SIMULATING THE SPREAD OF MALARIA: A CELLULAR AUTOMATON BASED MATHEMATICAL MODEL & A PROTOTYPE SOFTWARE IMPLEMENTATION

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(ABSTRACT)

Every year three million deaths are attributed to malaria, of which one-third are of children. Malaria is a vector-borne disease, where a mosquito acts as the vector that transmits the disease. In the last few years, computer simulation based models have been used effectively to study the vector population dynamics and control strategies of vector-borne diseases. Typically, these models use ordinary differential equations to simulate the spread of malaria. Although these models provide a powerful mechanism to study the spread of malaria, they have several shortcomings. The research in this thesis focuses on creating a simulation model based on the framework of cellular automata, which addresses many shortcomings of previous models. Cellular automata are dynamical systems, which are discrete in time and space. The implementation of the model proposed can easily be integrated with EpiSims/TRANSIMS. EpiSims is an epidemiological modeling tool for studying the spread of infectious diseases; it uses social contact network from TRANSIMS (A Transport Analysis and Simulation System). Simulation results from the prototype implementation showed qualitatively correct results for vector densities, diffusion and epidemiological curves.

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Chapter 1

Introduction

1.1 Motivation

Every year one to three million deaths are attributed to malaria out of which one-third are children [1]. Malaria is transmitted by the infected female *Anopheles* mosquito, which feeds on human blood. Malaria can be prevented and controlled if detected early. Computer simulation based models provide a powerful tool for studying the vector/mosquito population dynamics, the people vector interaction, and the effects of control strategies for malaria. We have included a detailed description of Vector-borne diseases focusing on malaria to give the reader an insight in the factors that should be addressed in a mathematical model.

1.2 Problem statement

Derive and implement a mathematical model within a simulation-based decision framework, that can be use to analyze and compare the effectiveness of many intervention scenarios that would otherwise be hard or impossible to conduct in real-life because of the time, risks or expenses involved.

1.3 Contribution of this Thesis

Many of the earlier approaches were based on differential equations. They made several assumptions such as complete mixing of the population, addressing fraction of the population as either infected or uninfected and many more. A cellular automaton based

model for malaria has made it easier to incorporate the appropriate mobility and interaction between vector and host. The distributed model introduces spatial variation in land type and temperature. It takes into account reproduction, survival, diffusion and biting rate for the vector mosquito and climatic factors such as wind.

The prototype model is implemented in C++ and can be used in conjunction with EpiSims/TRANSIMS. It is an extensible model which can include additional factors without breaking the design of the model. Examples include mapping of satellite images to density of mosquito population; specific modification of improvement in the host/vector interaction and more.

1.4 Thesis Organization

The remaining sections of this thesis are organized as follows. Chapter 2 discusses the background of the vector-borne diseases focusing on malaria from life cycle of the vector to projects around the globe for the prevention of the disease. Chapter 3 describes the earlier approaches to model and simulate the spread of malaria and some of their shortcomings. Chapter 4 introduces the concept of cellular automata and illustrates it with examples. Chapter 5 describes the background of Episims and TRANSIMS and how it is used to analyze the epidemics of various diseases. Chapter 6 describes our model which is based on cellular automata and the factors incorporated to overcome the limitations of the earlier approaches. Chapter 7 discusses the software implementation, test cases and results. Chapter 8 presents some ideas for future work and concludes this thesis. Finally, the bibliography is presented in Chapter 9.

Chapter 2

Vector-Borne Disease

A vector-borne disease, as the name suggests, is transmitted with the aid of a vector. The term vector refers to a medium, an arthropod or some other agent through which a pathogenic microorganism is transmitted from an infected individual to another uninfected individual. The mechanism of transmission involves at least three different living organisms, the pathological agents which can either be a bacteria, virus, and protozoa; the vector, generally arthropods such as ticks or mosquitoes; and the human host. Some domesticated or wild animals can act as reservoir for the pathogens till they are exposed to the susceptible human population.

Vector-borne diseases are the major health problem in the developing countries of Africa and Asia usually residing in the tropic and sub tropic regions. Almost half the population of the world is infected by the vector-borne diseases leading to high morbidity and mortality [2]. The transmission of many vector-borne diseases is affected by climatic factors. Infective agents and their vector organisms are sensitive to factors such as temperature, surface water, humidity, wind, soil moisture, and changes in forest distribution [3].

Many control programs were implemented globally to eradicate the vector-borne diseases. Most of these programs were successful outside Africa but the success was short-lived. The factors responsible for the resurgence of vector-borne diseases are complex. They include insecticide and drug resistance, changes in public health policy, emphasis on emergency response, de-emphasis of prevention programs, demographic and societal changes, and genetic changes in pathogens [4].

2.1 Types of vector-borne disease

Each vector-borne disease is associated with a specific pathogen and a vector which acts as a medium of transmission. The spread of the disease in a particular region depends on the adaptability of the vector to survive and grow in that region. From Table 1.1 we can see that some vector-borne diseases are more prevalent in specific regions due to the vector's ability to adapt in the specific environment and climate. For example, malaria is more prominent in the tropic and sub-tropic regions, since it provides a more conducive environment for the mosquito to grow and breed rapidly.

Disease	**Vector**	**Geographical Distribution**
Malaria	Mosquito	Tropics & Sub-tropics
Schistosomiasis	Water snail	Tropics & Sub-tropics
Lymphatic Filariasis	Mosquito	Tropics & Sub-tropics
African Trypanosomiasis (Sleeping Sickness)	Tsetse fly	Tropical Africa
Drancunculiasis (Guinea worm)	Crustacean (copepod)	South Asia, Arabian Peninsula, Central-West Africa
Leishmaniasis	Phlebotomine sandfly	Asia, Southern Europe, Africa, Americas
Onchoerciasis (River Blindness)	Blackfly	Africa, Latin America
AmericanTrypanosomiasis (Chagas disease)	Triatomine bug	Central & South America
Dengue	Mosquito	All Tropical Countries
Yellow Fever	Mosquito	Tropical South America, Africa

Table 1.1 Vector-borne diseases, associated vector and the region of prevalence [5]

2.2 Introduction to malaria

Malaria is a major life-threatening vector-borne disease transmitted through mosquitoes. The disease got its name from bad air (mal aria) as it was thought that the disease came from fetid marshes. Later in 1880, it was discovered that the real cause of malaria was *Plasmodium* a single cell parasite which can only be transmitted from one person to another by the bite of female *Anopheles* mosquito. The male *Anopheles* mosquitoes are not involved in disease transmission as they don't require blood to nurture eggs as their female counterparts do [6].

The disease is more prevalent in the tropic and sub-tropic regions of the world and causes more than 300 million acute illnesses and at least one million deaths annually [6]. People living in the world's poorest countries are at a high risk of malaria, which constitutes approximately more then 40% of the world's population. According to World Malaria Report 2005 [7] by World Health Organization (W.H.O.) 90% of deaths caused by malaria take place in Africa, primarily among young children, pregnant women and their unborn children. A child in Africa dies every 30 seconds because of malaria and those who survive the severe episode of malaria might suffer from learning impairments or brain damage [8].

Although malaria is spread by bites of female *Anopheles* mosquitoes, it can also spread by other means such as blood transfusions, organ transplants and sharing of needles by intravenous drug (IV drug) users [9].

2.3 Types of parasite

There are over 120 species of the parasite genus *Plasmodium* [10]. However, only four of these infect humans to cause malaria. These four species of *Plasmodium* parasites are *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*. *Plasmodium falciparum* can cause severe (life-threatening) malaria, and the other three species cannot. The details of the four main species of *Plasmodium* that infect humans with malaria are described below [9]:

1. *P. vivax* – They are found world wide but most commonly in India, Central and South America. The incubation period in the human body is approximately 8-13 days for the symptoms of the disease to become apparent. Infection by this parasite can sometimes lead to life-threatening rupture of spleen. They hide in liver and can return later once a person is infected [9].

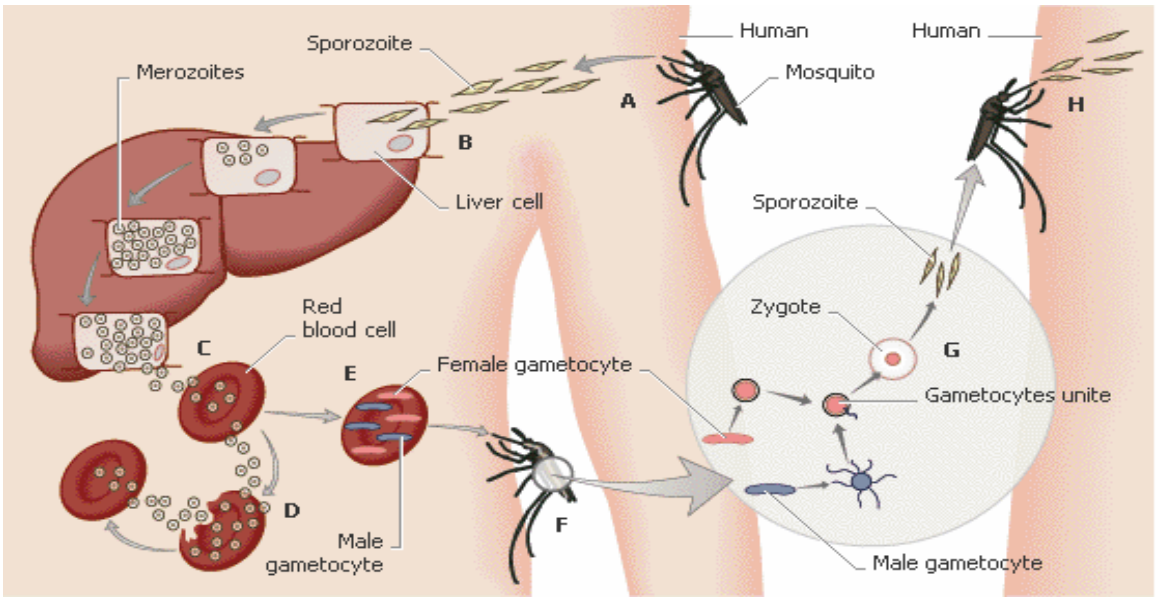
2. *P. ovale* – They are found mostly in Africa. This form of malaria has an incubation period of 8-17 days in the infected person and can hide in the liver of partially treated people and return later [9].

3. *P. malariae* – They are found in most part of the world but are less frequent than other forms of the malaria parasite. The incubation period for this parasite is 2-4 weeks in the infected person. If the disease is untreated, it can last for many years [9].

4. *P. falciparum* – They are responsible for the most life-threatening form of malaria and cause majority of the deaths in the world and are found worldwide. The incubation period for this parasite is 5-12 days. They are resistant to most of the drugs used to treat or prevent malaria [9].

2.4 Life cycle of malaria parasite

The life cycle of malaria is described in terms of development stages of the malaria parasite that takes place in different environments. The small single-cell organism has three to four different forms. Each form is specialized in living in a certain place such as mid gut, salivary glands of the mosquito, red blood cells, liver of the mammalian host etc.



Picture Courtesy: MSN Encarta [11]

Figure 2.1 Life cycle of malaria parasite

Figure 2.1 above explains the development phase of the malaria parasite. The infection begins when the malaria parasite enters the human body through the bite of the infected female *Anopheles* mosquito from its blood meal. The sporozoites [12] are transferred to a human host with the mosquito bite, injecting its saliva into the tiny blood vessels (A). The sporozoite travels with the blood to the liver and enters the liver cells (B). In the liver some of the sporozoites divide and become thousands of merozoites [13]. The merozoites enters the blood after being released from the liver cell and are taken by the red blood cells (C). In the red blood cells some of the merozoites turn into a ring formed trophozoites [14], which splits again to form schizonts [15]. The schizonts burst the red blood cells (D) at a certain moment, releasing the merozoite which in turn infects more red blood cells. Each burst of red blood cells is associated with violent rise of temperature and severe body chill as seen during the attacks in malaria [16]. The trophozoites that were left over during the division will develop into a sexual form, the male and female gametocyte (E) in the course of few days. The gametocyte is the form that infects mosquito and reproduces itself. When the uninfected mosquito has sucked blood (F) containing gametocytes, they pass into the salivary glands of the mosquito, where they develop into a new form, the sporozoites (G). The parasite matures inside the mosquito

until it reaches the stage where it can again infect a human host when the mosquito takes her next blood meal (H), 10 to 14 or more days later.

The incubation period (time from mosquito bite to development of the disease) is usually about 10 to 15 days. This period can be much longer depending on whether any anti-malarial medication has been taken. *Plasmodium ovale* and *Plasmodium vivax* can stay in dormant form known as hypnozoite in liver cell, which can cause relapses of the disease months and even years after the original disease (relapsing malaria) [17].

2.5 Factors influencing the transmission of malaria

The implementation of the thesis is based on various parameters explained in this section. The life cycle of parasitic organism and its associated vector-borne diseases in the ecological perspective is important in understanding and controlling these diseases [18-19]. According to M. Wilson [20] "Moreover, vector-borne diseases are part of a larger human ecology in which human social systems, economic activities, interactions with the environment, and lifestyles represent some of the key domains of interaction that affect infection and disease risk" . Any alteration in the environment either by natural phenomenon or human; can change the ecological balance and context within which disease hosts, vectors, and parasites breed, develop and transmit diseases [21-22]. Transmission and distribution of vector-borne diseases are greatly influenced by environmental and climatic factors. The vector-borne disease such as malaria is strongly affected by environmental factors influencing the abundance and survival of the vector. Indeed, Smith, K. et al. [23] attribute 70-90% of the risk of malaria to environmental factors. The variety and magnitude of environmental influences on malaria are enormous [20].

There are many effects of temperature on the transmission cycle of the malaria parasite *Plasmodium falciparum.* However, the effect on sporogonic period (n) [24-25] and mosquito survival (p) [24] are considered to be crucial [26-27]. The sporogonic period is the development phase of ookinete, the egg of the parasite, in the mid-gut of the anopheline mosquito. The lower limit of temperature depends on the number of the

mosquito surviving the incubation period (pn). The parasite becomes inactive at 16°C and the transmission is not likely to take place below 18°C, as very few adult mosquitos survive the 56 days required to complete the sporogony at that temperature. At 22°C sporogony is completed in less than 3 weeks and the mosquito survival is comparatively high to complete the transmission cycle. Hence temperatures below 18°C were considered to be unsuitable and above 22°C, stable and suitable for transmission. The sporogony cycle on an average lasts about 10 days, but shortens as the temperature increases [25, 28] becoming as short as five days when the temperature exceeds 32°C. The upper limit of temperature depends on the vector survival. Studies [29-30] have shown that temperature above 32°C causes high vector population turnover, weak individuals and high mortality. Thermal death for mosquitoes occurs around 40–42°C [31-32] and daily survival is zero at 40°C [24]. Humidity impacts the survival rate of the mosquito as well. Typically, mosquitoes do not live long enough to complete their transmission cycle in places where the relative humidity is consistently less than 60% [33, 85].

Deposition of mosquito eggs, and their maturation into larvae and then into ad ults, requires aquatic breeding sites, which is most of the time dependent on rainfall [34-35]. The time required for mosquito maturation shortens as temperature increases [34, 36]. The abundance of the mosquitoes post rainfall is determined by the temperature, which affects the duration of the aquatic stage of the mosquito's life cycle. Female mosquitoes start looking for the blood meal as soon as they enter in the adult stage and in that process the malaria parasite is ingested by the female mosquito with the blood. The proportions of infective mosquitoes [37] increases as the feeding frequency of the mosquitoes also increase with the temperature. At local scales within few 100 meters, the risk of malaria is determined by mosquito behavior and ecology, especially the distribution of blood-meal hosts and water [37]. Mosquitoes alternate between blood feeding and oviposition, and suitable host and water are heterogeneously distributed [38]. Thus, biting reflects that mosquitoes commute to complete its gonotrophic cycle [39].

Vectorial capacity is defined as the [40] "daily rate at which future inoculations arise from a currently infective case" and in general can be determined as the product of three parameters:

a) Biting rate, representing the incidence of biting contact between the mosquito and the people in terms of number of bites per person per night; this indicates the average number of vector females liable to become infected per case per day;
b) Expectation of infective life, or days of infective life per mosquito infected with the given parasite species;
c) Man biting habit or bites on man per day per individual female [41].

Webber and Edman [42] indicated that the probability of vector survival falls linearly from 1.0 to 0.5 when feeding success falls to zero i.e. when there is no host in the vicinity. Density-dependent host defensiveness appears to be the major host-related determinant of lifetime reproductive success for most blood-sucking insects, affecting the quantity of blood ingested and the probability that the vector lives to feed again; hence there must be intense pressure for vectors to evolve strategies to discriminate and feed on the least defensive hosts. [39]. Mobile population [23, 43-45] also introduces additional complications associated with administering health services to transient populations, inadequate medical follow-up and possible side effects. Although incomplete treatment can relieve fever, the underlying malarial infection persists as the migrant moves and potentially transmits the disease to other locations.

Temperature influences anopheline mosquito's feeding intervals, population density, longevity [25, 28, 46-47], and reproductive potential of the *Plasmodium* parasite [48]. Malaria transmission, however, is a complex interaction of many factors, including not only vector and parasite densities and behavior, but also land-use change [49], public health control measures [50-52], human migration [53-54], and drug resistance [55-58]. Difficulties in obtaining prompt treatment also enhance the probability of spread of disease. Woolhouse *et al.*[59] estimated that, on average, 20% of any host population contributes 80% of the net transmission potential

In general, there are three major factors influencing the transmission of malaria.

a) Natural environment factors such as temperature, altitude, rainfall and rivers

b) Man made environment factors such as deforestation, road construction, water control systems including dams, canals and irrigation systems, agricultural development, population movement and urbanization [60]

c) Socio-economic factors such as personal protection against mosquitoes and the quality of housing construction are important in explaining the distribution of malaria incidence [61].

2.6 Epidemics prediction.

Populations with little or no immunity are more vulnerable to malaria attack. Epidemics can occur among people of all age groups, which are at risk of death or severe disease. If the epidemics of *Plasmodium falciparum* are not controlled in a timely fashion, it can lead to have a devastating effect. As malaria epidemics occur in populations that are not normally exposed to the disease, or are exposed for only a short part of the year. Local health services are usually unprepared to predict, detect and control such epidemics in time, resulting in severe cases and high death rates. When control measures are taken, they are often too late and are implemented with minimal coordination and expertise, resulting in only a marginal benefit [62].

Combination of local epidemiological knowledge, socioeconomic and meteorological information can be used to predict the epidemics of malaria up to certain extent. Man-made epidemics can be predicted with some amount of precision and ease [62], examples in relation with irrigation projects, road constructions, and deforestation; compared to one arising from natural causes. World Health Organization (W.H.O.) is currently surveying and analyzing the natural causes of epidemics in seven African countries which tend to recur. The outcome of the analysis will form the basis of the prevention and control guidelines for World Health Organization (W.H.O.) in African Countries. One of the studies [63] showed that short-term predictions of *P. falciparum* cases using lagged weather and case incidence data performed well in identifying periods of increased

malaria cases. In the examined Ethiopian districts [63], weather-based predictors of malaria incidence are more useful in rural than in urban settings.

From the discussion in the previous sections (Section 2.4 – 2.5) of factors influencing spread of malaria and the life cycle of mosquito suggests that malaria cases should follow, at defined intervals, periods of increased temperature and increased rainfall. Moreover, because temperature accelerates several steps in the process of mosquito and parasite development, the time lag between the appearance of suitable weather conditions and the appearance of new malaria cases should shorten as temperature rises. At an average temperature of 20°C, the aquatic phase of the mosquito will be completed in about 28 days (five days for eggs to hatch and 23 days for the larva to develop into adult stage); and sporogony is completed in 28 days [64]. At this temperature, malaria cases should, therefore, appear 9–10 weeks following rainfall, assuming an average incubation period of about 10–16 days [64]. Similarly, in this situation, the number of malaria cases should be positively related to increases in temperature three to seven weeks beforehand during the aquatic and sporogony stages [64]. When the mean temperature is higher, the aquatic stage of mosquito and the sporogony cycle are completed in about 12 and 8 days respectively. In this relatively hot environment, malaria cases should appear 4–5 weeks following rainfall and the lag in the effect of temperature should also be shorter [64].

Comprehensive multi sectored epidemic warning systems that combine early detection, early warning and long-range forecasting are being developed by Roll Back Malaria (RBM) and its partners for supporting epidemic-prone countries [62]. Forecasting and early warning can strengthen local preparedness, and allow authorities and communities to use cost-effective and timely control options to prevent excessive deaths. It also helps to develop strategies for epidemic preparedness and emergency action.

2.7 Economic and social implication of malaria

According to economist Jeffrey Sachs [65] “The burden of malaria is enormous, there are 300 to 500 million cases every year; and between one to three million deaths, mostly of children, attributed to this disease [malaria]. Every 40 seconds a child dies of malaria,

resulting in a daily loss of more than 2000 young lives worldwide. These estimates render malaria the pre-eminent tropical parasitic disease and one of the top three killers among communicable diseases." Beyond mortality, malaria causes morbidity through fever, weakness, malnutrition, anemia, spleen diseases and vulnerability to other diseases. The health consequences of malaria vary in terms of severity, but the global impact of malaria on human health, productivity, and general well-being is profound. The joint mortality and morbidity impacts of malaria are estimated to be 45 million DALYs (disability adjusted life years) in 2000 or nearly 11% of all infectious diseases [66].

Malaria imposes substantive social and economic costs. It impedes economic development through several channels, including but certainly not limited to, quality of life, fertility, population growth, saving and investment, worker productivity, premature mortality and medical costs [65].

The various effects of malaria are outlined below:

2.7.1 Mortality

Estimating the number of deaths due to malaria is problematic [67-68]. It is perhaps not surprising that most studies do not attempt to capture any of the economic effects of death, focusing on the implications of morbidity alone. However, a wide range of immediate and long-term effects are thus excluded, ranging from funeral costs, to lost output of the deceased, subsequent changes in the organization of activities, and potentially the dissolution of the household or knock-on effects on the health of other household members [69].

2.7.2 Episodes of uncomplicated malaria

Estimates of the number of malaria episodes per year used to calculate direct and indirect morbidity costs are usually based on self-diagnosis or facility-based reports of febrile episodes, because uncomplicated malaria is typically treated on the basis of clinical symptoms alone [70-74]. Measuring costs associated with treating fever may therefore substantially overestimate the costs of malaria episodes.

2.7.3 Severe disease

Severe malaria has two major clinical syndromes: malaria with respiratory distress; and malaria with neurological disturbance, or cerebral malaria [75]. These occur primarily among children, but also affect adults in areas of low or unstable transmission. Although incidence of such severe disease is low, the cost implications of such episodes could be very high, and could have important implications for the individual household. Survivors of cerebral malaria may be left with neurological sequelae including weakness in the limbs, speech disorders, behavioral disorders, blindness, hearing impairment, cerebral palsy and epilepsy [67].

2.7.4 Anaemia

Malaria is an important cause of anaemia in many parts of Africa, most sub-Saharan [76]. The severe form is a life-threatening condition in young children and often warrants blood transfusion, which increases the risk of HIV infection [67]. In malaria-endemic areas, the incidence and age pattern of severe anaemia are strongly dependent on the intensity of *Plasmodium falciparum* transmission [77]. Malaria control trials have been associated with significant reductions in the prevalence of anaemia in children and pregnant women [52, 78]. There is good evidence on the association between iron deficiency anaemia (IDA) and poor performance in infant development scales, Intelligent Quotient (IQ) and learning tasks in pre-school children and educational achievement among school-age children [79-81]. Lozoff et al. [82] observed that IDA among infants predicted poorer performance in cognitive tests at a later developmental period. Iron supplementation has been associated with improvement in mental development scale scores in infants [83] and significant increases in school achievement scores [84]. However, it is not clear whether these findings for IDA apply equally to children with the type of anaemia [85] associated with malaria.

2.7.5 Malaria in pregnancy

Anaemia is also a harmful manifestation of malaria in pregnancy. Pregnant women are particularly vulnerable to malaria. Malaria infection during their first pregnancy,

experience an increased risk of maternal anaemia, abortion, stillbirth, and low birth weight due to both pre-maturity and intra-uterine growth retardation [86-89].

2.7.6 Interaction with other diseases

In addition to its direct role in morbidity and mortality, malaria is also thought to have a significant indirect effect in conjunction with other common diseases such as measles, respiratory infections, diarrhoeal disease and malnutrition, although the extent of the indirect impact is difficult to measure and not well understood. [90].

2.7.7 Intellectual development

Malaria significantly affects intellectual development through severe anaemia, epileptic seizures, and school absenteeism although the evidence is less. Variations in reasoning ability, cognitive skill, and years of schooling are considered to be important determinants of future variations in productivity and earnings of individuals [91-92], so the economic impact is likely to be significant.

2.7.8 Economic Cost

Economists have attempted to put an economic value on the burden of malaria by measuring the impacts on households and national economies [93**]**.

2.7.8.1 Household

Malaria imposes both direct and indirect costs at household level. Direct costs can be from a personal expenditure or a public expenditure. Personal expenditures include individual or family spending on insecticide treated mosquito nets (ITNs), doctors' fees, anti-malarial drugs, transport to health facilities, support for the patient and sometimes an accompanying family member during hospital stays. Public expenditures include spending by government on maintaining health facilities and health care infrastructure, publicly managed vector control, education and research. In some countries with a heavy malaria burden, the disease may account for as much as 40% of public health expenditure, 30-50% of inpatient admissions, and up to 50% of outpatient visits [62].

The indirect costs of malaria include lost productivity or income associated with illness or death. This might be expressed as the cost of lost workdays or absenteeism from formal employment and the value of unpaid work done in the home by both men and women. Indirect costs, which are typically harder to measure, include loss of work efficiency and time and work reallocation within the household. For children in particular, indirect costs also include nutritional deficiencies, cognitive and educational disabilities, and physical retardation. Pain and suffering are clearly substantial indirect costs but are perhaps most difficult to quantify and monetize. In general, long term effects such as child development and resistance are unknown [94]. In the case of death, the indirect cost includes the discounted future lifetime earnings of those who die.

2.7.8.2 National Economies

Malaria is estimated to cause a decline in economic growth in the range of 0.25% to 1.3% of per capita Gross National Product (GNP) growth in tropical countries, even after accounting for initial endowments, overall life expectancy and geographic location [65-66]. To the extent that slow economic growth limits funds for malaria control, there is a vicious cycle of poverty and malaria that diminishes economic opportunities for a large number of the world's inhabitants. Malaria affects the health and wealth of nations and individuals alike. In Africa, Malaria is a disease of poverty and a cause of poverty. For developing economies the gap in prosperity between countries with malaria and countries without malaria has become wider every single year [62]. Annual economic growth in countries with high malaria transmission has historically been lower than in countries without malaria. Economists believe that malaria is responsible for a 'growth penalty' of up to 1.3% per year in some African countries. When compounded over the years, this penalty leads to substantial differences in GDP between countries with and without Malaria and severely restrains the economic growth of the entire region [62].

2.8 Coping strategies

Strategies adopted by family members, friends and colleagues to minimize the effects of an illness on the welfare of all concerned are known as coping mechanism [69]. Sauerborn et al. [95] identified 11 different kinds of household coping behaviors in

response to illness episodes, seven for direct costs, and four for indirect costs of lost time. The most commonly used strategy for indirect cost was intra-household labor substitution in response to lost work time of household members. Most frequent coping methods used by households with direct costs are mobilizing cash reserves and savings, selling livestock, or receiving gifts from other households. Evidence of widespread use of such coping mechanisms in response to malaria episodes has been observed both within and outside Africa [96-99].

Strategies for coping with financial expenditure on treatment and prevention may have knock-on effects through depleted capital stock, lost savings and indebtedness. The sale of assets such as livestock potentially jeopardizes the household asset base, with households emerging more vulnerable and less able to cope with further crises [95]. A household without livestock and unable to rely on gifts may be forced to take out loans which could lead to serious debt and future impoverishment [69]. These knock-on effects ultimately affect supply or production through low saving and investment. Furthermore, this means that the causal relationship by which malaria affects the economy may not necessarily be through sick labor only, but also through lost capital and purchasing power.

The potential for labor substitution crucially affects the degree to which any loss of time is translated into a loss of output [100-101]. Unemployment and underemployment are common features of sub-Saharan economies, and farming is often undertaken communally, in households or extended families. In the event of temporary disability of a household member, the family workforce may provide a cushion for the period of absence of the disabled member, limiting the consequent loss of output. During some seasons, agricultural underemployment may be so prevalent that the time lost by sick individuals can be fully compensated for. Similarly in the industrial and service sectors, other members of the workforce may cover to some extent for sick colleagues. Even if market output is maintained, there may be costs associated with labor substitution, depending on the value of the activities from which the substituting labor is withdrawn [69].

The simple presence of malaria in a community or country also hampers individual and national prosperity due to its influence on social and economic decisions. The risk of contracting malaria in endemic areas can deter investment, both internal and external. It affects individual and household decision making in many ways that have a negative impact on economic productivity and growth. Some of the impacts are undeveloped tourist industry due to reluctance of travelers to visit malaria-endemic areas. Undeveloped markets due to trader's unwillingness to travel to and invest in malarious areas. Preference of individual farmers/households to plant subsistence crops rather than more labor intensive cash crops because of malaria's impact on labor during harvest season [102].

Private sector including the local and the international business operating in the malarious area can play an important role in supporting the malaria control measures. It will not only reduce levels of absenteeism and lost productivity, but also boosts labor, community and government relations. In the long term, increased productivity will encourage market expansion, boost household spending and change consumption patterns. By increasing the malaria control measures it can benefit many companies, especially those producing consumer goods or local service industries.

Some of the ways in which private companies can contribute vital resources and expertise to malaria control include providing capital for the current control programs, supporting research and development for new interventions and treatments of malaria, assisting in public education campaigns and creating market for insecticide treated bed nets and anti malarial drug using their marketing and business expertise [62].

2.9 Preventive measure to control malaria

Preventive measures can be divided into two major factors which include personal control and vector control. There is no reliable vaccine available against malaria at present. People traveling in the malarious areas should protect themselves by using anti-mosquito measures and by taking chemoprophylaxis to prevent malaria. Local people and public administration of endemic regions should take effective steps explained in this section to avoid epidemic of malaria.

2.9.1 Personal control

The best way to prevent the infection of malaria is to avoid the bites of *Anopheles* mosquitoes. *Anopheles* mosquitoes usually feed at night and hence Malaria is transmitted between dusk and dawn. When outdoors, one should wear clothing that covers the entire body such as long sleeves and long pants. For extra protection clothing can be treated with insecticide permethrin. Insect repellent can be used on the exposed skin, the most effective repellent contain 20% to 35% of DEET (N,N-diethylmethyltoluamide) [103]. Whenever inside the house, one should stay in well-screened areas as much as possible and spray insecticide in the living and sleeping areas.

2.9.1.1 Chemoprophylaxis

A preventive measure taken by tourists or locals in an area prone to Malaria epidemic is to use chemoprophylaxis drugs. One of the least appreciated aspects of chemoprophylaxis is the requirement for taking the drug before, during, and after exposure to malaria. Chemoprophylaxis should begin two weeks before travel to endemic areas to allow adequate blood levels to develop. This is true for all malaria prophylaxis drugs except for doxycycline, which should be initiated 1-2 days before exposure [103]. Prophylaxis must be continued for four weeks after leaving an endemic area to ensure that suppressive action is effective. The required four week time period is to ensure drug therapy exceeds the length of time needed for the incubation period in the liver.

The endemic region is classified into three regimens due to the following factors, drug resistance in specific locations and any allergic or other reactions to the anti malarial drug of choice to the person staying or traveling in that location. The three regimens are described below in detail.

1. Regimen A: Areas where chloroquine resistant P. falciparum has not been reported, once weekly use of chloroquine alone is recommended [103].
2. Regimen B: Areas where chloroquine resistant P. falciparum exists, mefloquine is recommended [103]. Mefloquine is usually well tolerated at prophylactic dosage, but should not be taken by individual with a history of seizures, severe psychiatric disorders, or those with cardiac conduction abnormalities.

3. Regimen C: Doxycycline is also recommended [103] for areas where chloroquine-resistant P. falciparum exists. It is the drug of choice for chemoprophylaxis in most parts of Southeast Asia. One of the most common side effects of doxycycline is adverse gastrointestinal symptoms, usually nausea or vomiting. This often leads to compliance problems. These side effects may be avoided by taking doxycycline with a meal. Other side effects include photosensitivity manifested by a severe sunburn reaction, and an increased frequency of monilial vaginitis. The sunburn reaction can be prevented by avoiding prolonged exposure to sunshine, or sunscreen use. Females taking doxycycline should be supplied with nystatin suppositories to treat possible yeast infections when they occur [103].

a. Terminal primaquine prophylaxis

Currently, primaquine is the only available drug for prevention of P. vivax and P. ovale relapse. As most endemic areas of the world have at least one of these species, terminal primaquine prophylaxis is recommended to eradicate hypnozoites (dormant form of disease) [104]

b. Chemoprophylaxis during pregnancy

Women who are pregnant should avoid travel to malarious areas. When travel must occur, chloroquine is safe to use in pregnancy. Proguanil has been used for several decades without adverse effects on the pregnancy or unborn fetus [105]. Mefloquine is not recommended for use during pregnancy by the Food and Drug Administration (FDA) but may be considered for use by females who are pregnant when exposure to chloroquine-resistant *P. falciparum* is unavoidable [106]. Doxycycline is contraindicated for malaria prophylaxis during pregnancy. Fetal effects include discoloration and dysplasia of teeth and inhibition of bone growth [104]. Tetracyclines are only indicated to treat life-threatening infections due to multi-drug resistant *P. falciparum* [104]. Primaquine should not be used during pregnancy, as it can be passed transplacentally to a G-6-PD deficient fetus, causing in utero hemolytic anemia. Chloroquine can be given once weekly until delivery, at which time primaquine can be given [107].

c. Pediatric chemoprophylaxis

Children should avoid travel to areas with chloroquine-resistant *P. falciparum*, unless a highly effective drug such as doxycycline [104] or mefloquine [108] can be administered.

2.9.1.2 Insecticides treated bed nets

Pyrethroid treatment for example Deltamethrin treated bed nets has shown a significant reduction in the transmission of malaria in the Kou valley, Burkina Faso [109] as well as reduction in child and infant mortality in some malaria endemic African countries [65, 110]. This reduction arose primarily because of a marked decrease in the sporozoitic index and a lower density of vectors. Thus, use of pyrethroid-impregnated bed nets by all members of the community appears to be a major tool in preventing transmission of malaria [109].

2.9.2 Vector Control

The goal of malaria vector control is to eliminate the anopheline population or reduce its population below the number required to sustain disease transmission. There are three main methods used to reduce mosquito populations:

2.9.2.1 Biological control

Several methods of biological control currently exist. One involves the introduction of Bacillus thuringiensis israelensis (BTI) [111], a mosquito bacterial pathogen, into a targeted mosquito population. Another requires the introduction of mosquito larvae-eating fish, *Gambusia spp*., [112] into breeding areas.

2.9.2.2 Elimination of breeding sites

Breeding sites can be made unsuitable for mosquito larvae through a variety of methods. These include increasing water flow or ditching, removing protective aquatic vegetation and regularly clean watering troughs. Other methods for elimination of breeding sites are frequently emptying any containers that accumulate water for more than 3 days such as discarded tires, potted plant saucers, pet bowls, wading pools [113-114]

2.9.2.3 Insecticides

Insecticides can be used in the following ways explained in detail below:

a. Chemical control of larvae.

Treatment of standing water with larvicides to kill larvae before they develop into mosquitoes is more effective than controlling adult mosquitoes. Solutions, emulsifiable concentrates, and suspensions are effective chemicals for the control of larvae with ground operated or aerial dispersal equipment. [115]

b. Chemical control of adult mosquitoes

Chemical control of adult mosquito is carried out in outdoors as well as in indoors, which is explained in detail below:

i. Outdoor control

The treatment of choice to control adult mosquitoes is ultra-low-volume spraying (ULV) [116]. ULV spraying provides adequate protection for limited periods of time. To provide continuous protection in large areas with many breeding sites, ULV insecticides must be applied on a repetitive schedule, typically twice a day or daily or every other day. As ULV insecticides are most effective against flying insects, spraying operations can be planned for dusk, after dark, and early morning (near sunrise). When properly applied, ULV treatments do not leave dangerous or unsightly deposits on trees, bushes, or terrain.

ii. Indoor Residual Spraying.

Indoor control of mosquitoes relies on aerosol sprays that have only a short-term effect [117], which must be re-applied whenever new mosquitoes enter the space. Another method of indoor control is the application of residual sprays to surfaces where mosquitoes rest, usually a permethrin or a long lasting spray recommended by a medical entomologist [118]. For porous surfaces such as brick or unfinished wood, suspension made with a water-mixable powder or a microencapsulated formulation can be used [119].

2.10 Global initiative to prevent the disease of malaria

There are many global projects in progress taking place to eradicate the spread of the Malaria; some of the selected initiatives are mentioned as follows:

2.10.1 P.falciparum Genome Sequencing Consortium

The *P.falciparum* Genome Sequencing Consortium [120] is collaboration among 3 sequencing centers: The Sanger Centre (U.K.), The Institute for Genomic Research/Naval Medical Research Institute (U.S.A.), and Stanford University (U.S.A.). It works on the sequencing of the *Plasmodium* genome, which can circumvent many of the difficulties related to malaria eradication and rapidly increases the knowledge about these parasites. This knowledge can be used to identify new targets for vaccine and drug development. *P. falciparam* and *Anopheles* mosquito's genome has recently been completed

2.10.2 Mapping Malaria Risk in Africa

The MARA/ARMA [121] collaboration was initiated to provide an Atlas of malaria for Africa, containing relevant information for rational and targeted implementation of malaria control. The objective of the MARA/ARMA is to map malaria risk in Africa through collection of published and unpublished malaria data and spatial modeling of malaria distribution, seasonality and endemicity; to disseminate relevant information to national and international decision makers and other end users, in a range of useful formats. And to develop capacity in malaria / health GIS.

2.10.3 Malaria Vaccine Initiative (MVI)

The MVI [122] was created through a grant of the Bill and Melinda Gates Foundation to Program for Appropriate Technology in Health (PATH). The objective of the MVI is to significantly accelerate the clinical development of promising malaria vaccine candidates.

The MVI is expected to lead field trials of one or more vaccine candidates; coordinate its efforts with malaria vaccine programs at various organizations and agencies; and identify gaps in current research efforts and apply resources to advance promising malaria vaccine candidates.

2.10.4 Asian Collaborative Training Network for Malaria (ACTMalaria)

The ACTMalaria [123] is an inter-country initiative between Bangladesh, Cambodia, China (Yunnan Province), Indonesia, Lao PDR, Malaysia, Myanmar, Thailand, and Vietnam. Its objective is to collect, develop, and disseminate training materials and to implement practical training courses to meet the needs of malaria control programs in Southeast Asia and the Mekong valley. It also aims to improve communication between these countries on malaria control problems affecting their common borders.

2.10.5 Medicines for Malaria Venture (MMV)

World Health Organizations (W.H.O.) new MMV [124] is a joint public-private sector initiative which aims to discover, develop and deliver new anti-malarial drugs in poor countries through effective public-private partnerships. There vision is to build a world in which affordable drugs will help eliminate the devastating effects of malaria and help protect the billions of people, especially children and pregnant women, at risk of this terrible disease.

2.10.6 Regional Malaria Control Programme in Cambodia, Laos and Vietnam

Regional Malaria Control Programme in Cambodia, Laos and Vietnam [125] is a joint effort with European Commission (EC), whose aim is to provide training to key health personnel, Research consultancy and Publication of Mekong Malaria Forum. The EC Programme assists government in decreasing morbidity and mortality due to malaria by

reinforcing capacities of national health systems through acquisition of knowledge and development of managerial skills of malaria control workers.

2.10.7 Roll Back Malaria (RBM) Partnership

The RBM [126] initiative was announced by World Health Organization (W.H.O.) in May 1998. It is a global strategy to improve health systems with the goal of a 50% reduction in malaria deaths by 2010. Following measures will be taken to achieve this goal: (a) increasing speedy access for people to effective treatment and means of protection from mosquito bites. (b) Enabling national authorities and non-governmental organizations to combat malaria intensifying efforts. (c) Developing new products for the prevention and treatment of malaria.

2.10.8 African Malaria Vaccine Testing Network (AMVTN)

The AMVTN [127] is a non-profit network established in 1995 in Arusha, Tanzania. Its objective is to provide a forum for scientists and policy makers involved in the planning, coordination, and execution of malaria vaccination trials in Africa. The expanded role include among others; creation of global awareness of the African malaria burden, advancement of essential human capacity for research and development of malaria intervention in Africa.

2.10.9 Multilateral Initiative on Malaria (MIM)

The MIM [128] is an alliance of organizations & individuals concerned with malaria. It aims to maximize the impact of scientific research against malaria in Africa, by facilitating global collaboration and coordination.

2.10.10 Malaria Research and Reference Reagent Resource Center (MR4)

The MR4 [129] was established to provide a central source of quality controlled malaria-related reagents and information to the international malaria research community. Materials available to qualified, registered users include parasites, mosquito vectors, antibodies, antigens, gene libraries, molecular probes and constructs.

Chapter 3

Models of Vector-Borne Diseases

Models of vector-borne diseases fall into two primary categories [130]:

1) Epidemiological models that focus on the reproductive rate of the disease, it is a mean number of secondary cases a typical single infected case will cause in a population with no immunity to the disease in the absence of interventions to control the infection.
2) Geographical models of vector distribution that match environmental characteristics with vector populations and/or disease outbreaks.

Both the models are important for understanding the spread of vector-borne diseases. The evolution and integration of the two traditions are critical in predicting changes in the incidence of vector-borne diseases due to climate change.

Epidemiological models have been developed to describe and predict various aspects of the life history of vector-borne diseases. Rogers [131] was the first to incorporate critical components of a parasite's intricate life cycle into a mathematical model and used it to predict the incidence of malaria within human populations. He provided the mathematical basis for the concepts of reproductive rate and the thresholds for transmission of disease but lacked the ability to adjust the variation due to seasonality and immunity. After decades of work Rogers [132] came with another model that incorporated the incubation and immune periods in the two host species and the variable efficiency of transmission of different pathogen species from the vertebrate to the vectors and vice versa.

Haile's study [133] examined the impact of climate change on vector-borne disease transmission in the United States. He reviewed several models that have been used to develop an understanding of vector population dynamics and disease transmission. Haile developed a model considering key effects of weather variables, which can be used to predict the transmission of malaria between the vector and human population. Rogers and Packer [134] also provided a good overview of vector-borne diseases, which includes a discussion of both epidemiological and geographic distribution models. They highlighted some of the complexities that arise in trying to predict changes in the reproductive rate of vector-borne diseases when introduced into new areas. They noted that the information available on the geographic distribution models has evolved from crude maps to the sophisticated use of data from weather stations and satellites to determine the key combination of variables needed to predict vector distribution.

Ecologists have considered the cycle of seasons in mathematical models of the population dynamics of infectious diseases. Models of populations with seasonally forced, dynamic interactions (births, deaths, aggregation, or disease transmission) reveal an array of possible responses, from simple yearly cycles, through cycles that repeat with longer periods, to irregular chaotic fluctuations. Some models also predict intermittent switching between different dynamic infectious disease behaviors. However, typical models consider only simple seasonal forcing functions such as mathematical functions that are periodic in time and therefore describe in a generic way the seasonal variation in the transmission rate or some other seasonal parameter; e.g. sine wave. There are some important exceptions to periodic mathematical functions; some models do incorporate more complicated seasonal forcing functions that describe the actual processes underlying the seasonal drivers of transmission. Examples are; models of childhood diseases that describe the regular stopping and starting of school terms [135-137] and recent malaria models that include the seasonal dynamics of mosquito births and pathogen incubation as functions of temperature and rainfall [138].

The present and future impact of climate change in infectious disease dynamics is a pressing but controversial subject [139-145]. Malaria is a major public health burden around the tropics [65, 144] with the potential to significantly increase in response to

climate change due to the role of temperature and rainfall in the population dynamics of its mosquito vector [143,146]. *Plasmodium falciparum* and *Plasmodium vivax* are the most important malaria species for humans, and their range is limited at high altitudes by low temperatures [147]; global warming could thus drive the geographical spread of the disease and produce an increase in incidence at higher-altitude sites.

Temperature is known to influence the mosquito life cycle and in particular the development rate of larvae and adult survival [148-149]. The mosquito model [150] is driven by both the original temperature time series and its de-trended counterpart for each site. The relative difference (RD) in the output of the model for the two temperature regimes shows that the mosquito dynamics significantly amplify the temperature increase. Parametric models closer in formulation to the approach of Hay *et al.* [151] also demonstrate significant (linear) trends.

3.1 Motivation for a new model

Traditional epidemiological research has focused on transmission rate based differential equation models on completely mixing populations which allows all the people to interact with each other. An attractive feature of this modeling approach is that, it allows one to obtain analytical expressions for a number of interesting parameters such as the numbers of sick, infected and recovered individuals in a population. But such a modeling approach does not capture the complexity of individual human interactions that serves as a mechanism for disease transmission. In addition, typically the number of different sub population types considered is small for analytical tractability. Parameters such as mixing rate and reproductive number is either unknown or hard to observe.

Other epidemiological models cannot easily capture the complexity of interactions between the host, the vector and their common environment. At the same time, specific modeling approaches makes it hard to take into account the effect of demographics such as age, resistance to disease and others. There are several parameters which are difficult to implement in the current mathematical framework such as relationship between transmission intensity and health outcomes, environment management of mosquito

resources, spread of malaria in rural and urban environments and relationship between age, health state, etc with the effect of mosquito inoculations. Oviposition behavior of mosquitoes has also been neglected.

A good model would incorporate the features of epidemiological as well as geographical models. Our cellular automaton based malaria model is more inclined towards the geographic models but can be extended to include the features of epidemiological model by integrating with EpiSims/TRANSIMS. EpiSims is an epidemiological modeling tool for studying the spread of infectious diseases which combines realistic estimates of population mobility, based on census and land-use data, with parameterized models for simulating the progress of a disease within an individual and of transmission between vector and individuals [152]. It helps the decision makers with information such as consequences of a biological attack or natural outbreak, demand for health services and feasibility and effectiveness of response options.

Chapter 4

Cellular Automata

This chapter explains the basics of Cellular Automata that forms the basis of our mathematical malaria model.

4.1. Introduction to Cellular Automata

Cellular automata are dynamical systems which are discrete in space and time. They operate on a uniform, regular lattice and are characterized by local interaction. They are generally attributed to Ulam [153] and von Neumann [154], who introduced the concept in the late forties to provide a realistic model for the behavior of complex systems. They used discrete models to study computability theory, mathematics, and biological systems [155-156]

The type of grid used to compute the state of the cell is one of the important properties of cellular automaton. The simplest grid is a one-dimensional line. In two dimensions square, triangular and hexagonal grids can be considered. The grid can be in any finite number of dimensions [157]. A cellular automaton consists of an infinite or finite, regular grid of cells, each in one of a finite number of states. The state of a cell at time t is dependent upon the state of its neighborhood cells at time $t - 1$. In our context the grid can be thought of as geographical region which is divided into small regions (cells). The two common type of neighborhood used for the computation of cellular automaton on the square grid are the Moore neighborhood [158] and the von Newmann neighborhood [159]. Every cell has a set of rules for updating their state based on the values in this neighborhood. Every time the rules are applied to the whole grid a new state generation is produced.

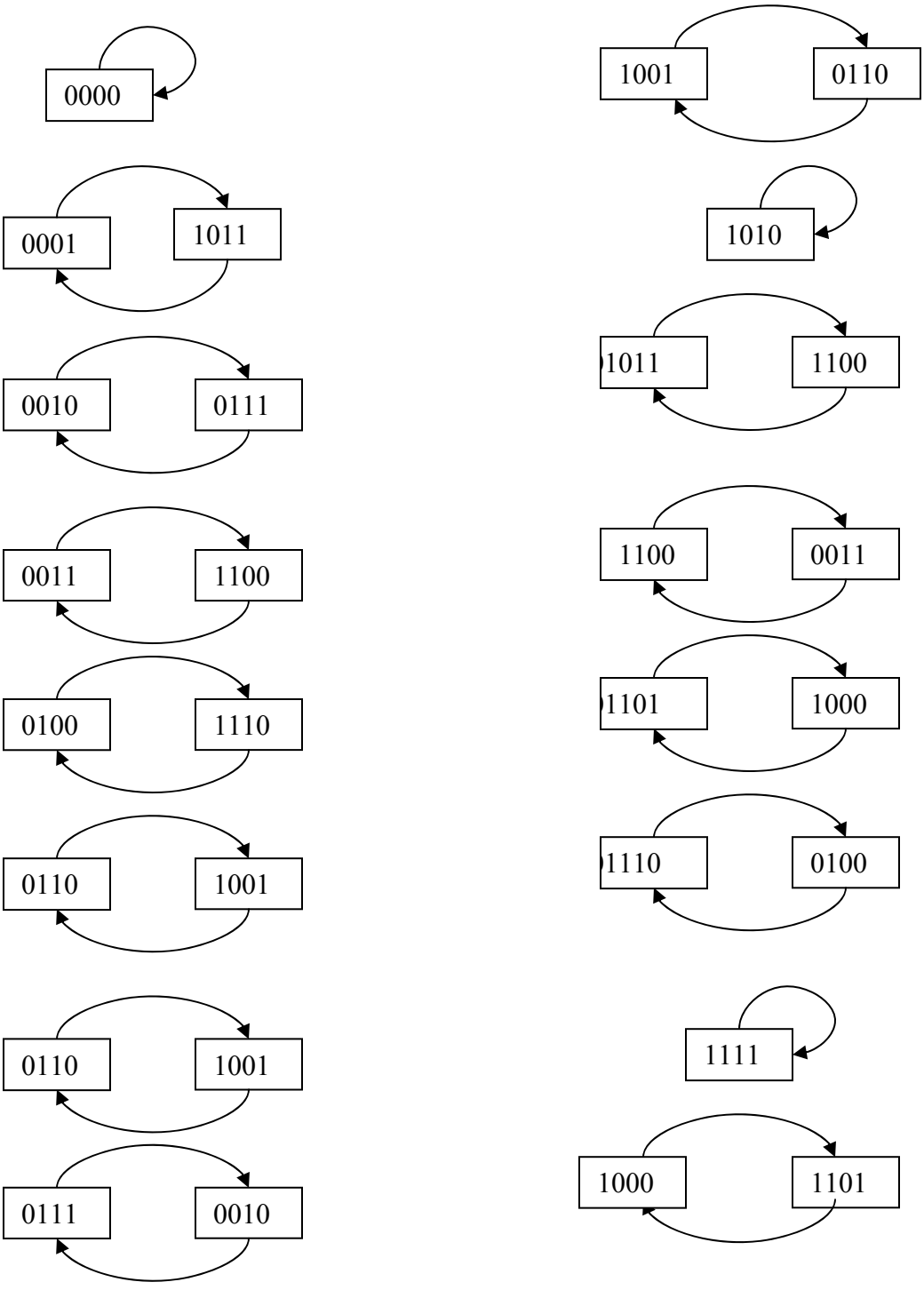


Figure 4.1 Phase space

The simplest type of cellular automaton is a binary, nearest-neighbor, one-dimensional automaton. Such automata are called elementary cellular automata [156, 158]. The Phase space shown in Figure 4.1 gives an example of the dynamics of an elementary cellular automaton given by the function $f : \{0,1\}^3 \rightarrow \{0,1\}$ where

$$f(X,Y,Z) = (X + Y + Z) MOD 2$$

The function of this example is the parity function. In the example all points are either fixed points or periodic points of period 2. A slightly more complicated class of cellular automata is the radius *r* one-dimensional cellular automata. In two dimensions, the best-known cellular automaton is Conway's game of life [160], discovered by J. H. Conway in 1970 which is explained later in this chapter.

4.2. Example: The Game of Life Cellular Automaton

The "Game of Life" is a binary totalistic cellular automaton with a Moore neighborhood. It is played on a square grid of cells and can be extended infinitely in every direction. A cell can be assumed to be live or dead. A live cell is shown by putting a marker on its square ($X_{i,j}$ = 1) and a dead cell is shown by leaving the square empty ($X_{i,j}$ = 0). Each cell in the grid has a neighborhood consisting of the eight cells in every direction including diagonals.

To apply the rules of game of life, we count the number of live neighbors for each cell. What happens next depends on this number according to the rules mentioned below.

- Rule 1: A dead cell with exactly three live neighbors becomes a live cell (birth).

  if $\sum_{i',j' \in N(i,j)} X(i',j') = 3$ and $X_{i,j} = 0$

  then $X_{i,j} = 0 \rightarrow X_{i,j} = 1$

  otherwise $X_{i,j} \rightarrow 0$.

- Rule 2: A live cell with two or three live neighbors stays alive (survival).

  If $\sum_{i',j' \in N(i,j)} X(i', j') = 2$ or 3 and $X_{i,j} = 1$

  then $Xi,j \rightarrow 1$

- Rule 3: A cell dies or remains dead (overcrowding (more then 3 neighbors alive) or loneliness (only one neighbor alive))

  If $\sum_{i',j' \in N(i,j)} X(i', j') < 2$ or > 3

  If $X_{i,j} = 1$

  then $X_{i,j} = 1 \rightarrow X_{i,j} = 0$

  else if $X_{i,j} = 0$

  then $X_{i,j} \rightarrow 0$

$t = 0$ $t = 1$ $t = 2$

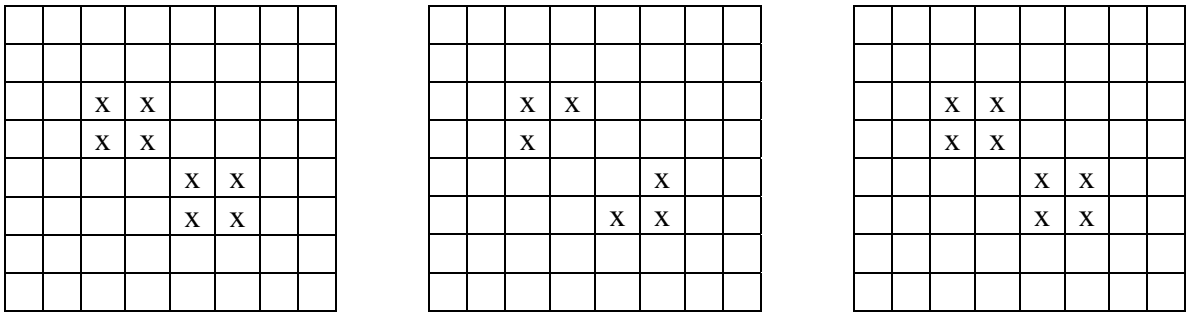


Figure 4.2 Example of "Game of Life"

In the above example referred in Figure 4.2 there are 8 cells alive at time $t = 0$. At time $t = 1$, two cells dies because of overcrowding (Rule 3) and the remaining cells stays alive by the virtue of Rule 2. At time $t = 2$ the dead cells becomes alive as they exactly had 3 live neighboring cells to make it alive (Rule 1).

Chapter 5

EpiSims/TRANSIMS

5.1 Introduction to EpiSims

EpiSims [161-166] models the spread of disease in urban areas, allowing for the assessment of prevention, intervention, and response strategies by simulating the daily movements of synthetic individuals within an urban region. EpiSims allows the user to specify the effects in detail of a pathogen on a specific person, and to assign different effects to various people based on demographic characteristics. In conjunction with population mobility models it can represent behavioral reactions to an outbreak, including official interventions.

EpiSims provides detailed information about every simulated person and the events happens to each person during the simulation including infection, incapacitation, and treatment along with a time stamp and current location. EpiSims can also produce a representation of the social network, i.e. the person-to-person contact patterns within the entire population and a description of the outbreak path over the social network [167]. It allows for efficient measuring of the structural properties of very large social networks. EpiSims uses TRANSIMS [168] as a mobility generator for a traffic dynamic model. TRANSIMS is an instance of a mobility generator inside the Simfrastructure framework [170].

5.2 What is TRANSIMS?

TRANSIMS is a (TRansportation ANalysis SIMulation System) simulation model developed at Los Alamos Laboratory [169]. It is capable of simulating every move of a person and vehicle in the large urban transportation network second by second.

Simfrastructure, which is the overlaying framework for TRANSIMS can represent and analyze interdependent urban infrastructures including public health, commodity market, transportation, energy, telecommunication etc. It has the unique ability to represent the entire urban population at the level of individuals including their activities, movements, locations and their interaction with others and physical infrastructure. A connected collection of such urban infrastructure simulations allow analysis of urban infrastructure interdependencies through integrated functional data flow architectures.

Figure 5.1 shows four interacting modules [171] of TRANSIMS Architecture that are used to generate the activities and the movements of the individual. They are the Population Generator, the Activity Generator, the Transportation Router and the Transportation Micro-simulator. These modules are listed in order of increasing fidelity and decreasing time scales. The Population Generator models interactions on time scales of months to years; the Activity Generator, weeks to days; the Transportation Router, hours to minutes, and the Transportation Micro-simulator, seconds. TRANSIMS uses the synthetic population and their associated activities generated within the Simfrastructure framework using service architecture.

Each module of TRANSIMS can itself be represented as a Sequential Dynamical Systems [172-174] and by composing these modules the entire system's specification is obtained. Using the feedback mechanism the complicated non-linearities and inter-dependencies are resolved. The Population synthesizer generates the synthetic population of households and individuals that are distributed demographically and geographically within a real large urban area using land-use data, demographic projections and census data.

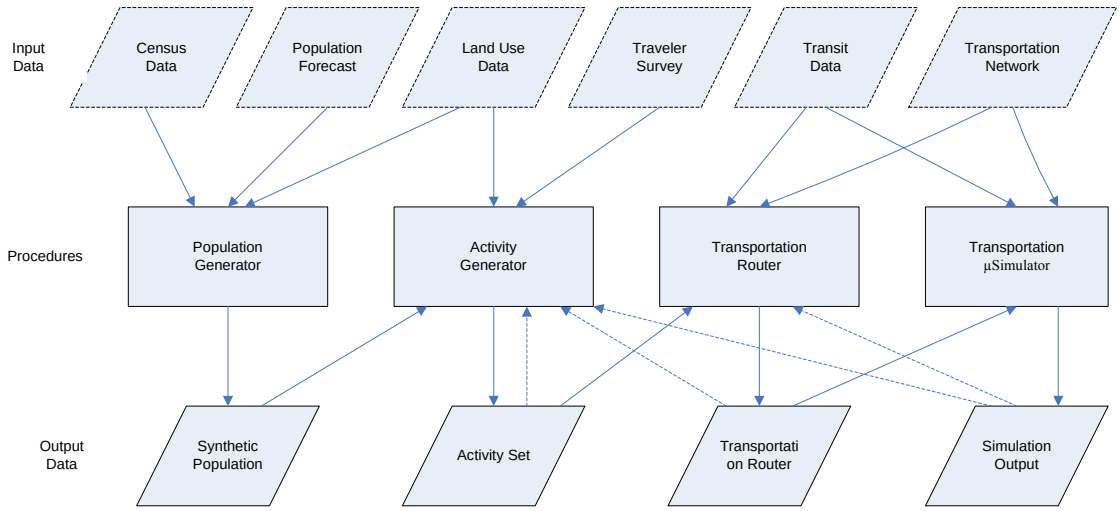


Figure 5.1 TRANSIMS Architecture.
(Figure is created based on the description in [171])

In a typical census data a joint demographic distribution can be reconstructed from the marginal distributions using an iterative proportional fitting (IPF) technique [175]. Each individual in an actual population is represented by one agent in the synthetic population, and these agents live at locations where persons in the real population with similar demographics would most likely live [176]. The synthetic households are described by all the data in the US Census Public Use Micro Data Samples (PUMS). This data includes: ages of the individuals, worker status of the individuals, and the household incomes. Information on the statistical methodology for generating this population may be found in [176].

Traveler surveys contain information on the itinerary and activity schedules of a number of households. Each list covers the activities of an individual over an entire day. These activities include activity type such as in-home, work, school, shopping, etc., start time, stop time, travel time to each activity, and travel mode(s). In addition to the household activity patterns, the data in these surveys include household demographics such as household size, household income and the number of household workers. By selecting one of the activity patterns from a survey and assigning it to the people in the synthetic household the Activity Generator builds an activity list for each household individual using statistical techniques. This is accomplished by matching the household's demographics with those from household travel survey and drawing a survey activity list

at random from all those with similar demographic characteristics. A statistical model determines which demographics are used in the matching process. In most cases, these variables include the household size, the number of workers in the household, and the ages of the children in the household, if any.

The activity locations are geographically spread around the urban area and number in tens to hundred thousands depending on the desired fidelity of the resulting model. A TRANSIMS model will require two activity locations for every block in the urban area. For each of these activity locations, the Activity Generator has land-use data as an input and the Activity Generator selects a likely location for each activity in a person's list using a gravity model [177] for each individual in the population. The Router determines the path the traveler takes across the transportation network to move from one activity location to another using the desired transportation mode. It also finds each traveler's fastest or cheapest cost route to each activity using as input the travel times on each link of the multi-modal transportation network. The micro-simulation is an agent based model that simulates the movement of vehicles along the paths given by the router using simple movement rules [178]. Each traveler's trip plan is executed second by second, simulating the concomitant movement of individuals throughout the transportation network, including their use of vehicles such as cars or buses. The stochastic cellular automata (particle-hopping) model [179-180] of individual vehicle interactions produces traffic dynamics calibration and validation against real world data [168]. Figure 5.2 explains a two way traffic model using cellular automata technique. The movement of each vehicle is dynamically modified according to its own speed, the speed of the neighboring vehicle and its distance from the neighboring vehicle in order to overtake. It also takes into consideration of accidents and construction work in the way.

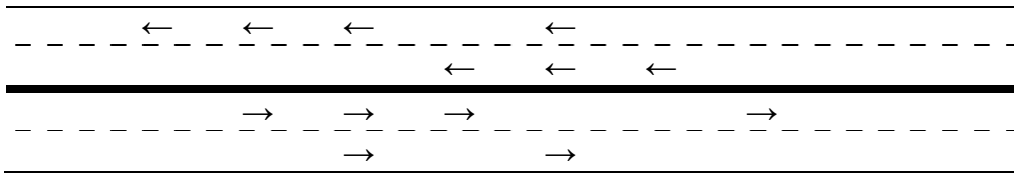


Figure 5.2 Two way traffic model using cellular automata

It will be very difficult for the low fidelity macro statistical models from the activity generator to produce a set of activities and locations that could be executed by the micro-simulation without some adjustment in their times or locations. The TRANSIMS framework feeds information back from a higher fidelity procedure to one of lower fidelity to produce a realistic, self- consistent set of activities, locations, and plans for everyone in the urban area. The main feedback pathways are shown as the dashed arrows in Figure 5.1; the feedback loop can be viewed as an algorithm for solving a large n-way game wherein travelers choose best paths for themselves in the context of all other travelers' choices until no better path can be found. The feedback is achieved using work-flows that facilitate the interactions between the processes with Simfrastructure and TRANSIMS. Information from a converged micro-simulation may be fed back to the activity generator to update the activity times, locations and/or transportation modes of those travelers who are unable to meet their itinerary.

A new user can easily substitute new routing method or a new way of assigning activity locations or a new driving logic; these changes will result in a new model of the transport system that will then need to be analyzed for producing realistic traffic, land use, activity patterns, etc.

5.3 Analyzing epidemics using EpiSims

EpiSims [181] is an epidemiological modeling tool for studying the spread of infectious diseases. EpiSims and its successor called SimDemics in conjunction with Simfrastructure simulate the spread of infectious disease in urban areas. It details the demographic and geographic distributions of disease and provides decision makers with information about (1) the consequences of a biological attack or natural outbreak, (2) the resulting demand for health services, and (3) the feasibility and effectiveness of response options. The system provides estimates of how disease will spread through a population depending on how it is introduced, how vulnerable people are, what responses are applied, and when responses are implemented. It takes into account the traffic model of a city to understand the social network of the people having individual schedule using a mathematical model TRANSIMS which produces estimates of social networks based on

the assumption that the transportation infrastructure constrains people's choices about where and when to perform activities [168]. It then estimates positions and activities of all travelers on a second-by-second basis.

The modeling environment associates a state of health with each individual being simulated. An individual's demographics determine his/her response to exposure and infection. For example, anyone over the age of 32 is assumed to have been vaccinated for smallpox. Exposure occurs in either of two ways: through contact with an infectious person or by visiting a contaminated location. The simulation user can introduce contamination at a location as an exogenous event in the simulation. Whether a person is infectious depends on when that person was exposed and its individual response to infection. By varying a few parameters, users can model many different diseases. A simulated person's state of health may affect his or her actions. They may seek treatment at a nearby hospital or clinic, or they may stay home instead of pursuing certain activities. In addition, the user may specify actions that affect simulated people, such as mass or targeted vaccination / treatment / prophylaxis and isolation. Targeted responses are automated within the simulations: people are chosen at a user-specified rate from a list of symptomatic people; their contacts are found by following their schedule; and the contacts are then treated and/or isolated.

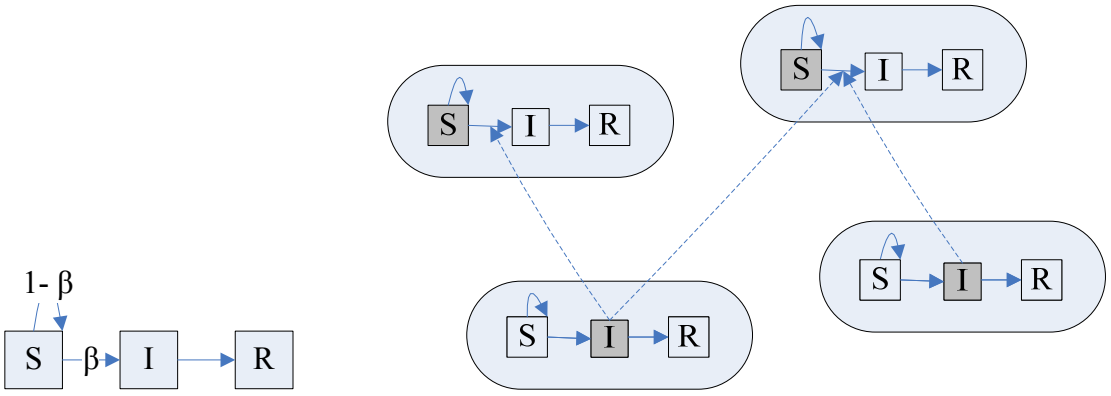
EpiSims uses a time-dependent bipartite labeled graph, which creates an individual graph for each time interval in the model and is capable of generating dynamic contact graphs at one-minute intervals, or as many as 1,440 graphs per day [182]. Consider an individual represented as vertex in the shape of a circle and a location (activity location) as another vertex in the shape of square. When an individual visits a location an edge is drawn between them, all the graphs are formed using this mechanism. Extreme detail was used in designing the EpiSims model, as it combines realistic estimates of population mobility, based on census and land-use data, with parameterized models for simulating the progress of a disease within a host and of transmission between hosts [152]. It comes up with accurate information for the creation of "synthetic" households that are assigned to the appropriate locations within a chosen U.S. locale by using statistical fitting technique

along with the census data. Many demographics available from census information, such as age, gender, etc., remain tied to the individuals in this simulated population and activities were assigned to each member of the household, such as work, home, school, and so on. Along with activity assignment is the assignment of location, arrival, and departure times. In this way, not only is the activity location information captured and taken into account, but also the information regarding transportation choices to and from the activity location is retrieved. The transportation information helps to estimates the positions and activities of all the travelers on a second-by-second basis. Activities taking place at a large enough location. For example a large office building or a university, end up requiring their own sub-location models, which EpiSims takes into account [182].

One of the many benefits of EpiSims is its amazing levels of details. Through its various parameters for health interactions, EpiSims designers established the ability to predict altered patterns of interaction that occur during an outbreak, including those of seeking medical treatment, obtaining Over the Counter (OTC) medications, confining themselves at home, or fleeing a geographic location. One of the downsides to this complexity, however, is the difficulty in generating data that can be worked with when using the model in its entirety. In the network configuration of this model, both people and locations represented as nodes and edges between them indicating the presence of a person at a particular location.

The mathematical model for EpiSims can be described as a coupled probabilistic timed finite state machine (PTFSM) Architecture [176]. Each individual is associated with a timed probabilistic finite state machine, the state transitions are probabilistic and the transitions may be timed i.e. they may occur at a specified time after the previous transition or there may be a fixed probability of transition for each discrete time interval. The social contact network derives the coupling between automata to other automata. Each person is associated with a probabilistic timed finite state machine (PTFSM) that represents the host's reaction to exposure to a pathogen, the within-host "disease model". In principle, each host can have a different PTFSM. More commonly, subsets of people determined by demographics such as age are assigned a single parameterized PTFSM and

individuals are assigned values for the parameters at random from an appropriate distribution.



(a) (b)

Figure 5.3(a) A finite state machine representation of the within host disease model. 5.3(b) Coupled Probabilistic Timed Transition System
(Figure is created based on the description in [183])

Figure 5.3 (a) shows an identical non-parametric PTFMS for each person. Within host disease models for those individuals, who are not immune by definition have transition out of the "susceptible" state in common. Figure 5.3 (b) shows the probability associated with this transition, affected by interaction with other people. The coupled probabilistic timed finite state machine is generated by coupling individual PTFSMs for each individual in a manner dictated by the social network. The PTFSM for each individual is restricted to three states analogous to the simplest coupled-rate-equation models of epidemiology for simplicity. The states represent Susceptible, Infected, and Recovered (or Removed) people, and are labeled S, I, and R, respectively. Infected people are also infectious. A time stepped model was chosen in which the duration of infection is constant across people and sets the time scale. In other words, after residing in state I for one time step, the person makes a transition to state R. Infected people are presumed also to be infectious. Each infectious person modifies the transition probability from S to I of every neighbor according to the duration of contact between them. The effect on transmission probability might also depend on other attributes of the people involved, such as age, contact, and activity type.

Chapter 6

Cellular Automaton based distributed model for malaria

Most of the mathematical models used in Malaria epidemic for representing the fraction of people infected with Malaria and the fraction of infected female mosquitoes used ordinary differential equations (ODE). However, they have several shortcomings as discussed in Chapter 3. Our model is based on the cellular automata framework, which makes it possible to take into account the geographic variations, modeling of individuals and integration with the EpiSims/TRANSIMS framework. Different features incorporated in our model are listed below:

1. Distributed grid model
   a. Cell environment state
   b. Cell vector state
2. Mosquito grid model
3. Diffusion/Vector mobility
4. Climate effects: Wind
5. Host mobility
6. Vector/Host interaction

6.1 Distributed grid model

Our model is constructed by superimposing a grid layer on the geographic region, whose minimum/maximum latitude and longitude values are known. The grid layer divides the geographic region into $m \times n$ number of cells depending on the size of the region and the

scale of the grid layer. Figure 6.1 shows a grid modeled geographical region. Unlike ODE models our model is a distributed model with cell specific information. Each cell in the grid model has been assigned properties for (a) environment and (b) vector (mosquito).

Image Courtesy : Local.live.com

Figure 6.1 Grid layout of small geographic region

6.1.1 Cell environmental state

The grid model of the geographic region assigns a mosquito density level to each cell depending on the classification of the land and the temperature of the region. Land is classified according to its characteristics such as farmland, pasture, swamp, forest, streams, road, shrubs, housing, industry and other man made structure, its usage and the possibility of the region being a breeding site. According to the study [184-185] various breeding sites such as slopes on riverbeds, riverbeds, borders of swamps, stagnant drains, and rivers have high density of mosquitoes. As discussed earlier in Chapter 2, climatic factors such as wind and temperature also play an important role in determining the density level. The survival rate of mosquitoes is very low below temperatures of 18 °C

and above 40°C and varies between these temperatures depending on the humidity of the region [33, 85].

6.1.2 Cell vector state

The density of mosquitos population in each cell is divided into three major classes depending on the physiological state and gender of the mosquito. A male mosquito does not play any role in the transmission of malaria; it stays in the uninfected health state throughout its life cycle. A female *Anopheles* mosquito changes its physiological state from uninfected to infected depending on its interaction with infected human host. As known, malaria is spread in the human populations via mosquitoes and not by direct contact between individuals. Similarly, the parasite of malaria is transferred from one mosquito to the other only through the medium of host that is through horizontal transmission instead of progeny that is vertical transmission [186].

6.2 Mosquito growth model

Mosquitoes in each geographic region cell have been assigned a reproduction and survival rate depending on the land type and temperature of that region. The reproduction rate can be modified to consider the effect of change in land type such as formation of water patches due to rain or change in temperature of the region. Also the survival rate can be changed for incorporating interventions such as use of insecticides/pesticides. Any change in the environmental factors indirectly affects the survival and reproduction rate of the mosquito. In equation (1) the density of vector population for each cell is calculated at time $t + 1$ considering the reproduction rate and the survival rate at time t with temperature T and land type L as

$$C_x(i, j, t+1) = C_x(i, j, t) \bullet r(i, j, T, L) + C_x(i, j, t) \bullet s(i, j, T, L) \quad \ldots (1)$$

where

$C_x(i, j, t)$ is the count of mosquitoes in the geographic region cell (i,j) at time t, $r(i, j, T, L)$ is the reproduction rate in the geographic region cell (i, j) depending on the

land type and temperature of the region and $s(i, j, T, L)$ is the survival rate in the geographic region cell (i, j) depending on the land type and temperature of the region.

Here $x \in \{f_i, f_u, m\}$ in the density variable is replaced by the gender and health state where f_i denotes the infected females, f_u denotes the uninfected females and m denotes the male mosquitoes (which stay uninfected throughout their life cycle)

6.3 Diffusion/Vector mobility

Mosquitoes diffuse in different directions from a geographic region cell refer to Figure 6.2 depending on their biting cycle [187]. They diffuse towards human settlement looking for blood meals, or quiet/isolated place such as walls or shrubs to relax/digest after meals or breeding sites such as empty cans/tires or water patches to lay eggs. We have incorporated the diffusion rate for male and female mosquitoes depending on geographic land classification. We can extend our model to incorporate the biting cycle if required in the diffusion rate. The cellular automaton computes the count of mosquito population in each cell at a given time t using the count of the current population and the net diffusion from the neighborhood cell at time $t - 1$ at regular intervals.

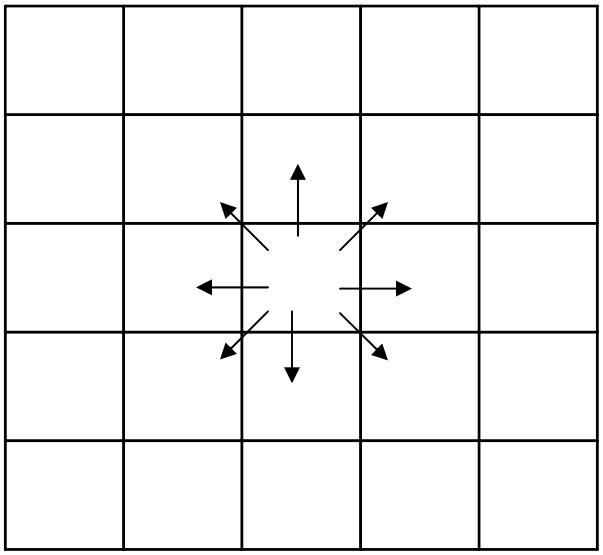


Figure 6.2 Diffusion to the neighboring cell.

The function *g(i,j,t)* in the equation (2) is the summation of net diffusion from the 8 neighboring cell using the Moore's neighborhood [158].

$$g(i,j,t) = \sum_{(i',j')\neq(i,j)} [D(i',j',i,j,t) - D(i,j,i',j',t)] \quad \ldots. (2)$$

Here $g(i,j,t)$ is the net diffusion to/from the 8 neighboring cell, $D(i,j,i',j',t)$ is the count of mosquitoes that leave cell (*i,j*) and enter cell (*i',j'*)at time t as result of diffusion to/from neighboring cell

6.4 Climate effects: Wind

Climatic factor such as wind can plays an important role in the transmission of the disease in certain circumstances. The direction and intensity of the wind affects the time required to spread the disease either by assisting or opposing the diffusion of vector population to the neighboring cell. Equation (3) incorporates the direction and the intensity of wind to calculate the net diffusion from 8 neighboring cell.

$$gw(i,j,t) = \sum_{(i',j')\neq(i,j)} [w((i,j)-(i',j')) \bullet D(i',j',i,j,t) - w((i',j')-(i,j)) \bullet D(i,j,i',j',t)] \ldots (3)$$

Here $w(d_1,d_2)$ is the wind factor for the direction (d_1,d_2).

For example the North East wind direction would have $w(d_1,d_2)$ coordinates as (1,1). The wind flows in the direction shown by the vector (1,1) and the wind intensity is used to adapt the diffusion rate in the direction of the wind as shown in Figure 6.3. The wind intensity for the remaining direction is normalized to ensure that the net diffusion is not more than the vector density population of the geographic region cell in consideration.

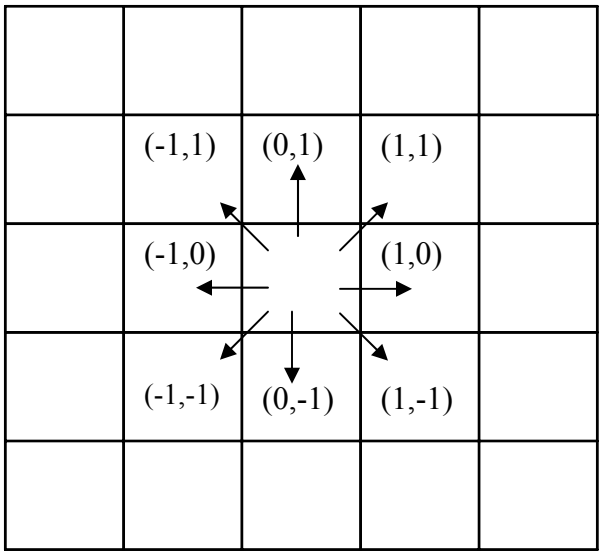


Figure 6.3 Diffusion to the neighboring cell with wind coefficient.

6.5 Host mobility

We have complemented the data for the individuals from TRANSIMS/EpiSims with malaria specific properties. These properties would be assigned to people in a manner similar to what is done in the population construction of TRANSIMS so as to be representative or statistically indistinguishable from actual survey data. These properties are age, gender, physical activity plus intensity level, pregnancy in case of adult female etc., and they play a crucial role in the susceptibility and transmission of disease. People move from one activity location to another in the given geographic region of consideration and this is where the host/vector exchange occurs. There are *n* numbers of activity location in a given geographic region such as school, home, office etc. Each individual has been assigned a schedule for mobility from one activity location to other and the duration it spends at each activity location. TRANSIMS and other mobility generators can be used to generate mobility schedule of each individual in the given geographic region.

6.6 Vector/Host interaction

The effect of vector/host interaction is analyzed by examining its effect on the probability of human exposure to the pathogen (P_1), which is the probability of at least one contact with an infected vector [188].

$$P_1 = 1 - (1 - k_v r)^n \qquad \ldots(4)$$

Here k_v is the proportion of vectors infected with the pathogen, n is the number of vector-human contacts (e.g., mosquito bites), and r is the bite effectiveness. The product $k_v \cdot r$ is the entomological inoculation rate, EIR

In Equation (4), the product $k_v \cdot r$ is the probability of contracting the parasite from one bite of mosquito. Therefore $(1 - k_v \cdot r)^n$ is probability of not contracting the parasite by n number of bites. The number of vector-human contacts is calculated by considering many factors such as the type of activity location; as different species of mosquitoes has different biting rate at a given time of the day at different activity location [189]. Other factors include pregnancy [190], age, body size, sex, disease status and physical activity [39]. The analysis assumes that a single infective contact (e.g., bite by an infected mosquito) is sufficient for transmission of the pathogen. This probabilistic approach to the likelihood of human encounter with an infected vector is related to the probabilistic portion of the Reed-Frost epidemic model [191]. Immunity factor in the human host and the mosquito has not been taken into consideration and can be included as a future project.

6.7 Integration with Episims

Our model has been designed focusing on integration with EpiSims in future. We can integrate our model with EpiSims in one of following ways

a. Offline integration
b. Full integration

6.7.1 Offline integration

EpiSims/TRANSIMS provides activity locations and a list of individuals with their schedules for each point in time. It monitors each individual's movement across different activity location and dynamically changes the schedule of the individual according to their health state. The software prototype implementation of the malaria model reads the input of individual's schedule and health state from EpiSims/TRANSIMS and outputs the health state of the individual after calculating the various parameters discussed in (Sect 6.2 – Sect. 6.6). Malaria model in conjunction with EpiSims/TRANSIMS is highly scalable and allows to model transmission at a high level of detail.

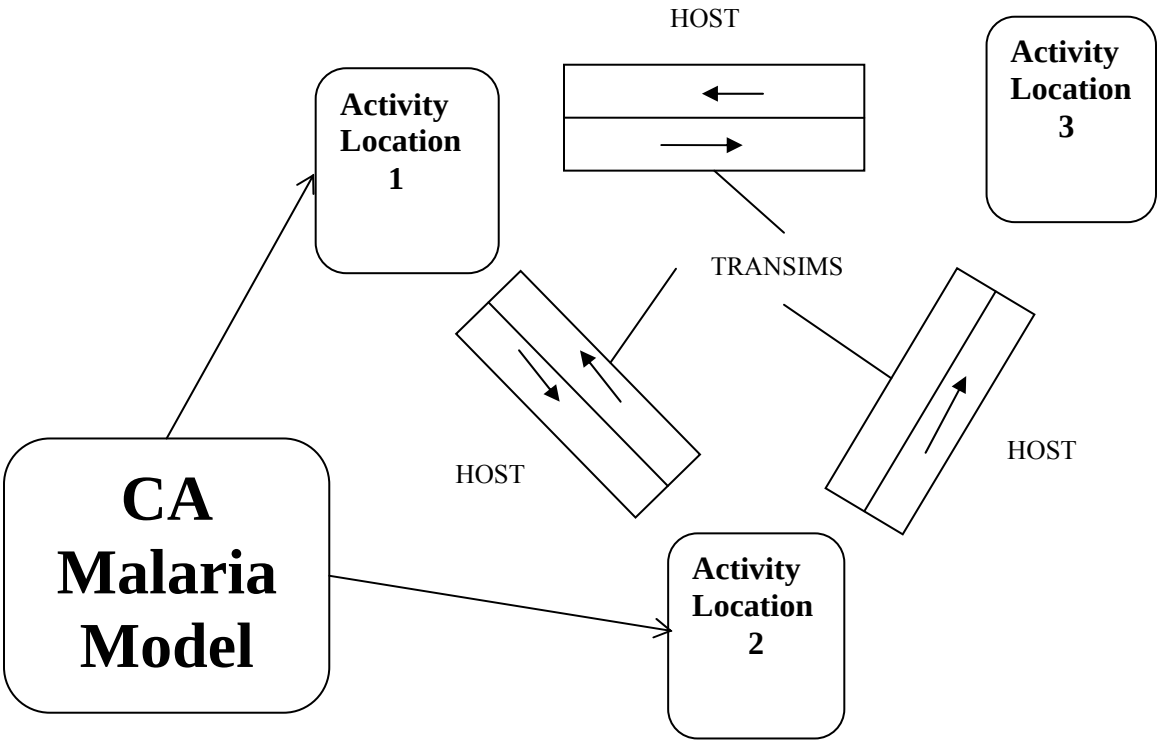


Figure 6.4 Integration with EpiSims/TRANSIMS using a CA based model for malaria.

6.7.2 Full integration

EpiSims/TRANSIMS has incorporated different disease model from small pox to influenza which were based on human to human contact whereas malaria can only be transmitted by means of a mosquito vector. By full integration of our malaria model

vector physiological state and the host health state can be dynamically modified and their traveling plans can be altered. Our malaria module will be running alongside EpiSims for its computation. For example, our model will identify the possibility of a host becoming infected when there is an interaction between the host and the vector and EpiSims will change the traveling schedule of the person to stay at home or visit a doctor. Figure 6.4 shows the model after integration with EpiSims/TRANSIMS. In this Figure our malaria model controls the activity location where a possible interaction between host and host can occurs. The mobility of host from one activity location to another location is controlled by TRANSIMS which is a mobility generator in the model and the EpiSims dynamically controls the change of health state and modifies the schedule of individual. Our model is principally aligned to the EpiSims/TRANSIMS, but will require some amount of work to for full integration.

Chapter 7

Software Implementation

7.1 Initialization

The software was designed as a prototype for simulating the spread of malaria incorporating major factors. It is a scalable, stand-alone module intended to be integrated with EpiSims to understand the epidemic of malaria in detail. The overview architecture of our prototype model is shown in Figure 7.1. In the initialization phase, grid coordinates of the region and number of geographic cells is defined. Area of the geographic cell is calculated in square meters from the above information. The wind factors such as direction and the intensity are specified by the user.

The computations are based on certain assumptions such as density of the mosquito population, reproduction rate of mosquitoes, survival rate of mosquitoes, vicinity of activity location to breeding sites, human host's health state and many other parameters. This data is provided to the module via input files. The input files can be modified according to the change in the condition of the region; such as increase or decrease in temperature, change in the land type from dry land to patches of water, use of interventions such as insecticides and others.

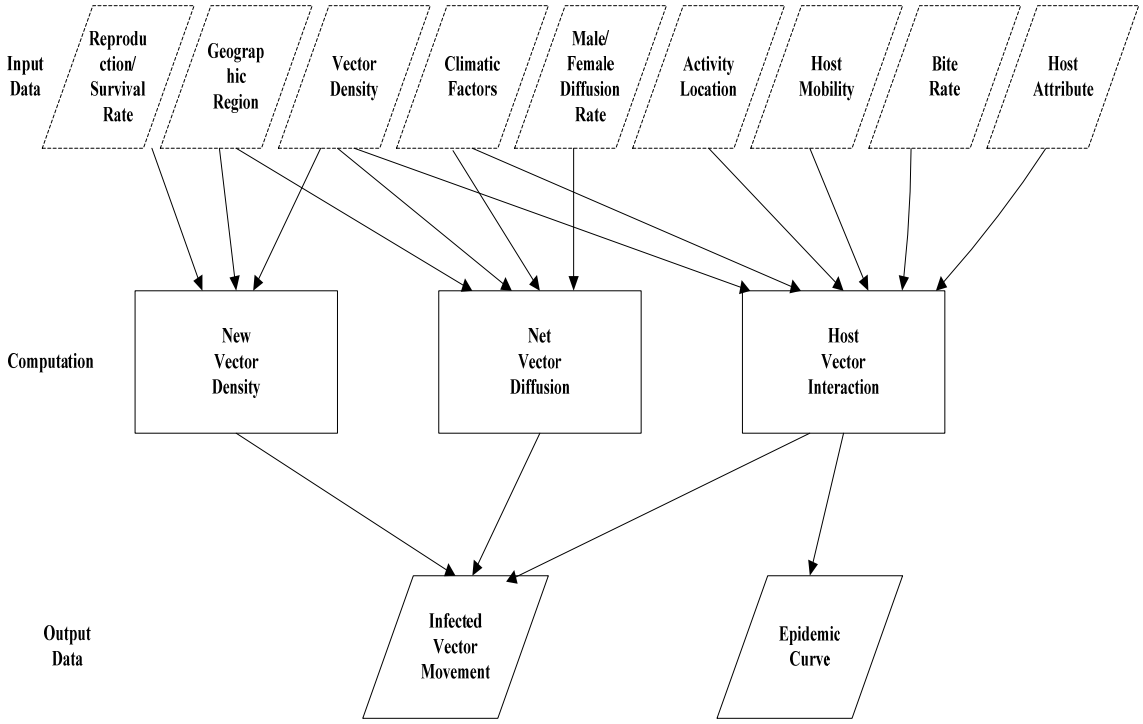


Figure 7.1 Architecture of malaria model

The input files which are read by the model are shown in the Figure 7.1 they include:

a. Reproduction/Survival rate: The reproduction and the survival rate of the given mosquito species is defined in this file and is a function of the temperature and the land classification.
b. Geographic Region: It is user specified input which provides the maximum/minimum grid coordinates values of latitude and longitude.
c. Vector density: This file defines the density of the mosquito population per square meter according to the type of land and the temperature of the region.
d. Climatic factor: It is a user-specified input which provides the direction and the intensity of the wind.
e. Male/Female diffusion rate: The male and female diffusion rate is provided in a separate file which varies according to the search for food/host blood meal and land type.

f. Activity location: The activity location is a place where there is a high probability of the human host being exposed to the malaria pathogen via mosquito vector. The input file provides the grid coordinates of the activity location and defines whether the location is indoors or outdoors.
g. Host mobility: This file provides schedule of the each individual during a given period of time, which is the person's movement from one activity location to other.
h. Bite rate: This input file provides the number of times a human is bitten in 1 second by a malaria infected mosquito. This value is dependent on temperature and land classification.
i. Host attribute: This input file contains person id, health state, age, gender, pregnancy in case of females, and the activity state of the individual which would be statistically similar to the survey data used in EpiSims/TRANSIMS.

The Host attribute, activity location and Host mobility file are similar to the ones used in EpiSims/TRANSIMS. The format can easily be adapted to facilitate the exact format of EpiSims/TRANSIMS. Geographic region cell, Activity location and each individual is initialized using the input files and initial instantiation of the grid location.

Each geographic region cell is assigned the initial density of mosquito population, reproduction rate and the survival rate from the input files according to the land classification and the temperature of the region. The activity location is initialized by determining the position in the geographic region along with the number of people present in that activity location at the initial time using the input files. Each person is also initialized with their personal attributes such as health state, age, pregnancy status in case of females, activity state and the initial activity location they are present in.

7.2 Computation

In this phase of the software prototype implementation different computation aspects of the model are taken into consideration. The class diagram in the Figure 7.2 and the sequence diagram in the Figure 7.3 can help us better understanding the architecture, flow and computation of the data.

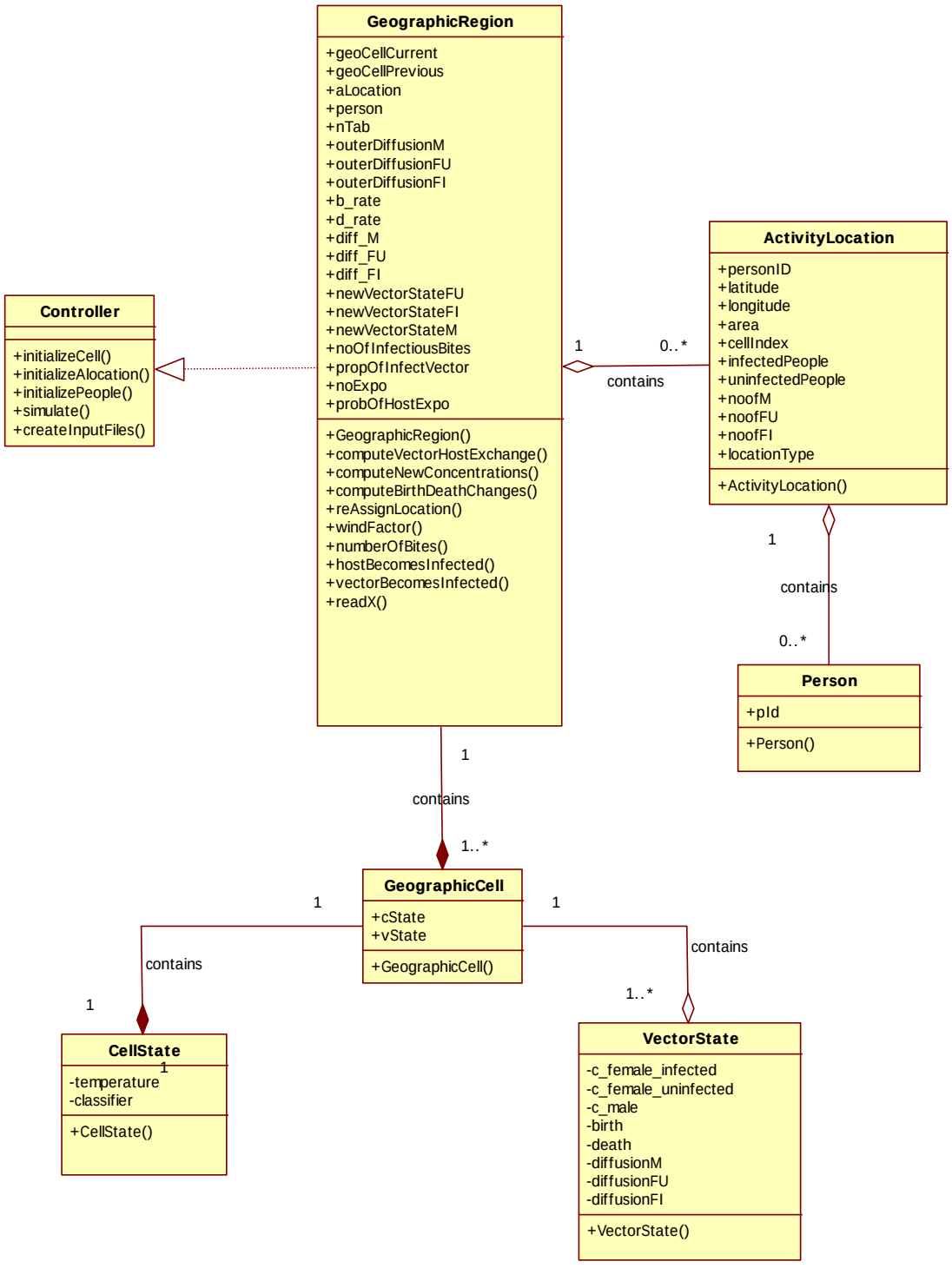


Figure 7.2 Class diagram of the implementation of the malaria model

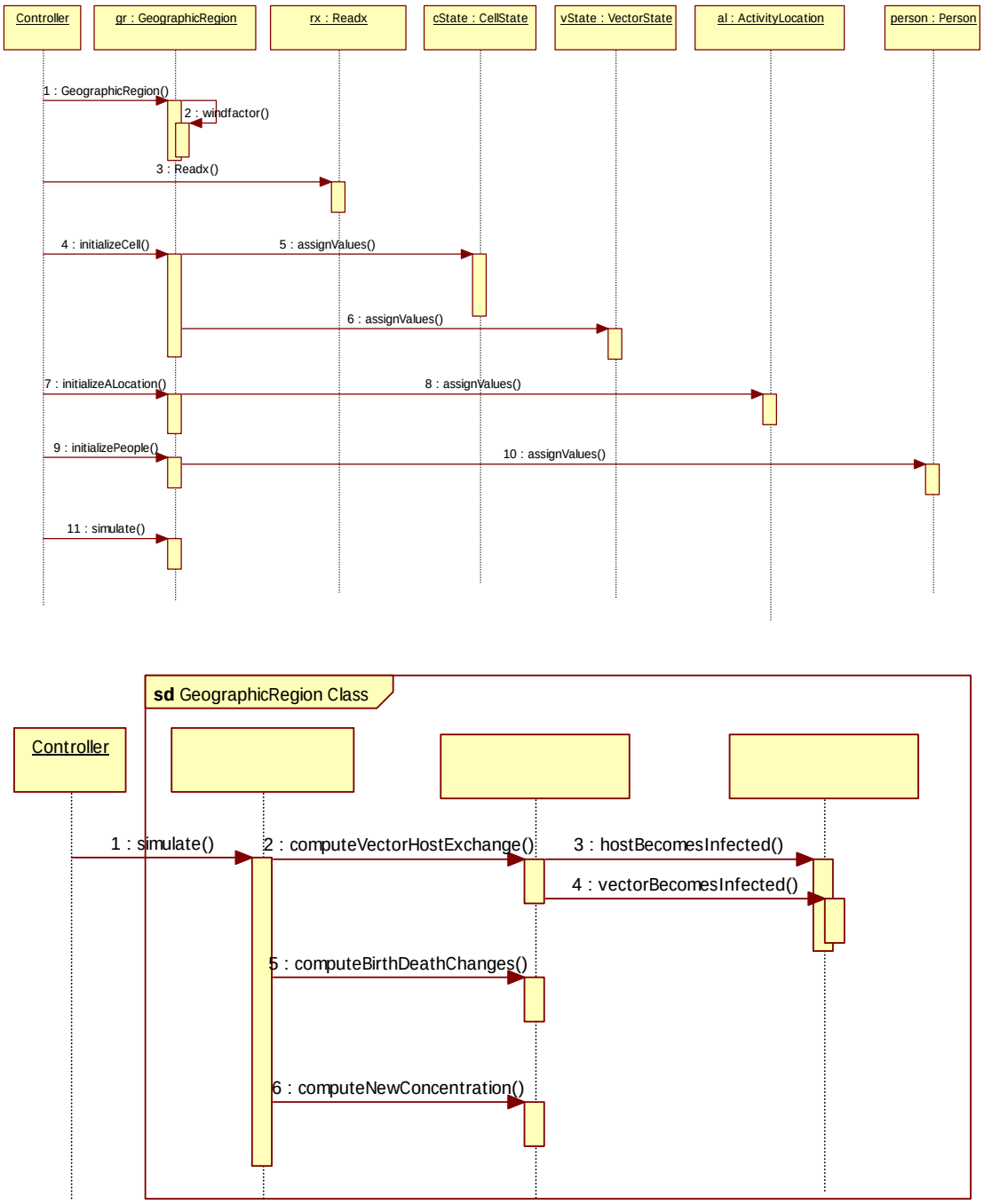


Figure 7.3 Sequence diagram of the implementation of the malaria model.

7.2.1 New vector density

As shown in the Figure 7.1 the computation of the new vector density requires the reproduction rate, survival rate, geographic region coordinates (including the type of land and temperature) and the original vector density of the geographic region. The vector

density is assumed depending on the temperature and the land classification. Equation 1 is used to calculate the new vector density at a regular interval specified by the user. This equation helps to better understand the effects of temperature, land type and other interventions such as insecticides in the transmission of the Malaria.

7.2.2 Net vector diffusion

Vector diffusion computation helps us to evaluate the movement of vector mosquito across different geographic region cells. Each geographic region cell is a different land type. Higher vector density in a particular geographic region cell will help us identify the potential breeding site and large number of host vector interaction for possible transmission of the disease, as calculated in equation (2). The climatic factor such as wind is also taken into consideration as referred in equation (3). We provide the male and female diffusion rate as an input depending on the land type. This rate can be modified to incorporate the biting cycle and time of the day for diffusion.

7.2.3 Host/Vector interaction

The host/Vector interaction is the central computation which helps us evaluate the increase in number of infected hosts and vectors for the epidemic of malaria. Host attributes, Activity location, Host mobility and Biting rate is provided as input file. The biting rate can be modified to evaluate the effect of temperature as referred in equation 4. Number of people in the given activity location and the vicinity to the breeding site will help us evaluate the rate at which the epidemic can spread.

7.3 Output and Visualization

The output of the software implementation is a set of tab delimited text files. This output files are used as input to *Mathematica* 5.2 [192] to visualize the results in a graphical format and interpret the outcome. The results obtained give a good insight on the factors responsible for the spread of malaria. One file gives the number of people infected in the region of consideration at different time steps. This file is visualized as an epidemic curve to find out the rate at which the epidemic can spread. The second group of files outputs the density of mosquito population in each geographic cell at different time. This group

of files is simulated in the grid layout format to view the movement of the infected mosquito and increase in its density population.

7.4 Test cases

We have carried out many test cases to evaluate factors discussed in section 2.6 responsible for the transmission of the disease. Few of the test cases are explained in detailed with the help of the visualized output.

Test case 1:
Robustness under scaling

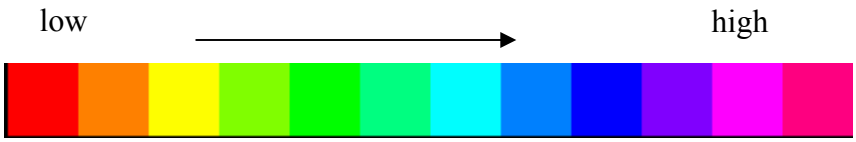
Test case 2:
Effects of diffusion

Test case 3:
Epidemic curves

Test case 4:
Effect of Mosquito Count in an Activity Location

7.4.1 Case1: Robustness under scaling

In this test case we try to evaluate the robustness of our model and implementation. We modify the number of grids in a given geographic region starting from 10 by 10 to 75 by 75 and show snapshots of the simulation at three different time steps in Figure 7.4 – 7.6. It was found that the model can qualitatively handle the scaling. Since the vector density for each geographic cell is assigned randomly we can not expect to see quantitative similarity between all the three scaled graphs. In Figure 7.4 – 7.6 (d) black color shows the higher density.



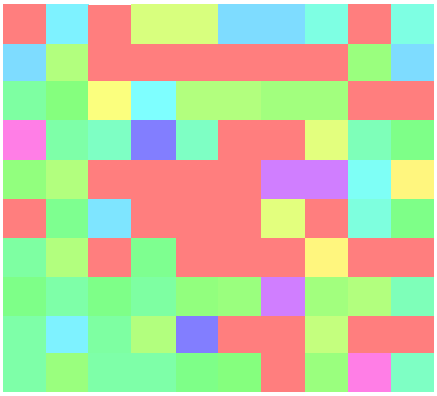


Figure 7.4 (a) Vector density movement across 10 x 10 grid at time t = 0 sec

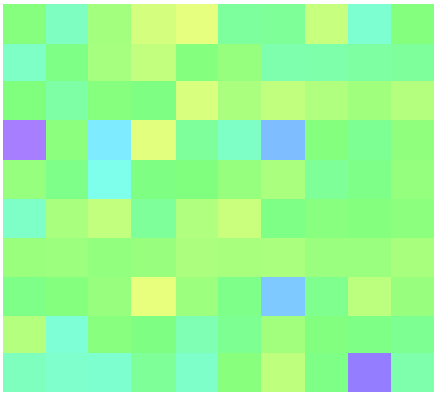


Figure 7.4 (b) Vector density movement across 10 x 10 grid at time t = 500 sec

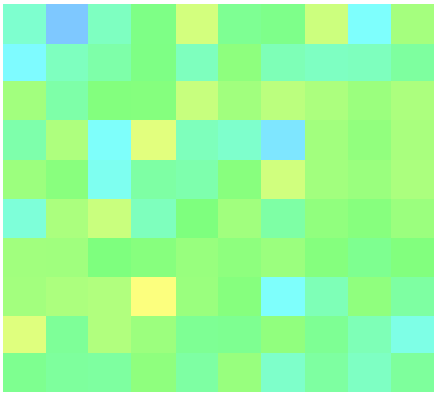


Figure 7.4 (c) Vector density movement across 10 x 10 grid at time t = 1000 sec

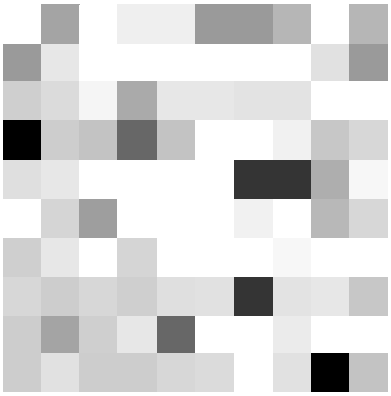
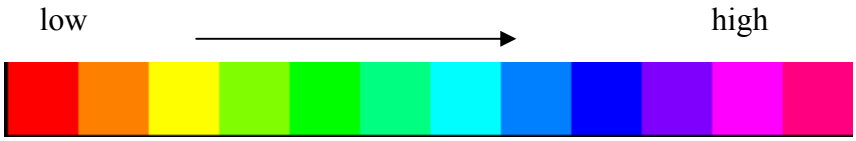


Figure 7.4 (d) Cell classification for expected mosquito count in 10x10 grid



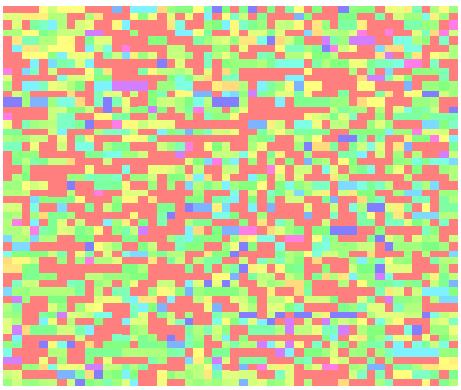


Figure 7.5 (a) Vector density movement across50 x 50 grid at time t = 0 sec

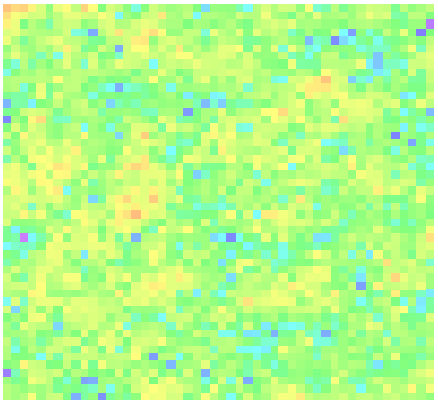


Figure 7.5 (b) Vector density movement across 50 x 50 grid at time t = 500 sec

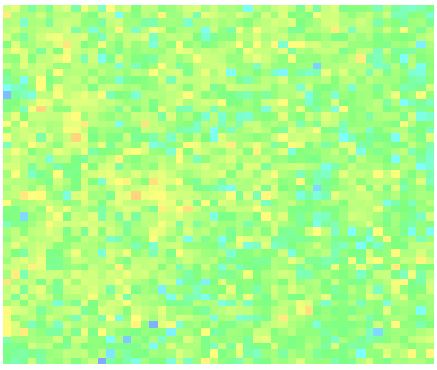


Figure 7.5 (c) Vector density movement across 50 x 50 grid at time t = 1000 sec

Figure 7.5 (d) Cell classification for expected mosquito count in 50x50 grid

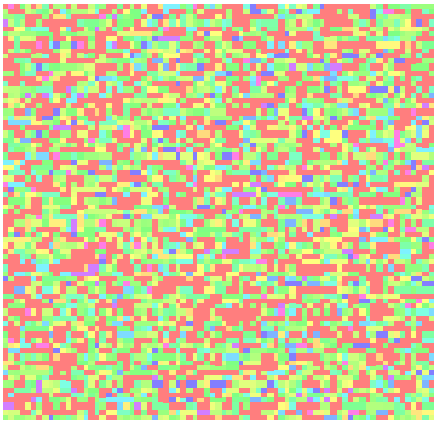


Figure 7.6 (a) Vector density movement across 75 x 75 grid at time t = 0 sec

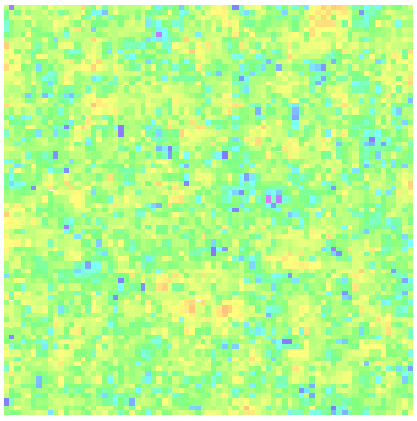


Figure 7.6 (b) Vector density movement across 75 x 75 grid at time t = 500 sec

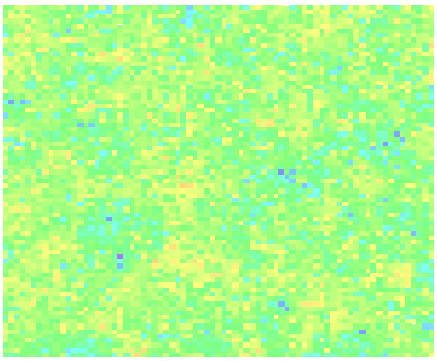


Figure 7.6 (c) Vector density movement across 75 x 75 grid at time t = 1000 sec

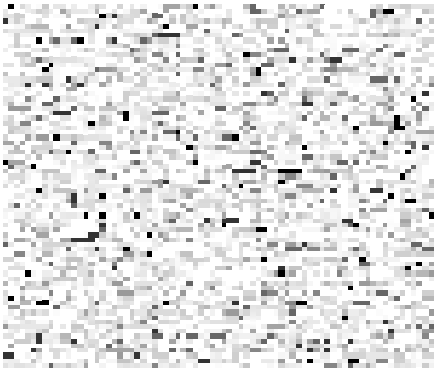
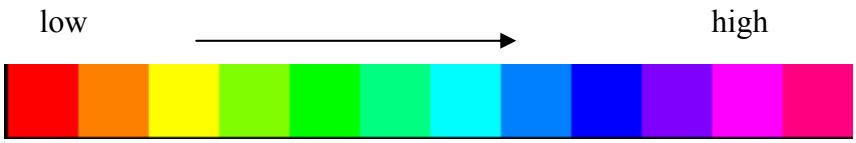


Figure 7.6 (d) Cell classification for expected mosquito count in 75x75 grid

7.4.2 Case 2: Effects of diffusion

In this case we try to evaluate the pattern of diffusion from one geographic region cell to the other. Mosquito diffuse either for breeding or blood meal. In the Figure 7.7 we try to diffuse mosquito from a farmland to human settlement and it was found that the mosquito diffuse in a large quantity towards human settlement without assistance of wind factor.



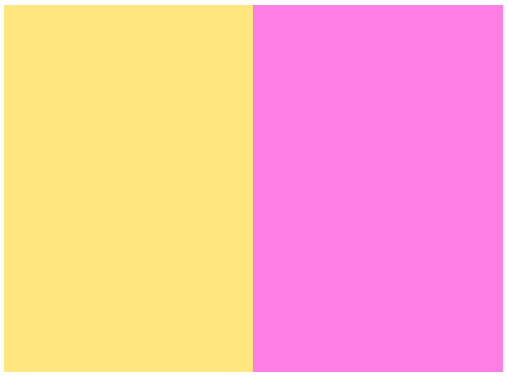


Figure 7.7 (a) Vector density movement across 50 x 50 grid at time t = 0 sec for diffusion

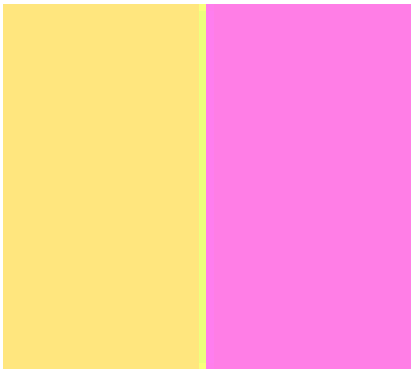


Figure 7.7 (a) Vector density movement across 50 x 50 grid at time t = 500 sec for diffusion

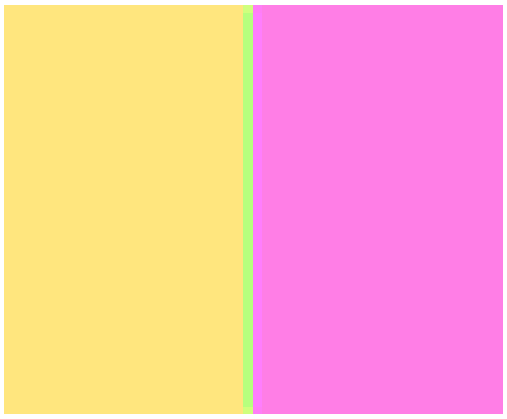


Figure 7.7 (c) Vector density movement across 50 x 50 grid at time t = 1000 sec for diffusion

7.4.3 Case 3: Epidemic curve

In this case we test the rate at which number of infected people increase with time in a given set of condition with assumed values. As the number of people in a given geographic region remains constant, the epidemic curve shows an increasing trend for the number of people being infected; as referred in Figure 7.8. This evolution is what one qualitatively would expect.

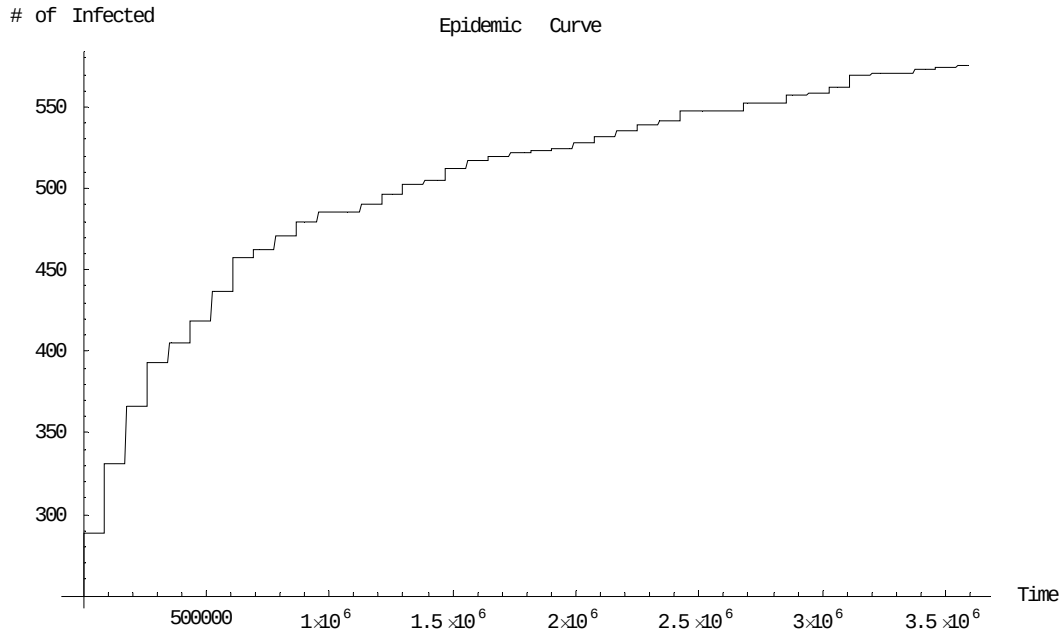


Figure 7.8 Epidemic curve

7.4.4 Case 4: Effect of mosquito count in an activity location

In this test case we try to vary the mosquito count in each activity location to understand the effect of density of vector population to the infection rate. It was found that the location with high mosquito counts have more infections than cells with lower mosquito counts, which was expected. Figure 7.9(a) (b) shows activity location 37 which has a higher mosquito count than location 31 as shown in Figure 7.10(a) (b).

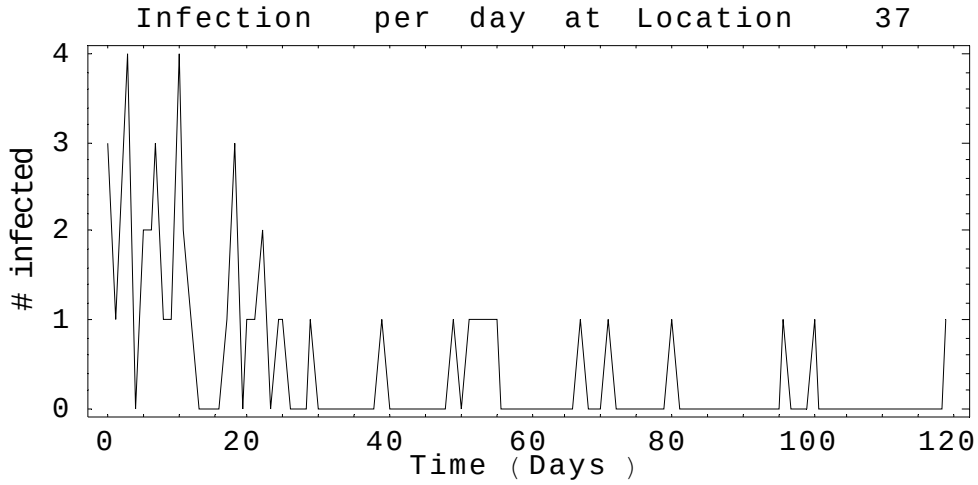


Figure 7.9 (a) Number of hosts getting infected on each day at location 37

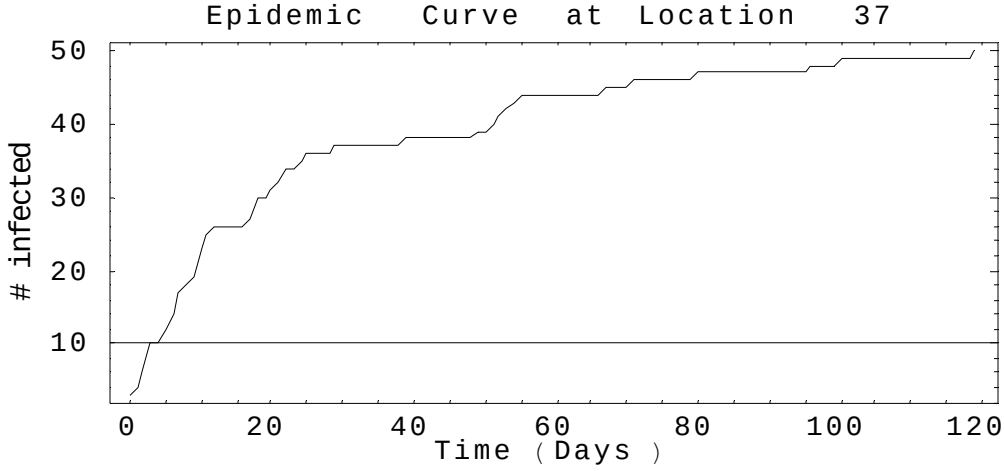


Figure 7.9 (b) Number of hosts infected with time at location 37

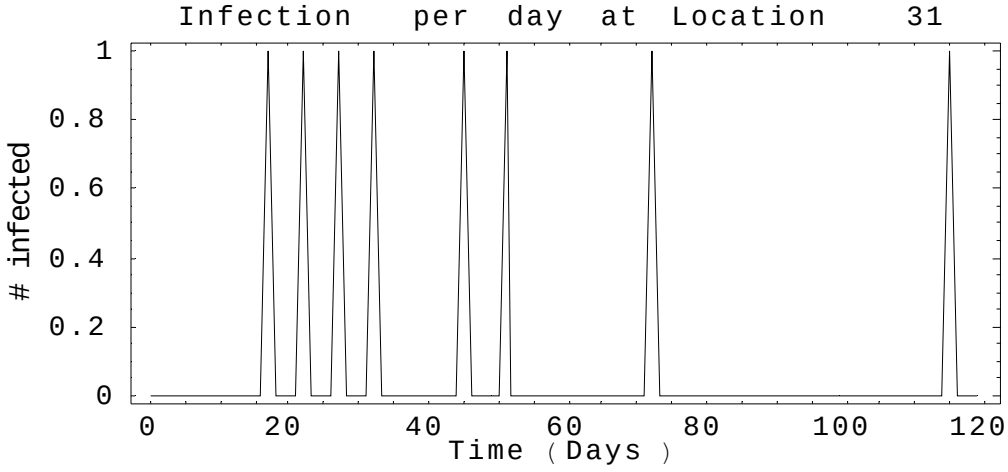


Figure 7.10 (a) Number of hosts getting infected on each day at location 31

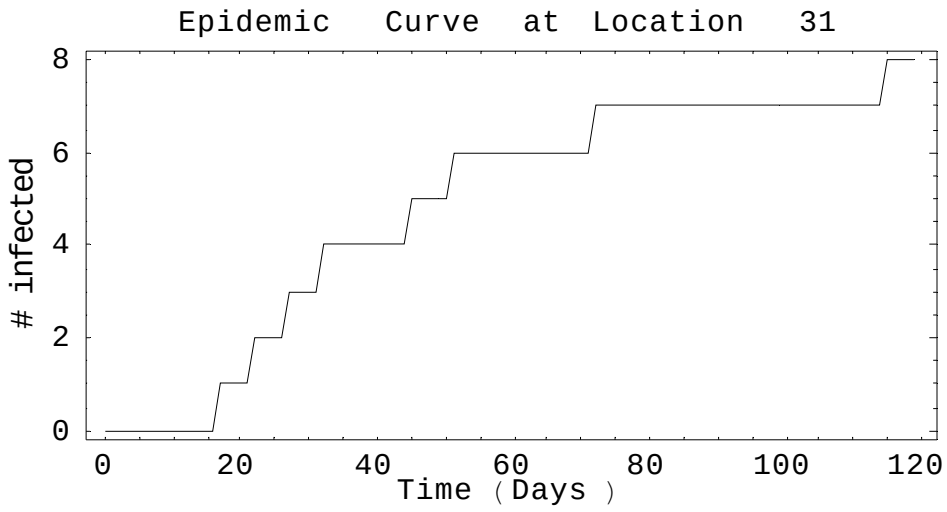


Figure 7.10 (b) Number of hosts infected with time at location 31

7.5 Calibration

In our prototype model some of the parameters are based on the values as specified in the papers reviewed in the literature surveys from specialist (K. Adasi) [193] and other values were estimated. Some of the assumptions on which our model is based are density of vector population, birth rate, death rate depending on temperature and land classification. One can calibrate the model with more accurate data without modifying the design of the model.

Chapter 8

Future work and Conclusion

8.1 Recommendation for Future work

Possible recommendations for future work which can be easily incorporated in the model without breaking the design of the model are

- Full integration of the model with the Episims/Transims.
- Mapping of satellite images to the density of vector population which can make it easier to differentiate between potential breeding sites and non breeding sites.
- More accurate interaction model incorporating e.g. biting cycle/season/rain/weather for longer duration of calculation
- Implement and study interventions (e.g. insecticides)

8.2 Summary and Conclusion

Malaria is not just a disease but an economic and social disease that burdens many nations globally. Many control measures have been implemented to eradicate the disease but very few have turned out to be effective and incur very high amount of money and time. Simulation helps in formulating strategies to control, which would have not been possible physically. Different simulation models have been built to understand different factors influencing the spread of the disease. These models either focus on the epidemiological aspects of the disease using ordinary differential equation or the geographical aspects. They assume complete mixing of the populations and address only a fraction of the population, which is either infected or uninfected. As a result, these

models were not able to focus on the individuals and have other shortcomings as explained in Section 3.1.

Our model combines the epidemiological as well as the geographical aspects of the spread of the disease. It can incorporate disease at individual level and can add features to model as required in understanding it better. The prototype software is implemented in such a way that it can be easily integrated in to EpiSims/TRANSIMS and can be scaled to a very large population focusing on each individual's level.

Chapter 9

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