

EXPLORING THE DYNAMICS OF GENE DRIVE MOSQUITOES WITHIN WILD POPULATIONS USING AN AGENT-BASED SIMULATION

Sureni Wickramasooriya^a, Imran Mahmood^b, Anisoara Calinescu^b, Michael Wooldridge^b, and Gregory Lanzaro^a

^aDepartment of Pathology, Microbiology and Immunology, University of California, Davis, USA

^bDepartment of Computer Science, University of Oxford, UK

ABSTRACT

Gene drive technology is emerging as a potentially powerful tool in combating vector-borne diseases – notably malaria. This study introduces an agent-based model (ABM) focused on the deployment of genetically engineered mosquitoes with gene drive (GEM) in Príncipe Island, Republic of São Tomé and Príncipe, an island nation in the Gulf of Guinea, West Africa. Grounded in empirical data from laboratory and field studies, our model forecasts the dynamics of mosquito populations central to devising efficacious GEM release strategies. The core objective is to evaluate the time required for GEMs to constitute 90% of the mosquito population and to elucidate their dispersal throughout the island. This research is instrumental in understanding GEM potential in controlling malaria vectors.

Keywords: genetically engineered mosquito (GEM), gene drive, agent-based model (ABM), geo-spatial simulation, complex agent interactions

1 INTRODUCTION

Integrated vector control programs have been deployed to control malaria throughout Africa. These programs include the use of insecticide-treated nets (ITNs), indoor residual spraying (IRS), activities targeting mosquito larvae, and distribution of antimalarial drugs [1, 2]. Despite partial success, the disease continues to claim a significant number of lives. In 2022, the World Health Organization reported 233 million cases with 619,000 deaths globally attributed to malaria [3].

The ongoing challenge underscores the critical need for more effective strategies to curtail malaria's prevalence in Africa. One innovative approach gaining traction is gene drive technology. This technique involves the introduction of genetically engineered mosquitoes to suppress or modify local disease-carrying populations [4, 5, 6, 7]. A population modification (sometimes referred to as population replacement) strategy is emerging as a promising solution [8]. This method entails the introduction and spread of genes which encode products that block the malaria parasite in the mosquito. The construct includes an autonomous Cas-9-based gene drive which biases transgene inheritance favoring its rapid increase in frequency over multiple generations and its spread throughout local mosquito populations via normal mosquito dispersal [9, 10, 11]. This strategy is currently being evaluated by the University of California Malaria Initiative (UCMI).

The UCMI is working, in collaboration with stakeholders, in the West African island nation of São Tomé and Príncipe as a site for conducting a trial of their GEM. The first release is proposed for the island of Príncipe. Here, we present a model of the potential outcome of this trial. Príncipe covers an area of 143.16 square kilometers and has a population of approximately 8,420 [12]. The climate is mostly tropical, characterized by a nine-month rainy season (September to May) and a dry season (June to August). There is only a

single malaria vector present on the island: *Anopheles coluzzii*. For the proposed trial, a total of 1512 genetically engineered, gravid, female *A. coluzzii* will be released in the city of 'Santo Antonio', Príncipe. These mosquitoes are expected to lay eggs on the same day of release. After 14 days, adult mosquitoes originating from these eggs will emerge. These adults will interact by mating with the wild-type, resident mosquitoes. As a consequence of the gene drive, nearly 100% of the progeny from these matings will inherit the malaria-blocking transgenes. This genetic integration should, over a relatively short number of generations, transform the wild mosquito population into one predominated by GEMs.

The impact of this integration is profound. As the local mosquito population becomes increasingly composed of GEMs, the number of mosquitoes capable of transmitting malaria is expected to decline sharply. This reduction could lead to a significant decrease, or even elimination, of malaria on the island. By utilizing genetic modification, this innovative approach targets the malaria parasite in the vector, but not the vector itself, which will persist in the environment after the parasite has been eliminated, thereby preventing malaria reintroduction.

Understanding how the GEM interacts with the wild mosquito population and how it spreads from the release site to neighboring communities is crucial for assessing the effectiveness of this strategy. To approach this question we developed a geospatial, heterogeneous, data-driven, agent-based model (ABM) to simulate the release of the UCMi GEM on the island of Príncipe. The proposed model implements the following features:

- (a) Initialization, growth and deaths of wild mosquito population in the selected area, given an average age of 21 days.
- (b) Progress through the life-cycle of mosquitoes: egg, larva, pupa and the emerged adult and keep track of the survivability of each form based on the environmental conditions and the survivability probability.
- (c) Simulating the movement patterns of mosquitoes using the ecological phenomenon and resistance surface, taking into account the elevation of the island and its land use.
- (d) Simulating the mating process of male and female mosquitoes, implementing the oviposition behaviour and the logic for gene inheritance.
- (e) Simulating the release of gravid female mosquitoes (GEM) at the designated site, 'Santo Antonio'.
- (f) Simulating the evolution of population through the interactions of agents of different genotypes (e.g., WW = wild, DD = GEM, DW = mixed).

The research focus and goal of this ABM is to analyze the dynamics of populations of different genotypes (WW , DD and DW), and to determine the time required for the GEM population ($DD + DW$) to achieve a frequency of 90% of the total *A. coluzzii* population at the study site. By analyzing population dynamics over time and space, this model aims to provide valuable insights into the dispersal patterns of GEMs, informing decisions about the broader impact and success (defined as the frequency of $DD + DW \geq 0.90$) of the UCMi GEM release strategy. It further allows for analysis to inform optimal release sites, number of releases, and optimal time of release.

The paper is structured as follows: Section 2 presents background concepts and literature review. In Section 3, we describe our proposed framework. The simulation results are presented in Section 4, and Section 5 reports conclusions arising from our results and outlines directions for future work.

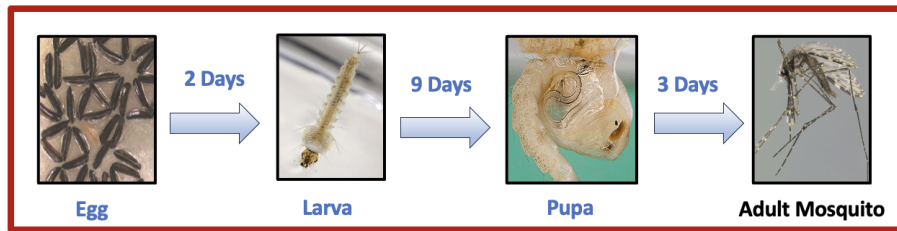


Figure 1: Visual guide to *A. coluzzii* life stages and transformations .

2 BACKGROUND AND LITERATURE REVIEW

2.1 Background

2.1.1 Malaria Vector *Anopheles coluzzii*

Malaria is transmitted through the bite of infected female mosquitoes belonging to the genus *Anopheles*. Of the roughly 530 species in this genus only 40 transmit malaria [13]. One of the most important malaria vector species is *Anopheles coluzzii* which transmits malaria throughout its range in west and central Africa.

The life cycle of *A. coluzzii* includes aquatic immature and terrestrial/aerial adult stages. Its life cycle begins with the egg stage. Eggs hatch approximately 2 days following oviposition. Newly hatched larvae pass through four larval stages, known as instars, before becoming pupae; a process that takes typically nine days. After an average of three days in the pupal stage, adult mosquitoes emerge (eclose) and fly off. The life cycle is illustrated in Figure 1. The duration of each stage was obtained by UCMI researchers from detailed life table experiments.

The seasonal behavior of *A. coluzzii* is primarily influenced by meteorological and geographical factors, especially temperature, relative humidity, and rainfall. This species exhibits a preference for regions at low to moderate elevations. Eggs are deposited and immature stages develop in clear and slowly moving or still freshwater, often in man-made sources. In this study, we evaluate the survival probabilities of mosquitoes from eggs to adult based on our own data and those obtained from Parham et al. (2012) [14]. We then integrate climate data, including monthly average temperature, rainfall, and relative humidity at the target field site, to provide a comprehensive understanding of the environmental conditions influencing mosquito life stages. This information is used to create a database containing daily survival probability for each stage throughout the year.

2.2 Literature Review

Modelling of the population dynamics and ecological consequences of a GEM with gene drive may be useful in assessing efficacy and identifying potential risks [15]. A vast number of gene drive models have been put forth over the past decade [16, 17]. Generally, these can be grouped into two types: epidemiological models and population genetic models. The former are frequently extensions of earlier vector-borne disease models that included mosquito-life history parameters [18, 19, 20, 21, 22, 23]. Outcomes generated from these models are typically expressed in terms related to disease reduction (epidemiological outcomes). Population genetic-based models focus on changes in allele frequencies resulting from environmental, demographic, and/or fitness effects [24, 25, 26, 27]. These models generate output in terms of gene frequencies (entomological outcomes).

Gene drive mechanisms, such as CRISPR/Cas9, have been developed to edit genes with the idea of conferring resistance to pathogens that cause vector-borne diseases. Burt (2003) [28] introduced gene drive

technology as a means to control mosquito populations. Multiple new developments, such as the work of Carballar-Lejarazu et al. [8, 29], have been undertaken to enhance the efficiency of vector-borne disease prevalence. These efforts aim to systematically pass on the genotype of the GEMs to new generations, disrupting disease transmission cycles effectively. Recognizing the potential population dynamics and ecological consequences of GEM in actual ecosystem settings before releasing them is crucial for identifying environmental impacts and conducting effective risk assessments [30]. In an effort to gain insight into the expected behavior of gene drive systems within real ecosystems, several modeling frameworks have recently been developed. To gain insight into the anticipated behavior of the gene drive systems within real ecosystems, several modeling frameworks have recently been developed. The *CIMSiM* model [18] stands out as one of the earliest gene drive simulation approaches. It is a spatially explicit simulation model originally crafted for investigating the population dynamics of *Aedes aegypti* mosquitoes, known vectors for the transmission of diseases such as dengue fever. Subsequently, the scope of the model broadened to encompass other vector-borne diseases, including the dynamics of malaria transmission. This weather-driven, dynamic life table simulation model aims to spread a specific genetic change within a population, potentially causing changes in the characteristics of the targeted species. The expanded edition *Skeeter Buster* [19, 20], demonstrates advanced capabilities in forecasting population dynamics and discerning the population genetics impacted by stochastic and spatial fluctuations in mosquito habitats. Despite its biologically rich modeling implementation, which comprehensively captures various aspects of mosquito ecology, this software is not available as an open-source tool and only facilitates a limited set of genetic control strategies. In 2011, Eckhoff [21] introduced a large-scale open-source individual-based model known as the *EMOD* malaria model. This model was specifically designed to simulate a gene drive system tailored for the *Anopheles gambiae* mosquito variety. The model includes distinctive parameter values tailored to this specific mosquito variety, as well as the influence of weather and the outcomes of various concurrent interventions. However, the task of adapting the *EMOD* model for other mosquito strains is complex and requires additional effort. The *MG-Drive* framework, another widely recognized model, is an extension of a mosquito ecology model initially proposed by Hancock and Godfray in 2007 [22]. This extended framework integrates genetic and spatial factors into its structure. Deredec, Godfray, and Burt adapted the model in 2011 [23] to explore homing gene drive systems, and later, in 2017, Marshall et al. [31, 32] applied it to investigate population-suppressing homing systems in the presence of resistant for drive.

2.2.1 The Agent-Based Model (ABM)

We discuss the significance of employing an ABM on a real-world scale, particularly its applicability in modeling the release, to this end. With the ongoing advancements in computational power, ABMs have undergone significant evolution, finding a diverse array of real-world applications and explorations in recent years [33]. In the context of ecology, a comprehensive review of recent literature highlights the increasing utilization of ABMs to address challenges that traditional equation-based methods struggle to effectively tackle [34]. ABM is applied to address the most complex ecological phenomena, as exemplified in recent research, such as analyzing the interaction between hosts and vectors in vector-borne diseases [35]. The key components of ABM including the collection of agents (or individuals) and the rules that define individual behaviors and interactions with other agents and the environment. This framework creates a customized artificial environment, populating it with individual entities, and enables researchers to simulate and analyze the interactions and behaviors, examining the micro-level dynamics within the system. Given that we are introducing gene drive mosquitoes, there is a keen interest in closely examining the micro-level dynamics to establish the rules governing the behavior of these mosquitoes. Considering the mentioned advantages, and to effectively model the introduction of GEM into the local mosquito population, we have proposed an agent-based modeling approach. In our ABM model, mosquitoes serve as the agents, and we integrate GIS data and mapping on Príncipe Island to illustrate the spatial distribution of these agents. Our framework

is briefly summarized in Figure 2, illustrating the components that align with the key elements: Agents, Environment, and Behavioral Rules.

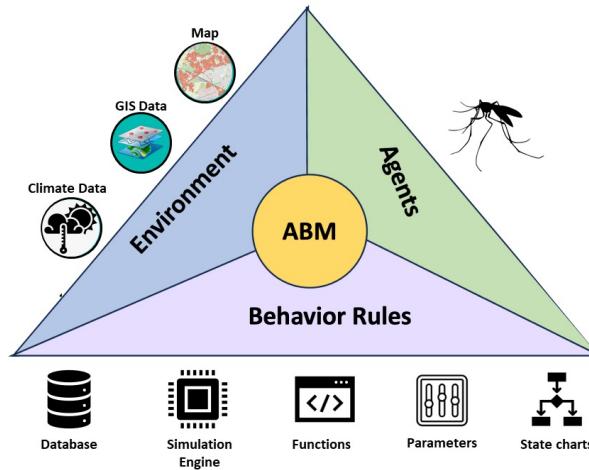


Figure 2: Agent-based model structure .

3 PROPOSED MODEL

In this section, we present our proposed ABM framework, which contains three layers as seen in Figure 2: (i) Life Cycle; (ii) Movements and Dispersal and (iii) Mating and Oviposition. Our intention has been to appropriately integrate laboratory and field data for a detailed micro-level analysis. These data were provided by the Vector Genetics Laboratory at the University of California, Davis. The subsequent sections provide a systematic discussion of the model structure for each layer.

3.1 Life Cycle and Behaviour

This layer in our proposed ABM deals with two distinct types of agents: female mosquitoes and male mosquitoes and integrates the rules and parameters governing their life cycle, from egg, to growth, and death. The life stages are visually represented in a state diagram (Figure 3a). Upon completing 14 days in the immature stages, an adult mosquito emerges from the pupal stage. Post-emergence, the initial behavior for both genders is 'moving and seeking food'. The transitions between stages align with the methodology outlined in Section 2.2.1, wherein each stage progresses based on a given survival probability. Transitions between stages linked into the dead state in the state chart are associated with mortality for the respective stage. A generic survivability function has been implemented to incorporate these probabilities, which can further be extended to account for environmental conditions and climate data.

3.2 Movements and Dispersal

In this layer the movements and dispersal of the female and male agents are implemented. The movement patterns of mosquitoes plays a crucial role in modeling dispersal, as it directly influences how individuals spread across the landscape. We hypothesize that land use and elevation are key factors that significantly impact mosquito movement. Resistance in ecology, specifically in the context of mosquito movements, refers to the factors or obstacles that impede or hinder the ability of mosquitoes to disperse or migrate within their environment. These factors can include physical, environmental, or ecological barriers that restrict the movement of mosquitoes from one location to another. The classification of resistance factors

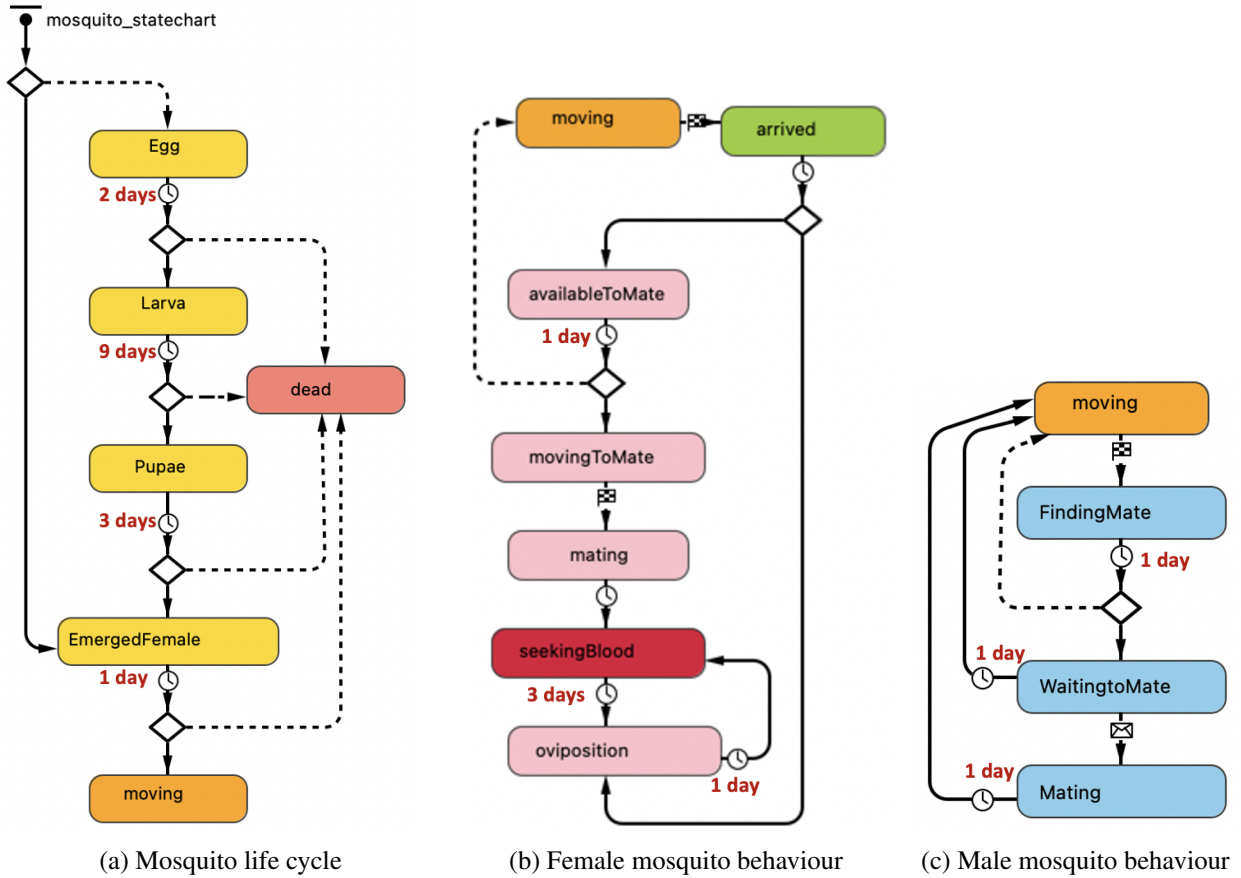


Figure 3: states chart for life-cycle, male and female behaviour .

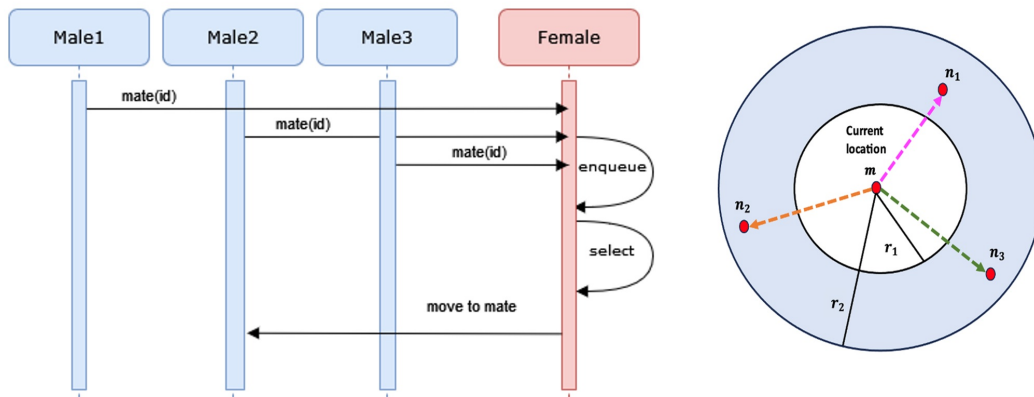


Figure 4: (a) mating process (b) agent flight region .

is outlined in Table 1. The movement resistance (R_k) at any given point k can be calculated by considering these factors. Specifically, to calculate the resistance at a particular point, we sum the product of resistance levels with the corresponding weight assigned to each factor.

$$R_k = (l_{ij} \cdot w_{ij})_{\text{Elevation}} + (l_{ij} \cdot w_{ij})_{\text{Land use}} \cdot \quad (1)$$

i is the longitude and j is the latitude of point k .

A. coluzzii is capable of flying the daily average distance ranging from $r_1 = 170$ meters to $r_2 = 1736$ meters, (unpublished data provided by VGL). Figure 4(b) illustrates a flight region where an individual travels from its current location, point m , to the point within the blue region (i.e., between r_1 and r_2) of the point n . The possible destination points are characterized by $\{n_1, n_2, n_3, \dots\}$. By assuming that the least cost path of the mosquito is proportional to the resistance and the distance to the destination, we modify the least cost equation introduced in [36], according to which, the new point is determined by optimizing the minimum cumulative resistance (MCR_{min} of the destination points n).

$$MCR_{min} = \min \{ (R_n - R_m) \times D_{mn} \} \cdot \quad (2)$$

D_{mn} is the distance between the points m and n .

This process ensures an efficient path from the starting location to a specific point, optimizing the mosquito's flight dynamics.

Table 1: Resistance Factor Classification .

Resistance Factor	Classification Index	Resistance Level l_{ij}	Weight w_{ij}
Elevation	40 meters-290 meters	1	0.5
	>290 meters or <40 meters	2	
Land Cover Type	Urban, Construction sites, coastal wetlands	1	0.5
	Vegetation, Arable, Permanent crops, shrub	2	
	Industrial, Artificial	3	
	Water bodies, Wetlands, Pastures, Forests	4	
	Open space	5	

Based on Equation 2, we implemented the movement using Algorithm 1. This retrieves the new point with least resistance, and is used by the mosquito agent to move to.

Algorithm 1 Movement Based on Elevation and Landcover .

Input: Current coordinates (latitude, longitude) of the agent, Target region for the agent to move within

Output: New point (coordinates) for the agent to move to

▷ These points represent potential new positions for the agent

1: Generate a set of random points within the region of radii r_1 and r_2 , as shown in figure 4(b)

2: **for** each random point generated **do**

3: Retrieve the elevation value and land-cover type at the current coordinates of the agent

▷ we use a GeoTools open-source library to fetch this data from the offline GIS datasets

4: Compute the 'cost of resistance' to move from the current position to this point.

5: **end for**

6: Compare the computed costs for all random points.

7: Select the point with the minimum cost of resistance.

▷ This is the most efficient path for the agent

8: **return** the new coordinates of the agent.

3.3 Mating and Oviposition

This layer deals with the implementation rules for mating and oviposition. Once a female mosquito arrives at its destination, it enters the arrived state. For the wild population type, the female mosquito assumes the *availableToMate* state, indicating readiness for mating. Conversely, if the mosquito is injected as a gravid female, then it directly transitions to the Oviposition state, signifying that the mosquitoes are now prepared to lay eggs (see Figure 3b). The male and female activities and transitions are illustrated in Figure 3c and Figure 3b respectively. After the movement is completed, male mosquitoes enter the *FindingMate* state, actively seeking potential female mates. This is implemented through message passing, where the male sends a message 'mate':'id' to all available (and ready to mate) females within a 50-meter range and transition into the *WaitingtoMate* state, anticipating a response from a female. If there is no response within 1 day, the male mosquito relocates to a different location, as illustrated in Figure 3c. Female mosquitoes, in the *availableToMate* state, get a number of 'mate' messages and queue them in a message queue. Then the female randomly select a male from the message queue (in future we plan to improve this random selection by incorporating female preferences towards male characteristics). After selection the female responds to the selected male by sending a response message and transitions into the *movingToMate* state, by moving towards the chosen male to initiate the mating process. The male when receives the female's response engage in the mating. This process is illustrated in a sequence diagram, as shown in Figure 4(a). During mating, the male shares its genotype with the female, a critical step for passing on genetic information to future offspring. Subsequently, after completing the mating state, male mosquitoes rest for a day before relocating, and the cycle repeats until their 21-day lifespan concludes.

The behavior of female mosquitoes is characterized by distinct phases. After engaging in mating, females transition to the *seekingBlood* state, actively seeking blood to facilitate the production of eggs. Subsequently, they enter a resting period of 3 days before initiating the egg-laying process. Female mosquitoes in the oviposition state lay their eggs during this phase. Following the release of eggs, the female mosquito returns to the *seekingBlood* state, preparing for the next egg production cycle after 3 days. This cycle is designed to run for three iterations, reflecting the concept that a female mosquito is capable of laying eggs three times during her lifetime. For the new offspring, their locations are set to the current instance where the oviposition female laid them, and their age is initialized to 0.

In this study, we are investigating two types of mosquito chromosomes: the local wild type (W), found naturally in the local mosquito population, and the modified gene drive type (D), designed to inhibit the transmission of the malaria pathogen. There are three genotype categories in our system: WW , representing mosquitoes with both wild-type chromosomes, typically the local wild; DD , indicating mosquitoes carrying exclusively the gene drive; and DW , signifying mosquitoes with one wild-type and one gene drive chromosome. Figure 5 illustrates the variation of genotypes based on the combination of chromosomes, while Table 2 demonstrates the probabilities of gene inheritance from parents to offspring resulting from cross-mating. We use the gene inheritance outputs developed by Marshall et al. [32] to determine the probabilities of inheritance. Subsequently, we select the potential offspring probabilities that represent the maximum probability among all combinations.

In the simulation, we initially release gravid female mosquitoes carrying the DD genotype, resulting in the offspring also having DD eggs. When these eggs mature and reach the reproductive stage, they can mate with either other mosquitoes carrying the DD genotype within the same cluster or with local wild-type mosquitoes carrying WW . As a result, the second generation is a mix of both DD mosquitoes (resulting from DD mating with DD) and a new genotype, DW – formed when DD mates with WW , marking the progression of the system. Importantly, both DW and DD mosquitoes are considered gene drive mosquitoes because they are incapable of transmitting malaria.

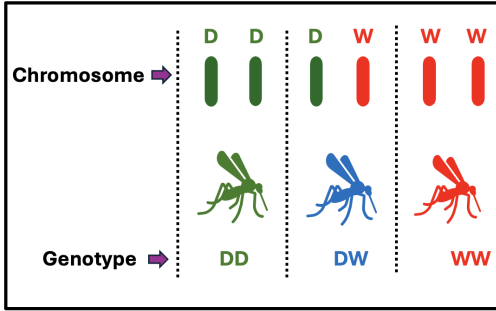


Figure 5: The figure illustrates three genotype categories of mosquitoes, DD (green), DW (blue), and WW (red) resulting from various combinations of chromosomes D (Drive) and W (Wild).

Cross-Mating genotypes	Offspring genotype
$DD \times DD$	DD
$DD \times DW$	DD
$DD \times WW$	DW
$DW \times DW$	DW
$DW \times WW$	DW
$WW \times WW$	WW

Table 2: The first column illustrates the genotypes of parents when they cross-mate, and the second column depicts the potential offspring genotypes resulting from the parental cross.

Initially, there is an increase in the number of DW mosquitoes, followed by an expected increase in DW mosquitoes resulting from the mating of DW and DD individuals. This trend reflects an efficient approach to malaria prevention by replacing the wild-type mosquitoes with gene drive mosquitoes. Table 2 outlines the potential genotypes with the highest likelihood for the offspring, based on the probabilities associated with all the combinations of parental cross-mating.

3.4 Initial wild mosquito population size

The UCMI team conducted field trials to investigate the distribution of *A. coluzzii* on the island of Príncipe. They found that *A. coluzzii* occurs predominantly in the northern part of the island. *A. coluzzii* is absent or rare in the southern portion of the island, which is covered by heavy forest and has very few human inhabitants. Accordingly, in this model, we constrained the distribution of mosquitoes to the upper part of the island. To determine the initial wild population size for our simulation, we utilized the results of two mark-release-recapture studies conducted in Santo Antonio, Príncipe, one during the wet and one during the dry season. The unpublished results from these trials (UCMI) are employed to determine the population size by integrating them into the population size estimation index – the Bailey index [37], as shown in Equation 3.

$$P = \frac{2m(c+1)}{(r+1)}. \quad (3)$$

where P – population size, m –marked and release female, r –recapture marked population size, c – total captured population size. The initial wild population size is 218,630, computed by taking the average of

Table 3: The estimated population size in wet and dry season .

Season	m	r	c	P
Wet	3750	35	1160	241875
Dry	5000	12	253	195385

the measure, P , in both wet and dry seasons (refer to Table 3).

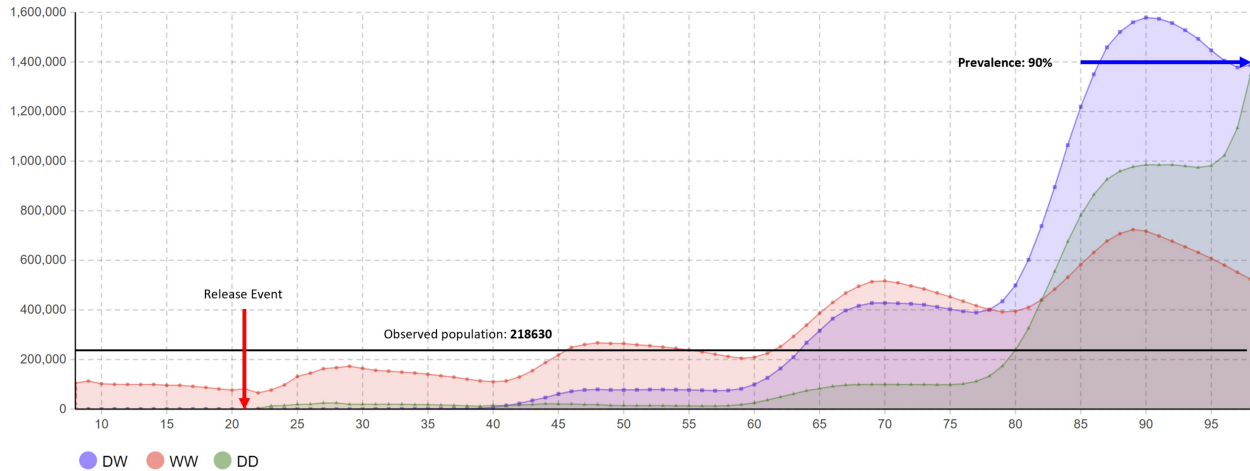


Figure 6: Simulation results .

4 SIMULATION RESULTS

We ran a series of simulation experiments with different initialization parameters (including initial wild population, their initial distributions and random initial ages). The simulation starts with an initial local wild population, characterized by the genotype *WW*, randomly distributed across the region. On day 21, 1512 GEM gravid females, carrying the gene drive eggs, are released. The gravid females released the eggs on the same day. Figure 6 shows a typical run of 100 days, where the wild population (shown in red) and GEM (shown in green and blue) are evolved over time. A spatial and temporal visualization of a simulation run is depicted in Figure 7. It shows the spawning of eggs (male=blue, female=red) after the release of gravid female (green). After the release of GEM, the system initially comprised only the GEM with the genotype *DD*. As time passed, the genotype *DW* emerged as a result of mating between *DD* and the local wild carrying *WW*. Both populations *DD* and *DW* increased, surpassing the local wild population. Ultimately, the leading population in the system became GEM, achieving 90% prevalence within 100 days.

These simulation results apparently show a continuous increase in the different genotypes, as a result of a snow-ball effect. Whereas the ecology data collected from the site shows a convergence towards the equilibrium of the local population. In this ABM framework, we used some simplistic assumptions such as mosquitoes deaths (age of an adult mosquito > 21), unlimited supply of food and no environmental conditions or external control measures. However, in the real-world, mosquito mortality is influenced by various factors, including vector control measures in the region and the availability of food, and unfavourable climate conditions. Hence, the population size does not tend to converge to an equilibrium state. An extension of our model to such external factors affecting mosquito mortality and reproduction, may impact the dynamics of the mosquito population. Also, once the actual experiment is performed we expect to receive real data from the test site about the mosquito movements, population growth, and reproduction which will help get a better hold on model calibration and validation. For the purpose of verification, we have conducted unit tests at the code level, integration tests and the layer level and system testing at the model level.

5 SUMMARY AND CONCLUSION

The research presented in this paper offers an in-depth analysis of the dynamics of gene drive mosquitoes release on the African island of Príncipe within the wild populations using an agent-based simulation. Utilizing an agent-based modeling and simulation framework, the study intricately explores the life cycle, behavior, movement, dispersal, mating, and oviposition of these genetically engineered mosquitoes, and their

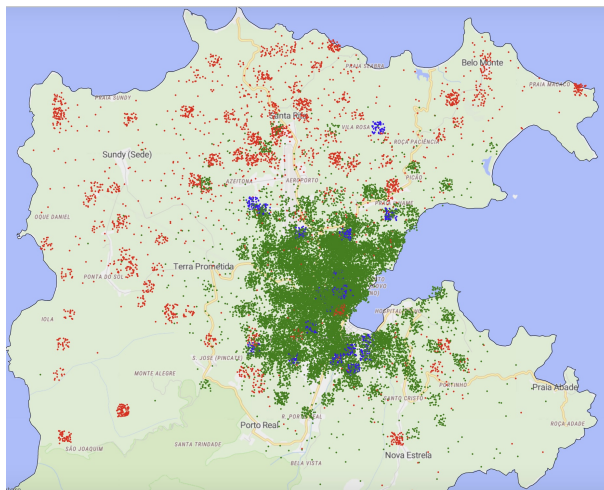


Figure 7: Visualization of the release site on day30 [red=WW, green=DD, blue=DW] .

interactions with the wild population. The proposed agent-based model contributes towards the cutting-edge, sustainable method to combat malaria using genetic engineering. The findings of this research are instrumental in developing and refining gene-drive mosquito release strategies at different target areas, and hence provide as a decision support framework.

Our proposed model can be conceived as a prototype. In future, we aim to enhance the precision and utility of this research by developing an open-source platform for the framework, hence aim at the high performance and scalability of the simulation model, and provide a more detailed and accessible tool for analyzing and implementing gene-drive mosquito release strategies. We further aim to apply different calibration techniques to improve our population dynamics, movements, dispersal and reproduction algorithms.

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AUTHOR BIOGRAPHIES

SURENI WICKRAMASOORIYA is a post-doctoral scholar in the Pathology, Microbiology, and Immunology Department at University of California, Davis School of Veterinary Medicine. She previously served as an Assistant Professor at Kansas Wesleyan University. She obtained her PhD from Clarkson

University in the United States. Her research focuses on population dynamics and modeling ecological problems. Email: sswickramasooriya@ucdavis.edu

IMRAN MAHMOOD is currently working as a Senior Postdoc Researcher at the Department of Computer Science, University of Oxford. He served at University of South Florida and Brunel University London as research fellow. He is a Tenured Associate Professor at the Department of Computing, School of Electrical Engineering and Computer Science (SEECs), National University of Sciences and Technology, (Pakistan); and Director of the Center for Research in Modeling & Simulation (CRIMSON). He is a IEEE senior member, ACM/SIGSIM Professional member, member society of operations research and global network of models of infectious disease agent study scientists (MIDAS). [Profile](#). Email: imran.hashmi@cs.ox.ac.uk

ANISOARA CALINESCU is an Associate Professor of Computer Science at the University of Oxford. Her main research interests are in modelling and reasoning about complex networked systems; the theory, practice, and methodology of agent-based modelling, including model calibration and validation, and using models for predictions. [Profile](#). Email: ani.calinescu@cs.ox.ac.uk

MICHAEL WOOLDRIDGE is a Professor of Computer Science at the University of Oxford. His main research interests are in agent-based modelling, multi-agent systems, and in particular, in the computational theory aspects of rational action in systems composed of multiple self-interested agents. His work is characterised by the use of techniques from computational logic, game theory, and social choice theory. [Profile](#). Email: michael.wooldridge@cs.ox.ac.uk

GREGORY LANZARO is a professor in the Pathology, Microbiology, and Immunology Department at University of California, Davis School of Veterinary Medicine. Previously he was a Professor at University of Texas Medical Branch and a post-doctoral scholar at University of California, Davis. He received his PhD at University of Florida. His research interests include the application of population genomics to the development of genetic-based strategies aimed at the elimination of malaria. [Profile](#). Email: gclanzaro@ucdavis.edu