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A sex-structured model of *Wolbachia* invasion to design sex-biased release strategies in *Aedes spp* mosquito populations

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Abstract

Laboratory experiments as well as some field essays have revealed that the intracellular bacterium *Wolbachia*, deliberately introduced in *Aedes spp* female mosquitoes, drastically reduces their vector competence for dengue virus and other pathogens. However, female mosquitoes infected with *Wolbachia* still need to ingest human blood while male mosquitoes, either wild or *Wolbachia*-carrying, do not bite people. Moreover, *Wolbachia*-carrying females may transmit the virus to people during blood-feeding, even though with a far less probability than the wild ones. Therefore, massive releases of *Wolbachia*-carrying females may increase both the nuisance and the epidemiological risk among human residents. In this paper, we propose a sex-structured model of *Wolbachia* invasion that brings forward the possibility of developing male-biased release strategies of *Wolbachia*-carriers leading to *Wolbachia* invasion. Thanks to this model, we study the minimal amount of mosquitoes necessary to complete this task, according to the relative sex-ratio of the released mosquitoes and to the release schedule. We also pay attention to the estimate of the time needed to achieve the ultimate population replacement.

Keywords: *Wolbachia* symbiont, sex-structured model, population replacement, *Aedes spp*, male-biased releases.

1 Introduction

Vector-borne diseases are an important threat around the world. Among them, dengue fever is the most challenging one in places where its principal transmitter, *Aedes aegypti*, is abundant. Indeed, *Aedes* females need blood-feeding by human blood (preferably) to mature their eggs before deposit. During these blood meals, the dengue virus may be passed from an infected female to a susceptible human

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host, or from an infected human to a susceptible female vector, giving rise to transmission cycle. For that reason, vector control has become an essential issue in many countries where dengue is endemic or circulating, and even in countries where *Aedes spp*, like *Aedes albopictus* and *Aedes polynesiensis* are either established (like in Southern Europe and South Pacific, respectively), or invading new places. Note also that *Aedes albopictus* is primary vector of Chikungunya, while *Aedes polynesiensis* is the primary vector of Lymphatic filariasis. In addition, through travels, human mobility has increased the risk of vector-borne diseases outside endemic areas.

In the 1950-th and later, the primary tool to control adult mosquitoes was adulticide. We know now that this was a huge mistake, as mosquitoes became more and more resistant, leading to an arms race between mosquitoes and chemical companies. At such a point, only very few insecticides are now authorized (only deltamethrin in France, for instance), if they have not become somehow ineffective in some places. Moreover, the use of adulticides is very detrimental to biodiversity, as they are not species-specific, and this is a crucial issue in biodiversity hotspots.

Then, larvicides have been developed to target mosquitoes at the larvae stages in breeding sites. However, while very efficient in laboratory conditions, their impact in the field can be very limited, because many breeding sites are not accessible. As larvicide, *Bacillus thuringiensis israelensis*, also called *Bti*, is the most well-known. However, this biological pesticide has recently raised concerns regarding its safety for crops, aquatic ecosystems, and other possible adverse side-effects [10].

In front of these drawbacks, people suggested species-specific, autocidal control methods, like the Sterile Insect Technique (SIT). This is an old biological control technique newly used against several agricultural pests and also against some mosquito species, including *Aedes spp*. It relies on mass releases of males sterilized by ionizing radiation, which will mate with wild females and transfer them their sterile sperm, resulting in a progressive decay of the targeted population. It is also possible to sterilize mosquito males using *Wolbachia* bacteria [23]. However, whatever the sterilization technique, SIT, while conceptually very simple, is complex to conduct in the field and at an industrial scale. The main objective, in general, is a drastic decrease in the population size or elimination. While in some places, elimination can be helpful, in other sites, the drastic reduction of the targeted mosquito population may favor the settlement of other mosquito species that can be more detrimental than the initial population. Whence the interest of replacing the wild mosquito population with a new population bearing a reduced vectorial capacity. Biologists have shown that such an operation is possible.

Indeed, laboratory experiments have revealed that the intracellular bacterium *Wolbachia*, deliberately introduced in *A. aegypti*, *A. albopictus* or *A. polynesiensis* female mosquitoes, drastically reduces the vector competence of the mosquito for dengue virus and other pathogens. In particular, focusing on

dengue, *Wolbachia* decreases the virulence of the dengue infection by increasing the incubation period or blocking the virus [4, 19, 25, 6, 9, 5]. *Wolbachia* is only transmitted maternally from a female to her offspring. Cytoplasmic incompatibility (CI) occurs when a female uninfected by *Wolbachia* is inseminated by an infected male, a mating that leads to inviable eggs. This grants a reproduction advantage to infected females against uninfected ones, facilitating the *Wolbachia* spread: see Table 1, page 5.

Several models have been developed and analyzed to study release strategies to ensure population replacement, thanks to different *Wolbachia* strains: see for instance [1, 2, 3, 7, 11, 12, 13, 16, 21, 24, 26, 27]. In the present paper, we provide a sex-structured model allowing us to study and size in detail the release process, enabling in particular to assess different male/female compositions all capable of achieving successful infection by *Wolbachia*.

The paper is organized as follows. In Section 2, we build a sex-structured model describing the dynamics of wild and *Wolbachia*-carrying mosquitoes and provide some general analysis results. Then, in Section 3, we study the existence of steady states for the model according to some threshold parameters. The stability/instability properties of these steady states are studied in Section 4. Finally, in Section 5, we provide numerical simulations to study some release scenarios and discuss the results. We focus especially on the minimal amount of mosquitoes necessary to achieve replacement, according to the relative sex-ratio of the released mosquitoes and to the schedule of the releases, and on estimating the time needed to achieve the population replacement. Concluding remarks are given in Section 6.

2 Formulation of the model

In 2019, Bliman *et al.* [8] have proposed a simple sex-structured model that describes the population dynamics of wild adult mosquitoes. This model relies on the following basic assumptions:

- (i) All females are equally able to mate.
- (ii) After only one mating, a female remains fertile all her life.

Let $M_n(t)$ and $F_n(t)$ denote the densities of wild male and female mosquitoes at each day $t \geq 0$. Using these variables, the mathematical formulation of the bidimensional model proposed in [8] is the following:

$$\begin{cases} \frac{dM_n}{dt} = r_n \rho_n F_n e^{-\sigma(M_n+F_n)} - \mu_n M_n, & (1a) \\ \frac{dF_n}{dt} = (1 - r_n) \rho_n F_n e^{-\sigma(M_n+F_n)} - \delta_n F_n, & (1b) \end{cases}$$

where $r_n \in (0, 1)$ denotes the primary sex ratio, $\rho_n > 0$ expresses the mean number of eggs produced by a single wild female on average per day, and $\mu_n, \delta_n > 0$ represent the natural mortality rates of wild

male and female insects, respectively. The exponential term in (1) models the direct and/or indirect competition effect at different stages (larvae, pupae, adults), through the parameter $\sigma > 0$. In this context, the smaller values of σ imply that a larger fraction of eggs may survive to adulthood, and its larger values express the stronger competition and/or the presence of fewer breeding sites, so that σ plays the role of a carrying capacity parameter.

Let us now suppose that, besides the population of wild mosquitoes $P_n(t) := M_n(t) + F_n(t)$, another population $P_w(t) := M_w(t) + F_w(t)$ of mosquitoes transinfected with *Wolbachia* symbiotic bacterium is present in the same locality. Notably, $M_w(t)$ and $F_w(t)$ define the numbers (or densities) at each day $t \geq 0$ of *Wolbachia*-carrying male and female insects, respectively.

To model the reproduction and interaction of both mosquito populations, it is worthwhile to recall [14, 22] that under favorable climatic conditions

- *Wolbachia* symbiotic bacterium is maternally inherited, i.e., it is transmitted from the *Wolbachia*-carrying female to all her offsprings;
- the presence of *Wolbachia* in the mosquito cells induces a particular reproductive phenotype of *cytoplasmic incompatibility* (CI¹)

Basing on these two distinctive features illustrated in Table 1, we now proceed to formulate a four-dimensional sex-structured model that describes the population dynamics of wild and *Wolbachia*-carrying mosquitoes:

$$\left\{ \begin{array}{l} \frac{dM_n}{dt} = r_n \rho_n \frac{F_n M_n}{M_n + \gamma M_w} e^{-\sigma(M_n + F_n + M_w + F_w)} - \mu_n M_n, \\ \frac{dF_n}{dt} = (1 - r_n) \rho_n \frac{F_n M_n}{M_n + \gamma M_w} e^{-\sigma(M_n + F_n + M_w + F_w)} - \delta_n F_n, \\ \frac{dM_w}{dt} = r_w \rho_w F_w e^{-\sigma(M_n + F_n + M_w + F_w)} - \mu_w M_w \\ \frac{dF_w}{dt} = (1 - r_w) \rho_w F_w e^{-\sigma(M_n + F_n + M_w + F_w)} - \delta_w F_w. \end{array} \right. \quad \begin{array}{l} (2a) \\ (2b) \\ (2c) \\ (2d) \end{array}$$

In the above formulation, the parameters bearing the subscript ‘w’ refer to the *Wolbachia*-carrying population and their meanings are similar to the parameters bearing the subscript ‘n’ that are included in the original bidimensional system (1), which corresponds to non-infected mosquitoes. In Eqs. (2a)-(2b), the positive parameter $\gamma \leq 1$ denotes the mating competitiveness of *Wolbachia*-carrying male mosquitoes that can be altered by some *Wolbachia* strains. Furthermore, the recruitment terms in (2a)-(2b) include only the successful matings of wild females F_n (i.e., those leading to production of the viable offspring), which occur with a probability $\frac{M_n}{M_n + \gamma M_w}$.

¹The CI phenotype ensures the absence of viable offspring originated from matings between uninfected females and *Wolbachia*-

Table 1: Illustration of the maternal transmission and the CI reproductive phenotype induced by *Wolbachia*.

		Mosquito offspring	
Adults		<i>Wolbachia</i> -infected ♀	Uninfected ♀
<i>Wolbachia</i> -infected ♂		Infected	Inviabile eggs
Uninfected ♂		Infected	Uninfected

Remark 1. *It is worthwhile to point out that the dynamical system (2) bears some resemblance with the sex-structured model introduced by Campo-Duarte et al. [12]. However, there is a principal difference laying in the definition of the recruitment terms or “birth functions”. Namely, the recruitment terms in (2) agree with the Ricker-type model studied in [8], whereas the recruitment terms employed in [12] stem from the harmonic-type “birth functions” that have been originally introduced in [18] for discrete-time models.*

System (2) can be written in the vector form as

$$\frac{d\mathbf{X}}{dt} = \mathbf{f}(\mathbf{X}), \quad \mathbf{X} := (M_n, F_n, M_w, F_w),$$

where the vector field $\mathbf{f} := (f_1(\mathbf{X}), f_2(\mathbf{X}), f_3(\mathbf{X}), f_4(\mathbf{X}))$ represents the right-hand side of the ODE system (2) and can be easily deduced.

Also, let us denote by $\mathbf{X}(t; \mathbf{X}_0)$ the solution of (2) engendered by the initial condition

$$\mathbf{X}_0 := (M_n(0), F_n(0), M_w(0), F_w(0)).$$

If the initial condition $\mathbf{X}_0 \in \mathbb{R}_+^4$ then it is easy to see that $\mathbf{X}(t; \mathbf{X}_0) \in \mathbb{R}_+^4$ for all $t \geq 0$. In effect, since

$$\left. \frac{dM_n}{dt} \right|_{M_n=0} = 0, \quad \left. \frac{dF_n}{dt} \right|_{F_n=0} = 0, \quad \left. \frac{dM_w}{dt} \right|_{M_w=0} \geq 0, \quad \left. \frac{dF_w}{dt} \right|_{F_w=0} = 0,$$

the positive invariance of \mathbb{R}_+^4 becomes obvious and it holds that $\mathbf{X}(t; \mathbf{X}_0) \geq \mathbf{0}$ for all $t \geq 0$ whenever $\mathbf{X}_0 \in \mathbb{R}_+^4$.

Moreover, we have the following result related to the uniform ultimate bound of all solutions to the system (2), expressed in terms of the norm $\|\mathbf{X}\|_1 := M_n + F_n + M_w + F_w$ in \mathbb{R}_+^4 .

Proposition 1. *The set*

$$\Omega := \left\{ \mathbf{X} = (M_n, F_n, M_w, F_w) \in \mathbb{R}_+^4 : \|\mathbf{X}\|_1 \leq \hat{P} \right\}, \quad \hat{P} := \frac{1}{\sigma} \ln \left(\frac{\max\{\rho_n, \rho_w\}}{\min\{\mu_n, \delta_n, \mu_w, \delta_w\}} \right) \quad (3)$$

is an attracting set. In other words, for any initial condition $\mathbf{X}_0 \in \mathbb{R}_+^4$,

$$\lim_{t \rightarrow +\infty} \text{dist}(\mathbf{X}(t; \mathbf{X}_0), \Omega) = 0, \quad \text{that is} \quad \limsup_{t \rightarrow +\infty} \|\mathbf{X}(t; \mathbf{X}_0)\|_1 \leq \hat{P}. \quad (4)$$

carrying males.

Proof. First, we note that along the trajectories of (2) it holds that

$$\begin{aligned} \frac{d\|\mathbf{X}\|_1}{dt} &\leq (\rho_n F_n + \rho_w F_w) e^{-\sigma\|\mathbf{X}\|_1} - \min\{\mu_n, \delta_n, \mu_w, \delta_w\} \|\mathbf{X}\|_1 \\ &\leq \left(\max\{\rho_n, \rho_w\} e^{-\sigma\|\mathbf{X}\|_1} - \min\{\mu_n, \delta_n, \mu_w, \delta_w\} \right) \|\mathbf{X}\|_1. \end{aligned}$$

For any trajectory and any $t \geq 0$, one thus has $\|\mathbf{X}(t; \mathbf{X}_0)\|_1 \leq x(t)$, where x is the solution of the comparison system

$$\frac{dx}{dt} = \max\{\rho_n, \rho_w\} \left(e^{-\sigma x} - e^{-\sigma \hat{P}} \right) x, \quad x(0) = \|\mathbf{X}_0\|_1.$$

As the latter converges towards \hat{P} except if $\|\mathbf{X}_0\|_1 = 0$, one deduces (4). \blacksquare

For subsequent use, let us define the four following quantities:

$$Q_n^M := \frac{r_n \rho_n}{\mu_n}, \quad Q_n^F := \frac{(1-r_n) \rho_n}{\delta_n}, \quad Q_w^M := \frac{r_w \rho_w}{\mu_w}, \quad Q_w^F := \frac{(1-r_w) \rho_w}{\delta_w}. \quad (5)$$

These positive constants represent the *basic offspring numbers* related to the four sub-populations of mosquitoes. It is worthwhile to recall that the basic offspring number expresses an average number of descendants produced by one individual during his/her lifespan in the absence of intraspecific competition. Thus, Q_n^M (resp. Q_n^F) denotes the average number of wild male (resp. female) descendants produced by one wild male (resp. female) mosquito during his (resp. her) lifespan. The definitions of Q_w^M and Q_w^F are interpreted likewise for the *Wolbachia*-carrying sub-population of male and female insects.

3 Existence of equilibrium points

The equilibrium points of (2) are nonnegative solutions of the following system of algebraic equations:

$$\begin{cases} 0 = r_n \rho_n \frac{F_n M_n}{M_n + \gamma M_w} e^{-\sigma(M_n + F_n + M_w + F_w)} - \mu_n M_n, & (6a) \end{cases}$$

$$\begin{cases} 0 = (1-r_n) \rho_n \frac{F_n M_n}{M_n + \gamma M_w} e^{-\sigma(M_n + F_n + M_w + F_w)} - \delta_n F_n, & (6b) \end{cases}$$

$$\begin{cases} 0 = r_w \rho_w F_w e^{-\sigma(M_n + F_n + M_w + F_w)} - \mu_w M_w, & (6c) \end{cases}$$

$$\begin{cases} 0 = (1-r_w) \rho_w F_w e^{-\sigma(M_n + F_n + M_w + F_w)} - \delta_w F_w. & (6d) \end{cases}$$

The existence of nonnegative solutions of (6) is closely related with the values of basic offspring numbers introduced by (5), and their coordinates can be expressed in terms of Q_n^M, Q_n^F, Q_w^M , and Q_w^F . The latter is summarized by the following result.

Theorem 1. *The dynamical system (2) admits exactly the following nonnegative equilibria:*

- *The trivial equilibrium point $\mathbf{E}_0 := (0, 0, 0, 0)$ that exists regardless of the values of Q_n^M, Q_n^F, Q_w^M , and Q_w^F .*

- A fully non-infected equilibrium point $\mathbf{E}_n := (M_n^\#, F_n^\#, 0, 0)$ that exists if and only if $Q_n^F > 1$, and its positive coordinates are

$$M_n^\# = \frac{Q_n^M}{Q_n^M + Q_n^F} \frac{1}{\sigma} \ln Q_n^F, \quad F_n^\# = \frac{Q_n^F}{Q_n^M + Q_n^F} \frac{1}{\sigma} \ln Q_n^F. \quad (7)$$

- A fully infected equilibrium point $\mathbf{E}_w := (0, 0, M_w^\#, F_w^\#)$ that exists if and only if $Q_w^F > 1$, and its positive coordinates are

$$M_w^\# = \frac{Q_w^M}{Q_w^M + Q_w^F} \frac{1}{\sigma} \ln Q_w^F, \quad F_w^\# = \frac{Q_w^F}{Q_w^M + Q_w^F} \frac{1}{\sigma} \ln Q_w^F. \quad (8)$$

- A strictly positive coexistence equilibrium point $\mathbf{E}_c := (M_n^c, F_n^c, M_w^c, F_w^c)$ that exists if and only if $Q_n^F > Q_w^F > 1$ and its coordinates can be expressed as

$$M_n^c = \frac{\gamma}{\sigma \Delta_c} Q_n^M Q_w^M Q_w^F \ln Q_w^F, \quad (9a)$$

$$F_n^c = \frac{\gamma}{\sigma \Delta_c} Q_n^F Q_w^M Q_w^F \ln Q_w^F, \quad (9b)$$

$$M_w^c = \frac{1}{\sigma \Delta_c} Q_n^M Q_w^M (Q_n^F - Q_w^F) \ln Q_w^F, \quad (9c)$$

$$F_w^c = \frac{1}{\sigma \Delta_c} Q_n^M Q_w^F (Q_n^F - Q_w^F) \ln Q_w^F, \quad (9d)$$

where

$$\Delta_c := Q_n^M (Q_n^F - Q_w^F) (Q_w^M + Q_w^F) + \gamma Q_w^M Q_w^F (Q_n^M + Q_n^F). \quad (10)$$

In general terms, Theorem 1 states that system (2) may admit one, two, three or four equilibria depending on the underlying positive values of Q_n^F and Q_w^F . Figure 1 resumes the results of Theorem 1 by displaying five regions (I–V) in the positive quadrant of the (Q_n^F, Q_w^F) -plane that admit one, two, three or four nonnegative equilibria. Namely, when $Q_n^F \leq 1$ and $Q_w^F \leq 1$, only the trivial equilibrium \mathbf{E}_0 exists (see Region I in Figure 1). Two nonnegative equilibria \mathbf{E}_0 and \mathbf{E}_n (resp. \mathbf{E}_0 and \mathbf{E}_w) exist when $Q_n^F > 1 \geq Q_w^F$ (resp. $Q_n^F \leq 1 < Q_w^F$) that corresponds to the Region II (resp. Region III). When $1 < Q_n^F \leq Q_w^F$ (Region IV), three nonnegative equilibria \mathbf{E}_0 , \mathbf{E}_n , and \mathbf{E}_w exist, while $1 < Q_w^F < Q_n^F$ (Region V) ensures existence of four nonnegative equilibria \mathbf{E}_0 , \mathbf{E}_n , \mathbf{E}_w , and \mathbf{E}_c .

Proof. (Theorem 1). Clearly, the trivial equilibrium $\mathbf{E}_0 \in \Omega$ is a solution of the algebraic system (6), and it exists for any positive values of Q_n^M , Q_n^F , Q_w^M , and Q_w^F . This equilibrium corresponds to the extinction of all sub-populations of mosquitoes. Notice that for any solution (M_n, F_n, M_w, F_w) of the system (6), it holds that

$$M_n = 0 \Leftrightarrow F_n = 0 \quad \text{and} \quad M_w = 0 \Leftrightarrow F_w = 0.$$

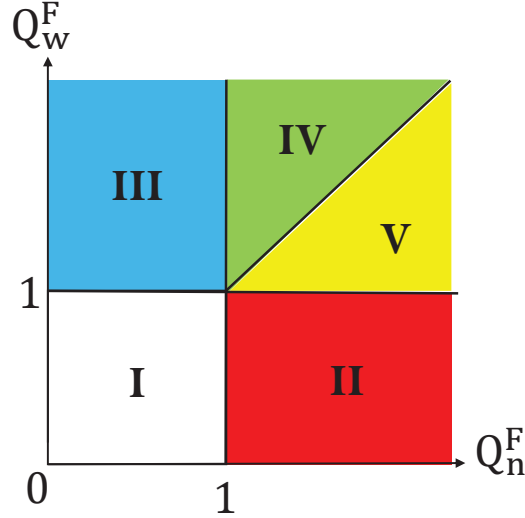


Figure 1: Existence of nonnegative equilibria of the system (2): only the trivial equilibrium E_0 exists in the Region I (uncolored), two equilibria (E_0 and either E_n or E_w) exist in the Regions II and III, respectively (red- and blue-colored), three equilibria E_0, E_n , and E_w exist in the Region IV (green-colored), and four equilibria E_0, E_n, E_w , and E_c exist in the Region V (yellow-colored).

In the absence of *Wolbachia*-infected sub-populations ($M_w = F_w = 0$), the positive coordinates $M_n^\#, F_n^\#$ of the fully non-infected equilibrium E_n are solutions of the bidimensional sub-system

$$\begin{cases} 0 = r_n \rho_n F_n^\# e^{-\sigma(M_n^\# + F_n^\#)} - \mu_n M_n^\#, & (11a) \\ 0 = (1 - r_n) \rho_n F_n^\# e^{-\sigma(M_n^\# + F_n^\#)} - \delta_n F_n^\#. & (11b) \end{cases}$$

From (11b), we get

$$\frac{\delta_n}{(1 - r_n) \rho_n} = e^{-\sigma(M_n^\# + F_n^\#)} < 1$$

which requires

$$Q_n^F = \frac{(1 - r_n) \rho_n}{\delta_n} > 1 \quad (12)$$

for obtaining a feasible (positive) solution that fulfills

$$M_n^\# + F_n^\# = \frac{1}{\sigma} \ln Q_n^F. \quad (13)$$

From (11a), we then deduce

$$\frac{F_n^\#}{M_n^\#} = \frac{\mu_n}{r_n \rho_n} e^{\sigma(M_n^\# + F_n^\#)} = \frac{Q_n^F}{Q_n^M}. \quad (14)$$

Finally, from the relationships (13) and (14), we have

$$\begin{pmatrix} 1 & 1 \\ -Q_n^F & Q_n^M \end{pmatrix} \begin{pmatrix} M_n^\# \\ F_n^\# \end{pmatrix} = \begin{pmatrix} \frac{1}{\sigma} \ln Q_n^F \\ 0 \end{pmatrix} \quad (15)$$

meaning that $M_n^\#, F_n^\#$ are in one-to-one correspondence with the solutions of (15). Moreover,

$$\Delta_n := \det \begin{vmatrix} 1 & 1 \\ -Q_n^F & Q_n^M \end{vmatrix} = Q_n^M + Q_n^F \neq 0.$$

Therefore, when (12) holds, linear system (15) has a unique solution (7) that can be obtained directly by Cramer's rule.

Similarly, in the absence of non-infected sub-populations ($M_n = F_n = 0$), the positive coordinates M_w^\sharp, F_w^\sharp of the fully infected equilibrium \mathbf{E}_w are solutions of the bidimensional sub-system

$$\begin{cases} 0 = r_w \rho_w F_w^\sharp e^{-\sigma(M_w^\sharp + F_w^\sharp)} - \mu_w M_w^\sharp, & (16a) \\ 0 = (1 - r_w) \rho_w F_w^\sharp e^{-\sigma(M_w^\sharp + F_w^\sharp)} - \delta_w F_w^\sharp. & (16b) \end{cases}$$

This system is formally identical to (11), and its unique positive solution (M_w^\sharp, F_w^\sharp) renders the explicit expressions (8) for M_w^\sharp and F_w^\sharp under the condition

$$Q_w^F = \frac{(1 - r_w) \rho_w}{\delta_w} > 1. \quad (17)$$

Let us now establish the conditions for existence of the strictly positive equilibrium $\mathbf{E}_c = (M_n^c, F_n^c, M_w^c, F_w^c)$.

From (6d), we have

$$\frac{1}{Q_w^F} = \frac{\delta_w}{(1 - r_w) \rho_w} = e^{-\sigma(M_n^c + F_n^c + M_w^c + F_w^c)} < 1, \quad (18)$$

which requires (17) to be fulfilled together with

$$M_n^c + F_n^c + M_w^c + F_w^c = \frac{1}{\sigma} \ln Q_w^F. \quad (19)$$

Also, from (6c) we have

$$\frac{F_w^c}{M_w^c} = \frac{\mu_w}{r_w \rho_w} e^{\sigma(M_n^c + F_n^c + M_w^c + F_w^c)} = \frac{Q_w^F}{Q_w^M}. \quad (20)$$

and from (6b) we get

$$\frac{1}{1 + \gamma \frac{M_w^c}{M_n^c}} = \frac{\delta_n}{(1 - r_n) \rho_n} e^{\sigma(M_n^c + F_n^c + M_w^c + F_w^c)} = \frac{Q_w^F}{Q_n^F} \Rightarrow \frac{Q_n^F}{Q_w^F} = 1 + \gamma \frac{M_w^c}{M_n^c}, \quad (21)$$

so we obtain then

$$M_n^c + \gamma M_w^c = \frac{Q_n^F}{Q_w^F} M_n^c \quad \text{and} \quad M_w^c = \frac{Q_n^F - Q_w^F}{\gamma Q_w^F} M_n^c. \quad (22)$$

Thus, because of (17), the existence of a strictly positive equilibrium requires to impose the condition

$$Q_n^F > Q_w^F > 1. \quad (23)$$

Under this condition and using (21), one gets from (6a) that

$$\frac{F_n^c}{M_n^c} = \frac{\mu_n}{r_n \rho_n} e^{\sigma(M_n^c + F_n^c + M_w^c + F_w^c)} \left(1 + \gamma \frac{M_w^c}{M_n^c} \right) = \frac{Q_w^F}{Q_n^M} \frac{Q_n^F}{Q_w^F} = \frac{Q_n^F}{Q_n^M}. \quad (24)$$

Finally, from equations (19), (20), (22), and (24), we have

$$\begin{pmatrix} 1 & 1 & 1 & 1 \\ 0 & 0 & Q_w^F & -Q_w^M \\ Q_n^F - Q_w^F & 0 & -\gamma Q_w^F & 0 \\ Q_n^F & -Q_n^M & 0 & 0 \end{pmatrix} \begin{pmatrix} M_n^c \\ F_n^c \\ M_w^c \\ F_w^c \end{pmatrix} = \begin{pmatrix} \frac{1}{\sigma} \ln Q_w^F \\ 0 \\ 0 \\ 0 \end{pmatrix}. \quad (25)$$

Thus, the coordinates $M_n^c, F_n^c, M_w^c,$ and F_w^c of \mathbf{E}_c are in one-to-one correspondence with the positive solutions of linear system (25). Furthermore, the determinant of this linear system (25) is exactly Δ_c given by (10), that is,

$$\begin{aligned} \Delta_c &:= \begin{vmatrix} 1 & 1 & 1 & 1 \\ 0 & 0 & Q_w^F & -Q_w^M \\ Q_n^F - Q_w & 0 & -\gamma Q_w^F & 0 \\ Q_n^F & -Q_n^M & 0 & 0 \end{vmatrix} \\ &= Q_n^M (Q_F - Q_{F,w}) (Q_{M,w} + Q_{F,w}) + \gamma Q_{M,w} Q_{F,w} (Q_M + Q_F), \end{aligned}$$

and it is strictly positive under the condition (23). Therefore, linear system (25) has a unique solution $(M_n^c, F_n^c, M_w^c, F_w^c)$ that matches (9) and can be obtained by direct application of Cramer's rule. ■

Remark 2. *It can be verified that every possible equilibrium point pertains to the absorbing set Ω , defined in (3), together with the positive constant \hat{P} . Clearly, $\|\mathbf{E}_0\| = 0$ meaning that $\mathbf{E}_0 \in \Omega$. For the boundary equilibrium \mathbf{E}_n and bearing in mind that $Q_n^F > 1$ together with formula (4), we have*

$$\|\mathbf{E}_n\| = M_n^\# + F_n^\# + 0 + 0 = \frac{1}{\sigma} \ln Q_n^F = \frac{1}{\sigma} \ln \left(\frac{(1 - r_n)\rho_n}{\delta_n} \right) \leq \hat{P}$$

meaning that $\mathbf{E}_n \in \Omega$. Similar rationale can be used to show that $\mathbf{E}_w \in \Omega$ when $Q_w^F > 1$. Finally, when $1 < Q_w^F < Q_n^F$ we have

$$\|\mathbf{E}_c\| = M_n^c + F_n^c + M_w^c + F_w^c = \frac{1}{\sigma} \ln Q_w^F = \frac{1}{\sigma} \ln \left(\frac{(1 - r_w)\rho_w}{\delta_w} \right) \leq \hat{P}$$

that implies $\mathbf{E}_c \in \Omega$.

4 Stability properties

Stability properties of the dynamical system (2) are naturally related to the values of Q_n^F and Q_w^F that define the existence of its nonnegative equilibria (see Theorem 1 and Figure 1). The overview of the situation is given in the following statement.

Theorem 2. *The stability properties of the equilibrium points exhibited in Theorem 1 are as follows.*

- *When the extinction equilibrium \mathbf{E}_0 is the only equilibrium of system (2), it is globally asymptotically stable (GAS). It is otherwise unstable.*
- *When the fully non-infected equilibrium \mathbf{E}_n exists, it is locally asymptotically stable (LAS) if $Q_n^F > Q_w^F$ and is unstable if $Q_n^F < Q_w^F$.*
- *When the fully infected \mathbf{E}_w exists, it is locally asymptotically stable (LAS).*
- *When the coexistence equilibrium \mathbf{E}_c exists, it is unstable.*

Using Figure 1, the results of Theorems 1 and 2 may be summarized as follows. When $Q_n^F \leq 1$ and $Q_w^F \leq 1$, only the trivial equilibrium \mathbf{E}_0 exists, and it is GAS (see Region I in Figure 1). When $Q_n^F > 1 \geq Q_w^F$, two nonnegative equilibria \mathbf{E}_0 and \mathbf{E}_n exist, with \mathbf{E}_0 unstable and \mathbf{E}_n LAS (Region II). When $Q_n^F \leq 1 < Q_w^F$, two nonnegative equilibria \mathbf{E}_0 and \mathbf{E}_w exist, with \mathbf{E}_0 unstable and \mathbf{E}_w LAS (Region III). When $1 < Q_n^F \leq Q_w^F$ (Region IV), three nonnegative equilibria \mathbf{E}_0 , \mathbf{E}_n , and \mathbf{E}_w exist, with \mathbf{E}_0 and \mathbf{E}_n unstable and \mathbf{E}_w LAS. Last, when $1 < Q_w^F < Q_n^F$ (Region V) four nonnegative equilibria exist \mathbf{E}_0 , \mathbf{E}_n , \mathbf{E}_w , and \mathbf{E}_c , with \mathbf{E}_0 and \mathbf{E}_c unstable and \mathbf{E}_n and \mathbf{E}_w LAS.

Notice that Theorem 2 does not assess the possibility of global asymptotic stability of \mathbf{E}_n when this equilibrium is the only one to exist, in addition to \mathbf{E}_0 . The same remark applies to \mathbf{E}_w . Indeed, such situations are of no practical interest here, as they presuppose that one of the two populations is not viable.

For sake of readability, the proof of Theorem 2 is decomposed in four steps, Propositions 2, 3, 4 and 5 below, which treat respectively the cases of \mathbf{E}_0 , \mathbf{E}_n , \mathbf{E}_w and \mathbf{E}_c .

To perform the stability analysis of all possible nonnegative equilibria of the system (2), let us define for future use the Jacobian matrix of the system (2)

$$\mathbb{J}(\mathbf{X}) := \frac{\partial \mathbf{f}(\mathbf{X})}{\partial \mathbf{X}} = \begin{pmatrix} J_{11} & J_{12} & J_{13} & J_{14} \\ J_{21} & J_{22} & J_{23} & J_{24} \\ J_{31} & J_{32} & J_{33} & J_{34} \\ J_{41} & J_{42} & J_{43} & J_{44} \end{pmatrix} \quad (26)$$

where $\mathbf{X} = (M_n, F_n, M_w, F_w)$, $\mathbf{f} = (f_1(\mathbf{X}), f_2(\mathbf{X}), f_3(\mathbf{X}), f_4(\mathbf{X}))$ represents the right-hand side of (2), and the precise expressions for J_{ij} , $i, j = 1, 2, 3, 4$ are provided in Appendix A. The Jacobian matrix \mathbb{J} is defined in every point of \mathbb{R}_+^4 except in \mathbf{E}_0 .

Our study will commence by analyzing the stability properties of the trivial equilibrium \mathbf{E}_0 that exists for all positive values of basic offspring numbers Q_n^F and Q_w^F defined by (5). In this context, we formulate the following result.

Proposition 2. *If $Q_n^F \leq 1$ and $Q_w^F \leq 1$, the trivial equilibrium $\mathbf{E}_0 = (0, 0, 0, 0)$ is GAS. If $Q_n^F > 1$ or $Q_w^F > 1$ (see Regions II, III, IV, and V in Figure 1), the trivial equilibrium \mathbf{E}_0 is unstable but there always exists a trajectory converging to \mathbf{E}_0 meaning that \mathbf{E}_0 is not a repeller.*

Proof. Let $Q_n^F \leq 1$. From the equation (2b) it is obtained that

$$\frac{dF_n}{dt} \leq \delta_n \left(Q_n^F e^{-\sigma(M_n + F_n + M_w + F_w)} - 1 \right) F_n \leq \delta_n \left(Q_n^F e^{-\sigma F_n} - 1 \right) F_n.$$

Let $\varepsilon > 0$. There exists $\alpha > 0$ such that $F_n \in [0, \varepsilon]$ implies $e^{-\sigma F_n} \leq 1 - \alpha F_n$. Therefore, as long as $F_n < \varepsilon$ and $Q_n^F \leq 1$, one has

$$\frac{dF_n}{dt} \leq \delta_n \left(Q_n^F e^{-\sigma F_n} - 1 \right) F_n \leq -\delta_n \left(1 - Q_n^F + \alpha Q_n^F F_n \right) F_n \leq -\alpha \delta_n Q_n^F F_n^2.$$

implying that F_n converges to 0, and so does M_n . A similar rationale can be used to prove that F_w converges to 0 when $Q_w^F \leq 1$ and so does M_w . Altogether, we have proved that, under the conditions $Q_n^F \leq 1$ and $Q_w^F \leq 1$ (Region I in Figure 1), the trajectories of the system (2) engendered by *any* nonnegative initial conditions converge to \mathbf{E}_0 . The latter implies that \mathbf{E}_0 is GAS when $Q_n^F \leq 1$ and $Q_w^F \leq 1$.

Note that $\mathbb{J}(\mathbf{E}_0)$ cannot be directly calculated. However, the division by zero can be avoided by applying the technique proposed in [12]. Let us first evaluate the Jacobian matrix for $M_n = \epsilon > 0, F_n = M_w = F_w = 0$ and then examine its limit when $\epsilon \rightarrow 0^+$. According to the expressions provided in Appendix A, we have

$$\mathbb{J}(\epsilon, 0, 0, 0) = \begin{pmatrix} -\mu_n & r_n \rho_n e^{-\sigma \epsilon} & 0 & 0 \\ 0 & (1 - r_n) \rho_n e^{-\sigma \epsilon} - \delta_n & 0 & 0 \\ 0 & 0 & -\mu_w & r_w \rho_w e^{-\sigma \epsilon} \\ 0 & 0 & 0 & (1 - r_w) \rho_w e^{-\sigma \epsilon} - \delta_w \end{pmatrix},$$

and the eigenvalues of this upper-triangular matrix are located on its main diagonal. As $\epsilon \rightarrow 0^+$, these eigenvalues become

$$\lambda_1^0 = -\mu_n, \quad \lambda_2^0 = \delta_n(Q_n^F - 1), \quad \lambda_3^0 = -\mu_w, \quad \lambda_4^0 = \delta_w(Q_w^F - 1).$$

Notably, $\lambda_1^0 < 0$ and $\lambda_3^0 < 0$ while the signs of λ_2^0 and λ_4^0 are defined by Q_n^F and Q_w^F . Namely, $Q_n^F > 1$ (resp. $Q_w^F > 1$) implies that $\lambda_2^0 > 0$ (resp. $\lambda_4^0 > 0$). The latter ensures instability of \mathbf{E}_0 when $Q_n^F > 1$ or $Q_w^F > 1$ (i.e., outside the Region I given in Figure 1).

The presence of two negative eigenvalues, $\lambda_1^0 < 0$ and $\lambda_3^0 < 0$, implies that \mathbf{E}_0 is not a repeller. Furthermore, the system trajectories engendered by $M_n(0) > 0, F_n(0) = 0, M_w(0) > 0, F_w(0) = 0$ converge to \mathbf{E}_0 even though it holds that $Q_n^F > 1$ and $Q_w^F > 1$. ■

It is worthwhile to highlight that Proposition 2 is biologically meaningful. Recall that $Q_n^F \leq 1$ (resp. $Q_w^F \leq 1$) expresses that one wild (resp. *Wolbachia*-carrying) female mosquito produces on average at most one female descendant during her lifespan. Under such assumption(s), it is expected that the wild (resp. *Wolbachia*-carrying) mosquito population will be eventually driven toward extinction, i.e., to $(M_n, F_n) = (0, 0)$ (resp. to $(M_w, F_w) = (0, 0)$). Thus, if $Q_n^F \leq 1$ and $Q_w^F \leq 1$ are fulfilled simultaneously, then \mathbf{E}_0 is the only reachable equilibrium, and it corresponds to the extinction of both mosquito populations. Alternatively, if $Q_n^F > 1$ and $Q_w^F \leq 1$ (resp. $Q_n^F \leq 1$ and $Q_w^F > 1$) are fulfilled, Theorem 1 establishes the existence of another equilibrium \mathbf{E}_n (resp. \mathbf{E}_w) in the Region II (resp. Region III) presented in Figure 1. The latter induces instability of \mathbf{E}_0 and encourages persistence of one mosquito population.

Let us now examine the stability properties of the fully non-infected equilibrium $\mathbf{E}_n = (M_n^\#, F_n^\#, 0, 0)$ defined by (7) that exists only if $Q_n^F > 1$.

Proposition 3. When $Q_n^F > 1$, the fully non-infected equilibrium $\mathbf{E}_n = (M_n^\#, F_n^\#, 0, 0)$ is LAS if $Q_n^F > Q_w^F > 1$ or $Q_n^F > 1 \geq Q_w^F$ (Regions II and V in Figure 1), and it is unstable if $Q_w^F \geq Q_n^F > 1$ (Region IV in Figure 1).

Proof. First, we assume that $Q_n^F > 1$ holds for the parameters of the model (2). Let $J_{ij}^n, i, j = 1, 2, 3, 4$ denote the entries of $\mathbb{J}(\mathbf{E}_n)$. Using the expressions for J_{ij} provided in Appendix A, it is easy to deduce that

$$J_{31}^n = J_{32}^n = J_{41}^n = J_{42}^n = J_{43}^n = 0.$$

Therefore, $\mathbb{J}(\mathbf{E}_n)$ admits the following structure:

$$\mathbb{J}(\mathbf{E}_n) = \begin{pmatrix} \mathcal{A}_{(2 \times 2)}^n & \mathcal{B}_{(2 \times 2)}^n \\ \mathcal{O}_{(2 \times 2)}^n & \mathcal{C}_{(2 \times 2)}^n \end{pmatrix} = \begin{pmatrix} -\mu_n \left(1 + \frac{Q_n^M \ln Q_n^F}{Q_n^M + Q_n^F} \right) & \mu_n \frac{Q_n^M}{Q_n^F} \left(1 - \frac{Q_n^F \ln Q_n^F}{Q_n^M + Q_n^F} \right) & J_{13}^n & J_{14}^n \\ -\delta_n \frac{Q_n^F \ln Q_n^F}{Q_n^M + Q_n^F} & -\delta_n \frac{Q_n^F \ln Q_n^F}{Q_n^M + Q_n^F} & J_{23}^n & J_{24}^n \\ 0 & 0 & -\mu_w & J_{34}^n \\ 0 & 0 & 0 & \delta_w \left(\frac{Q_w^F}{Q_n^F} - 1 \right) \end{pmatrix}.$$

To show that \mathbf{E}_n is LAS in the Regions II and V given in Figure 1, it suffices to prove that all eigenvalues $\lambda_i^n, i = 1, 2, 3, 4$ of $\mathbb{J}(\mathbf{E}_n)$ have negative real part under the condition $Q_n^F > Q_w^F > 1$. Given the block structure of $\mathbb{J}(\mathbf{E}_n)$, its eigenvalues are the eigenvalues of the blocks $\mathcal{A}_{(2 \times 2)}^n$ and $\mathcal{C}_{(2 \times 2)}^n$.

To define the signs of two eigenvalues of $\mathcal{A}_{(2 \times 2)}^n$, let us recall that λ_1^n and λ_2^n have strictly negative real parts if and only if the trace of $\mathcal{A}_{(2 \times 2)}^n$ is strictly negative while its determinant is strictly positive.

Effectively,

$$\begin{aligned} \text{trace } \mathcal{A}_{(2 \times 2)}^n &= -\mu_n \left(1 + \frac{Q_n^M \ln Q_n^F}{Q_n^M + Q_n^F} \right) - \delta_n \frac{Q_n^F \ln Q_n^F}{Q_n^M + Q_n^F} < 0, \\ \det \mathcal{A}_{(2 \times 2)}^n &= \mu_n \delta_n \frac{Q_n^F \ln Q_n^F}{Q_n^M + Q_n^F} \left[1 + \frac{Q_n^M \ln Q_n^F}{Q_n^M + Q_n^F} + \frac{Q_n^M}{Q_n^F} - \frac{Q_n^M \ln Q_n^F}{Q_n^M + Q_n^F} \right] \\ &= \mu_n \delta_n \frac{Q_n^F \ln Q_n^F}{Q_n^M + Q_n^F} \frac{(Q_n^M + Q_n^F)}{Q_n^F} = \mu_n \delta_n \ln Q_n^F > 0. \end{aligned}$$

Therefore, as long as $Q_n^F > 1$, we have $\Re(\lambda_1^n) < 0$ and $\Re(\lambda_2^n) < 0$.

The eigenvalues $\lambda_3^n < 0$ and $\lambda_4^n < 0$ of the upper-triangular block $\mathcal{C}_{(2 \times 2)}^n$ are located on its main diagonal:

$$\lambda_3^n = -\mu_w < 0, \quad \lambda_4^n = \delta_w \left(\frac{Q_w^F}{Q_n^F} - 1 \right),$$

Notably, $\lambda_4^n < 0$ if $Q_n^F > Q_w^F$ (with either $Q_w^F \leq 1$ or $Q_w^F > 1$) and \mathbf{E}_n is LAS under this condition, i.e., in the Regions II and V given in Figure 1. However, if $Q_w^F > Q_n^F > 1$, we have that $\lambda_4^n > 0$ meaning that \mathbf{E}_n becomes unstable in the Region IV of Figure (1). ■

To establish the stability properties of the fully infected equilibrium $\mathbf{E}_w = (0, 0, M_w^\#, F_w^\#)$ defined by (8) that exists only if $Q_w^F > 1$, we formulate and prove the following result.

Proposition 4. *When $Q_w^F > 1$, the fully infected equilibrium $\mathbf{E}_w = (0, 0, M_w^\#, F_w^\#)$ is LAS regardless of the positive value of Q_n^F , that is, in Regions III, IV, and V plotted in Figure 1.*

Proof. First, we assume that $Q_w^F > 1$ holds for the parameters of the model (2). Let $J_{ij}^w, i, j = 1, 2, 3, 4$ denote the entries of $\mathbb{J}(\mathbf{E}_w)$. Using the expressions for J_{ij} provided in Appendix A, it is easy to deduce that

$$J_{12}^w = J_{13}^w = J_{14}^w = J_{21}^w = J_{23}^w = J_{24}^w = 0.$$

Therefore, $\mathbb{J}(\mathbf{E}_w)$ admits the following structure:

$$\mathbb{J}(\mathbf{E}_w) = \begin{pmatrix} \mathcal{A}_{(2 \times 2)}^w & \mathcal{O}_{(2 \times 2)}^w \\ \mathcal{B}_{(2 \times 2)}^w & \mathcal{C}_{(2 \times 2)}^w \end{pmatrix} = \begin{pmatrix} -\mu_n & 0 & 0 & 0 \\ 0 & -\delta_n & 0 & 0 \\ J_{31}^w & J_{32}^w & -\mu_w \left(1 + \frac{Q_w^M \ln Q_w^F}{Q_w^M + Q_w^F}\right) & \mu_w \frac{Q_w^M}{Q_w^F} \left(1 - \frac{Q_w^F \ln Q_w^F}{Q_w^M + Q_w^F}\right) \\ J_{41}^w & J_{42}^w & -\delta_w \frac{Q_w^F \ln Q_w^F}{Q_w^M + Q_w^F} & -\delta_w \frac{Q_w^F \ln Q_w^F}{Q_w^M + Q_w^F} \end{pmatrix}.$$

To show that \mathbf{E}_w is LAS whenever it exists (i.e., in the Regions III, IV, and V given in Figure 1), it suffices to prove that all eigenvalues $\lambda_i^w, i = 1, 2, 3, 4$ of $\mathbb{J}(\mathbf{E}_w)$ have negative real part under the condition $Q_w^F > 1$ and regardless of the value of Q_n^F . Given the block structure of $\mathbb{J}(\mathbf{E}_w)$, its eigenvalues are the eigenvalues of the blocks $\mathcal{A}_{(2 \times 2)}^w$ and $\mathcal{C}_{(2 \times 2)}^w$. Clearly, the eigenvalues of $\mathcal{A}_{(2 \times 2)}^w$ are always negative, that is,

$$\lambda_1^w = -\mu_n < 0, \quad \text{and} \quad \lambda_2^w = -\delta_n < 0.$$

Furthermore, λ_3^w and λ_4^w have negative real parts if and only if the trace of $\mathcal{C}_{(2 \times 2)}^w$ is strictly negative

while its determinant is strictly positive. In fact,

$$\begin{aligned}\text{trace } \mathcal{C}_{(2 \times 2)}^w &= -\mu_w \left(1 + \frac{Q_w^M \ln Q_w^F}{Q_w^M + Q_w^F} \right) - \delta_w \frac{Q_w^F \ln Q_w^F}{Q_w^M + Q_w^F} < 0, \\ \det \mathcal{C}_{(2 \times 2)}^w &= \mu_w \delta_w \frac{Q_w^F \ln Q_w^F}{Q_w^M + Q_w^F} \left[1 + \frac{Q_w^M \ln Q_w^F}{Q_w^M + Q_w^F} + \frac{Q_w^M}{Q_w^F} - \frac{Q_w^M \ln Q_w^F}{Q_w^M + Q_w^F} \right] \\ &= \mu_w \delta_w \frac{Q_w^F \ln Q_w^F}{Q_w^M + Q_w^F} \frac{(Q_w^M + Q_w^F)}{Q_w^F} = \mu_w \delta_w \ln Q_w^F > 0.\end{aligned}$$

Thus, we have $\Re(\lambda_3^w) < 0$ and $\Re(\lambda_4^w) < 0$ as long as $Q_w^F > 1$. Therefore, \mathbf{E}_w is LAS whenever it exists and regardless of the value of Q_n^F . ■

From Propositions 3 and 4 we conclude that both \mathbf{E}_n and \mathbf{E}_w are LAS in the Region V (see Figure 1) where it holds that $Q_n^F > Q_w^F > 1$, while Region IV (where $Q_w^F \geq Q_n^F > 1$) contains only one locally asymptotically stable equilibrium \mathbf{E}_w together with two unstable equilibria $\mathbf{E}_0, \mathbf{E}_n$. Both conclusions are quite meaningful from a biological standpoint. When it holds that $Q_n^F > 1$ and $Q_w^F > 1$ (Regions IV and V in Figure 1), both mosquito sub-populations (with and without *Wolbachia*) are regarded as naturally persistent, meaning that one female insect produces more than one female descendant during her lifespan, and that each sub-population will persist at the low density (or in the absence) of the other.

However, the relationship $Q_w^F \geq Q_n^F > 1$ implies that a *Wolbachia*-infected female is capable of producing more female descendants than a non-infected female. Additionally, the CI reproductive phenotype enables *Wolbachia*-infected females to produce viable offspring after mating with non-infected males, while non-infected females fail to produce viable offspring after mating with *Wolbachia*-infected males. In other words, under the condition $Q_w^F \geq Q_n^F > 1$ (Region IV in Figure 1), *Wolbachia*-infected insects benefit not only from their CI-enabled reproductive advantage but also exhibit a better individual fitness $Q_w^F \geq Q_n^F$. In this case, the outcome of the inter-species competition is strongly biased towards the survival of *Wolbachia*-infected sub-population together with an ultimate extinction of the non-infected sub-population.

On the other hand, the condition $Q_n^F > Q_w^F > 1$ implies that a non-infected female has a better individual fitness (higher fertility and/or longevity) than an infected one whenever there are sufficient males to mate with. However, the reproductive fitness of non-infected females can be jeopardized by the relative scarcity (or low frequency) of non-infected males. Notably, at lower frequencies of non-infected male insects, the probability of matings between non-infected females and infected males becomes higher and so does the probability of producing inviable offspring. Therefore, a lower individual fitness of *Wolbachia*-infected females ($Q_n^F > Q_w^F$) can be compensated by the CI-phenotype granting them the capability to produce viable and *Wolbachia*-infected descendants after mating with either infected or non-infected males. In this case, the dynamical system (2) exhibits bistability (both boundary equilibria

\mathbf{E}_n and \mathbf{E}_w are LAS in Region V given in Figure 1), and the outcome of the inter-species competition depends on the frequency of *Wolbachia* infection in the total mosquito population. The latter fully agrees with previous results obtained for other models of *Wolbachia* invasion formulated either in terms of the infection frequency [2, 21, 24] or competitive population dynamics [1, 3, 7, 11, 12, 13, 16, 26, 27].

As stated in Theorem 1, Region V also contains the strictly positive equilibrium \mathbf{E}_c besides \mathbf{E}_0 (which is unstable) and $\mathbf{E}_n, \mathbf{E}_w$ (that are LAS). The following result describes the stability properties of the strictly positive equilibrium \mathbf{E}_c that exists only in Region V where $Q_n^F > Q_w^F > 1$.

Proposition 5. *The strictly positive equilibrium $\mathbf{E}_c = (M_n^c, F_n^c, M_w^c, F_w^c)$ defined by (9) is always unstable whenever it exists.*

Proof. As stated by Theorem 1, \mathbf{E}_c exists only if $Q_n^F > Q_w^F > 1$ (i.e., in the Region V given in Figure 1). To prove its instability, it is sufficient to show that $\mathbb{J}(\mathbf{E}_c)$ has at least one strictly positive eigenvalue. In this context, let us recall that $\det \mathbb{J}(\mathbf{E}_c) = \prod_{i=1}^4 \lambda_i^c$, where $\lambda_i^c, i = 1, 2, 3, 4$ denote the eigenvalues of $\mathbb{J}(\mathbf{E}_c)$. Therefore, showing that $\det \mathbb{J}(\mathbf{E}_c) < 0$ would imply the presence of one (or three) positive eigenvalues of $\mathbb{J}(\mathbf{E}_c)$, and the instability of \mathbf{E}_c will be proven.

To evaluate the components $J_{ij}^c, i, j = 1, 2, 3, 4$ of the Jacobian matrix $\mathbb{J}(\mathbf{E}_c)$, let us first express the coordinates F_n^c, F_w^c of \mathbf{E}_c in terms of M_n^c, M_w^c

$$F_n^c = \frac{Q_n^F}{Q_n^M} M_n^c, \quad F_w^c = \frac{Q_w^F}{Q_w^M} M_w^c \quad (27)$$

and then make use of the relationships

$$\frac{M_n^c}{M_n^c + \gamma M_w^c} = \frac{Q_w^F}{Q_n^F}, \quad e^{-\sigma(M_n^c + F_n^c + M_w^c + F_w^c)} = \frac{1}{Q_w^F}, \quad (28)$$

derived from (18), (21). Having performed some heavy calculations (presented in Appendix A), we obtain

$$\mathbb{J} \left(M_n^c, \frac{Q_n^F}{Q_n^M} M_n^c, M_w^c, \frac{Q_w^F}{Q_w^M} M_w^c \right) = \quad (29)$$

$$\begin{pmatrix} -\mu_n \left(\frac{Q_w^F}{Q_n^F} + \sigma M_n^c \right) & \mu_n \left(\frac{Q_n^M}{Q_n^F} - \sigma M_n^c \right) & -\mu_n \left(\gamma \frac{Q_w^F}{Q_n^F} + \sigma M_n^c \right) & -\mu_n \sigma M_n^c \\ \delta_n \frac{Q_n^F}{Q_n^M} \left(1 - \frac{Q_w^F}{Q_n^F} - \sigma M_n^c \right) & -\delta_n \frac{Q_n^F}{Q_n^M} \sigma M_n^c & -\delta_n \frac{Q_n^F}{Q_n^M} \left(\gamma \frac{Q_w^F}{Q_n^F} + \sigma M_n^c \right) & -\delta_n \frac{Q_n^F}{Q_n^M} \sigma M_n^c \\ -\mu_w \sigma M_w^c & -\mu_w \sigma M_w^c & -\mu_w \left(1 + \sigma M_w^c \right) & \mu_w \left(\frac{Q_w^M}{Q_w^F} - \sigma M_w^c \right) \\ -\delta_w \frac{Q_w^F}{Q_w^M} \sigma M_w^c & -\delta_w \frac{Q_w^F}{Q_w^M} \sigma M_w^c & -\delta_w \frac{Q_w^F}{Q_w^M} \sigma M_w^c & -\delta_w \frac{Q_w^F}{Q_w^M} \sigma M_w^c \end{pmatrix}$$

and

$$\det \mathbb{J}(\mathbf{E}^c) = \mu_n \delta_n \mu_w \delta_w \sigma M_w^c \left[-\gamma \frac{Q_w^F}{Q_n^F} \left(\frac{Q_n^F}{Q_n^M} + 1 \right) - \left(1 - \frac{Q_w^F}{Q_n^F} \right) \left(\frac{Q_w^F}{Q_w^M} + 1 \right) \right].$$

Let us recall that \mathbf{E}_c exists only if $Q_n^F > Q_w^F > 1$ (see Region V in Figure 1). Therefore, $\det \mathbb{J}(\mathbf{E}^c) < 0$ and \mathbf{E}_c is always unstable whenever it exists. ■

According to Proposition 5, the coexistence of both mosquito sub-populations cannot be sustained. From a biological standpoint, this conclusion is consensual with the so-called *principle of competitive exclusion* induced by the frequency-dependent Allee effect [17] which basically states that only one of two species competing for the same resources, including mating opportunities, should ultimately survive and persist.

To complete this section, let us emphasize that a thorough theoretical analysis of the stability properties of the system (2) constitutes the major result of this paper, and fills the gap left by the authors of [12] where the stability of a resembling sex-structured model have been studied only by a numerical approach based on the Monte-Carlo method.

5 Numerical simulations and discussion

We will now derive some simulations in order to illustrate the previous theoretical results, and to discuss some release scenarios, taking into account the epidemiological status of the place where the replacement needs to occur. We stress that no epidemiological aspect is envisioned here, a complete study of this subject, of key importance of course, will be provided in a further article.

Two important features must be taken into account: first, the *Wlb-mosquito*² production capacity necessary to produce a unique initial release or several releases, every week or every two weeks; second, the *epidemiological status* at the place and time where the releases are to be done: clearly, if an epidemic is ongoing or if the place is located in an endemic area, the release of numerous *Wlb*-females will increase the basic reproduction number \mathcal{R}_0 , and thus boost the epidemic, so that it seems preferable to release more *Wlb*-males than *Wlb*-females. On the contrary, releasing females is less challenging in an inter-epidemic period. However, the inhabitants may complain about the increase of nuisance due to female bites, so that, again, the release of more *Wlb*-males than *Wlb*-females seems to be the best choice. In this regard, we remind that various approaches have been developed or are under development for the sex-separation of the *Aedes* mosquito at the egg stage (see [20] and references therein).

For the subsequent simulations, we consider the parameter values summarized in Table 2, page 18. In this table, the factor 0.9 used in the *Wlb*-parameters values is taken from [14] and reflects the fitness reduction of *Wlb*-mosquitoes.

With the parameter values taken from [8], we have $Q_n^M \approx 56.87$ and $Q_n^F \approx 75.83$. At equilibrium, the wild mosquito population is $\mathbf{E}_n = (M_n^\#, F_n^\#, 0, 0)$ with $M_n^\# \approx 5.194 \times 10^3$ and $F_n^\# \approx 6.925 \times 10^3$ individuals per hectare (ha). For *Wlb*-mosquitoes, the basic offspring numbers are lower, i.e., $Q_w^M \approx 46.07$ and $Q_w^F \approx 61.42$.

²Here and in the sequel, the term *Wlb*- refers to mosquitoes infected by the *wMel* strain of *Wolbachia*.

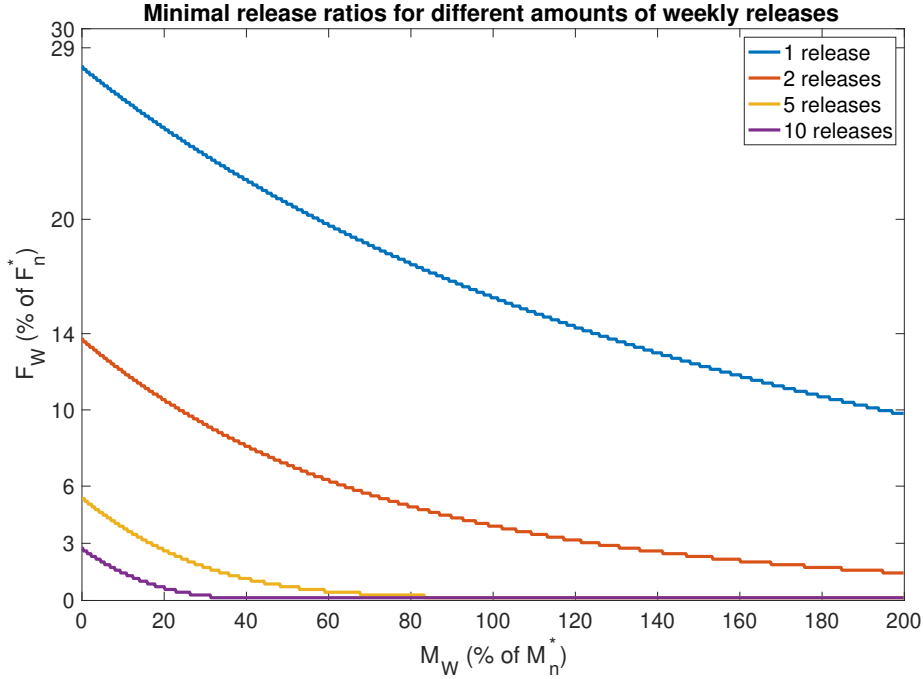


Figure 2: Minimal release ratios of *Wlb*-mosquitoes to ensure convergence to E_w for different initial weekly release(s) scenarios

Since $1 < Q_w^F < Q_n^F$, we are in the case of Region V (see Fig. 1, page 8), where two stable equilibria E_n and E_w co-exist. Thus, being in the basin of attraction of E_w or E_n will depend on the release size(s) and periodicity. To explore this feature, the next figures show the minimal release ratios of *Wolbachia*-carrying males and females necessary to realize successful invasion. These curves have been obtained numerically, through repeated simulations of system (2).

In Fig. 2, page 18, we consider either a unique release or 2, 5, and 10 consecutive weekly releases, while Figs. 3 and 4 on pages 19 and 20 exhibit similar results for semi-monthly and monthly releases,

Table 2: Parameters of the entomological model (2) borrowed from [8, 14]

Parameter	Value	Description
$r_n = r_w$	0.5	adult sex ratio
ρ_n	4.55	fecundity of wild female mosquitoes
ρ_w	4.55×0.9	fecundity of <i>Wolbachia</i> -carrying female mosquitoes
μ_n	0.04	natural mortality rate for wild male mosquitoes
δ_n	0.03	natural mortality rate for wild female mosquitoes
μ_w	0.04/0.9	natural mortality rate for <i>Wolbachia</i> -carrying male mosquitoes
δ_w	0.03/0.9	natural mortality rate for <i>Wolbachia</i> -carrying female mosquitoes
γ	1	mating competitiveness of <i>Wolbachia</i> -carrying mosquitoes
σ	3.57×10^{-4}	carrying capacity parameter for 1 ha

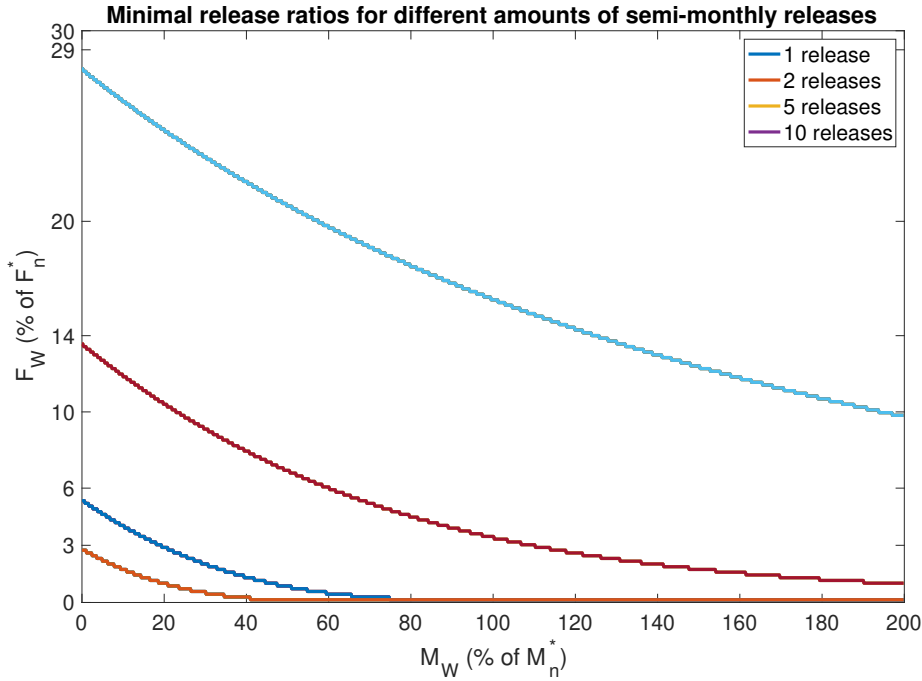


Figure 3: Minimal release ratios of *Wlb*-mosquitoes to ensure convergence to E_w for different initial semi-monthly release(s) scenarios

respectively. The four curves at each figure provide the minimal quantities of *Wlb*-females and *Wlb*-males to be released in order to reach equilibrium E_w , in each of the four situations. These quantities are expressed as proportions of the wild female and male equilibrium values. Notice that the *total* released sizes may be obtained easily by multiplying the nominal values by the number of releases.

One observes that, for a unique release, replacement may occur with the release of a quantity of *Wlb*-females as small as 29% of the equilibrium size of the wild females per ha, that is 2 082 *Wlb*-females per ha, and no *Wlb*-males at all. Another option is to release 20% of *Wlb*-females and at least 60% of *Wlb*-males, that is, 1 385 *Wlb*-females and 3 117 *Wlb*-males. If the area to treat is very large, thousands of hectares, this requires the production of a vast amount of *Wlb*-mosquitoes.

Also and as said previously, when a vector-borne disease virus, like the dengue virus is circulating, releasing too many females is problematic. It was shown in [15] that releasing (sterile) females can increase the basic reproduction number, i.e., $\mathcal{R}_0 \gg 1$, and thus ignite an epidemic. The same disturbing effect may, of course, occur with the replacement method studied here, and this is why it is necessary to reduce the amount of *Wlb*-females in the releases. To do that, other strategies are possible, like releasing smaller quantities of *Wlb*-mosquitoes during 2, 5, or 10 weeks: see Fig. 2, page 18.

Minor releases over 10 consecutive weeks are also possible; for instance, only 3% of *Wlb*-females and 10% of *Wlb*-males (compared to the respective equilibrium levels), that is, 208 *Wlb*-females and 520 of

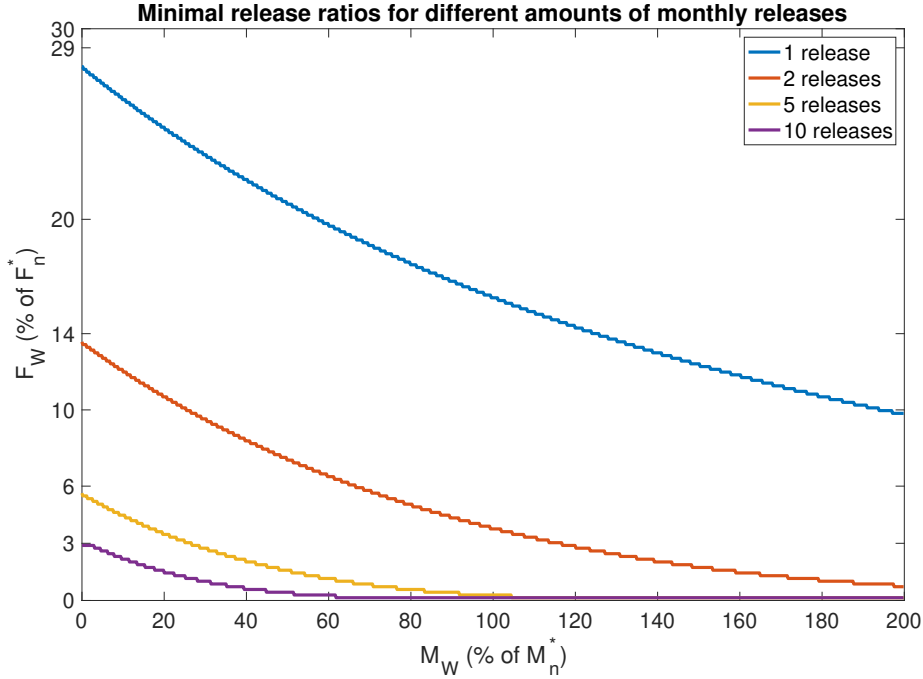


Figure 4: Minimal release ratios of *Wlb*-mosquitoes to ensure convergence to E_w for different initial monthly release(s) scenarios

Wlb-males per hectare. It is also possible to consider even smaller *Wlb*-female releases, like 1%, and 35% of *Wlb*-males.

Since the lifespans of wild and *Wlb*-mosquitoes are supposed to be longer than a week (up to a month), we have also displayed in Fig. 3, page 19 and Fig. 4, page 20 that semi-monthly and monthly releases provide almost similar results to weekly releases. Our simulations show certain flexibility in determining the release strategy to treat huge areas. Namely, the release strategy can be adapted to account for the time needed for mass rearing of *Wlb*-mosquitoes or possible failures in the weekly production. This is quite important from a practical point of view.

While it seems better to perform male-biased releases from the epidemiological point of view, it is also essential to assess the time of the population replacement for the different ratios of males and females considered. In the sequel, we assume by convention that the population replacement is achieved satisfactorily when $F_n + M_n < 1$. Notice that releasing a larger quantity of infected mosquitoes induces a faster replacement. However, this trend is limited by the natural mortality of the wild mosquitoes present at the beginning of the campaign³.

In Fig. 5, page 21, we show results corresponding to weekly, semi-monthly, and monthly releases.

³This may be seen easily from system (2), which implies $\frac{dM_n}{dt} \geq -\mu_n M_n$, $\frac{dF_n}{dt} \geq -\delta_n F_n$, therefore imposing a limitation to the extinction speed of the uninfected population.

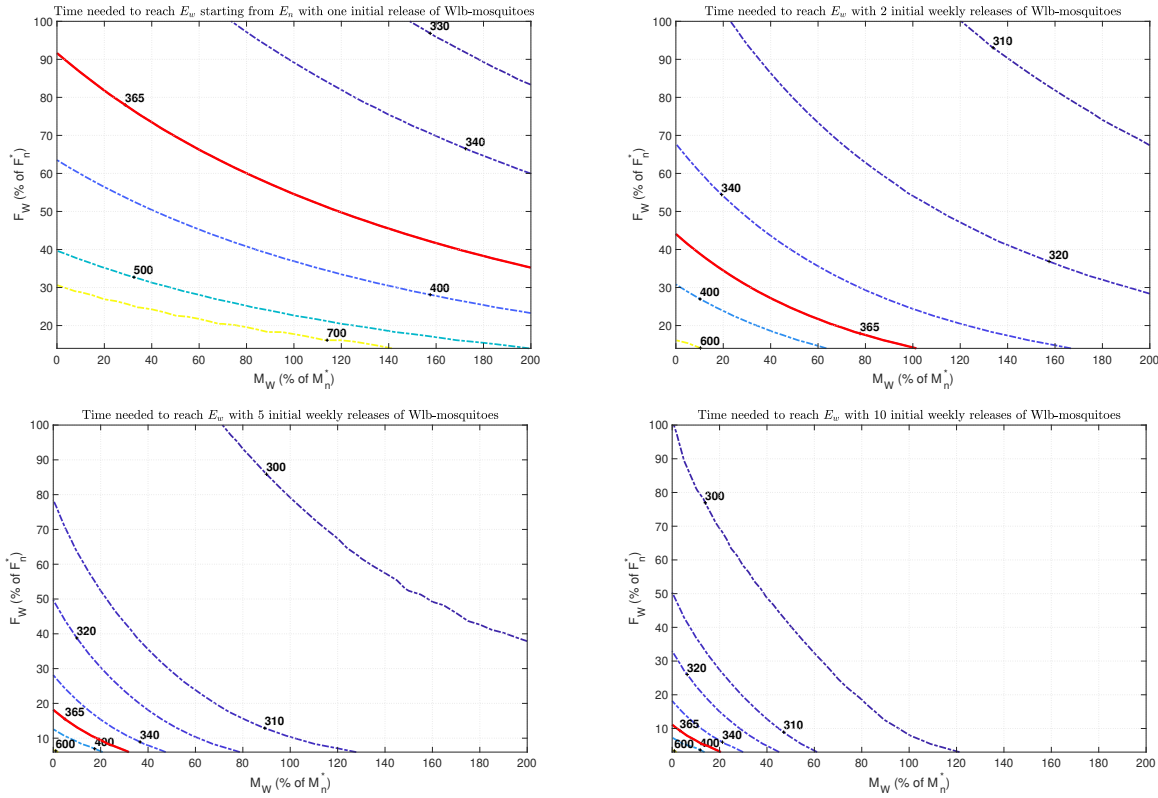


Figure 5: Minimal time to reach E_w for different weekly release(s) scenarios

The explored range of values includes all proportions of released *Wlb*-females between 0 and 100% and *Wlb*-males between 0 and 200% (relative to the wild mosquito equilibrium values). The red level-set curve in each of these figures indicates when one year time is needed to reach the population replacement.

For all simulations, the quickest treatment duration appearing on the figures (achieved with the largest release, that is 100% *Wlb*-females and 200% *Wlb*-males) is about 292 days. If the production capacity is sufficient, then the one-release strategy is feasible, achieving replacement in less than a year. Otherwise, our simulations show that we can adapt the release strategy in order to realize replacement in less than a year with releases of manageable size. For instance, if a constraint is to release an amount of *Wlb*-females smaller, say than 5%, then 5 weekly releases with at least 32% of *Wlb*-males or 10 weekly releases with at least 21% of *Wlb*-males are sufficient to reach replacement in less than a year (see Fig. 5, two lower charts).

Fig. 6, page 22 and Fig. 7, page 23 show similar results. Fig. 7 shows, for example, that 5 monthly releases of 10% of *Wlb*-females and 20% of *Wlb*-males achieve population replacement in less than 500 days: in such an option, time should not be a strong constraint.

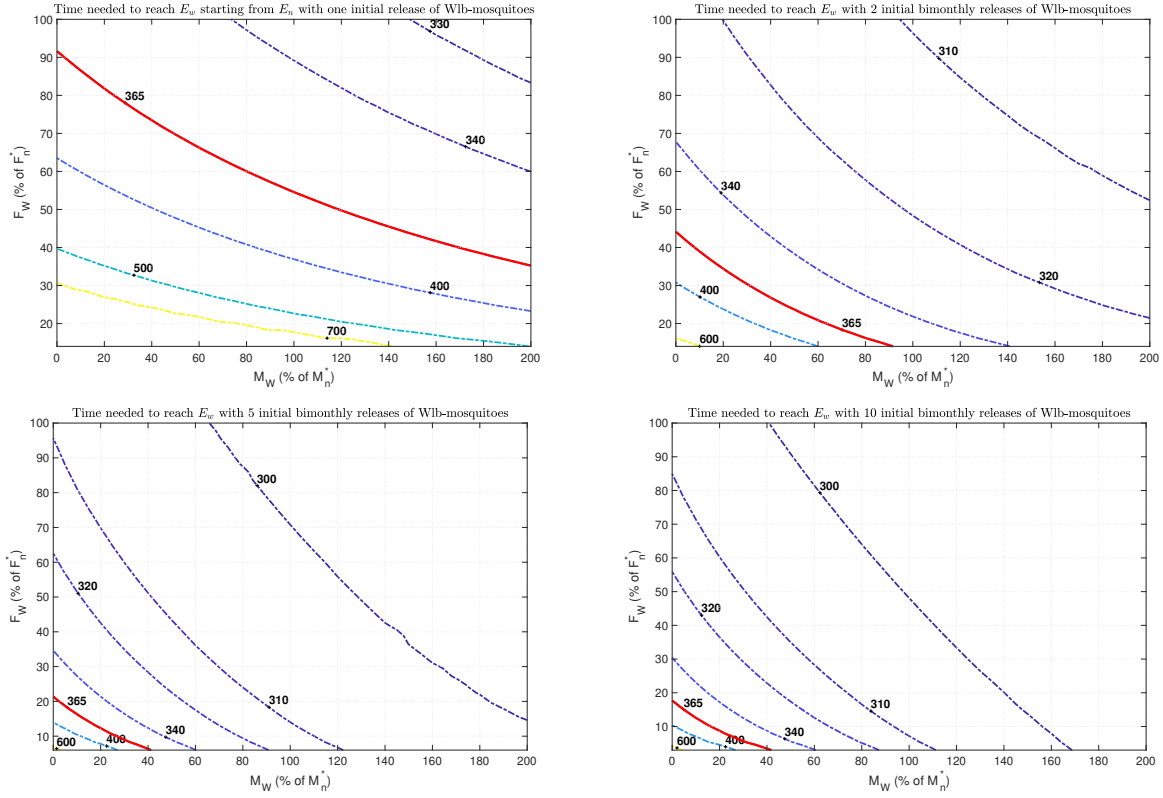


Figure 6: Minimal time to reach E_w for different semi-monthly release(s) scenarios

6 Conclusions

In this paper, we studied a generic sex-structured full *Wolbachia* replacement model that describes the interaction between a wild and a *Wolbachia*-carrying *Aedes* population. Our analysis reveals that, even if the *Wolbachia*-carrying population has lower individual fitness than the wild population, the CI-reproductive phenotype grants an advantage to drive the system from a wild population to the *Wolbachia*-carrying population, provided that a suitable release strategy is considered. Since sex-separation is not a practical issue, adjusting independently the quantities of male and female mosquitoes is a realistic option, which the proposed model allows to study.

Simulations show that replacement is achievable within the same time span, while reducing substantially the amount of *Wolbachia*-carrying females through adequate releases of *Wolbachia*-carrying males. Indeed, the male-biased strategy is more advisable, especially when a vector-borne disease virus, like the dengue virus, is circulating, as it reduces the epidemiological risk without increasing the nuisance caused by the female bites.

Last but not least, we also show that the strategies consisting of several releases every week, every two weeks, or every month are efficient when appropriately sized, and can be helpful for field releases

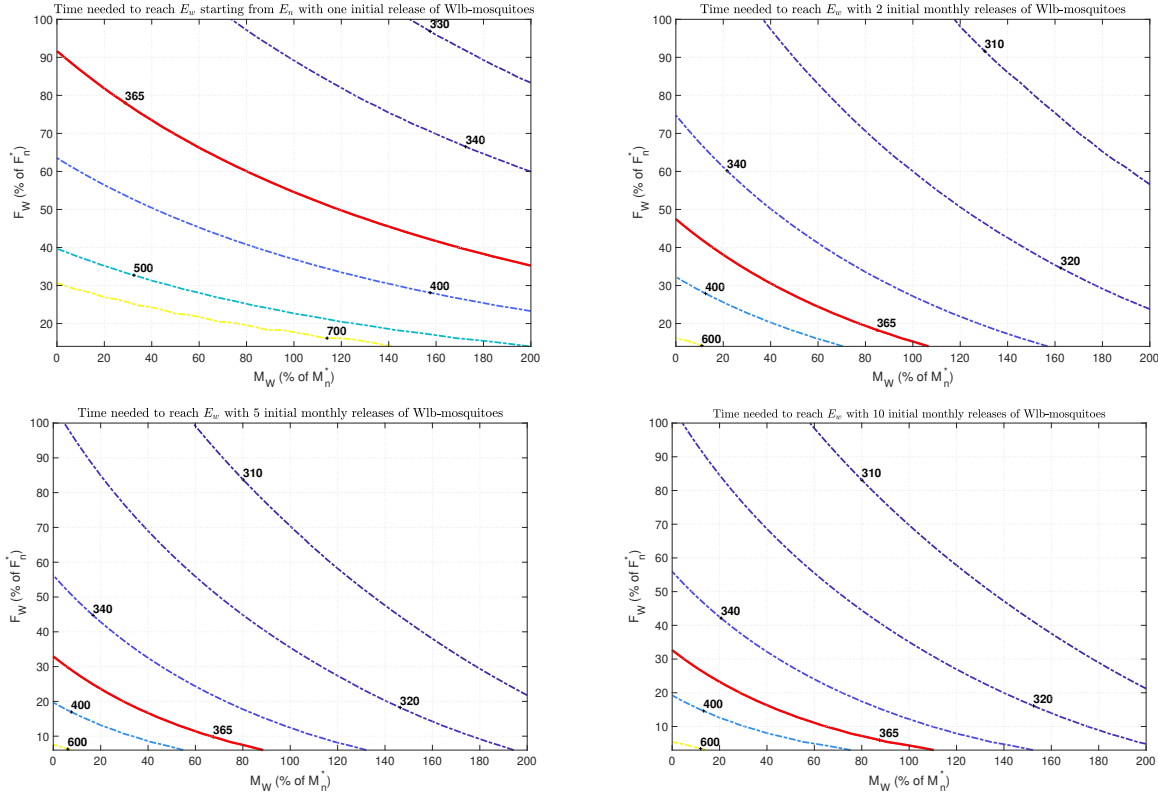


Figure 7: Minimal time to reach E_w for different monthly release(s) scenarios

in large areas, when the capacity for production of *Wolbachia*-carrying mosquitoes is limited.

Of course, field releases would be more than welcome to test the different release strategies. As a further development, we plan to couple the proposed replacement model with an epidemiological model of dengue transmission, for instance, in order to study the impact of population replacement on the epidemiological risk, in different conditions and for different *Wolbachia* strains.

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Appendix A: Jacobian matrix evaluated in E_C and its determinant

The components $J_{ij}, i, j = 1, 2, 3, 4$ of the Jacobian matrix (26) are given by the following expressions:

$$\begin{aligned}
J_{11} &= \frac{\partial f_1}{\partial M_n} = r_n \rho_n F_n \frac{\gamma M_w - \sigma M_n (M_n + \gamma M_w)}{(M_n + \gamma M_w)^2} e^{-\sigma(M_n + F_n + M_w + F_w)} - \mu_n, \\
J_{12} &= \frac{\partial f_1}{\partial F_n} = r_n \rho_n \frac{M_n(1 - \sigma F_n)}{M_n + \gamma M_w} e^{-\sigma(M_n + F_n + M_w + F_w)}, \\
J_{13} &= \frac{\partial f_1}{\partial M_w} = -r_n \rho_n \frac{M_n F_n (\gamma + \sigma (M_n + \gamma M_w))}{(M_n + \gamma M_w)^2} e^{-\sigma(M_n + F_n + M_w + F_w)}, \\
J_{14} &= \frac{\partial f_1}{\partial F_w} = -r_n \rho_n \frac{\sigma M_n F_n}{M_n + \gamma M_w} e^{-\sigma(M_n + F_n + M_w + F_w)}, \\
J_{21} &= \frac{\partial f_2}{\partial M_n} = (1 - r_n) \rho_n F_n \frac{\gamma M_w - \sigma M_n (M_n + \gamma M_w)}{(M_n + \gamma M_w)^2} e^{-\sigma(M_n + F_n + M_w + F_w)}, \\
J_{22} &= \frac{\partial f_2}{\partial F_n} = (1 - r_n) \rho_n \frac{M_n(1 - \sigma F_n)}{M_n + \gamma M_w} e^{-\sigma(M_n + F_n + M_w + F_w)} - \delta_n, \\
J_{23} &= \frac{\partial f_2}{\partial M_w} = -(1 - r_n) \rho_n \frac{M_n F_n (\gamma + \sigma (M_n + \gamma M_w))}{(M_n + \gamma M_w)^2} e^{-\sigma(M_n + F_n + M_w + F_w)}, \\
J_{24} &= \frac{\partial f_2}{\partial F_w} = -(1 - r_n) \rho_n \frac{\sigma M_n F_n}{M_n + \gamma M_w} e^{-\sigma(M_n + F_n + M_w + F_w)}, \\
J_{31} &= \frac{\partial f_3}{\partial M_n} = -r_w \rho_w \sigma F_w e^{-\sigma(M_n + F_n + M_w + F_w)} = \frac{\partial f_3}{\partial F_n} = J_{32}, \\
J_{33} &= \frac{\partial f_3}{\partial M_w} = -r_w \rho_w \sigma F_w e^{-\sigma(M_n + F_n + M_w + F_w)} - \mu_w, \\
J_{34} &= \frac{\partial f_3}{\partial F_w} = -r_w \rho_w (1 - \sigma F_w) e^{-\sigma(M_n + F_n + M_w + F_w)}, \\
J_{41} &= \frac{\partial f_4}{\partial M_n} = -(1 - r_w) \rho_w \sigma F_w e^{-\sigma(M_n + F_n + M_w + F_w)} = \frac{\partial f_4}{\partial F_n} = J_{42} = \frac{\partial f_4}{\partial M_w} = J_{43}, \\
J_{44} &= \frac{\partial f_4}{\partial F_w} = (1 - r_w) \rho_w (1 - \sigma F_w) e^{-\sigma(M_n + F_n + M_w + F_w)} - \delta_w.
\end{aligned}$$

Using the expression (27), (28) we proceed to evaluate the components $J_{ij}^c, i, j = 1, 2, 3, 4$ of $\mathbb{J}(E_C)$, whose values are given in the formulas (9). In the subsequent computations, are used repeatedly the values of $M_n^c + F_n^c + M_w^c + F_w^c$ given in (19) and the value of $M_n^c + \gamma M_w^c$ given in (22), as well as the

properties expressed in identities (20), (21) and (24).

$$\begin{aligned}
J_{11}^c &= r_n \rho_n \frac{Q_n^F}{Q_n^M} M_n^c \frac{\gamma \frac{Q_n^F - Q_w^F}{\gamma Q_w^F} M_n^c - \sigma (M_n^c)^2 \frac{Q_n^F}{Q_w^F}}{\left(M_n^c \frac{Q_n^F}{Q_w^F} \right)^2 Q_w^F} - \mu_n = \frac{r_n \rho_n}{Q_n^M} \frac{\left(Q_n^F - Q_w^F - \sigma Q_n^F M_n^c \right)}{Q_n^F} - \mu_n \\
&= \frac{r_n \rho_n}{\mu_n} \frac{\mu_n}{Q_n^M} \left(1 - \frac{Q_w^F}{Q_n^F} - \sigma M_n^c \right) - \mu_n = \mu_n \left(1 - \frac{Q_w^F}{Q_n^F} - \sigma M_n^c - 1 \right) = -\mu_n \left(\frac{Q_w^F}{Q_n^F} + \sigma M_n^c \right); \\
J_{12}^c &= r_n \rho_n \frac{Q_w^F}{Q_n^F} \left(1 - \sigma \frac{Q_n^F}{Q_n^M} M_n^c \right) \frac{1}{Q_w^F} = \frac{r_n \rho_n}{\mu_n} \frac{\mu_n}{Q_n^M} \left(\frac{Q_n^M}{Q_n^F} - \sigma M_n^c \right) = \mu_n \left(\frac{Q_n^M}{Q_n^F} - \sigma M_n^c \right); \\
J_{13}^c &= -r_n \rho_n \left(\frac{Q_w^F}{Q_n^F} \right)^2 \frac{Q_n^F}{Q_n^M} \frac{\left(\gamma + \sigma \frac{Q_n^F}{Q_w^F} M_n^c \right)}{Q_w^F} = -\frac{r_n \rho_n}{\mu_n} \frac{\mu_n}{Q_n^M} \frac{Q_w^F}{Q_n^F} \left(\gamma + \sigma \frac{Q_n^F}{Q_w^F} M_n^c \right) \\
&= -\mu_n \left(\gamma \frac{Q_w^F}{Q_n^F} + \sigma M_n^c \right); \\
J_{14}^c &= -r_n \rho_n \frac{Q_w^F}{Q_n^F} \frac{Q_n^F}{Q_n^M} \frac{\sigma M_n^c}{Q_w^F} = -\frac{r_n \rho_n}{\mu_n} \frac{\mu_n}{Q_n^M} \sigma M_n^c = -\mu_n \sigma M_n^c; \\
J_{21}^c &= (1 - r_n) \rho_n \frac{Q_n^F}{Q_n^M} M_n^c \frac{\gamma \frac{Q_n^F - Q_w^F}{\gamma Q_w^F} M_n^c - \sigma (M_n^c)^2 \frac{Q_n^F}{Q_w^F}}{\left(M_n^c \frac{Q_n^F}{Q_w^F} \right)^2 Q_w^F} = \frac{(1 - r_n) \rho_n}{Q_n^F} \frac{\left(Q_n^F - Q_w^F - \sigma Q_n^F M_n^c \right)}{Q_n^M} \\
&= \frac{(1 - r_n) \rho_n}{\delta_n} \frac{\delta_n}{Q_n^M} \left(1 - \frac{Q_w^F}{Q_n^F} - \sigma M_n^c \right) = \delta_n \frac{Q_n^F}{Q_n^M} \left(1 - \frac{Q_w^F}{Q_n^F} - \sigma M_n^c \right); \\
J_{22}^c &= (1 - r_n) \rho_n \frac{Q_w^F}{Q_n^F} \left(1 - \sigma \frac{Q_n^F}{Q_n^M} M_n^c \right) \frac{1}{Q_w^F} - \delta_n = \frac{(1 - r_n) \rho_n}{\delta_n} \frac{\delta_n}{Q_n^F} \left(1 - \sigma \frac{Q_n^F}{Q_n^M} M_n^c \right) - \delta_n \\
&= \delta_n \left(1 - \sigma \frac{Q_n^M}{Q_n^F} M_n^c - 1 \right) = -\delta_n \frac{Q_n^F}{Q_n^M} \sigma M_n^c; \\
J_{23}^c &= -(1 - r_n) \rho_n \left(\frac{Q_w^F}{Q_n^F} \right)^2 \frac{Q_n^F}{Q_n^M} \frac{\left(\gamma + \sigma \frac{Q_n^F}{Q_w^F} M_n^c \right)}{Q_w^F} = -\frac{(1 - r_n) \rho_n}{\delta_n} \frac{\delta_n}{Q_n^M} \left(\gamma \frac{Q_w^F}{Q_n^F} + \sigma M_n^c \right) \\
&= -\delta_n \frac{Q_n^F}{Q_n^M} \left(\gamma \frac{Q_w^F}{Q_n^F} + \sigma M_n^c \right); \\
J_{24}^c &= -(1 - r_n) \rho_n \frac{Q_w^F}{Q_n^F} \frac{Q_n^F}{Q_n^M} \frac{\sigma M_n^c}{Q_w^F} = -\frac{(1 - r_n) \rho_n}{\delta_n} \frac{\delta_n}{Q_n^M} \sigma M_n^c = -\delta_n \frac{Q_n^F}{Q_n^M} \sigma M_n^c; \\
J_{31}^c &= -r_w \rho_w \sigma \frac{Q_w^F}{Q_w^M} M_w^c \frac{1}{Q_w^F} = -\frac{r_w \rho_w}{\mu_w} \frac{\mu_w}{Q_w^M} \sigma M_w^c = -\mu_w \sigma M_w^c = J_{32}^c; \\
J_{33}^c &= -r_w \rho_w \sigma \frac{Q_w^F}{Q_w^M} M_w^c \frac{1}{Q_w^F} - \mu_w = -\frac{r_w \rho_w}{\mu_w} \frac{\mu_w}{Q_w^M} \sigma M_w^c - \mu_w = -\mu_w \left(1 + \sigma M_w^c \right); \\
J_{34}^c &= r_w \rho_w \left(1 - \sigma \frac{Q_w^F}{Q_w^M} M_w^c \right) \frac{1}{Q_w^F} = \frac{r_w \rho_w}{\mu_w} \frac{\mu_w}{Q_w^F} \left(1 - \sigma \frac{Q_w^F}{Q_w^M} M_w^c \right) = \mu_w \left(\frac{Q_w^M}{Q_w^F} - \sigma M_w^c \right); \\
J_{41}^c &= -(1 - r_w) \rho_w \sigma \frac{Q_w^F}{Q_w^M} M_w^c \frac{1}{Q_w^F} = -\frac{(1 - r_w) \rho_w}{\delta_w} \frac{\delta_w}{Q_w^M} \sigma M_w^c = -\delta_w \frac{Q_w^F}{Q_w^M} \sigma M_w^c = J_{42}^c = J_{43}^c;
\end{aligned}$$

$$\begin{aligned}
J_{44}^c &= (1 - r_w)\rho_w \left(1 - \sigma \frac{Q_w^F}{Q_w^M} M_w^c\right) \frac{1}{Q_w^F} - \delta_w = \frac{(1 - r_w)\rho_w}{\delta_w} \frac{\delta_w}{Q_w^F} \left(1 - \sigma \frac{Q_w^F}{Q_w^M} M_w^c\right) - \delta_w \\
&= \delta_w \left(1 - \sigma \frac{Q_w^F}{Q_w^M} M_w^c - 1\right) = -\delta_w \frac{Q_w^F}{Q_w^M} \sigma M_w^c.
\end{aligned}$$

Let us now introduce some useful repeating patterns that appear in the above formulas:

$$A := \frac{Q_n^F}{Q_n^F}, \quad B := \frac{Q_n^F}{Q_n^M}, \quad C := \frac{Q_w^F}{Q_w^M}, \quad D := \sigma M_n^c, \quad E := \sigma M_w^c. \quad (\text{A-1})$$

Using these patterns, the Jacobian matrix (29) evaluated in \mathbf{E}_c can be written as

$$\mathbb{J}(\mathbf{E}_c) = \begin{pmatrix} -\mu_n(A + D) & \mu_n \left(\frac{1}{B} - D\right) & -\mu_n(\gamma A + D) & -\mu_n D \\ \delta_n B(1 - A - D) & -\delta_n B D & -\delta_n B(\gamma A + D) & -\delta_n B D \\ -\mu_w E & -\mu_w E & -\mu_w(1 + E) & \mu_w \left(\frac{1}{C} - E\right) \\ -\delta_w C E & -\delta_w C E & -\delta_w C E & -\delta_w C E \end{pmatrix}$$

To compute the determinant of $\mathbb{J}(\mathbf{E}_c)$, one may proceed as follows.

$$\begin{aligned}
\det \mathbb{J}(\mathbf{E}_c) &= \begin{vmatrix} -\mu_n(A + D) & \mu_n \left(\frac{1}{B} - D\right) & -\mu_n(\gamma A + D) & -\mu_n D \\ \delta_n B(1 - A - D) & -\delta_n B D & -\delta_n B(\gamma A + D) & -\delta_n B D \\ -\mu_w E & -\mu_w E & -\mu_w(1 + E) & \mu_w \left(\frac{1}{C} - E\right) \\ -\delta_w C E & -\delta_w C E & -\delta_w C E & -\delta_w C E \end{vmatrix} \\
&= -\frac{\delta_w C}{\mu_w} \begin{vmatrix} -\mu_n(A + D) & \mu_n \left(\frac{1}{B} - D\right) & -\mu_n(\gamma A + D) & -\mu_n D \\ \delta_n B(1 - A - D) & -\delta_n B D & -\delta_n B(\gamma A + D) & -\delta_n B D \\ -\mu_w E & -\mu_w E & -\mu_w(1 + E) & \mu_w \left(\frac{1}{C} - E\right) \\ \mu_w E & \mu_w E & \mu_w E & \mu_w E \end{vmatrix} \\
&\quad \text{(by multiplication of the 4th row by } -\frac{\mu_w}{\delta_w C}\text{)} \\
&= -\frac{\delta_w C}{\mu_w} \begin{vmatrix} -\mu_n(A + D) & \mu_n \left(\frac{1}{B} - D\right) & -\mu_n(\gamma A + D) & -\mu_n D \\ \delta_n B(1 - A - D) & -\delta_n B D & -\delta_n B(\gamma A + D) & -\delta_n B D \\ -\mu_w E & -\mu_w E & -\mu_w(1 + E) & \mu_w \left(\frac{1}{C} - E\right) \\ 0 & 0 & -\mu_w & \frac{\mu_w}{C} \end{vmatrix} \\
&\quad \text{(by addition of the 3rd row to the 4th one)}
\end{aligned}$$

$$= \frac{\delta_w C}{\mu_w} \frac{\delta_n B}{\mu_n} \begin{vmatrix} -\mu_n(A+D) & \mu_n \left(\frac{1}{B} - D \right) & -\mu_n(\gamma A + D) & -\mu_n D \\ \mu_n(A+D-1) & \mu_n D & \mu_n(\gamma A + D) & \mu_n D \\ -\mu_w E & -\mu_w E & -\mu_w(1+E) & \mu_w \left(\frac{1}{C} - E \right) \\ 0 & 0 & -\mu_w & \frac{\mu_w}{C} \end{vmatrix}$$

(by multiplication of the 2nd row by $-\frac{\mu_n}{\delta_n B}$)

$$= \frac{\delta_w C}{\mu_w} \frac{\delta_n B}{\mu_n} \begin{vmatrix} -\mu_n & \frac{\mu_n}{B} & 0 & 0 \\ \mu_n(A+D-1) & \mu_n D & \mu_n(\gamma A + D) & \mu_n D \\ -\mu_w E & -\mu_w E & -\mu_w(1+E) & \mu_w \left(\frac{1}{C} - E \right) \\ 0 & 0 & -\mu_w & \frac{\mu_w}{C} \end{vmatrix}$$

(by addition of the 2nd row to the 1st one)

$$= \frac{\delta_w C}{\mu_w} \frac{\delta_n B}{\mu_n} \begin{vmatrix} -\mu_n \left(1 + \frac{1}{B} \right) & \frac{\mu_n}{B} & 0 & 0 \\ \mu_n(A-1) & \mu_n D & \mu_n(\gamma A + D) & \mu_n D \\ 0 & -\mu_w E & -\mu_w(1+E) & \mu_w \left(\frac{1}{C} - E \right) \\ 0 & 0 & -\mu_w & \frac{\mu_w}{C} \end{vmatrix}$$

(by subtracting the 2nd column from the 1st one)

$$= \frac{\delta_w C}{\mu_w} \frac{\delta_n B}{\mu_n} \begin{vmatrix} -\mu_n \left(1 + \frac{1}{B} \right) & \frac{\mu_n}{B} & 0 & 0 \\ \mu_n(A-1) & \mu_n D & \mu_n(\gamma A + D + CD) & \mu_n D \\ 0 & -\mu_w E & -\mu_w E(1+C) & \mu_w \left(\frac{1}{C} - E \right) \\ 0 & 0 & 0 & \frac{\mu_w}{C} \end{vmatrix}$$

(by adding the 4th row multiplied by C to the 3rd one)

Given the fact that all constants are positive, see (A-1), the sign of $\det \mathbb{J}(\mathbf{E}_c)$ is the sign of the 3×3 determinant that appears after developing with respect to the 4th row, that is

$$\begin{aligned} & \begin{vmatrix} -\mu_n \left(1 + \frac{1}{B} \right) & \frac{\mu_n}{B} & 0 \\ \mu_n(A-1) & \mu_n D & \mu_n(\gamma A + D + CD) \\ 0 & -\mu_w E & -\mu_w E(1+C) \end{vmatrix} \\ &= \mu_w E \begin{vmatrix} -\mu_n \left(1 + \frac{1}{B} \right) & \frac{\mu_n}{B} & 0 \\ \mu_n(A-1) & \mu_n D & \mu_n(\gamma A + D + CD) \\ 0 & -1 & -(1+C) \end{vmatrix} \\ &= \mu_w E \begin{vmatrix} -\mu_n \left(1 + \frac{1}{B} \right) & \frac{\mu_n}{B} & 0 \\ \mu_n(A-1) & 0 & \mu_n \gamma A \\ 0 & -1 & -(1+C) \end{vmatrix} \end{aligned}$$

(by addition of the 3rd row multiplied $\mu_n D$ by to the 2nd one)

The coefficient $\mu_w E$ is positive, so the sign of $\det \mathbb{J}(\mathbf{E}_c)$ is the sign of the determinant that appears

in the previous formula. The computation of the latter yields

$$\begin{aligned} \begin{vmatrix} -\mu_n \left(1 + \frac{1}{B}\right) & \frac{\mu_n}{B} & 0 \\ \mu_n(A-1) & 0 & \mu_n \gamma A \\ 0 & -1 & -(1+C) \end{vmatrix} &= -\mu_n^2 \gamma A \left(1 + \frac{1}{B}\right) + \mu_n^2 (A-1) \frac{1}{B} (1+C) \\ &= \mu_n^2 \frac{1}{B} \left(-\gamma A(B+1) + (A-1)(C+1)\right). \end{aligned}$$

Thus, we have

$$\begin{aligned} \det \mathbb{J}(\mathbf{E}_c) &= \frac{\delta_w C}{\mu_w} \frac{\delta_n B}{\mu_n} \frac{\mu_w}{C} \mu_w E \mu_n^2 \frac{1}{B} \left(-\gamma A(B+1) + (A-1)(C+1)\right) \\ &= \mu_n \delta_n \mu_w \delta_w E \left(-\gamma A(B+1) - (1-A)(C+1)\right). \end{aligned}$$

Finally, using the patterns defined by (A-1) we obtain

$$\det \mathbb{J}(\mathbf{E}^c) = \mu_n \delta_n \mu_w \delta_w \sigma M_w^c \left[-\gamma \frac{Q_w^F}{Q_n^F} \left(\frac{Q_n^F}{Q_n^M} + 1 \right) - \left(1 - \frac{Q_w^F}{Q_n^F} \right) \left(\frac{Q_w^F}{Q_w^M} + 1 \right) \right] < 0$$

whenever \mathbf{E}_c exists, that is, whenever it is fulfilled that

$$Q_n^F > Q_w^F > 1.$$

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