AGENT BASED MODELING OF MALARIA

C. Illangakoon, R.D. McLeod
Department of Electrical and Computer Engineering
University of Manitoba
Winnipeg, MB, Canada

M.R. Friesen
Design Engineering
University of Manitoba
Winnipeg, MB, Canada

***Abstract*— This work explores the utility of an agent based model (ABM) for studying malaria prevalence and transmission. Malaria is a life-threatening disease caused by Plasmodium parasites that are transmitted to humans through the bites of infected female mosquitoes of the genus Anopheles. According to the WHO, malaria caused an estimated 627,000 deaths in 2012 (with an uncertainty range of 473,000 to 789,000), mostly among African children [1][2]. Increased malaria prevention and control measures are the focus of much research and have already dramatically reduced the malaria burden in many places. Through the use of technology and high-resolution modeling and simulation, an even better understanding of prevention and control measures may be obtained.**

***Keywords*— Agent based modeling, SEIR, Malaria.**

I. INTRODUCTION

Modeling of malaria transmission is complicated due to a number of factors. These include an individual's behavior and movement patterns, the mosquito's behaviour and movement patterns, and the life cycle of the parasite itself. Each of these are also dependent upon the environment.

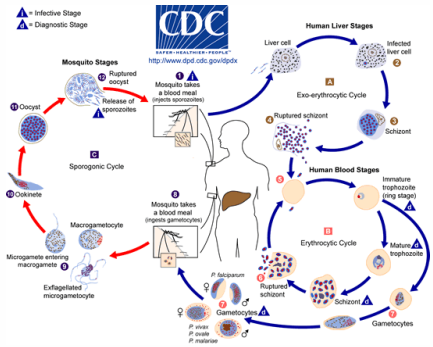

Fig.1. Relationship among factors affecting the malaria lifecycle [3].

Other aspects of the risk factors for spreading the disease can be correlated to social conditions and demographics of various regions and the movement of individuals between them.

These complex factors nonetheless make the modeling of malaria transmission well suited to interacting agent based modeling (ABM) and simulation. In ABM, individuals (agents) have associated states such being susceptible, exposed, or infected. In turn, these states have associated latencies or incubation periods. Mosquitos also have states associated with their life cycle, and the parasite's lifecycle involves both the mosquito and human as hosts. This complex interaction is depicted in Fig. 1. In ABM, the individual interactions of agents to other agents and to their environments are accounted for. One of the objectives of simulation and modeling is to assess the efficacy of public health policy or infection mitigation strategies. Mitigation strategies may include, when and where larviciding, netting, or the use of insecticide treated netting.

The most important aspects of Fig.1 with respect to ABM are as follows:

1) A malaria-infected female Anopheles mosquito inoculates sporozoites into the human host. (From an ABM perspective, this is a probabilistic contact-based transmission. The human agent transitions from being susceptible to exposed).

2-4) Sporozoites infect human liver cells and mature into schizonts, which rupture and release merozoites. (From an ABM perspective this is a delay or latent period of time, where the individual remains in the exposed state for a period between 5-16 days.)

5-7) Merozoites infect human red blood cells. Some parasites differentiate into sexual erythrocytic stages (gametocytes). The blood stage parasites are responsible for the clinical manifestations of the disease. (From an ABM perspective, the human agent will move from exposed to being infectious, this differentiation of parasites is from 1-3 days.)

8-11) The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an Anopheles mosquito during a blood meal on a human. While in the mosquito's stomach, the microgametes penetrate the macrogametes, generating zygotes. The zygotes in turn become motile and elongated (ookinetes) which invade the midgut wall of the mosquito where they develop into oocysts. (From an ABM perspective the mosquito agent would have moved from susceptible to exposed)

12-1) The oocysts grow, rupture, and release sporozoites, which make their way to the mosquito's salivary glands. Inoculation of the sporozoites into a new human agent perpetuates the malaria life cycle. (From an ABM perspective, this is a delay or latent period of time which may last between 8-15 days, where the mosquito agent would have moved from exposed to infectious)

The mosquito agents will also have a birth and death (lifecycle) state associated with the equilibrium population of mosquitoes in that region which is also impacted by environmental conditions and seasonality.

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In these complex interactions, the modeling opportunities are apparent, including the potential for technologies that may be useful in establishing data baselines that can be used to refine the models (for example, mobile apps in which users self-report general mosquito prevalence that can be correlated to official trap counts). Another complicating factor is that in latencies such as from stages 8-11, there is strong temperature dependence as well as a relationship between temperature and the life cycle of the insect [4].

II. Literature Review

This literature review primarily overviews the mathematical models associated with mosquito borne illnesses as well those associated with more traditional epidemiological models, followed by brief description of ABMs.

Traditionally, disease and infection models were differential or difference equation based and related to (focused on) populations rather than individuals. Smith et al. [5] provide a thorough discussion and chronological overview of the development on mosquito parasite models known as Ross-McDonald models. An example of a Ross type model [6] is as follows:

$$\frac{dI_h}{dt} = abmI_m(1 - I_h) - rI_h$$
$$\frac{dI_m}{dt} = acI_h(1 - I_m) - \mu_2 I_m$$

The model above relates the population of infectious mosquitos to the population of infected humans. Improved models [7][8][9] attempt to incorporate latencies or incubation periods associated with both the mosquito and human, as discussed in the overview of the mosquito-parasite-human cycle.

$$\frac{dI_h}{dt} = abI_m(t - \tau_1)(1 - I_h(t - \tau_1))e^{d_1\tau_1} - d_1 I_h(t)$$
$$\frac{dI_m}{dt} = acI_h(t - \tau_2)(1 - I_m(t - \tau_2))e^{d_2\tau_2} - d_2 I_m(t)$$

In the work of [9], modeling efforts show that the basic reproduction number is a decreasing function of the latencies, and those interventions that increase incubation periods in either humans or mosquitos (via medicine or control measures) could reduce the prevalence of infection. Parameter descriptions for above equations above can be found in [10].

These models are continually being refined to include additional parameters associated with environmental conditions. Malaria is among the many mosquito borne diseases that have been affected by climate, since warm and moist climates are most conductive to mosquito propagation and survival. In most cases, increased comprehensiveness usually imposes numerical simulations to otherwise analytically intractable solutions.

In the case of mathematical models associated with more familiar human diseases such as influenza and other respiratory-infections, the SEIR(S) models of Kermack and McKendrick [11] are most widely cited, albeit heavily influenced by earlier work of Ross.

Related work [12] includes a simulator of a SEIRS model. The SEIRS model, models the flow of people between four states: susceptible (S), exposed (E), infected (I), and resistant (R). Each of those variables represents the number of people in those groups. The parameters partially control how fast people move from being susceptible to exposed (β), from exposed to infected (σ), and from infected to resistant (γ). The SEIR model typically has two additional parameters: one is the background mortality (μ) which is unaffected by disease-state, while the other is vaccination (η). The vaccination moves people from the susceptible to resistant directly, without becoming exposed or infected. Although malaria vaccines are an intensive area of research, at this time there is no practical or effective vaccine in clinical practice.

The SEIRS model differs from the SEIR model by setting immunity to be a temporary condition rather than permanent, and thus letting recovered individuals lose their immunity over time and re-entering the susceptible state (final S in SEIRS). The rate at which people lose their immunity is governed by the parameter ρ. The Plasmodium parasite requires both human and mosquito for its life cycle to complete. In malaria models, therefore, these SEIRS compartments have been applied to both human (host) and vector (mosquito) [10].

These population-based compartmental models have evolved to modeling subgroups within a population, which still do not consider each individual agent but rather groups of agents.

$$\frac{dS}{dt} = \mu(N - S) - \beta\frac{SI}{N} - \nu S + \rho R$$
$$\frac{dE}{dt} = \beta\frac{SI}{N} - (\mu + \sigma)E$$
$$\frac{dI}{dt} = \sigma E + (\mu + \gamma)I$$
$$\frac{dR}{dt} = \gamma I - \mu R + \nu S - \rho R$$
$$N = S + E + I + R$$

The Ross type model typically divides the human population into susceptible (S_h) and infected (I_h) compartments, with the infected class returning to susceptible class, again leading to the SIS structure. The mosquito population also has only two compartments (S_m, I_m), as they do not recover from infection due to their short life span, and follow the SI structure [10].

In effect, these types of models present a hierarchy in which the models of the Ross-MacDonald type couple mosquitos and humans while the models of Kermack and McKendrick typically concern populations of humans and their health states or compartments.

ABMs take the subgroups within a population to the point where each individual is its own compartmental state machine. Just as with the equations associated with entire populations (or sub-populations) discussed above, an ABM essentially discretizes a population to that of individuals, each governed

by interacting stochastic processes. In the most general case, the ABM discretizes the population into individuals as well as localizing them in both space and time.

Of greater interest in terms of advancing humanitarian applications of technology is the role that technology may play to increase the utility of ABMs when applied to the complex disease models associated with malaria. ABM is a relatively newcomer to the simulation and modeling world. Its foundational premise is to model all agents (individuals) with the model with as much fidelity as possible, defining agents by naturalistic and realistic behaviours and interactions with other agents and with their environment. The modeling of parasite dispersal is also very important, although less amenable to technologies that provide human movement patterns.

Thus, there is considerable interest an opportunity to integrate agent based models in order to account for the mosquito-parasite-human cycle as well as social, environmental and human mobility factors. The most likely manifestation of ABM associated with mosquito borne disease will likely be a hybrid of equation based human mosquito interactions within regions, combined with individual ABMs of actual individuals that also capture human movement patterns.

A major and most recent boost to the use and efficacy of an ABM is the considerable data that is becoming available for use within an ABM, primarily in defining agent (human) movements. These data sources are most often tertiary to their initial collection purposes (for example, cellular network data, and location-based mobile app user data). A subsequent section will discuss the emerging sources of data and their utility and the potential for integration within an ABM framework for modeling the spread of infectious diseases.

III. Model Improvements

In the literature review, the importance of incorporating biological factors was noted. In the Ruan-2008 model [9], the basic reproduction number decays exponentially with the latency. This indicates the importance of latency to the accuracy of a model. In brief, the latency is the time duration taken for an infected parasite host (human/mosquito) to become infectious (able to transmit the disease). See [9] and [13] for details. The parasite development rate inside the mosquito body can highly influence malaria spreading. A female Anopheles lives usually 3-4 weeks. Hence, the latency will determine the infectious duration of the mosquito. A slow development of parasites may even prevent the mosquito becoming infectious at all. When determining parasite development inside the mosquito body, the atmospheric temperature is a sensitive influencing factor [14].

A temperature-dependent parasite development model, proposed in [15], is used as illustrated in Fig.2. The incubation period for malaria parasites within the mosquito is extremely temperature-sensitive and therefore temperature is a major determinant of malaria risk.

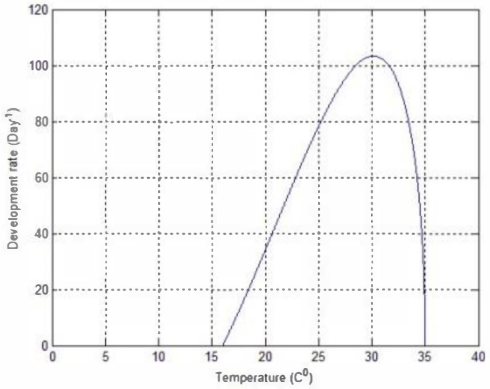

Fig.2. Development Rate vs Temperature Model

Temperature-based malaria transmission is generally incorporated into models using mean monthly or daily temperatures. However, temperature fluctuates through the daily cycle. In [15], it is shown that temperature fluctuation can substantially alter the incubation period of the parasite (i.e., latency period). Therefore, emerging models should take diurnal temperature variation into consideration. An example model illustrating diurnal temperature variation as per [15] is illustrated in Fig.3.

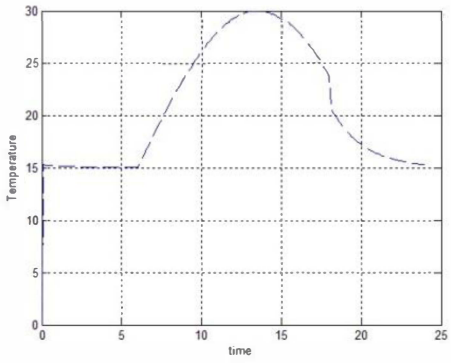

Fig.3. Temperature Variation Model

The above two model enable calculation of cumulative growth of parasites inside the mosquito body. The cumulative growth is calculated over 15 min intervals. Fig.4 shows growth rate over a period of year (the mean daily temperature is indicated). The curve in blue shows the growth rate (per day) considering mean temperature (i.e., assuming temperature remains constant), whereas the curve in red shows the growth rate considering diurnal temperature fluctuation. We notice that at low-mean temperatures the growth rate is underestimated with constant mean temperature and overestimated at high-mean temperatures. This is due to the fact that fluctuation around high-mean temperatures slows down the development process, whereas fluctuations around low-mean temperatures speeds the parasite development compared to constant mean temperature.

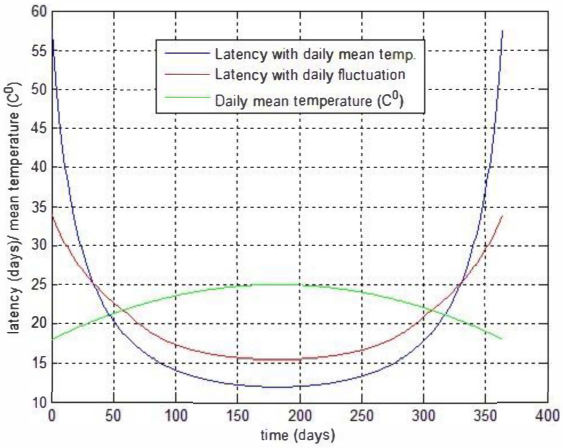

Fig.4. Latency against Temperature

These types of model refinements will yet further both equation based and agent based models. In the work of [16], the variation in latencies is recognized as an important factor in obtaining a biological interpretation to the basic reproduction number. Here it was recognized that the latencies of the malaria parasite in mosquitoes may differ from individual to individual, as do the latencies in humans. These are further refinements upon discrete latencies as investigated in [13]. It is widely recognized that analytical models that provide biological interpretation of disease spread determinants such as factors associated with basic reproduction are very useful. ABMs however provide the opportunity to complement and validate analytical models while holding the possibility of increased model fidelity or accuracy.

Following these observations, facilitates the creation of an ABM that takes temperature dependent latency, latency variations and human mobility into consideration. In [17] it is recognized that "Human movements contribute to the transmission of malaria on spatial scales that exceed the limits of mosquito dispersal. Identifying the sources and sinks of imported infections due to human travel and locating high-risk sites of parasite importation could greatly improve malaria control programs." With this in mind, the state or flow chart of an individual or human agent would be that of Fig. 5.

This type of stochastic state machine for an agent is even more complicated as symptoms of malaria can recur after varying symptom-free periods. Recurrence can be classified as recrudescence, relapse, or reinfection. Recrudescence is when symptoms return after a symptom-free period caused by parasites surviving in the blood. Relapse is when symptoms reappear after the parasites have been eliminated from blood but persist as dormant hypnozoites in liver cells. Reinfection means that a new parasite was introduced [18].

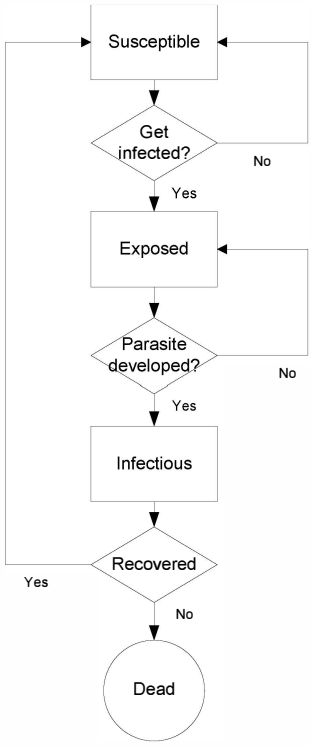

Fig.5. Flow chart of a human agent.

In this model a human is a mobile agent. Agents are described by their health status namely susceptible, exposed (infected but not yet infectious) and infectious. And there are variables assigned to keep track of location, duration of sickness, and parasite latency duration. In the modern world, with the advanced transportation systems, human mobility is a prevailing factor in disease spread phenomenon. In malaria spreading, both human and mosquito mobility can affect the dynamics of the disease. Here it is assumed that mosquito mobility is quite negligible, and that mosquitoes are spatially static. However, parasite importation and exportation, from region to region, through human mobility is considerable [17].

Similar to the flow chart for the human agent would be one associated with a mosquito agent as shown in Fig. 6. In the case of the mosquito agent, although natural dispersal may be a factor, parasite importation and exportation through human movement are seen to be significantly larger contributors to parasite dispersal than that of mosquitos themselves. In addition to temperature and diurnal temperature induced parasite development latencies, it is also important to include seasonal and environmental variation when attempting to model mosquito populations.

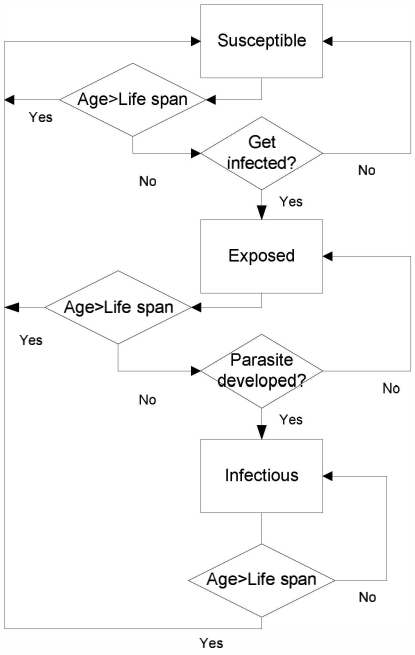

Fig.6. Flow chart of a mosquito agent.

Upon a female Anopheles mosquito taking a blood meal from an infected human, a susceptible agent (mosquito) transits into the exposed state, in which it stays until parasites are fully developed. Finally the mosquito spends its remaining time being infectious, which contributes to the parasite rate at a given time. A dead mosquito will immediately go to the susceptible state (i.e. a new-born mosquito). This will ensure a constant mosquito population at that period of time. Although it may be impractical to associate an agent with individual mosquitos, a model that aggregates the geographically dispersed mosquito population into spatial patches would be a computational alternative [19].

The final aspect associated with malaria spreading patterns would be that associated with human mobility patterns. As an initial and preliminary foray into this modeling, a four city model is being developed. For this simulation a region with four cities, with initial parasite rates, is considered. City-A is the capital and it is frequently visited by other cities. City-C has higher parasite rates. And the other two cities have moderate parasite rates. An illustration of the region is given in Fig. 7.

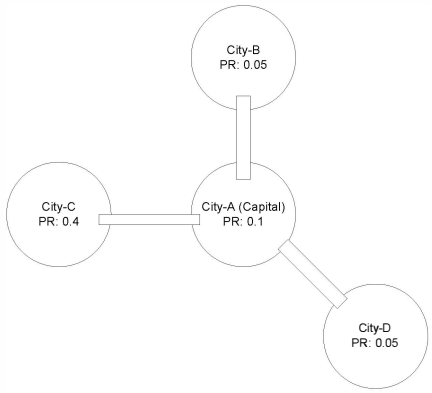

Fig.7. Simulation setup: The four-city region.

At the time of writing several preliminary simulation runs have been undertaken. It is expected that these results will be available by the conference dates. The next section provides some additional insight into technologies that can be used to aid in generating human movement patterns.

IV. Data Sources

In an ongoing effort to better understand the complex dynamics of malaria spread, one of the most important aspects of improved modeling is to integrate real human movement patterns in defining agent behaviours and interactions within an ABM. The most obvious source of data for human movement patterns is information derived from cellular service providers in the data that represents the geographical location of a cellular phone over time as an excellent proxy for its user's movements. This has been demonstrated in the data collected in various studies, with of the most ambitious being that of Wesolowski et al. [17]. The types of records in [17] provide a snapshot of the location of a person in Kenya over 2008-2009. Data were collected in relation to text or calls that a person made from a cellular device. There is also additional cellular data that is more frequently recorded than that associated with an actual call or text which conceivably could be of greater utility in generating human movement patterns.

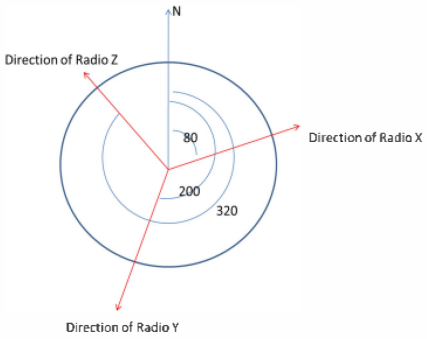

Fig.8. Cellphone tower with three radios covering 120 degrees each.

The cellular service provider knows which cellular antenna sector a phone is within at all times (regardless of voice or text calls being made) as a matter of requiring this information to place a call or deliver a text. For example, a cell tower with three sectors is shown in Fig.8. Within this reference, a person's cell phone is typically associated with a sector. These sectors are of various size and coverage area, typically governed by density. The records associated with cellular network administration are denoted AAA (authentication, authorization and accounting). The AAA protocol is tailored to distributed systems for controlling which users are allowed access to which services, and tracking which resources they have used. These records are maintained for cell phones which are powered on and can be collected with fairly fine temporal resolution (15 minute temporal resolution is representative). The primary purpose of this data is to provide service to customers as well as to obtain accounting information. Combining the network data from the cellular service provider with the information on cell towers and their sectors allows for fairly fine grained spatial resolution of cellphone trajectories. Fig.9 is a cell phone tower layout for the city of Winnipeg MB, Canada.

In Fig.9, a Voronoi diagram (red lines) divides space into a number of regions which when combined with cell tower antenna sectors provides a reasonable estimate of the location of the cell phone at a given time. From these data, trajectories of users can be overlaid to provide information on fairly fine grained movement patterns. Once trajectories are calculated for a larger number of subscribers over a longer period, actual mobility patterns become apparent.

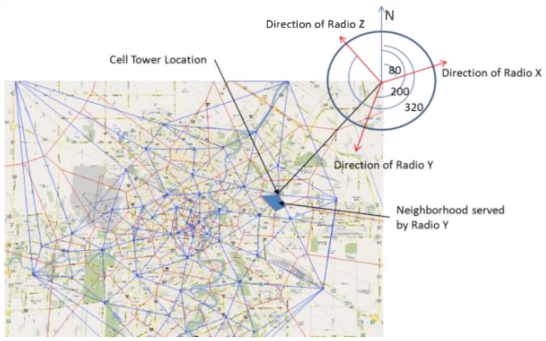

Fig.9. Cellphone tower with three radios covering 120 degrees each.

The following two You-tube videos illustrate some of the animations of movement patterns extracted from cell phone trajectory data:

- [www.youtube.com/watch?v=cOJZKzy0XBY],
- [https://www.youtube.com/watch?v=mUee-tFv1uE].

The former is based on movement patterns over a large geographic area whereas the latter coerces cellphone trajectories onto a street level topology within an urban area.

Another source of data to inform agent behaviours within an ABM is via voluntary crowdsourcing. An app would be one that records a person's proximity to an antenna sector as well as received signal strength, both accessible to the app via a suitable API. These data could be used to augment other types of data related to human mobility.

One of the major difficulties with crowdsourcing is a return for participation. The Kenya data [17] was obtained through a collaborative program where mobile phone data were provided by the leading mobile phone service provider in Kenya, representing 92% of market share at the time of data collection. The research was supported by both NSF as well as the Bill and Melinda Gates Foundation, again illustrating that obtaining data of this nature is not bound by a technological constraints but does require the will and effort of humanitarian organizations.

V. Concluding Remarks

We are just now beginning to see the emergence of ABMs being applied to improving malaria modeling [20][21], although at present these models are considered primitive in comparison to the promise of ABM. Technology will soon allow the incorporation of inordinate amounts of real data to generate highly realistic and precise ABMs. These data are becoming available largely through cell phones which are ubiquitous and proxy well for individuals. There will still exist challenges for ABMs in terms of fusing data related to human movement patterns, climate as well as factors impacting latency modeling such as such as diurnal temperature variations. Additional challenges will be related to developing practical hybrid models integrating both equation based population methods as well as individual models. One last point should be made as it relates to the promising use of smartphones, not for tracking, but rather early malaria detection and bio-surveillance [22].

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