

**Malaria in the Amazon:  
An Agent-Based Approach to Epidemiological  
Modeling of Coupled Systems**

by

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## Abstract

The epidemiology of malaria considers a complex set of local interactions amongst host, vector, and environment. A history of reemergence, epidemic transition, and ensuing endemic transmission in Iquitos, Peru reveals an interesting case used to model and explore such interactions. In this region of the Peruvian Amazon, climate change, development initiatives and landscape fragmentation are amongst a unique set of local spatial variables underlying the endemicity of malaria. Traditional population-based approaches lack the ability to resolve the spatial influences of these variables. Presented is a framework for spatially explicit, agent-based modeling of malaria transmission dynamics in Iquitos and surrounding areas. The use of an agent-based model presents a new opportunity to spatially define causal factors and influences of transmission between mosquito vectors and human hosts. In addition to spatial considerations, the ability to model individual decisions of humans can define socio-economic and human-environment interactions related to malaria transmission. Three interacting sub-models representing human decisions, vector dynamics, and environmental factors comprise the model. Feedbacks between the interacting sub-models define individual decisions and ultimately the flexibility that will allow the model to function in a diagnostic capacity. Sensitivity analysis and simulated interactions are used to discuss this diagnostic capability and to build understanding of the physical systems driving local transmission of malaria.

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# Chapter 1

## Introduction

In the Amazonian region of Peru there is growing concern over reemergent malaria that is currently responsible for the second largest transmission rate in South America (Branch et al., 2005; Guarda et al., 1999; Guthmann et al., 2002; Pinedo-Cancino et al., 2006; Roberts et al., 1997; Roper et al., 2000; Roshanravan et al., 2003; Vittor et al., 2006). Reemergent Malaria in the Peruvian Amazon has been observed in a variety of epidemiological events including sustained endemic transmission and epidemic outbreaks. Alarmingly, these events have increased in frequency during the past two decades in spite of modern control measures. A majority of the observed cases in the Amazon have originated from the department of Loreto, a populated expanse of land accessible only by air or boat (Guarda et al., 1999). During the later part of the 1990s nearly half of all malaria infections reported in Peru occurred in this region (Arata et al., 1999). The capital city of the Loreto region, Iquitos, and its surrounding areas are substantially populated and well connected relative to other Amazonian regions. These attributes as well as additional local causal mechanisms have placed the region at additional risk for epidemic and endemic malaria transmission events. A widely recognized epidemic from 1995 to 1998 raised serious questions about local factors of reemergence and sustained transmission of malaria in areas surrounding Iquitos (Bautista et al., 2006; Branch et al., 2005; Guarda et al., 1999)

Concern over this epidemic as well as sustained transmission in the area generated a significant amount of literature from epidemiology and public health communities around the world. Much of this research attempted to identify and discuss causal factors promoting reemergence and sustained transmission of malaria in and around Iquitos. Despite the volume of research, consensus was not reached on the causal factors or mechanisms driving reemergence in the Iquitos area. Among the

identified causal mechanisms are a slue of anthropogenic, biological, climatic, and environmental changes including habitat modification (Bautista et al., 2006), land use change (Bradley and Altizer, 2007; Derraik and Slaney, 2007; Patz et al., 2004), variation in regional climate (Martens et al., 1999; Rogers and Randolph, 2006) and immunology (Patz and Reisen, 2001). The range of causal factors explored by this research presents an interesting case requiring novel tools to test hypothesis and resolve physical systems driving local transmission dynamics.

Resolution of the interaction space defining local transmission dynamics demands methods capable of modeling a multitude of underling physical systems. The desired set of systems form a complex set of interactions amongst host, vector, and environmental factors local to where malaria occurs (Bruce-Chwatt, 1987). Analysis of the behaviors generated by these systems and the interaction space they define can be used to promote understanding of physical systems and their roles in epidemiological events. Unfortunately prior research has accomplished little in the understanding of coupled physical systems and their role in the transmission of malaria in the Iquitos area. The malaria in the amazon (MIA) project attempts to bridge the gap between previously identified casual mechanisms and their role in coupled physical systems of transmission. To accomplish this, agent based models (ABMs) will be presented as a novel approach to simulation of interactions amongst mosquitoes, and humans within a spatially explicit environment.

The novel tool presented in ABMs have shown considerable promise in the simulation of coupled human-environmental systems (Deadman et al., 2004) and hold promise for use in epidemiology (Bian, 2004). Here, individual representations of humans and mosquitoes are generated within the model domain as agents. Agents each have a unique set of attributes that change in response to interactions within the model. Agents make autonomous decisions based on assimilated knowledge from geographically referenced environmental models, as well as interactions with other agents. Simulation of agents within this environment can potentially enable observation and analysis of causal mechanisms as part of a coupled human-vector-environment system. More importantly, changes in agent attributes can be observed in relation to the dynamics of environmental, social, or vector systems within the model. Previously identified frameworks for agent-based spatially explicit epidemiological models (Bian, 2004; Roche et al., 2008) hold great potential to be extended upon in the study of historic epidemiological events in Iquitos. Thus, MIA will document the development of a novel agent-based method to be used as a diagnostic tool for exploring causal mechanisms and their role in transmission dynamics of the Iquitos epidemic.

## 1.1 Goals and Objectives

The ultimate goal of MIA is to develop a tool to contribute greater understanding to the physical systems driving localized malaria transmission in the Amazon. The novel approaches developed in MIA will bring spatial understanding to the relationships between malarial events and previously identified environmental, climatic, and anthropogenic causal factors. As an intermediary to increased understanding, MIA, will attempt to answer the question: Can a novel modeling methodology be developed to resolve local causal factors or mechanisms generated in coupled human-vector-environmental systems? Additionally, this research seeks to assess the potential of said methods as diagnostic tools by identifying research gaps and relating them to future questions. To answer these questions a series of operational goals are established to help access them:

- Develop a novel agent-based method for simulation of malaria transmission
- Couple physical models representing the dynamics of mosquitoes, humans, and their physical environment into a single domain
- Devise methods for observation of emergent behaviors resulting from individual level interactions amongst the coupled systems
- Assess the effects of individual parameterizations within the model domain through sensitivity analysis and comparison to traditional methods in epidemiology
- Identify and foster understanding of localized causal mechanisms as products of the diagnostic capabilities of the developed model
- Explore previously identified local causal mechanisms including climate and anthropogenic change as components of the coupled human-vector-environmental system

MIA will provide reproducible methods that will access these goals within the localized environment of the suburban communities surrounding Iquitos. A commitment is made to encourage adaptability in the model structures so that analysis and understanding can be extended to additional study areas requiring diagnostic capabilities provided by MIA. Additionally, the products of MIA and the methodologies developed will be discussed exclusively as diagnostic tools rather than predictive measures. This will be maintained to ground the capabilities of the model and discourage misinterpretation of results.

## 1.2 Motivation for Research

Martens et al. (1999) described malaria as “the most important vector born disease in the world”. Arguably this statement is qualified as upwards of 3.3 billion people are at risk of contracting malaria around the world (Aregawi et al., 2008). The global reach of malaria is vast not only in population but physical area affecting parts of Africa, Asia, Middle East, Central America, South America and Oceania. Cases world wide in 2006 were estimated to be 247 million across these areas (Aregawi et al., 2008). Additionally, nearly one million of those infected each year die. The burden of Malaria extends well beyond its mortality rate as the incapacitating nature of the infection can bring loss of financial capabilities to the households affected. These issues are compounded when transmission occurs in less developed nations where financial difficulties are already a burden of everyday life.

Simulations such as the one preposed in MIA provide tools for policy makers and scientists alike to negate the impact of future epidemiological events by understanding causal mechanisms. Once identified, attempts can be made to devise methods of control to address specific causal mechanisms in the localities studied. Control measures and policy changes can be enacted on a virtual population prior to subjecting the physical population to said changes. In this, MIA, is driven not only to provide methods for analysis of human-vector-environmental interactions in Iquitos but also to further the worldwide fight of malaria.

## 1.3 Structure of Thesis

The structure of this thesis will guide the reader though a series of introductory chapters prior to discussion of the model structure and analysis of MIA’s products. Chapter 2 provides discussion of the study area, its epidemiological history, and the local considerations of malaria transmission. Additionally, this chapter will provide introduction to the previous research completed in the Iquitos area. Chapter 3 reviews methods in epidemiological modeling through traditional approaches and modern adaptations. This chapter will also introduce ABMs in epidemiology and provide discussion as to how MIA intends to utilize this approach. Chapter 4 discusses the specific components used to develop the methodologies of MIA. This will include discussion of procedures utilized in the coupled systems approach to simulation of the transmission of malaria. Chapter 5 presents the simulation results of the MIA model in a concise manor with discussion how they relate to the Iquitos

epidemic. This will be completed as a series of simulation scenarios testing various aspects of MIA. Finally, chapter 6 provides discussion of the model contributions, limitations, and newly generated research questions.

# Chapter 2

## Malaria in the Peruvian Amazon

### 2.1 Introduction

To satisfy the goals of this study, and encourage greater understanding of human-vector-environmental systems, an intimate understanding of local conditions must first be established. The considerations discussed here will inform parameterizations, interaction processes, and mathematical models essential to the abstraction process defining physical systems within MIA. Strong understanding of local conditions driving these physical systems will encourage complexity as a product of informed interaction space design. To achieve the desired level understanding a historic perspective of Iquitos and its surrounding areas will be compiled. Efforts will be made to document the people of the area and the physical environment they reside in. Moreover, the epidemiological history of the area will be discussed as an important component of this history. Prior epidemic and endemic transmission of malaria will be discussed highlighting local considerations of epidemiology. Previously documented causal factors and mechanisms will be discussed as components of this history and the physical systems driving transmission. Environmental and social considerations influencing local transmission dynamics will be introduced as components of these systems. This discussion will serve to identify and discuss a preliminary set of assumptions that will be utilized to formulate the basis of MIA.

### 2.2 The Iquitos Study Area

Found in the northern Peruvian Amazon, the region of Loreto comprises nearly one fourth of the country's entire area (Guarda et al., 1999). This vast expanse of land

covering 368,852 km<sup>2</sup> is home to a population of 884,144 (Instituto Nacional de Estadística e Informática, 2007). When compared with Peru as a whole this region has a relatively low density of approximately 2.4 persons/km<sup>2</sup> (Instituto Nacional de Estadística e Informática, 2007). Despite this low regional density, several areas of substantial population can be found clustered around regional infrastructure. Amongst these areas is the Maynas province found in the north-east of Loreto, sharing borders with Ecuador and Colombia. Within the Maynas province the highest population density of the Loreto region is found, namely it's capital and largest urban center, Iquitos.

The city of Iquitos is a longstanding urban area in the Amazon home to nearly half of all inhabitants in the Loreto region. Additionally, there are several villages, much smaller in comparison, in close proximity to the city proper of Iquitos. The physical location of the study area is most notably distinguished by its proximity to three major rivers. The Iquitos area is bordered by the Amazon river to the east, the Itaya river to the south, and Nanay river to the north (Turell et al., 2005). The climate of Iquitos is typical of rainforest regions with high temperatures and humidity throughout the year (Vittor et al., 2006). Seasonal variation in temperature is minimal ranging from 24°C to 28°C. Due to this, seasonality is best defined in terms of precipitation where a rainy season begins in January and continues through May or June (Vittor et al., 2006). Conversely, a dry season comprises the rest of the year with the exception of November.

Historical records of the area date back as far as 1842 when Iquitos existed as a village of 200 inhabitants (Kalliola and Paitán, 1998). A boom in population occurred during 1903, coinciding with the advancement of rubber exploitation in the area (Kalliola and Paitán, 1998). The surge of newly found wealth generated by primary resource extraction caused significant migration to the area. The initial boom in population faded near the end of World War I as demands for rubber dwindled. In the years following logging, mining, and agriculture emerged as the dominant industries in Iquitos and its neighboring areas (Vittor et al., 2006). These industries would sustain Iquitos until the 1950's, when oil and drug trafficking came to generate much of the income within the area. More recent increases in population were driven by relocation programs promoted by the federal government throughout the 1980s (Singer and de Castro, 2001). Furthermore, increased military presence, migration from the Andes, and infrastructure projects have continued to contribute to migration (Serra-Vega, 1990).

One of the most important infrastructure projects in the Iquitos area has been the Iquitos-Nauta road which connects the two port cities it is named after (Vittor



et al., 2006). The road itself, while only 95 km long, has significantly improved access to the area and has ultimately contributed to increased mobility of the local people. Local development and population growth associated with the construction of the road coincided with significant deforestation in the area. The heaviest deforestation has occurred in areas alongside the Iquitos-Nauta road, as new migration expands or establishes communities. These communities have engaged in expansive agriculture, resource extraction, and urbanization projects requiring reclaimed land. The continual deforestation in the area has produced an average annual loss of 4,257 hectares between 1983 and 1995 (Gomez-Romero and Tamariz-Ortiz, 1998). The areas served by this road will be of particular interest to MIA as they have been associated with the reemergence of malaria. Due to this, MIA will concentrate on the suburban communities found outside of Iquitos utilizing this transportation corridor (Figure 2.1).



Figure 2.1: The suburban community of Zungarococha

One such area outside the city proper of Iquitos is the suburban community of Zungarococha, located 5 km south-west of the urban center. Zungarococha is composed of four small villages located along the Nanay river with access to the

Iquitos-Natua road. Zungrococha village (ZG), Puerto Almendra (PA), Ninarumi (NR), and Llanchama (LC) make up this suburban community and have an approximate population of 2,200. These small urban centers are of interest as they have been previously identified as high transmission areas for malaria and potential sources of the initial reemergence (Guarda et al., 1999; Roper et al., 2000). Furthermore, the proximity of local urbanization to forest and peri-urban areas will allow previously established hypothesis to be tested within a community sharing a common history with Iquitos (Arata et al., 1999). A study of the epidemiological history of Iquitos and this suburban community will reveal many opportunities to explore unique local transmission dynamics.

## 2.3 Local Epidemiological History

### 2.3.1 Malaria Transmission Dynamics

Malaria is a vector-borne disease, necessitating a third party to complete transmission between humans. This cycle of transmission is initiated when the bite of an *Anopheles* mosquito draws blood from a human infected with the parasite causing malaria. If the mosquito survives long enough for the parasite's incubation period to elapse it will be able to transmit to humans via successive bites. Mosquitoes in the study area are capable of carrying and transmitting two different parasites which cause malaria: *Plasmodium falciparum* and *Plasmodium vivax*. Each parasite is associated with a different intensity of symptoms, the worst of which are caused by *Plasmodium falciparum*. Differences in *Anopheles* sub-species behavior and biological function can cause the dynamics of the transmission process to vary. As result, it is important for the modeling process to understand the specifics of the dominant local vector.

The vector of interest in the Iquitos study area and the MIA model is *A. darlingi*. Much like other regions of South America (da Rocha et al., 2008; Girod et al., 2008; Olson et al., 2009), the recent rise of *A. darlingi* in Iquitos has been strongly associated with increases in malaria infection rates (Arata et al., 1999). Prior to 1993 there was no evidence of *A. darlingi* in the Iquitos or the Loreto region. Since then the vector has become the predominate sub-species of mosquito and primary vector of malaria in the area. *A. darlingi* has been identified as a highly proficient vector by numerous authors (Roberts et al., 2002; Roper et al., 2000; Tadei et al., 1998). Moreover, the recent emergence of *P. falciparum* has been attributed to

the dominance of the primary vector *A. darlingi* (Branch et al., 2005; Roshanravan et al., 2003; Vittor et al., 2006). These observations are important to understanding the epidemiological history of Iquitos and will now be used to discuss the Iquitos epidemic.

### 2.3.2 The Iquitos Epidemic

Since the early 1990s, the region of Loreto and more specifically its capital, Iquitos, have been the epicenter of reemergent malaria in the Peruvian Amazon (Bautista et al., 2006). Following what was thought to be a drastic reduction in malaria cases, an epidemic occurred in the mid 1990's that eventually led to endemic transmission in the area. The epidemiological history of the Loreto region has been described as heavily intertwined with the demographic evolution of its capital city Iquitos (Vittor et al., 2006). Furthermore, the history of the region reveals an extended timeline of past epidemics, malarial control campaigns, and reemergence (Guarda et al., 1999). Understanding these events can potentially provide insight to interactions that have driven past epidemiological events.

The city of Iquitos and its surrounding areas have a unique history of transmission as reflected in the diversity of infection levels over the last half century. The first indicators of this diversity were noted during an epidemic transmission event in 1944. During this event epidemic transmission was observed resulting in 95,000 confirmed cases of malaria in the Loreto region (Guarda et al., 1999). This epidemiological event coincided with a significant influx of migration to the area, as previously discussed, due to expanding resource extraction. Elevated malarial activity in the Loreto region would continue into the 1960s, as the initial epidemic faded and sustained endemic transmission occurred. Transmission during this period occurred at much lower rates, but a constant reservoir of infected humans and mosquitoes remained. As a reactionary measure, government intervention in 1965 implemented source, chemical, and biological control strategies to limit mosquito populations and decrease vector transmission of malaria in the Iquitos area (Branch et al., 2005; Vittor et al., 2006). The primary methods of control were insecticides, pyrethroids, and most notably DDT, to actively limit mosquito populations.

Active control campaigns were highly successful in reducing mosquito populations in and around Iquitos. This was reflected in a sharp decline of malaria cases as annual infections dwindled to 1,500 (Guarda et al., 1999). These impressive results would continue for almost twenty years as the programs were maintained. During the 1980's campaigns fell into disrepair and eventually were abandoned (Branch

et al., 2005). Furthermore, the use of DDT as a control measure ceased during this time period. Two distinct events would occur following the discontinuation of these campaigns, and have been explored as pre-cursors to the ensuing epidemic. Firstly, without active control campaigns limiting mosquito habitat, new sub-species were allowed to migrate from other Amazonian regions. *A. darlingi*, a proficient vector of malaria, previously undocumented in the Iquitos area, was detected in the early 1990's (Branch et al., 2005). In addition to this new vector, *P. falciparum*, a parasite causing malaria that was previously thought to have been eradicated, reemerged. Newly emergent *P. falciparum* was first detected in the suburban community of Padrecocha in 1991 eventually leading to 140 confirmed cases (Guarda et al., 1999). By 1992 *P. falciparum* had established itself in the Iquitos area with sustained transmission (Roper et al., 2000).

Following these observed epidemiological changes, the Loreto region and city of Iquitos experienced their largest epidemic transmission event lasting from 1995 until 1998 (Figure 2.2). During the observed epidemic transmission a peak of 54,290 *P. falciparum* and 121,268 total cases were recorded (Branch et al., 2005; Guarda et al., 1999). This unprecedented increase would subside in 1998 after transitioning once again into low level transmission sustained by a reservoir of infected individuals. Much of the drop in 1998 has been attributed to control measures activated as a reactionary measure by the Peruvian government (Roshanravan et al., 2003). The Loreto region has since seen endemic transmission ranging between 5 and 50 cases per 1000 persons (Branch et al., 2005). Retrospective analysis reveals several local conditions that may have played a role in the epidemic event. Resolution of the interaction space defining these roles will first require consideration of the local dynamics underling the epidemiological history of Iquitos.

## 2.4 Local Epidemiological Considerations

### 2.4.1 Environmental Considerations

#### Anthropogenic Change

A variety of anthropogenic factors altering the physical state of the environment can be found around the Iquitos areas. These factors refer to changes of the physical environment as a result of human activity. Different human activities carry varying degrees of impact, but in general have had negative ramifications for the local

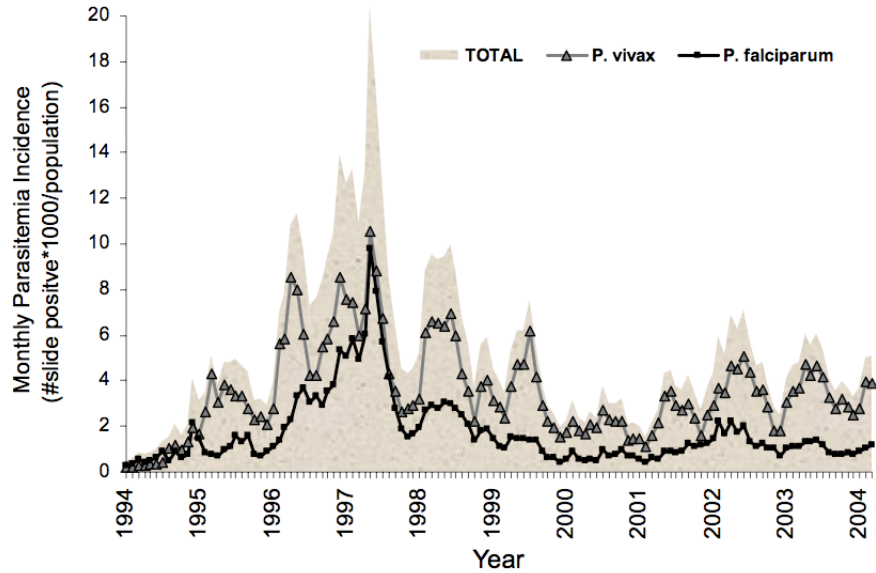


Figure 2.2: The Loreto epidemic (Branch et al., 2005)

environment. In the Iquitos area many of these changes are a direct result of agriculture, resource extraction, and infrastructure development (Guarda et al., 1999). The presence of these activities, and their associated anthropogenic change, have been identified as potential catalysts for increased risk of epidemic transmission (Vittor et al., 2006). One such product of human activity that holds potential for increased vectorial capacity and epidemiological activity is deforestation.

The relationship between deforestation and disease is not specific to malaria and has been associated with a wide range of vector borne diseases (Walsh et al., 1993). Indirectly, deforestation has the potential to increase disease transmission by creating or expanding the habitat of the primary vector (Conn et al., 2002). The primary vector in Iquitos, *A. darlingi*, is known to utilize these anthropogenic habitats including irrigation channels, pastures, rice fields, and roadsides (Vittor et al., 2006). As many activities generating these types of habitats occur in the Iquitos area there is potential for a greater vector population as access to breeding areas is increased. Public infrastructure projects such as road construction accelerate changes leading to increased habitats and vectorial capacity (Patz et al., 2000). Moreover, proximity of new or expanded habitats to humans has the added effect of increasing biting rates. Reclamation of the Amazon forest to facilitate human activities such as agriculture often decreases the distance between human residences, thus promoting increased interactions and transmission opportunities.

Previous studies of vector ecology in the Amazon sampled *Anophales* larvae and

adults in areas where human activity has altered the landscape (Tadei et al., 1998). Their research identified *A. darlingi* as highly associated with areas altered by human activity, including agricultural activities and urbanization. Utilizing traps to sample adult and larval stage mosquitoes, population was characterized across several land coverage types. Areas sampled with human activity were observed to have active *A. darlingi* populations in 93% of locations. Undisturbed areas sampled has an astonishing 0% occurrence of *A. darlingi* larvae or adults. Unfortunately a small number of samples were taken at undisturbed locations ( $n = 5$ ) raising questions of bias in the results. Regardless of potential errors, this study suggests that the alteration of land by humans played a significant role in the reemergence of *A. darlingi*.

Vittor et al. (2006) attempted to explore the same relationship utilizing spatial analysis of human-biting rates, malaria distributions, and the degree of deforestation. This research concentrated on the areas surrounding Iquitos and the local vectors found there. The methods employed utilized a series of traps to estimate human biting across stratified land coverage types. In heavily deforested areas human biting rates for *A. darlingi* were observed at 6.5 bites per person per 6 hour period. With increasing forestation, biting rates approached 0 as traps were placed completely within the forest. Other *Anophales* mosquitoes including *A. triannulatus* were observed to have significant biting rates within the same forested areas. These results suggested that *A. darlingi* prefers meals and travel in deforested areas. The feeding preferences documented for *A. darlingi* will be utilized as parameters driving the mosquito model implemented by MIA.

## Climate Variability

Transmission is effected by changes in temperature and rainfall, expressed as variation in mosquito survival, parasite incubation, and habitat dynamics (Craig et al., 1999). Regional climate variability plays an important role in the local transmission of infectious diseases, but currently presents great uncertainty in its long term effects (Patz et al., 2005). The uncertainty that climate variability introduces may be discussed in terms of local and inter-annual events. More specifically, long term variation in local temperature and rainfall and the effects of El Niño are possible sources of variation in local malaria transmission.

Estimates of increase in global average temperature, due to changes such as enhanced greenhouse effect, range from 1.5°C to 4.5°C by 2100 (Intergovernmental Panel on Climate Change, 2001). These changes in temperature can potentially en-

courage or mitigate malaria transmission as a product of variation in the mosquito population, incubation, and feeding. While long term local changes in temperature may represent only small increases in temperature, these are important in consideration of mosquito population dynamics. In the range of 18°C to 26°C changes of a single degree can influence the life span of a mosquito by more than a week (Depinay et al., 2004). Increased mosquito life span can potentially provide additional opportunities for transmission by increasing total population and the number of bloodmeals each mosquito acquires. As these changes require significant time-frames to unfold it is unlikely that an abrupt epidemic could be caused by it. These aspects of local climatic change will be directly observed though model structures controlling environmental attributes of the physical environment.

In addition to long term climatic variation, inter-annual variability has been associated with changes in transmission. Several examples of transmission variation have been associated inter-annual events, specifically during the El Niño phenomena. These events have taken place in Columbia (Bouma et al., 1997), Venezuela (Bouma and Dye, 1997), Sri Lanka (Bouma and Vanderkay, 1996), and Uganda (Hay et al., 2002; Lindblade et al., 1999). Many of these regions experienced a significant increase in precipitation possibly increasing habitat of local vectors. In 1997 the El Niño phenomena was experienced in the Loreto region resulting in an extended dry season (Guarda et al., 1999). This was a contrasting effect to costal regions in Peru who experienced increased rainfall. The resulting changes had the effect of drying potential habitats but also provided increases in temperature that would foster longevity in the surviving population. These considerations can be explored as a component of the climatic model framework to bring understanding to El Niño as a factor of variation in transmission.

## Mosquito Dynamics

Review of the biological functions and feeding characteristics of the dominate local vector *A. darlingi* reveals several practices favorable to transmission of malaria between humans. The transmission capabilities of *A. darlingi* benefit from it's highly anthropophilic nature (Arata et al., 1999; Roberts et al., 2002). *A. darlingi* will take preference in acquiring its bloodmeals from humans. This is opposed to other *Anophales* mosquitoes who will much more readily acquire blood from animals found in forested areas or livestock. Moreover, *A. darlingi* is highly endophagic relative to other sub-species found in the area. Without hesitation *A. darlingi* will seek bloodmeals indoors where as most vectors will remain outdoors (Roberts et al.,

2002). The construction of homes in the Iquitos area often incorporate open air access allowing for greater proximity to humans. As result of these preferences in feeding *A. darlingi* has greater exposure to humans and therefore greater potential for transmission of the parasite causing malaria.

Human contact with *A. darlingi* generally occurs between the hours of 7 and 12 pm when feeding is most intense. A local study of *A. darlingi* feeding revealed a unimodal distribution of biting with a peak occurring between 9 and 10 pm (Roshanravan et al., 2003). Biting continues through midnight but dwindles as this time is approached. Here, an interesting model consideration is noted as human activity during these hours is often limited to the indoors. As people are indoors their exposure to vectors which do not feed indoors is limited. Finally, parasite sporozoites found in the salivary glands of *A. darlingi* have been found at significant rates compared to other *Anophales* mosquitoes (de Oliveira-Ferreira et al., 1990). Sporozoites are the necessary stage in the parasites life-cycle for transmission to occur from a mosquito to human. Moreover, *A. darlingi* is a competent vector of both parasites causing malaria in the Iquitos area, *P. falciparum* and *P. vivax*. These coupled attributes and abilities of *A. darlingi* allow it to be an extremely proficient vector of malaria to humans in Iquitos.

## 2.4.2 Social Considerations

### Age, Sex, and Occupation

While environmental concerns have been the primary focus of researchers in the Iquitos area there are several social considerations that should be simulated within the model domain. Within the demographic structure of Iquitos and its surrounding areas there has been observed variation in infection rate amongst age, sex and occupational cohorts (Guarda et al., 1999; Roper et al., 2000). Two distinct groupings of people stood out in this research as being affected by malaria: those over 60 and working age individuals.

Working age individuals are exposed to increased vectors interaction because of the proximity of many jobs to mosquito habitats. In the Iquitos area this is a product of the reliance on resource extraction and agriculture. These activities place individuals participating at increased risk of malaria because of their proximity to vector habitats. Increased malaria rates due to occupation was particularly prevalent in males as many of these occupations are traditionally held by them in



Iquitos. Additionally, those aged over 60 are susceptible because of immunity issues associated with the aging process.

## **Infection and Treatment**

Of considerable merit is the evaluation of symptomatic presentation in humans and how individuals deal with with symptoms. Roper et al. (2000) found that the mean duration of symptoms was two days with a standard deviation of two days once treatment was sought. Those not acquiring aid were not included in the calculation as there was no recoded data. More useful to model parameterization is understanding of recovery as a component of not only time after treatment but the entire timeframe from initial transmission. This will be discussed later as a component of the mathematical model. Additionally, there is widespread resistance to chloroquine in the area and as result alternative methods are often employed to treat malaria in Iquitos. Seven day treatments of sulfadoxine, pyrimethamine and primaquine are typically used (Roper et al., 2000). Treatment is free but patients must seek supervised medical care on a daily basis in order for their medication to be administered. These requirements may be unattractive to persons who lack mobility or cannot afford to miss work for treatment.

The Ministry of Health in Peru does not allow private pharmacies to dispense anti-malarial drugs to symptomatic patients(Roper et al., 2000). This requirement has been put into place to reduce mishandling of treatment which can result in pharmaceutical resistance in local parasites. Even though these policies are in place there is little to no enforcement or monitoring of the situation. It has been documented that one can easily purchase the same anti-malarial drugs that are available at Ministry of Health facilities at pharmacies or shops in and around Iquitos. This is alarming, as misuse of such drugs can increase the prevalence of resistance strains of the parasites within the community. These increases occur when options for treating malaria are reduced due to resistances or available options become too expensive or ineffective. Increased resistance within an already endemic community will serve to further perpetuate the situation.

## **2.5 Chapter Summary**

Malaria in the Peruvian Amazon is a complex system with many considerations. Understanding of the physical environment, the people who reside within it, and

the mosquito population they interact with presents many causal mechanisms that may be explored through MIA. Understanding of anthropogenic change and the habitats it generates will be of considerable value to the construction of MIA. This highly spatial mechanism can potentially offer resolve to the spread of transmission during prior epidemiological events. Moreover, the dynamics of the mosquito population are an extremely important component of the modeling system. These considerations and potential causal mechanism will be explored as components of a larger system of understanding.

# Chapter 3

## Epidemiological Modeling of Coupled Systems

### 3.1 Introduction

Modeling is often described as an iterative process whereby an attempt is made to refine scope, test hypothesis', define causal understanding, provide quantification, test reliability, and in some cases assist in policy analysis (Sterman, 2000). MIA attempts to do just this in its generalization of complex systems as an epidemiological model. As a whole, this process can be conceptualized as a set of refinements with the ultimate goal of satisfying requirements for realism, robustness, flexibility, clarity, and reproductive ability (Homer and Hirsch, 2006). While concerned with these requirements, MIA concentrates on expanding realism as a product of complexity and providing flexibility in the form of modular design. To achieve the desired levels of complexity a novel approach that encourages discussion of traditional methods and novel adaptations is utilized. Here, isolation of specific vulnerabilities in past methodologies and the discussion of novel approaches will dictate areas of focus in MIA. Once identified these gaps in knowledge or architecture of epidemiological modeling can be addressed in the hopes of using adapted methods to understand causal mechanisms of reemergent malaria in Iquitos.

This chapter and its discussion of epidemiological modeling will allow the reader an opportunity to access the concepts utilized the in construction of MIA. A survey of theoretical research and methodologies in traditional epidemiology will first be used to identify the assumptions of basic transmission modeling. Processes of abstraction in transmission and specific mathematical models will be introduced to

illustrate the breadth of approaches available. Deconstruction of model architecture through analysis of strengths and weaknesses will serve to assimilate the best practices of past methods into MIA's approach. Additionally, adaptations utilized in the transition to modern epidemiological modeling will be discussed as intermediate steps to MIA's approach. The concept of an agent-based model (ABM) will be introduced as a paradigm and potential tool for exploration of epidemiological events and causal factors. A thorough review of agent-based reference models, past implementations, and discussion of the merits of individual analysis will be used to explain the current conceptualization of MIA. Moreover, this chapter will give insight to the specifics of ABM implementation in MIA and how past research has been adapted to facilitate this.

## **3.2 Epidemiology and Modeling**

The notion of epidemiological modeling references much more than the simulation of transmission effects amongst a host population. Rather the complex systems that many researchers seek to characterize contain a near infinite number of parameterizations and attributes that address the nuances of disease transmission amongst humans. The tools utilized in epidemiological modeling are required to capture the dynamics of not only host interactions but also those occurring in a much larger interaction space. This enhanced interaction space can include events between hosts and the physical environment, and the feedbacks effects generated as result of these interactions. To facilitate the abstraction process of these physical systems many methods have been developed to provide greater understanding of the interaction spaces involved. The modern tools used to accomplish this are very much a product of the past and as such there is great utility in understanding of the traditional theoretical and design concepts behind them.

### **3.2.1 Traditional Methods in Epidemiological Modeling**

Traditional methods in epidemiological modeling have relied on the use of mathematical models known as dynamic equation (Auchincloss and Roux, 2008) or differential equation models (Rahmandad and Sterman, 2008). Bound by a set of differential equations, infectious risk states are modeled as trends within an entire population (Anderson and May, 1991; Kermack and McKendrick, 1991; Rao et al., 2009). Each differential equation is used to resolve a rate of change as proportional

to a set of input parameters. Here, the equation set typically will be used to model individual risk states within a segmented population as susceptible, infected, or recovered (SIR). Implemented is an exhaustive measure of transition of an infectious agent through a population within a simulated epidemiological event. In a basic implementation of this model type, three governing differential equations model the change in population size found at each risk state:

$$\frac{dX}{dt} = \mu N - [\lambda(t) + \mu]X(t) \quad (3.1)$$

$$\frac{dY}{dt} = \lambda X - (v + \mu)Y(t) \quad (3.2)$$

$$\frac{dZ}{dt} = vY - \mu Z(t) \quad (3.3)$$

Within this equation set,  $X(t)$ ,  $Y(t)$ , and  $Z(t)$  are representative of the number of individuals within the model domain who are susceptible, infected, or recovered respectively at time,  $t$ . Birth and death rates, a force of infection, and recovery rates are parameterized as  $\mu$ ,  $\lambda$ , and  $v$  respectively. Force of infection is representative of the number of secondary infections resulting from a infected individual. A critical value exists where force of infection produces more new infections than are compensated for by those recovering. Modelers utilize this as an indicator of sustained transmission potentially signifying the presence of an epidemic. The input parameters of the equation set can be adjusted by means of sensitivity analysis for calibration of the model domain with local observations. Produced from the equation set are stocks and flows of transitioning population amongst the risk states (Auchincloss and Roux, 2008). Figure 3.1 illustrates how the differential equation set is applied to the segmented population simulating transition. Summation of the individuals within all cohorts is equal to the total population. This occurs because all individuals are considered to be susceptible in this traditional framework. The possible outcomes of this type of model are shown in figure 3.2 as proportions of susceptible and infected populations through the course of an epidemic event. Steep trajectories found in this phase plane occur when significant populations of infected individuals exist within the model. Epidemic events would be associated with these steep trajectories where recovery rates have been eclipsed by new infections.

While dated in application, dynamic equation models have been utilized extensively in epidemiology (Bolker and Grenfel, 1993; Hethcote, 2000; Lloyd, 2001),

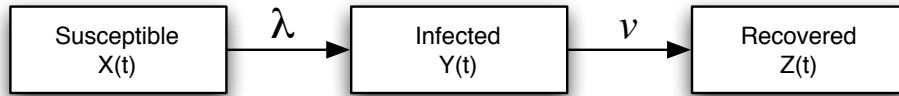


Figure 3.1: Simple SIR model

host-vector diseases (Feng and Velasco-Hernández, 1997), and malaria transfer simulation (Depinay et al., 2004; Ngwa, 2004; Wyse et al., 2007). Many of these models employ a common base in the compartmental SIR model structure as originally proposed by Kermack and McKendrick (1991) and popularized by Anderson and May (1991). The traditional SIR model discussed above has seen extensive modification in years past illustrating its potential to adapt to increasing demands of complexity in epidemiology (Anderson and May, 1991). Such changes include the addition of supplementary risk states representing individuals who are infected but not yet able to transmit the infection (Wyse et al., 2007). Moreover, aspects of heterogeneity including social behavior and susceptibility have been addressed by increasing the total number of compartments in the model domain (Roberts and Heesterbeek, 1993). This augmentation of traditional SIR models with equation sets numbering in the hundreds has become increasingly common as demands for descriptive complexity increase (Homer and Hirsch, 2006). Regardless of past utilization these traditional approaches in epidemiological modeling have not escaped criticism.

The aforementioned popularity of dynamic equation models in epidemiology has just as much to do with a lack of reference models outside of this basic approach (Roche et al., 2008), as it does with the extensive availability of documentation and ease of implementation (Anderson and May, 1991). Despite its ease of use and potential adaptability several researchers have commented on the serious limitations inhibiting the ability of dynamic equation models to produce useful results in complex systems (Auchincloss and Roux, 2008; Roche et al., 2008). Critics have gone as far as to refer to SIR implementations as “toy” models signifying the need for change in epidemiological modeling (Roche et al., 2008). Furthermore, the primary means of adaptation, expansive differential equation sets, can become unmanageable due of the vast number of parameterizations required (Auchincloss and Roux, 2008; Roche et al., 2008).

Further criticism of traditional methods can be generated with discussion of the basic assumption set utilized. A population based approach, such as dynamic equation modeling of epidemiological events requires a set of rigid assumptions to

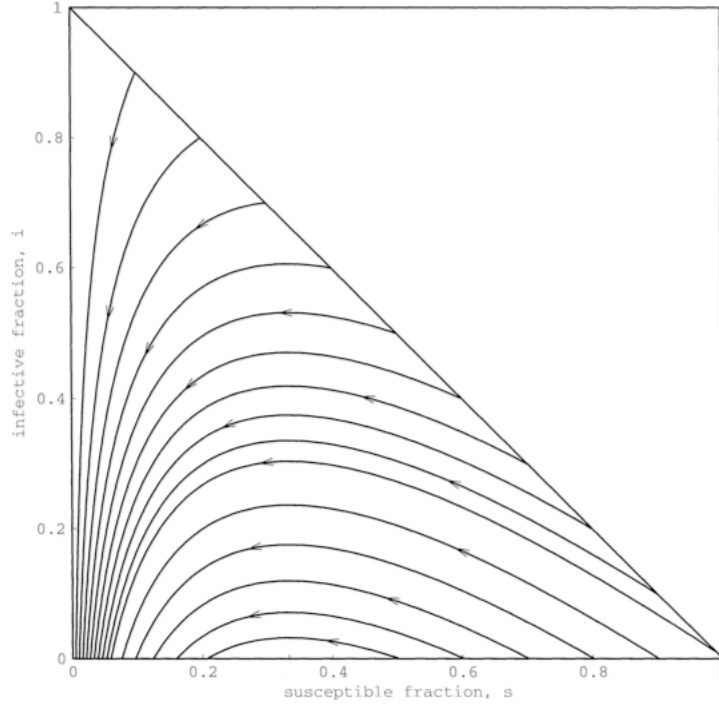


Figure 3.2: Trajectories of traditional SIR models (Hethcote, 2000)

relate individuals to the context of a population. Bian (2004) summarizes these assumptions as four basic rules used in population based models. Firstly, all individuals within the model are assumed to be identical whereby heterogeneity of susceptibility is not considered. This assumption explicitly ignores host specific vulnerabilities in humans such as age (Breman, 2001; Marsh et al., 1995; Snow et al., 1999) and occupation (Guthmann et al., 2001; Ongecha et al., 2006). Moreover, host specific immunities and protections rely on simplified global parameters which can compromise local scale heterogeneity of humans (McKenzie, 2000). Interactions amongst individuals occur globally within the model domain meaning that spatial adjacency is not considered as a limiting factor. Lack of local spatial context disregards the finite number of interactions hosts are capable of due to spatial adjacency. Rather than address the spatial context of hosts, a uniform spatial distribution is assumed in most dynamic equation models. Due to this, previously identified clustering properties of malaria in settlements and around access to infrastructure are ignored (Carter et al., 2000). Finally it is assumed that contact between individuals occurs equally as all individuals are identical. This, as with all assumptions of this model structure, inherently limits spatial analysis and resolution of causal factors within localized study areas.

The continued use of dynamic equation models in epidemiology has been cautioned as limitations will continue to inhibit complexity and understanding of causal factors (Bian, 2004). These problems of complexity are compounded when addressing coupled human-environment interactions as a function of malaria distribution. Additional methodologies must be explored or developed to resolve the desired interactions across multiple spatial interaction spaces. The requirements noted here have caused divergent paths between traditional epidemiological modeling of directly transmitted diseases and vector transmitted diseases such as malaria. While sharing many commonalities, the divergent research path of malaria modeling has been quicker to adapt new tools because of its specific requirements. As a result, past methods and adaptations in the simulation of malaria should be explored as an intermediary prior to the discussion of newer methods.

### 3.2.2 Traditional Methods in Malaria Modeling

The use of traditional epidemiological methods in the modeling of malaria is problematic because unlike directly transmitted diseases multiple population sets hold the ability to host to the infectious agent (McKenzie, 2000). If applied to traditional epidemiology the modeling of malaria must be completed with both humans and mosquitoes represented as hosts in a dually-compartmentalized population. Much of the preliminary work in modeling of malaria transmission can be traced back to the work of Ronald Ross (1910). His pioneering research was able to illustrate that malaria was transmitted by *Anopheles* genus of mosquitoes. This was against a common misconception that the source of malaria transmission was contaminated water (Hurley, 1905). Additionally, Ross (1910) was able to show that significant reductions in malaria infections did not require the complete eradication of the transmitting vector but rather a reduction below a threshold reproduction rate. This work would largely go ignored at the time with few of his contemporaries giving consideration to his research and mathematical models (McKenzie and Samba, 2004).

It was not until the 1950's that researchers such as Macdonald (1957) would revive and continue the important work Ross had begun. Research published by both Ross (1910) and Macdonald (1957) utilized a compartmental approach similar to the previously discussed SIR model. The way in which compartmental SIR models can be applied to an indirectly transmitted diseases needs to be carefully considered because of the two interacting populations. Due to this, any simulation of the interaction space must first consider the risk states of each populations sepa-



rately in order to simulate stocks and flows of the parasite through each population. These models are then coupled in order to simulate transfer between human and mosquito populations:

$$\frac{dx}{dt} = ab\frac{M}{N}y(1-x) - \gamma x \quad (3.4)$$

$$\frac{dy}{dt} = acx(1-y) - \mu y \quad (3.5)$$

Here,  $x$  and  $y$  represent the fraction of infected humans and mosquitoes;  $a$  is the biting rate of mosquitoes on humans as a per capita;  $b$  is a measure of probability describing the chance of a bite from an infected mosquito transmitting to a human,  $c$  is the inverse probability that a mosquito biting an infected human will receive the parasite;  $\gamma$  is the human recovery rate;  $\mu$  is the mosquito death rate; and finally  $M/N$  is the ratio of malaria free female mosquitoes to humans (Roberts and Heesterbeek, 2003). As the differential equation set utilized in the traditional SIR model estimated infected population within a single set of hosts, this set of equations couples the two population estimating transmission of between them. To estimate the secondary infections and ultimately the potential for epidemic transmission this basic model utilizes the basic reproduction ratio,  $R_0$ :

$$R_0 = \frac{M}{N} \frac{a^2bc}{\gamma\mu} \quad (3.6)$$

If  $R_0 > 1$  the number of infected in the population will increase, if  $R_0 < 1$  the cases will decrease (Smith et al., 2007). Utilized as a metric in epidemiological events, values greater than one hold potential to indicate an epidemic event, as the number of secondary cases will exceed the clearing rate. This would indicate that there is a sustainable reservoir of infected humans and mosquitoes within the simulated populations. When utilized as a measure to assess the effectiveness of control campaigns, goals are set to lower the value of  $R_0$  to less than one. If the basic reproduction rate is lowered to this level, transmission will not be sustainable and will eventually lead to eradication of the infectious agent.

Macdonald's work, as with the work of Ross before him, failed to consider the population dynamics of humans and *Anopheles* mosquitoes (McKenzie, 2000). The basic differential equation set assumes a static population, ageless, and unsusceptible to successive reinfections or immunities. Furthermore, little consideration was given to the abstraction of physical processes involved in the life cycle of the

parasites causing malaria. Ross (1910) wrote of his own model:

“Such calculations may appear far-fetched to many, but they are useful, not so much for numerical estimates yielded by them, but because they give more precision to our ideas and a guide for future investigations”

His analysis of his own work highlights many of the short comings of traditional methods in malaria modeling, but provides necessary focus on the diagnostic utility of these past implementations. Moreover, his view that the value of dynamic equation models is in their ability to provide precision in future investigations is valuable, as detailed analysis of these models has isolated several gaps in knowledge. Influence of this pioneering work in diagnostics of causal factors of malaria transmission can be seen in much of the research today. Products of such models have been used extensively to aid in decision-making by providing analysis of proposed control strategies and retrospective analysis of causal factors (McKenzie, 2000). While powerful, these models, which are primarily based in biology, could be linked to social or economic models to provide greater insight (McKenzie, 2000). Thanks to modern computing power there is potential for compartmental models to facilitate this and to be brought down to individual level (McKenzie and Samba, 2004). Computational modeling has established itself as the preferential tool for the exploration of interaction complexities involved with epidemiological events (Roche et al., 2008). MIA proposes to harness the power of individual based analysis to address many of the inadequacies of traditional methods in epidemiological modeling. ABMs will be employed as a tool to facilitate this adaptation of malaria modeling. As such, a thorough review of ABMs and how they can be applied within the MIA framework is warranted.

### **3.3 Agent-Based Modeling**

Agent-based modeling provides a platform that can be used to simulate disaggregated decisions amongst individuals within a spatially explicit environment (Parker et al., 2003). This basic principle contrasts against the assumptions of the previously discussed population-based methods. Dynamic equation models often aggregate analysis to the population level as an inherent product of their equation sets. Conversely, ABMs observe and define model procedures at an individual or “agent” level. Agents are treated as unique entities capable of making informed

decisions based upon information gathered through interactions. This level of analysis is promoted in the ABM in the hopes of observing emergent behaviors between interacting agents that would otherwise be lost in aggregation.

Prior to understanding how such analysis can be applied to epidemiology a basic understanding of what an agent is must be developed. To answer this Grimm et al. (2005) ask what makes James Bond an agent? The answer resolves both cases: they have a clear set of goals, make autonomous decisions to reach their goals, and are able to adapt their decisions rapidly in response to information they collect. Examples of such agents are all around us but in the context of MIA humans and mosquitos fit this description. The abstraction of an agent requires an object centric approach not to be confused with the popular software paradigm object-oriented programming (Jennings, 2000). In this approach specific coding structures are utilized to create unique objects within the model domain able to store and maintain attributes as tangible representations of real-world parameterizations. The agent is then held as this object within a spatially explicit environment throughout its procedural lifespan. While divergent in application, agents are bound by a set of commonalities that can be used to define its purpose in a model:

- Agents have the ability to act as autonomous entities within the model domain
- Each agent has an associated set of attributes or characteristics
- Agents are given spatial context through the use of coordinate systems, normal grids, or social networks
- Each agent's procedural tasks are formed from a set of characteristics and rules

The commonalities presented here provide a basis for the unique assumption set employed by the ABM process. Intrinsic individuality maintains that all agents differ as a product of their unique set of attributes. This reflects heterogeneity of populations, as contrasted with previous assumptions utilized by dynamic equation models. Moreover, spatial context provides the means for local interactions in and amongst agents and their surroundings. Attention is drawn to this assumption as it strongly counters the global interaction space maintained in dynamic equation models. Finally, the autonomous actions of agents foster complexity in the decision making process.

Agents within the model need not be representative only of living organisms rather they can be used to abstract any perception or understanding of physical

systems in a broadest sense (Sanders, 2007). A wide range of agent types including parcels of land (Deadman et al., 2004), fluids (Xiang et al., 2004), and geomorphic processes (Guthrie et al., 2008) have been utilized in the past. Social structures have also been extended to agent-based representations including supply chains (Hanafizadeh and Sherkat, 2009). The above set of commonalities and assumptions of ABMs provides a basis upon which the MIA model can be extended to address specific gaps of knowledge and complexity in the modeling of malaria.

### 3.3.1 Relevancy of Agent-Based Modeling in Epidemiology

A pioneer in complexities research, Wolfram (1984a), suggested that complex systems in nature were a product of interactions amongst many simple, identical, components. He felt that our understanding of these components was advanced but the mechanisms of interaction amongst them, fostering complexity, were relatively unknown. He suggested a discrete dynamical system known as cellular automata (CA) to advance understanding of the complexities resulting from their interaction. CA utilizes a grid based system with prescribed rule sets, and local interactions to develop understanding of complex patterns in physical or biological systems (Wolfram, 1984b). This was an important advancement in complexities research as it provided an object-based conceptualization of physical systems and an alternative to differential equation models. Despite the benefits of CA, the components of malaria transmission exemplify a measure of heterogeneity that if applied to CA could be lost in its simplicity. Moreover, systems comprising MIA's interaction space would be limited by localized interactions imposed by a CA. Abstraction of Humans and mosquitoes will require integration of a vast number of states beyond the scope of traditional CA. Due to these limiting factors a true CA will not be used in MIA. Notwithstanding, the pioneering ideas developed in this work such spatially explicit objects have been extended to ABMs and will be used to reinforce MIA.

ABMs hold potential to extend the advancements of CA to epidemiological simulation of coupled systems. This has been reinforced in previous literature which defines ABMs as tools showing considerable promise in the simulation of coupled human-environmental systems (Deadman et al., 2004). The use of ABMs in epidemiological modeling promotes a novel conceptualization of the interactions amongst hosts by providing facilities to simulate individual heterogeneity. This is important when considering the complex interaction space of coupled systems encompassing humans, mosquitoes, and the physical environment. Perhaps the

most valuable products of the ABM process are not generated from direct observation of individuals but rather from the products of interactions between them. Emergent behaviors, whereby observations from the interaction space are generated from interactions between individuals and their physical environment, can provide a novel understanding of causal mechanisms otherwise lost in population-based analysis. These emergent behaviors are a product of not only parameterizations of the model domain but are generated by the autonomous actions of the agents. A majority of dynamic equation models do not begin to consider the resolution of causal mechanisms, but only provide direct estimates of the affected population size (Bian, 2004). As the transmission of malaria is a product of the interactions between two sets of individuals an agent-based approach can be useful to highlight the mechanics found in the physical processes facilitating transmission.

### 3.3.2 Agent-based Modeling in Epidemiology

Several studies utilizing agent-based methodologies had have been published for directly transmitted diseases including the spread of avian flu in Southeast Asia (Ferguson et al., 2005), and localized smallpox outbreaks (Eubank et al., 2004). Unfortunately, these studies have been vague in their methods and employ complex procedures to estimate transmission amongst individuals. For these reasons the model structures employed in these studies have not been reproducible. While operating at the individual level these models do not necessarily fit the basic assumptions of ABMs as they lack spatial context or rely on rigid rule sets to define interactions amongst agents. Regardless of the results presented in these studies they have done little for the ABM community in epidemiology. Authors responded to this situation by proposing reference models for ABMs in epidemiology. Proposals for this standardization were developed by Bian (2004), and later by Roche et al. (2008). Their standardized frameworks attempted for the first time to provide researchers with easily replicated or adapted methods for spatially explicit investigation of causal factors and mechanisms.

Bian (2004) sought to define transmission as a network function amongst agents within the model domain. Measures of adjacency and social networking between agents form the basis for this transmission function. Testing of this methodology showed encouraging results promoting the use of ABMs as a method of increasing complexity. Figure 3.3 shows the running results of one such testbed against traditional methods in epidemiology. Bian (2004) highlighted the ill effects of the assumption set used in traditional epidemiological modeling by showing an overop-

timistic infection rates and timing as result of global mixing. The agent-based approach produced a longer, sustained period of epidemic with lower total infections. This was a direct result of localized contact of agents, limiting each to finite interaction space. Also important in this study was the analysis of spatial clustering, which was largely resolved due to the interaction assumptions used in ABMs. Bian (2004) iterates that her proposed framework can be amended to vector-borne infectious diseases but that it requires modeling of both human and vectors as previously discussed. While this work diligently documented the benefits of an ABM, and outlined what the theoretical constructing of such a system would entail, it failed to provide the specific means of implementation.

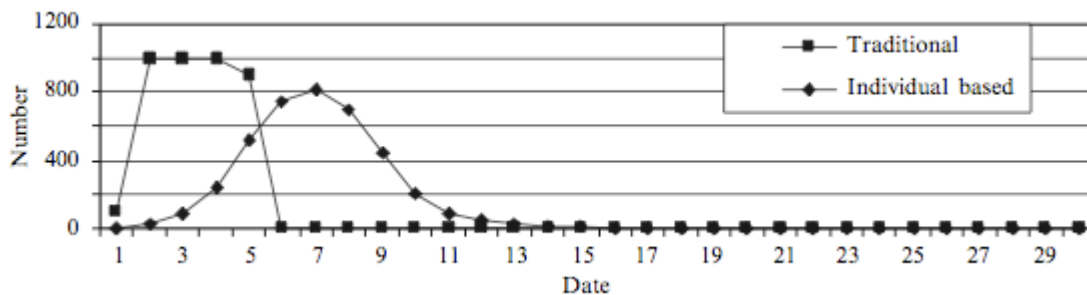


Figure 3.3: Traditional and individually-based model comparison (Bian, 2004)

The work of Roche et al. (2008) appeared several years later, striving to promote turn-key methods in epidemiological modeling. Tired of lackluster documentation and complex approaches, the authors of this study proposed a standard agent-based methodology for modeling of vector-borne diseases. As apposed to the work of Bian (2004), this framework was to be used explicitly for diseases communicated by vectors, as is the case of malaria. Inspired by the traditional SIR methods previously mentioned, segmented populations were extended to individual analysis amongst multiple sets of hosts. They attempted to illustrate the adaptable nature of this implementation by integrating representative environmental landscapes and parallel computing aspects as optional components of the framework.

The framework was created in the Java programming language, implementing a functional ABM with the Swarm simulation toolkit (Minar et al., 1996). Object abstractions of parasites and hosts were utilized to form the agent classes within the model domain. The complete source code including functional examples were released with the paper to allow researchers an opportunity to adapt their framework to current research. The end result was a simplistic implementation of an ABM for transmission of vector-borne diseases. While platform independent, the Swarm toolkit it utilizes was originally developed in the mid 1990s and has since been

replaced by a new generation of potentially more powerful tools. At the time of the MIA, no literature had yet utilized the methods proposed by Roche et al. (2008). Despite poor adaptation of reference models in agent-based epidemiology, there are several encouraging studies that have been able to bring theoretical frameworks into practical application in the simulation of malaria transmission.

### 3.3.3 Applied Agent-Based Malaria Modeling

Recently two studies have attempted to implement an ABM to simulate malaria transfer dynamics at local scales. These early adopters of ABMs in the simulation of malaria transfer were able to extend conceptual designs and existing mathematical models into functional systems. Prior to these studies, such modeling efforts remained only as reference frameworks lacking real-world application. This was due in part to a lack of adequate field data for parameterization as well as restrictions imposed by computing resources. Extensive field work and embedded mathematical models were coupled with existing agent-based methods to enable abstraction of epidemiology and malaria transmission. Contrasting in purpose these two approaches may be used as reference points in the construction of MIA. Discussion will be given to the merits of these studies as precursors and potential references for future ABMs in malaria transmission. Additionally, their work will be compared and contrasted to the proposed methodologies of MIA.

The first of the two studies concentrated on risk assessment by examining potential reemergence of malaria in southern France. The model as implemented by Linard et al. (2009) was created as a reactionary measure to the detection of local autochthonous transmission in 2006. Autochthonous transmission indicates that the transfer was localized between hosts in the study area and not a result of importation. This drew considerable attention as malaria was thought to have been eradicated in the wake of previous vector eradication campaigns. Even with the identification of recent localized transmission the authors indicate that the assumed risk of local malaria re-emergence is low (Poncon et al., 2007). Due to this the framework did not seek to identify reemergence temporally but rather was an exercise in spatial analysis of causal factors and emergent behaviors driving risk analysis. An immediate parallel can be drawn to the priorities of the MIA in the creation of an infrastructure for diagnostic modeling.

Their model, MALCAM, was tasked with estimating spatial and temporal variation in actual biting rates (ABR) between mosquitoes and humans over a single season (May to October). This approach borrows from traditional metrics of

epidimicy such as  $R_0$ , or basic reproductivity, estimated from local variables such as biting rates (Smith et al., 2007). Sensitivity analysis tests showed that mosquito reproduction and mortality greatly influenced contacts between mosquitoes and humans. Unsurprisingly these parameters control the abundance of mosquitoes found in the model and thus increase opportunities for biting to occur. The emergent behaviors shown in these results are promising as they show similar changes to the pioneering work of Ross (1910). Using ABMs to accomplish this has the added value of producing spatial results in which clusterings can be observed.

As apposed to studies considering reemergent malaria in topical regions, climate change is not a driving factor in the malaria transmission model of MALCAM. Rather, land use change is assumed as the primary factor behind potential reemergence. This is related to extensive local rice farming that has provided expansive habitat space for the primary vector *A. hyrcanus*. It was presumed that habitat extension would allow for an increased carrying capacity within the local environment, encouraging an increased vector population. Thus, an interesting case has been submitted for diagnostic modeling of an epidemiological event within an environment contrasting to that of MIA. The research completed here promoted a strong case for the use of sensitivity testing of input parameters to understand how land use and other biological factors could drive reemergence. Figure 3.4 shows the sensitivity analysis of several biological input parameters in MALCAM. Each was tested 20% above and below the default input parameter. As was previously suggested, sensitivities in reproduction and mortality rates of mosquitoes has a exponential relationship with actual biting rates simulated in the model domain. A 20% increase in reproduction of mosquitoes results in a near 300% increase in biting rates simulated. This reinforced the need to implement polices that could negatively impact the reproductive cycles of the mosquitoes themselves and reduce available habitat space.

MALCAM uses a set of mathematical models to drive population dynamics of mosquitoes that was calibrated with in-situ measurements and biological specifics of the primary vector in the study area. For these reasons, as well as an assumed non-endemic population, the possibility of extending this model to epidemic/endemic regions such as the Peruvian Amazon are limited. Furthermore, specific vulnerabilities of the MALCAM model restrict mosquito habitat space to rice fields with no consideration of precipitation or hydrological variation within the abstracted physical environment. Notwithstanding, the design concepts employed by the authors of this study, as well as their testing rigor, provide valuable insight into the design of an ABM for malaria transmission.



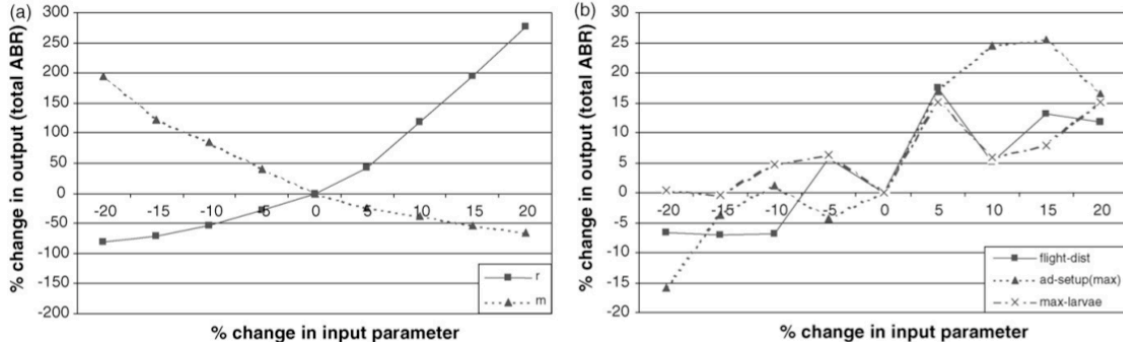


Figure 3.4: Sensitivity analysis of reproduction ( $r$ ), mortality ( $m$ ), maximum flight distance ( $flight-dist$ ), initialization conditions ( $ad-setup(max)$ ) and carrying capacity ( $max-larvae$ ) (Linard et al., 2009)

Developed around the same time as MALCAM, Bomblies et al. (2008) presented a coupled hydrological-entomological model to assess local scale malaria transmission in the village of Banizoumbou, Niger. Their model attempted to extend an existing individually-based mathematical model developed by Depinay et al. (2004) that was capable of simulating mosquito population dynamics. The applied mathematical framework included procedures for estimation of mosquito mortality, reproduction, vectorial capacity, and controlling habitat dynamics. The integration of this mathematical modeling system developed by Depinay et al. (2004) placed the model at a considerable level of complexity over the previous efforts of MALCAM. As the local study area is a desert-fringe environment the hydrological dynamics strongly drive habitat generation and ultimately mosquito population size. The model was calibrated with extensive field work that included mosquitos collected from light traps, soil sampling, and extensive meteorological monitoring. As result of their efforts the model was able to accurately simulate mosquito habitats and population. Despite their successes, the authors identify a limitation of the model as not being able to “perfectly reproduce weekly CDC light trap measurements” (Bomblies et al., 2008). This is consistent with the tone of the paper throughout, as consideration of the diagnostic capabilities of the model are used primarily as metrics for the predictive capabilities of the model.

While each of these ABMs utilized climatic data including temperature to assist in the modeling of transmission little consideration was given to the the effects of local climate variability. Each study identified a relationship between climatic variability and specific physical systems but failed to explore how local observations tied into larger climate systems. This can be attributed to the restricted temporal scale of each model which limited the potential to assess climate change over time

as a component of malaria transmission. MIA will attempt to extend analysis of climatic variability into a larger context as a component of global climate change and its effects on local vector populations and malaria transmission.

### **3.3.4 MIA Agent-Based Approach**

The approach in MIA merges the theories used in traditional epidemiological modeling, such as SIR, with the spatially explicit individual level analysis of ABMs. The proposed system will characterize two sets of agents in mosquitoes and humans. These agent sets will be used to model transfer dynamics through the interactions that occur between the two sets of agents. Additionally, a spatially explicit environment will be created to provide agents a common space within which agents can interact and gather information.

Each set of agents will have attached attributes to indicate their current risk state as well as a vast number of ancillary states abstracting population dynamics, biological functions, and environmental interactions. This disaggregation will allow for greater control of biological drivers and possibly facilitate an increase in model complexity through refinement of physical system interactions. The interaction rules and procedural lifespan of each agent will be driven by a series of mathematical models and heuristic rule sets.

## **3.4 Chapter Summary**

Comparative analysis of traditional methods in epidemiology and novel approaches such as ABMs show accessible gaps in research in the modeling of malaria transmission. Specific issues identified through the prior discussion include:

- Restricted complexity because of rigid assumption sets employed in traditional epidemiological modeling
- Compromises in prior implementations can be accommodated by using novel hybrid approaches and enhanced resolution of the level of analysis
- ABMs can be exploited to access emergent behaviors and extend understanding of physical systems.

- Past implementations of ABMs in epidemiology and malaria have assessed many research gaps and as a whole can be synthesized to devise a novel approach to transmission modeling.

MIA will attempt to address many of these shortcomings through the introduction of novel methods that incorporate traditional approaches with the agent-based paradigm of modeling. Even with potential solutions in sight, the cognitive burden of understanding model behavior can often become a restrictive cost of increasing complexity in modeling (Rahmandad and Sterman, 2008). Several researchers of the past have understood this basic principle in epidemiological modeling, and MIA will attempt to empathize this in its methodologies and discussion. Carrying forward the base of understanding established in this chapter, focus will now be turned to the specific methodologies employed in MIA to illustrate the conceptualization of the novel approach synthesized from the lessons of the past.

# Chapter 4

## Methodology

As an exercise in model building and implementation, the methodologies utilized in MIA are presented in detail to draw attention to the complexities of interaction amongst its abstracted physical systems. Focus is given to the coupled nature of sub-model structures demonstrating an integrated approach to physical modeling of human-mosquito-environment interactions. This approach aims to address how specific research questions have been accessed through the construction of the model. Development and implementation of the model is described in this chapter, utilizing the overview, design concepts, and details (ODD) protocol for individually based models (Grimm et al., 2006). The complex integrated nature of the MIA model demands standardized descriptive structures for abstraction of model processes and mathematical sub-systems. A general purpose overview of the model's structure will be given in the methodological purpose, platform description, explanation of state variables, and process-scheduling definition. Conceptual design is then discussed to demonstrate theoretical processes as related to specific model structures and parameterizations. Lastly, detailed discussion of model initialization, input, and sub-model processes will be developed to finalize understanding of the MIA model implementation.

### 4.1 Overview

#### 4.1.1 Purpose

From a methodological perspective the model strives to abstract physical systems into either mathematical models or heuristic rule sets. These model constructs are

responsible for providing the means to observe emergent behaviors resulting from simulated individuals. Developed structures and abstractions in the model serve as feedbacks to additional systems of simulation that comprise a larger conceptualization of the processes involved in malaria transmission. It is in analysis of the connections amongst processes that hypothesis testing and analysis of emergent behaviors can best be observed. In the case of MIA, the construct of modeling implies not a tool of historical epidemiology but rather an avenue for systematic exploration of processes and feedbacks driving interactions of interest. The forthcoming methodologies seek to provide the basis for a spatially explicit ABM of malaria transmission dynamics and the procedures necessary to utilize the model as a diagnostic tool.

### 4.1.2 Platform

The development platform of MIA can be broken down into two main components of processing and data handling (Figure: 4.1). The model processing platform is created in a Java programming environment (Gosling et al., 2005) utilizing the Java implementation of the recursive porous agent simulation toolkit otherwise known as REPAST (Collier, 2003). The REPAST toolkit offers an open source platform for development and deployment of ABMs. REPAST provides facilities for controller, scheduler, action, and agent processing (North et al., 2006) which is used heavily to coordinate the model at the system level. Structures in the programming platform, other than those provided by REPAST, were developed as original code of this project. These structures were also created in a Java environment utilizing an object oriented programming approach. Working in a Java environment allows for strong coupling of third party open source facilities for data handling purposes. The model takes advantage of this by structuring data handling as a two part process. A coupled MySQL database (MySQL, 2009) gathers and stores global and agent states at each time step. Database entries then are processed using the R statistical language (R Development Core Team, 2009). The R statistical language provides strong aptitude for statistical processing that is utilized to present results and drive discussion. Much like the processing platform, structures utilized to couple third party data handling software were developed as original code for MIA.

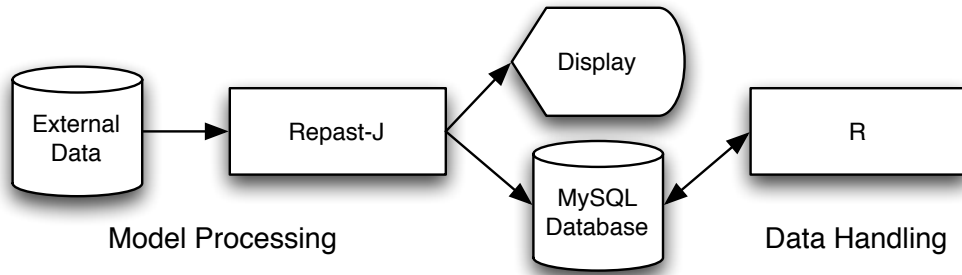


Figure 4.1: MIA model platform

### 4.1.3 State Variables and Scales

MIA is characterized by five hierarchal levels where individuals (agents), households, habitats, population, and environment are observed as model components. Each level of analysis offers a different perspective to the desired interaction properties in the model by capturing a unique set of state variables. The processing tasks assigned at each level are contrasting in approach and require sub-model specific structures to govern their behaviors and methods of simulation.

The individual level forms the basis of all ABMs by abstracting individual entities as agent objects with a unique set of state variables dictated by their interactions in the model domain. An assumption that all agents are able to make decisions or follow rule sets independently across time is maintained at the individual level. An individual may only be considered at a single spatially explicit location during discrete temporal events within the model domain. The model structure considers two unique classes of physically based agents in humans and mosquitoes. Each class of agents is characterized by a set of state variables inherited from their agent type. Human agents are characterized with a set of state variables including identification number, location coordinates, age, sex, occupation, and malarial state (see table 4.1). Human agents that have not completed their 15<sup>th</sup> year of life are considered to be children, and all others adults. Human children carry an identical set of state variables as their adult agent counterparts but are limited in occupation and utilize different mortality rates. Stochastic simulations and heuristic rule sets of a human sub-model determine the actions of agents in the model and facilitate changes in state variables.

Also considered at the individual level of analysis are adult-stage mosquitoes. Adult-stage mosquitoes have emerged from aquatic-stage simulation to be discussed

Table 4.1: Human agent attributes

Variable	Data Type	Description
ID	Integer	Unique Identifier
x	Integer	Current X coordinate
y	Integer	Current Y coordinate
homeY	Integer	Household X coordinate
homeX	Integer	Household Y coordinate
age	Integer	Agent age in years
stepsToLive	Integer	Simulated year of death
sex	Integer	Sex of agent
occupation	Integer	Occupation of agent
hasMalaria	Boolean	True if agent is infected
isInfectious	Boolean	True if agent is infectious
isSymptomatic	Boolean	True if agent is symptomatic
stepsSinceInfection	Integer	Tracking for incubation period

in the mosquito sub-model becoming flying agents. Mosquitoes at the adult-stage inherit a different set of state variables unique to their agent type. This set of state variables is comprised of a identification number, geographic location, gonotrophic cycle status, and malarial status (see table: 4.2). A series of tasks directed by an adult mosquito sub-model are completed to simulate interactions and development within the model domain. Simulation at the individual level generates hundreds of thousands of unique instances representing each adult mosquito or human in the model. This produces rich data sets detailing the interactions of individuals but is also the most computationally expensive level of observation. Due to this, additional levels of analysis are utilized to observe and simulate smaller scale processes in the MIA model.

The second tier of analysis is comprised of two related units of aggregation: households and habitats. A household is defined as a spatially explicit unit that can be occupied by a group of human agents during any time period of a model run. The household unit is characterized by state variables including identification number, location coordinates, agents residing in the household, and the presence of aquaculture. The agents composing this unit are considered a family unit and are related within the model domain. The existence of the household unit is reliant on it being occupied by human agents. If the number of human agents becomes zero at any point during the model run the household unit is abandoned. In this state the household can be colonized by new families dynamically imported into the study site by migration or human agents already operating within the study

Table 4.2: Mosquito agent attributes

Variable	Data Type	Description
ID	Integer	Unique Identifier
x	Integer	Current X coordinate
y	Integer	Current Y coordinate
xX	Integer	Temporary movement variable
yX	Integer	Temporary movement variable
gonotropicCycle	Double	Monitoring of gonotropic cycle
isOvipositing	Boolean	True if laying eggs during step
isInfectious	Boolean	True if agent can transmit
isInfected	Boolean	True if agent is infected
hasBitten	Boolean	True if agent bit human
eggsLaid	Integer	Count of eggs laid in current cycle
stepsSinceInfection	Integer	Tracking for incubation periods

site. The aquaculture state of the household describes aquatic farming practices and is dependent on the actions of the agents inhabiting the household and model initialization parameters. Currently, the household level exists purely for statistical purposes. Simulated household decisions are not made based upon the individuals who reside within in it but in the future may be modified to do so.

As humans inhabit household units, mosquitoes utilize habitats in the model to accommodate their biological processes. Habitats are represented in the model as geographical units with embedded sub-models to facilitate tasks including the laying of eggs (oviposition) and simulation of aquatic-stage mosquito development. The spatial characteristics of a habitat unit are bound by the normal grid cell size used to represent the physical environment. In contrast to adult-stage mosquitoes who are simulated as agents, immature or aquatic-stage mosquitoes are simulated as aggregate units within a grid cell habitat. This process requires an embedded mathematical model to govern development of the immature mosquitoes within each habitat. Due to this, mosquito habitats are a complicated units of analysis and hold potential for uncertainty if improperly parameterized. Utilizing a large set of variables, habitats are characterized with states of water dynamics, immature mosquitoes dynamics (eggs, larvae, pupae) and local development rates. Unlike households, habitats do not require the presence of individual agents for their operation. Habitat simulation is completed iteratively throughout the entire run of the model. This ensures that the embedded models are ready for aquatic-stage simulation at any point of a model run.

Aggregate analysis of trends in groups of individuals, households, or habitats



is handled by the model at the population level. Human agents at the population level are characterized by size, number of households, and infection rates. These observations can be accessed in a spatial fashion for observation of trends over time and space. The same set of variables is used to characterize adult mosquitoes in addition to biting rates, global gonotropic cycling estimates, and oviposition rates. Aquatic-stage mosquitoes can also be observed at the population level characterized by total population at egg, larval, and pupal stages of development. Population level analysis provides important observational tools allowing for analysis of parameterization changes made at the individual level in relation to expected results in the study site.

All previously discussed levels of the model exist within the final and the highest order of the model, the environment. The environmental sub-model governs this level of the model and provides a spatially explicit representation of the study area including land cover types and climatic conditions. A regular grid is used to define the spatial locations found within the environmental level. The environment is characterized by state variables including temperature, barometric pressure, relative humidity, time of sun rise/set, precipitation, and land cover type. More importantly all lower tier elements of the model are bound by the limits of the environment existing within its domain. The resulting product generates a space in which interactions amongst agents or between agents and the environment can be simulated in a spatially explicit fashion. The environmental level provides coupling structures for all sub-models and is the true interface through which emergent behaviors can be observed in the MIA model.

#### **4.1.4 Processes Overview and Scheduling**

Three interacting sub-models abstract human, mosquito, and environmental systems to retrospectively simulate the dynamics of malaria transfer in the MIA model (Figure: 4.2). The implemented model structure separates processes into these three primary categories corresponding to physical systems targeted in the research questions. Each of the three major components is governed by a sub-model that simulates known processes and provides process coupling. To simulate physical systems each sub-model generates a series of tasks which are completed as discrete time steps.

The discrete time steps in MIA contain five programming structures which facilitate the tasks required to simulate the human, mosquito, and environmental

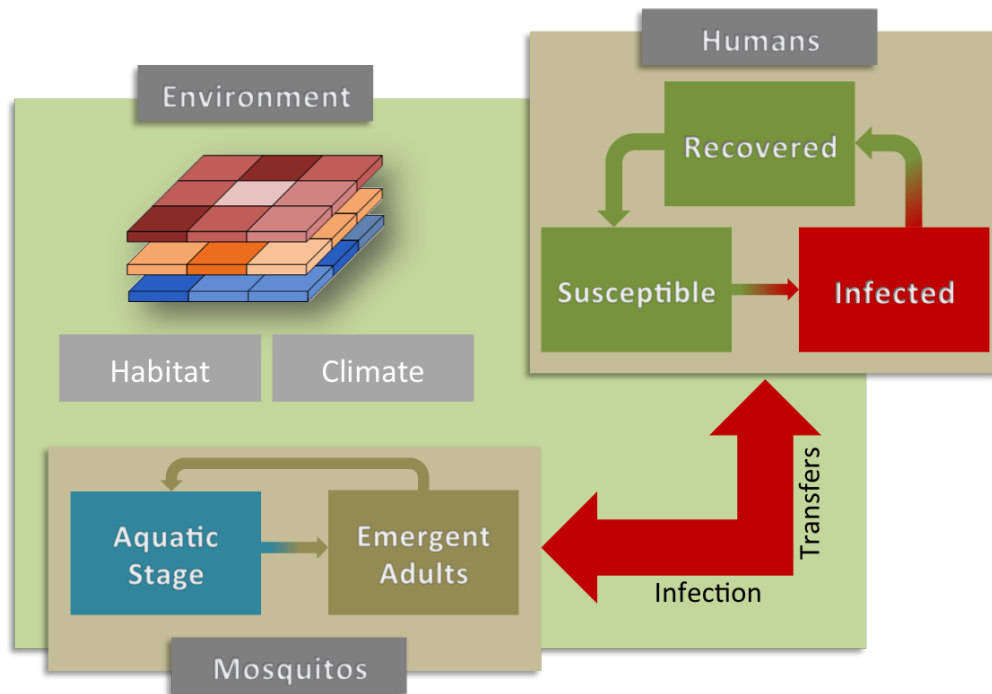


Figure 4.2: MIA model conceptualization

sub-models. Figure 4.3 illustrates the order of these tasks in a UML sequence diagram. Tasks to be simulated are shown as elements of the previously discussed hierarchal levels. An additional level known as the scheduler is added to represent system level processing of the MIA model. While not a unit of analysis its purpose is to coordinate the model sequencing during each time step using the REPAST controller. The scheduling sequence at each time step begins with an update of global variables including temperature, carrying capacities, and development rates. Following the global update human and mosquito sub-models are updated to reflect changes in population based upon the updated state variables from the previous step or initialization parameters. This sequence provides an estimation of population size and generates new mosquito agents. Finally, the primary model stepping iterates through each human and mosquito agent simulating sub-model tasks at the agent level. The tasks of each human and mosquito agent are completed asynchronously in an attempt to characterize interactions between the two sets of individuals replicating the dynamics of the physical environment.

Time in MIA is addressed using discrete steps representative of a 24 hour period. This global stepping corresponds with the course requirements of the model as a whole. Specific sub-model elements are allowed to simulate at finer temporal scales to satisfy their particular requirements. The results of sub-scale elements

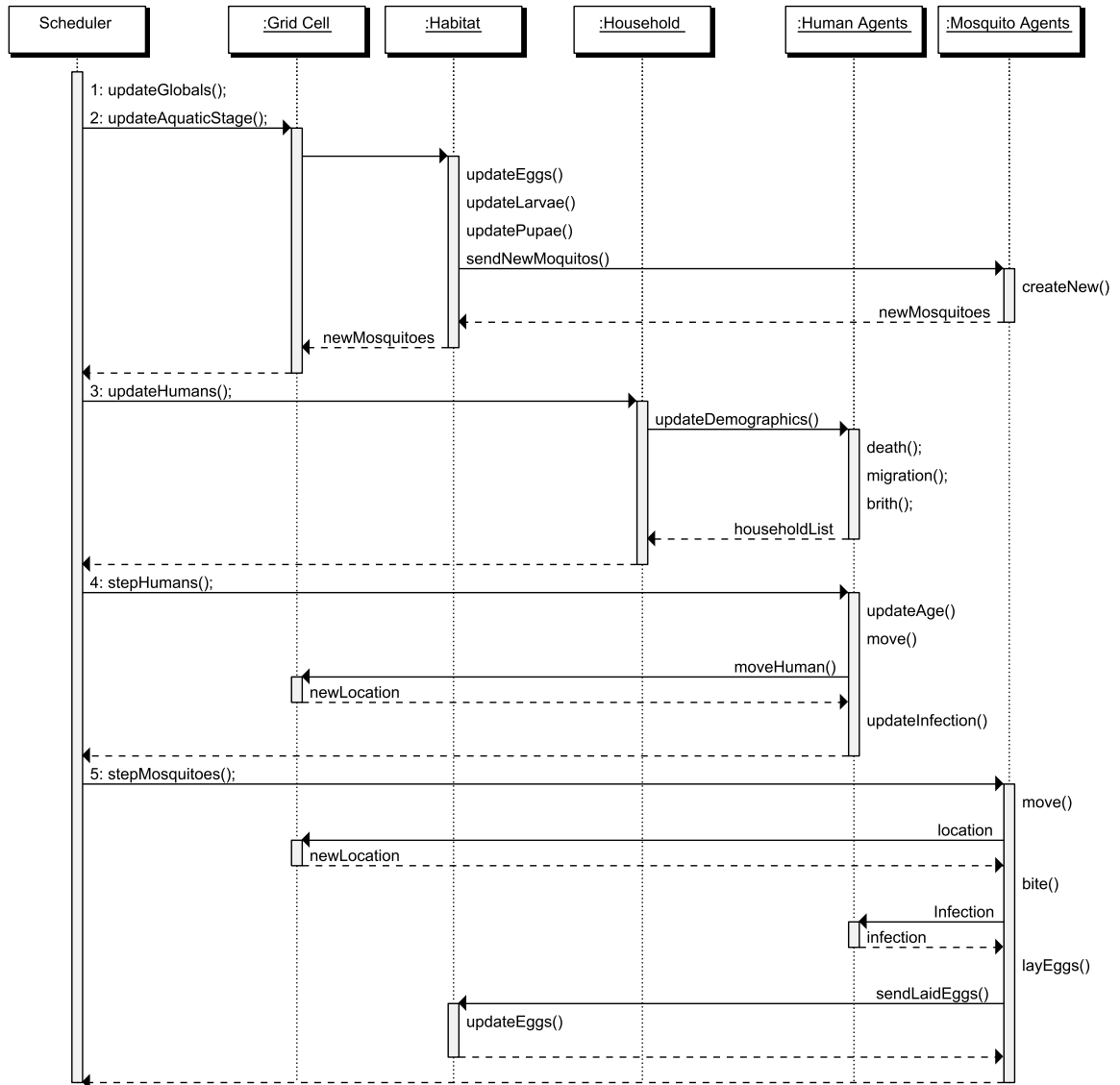


Figure 4.3: UML sequence diagram

are aggregated to correspond with MIA’s global temporal resolution. For example, a structural element such as the mathematical model governing aquatic-stage development requires that each hour of the day be simulated. Thus this process is allowed to iterate within each step to produce an aggregate measure of development based upon hourly estimates. This structuring of temporal scale is utilized to correspond with the temporal availability of climatic data and the computational capacity of the systems used to simulate the model.

## **4.2 Design Concepts and Details**

### **4.2.1 Sensing**

Sensing is an important concept in the model referring to the proprietary methods used by agents to gather information about their surrounding environment. Mosquito agents utilize sensing feedbacks from environmental and human systems to simulate their behavior and development. These sensing abilities extend to enable detection of variables including human presence, and detection of suitable breeding sites. Mosquito agents will make decisions based upon the variable information and stochastic processes gathered from their sensing abilities. Human agents are assumed to have abilities to sense their surroundings, including locational and household information. Additionally human agents are aware of their infectious status through the presentation of symptoms such as fever.

### **4.2.2 Interaction**

The model as a whole is driven by the interactions amongst agents and their environment. Interactions are facilitated through the grid spaces generated by the environmental model. Spatially explicit grid cells can be occupied by agents and attributes so that sensing can occur and interactions develop. These feedbacks are utilized by the mosquito agents to ultimately generate the interaction that the model seeks to characterize, biting, and the potential transfer of malaria. Agents have the ability to modify their environment but are also influenced by changes in the environment. Emergent behavior simulated between agents is largely a product of these cycles of modification, reaction, and adaptation as generated in interaction. Concepts of space and time are maintained as discreet locations and temporal events with all interactions.

### 4.2.3 Stochasticity

The MIA model relies on several stochastic processes to introduce variability into deterministic mathematical models. Gaussian and weighted uniform probability distributions are used to consider heterogeneity in agent state variables and attributes. Additionally some variables describing mosquito development are stochastically generated as discussed later as sub-model structure.

### 4.2.4 Model Initialization

In order to bring the model to a stable state several elements require initialization. Human agents are randomly generated and assigned to households based on known population size at the initialization date of the model. This process utilizes known population distributions to assign ages and expiry dates to human agents spawned during initialization. Agents generated after initialization will be assumed either new born or simulated migrants with an assigned age. Households are allocated across land coverage types based upon known urbanization rates from Peruvian census data. The exact locations of households are randomly generated within each land cover type. Additionally aquaculture pools are assigned to random households at the onset of the model based upon the requirements of the simulation type.

The mosquito population at initialization is set to fifty adult stage mosquitos with no aquatic-stage population. Each is randomly placed in a habitat in the study site. Testing of the model with smaller numbers in many cases failed to reach steady state. The minimum selected here ensures that a steady state is reached within the model. With this initialization the model requires approximately six to eight months to reach a steady state. The results produced from the first year of the model are not considered in analysis because of this. The effect of the initialization processes carries potential uncertainties which necessitate sensitivity testing. Steps will be taken in the discussion of the model results to provide analysis of these uncertainties.

## 4.3 Environmental Sub-Model

The environmental sub-model (ESM) is the most important sub-system of the MIA model because of its spatially explicit nature. Utilized to create a coupling interface,

the ESM facilitates interactions amongst sub-model simulation spaces. Conceptually, the ESM is a spatially explicit representation of the physical environment found within the study area. A “world” object is generated and utilized as a container for agents and spatial variables much in the same way we live and interact within our physical environment (Roche et al., 2008). Spatial interactions between agents and the physical environment can then be simulated though time and space when coupled in the larger context of the model. To define the model’s “world” the ESM generates cellular landscapes or grids in which agents and environmental attributes are given spatial context. As each type of agent has it’s own environmental considerations a cellular landscape is generated to address the specific needs of each governing sub-model. Georectification is implemented to ensure that locations in any of the cellular landscapes relate the same physical location. This has been completed to allow interactions not only within but amongst cellular landscapes. Computationally, each grid is managed as a matrix, storing cell values and variables in memory during the model run. The following section documents the inputs utilized in the generation of each grid and methodologies used to create environmental simulation space.

### **4.3.1 Sub-Model Inputs**

The primary input of the ESM is based on satellite imagery acquired by the Landsat series of space-borne optical sensors. Images were acquired on November 11th, 1987, August 5th, 1993, and July 6th, 1996 from the thematic mapper (TM) sensor of Landsat 5, and May 31st, 2001 from the enhanced thematic mapper (ETM+) of Landsat 7. Prior to assimilation of these images into the model a series of pre-processing steps are completed to prepare the data. A process of image to image rectification is completed to ensure that grid cells in each of the images are representative of the same location in the physical environment. Permanent urban features such as a road network intersections, airport runways, and building features were utilized as reference points between each image. Due to a lack of locally available ground control points the accuracy of coordinate systems in relation to real world locations cannot be presently ensured. This does not concern the model as certainty of image to image rectification allows for minimal errors in observation of changes over time. A root mean square error rate of less than one pixel was maintained in both the X and Y planes to ensure accuracy in the image to image rectification process.

### 4.3.2 Environmental Simulation

Simulation of the physical environment in this sub-model is completed in three steps, generating a number of cellular landscapes. Environmental and human grid spaces are derived from satellite imagery detailing specific land coverage types of the physical environment within the model. These grid spaces are similar and will be discussed together in regards to their creation. Next a grid space abstracting mosquito habitat is created based on the products of the environmental and human grid spaces. Each grid space consists of a 240 by 180 regular grid at a spatial resolution of 30 m x 30 m. The grid space resolution is a compromise between complexity and computational overhead. The spatial resolution selected comes from the native resolution of the the satellite imagery providing a reasonable space in which habitats and agent tasks can be simulated. Refinement of the spatial resolution would add computational overhead by compounding grid based calculations in relation to the number of additional cells. Considering the already significant computational requirements of an agent-based model the native resolution of the satellite serves as an adequate compromise.

#### Environmental and Human Grid Space

To simulate human agency with spatial consideration, the model requires geographic definition of areas suitable for agents to occupy. The ESM accomplishes this by creating a grid space where agents occupy grid cells based upon known land coverage types. Rulesets are extended to isolate cells acceptable for habitation and the establishment of household structures. The ESM utilizes land coverage types including urban and peri-urban for the initial human habitation ruleset. Additionally, land cover types of forest, bare ground, and water are processed to complete the model representation of the physical environment. The rendered spatially explicit land covers, coupled with known urbanization rates, is utilized to estimate spatial population distributions throughout the study site.

Generating these land cover classifications requires Landsat 5 and 7 satellite imagery to be assimilated into the model. Images from the Landsat series prior to processing have a swath 185 km wide (Jensen, 2000). Due to this, unprocessed images represent areas much larger than the observed study site in the MIA model. A sub-set of the image is made for the 8 km x 4 km study area focused on the Zungarococha suburban communities. Here, each image is bound by bound by a coordinate set found in the north west at  $73^{\circ} 24' 52''$  W,  $3^{\circ} 49' 27''$  S and south-east

at  $73^{\circ} 20' 23''$  W,  $3^{\circ} 51' 43''$  S.

The TM and ETM+ sensors used to acquire Landsat 5 and 7 imagery respectively capture seven bands of visual and infrared data (Jensen, 2000). For the purposes of the land cover classification in the model only four bands are selected including red, green, and blue visual spectrum data as well as near infrared data. To increase contrast and help in the classification process a normalized vegetation index (NDVI) is calculated based upon observed red and near infrared data. Classification of land cover types is processed using PCI geomatica (PCI Geomatics, 2002) with an k-means unsupervised classification. From the iterative unsupervised classification 16 initial classes are generated and aggregated to five possible land cover types: bare ground, forested, peri-urban, urban, and water. Classifications are completed for all available imagery and made available to the model domain between time steps of acquisition as ASCII grids. The generated environmental grid is made available to the entire model to aid in other sub-model simulations.

The preprocessing steps described above are completed using third party software and are not internally coupled with the MIA model. Due to this there is no automation of these processes and the data must be prepared manually prior to assimilation by the ESM. One of the operational goals of MIA in the future should be the elimination of reliance on closed source applications and coupled automation of preprocessing.

## **Mosquito Grid Space**

The mosquito grid space represents possible habitat locations for adult and aquatic-stage mosquitoes in MIA. Identification of these habitats relies on understanding of the requirements and preferences of local mosquitoes for completion of their biological functions. Adult mosquitos laying their eggs and developing immature mosquitoes require aquatic environments (Guarda et al., 1999; Roshanravan et al., 2003). Keeping this in mind the MIA model provides two possible structures for habitation: water edge environments and aquaculture.

The model uses the previously completed land use classifications to identify existing bodies of water. An edge detection algorithm extracts cells bordering known bodies of water which are added to the mosquito grid space. These locations have an assumed presence of water providing favorable habitats for mosquito agents and aquatic-stage simulation. The locations of aquaculture ponds are simulated through the model initialization and are allocated to households randomly in the



study area. As these ponds often have stagnate water sources preferable to mosquito habitation they are added to the grid space.

Indeed there are many sub-scale mosquito habitats that are unaccounted for in the model including but not limited to discarded tires, wells, and sources of standing water. The processes currently utilized are in place to accomplish the proof of concept goals of the first generation MIA model and will not consider sub-scale habitats. These hydrological complexities and possible strategies to resolve them will be discussed as a model limitation at the conclusion of the paper.

## 4.4 Mosquito Sub-Model

In the modeling of transmission the actions of mosquitoes are simulated to observe emergent behaviors between potential hosts of the parasite causing malaria. Long before one can consider these potential interactions between hosts, discrete events such as blood meals, dispersal, egg laying, and immature mosquito development must be considered to simulate local mosquito population dynamics. A set of rules and mathematical models governing these actions allow for physical processes to be parameterized, simulated, and observed. Simulation of these discrete events along with the tracking agent state variables, such as the infectious status, are utilized as feedbacks in the dynamic simulation prior to transmission. Finally, transmission can be conceptualized as series of events where successive bloodmeals of a mosquito can transfer the parasite causing malaria from one human host to another.

The mosquito sub-model considers these processes as a simulation the mosquito's lifespan. The mosquitoes life is divided into two major cohorts: aquatic and adult. Due to the contrasting nature of aquatic-stage and adult-stage development two separate modeling techniques are utilized to simulate these stages. MIA has taken local environmental and biological considerations and applied them to existing mathematical models and heuristic rule sets to simulate each of the development stages. To explain the modeling techniques utilized, discussion will be given to the data inputs, aquatic-stage simulation, adult-stage simulation, and their parameterizations.

### 4.4.1 Sub-Model Inputs

A primary meteorological data set and a variety of internal parameters generated from coupled sub-models are used to drive the mosquito sub-model. Meteorological

data is assimilated directly into the mosquito sub-model for use in the physically-based mathematical models. This data was acquired from a meteorological tower located at the Iquitos airport approximately 4 km North-East of the study site at  $3^{\circ} 45' 0''$  S,  $73^{\circ} 13' 48''$  W. This station was selected because of the large number of variables and temporal coverage available. In rare cases where data was missing replicate data from prior periods was used to make averaged estimates. Air temperature (min, max, mean), relative humidity, and precipitation are used in the mosquito sub model. Climatic variables are considered to be uniform across the entire study site but can be adjusted for specific grid cell habitats utilizing the input parameter space of the model. Model parameters abstracting environmental considerations such as shading, cloud cover, and pool depth can be applied via this interface in future generations of MIA.

#### 4.4.2 Aquatic-Stage Simulation

The modeling of the aquatic-stage relies on an understanding of immature mosquito development and how spatiotemporal variables can influence development at each stage. The local vector of malaria, *A. darlingi*, much like other mosquitoes, has three basic aquatic stages of development. Starting as an egg the immature mosquito hatches and enters the first larval stage (L1). As the larvae grows it completes three additional larval stages (L2-L3-L4) until it develops into a pupae. Finally, surviving the pupae stage, it will emerge as a flying adult-stage mosquito. Each stage of development is governed by complex set of determining variables such as temperature, moisture, nutrients, predation, and dispersal (Depinay et al., 2004; Girod et al., 2008; Grieco et al., 2007; Turell et al., 2008). The aquatic-stage model is used to estimate development at egg, larvae, and pupae stages in relation to these variables within the model. To do so the aquatic-stage model is embedded at each grid cell previously identified as favorable habitat in the ESM. Initialization of the aquatic-stage model occurs when an adult-stage mosquito lays eggs at in one of these grid cells. Figure 4.4 illustrates this process where previously laid eggs from mosquito agents are used as input for the embedded aquatic-stage model. The embedded aquatic-stage model consists of three major components used to estimate aquatic-stage sub-populations: (1) development, (2) carrying capacity, and (3) mortality.

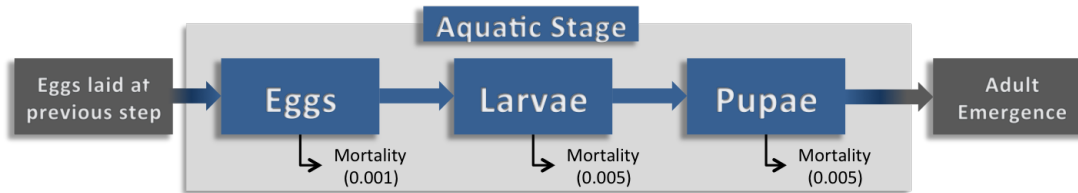


Figure 4.4: Aquatic-stage sub-model

### Aquatic-Stage Development Model

The embedded aquatic-stage simulation utilizes a mathematical model pioneered by Depinay et al. (2004) for estimation of development and aquatic-stage sub-populations at each grid cell. Derived from mosquito development, environmental, and field validation data in Africa with *A. gambiae* the model of Depinay et al. (2004) simulates internal biological processes of the mosquito to simulate development. Incorporation of local climatic and biological parameters unique to each stage of development drives estimation of sub-populations transitioning between stages of development. While the model of Depinay et al. (2004) was not intentionally built for study sites in South America or the Peruvian Amazon, the assumptions of the mathematical model are not geographically exclusive to the areas in which it has been previously applied. Moreover, the mathematical model is adaptive in that it can be parameterized to incorporate the attributes of local mosquito populations and environmental conditions (Bomblies et al., 2008).

Depinay et al. (2004) describes development of mosquitoes as a temperature dependent function over time where  $T_{tk}$  is the temperature over a specific time interval,  $k$ , as shown in equation 4.1. This mathematical model is based on the assumption that mosquitoes are poikilothermic, meaning that their internal temperature varies in accordance with the ambient temperature of their direct environment (Hildebrand and Goslow, 2001). This is an important concept as poikilothermic organisms are sensitive to small changes in temperature due to their inability to govern their internal temperature (Depinay et al., 2004). Due to this an ambient change of even a single degree can result in large changes in a mosquito's life span. These changes in life span are a direct result of changing reaction rates of enzymes important for development within the mosquito in relation to ambient temperatures (Sharpe and Demichele, 1977). The basis of understanding prior to the model of Depinay et al. (2004) was extended by Sharpe and Demichele (1977) who first derived a reaction kinetics model for poikilotherms using three assumptions of analysis:

1. A single control enzyme regulates development. Observed reaction rates of this enzyme determines development rates of an organism.
2. The product of concentration of active enzymes and the associated rate constants have a proportional development rate associated them.
3. Three states exist for the control enzyme. This includes two temperature dependent inactivations states and an active state.

The model is developed from these assumptions by simulating the three possible states of control enzymes in the organism population. This produces an estimate of concentrations found to be active or inactive which are used to estimate a proportional rate of development as per the second assumption. The mathematical model assumes that this is the only control enzyme regulating development and the products of the mathematical model determine the development of the organisms satisfying the first assumption. Knowing mosquitoes are poikilothermic, the reaction kinetics model was adapted by Depinay et al. (2004) and is applied to aquatic-stage populations with known ambient water temperature of their habitat to estimate development. The temperature dependent development of the poikilothermic mosquitoes is estimated as  $r(T)$  resolved in equation 4.2.

$$d_k = r(T_{tk}) \cdot \Delta t_k. \quad (4.1)$$

$$r(T) = \frac{\rho_{25^\circ C} \cdot \frac{T}{298} \cdot \exp\left[\frac{\Delta H_A^\ddagger}{R} \cdot \left(\frac{1}{298} - \frac{1}{T}\right)\right]}{1 + \exp\left[\frac{\Delta H_L}{R} \cdot \left(\frac{1}{T_{\frac{1}{2}L}} - \frac{1}{T}\right)\right] + \exp\left[\frac{\Delta H_H}{R} \cdot \left(\frac{1}{T_{\frac{1}{2}H}} - \frac{1}{T}\right)\right]} \quad (4.2)$$

In this equation  $\rho_{25^\circ C}$  is a known development rate per hour at a temperature of  $25^\circ C$  with no inactivation of the control enzymes;  $T$  is the ambient temperature ( $^\circ K$ ) of the mosquitoes direct environment. The remainder of the equation relies on an understanding of enthalpy of activation where  $\Delta H_A^\ddagger$  relates to the reaction catalyzed by the control enzyme ( $cal \cdot mol^{-1}$ );  $\Delta H_L$  is the change associated with low temperature ( $cal \cdot mol^{-1}$ );  $\Delta H_H$  is the change associated with high temperature ( $cal \cdot mol^{-1}$ );  $T_{\frac{1}{2}H}$  represents the temperature at which 50% of control enzymes are inactivated because of high temperatures; inversely  $T_{\frac{1}{2}L}$  represents 50% inactivation due to low temperature; and  $R$  is the universal gas constant ( $1.987 cal \cdot mol^{-1}$ ) (Depinay et al., 2004).

Development rates are calculated independently at the beginning of each time step for all aquatic-stages using a set of parameters defined in table 4.3. Sequential

calculations are completed to estimate the size of the sub-population transitioning from one stage to another based on the sub-population size of the previous step multiplied against the calculated development rate. Equation 4.2 produces the hourly estimation of the development variable needed to transition sub-populations in this manner. To match the temporal resolution of the model the development product is aggregated as observed in equation 4.3 producing a measure of cumulative development.

Table 4.3: Developmental rate parameters

	$\rho_{25^{\circ}C}$	$\Delta H_A^{\neq}$	$\Delta H_L$	$T_{\frac{1}{2}L}$	$\Delta H_L$	$T_{\frac{1}{2}H}$
<b>Egg</b>	0.0413	1	-170644	288.8	1000000	313.3
<b>Larvae</b>	0.037	156684	-229902	286.4	822285	313.4
<b>Pupae</b>	0.034	1	-154394	288.8	554707	313.8

$$CD(t_n) = \sum_n^{k-1} d_k \quad (4.3)$$

Completion at any of the development stages is defined as  $CD(t_n) > CD_f = 1$ , where cumulative development is greater than one. It has been suggested that completion be addressed as a stochastic process to model variability in development (Bomblies et al., 2008; Depinay et al., 2004). Equation 4.4 implements this suggestion by modeling variability with the addition of a normal random variable ( $G$ ) with a mean of 0 and standard deviation of 10%. The new estimation of completion is defined as cumulative development greater than one with the addition of a randomly generated parameter from the normal distribution.

$$CD(t_n) > CD_f = 1 + G(0, 0.1) \quad (4.4)$$

## Carrying Capacity

The methods demonstrated thus far for estimating aquatic-stage populations consider only temperature as a factor. To properly estimate aquatic-stage populations consideration must be given to additional regulatory mechanisms limiting population. In this regard there is a need to estimate nutrient competition in aquatic habitats by defining carrying capacity. Each grid cell habitat has a finite availability of nutrients and if the feeding requirements of aquatic-stage mosquitoes exceed

these requirements development will not be sustainable. Carrying capacity is applied as a regulatory mechanism to larval stages as they are the only aquatic stage that require ingestion of nutrients for development. Larval stages are sensitive to nutrient competition because of the length of the larval stage relative to egg and pupae stages and the relationship to final adult weight (Hoshen and Morse, 2004). Prolonged nutrient deficiency will drastically limit larval development until a sustainable state is reached in the system. Reflecting the model of Depinay et al. (2004) aquatic-stage populations are limited by estimation of nutrient competition,  $C$ .

$$C = \left( \frac{e - w}{e} \right) \quad (4.5)$$

Equation 4.5 resolves nutrient competition,  $C$ , where  $e$  is a parameterized carrying capacity ( $\text{mg}\cdot\text{m}^{-2}$ ) and  $w$  is the summation of larval biomass in the habitat. It is assumed that no grid cell will have 100% of its surface favorable for larval development and a maximum carrying capacity of 3000 mg per grid cell is set. If this is not assumed a 30 x 30 grid cell would sustain an aquatic population of over 300,000 larvae which is well beyond the estimated densities found in the study site (Turell et al., 2008). Once calculated the current larval population and the nutrient competition parameter will define the carrying capacity limited larval population at each time step. The procedure generates a logarithmic relationship between the maximum carrying capacity and the larval population. This is desirable so hard thresholds are not imposed on the simulation allowing for a more natural representation of the real world systems.

## **Mortality**

Mortality is the final regulatory mechanism used to simulate aquatic-stage development. Sources of mortality unrelated to carrying capacity or temperature dependent development are integrated as model parameterizations for aquatic-stage simulation. These include egg-larvae-pupae specific death rates, cannibalism, and predation. Stage specific death rates have been adapted from previous literature as daily or hourly measures. The parameters are used in the model during each step by removing a percentage of the population based upon the documented rate. Cannibalism is modeled at each iteration of the mosquito sub-model where L1 larvae are eaten by L4 larvae. Additionally predation is modeled as a simple percentage of the total population removed at each step.

## Parameterization

The discussed elements of the mosquito sub-model require definition of a variety of parameters to drive simulation. As the sub-model draws largely on the work of Depinay et al. (2004) and Bomblies et al. (2008), many of the initial parameter values are a product of their work. Table 4.4 details the parameterizations used in the aquatic-stage sub-model. The parameterizations listed here are the initial conditions used to test the model. Parameters will be tested by using sensitivity analysis during the discussion of results.

Table 4.4: Aquatic-stage simulation parameters

Variable	Value	Unit	Reference
Weight of L1 Larvae	0.02	mg	Depinay et al. (2004)
Weight of L2 Larvae	0.16	mg	Depinay et al. (2004)
Weight of L3 Larvae	0.30	mg	Depinay et al. (2004)
Weight of L4 Larvae	0.45	mg	Depinay et al. (2004)
Carrying capacity of habitat	300	mg m <sup>-2</sup>	Bomblies et al. (2008)
Egg death rate	0.01	h <sup>-1</sup>	Depinay et al. (2004)
Larval death rate	0.005	h <sup>-1</sup>	Depinay et al. (2004)
Pupae death rate	0.005	h <sup>-1</sup>	Depinay et al. (2004)
Predation	0.005	h <sup>-1</sup>	Depinay et al. (2004)
Cannibalism rate of L1 larvae	0.0008	h <sup>-1</sup>	Bomblies et al. (2008)

### 4.4.3 Adult-Stage Simulation

At the beginning of each model time step newly emergent mosquito agents are generated, added to the model domain, and tracked as individuals based upon simulated completion of the pupae aquatic-stage. As previously discussed, a prescribed sequence of events is simulated for each mosquito where an agent seeks a bloodmeal, bites, rests, lays eggs (oviposition), and repeats until death. Each event type and related interactions are modeled in MIA to drive the actions of mosquito agents. The sub-model assumes that all adult-stage mosquitoes are fertilized immediately after emergence, and thus is not a limiting factor in the sub-model (Hoshen and Morse, 2004). As in the aquatic-stage model only female mosquitoes will be simulated. This subsection details the modeling procedures utilized to simulate each task including the biological parameterization of adult-stage mosquitoes.

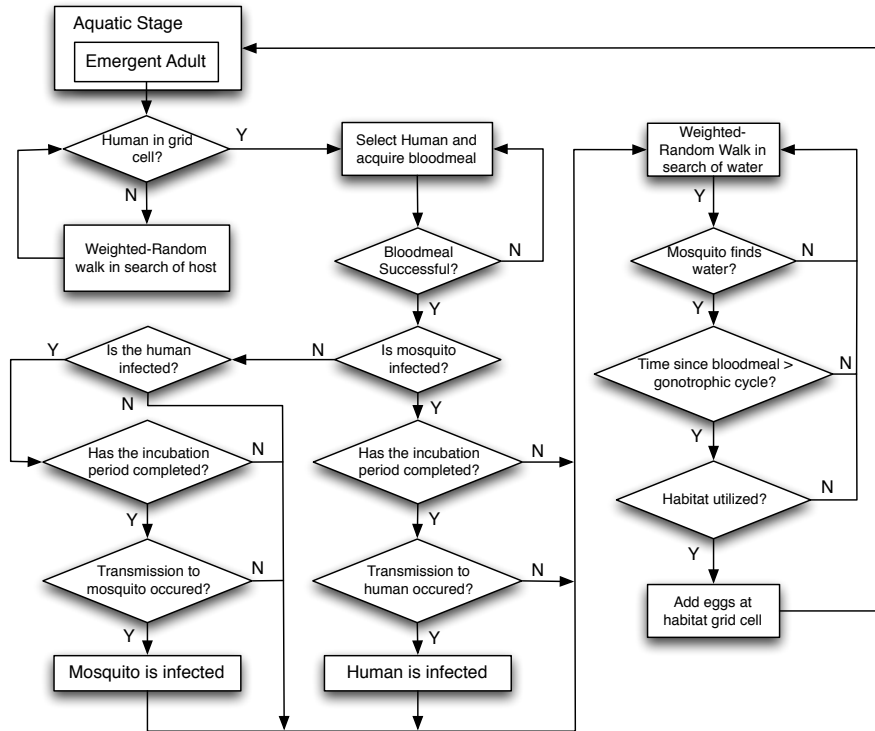


Figure 4.5: Adult-stage mosquito behavior. Adapted from (Bomblies et al., 2008).

### Bloodmeal Simulation

Assuming immediate fertilization, simulated female mosquitoes require intake of protein to catalyze the development of their fertilized eggs (Hoshen and Morse, 2004). To acquire the required protein a female mosquito will seek a host to draw a bloodmeal. *A. darlingi* is anthropophilic meaning it has a preference for bloodmeals acquired from human hosts (Roberts et al., 2002). This has much to do with the mosquitoes approach to acquiring bloodmeals where it will bite not only in its own habitat but will also enter human homes to do so (Branch et al., 2005; Charlwood, 1996). Within the first 24 hours after emergence the mosquito will begin searching for its first bloodmeal (Depinay et al., 2004).

To find its first bloodmeal the mosquito agent is directed by a series of weighted-random movements. In the model domain these movements are simulated as transitions from cell to cell in the ESM grid space. While little is known about the movements of mosquitoes it has been suggested that movement is influenced by variables such as wind, visual cues, sensing of carbon dioxide, and land cover type. At the present time there is inadequate data to simulate the complex influences of wind and as such is not considered in the model. Additionally, inclusion of carbon



dioxide modeling has been deemed excessive to the current model complexity as the procedures required to simulate this are sub-grid scale to the environmental model. As result mosquito movement is restricted in the adult-stage sub-model with parameterization of maximum distance, preference in land cover type, and proximity to human agents.

Previous literature indicates that mosquitoes can travel anywhere from 1 km to 2.5 km per day depending on climatic and environmental conditions (Linard et al., 2009; Service, 1997). These observations are incorporated as a limiting parameter of each mosquito agent in their search for bloodmeals. An agent-based parameter establishes the maximum distance that can be traveled in a day by a mosquito agent. Variability is modeled in the system as a random normal variable with a standard deviation of 10%. The simulated variation is added to the parameterized maximum distance of flight to establish the maximum distance an agent will travel in search of a human host. The spatial resolution of the model is utilized to define units of distance in the model where a transition from cell to cell comprises a total of 30 m traveled.

Next, preference to land cover types where human activity occurs is given to the agents through a weighting parameter. A queen's case neighborhood analysis around the mosquito is used analyze its surrounding land coverage types. This model parameterization equates to an approximate 30 m vision for the mosquito. Once the coverage types around the mosquito have been identified they are assigned weights utilizing a statistical selector. Slight preference is given to coverage types associated with human activity. This causes the mosquitoes to be pulled towards peri-urban or urban land cover types when seeking bloodmeals.

Mosquitoes can sense carbon dioxide up to a maximum distance of 20 m (Kettle, 1995). Rather than simulate carbon dioxide sources as emitted by humans this is parameterized into the model as an assumption that mosquito agents are only capable of attraction to a human agent if they are located in the same grid cell. Due to the size of the grid space the sensing capabilities of the mosquito are sub-scale and currently are assumed to extend to 30 m. If humans are detected by the mosquito in the same cell a random human in the grid cell will be selected by the mosquito and bit.

The mosquito agent will search for a human host for a maximum of three model steps before it is assumed that a bloodmeal was taken from an animal source another source. By this time 80% of all mosquitoes in the model will have taken a bloodmeal from a human agent. In the real world not all bloodmeals allow for full development

of eggs and mosquitoes in this situation are described as pre-gravid (Lyimo and Takken, 1993). Pre-gravid processes are ignored in the model and all bloodmeals are assumed to initiate and sustain egg development. This may produce overestimation but due to lack of documented parameterization pre-gravid considerations could contribute unnecessary model uncertainties if included. Once the mosquito has acquired its bloodmeal through a bite two possible processes are activated where egg development is initiated and/or intrinsic incubation of malaria begins if the human host was infected.

### Egg Development and Oviposition Simulation

As per previous assumptions, if a mosquito agent completes a bloodmeal internal egg development is catalyzed by the ingestion of protein. As per previous assumptions, if a mosquito agent completes a bloodmeal, a process of internal egg development is catalyzed by the ingestion of protein. The period of development occurring here is known as the gonotrophic cycle and describes the time required between a completed bloodmeal and oviposition. This cycle in tropical climates typically takes 2 to 2.5 days to complete. As in aquatic-stage development, egg development is a temperature dependent process governed by equation 4.2. The input parameters in table 4.5 and the equation produce a hourly measure of development. A measure of cumulative development is calculated much the same as equation 4.3. Once cumulative development reaches a value of 1 or greater the gonotrophic cycle is completed and the mosquito agent can oviposit.

Table 4.5: Gonotrophic cycle parameters

	$\rho_{25^{\circ}C}$	$\Delta H_A^{\neq}$	$\Delta H_L$	$T_{\frac{1}{2}L}$	$\Delta H_L$	$T_{\frac{1}{2}H}$
Egg development	0.034	1	-154394	288.8	554707	313.8

Oviposition can only take place in the aquatic habitats defined by the ESM. To find these habitats the mosquito agent will again utilize weighted-random movements in its search. Rather than weighting being placed on human centric environments, weighting is allocated to draw the mosquito towards possible habitats. The mosquito agent will then assess a predetermined probability distribution to decide if it will utilize the habitat. If this process is successful it will lay its eggs adding them to the aquatic-stage embedded sub-model at that grid cell location. Mosquito agents will continue to search for habitat until a successful oviposit or they are removed from the simulation. If literature becomes available to support

temporal thresholds for oviposition agents can be guided towards adequate habitats within specific time frames.

### **Intrinsic Incubation Simulation**

When considering the simulation of bloodmeals, parasite transfers can occur not only from the mosquito to the human but also from the human to the mosquito. This is an important aspect in the modeling of human malaria as the initial infection of a mosquito is based upon acquisition from a bloodmeal of an infected human. In this preliminary implementation of the MIA model parasite transfers from humans to mosquitos are assumed to occur at a rate of 90% per bloodmeal. While arbitrary, previous literature has described to the local vector as extremely proficient. Due to this, not all mosquitoes taking a bloodmeal from infected human agents will acquire the parasite. The process success rate has been parameterized in the sub-model structure meaning that if additional information is acquired new generations MIA can be made to incorporate infection success rates.

A mosquito who has acquired a parasite from a human bloodmeal does not immediately become infectious. An incubation period is required for the transition of the parasite in the midgut of the mosquito to its salivary glands for transmission. This transition has been described as a degree day dependance where the development of sporozoites in the salivary glands requires 111 degree days above 16°C calculated as (Detinova, 1962):

$$n = \frac{DD}{T - T_{min}} \quad (4.6)$$

Where DD is the number of degree days required for incubation and T is the temperature. The progression of incubation is tracked within each mosquito agent. Once elapsed agents will be able to the transmit of the parasite back to humans in subsequent bloodmeals. The infectious status of the mosquito will remain unchanged until its death once a parasite has moved to the salivary glands.

### **Mortality**

The daily survival of the mosquito agent is temperature dependent (Hoshen and Morse, 2005). *Anopheles* best survive in temperatures ranging from 20 to 25°C (Martens and Millstone, 1998). Temperatures exceeding these thresholds significantly affect the mosquitoes daily survival. Mosquito lifespan in MIA is modeled

by subjecting the mosquito agent to a survivability measure at each time step. Martens and Millstone (1998) defined this daily survivability as  $p$  in equation 4.7:

$$p = \exp\left(\frac{-1}{-4.4 + 1.31T_d - 0.03T_d^2}\right) \quad (4.7)$$

Here the temperature dependent survivability is resolved where  $T_d$  is the average temperature of the previous step. At the beginning of each time step all agents surviving the prior step are subjected to the survivability measure. To do this a uniform random number is generated between 0 and 1. If the the randomly generated number is higher than the calculated survival threshold the mosquito is unsuccessful in its attempt at survival. If they are unsuccessful in surviving the step they are removed from the model domain.

## Parameterization

Much like the aquatic-stage, adult-stage simulation requires a multitude of input parameters to drive the sub-model processes. The numerical parameterizations used in the adult-stage simulation are shown in table 4.6. The initial parameters draw from a variety of sources that have conducted processes specific studies to aid in parameterization.

Table 4.6: Adult-stage simulation parameters

Variable	Value	Unit	Reference
Maximum flight distance	65	m h <sup>-1</sup>	Bomblies et al. (2008)
Mean flight distance	15	m h <sup>-1</sup>	Bomblies et al. (2008)
Carrying capacity of habitat	300	mg m <sup>2</sup>	Bomblies et al. (2008)
Intrinsic incubation period	111	Degree Days	Detinova (1962)
Inoculation efficiency	0.90		Hoshen and Morse (2005)
Human biting rate	0.90		Branch et al. (2005)
Habitat selection	0.90		Bomblies et al. (2008)

## 4.5 Human Sub-Model

The simulated actions of mosquitoes in MIA comprise only part of the interaction space found in the transmission of malaria. To complete the interaction space a human sub-model is deployed to emulate the demographic transitions and the

actions of individual humans. In the human sub-model individuals are abstracted as agents and associated with a set of state variables. Agents and attributes are tracked through time and space to model interactions between the two agent types and the environment. Each human agent finds spatial definition by its location within a single grid cell of the human grid space produced by the ESM.

The time period considered for simulation of human agents is based upon the biting habits of *A. darlingi*. These mosquitoes will actively seek bloodmeals at night with the most intense period of biting found around 10 pm (Silver and Service, 2008). As the primary focus of MIA is tightly coupled with time periods of intense mosquito activity consideration of human actions outside of this time period add unnecessary complexity. Therefore, all human agent activities are simulated only for the time period where *A. darlingi* is active. Simulation of night time hours enables a reasonable assumption that human activity is limited to the indoors. Thus a majority of human agents will be considered immobile while existing within the model.

#### 4.5.1 Sub-Model Inputs

The human sub-model requires local demographic information to drive simulation. Here, Peruvian national census data is used including age distributions, death by age distributions, population by year, and sex ratios. A majority of the data used was extracted from the 2005 census. Many of these distributions and ratios are not used directly by the sub-model but rather parameterize a weighted selector for creation of weighted uniform distributions.

#### 4.5.2 Human Agent Simulation

##### Demographic Simulation

Simulation of a human agent's life in MIA is reliant on external information about demographic distributions local to the study site. As mentioned previously peruvian census data is used to drive the human demographic systems of MIA. Demographic simulation in the model considers variables including deaths, births, and migration. Population change at each time step is calculated as:

$$P_{change} = b - d + m_{in} - m_{out} \quad (4.8)$$

Where  $P_{change}$  is the change in population since last step;  $b$  is the the number of new births;  $d$  is the number of deaths;  $m_{in}$  is the number of new migrants; and  $m_{out}$  is the number of people who have migrated out of the model domain. The total population at the current time step can then be calculated as  $P = P + P_{change}$ . These population dynamics are driven by the changes of state simulated at the agent level of the model as a product processed census distributions.

At the beginning of each time step, the components making up population change are updated for each human agent. A known birth rate per population of 1000 is used to estimate the the number of new births to be added to the simulation at the beginning of every model step. If a positive number is calculated new agents are added to the model and are give an expiry date based on a weighted random variable assigned from the selector. The weighted selector is parametrized with a known distribution of death by age from census data. After the year of death has been calculated a specific day is generated from a uniform distribution of 365 days.

The death of an agent is simulated by comparing the expiry date of the agent to the models current step date. If the two values are the same, the agent is removed from MIA prior to the beginning of the current step. Additionally, the agent is removed from any household that it belonged to. While the structures to accommodate human demographics are rough in implementation it is important to consider the lifespan of a human relative to the model length. This makes small variations minor in comparison to potential uncertainties in mosquito lifespan. Malaria will not be considered as a factor in mortality because of the low annual rates. Previous literature has documents annual deaths due to malaria from 1.3 to 1.8 per 1000 in Loreto during epidemic years (Guarda et al., 1999). Moreover, the census data utilized to generate the distributions driving agent deaths already considers all sources of mortality, including malaria.

## Infectious State Simulation

The population of human agents adopts a traditional epidemiological conceptualized in regards to infectious status as the following:

$$P = P_s + P_e + P_i \tag{4.9}$$

Where  $P$  is the total population;  $P_s$  are susceptible individuals;  $P_e$  are exposed individuals; and  $P_i$  are those who are infectious. These three divisions of the population represent the three possible states that human agents can have. A

majority of the human agent population can be found in the susceptible state as immunities are not considered in the model. Immunities could easily be integrated as an agent attribute once data can be organized to document rates occurring in Iquitos. Additionally individuals who have recovered from a malaria infection become susceptible for the same reason.

Exposed human agents are those who have been bitten by an infected mosquito and a successful transfer of the parasite has occurred. This is reflected by a change in the infected state variable tracked within each human agent. Changes to an individual's infected state initiate an incubation period that governs transition to the infectious state from the exposed. The incubation period models the required time for the appearance of gametocytes in the human's blood. The presence of gametocytes is required for the human agent to become infectious to biting mosquitoes. Incubation has been parameterized as a two week period before the agent will become infectious based on previous literature (Bomblies et al., 2008). Once this period has elapsed the agent will change states from exposed to infectious.

Exit from the infectious state of human agents is modeled after natural clearing processes which are very slow lasting up to one year (Hoshen and Morse, 2005). At the beginning of each step infected human agents generate a uniform random number and compare it to a known clearing rate. If the number is lower than the clearing rate the infection is carried forward to the next time step. In MIA the clearing rate has been parameterized as 0.12 per step (Hoshen and Morse, 2004). This representation does not currently consider distances to medical care or available services but can be amended to incorporate this in future model builds. All agents are assumed to be capable of clearing and no malaria related mortality is introduced into the model.

# Chapter 5

## Simulation Results and Discussion

### 5.1 Introduction

The MIA framework has been designed to allow for the testing of a variety of scenarios within the model domain. Each simulation consists of a specific parameterization aimed at enabling observation of targeted transmission dynamics or causal mechanisms. The simulations documented in this chapter facilitate three primary roles: sensitivity testing of key parameters, observation of localized transmission effects, and climate variability analysis. The first simulation type focuses on the effects of individual parameters within the model domain by assessing how synthetic variation relates to global behavior and uncertainty. Simulation runs enabling observation of localized transmission generate the primary result set of MIA. Moreover, this simulation type will attempt to assess the model as a diagnostic tool driven by currently available data sources. The resulting output is used as the basis of discussion for emergent behaviors documented through the models interaction processes. Efforts will be made to relate results to previously documented causal factors in order to comment on the diagnostic abilities of the model. Finally, the model will be tested in the context of climate variability and discussed as a component of regional climate.

Each simulation run in MIA generates an extensive set of results which are written to a database for later analysis. As previously discussed this is facilitated through coupling of a mySQL database, the R statistical language, and MIA. The database system is capable of capturing data at several levels of analysis including individual, household, and domain. As a result, exceptional amounts of data are generated during each step of a simulation. Specific elements of this output will be



used to highlight trends relevant to each simulation type. By this process a primary set of is data generated from individual interactions of mosquitoes, humans and their physical environment. Simulated results pertaining to mosquito population, parasitic capacity, biting rates, and reproductivity will be discussed as components of this output. The products of the ESM will also be discussed in relation to aquatic stage mosquitoes and their habitat utilization. Additionally, data pertaining to human infection rates and population dynamics will be presented as a component of these systems interactions.

## 5.2 Sensitivity Analysis

One of the potential consequences of increased complexity is the introduction of uncertainty in model structure and parameter estimation (Xu and Gertner, 2008). As MIA strives to conceptualize and simulate complexities previously unaddressed in epidemiology this issue is of considerable concern to the model. Approximation of these uncertainties in parameter estimation can be accomplished with methods of sensitivity analysis (Henderson-Sellers and Henderson-Sellers, 1996). A basic implementation of sensitivity testing allows variation in a single parameter while holding the remaining parameters constant. Consideration is then given to model outputs to detect irregularities or instabilities resulting from the imposed changes. MIA will utilize this approach to evaluate the sensitivity of the model to key parameters previously identified as possible sources of uncertainty. A selection of attributes including mosquito mortality, flight distance, and ecological carrying capacity will be tested.

Sensitivity analysis is an important pre-cursor to model validation as it can identify undesirable instabilities found in model outputs usually as one of two distinct cases (Henderson-Sellers and Henderson-Sellers, 1996). Firstly, observed sensitivity in model outputs can suggest that the model is finely tuned to a specific value. This is observed as drastic changes in output when variability is applied to a parameter. Such parameter over-fittings can compromise the heterogeneity of an abstracted system by restricting the utility of the model to a small range of inputs. A second case exists where model sensitivities are representative of real world systems and changes within modeled systems reflect those in the physical system characterized. This case is preferable but due to the complexities of coupled systems instabilities can be lost in the vast interaction space created by the model. In the context of MIA undesirable sensitivity or instabilities can be a product of the embedded math-

emathical models, model couplings, or local scale variability unaccounted for. MIA will apply sensitivity analysis in the hope that exploration of these model dynamics will enable greater understanding of interactions and limit uncertainties in it's human-mosquito-environmental systems. Additionally, sensitivity analysis enables the isolation of specific model weakness that may be addressed in later research.

### 5.2.1 Mosquito Mortality

Previous research (Bomblies et al., 2008; Linard et al., 2009) indicated that significant variance in mosquito population and more importantly actual biting rates (ABR) could be observed in model outputs when sensitivity testing was applied to mosquito mortality. This echos the observations of Ross (1910) who documented vector mortality as a critical parameter utilized to impact malaria transmission during control campaigns. A hypothesis may be formulated that if mortality is varied in MIA significant changes in mosquito population and ABR will be simulated. In order to test this hypothesis a series of model runs are completed in which the mathematical model controlling mosquito mortality is augmented with an external forcing parameter. Implemented in cohorts of 5%, modification to the parameter controlling mosquito mortality is applied at  $\pm 20\%$ . The external forcing parameter is added to the calculated mosquito mortality at the beginning of each step. Finally, each cohort test is iterated ten times and the results are averaged amongst them. To observe the global effect of this change, ABR and mosquito populations are calculated as averaged daily rates over the entire model run. The condensed numerical results are presented in table 5.2 documenting the changes in average ABR and mosquito population relative to variation in mosquito survivability.

Table 5.1: Mosquito mortality testing

	ABR	Change(%)	Population	Change (%)
-20%	126	-63.9	543	-78.4
-15%	179	-48.7	809	-67.8
-10%	193	-44.7	1015	-59.6
-5%	218	-37.5	1386	-44.8
0%	349	0.0	2511	0.0
+5%	350	0.3	4424	76.2
+10%	581	66.5	25514	916.1
+15%	606	73.6	38794	1445.0
+20%	721	106.6	42124	1577.6

As expected, changes in both ABR and mosquito population occur relative to

changes in mosquito mortality. Noteworthy are the drastic increases in the mosquito population simulated at and beyond an increase of 10% in mosquito life span. Further sensitivity testing utilizing fine cohorts revealed that exponential growth occurred as this threshold in mortality was approached. Investigation of agent life span associated with the simulated increases reveals an unrealistic scenario promoting instability in the mathematical model. Increases such as this elevate what would normally be a daily survival in the low to mid 80% to an astounding 95% or higher daily probability of survival for each mosquito agent. With synthetically generated daily survival above 95% mosquito agents can live lives upwards of three weeks and are able to partake in successive bloodmeals well beyond documented or plausible rates. Thus, results beyond an increase of 10% are extremely unlikely to occur and should be considered the upward bounds of model stability in mosquito mortality. Graphing these results shows a smooth relationship abruptly ended with exponential growth as the simulation approaches +10% (see figure: 5.1).

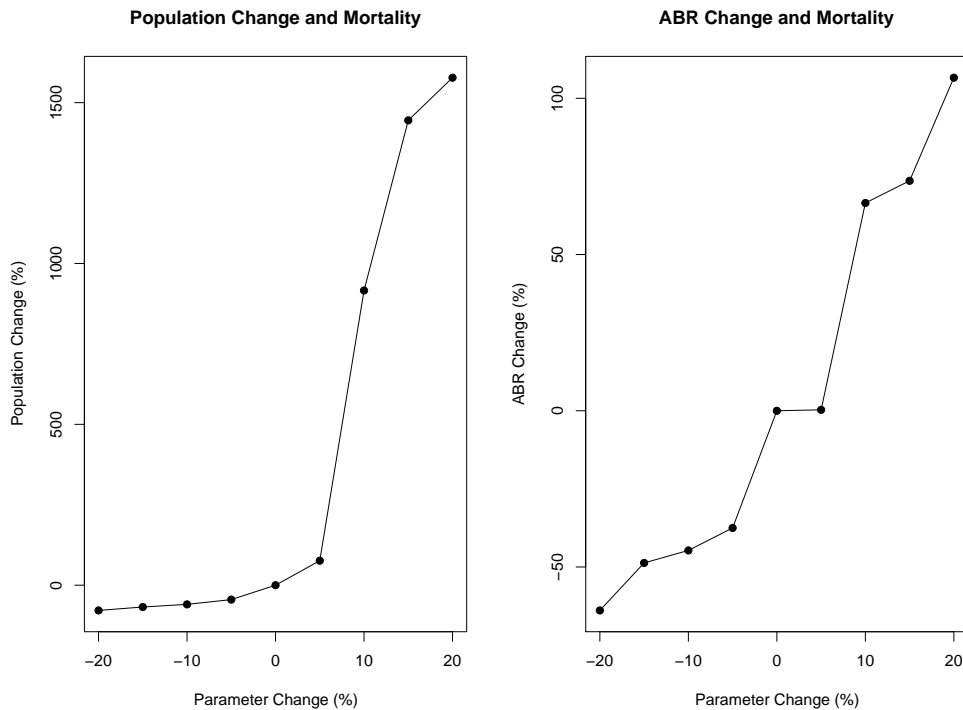


Figure 5.1: Mosquito mortality sensitivity analysis

Encouragingly, these same issues are not associated with reductions or small increases in the daily survival of mosquito agents. Relative change in population and ABR to survival presents a positive correlation reminiscent of those discussed by previous authors (Bomblies et al., 2008; Linard et al., 2009). In the most extreme

case the average population is reduced to  $1/5^{th}$  of an unaltered run. Contrary to the previous results this change is gradual. The areas of stability generated through the mortality parameter suggest that the model maybe affected by outliers. Consultation of the previously discussed parameters of mosquito mortality show that temperature is the primary factor in mosquito lifespan. As the climate is constant year round in Iquitos there is little concern that potential outliers will drastically effect model results.

## 5.2.2 Mosquito Flight Distance

Aside from the biological functions of mosquitos there are several behavioral parameters governing mosquito agent feeding. One such parameter is the maximum flight distance assigned to each mosquito agent. This parameter is of interest as each mosquito has access to a finite number of humans and habitats defined by the distance they are able to travel each step. Modification of this parameter could expose the agent to additional interactions which otherwise would be unavailable. Lack of documentation of local mosquito travel patterns makes this issue all the more pressing. To test the sensitivity of this parameter simulations similar to those completed in the testing of mortality are employed. A summary of the simulated results is presented in table 5.2 as both changes in ABR and mosquito population.

Table 5.2: Mosquito flight distance testing

	ABR	Change(%)	Population	Change (%)
-20%	314	2.9	2363	1.3
-15%	290	-5.1	2291	-1.8
-10%	301	-1.4	2338	0.2
-5%	309	1.5	2352	0.9
0%	305	0	2332	0
+5%	296	-2.9	2312	-0.9
+10%	294	3.8	2310	-1.0
+15%	287	-6.1	2279	-2.3
+20%	296	-3.0	2318	-0.6

The resulting changes in both ABR and mosquito population are miniscule when compared to those generated from increased mortality. Moreover, there is no specific relationship observed between changes in maximum flight distance and ABR or population. Rather the results seem to present themselves only as noise within a small range of change. While these results might suggest that the maximum

flight distance is arbitrary there are several interactions that must be considered to substantiate this claim.

Analysis of individual mosquito flights show that a majority of individuals do not utilize the maximum flight distance. Rather, shorter range habitats or meals are selected prior to the limit being reached. This underutilization of the parameter may be a result of indirect model structures, such as the directional weighting system, and biting preference. These methods cumulatively define when mosquito agents engage in interactions and could promote overoptimistic simulation. Overoptimistic simulation of interaction implies that the mosquito agent will participate in a simulated interaction more readily than in the abstracted physical system. Here, weighted movements can cause agents to be drawn towards interactions before the maximum flight distance is reached. Moreover, parameters such as biting preference which use rigid statistical thresholds can promote overoptimistic simulation of interactions due to a lack of local parameterization. Both model structures would benefit from the integration of in situ observations to refine model variability and interaction mechanics currently generating the simulated noise.

Unfortunately the noise exhibited in the sensitivity test raises more questions than answers. The noise simulated in this parameter is likely not a product of a lone parameterization but rather the complex interaction space generated by the coupled system. Problems such as this are related to the previously discussed issues of increasing complexity where uncertainties become a product of the interaction space.

### **5.2.3 Ecological Carrying Capacity**

Outside of the parameterization of individual mosquitos, the environmental sub-model's parameter space holds potential to influence global outputs. Amongst the driving factors of habitat simulation, ecological carrying capacity demonstrates a limiting parameter capable of introducing uncertainty. Enacted to stabilize variance, this parameter drives a logarithmic transformation of the immature mosquito population within each simulated habitat. While this ensures abrupt restrictions of population are not encountered it can potentially encourage misestimation. This is most likely to occur during periods of increased temperature where the limiting properties of the carrying capacity will have greater influence on larval development (Depinay et al., 2004). The ecological carrying capacity parameter defines the total biomass that can be sustained in a simulated habitat. Internal estimation of a habitats biomass is completed as a summation of larval mosquito weight. The weights

utilized in this calculation (Table 4.3) have been adopted from studies outside of Iquitos. As these calculations number in the millions during a simulation uncertainties, specifically the lack of local parameterization, may become compounded over an entire run. As larval mosquito populations are a product of the habitats governed by this parameter sensitivity testing is warranted to document its influence on global outputs.

Unlike maximum flight distance there is an observable relationship between the ecological carrying capacity and mosquito population. A 20% increase in ecological carrying capacity results in a 17.6% increase in mosquito population. Conversely a 20% reduction in ecological carrying capacity results in a 18.6% reduction in mosquito population. To a slightly lesser extent ABR also has a relationship with ecological carrying capacity resulting in a 17.2% increase in biting at 20% increased capacity. The resulting changes in biting appear to saturate above and below a 10% change in ecological carrying capacity (Figure 5.2). The observed saturation may suggest that the sensitivity of the parameter is tightly coupled with local parameterization requiring additional study of mosquito dynamics to elevate this issue.

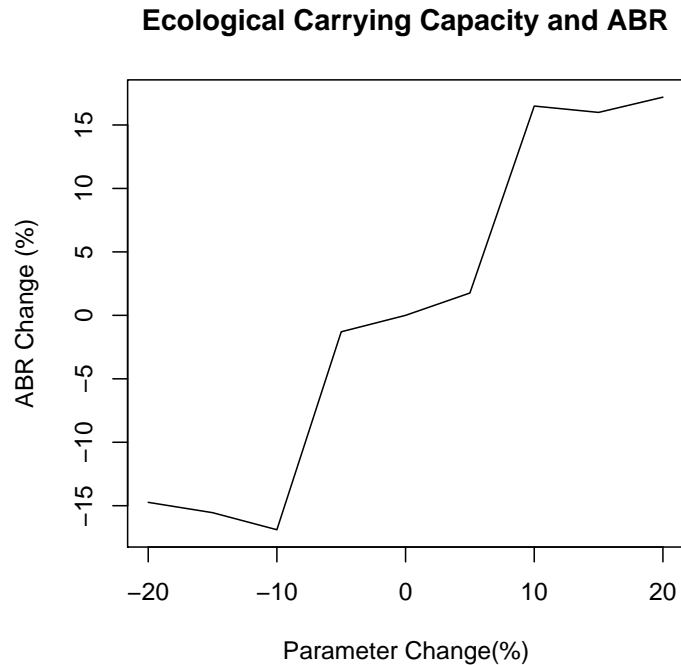


Figure 5.2: Ecological carrying capacity sensitivity analysis

A tangible relationship to the real world exists through this parameter that

could be used to test policy and control measures. Previous studies of nutrient availability found strong relationships between immature mosquito population and the availability of algae (Kaufman et al., 2006), and maize pollen (Ye-Ebiyo et al., 2003). The carrying capacity is conceptually a product of available nutrients and the biological requirements of the habitat. Local reduction strategies could be implemented within the model to test the capabilities of said programs. The sensitivity sweep suggests that programs capable to reducing the carrying capacity of habitats between 5% and 10% would see comparable reductions in local biting. As with previous results these findings must be handled carefully until steps can be taken to validate the model structures producing them.

## 5.3 Dynamics of Local Transmission

MIA, through its operational goals, has sought to develop modeling structures capable of enabling agent-based modeling of epidemiology. These structures outline the abstraction of human-vector-environmental coupled systems and provide several output types useful to observation of local transmission. Their construction and primary sensitivity testing complete, an opportunity exists to apply MIA in a study site specific simulation. The following explores the simulation capabilities of MIA through analysis of its primary result set, transmission scenarios, and visualizations.

### 5.3.1 MIA Primary Simulation Results

#### Mosquito Population Dynamics

Disregarding the period required for model initialization MIA produces a result set for years including and after 1993. This time period is representative of the years immediately prior to and during the most recent epidemic transmission event. Here, MIA is used to explore causality and generate discussion of the models diagnostic capabilities. Unlike previous sensitivity analysis this simulation is averaged over fifty iterations of the MIA model in an attempt to minimize outliers. The decision to assess the model as an iterative approach stems from previously observed uncertainties in sensitivity analysis. Rather than enabling water edge habitats discussed in methods, only those in proximity to human habitats have been used. This effectively reduces the available habitat by approximately 75%, relegating habitation to urban and peri-urban environments. Largely bound by hardware and software

limitations currently imposed on MIA, this modification helps maintain a computationally manageable number of agents. As replication of population is not as important as the identification of emergent trends this model condition can be utilized without compromising assessment of MIA's diagnostic capabilities. Each model run is initialized with 350 human households, resulting in a human population of approximately 2,000. Finally, habitats are seeded randomly with a total of 500 adult-stage mosquito agents. With this set of conditions MIA is allowed to simulate the dynamics of transmission local to the study area.

The simulated mosquito population is presented in figure 5.3 as daily summation of adult mosquito agents. The interaction space generated by this simulation maintained an average of 24,951 mosquito agents during each step. Additionally a maximum of 31,904 mosquito agents were simulated. Within the results, interesting model behaviors appear as two distinct trends in mosquito population. Here, substantial differences in seasonal populations are simulated in years prior to, and during the epidemic. Initially, seasonality in mosquito population appears to have been captured by the model as oscillations between wet and dry seasons. Years prior to the epidemic show reduction in mosquito population between June and November. This period of time corresponds with the dry season in Iquitos and is in agreement with previously documented seasonal reductions in *A. darlingi* (Guarda et al., 1999).

Contrasting trends in mosquito population between 1993 and 1996 become apparent when plotted in twelve month segments (Figure 5.4). Again during 1993 and 1994 discernible reductions in population are simulated during the dry months. Although the trends amongst these two years appear similar they are not synchronized temporally with the minimum population of 18,915 occurring during August of 1993 and 19,066 in July of 1994. A much different trend is simulated during 1995 resulting in a muted seasonal oscillation during the dry months. During the dry season a minimum of 22,029 mosquitos were simulated, a 13.5% increase over the previous low during the same time period. Interestingly the simulated reduction pales in comparison to the gains in population simulated during this same period. Here, three substantial increases in population occur during the months of January, April, and October causing the population to approach or exceed 30,000. Two of the three simulated increases exceed the maximum population in the two previous years. These increases and lack of dry season recession result in a 5.4% daily increase in mosquito population over the previous two years.

The simulated changes in population during 1995 result in 500,000 additional mosquitoes entering the model domain during that year. The muted seasonal oscil-



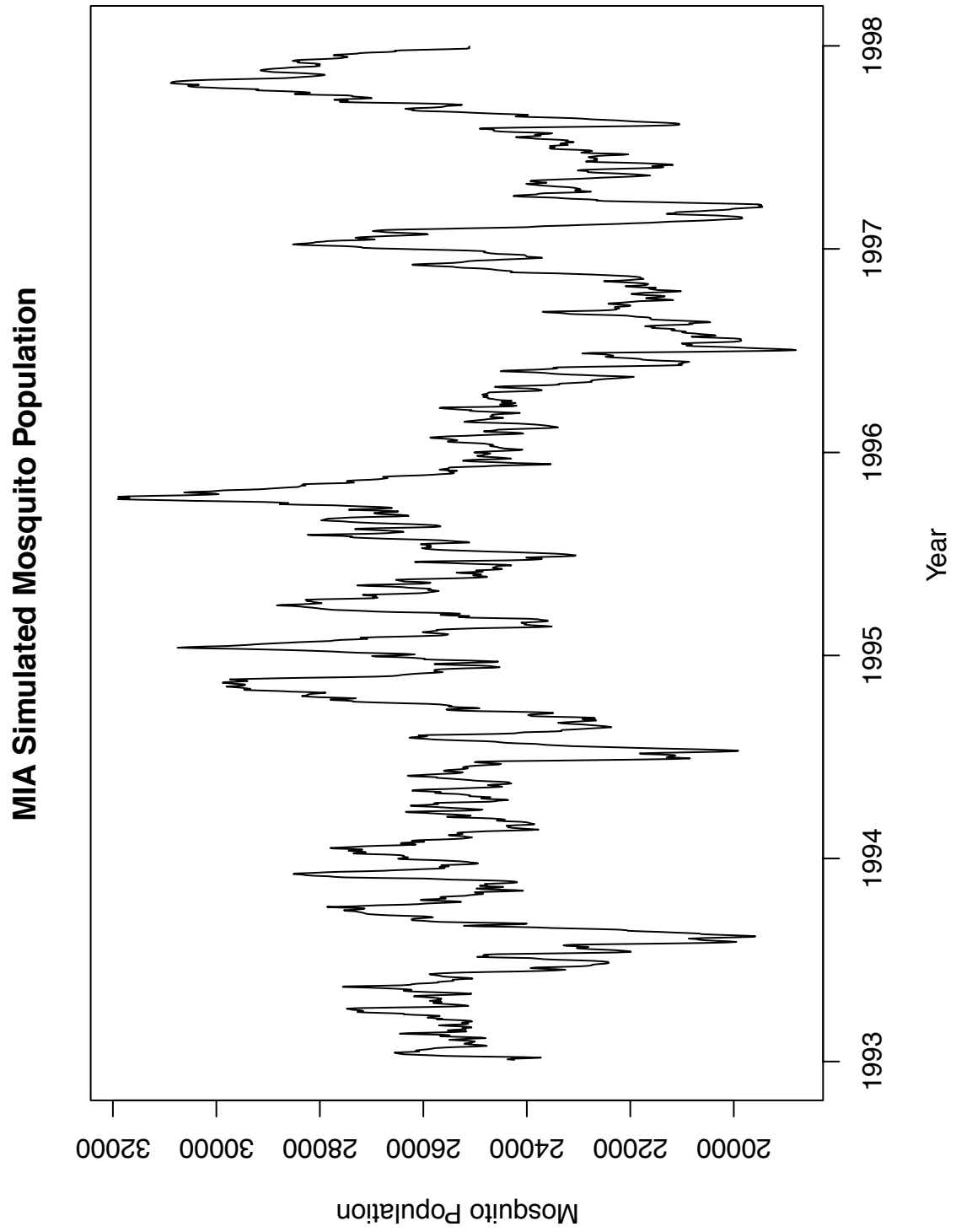


Figure 5.3: MIA simulated mosquito population

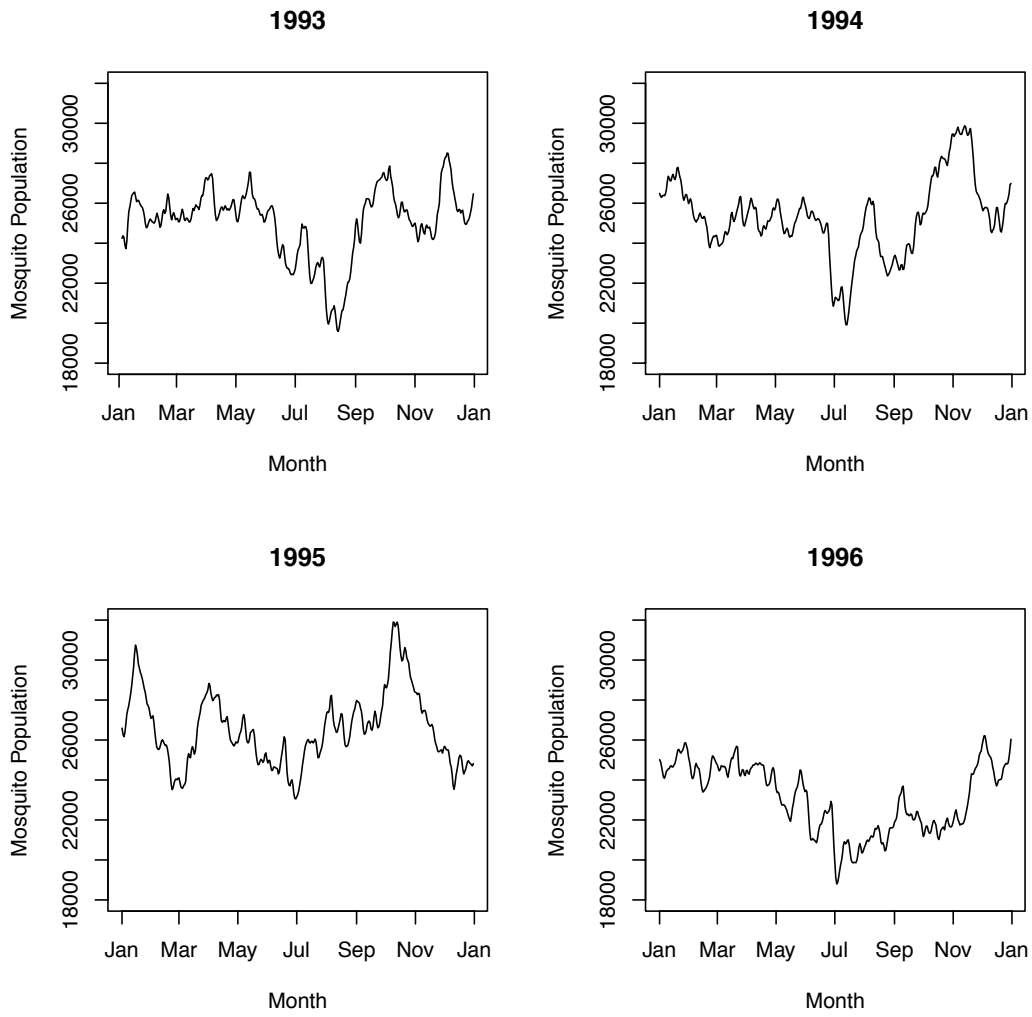


Figure 5.4: Four year comparison of MIA simulated mosquito population

lations and substantial increases facilitating this changes appears to coincide with beginning of the Iquitos epidemic. While this result does not imply causation it's existence warrants additional investigation into the factors driving the simulated trends. One such route of exploration exists in observation of the environmental sub-model and its climatic outputs during this period. Here, previously discussed climatic interactions hold potential to drive mosquito population in response to variation in temperature and precipitation. Analysis of the climatic simulation shows that during this period the mean temperature within the study site rose from 25.51°C in 1993 to 25.95°C in 1995. Previously discussed as a component of climate variability, the work of Depinay et al. (2004) suggested that changes of even a single degree in the range of 18°C to 26°C can result in extension of the mosquitos life span by more than a week. The 0.44°C change in mean temperature found in MIA is then a justifiable catalyst for increased vectorial capacity as this was a persistent factor of change throughout the year. Moreover, total precipitation during 1995 increased to 3,047 mm over previous totals of 2,393 mm in 1993 and 2,338 in 1994. These gains in precipitation could potentially create new or reinforce existing habitats encouraging increases in mosquito population. The results generated in the simulation, while not validated, suggest conditions conducive to increased vectorial activity in the area signifying a potential catalyst for increased transmission. Moreover, the reactive simulation trends provide a positive indicator for structural validation as documented environmental interactions have been captured by the model.

Undiscussed thus far have been the dynamics of mosquito population just prior the peak of the epidemic in 1997. Contrary to the elevated numbers simulated at the onset of the epidemic, the trend during 1996 appears to exhibit a general reduction in population over prior years. This is reflected in a 13% reduction of daily mean population to 23,074 mosquito agents. As with prior variation in the simulated population, climate appears to have played a large role during this period. The elevated temperatures observed during the previous year were reduced slightly to 25.61 °C. Interestingly, yearly precipitation during 1996 increased to 3,177 mm contrary to commentary from previous authors. Further investigation of precipitation patterns during 1996 reveals that 520 mm of the total precipitation observed can be attributed to three large rain events. Without these rain events the total precipitation for the year is similar to the years prior to the epidemic. As the quality of this data set is unknown the impact of these large rain events is questionable and will require future research to investigate the validity of their role in population dynamics.

After the simulated reduction in mosquito population a rebound was simulated during 1997. Unfortunately this simulated change in mosquito population potentially illustrates one of the main limitations of MIA. While plausible, the simulated increase in population occurs during the well documented El Niño phenomena. El Niño in Iquitos was associated with an extended dry period which could drastically impact mosquito habitat. This is potentially reflected in the simulation as a stabilization of population from mid April until September. Here, stabilization throughout the extended dry season does not emulate previous minimums simulated during previous dry season oscillation. While increased temperatures are conducive to increases in mosquito population, coupled with reductions in precipitation, habitats would hold little potential to support such gains in population. At the least this should be emulated in trend as a substantial reduction in aquatic-stage mosquitos. The true impact of this issue cannot be assessed until limitations of both data availability and hydrological simulation are resolved. These issues will be discussed as limitations of MIA and provide insight into potential solutions.

### **Mosquito Biting Dynamics**

MIA's structure, sensitivity analysis, and discussion of previous literature have all made apparent the positive relationship between mosquito population and biting. Due to this, previously simulated increases in mosquito population should be reflected as increases in human biting by mosquito agents. This potential result is of interest as increases in biting will create additional opportunities for transmission. Sharp increases in biting during the simulation will therefor have potential for creating substantial transmission events that may provide insight into the Iquitos epidemic. Figure 5.5 presents the daily human biting rates as simulated by MIA. The presented results are not representative of total mosquito biting as agents are free to feed from sources other than humans. Agents making the decision to feed on sources other than humans exist only in small numbers because of the anthropophilic nature of the primary local vector *A. darlingi*. Coupled with the model's simulation of mosquito-human transmission, non-human interactions will not be considered for analysis at this time.

The expected relationship between these two variables is realized in a correlation coefficient from linear regression of 0.85  $R^2$ . The anthropophilic nature of *A. darlingi* causes human biting to be very reactive to increases in population because of their preference for human meals over animals. Moreover, there is minimal lag between population increases and biting as each agent will seek a bloodmeal

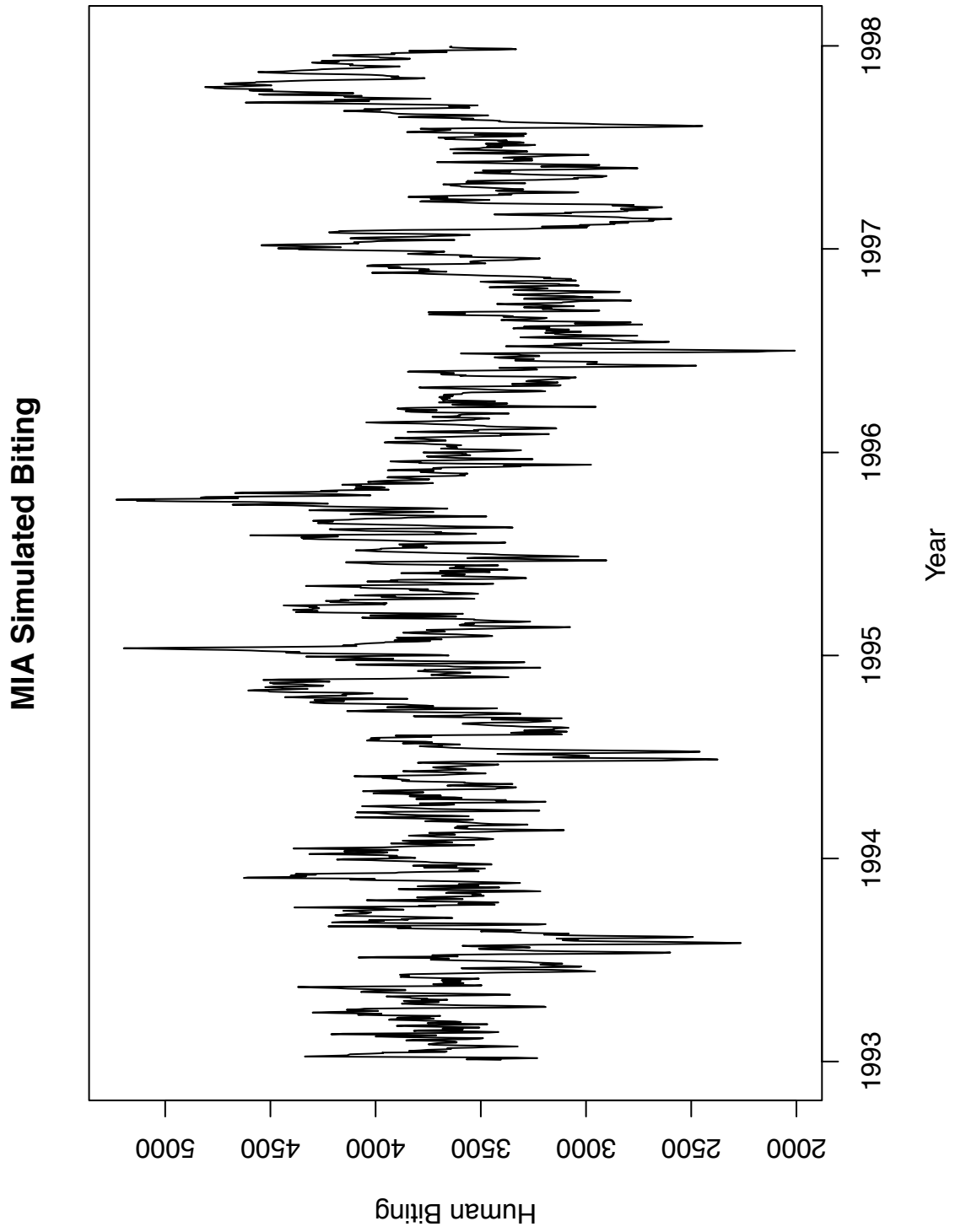


Figure 5.5: MIA simulated mosquito biting

within one model step of their initial emergence. As expected increased feeding is simulated during 1995 corresponding with the previously documented increases of mosquito population during the same period. Simulated increases in biting during this period are not only a product increased mosquito population but are also a result of the biological response to observed increases in temperature by each mosquito agent. Here, the gonotrophic cycle of each agent was accelerated relative to increased temperature as a product of the mathematical model governing this process. As result, the time needed by each mosquito agent for egg development and oviposition was significantly reduced. Within the lifespan of a mosquito agent this caused an increase in frequency of these events necessitating additional blood-meals. The resulting agent behavior produces additional need for protein intake reflected as increased biting in the model.

Additionally, two large increases in biting are simulated at short lags after previously discussed increases in population during 1994 and 1995. Finally, the population dynamics discussed during 1996 and 1997 have caused substantial decreases in mosquito biting. These biting rates will need to be addressed in future research to verify if instabilities in population previously discussed are in fact causing serious misestimation during inter-annual climate events. Overall the simulated trends in mosquito population and human biting seem to reflect variation as a product of a large interaction space.

### **5.3.2 MIA Transmission Scenarios**

Evaluation of MIA would be incomplete without discussion of it's ability to simulate malaria transmission within the virtual population. Here, the coupled nature of MIA is truly tested as transmission is a product of every system, structure, and parameterization of the model. Simulation of this interaction space generates biting events between mosquito and human agents, some of which result in transmission of malaria. The model is then capable of tracking infections resulting from successful interactions through changes in human state. This complex interaction space driving transmission has been discussed previously as sub-system components but not yet as a model result. Contrary to previous analysis, an iterative approach can cause the dynamics of unique transmission scenarios to be lost in aggregation. Thus, rather than discussing transmission as an iterative measure, specific trends in model output will be highlighted to identify potential epidemiological events. Consideration will now be given to a selection of scenarios, discussed as reoccurring trends in MIA's transmission output.

Two emergent transmission scenarios resulting from model interactions are presented in figure 5.6. While unique, each represents a reoccurring scenario simulated in several model iterations. The first scenario simulates an acute transmission event occurring during the later part of 1995. The initial conditions of this scenario simulate a small number of cases prior to 1995. This is similar to the Iquitos epidemic where several clusters of emergent low level transmission were observed prior to the epidemic. These initial transmission events fail to gain momentum within the simulation and are cleared from the study site within weeks of the initial case. Initial events such as this suggest an insufficient number of infectious humans to enable sustained transmission within the model domain. Moreover, this result indicates a low incidence of secondary infection. The absence of transmission is abruptly ended midway through 1995 when a simulated increase generates over twenty infected agents. Here a process spanning nearly two months causes the transmission to change from intermittent to sustained transmission effecting nearly 1% of the total human population. The change in infections corresponds with simulated increases in mosquito population and biting in relation to climatic variability during this period. Increases in mosquito population enable adequate transmission to establish a sustainable reservoir of human infections. Once this occurs sustained transmission is enabled and continues through the end of the simulation. Smaller variances in infections are simulated throughout the remainder of the run but do not reach the magnitude of the initial outbreak.

The second transmission scenario of interest simulates a sustained event throughout the observed epidemic years in Iquitos. This trend in transmission suggests a persistent reservoir of infected human agents throughout the simulation potentially in the same manner as the observed endemic transmission in Iquitos (Guarda et al., 1999). In addition to this initial observation, two interesting behaviors emerge during sustained transmission causing an acute increase in infection followed by a recession. Prior to the simulated peak in malaria cases a seasonal oscillation effect is simulated during the first two years. This is in agreement with previously discussed emergent behaviors impacting mosquito population and biting during dry periods. Directly after these events a strong increase in infection is simulated at the end of 1994 and beginning of 1995. This increase is a result of the increased mosquito activity simulated during the previously discussed climatic changes during this period. Elevated rates of infection continue until mid 1996 when a drop in cases is simulated corresponding with the El Niño phenomena. This decrease seems to contradict the observed increases in malaria during the same period in Loreto. As discussed in mosquito population dynamics this may be result of uncertainties in

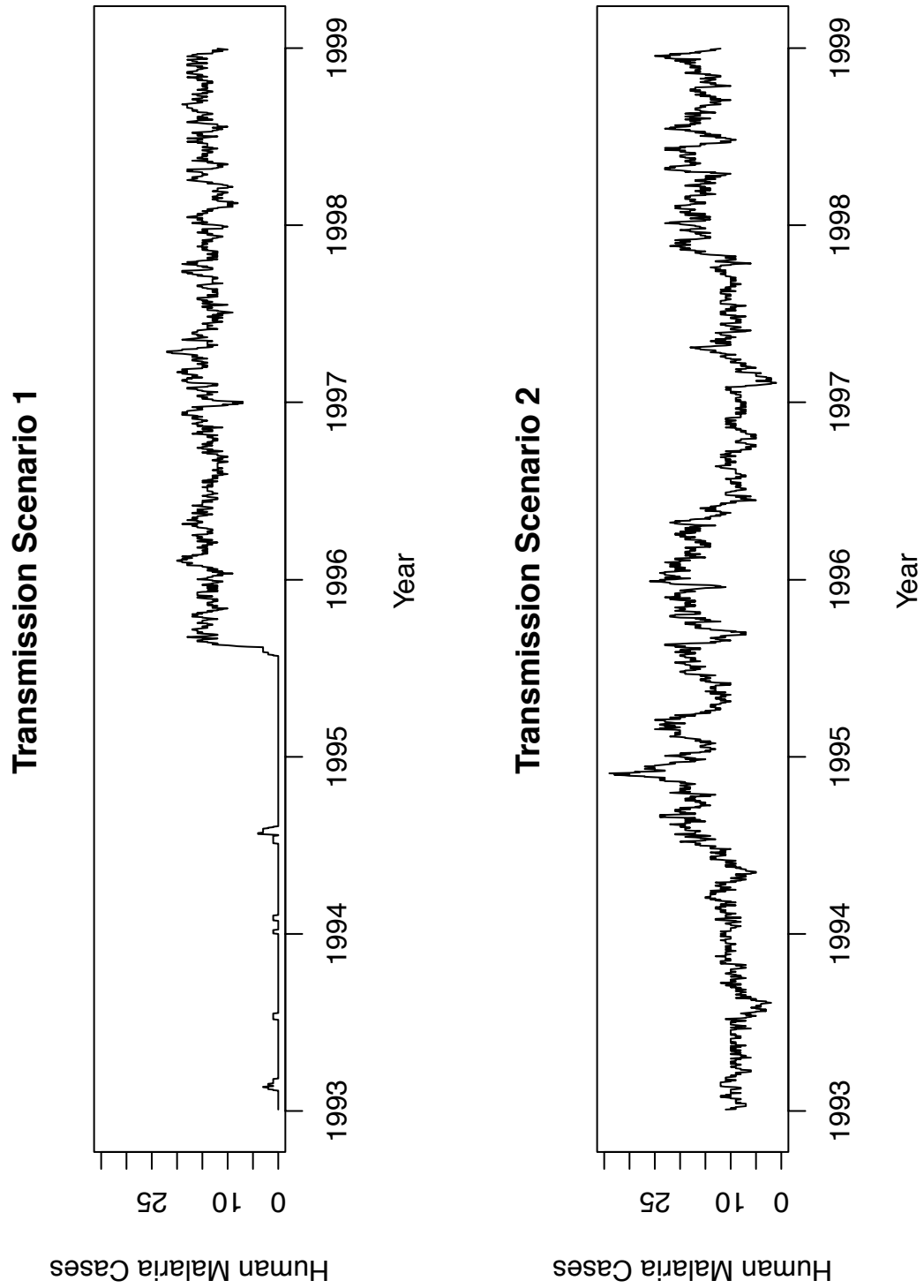


Figure 5.6: MIA simulated malaria cases



habitat simulation causing underestimation of mosquito population. Future consideration will need to be given to the uncertainties associated with habitat mechanics and climatic interactions to resolve the potential issues simulated here.

The simulated scenarios discussed here generate interesting dynamics of transmission that in the future can potentially be used to validate the structural composition of MIA. The simulation space was unable to reproduce the specific transmission dynamics of Iquitos epidemic in 1997 but it must be recognized that this was never the intention of MIA. Rather the reactive structural composition of MIA has shown that several abstracted systems respond to their intended environmental and behavioral interactions. Due to this there is promise that such systems can be refined in the future to produce meaningful results for the Iquitos area. The dynamics generated here suggest parameterizations including human agent recovery, parasite incubation, and climatic interactions, should be reevaluated within the model. Here there is an obvious need to parameterize these elements based on in situ observations and clinical data gathered during the epidemic event.

### 5.3.3 MIA Spatial Visualization

While a majority of outputs discussed thus far have been empirically based the spatially explicit nature of the model allows for visualization of agent locational information. These visualizations can be used as qualitative measures to observe movement and clustering of mosquito agents over time. One area of the MIA that benefits from this type of observation is the dispersion of adult-stage mosquito agents. Introduced in methodology, each mosquito agent is assigned a weighted movement grid to govern searches for bloodmeals or breeding habitats. The weighted movement routines were implemented to reflect prior research suggesting that higher concentrations of *A. darlingi* could be found in deforested or peri-urban land coverage types (Johnson et al., 2008; Vittor et al., 2006). The same research indicated little prevalence of *A. darlingi* in forested areas reinforcing its preference to deforested areas. The weighted grids were parameterized to reflect these attributes and draw mosquito agents towards urban and peri-urban environments.

Figure 5.7 illustrates the spatial distribution of mosquito agents during an arbitrary step of a simulation run. Mosquito agents are shown in red and human agents in black. Coverage types are differentiated by colour with forest as green, peri-urban as teal, urban as grey, and water as blue. The simulated distribution of mosquito agents is a culmination of parameters including maximum flight distance, human subject preference, habitat selection, and land coverage preference. While

in the future spatial statistics can be used to assess these distributions, currently only qualitative measures have been employed in analysis

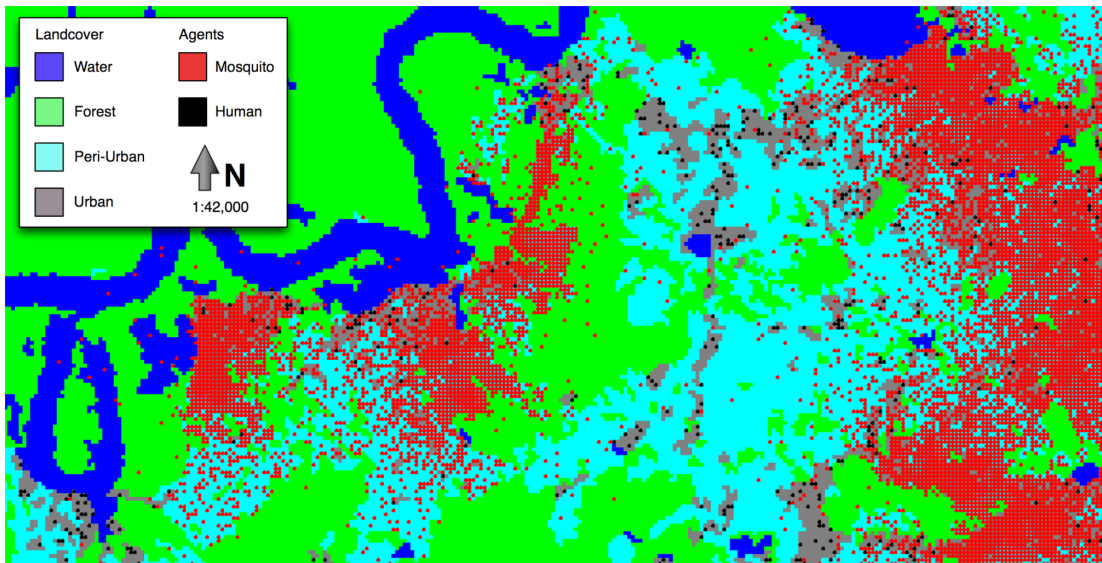


Figure 5.7: MIA visualization of mosquito dispersion

Clusters of mosquito agents are most apparent in areas where available habitat has been saturated. Here the edges of the river, ponds, and small lakes promote clustering of the mosquito population. This clustering is a product of anthropophilic nature of *A. darlingi*, land coverage preference, proximity to habitat, and the programming structures utilized to simulate these traits. Mosquitos in their dispersion make decisions to utilize land coverage types associated with human activity rather than move through forested areas. It is in these choices that the influences of anthropogenic change are apparent in the spatial dispersion of mosquito agents. Visually, corridors created by deforestation can be identified as facilitating movement of mosquitos from habitat area to another. In an area where transmission of malaria is driven by human movement this additional dynamic stands to promote short range expansion of malaria transmission.

## 5.4 Climate Variability

Climate variability is the final simulation role in which MIA will be tested. This role is considered because of the growing number of studies exploring the relationships between climate and disease (Derraik and Slaney, 2007; Hay et al., 2002; Martens et al., 1999, 1997; Patz et al., 2005, 2004; Rogers and Randolph, 2006). Many of

these studies have identified changes in regional climate as an important factor in increased transmission of vector-borne diseases. As malaria relies on this type of transmission MIA can be utilized to test the local effects of climate variability on transmission dynamics. In this regard, steps will be taken to document changes in output as result of variation in the simulated climate and the interaction dynamics it facilitates.

Authors including Martens (1998) and Jetten et al. (1996) recognized the importance of climate variability and applied climate scenarios to traditional epidemiological models of malaria. These studies utilized regional climate models to forecast changes in temperature and precipitation. Forecasted climate data was then used to drive existing malaria transmission models to gauge epidemic potential as a product climatic variability. In the absence of the facilities to forecast climatic variation MIA will attempt assess the impact of variation in regional climate by applying plausible scenarios to retrospective data. While this gives little indication of how future epidemics may unfold in relation to regional climate it can potentially provide useful insight into how changes effect larger systems of transmission in Iquitos.

Within the range of previously discussed IPCC estimates, retrospective simulation of climate variability scenarios is completed. Six simulation scenarios are tested to gauge a single habitat response to increases of 1°C. Each simulation is iterated a total of ten times and the results averaged amongst them. The generated simulation space can be viewed in table 5.3 as population trends between each of the six scenarios. The simulation results illustrate a strong relationship to increased mosquito activity, biting, and potentially transmission opportunities as results of plausible increases in temperature in current climate scenarios.

Table 5.3: MIA climate change results

	ABR	Change(%)	Mosquito Population	Change (%)
0°C	323	0.0	2443	0.0
+1°C	395	22.3	2843	16.4
+2°C	473	46.3	3284	34.4
+3°C	619	91.6	3816	56.2
+4°C	561	73.7	3944	61.5
+5°C	666	106.2	4403	80.2

The simulated increases are a result of the role temperature plays within the model. Several model structures such as development of mosquitos agents, and immature population dynamic are driven by this parameter. Thus even small increases can

result in large changes in population by effecting mosquito emergence rates and survivability. The simulated increases in daily population are concerning when viewed in the context of MIA's previously discussed climatic relationships. Previous analysis pointed to large increases in mosquito populations just prior to the epidemic as related to less than half a degree change in temperature. In the same capacity the simulated results from an increase of just 1°C could produce an more than 1,000,000 additional mosquito agents within a span of a year. If small increase of 1°C were to occur even as an inter-annual effect it could greatly increases the chances epidemic transmission. Malaria transmission scenarios produced from this single habitat response should not be given consideration until measures can be taken to optimize model structures and test climatic change without habitat restriction. Future generations of MIA with the ability to test and validate such findings should utilize forecasted climate data to simulate mosquito and transmission dynamics.

# Chapter 6

## Conclusions

The results generated by MIA present a glimpse of the potential this prototype model has to offer. Limited in several respects, the first generation of MIA stands as a proof of concept and exercise in model building. The simulated results appear to be a cumulative product of deforestation, dominance of *A. darlingi*, expansive habitat, preferable climatic conditions, and season oscillations. While not yet validated these results show encouraging trends and exhibit model behaviors hinting at causal mechanisms. The thesis will now conclude with insights and commentary regarding how MIA has contributed, its limitations, and recommendations for the future.

### 6.1 Contributions

At the onset of this thesis a set of operational goals were established as a guide to address the research questions at hand. While ambitious, several of these goals have been achieved and tangible products exist because of them. In this regard MIA was developed and deployed as novel agent-based methodology for simulation of malaria transmission. This was accomplished using coupled physical systems, facilities for observation of emergent behaviors, and testing environments to assess model sensitivities. Regardless of the outcome of future validation, the interaction space and framework established in MIA can be parameterized and modified to meet the needs of successive generations of the model. Moreover, MIA has only begun to foster understanding of localized causal mechanisms in the Iquitos area. The full potential of MIA as a diagnostic tool will not be realized until successive generations are able to address the limitations of this prototype. At the least

MIA has addressed the remaining goals by generating intimate discussion of the limitations hindering its progress.

This thesis asked the question: Can a novel modeling methodology be developed to resolve local causal factors or mechanisms generated in coupled human-vector-environmental systems? The answer to this question is perhaps the greatest contribution of MIA. A flexible framework for agent-based simulation of malaria transmission has been created from theoretical concepts and existing physical models. MIA is one of very few examples of practical application of an agent based model in epidemiology, and even more so in transmission of malaria. Moreover, MIA is the only example of agent-based multi-year simulation of local scale malaria transmission dynamics. While this model is by no stretch perfect a large number of its limiting factors are known and through discussion of these issues the future of the model can be established.

## **6.2 Limitations**

### **6.2.1 Local Parameterization, Data, and Bias**

The three limitations covered in of this sub-section are inter-related and comprise a reoccurring theme limiting the potential of MIA. One of the primary limitations of MIA throughout the course of this research has been the lack of local parameterization for the Iquitos area. This is reflected in the number of parameterizations imported from studies of malaria centered outside of Iquitos and South America. Individual parameterizations from larval weight to mortality suffer from a lack of local parameterization. While literature seems to demonstrate inter-species variability in mosquitoes as minimal, even small uncertainties can quickly become unmanageable and cause instability in results. Environmental system parameters such as ecological carrying capacity would benefit from local knowledge and allow for emergent behaviors to reflect real world complexities. Moreover, where sources of local data do exist, such as satellite imagery and climatic data, there is a need to extend the availability of these resources to the model. Limiting the number of observations available to the model can potentially increase the impact of uncertainties in the small data sets available. Building a database of local knowledge will not only allow for refinement of physical systems simulation but also provide a basis for validation of model results and analysis. Currently many of the trends and simulated behaviors found in MIA cannot be substantiated until field data

validates the parameterizations utilized.

In addition to unavailability of data, a lack of exposure of this researcher to the local study site carries an assumption of bias from the literature and data utilized in development and analysis. In this, uncertainties encountered and undocumented in prior research become the burden of MIA until steps can be taken to expose this research to local study and validation. At the onset of MIA hopes were high for external resources to alleviate these issues but due to unforeseen circumstances MIA was relegated to freely acquired resources. Moreover, comparable projects in the past have been undertaken by teams of multiple researchers. The limited time of a master student to accomplish the ambitious goals of this project have become as much of a limitation as the prior mentioned issues.

## 6.2.2 Hydrological Modeling

While MIA is capable of simulating habitat level biology it lacks methods for dynamic generation and elimination of habitat objects. In the absence of such methods MIA is susceptible to overestimations of mosquito populations during the dry seasons and underestimations during the wet season. This issue was of particular interest during 1997 when the El Niño phenomena generated an extended dry season but did not reflect previous lows in seasonal oscillation. Evaporation of resting water or reduction of soil moisture during these events could eliminate entire immature mosquito populations developing in these habitats. Events such as this would drastically limit populations creating variability currently inaccessible to MIA. The effect of such limitations may be enhanced in wet environments such as those studied in MIA.

The coupling of a hydrological model with MIA could elevate this issue by providing overland flow and soil moisture estimates to the habitat simulation structures. Coupled with enhanced resolution of the simulation grid space a hydrological model could enable MIA to react to precipitation events which could cause drastic shifts in population. The timeframe for change would be in the scale of approximately one week as a product by the immature mosquitoes development simulated during and after an event. Unfortunately the addition of a system such as this would be a large undertaking requiring significant understanding of hydrological modeling and coupled physical systems. The environmental sub-model would not require serious retooling but steps would need to be taken to make sure that message passing interfaces were established between the connected systems. Previous work by Bomblies et al. (2008) appears to have successfully undertaken this feat.

As their approach applied hydrological modeling in a water scarce region significant testing would be required prior to introducing it to a rainforest region. Regardless, the current modular design of MIA would allow for the coupling of a hydrological modeling systems such as the one utilized by Bomblies et al. (2008). The inputs necessary including precipitation, evapotranspiration, and elevation data are readily available from the existing data set employed by MIA.

As alternative to this approach several authors have suggested the use of remote sensing as a tool to model mosquito habitats (Achee et al., 2006; Atkinson and Graham, 2006; Hay et al., 2006; Kalluri et al., 2007; Omumbo et al., 2005; Zeilhofer et al., 2007). This approach relies on relating in situ characterization of preferable habitats to spectral responses in satellite imagery. Characteristics such as soil moisture and land cover type have been derived from satellite imagery and used to produce fuzzy measures of habitat capacity. Habitat classification such as this could be easily integrated because of MIA's existing use of grids in the ESM. Unfortunately, a majority of these studies are temporally static providing only a single observation. Habitats within MIA's study site are highly reactive to temperature and precipitation events resulting in acute variability. Without a high temporal resolution of imagery the desired dynamic changes would be left unresolved. This limitation offers a simple but expensive solution by increasing availability of satellite imagery within the model. Moreover, interpolation methods could be utilized to estimate habitats between observations based on climatic inputs. Prior to implementation of a remote sensing based solution a study would be required to identify the minimum temporal resolution necessary to advance habitat generation and elimination in MIA.

### **6.2.3 Sub-Scale Variability**

MIA is spatially explicit, but the grid system employed to facilitate this may be a limiting factor. More specifically, the common grid cell resolution used with MIA's coupled systems is a compromise in resolution potentially ignoring microhabitats and small-scale variability. This may be problematic in light of literature suggesting microhabitats and small-scale variability play a significant role in mitigating stress of a mosquito population and promoting increased survivability (Okech et al., 2003). These habitats exist in a variety of forms within the study site including tire tracks, surface run-off, and ditches. In MIA, microhabitats would be of particular interest during climatic extremes and inter-annual oscillations as habitat is a significant limiting factor of mosquito population. Currently MIA does not possess the spatial



resolution to consider the influence of microhabitats. Instead it uses aggregate measures to estimate multiple habitats within a single grid cell. Changes to increase the spatial resolution of MIA would require resampling of all grid based data and adjustment of internal parameterizations.

The first consideration prior to such changes is the potential for diminishing returns with increasing complexity. As previously mentioned in sensitivity analysis the complex interaction space formed amongst the interacting systems can cause uncertainties to become lost in the results and worse yet diminish the ability of those interpreting the results to generate useful discussion. As the physical characterization of these small-scale systems would be accompanied by large uncertainties the potential benefits to the model could be outweighed by convolution in results. In the case of sub-scale variability simplicity may offer a better solution until efforts can be made to assess potential of additional structures fostering complexity. The second consideration is the increased computational overhead resulting from increased spatial resolution. Increasing grid cell resolution would result in substantial increases in the number of grid cells which need to be processed during each step. The problem of computational overhead is not unique to sub-scale issues and will be discussed now as a limitation of the model.

#### **6.2.4 Computational Overhead**

The simulation space of MIA revealed that the computational demands of such systems exceed that of current desktop computing. Parry and Evans (2008) suggested two potential solutions to allow for simulation of millions of agents in applications such as MIA. These methods included the use of mathematically derived super-individuals or hardware based parallel computing. Originally proposed by Scheffer et al. (1995), super-individuals are an aggregate modeling approach whereby individuals are grouped together in an effort reduce the total number of objects simulated. Forgoing individual heterogeneity, this approach implies that observed phenomena are not a primary product of individual behavior. The changes needed to implement this approach do not necessitate model reformation but require changes to be made to the model structure (Scheffer et al., 1995). These changes can potentially influence model results as individual heterogeneity is lost in the applied aggregate functions. Parry and Evans (2008) proposed an example where aphids agents born at the same grid location would be grouped as super-individuals. Their actions, mortality, and spatial context are then facilitated though aggregate statistical measures instead of individualistic parameterizations. Noted complications

of this modeling approach included temporal variability, underestimation of population, unwanted spatial clustering, and inadequate dispersion. Moreover, the observed Issues were compounded as the number of agents increases in the simulation.

Parry and Evans (2008) concluded that while easier to implement, super-individuals are inappropriate in simulations with interactive agents. This is especially true in spatial models such as MIA where the individual spatial actions of agents drive emergent behaviors. The loss of spatial interaction properties desired in these models negates the potential gains in model runtime. Alternatively a hardware based solution was proposed in parallel computing, offering decreased computing time without alteration of model results. Parallel computerizing allows for the computationally tasking elements to be distributed amongst a cluster of computers, balancing the load over many processors. This solution requires hardware and interconnectivity be available but also that a software interface be employed to distribute tasks amongst the available hardware. Solving these requirements would be a major undertaking to the MIA project but offer large gains if implemented. Parallelization is an extremely attractive option as asynchronous mosquito agents could easily be adapted to this type of processing. The shared hierarchal academic research computing network (SHARCNET) of Ontario have recently deployed MPJ express, a java based message passing interface to allow for parallelization of REPAST based models. Unfortunately these systems have only become available at the conclusion of MIA's testing and have not been utilized as of yet.

### **6.3 Recommendations for Research**

MIA has great potential to evolve and respond positively to additional research by refining complexities and parameterizations. The work completed thus far has shown successes in transitioning theoretical agent-based epidemiological modeling into practical application. As the vast majority of effort in the research has focused on construction of these modeling structures there is near limitless potential to refine and integrate new methods to enhance the established core. A majority of changes required to facilitate this advancement have been discussed as uncertainties in data or model structures. Successive generations of MIA will need to address these issues in order to move past the limitations of the current generation. Three primary issues exist which will require immediate attention in the next generation of MIA:

- Integration of hydrological modeling and exploration sub-scale variability
- Parallelization of model structures to allow for high performance computing
- Local parameterization of mosquito, human, and environmental sub-models with in situ data

The potential solutions to these issues will require significant investment of time and funds. The preliminary work has already been completed for hydrological modeling and parallelization but will required additional expertise in the future. Encouragingly previous literature has shown sufficient gains can be made through these additions (Bomblies et al., 2008; Parry and Evans, 2008). Collection of in-situ data will be the most challenging of these additions requiring significant field work and external funding to facilitate it. Regardless of cost, the addition of in situ observations would allow for local parameterization and most importantly validation. This will give direction to future generations by isolating weakness and identifying sources of uncertainty in MIA. A gamut of secondary recommendations exist and should be consideration during the construction of the next generation of MIA. First efforts should be made to incorporate traditional epidemiological metrics. This will enable commentary from academics foreign to modeling and provide a tool for communication model results. Additionally, these results should be presented with enhanced visualizations to reflect spatial distributions of population and infection.

## 6.4 The Future

Looking beyond limitations, several advancements could allow MIA to evolve in it's role as a tool of spatial epidemiology. This is perhaps most apparent in the coding structures utilized by MIA. While implemented to simulate the transmission of malaria, model code could easily be adapted to simulate a multitude of vector-borne diseases. This may be of interest to researchers examining spatial transmission of dengue fever, or in the case of Ontario, emergent west Nile virus. Additionally, MIA can be adapted to new study sites because of its versatile parameter space. Given adequate data this parameter space could be adapted to consider a large number of terrestrial study sites. If the dominant vector in new study sites is different than MIA, additional *Anophales* sub-species could be considered with retooling of the agent parameter space. If multiple vectors are found in the study area this can

be accommodated by adding additional agent classes and parameterizing each to specific sub-species. These potential roles illustrate the adaptability of MIA and promote use well beyond it's current scope.

MIA, despite it's potential for advancement, is a prototype and should be treaded as such. Sensitivity analysis may have provided the greatest insights to prescribe the use of the current generation of MIA. Here, parameters exhibit reactions to real world phenomena, potential over-fittings, and interaction space noise. Results such as this must be interpreted as indicators of uncertainly warranting substantial investigation into the models validity. Moreover, these results my be indicative of a much larger problem in excessive complexity. While the intentions of MIA were to foster complexity in design, a potential overshoot of this goal could drive noise as result of cumulative uncertainties. As a guideline, the results produced by MIA should be handled with care. Their usefulness in applications outside of validation are not substantiated and could potentially foster misinterpretation. Due to this the first generation of MIA should be used as a guide in model design to encourage future generations of ABMs in epidemiology.

# Appendix A

## Abbreviations and Acronyms

### A.1 List of Abbreviations

*A.* - Anophales

*P.* - Plasmodium

### A.2 List of Acronyms

ABM(s) - Agent-based model(s)

ABR - Actual biting rate

CA - Cellular automata

DDT - Dichlorodiphenyltrichloroethane

ESM - Environmental sub-model

MIA - Malaria in the Amazon

ODD - Overview, design concepts, details

REPAST - Recursive porous agent simulation toolkit

SHARCNET - Shared hierarchal academic research computing network

SIR - Susceptible, infected, recovered

UML - Unified modeling language

# Appendix B

## Temperature Calculations

### B.1 Hourly between sunrise and sunset

$$T_t = T_{min} + (T_{max} - T_{min}) \cdot \sin \cdot \left( \pi \cdot \frac{t - t_{sr}}{D + A} \right) \quad (\text{B.1})$$

Where  $T^t$  is an estimation of temperature in °C at hour  $t$ .  $T^{min}$  is the minimum temperature of the day,  $T^{max}$  is the maximum,  $t^{sr}$  is the hour of sunrise,  $D$  is the number of hours of sunlight, and  $A$  is two times the maximum temperature after midday (Jetten et al., 1996).

### B.2 Hourly temperature after sunset

$$T_t = \frac{T_{min} - T_{Ss} \cdot e^{-N/\tau} + (T_{Ss} - T_{min}) \cdot e^{(t/T_{Ss})/\tau}}{1 - e^{-N/\tau}} \quad (\text{B.2})$$

Where  $T^{Ss}$  is temperature at sunset,  $N$  is the number of hours without sunlight,  $T^{Ss}$  is the hour of sunset, and  $\tau$  is a nocturnal time constant (Jetten et al., 1996). An estimate of 4 hours was used to set the nocturnal time constant.

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