D., Ojwang, G., Mwangangi, J. M., Nzovu, J. G., Githure, J. I., Yan, G., and Beier, J. C. (2007). Estimating dispersal and survival of *Anopheles gambiae* and *Anopheles funestus* along the Kenyan coast by using mark-release-recapture methods. *Journal of Medical Entomology*, 6(44):923–9.

Minakawa, N., Seda, P., and Yan, G. (2002). Influence of host and larval habitat distribution on the abundance of African malaria vectors in western Kenya. *The American Journal of Tropical Medicine and Hygiene*, 67(1).

Moore, S. J., Darling, S. T., Sihuincha, M., Padilla, N., and Devine, G. J. (2007). A low-cost repellent for malaria vectors in the americas: results of two field trials in guatemala and peru. *Malaria Journal*, 6.

Mukabana, W. R., Takken, W., Coe, R., and Knols, B. G. (2002). Host-specific cues cause differential attractiveness of Kenyan men to the African malaria vector *Anopheles gambiae*. *Malaria Journal*, 1:17.

Muturi, E. J., Burgess, P., and Novak, R. (2008). Malaria vector management: where have we come from and where are we headed? *The American Journal of Tropical Medicine and Hygiene*, 78.

Mwandawiro, C., Boots, M., Tuno, N., Suwonkerd, W., Tsuda, Y., and Takagi, M. (2000). Heterogeneity in the host preference of Japanese encephalitis vectors in Chiang Mai, northern Thailand. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 94(3):238 – 242.

Mwangangi, J. M., Kahindi, S. C., Kibe, L. W., Nzovu, J. G., Luethy, P., Githure, J. I., and Mbogo, C. M. (2011). Wide-scale application of Bti/Bs biolarvicide in different aquatic habitat types in urban and peri-urban Malindi, Kenya. *Parasitology Research*, 108:1355 – 1363.

Ngwa, G. A. (2006). On the population dynamics of the malaria vector. *Bulletin of Mathematical Biology*, 68(8):2161 – 2189.

Nourridine, S., Teboh-Ewungkem, M. I., and Ngwa, G. A. (2011). A mathematical model of the population dynamics of disease - transmitting vectors with spatial consideration. *Journal of Biological dynamics*, 5(4):335 – 365.

Okogun, G. (2005). Life-table analysis of *Anopheles* malaria vectors: generational mortality as tool in mosquito vector abundance and control studies. *Journal of Vector borne Diseases*, 42(2).

Okumu, F., Govella, N., Moore, S., Chitnis, N., and Killeen, G. (2010). Potential benefits, limitations and target product-profiles of odor-baited mosquito traps for malaria control in Africa. *PloS ONE*, 5(7).

Okuyama, T. (2008). Intraguild predation with spatially structured interactions. *Basic and Applied Ecology*, 9:135 – 144.

O'Sullivan, D. and Perry, G. L. (2009). A discrete space model for continuous space dispersal processes. *Ecological Informatics*, 4:57 – 68.

Otero, M., Schweigmann, N., and Solari, H. G. (2008). A Stochastic Spatial Dynamical Model for *Aedes Aegypti*. *Bulletin of Mathematical Biology*, 70(5):1297 – 325.

Otero, M., Solari, H. G., and Schweigmann, N. (2006). A stochastic population dynamics model for *Aedes Aegypti*: formulation and application to a city with temperate climate. *Bulletin of Mathematical Biology*, 68(8).

Oxborough, R. M., Mosha, F. W., Matowo, J., Mndeme, R., Feston, E., Hemingway, J., and Rowland, M. (2008). Mosquitoes and bednets: testing the spatial positioning of insecticide on nets and the rationale behind combination insecticide treatments. *Annals of Tropical Medicine and Parasitology*, 102(8).

Papke, L. E. and Wooldridge, Jeffrey, M. (1996). Econometric methods for fractional response variables with an application to 401(K) plan participation rates. *Journal of applied econometrics*, 11:619 – 632.

Pates, H. and Curtis, C. (2005). Mosquito behaviour and vector control. *Annual Review of Entomology*, 50:53 – 70.

Pigott, D. M., Atun, R., Moyes, C. L., Hay, S. I., and Gething, P. W. (2012). Funding for malaria control 2006?2010: A comprehensive global assessment. *Malaria Journal*, 11:246.

Raffy, M. and Tran, A. (2005). On the dynamics of flying insects populations controlled by large scale information. *Theoretical Population Biology*, 68:91 – 104.

RBM (2008). The global malaria action plan. Technical report, Roll Back Malaria Partnership.

RBM (2013). Minutes of Roll Back Malaria (RBM) vector control working group 8th annual meeting. *Roll Back Malaria Partnership*, Link:http://www.rollbackmalaria.org/mechanisms/vcwg.html.

Reynolds, A. M. and Frye, M. A. (2007). Free-flight odor tracking in drosophila is consistent with an optimal intermittent scale-free search. *PLoS ONE*, 2.

Ross, R. (1905). The logical basis of the sanitary policy of mosquito reducation. *Science*, XXII(570).

Ross, R. (1915). Some a priori pathometric equations. *The British Medical Journal*, 1:546 – 447.

Rowland, M., Downey, G., Rab, A., Freeman, T., Mohammad, N., Rehman, H., Durrani, N., Reyburn, H., Curtis, C., Lines, J., and Fayaz, M. (2004). DEET mosquito repellent provides personal protection against malaria: a household randomized trial in an afghan refugee camp in pakistan. *Tropical Medicine and International Health*, 9(3):335 – 342.

Sambo, L. G., Ki-Zerbo, G., and Kirigia, J. M. (2011). Malaria control in the African Region: perceptions and viewspoints on proceedings of the Africa Leaders Malaria alliance (ALMA). *BMC Proceedings*, 5(Suppl 5).

Sattler, M. A., Mtasiwa, D., Kiama, M., Premji, Z., Tanner, M., Killeen, G. F., and Lengeler, C. (2005). Habitat characterization and spatial distribution of *Anopheles sp.* mosquito larvae in Dar es salaam (Tanzania) during an extended dry period. *Malaria Journal*, 4.

Saul, A. (2003). Zooprophylaxis or zoopotentiation: the outcome of introducing animals on vector transmission is highly dependent on the mosquito mortality while searching. *Malaria Journal*, 2(3).

Service, M. W. (1997). Mosquito dispersal - The long and the short of it. *Journal of medical entomology*, 34(6).

Service, M. W. (2004). *Medical Entomology for Students*. Cambridge University Press, Third edition.

Sinka, M. E., Bangs, M. J., Manguin, S., Rubio-Palis, Y., Chareonviriyaphap, T., Coetzee, M., Mbogo, C. M., Hemingway, J., Patil, A. P., Temperley, W. H., Gething, P. W., Kabaria, C. W., Burkot, T. R., Harbach, R. E., and Hay, S. I. (2012). A global map of dominant malaria vectors. *Parasites and Vectors*, 5:69.

Smallegange, R. C., Qiu, Y. T., van Loon, J. J. A., and Takken, W. (2005). Synergism between ammonia, lactic acid and carboxylic acids as kairomones in the host-seeking behaviour of the malaria mosquito *Anopheles gambiae sensu stricto* (diptera: Culicidae). *Chemical Senses*, 30(2).

Smith, D. L., Dushoff, J., and McKenzie, F. E. (2004). The Risk of a Mosquito-Borne Infection in a Heterogeneous Environment. *PLoS Biology*, 2(11).

Smith, D. L., Hay, S. I., Noor, A. M., and Snow, R. W. (2009). Predicting changing malaria risk after expanded insecticide-treated net coverage in Africa. *Trends in Parasitology*, 25(11).

Smith, T., Charlwood, J. D., Takken, W., Tanner, M., and Spiegelhalter, D. J. (2002). Mapping the densities of malaria vectors within a single village. *Acta Trop*, 59:1 –18.

Stoddard, S. T., Forshey, B. M., Morrison, A. C., Paz-Soldan, V. A., Vazquez-Prokopec, G. M., Astete, H., Reiner, Jr, R. C., Vilcarromero, S., Elder, J. P., Halsey, E. S., Kochel, T. J., Kitron, U., and Scott, T. W. (2012). House-to-house human movement drives dengue virus transmission. *PNAS*, Early Edition.

Stoddard, S. T., Morrison, A. C., Vazquez-Prokopec, G. M., Soldan, V. P., Kochel, T. J., Kitron, U., Elder, J. P., and Scott, T. W. (2009). The role of human movement in the transmission of vector-borne pathogens. *PLoS Neglected Tropical Diseases*, 3(7).

Su, M., Li, W., Li, Z., Zhang, F., and Hui, C. (2009). The effect of landscape heterogeneity on host-parasite dynamics. *Ecological Research*, 24(4):889 – 896.

Takahashi, L. T., Maidana, N. A., Ferreira, W., Pulino, P., and Yang, H. M. (2005). Mathematical models for the *Aedes aegypti* dispersal dynamics: travelling waves by wing and wind. *Bulletin of Mathematical Biology*, 67:509528.

Takken, W. (2002). Do insecticide-treated bednets have an effect on malaria vectors? *Tropical Medicine and International Health*, 7(12).

Takken, W. and Knols, B. G. J. (1999). Odor-mediated behavior of afrotropical malaria mosquitoes. *Annual Review of Entomology*, 44:131–157.

Takken, W. and Verhulst, N. (2013). Host preferences of blood-feeding mosquitoes. *Annual Review of Entomology*, 58:433 – 453.

Tatem, A. J., Qiu, Y., Smith, D. L., Sabot, O., Ali, A. S., and Moonen, B. (2009). The use of mobile phone data for the estimation of the travel patterns and imported *Plasmodium falciparum* rates among Zanzibar residents. *Malaria Journal*, 8:287.

Tatem, A. J., Rogers, D. J., and Hay, S. I. (2006). Estimating the malaria risk of African mosquito movement by air travel. *Malaria Journal*, 57:5.

Thomson, N. A. and Ellner, S. P. (2003). Pair-edge approximation for heterogeneous lattice population models. *Theoretical Population Biology*, 64(3):271 – 280.

Tran, A. and Raffy, M. (2006). On the dynamics of dengue epidemics from large-scale information. *Theoretical Population Biology*, 69:3–12.

Tsonis, A. A., Swanson, K. L., and Wang, G. (2008). Estimating the clustering coefficient in scale-free networks on lattices with local spatial correlation structure. *Physica A*, 387.

van den Driessche, P. and Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180(1-2).

Vazquez-Prokopec, G. M., Kitron, U., Montgomery, B., Horne, P., and Ritchie, S. A. (2010). Quantifying the spatial dimension of dengue virus epidemic spread within a tropical urban environment. *PLoS Negl Trop Dis*, 4:1 –18.

Vinatier, F., Tixier, P., Duyck, P.-F., and Lescourret, F. (2011). Factors and mechanisms explaining spatial heterogeneity: a review of methods for insect populations. *Methods in Ecology and Evolution*, 2.

Westerberg, L., Ostman, O., and Wennergren, U. (2005). Movement effects on equilibrium distributions of habitat generalists in heterogeneous landscapes. *Ecological Modelling*, 188:432 – 447.

White, M. T., Griffin, J. T., Churcher, T. S., Ferguson, N. M., Basez, M.-G., and Ghani, A. C. (2011). Modelling the impact of vector control interventions on *Anopheles gambiae* population dynamics. *Parasites and Vectors*, 4(153).

WHO (2004). Global strategic framework for integrated vector management. Technical report, World Health Organization, Geneva.

WHO (2006). Indoor residual spraying: Use of indoor residual spraying for scaling up global malaria control and elimination. Technical report, World Health Organization.

WHO (2007). Insecticide-treated mosquito nets: a WHO position statement. Technical report, World Health Organization.

WHO (2011). World Malaria Report. Technical report, World Health Organization, Geneva.

WHO (2012). World Malaria Report. Technical report, World Health Organization, Geneva.

Worrall, E., Connor, S. J., and Thomson, M. C. (2007). A model to simulate the impact of timing, coverage and transmission intensity on the effectiveness of indoor residual spraying (IRS) for malaria control. *Tropical Medicine and International Health*, 12(1).

Yakob, L. and Yan, G. (2009). Modeling the effects of integrating larval habitat source reduction and insecticide treated nets for malaria control. *PLoS ONE*, 4(9).

Yakob, L. and Yan, G. (2010). A network population model of the dynamics and control of African malaria vectors. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 104(10):669 – 675.

Yaro, A. S., Dao, A., Adamou, A., Crawford, J. E., Ribeiro, J. M. C., Gwadz, R., Traore, S. F., and Lehmann, T. (2006). The distribution of hatching time in *Anopheles gambiae*. *Malaria Journal*, 5:19.