Modelling Allee Effects in a Transgenic Mosquito Population During Range Expansion

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(ABSTRACT)

Mosquitoes are vectors for many diseases that cause significant mortality and morbidity across the globe such as malaria, dengue fever and Zika. As mosquito populations expand their range into new areas, they may undergo mate-finding Allee effects such that their ability to successfully reproduce becomes difficult at low population densities. With new technology, creating target specific gene modification may now be a viable method for mosquito population control. We develop a mathematical model to investigate the effects of releasing transgenic mosquitoes into newly established low-density mosquito populations. Our model consists of two life stages (aquatic and adult), which are further divided into three genetically distinct groups: heterogeneous and homogeneous transgenic alleles that cause female infertility and a homogeneous wild type. We perform analytical and numerical analyses on the equilibria to determine the level of saturation needed to eliminate mosquitoes in a given area. This model demonstrates the potential for a gene drive system to reduce the spread of invading mosquito populations.

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(GENERAL AUDIENCE ABSTRACT)

Mosquitoes spread many diseases that cause significant death across the globe such as malaria, dengue fever and Zika. As mosquito populations expand their range into new areas, they may not be able to successful reproduce at small population. With new technology, creating target specific gene modification may now be a viable method for mosquito population control. We develop a mathematical model to investigate the effects of releasing mosquitoes which have a gene modification into newly established low-density mosquito populations. Our model consists of two life stages (aquatic and adult), which are further divided into three genetically distinct groups. We perform analytical and numerical analyses on the equilibria to determine the level of saturation needed to eliminate mosquitoes in a given area. This model demonstrates the potential for a gene modified mosquito to reduce the spread of invading mosquito populations.

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Chapter 1

Introduction

Mosquitoes have been labeled the deadliest animal [46] as more than half a million people die each year from mosquito-borne diseases, including dengue and malaria [92, 93]. Methods such as insecticide-treated mosquito nets, indoor residual spraying, space treatment, and larvicide application have led to significant headway in disease control by directly targeting the mosquito populations [40, 90]. However, there are limitations to these methods. For example, extensive usage of common insecticides has led to mosquitoes rapidly acquiring resistance [49]. It is not a straightforward task to replace insecticides used in treated mosquito nets, as they require low toxicity due to their close proximity to humans [49]. Effective control of mosquito populations may consequently require novel measures to supplement existing tactics.

Beyond the rise of insecticide resistance, mosquito populations continue to expand into new territory and increase in density in other locations, further altering the potential for profound impacts on local transmission dynamics of vector-borne diseases. In the last 30 years, for example, *Aedes albopictus* has spread from Southeast Asia to Africa, Europe and the Americas due in part to an increase in global shipping [35]. In 2017, the Center for Disease Control showed an increased rate of geographic spread of *Aedes albopictus* and *Aedes aegypti* in the United States [18]. Although *Anopheles gambiae* have not spread outside of Africa, their geographical range has shifted [81]. While mosquitoes are endemic to many locations, other places observe seasonal variation in their populations. As temperatures continue to increase globally, African highlands have observed increases in mosquito populations [59]. A study in Peru also revealed that weather is related to variation in *Aedes aegypti* populations and, importantly, has direct consequences on the transmission of dengue virus between humans and vectors [15]. Although eliminating mosquitoes that serve as disease vectors is insurmountable in many locations, minimizing their spatial spread to new areas may be a viable option.

One method that shows promise in facilitating control of mosquito populations and the infectious diseases they carry is the release of transgenic or otherwise genetically altered

mosquitoes [5, 37]. Manipulation of mosquito genetics has already been undertaken using the CRISPR-Cas9 system [30, 37], such as on an *Anopheles stephensi* gene that exhibits anti-*Plasmodium falciparum* effects [30]. In *Anopheles gambiae*, three recessive genes have been identified that produce female sterility. Using CRISPR-Cas9 constructs that function as a gene drive system, they observed transmission rates of these genes at over 90% [37]. *Gene drive* occurs when a gene is inherited with greater probability, then predicted by traditional Mendelian inheritance, where each gene has the same probability of being passed on to progeny. As the gene that creates infertility is more favorably inherited than the gene that does not, these results suggest that it is biologically feasible to use gene drive to express infertility in female *Anopheles* mosquitoes.

An additional feature of the population dynamics that may play a crucial role in the design and implementation of control via transgenic mosquitoes is the impact of low population density on the the ability of mosquitoes to successfully find a mate. Low population densities are most likely to occur as mosquitoes move into new territories and, consequently, this may generate a mate-finding Allee effect. More generally, an *Allee effect* is the loss of fitness or ability to reproduce due to decreased population size and arises from several mechanisms including mate-finding failure, foraging efficiency, and predation [12]. In particular, *strong Allee effects* exist if there is a population threshold below which *per capita* growth rates become negative [79]. Mosquitoes may have a naturally occurring Allee effect supported by evidence of skip oviposition in *Aedes aegypti* [95]. This preference implies that larvae survival may decrease with a low population density, suggesting the presence of an Allee effect.

In the next chapter, we discuss biological the background necessary for the model development, including information about mosquitoes life cycles, gene drive and Allee Effect. In Chapter 3, we discuss previous mathematical models of mosquitoes and include mathematical representation of Allee effects in literature. In Chapter 4, we build the basic mosquito population model, find equilibria, and analyze the stability of this model. In Chapter 5, we introduce mosquitoes with a gene drive allele that causes partial sterility. We find and analyze the stability of a subset of equilibria of this model and present numerical simulation results. In Chapter 6, we look at extensions to the model to include migration and a way to evaluate the spread of disease. In the final chapter, we discussion the feasibility of limiting invading mosquitoes with the use of gene drive mosquitoes. The majority of this work will be published in the Journal of Biological Dynamics [85].

Chapter 2

Biological Background

2.1 Mosquito life cycle

Mosquitoes have complicated life cycles with several distinct phases of development. They begin as eggs that are laid in an aquatic environment. After hatching, they enter the first of four sequential larval stages, all of which occur in the aquatic environment. They molt between each stage and emerge larger in the next stage. Following the larval transitions, the mosquitoes enter the final aquatic stage: pupa. They emerge from the pupal stage as adults [20]. Figure 2.1 shows the mosquito life cycle (reproduced from [83]).

Although mosquitoes are known for their pesky bites, all adult mosquitoes require sugar from plants as nutrients while only female mosquitoes take a blood meal. The blood is necessary for the development of their eggs. Typically females follow a regular sequence of events prior to egg laying. This begins by looking for a host for a blood meal. Once a female mosquito gets an adequate blood meal, digestion of blood takes two to three days, which is called the resting phase. Then a female will oviposit or lay the eggs. This sequence of events - feeding, resting and egg laying - is known as the *gonotrophic cycle* and occurs repeatedly throughout the adult female lifespan. Typically, females only need one blood meal per gonotrophic cycle. Furthermore, female mosquitoes only need to mate a single time in their life [73].

A substantial body of research exists on how mosquito life history traits vary with environmental conditions such as temperature, nutrient availability or density. Of the over 3000 species of mosquitoes, three main genera spread disease: *Culex*, *Anopheles* and *Aedes*. Due to their importance in disease transmission, we specifically focus on three species: *Aedes aegypti*, *Aedes albopictus*, and *Anopheles gambiae*. The first two are *Aedes* mosquitoes that are primary vectors of Zika and dengue fever. The last one is the primary vector for malaria, which kills hundreds of thousands of people every year. Below we discuss in detail each of these species.

Aedes Aegypti

Aedes aegypti are an important species as they are one of the primary vectors for viral infections including dengue, Zika, and chikanguna. They are primarily found in tropical climates, and historically lived in forested areas. With increased global urbanization of forest, *Aedes aegypti* are now commonly found in artificial containers near human populations [36, 86].

The persistence of *Aedes* mosquitoes may be attributed to the resilience of their eggs, which can remain desiccated for up to eight months prior to hatching [16]. In general, *Aedes aegypti* are estimated to lay on average 100 eggs per gonotrophic cycle [16], which happens about every 3 days [69]. Although their ability to have large amount of durable eggs, makes them robust, they struggle in cool temperatures. Studies show their larvae develop at temperatures ranging from 15 - 34°C, with very few larvae developed at or below 15°C [75]. In addition to poor larval survival at low temperatures, larval development time is significantly delayed. The median time at 15°C was 58 days while at 34°C it was six days [75]. There are other factors, in addition to temperature, that may have effected the length of larvae development, such as available food source and population density [22].

Aedes Albopictus

Aedes albopictus are another important vector for viral infections. Despite an expansive territory in Africa, the Americas, Asia, Europe, Australia, and the Pacific Islands [35], they are less influential in viral transmission than *Aedes aegypti*, as they prefer to bite animals. Unlike some other species that primarily bite at night, *Aedes albopictus* will bite anytime, although mainly during the morning and evening [70]. They can also survive when temperatures drop to as low as -5°C [70].

There is a lot of variation in measurements of the number of eggs laid and how often. As an example, it is reported that *Aedes albopictus* oviposit 15 to 110 eggs per gonotrophic cycle [14]. The average length of gonotrophic cycle was shown to be around four days, but varied significantly with temperature [25].

Similar to *Aedes aegypti*, the larvae of *Aedes albopictus* will develop at temperatures ranging from 12-35°C [14, 25], but the greatest chance of survival is in intermediate temperates [25]. Development time follows a non-monotonic curve, as the temperature is increased from 15°C to 30°C the development time decreases, but then increases over the range of 30°C to 35°C. Additionally, a greater density of larvae experience increase development time [14].

Survival rates are an important determinant of the capacity of mosquitoes to transmit disease. Life expectancy was modeled for *Aedes albopictus* to be between 20 and 38 days for females, but 15 to 31 for males (at 35°C and 15°C respectively) [25]. Overall adult survival is greater at cooler temperatures. There is evidence that temperature can effect the ratio of male and female mosquitoes. Two different studies that varied temperature found the percent of female *Aedes albopictus* larvae was less than males except at the highest temperature measured. One of these studies found the ratio of males to females to be 2 to 1 [14, 25].

Anopheline gambiae

Anopheline gambiae are the primary vector for malaria transmission, although they do not transmit the viral infections that *Aedes* mosquitoes transmit. Despite their importance for malaria transmission, *Anopheline* mosquitoes are less robust to lab breeding than *Aedes* mosquitoes, so there exist fewer studies at controlled temperatures. Most studies tend to be in the wild at specific locations, where temperatures vary. A study in Mauritius, found that *Anopheline gambiae* larvae showed no activity at temperatures below 16.5°C and died at temperatures above 41°C.

Similar to *Aedes* mosquitoes, there is a non-monotonic relationship between larval development time and temperature [44], with survival of larvae highest at intermediate temperatures [61]. The average development time of larvae is between 8-12 days. As the density of larvae increases the development time increases and the average mass of each larva decreases [34]. Another effect on larvae raised in higher temperatures, is that as adults they lay fewer eggs [19].

When considering adult *Anopheline gambiae*, temperature, location, and food all impact their lifespan. In various locations, adults were found to have life spans from 4 to 23 days [64, 66] with an average of approximately 12 days [66]. Available food increases the lifespan of the mosquito, as a study restricting the diets of *Anopheline gambiae* showed they lived as short as two days with limited sugar. Those with a large amounts of sugar in their diet lived as long as 30 days [31]. Lifespan effects the number of gonotrophic cycles completed. One mosquito was found to have completed 12 cycles, although only 1% of those collected had completed 7 or more cycles [33]. A single gonotrophic cycle lasts about every three days *Anopheline gambiae* [33], so completing 12 cycles means that the mosquito may have been older than 30 days.

2.2 Insect Control

As mosquitoes are the deadliest animals in the world [46], an array of different techniques are in use to control mosquitoes, including insecticide-treated mosquito nets, indoor residual spraying, space treatment, and larviciding [90]. Insecticide-treated mosquito nets and indoor residual spraying have been the main focus of recent mosquito control. As a result, mosquitoes are becoming resistant to the most common insecticides. Furthermore, as only a limited number of compounds can be used in close proximity to humans, the chemicals currently used in insecticide-treated mosquito nets will be hard to replace [49]. As mosquitoes become more resistant to current insecticides, new ways to control mosquito population are needed.

2.2.1 Sterile Insect Technique

In light of the need for new control measures the Sterile Insect Technique (SIT) is one method that has been proposed. SIT works through the sterilization of male insects and their subsequent release into the wild population. Wild females then mate with sterile males and are unable to produce offspring [27]. Sterile insects, as a form of pest control, were first introduced by three different sources in the 30s and 40s, A.S. Serebrovskii at Moscow State University, F.L. Vanderplank field research station in Tanzania, and E.F. Kipling from the US department of Agriculture. Of these researchers, only Kipling's research, implemented by Baumhover, was successful in releasing the idea [47]. Baumhover sterilized screwworms through radiation, and then released them on the island Curacao. They released between 175 to 727 sterile males per square mile of the entire island for a five month period. The program was ceased once eight weeks of collection showed no screwworms [8, 48]. SIT has proven to be useful in eliminating vectors such as the screwworm fly, Mediterranean fruit fly, and pink bollworm in places such as the United States, Libya, Mexico, and Central America [2].

Baumhover's experiment has been reproduced with other insects. In the 1970s, 4.3 million *Anopheles albimanus* sterilized mosquitoes were released in El Salvador over a five month period [3]. During the most successful months (September and October) of the release program, they only caught two mosquitoes, which was a significant decrease from the 1000+ females caught in the same months in other years. Following the experiment, it took four months for the population to return to normal densities [60]. More recently from 2005 to 2009, five trial releases of sterile *Aedes albopictus* occurred in Italy. They found that releasing between 896 to 1,590 sterile males per hectare per week, the mosquito population was approximately 70-80% sterile with significant reduction of mosquitoes measured by trapping methods [11].

Despite the apparent success of SIT, one of the largest drawbacks is that the sheer number of mosquitoes required to maintain control is large and they must be introduced continually. For example, the study in Italy released approximately two million mosquitoes [11]. In another experiment, the number were even greater. The need for massive releases means that a facility needs to be able to raise large amount of mosquitoes on a regular basis. Another issue involves transporting and releasing the mosquitoes, a process that is inefficient and labor intensive [51]. Furthermore, sterilization itself can be difficult. Mosquito populations are less receptive to the invasion of irradiated males as they have low mating fitness [6, 50]. To combat this, researchers have found that giving the mosquitoes, specialized diets can help increase the size of the lab raised mosquitoes which makes them more competitive sexually [51, 68]. Finally, the release of sterilized mosquitoes is not always successful. When full removal of the population is not achieved, the mosquito population can rapidly bounce back. After four months the El Salvador mosquito population was back to the original size [60].

2.2.2 Gene drive

One solution to alleviate the need of massive mosquito releases is to design a system where a gene causing infertility naturally spreads through the mosquito population. In particular, if this gene could spread through a population at a greater than Mendelian inheritance, i.e. increasing its frequency in each subsequent generation, the impact would be even greater. This idea is know as *gene drive* [38].

When developing SIT, A.S. Serebrovskii was researching a specific sterilization technique through the alteration of genetic material via chromosomal translocation [47]. In this case, insects with heterozygous chromosomal translocation were semi-sterile where as translocation homozygotes were fully sterile [23]. C.F. Curtis expanded this idea, which later became known as genetic underdominance [38]. Since then several ways to genetically modify insects have been suggested, such as transposable elements, meiotic drive genes, and homing endonuclease genes [76].

A relatively recent method co-opted to introduce sterilized genes is the CRISPR-Cas9 system. This method induces a site specific double strand DNA break where a new gene can be inserted. CRISPR-Cas9 has been used successfully to insert genes of interest into *Anopheles* mosquitoes. An anti-*Plasmodium falciparum* gene was inserted into *Anopheles stephensi* [30]. While in *Anopheles gambiae*, Hammond et. al. identified three recessive genes that produce female sterility where they found transmission rates of the gene at >90% [37]. Although the initial experiment showed positive results with greater than Mendelian inheritance, two forms of natural resistance have arisen, cleavage repair by nonhomologous end joining and *de novo* mutations [72].

2.3 Allee Effect

Some organisms exhibit a reduction in fecundity at low population density. Ribbed mussels group together in inter-tidal areas. The greater the density of mussels in an area, the probability of surviving increases, since larger groups reduce the chances of predation from crabs and death from ice in the winter [13]. African wild dogs grow up in packs that depend on each other for basic necessities. Raising the young is not just the parents responsibility; others in the pack will feed and watch young pups that are not their own. The dogs forage together and defend as a group. Due to the importance of community, there exist some threshold size at which the population growth decreases without a large enough pack [21]. Male fruit flies release a pheromone that causes mating adults to aggregate. It has been shown that this increased density of adults improves the survival rates of their larvae [87]. All three of these examples demonstrate cases where increasing the density of a population, increases the probability of survival, a phenomenon known as an Allee effect.

An *Allee effect* is the loss of fitness or ability to reproduce due to decreased population size and arises from several mechanisms including mate-finding failure, foraging efficiency, and predation [12]. The term is named after W. C. Allee who first discussed the phenomenom that the growth rate of flour beetles was higher at intermediate than at low population densities [1]. The overall effect on growth rate is called the *demographic Allee effect*, while factors that decrease fitness when population size is low are known as *component Allee* effects. For example, cooperative breeding, foraging and anti-predator behavior are each individual component Allee effects, but the demographic Allee effect refers to the combined consequence of all of these component Allee effects. A *strong Allee effect* exists if there is a population threshold below which *per capita* growth rates become negative [79]. Studies on gypsy moths found a naturally occurring strong Allee effect. This knowledge has been manipulated to decrease the spread of this invasive species by implementing measures to force gypsy moth population below the threshold [89].

Mosquitoes may have a naturally occurring Allee effect. In William et. al. [95], *Aedes aegypti* show evidence of skip oviposition, where a female does not release her entire set of eggs, but retains some to deposit at a different location. The preference to lay eggs in the presence of an intermediate density of eggs rather than locations with few eggs implies that larvae survival may decrease with a low population density and suggest the presence of an Allee effect. A commonly observed Allee effect is the inability to find a mate at lower population levels. Even if there are equal numbers of male and female individuals in an area, if they are spread far apart, a female will spend additional time searching for or may not be able to locate a mate. We expect this to be the case in areas with low mosquito population density, such as occurs during range expansion. This is the Allee effect that we consider in our model.

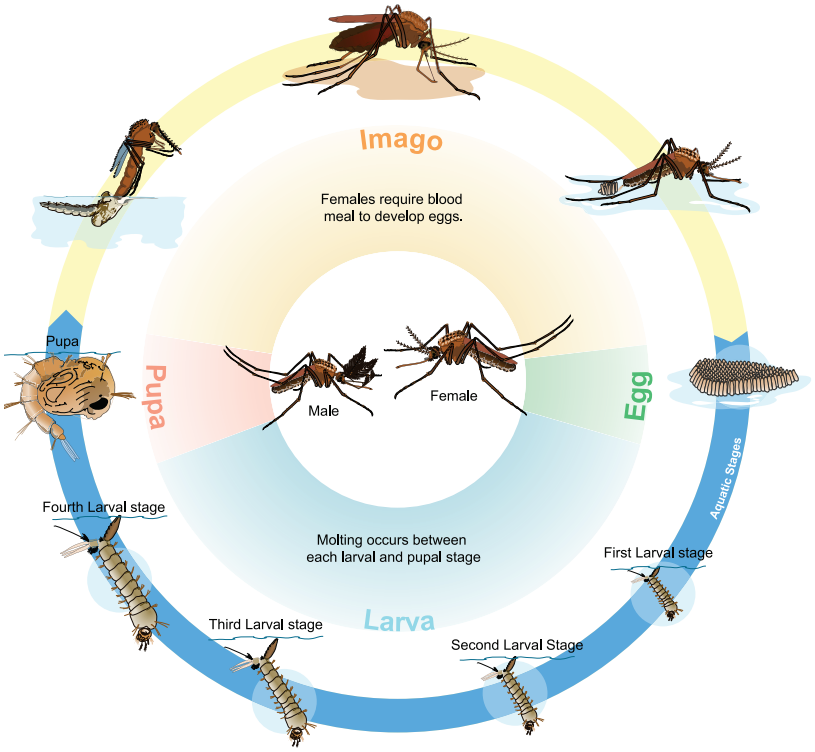


Figure 2.1: **Mosquito Life Cycle**: Mosquitoes have a complicated life cycle with several distinct phases of development. Mosquitoes begin as eggs that are laid in an aquatic environment. After hatching, they enter the first of four sequential larval stages, all of which occur in the aquatic environment. They molt between each stage and emerge larger in the next stage. Following the larval transitions, the mosquitoes enter the final aquatic stage: pupa. They emerge from the pupal stage as imago, which means adults. (Open source image reproduced from [83].)

Chapter 3

Mathematical Background

Mathematical models to study mosquito populations have a rich history. In particular, modeling mosquito population dynamics can be a useful tool to understand how to reduce the spread of these disease. The first mosquito model was introduced by Ronald Ross in 1905 to understand the best way to combat malaria. Using his model, he showed that reducing laval breeding sites would reduce mosquito population size [77]. Ross's original one-dimensional model considered the number of humans infected at some future time based on the proportion of mosquitoes capable of passing on malaria and number of currently infected people [74]. His second model additionally included a separate population for mosquitoes. These ideas were refined decades later by George Macdonald [77]. A suite of models combining the work of Ross and Macdonald has been the basis of much future work modeling mosquito transmitted pathogens, known as the "Ross-Macdonald" model [77].

3.1 General mosquito life cycle models

Many models of mosquito population growth have been considered with various questions in mind. We introduce several models of the mosquito life cycle. As the models are similar in format we provide the variables and parameters that are consistent among the models in Tables 3.1 and 3.2, respectively. Parameters that only appear in one model will be discussed in the text alongside that model.

3.1.1 Compartment models of the life cycle

Many recent models include a detailed model of the life cycle in order to enable the modeling of specific control methods. One such model by White et. al. [88] is composed of three equations for the aquatic stages — one for each of egg, larva and pupa — along with adult

Table 3.1: Variables found in the models.

Symbol	Description
J	aquatic class
E	egg class
L	larval class
P	pupal class
A	adult class
F	female adult class
M	male adult class
Y	non egg laying (young) female adult class
S	sterile male adult class

Table 3.2: Parameters used in the models.

Symbol	Description
β	Eggs laid per female
α_i	rate of transition from group $i \in \{J, F, Y, \dots\}$
r	Proportion females
μ_i	constant mortality rate of group $i \in \{J, F, Y, \dots\}$
μ_{0_i}	Density-dependent mortality rate$i \in \{J, F, Y, \dots\}$
K	carrying capacity of aquatic stages
b	rate of release of number of sterile insects
δ	Allee constant

females as follows

$$\begin{aligned}
\frac{dE}{dt} &= \beta F - \alpha_E E - \mu_{0_E}(1 + \frac{E+L}{K})E, \\
\frac{dL}{dt} &= \alpha_E E - \alpha_L L - \mu_{0_L}(1 + \frac{g(E+L)}{K})L, \\
\frac{dP}{dt} &= \alpha_L L - \alpha_P P - \mu_P P, \\
\frac{dF}{dt} &= \frac{1}{2}\alpha_P P - \mu_F F.
\end{aligned}$$

The only nonlinear terms appearing in this model are those accounting for density dependent growth restriction in the egg and larval compartments. For example, g is the proportion that determines density dependence of larval stage to differ from that in the egg stage. This model is used to consider the impact of insecticide treated bed nets and indoor residual spray, both current popular interventions [88].

3.1.2 Fixed delays during development

Standard compartmental ordinary differential equation models betray biological processes by nearly instantaneous transition of a proportion of the individuals. However, mosquito larva require at least several days of development before they can mature to pupae and then adults. To properly account for this, some models, such as Hancock et. al. [39] introduce delay differential equations.

In the following model, they only consider female mosquitoes at all stages and τ_i is the time delay for a given stage i, where $i \in \{E, L, P\}$ and θ, is the probability of surviving the pupa stage.

$$\begin{aligned}
\frac{dL}{dt} &= \beta F(t-\tau_E) - \alpha_L F(t-\tau_E-\tau_L)\omega(t) - (\mu_L + \mu_0 L(t))L(t), \\
\frac{dF}{dt} &= \alpha_L \theta F(t-\tau_E-\tau_L-\tau_P)\omega(t) - \mu_F F(t), \\
\omega(t) &= \exp\left(-\int_{t-\tau_L}^{t} \mu_0 L(x)\, dx\right).
\end{aligned}$$

This paper uses the model to consider malaria infection of mosquitoes [39].

3.1.3 Extensions of simple models of the life cycle

J. Li has used several simple models to study the impact of sterile mosquitoes [53, 55, 57, 54, 56]. One of her basic population models [56] only includes juvenile and adult stages

$$\begin{aligned}
\frac{dJ}{dt} &= \beta A - \frac{\alpha_J J}{1+J} - (\mu_J + \mu_0 J)J, \\
\frac{dA}{dt} &= \frac{\alpha_J J}{1+J} - \mu_A A.
\end{aligned}$$

She has extended her basic model to include an Allee effect in the birth term [56] as follows

$$\begin{aligned}
\frac{dJ}{dt} &= \frac{\beta A}{A+\delta} A - \frac{\alpha_J J}{1+J} - (\mu_J + \mu_0 J)J, \\
\frac{dA}{dt} &= \frac{\alpha_J J}{1+J} - \mu_A A.
\end{aligned}$$

She then includes sterile insect releases into the model, which will be discussed in the next section.

3.2 Sterile Mosquitoes and Gene Drive Models

In this section we focus on models which consider reducing the population of mosquitoes using Sterile Insect Technique.

3.2.1 Two-stage model

The first mathematical models for sterile insects with two life stages and density dependence in the larval stage was done by Miller and Weidhaas (1974) and by Prout (1978) [7]. These were generalized by Barclay [7] as

$$\begin{aligned}
\frac{dJ}{dt} &= (\beta - k(A+S))\frac{A}{A+S} - (\alpha_J + \mu_{0_J} J)J, \\
\frac{dA}{dt} &= ((\alpha_J - c_0) - c_1 J)J - (\mu_A + \mu_{0_A}(A+S))A, \\
\frac{dS}{dt} &= b - \mu_S S - \mu_{0_A}(A+S)A.
\end{aligned}$$

The parameter c_0 and c_1 are constant and density dependence mortality, respectively, of juveniles, whom do not transition to adult. The k is a density dependent term of birth and can be thought of as the reciprocal of carrying capacity, $k = \frac{1}{K}$. In the paper he shows that density dependence creates two positive equilibria. He notes that without density dependence, insects will not likely achieve a controlled population level of lower level [7].

3.2.2 Female age-structured model

Since young females cannot give birth, extensions of this form have included an intermediate class for females. This allows a delay before females can contribute to the aquatic class. An example of this extension [3] is

$$\begin{aligned}
\frac{dJ}{dt} &= \beta F - (\alpha_J + \mu_J + \mu_0 J)J, \\
\frac{dY}{dt} &= r\alpha_J J - (\alpha_Y + \mu_Y)Y, \\
\frac{dF}{dt} &= \frac{\alpha_Y Y}{M+S} - \mu_F F, \\
\frac{dM}{dt} &= (1-r)\alpha_J J - \mu_M M, \\
\frac{dS}{dt} &= b - \mu_S S.
\end{aligned}$$

3.2.3 Delayed egg laying model

In addition to the known lags due to development, there is also a delay between blood feeding and laying eggs. To account for this, some models include the time it takes females to search for a blood meal F_f and allow for resting F_r and then females that are breeding F_b such as

$$\begin{aligned}
\frac{dJ}{dt} &= \beta(1-\frac{J}{K})F_b - (\alpha_J + \mu_J)J,\\
\frac{dY}{dt} &= r\alpha_J J - (\mu_Y + \alpha_Y)Y,\\
\frac{dF_f}{dt} &= \alpha_{F_b}F_b + \frac{M+fS}{M+S}\alpha_Y Y - (\alpha_{F_f} + \mu_F)F_f,\\
\frac{dF_r}{dt} &= \alpha_{F_f}F_f - (\alpha_{F_r} + \mu_F)F_f,\\
\frac{dF_b}{dt} &= \alpha_{F_r}F_r - (\alpha_{F_b} + \mu_F)F_b,\\
\frac{dM}{dt} &= (1-r)\alpha_J J - \mu_M M,\\
\frac{dS}{dt} &= -\mu_S S.
\end{aligned}$$

This model allows the sterile males to be only partially sterile, so that f is the efficiency of a sterile mosquito breeding. They consider a pulsed release of the sterile males in their model.

3.2.4 Extension of basic models

Returning to the Li suite of models, we focus on her recent inclusion of sterile mosquitoes [56] as

$$\begin{aligned}
\frac{dJ}{dt} &= \frac{\beta A}{A+S}A - \frac{\alpha_J J}{1+J} - (\mu_J + \mu_0 J)J,\\
\frac{dA}{dt} &= \frac{\alpha_J J}{1+J} - \mu_A A,\\
\frac{dS}{dt} &= B(S) - \mu_S S.
\end{aligned}$$

The function $B(S)$ represents the release of sterile mosquitoes. As sterile mosquitoes, by definition, cannot persist in population they need to be continually released. This paper considers several different forms of $B(S)$ and tries to optimize release. She considers three different forms of release $B(S)$: a constant release b; proportional release bA; and proportional release with saturation $\frac{bA}{1+A}$. We use the Li model [56] as a basis for our own work.

3.3 Allee Effect

Allee effects have been modeled previously in different ways. We include biological and mathematical justification for the type of Allee effect we incorporate.

A simple description of finding a mate assumes that the probability of a female finding a mate is directly proportional to the number of males available, n. This is reasonable when the number of males and females is large and the population is well mixed, which is not always the case. Another way to look at the chance of mating is to consider random collision. If we assume a one to one ratio of males and females, then the number of males is n and the number of females is n. The probability that a pair is made is proportional to n^2 [84].

3.3.1 Polygamous Mating

To begin, we will discus pair making in the context of polygamous mating [26] even though mosquitoes only mate once. We then consider polygamous mating with the assumption of only a single mating.

We assume that sex ratio is constant and that the probability of finding a mate is proportional to the area searched and the amount of times previously mated. Let δ be a function of the number of times previously mated, denoted by x, with $\delta(0) = b$ where b is a constant. In order for δ to make biological sense, we require $\delta(x) = 0$ when $x < 0$. Given a to be the area searched, M is the density of males, and $X(a)$ is the number of times a female mates, then the probability of a female mating an additional time is

$$P[X(a + \Delta a) = x + 1 \mid X(a) = x] = \delta(x)M\Delta a.$$

With the assumption of the probability as above, the forward difference equation is used to estimate the derivative as

$$\frac{dp_x(a)}{da} = \delta(x-1)Mp_{x-1}(a) - \delta(x)Mp_x(a) \tag{3.1}$$

where $P[X(a) = x] = p_x(a)$ [26].

Notice that if no area is searched ($a = 0$), no mating will occur ($x = 0$), i.e. the probability of not finding a mate when no area is searched is one, $p_0(0) = 1$. Using the integrating factor $e^{\delta(x)na}$ and the initial condition $p_0(0) = 1$ we can solve Equation 3.1 with $x = 0$ for $p_0(a)$ as

follows

$$\begin{aligned}
e^{\delta(x)Ma}\frac{dp_x(a)}{da} + \delta(x)ne^{\delta(x)Ma}p_x(a) =& \delta(x-1)Me^{\delta(x)Ma}p_{x-1}(a)\\
e^{\delta(0)Ma}\frac{dp_0(a)}{da} + \delta(0)ne^{\delta(0)Ma}p_0(a) =& \delta(-1)Me^{\delta(0)Ma}p_{-1}(a)\\
\frac{d}{da}(e^{bMa}p_0(a)) =& 0\\
\int_0^a \frac{d}{ds}(e^{bMs}p_0(a))ds =& 0\\
e^{bMa}p_0(a) - e^{bM0}p_0(0) =& 0\\
e^{bMa}p_0(a) =& 1\\
p_0(a) =& e^{-bMa}
\end{aligned}$$

Now we consider Equation 3.1 for any x, rather than just $x = 0$ as above,

$$\begin{aligned}
e^{\delta(x)Ma}p_x(a) =& \int_0^a \delta(x-1)Me^{\delta(x)Ms}p_{x-1}(s)ds\\
p_x(a) =& e^{-\delta(x)Ma}\delta(x-1)n\int_0^a e^{\delta(x)Ms}p_{x-1}(s)ds
\end{aligned} \tag{3.2}$$

By assuming the function $\delta(x)$ takes the form of the first two terms of Taylor series expansion, Dennis et. al. [26] explored three different forms of δ. Since we are interested in Allee effects, we specifically interested in small populations, so the Taylor series expansion is centered around zero

$$\delta(x) = \delta(0) + x\delta'(0) + \ldots \approx b + cx$$

The three cases for δ can be simplified to consider when $c > 0, c < 0$ and $c = 0$ [26].

Probability of Mating

Regardless of the choice of c, the probability of not finding a mate is given as $p_0(a) = e^{-bMa}$, which means that mating occurs with probability $1 - e^{-\theta M}$ where $\theta = ba$. Often this simplifying view of mating is used in mathematical models [32, 71, 65]. When mosquitoes mate, the males' spermatozoa contains a substrate, that makes the female resistant to future copulations. One mating event is sufficient to fertilize several batches of eggs [10], which makes this distribution sufficient for mosquitoes.

We have defined $\theta = ab$, so that mating is proportional to area searched a [63], but a could also be seen as a mating detection distance instead [29]. One modification is to include the

parameter β to modify the strength of the Allee effect, so that the probability of mating is now $1-(1-\beta)e^{-M\theta}$ [12].

Now we will assume that the probability a mosquito mates is $1-e^{-\theta M}$ where θ is the amount of area searched by a female mosquito. Instead of assigning a value to θ, we will assume that θ is a random variable with a continuous probability distribution. Let D be the average area searched by a female, which means that the expected value is $\frac{1}{D}$ mosquitoes per area. We will use the exponential distribution [24]

$$f\left(\theta \;\middle|\; \frac{1}{D}\right) = \begin{cases} \frac{e^{-\frac{\theta}{D}}}{D} & \theta > 0 \\ 0 & \theta \leq 0 \end{cases} \tag{3.3}$$

We multiply Equation 3.3 by the probability of finding at least one mate, so that the probability that a female mosquito will mate after searching θ area is

$$f(\theta) = \begin{cases} \frac{e^{-\frac{\theta}{D}}}{D}(1-e^{-M\theta}) & x \in \mathbb{N} \cup \{0\} \text{ and } \theta > 0 \\ 0 & \text{otherwise.} \end{cases}$$

We are interested in the proportion of mosquitoes that mate regardless of the area searched by that particular mosquito, which can be found by taking the integral from zero to infinity with respect to θ for $x \neq 0$ [24, 63] as

$$\int_0^\infty \frac{e^{-\theta/D}}{D}(1-e^{-M\theta})d\theta = \frac{M}{M+1/D}. \tag{3.4}$$

Ecological applications

In ecology this functional form is similar to a Holling type II functional response developed for predator-prey models. Initially Holling described four different functional responses as seen in the study of animal predation on a sawfly [41]. He then developed the mathematical form by assuming that the density of the predators (y) is proportional to the density of prey (x) and time spent searching. Letting T be the time available for searching for prey and b be time it takes to eat and rest after eating, then the time left for a predator to still search will be $T-by$. Thus, the density of predators is $y = a(T-by)x$ where a is the rate of successfully catching prey [42]. Solving for y, Holling finds

$$y = \frac{Tax}{1+abx}.$$

By fitting sawfly data to this functional form, Holling demonstrates its biological relevance [42].

Equation 3.4, the rectangular hyperbole, is also known in Michaelis-Menten kinetics as relating the rate of change of enzymes reaction to the concentration of the enzyme-substrate complex [45]. Michaelis and Menten measured the reaction of sucrose (S) converting to fructose (F) and glucose (G) with the following reaction

$$E + S \overset{K_s}{\longleftrightarrow} ES \overset{c}{\rightarrow} E + G + F,$$

where E is the enzyme and K_s is the equilibrium dissociation constant and c is a constant. The parameter ES is the enzyme-substrate complex. In 1913, they published their work were they proposed that the rate of reaction ν can be written as

$$\nu = \frac{cE_0S}{S + K_s}$$

where E_0 is the initial enzyme amount. Now it is known that cE_0 is equal to maximum rate of change of the reaction [45].

These functional forms are used in models with an Allee effect [43, 63] including mosquito models [54, 56]. With more complex forms of cooperation, the model can include a cooperation term w as

$$\frac{M^w}{M^w + \delta}. \qquad [43]$$

Introducing Allee effects

A simple form of a mate finding Allee effect can be represented by

$$\frac{M}{M + \delta} = \frac{rA}{rA + \delta}.$$

We use this form in our model of mate finding Allee effects where δ is the Allee constant. A larger Allee constant δ corresponds to a stronger Allee effect. This means that if we expect it to be harder for mosquitoes to find a mate, δ will be greater. This form always gives a strong Allee effect. See Figure 3.1, to see the growth rate with a strong Allee effect, which is when growth rate is negative for some lower population level. The Allee Threshold is the point at which growth rate switches from negative to positive.

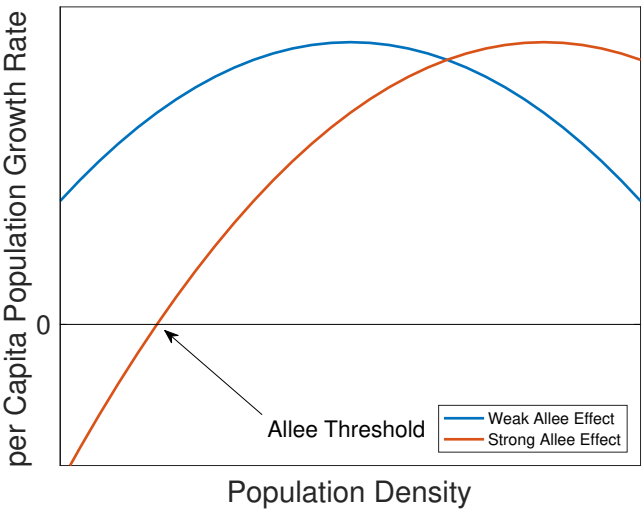


Figure 3.1: Per capita population growth rate that exhibit an Allee effect. The blue line has a negative growth rate below the Allee Threshold, known as a strong Allee effect. The blue line shows a weak Allee effect.

Chapter 4

Mosquito Population Model

We develop a continuous-time model of the mosquito life cycle comprised of aquatic (J) and adult (A) classes. Egg, larvae, and pupae stages are included in the single aquatic class (J), as in previous work [7, 56].

We let r be the proportion of the adults that are males, and thus $1-r$ fraction of adults are females. Females have an associated fecundity of β eggs, and transitions from the aquatic class to the adult class occurs at rate α. We assume there are constant death rates μ_1 and μ_2 for the aquatic class and adult class, respectively. As there is evidence of density dependent death in the first larval stage [28], we additionally assume that the aquatic class (J) has an associated density dependent death rate μ_0 which is in line with previous mosquito models [3, 7, 88]. Thus, in the absence of Allee effects our model is given by

$$\begin{aligned} \frac{dJ}{dt} &= (1-r)\beta A - (\mu_1 + \mu_0 J)J - \alpha J, \\ \frac{dA}{dt} &= \alpha J - \mu_2 A. \end{aligned} \tag{4.1}$$

We introduce a mate finding Allee effect using the functional form $\dfrac{rA}{rA+\delta}$ where δ is the Allee constant. Here, δ dictates the strength of the Allee effect so that a larger value indicates a stronger Allee effect. Thus, our basic model with an Allee effect is

$$\begin{aligned} \frac{dJ}{dt} &= \frac{r(1-r)\beta}{rA+\delta}A^2 - (\mu_J + \mu_0 J)J - \alpha J, \\ \frac{dA}{dt} &= \alpha J - \mu_A A. \end{aligned} \tag{4.2}$$

Notice that Models (4.1) and (4.2) are identical when $\delta = 0$ (i.e. there is no Allee effect).

4.1 Equilibria of Basic Model

To ensure biological realism, we assume all parameter values are positive.

Proposition 1. *In the absence of an Allee effect ($\delta = 0$), the basic model of mosquito population dynamics has two possible equilibria. The first corresponds to population extinction, $(J^*, A^*) = (0, 0)$; and the second is a non-zero equilibrium, $(J^*, A^*) = (\frac{\mu_A}{\alpha} A_b^*, A_b^*)$ where*

$$A_b^* = \frac{\alpha^2(1-r)\beta - \alpha\mu_J\mu_A - \alpha^2\mu_A}{\mu_0\mu_A^2}.$$

Proof. If we set the right-hand side of the differential equations in 4.1 to zero, we get

$$J^* = \frac{\mu_A}{\alpha} A_b^*$$

from the adult equation. Substituting this into the aquatic class equation, we see

$$A_b^* \left((1-r)\beta - (\mu_J + \mu_0 \frac{\mu_A}{\alpha} A_b^*) \frac{\mu_A}{\alpha} - \alpha \frac{\mu_A}{\alpha} \right) = 0.$$

So then considering the nonzero equilibrium, we have

$$\begin{aligned} (1-r)\beta - (\mu_J + \mu_0 \frac{\mu_A}{\alpha} A_b^*) \frac{\mu_A}{\alpha} - \mu_A &= 0 \\ \mu_0\mu_A^2 A_b^* &= \alpha^2(1-r)\beta - \alpha\mu_J\mu_A - \alpha^2\mu_A \\ A_b^* &= \frac{\alpha^2(1-r)\beta - \alpha\mu_J\mu_A - \alpha^2\mu_A}{\mu_0\mu_A^2} \end{aligned}$$

□

Proposition 2. *Consider equilibrium values (J^*, A^*) of our system when $\delta > 0$. Three equilibria are possible.*

The extinction equilibrium always exists and there is a saddle node bifurcation when

$$s^2 = 4r\alpha\delta\mu_0\mu_A^3(\mu_J + \alpha).$$

If $s^2 > 4r\alpha\delta\mu_0\mu_A^3(\mu_J + \alpha)$, two nonzero equilibria exist with the opposite sign as s,

$$s := \mu_0\mu_A^2\delta + \alpha^2\mu_A r + \alpha\mu_J\mu_A r - \alpha^2 r(1-r)\beta.$$

Proof. The extinction equilibrium always exists $(J^*, A^*) = (0, 0)$. To find nonzero equilibria (where $A^*, J^* \neq 0$), we set each differential equation to zero. Setting the adult mosquito equation to zero we get

$$\begin{aligned} \alpha J - \mu_A A &= 0, \\ J^* &= \frac{\mu_A}{\alpha} A^*. \end{aligned} \tag{4.3}$$

Now we set the aquatic class to zero, so

$$\frac{r(1-r)\beta}{rA+\delta}A^2 - (\mu_J + \mu_0 J)J - \alpha J = 0.$$

We now combine this with Equation (4.3) to find

$$\frac{r(1-r)\beta}{rA+\delta}A^2 - (\mu_J + \mu_0\frac{\mu_A}{\alpha}A)\frac{\mu_A}{\alpha}A - \alpha\frac{\mu_A}{\alpha}A = 0$$

Assume $A \neq 0$, we divide by A and get

$$\frac{r(1-r)\beta}{rA+\delta}A - \frac{\mu_J\mu_A}{\alpha} - \frac{\mu_0\mu_A^2}{\alpha^2}A - \mu_2 = 0$$
$$\frac{\alpha r(1-r)\beta}{rA+\delta}A - \mu_J\mu_A - \frac{\mu_0\mu_A^2}{\alpha}A - \mu_A\alpha = 0$$

$$\frac{\alpha r(1-r)\beta}{rA^*+\delta}A^* = \mu_J\mu_A + \frac{\mu_0\mu_A^2}{\alpha}A^* + \mu_2\alpha \tag{4.4}$$

$$\alpha^2 r(1-r)\beta A - \mu_0\mu_A^2(rA+\delta)A - \alpha\mu_J\mu_A(rA+\delta) - \alpha^2\mu_A(rA+\delta) = 0$$
$$\mu_0\mu_A^2 rA^2 + \left(\mu_0\mu_A^2\delta + \alpha^2\mu_A r + \alpha\mu_J\mu_A r - \alpha^2 r(1-r)\beta\right)A + \alpha\mu_A\delta(\mu_J+\alpha) = 0 \tag{4.5}$$

Let $s := \mu_0\mu_A^2\delta + \alpha^2\mu_A r + \alpha\mu_J\mu_A r - \alpha^2 r(1-r)\beta$ and solve Equation 4.5 by the quadratic equation. Thus, we have two possible equilibria, which are

$$A^* = \frac{-s \pm \sqrt{s^2 - 4r\alpha\delta\mu_0\mu_A^3(\mu_1+\alpha)}}{2\mu_0\mu_A^2 r}.$$

To have two nonzero equilibria, the discriminant must be non-negative. This shows that if $s^2 < 4r\alpha\delta\mu_0\mu_A^3(\mu_J+\alpha)$, we will only have the extinction equilibrium and when $s^2 = 4r\alpha\delta\mu_0\mu_A^3(\mu_J+\alpha)$, we will have a single nonzero equilibrium with the same sign as $-s$. This indicates a saddle node bifurcation.

Now in order to find the sign of the nonzero equilibria, we first assume that $-s > 0$. Since all parameters are positive, we have

$$-4r\alpha\delta\mu_0\mu_A^3(\mu_J+\alpha) < 0$$
$$s^2 - 4r\alpha\delta\mu_0\mu_A^3(\mu_J+\alpha) < s^2$$

We ignore the positive solution, since we are considering the case $-s > 0$

$$\sqrt{s^2 - 4r\alpha\delta\mu_0\mu_A^3(\mu_J + \alpha)} < -s$$
$$-s - \sqrt{s^2 - 4r\alpha\delta\mu_0\mu_A^3(\mu_J + \alpha)} > 0$$

So with the assumption that $-s > 0$, we will have two positive equilibriums. Following the same reasoning, if $s > 0$, then we will have two negative equilibriums, which are not of biological relevance. □

4.2 Stability of Equilibriums

Proposition 3. *When $\delta = 0$, there is a transcritical bifurcation when*

$$r_1 := \frac{\alpha(1-r)\beta}{\alpha\mu_A + \mu_J\mu_A} = 1.$$

Proof. Assuming there is no Allee effect, when $\delta = 0$, from Proposition 1, we know there are two equilibria. Stability is found by calculating finding the eigenvalues of the Jacobian matrix ($\mathcal{J}$).

$$\mathcal{J}(J^*, A^*) = \begin{pmatrix} -\alpha - \mu_J - \frac{2\mu_0\mu_A}{\alpha}A^* & (1-r)\beta \\ \alpha & -\mu_A \end{pmatrix}$$

The trace will always be negative. The determinant is $\mu_A(\alpha + \mu_J + \frac{2\mu_0\mu_A}{\alpha}A^*) - \alpha(1-r)\beta$, so when it changes from positive to negative, the stability changes. Let us first consider when $A^* = 0$ and assume the determinant is positive. Then,

$$\alpha\mu_A + \mu_J\mu_A + \frac{2\mu_0\mu_A^2}{\alpha} \cdot 0 - \alpha(1-r)\beta > 0$$
$$1 > \frac{\alpha(1-r)\beta}{\alpha\mu_A + \mu_J\mu_A}$$

The non-zero equilibrium is locally stable when $r_1 < 1$ and thus unstable when $r_1 > 1$.

Now we consider whether or not $(J^*, A^*) = (\frac{\mu_A}{\alpha}A_b^*, A_b^*)$ is locally stable.

$$\alpha\mu_A + \mu_J\mu_A + \frac{2\mu_0\mu_A^2}{\alpha} \cdot \left(\frac{\alpha^2(1-r)\beta - \alpha\mu_J\mu_A - \alpha^2\mu_A}{\mu_0\mu_A^2}\right) - \alpha(1-r)\beta > 0$$
$$\alpha\mu_A + \mu_J\mu_A + 2\alpha(1-r)\beta - 2\mu_J\mu_A - 2\alpha\mu_A - \alpha(1-r)\beta > 0$$
$$\alpha(1-r)\beta > \mu_J\mu_A + \alpha\mu_A$$
$$\frac{\alpha(1-r)\beta}{\mu_J\mu_A + \alpha\mu_A} > 1$$

This shows that if $r_1 > 1$, we have stability of the nonzero equilibria and instability of the extiction equilbria. If $r_1 > 1$, the opposite is true, i.e. the extinction equilbrium is unstable and $(J^*, A^*) = (\frac{\mu_2}{\alpha}A_b^*, A_b^*)$ is locally stable.

□

Proposition 4. *When $\delta > 0$, the extinction equilibrium is always locally stable.*

Proof. Now we will consider the stability when $\delta > 0$. The Jacobian is

$$|\mathcal{J}(J^*, A^*) - \lambda I| = \begin{vmatrix} -\alpha - \mu_J - \frac{2\mu_0\mu_A}{\alpha}A^* - \lambda & \frac{r(1-r)\beta A^*(rA^*+2\delta)}{(rA^*+\delta)^2} \\ \alpha & -\mu_A - \lambda \end{vmatrix} \tag{4.6}$$

$$= (\alpha + \mu_J + \frac{2\mu_0\mu_A}{\alpha}A^* + \lambda)(\mu_A + \lambda) - \frac{\alpha r(1-r)\beta A^*(rA^*+2\delta)}{(rA^*+\delta)^2} \tag{4.7}$$

$$= \lambda^2 + (\alpha + \mu_J + \mu_A + \frac{2\mu_0\mu_A}{\alpha}A^*)\lambda + \alpha\mu_A + \mu_J\mu_A + \frac{2\mu_0\mu_A^2}{\alpha}A^* - \frac{\alpha r(1-r)\beta A^*(rA^*+2\delta)}{(rA^*+\delta)^2} \tag{4.8}$$

Considering the trivial equilibrium $(J^*, A^*) = (0, 0)$ and evaluating the eigenvalues of the Jacobian we find

$$\lambda^2 + (\alpha + \mu_J + \mu_A)\lambda + \alpha\mu_A + \mu_1\mu_A = 0,$$
$$(\lambda + \alpha + \mu_J)(\lambda + \mu_A) = 0.$$

This means our eigenvalues are $\lambda_1 = -\alpha - \mu_J$ and $\lambda_2 = -\mu_A$. As all parameters are positive, the eigenvalues are always negative, indicating the extinction equilibrium is always locally stable. □

Proposition 5. *Given that $s^2 > 4r\alpha\delta\mu_0\mu_A^3(\mu_J + \alpha)$, $s < 0$ and $\delta > 0$, we know that the one larger in magnitude, A_1^*, is locally stable and the non-zero equilibrium smaller in magnitude, A_2^*, is unstable.*

Proof. It is sufficient to test if the trace($\mathcal{J}$) < 0 and determinant($\mathcal{J}$) > 0 for local stability. Considering 4.6, the trace is always negative for biologically realistic parameters and equilibria, so if the determinant is positive, i.e.

$$\alpha\mu_A + \mu_J\mu_A + \frac{2\mu_0\mu_A^2}{\alpha}A^* - \frac{\alpha r(1-r)\beta A^*(rA^*+2\delta)}{(rA^*+\delta)^2} > 0,$$

the equilibrium will be locally stable. Let us assume that we have positive equilibrium, guaranteed when

$$s := \mu_0\mu_A^2\delta + \alpha^2\mu_A r + \alpha\mu_J\mu_A r - \alpha^2 r(1-r)\beta < 0$$

as noted in Proposition 2.

Then, we can rearrange determinant($\mathcal{J}$) as follows

$$\alpha\mu_A + \mu_J\mu_A + \frac{2\mu_0\mu_A^2}{\alpha}A^* - \frac{\alpha r(1-r)\beta A^*\left(rA^*+2\delta\right)}{(rA^*+\delta)^2}$$
$$= \alpha\mu_A + \mu_J\mu_A + \frac{2\mu_0\mu_A^2}{\alpha}A^* - \frac{\alpha r(1-r)\beta A^*}{rA^*+\delta}\frac{rA^*+2\delta}{rA^*+\delta} \tag{4.9}$$

From equivalences of our non-zero equilibrium, (Equation 4.4), we know that Equation 4.9 is equal to

$$\begin{aligned}
&\alpha\mu_A + \mu_J\mu_A + \frac{2\mu_0\mu_A^2}{\alpha}A^* - \left(\mu_J\mu_A + \frac{\mu_0\mu_A^2}{\alpha}A^* + \mu_A\alpha\right)\frac{rA^*+2\delta}{rA^*+\delta} \\
&= \frac{\mu_0\mu_A^2}{\alpha}A^* + \left(\alpha\mu_A + \mu_J\mu_A + \frac{\mu_0\mu_A^2}{\alpha}A^*\right)\left(1 - \frac{rA^*+2\delta}{rA^*+\delta}\right) \\
&= \frac{\mu_0\mu_A^2}{\alpha}A^* + \left(\alpha\mu_A + \mu_J\mu_A + \frac{\mu_0\mu_A^2}{\alpha}A^*\right)\left(\frac{-\delta}{rA^*+\delta}\right) \\
&= \left(1 - \frac{\delta}{rA^*+\delta}\right)\frac{\mu_0\mu_A^2}{\alpha}A^* - \frac{\delta\left(\alpha\mu_A + \mu_J\mu_A\right)}{rA^*+\delta} \\
&= \frac{r\mu_0\mu_A^2(A^*)^2}{\alpha(rA^*+\delta)} - \frac{\delta\mu_A(\alpha+\mu_J)}{rA^*+\delta} \\
&= \frac{r\mu_0\mu_A^2(A^*)^2 - \alpha\delta\mu_A(\alpha+\mu_J)}{\alpha(rA^*+\delta)} \\
&= \frac{r\mu_0\mu_A^2}{\alpha(rA^*+\delta)}\left((A^*)^2 - \frac{\alpha\delta(\alpha+\mu_J)}{r\mu_0\mu_A}\right) \\
&= \frac{r\mu_0\mu_A^2}{\alpha(rA^*+\delta)}\left((A^*)^2 - \frac{4r\mu_0\mu_A^3\alpha\delta(\alpha+\mu_J)}{(2r\mu_0\mu_A^2)^2}\right).
\end{aligned}$$

So we see that if

$$(A^*)^2 - \frac{4r\mu_0\mu_A^3\alpha\delta(\alpha+\mu_J)}{(2r\mu_0\mu_A^2)^2} > 0, \tag{4.10}$$

then the determinant($\mathcal{J}$) is positive and we have a locally stable positive equilibrium. To evaluate when this occurs, let the two nonzero equilbria be written as

$$A^* = \frac{-Q - W + Z \pm \sqrt{(Q+W-Z)^2 - 4QW}}{2\mu_0\mu_A^2 r} \tag{4.11}$$

where

$$\begin{aligned}
Q &= \mu_0\mu_A^2\delta, \\
W &= \alpha\mu_A r(\alpha+\mu_J), \\
Z &= \alpha^2 r(1-r)\beta.
\end{aligned}$$

From assumptions, we require

$$\begin{aligned} s^2 - 4r\alpha\delta\mu_0\mu_A^3(\mu_J + \alpha) &\geq 0, \\ s &< 0. \end{aligned}$$

This means that

$$\begin{aligned} (*) \qquad (Q + W - Z)^2 - 4QW &\geq 0, \\ (**) \qquad Z &> Q + W. \end{aligned}$$

Now if we plug A^* into the condition found from (4.10), we have the following

$$\begin{aligned} &\left(\frac{-Q - W + Z \pm \sqrt{(Q + W - Z)^2 - 4QW}}{2\mu_0\mu_A^2 r}\right)^2 - \frac{4QW}{(2r\mu_0\mu_A^2)^2} \\ &\quad = \frac{\left(-Q - W + Z \pm \sqrt{(Q + W - Z)^2 - 4QW}\right)^2 - 4QW}{(2\mu_0\mu_A^2 r)^2} \\ &\quad = \frac{(-Q - W + Z)^2 - 4QW + (Q + W - Z)^2 - 4QW}{(2\mu_0\mu_A^2 r)^2} \qquad (4.12) \\ &\qquad + \frac{\pm 2(-Q - W + Z)\sqrt{(Q + W - Z)^2 - 4QW}}{(2\mu_0\mu_A^2 r)^2} \qquad (4.13) \\ &\quad = \frac{2\left((-Q - W + Z)^2 - 4QW \pm (-Q - W + Z)\sqrt{(Q + W - Z)^2 - 4QW}\right)}{(2\mu_0\mu_A^2 r)^2}. \qquad (4.14) \end{aligned}$$

From (*), we know that the term on line (4.12) is positive. Considering only the larger equilibrium value A_1^*, we can also say that that the term on line (4.13) is positive. This implies (4.10) will be positive. This means the determinant($\mathcal{J}$) is positive and A_1^* is locally stable.

We now want to determine the stability of A_2^*. Since all parameters will be positive, then $Q, W, Z > 0$. Thus,

$$\begin{aligned} -4QW &< 0 \\ (-Q - W + Z)^2 - 4QW &< (-Q - W + Z)^2 \\ \sqrt{(-Q - W + Z)^2 - 4QW} &< -Q - W + Z \\ \sqrt{(-Q - W + Z)^2 - 4QW}\sqrt{(-Q - W + Z)^2 - 4QW} &< (-Q - W + Z)\sqrt{(-Q - W + Z)^2 - 4QW} \\ (-Q - W + Z)^2 - 4QW &< (-Q - W + Z)\sqrt{(-Q - W + Z)^2 - 4QW} \end{aligned}$$

$$(-Q - W + Z)^2 - 4QW - (-Q - W + Z)\sqrt{(-Q - W + Z)^2 - 4QW} < 0. \qquad (4.15)$$

Now if we consider only the smaller equilibrium value A_2^*, we see that (4.14) is negative due to (4.15). Thus, given a positive A_2^*, (4.10) will be negative, demonstrating determinant($\mathcal{J}$) is negative and A_2^* is unstable. □

Chapter 5

Gene Drive Model

We extend our basic model to consider the effect of including and releasing transgenic mosquitoes into the population. Specifically, we consider transgenic mosquitoes that harbour a trait causing sterility that can be expressed by a single gene determined by two alleles [30]. We assume transmission of the gene does not follow Mendelian inheritance.

Let W denote the naturally occurring 'wild type' allele and D the new allele, which inhibits fertility and displays the gene drive phenomenon. Adults are categorised by their allele representation as denoted by subscripts. We assume that A_{WW} individuals reproduce as before, but all homogeneous gene drive females (A_{DD}) have an associated fertility cost (where f_d is defined as the fraction of fertility of the homogeneous females). The alleles are co-dominant so that A_{DW} may have some fitness cost (where f is defined as the fraction of fertility of the heterogeneous females). We impose parameter bounds for fitness such that $0 \leq f_d, f \leq 1$. The total adult population is now given by $A = A_{WW} + A_{DW} + A_{DD}$.

From the basic model, a proportion $\dfrac{rA}{rA+\delta}$ of females successfully mate where rA represents the total number of adult males in the population, which can be broken down by the type of male so that

$$\frac{rA}{rA+\delta} = \frac{rA_{WW}}{rA+\delta} + \frac{rA_{DW}}{rA+\delta} + \frac{rA_{DD}}{rA+\delta}.$$

The fecundity for females of type A_{WW} is β. Due to a fitness cost, heterogeneous females (A_{DW}) have a fecundity that is a fraction f of that for A_{WW} females (i.e. $f\beta$). Under these assumptions, for example, the probability that a single female type DW mates with a type WW male is $\left(\dfrac{rA_{WW}}{rA+\delta}\right)$, and the female produces $f\beta(1-r)$ eggs.

Gene drive allows for alleles to be spread at a greater rate than Mendelian inheritance. We will assume that x is the strength of spread of the new allele where $0.5 \leq x \leq 1$. When $x = 0.5$, the gene exhibits normal Mendelian inheritance. The contribution of each adult

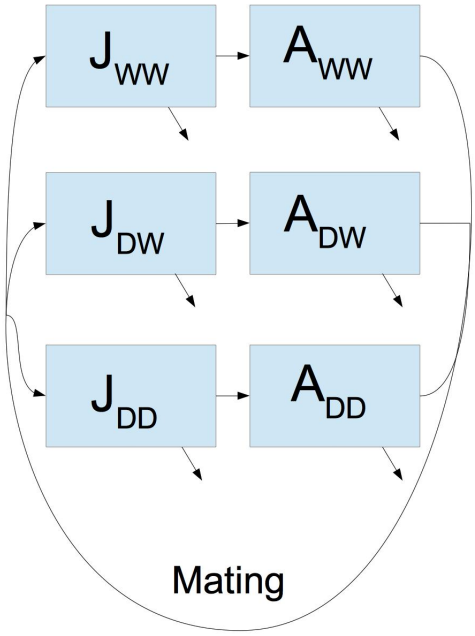


Figure 5.1: **Schematic of the mosquito life-cycle model.** Aquatic stages (J) and adult stages (A) are denoted by their genetic composition: wild type (W) or gene drive (D). All mating crosses are possible and the offspring are generated according to Table 5.1. Mortality occurs with at a density-dependent rate from the aquatic stages and a constant rate from the adults stages, both denoted by a diagonal arrow. (Created by V. Brown)

class to the aquatic population is found by considering all possible matings as follows

$$\beta A_{female}\left(\frac{A_{male}}{A_{male}+\delta}\right) = \beta(1-r)\left(A_{WW}+fA_{DW}+f_dA_{DD}\right)\left(\frac{r\left(A_{WW}+A_{DW}+A_{DD}\right)}{rA+\delta}\right).$$

We then split up the offspring of each male-female pairing into the appropriate aquatic group. For example, a heterogeneous gene drive (A_{DW}) male mating with a homogeneous wild type (A_{WW}) female, produces only two types of offspring: homogeneous wild (J_{WW}) or heterogeneous gene drive (J_{DW}). Based on the strength of the gene drive, a proportion of the offspring $(1-x)$ are homogeneous wild type and the others (x) are heterogeneous gene drive. Figure 5.1 is a schematic of the mating pairs and their offspring. Details of each mating are provided in Table 5.1.

Table 5.1: **Origin of aquatic populations from crosses of wild type and gene drive adults.**

		Fraction Progeny			Coming from
Female	Male	WW	DW	DD	Adults
WW	WW	1	0	0	$\beta(1-r)A_{WW}\left(\frac{rA_{WW}}{rA+\delta}\right)$
WW	DW	$(1-x)$	x	0	$\beta(1-r)A_{WW}\left(\frac{rA_{DW}}{rA+\delta}\right)$
WW	DD	0	1	0	$\beta(1-r)A_{WW}\left(\frac{rA_{DD}}{rA+\delta}\right)$
DW	WW	$(1-x)$	x	0	$f\beta(1-r)A_{DW}\left(\frac{rA_{WW}}{rA+\delta}\right)$
DW	DW	$(1-x)^2$	$2x(1-x)$	x^2	$f\beta(1-r)A_{DW}\left(\frac{rA_{DW}}{rA+\delta}\right)$
DW	DD	0	$(1-x)$	x	$f\beta(1-r)A_{DW}\left(\frac{rA_{DD}}{rA+\delta}\right)$
DD	WW	0	1	0	$f_d\beta(1-r)A_{DD}\left(\frac{rA_{WW}}{rA+\delta}\right)$
DD	DW	0	$(1-x)$	x	$f_d\beta(1-r)A_{DD}\left(\frac{rA_{DW}}{rA+\delta}\right)$
DD	DD	0	0	1	$f_d\beta(1-r)A_{DD}\left(\frac{rA_{DD}}{rA+\delta}\right)$

Our full model with gene drive is given by

$$\begin{aligned}
\frac{dJ_{WW}}{dt} &= \frac{\beta(1-r)r}{rA+\delta}\Big(A_{WW}^2 + (1-x)(f+1)A_{DW}A_{WW} + (1-x)^2 f A_{DW}^2\Big) \\
&\qquad - \Big(\mu_J + \mu_0(J_{WW}+J_{DW}+J_{DD})\Big)J_{WW} - \alpha J_{WW}, \\
\frac{dJ_{DW}}{dt} &= \frac{\beta(1-r)r}{rA+\delta}\Big(x(1+f)A_{WW}A_{DW} + (1+f_d)A_{WW}A_{DD} + 2x(1-x)fA_{DW}^2 \\
&\qquad + (1-x)(f+f_d)A_{DW}A_{DD}\Big) \\
&\qquad - \Big(\mu_J + \mu_0(J_{WW}+J_{DW}+J_{DD})\Big)J_{DW} - \alpha J_{DW}, \\
\frac{dJ_{DD}}{dt} &= \frac{\beta(1-r)r}{rA+\delta}\Big(fx^2A_{DW}^2 + x(f+f_d)A_{DD}A_{DW} + f_dA_{DD}^2\Big) \\
&\qquad - \Big(\mu_J + \mu_0(J_{WW}+J_{DW}+J_{DD})\Big)J_{DD} - \alpha J_{DD},
\end{aligned}$$

$$\begin{aligned}
\frac{dA_{WW}}{dt} &= \alpha J_{WW} - \mu_A A_{WW}, \\
\frac{dA_{DW}}{dt} &= \alpha J_{DW} - \mu_A A_{DW}, \\
\frac{dA_{DD}}{dt} &= \alpha J_{DD} - \mu_A A_{DD}.
\end{aligned} \tag{5.1}$$

5.1 Analysis of dynamics with transgenic mosquitoes

In the full model including gene drive, it is difficult to find a comprehensible analytical solution. The extinction equilibrium ($A_{WW} = A_{DW} = A_{DD} = J_{WW} = J_{DW} = J_{DD} = 0$) always exists. Here we consider four non-extinction equilibria that occur when $A_{DW} = J_{DW} = 0$.

Proposition 6. *If the equilbrium of $A^*_{DW} = J^*_{DW} = 0$, there are five possible equilbria: the extinction equilbrium, two equilbria where $A^*_{DD} \neq 0$ and two where $A^*_{WW} \neq 0$.*

Proof. At equilibrium, the differential equation for J_{DW} becomes

$$\frac{dJ_{DW}}{dt} = \frac{\beta(1-r)r}{rA+\delta}\Big((1+f_d)A_{WW}A_{DD}\Big) = 0.$$

Notice that the equilibrium for $\frac{dJ_{DW}}{dt} = 0$ only occurs if either $A_{WW} = 0$ or $A_{DD} = 0$. First, if $A_{DD} = 0$, as we are under the assumption of $A_{DW} = 0$, we return to the same results as the basic model. We showed in Prop. 2, this will have three possible equilibria including the extinction equilibrium.

Thus, we consider the case where $A_{WW} = 0$, in addition to $A_{DW} = 0$. This makes $\frac{dJ_{WW}}{dt} = \frac{dA_{WW}}{dt} = 0$, so the only equations which are not already zero are $\frac{dJ_{DD}}{dt}$ and $\frac{dA_{DD}}{dt}$. So setting $\frac{dA_{DD}}{dt} = 0$, we get

$$J^*_{DD} = \frac{\mu_A}{\alpha}A^*_{DD}.$$

Now plugging this into $\frac{dJ_{DD}}{dt}$ and setting to zero, we have

$$\begin{aligned}\frac{dJ_{DD}}{dt} = \frac{\beta(1-r)r}{rA+\delta}\Big(fx^2A^2_{DW} + x(f+f_d)A_{DD}A_{DW} + f_dA^2_{DD}\Big)& \\ - \Big(\mu_J + \mu_0(J_{WW} + J_{DW} + \frac{\mu_A}{\alpha}A^*_{DD})\Big)\frac{\mu_A}{\alpha}A_{DD} - \alpha\frac{\mu_A}{\alpha}A_{DD} = 0&\end{aligned}$$

Plugging in other equilibria values,

$$A_{DD}\left(\frac{\alpha\beta(1-r)rf_d}{rA_{DD}+\delta}A_{DD} - \mu_J\mu_A - \frac{\mu_0\mu_A^2}{\alpha}A_{DD} - \alpha\mu_A\right) = 0$$

We are considering when $A^*_{DD} \neq 0$, so

$$\begin{aligned}\alpha^2\beta(1-r)rf_dA_{DD} + \left(-\alpha\mu_J\mu_A - \mu_0\mu_A^2A_{DD} - \alpha^2\mu_A\right)(rA_{DD}+\delta) = 0& \\ -r\mu_0\mu_A^2A^2_{DD} + \left(\alpha^2\beta(1-r)rf_d - r\alpha\mu_A(\mu_J+\alpha) - \delta\mu_0\mu_A^2\right)A_{DD} - \alpha\delta\mu_A(\mu_J+\alpha) = 0&\end{aligned}$$

We obtain the following equilibria for A_{DD}

$$A^*_{DD} = \frac{-1}{2r\mu_0\mu_A^2}\Bigg(\delta\mu_0\mu_A^2 - \alpha^2\beta(1-r)rf_d + r\alpha\mu_A(\alpha+\mu_J) \\ \pm \sqrt{(\alpha^2\beta(1-r)rf_d - \mu_A(r\alpha(\alpha+\ \mu_J) + \delta\mu_0\mu_A))^2 - 4r\alpha\delta\mu_0(\alpha+\mu_J)\mu_A^3}\Bigg). \quad (5.2)$$

□

The equilibria are not dependent on the fertility of the heterozygotes f, but the stability of these equilibria do change based on the parameter f. We examine the stability of these equilibria where $0 \leq f_d, f \leq 1$ and $\delta = 0$ or 150. Biologically if $A_{DD} < 1$, only a fraction of a mosquito exists, so will only discuss results where there is at least one mosquito.

Proposition 7. *The extinction equilibrium is always locally stable.*

Proof. To begin, we examine the extinction equilibrium in the Jacobian and find using Mathematica that there are only two eigenvalues, $-\alpha - \mu_J$ and $-\mu_A$, each with multiplicity of three. Thus, under our assumption of positive parameter values, the extinction equilibria is always locally stable. □

Proposition 8. *The stability of $A_{WW} > 0$ equilibrium depends on δ, f, and x.*

Proof. Consider $A^*_{WW} > 0$ and $J^*_{WW} > 0$ with all other populations zero. We find with the assistance of Mathematica the following eigenvalues of the Jacobian, written in terms of A^*_{WW}, as

$$\begin{aligned}
\lambda_1 &= -\mu_A, \\
\lambda_2 &= -\left(\frac{\alpha^2 + \alpha\mu_J + \mu_0\mu_A A^*_{WW}}{\alpha}\right), \\
\lambda_{3,4} &= -\left(\frac{Q_1 + r\mu_0\mu_A(A^*_{WW})^2 + (\delta\mu_0\mu_A + r\alpha(\alpha+\mu_J+\mu_A))A^*_{WW} \pm \sqrt{Q_3}}{Q_2}\right), \\
\lambda_{5,6} &= -\left(\frac{Q_1 + 2r\mu_0\mu_A(A^*_{WW})^2 + (2\delta\mu_0\mu_A + r\alpha(\alpha+\mu_J+\mu_A))A^*_{WW} \pm \sqrt{Q_4}}{Q_2}\right), \qquad (5.3)
\end{aligned}$$

where

$$
\begin{aligned}
Q_1 &= \alpha^2\delta + \alpha\delta\mu_J + \alpha\delta\mu_A,\\
Q_2 &= 2\alpha(rA^*_{WW} + \delta),\\
Q_3 &= (rA^*_{WW} + \delta)\Big(\alpha^2\delta(\alpha + \ \mu_J - \mu_A)^2 + r\mu_0^2\mu_A^2(A^*_{WW})^3 + \mu_0\mu_A(2r\alpha(\alpha+\mu_J-\mu_A) + \delta\mu_0\mu_A)(A^*_{WW})^2\\
&\quad + \alpha(-4(1+f)r^2x\alpha^2\beta + r\alpha(\alpha^2 + (\mu_J-\mu_A)^2 + 2\alpha(2(1+f)x\beta + \mu_J - \mu_A))\\
&\quad + 2\delta\mu_0(\alpha+\mu_J-\mu_A)\mu_A)A^*_{WW}\Big),\\
Q_4 &= \alpha^2\delta^2(\alpha+\mu_J-\mu_A)^2 + 4r^2\mu_0^2\mu_A^2(A^*_{WW})^4 + 4r\mu_0\mu_A(r\alpha(\alpha+\mu_J-\mu_A) + 2\delta\mu_0\mu_A)(A^*_{WW})^3\\
&\quad + 2A^*_{WW}\alpha\delta(-4r^2\alpha^2\beta + r\alpha(\alpha^2 + (\mu_J-\mu_A)^2 + 2\alpha(2\beta+\mu_J-\mu_A)) + 2\delta\mu_0(\alpha+\mu_J-\mu_A)\mu_A)\\
&\quad + (-4r^3\alpha^3\beta + r^2\alpha^2(\alpha^2 + (\mu_J-\mu_A)^2 + 2\alpha(2\beta+\mu_J-\mu_A)))(A^*_{WW})^2\\
&\quad + (8r\alpha\delta\mu_0(\alpha+\mu_J-\mu_A)\mu_A + 4\delta^2\mu_0^2\mu_A^2)(A^*_{WW})^2.
\end{aligned}
$$

Given positive parameters, as well as $\mu_J > \mu_A$ and $A_{WW} > 0$, then four of the eigenvalues are always negative, i.e. $\lambda_{1,2,3,5} < 0$. It is possible for λ_4 and λ_6 to be positive. When either of these eigenvalues are positive, the equilibrium would be unstable. Both λ_4 and λ_6 are dependent on the Allee constant δ. In addition, λ_4 is also dependent on the level of gene drive x and the heterozygous fertility f. Based on parameter values (Table 5.2), we can determine numerically where stability changes. □

Table 5.2: **Parameter ranges and a specific parameter set for *Anopheles gambiae* at 26°C.** The origin of the parameter ranges and †references are found in the text. The density-dependent and independent mortality for the aquatic stage of *Anopheles gambiae* varied widely in the literature, as noted in the text. Below the horizontal line are parameters for which *Anopheles* specific parameterization does not exist so standard values used are listed.

			Anopheles gambiae	
Symbol	Description	Range†	Value	Reference
β	Eggs laid per female	$[50/4, 122/2]$	$100/3$	[33, 62]
r	Proportion males	$[0.5, 0.55]$	0.50	[82]
μ_0	Density-dependent mortality rate	$[3\cdot10^{-6}, 0.5]$	0.05	-
μ_J	Mortality rate for aquatic stage	$[0.05, 0.8]$	0.2	-
μ_A	Mortality rate for adults	$[1/30, 1/8]$	$1/23$	[67]
α	Maturation rate	$[1/30, 1/8]$	$1/9.8$	[9]
δ	Allee constant	$[0, 250]$	0	-
$1-f$	Fertility cost of A_{DW}	[0,1]	0.5	-
$1-f_d$	Fertility cost of A_{DD}	[0,1]	0	-
x	Gene drive strength	[0.5,1]	0.5	-

Stability of the gene drive only equilibrium

Proposition 9. *The stability of $A_{DD} > 0$ equilibria depends on x, δ, f, and f_d.*

Proof. Consider $A_{DD} > 0$ and $J_{DD} > 0$ with all other populations zero. We find with the assistance of Mathematica the following eigenvalues of the Jacobian, written in terms of A^*_{DD}, as

$$\begin{aligned}
\lambda_1 &= -\mu_A, \\
\lambda_2 &= -\left(\frac{\alpha^2 + \alpha\mu_J + \mu_0\mu_A A^*_{DD}}{\alpha}\right), \\
\lambda_{3,4} &= -\left(\frac{Q_1 + r\mu_0\mu_A(A^*_{DD})^2 + (\delta\mu_0\mu_A + r\alpha(\alpha+\mu_J+\mu_A))A^*_{DD} \pm \sqrt{Q_6}}{Q_5}\right), \\
\lambda_{5,6} &= -\left(\frac{Q_1 + 4r\mu_0\mu_A(A^*_{DD})^2 + 2(\delta\mu_0\mu_A + r\alpha(\alpha+\mu_J+\mu_A))A^*_{DD} \pm \sqrt{Q_7}}{Q_5}\right),
\end{aligned}$$

where

$$\begin{aligned}
Q_5 &= 2\alpha(rA^*_{DD} + \delta) \\
Q_6 &= (rA^*_{DD} + \delta)\Big(\alpha^2\delta(\alpha + \ \mu_J - \mu_A)^2 + (A^*_{DD})^3 r\mu_0^2\mu_A^2 + \mu_0\mu_A(2r\alpha(\alpha+\mu_J-\mu_A) \ + \delta\mu_0\mu_A)(A^*_{DD})^2 \\
&\quad + \alpha(4(f+f_d)r^2(-1+x)\alpha^2\beta + 2\delta\mu_0(\alpha+\mu_J-\mu_A)\mu_A + r\alpha(\alpha^2 + (\mu_J-\mu_A)^2)A^*_{DD} \\
&\quad - 2\alpha^2(2f(-1+x)\beta + 2f_d(-1+x)\beta - \mu_J + \mu_A)A^*_{DD}\Big), \\
Q_7 &= \alpha^2 \ \delta^2(\alpha+\mu_J-\mu_A)^2 + 16r^2\mu_0^2\mu_A^2(A^*_{DD})^4 + 16r\mu_0\mu_A(r\alpha(\alpha+\mu_J- \ \mu_A) + \delta\mu_0\mu_A)(A^*_{DD})^3 \\
&\quad + 4\alpha\delta(-2f_d r^2\alpha^2\beta + r\alpha(\alpha^2 + (\mu_J-\mu_A)^2 + 2\alpha(f_d\beta + \mu_J - \mu_A)) + \delta \ \mu_0(\alpha+\mu_J-\mu_A)\mu_A)A^*_{DD} \\
&\quad + 4(-2f_d r^3\alpha^3\beta + r^2\alpha^2(\alpha^2 + (\mu_J-\mu_A)^2 + 2\alpha(f_d\beta + \mu_J - \mu_A)) + 4r\alpha\delta\mu_0(\alpha+\mu_J-\mu_A)\mu_A)(A^*_{DD})^2 \\
&\quad + 4\delta^2\mu_0^2\mu_A^2(A^*_{DD})^2.
\end{aligned}$$

Similar to the stability of wild type, we find that given positive parameters, as well as $\mu_J > \mu_A$, and $A^*_{DD} > 0$, then all of the eigenvalues are always negative, except λ_4 and λ_6. Both λ_4 and λ_6 are dependent on the gene drive strength x, Allee constant δ, and the fertility of the homozygous gene drive females f_d. Additionally, λ_4 is dependent on the heterozygous fertility f. Based on parameter values (Table 5.2), we can determine numerically where stability changes. □

Absence of an Allee effect

Consider the case when there is no Allee effect $\delta = 0$, There can exist one positive A_{WW} equilibrium and one positive A_{DD} equilibrium in addition to the extinction equilibrium. As we are working under the assumption $A_{DW} = J_{DW} = 0$ there are no positive equilibria where

both A_{WW} and A_{DD} co-exist. The stability of the A_{WW} equilibrium depends on the gene drive x and the fertility of the heterozygotes f.

Numerical Result 5.1.1. *In the case of the parameters from Table 5.2, the wild type only equilibrium is locally stable when* $x < \frac{1}{1+f}$.

Using the eigenvalues in Equation 5.3, found in Mathematica, we again note that $\lambda_{1,2,3,5} < 0$ for all positive eigenvalues and when $A_{WW} > 0$, $A_{DD} = 0$ and $A_{DW} = 0$. Thus when plugging in the specific parameters listed in Table 5.2 (with $\delta = 0$) and f and x remain variables. We find that $\lambda_6 < 0$, so then we set $\lambda_4 < 0$ and solve for x using $A^*_{WW} > 0$ using Mathematica. We find that when $x < \frac{1}{1+f}$ all eigenvalues will be negative, and thus the wild type only equilibrium is locally stable.

Notice that the stability is not affected by the fertility of the homozygotes f_d. In contrast, the stability of the A_{DD} equilibrium additionally depends on the fertility of the homozygotes f_d as well as the gene drive x and the fertility of the heterozygotes f. Furthermore, with the chosen parameter set (Table 5.2) when $x < \frac{1}{1+f}$, there exists multi-stability between the wild type only, gene drive only, and extinction equilibria. In other words, the initial conditions determine when the adult population will be composed entirely of A_{WW} or A_{DD} mosquitoes (or no mosquitoes).

When $x > \frac{1}{1+f}$, the only possible equilibria either are composed entirely of gene drive homozygous mosquitoes or no mosquitoes at all, i.e. extinction. There is a clear division of this space into where the gene drive equilibrium is locally stable or unstable, but the analytical formula is complicated and rather uninformative.

Numerical Result 5.1.2. *Given parameters from Table 5.2, The A_{DD} equilibrium is unstable when*

$$x > \frac{1}{f + f_d}\left(-3.86 \cdot 10^{-3} + f + 0.5 f_d - 0.5\sqrt{5.97 \cdot 10^{-5} - 1.55 \cdot 10^{-2} f_d + f_d^2}\right).$$

Note, these values were computed in Mathematica and rounded.

Presence of an Allee effect

When an Allee effect is included, ($\delta \neq 0$), more equilibria are possible. For example, consider $\delta = 150$, with the parameterisation in Table 5.2. There are at least five possible equilibria: the extinction equilibria, two positive equilibria with only wild type mosquitoes ($A_{WW} > 0$) and two positive equilibria with only gene drive homozygotes ($A_{DD} > 0$).

Proposition 10. *The latter two equilibria are only real and positive when*

$$f_d > \frac{\mu_A\left(r\alpha(\alpha + \mu_J) + \delta\mu_0\mu_A\right) + 2\sqrt{r\alpha\delta\mu_0(\alpha + \mu_J)\mu_A^3}}{\alpha^2\beta r(1 - r)}$$

Proof. Looking at Equation 5.2, and asuuming that $A^*_{DD} > 0$,

$$(\alpha^2\beta(1-r)rf_d + \mu_A(r\alpha(\alpha + \ \mu_J) + \delta\mu_0\mu_A))^2 - 4r\alpha\delta\mu_0(\alpha+\mu_J)\mu_A^3 > 0,$$
$$(\alpha^2\beta(1-r)rf_d - \mu_A(r\alpha(\alpha + \ \mu_J) + \delta\mu_0\mu_A))^2 > 4r\alpha\delta\mu_0(\alpha+\mu_J)\mu_A^3.$$

Now since we assume that $A^*_{DD} > 0$, looking at 5.2, this means that,

$$\alpha^2\beta(1-r)rf_d - \delta\mu_0\mu_A^2 - r\alpha\mu_A(\alpha+\mu_J) > 0.$$

Then when we square root both sides we know that the left side will be positive, so

$$\alpha^2\beta(1-r)rf_d - \mu_A(r\alpha(\alpha + \ \mu_J) + \delta\mu_0\mu_A) > 2\sqrt{r\alpha\delta\mu_0(\alpha+\mu_J)\mu_A^3},$$
$$\alpha^2\beta(1-r)rf_d > \mu_A(r\alpha(\alpha + \ \mu_J) + \delta\mu_0\mu_A) + 2\sqrt{r\alpha\delta\mu_0(\alpha+\mu_J)\mu_A^3},$$
$$f_d > \frac{\mu_A(r\alpha(\alpha + \ \mu_J) + \delta\mu_0\mu_A) + 2\sqrt{r\alpha\delta\mu_0(\alpha+\mu_J)\mu_A^3}}{\alpha^2\beta(1-r)r}.$$

□

Numerical Result 5.1.3. *With the parameterisation from Table 5.2, when $f_d \lessapprox 0.243$, the gene drive only equilibrium does not exist.*

We substituted the parameter values into Proposition 10 and used Mathematica to obtain this numerical result.

Numerical Result 5.1.4. *Given parameters from Table 5.2 with Allee effect ($\delta = 150$), the larger equilibrium in magnitude for A_{WW} and A_{DD} demonstrates qualitatively similar local stability patterns to those observed for the non-zero equilibrium in the basic model. The smaller A_{WW} equilibrium is always unstable.*

We find that only λ_4 has the possibility to be positive. We solve this in Mathematica, and find for the larger nonzero A_{WW} equilibrium that when $x < \frac{1}{1+f}$ it is locally stable. Notice that this is the same when $\delta = 0$. The eigenvalue is dependent on δ, but numerically we see that its dependence is minimal.

We find that for the parameters in Table 5.2, that $\lambda_6 > 0$ for the smaller A_{WW} equilibrium. Thus it is always unstable. □

Numerical Result 5.1.5. *The smaller A_{DD} equilibrium has more complicated stability changes, which we only determine numerically.*

Coexistence equilibria

Conjecture 5.1.6. *There exists equilibria where $A_{WW}, A_{DW}, A_{DD} > 0$ in our system.*

However, these are analytically difficult to determine. For particular parameter sets we find locally stable coexistence equilibria numerically, for example in the lower right in Figure 5.7. In addition, there are multiple equilibria that are not biologically relevant, i.e. $A_i < 0$ with $i \in \{WW, DW, DD\}$.

5.2 Numerical Results

Parameter ranges

Parameter values are highly species specific and dependent on many factors including temperature, diet, and mosquito size. We consider mosquitoes of genus *Anopheles* and *Aedes*, and specifically focus on *Anopheles gambiae*, as these mosquitoes are primary vectors for the diseases that cause significant global public health impact [17, 91, 92, 94, 70, 93]. We set upper and lower bounds for each parameter based on published experimental data, and vary the parameters within these bounds (Table 5.2). Based on temperature-specific data, we also fix a specific parameter set for *Anopheles gambiae* at approximately 26°C as a baseline (Table 5.2).

Parameters are ascertained from the life history of mosquitoes. The fecundity β is determined by both the number of eggs per gonotrophic cyclic (approximately 50 to 122 eggs per gonotrophic cycle) and the number of days in a gonotrophic cycle (laying every 2 to 4 days in favourable environmental conditions) [14, 19, 25, 33]. The proportion of males r is similar or slightly higher than females [14, 25]. The transition from eggs to adults α takes between 8 and 30 days [9, 25, 75, 82]. Adult mosquito life expectancy, related to adult mortality rate μ_A, varies between 8 and 30 days [4, 67, 78]. Survival of larvae to adulthood, related to aquatic mortality rate μ_J, is extremely temperature dependent and can vary from 3% to 93% [9, 25, 75, 82]. Determining the density-dependent mortality rate from experimental evidence is more challenging. Previous estimates for this parameter vary significantly [28, 52], so we allow μ_0 to vary over a broad range of values.

The value of the Allee constant δ is not known for mosquitoes, although there exist estimates for other insect species. For example, in a study on gypsy months in different states, two different Allee threshold values were determined: 0.78% and 3.1% of the estimated carrying capacity [80]. As a result, we assume the mate-finding Allee effect, if it exists, to be a small percentage of the carrying capacity. We choose δ such that the Allee effect is at most 15%. We run all simulations with $\delta = 0$ and $\delta \in [50, 250]$.

Parameter variation

We use Latin Hypercube Sampling (LHS) and filter our parameterisation based on biologically-derived criteria in the absence of gene drive. Specifically, we use $n = 225$ LHS samples and

a two-step filter process on the data. The first filter step chooses parameter sets such that there exist only non-zero equilibria that are real and positive. This amounts to only allowing parameter sets which fall to the left of the bifurcation value (star in Figure 5.2a). Approximately 85% of the total LHS samples are retained. Biologically if there exists a mate-finding Allee effect, we expect the number of mosquitoes necessary to find a mate to be relatively small compared to the carrying capacity. The relative Allee effect can be calculated as A_1^*/A_2^*.

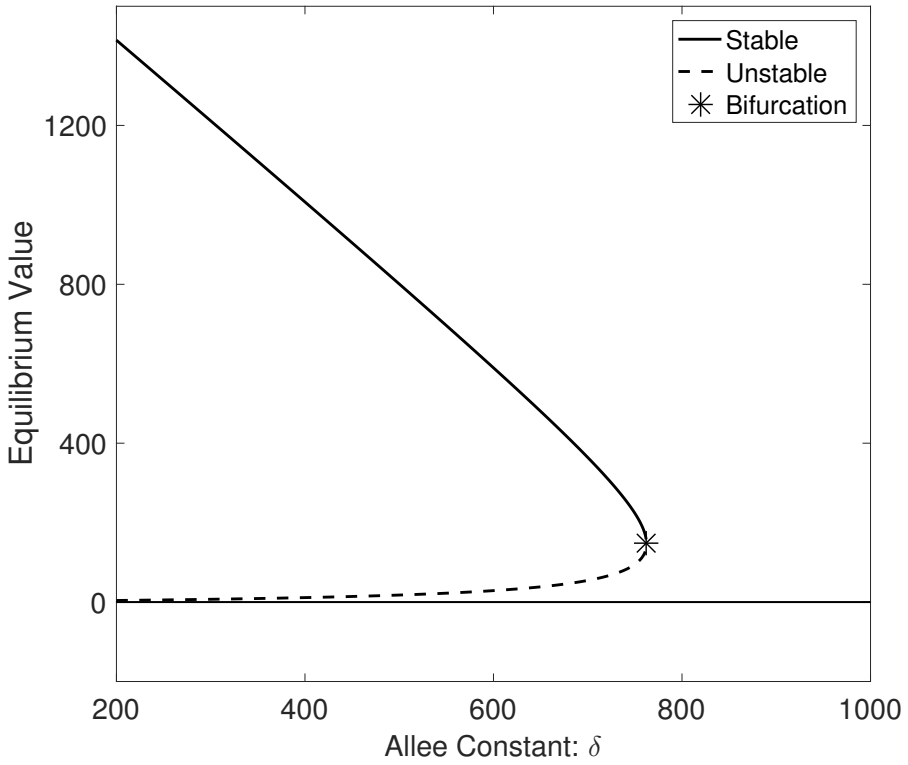
We therefore use a second step in our filter process to refine our parameter sets to those with relative Allee effects of less than 15%. This retains $\sim 99\%$ of the parameter sets from the first stage of the filter process. In total, we are left with 190 parameter sets that fulfill both criteria. We show the proportion of parameters in a particular interval based on positive equilibria or non-positive equilibria (Figure 5.3).

Simulation results

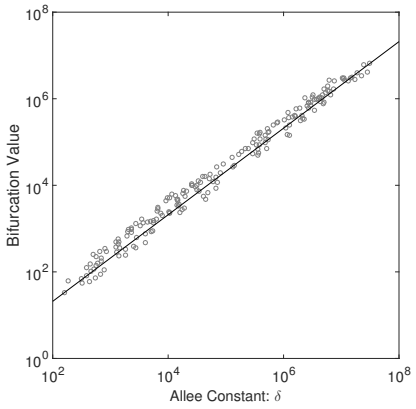
We carry forward the parameterisation from the basic model for the gene drive model. We vary all the additional parameters found in the gene drive model: x, f, and f_d. We assume greater-than-Mendelian inheritance bias of the gene drive allele, i.e. $x > 0.5$. We consider the effect of the gene drive allele on the fertility of mosquitoes, such that $0 \leq f, f_d \leq 1$.

To begin, we fixed the fertility of heterozygotes to be $f = 0.5$ and homozygous gene drive to be $f_d = 0$, and varied the gene drive strength for our parameter sets. We numerically determined the equilibria of the gene drive model with an initial population size set just above the Allee threshold A_1^* found from the basic model. In Figure 5.4, the parameter sets are ordered by the non-zero equilibrium from the basic model without an Allee effect, although the relative Allee effect (A_1^*/A_2^*) gives a similar ordering (not pictured). From Figure 5.4, we find that gene drive must be stronger than 95% to drive the population to extinction in most parameter sets. At lower values of the equilibrium of the basic model increases, particularly when an Allee effect is present (further to the left in Figure 5.4b), a lower level of gene drive is sufficient to achieve elimination of the mosquito population. Notice that parameter sets which produce nearly identical equilibrium values, and are thus ordered sequentially along the x-axis, may require very different levels of gene drive to reach extinction (Figure 5.4). The reason for this variation in gene drive requirements is due to the values of individual parameters that differ between the parameter sets.

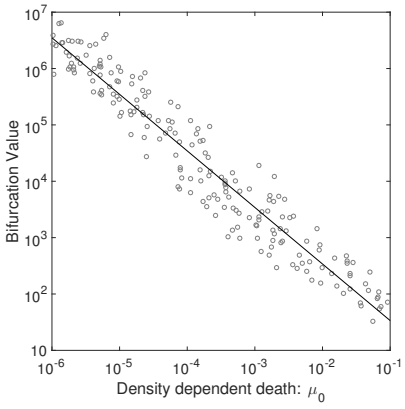
Next we relaxed our assumption on the fertility of heterozygotes, while the fertility of gene drive homozygotes remain fixed at zero ($f_d = 0$), and varied gene drive strength. All other parameters were fixed to the *Anopheles* specific parameters found in Table 5.2. Elimination was observed for a wide range of f when gene drive was above 95% (Figure 5.5), regardless of the inclusion of an Allee effect. In the absence of an Allee effect, we find that based on the initial conditions, the adult population becomes either all wild type mosquitoes A_{WW} or all homozygous gene drive type A_{DD} (Figure 5.5a). In the presence of an Allee effect, we find that the population equilibrium decreases in all instances where gene drive mosquitoes



(a) Strength of Allee effect



(b)



(c)

Figure 5.2: **Equilibrium values and stability change with Allee effect and density-dependent mortality.** (a) A bifurcation diagram as the Allee constant δ varies. The equilibrium value at the bifurcation, marked by a star in (a), is highly correlated with the Allee constant (b) and density-dependent mortality (c). The diagram in (a) is computed with the parameters from Table 5.2. The LHS parameter sets were used to calculate the bifurcation values for (b) and (c). Parameter sets are the same as those used in Figure 5.4

previously dominated (Figure 5.5b). Notice, that there is a minimum level of fertility of heterozygotes for persistence of the gene drive population. Below this level mosquitoes with gene drive alleles lack sufficient progeny, so the allele cannot be passed on to the next generation (Figure 5.5, lower left corner).

To consider variation in the fertility of both gene drive homozygotes and heterozygotes, we assume presence of an Allee effect and examine three scenarios of gene drive strength: 50%, 80% and 95%. Under Mendelian inheritance ($x = 0.5$), the wild type only equilibrium is locally stable for all levels of homozygous and heterozygous fertility (Figure 5.6a). Depending on the initial conditions, however, it is also possible to reach a gene drive only equilibrium, as a region of multi-stability is present in the system. Furthermore, the region where only the wild type population exists is divided into two distinct regions: where no gene drive equilibrium is possible ($f_d \lessapprox 0.243$) and where the equilibrium is unstable.

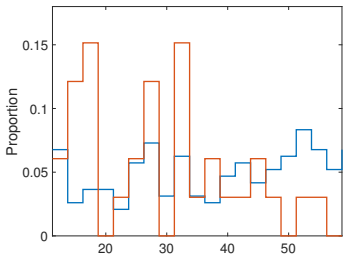
In the presence of gene drive ($x > 0.5$) the region where the wild type only equilibrium is locally stable shrinks to low values of the heterozygous fertility, f (Figure 5.6bc). For larger heterozygous fertility $f \gtrapprox 30\%$ and low homozygous fertility $f_d \lessapprox 24\%$ extinction is predicted assuming no heterozygous equilibria are possible, i.e. $A_{DW} = J_{DW} = 0$ (Figure 5.6bc, lower right corner). Our biological expectation is a monotonic increase of the fertility trait from heterozygotes to homozygotes. If we restrict ourselves to that region, below the $y = x$ line in Figure 5.6, we see that it is a region that is dominated by extinction and gene drive only equilibria.

A detailed numerical examination of our model with an Allee effect supports our analytical results under our simplifying assumption of no heterozygotes. We discuss in detail when gene drive strength is 80%, but similar results occur for all gene drive considered (not pictured). In regions of known bi- or multi-stability our initial levels of gene drive or wild type mosquitoes matter (Figure 5.7a-b, upper left corner). When the wild type population excludes the gene drive population, an identical wild type equilibrium is reached regardless of the fertility of the homozygous gene drive population. In contrast, when the gene drive population excludes the wild type population, the equilibrium population size is dependent on the fertility of both the heterozygotes and the homozygous gene drive population. When fertility of the gene drive population is very low (i.e. $f, f_d \lessapprox 0.2$) then the population may get pushed below the Allee threshold causing it to crash (Figure 5.7b). Finally, in our numerical examination we also observe the persistence of population where we predicted the extinction of the population. This is due to the presence of co-existence equilibrium (Figure 5.7, positive values in the lower right). These co-existence equilibria require the persistence of the heterozygous population, i.e. $A_{DW}, J_{DW} > 0$. We show examples of temporal population levels based on different gene drive levels and fixing heterozygous fertility set to $f = 0.3$ and all parameters set as in Table 5.2. We see all possible equilibrium types discussed with an initial population of 50 mosquitoes and releasing 10 gene drive mosquitoes. We see only wild type survive, When gene drive is $x = 0.7$ (Figure 5.8a). Then increasing gene drive to $x = 0.8$, we have co-existance (Figure 5.8b), and then when $x = 0.9$, we only have gene drive mosquitoes at a much lower population level (Figure 5.8c). Then when $x = 0.99$, we have extinction (Figure

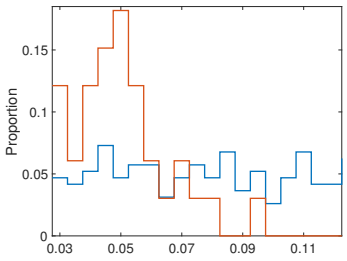
5.8d).

Numerical simulations where run in MatLab using ode45 (Figures 5.4, 5.5, 5.7, and 5.8). Then the final three adult populations (A_{WW}, A_{DW}, and A_{DD}) were summed. The final populations were plotted using imagesc (Figures 5.4, 5.5, and 5.7). For the latin hypercube sampling, the function lhs was used. For density dependent death rate of larvae μ_0 the bounds were transformed using log base 10. The Figure 5.3 was created using the function hist. All code has been uploaded to GitHub and is available at

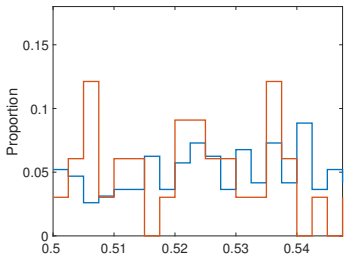
https://github.com/melody289/genedrivemosquito.



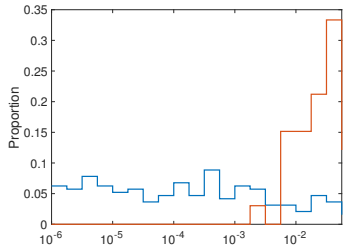
(a) β: Egg laying rate



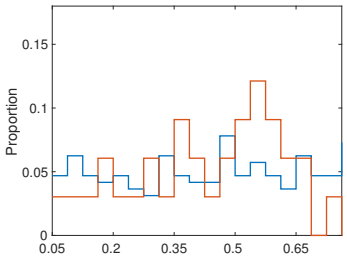
(b) α: Transition rate



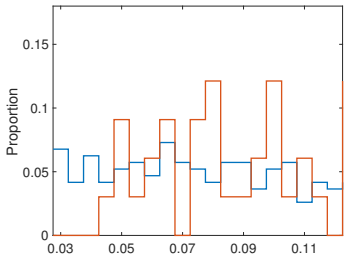
(c) r: Male percent



(d) μ_0: Density dependent death rate



(e) μ_J: Constant death rate



(f) μ_A: Adult death rate

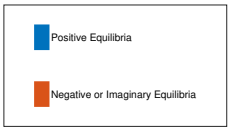
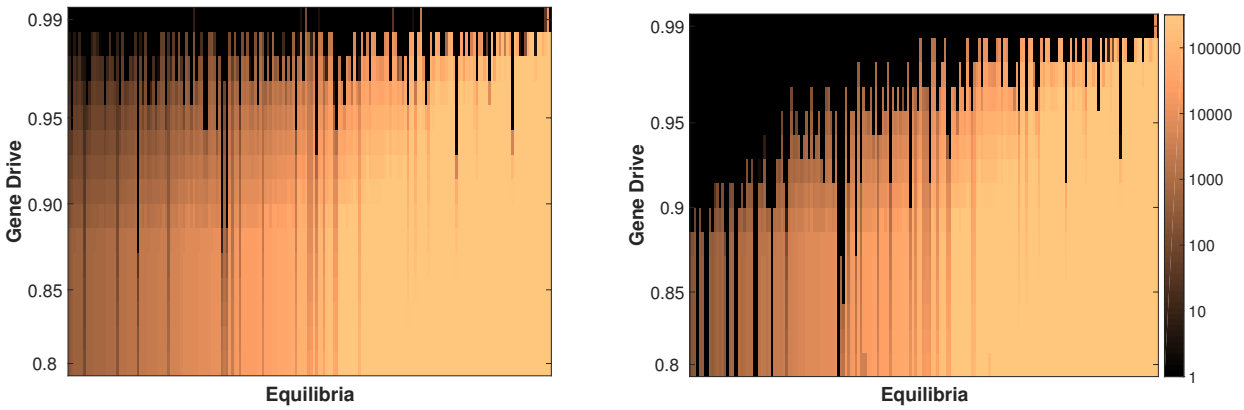


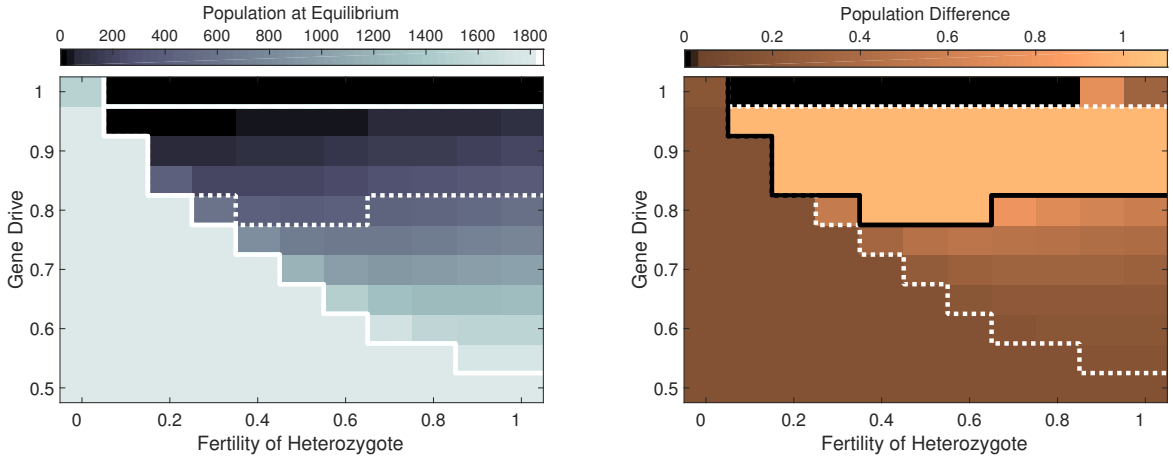
Figure 5.3: **Parameter Spread using latin hypercube sampling**. After taking a sample of 225 various parameters in the bounds on Table 5.2, we separated those parameter sets that give positive equilibria versus non-positive equilibria and show histograms of the proportion of value of the parameters.



(a) No Allee Effect, $\delta = 0$

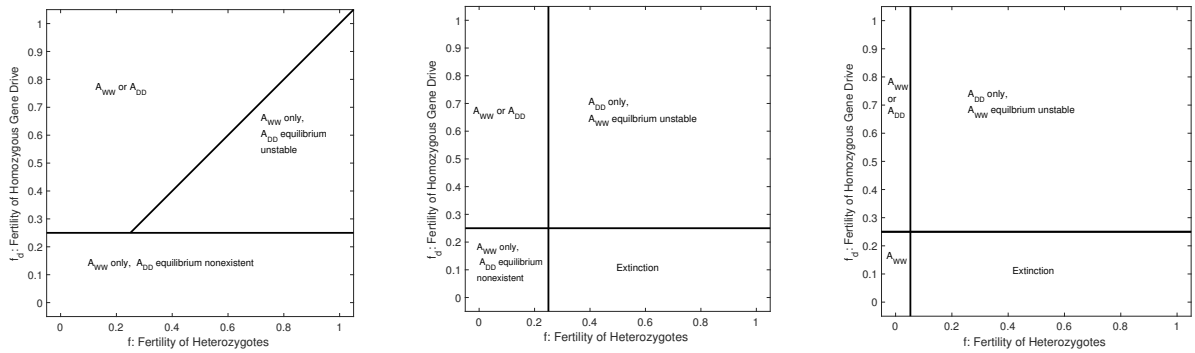
(b) Allee Effect, $\delta = 150$

Figure 5.4: **Effect of varying gene drive on the equilibrium of the full model.** (a) Without an Allee effect, gene drive stronger than 95% is necessary for extinction with most parameter sets. (b) With an Allee effect, population extinction is attained for a wider range of gene drive strengths. The color represents the equilibrium population size, with brighter colors associated with larger population size (visualized on a log-scale). Parameter sets are ordered on the x-axis by their equilibrium population size when $\delta = 0$. Parameters are found in Table 5.2.



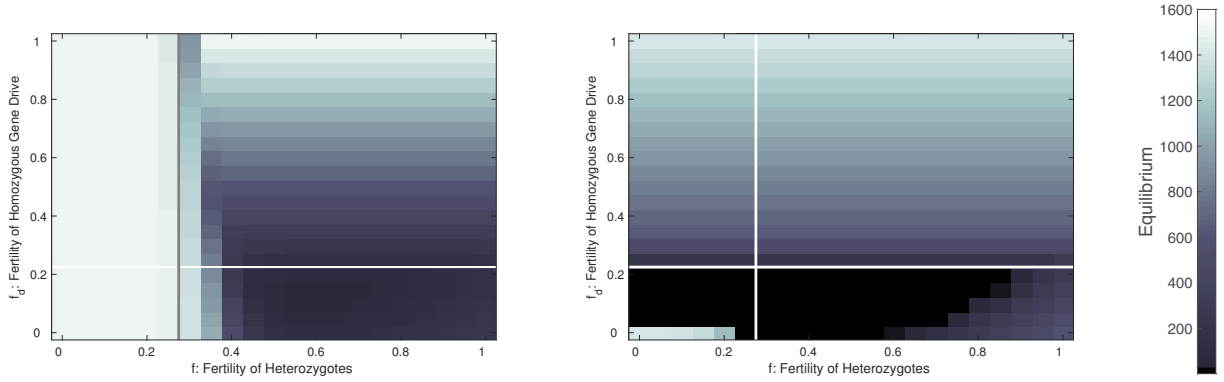
(a) No Allee Effect ($\delta = 0$) (b) Change in population with Allee Effect ($\delta = 150$)

Figure 5.5: **Equilibrium for the full model when gene drive strength and heterozygous fertility are varied.** (a) The equilibrium size when there is no Allee effect and (b) the fraction reduction in the population size when the Allee constant is $\delta = 150$. Darker colors indicate smaller population size in (a) or smaller change in the presence of an Allee effect (b). Solid lines separate the space into regions with qualitatively different equilibria. Dashed lines show the regions on the other plot, for ease of comparison. Parameters from Table 5.2.



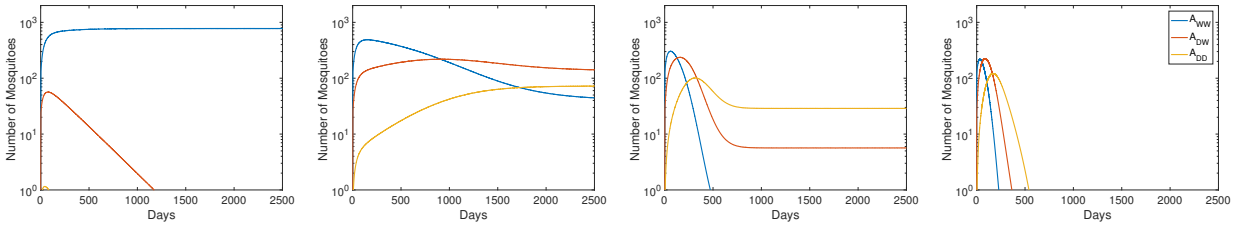
(a) $x = 0.5$ (b) $x = 0.8$ (c) $x = 0.95$

Figure 5.6: **Bifurcation diagrams of the full model when varying both heterozygous and homozygous fertility but assuming the absence of heterozygotes.** In the presence of an Allee effect ($\delta = 150$), the regions of existence and stability change with increasing gene drive strength, x: (a) 50%, (b) 80%, and (c) 95%. Below the horizontal line $f \lessapprox 0.243$ a non-zero equilibrium does not exist for the gene drive population. To the left of the vertical line in (b) and (c) the wild type only equilibrium is not stable. All other parameters from Table 5.2. Note: we assume $A_{DW} = J_{DW} = 0$ for the determination of equilibria and stability.



(a) $A_{DD_0} < A_{WW_0}$ (b) $A_{DD_0} > A_{WW_0}$

Figure 5.7: **Adult population size after three years when varying both heterozygous and homozygous fertility.** The plots differ only in their initial levels of adult homozygous mosquitoes: (a) larger initial size of the wild type population relative to the gene drive population, $A_{WW} = 500$, $A_{DD} = 10$; (b) a larger initial size of the gene drive population $A_{WW} = 10$, $A_{DD} = 500$. Here a gene drive strength of 80% and an Allee effect with Allee constant $\delta = 150$ are assumed. All other parameters from Table 5.2. The bifurcation lines in the absence of a heterozygous population (from Figure 5.6) are overlaid.



(a) Gene drive $x = 0.7$ (b) Gene drive $x = 0.8$ (c) Gene drive $x = 0.9$ (d) Gene drive $x = 0.99$

Figure 5.8: **Temporal dynamics with varying gene drive**: We increase x(gene drive) to show temporal dynamics with the heterozygous fertility set to $f = 0.3$. All other parameters are the same as those listed in Table 5.2.

Chapter 6

Model Extensions

The goal of this paper is to model the reduction or elimination of invading mosquitoes in the hopes of decreasing disease spread. We investigate this idea further in two ways, presenting a model that includes migrating mosquitoes and looking at the basic reproductive number R_0.

6.1 Gene drive model with migration

In our models presented previously, we ignored the continued invasion of mosquitoes. The assumption of a single event populating a new population is biologically possible if a batch of eggs that hatch at approximately the same time are laid in a new area. To consider the continue invasion of mosquitoes, we adapted our basic model to include a time-decaying adult migration term:

$$\begin{aligned}\frac{dJ}{dt} &= \frac{r(1-r)\beta}{rA+\delta}A^2 - (\mu_J + \mu_0 J)J - \alpha J,\\ \frac{dA}{dt} &= \alpha J - \mu_A A + M,\\ M &= m_0 e^{-ct},\end{aligned}$$

where M is the migration rate of adult mosquitoes; c is the deceleration of migrating mosquitoes into the area, i.e. the rate mosquitoes lose interest in migrating; and m_0 is the initial size of the migrating mosquito population. As under these assumptions the migrating population will eventually disappear, the addition of migration in this form does not affect the asymptotic dynamics. However, the decaying migration does effect the transient dynamics of the mosquito population.

We also make a similar adaptation to the gene drive model, i.e. the addition of an extra

equation for the migrating adult population, resulting in the system

$$\begin{aligned}
\frac{dJ_{WW}}{dt} &= \frac{\beta(1-r)r}{rA+\delta}\left(A_{WW}^2 + (1-x)(f+1)A_{DW}A_{WW} + (1-x)^2 f A_{DW}^2\right) \\
&\qquad - (\mu_J + \mu_0 J)J_{WW} - \alpha J_{WW}, \\
\frac{dJ_{DW}}{dt} &= \frac{\beta(1-r)r}{rA+\delta}\Big[x(1+f)A_{WW}A_{DW} + (1+f_d)A_{WW}A_{DD} + 2x(1-x)fA_{DW}^2 \\
&\qquad + (1-x)(f+f_d)A_{DW}A_{DD}\Big] - (\mu_J + \mu_0 J)J_{DW} - \alpha J_{DW}, \\
\frac{dJ_{DD}}{dt} &= \frac{\beta(1-r)r}{rA+\delta}\left(fx^2 A_{DW}^2 + x(f+f_d)A_{DD}A_{DW} + f_d A_{DD}^2\right) \\
&\qquad - (\mu_J + \mu_0 J)J_{DD} - \alpha J_{DD},
\end{aligned}$$

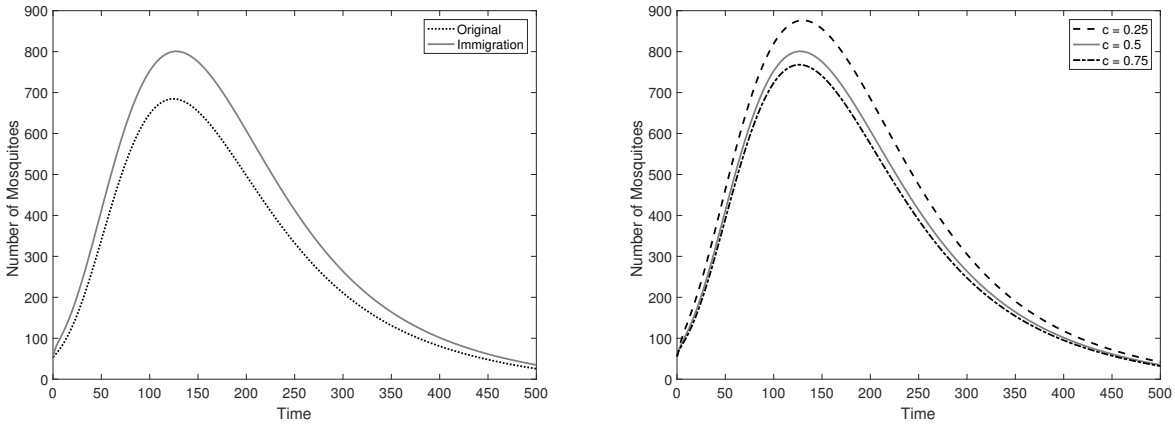
$$\begin{aligned}
\frac{dA_{WW}}{dt} &= \alpha J_{WW} - \mu_A A_{WW} + M, \\
\frac{dA_{DW}}{dt} &= \alpha J_{DW} - \mu_A A_{DW}, \\
\frac{dA_{DD}}{dt} &= \alpha J_{DD} - \mu_A A_{DD}, \\
M &= m_0 e^{-ct}
\end{aligned}$$

where $J = J_{WW} + J_{DW} + J_{DD}$, $A = A_{WW} + A_{DW} + A_{DD}$, and all other parameters are defined as in the gene drive model. All migrating mosquitoes are assumed to be wild type.

All equilibria remain unchanged, but in the regions of multiple stability, the locally stable equilibria that is reached may change due to the altered initial conditions. In other words, the migrating population contributes to the wild type population and acts like a larger initial influx of wild type mosquitoes. In addition, the inclusion of migrating mosquitoes can produce large changes in the transient behavior (Fig. 6.1).

6.2 Basic Reproductive Number: R_0

We now present a simple model to represent spread of a disease from mosquitoes to humans. The goal is to find a simple threshold of whether, in the expansion of mosquitoes territory, the disease will spread. Let H_s represent humans which are susceptible to a disease and H be infectious individuals with a total population of humans as $N = H_s + H$. Once a person is recovered, they will return to the susceptible class at a rate γ, such that people do not acquire immunity. A_s and A_i are susceptible and infectious mosquitoes, respectively, where $A = A_i + A_s$ is the total population of adult mosquitoes at a given time. From the basic model new adult mosquitoes αJ will be in the susceptible class. The death rate of adult mosquitoes



(a) With and without migration

(b) Variable decay of migration

Figure 6.1: **Transient dynamics of the model with and without migration.** (a) The inclusion of immigrating mosquitoes ($m_0 = 10$, $c = 0.5$) boosts the transient mosquito population. (b) The rate of decay of migration c affects the size of the transient peak. Parameters from Table 5.2 with $f = 0.5$, $f_d = 0$, and $x = 0.9$.

is μ_A. Once a mosquito becomes infectious, the mosquito will die in this class at the same rate as a susceptible one (μ_A). Let b_h be the rate at which a person is bitten per time and b_m be the number of times a mosquito bites per time. We assume conservation of biting as done elsewhere [58], which means that the total number of bites taken by mosquitoes is the same as the total number of bites received by humans $b_m A = b_h N$. Infected mosquitoes transmit the virus with a probability of β_m, while humans infect mosquitoes with β_h probability. So then the force of infection for a human is $\lambda_h = \frac{\beta_m b_h A_i}{A} = \frac{\beta_m b_m A_i}{N}$ and for mosquitoes is $\lambda_m = \frac{\beta_h b_m H}{N} = \frac{\beta_h b_h H}{A}$. Our full model becomes:

$$\begin{aligned}
\frac{dA_s}{dt} &= \alpha J - \lambda_m A_s - \mu_A A_s, \\
\frac{dA_i}{dt} &= \lambda_m A_s - \mu_A A_i, \\
\frac{dH_s}{dt} &= \gamma H - \lambda_h H_s, \\
\frac{dH}{dt} &= \lambda_h H_s - \gamma H.
\end{aligned}$$

We will assume a fixed number of people, so there will be no deaths or births during the time of the infection, so $H_s = N - H$. Our system reduces to

$$\begin{aligned}\frac{dA_s}{dt} &= \alpha J - \lambda_m A_s - \mu_A A_s \\ \frac{dA_i}{dt} &= \lambda_m A_s - \mu_A A_i \\ \frac{dH}{dt} &= \lambda_h (N - H) - \gamma H\end{aligned}$$

We find R_0 as defined by the number of new infectious mosquitoes in the context of a completely susceptible population. We use the next generation method, which only requires the infectious classes (A_i and H), to get $R_0 = \sqrt{\frac{\beta_m \beta_h b_m^2}{\mu_A \gamma N} A_s}$. The R_0 derived using the next generation method is a geometric mean of R_0 for both vector and host individually. For example, if one infected mosquito infects 3 humans, and those three humans infect 5 mosquitoes each then $R_0 = \sqrt{5 \cdot 3}$ [55]. If $R_0 < 1$, an infection will not spread through a population.

Considering our model with the parameters chosen from Table 5.2, we expect an equilibrium of approximately 1800 mosquitoes and if we include an Allee effect where $\delta = 150$, we find the equilibrium is approximately 1500 mosquitoes. Thus we might find that, if there is a naturally occurring mate finding Allee effect, that R_0 in its presence would be 91% of the original R_0 as can be seen by

$$\frac{\sqrt{\frac{\beta_m \beta_h b_m^2}{\mu_A \gamma N} 1500}}{\sqrt{\frac{\beta_m \beta_h b_m^2}{\mu_A \gamma N} 1800}} \approx 0.91.$$

Assuming an Allee effect exists, if we consider releasing gene drive mosquitoes where the gene spreads at a rate of 80% ($x = 0.8$), the fertility of heterozygotes is 30%, and homozygotes gene drive= have no fertility. The population does not become extinct, but the equilibrium population size becomes approximately 600. This pushes the R_0 even lower, approximately 63% of the R_0 without gene drive, i.e.

$$\frac{\sqrt{\frac{\beta_m \beta_h b_m^2}{\mu_A \gamma N} 600}}{\sqrt{\frac{\beta_m \beta_h b_m^2}{\mu_A \gamma N} 1500}} \approx 0.63.$$

In certain contexts, this could be strong enough to push R_0 below one and to stop the spread of a disease.

Chapter 7

Conclusion

In this paper, we examined the impact of a novel control method on an invading mosquito population. Releasing sterile mosquitoes has been modelled previously; however one of the biggest issues with sterile release is the success of the released mosquitoes in competing with the native populations. For this to be successful, most models show a need for continual releases of sterile mosquitoes. A more efficient method would be if the gene of sterility could spread through the population. To investigate this, we developed a mathematical model of mosquito populations and then introduced gene drive. Our results show that it can be effective, but the drive through the population needs to be at a high level to guarantee conditions that will stop invasion of wild mosquitoes. Overall, if gene drive is over 99% then for all parameter values considered it will prove effective. This high level of gene drive is unlikely in reality (although rates of greater than 90% gene drive have been observed experimentally) as resistance of the gene in the host may occur [37]. However, our model shows that even with Mendelian inheritance (gene drive of 50%), it is possible to eliminate the invading mosquito population under certain conditions. In particular, if a strong Allee effect exists in mosquitoes, the use of gene drive is much more effective.

Preventing the invasion of mosquitoes into new territories will impact their ability to spread disease to those areas. In most infectious disease modelling, spread of the disease is quantified by the reproduction number R_0. When calculating R_0 for mosquito-borne diseases, the population of mosquitoes is an important component.

A strong Allee effect decreases the population number, which decreases R_0. Coupled with the effects of introducing gene drive into an invading mosquito population, our results suggest gene drive can offer a viable method of control in the efforts to reduce mosquito-borne diseases.

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