Evaluation of Zika Vector Control Strategies Using Agent-Based Modeling

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Abstract. Aedes Aegypti is the vector of several deadly diseases, including Zika. Effective and sustainable vector control measures must be deployed to keep A. aegypti numbers under control. The distribution of A. Aegypti is subject to spatial and climatic constraints. Using agent-based modeling, we model the population dynamics of A. aegypti subjected to the spatial and climatic constraints of a neighborhood in the Key West. Satellite imagery was used to identify vegetation, houses(CO₂ zones) both critical to the mosquito lifecycle. The model replicates the annual fluctuation of adult population sampled through field studies and approximates the population between 1 per 12m² during summer and 1 per 59 m² during winter. We then simulate two biological vector control strategies: 1) Release of Insects carrying a Dominant Lethal gene (RIDL) and 2) Wolbachia infection. Our results support the sustainability of Wolbachia infection within the population from the year of treatment onto the next. For the assessment of these two strategies, our approach provides a realistic simulation environment consisting of male and female Aedes aegypti, breeding spots, vegetation and CO₂ sources.

1 Introduction

Zika, first identified in Central Africa as a sporadic epidemic disease, has grown into a pandemic with cases reported from every continent within the span of a year. South America is currently most heavily hit with over 4200 suspected cases reported in Brazil itself [1]. The primary vector of the Zika virus is the Aedes Aegypti mosquito also responsible for the spread of yellow fever, dengue, malaria and chikungunya.

At the time of writing, the Centers for Disease Control has issued several reports warning the public of the potential devastation of public health that Zika poses in the US. Florida’s warm and humid environment, in particular, provides an excellent breeding ground for A. Aegypti. Public health administration departments like the Florida Keys Mosquito Control District have been monitoring

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and controlling mosquito populations in the region. In addition to the traditional population control methods such as destruction of breeding ground through public cleanups, DDT/insecticide spraying, etc. two biological methods have gained popularity in recent years. The first, the Release of Insects carrying a Dominant Lethal gene (RIDL), involves the release of a large number of genetically engineered mosquitoes into the wild [11]. RIDL uses a ‘suicidal’ gene which prevents the offspring of the genetically modified mosquito from maturing into adulthood.

The second method, an incompatible insect technique (IIT), involves the release of mosquitoes infected with the intracellular bacteria, Wolbachia pipentis, which occurs naturally in insects. However at high concentrations, Wolbachia has been proven to reduce the adult lifespan of A. aegypti by upto 50% [19].

Both vector control techniques have potential long-term difficulties despite their ability to reduce mosquito numbers upon release. The inability of offspring resulting from RIDL to survive into adulthood also means that the Dominant Lethal gene will not be inherited [24]. Therefore, regular releases must be made to maintain long-term sustainability of this approach. On the other hand, Wolbachia infection may transmitted from parent to child through reproduction and remain in the population throughout generations. Yet, spatial and climatic constraints may limit Wolbachia-infected adults from finding mates in the wild or result in infected females being killed off prior to ovipositioning. The production of large volumes of RIDL or Wolbachia-infected A. aegypti may be costly. Attempts to establish a sustained infection of Wolbachia within A. aegypti populations in the wild have been attempted [21]. Therefore, identifying the long-term sustainability and required release volumes of mosquitoes is important.

Despite the difficulty of suppressing the mosquito population as a whole, A. aegypti is quite vulnerable to climatic and spatial conditions on an individual scale. In particular, the fetal/aquatic lifespan (time spent in egg, larval and pupal stages), adult lifespan, mortality rates and probability of emergence are highly sensitive to variations in the temperature. The Key West, despite having a tropical climate with a yearly average temperature range of 10 °C, has been shown to have a reasonable fluctuation in mosquito population throughout the year.

In addition to climatic variations, mosquito survival is heavily dependent on abundance of vegetation, human hosts and breeding sites. The male mosquito depends on vegetation for food, while it is the female mosquito that feeds on the blood of mammals. The female mosquito is attracted to hosts by CO₂ and pheromone emissions and can detect hosts from upto 30m away [8,12]. Vegetation zones must be within reasonable proximity of host locations in order for males to be able to reach females for mating. Finally, there must be an abundance of breeding sites (exposed stagnant water) upon which females must oviposition (lay eggs).

In an effort to identify the sustainability of the two vector control techniques, we use agent-based modeling to simulate the yearly fluctuation of mosquito population dynamics in the Key West. A suburban neighborhood is selected and segmented into vegetation, houses (CO₂ zones) and breeding zones to capture
the spatial constraints experienced by the local mosquito population. Satellite imagery of the neighborhood is processed to identify the exact location of these zones. In addition to the spatial constraints, the monthly temperature variation of the Key West is also simulated as a climatic constraint. Mosquito agents are released into this environment and their population characteristics are observed throughout time. After validating the yearly adult population fluctuation produced by this model, we use it to simulate and compare the two vector control strategies mentioned.

2 Background

A. aegypti has four life stages and undergoes metamorphosis between these stages. The first three life stages (egg, larva and pupa) are spent in water while the final stage (adult) is spent as an airborne insect. Adult females feed on blood of mammal hosts, while males gain nutrition from vegetation. Female mosquitoes are attracted to hosts through CO$_2$ and pheromones upon which they perform a process known as klinotaxis to reach their host. The female A. aegypti prefers to lay eggs closer to urban areas and is considered a domestic pest.

For the purpose of this study climatic constraints on mosquito population are considered to occur through varying monthly temperature. Field studies of A. aegypti in the wild and laboratory experiments have established the relationships of average temperature and mortality rates, probability of adult emergence from pupa and life stage durations. There are several studies in the literature [25,5], which have fit mathematical models relating aquatic/fetal mortality, adult mortality, fetal duration, adult duration and probability of emergence with temperature. Brady et al. [5] found that a much longer duration of adult lifespan was observed in laboratory experiments than in the wild, indicating that the non-climatic constraints played a significant role on the mortality of A. aegypti.

The variety of mosquito population dynamics modeling in the literature includes analytical models, differential equation models and ABMs. ABMs differ from the other models by capturing the spatial interactions among individuals which emerge into macro scale results of small changes in individual characteristics or behaviors of the agents. Our approach employs a spatial model of the A. aegypti population by integrating an ABM with geographic information. Spatial models are used in epidemiology to study population dynamics or to evaluate methods for population control. Evans and Bishop [11] propose a spatial model with pulsed releases to observe the effects of different mosquito release strategies in Aedes aegypti population control. The approach presents a mathematical model to replicate the release strategies and identifies the spatially uniform equilibria of the model. The results of the model show the importance of release pulse frequency, number of release sites and the threshold values for release volume.

Another spatial approach for simulating Aedes aegypti population is SimPopMosq [3], an ABM of representative agents for mosquitoes, some mammals and objects found in urban environments. Two real experimental databases are used to calibrate the parameters used in the simulations. SimPopMosq is used
to study the active traps as a population control strategy and includes no sterile insect agents or techniques. The framework by Arifin et al. [4] integrates an ABM with a geographic information system (GIS) to provide a spatial system for exploring epidemiological landscape changes. However, the ABM used in the framework is designed for the population dynamics of the malaria vector Anopheles gambiae. Lee et al. [18] also investigate the influence of spatial factors such as the release region size on population control. The method uses a mathematical model to study the relation among the location related parameters. Isidoro et al. [15] used LAIS framework to evaluate the RIDL for Aedes aegypti population. The ABM includes independent decision-making agents for mosquitoes and pre-determined rule based elements for environmental objects such as oviposition spots. However the model lacks important factors such as a realistic map or temperature effects.

There are also approaches integrating the mosquito population control models with epidemic models. Deng et al. [9] proposed an ABM to simulate the spread of dengue, the main vector of which is Aedes aegypti as well. The mobility of the mosquitoes in this model are defined by a utility function, which is affected by the population, wind and landscape features. However, the model lacks a granular spatial discretization and only a small number of agents are used. Moulay and Pigne [20] studied Chikungunya epidemic with a metapopulation network model representing both mosquito and human dynamics on an island. The model is created by considering both the density and mobility of populations and their effects on the transmission of the disease.

3 Methodology

We model the population dynamics of mosquitoes in an agent-based model implemented in RePast Simphony [22] consisting of agents embodying the behavior of A. aegypti and feeding and breeding off of designated zones in a geographical environment with monthly changes in average temperature. The distribution of the zones provided spatial constraints on the total population while changing temperature applied climatic constraints. Zones were either locations with CO$_2$ (human hosts), vegetation or breeding sites. The distribution of these zones were determined using geographical analysis of a suburban neighborhood in Key West, Florida. The monthly average temperature in Key West was obtained from [2].

3.1 Life Stages, Processes, Circadian Rhythm and Behavior Modes

The life stages of A. aegypti are simulated in our model. The lifecycle of the simulated mosquito agents is described in Fig. 1. For the purpose of our study, the egg, larva, and pupa stages were considered as a single stage, FETAL, and considered to be inanimate. During the FETAL stage the mosquito remains within the confines of the breeding site. A FETAL has a probability of dying $M_F$ (mortality rate, probability of maturing: $P_M = 1 - M_F$). Once the FETAL agent has survived for $D_f$ days, it emerges into an adult. Emergence is probabilistic
and there is $M_E$ chance of death during emergence (probability of emergence: $P_E = 1 - M_E$).

![Lifecycle of the mosquito agent](image)

**Fig. 1.** Lifecycle of the mosquito agent.

Emerged ADULTs live for $D_A$ days. ADULTs may die during their life processes or due to old age at a rate of $M_A$. New FETALs are created through reproduction with a probability of $P_R$. $P_R$ depends on an individual adult’s ability to find food sources, feed, seek mates, mate successfully, seek breeding zones and oviposition. These processes are constrained by the spatial distribution of the zones and restriction of $D_A$ due to temperature. Further, mating success is probabilistic (probability of successful mating: $p_m$). Adult females may be killed by human hosts while feeding (daily probability of female being killed by human host: $p_h$). $M_A$ and $P_R$, are therefore, subject to various factors and highly variable depending on the individual mosquito’s sex, location in relation to other mosquitoes, location in relation to zones and the temperature of the environment. However, precalculation of $M_A$ and $P_R$ are not required due to the computational nature of agent-based modeling.

In our model, all adult mosquitoes emerge from the FETAL process into the FOODSEEKING process. As shown in Figure 2, when in range of an appropriate food source, the agent switches to the FOODENCOUNTERED process. The female mosquito searches for blood meals by seeking out CO$_2$ sources within the environment, while males seek out vegetation zones. After a period of feeding, the mosquitoes enter the mating phases. The female mosquito agents transition to RESTING until fertilization, upon which she enters the OVIPOSITIONING phase. Meanwhile, male mosquitoes enter the MATING phase and seek
out potential mates, until their energy is depleted upon which they enter the RESTING phase. This completes the daily rhythm of the mosquito.

There are certain conditions of satisfaction for the mosquito agents to transition from one process to another as described in Figure 2. In order for a mosquito to enter into any of the processes described above other than the FETAL process, it must be in the ADULT phase. In order for a female to produce eggs, it must have enough energy or be fed. To enter OVIPOSITIONING, the female must also be fertilized by a male mate.

![State diagram for the adult mosquito agent.](image)

The adult mosquito agents in the model follow a daily rhythmic behavior depending on their current state. A. aegypti circadian rhythms reported by Chadee [6] demonstrated that blood feeding, oviposition, sugar feeding and copulation occurred mostly between 06-09 hours and between 16-18 hours. The mosquitoes rest for the remaining time of the day except atypical biting. Hence, the daily time was partitioned into eight equal segments in our model. Following the information given by Chadee [6], ovipositioning was allowed during the second and fifth segments of the day while feeding was allowed during the second, third, fifth and sixth segments of the day.

### 3.2 Geographical Environment

The simulations were run on a suburban neighborhood (Lat: -81.78095, Lon: 24.55350) in the Key West, FL. An area of 29584 m$^2$ was simulated consisting of two blocks of housing. Satellite imagery was obtained through Google Earth and processed using QGIS (Fig. 3 top-left). After geomapping of the satellite image and noise cancelation, the image was converted to grayscale and segmented through a k-means unsupervised learning algorithm searching for two classes by pixel intensity (Fig. 3 top-right). The resulting polygons were then overlain with a regular grid of points. Each point having 10m spacing between them. The points were then classified according to which class of polygon they intersected on
the map image. The result was a representation of the distribution of vegetation zones and urban areas in this neighborhood (Fig. 3 bottom-left).

Fig. 3. Satellite imagery of the suburban neighborhood simulated in the study being processed and converted to zones simulation in RePast.

The point layer was then imported into Repast as an ESRI shapefile. Each point was then made the center of a circular vegetation zone or CO$_2$ source with radius ($R_C$) or ($R_V$), respectively.

The prevalence of breeding zones depended on the house index (breeding sites per house per week) in the region. The average house index as reported by FKMCD was approximately 20% in 2010 [10,17]. Accordingly, 20% of the CO$_2$ zones were, randomly, also designated as breeding zones with radius ($R_B$). An example of the distribution of zones within the simulated region is shown in (Fig. 3) bottom-right.

3.3 Vector Control Strategies

Superinfection of mosquito populations in the wild with the naturally occurring intracellular bacteria, Wolbachia (also referred to as Incompatible Insect Technique (IIT)) result in Cytoplasmic Incompatibility. Crosses between infected
males and uninfected females result in no offspring and has been used in suppression of mosquito populations in the wild [26]. Most pathogens transmitted by mosquitoes require a development period before they can be transmitted to a human host [19]. The time period from pathogen ingestion to potential infectivity, the extrinsic incubation period (EIP), is about 10 days for Zika. Wolbachia has been shown to reduce the lifespan of A. aegypti by upto 50% [19]. Reduced life time of adult female mosquitoes leads to a reduction in the probability of adult female mosquitoes biting humans and resulting mitigates the transmission of vector-borne disease such as Zika. Sustained Wolbachia infection has been induced in wild mosquito populations by releasing infected females (crosses between infected females and uninfected or infected males results in Wolbachia infected offspring) [16, 14, 19].

On the other hand, RIDL depends on the artificial genetic alteration of the mosquito to become dependent on tetracycline. Mosquitoes reared in the laboratory are provided on tetracycline and then released into the wild. The resulting offspring die before reaching adulthood due to the absence of tetracycline in the wild. RIDL mosquitoes are usually male, to avoid increasing human-biting mosquitoes by releasing females [13]. Further, unlike Wolbachia infection, female release is unnecessary since a sustained introduction of RIDL cannot be maintained as all offspring are killed. Potential disadvantages of RIDL have been discussed in [24].

Mosquito agents in the model could be infected with Wolbachia. Mating between uninfected females and infected males results in $DA = 0$ for all offspring. Mating between infected females and uninfected/infected males results in all offspring being infected with Wolbachia. $DA$ of these offspring will be halved.

Mosquito agents may carry the RIDL gene. Only released RIDL mosquitoes will be able to survive in the environment as adults. All children resulting from a RIDL parent will inherit RIDL and set $DA = 0$. Finally, for RIDLs $PM = 0.5$ as reported in [24].

4 Experiments

The agent-based model was validated against actual weekly catch rates of the Aedes aegypti population in the Key West. The validated model was then used to evaluate the two control strategies (RIDL and Wolbachia infection) over a simulated period of two years. For every experiment, the simulation was allowed to run for 2 simulation years prior to data collection, in order to allow the agents to fit the constraint patterns of the environment. Data collection was performed after the 2nd simulation year and performed for 2 simulation years. FKMCD [10, 17] indicates the mean maximum of Aedes Aegypti caught in traps set up near households is 20 per trap per night. Hence, our simulations were initialized with 20 larvae in each breeding site. Values of the other parameters used in all simulation experiments and their sources are listed in table 1.
Table 1. Parameters used in the model (T: Monthly Temperature)

| Parameter Definition                                      | Value       | Source |
|-----------------------------------------------------------|-------------|--------|
| $spd$ displacement speed                                   | 0.5 - 1 m/s | [3,8]  |
| $D_{f1}$ Mean duration of egg stage                        | $f(T)$      | [23]  |
| $D_{f2}$ Mean duration of larval and pupal stages         | $f(T)$      | [23]  |
| $D_F$ Mean duration of FETAL stage                         | $D_{f1} + D_{f2}$ |        |
| $D_A$ Mean duration of ADULT stage                         | $f(T)$      | [23]  |
| $M_F$ FETAL mortality rate                                 | 0.3         | [23]  |
| $m_i$ Probability of successful emergence                  | 0.3         | [23]  |
| $r_c$ Detection range for CO$_2$ zones                    | 30 m        | [3,8] |
| $r_v$ Detection range for vegetation zones                 | 30 m        | [3,8] |
| $r_b$ Detection range for breeding zones                   | 30 m        | [3,8] |
| $r_m$ Detection range for mates                            | 30 m        | [3,8] |
| $r_m$ Number of mates per male per day                     | 5           | [7]   |
| $r_m$ Probability of successful mating                      | 0.7         | [3]   |
| $r_m$ Number of times a female can lay eggs in one lifetime| 5           | [7]   |
| $r_m$ Eggs laid in one oviposition                          | 63          | [11]  |
| $r_m$ Duration of one oviposition                           | 3-4 days    | [11]  |
| $d_w$ ADULT duration decrease due to Wolbachia             | 50%         | [19]  |
| $d_l$ ADULT duration decrease due to lethal gene           | 100%        | [24]  |
| $d_m$ Mating success of RIDL males                          | 50%         | [24]  |

4.1 Model Validation

As a sampling of the total population of A. aegypti in the wild, the catch rate of mosquitoes is directly correlated to the actual population of mosquitoes in the region being tested. We used mosquito catch rates in the Key West as an empirical stylized fact to validate the trend in mosquito population throughout the year as generated by our model. The same trend was expected, and the predicted numbers resulting from the simulation represent the actual number of mosquitoes that can thrive with the given spatial and climatic constraints in the region. FKMCD has performed trapping and counts of mosquito and larval population in the Key West and have reported that the catch rate of A. aegypti (mosquito caught per trap per night) varies at peak of 10-20 individuals during the months of June to September when the climate is warmer and more humid. The highest reported catch rate is 20 mosquitoes in August, 2010 [10]. In the colder and drier months between October and May the catch rate tends to stay below 10.

For validation, we performed multiple runs of our model and compared the aggregate adult population numbers with the trends seen in the actual catch rates throughout the year. The model was made to simulate 2 years prior to data collection. During this initialization phase, the trend in population of mosquitoes settled down to fit the spatial and climatic constraints of the model. Years 3, 4 and 5 were used for comparison for validation. For robustness of results this
process was repeated with different numbers of initial mosquitoes (20, 40, 60 and 100) per breeding zone. The parameters for the spatial and climatic constraints were kept fixed as specified in table 1. The simulation output matched the annual fluctuation reported in [10] with large numbers of adult mosquitoes during the warmer months and a sharp decline during the colder months. Our results show that with the spatial and climatic constraints found in a typical Key West neighborhood, a maximum of around 2400 mosquitoes may be present in the summer months. We also see that the adult population manages to remain above 500 during the colder months, preventing extinction of the species (Fig. 4).

4.2 Vector Control Evaluation

We adopt a mosquito release strategy similar to that employed in [21] for a field study on establishing Wolbachia infection in the A. aegypti population in Machans Beach, Australia. Using the same ratio of females to male released in [21], we made 4 releases of Wolbachia infected mosquito agents (1300 males and 420 females per release) over 4 months starting from the July of the first year. Releases were conducted from a randomly selected breeding zone for each run. Separately, a total of 1720 RIDL males were released using the same release pattern as for the Wolbachia case to simulate the release of RIDL into the wild. For comparison, a control experiment, where no vector control strategies were
applied was conducted. In each of the three cases mentioned, the simulation was seeded with 20 mosquitoes and allowed to settle for two years after which data was collected. Data was aggregated over ten runs of each case.

Fig. 5. Comparison of vector control strategies on the number of female mosquitoes over a period of three years.

It was seen that immediately following the final release of both RIDL and Wolbachia, the number of female mosquitoes reported was dropped lower than when no control strategy was employed (Fig. 5 first year Sep to Dec). However, considering the number of mosquitoes released in order to achieve this decrease (approximately 50 for RIDL and 100 for Wolbachia), the result was insignificant.

Fig. 6 demonstrates the sustainability of both vector control strategies over the year of release. As RIDL could not be inherited into the next generation, the number of RIDL mosquitoes dropped rapidly within the period of a month. However, Wolbachia was inherited into the resulting generations and continued to persist throughout the year of release and onto the next.
Conclusion

We have designed an agent-based model of the mosquito population in the Key West, Florida in an effort to address the control of the Zika pandemic. The primary vector of Zika, Aedes aegypti was modeled on a geographical space representing a suburban neighborhood. By using satellite imagery we have captured the spatial distribution of houses (CO2 zones), vegetation zones and breeding sites. Additionally, we have simulated the monthly variation in temperature in the Key West. Using these spatial and climatic constraints the annual cycle of the mosquito population has been replicated by this model to match the weekly catch rates reported in field studies. It was shown that the spatial and climatic constraints in the Key West allowed for a maximum of approximately 2400 mosquitoes in the summer months yet maintained a low of above 500 during the winter months.

Two vector control strategies were implemented on top of this model. The first strategy, Release of Insects carrying a Dominant Lethal gene (RIDL), involved releasing males that would produce offspring that could not survive into adulthood. If these males competed successfully with wild males for mates, then the population would reduce as a result. The second technique was the release of Wolbachia infected mosquitoes. Infected males that mated with uninfected females would result in dead offspring, while infected females would produce offspring with Wolbachia infection. The volumes of Wolbachia infected males and females released were determined using the ratios applied in a field study [21]. The total volume of RIDL males released was equal to the total Wolbachia infected mosquitoes released. Despite a slight drop in the total female population, there was no significant change observed. This may be due to the lack of volume of males with each release.

However, it was observed that after the release of Wolbachia infected mosquitoes, the infection persisted in the population as observed by [21]. On the other hand,
the number of RIDL mosquitoes returned to 0 after one mosquito-lifetime had passed, with every release. In other words, introduction of Wolbachia into the population proved to be a potentially sustainable vector control strategy in comparison to RIDL.

Importantly, this model can be used to simulate what-if scenarios to experiment with the release volumes and frequencies of vector control strategies for A. aegypti. The spatial and climatic constraints captured in this model allow it to closely represent the distribution of A. aegypti in Key West and the same technique can be applied for any geographical location.

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