Optimal Control Approach to Developing Sex-Structured Release Strategies For Dengue Prevention

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Abstract

Dengue Fever is widespread in warm, tropical regions, putting nearly half the world's population at risk. It spreads primarily through bites of infected female *Aedes Aegypti* and *Aedes Albopictus* mosquitoes, which acquire the virus from infected humans and continue the cycle through further bites. Each year, over 100 million people are infected with dengue, with symptoms varying in intensity. This makes disease control essential to eliminate deadly cases. *Wolbachia* are maternally transmitted bacteria present in about 60 percent of arthropods. When introduced into mosquito vectors like *Aedes Aegypti*, they reduce disease transmission by lowering mosquito fitness, fertility, and causing cytoplasmic incompatibility. These effects make Wolbachia a valuable biological control, though different strains vary in how successfully they spread in wild mosquito populations.

We propose a two sex-structured dynamical models for mosquito populations: (1) a mosquito-only system modeling interactions between wild and *Wolbachia*-infected males and females, and (2) an extended system coupling these dynamics with a human compartment (infected) to capture dengue transmission. An optimal control problem was formulated to identify time-dependent release strategies for *Wolbachia*-infected female and male mosquitoes. The goal is to minimize a cost functional that reflects both biological and operational objectives: reducing the number of dengue-infected humans, limiting the intensity of mosquito releases, and accounting for baseline introduction costs. The dynamics of different *Wolbachia* strains were explored to assess their potential for long-term population replacement and vector control.

Keywords *Wolbachia*, dengue, *Aedes aegypti*, sex-structured model, optimal control

Contents

1 Introduction

1.1 Why Study *Wolbachia*?

In recent decades, biologists and mathematical modelers have collaborated to contain disease epidemics. Mosquitoes, specifically the *Aedes aegypti* subtype, are considered some of the most common yet harmful disease vectors. Out of 3,500 different mosquito subtypes, *Ae. aegypti* are often responsible for spreading many deadly diseases [37]. Females have evolved to target humans and are notorious carriers of disease including, but not limited to, dengue, yellow fever, and chikungunya [14]. In particular, dengue is a mosquito-borne illness that can harbor mild flu-like symptoms,turning potentially deadly within days, resulting in ailments ranging from high fever to internal bleeding with organ failure [27]. As of 2024, researchers and medical professionals speculate that approximately half of the entire world is at risk for contracting dengue, with 100-400 million cases occurring each year [52]. Due to such a high volume of cases, preventative measures have been introduced to high-risk areas. However, there is no effective long-term cure for preventing dengue, with the TAK-003 (QDenga) vaccine working only for individuals who have previously been infected with one of the four dengue serotypes [53]. As medical technology continues to develop to help human recovery from dengue, directly controlling *Aedes aegypti* populations has attracted considerable interest as a method for dengue infection prevention.

Aedes aegypti, commonly referred to as the "dengue mosquito", are a type of mosquito found in tropical and subtropical regions of the world, such as South America. Originating in Sub-Saharan Africa, they have evolved into an invasive species in temperate regions around the world [46]. *Ae. aegypti* contributed significantly to the Yellow Fever epidemic in the 1600s as consequence of the slave trade which transplanted these mosquitoes into the New World [35]. Following this introduction, *Ae. aegypti* have continued to migrate and spread arboviruses in much of the Americas. Soon after, dengue fever began to appear, generating outbreaks it distinct regions [12]. Characteristically, *Ae. aegypti* present between 4-7 mm long, are identifiable via their white scale arches, and remain active year-round near dense cities with limited dispersal capacity [14]. Female *Ae. aegypti* require blood meals to viably produce eggs, infecting humans with disease while feasting. During this process, females recognize chemical signals emitted by mammals, such as carbon dioxide or ammonia, which they follow to find blood meal opportunities. *Ae. aegypti* are uniquely resilient, being able to persist through unfavorable weather for extreme periods of time through a process called quiescence. As a result, eggs can survive in drastic dry and cold weather conditions, and on occasion, are able to remain dormant for more than a year until exposed to water [44]. Furthermore, *Ae. aegypti* saliva allows for human pathogens such as dengue to develop, providing a successful means for spread in human populations [37]. Thus, *Ae. aegypti* function as an ideal vector of disease for arboviruses, thereby suggesting that control of their population is a practical method disease prevention.

Aedes aegypti are associated with the spread of arboviruses due to their close proximity to dense cities [46], making humans an easy target for blood meal. With the current rate at which *Ae. aegypti* spread dengue, this species has become the main subject of countless studies on disease control. Vector control is a sought-after technique that aims to manipulate mosquito populations, preventing epidemics from occurring in societies where *Aedes aegypti* are established. Primarily, vector control aims to genetically alter or decrease the number of vectors, so that the spread of given disease is decreased [38] .

Although there exist multiple ways to exterminate disease-carrying mosquito populations through insecticides [48] or by genetically modifying their fertility through CRISPR technology in laboratories [20], many of these programs have limited impact due to constraints in resources. Therefore, it has become crucial to identify ways to maximize the efforts of controlling mosquito populations while accounting for the costs of such techniques, whether those costs be monetary or environmental. In recent time, researchers have identified a set of bacteria that alter the microbiome of *Ae. aegypti*, called *Wolbachia*. *Wolbachia pipientis* is an endosymbiotic bacterium that affects a wide range of arthropods' reproductive systems [51]. Studies have indicated that *Wolbachia* is an effective method for inhibiting the spread of RNA viruses such as dengue and yellow fever by reducing the viral load of disease, as well as the viability of disease-carrying offspring [29]. Naturally, the rearing of *Wolbachia* in *Ae. aegypti* has gained traction as a method to hamper vector populations. Three *Wolbachia* strains of interest, *WMelPop-CLA, WMel*, and *wAlbB*, have been shown to decrease the relative fitness of *Ae. aegypti* and affect the reproduction process of *Ae. aegypti* [19]. As such, introduction of *Wolbachia* to *Aedes aegypti* has been used as a way to manage dengue-infected populations. A randomized controlled trial was performed by the World Mosquito Program in Indonesia demonstrated a 77% reduction in dengue incidence and 86% reduction in hospitalizations [39]. It is a proven effective method, but more details are needed for release plans.

While *Wolbachia* does not naturally occur within *Ae. aegypti* populations, infection of *Ae. aegypti* with *Wolbachia* is a well-established process. Laboratories will catch mosquitoes, provide adequate conditions for females to lay eggs, then finally inject *Wolbachia* into the eggs [32]. When performed successfully, these eggs grow into fully-fledged adults that are infected with a *Wolbachia* strain, drastically decreasing infection-transmission rates, and once released into the wild, have the capacity to infect wild *Ae. aegypti* populations with *Wolbachia*.

1.2 Mechanics of *Wolbachia*

Wolbachia is transmitted maternally through *Ae. aegypti*, suppressing DENV viral load and reducing viability of offspring. Cytoplasmic incompatibility (CI) is a phenomenon that occurs when an *Ae. aegpyti* is infected with a *Wolbachia* strain, rendering infected males unable to produce viable offspring with **uninfected** females. This illustrates the reproductive advantage of infected females when there is a presence of male carriers [45]. When a mosquito is infected, *Wolbachia* encourages the production of cidB genes, disrupting male chromosome condensation and stopping embryos from fully developing [15].

Wolbachia blocks virus replication and transmission through a variety of mechanisms and complications. *Wolbachia* bacteria trigger immune responses within the mosquito that impede DENV replication. Beyond this, *Wolbachia* compete with DENV for cellular resources [45]. Typically, the mosquito gut and salivary glands are analyzed for the presence of DENV using quantitative polymerase chain reaction (qPCR). The lower the viral load observed, the more effective the control.

Table 1: Offspring Viability Outcomes of *Wolbachia* and Wild Mosquito Reproduction

Gender	**Non-Infected Male**	***Wolbachia*-Infected Male**
Non-infected Female	Non-Infected Offspring	Deceased Offspring
***Wolbachia*-Infected Female**	Infected Offspring	Infected Offspring

Table 1 illustrates the outcome of offspring depending on parental infection of *Wolbachia*. While two non-infected or *Wolbachia*-infected parents produce non-infected and *Wolbachia*-infected offspring respectively, interesting results arise when parent phenotypes are mixed. If a *Wolbachia*-infected male mates with a non-infected female, the offspring will be non-viable via cytoplasmic incompatibility. On the other hand, when a non-infected male mosquito mates with a *Wolbachia*-infected female mosquito, offspring are *Wolbachia*-carriers due to vertical transmission. This favoring of *Wolbachia*-infection is of utmost importance to most modeling efforts, as it significantly dictates the dynamics of *Wolbachia* persistence when introduced to wild mosquito populations.

In particular, the proportion of *Wolbachia*-carrying males to females introduced can greatly impact whether release programs are successful in establishing *Wolbachia* in a selected mosquito population. Currently, there exist two main approaches to releasing *Wolbachia*-infected mosquitoes: release males only or a mixture of both sexes [33]. However, research on mixed releases is sparse, with general strategies being exploratory by nature.

1.3 Release Programs and Techniques

Following the success of the artificial introduction of *Wolbachia* to *Ae. aegypti*, many countries began implementing ways to release *Wolbachia*-infected mosquitoes against wild populations. In Singapore, the National Environment Agency constructed various sites to release male *Wolbachia*-carrying mosquitoes twice a week, decreasing the local *Ae. aegypti* populations [31]. Colombia has deployed drones designed to disperse 150 mosquitoes every 50 meters over the city of Cali [32]. In fact, the infection of *Wolbachia* into *Ae. aegypti* has prompted the creation of the World Mosquito Program which is focused on using *Wolbachia* biological control to manage wild mosquito populations in countries of Latin America, Oceania, and Asia [40]. Despite the success of multiple release programs, persistence of *Wolbachia* in larger mosquito populations for long periods of time has remained difficult to attain. Namely, Rio de Janeiro has struggled to maintain a sufficient number of *Wolbachia*-infected *Ae. aegypti*, leading to a dwindling prevalence of the *w*Mel strain after 29 months of introduction [36]. Release rates, distribution of release, and many other factors are crucial determinants of what become successful (and unsuccessful) programs.

Intertwined with these release tactics is the choice of *Wolbachia* strain used to infect mosquitoes. Currently, there are multiple *Wolbachia* strains being used as biological controls. Of them, three offer unique strengths and weaknesses and are most commonly used in the field: *w*MelPop, *w*Mel, and *w*AlbB. In general, a strain that causes greater suppression of viral load and incidence of cytoplasmic incompatibility tends to also impose a higher fitness cost on the mosquito, thereby complicating establishment of a population of *Wolbachia*-infected mosquitoes.

Table 2: Egg Viability, Fitness, and Disease-Transmission Differences Among *Wolbachia* Strains

wAlbB	**wMel**	**wMelPop**
Moderate Egg Viability	High Egg Viability	Minimal Egg Viability
Minimal Fitness Cost	Low Fitness Cost	High Fitness Cost
Low Viral Impedance	Moderate Viral Impedance	High Viral Impedance

Noticeably, *w*MelPop has a significant, negative effect on mosquito fitness, with decreased fecundity, impaired blood feeding, and increased egg mortality all contributing to a higher fitness cost and reduced egg viability for *w*MelPop-infected mosquitoes [41]. However, it does exhibit a strong suppression of most of a given virus within the mosquito [4]. Comparatively, *w*Mel is more widely used for *Wolbachia* control methods [16]. Utilized by the World Mosquito Program [50], *w*Mel is more effective at spreading throughout a population than wMelPop is. Despite the fact that wMel does not impede virus replication as optimally as wMelPop, the relatively small fitness costs allow for complete population replacement over time. wAlbB is another effective strain, though less commonly used than wMelPop or wMel. Its viral impedance effects, while significant, are less than that of wMel and far less compared to wMelPop. However, its minimal fitness costs and characteristic heat-resistance make it desirable for certain circumstances. *Aedes aegypti* mosquitoes are particularly fond of high temperature climates, leading to survivability issues for certain strains of *Wolbachia*. wAlbB circumvents this issue, thriving in temperatures that other strains are incapable of tolerating [25]. Thus, in regions where wMel or wMelPop are not feasible, wAlbB is a necessity. Table 3 contains parameter values for both wMel and wAlbB, relative to normal uninfected mosquitoes.

1.4 Developing Questions and Aims

With the recent developments produced by studies focusing on disease vector control, it has become increasingly important to consider the most cost-effective ways to successfully spread *Wolbachia* to wild mosquito populations. Other research endeavors have examined different *Wolbachia* strains [16], methods of infected mosquito release [17], and many more seek to improve the efficacy of release programs worldwide. Certain studies have indicated the importance of releasing a greater proportion of male mosquitoes compared to females [17], but very few have formally approached the difficult task of optimizing these sex-structured releases. As such, we have formulated the following questions:

- What proportion of male and female mosquitoes would minimize the cost of treating people infected with dengue while at the same minimizing the number of resources used to release mosquitoes?
- How can various *Wolbachia* strains be utilized in mosquito releases for different endemic dengue scenarios?

This problem can be approached by way of optimal control theory, wherein our objective is to minimize a weighted integral over time, combining the human infection burden and the squared release rates of infected females and males (as control variables). In doing so, this approach allows for the determination of optimal release strategies that account for the sex of the *Wolbachia*-infected mosquitoes. Furthermore, beyond this specific problem, our aim is to understand the general dynamics of *Wolbachia* and dengue in a local setting where release programs would be most beneficial.

2 The Sex-Structured Model

Adjacent research has ventured into solving a similar realm of questions as posed in 1.4. One study performed a related analysis by distinguishing mosquitoes based on sex and comparing two different *Wolbachia* strains on their persistence against a population of wild mosquitoes, with the intent to inhibit the spread of dengue in humans [6]. Despite such similarities to the model to be presented in Section 2.1, certain assumptions and the resulting construction of the model make it fundamentally different. Their model uses a "harmonic form" birth function, employing an exponential factor to denote the four stages of the *Ae. Aegypti* life cycle. Further, their human compartment contains a recovered state for dengue cases. As such, the model of Section 2.1 presented in this paper introduces a unique approach that focuses solely on adult mosquitoes, which is later extended to incorporate human infection with dengue in Section 3.

Previous *Wolbachia*-release studies have taken into account various elements that affect the establishment of the *Wolbachia* among wild mosquito populations. Naturally, the most common way to capture the dynamics of *Wolbachia* in wild mosquito populations is through a system of ordinary differential equations. Factors such as sex, the life cycle of a mosquito, location, and mosquito-human interaction lead to distinct parameters and construction of systems. In this paper, the aim is to generate release methods based on sex. There are numerous versions of sex-structured species models [30], but the focus of our model is on adult mosquito populations, provided adult, female mosquitoes are the primary vector of dengue.

2.1 Derivation of the Sex-Structured Model

In Vicencio, Vasilieva, and Gardajo's *Wolbachia* bi-dimensional model [49], separation of mosquitoes into two stages, non-infected ($N(t)$) and *Wolbachia*-infected ($W(t)$), provides the compartments of their system. Consequently, they develop the following differential equation system:

$$\frac{dN}{dt} = \rho_N N \left(\frac{N}{N+W}\right) - \alpha_N N - \beta_N N(N+W), \tag{1}$$

$$\frac{dW}{dt} = \rho_W W - \alpha_W W - \beta_W W(N+W). \tag{2}$$

This model establishes an effective method of monitoring mosquitoes based on their level of infection, as well as understanding the general dynamics of *Wolbachia*. However, it overlooks the impact of cytoplasmic incompatibility that occurs between the different classes of mosquitoes based upon sex.

Table 3 includes the parameters used in both [49] and our expanded model. Addressing the fitness impacts of *Wolbachia*, the sex-structured model is first implemented with parameters adjusted for the wMelPop strain. On average, this strain reduces the total lifespan of a wild mosquito by half. Fecundity of *Wolbachia*-infected mosquitoes with this given strain is also diminished [5]. Parameters f and q represent the proportion of females born, based on *Wolbachia* infection level. It is important to note that the compliment of each of the two parameters can be used to calculate the proportion of males for each respective group. Certain strains of *Wolbachia* have been shown to decrease the number of male mosquitoes due to increased female longevity and feminization [34], thereby meaning that females tend to dominate once a population is infected with *Wolbachia*. Asgharian *et. al* has found the ratio of 1:1.8 for male to female *Wolbachia*-infected mosquitoes.

Table 3: Parameter Descriptions for the Sex-Structured Model

Parameter	Description	Units	Value	Reference
ρ_N	Fecundity of Uninfected Insects	time^{-1}	4.55	[13], [5]
ρ_W	Fecundity of Infected Insects	time^{-1}	$0.5 \times \rho_N = 2.27$	[28], [18], [21]
α_N	Natural mortality rate of Uninfected Insects	time^{-1}	0.03333	[13], [5]
α_W	Natural mortality rate of Infected Insects	time^{-1}	$2 \times \alpha_N = 0.06666$	[28], [18], [21]
β_N	Competition of Uninfected Insects	(mosquito $\times$ time)$^{-1}$	2.61258×10^{-3}	[49]
β_W	Competition of Infected Insects	(mosquito $\times$ time)$^{-1}$	3.12792×10^{-3}	[11], [10]
f	Female birth proportion for uninfected	scalar	0.5	[24]
q	Female birth proportion for infected	scalar	0.5556	[34], [3]

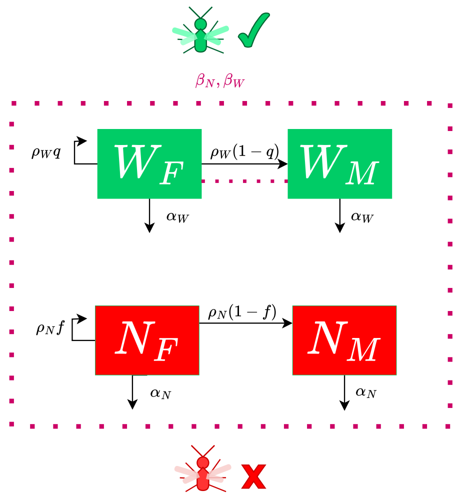
Furthermore, the model presented adheres to the following constructions and assumptions:

1. $N(t) = N_F(t) + N_M(t)$ is the total wild (uninfected) mosquito population. $W(t) = W_F(t) + W_M(t)$ is the total *Wolbachia*-infected mosquito population.
2. $\dfrac{1}{\alpha_N}$ and $\dfrac{1}{\alpha_W}$ are the average lifespan for wild and *Wolbachia*-infected mosquitoes, respectively.
3. $\dfrac{N}{N+W}$ denotes the probability of two wild (uninfected) mosquitoes mating.
4. $\rho_N > \alpha_N$, or the rate of natural births, is greater than the mortality rate for wild (uninfected) mosquitoes.
5. $\rho_W > \alpha_W$, or the rate of natural births, is greater than the mortality rate for *Wolbachia*-infected mosquitoes.
6. $\rho_W \leq \rho_N$ and $\alpha_W \geq \alpha_N$, display the potential fitness level effects different strains may impose.
7. The life cycle of a mosquito is simplified and excludes stages (i.e. egg, larvae, pupa).

Although Vicencio *et.al*'s model focuses on two *Wolbachia* infection levels for *Ae. aeypgti*, it overlooks the effects cytoplasmic incompatibility has on populations once *Wolbachia* is released.

In order to account for the effects *Wolbachia* with respect to sex, we split our model, creating four compartments accounting for all combinations of sex and *Wolbachia* infection. That is, each compartment for *Wolbachia*-infection can be divided into a female and a male category, leaving us with wild (uninfected) females (N_F), wild (uninfected) males (N_M), *Wolbachia*-infected females (W_F), and *Wolbachia*-infected males (W_M).

Figure 1: Schematic of the Sex-Structured Model



The Sex-Structured Model (2025):

$$
\begin{aligned}
\frac{dN_F}{dt} &= \rho_N f N_F \left(\frac{N_M}{N_M + W_M}\right) - \alpha_N N_F - \beta_N N_F (N_F + N_M + W_F + W_M), \\
\frac{dN_M}{dt} &= \rho_N (1-f) N_F \left(\frac{N_M}{N_M + W_M}\right) - \alpha_N N_M - \beta_N N_M (N_F + N_M + W_F + W_M), \\
\frac{dW_F}{dt} &= \rho_W q W_F - \alpha_W W_F - \beta_W W_F (N_F + N_M + W_F + W_M), \\
\frac{dW_M}{dt} &= \rho_W (1-q) W_F - \alpha_W W_M - \beta_W W_M (N_F + N_M + W_F + W_M).
\end{aligned} \tag{3}
$$

In practice, this new model makes further assumptions about *Aedes aegypti*. By assumption, there exists perfect cytoplasmic incompatibility in the model, that is, regardless of *Wolchabia* strain, reproduction of female *Wolbachia*-infected msoquitoes always results in *Wolbachia*-infected offspring and reproduction of *Wolbachia*-infected males with wild (uninfected) females produces unviable offspring [49].

2.2 Analytical Results of the Sex-Structured Model

Proposition 1: The Sex-Structured Model is well-posed.

Proof. With the assumptions of (3), note,

$$
\begin{aligned}
\left.\frac{dN_F}{dt}\right|_{N_F=0} &= 0 \\
\left.\frac{dN_M}{dt}\right|_{N_M=0} &= 0 \\
\left.\frac{dW_F}{dt}\right|_{W_F=0} &= 0 \\
\left.\frac{dW_M}{dt}\right|_{W_M=0} &= p_W(1-q)W_F \geq 0.
\end{aligned}
$$

This means for all subpopulations of mosquitoes considered, no subpopulation ever becomes negative, because when each subpopulation is 0, their rate of change is nonnegative. That is, the Sex-Structured Model is invariant in the positive cone $\mathbb{R}_+^4$, as desired.

In addition to the positive invariance of the Sex-Structured model, it is also true that its solutions are bounded. This can be proven by showing that each subpopulation must be bounded. Here, we use the assumption of the non-negativity of each subpopulation which follows from the prior result that confirmed the positive invariance of the Sex-Structured model.

For the wild female mosquito population,

$$
\begin{aligned}
\frac{dN_F}{dt} &= \rho_N f N_F \left(\frac{N_M}{N_M + W_M}\right) - \alpha_N N_F - \beta_N N_F P \\
&\leq \rho_N N_F - \alpha_N N_F - \beta_N N_F^2 \\
&= \beta_N N_F \left(\frac{\rho_N - \alpha_N}{\beta_N} - N_F\right).
\end{aligned}
$$

Therefore,

$$
\left.\frac{dN_F}{dt}\right|_{N_F=\tilde{N}_F} \leq 0
$$

and $\frac{dN_F}{dt} < 0$ when $N_F > \tilde{N}_F$ where $\tilde{N}_F := \frac{\rho_N - \alpha_N}{\beta_N}$.

Intuitively, this inequality establishes a representation of logistic growth that identifies what can be considered as a "carrying capacity" of N_F. However, $\tilde{N}_F$ is not the true "carrying capacity" of N_F given the inequality constructed in the second line. Still, provided

$$
\left.\frac{dN_F}{dt}\right|_{N_F>\tilde{N}_F} < 0,
$$

then for any $t, N_F(t) \leq \max\left\{\tilde{N}_F, N_F(0)\right\}$. Capitalizing on the non-negativity of N_F, it follows that for any t

$$
\begin{aligned}
0 \leq N_F(t) &\leq \max\left\{\tilde{N}_F, N_F(0)\right\} \\
|N_F(t)| &\leq \max\left\{\tilde{N}_F, N_F(0)\right\}.
\end{aligned}
$$

Thus, N_F is bounded. Let the upper bound of N_F be denoted as $N_F^{\max}$.

By a similar argument, for the wild male mosquito population, N_M,

$$
\begin{aligned}
\frac{dN_M}{dt} &= \rho_N f N_F \left(\frac{N_M}{N_M + W_M}\right) - \alpha_N N_M - \beta_N N_M P \\
&\leq \rho_N N_F N_M - \alpha_N N_M - \beta_N N_M^2 \\
&\leq \beta_N N_M \left(\frac{N_F^{\max}\rho_N - \alpha_N}{\beta_N} - N_M\right)
\end{aligned}
$$

for which it can be seen

$$
\left.\frac{dN_M}{dt}\right|_{N_M = \tilde{N}_M} \leq 0
$$

and $\dfrac{dN_M}{dt} < 0$ when $N_M > \tilde{N}_M$ where $\tilde{N}_M := \dfrac{N_F^{\max}\rho_N - \alpha_N}{\beta_N}$.

Continuing the same process as done before, for any $t, N_M(t) \leq \max\left\{\tilde{N}_M, N_M(0)\right\}$. It then follows that for any t

$$
\begin{aligned}
0 \leq N_M(t) &\leq \max\left\{\tilde{N}_M, N_M(0)\right\} \\
|N_M(t)| &\leq \max\left\{\tilde{N}_M, N_M(0)\right\},
\end{aligned}
$$

thereby showing N_M is bounded.

This shows the boundedness of the wild mosquito populations, so all that is left to show is the boundedness of the *Wolbachia*-infected populations, which uses the same argument as before. Beginning with the *Wolbachia*-infected female population, W_F, realize,

$$
\begin{aligned}
\frac{dW_F}{dt} &= \rho_W q W_F - \alpha_W W_F - \beta_W W_F P \\
&\leq \rho_W W_F - \alpha_W W_F - \beta_W W_F^2 \\
&= \beta_W W_F \left(\frac{\rho_W - \alpha_W}{\beta_W} - W_F\right),
\end{aligned}
$$

implying

$$
\left.\frac{dW_F}{dt}\right|_{W_F = \tilde{W}_F} \leq 0
$$

and $\dfrac{dW_F}{dt} < 0$ when $W_F > \tilde{W}_F$ where $\tilde{W}_F := \dfrac{\rho_W - \alpha_W}{\beta_w}$.

So, for any $t, W_F(t) \leq \max\left\{\tilde{W}_F, W_F(0)\right\}$. It then follows that for any t

$$\begin{aligned}0 \leq W_F(t) &\leq \max\left\{\tilde{W}_F, W_F(0)\right\}\\ |W_F(t)| &\leq \max\left\{\tilde{W}_F, W_F(0)\right\}.\end{aligned}$$

proving W_F is bounded. Let the upper bound of W_F be denoted as $W_F^{\max}$.

Finally, for *Wolbachia*-infected male population, W_M,

$$\begin{aligned}\frac{dW_M}{dt} &= \rho_W q W_F - \alpha_W W_M - \beta_W W_M P\\ &\leq \rho_W W_F^{\max} - \alpha_W W_M\\ &= \alpha_W \left(\frac{W_F^{\max}\rho_W}{\alpha_W} - W_M\right),\end{aligned}$$

indicating

$$\left.\frac{dW_M}{dt}\right|_{W_M=\tilde{W}_M} \leq 0$$

and $\dfrac{dW_M}{dt} < 0$ when $W_M > \tilde{W}_M$ where $\tilde{W}_M := \dfrac{W_F^{\max}\rho_W}{\alpha_W}$.

Therefore, it must be for any $t, W_M(t) \leq \max\left\{\tilde{W}_M, W_M(0)\right\}$. Consquently, for any t,

$$\begin{aligned}0 \leq W_M(t) &\leq \max\left\{\tilde{W}_M, W_M(0)\right\}\\ |W_M(t)| &\leq \max\left\{\tilde{W}_M, W_M(0)\right\},\end{aligned}$$

showing W_M is bounded.

That is, the compact set

$$\chi := \{(N_F, N_M, W_F, W_M) \in \mathbb{R}_+^4 : 0 \leq N_F \leq \tilde{N}_F, 0 \leq N_M \leq \tilde{N}_M, 0 \leq W_F \leq \tilde{W}_F, 0 \leq W_M \leq \tilde{W}_M\}$$

acts as an absorbing set of trajectories and is invariant. Thus, the Sex-Structured model is well-posed.

Determining the equilibria and the stability of equilibria is an important way to understand the dynamics and interplay of the four subpopulations of mosquitoes considered. In the Sex-Structured model, there exist three distinct equilibria $\mathscr{E}_{\boldsymbol{N}}, \mathscr{E}_{\boldsymbol{W}}, \mathscr{E}_{\boldsymbol{C}}$, denoting equilibria where only wild mosquitoes persist, only *Wolbachia*-infected mosquitoes persist, and finally, coexistence of wild and *Wolbachia*-infected mosquitoes. However, analytical solution for the equilibria and stability is only possible for $\mathscr{E}_{\boldsymbol{N}}$ and $\mathscr{E}_{\boldsymbol{W}}$, while stability for $\mathscr{E}_{\boldsymbol{C}}$ is shown in 2.3.

Proposition 2: The Sex-Structured Model offers two non-coexistence and one coexistence equilibria that attain different thresholds for stability.

Proof. An equilibrium point, $\mathscr{E} = (N_F^*, N_M^*, W_F^*, W_M^*)$, for our system will satisfy

$$\left.\frac{dN_F}{dt}\right|_{(N_F,N_M,W_F,W_M)=\mathscr{E}} = 0$$
$$\left.\frac{dN_M}{dt}\right|_{(N_F,N_M,W_F,W_M)=\mathscr{E}} = 0$$
$$\left.\frac{dW_F}{dt}\right|_{(N_F,N_M,W_F,W_M)=\mathscr{E}} = 0$$
$$\left.\frac{dW_M}{dt}\right|_{(N_F,N_M,W_F,W_M)=\mathscr{E}} = 0.$$

Consider $\mathscr{E}_{\boldsymbol{N}} := \left(N_F^{\mathscr{E}_N}, N_M^{\mathscr{E}_N}, W_F^{\mathscr{E}_N}, W_M^{\mathscr{E}_N}\right)$ where

$$N_F^{\mathscr{E}_N} = -\frac{f(\alpha_N - f\rho_N)}{\beta_N}, \quad N_M^{\mathscr{E}_N} = \frac{(f-1)(\alpha_N - f\rho_N)}{\beta_N}, \quad W_F^{\mathscr{E}_N} = W_M^{\mathscr{E}_N} = 0.$$

If $W_M = W_F = 0$, then $\dfrac{dW_M}{dt} = \dfrac{dW_F}{dt} = 0$.

Now, if $N_F = -\dfrac{f(\alpha_N - f\rho_N)}{\beta_N}$ and $N_M = \dfrac{(f-1)(\alpha_N - f\rho_N)}{\beta_N}$,

$$\begin{aligned}
\frac{dN_F}{dt} &= \rho_N f\left(\frac{-f(\alpha_N - f\rho_N)}{\beta_N}\right) - \alpha_N\left(\frac{-f(\alpha_N - f\rho_N)}{\beta_N}\right) - \beta_N\left(\frac{-f(\alpha_N - f\rho_N)}{\beta_N}\right)\left(\frac{-(\alpha_N - f\rho_N)}{\beta_N}\right)\\
&= \frac{-f(\alpha_N - f\rho_N)}{\beta_N}(\rho_N f - \alpha_N) - \frac{-f(\alpha_N - f\rho_N)}{\beta_N}(\rho_N f - \alpha_N)\\
&= 0, \quad \text{as desired.}
\end{aligned}$$

Further, $\dfrac{dN_M}{dt} = \rho_N(1-f)N_F - \alpha_N N_M - \beta_N N_M(N_F + N_M)$ provided $W_F = W_M = 0$. Substituting N_F and N_M from above,

$$\begin{aligned}
\frac{dN_M}{dt} &= \rho_N(1-f)N_F - \alpha_N N_M - \beta_N N_M(N_F + N_M)\\
&= \frac{(f-1)(\alpha_N - f\rho_N)}{\beta_N}(\rho_N f - \alpha_N) - \frac{(f-1)(\alpha_N - f\rho_N)}{\beta_N}(\rho_N f - \alpha_N)\\
&= 0.
\end{aligned}$$

Thus,

$$\mathscr{E}_{\boldsymbol{N}} = \left(-\frac{f(\alpha_N - f\rho_N)}{\beta_N}, \frac{(f-1)(\alpha_N - f\rho_N)}{\beta_N}, 0, 0\right)$$

is a valid equilibrium. Moreover, as $N_F, N_M, W_F, W_M \geq 0$, it follows that

$$\alpha_N - f\rho_N < 0 \implies \frac{f\rho_N}{\alpha_N} > 1.$$

Take $Q_N := \dfrac{f\rho_N}{\alpha_N}$. Biologically, this means that $\mathscr{E}_{\boldsymbol{N}}$ is only feasible provided the average number female wild mosquitoes birthed over a given time step is greater than the average death of wild mosquitoes over the same time step. In essence, a population of wild mosquitoes must be able to sustain itself, which is biologically reasonable to require.

The standard methodology for analyzing the stability of $\mathscr{E}_{\boldsymbol{N}}$ requires the eigenvalues of the Jacobian, J, of (3) evaluated at $\mathscr{E}_{\boldsymbol{N}}$, where in this case,

$$\begin{pmatrix} \sigma_5 - N_F\beta_N - \sigma_3 - \alpha_N & -\frac{N_F(\beta_N N_M^2 + 2\beta_N N_M W_M + \beta_N W_M^2 - f\rho_N W_M)}{(N_M+W_M)^2} & -N_F\beta_N & -N_F\beta_N - \frac{N_F\sigma_5}{(N_M+W_M)} \\ -N_M\beta_N - N_M\sigma_4 & \sigma_1 - N_M\beta_N - \sigma_3 - N_F\sigma_4 - \alpha_N & -N_M\beta_N & \sigma_1 - N_M\beta_N \\ -W_F\beta_W & -W_F\beta_W & q\rho_W - W_F\beta_W - \alpha_W - \sigma_2 & -W_F\beta_W \\ -W_M\beta_W & -W_M\beta_W & -W_M\beta_W - \rho_W(q-1) & -\alpha_W - W_M\beta_W - \sigma_2 \end{pmatrix}$$

is the Jacobian matrix, J, and

$$\begin{aligned} \sigma_1 &= \frac{N_F\, N_M\, \rho_N\, (f-1)}{(N_M + W_M)^2}, \\ \sigma_2 &= \beta_W\, P, \\ \sigma_3 &= \beta_N\, P, \\ \sigma_4 &= \frac{\rho_N(f-1)}{N_M + W_M}, \\ \sigma_5 &= \frac{N_M f \rho_N}{N_M + W_M}. \end{aligned}$$

The eigenvalues, $\boldsymbol{\lambda}$, of J associated to $\mathscr{E}_{\boldsymbol{N}}$ are

$$\boldsymbol{\lambda}\left(J(\mathscr{E}_{\boldsymbol{N}})\right) = \begin{pmatrix} \frac{\alpha_N\,\beta_W - \alpha_W\,\beta_N - \beta_W\,f\,\rho_N + \beta_N\,q\,\rho_W}{\beta_N} \\ \alpha_N - f\,\rho_N \\ -f\,\rho_N \\ -\frac{\alpha_W\,\beta_N - \alpha_N\,\beta_W + \beta_W\,f\,\rho_N}{\beta_N} \end{pmatrix}.$$

For $\mathscr{E}_{\boldsymbol{N}}$ to be a stable equilibrium, all eigenvalues $\boldsymbol{\lambda}\left(J(\mathscr{E}_{\boldsymbol{N}})\right)$ must be negative. This requires specific thresholds that the parameters of the Sex-Structured model must fulfill in order for $\mathscr{E}_{\boldsymbol{N}}$ to be stable. Identification of these thresholds can provide a stronger sense of the biological conditions the wild mosquitoes must attain for sufficient overtake of the *Wolbachia*-infected mosquito populations (and vice versa). The third eigenvalue satisfies $-f\rho_N < 0$ and the second eigenvalue $\alpha_N - f\rho_N < 0$ as $Q_N > 1$. Also, $\alpha_N\beta_W - \alpha_W\beta_N - \beta_W f\rho_N < \alpha_N\beta_W - \alpha_W\beta_N - \beta_W f\rho_N + \beta_N q\rho_W$. So, it suffices to find the threshold for which the first eigenvalue is less than 0, as this implies that the last eigenvalue is also negative.

We want $\alpha_N\beta_W - \alpha_W\beta_N - \beta_W f\rho_N + \beta_N q\rho_W < 0$, so it follows:

$$
\begin{aligned}
\alpha_N\beta_W - \alpha_W\beta_N - \beta_W f\rho_N + \beta_N q\rho_W &< 0 \\
\alpha_N\beta_W + \beta_N q\rho_W &< \alpha_W\beta_N + \beta_W f\rho_N \\
\frac{\alpha_N\beta_W + \beta_N q\rho_W}{\alpha_W\beta_N + \beta_W f\rho_N} &< 1 \\
\frac{\alpha_W\beta_N + \beta_W f\rho_N}{\alpha_N\beta_W + \beta_N q\rho_W} &> 1 \\
\frac{\frac{\alpha_W\beta_N}{\alpha_N\beta_W} + Q_N}{1 + \frac{\beta_N q P_W}{\alpha_N\beta_W}} &> 1 \\
\frac{\alpha_W\beta_N}{\alpha_N\beta_W} + Q_N &> 1 + \frac{\alpha_W\beta_N}{\alpha_N\beta_W} Q_W \\
Q_N &> 1 + C(Q_W - 1)
\end{aligned}
$$

where $C := \dfrac{\alpha_W\beta_N}{\alpha_N\beta_W}, Q_W := \dfrac{q\rho_W}{\alpha_W}$. Therefore, the threshold of stability for $\mathscr{E}_{\boldsymbol{N}}$ is $Q_N > 1 + C(Q_W - 1)$.

Next, consider $\mathscr{E}_{\boldsymbol{W}} := \left(N_F^{\mathscr{E}_W}, N_M^{\mathscr{E}_W}, W_F^{\mathscr{E}_W}, W_M^{\mathscr{E}_W}\right)$ where

$$
N_F^{\mathscr{E}_W} = N_M^{\mathscr{E}_W} = 0, \quad W_F^{\mathscr{E}_W} = -\frac{q(\alpha_W - q\rho_W)}{\beta_W}, \quad W_M^{\mathscr{E}_W} = \frac{(\alpha_W - q\rho_W)(q-1)}{\beta_W}.
$$

Here, when $N_F = N_M = 0$,

$$
\frac{dN_F}{dt} = \frac{dN_M}{dt} = 0.
$$

It follows that when

$$
W_F = -\frac{q(\alpha_W - q\rho_W)}{\beta_W}, \quad W_M = \frac{(\alpha_W - q\rho_W)(q-1)}{\beta_W},
$$

$$
\begin{aligned}
\frac{dW_F}{dt} &= \rho_W q\left(\frac{-q(\alpha_W - q\rho_W)}{\beta_W}\right) - \alpha_W\left(\frac{-q(\alpha_W - q\rho_W)}{\beta_W}\right) - \beta_W\left(\frac{-q(\alpha_W - q\rho_W)}{\beta_W}\right)\left(\frac{-(\alpha_W - q\rho_W)}{\beta_W}\right) \\
&= \frac{-q(\alpha_W - q\rho_W)}{\beta_W}(\rho_W q - \alpha_W) - \frac{-q(\alpha_W - q\rho_W)}{\beta_W}(\rho_W q - \alpha_W) \\
&= 0, \\
\frac{dW_M}{dt} &= \rho_W(1-q)\left(\frac{-q(\alpha_W - q\rho_W)}{\beta_W}\right) - \alpha_W\left(\frac{(q-1)(\alpha_W - q\rho_W)}{\beta_W}\right) - \beta_W\left(\frac{(q-1)(\alpha_W - q\rho_W)}{\beta_W}\right)\left(\frac{-(\alpha_W - q\rho_W)}{\beta_W}\right) \\
&= \frac{(q-1)(\alpha_W - q\rho_W)}{\beta_W}(\rho_W q - \alpha_W) - \frac{(q-1)(\alpha_W - q\rho_W)}{\beta_W}(\rho_W q - \alpha_W) \\
&= 0, \quad \text{as desired.}
\end{aligned}
$$

Therefore,

$$
\mathscr{E}_{\boldsymbol{W}} = \left(0, 0, -\frac{q(\alpha_W - q\rho_W)}{\beta_W}, \frac{(\alpha_W - q\rho_W)(q-1)}{\beta_W}\right)
$$

is a valid equilibrium. Further, as it has been shown that $N_F, N_M, W_F, W_M \geq 0$,

$$\alpha_W - q\rho_W < 0 \implies Q_W > 1.$$

Intuitively, this implies that $\mathscr{E}_{\boldsymbol{W}}$ is only feasible provided the average number female *Wolbachia*-infected mosquitoes birthed over a given time step is greater than the average number of deaths of *Wolbachia*-infected mosquitoes over the same time step.

With the same Jacobian, J, the eigenvalues, $\boldsymbol{\lambda}$, of J associated to $\mathscr{E}_{\boldsymbol{W}}$ are

$$\boldsymbol{\lambda}\,(J(\mathscr{E}_{\boldsymbol{W}})) = \begin{pmatrix} \alpha_W - q\,\rho_W \\ -q\,\rho_W \\ -\frac{\alpha_N\,\beta_W - \alpha_W\,\beta_N + \beta_N\,q\,\rho_W}{\beta_W} \\ -\frac{\alpha_N\,\beta_W - \alpha_W\,\beta_N + \beta_N\,q\,\rho_W}{\beta_W} \end{pmatrix}$$

Here, $-q\rho_W < 0$ and $\alpha_W - q\rho_W < 0$ as $Q_W > 1$. The last two eigenvalues are the same, so for $\mathscr{E}_{\boldsymbol{W}}$ to be stable, we need $\alpha_W\beta_N - \alpha_N\beta_W - \beta_N q P_W < 0$. However, $\alpha_W\beta_N - \alpha_N\beta_W - \beta_N q P_W = \beta_N\,(\alpha_W - q\rho_W) - \alpha_N\beta_W$. Therefore, since $\alpha_W - q\rho_W < 0$ and $-\alpha_N\beta_W < 0$, then $\alpha_W\beta_N - \alpha_N\beta_W - \beta_N q P_W < 0$. Consequently, the only threshold condition needed for the stability of $\mathscr{E}_{\boldsymbol{W}}$ is $Q_W > 1$.

Finally, for $\mathscr{E}_{\boldsymbol{C}} = (N_F^{\mathscr{E}_C}, N_M^{\mathscr{E}_C}, W_F^{\mathscr{E}_C}, W_M^{\mathscr{E}_C})$ where

$$\begin{aligned} N_F^{\mathscr{E}_C} &= -\frac{f\,(\alpha_W - q\,\rho_W)\,(q-1)\,\sigma_3}{\sigma_1} \\ N_M^{\mathscr{E}_C} &= \frac{(1-f)\,(\alpha_W - q\,\rho_W)\,(q-1)\,\sigma_3}{\sigma_1} \\ W_F^{\mathscr{E}_C} &= \frac{q\,(\alpha_W - q\,\rho_W)\,(f-1)\,\sigma_2}{\sigma_1} \\ W_M^{\mathscr{E}_C} &= \frac{(q-1)\,(\alpha_W - q\,\rho_W)\,(f-1)\,\sigma_2}{\sigma_1} \end{aligned}$$

and

$$\begin{aligned} \sigma_1 &:= \beta_W\left(\beta_N q^2 \rho_W - \alpha_N\beta_W f + \alpha_W\beta_N f + \alpha_N\beta_W q\right) \\ \sigma_2 &:= \alpha_N\beta_W - \alpha_W\beta_N - \beta_W f \rho_N + \beta_N q \rho_W \\ \sigma_3 &:= \alpha_N\beta_W - \alpha_W\beta_N + \beta_N q \rho_W, \end{aligned}$$

it can be shown that $\mathscr{E}_{\boldsymbol{C}}$ is a valid equilibrium. However, solution to the stability of $\mathscr{E}_{\boldsymbol{C}}$ is left to 2.3.

2.3 Numerical Results of the Sex-Structured Model

Following the classification of equilibria and their stability in 2.2, numerical determination of the stability of $\mathscr{E}_{\boldsymbol{C}}$ was necessitated. Numerical simulations suggest that there is not a stable coexistence equilibrium when utilizing the *w*MelPop strain for biological control of *Ae. aegypti* populations. The following phase plots were constructed to corroborate the numerical findings,

Figure 2: Phase portraits for mosquito populations: wild mosquitoes (left) and *Wolbachia*-infected mosquitoes (right).

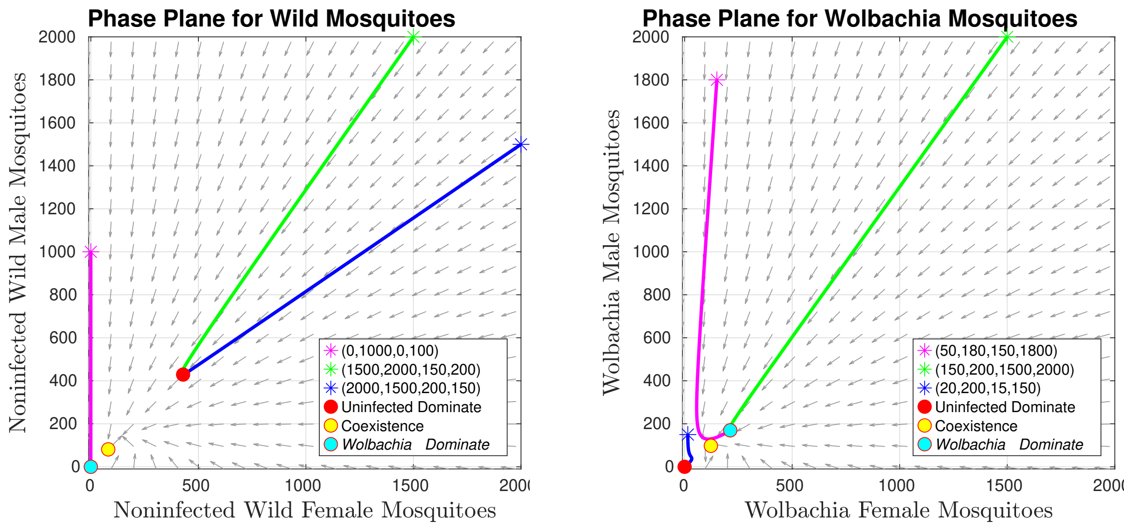
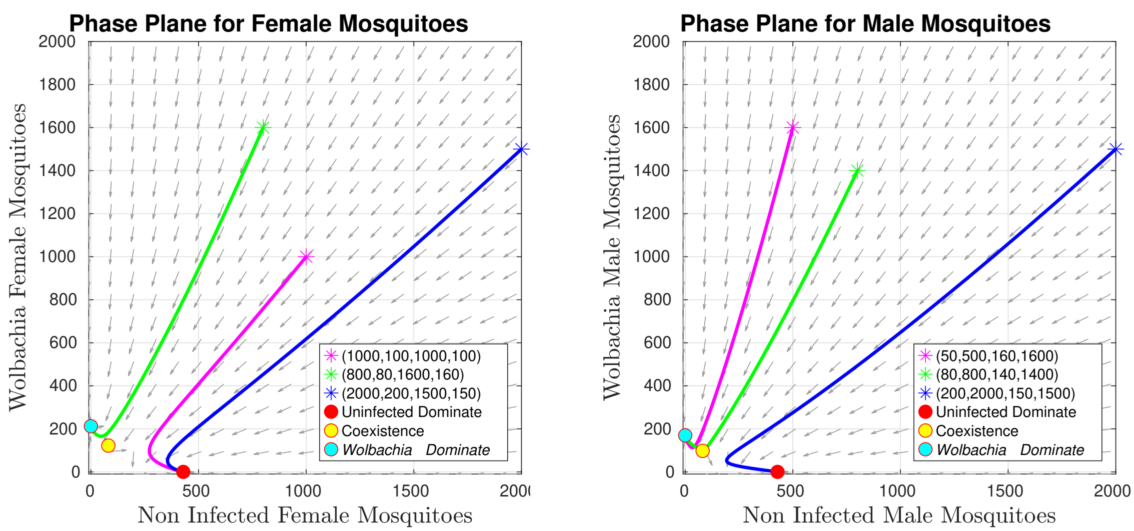


Figure 3: Phase portraits for mosquito populations: female mosquitoes (left) and male mosquitoes (right).

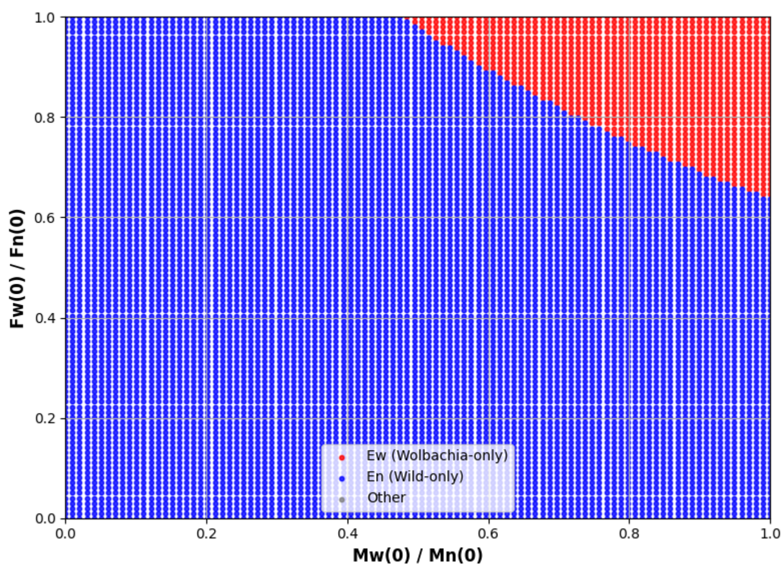


suggesting the populations never converge to a stable coexistence point. That is, only one-winner equilibria are feasible to have stable conditions as explored in 2.2.

Figure 2 demonstrates the three distinct equilibrium points found in 2.2 when the wMelPop strain is used, with the horizontal axis representing female mosquitoes and the vertical axis for male mosquitoes. Initial conditions are selected at random. There is the potential to go towards one winner equilibria, where one *Wolbachia* infection level dominates. On the other hand, the coexistence equilbrium follows as being unstable, as no initial condition values will remain nor attract there indefinitely. One important aspect to note is that the equilibria appear in a line for the Figure 2 phase portraits as a result of plotting by *Wolbachia* infection level. That is, the populations of the opposing *Wolbachia* infection level cannot be seen, and only relationships between mosquitoes of the same infection level are compared.

Alternatively, Figure 3 contains phase plots constructed with respect to sex. The horizontal axis accounts for wild (uninfected) mosquitoes while the vertical axis represents *Wolbachia*-infected mosquitoes. A similar pattern for our fixed points is seen in both provided the each portrait differentiates between *Wolbachia* infection levels. Alike to the previous phase portraits, initial conditions may go towards a one-winner equilibria but will never remain in the coexistence fixed point, $\mathscr{E}_{\boldsymbol{C}}$.

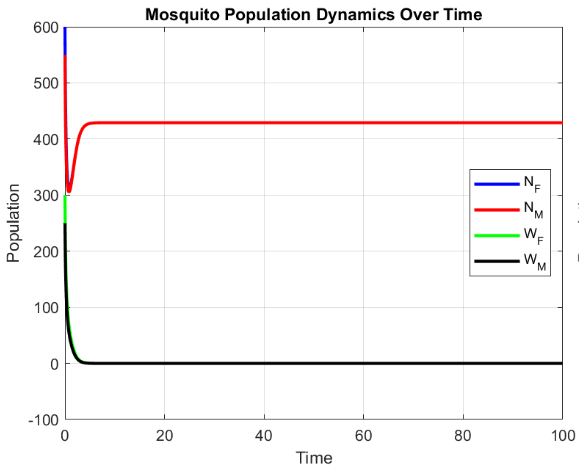
Figure 4: Basin of attraction plot showing convergence dynamics between mosquito population equilibria of 2.2.

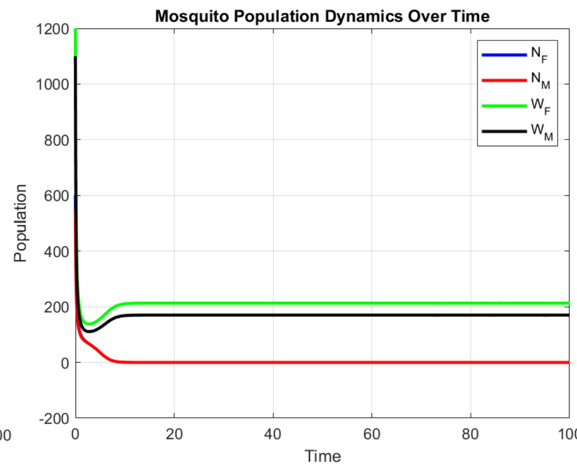


In Figure 4, the basin of attraction plot visualizes the two non-coexistence equilibria sufficiently and further confirms that the coexistence fixed point, $\mathscr{E}_{\boldsymbol{C}}$, is unstable. The horizontal axis contains the ratio of male *Wolbachia*-infected mosquitoes to male wild mosquitoes, with the vertical axis replicating this for females, respectively. The red area represents wild-free equilibrium, $\mathscr{E}_{\boldsymbol{W}}$: only *Wolbachia*-infected mosquitoes persist, whereas the blue area represents *Wolbachia*-free equilibrium, $\mathscr{E}_{\boldsymbol{N}}$. Recognize there exists no gray area, which would have represented the coexistence equilibrium, given it had been stable for some choice of parameters for (3). That is, we are lead to believe that there is no stable coexistence equilibrium; only asymptotic domination by one population or another.

In order to capture an example of these dynamics tending towards the equilibria $\mathscr{E}_{\boldsymbol{W}}$ and $\mathscr{E}_{\boldsymbol{N}}$, Figure 5 depicts the one-winner equilibrium scenarios. For the first plot (left), it is seen that in-

Figure 5: Simulations for Mosquito Populations, *Wolbachia* free equilibrium (left) and wild non-infected free (right).





troducing *Wolbachia*-infected mosquitoes in numbers less than the total wild mosquito population, regardless of sex, leads to the wild (uninfected) population winning out. Namely, there is an insufficient amount of *Wolbachia* being spread to the wild mosquito population for it to overtake. On the other hand, for the second plot, when the number of *Wolbachia*-infected mosquitoes introduced sufficiently outnumbers the wild population (in this case, approximately $\times 1.5$), population replacement by *Wolbachia* occurs. It is also seen that the total population of *Wolbachia*-infected mosquitoes when *Wolbachia* overtakes is also smaller, reflecting the reduced lifespans that occur as a result of the fitness impacts of the wMelPop strain [41].

3 The Dengue - *Wolbachia* Model

3.1 Derivation of the Dengue - *Wolbachia* Model

Although the Sex-Structured Model (3) provides a way to understand the dynamics of *Wolbachia* once introduced to a population of wild mosquitoes, it lacks a connection to the dynamics of dengue infection in both mosquito and human populations. To account for the spread of dengue, the Dengue-*Wolbachia* Model (4) builds upon the Sex-Structured Model by introducing a simplified Ross-Macdonald model to account for dengue transmission [26].

This extended model contains the parameters acknowledged in Table 3, but introduces three new parameters to account for the inclusion of dengue transmission during human and mosquito interactions.

Table 4: Parameter Descriptions for the Dengue-*Wolbachia* Model

Parameter	**Description**	**Units**	**Value**
μ_N	Rate of human $\rightarrow$ mosquito transmission	$(\text{time} \times \text{human})^{-1}$	$0.0834 \times 0.3352 = 0.02795568$
μ_H	Rate of mosquito $\rightarrow$ human transmission	$(\text{time} \times \text{mosquito})^{-1}$	$0.2499 \times 0.3352 = 0.08376648$
α_H	Dengue recovery rate in humans	time^{-1}	0.1

Given that dengue transmission is highly dependent on the locality of the disease, note that Table 4 uses parameters estimated from Cali, Colombia, which is actively engaged in ongoing *Wolbachia* release programs [2]. Several surges of dengue cases have occurred in the past decade, with all four dengue strains being active [42]. Despite these parameters stemming from a specific city, *Ae. aegypti* target similar subtropical regions of the world, making such parameters likely amenable to broader geographical regions.

As discussed in Section 1.3, besides the *w*MelPop strain, *w*Mel and *w*AlbB are also of interest. Their respective birth and mortality rates will be implemented in the Dengue - *Wolbachia* model to see how the dynamics of such strains alter the dynamics of the overall mosquito population. Table 5 provides these parameter values as a proportion of wild mosquito birth and mortality rates ρ_N and α_N [55].

Table 5: *w*Mel, *w*Alb Parameters

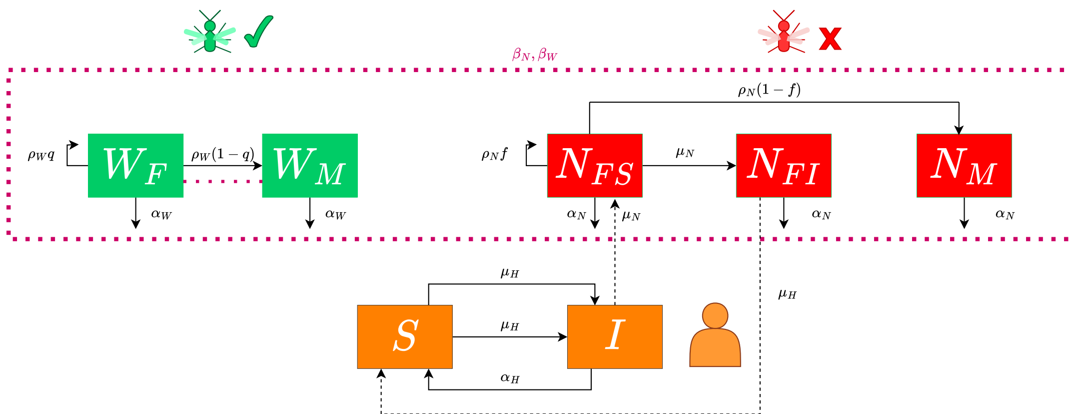
Strain	ρ_W	α_W
*w*Mel	$0.9 \times \rho_N$	$1.1 \times \alpha_N$
*w*AlbB	$0.85 \times \rho_N$	$\approx \alpha_N$

Interestingly, *w*AlbB has little penalty on the wild mosquito death rate, α_N, only birth rate, ρ_N. This is occurs as *w*AlbB's primary "cost" to the mosquito comes in the form of egg viability instead survivability directly. Compared to *w*MelPop, *w*Mel and *w*AlbB have growth and death rates that are relatively close to those seen among wild mosquito populations. The trade-off, as seen in Section 1.3, is how effectively these strains suppress DENV replication and transmission.

For the purposes of this paper, however, we assume that all strains suppress the virus equally as effective as the wMelPop strain.

In order to demonstrate how various strains impact the spread of dengue among human and mosquito populations, a new model must be created, branching from (3). For this model, we assume that only wild female mosquitoes are capable of transmitting dengue, and *Wolbachia*-infected mosquitoes are **perfectly incapable** of spreading dengue. With these assumptions, there are five subpopulations of mosquitoes. These include dengue-infected wild females, N_{FI}, dengue-susceptible wild females, N_{FS}, wild males, N_M, *Wolbachia*-infected females, W_F, and *Wolbachia*-infected males, W_M. Further, by a simple version of the Ross-Macdonald Model [26], the model introduces simple dynamics for dengue infection in humans. In doing so, we account for two classes of human dengue infection: susceptible (S) and infectious (I). Underlying these classes is the assumption that any human - upon recovery from dengue - is immediately susceptible once again [8]. Additionally, we assume that our human population, H, is constant.

Figure 6: Schematic of Dengue-*Wolbachia* Model



The Dengue-*Wolbachia* Model (2025):

$$\begin{aligned}
\frac{dN_{FS}}{dt} &= \rho_N f(N_{FI}+N_{FS})\left(\frac{N_M}{W_M+N_M}\right) - \alpha_N N_{FS} - \beta_N N_{FS}P - \mu_N N_{FS}I,\\
\frac{dN_{FI}}{dt} &= \mu_N N_{FS}I - \alpha_N N_{FI} - \beta_N N_{FI}P,\\
\frac{dN_M}{dt} &= \rho_N(1-f)(N_{FI}+N_{FS})(\frac{N_M}{W_M+N_M}) - \alpha_N N_M - \rho_N N_M P,\\
\frac{dW_F}{dt} &= \rho_W q W_F - \alpha_W W_F - \beta_W W_F P,\\
\frac{dW_M}{dt} &= \rho_W(1-q)W_F - \alpha_W W_M - \beta_W W_M P,\\
\frac{dI}{dt} &= \mu_H(H-I)N_{FI} - \alpha_H I.
\end{aligned} \tag{4}$$

Implicitly, the Dengue-*Wolbachia* Model holds the assumption that dengue is evenly spread within the wild mosquito population. This model also carries over the simplifications associated with *Wolbachia*-infection assumed in (3). That is, only wild (uninfected with *Wolbachia*) female mosquitoes are capable of spreading dengue to humans. Due to this assumption, we construct two compartments for wild female mosquitoes: dengue-susceptible (N_{FS}) and dengue-infected (N_{FI}). Here, we assume that there exists no vertical transmission of dengue among wild mosquitoes.

3.2 Analytical Results of the Dengue-*Wolbachia* Model

Proposition 3: The Dengue -*Wolbachia* Model is well-posed.

Proof. With the assumptions of the Dengue-*Wolbachia* Model (4), it immediately follows by the same argument as used in Section 2.2 that all mosquito subpopulations of the Dengue-*Wolbachia* Model are positively invariant. Thus, we must show that I is positively invariant. Recognize,

$$\left.\frac{dI}{dt}\right|_{I=0} = \mu_H H N_{FI} \geq 0,$$

implying I is positively invariant. Therefore, the Dengue-*Wolbachia* Model is invariant in the positive cone $\mathbb{R}^6_+$, as desired.

Next, boundedness of the Dengue-*Wolbachia* Model can be shown by proving that each subpopulation must be bounded. Conveniently, all the mosquito populations are bounded as a result of the boundedness of the Sex-Structured Model. This follows easily from the construction that all wild female mosquitoes N_F, satisfy $N_F = N_{FS} + N_{FI}$. Therefore, we need only show the boundedness of the infected human population. It follows

$$
\begin{aligned}
\frac{dI}{dt} &= \mu_H (H - I) N_{FI} - \alpha_H I \\
&\leq \mu_H (H - I) N_{FI}^{\max} - \alpha_H I \\
&= \mu_H H N_{FI}^{\max} - \mu_H I N_{FI}^{\max} - \alpha_H I \\
&= (\mu_H N_{FI}^{\max} + \alpha_H) \left(\frac{\mu_H H N_{FI}^{\max}}{\mu_H N_{FI}^{\max} + \alpha_H} - I \right)
\end{aligned}
$$

for which it is seen

$$
\left. \frac{dI}{dt} \right|_{I = \frac{\mu_H H N_{FI}^{\max}}{\mu_H N_{FI}^{\max} + \alpha_H}} \leq 0
$$

and $\dfrac{dI}{dt} < 0$ when $I > \dfrac{\mu_H H N_{FI}^{\max}}{\mu_H N_{FI}^{\max} + \alpha_H}$.

So, following the same structure of the proof of boundedness of the Sex-Structured Model, for any $t, I(t) \leq \max\{\tilde{I}, I(0)\}$ where $\tilde{I} = \frac{\mu_H H N_{FI}^{\max}}{\mu_H N_{FI}^{\max} + \alpha_H}$. It then follows that for any t

$$
\begin{aligned}
0 \leq I(t) &\leq \max\{\tilde{I}, I(0)\} \\
|I(t)| &\leq \max\{\tilde{I}, I(0)\}.
\end{aligned}
$$

thereby showing I is bounded. Hence, the Dengue-*Wolbachia* Model (4) is bounded, and consequently, is well-posed.

The Dengue-*Wolbachia* system admits two new sets of equilibrium points with respect to dengue: endemic and dengue-free equilibria. In the case where there exists no dengue infection within the system (i.e. $N_{FI} = 0$ and $I = 0$), we recover the Sex-Structured Model, leading to the conclusion that any dengue-free equilibrium point follows the same thresholds for stability shown in Section 2.2. Since our primary motivation is understanding how to eliminate dengue in human and mosquito populations, the main focus will be on the dengue-free equilibria.

To develop a deeper understanding of the spread of dengue in the Dengue-*Wolbachia* Model, the basic reproduction number ($\mathscr{R}_0$) can be used to understand when dengue becomes endemic. Unlike $\mathscr{R}_0$ values for traditional models, $\mathscr{R}_0$ calculated for this model takes into account both mosquito and human populations infected with dengue. When $\mathscr{R}_0 > 1$, the disease is considered endemic. For the Dengue-*Wolbachia* model, there are two dengue-free fixed points, resulting in two $\mathscr{R}_0$ values.

Proposition 4: The dengue-free equilibria for wild mosquito domination results with

$$\mathscr{R}_0 = \frac{H\mu_H\mu_N\alpha_N(Q_N-1)}{\alpha_H\rho_N\beta_N}.$$

Proof. We proceed with the Van den Driessche and Watmough approach and create a next generation matrix to solve for $\mathscr{R}_0$ [26]. The "infected" compartments consist of dengue-infected wild female mosquitoes and dengue-infected humans. All other derivatives of states are considered non-infected and will not be accounted for in the next generation matrix determination. So, we have

$$\frac{dN_{FI}}{dt} = \mu_N N_{FS} I - \alpha_N N_{FI} - \beta_N N_{FI} P,$$
$$\frac{dI}{dt} = \mu_H (H-I) N_{FI} - \alpha_H I.$$

The rate of new infections ($\mathscr{F}_i$) and other transitional terms ($\mathscr{V}_i$) can be put into matrices

$$\mathscr{F}_i = \begin{bmatrix} \mu_H N_{FS} I \\ \mu_H (H-I) N_{FI} \end{bmatrix},$$

$$\mathscr{V}_i = \begin{bmatrix} \alpha_N N_{FI} + \beta_N N_{FI}(N_{FS} + N_{FI} + N_M + W_F + W_M) \\ \alpha_H I \end{bmatrix}.$$

Recall that there are two disease-free equilbria. Take

$$\mathscr{E}_{\boldsymbol{N}} = (0, \frac{f(f\rho_N - \alpha_N)}{\beta_N}, \sigma_4, 0, 0, 0)$$

where

$$\sigma_4 = \frac{(f-1)(\alpha_N - f\rho_N)}{\beta_N} = \frac{(1-f)(f\rho_N - \alpha_N)}{\beta_N}.$$

Linearizing around each disease-free equilibrium in new dengue infections, results in

$$F_N = \begin{bmatrix} 0 & -\frac{f\mu_N(\alpha_N - f\rho_N)}{\beta_N} \\ H\mu_H & 0 \end{bmatrix}.$$

Similarly, the same is done for the transitional terms

$$V_N = \begin{bmatrix} \alpha_N - \beta_N(\frac{f(\alpha_N - f\rho_N)}{\beta_N} - \frac{(\alpha_N - f\rho_N)(f-1)}{\beta_N}) & 0 \\ 0 & \alpha_H \end{bmatrix}.$$

F_N and V_N are utilized to solve for the next generation matrix.

$$K_N = F_N V_N^{-1} = \begin{bmatrix} 0 & -\frac{f\mu_N(\alpha_N - f\rho_N)}{\beta_N\alpha_H} \\ \frac{H\mu_H}{f\rho_N} & 0 \end{bmatrix}.$$

To find each $\mathscr{R}_0$, the spectral radius for matrix K ($\rho(K_i)$) is used to find

$$\mathscr{R}_0 = \rho(K_N) = \frac{H\mu_H\mu_N\alpha_N(f\rho_N - \alpha_N)}{\alpha_H\rho_N\beta_N}$$

$$= \frac{H\mu_H \mu_N \alpha_N (Q_N - 1)}{\alpha_H \rho_N \beta_N}$$

In the case of the Dengue-*Wolbachia* Model, $\mathscr{R}_0$ shows the spread of dengue in both mosquito and human populations. In order for dengue to persist in a community, there must exist a sufficient amount of dengue-infected wild female mosquitoes, denoted by $Q_N = \dfrac{f\rho_N}{\alpha_N}$.

Proposition 5: The dengue-free equilibria for *Wolbachia*-infected mosquito domination results with

$$\mathscr{R}_0 = 0.$$

Proof. Similarly, $\mathscr{R}_0$ can be shown for *Wolbachia*-infected mosquito establishment. We proceed with the same method, meaning $\mathscr{F}_i$ and $\mathscr{V}_i$ remain the same. In the *Wolbachia* domination scenario, the equilibrium is as follows:

$$\mathscr{E}_{\boldsymbol{W}} = (0, 0, 0, \sigma_6, \sigma_3, 0)$$

where

$$\sigma_3 = \frac{(\alpha_W - q\rho_W)(q-1)}{\beta_W},$$

$$\sigma_6 = \frac{-q(\alpha_W - q\rho_W)}{\beta_W}.$$

We linearize around the disease-free equilibria again for F_W and V_W and attain

$$F_W = \begin{bmatrix} 0 & 0 \\ H\mu_H & 0 \end{bmatrix},$$

$$V_W = \begin{bmatrix} \alpha_N - \beta_N\left(\frac{q(\alpha_W - q\rho_W)}{\beta_W} - \frac{(\alpha_w - q\rho_W)(q-1)}{\beta_W}\right) & 0 \\ 0 & \alpha_H \end{bmatrix}.$$

Both F_W and V_W can be used to solve for the next generation matrix once again, so

$$K_W = F_W V_W^{-1} = \begin{bmatrix} 0 & 0 \\ \frac{H\beta_W \mu_H}{\alpha_N \beta_W - \alpha_W \beta_N + q\beta_N \rho_W} & 0 \end{bmatrix}.$$

Lastly, the spectral radius can be used to find $\mathscr{R}_0$

$$\mathscr{R}_0 = \rho(K_W) = 0.$$

As expected, due to the assumption of perfect cytoplasmic incompatibility, dengue is unable to spread in both mosquito and human populations, resulting in $\mathscr{R}_0 = 0$. Thus, no dengue exists in the community.

3.3 Sensitivity Analysis for $\mathscr{R}_0$

The basic reproduction number $\mathscr{R}_0$ characterizes the expected number of secondary dengue infections generated by a single infectious individual introduced into a wholly susceptible population. For the mosquito–human subsystem considered here, it is given by

$$\mathscr{R}_0 = \frac{H\,\mu_H\,\mu_N\big(f\,\rho_N - \alpha_N\big)}{\alpha_H\,\rho_N\,\beta_N}, \tag{5}$$

where each parameter is defined in Table 6, and this was shown in Section 3.2. An outbreak is possible when $\mathscr{R}_0 > 1$, and disease fails to persist when $\mathscr{R}_0 < 1$. It is important to specify that the $\mathscr{R}_0$ provided here accounts for both human and mosquito populations, showing persistance in both as a whole.

To identify which biological processes exert the greatest influence on $\mathscr{R}_0$, we compute *normalized forward sensitivity indices.* For a generic parameter p the index is defined as

$$\Upsilon_p \;:=\; \frac{\partial \mathscr{R}_0}{\partial p}\cdot\frac{p}{\mathscr{R}_0}. \tag{6}$$

This dimensionless quantity measures the relative change in $\mathscr{R}_0$ resulting from a relative change in p. Thus:

- $\Upsilon_p > 0$ – increasing p increases $\mathscr{R}_0$;
- $\Upsilon_p < 0$ – increasing p decreases $\mathscr{R}_0$;
- $|\Upsilon_p| = 1$ – a 1% change in p produces a 1% change in $\mathscr{R}_0$.

Differentiating (5) symbolically yields the indices compiled in Table 6. Parameters whose indices equal ± 1 have a linear (one-to-one) influence on $\mathscr{R}_0$, whereas those with fractional indices impart a sub-linear effect.

Table 6: Normalized forward sensitivity indices Υ_p for each parameter of $\mathscr{R}_0$.

Parameter	**Definition of Υ_p**	**Simplified Expression**
H	$\Upsilon_H = \dfrac{\partial R_0}{\partial H} \cdot \dfrac{H}{R_0}$	1
μ_h	$\Upsilon_{\mu_h} = \dfrac{\partial R_0}{\partial \mu_h} \cdot \dfrac{\mu_h}{R_0}$	1
μ_n	$\Upsilon_{\mu_n} = \dfrac{\partial R_0}{\partial \mu_n} \cdot \dfrac{\mu_n}{R_0}$	1
f	$\Upsilon_f = \dfrac{\partial R_0}{\partial f} \cdot \dfrac{f}{R_0}$	$\dfrac{f\rho_n}{f\rho_n - \alpha_n}$
ρ_n	$\Upsilon_{\rho_n} = \dfrac{\partial R_0}{\partial \rho_n} \cdot \dfrac{\rho_n}{R_0}$	$\dfrac{\alpha_n}{f\rho_n - \alpha_n}$
α_n	$\Upsilon_{\alpha_n} = \dfrac{\partial R_0}{\partial \alpha_n} \cdot \dfrac{\alpha_n}{R_0}$	$\dfrac{\alpha_n}{\alpha_n - f\rho_n}$
α_h	$\Upsilon_{\alpha_h} = \dfrac{\partial R_0}{\partial \alpha_h} \cdot \dfrac{\alpha_h}{R_0}$	-1
β_n	$\Upsilon_{\beta_n} = \dfrac{\partial R_0}{\partial \beta_n} \cdot \dfrac{\beta_n}{R_0}$	-1

Figure 7: Sensitivity analysis of R_0 with respect to the female reproductive rate, ρ_n.

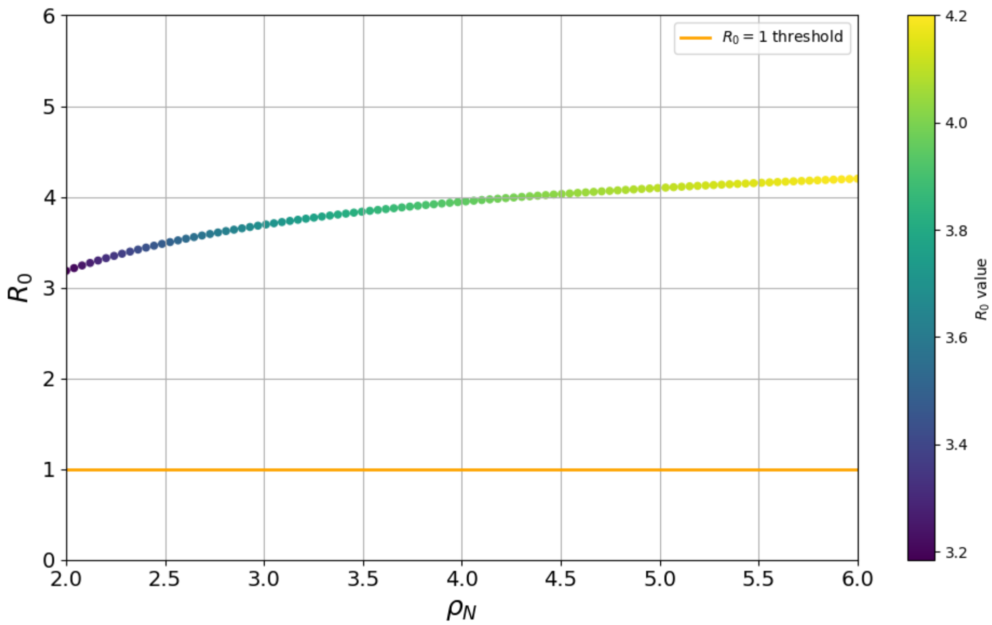
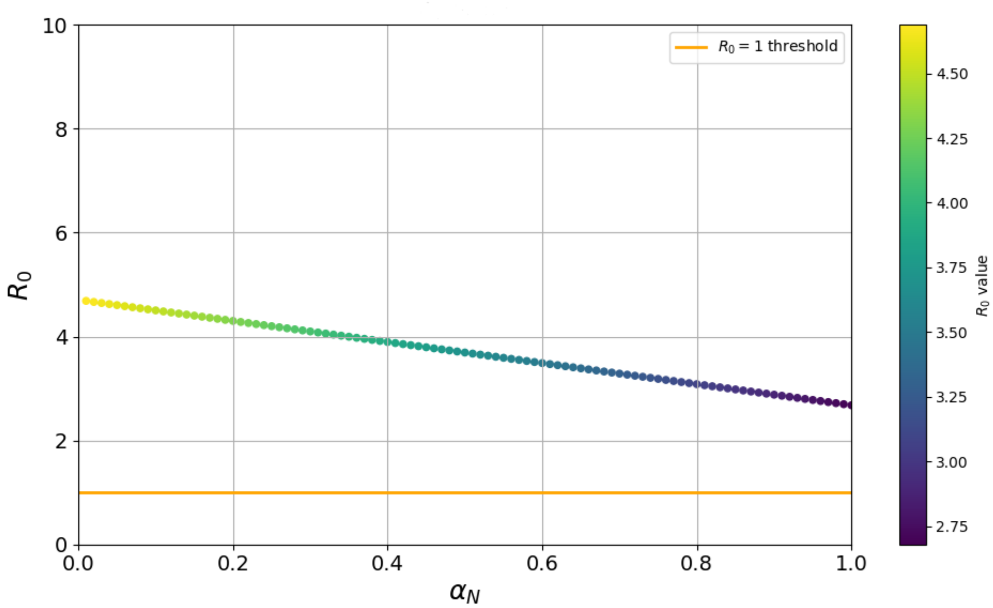


Figure 8: Sensitivity analysis of R_0 with respect to the mortality rate, α_n.



The red and orange lines in the above figures correspond to the thresholds $\mathscr{Q}_N = 1$ and $\mathscr{R}_0 = 1$, respectively. Here, $\mathscr{Q}_N$ denotes the critical threshold for wild mosquito persistence, while $\mathscr{R}_0$ represents the natural reproductive number for dengue transmission.

Increasing ρ_N raises both $\mathscr{Q}_N$ and $\mathscr{R}_0$, enhancing wild mosquito persistence and dengue transmission potential. Conversely, increasing α_N lowers both $\mathscr{Q}_N$ and $\mathscr{R}_0$, making it less likely for wild mosquitoes to persist and dengue to spread. Thus, effective interventions that elevate mortality or suppress fecundity in wild mosquitoes can reduce the system's tendency toward dengue outbreaks.

Alongside a sensitivity test for $\mathscr{R}_0$, a basin of attraction analysis is performed in Section 3.4 to investigate how initial population compositions influence long-term dynamics. The results reveal distinct regions of the phase space that lead to different equilibrium, wild-only or *Wolbachia*-only, depending on release conditions and model parameters of a given strain.

3.4 Numerical Results of Dengue-*Wolbachia* Model

Figure 9: Basin of attraction plots for female and male *Wolbachia*-infected mosquitoes across three different strains, *w*MelPop, *w*Mel, and *w*AlbB (left to right), showing the corresponding final number of infected humans I.

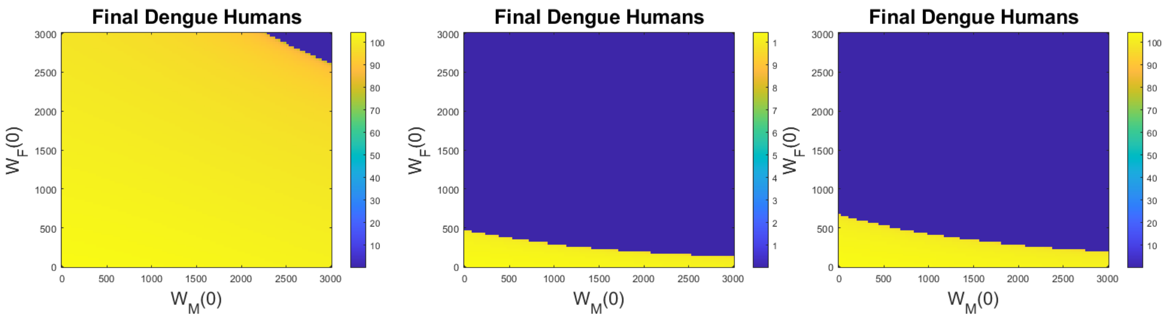
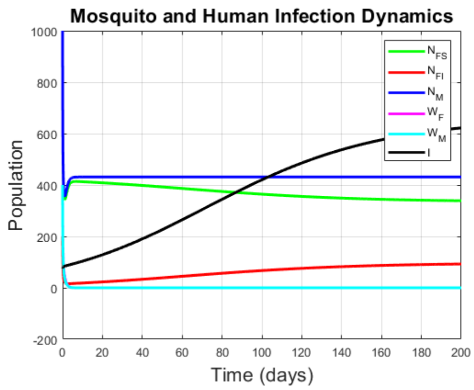


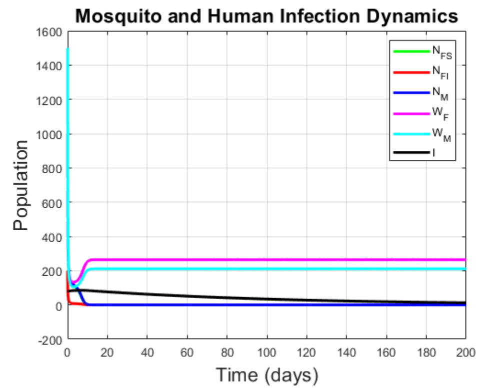
Figure 9 illustrates the basins of attraction for different initial conditions under the Dengue-*Wolbachia* Model. These visualizations help determine which equilibrium—wild-only, *Wolbachia*-only, or coexistence—the system converges to, based on varying initial population densities. The basins underscore the sensitivity of the system to initial population composition and the importance of exceeding release thresholds for successful *Wolbachia* establishment. The first figure for *w*MelPop indicates a high number of *Wolbachia* infected mosquitoes of both sexes must be released in order to eliminate dengue in humans successfully. The second figure for *w*Mel is the strain that requires the smallest proportion of male and female infected mosquitoes to eradicate dengue. *w*AlbB, illustrated in the third figure, requires slightly more than *w*Mel to function effectively.

Figure 10 below contains standard population dynamics plots. These depict the changes that occur for the two winner equilibrium points, now taking into account dengue infection. When the noninfected mosquitoes dominate, infection levels in humans, denoted by a black line on the graphs, begin to escalate overtime. When the *Wolbachia* infected mosquitoes dominate, then the reverse occurs and infection levels in humans begin to decrease at a slower rate. The simulations further push the implication of *Wolbachia* being a necessary tool to help diminish dengue cases in communities. Notice that releasing male *Wolbachia* infected mosquitoes is not necessary for total population replacement with the *w*Mel and *w*AlbB strains, just as in Figure 9.

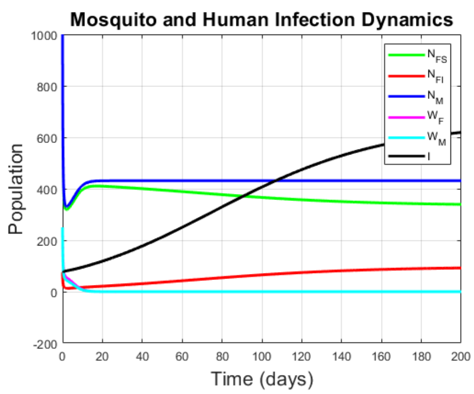
Figure 10: Dynamics for mosquito and human infections for *Wolbachia*-free equilibrium (left) and wild-free equilibrium (right).



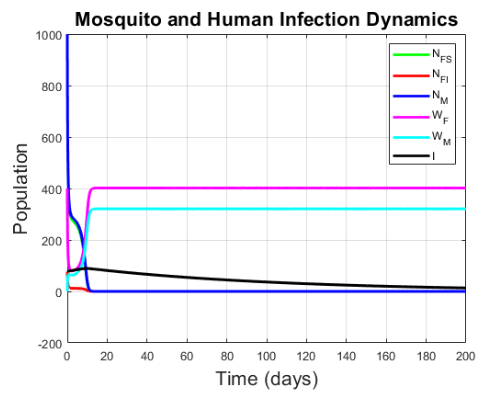
wMelPop, Low Initial Population



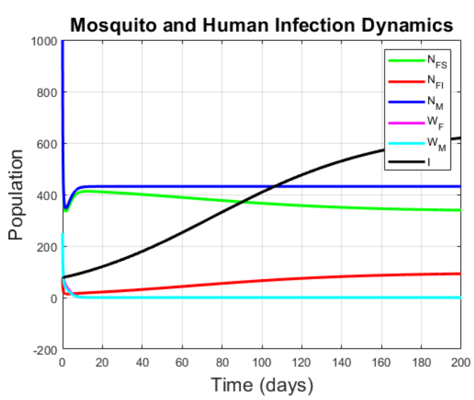
wMelPop, High Initial Population



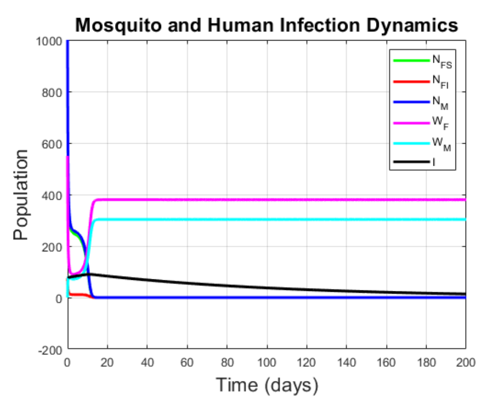
wMel, Low Initial Population



wMel, High Initial Population



wAlbB, Low Initial Population



wAlbB, High Initial Population

4 Optimal Control of the Dengue - *Wolbachia* Model

4.1 Optimal Control Problem Formalization and Characterization

Minimizing the number of individuals and wild mosquitoes with dengue presents the primary motivation for introducing an optimal control problem in the Dengue-*Wolbachia* Model. *Wolbachia*-infected mosquitoes are the main mode of biological control to reduce viral replication of dengue and control mosquito populations [29]. However, ideal strategies for the local, targeted release of *Wolbachia*-infected mosquitoes that most effectively reduce dengue are difficult to establish. Alternative dynamical representations of dengue and *Wolbachia* interplay have approached this optimal control problem and identified general schemes for the release of *Wolbachia*-infected mosquitoes [6]. Yet, it remains unanswered as to whether there exists a favorable release strategy that accounts for the sexes of the *Wolbachia*-infected mosquitoes. This question forms the basis of the proposed optimal control problem. That is, this problem focuses on identifying distinct, optimal release strategies of male and female *Wolbachia*-infected mosquitoes that minimize the "costs" of human infection and mosquito release. Given this problem considers the release of *Wolbachia*-infected male and female mosquitoes, the dynamics of W_F and W_M in the dengue-*Wolbachia* model will be altered. Naturally, this optimal control problem is carried out on the time interval $[0, T]$. Defining L_F and L_M to be the maximum rates of *Wolbachia*-infected mosquitoes released per day for female and male mosquitoes, respectively, it follows that $\frac{dW_F}{dt}, \frac{dW_M}{dt}$ are redefined as

$$\begin{aligned}
\frac{dW_F}{dt} &= \rho_W q W_F - \alpha_W W_F - \beta_W W_F P + u_1 L_F,\\
\frac{dW_M}{dt} &= \rho_W (1-q) W_F - \alpha_W W_M - \beta_W W_M P + u_2 L_M,
\end{aligned}$$

where $0 \leq u_1(t), u_2(t) \leq 1$, $\forall t \in [0, T]$. u_1, u_2 are the controls of the optimal control problem, where each is a piecewise continuous function, satisfying $u_1, u_2 : [0, \infty) \to [0, 1]$. u_1, u_2 represent the proportion of the maximum rate of *Wolbachia*-infected mosquitoes to be released on a given day t. The set of all admissible controls can be defined as $\mathscr{A} := \left\{u \in L^1(0, T) : u(t) \in [0, 1]\right\}$. Hence, the system dynamics that govern the optimal control problem are

$$\begin{aligned}
\frac{dN_{FS}}{dt} &= \rho_N f(N_{FI} + N_{FS}) \left(\frac{N_M}{W_M + N_M}\right) - \alpha_N N_{FS} - \beta_N N_{FS} P - \mu_N N_{FS} I,\\
\frac{dN_{FI}}{dt} &= \mu_N N_{FS} I - \alpha_N N_{FI} - \beta_N N_{FI} P,\\
\frac{dN_M}{dt} &= \rho_N (1-f)(N_{FI} + N_{FS}) \left(\frac{N_M}{W_M + N_M}\right) - \alpha_N N_M - \beta_N N_M P,\\
\frac{dW_F}{dt} &= \rho_W q W_F - \alpha_W W_F - \beta_W W_F P + u_1 L_F,\\
\frac{dW_M}{dt} &= \rho_W (1-q) W_F - \alpha_W W_M - \beta_W W_M P + u_2 L_M,\\
\frac{dI}{dt} &= \mu_H (H - I) N_{FI} - \alpha_H I.
\end{aligned}$$

For ease of notation, define

$$\boldsymbol{u}(t) = [u_1(t), u_2(t)],$$
$$\boldsymbol{f}(\boldsymbol{x}(t), \boldsymbol{u}(t)) = \left[\frac{dN_{FS}}{dt}, \frac{dN_{FI}}{dt}, \frac{dN_M}{dt}, \frac{dW_F}{dt}, \frac{dW_M}{dt}, \frac{dI}{dt}\right].$$

Therefore, the optimal control problem can be established as

$$J(\boldsymbol{u}^*) = \min_{\boldsymbol{u}} \int_0^T \left[a_0 I + \frac{1}{2}a_1 u_1^2(t) + \frac{1}{2}a_2 u_2^2(t)\right] dt \tag{7}$$

where $a_0, a_1, a_2 \in \mathbb{R}_+$, subject to $\boldsymbol{f}(\boldsymbol{x}(t), \boldsymbol{u}(t))$ with initial conditions $\boldsymbol{x}(0) = \boldsymbol{x}_0$. $\boldsymbol{u}^*$ represents the optimal controls that minimize the given functional, J. For future use, define $g(\boldsymbol{x}(t), \boldsymbol{u}(t)) = a_0 I + a_1 u_1^2(t) + a_2 u_2^2(t)$. The functional, J, is constructed to incorporate infected humans with the term $a_0 I$ and release strategies with u_1^2 and u_2^2, respectively. Therefore, minimization of this functional should provide a relevant choice of controls that reflects the desire to minimize both the number of infected humans and mosquitoes released. Noticeably, the controls are squared for ease of proving the existence of an optimal control and associated state, $(\boldsymbol{u}^*, \boldsymbol{x}^*)$.

After formulating the optimal control problem, it is natural to guarantee the existence of an optimal pair, $(\boldsymbol{u}^*(t), \boldsymbol{x}^*(t))$, for the specific problem. Existence of an optimal pair is proven by inciting the *Filippov-Cesari Existence Theorem* [26].

Proposition 6: The optimal control problem of the Dengue-*Wolbachia* Model has an optimal pair.

Proof. Proving that the desired optimal control problem (7) has an optimal pair $(\boldsymbol{u}^*(t), \boldsymbol{x}^*(t))$ amounts to satisfying the three conditions required of the *Filippov-Cesari Existence Theorem* [26]. First, it must be shown that

$$N(t, \boldsymbol{x}) = \{(g(\boldsymbol{x}, \boldsymbol{u}) + \xi, \boldsymbol{f}(\boldsymbol{x}, \boldsymbol{u})) : \xi \leq 0, \boldsymbol{u}(t) \in [0, 1]\}$$

is convex for every $(t, \boldsymbol{x})$. By construction, $g(\boldsymbol{x}, \boldsymbol{u})$ is convex, thus $g(\boldsymbol{x}, \boldsymbol{u}) + \xi$ is convex for any $\xi \leq 0$. Also, recognize that $\boldsymbol{f}(\boldsymbol{x}, \boldsymbol{u})$ is affine with respect to $\boldsymbol{u}$. Therefore, it easily follows that $N(t, \boldsymbol{x})$ must be convex for any $(t, \boldsymbol{x})$.

Next, the codomain of $\boldsymbol{u}$ is required to be compact. Since we have $\boldsymbol{u} : [0, \infty) \to [0, 1]$, then by the *Heine-Borel Theorem* [43], the codomain of $\boldsymbol{u}$ is compact, as desired.

Finally, there must exist a constant $K > 0$ such that $||\boldsymbol{x}(t)|| \leq K$ for all $t \in (0, T)$ and all admissible pairs $(\boldsymbol{x}, \boldsymbol{u})$. Even with the redefinitions of $\frac{dW_F}{dt}$ and $\frac{dW_M}{dt}$, this new model is well-posed. Importantly, this means that all state variables of $\boldsymbol{f}(\boldsymbol{x}, \boldsymbol{u})$ are bounded. Let the upper bounds of each state variable be denoted as such

$$\boldsymbol{x}^{\max} = [N_{FS}^{\max},\ N_{FI}^{\max},\ N_M^{\max},\ W_F^{\max},\ W_M^{\max},\ I^{\max}].$$

Take $M := \max\{N_{FS}^{\max},\ N_{FI}^{\max},\ N_M^{\max},\ W_F^{\max},\ W_M^{\max},\ I^{\max}\}$. Then it follows:

$$
\begin{aligned}
||\boldsymbol{x}(t)|| &\leq ||\boldsymbol{x}^{\max}|| \\
&= \sqrt{(N_{FS}^{\max})^2 + (N_{FI}^{\max})^2 + (N_{M}^{\max})^2 + (W_{F}^{\max})^2 + (W_{M}^{\max})^2 + (I^{\max})^2} \\
&\leq \sqrt{6M}.
\end{aligned}
$$

So, $K = \sqrt{6M}$.

Therefore, by the *Filippov-Cesari Existence Theorem* [26], there exists an optimal pair $(\mathbf{x}^*(t), \mathbf{u}^*(t))$, where $\mathbf{u}^*(t) \in \mathscr{A}$.

Next, characterization of the optimal controls is necessary. Namely, computing the solutions to the optimal control problem is done by way of the *Pontryagin Maximum Principle* [22, 26]. This converts the problem of minimizing (respectively, maximizing) a given functional, J, into minimizing (respectively, maximizing) what is called the Hamiltonian, $H(t, \boldsymbol{x}, \boldsymbol{u}, \boldsymbol{\lambda}) = g(t, \boldsymbol{x}, \boldsymbol{u}) + \boldsymbol{\lambda} \cdot \boldsymbol{f}(t, \boldsymbol{x}, \boldsymbol{u})$, where $\boldsymbol{\lambda}$ is a vector of piecewise differentiable adjoints [22].

Proposition 7: The optimal controls of the Dengue-*Wolbachia* Model problem admit the following characterizations:

$$
\begin{aligned}
u_1^*(t) &= \min\left\{1, \max\left\{\frac{-\lambda_4 L_F}{a_1}, 0\right\}\right\}, \\
u_2^*(t) &= \min\left\{1, \max\left\{\frac{-\lambda_5 L_M}{a_2}, 0\right\}\right\}.
\end{aligned}
$$

Proof. Suppose $(\boldsymbol{u}^*, \boldsymbol{x}^*)$ are an optimal pair for the minimization problem (7). Since $(\boldsymbol{u}^*, \boldsymbol{x}^*)$ is an optimal pair, then

$$
J(\boldsymbol{u}^*, \boldsymbol{x}^*) \leq J(\boldsymbol{u}, \boldsymbol{x}^*)
$$

for any choice of $\boldsymbol{u}$.

By the *Pontryagin Maximum Principle* [22], as $(\boldsymbol{u}^*, \boldsymbol{x}^*)$ is an optimal pair, there exists an adjoint vector $\boldsymbol{\lambda}$ - consisting of piecewise differentiable adjoint functions - such that

$$
\begin{aligned}
\left.\frac{\partial H}{\partial u_1}\right|_{u_1 = u_1^*} &= a_1 u_1^*(t) + \lambda_4(t) L_F = 0 \\
\left.\frac{\partial H}{\partial u_2}\right|_{u_2 = u_2^*} &= a_2 u_2^*(t) + \lambda_5(t) L_M = 0
\end{aligned}
$$

where the Hamiltonian, H, satisfies

$$
H = g + \boldsymbol{f} \cdot \boldsymbol{\lambda}
$$

and the adjoint vector $\boldsymbol{\lambda}(t)$ satisfies

$$
\boldsymbol{\lambda}'(t) = -\frac{\partial H}{\partial \mathbf{x}}, \qquad \boldsymbol{\lambda}(T) = 0.
$$

The Hamiltonian, H, is given by

$$\begin{aligned}
H(t,\boldsymbol{x},\boldsymbol{u},\boldsymbol{\lambda}) &= g(t,\boldsymbol{x},\boldsymbol{u}) + \boldsymbol{\lambda}\cdot\boldsymbol{f}(t,\boldsymbol{x},\boldsymbol{u}) \\
&= a_0 I(t) + \frac{a_1}{2}u_1^2(t) + \frac{a_2}{2}u_2^2(t) + a_3 \\
&+ \lambda_1(t)\frac{dN_{FS}}{dt} + \lambda_2(t)\frac{dN_{FI}}{dt} \\
&+ \lambda_3(t)\frac{dN_M}{dt} + \lambda_4(t)\frac{dW_F}{dt} \\
&+ \lambda_5(t)\frac{dW_M}{dt} + \lambda_6(t)\frac{dI}{dt}.
\end{aligned}$$

Thus, it follows that

$$\begin{aligned}
\frac{\partial^2 H(t,\boldsymbol{x},\boldsymbol{u},\boldsymbol{\lambda})}{\partial u_1^2} &= a_1 > 0, \\
\frac{\partial^2 H(t,\boldsymbol{x},\boldsymbol{u},\boldsymbol{\lambda})}{\partial u_2^2} &= a_2 > 0.
\end{aligned}$$

That is, H is convex at $\boldsymbol{u}^*$, so H attains a minimum at $\boldsymbol{u}^*$. Namely, $H(t,\boldsymbol{x}^*,\boldsymbol{u},\boldsymbol{\lambda}) \geq H(t,\boldsymbol{x}^*,\boldsymbol{u}^*,\boldsymbol{\lambda})$ for any choice for $\boldsymbol{u}$. Solving for ${u_1}^*$ and ${u_2}^*$, the characterization follows as

$$u_1^*(t) = \begin{cases} 0 & \text{if } \dfrac{\partial H}{\partial u_1} > 0 \\ \dfrac{-\lambda_4 L_F}{a_1} & \text{if } \dfrac{\partial H}{\partial u_1} = 0 \\ 1 & \text{if } \dfrac{\partial H}{\partial u_1} < 0 \end{cases} \quad u_2^*(t) = \begin{cases} 0 & \text{if } \dfrac{\partial H}{\partial u_2} > 0 \\ \dfrac{-\lambda_5 L_M}{a_2} & \text{if } \dfrac{\partial H}{\partial u_2} = 0 \\ 1 & \text{if } \dfrac{\partial H}{\partial u_2} < 0 \end{cases}$$

which can be neatly written as

$$\begin{aligned}
u_1^*(t) &= \min\left\{1, \max\left\{\frac{-\lambda_4 L_F}{a_1}, 0\right\}\right\} \\
u_2^*(t) &= \min\left\{1, \max\left\{\frac{-\lambda_5 L_M}{a_2}, 0\right\}\right\}.
\end{aligned}$$

4.2 Numerical Results of Optimal Control

Following characterization of the optimal controls, solution of the optimal control problem (7) is approachable. Analytical and closed-form solution is not feasible, so numerical solution is proposed for this problem. The GPOPS-II Next-Generation Optimal Control Software is used to calculate the optimal control solutions and is implemented through MATLAB [23]. GPOPS-II employs *Radau Pseudospectral Method*, subverting the need for numerical integration.

For solution of optimal controls, multiple scenarios of dengue infection in local human and wild mosquito populations are considered. As before, scenarios are situated in Cali, Colombia. Initial conditions and bounds are established by choice of parameters on the given mosquito population, which vary with respect to strain. We consider three strains, wMelPop, wMel, and **w**AlbB. *Arias-Castro, et. al* established estimated relationships between populations of *Ae. aegypti* and humans, as well as dengue infection proportions of human and mosquito populations in Cali, Colombia [2]. Our optimal control solutions will adopt these relationships and are illustrated in Table 7. However, in order to benefit from these relationships, an upper bound on the total population of mosquitoes must be identified.

Proposition 8: The total population of mosquitoes, P, is bounded by $\frac{\rho_N - \alpha_N}{\beta_N}$.

Proof. Taking $P = N_{FS} + N_{FI} + N_M + W_F + W_M$. Note,

$$\begin{aligned}
\frac{dP}{dt} &= \rho_N f(N_{FI} + N_{FS}) \left(\frac{N_M}{W_M + N_M} \right) - \alpha_N N_{FS} - \beta_N N_{FS} P - \mu_N N_{FS} \\
&+ \mu_N N_{FS} I - \alpha_N N_{FI} - \beta_N N_{FI} P \\
&+ \rho_N (1-f)(N_{FI} + N_{FS}) \left(\frac{N_M}{W_M + N_M} \right) - \alpha_N N_M - \beta_N N_M P \\
&+ \rho_W q W_F - \alpha_W W_F - \beta_W W_F P + u_1 L_F \\
&+ \rho_W (1-q) W_F - \alpha_W W_M - \beta_W W_M P + u_2 L_M \\
&\leq \rho_N P - \alpha_N P - \beta_N P^2 \\
&= \beta_N P \left(\frac{\rho_N - \alpha_N}{\beta_N} - P \right).
\end{aligned}$$

Thus, $|P| \leq \frac{\rho_N - \alpha_N}{\beta_N}$.

With an upper bound on the total population of *Ae. aegypti* identified, the following initial conditions and parameter values are constructed for the three different scenarios of strain use. wMelPop introduction is examined, followed by wMel and wAlbB. The parameters used for the previous two strains are estimated based on their effects when compared to wMelPop, as shown in Table 5.

Table 7: Optimal Control Parameter Descriptions

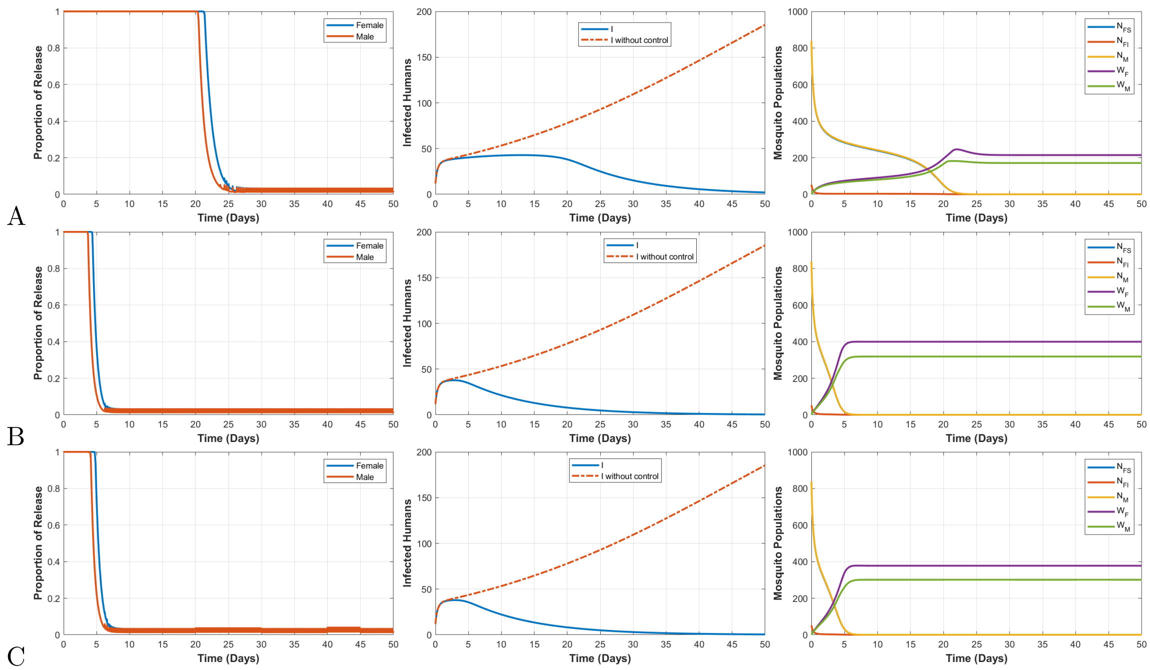
Parameter	Description	Value	Units	Reference
L_F	Maximum release rate for female *Wolbachia*-infected mosquitoes.	80	mosquito $\times$ (time)$^{-1}$	Assumed
L_M	Maximum release rate for male *Wolbachia*-infected mosquitoes.	80	mosquito $\times$ (time)$^{-1}$	Assumed
H	Total human population.	$1.4727 \times \dfrac{\rho_N - \alpha_N}{\beta_N}$	human	[2]
a_0	Weight placed on infected humans, I.	$\frac{1000}{H}$	-	Assumed
a_1	Weight placed on u_1.	1	-	Assumed
a_2	Weight placed on u_2.	1	-	Assumed
T	Length of release program.	50	-	Assumed

The maximum release rates for males and females, L_F and L_M, are considered to be equal in the simulations. The total human population, H, and mosquito population, P, are difficult to establish. However, a value for each can be determined by using the estimated ratio of humans to wild mosquitoes when we assume the total wild mosquito population is the upper bound proved earlier [2]. The weights, a_0, a_1, a_2, placed on each term of the integrand g of (7) are first normalized and then scaled with respect to importance of minimization. The main goal is to minimize the number of dengue cases, a_0 is set to be the strongest of the three weights, provided the scale of I far exceeds that of u_1, u_2. In Table 8, the initial conditions presented are based on *Arias et.al*'s parameter estimation [2].

Table 8: Initial conditions used for the optimal control solutions of all strains.

Initial Condition	Value	Units
$N_{FS}(0)$	$0.485 \times 1.4727 \times H$	mosquito
$N_{FI}(0)$	$0.03 \times 1.4727 \times H$	mosquito
$N_M(0)$	$0.485 \times 1.4727 \times H$	mosquito
$W_F(0)$	0	mosquito
$W_M(0)$	0	mosquito
$I(0)$	$0.01 \times H$	human

Figure 11: Optimal control solutions for wMelPop, wMel, and wAlbB scenarios.



In Figure 11, A is assigned to wMelPop, B to wMel, and C to wAlbB. The first column identifies the optimal controls, u_1^* and u_2^*, for each choice of strain. Interestingly, regardless of strain, all optimal controls show that maximal female releases – indicated by the blue line – should be prolonged for 1-3 days longer than maximal male releases. The second column of graphs shows infection levels of humans with and without controls when a specific strain is utilized. All scenarios showcase a significant decrease in dengue cases as a result of control use. Note, the orange, dotted line represents the infected human counts when there is no intervention with *Wolbachia* release. Notably, the wMelPop strain takes the longest for the effects of *Wolbachia* to become apparent, likely stemming from its significant fitness impacts. However, both wAlbB and wMel strains share similar release strategies with respect to controls and infection prevention. Finally, the third column contains the mosquito subpopulation dynamics, with establishment of *Wolbachia*-infected subpopulations occurring at the end of the optimal release programs for each scenario.

4.3 Cost Effectiveness Analysis of Optimal Release Programs

One of the drawbacks inherent to mosquito release programs is the cost that communities incur by participating in such programs. One study estimated that it would cost \$171.3 million U.S. dollars to implement *Wolbachia* release programs in ten diverse cities across the world, with the majority of the costs coming from preparation and first release stages [47]. Especially in less-fortunate regions, these costs can greatly dictate whether *Wolbachia* release can even occur in the first place. In order to develop *Wolbachia* release programs that are both effective and accessible, it is crucial to discover the most cost-effective release methods. Cost-effectiveness analysis examines the efficacy of healthcare interventions comparatively through cost and benefit [7]. In the analysis presented, the costs and benefits are measured in arbitrary units and the optimal release programs of the three strains of *Wolbachia* are compared to when no program is implemented.

Using the GPOPS-II software, values for cost and benefits for each strain can be calculated. When there is no control, the total infections that occur within the time window, T, is ≈ 4945.21. Benefits are calculated by subtracting the number of infections with a control strategy from those when no strategy is employed. To compare the cost-effectiveness of each strain, the average cost-effectiveness ratio (ACER) is used. ACER values can be calculated as follows. For our problem, we define

$$ACER = \frac{\int_0^T [a_1 u_1 + a_2 u_2]\, dt}{\int_0^T \hat{I}(t)\, dt - \int_0^T I(t)\, dt}.$$

Put simply, ACER calculates the cost of a strategy over benefits. Here, cost can be naively thought of as relative to the quantity of mosquitoes released during a program. A lower ACER value signifies better cost-effectiveness, as we wish maximize benefits (prevented human dengue infections) and minimize the costs of our control strategy (mosquito release).

Table 9: Cost Effective Analysis Values

Strain	**Cost**	**Benefits**	**ACER**
wMelPop	44.632	675.603	0.0119
wMel	10.573	1349.778	0.0024
wAlbB	11.617	1335.148	0.0026
No control	0	0	-

wMelPop is shown to be the most burdensome in terms of higher cost and lower benefits. Such results likely stem from the fact that this strain greatly reduces a mosquito's lifespan, requiring a program to release a greater bulk of infected mosquitoes. On the other hand, both wMel and wAlbB result in reduced costs, with wMel requiring the least expenditures. Similarly, wMel holds the greatest benefits value. Consequently, wMel holds the smallest ACER score, deeming it as the most cost-effective strain for our determined optimal release programs. This ACER result corresponds well with the fact that many release programs, including releases done by the World Mosquito program, prefer to use the wMel strain due to its optimal phenotypes that effectively hamper dengue transmission [50].

As highlighted with this analysis, programs and researchers are urged to take into account the strain that best fits the needs of the region they are working in. Provided viral load suppression and imperfect cytoplasmic incompatibility are not accounted for in the optimal control solutions nor the construction of the Dengue-*Wolbachia* Model, this analysis is not necessarily reflective of the true costs and benefits of optimal release programs when structured based on sex. Furthermore, other variations of *Wolbachia* strains such as those who have heat-resistance and super-infection may provide more effective methods of release, thereby necessitating further cost-effectiveness analysis [1].

5 Discussion and Conclusion

In this study, a mathematical model was built to investigate how the release of mosquitoes infected with the *Wolbachia* bacterium affects the spread of dengue fever. Unlike previous models, the first model introduced included sex-specific interactions. *Wolbachia* alters how mosquitoes reproduce through cytoplasmic incompatibility. Therefore, our model incorporated factors for rates on this biological control, addressing the interaction between male and female mosquitoes of different *Wolbachia* infection states. Taking into account the biological differences that occur based on the sex of a mosquito is crucial because *Wolbachia* affects male and female reproductive process distinctly. Through the Sex-Structured Model (3), the discovery of "one-winner" equilibrium points allowed for further analysis of best *Wolbachia* release proportions based on sex. Using simulations, observations in the long term dynamics of mosquito subpopulations can be made to speculate the change of releases over time. Under favorable conditions, *Wolbachia*-infected mosquitoes can thrive and lead to reduced dengue cases.

Unleashing *Wolbachia*-infected mosquitoes into wild populations has proven to be an effective method in reducing the spread of dengue in human populations. Based on the analysis conducted on the Sex-Structured model, the number of mosquitoes needed for *Wolbachia* to overtake is substantial when using the wMelPop strain. Despite such drastic numbers needed, population replacement requires a large quantity of female *Wolbachia*-infected mosquitoes. Females who carry *Wolbachia* are the main drivers of population replacement. Males with the infection are not useful for spreading the infection directly, but instead sabotaging the wild population due to cytoplasmic incompatibility, thus reducing the number of wild mosquitoes in the system as they cannot reproduce effectively with *Wolbachia*-infected males.

Through the development of our optimal control problem (7), the different outcomes of dengue persistence in the Dengue-*Wolbachia* Model were not clear cut. Regardless of the strains used, all optimal release programs demonstrated a similar trend. The ideal release strategy, with the provided weights, is to extend the maximal release of females approximately two days past the males. However, all results are based on the assumption that the strains tested maintain the same viral suppression effect.

The models presented in this paper have various limitations. Despite the analysis of each *Wolbachia* strain, many parameters could be adjusted to more precisely account for the impacts on mosquito health. Furthermore, more work can be done to implement new parameters to the model that consider changes in location, season, temperature, *Wolbachia* transmission, and viral suppression. For instance, the wAlbB strain survives better in warmer climates compared to other *Wolbachia* strains, allowing it to propagate itself in regions where wMel and wMelPop would fail [25]. By tweaking the models for varying circumstances, accurate results can be made for efficient release programs for more distinct scenarios. Additionally, more can be done to include the effects of different dengue strains. While variability in fitness between strains is included in the model, viral suppression and lack of maternal transmission of *Wolbachia* are assumed to be perfect. For example, the parameter μ_H, the rate of mosquito-to-human dengue transmission, can be varied based on the strain chosen. By looking for more suitable parameters and changing the values of existing ones, the optimal control problem may admit new and unique release strategies.

5.1 Practical Implications

The findings presented in this paper can be applied to *Wolbachia* release programs, with the specific aim of alleviating the stress dengue adds to lower socioeconomic regions. Areas at high-risk for dengue are more likely to be lower income communities with inadequate housing and risky sanitation levels [9, 54]. Such unfavorable conditions often put people at risk of contracting dengue fever. With this in mind, it has become ever more important to combat dengue with cost-minimizing strategies that both lower the number of dengue infections while releasing *Wolbachia*-infected mosquitoes. The cost-effectiveness analysis indicates that the World Mosquito Program's preferred *w*Mel strain is the most capable of lowering dengue cases, while using the least amount of resources. Nevertheless, programs should take into account the region's climate and time of year for their release when selecting a strain. Programs can incorporate extending the maximal release of *Wolbachia*-infected females past the duration of maximal male release to successfully establish *Wolbachia* in local mosquito populations.

Ultimately, this work showcases a new methodology for determining optimal release programs of *Wolbachia*-infected mosquitoes, which necessitates application in the field.

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