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OPTIMAL CONTROL FOR ENHANCEMENT OF *WOLBACHIA* FREQUENCY AMONG *AEDES AEGYPTI* FEMALES

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Abstract: In this paper, we propose and thoroughly analyze the ODE model that describes the competition between wild *Aedes aegypti* female mosquitoes and those carrying *Wolbachia* bacterial symbiont in the same locality. Using this model in the context of optimal control, we further propose feasible strategies for replacing the wild population with *Wolbachia*-carriers. The latter is known as *Wolbachia*-based biocontrol aimed at prevention of various arboviral infections (such as dengue, chikungunya, and zika diseases), given that *Wolbachia* drastically reduces the mosquito ability to acquire arboviral infections.

AMS Subject Classification: 92D25, 49N90, 92D99
Key Words: *Aedes aegypti*, *Wolbachia*, biological control, optimal control

1. Introduction

Aedes aegypti is an invasive mosquito species which is present in all tropical and sub-tropical regions worldwide [6]. Its abundance is strongly correlated with persistence of arboviral infections caused by dengue (DENV1-5), chikungunya

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(CHIKV), and zika (ZIKV) viruses. These viruses are transmitted by *Aedes aegypti* females during their blood meals taken on human individuals. Nowadays, arboviral infections have the tendency to spread into new geographic areas following the on-going proliferation of *Aedes aegypti* mosquitoes [1].

There is solid evidence [8, 9, 10, 22, 31, 35] that transmissibility of different arboviral infections can be drastically reduced when their transmitters (i.e., *Aedes aegypti* females) carry an intracellular bacterial symbiont of *Wolbachia* (its comprehensive description can be found in [6, p.437])). This biological agent, maternally inherited by the offspring at eggs stage, also induces a distinctive reproductive phenotype known as *cytoplasmic incompatibility* (CI)[1].

Even though the presence of *Wolbachia* has never been detected in wild populations of *Aedes aegypti* mosquitoes [28], many scholars assert that this mosquito species is susceptible to so-called *Wolbachia* "transinfection", i.e. a deliberate infection of wild mosquito eggs by the *Wolbachia* pathogen taken from other insect species [21, 36]. This process is usually carried out in laboratory conditions and can be viewed as "cultivation" of *Wolbachia*-carrying mosquitoes.

In recent years, *Wolbachia*-based biocontrol has emerged as a very promising method of insect control that is environmentally friendly, safe to human health and potentially cost effective [10, 11, 12, 22, 35]. This method of control preserves the natural ecosystems and it is completely safe for humans. There is solid proof [16, 24] that

- *Wolbachia* cannot be transferred to humans through the bite of infected mosquitoes;
- *Wolbachia* only invades insect species, as well as spiders, mites, and terrestrial crustaceans;
- *Wolbachia* is not transferred to plants, water, soil, or earthworms;
- *Wolbachia* is non-transferrable horizontally through predator-prey interaction.

All the above makes *Wolbachia*-based biocontrol even more appealing in the context of prevention of different arboviral infections.

The principal objective of this paper is to apply the modeling framework of optimal control theory for replacing the wild populations of *Aedes aegypti*

[1]CI phenotype causes inviability of offspring originated from matings between uninfected females and infected males and confers the (relative) reproductive advantage to infected females since they produce viable offspring after mating with either infected or uninfected males; see more details in [6, p.450].

mosquitoes with those carrying *Wolbachia*. For this purpose, we propose a simple stylized model (see Section 2) that describes the population dynamics of *Aedes aegypti* mosquitoes. For the sake of simplicity, our model includes only female compartments which are transmitters of different arboviral infections (male mosquitoes do not bite people and, therefore, they do not transmit arboviral infections). The model considers the competition between uninfected and *Wolbachia*-infected females for the same resources (food, breeding sites, etc.) and assumes their density-dependence.

Additionally, our model comprises so-called "Allee effect" or *critical depensation*(see, e.g., [17, 26] or other similar textbooks) which exhibit uninfected mosquitoes at high frequencies of *Wolbachia*. This effect was observed in other models describing *Wolbachia* invasion [3, 29, 34].

In Section 3 we discard the case of constant control input and then formulate the problem of optimal control where the control action is defined by the number of *Wolbachia*-infected female mosquitoes to be released into the wild *Aedes aegypti* populations at a daily basis. The final goal is to replace the wild mosquito population by the *Wolbachia*-infected ones while minimizing the total costs related to this control action.

Section 4 is devoted to the numerical solution of the optimal control problem formulated in the preceding section and interpretation of the results. All numerical calculations have been carried out using the entomological parameters of *wMelPop* strain of *Wolbachia*, which is regarded as the best blocker of dengue and other arboviruses [9, 22, 35] but possesses an extremely high fitness cost [14, 20, 25, 27] (in other words, this particular strain is rather difficult to establish in wild mosquito populations). Finally, Section 5 presents the conclusions and final comments.

2. Modelling Framework

We start by presenting the general framework for mosquito population dynamics. Let $N_f(t)$ denote the total number of female *Aedes aegypti* mosquitoes present at day t in some locality. According to [19], the mosquito birth rate can be expressed as

$$h(N_f) = \Psi_f - \frac{r_f}{K} N_f, \tag{1}$$

where Ψ_f is the natural birth rate in the absence of density dependence, $r_f = \Psi_f - \delta_f$ is the intrinsic growth rate of female mosquitoes in the absence of density dependence, δ_f is the natural death rate in the absence of density dependence, K is the carrying capacity of the mosquitoes in the locality.

The negative term in (1) expresses the density dependence that arises in mosquito populations due to a limited availability of breeding sites and competition between larvae [13, 18]. Then the evolution of N_f in time can be described by the following differential equation:

$$\begin{aligned} \frac{dN_f}{dt} &= h(N_f)N_f - \delta_f N_f = \left(\Psi_f - \frac{r_f}{K}N_f\right)N_f - \delta_f N_f \\ &= r_f\left(1 - \frac{N_f}{K}\right)N_f, \end{aligned} \tag{2}$$

which is also generally known as *logistic equation*. It is worthwhile to note that the sex-structured model developed in [4] also confirms the population of female mosquitoes has "almost" logistic behavior.

When *Wolbachia*-infected mosquitoes, $N_w(t)$ are introduced in the same locality, they have to compete with uninfected ones for mating opportunities, food resources, and breeding sites. Under this conditions, the logistic model (2) should be transformed into a competition model described, e. g., in [2].

Additionally, several scholars observed that uninfected individuals exhibit so-called Allee effect or critical depensation at high Wolbachia frequencies [3, 29, 34]. In other words, if the density of wild mosquitoes $N_f(t)$ drops below some critical threshold $0 < K_0 < K$ while *Wolbachia*-carries have a relatively high density, the population of wild mosquitoes will be gradually driven towards extinction. Such threshold K_0 is sometimes referred to as "minimum viable population size", which is necessary for survival and/or persistence of biological species [26]. This effect is attributed to CI reproductive phenotype induced by Wolbachia in wild insect populations. In effect, at high *Wolbachia* frequencies,

(a) a wild female has more opportunities to mate with a *Wolbachia*-carrying male (rather than wild one) and her offspring will result unviable due to CI phenotype;

(b) a wild male has more opportunities to mate with a *Wolbachia*-carrying female (rather than wild one) whose offspring will be infected with *Wolbachia* due to maternal transmission.

The foregoing arguments allow us to propose the following population dynamics model that comprises the competition between wild and *Wolbachia*-carrying females and exhibit the Allee effect with respect to wild mosquitoes at high *Wolbachia* frequencies:

$$\frac{dN_f}{dt} = \left(r_f - \frac{r_f N_f}{K} - \frac{r_w N_w}{K}\right)N_f\left(\frac{N_f}{K_0} - 1\right) \tag{3a}$$

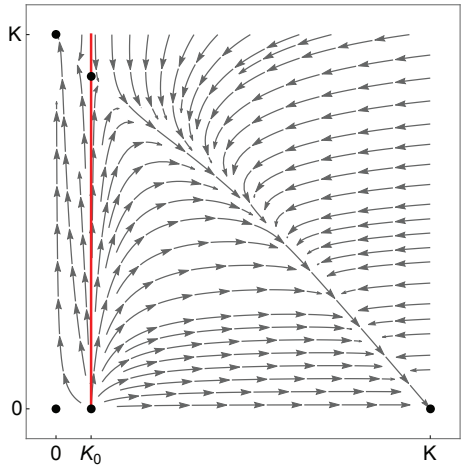

Figure 1: Phase portrait of the system (3) in the plane (N_f, N_w) and its five steady states (black points).

$$\frac{dN_w}{dt} = \left(r_w - \frac{r_f N_f}{K} - \frac{r_w N_w}{K}\right) N_w \tag{3b}$$

Here $r_f = \Psi_f - \delta_f$ has the same meaning as in (2) while $r_w = \Psi_w - \delta_w > 0$ denotes the intrinsic growth rate of *Wolbachia*-infected mosquitoes with Ψ_w and δ_w standing for their natural birth and death rates in the absence of density dependence, respectively. The carrying capacity K is now shared by both populations, and K_0 defines the threshold of minimum viable population size of uninfected mosquitoes that refers to Allee effect.

It is worthwhile to note that *wMelPop* strain of *Wolbachia* may significantly reduce the host longevity without altering much its fecundity [21, 37]. Therefore, it is fair to suppose further on that

$$\delta_w > \delta_f, \quad \Psi_w \approx \Psi_f, \quad 0 < r_w < r_f. \tag{4}$$

and then proceed to analyze the asymptotic behavior of the system (3).

Theorem 1. *Under the conditions* (4)*, dynamical system* (3) *has five equilibrium points (see Figure 1) in the region* $\mathbb{R}^2_+$ *of biological interest, namely:*

$$\left(N_f^{(1)}, N_w^{(1)}\right) = (0,0), \quad \left(N_f^{(2)}, N_w^{(2)}\right) = (K_0, 0), \quad \left(N_f^{(3)}, N_w^{(3)}\right) = (K, 0),$$

$$\left(N_f^{(4)}, N_w^{(4)}\right) = \left(K_0, K - \frac{r_f}{r_w} K_0\right), \quad \left(N_f^{(5)}, N_w^{(5)}\right) = (0, K) \tag{5}$$

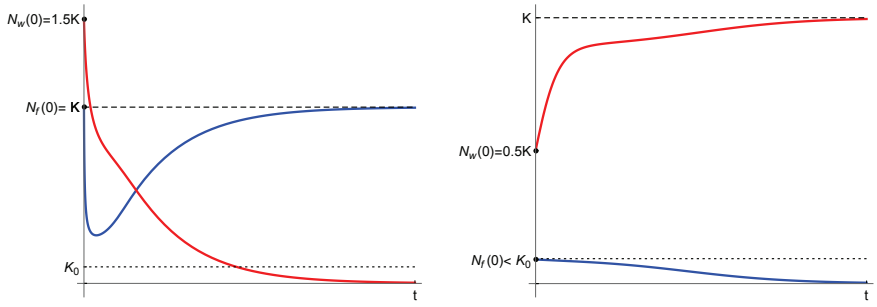

Figure 2: Trajectories of the system (3) reaching the points of attraction $\left(N_{\mathbf{f}}^{(3)}, N_{\mathbf{w}}^{(3)}\right) = (K, 0)$ *(Left)* and $\left(N_{\mathbf{f}}^{(5)}, N_{\mathbf{w}}^{(5)}\right) = (0, K)$ *(Right)*. Here the blue curves correspond to the populations of uninfected mosquitoes $N_{\mathbf{f}}(t)$ while the red curves denote the populations of *Wolbachia*-carriers $N_{\mathbf{w}}(t)$.

Among them, there are two asymptotically stable equilibria

$$\left(N_f^{(3)}, N_w^{(3)}\right) = (K, 0) \quad \text{and} \quad \left(N_f^{(5)}, N_w^{(5)}\right) = (0, K),$$

and only one of them can be reached when $t \to \infty$ *according to the initial conditions* $N_f(0) > 0, N_w(0) > 0$ *assigned to the system* (3)*, namely:*

- *If* $N_f(0) > K_0$ *and* $N_w(0) > 0$ *then* $\left(N_f^{(3)}, N_w^{(3)}\right) = (K, 0)$ *will be reached when* $t \to \infty$ *(see Figure 2* (Left)*).*
- *If* $0 < N_f(0) < K_0$ *and* $N_w(0) > 0$ *then* $\left(N_f^{(5)}, N_w^{(5)}\right) = (0, K)$ *will be reached when* $t \to \infty$ *(see Figure 2* (Right)*).*

Proof. Formal and detailed analysis of all steady states (5) is given in Appendix A. Here we just add that the vertical red line $N_f = K_0$ (that passes through $\left(N_f^{(2)}, N_w^{(2)}\right) = (K_0, 0)$ and $\left(N_f^{(4)}, N_w^{(4)}\right) = \left(K_0, K - \frac{r_{\mathbf{f}}}{r_{\mathbf{w}}} K_0\right)$, see Figure 1) separates two basins of attraction. Effectively, the area on the right-hand side from this line corresponds to the attraction basin of $\left(N_f^{(3)}, N_w^{(3)}\right) = (K, 0)$, while the attraction basin of $\left(N_f^{(5)}, N_w^{(5)}\right) = (0, K)$ lies on the left-hand side from the red line $N_f = K_0$. The initial conditions lying on this line, as well as those located on the axes are not of interest to our further analysis (however, they are discussed in Appendix A). □

In essence, Theorem 1 states that it is infeasible to replace wild mosquitoes with *Wolbachia*-carriers in infinite time unless the initial density of wild mosqui-

toes is below their minimum viable population size. The latter is hardly expected in practice since wild mosquitoes possess high degree of survivorship and have strong capacities for proliferation. Therefore, it is fair to suppose for practical purposes that the initial density of uninfected mosquitoes is somewhat close to their carrying capacity, that is, $N_f(0) \approx K$. Thus, no matter how many *Wolbachia*-carriers are release at $t = 0$, they all disappear from the system as $t \to \infty$ (see Figure 2 *(Left)*) if no successive releases are carried out. In the following section, we discuss this issue in more details.

3. Optimal Control Approach and Release Policies

In the previous section, it was clearly shown that a massive nonrecurrent release (also known as *inundative*) of even a huge number of *Wolbachia*-carriers into the target locality would do no good for the population replacement (see Figure 2 *(Left)*). Therefore, one should think of periodical (or so-called *inoculative*) releases. The latter can be done in two different ways, and we consider both of them in this section.

3.1. Constant Number of Mosquitoes to be Released

Let $\hat{u} > 0$ be a number of *Wolbachia*-carrying females that can be produced in laboratory conditions per unit time (daily, for example). Then at each day t, $\hat{u}$ *Wolbachia*-carriers should be released in the target locality. In mathematical terminology, the dynamical system (3) is now transformed into the new one, which accounts for daily constant releases of *Wolbachia*-infected females:

$$\frac{dN_f}{dt} = \left(r_f - \frac{r_f N_f}{K} - \frac{r_w N_w}{K}\right) N_f \left(\frac{N_f}{K_0} - 1\right) \tag{6a}$$

$$\frac{dN_w}{dt} = \left(r_w - \frac{r_f N_f}{K} - \frac{r_w N_w}{K}\right) N_w + \hat{u} \tag{6b}$$

with initial conditions

$$N_f(0) = \bar{K}, \qquad N_w(0) = 0 \tag{7}$$

where $\bar{K}$ stays close to K without exceeding it ($\bar{K} \leq K$). It is worthwhile to note that initial conditions (7) correspond to a real-life situation, so there is no practical sense to consider other setting for initial conditions.

Obviously, the positive constant input $\hat{u}$ in (6b) now impedes the extinction of *Wolbachia*-carriers from the system when $t \to \infty$. It is also clear that all

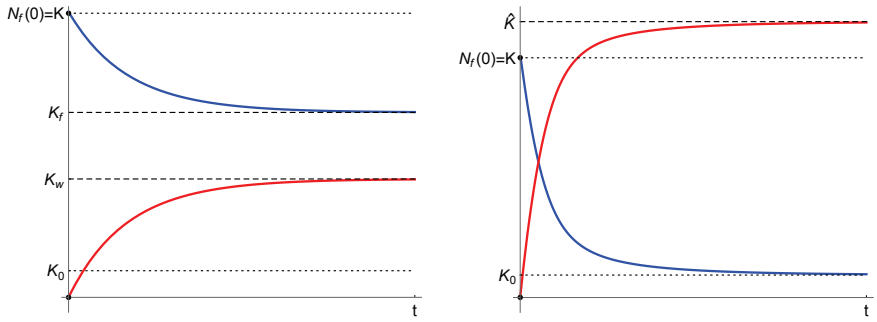

Figure 3: Trajectories of the system (6) reaching the steady states $\left(\hat{N}_{\mathsf{f}}^{(1)}, \hat{N}_{\mathsf{w}}^{(1)}\right) = (K_{\mathsf{f}}, K_{\mathsf{w}})$ *(Left)* and $\left(\hat{N}_{\mathsf{f}}^{(2)}, \hat{N}_{\mathsf{w}}^{(2)}\right) = (K_0, \hat{K})$ *(Right)* under limited and abundant daily releases $\hat{u}$, respectively. Here the blue curves correspond to the populations of uninfected mosquitoes $N_{\mathsf{f}}(t)$ while the red curves denote the populations of *Wolbachia*-carriers $N_{\mathsf{w}}(t)$.

equilibria of this new dynamical system should essentially depend on the value of $\hat{u}$. Effectively, the trajectories of the system (6) originated from the initial conditions (7) should reach one of the following steady states:

$$\left(\hat{N}_f^{(1)}, \hat{N}_w^{(1)}\right) = \left(K - \frac{r_w\,\hat{u}}{r_f(r_f - r_w)}, \frac{\hat{u}}{r_f - r_w}\right),$$

$$\left(\hat{N}_f^{(2)}, \hat{N}_w^{(2)}\right) = \left(K_0, \frac{1}{2}\left[K - \frac{r_f}{r_w}K_0 + \sqrt{\left(K - \frac{r_f}{r_w}K_0\right)^2 + \frac{4K}{r_w}\hat{u}}\right]\right)$$

From the above expressions, it is clearly seen that both steady states imply coexistence of uninfected mosquitoes and *Wolbachia*-carriers. For a (relatively) small value of $\hat{u}$, the point $\left(\hat{N}_f^{(1)}, \hat{N}_w^{(1)}\right)$ will be reachable when $t \to \infty$ (see Figure 3 *(Left)*, where K_f and K_w denote the components of this steady state). On the other hand, if $\hat{u}$ is (relatively) large, then the point $\left(\hat{N}_f^{(2)}, \hat{N}_w^{(2)}\right)$ will be reached (see Figure 3 *(Right)*, where $\hat{K}$ denotes the second component of this steady state).

In both cases, we see that $N_f(t)$ never drops below K_0. The latter implies that if constant release is suspended starting from some $0 < T < \infty$, the uninfected mosquitoes would gradually recover while the *Wolbachia*-carriers would be driven towards extinction. Therefore, neither scenario is suitable for applying in practice.

As an alternative, we propose another approach based on the optimal control modelling framework, which is presented in the next subsection.

3.2. Variable Number of Mosquitoes to be Released Daily

In order to formulate the problem of optimal control, we have to introduce the control variable $u(t) : [0,T] \mapsto [0,u_{\max}]$ that stands for the time-dependent number of *Wolbachia*-infected female mosquitoes to be released at the day t. Here $0 < T < \infty$ denotes the finite horizon of our control action. The purpose of control action is to find an optimal number $u^*(t) \in [0,u_{\max}]$ of *Wolbachia*-carriers to be release at each day $t \in [0,T]$ in order to satisfy the terminal endpoint condition

$$N_f(T) = K_0 - \varepsilon \tag{8}$$

while minimizing the objective functional

$$\min_{0 \le u(t) \le u_{\max}} \mathcal{J}(u) = \min_{0 \le u(t) \le u_{\max}} C\left[N_F(T) - (K_0 - \varepsilon)\right] + \frac{1}{2}\int_0^T u^2(t)dt \tag{9}$$

over the set of all possible solutions to the dynamical system

$$\frac{dN_f}{dt} = \left(r_f - \frac{r_f N_f}{K} - \frac{r_w N_w}{K}\right) N_f \left(\frac{N_f}{K_0} - 1\right) \tag{10a}$$

$$\frac{dN_w}{dt} = \left(r_w - \frac{r_f N_f}{K} - \frac{r_w N_w}{K}\right) N_w + u(t) \tag{10b}$$

with initial conditions

$$N_f(0) = \bar{K}, \qquad N_w(0) = 0 \tag{11}$$

The first summand in (9) (that is, terminal term of $\mathcal{J}(u)$) is included in order to facilitate the fulfilment of the end-point condition (8), while the second summand (that is, integral term of $\mathcal{J}(u)$) expresses the overall costs of cultivation of the *Wolbachia*-carriers in laboratory condition. Here we have supposed that production cost of one mosquito is normalized to unity. The role of $\varepsilon > 0$ in (8), (9) is to guarantees that, starting from $t = T$, the population of uninfected mosquitoes be lower than their minimum viable population size, that is, $N_f(t) < K_0$. When the terminal condition (8) is reached, the release policy can be safely suspended since population of uninfected mosquitoes $N_f(t)$ will gradually become extinct for $t > T$ and all wild mosquitoes will be ultimately replaced by those carrying *Wolbachia*.

Parameter	Value	References
Ψ_{f}	0.2151	[4, 5, 7, 23]
Ψ_{w}	0.2151	[4, 15]
δ_{f}	0.03	[4, 30, 32, 33]
δ_{w}	0.06	[4, 21]
K	320	[4]
$\bar{K}$	300	assumed
K_0	30	assumed
ε	1	assumed
C	10 000	assumed

Table 1: Parameter values assumed for numerical solution of the optimal control problem (8)–(11)

The optimal control problem (8)–(11) can only be solved numerically. For this purpose, we have employed the next-generation optimal control software package GPOPS-II[2] designed for MATLAB platform. Next section displays the results of our numerical computations.

4. Numerical Results and Discussion

Numerical solution of the optimal control problem formulated above requires to define the values of constant parameters which appear in (8)–(11) in accordance to scientific evidence gathered in this field. In particular, *wMelPop* strain of *Wolbachia* (which is considered the best one for control of arboviral infections [9, 22, 35]) has high fitness cost is rather difficult to establish in wild mosquito populations [14, 20, 25, 27]. Here we assume the challenge to solve the optimal control problem (8)–(11) with numerical value of *Wolbachia*-related parameters corresponding to *wMelPop* strain. Table 1 provides such values together with corresponding references.

It is worthwhile to note that mosquitoes' birth and death rates (Ψ_f, Ψ_w, δ_f, δ_w) are measured in day^{-1} while the carrying capacity K, the initial quantities $N_f(0), N_w(0)$, and the minimum viable population size K_0 are expressed in absolute numbers of individuals (for example, thousands of mosquitoes in accordance with [4]). The values of weight parameter C should be sufficiently large for the terminal term of the objective functional (9) to serve as a penalty

[2]See more details regarding GPOPS-II package at its official web-site: http://www.gpops2.com/

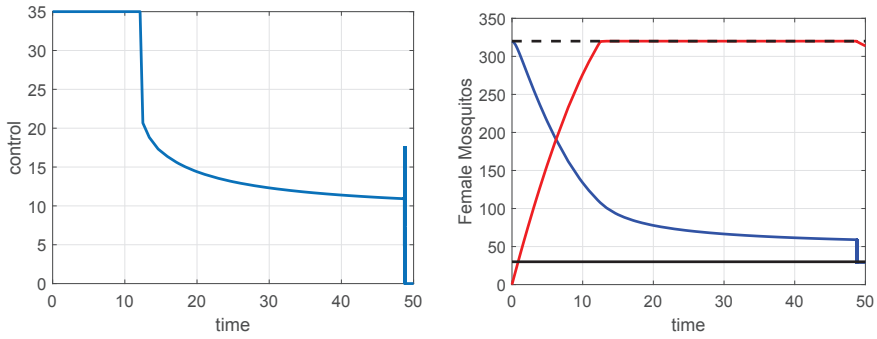

Figure 4: **Scenario A:** optimal release strategy $u^*(t)$ *(Left)* and the corresponding trajectories $\left(N_{\mathsf{f}}^*(t), N_{\mathsf{w}}^*(t)\right)$ of the system (10) *(Right)*. Here the blue curves correspond to the populations of uninfected mosquitoes $N_{\mathsf{f}}(t)$ while the red curves denote the populations of *Wolbachia*-carriers $N_{\mathsf{w}}(t)$.

for violation of the end-point condition (8).

It can be intuitively perceived that there is a certain tradeoff between the policy finite horizon T and the maximum capacity of daily releases $u_{\max}$. Effectively, when one of these quantities (or both of them) are too small, the problem of optimal control (8)–(11) becomes infeasible.

On the other hand, Figure 3 suggests that the maximum daily release capacity of *Wolbachia*-carriers, $u_{\max}$, should be sufficiently large in order to guarantee a fast proliferation of *Wolbachia*-infected mosquitoes. The latter may result in a (temporal) overpopulation of mosquitoes (see Figure 3 *(Right)*) than may not be tolerated by human population in a target locality. To avoid such situation, we impose an additional condition of $N_w(t) < K$ for all $t \in [0, T]$ for numerical solution of the optimal control problem (8)–(11)[3].

Taking into account the above arguments, we have decided to consider here two scenarios, namely:

Scenario A. Short-term policy for population replacement based on abundant daily releases: $T = 50$ days, $u_{\max} = 35$ thousands of *Wolbachia*-carriers per day.

Scenario B. Longer-term policy for population replacement based on moderate daily releases: $T = 140$ days, $u_{\max} = 20$ thousands of *Wolbachia*-carriers per day.

[3]The GPOPS-II software package allows to introduce this type of conditions.

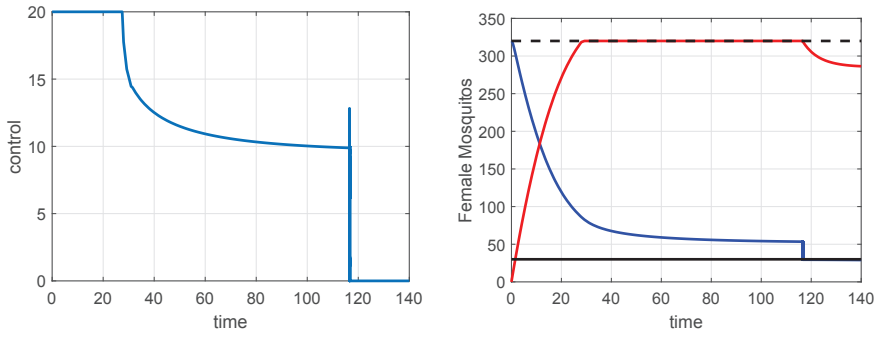

Figure 5: **Scenario B:** optimal release strategy $u^*(t)$ *(Left)* and the corresponding trajectories $\left(N_{\mathsf{f}}^*(t), N_{\mathsf{w}}^*(t)\right)$ of the system (10) *(Right)*. Here the blue curves correspond to the populations of uninfected mosquitoes $N_{\mathsf{f}}(t)$ while the red curves denote the populations of *Wolbachia*-carriers $N_{\mathsf{w}}(t)$.

The results of numerical solution for both scenarios are displayed by Figures 4 and 5, respectively. The optimal release strategies, $u^*(t)$, have a similar structure in both cases (see the left-hand sides of Figures 4 and 5).

Thus, in case of **Scenario A** it is optimal to release the maximum of $u_{\max} = 35$ thousands of *Wolbachia*-carriers per day during first 12 days of the policy implementation ($t \in [0, 12]$). At $t = 13$, the number of released mosquitoes is reduced to 20 thousands. Then, during the consequent 33 days (that is, from $t = 13$ to $t = 48$), the daily number of released *Wolbachia*-carriers should be gradually from 20 thousands to 11 thousands. Afterwards, at $t = 48$, a inundative release of $17,5$ thousands must be performed and from the day 49 all releases are suspended.

Under this strategy, the population of uninfected mosquitoes will drop, by the day $t = 13$, to about 30% of their initial quantity while the *Wolbachia*-carriers will reach the carrying capacity K. Then, during the following 33 days, the number of wild mosquitoes will steady decline towards K_0 with *Wolbachia*-infected ones staying at K. The inundative release at $t = 48$ should push the population of uninfected mosquitoes below K_0 in order to fulfill the end-point condition (8) at $t = T = 50$. Once we have that $N_f(t) < K_0$, the population of wild mosquitoes will be driven towards extinction.

The results of numerical solution for **Scenario B** have a similar interpretation, but this release policy requires for a longer time of implementation. Figure 5 shows that it is optimal to release the maximum of $u_{\max} = 20$ thousands of *Wolbachia*-carriers per day during first 27 days of the policy implementation ($t \in [0, 27]$). At $t = 28$, the number of released mosquitoes is reduced to $14,5$

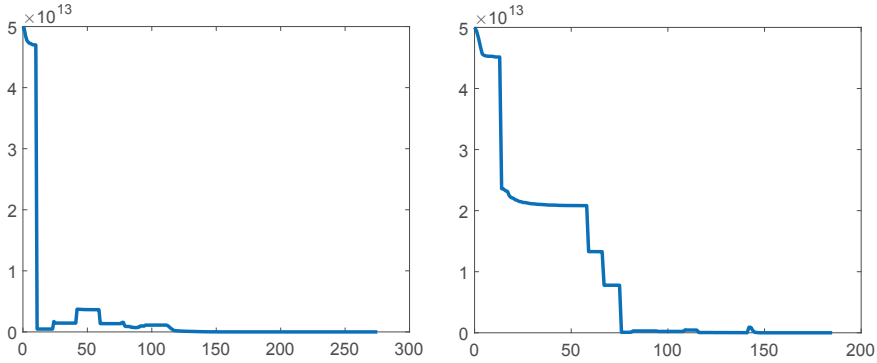

Figure 6: Value of the objective functional (9) for **Scenario A:** with 275 iterations *(Left)* and **Scenario B:** with 185 iterations *(Right)*.

thousands. Then, during the consequent 87 days (that is, from $t = 28$ to $t = 115$), the daily number of released *Wolbachia*-carriers should be gradually from $14,5$ thousands to 10 thousands. Afterwards, at $t = 115$, a inundative release of 14 thousands must be performed and from the day 117 all releases are suspended.

Under this strategy, the population of uninfected mosquitoes will be reduced, by the day $t = 29$ to about 30% of their initial quantity while the *Wolbachia*-carriers will reach the carrying capacity K. Then, during the following 87 days, the number of wild mosquitoes will steady decline towards K_0 with *Wolbachia*-infected ones staying at K. The inundative release at $t = 115$ should push the population of uninfected mosquitoes below K_0 in order to fulfill the end-point condition (8) at $t = T = 140$. Once we have that $N_f(t) < K_0$, the population of wild mosquitoes will be driven towards extinction.

Solution of the optimal control problem (8)–(11) with numerical accuracy of $\epsilon = 10^{-4}$ was found by GPOPS-II software in 275 and 185 for **Scenarios A** and **B**, respectively (see Figure 6). It worthwhile to note that, in both cases, the numerical algorithm implemented by GPOPS-II software package was capable of jumping out of several local minima and was able to continue the computation.

Additionally, we have estimated the overall quantity $M\left(u^*(t)\right)$ of *Wolbachia*-carrying females that must be cultivated in laboratory conditions to implement both scenarios:

$$M\left(u^*(t)\right) = \int_0^T u^*(t)dt = \begin{cases} 9.0617 \times 10^2 & \text{for} \quad \textbf{Scenario A} \\ 1.5384 \times 10^3 & \text{for} \quad \textbf{Scenario B} \end{cases}$$

The latter implies that **Scenario A** need less *Wolbachia*-carriers (and also less time!) than **Scenario B**. Therefore, **Scenario A** should be considered more cost-effective under the given setting of the model.

Effectively, we have no viable data regarding the maximum number of *Wolbachia*-carrying females which can be cultivated daily in laboratory conditions. However, one thing is very clear: this number should be sufficiently high. Thus, if we try to use $u_{\max} < 20$ under the current values of the model parameters given in Table 1, the optimal control problem (8)–(11) becomes infeasible even when the final time $T = 140$ was extended. Nonetheless, other trials performed with $u_{\max} \in (20, 35)$ and $T \in (50, 140)$ have resulted feasible, and their outcomes are similar to those obtained for **Scenarios A** and **B**. These trials have helped us to reveal an implicit relationship between $u_{\max}$ and T when other parameters of the model were kept unchanged. This relationship basically states that lower values of $u_{\max}$ require longer time T for policy implementation, which is rather logical and expected conclusion. The latter implies that our optimal control model proposed in this paper is in line with common sense.

5. Conclusions and Final Comments

In this paper, we have presented a competition model that describes the population dynamics of two interacting populations — wild (or *Wolbachia*-free) *Aedes aegypti* females and those carrying *Wolbachia*. This model accounts for so-called Allee effect which is exhibited by wild females at high frequencies of the *Wolbachia*-infected ones. It was shown that the coexistence of these two populations is unstable and should not be expected in practice. Additionally, it was demonstrated that the persistence of one or another population essentially depends on the initial population sizes of both populations.

Our principal goal was to propose a viable policy for replacing the wild population of *Aedes aegypti* females with *Wolbachia*-carriers by performing daily releases of *Wolbachia*-infected females in target locality. This policy should ultimately ensure the gradual extinction of uninfected mosquitoes after the releases are suspended.

The latter was done using the optimal control modelling framework and two viable release strategies were obtained: one that requires abundant releases but can be accomplished in a relative short period of time (50 days, **Scenario A**) and another that needs a moderate number of *Wolbachia*-carriers for daily releases but requires more time for implementation (140 days, **Scenario B**).

Both proposed strategies are feasible for implementation in practice and

possess a similar structure. However, the final choice should be done by a decision-maker in accordance with an actual daily capacity of the laboratory where *Wolbachia*-carriers are cultivated (i.e., parameter $u_{\max}$ in our optimal control model).

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Appendix A: Stability Analysis of the Dynamical System (3)

Five equilibria given by (5) are solutions of the nonlinear algebraic system

$$\begin{aligned} F_1(N_f, N_w) &= \left(r_f - \frac{r_f N_f}{K} - \frac{r_w N_w}{K}\right) N_f \left(\frac{N_f}{K_0} - 1\right) = 0, \\ F_2(N_f, N_w) &= \left(r_w - \frac{r_f N_f}{K} - \frac{r_w N_w}{K}\right) N_w = 0. \end{aligned}$$

Stability properties of these equilibria can be defined by the signs of eigenvalues of Jacobian matrix

$$\mathbb{J}(N_f, N_w) = \begin{pmatrix} \dfrac{\partial F_1}{\partial N_f} & \dfrac{\partial F_1}{\partial N_w} \\ \\ \dfrac{\partial F_2}{\partial N_f} & \dfrac{\partial F_2}{\partial N_w} \end{pmatrix} \tag{A-12}$$

evaluated at each equilibrium.

It is easy to verify that the components of $\mathbb{J}(N_f, N_w)$ are:

$$\begin{aligned} \frac{\partial F_1}{\partial N_f} &= -\frac{r_f}{K}\left(\frac{N_f}{K_0} - 1\right) N_f + \left(\frac{2N_f}{K_0} - 1\right)\left(r_f - \frac{r_f N_f + r_w N_w}{K}\right), \\ \frac{\partial F_1}{\partial N_w} &= -\frac{r_w}{K}\left(\frac{N_f}{K_0} - 1\right) N_f, \\ \frac{\partial F_2}{\partial N_f} &= -\frac{r_f}{K} N_w, \\ \frac{\partial F_2}{\partial N_w} &= r_w - \frac{r_f}{K} N_f - \frac{2r_w}{K} N_w. \end{aligned}$$

Let us denote by $\lambda_1^{(i)}, \lambda_2^{(i)}$ the eigenvalues of $\mathbb{J}^{(i)} = \left(N_f^{(i)}, N_w^{(i)}\right)$, that is, the Jacobian matrix (A-12) evaluated at the i-th equilibrium point for each $i = 1, 2, 3, 4, 5$. Now we proceed to revise the signs of these eigenvalues for each i.

1. At the first equilibrium point $\left(N_f^{(1)}, N_w^{(1)}\right) = (0, 0)$ we have that

$$\mathbb{J}^{(1)} = \mathbb{J}(0,0) = \begin{pmatrix} -r_f & 0 \\ 0 & r_w \end{pmatrix}$$

with

$$\lambda_1^{(1)} = -r_f < 0 \quad \text{and} \quad \lambda_2^{(1)} = r_w > 0.$$

Therefore, $\left(N_f^{(1)}, N_w^{(1)}\right) = (0, 0)$ is an unstable equilibrium (saddle point). It is worthwhile to note that $(0, 0)$ can be reached from the initial conditions $N_f(0) < K_0, N_w(0) = 0$ (i.e., in absence of *Wolbachia*-infected mosquitoes and supposing very low initial densities of wild mosquitoes), which is highly unlikely.

2. At the second equilibrium point $\left(N_f^{(2)}, N_w^{(2)}\right) = (K_0, 0)$ we have that

$$\mathbb{J}^{(2)} = \mathbb{J}(K_0, 0) = \begin{pmatrix} \dfrac{(K - K_0)r_f}{K} & 0 \\ 0 & r_w - \dfrac{K_0 r_f}{K} \end{pmatrix}$$

with

$$\lambda_1^{(2)} = \frac{(K - K_0)}{K} r_f > 0 \quad \text{and} \quad \lambda_2^{(2)} = r_w - \frac{K_0 r_f}{K}.$$

Here the sign of $\lambda_2^{(2)}$ is undefined. However, the positiveness of $\lambda_1^{(2)}$ clearly indicates that $\left(N_f^{(2)}, N_w^{(2)}\right) = (K_0, 0)$ is an unstable equilibrium (saddle point if $\lambda_2^{(2)} < 0$ or nodal repeller if $\lambda_2^{(2)} > 0$). In practical terms, one can expect that $\lambda_2^{(2)} > 0$ since $K \gg K_0$ while r_f slightly exceeds r_w. Therefore, this steady state can be reached only when $N_f(0) = K_0, N_w(0) = 0$ which is not of interest to our analysis.

3. At the third equilibrium point $\left(N_f^{(3)}, N_w^{(3)}\right) = (K, 0)$ we have that

$$\mathbb{J}^{(3)} = \mathbb{J}(K, 0) = \begin{pmatrix} -\dfrac{(K - K_0)}{K_0} r_f & -\dfrac{(K - K_0)}{K_0} r_w \\ 0 & -r_f + r_w \end{pmatrix}$$

with

$$\lambda_1^{(3)} = -\frac{(K-K_0)}{K_0} r_f < 0 \quad \text{and} \quad \lambda_2^{(3)} = -r_f + r_w < 0.$$

Therefore, $\left(N_f^{(3)}, N_w^{(3)}\right) = (K, 0)$ is a locally asymptotically stable equilibrium (nodal attractor).

4. At the fourth equilibrium point $\left(N_f^{(4)}, N_w^{(4)}\right) = \left(K_0, K - \frac{r_f}{r_w} K_0\right)$ we have that

$$\mathbb{J}^{(4)} = \mathbb{J}\left(K_0, K - \frac{r_f}{r_w} K_0\right) = \begin{pmatrix} r_f - r_w & 0 \\ r_f \left(\frac{r_f K_0}{r_w K} - 1\right) & \frac{r_f K_0}{K} - r_w \end{pmatrix}$$

with

$$\lambda_1^{(4)} = r_f - r_w > 0 \quad \text{and} \quad \lambda_2^{(4)} = \frac{r_f K_0}{K} - r_w.$$

Here the sign of $\lambda_2^{(4)}$ is undefined. However, the positiveness of $\lambda_1^{(4)}$ clearly indicates that $\left(N_f^{(4)}, N_w^{(4)}\right) = \left(K_0, K - \frac{r_f}{r_w} K_0\right)$ is an unstable equilibrium (saddle point if $\lambda_2^{(4)} < 0$ or nodal repeller if $\lambda_2^{(4)} > 0$). In practical terms, one can expect that $\lambda_2^{(4)} < 0$ since $K \gg K_0$. Therefore, this steady state can be reached only when $N_f(0) = K_0$ while $N_w(0)$ takes any positive value. However, there no reasonable grounds to expect that wild mosquitoes be exactly at their minimum viable population size at $t = 0$.

5. At the fifth equilibrium point $\left(N_f^{(5)}, N_w^{(5)}\right) = (0, K)$ we have that

$$\mathbb{J}^{(5)} = \mathbb{J}(0, K) = \begin{pmatrix} r_w - r_f & 0 \\ -r_f & -r_w \end{pmatrix}$$

with

$$\lambda_1^{(5)} = r_w - r_f < 0 \quad \text{and} \quad \lambda_2^{(5)} = -r_w < 0.$$

Therefore, $\left(N_f^{(5)}, N_w^{(5)}\right) = (0, K)$ is a locally asymptotically stable equilibrium (nodal attractor).