Monotone Dynamical Systems and Some Models of *Wolbachia* in *Aedes aegypti* Populations

G. Sallet [*] — A. H. B Silva Moacyr [**]

[*] Département Institut Élie Cartan, UMR 7502
Université de Lorraine, 57045 Metz Cedex 01, France
Gauthier.Sallet@univ-lorraine.fr

[**] Département Escola de Matemática Aplicada,
Fundação Getulio Vargas,
Praia de Botafogo 190, Rio de Janeiro, RJ Brésil, 22250-040
moacyr@fgv.br

ABSTRACT. We present a model of infection by *Wolbachia* of an *Aedes aegypti* population. This model is designed to take into account both the biology of this infection and any available data [30, 38]. The objective is to use this model for predicting the sustainable introduction of this bacteria. We provide a complete mathematical analysis of the model proposed and give the basic reproduction ratio $\mathcal{R}_0$ for *Wolbachia*. We observe a bistability phenomenon. Two equilibria are asymptotically stable : an equilibrium where all the population is uninfected and an equilibrium where all the population is infected. A third unstable equilibrium exists. We provide a lower bound for the basin of attraction of the desired infected equilibrium. We are in a backward bifurcation situation. The bistable situation occurs with natural biological values for the parameters.

RÉSUMÉ. Nous présentons un modèle d'infection par *Wolbachia* d'une population d' *Aedes aegypti*. Ce modèle est conçu pour à la fois prendre en compte la biologie de l'infection mais aussi les données d'une expérimentation sur le terrain [30, 38]. L'objectif est d'utiliser ce modèle pour prévoir l'introduction permanente de cette bactérie dans la population de moustiques. Nous donnons une analyse mathématique complète du modèle proposé avec le calcul du taux de reproduction de base $\mathcal{R}_0$ pour *Wolbachia*. On observe un phénomène de bistabilité. Deux équilibres sont asymptotiquement stables : un équilibre où toute la population est non infectée et un équilibre où toute la population est infectée. Un troisième équilibre instable existe. Nous donnons un encadrement pour le bassin d'attraction de l'équilibre souhaité. Il s'agit d'une situation de bifurcation rétrograde. Cette situation apparaît pour des valeurs biologiquement normales des paramètres.

KEYWORDS : Mathematical epidemiology, Wolbachia, Aedes, dynamical systems, stability, ODE.

MOTS-CLÉS : Épidémiogie mathématique, Wolbachia, Aedes, systèmes dynamiques,stabilité, EDO.

1. Introduction

Wolbachia is a bacterium which infects arthropod species, including a high proportion of insects (60% of species). Its interactions with its hosts are often complex, and in some cases it is considered as an endosymbiont.

The unique biology of *Wolbachia* has attracted a growing number of researchers interested in questions ranging from the evolutionary implications of infection through to the use of this agent for pest and disease control : a public web site has been funded by the National Science Foundation of Australia (`http://www.wolbachia.sols.uq.edu.au/about.cfm`), and a research in pubmeb (`http://www.ncbi.nlm.nih.gov/pubmed`) typing `wolbachia` gives 1315 results.

The bacterium was identified in 1924 by M. Hertig and S. B. Wolbach in *Culex pipiens* [26].

While *Wolbachia* is commonly found in many mosquitoes it is absent from the species that are considered to be of major importance for the transmission of human pathogens. The successful introduction of a life-shortening strain of *Wolbachia* into the dengue vector *Aedes aegypti* that decreases adult mean life has recently been reported [9, 20, 25, 42, 43, 49, 67].

Moreover it is estimated that the population of mosquitoes harboring *Wolbachia* is less efficient to transmit dengue [30, 43, 62].

Then it is considered that using *Wolbachia* can be a viable option for controlling the incidence of the dengue. This is peculiarly interesting since this approach is twofold : decreasing the population of mosquitoes and decreasing the transmission. Other approaches like Sterile Insect Techniques (SIT) [1, 15] act uniquely on population level. SIT consists to release sterile males (either irradiated males or genetically modified) competing with wild ones. A drawback of this technique is the need to release continuously sterile males. On the contrary the successful establishment of *Wolbachia* infected population, in theory, does not require continuous release.

In [18] a model is considered, to investigate the possibility for *Wolbachia* to invade a general population of hosts.

The reference [9] develops discrete models to predict the severity of adult life-shortening and in turn are used to estimate the impact on the transmission of dengue virus.

Reference [12] proposes a continuous-discrete model to predict invasion and establishment in a population.

A discrete model for establishment in a host population is studied in [16].

The authors of [24, 25] use integral delay-equation model and two stage population structure (juvenile/adult) to represent dynamics of spread in a host population.

Leslie matrix discrete model is used in [49].

Reference [57] considers discrete generations models.

Finally, in [52], reaction–diffusion and integro-difference equation models are used to model the spatio-temporal spread of *Wolbachia* in *Drosophila simulans*.

Our model, unlike those mentioned above, takes into account the totality of the population dynamics of mosquitoes, incorporating the three mosquito life-stages: egg, larva, and pupa. The adult life-stage is subdivided into three compartments: composed of young female mosquitoes (aged 1–5 days, not mated, that do not yet lay eggs), mature female and male mosquitoes. The reason is to take into account both the particular biology of *Wolbachia* and the possibility to incorporate biological data [38]. In many models some compartments are lumped : E, L and P in an aquatic stage in [1], L and P in [66]. When having access to data we obtain numbers for Eggs, Larvae and Pupae. This is the reason for our choice. When compartments are lumped it is very difficult to interpret these data to obtain figures for the lumped compartments.

This paper is organized as follows : In section 2 we study dynamics of a population of *Aedes aegypti*, incorporating the Egg, Pupae, Larvae, immature and mature female. As said one rationale for the introduction of two stages in female is to model, in the sequel, the cytoplasmic incompatibility induced by *Wolbachia* infection. We analyze completely this model. Section 3 is devoted to a complete model adapted for the characteristics of *Wolbachia*. A complete analysis is given and bistability and backward bifurcation are proven.

2. Population dynamics of wild *Aedes* mosquito

Before presenting and analyzing the model of infection with *Wolbachia* we will need some preliminaries and some results that will be used in the sequel.

2.1. The model

The life cycle of a mosquito consists of two main stages: aquatic (egg, larva, pupa) and adult (with males and females). After emergence from pupa, a female mosquito needs to mate and get a blood meal before it starts hatching eggs. Then every $4 - -5$ days it will take a blood meal and lay $100 - -150$ eggs at different places ($10 - -15$ per place). For the mathematical description, our model is inspired by the models considered in [14, 15]. However, for biological applications, our model introduce the complete stages.
However we will consider three aquatic stages, where the authors [15, 1] lump the three stages into a single aquatic stage. The rationale is to prepare for a subsequent model with infection by *Wolbachia*. Furthermore, we split the adult stage into three sub-compartments, males, immature female and mature female which leads to the following compartments:

- – Eggs E;
- – Larvae L;
- – Pupae P;
- – Males M;

– Young immature females Y; we consider a female to be in the Y compartment from its emergence from pupa until her gonotrophic cycle has began, that is the time of mating and taking the first blood meal, which takes typically $3 - -4$ days.

– Mature females F, i.e., fertilized female.

Parameters μ_E, μ_P, μ_Y, μ_F and μ_M are respectively the death rate of eggs, larvae, pupae, immature female, mature females and males. The parameters η_E, η_L, η_P , β are the respective rate of transfer to the next compartment. The parameter ν is the sex ratio. In this model, we use a density dependent death rate for the larvae stage since mosquitoes larvae (anopheles and aedes) are density sensitive, which imply an additional density mortality rate. We assume that eggs emergence is influenced by larvae density. The development is regulated by a carrying capacity effect depending on the occupation of the available breeding sites. The parameter C is the carrying capacity related to the amount of available nutrients and space. Such an hypothesis is appropriate since mosquitoes only have access to a finite number of potential breeding sites, and density-dependent larval survival has been demonstrated at such sites. The parameter ϕ is the average amount of eggs laid per fertilized female per unit of time.

Mating is a complex process that is not fully understood. However, as discussed in [1] and references therein, the male mosquito can mate practically through all its life. A female mosquito needs one successful mating to breed lifelong [31]. It is admitted that mosquitoes locate themselves in space and time to ensure they are available to mate. Therefore, it is reasonable to assume that in any case the immature female will mate and afterwards move to compartment F , or die. Thus a parameter like $\frac{1}{\beta + \mu_Y}$ can represents the mean time given by length of the first gonotrophic cycle of a female, i.e., the interval from immediately after the mating to the first blood meal.

We assume that all the parameters are constant. In reality, the mosquito population varies seasonally. Nevertheless, such a model should be a good approximation for a definite season.

$$
\begin{cases}
\dot{E} & = \phi\,F - (\mu_E + \eta_E)\,E \\[2mm]
\dot{L} & = \eta_E\,E\left(1 - \dfrac{L}{C}\right)^+ - (\mu_L + \eta_L)\,L \\[2mm]
\dot{P} & = \eta_L\,L - (\mu_P + \eta_P)\,P \\[2mm]
\dot{Y} & = \nu\,\eta_P\,P - (\beta + \mu_Y)\,Y \\[2mm]
\dot{F} & = \beta\,Y - \mu_F\,F \\[2mm]
\dot{M} & = (1 - \nu)\,\eta_P\,P - \mu_M\,M,
\end{cases}
\tag{1}
$$

where we have denoted by $\left(1 - \dfrac{L}{C}\right)^+$ the positive part of the function, i.e.,

$$\left(1 - \frac{L}{C}\right)^+ = \begin{cases} 1 - \dfrac{L}{C} & \text{if } L \leq C \\[2ex] 0 & \text{if } L > C \end{cases}$$

This choice is for the rationale of modelling : female *Aedes* choose their breeding site, hence value of egg hatching, in function of the availability of food and concentration of larvae. When $L > C$ having a egg hatching rate negative would be dubious. The choice of this function, $(1 - \dfrac{L}{C})$ with carrying capacity, is not new and has been already extensively used [15, 14]. We will study elsewhere a model with intraspecific competition for larvae [37].

We denote by X a vector of the state space of this system.

$$X^T = (E, L, P, Y, F, M),$$

The domain

$$\mathcal{D} = \{X \in \mathbb{R}_+^6 \mid L \leq C\}$$

is a closed positively invariant absorbing set. Absorbing means that any trajectory of (1) enters the interior of $\mathcal{D}$. Then throughout the remaining of this paper we will limit our analysis to $\mathcal{D}$.

2.2. Analysis of the model

In this section we will study the stability of the model and use one of his characteristic monotonicity. Monotonicity is a property shared by many biological models. For the convenience of the reader we recall some properties of monotone systems

2.2.1. Monotone dynamical systems

Consider an ODE

$$\dot{x} = f(x) \tag{2}$$

defined on a positively invariant set U (i.e., any trajectory starting in U, stays in U). We denote by $\phi_f(x)$ the flow f of this ODE, or in other words the trajectory at time t starting from x. We assume, to avoid complications, that this is defined for any $t \geq 0$ (this will be the case our system). We consider the standard partial order on $\mathbb{R}^n$ and the corresponding notations : $x \leq y \iff$ for all i $x_i \leq y_i$, $x < y$ if $x \leq y$ and $x \neq y$ and finally $x \ll y \iff$ for all i, $x_i < y_i$.

System (2) is called monotone if $x \leq y$ implies $\phi_t(x) \leq \phi_t(y)$ [29, 28]. If f is $\mathcal{C}^1$ this is equivalent to saying that the Jacobian of f, $Jac(x) = \left(\dfrac{\partial f_i(x)}{\partial x_j} \right)_{1 \leq i,j \leq n}$ is a Metzler matrix. A Metzler matrix is a matrix whose off-diagonal terms are nonnegative.

System (2) is called strongly monotone if $x < y$ implies $\phi_t(x) \ll \phi_t(y)$ for any $t > 0$. System (2) is strongly monotone if the Jacobian is irreducible. There is a simple algorithm to check if a Metzler matrix A is irreducible. The associated digraph $G(A)$ of a $n \times n$ matrix A, consists of n vertices $1, \ldots j$ where an edge leads from j to i if and only if $a_{ij} \neq 0$. A matrix A is irreducible iff its associated digraph is strongly connected, which means that for any ordered pair (j,i) of vertices of $G(A)$, there exists a sequence of oriented edges (a path) which leads from i to j.
We can use a different partial order associated to a cone. Let $K = \mathbb{R}_+^k \times -(\mathbb{R}_+^{n-k})$ and the associated order defined by $x \leq_K y \iff y - x \in K$, $x \ll y \iff y - x \in \overset{\circ}{K}$.
The notion of monotony for this order $\leq_K$ will called of type K : monotone systems of type K.

2.2.2. Monotonicity of the mosquito model (1)

Computing the Jacobian of (1) gives

$$
A(X) =
\begin{bmatrix}
-(\mu_E + \eta_E) & 0 & 0 & 0 & \phi & 0 \\
\eta_E \left(1 - \dfrac{L}{C}\right)^+ & -(\mu_L + \eta_L + \dfrac{\eta_E}{C} E) & 0 & 0 & 0 & 0 \\
0 & \eta_L & -(\mu_P + \eta_P) & 0 & 0 & 0 \\
0 & 0 & \nu\,\eta_P & -(\beta + \mu_Y) & 0 & 0 \\
0 & 0 & 0 & \beta & -\mu_F & 0 \\
0 & 0 & (1-\nu)\,\eta_P & 0 & 0 & -\mu_M
\end{bmatrix}.
$$

This Jacobian on $\mathcal{D}$ is a Metzler matrix, hence (1) is a monotone system. We can discard the last equation since M_W does not occur in the other equations. The reduced system is then strongly monotone if $L < C$.

2.2.3. Stability Analysis

Using the concept in demography introduced by Böckh, we can define a basic offspring number as the mean number of females born from one female during its entire reproductive life. This can be computed using the methods of [60] (where the transmission term is given by ϕF) or by looking at the equations.
Using (1) we obtain easily that

$$\mathcal{R}_{0,\text{offsp}} = \frac{\phi}{\mu_F} \frac{\eta_E}{\mu_E + \eta_E} \frac{\eta_L}{\mu_L + \eta_L} \frac{\nu\,\eta_P}{\mu_P + \eta_P} \frac{\beta}{\beta + \mu_Y}.$$

When $\mathcal{R}_{0,\text{offsp}} \leq 1$ the only equilibrium is the origin. When $\mathcal{R}_{0,\text{offsp}} > 1$, a second positive equilibrium exists $(E^*, L^*, P^*, Y^*, F^*, M^*)^T$.

We can express all the components as positive linear expressions of P^*

$$L^* = \frac{\mu_p + \eta_p}{\eta_L} P^*, \qquad\qquad Y^* = \frac{\nu\,\eta_P}{\beta + \mu_Y} P^*, \qquad (3)$$

$$F^* = \frac{\beta}{\beta + \mu_Y} \frac{\nu\,\eta_P}{\mu_F} P^*, \qquad M^* = \frac{(1-\nu)\,\eta_P}{\mu_M} P^* \qquad (4)$$

$$E^* = \frac{\phi}{\mu_E + \eta_E} \frac{\beta}{\beta + \mu_Y} \frac{\nu\,\eta_P}{\mu_F} P^*. \qquad (5)$$

Finally, replacing in the equation $\dot{L} = 0$, we get

$$P^* = \frac{\mathcal{R}_0 - 1}{\mathcal{R}_0} \frac{C\,\eta_L}{\mu_P + \eta_P} \qquad (6)$$

For a future use we will need positively compact invariant sets for (1) when $\mathcal{R}_{0,\text{offsp}} > 1$ and when $\mathcal{R}_{0,\text{offsp}} \leq 1$. In accordance with these notations the closed order interval $[a, b]$ is

$$[\,a, b\,] = \{x \in \mathbb{R}^n \mid a \leq x \leq b\}$$

We will also denote by $X^* = (E^*, L^*, P^*, Y^*, F^*, M^*)^T \gg 0$.

Proposition 2.1

When $\mathcal{R}_{0,\text{offsp}} > 1$, for any s and any θ such that $0 < s < 1$ and $1 < \theta$ the closed order intervals

$$[\,s\,X^*,\ \theta\,X^*\,]$$

are positively invariant compact subsets of the positive orthant for system (1)

When $\mathcal{R}_{0,\text{offsp}} \leq 1$, there exists $X_k \gg 0$ such that the order intervals $[0, \theta\,X_k]$ are positively invariant compact subsets of the positive orthant for any $\theta \geq 1$.

Proof

We remark that the vector field associated to (1), $A(X)\,X = f(X)$, is strictly sublinear. In other words this means that for any $X \gg 0$ and any $0 < \lambda < 1$ we have

$$\lambda\,f(X) < f(\lambda\,X).$$

From sublinearity we immediately obtain $f(s\,X^*) > 0$ and $f(\theta\,X^*) < 0$. Using the proof of Proposition 2.1 we then obtain that $[\,s\,X^*,\ \theta\,X^*\,]$ is positively invariant by the monotone system (1).

When $\mathcal{R}_{0,\text{offsp}} \leq 1$ we choose $L_k = C$, $P_k = 2\,\dfrac{\eta_L}{\mu_P + \eta_P}\,L_k$, $Y_k = 2\,\dfrac{\nu\,\eta_P}{\beta + \mu_U}\,P_k$,

$F_k = 2\,\dfrac{\beta}{\mu_F}\,Y_k$, $M_k = 2\dfrac{(1-\nu)\,\eta_P}{\mu_M}\,P_k$ and $E_k = 2\dfrac{\phi}{\mu_E + \eta_E}\,F_k$. If we define $X_k = (E_k, L_k, P_k, Y_k, F_k, M_k)^T$ we have $f(X_k) \ll 0$. By the same argument as before the order interval $[0,\ X_k]$ is a positively invariant absorbing set.

This proves that all the trajectories are bounded.

∎

We can now give the main result of this section

Theorem 2.1
If $\mathcal{R}_{0,\text{offsp}} < 1$ the origin is globally asymptotically stable in the nonnegative orthant $\mathbb{R}_+^n$. In other words the mosquito population goes to extinction.

If $\mathcal{R}_{0,\text{offsp}} > 1$ the positive equilibrium X^* is globally asymptotically stable on the nonnegative orthant minus the M-axis.

Proof
Since M does not appear in the 5 first equations, to study the stability of system (1) it is sufficient to consider the first 5 equations. In this case the system is strictly monotone and strictly sub-linear. Moreover Proposition 2.1 shows that all the trajectories are bounded. We can apply Theorem 6.1 of [27], with a simple adaptation to strict sub linear systems. Hence all trajectories tend to the origin or else there is a unique equilibrium $X^* \gg 0$ and all trajectories in $\mathbb{R}_+^5 \setminus \{0\}$ tend to X^*.

The origin is stable when $\mathcal{R}_{0,\text{offsp}} < 1$. On the other hand X^* is stable when $\mathcal{R}_{0,\text{offsp}} > 1$ and the origin is unstable. It is sufficient to consider the Jacobian at the equilibrium. Since we will have to do again these computations we refer to a subsequent section (3.4.1), where the stability of these matrices are proved. Actually the Jacobian computed at the positive equilibrium is given by matrix A_{11} in (3.4.1). The stability of A_{11} is proven in this section.

When $\mathcal{R}_{0,\text{offsp}} \leq 1$ we have only one equilibrium, which is the origin, in a set where the system is strongly monotone. Then using Theorem 10.3 of Hirsch [28] we obtain the global stability of the origin, in the open domain $L < C$. Since this domain is absorbing this proves the global asymptotic stability.

∎

For further reference we will denote by $f(X, \phi, \mu_F, \mu_K)$ the vector field on $\mathbb{R}^6$ associated to (1). This is to stress some particular parameters which will be of importance later on.

3. A complete model

We will now consider a model of infection of *Wolbachia* in an *Aedes* population. We assume that the wild population, when *Wolbachia* is not present, is sustainable. This means that $\mathcal{R}_{0,\text{offsp}} > 1$.

Our model take into account cytoplasmic incompatibility, which is outlined in the following table :

Reproduction			
		♂	
		Infected	Uninfected
♀	Infected	Infected	Infected
	Uninfected	Sterile	Uninfected

This phenomenon causes embryos from Wolbachia-uninfected females to die when they are mated with infected males whereas infected females are not affected in this manner[6, 30].

We index by U or W respectively the uninfected and infected stages. With this notation, the compartment of F_{WU} is the compartment of infected females fertilized by uninfected males, F_{WW} the compartment of infected females fertilized by infected males, F_{UU} the females resulting of mating between uninfected individuals. We denote by $F_W = F_{WU} + F_{WW}$ the compartment of infected female. Finally F_{UW} is the uninfected female fecundated by an infected male. We assume that cytoplasmic incompatibility is complete and this implies that this last compartment is constituted with sterile females. The assumption of complete CI is consistent with laboratory data [62]. Furthermore, based on this data, we also assume perfect maternal transmission of wMel infection. wMel is a peculiar strain of *Wolbachia* [5].

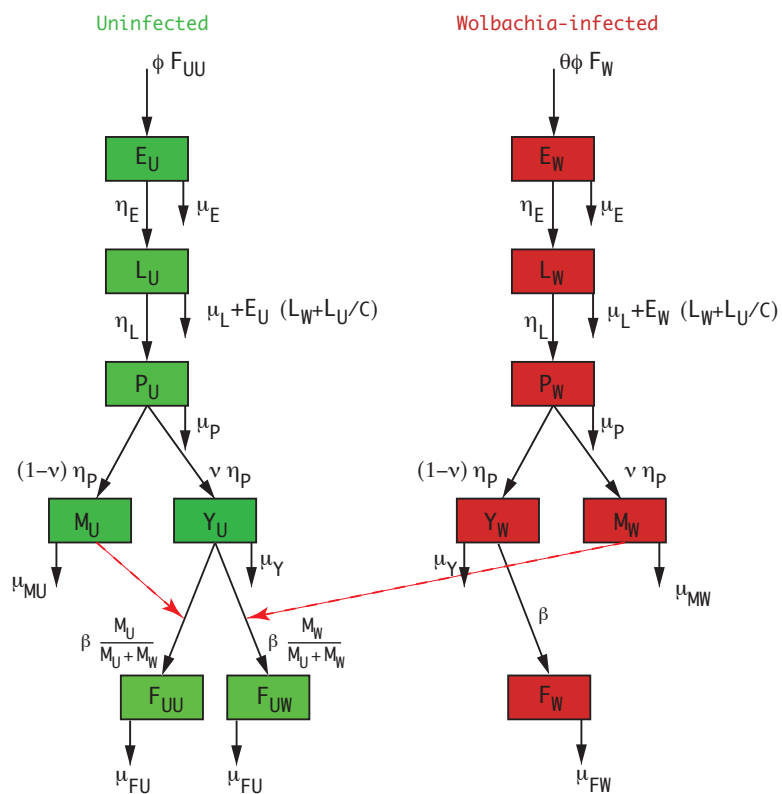These assumptions lead to the following system, defined on a subset of $\mathbb{R}_+^{13}$ whose flow graph is

Figure 1. *The Flow graph of Wolbachia system*

We split the system into two subsystems

$$
\left\{
\begin{aligned}
\dot{E}_U &= \phi\, F_{UU} - (\mu_E + \eta_E)\, E_U \\[2mm]
\dot{L}_U &= \eta_E\, E_U \left(1 - \frac{(L_U + L_W)}{C}\right)^{+} - [\eta_L + \mu_L]\, L_U \\[2mm]
\dot{P}_U &= \eta_L\, L_U - (\mu_P + \eta_P)\, P_U \\[2mm]
\dot{Y}_U &= \nu\, \eta_P\, P_U - (\beta + \mu_Y)\, Y_U \\[2mm]
\dot{F}_{UU} &= \beta\, Y_U\, \frac{M_U}{M_U + M_W} - \mu_{FU}\, F_{UU} \\[2mm]
\dot{M}_U &= (1 - \nu)\, \eta_P\, P_U - \mu_{MU}\, M_U \\[2mm]
\dot{E}_W &= \theta\, \phi\, F_W - (\mu_E + \eta_E)\, E_W \\[2mm]
\dot{L}_W &= \eta_E\, E_W \left(1 - \frac{(L_U + L_W)}{C}\right)^{+} - [\eta_L + \mu_L]\, L_W \\[2mm]
\dot{P}_W &= \eta_L\, L_W - (\mu_P + \eta_P)\, P_W \\[2mm]
\dot{Y}_W &= \nu\, \eta_P\, P_W - (\beta + \mu_Y)\, Y_W \\[2mm]
\dot{F}_W &= \beta\, Y_W - \mu_{FW}\, F_W \\[2mm]
\dot{M}_W &= (1 - \nu)\, \eta_P\, P_W - \mu_{MW}\, M_W,
\end{aligned}
\right. \tag{7}
$$

and

$$
\dot{F}_{UW} = \beta\, Y_U\, \frac{M_W}{M_U + M_W} - \mu_{FU}\, F_{UW}. \tag{8}
$$

Since F_{UW} (sterile female) does not appear in the other equations, due to cytoplasmic incompatibility, the asymptotic behavior of the complete system can be reduced to the behavior of system (7), with (8) discarded. From now on, we will consider this reduced system. We will also restrict to the domain

$$
\mathcal{D} = \{X \mid L_U + L_W \leq C\}. \tag{9}
$$

We have bounded cœfficients ($0 \leq \dfrac{M_U}{M_U + M_W} \leq 1$). Then in equations (7) we replace $\dfrac{M_U}{M_U + M_W}$ by

$$h(M_U, M_W) = \begin{cases} \dfrac{M_U}{M_U + M_W} & \text{if } M_U + M_W > 0 \\[3mm] 0 & \text{if } M_U = M_W = 0 \end{cases}$$

System (7) is defined on $\mathbb{R}_+^{12} \setminus \{M_U = M_W = 0\}$.

We will denote by $X = (X_U, X_W) \in \mathbb{R}_+^6 \times \mathbb{R}_+^6$ the components of the state of the system and we decompose accordingly the vector field in $f = (f_U, f_V)$. X_U corresponds to the uninfected variables and X_W corresponds to the *Wolbachia*-infected variables. System (7) can be written evidently

$$\begin{bmatrix} \dot{X}_U \\ \dot{X}_W \end{bmatrix} = \begin{bmatrix} A_U(X) & 0 \\ 0 & A_W(X) \end{bmatrix} \begin{bmatrix} X_U \\ X_W \end{bmatrix}$$

With this choice the vector is globally Lipschitz and the nonnegative orthant $\mathbb{R}_+^{12}$ is positively invariant.
We will need, later on, to identify the invariant faces of $\mathbb{R}_+^{12}$. It is clear that the only faces positively invariant are the four faces

$$\{0\}^5 \times \mathbb{R}_+ \times \mathbb{R}^6 \ , \ \mathbb{R}_+^6 \times \mathbb{R}_+ \times \{0\}^5 \ , \ \{0\}^6 \times \mathbb{R}^6 \ , \ \mathbb{R}_+^6 \times \{0\}^6$$

of dimension $7, 7, 6, 6$. We observe that the critical face $\{M_U = M_W = 0\}$ is not positively invariant.

We assume that *Wolbachia* has an impact on a stage when it is ascertained in litterature. However it would be straightforward to study a model for which *Wolbachia* has an impact on each stage. We incorporate a reduction of the mean life of the adult male and female mosquito as quoted in the literature [9, 20, 25, 42, 43, 49, 67]. Then we denote by μ_{FW} and μ_{MW} respectively the death rate of female and male infected by *Wolbachia*. We also introduce a competition, for mating, between infected male and uninfected male.
In this model E_U, E_W are the eggs compartments, respectively uninfected and infected. According to the literature, there is no apparent difference between infected and uninfected eggs [39] . So we denote respectively by μ_E and η_E the common death rate and the transition into the larvae compartments.
Similarly L_U and L_W are the larval compartments. In this case we introduce an intraspecific competition between larvae. Again, it seems that there is no known difference between infected and uninfected larvae [39]. Then we denote by μ_L and η_L the common death rate and transition rate to pupae compartments.
We denote by P_U and P_W the uninfected and infected pupae compartments.
We also introduce a factor $\theta \leq 1$ to consider an eventual decrease of the amount of laid eggs by an infected female [30, 41, 42, 62, 67].

We consider this model in the nonnegative orthant minus the set defined by $\{M_U = M_W = 0\}$. The nonnegative orthant is clearly positively invariant by this system. We can define the value of our system to be 0 at the origin, since the absence of population is a singular point. Note that our vector field cannot be prolongated continuously on the nonnegative orthant. However all the trajectories are defined on our domain. The competition between males results in the loss of monotonicity.

3.1. Equilibria

3.1.1. Uninfected equilibrium : *Wolbachia* free equilibrium

When there is no infection in the mosquito population, i.e., $E_W = L_W = P_W = Y_W = F_W = F_{UW} = M_W = 0$, model (7) reduces to model (1) of mosquito population. Then in the sequel we will assume that $\mathcal{R}_{0,\text{offsp}} > 1$. For this model the basic offspring number is

$$\mathcal{R}_{0,\text{offsp},U} = \frac{\phi}{\mu_{FU}} \frac{\eta_E}{\mu_E + \eta_E} \frac{\eta_L}{\mu_L + \eta_L} \frac{\nu\,\eta_P}{\mu_P + \eta_P} \frac{\beta}{\beta + \mu_Y}.$$

In this case there is an equilibrium on the boundary of the nonnegative orthant whose components are given by (3, 6), with the evident adaptation of notations corresponding to the vector field $f(X, \phi, \mu_{FU}, \mu_{MU})$.

This equilibrium corresponds to a population free of infection. We will call this equilibrium the WFE (*Wolbachia* free equilibrium). The WFE is expressed by $(X_U^*, 0)$ where X_U^* is given by (3, 6) with μ_F, μ_M replaced by μ_{FU}, μ_{MU} in the formulas.

3.1.2. Completely *Wolbachia*-Infected equilibrium

In a similar way if $E_U = L_U = P_U = Y_U = F_{UU} = M_U = 0$ the system reduces to a system like (1) with different parameters. Actually this corresponds to the vector field $f(\theta\,\phi, \mu_{FW}, \mu_{MW})$. Then we define a basic offspring number for the completely infected population

$$\mathcal{R}_{0,\text{offsp},W} = \frac{\theta\,\phi}{\mu_{FW}} \frac{\eta_E}{\mu_E + \eta_E} \frac{\eta_L}{\mu_L + \eta_L} \frac{\nu\,\eta_P}{\mu_P + \eta_P} \frac{\beta}{\beta + \mu_Y}.$$

In this case there is an equilibrium on the boundary of the nonnegative orthant given by

$$P_W^* = \frac{C\,\eta_L}{\mu_P + \eta_P} \frac{(\mathcal{R}_{0,\text{offsp},W} - 1)}{\mathcal{R}_{0,\text{offsp},W}} \tag{10}$$

$$L_W^* = \frac{\mu_P + \eta_P}{\eta_L} \, P_W^*, \qquad Y_W^* = \frac{\nu \, \eta_P}{\beta + \mu_Y} \, P_W^*, \tag{11}$$

$$M_W^* = \frac{(1 - \nu) \, \eta_P}{\mu_{MW}} \, P_W^* \qquad F_W^* = \frac{\beta}{\beta + \mu_Y} \, \frac{\nu \, \eta_P}{\mu_{FW}} \, P_W^*, \tag{12}$$

$$F_{UW}^* = 0, \qquad E_W^* = \frac{\theta \, \phi}{\mu_E + \eta_E} \, \frac{\beta}{\beta + \mu_Y} \, \frac{\nu \, \eta_P}{\mu_{FW}} \, P_W^* \tag{13}$$

In the sequel, we will refer to this equilibrium as the "Completely *Wolbachia*-Infected Equilibrium" (CWIE).

Since we are addressing the issue of the sustainable establishment of *Wolbachia* we will assume in what follows that $\mathcal{R}_{0,\text{offsp},W} > 1$.

3.1.3. A coexistence equilibrium

We remark that

$$\mathcal{R}_{0,\text{offsp},W} = \frac{\theta \, \mu_{FU}}{\mu_{FW}} \, \mathcal{R}_{0,\text{offsp},U} < \mathcal{R}_{0,\text{offsp},U}.$$

This inequality implies that the infected population, as actually observed, would be smaller that the uninfected population.

We denote by $\mathcal{R}_{0,W} = \dfrac{\theta \, \mu_{FU}}{\mu_{FW}} < 1$. We will justify, later on that this notation: $\mathcal{R}_{0,W}$ is actually the basic reproduction ratio [60] for *Wolbachia* in the mosquito population.

Then

$$\mathcal{R}_{0,\text{offsp},W} = \mathcal{R}_{0,W} \, \mathcal{R}_{0,\text{offsp},U} < \mathcal{R}_{0,\text{offsp},U}. \tag{14}$$

We assume that $\mathcal{R}_{0,\text{offsp},W} > 1$. In this case a coexistence equilibrium exists in the positive orthant. The components P_U and P_W are given by

$$P_{U,\text{coex}} = C \, \frac{\eta_L}{\eta_P + \mu_P} \, \frac{\theta \, \mu_{FU} \, \mu_{MU}}{\mu_{MW} \, [\mu_{FW} - \theta \, \mu_{FU}] + \theta \, \mu_{FU} \, \mu_{MU}} \, \frac{(\mathcal{R}_{0,\text{offsp},W} - 1)}{\mathcal{R}_{0,\text{offsp},W}} \tag{15}$$

$$P_{W,\text{coex}} = C \, \frac{\eta_L}{\eta_P + \mu_P} \, \frac{\mu_{MW} \, (\mu_{FW} - \theta \, \mu_{FU})}{\mu_{MW} \, [\mu_{FW} - \theta \, \mu_{FU}] + \theta \, \mu_{FU} \, \mu_{MU}} \, \frac{(\mathcal{R}_{0,\text{offsp},W} - 1)}{\mathcal{R}_{0,\text{offsp},W}} \tag{16}$$

These two components are positive with our hypotheses. The remaining components can be expressed in terms of these two as follows:

$$L_{U,\text{coex}} = \frac{\mu_P + \eta_P}{\eta_L} \, P_{U,\text{coex}}, \qquad L_{W,\text{coex}} = \frac{\mu_P + \eta_P}{\eta_L} \, P_{W,\text{coex}}, \tag{17}$$

$$Y_{U,\text{coex}} = \frac{\nu \, \eta_P}{\beta + \mu_Y} \, P_{U,\text{coex}} \,, \qquad Y_{W,\text{coex}} = \frac{\nu \, \eta_P}{\beta + \mu_Y} \, P_{W,\text{coex}} \,, \tag{18}$$

$$M_{U,\text{coex}} = \frac{(1-\nu) \, \eta_P}{\mu_{MU}} \, P_{U,\text{coex}}, \qquad M_{W,\text{coex}} = \frac{(1-\nu) \, \eta_P}{\mu_{MW}} \, P_{W,\text{coex}}. \tag{19}$$

$$\tag{20}$$

$$F_{UU,\text{coex}} = \frac{\beta \, \nu \, \eta_P \mu_{MW}}{\mu_{FU} \, (\mu_{MU} \, P_{W,\text{coex}} + \mu_{MW} \, P_{U,\text{coex}}) \, (\beta + \mu_Y)} \, P_{U,\text{coex}}^2, \tag{21}$$

$$F_{W,\text{coex}} = \frac{\beta \, \nu \, \eta_P}{\mu_{FW} \, (\beta + \mu_Y)} \, P_{W,\text{coex}}, \tag{22}$$

$$E_{U,\text{coex}} = \frac{\beta \, \nu \, \phi \, \eta_P \, \mu_{MW}}{\mu_{FU} \, (\mu_{MU} \, P_{W,\text{coex}} + \mu_{MW} \, P_{U,\text{coex}}) \, (\beta + \mu_Y) \, (\mu_E + \eta_E)} \, P_{U,\text{coex}}^2, \tag{23}$$

$$E_{W,\text{coex}} = \frac{\beta \, \nu \, \phi \, \theta \, \eta_P}{\mu_{FW} \, (\beta + \mu_Y) \, (\mu_E + \eta_E)} \, P_{W,\text{coex}}. \tag{24}$$

3.2. Monotonicity of the system

In this section we will prove that our system is monotone for an order $\leq_K$ on the closed absorbing positively invariant set $\mathcal{D}$ (see 9) and strongly monotone on a dense subset of $\mathcal{D}$.

We claim that system (7) is monotone relatively to the cone $K = \mathbb{R}_+^6 \times -(\mathbb{R}_+^6)$ [53].
The Jacobian is given by the matrix block

$$J(X) = \begin{bmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{bmatrix}$$

partitioned in 6×6 blocks. The blocks are given by

$$J_{11} = \begin{bmatrix} -(\mu_E + \eta_E) & 0 & 0 & 0 & \phi & 0 \\ \eta_E \left(1 - \frac{L_U + L_W}{C}\right) & -(\eta_L + \mu_L + \frac{\eta_E}{C} E_U) & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P + \mu_P) & 0 & 0 & 0 \\ 0 & 0 & \nu \, \eta_P & -(\beta + \mu_Y) & 0 & 0 \\ 0 & 0 & 0 & \beta & -\mu_{FU} & 0 \\ 0 & 0 & (1-\nu) \, \eta_P & 0 & 0 & -\mu_{MU} \end{bmatrix}$$

$$
J_{12} = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 \\
0 & -\frac{\eta_E}{C} E_U & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -\beta \frac{M_U Y_U}{(M_U + M_W)^2} \\
0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}
$$

$$
J_{21} = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 \\
0 & -\frac{\eta_E}{C} E_W & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}
$$

$$
J_{22} = \begin{bmatrix}
-(\mu_E + \eta_E) & 0 & 0 & 0 & \theta\,\phi & 0 \\
\eta_E \left(1 - \frac{L_U + L_W}{C}\right) & -(\eta_L + \mu_L + \frac{\eta_E}{C} E_W) & 0 & 0 & 0 & 0 \\
0 & \eta_L & -(\eta_P + \mu_P) & 0 & 0 & 0 \\
0 & 0 & \nu\,\eta_P & -(\beta + \mu_Y) & 0 & 0 \\
0 & 0 & 0 & \beta & -\mu_{FW} & 0 \\
0 & 0 & (1-\nu)\,\eta_P & 0 & 0 & -\mu_{MW}
\end{bmatrix}
$$

Let P the diagonal matrix defined by

$$
P = \mathrm{diag}(1, 1, 1, 1, 1, 1, -1, -1, -1, -1, -1 - 1)
$$

Then

$$
P\, Jac(X)\, P = \begin{bmatrix} J_{11} & -J_{12} \\ -J_{21} & J_{22} \end{bmatrix}
$$

which is a Metzler matrix. This proves our claim.
We will denote by $\leq_K$ the order corresponding to the cone K. Using the standard order on $\mathbb{R}^6$, we have the relation

$$
(X_U, X_W) \leq_K (Y_U, Y_W) \iff X_U \leq Y_U \; ; \; X_W \geq Y_W
$$

The system is clearly strongly monotone on the interior of the domain $\mathcal{D}$.
For the convenience of the reader we draw the graph of the Jacobian, to justify our claims.
It is straightforward that the digraph is strongly connected. We plot the negative links
in red. There exists an algorithm to identify if a system is monotone relatively to an
alternative cone. In the non oriented graph, the negative links are identified. There exists
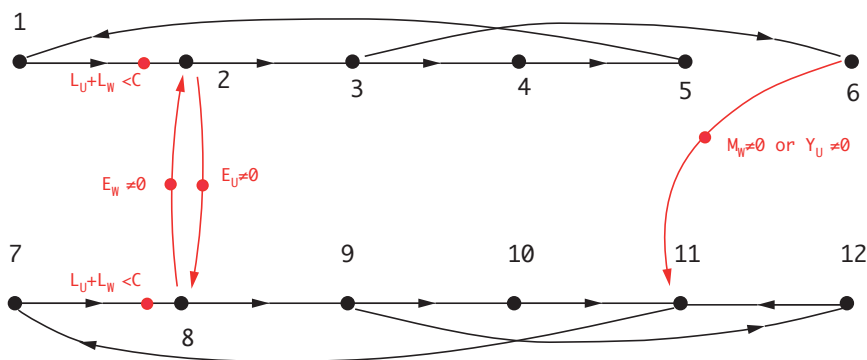a cone iff any loop contains an even number of negative links.

Figure 2. *The links that can vanish are with a red dot*

It is clear that this graph is strongly connected in the interior of $\mathcal{D}$, which proves the
strong monotonicity. Some red links are necessary to obtain strong connectivity. Then
our system will be monotone and strongly connected on the domain

$$\mathcal{B} = \{X \in \mathbb{R}^{12} \mid 0 \leq L_U + L_W < C \; ; \; 0 < E_W \; ; 0 < M_U \; ; 0 < Y_U\}$$

We have $\overset{o}{\mathcal{D}} \subset \mathcal{B}$. However we have already identified the 4 invariant faces of the nonneg-
ative orthant. Our system is strongly monotone on the nonnegative orthant minus these 4
faces.
We also observe (for the non oriented graph) that every closed loop has an even number
of red edges, which proves the monotonicity for a alternative cone [53].
We observe also that our system is strictly sub linear for the classical order on $\mathbb{R}^{12}$ in the
domain $\mathcal{D}$.

3.3. Invariance and Forward boundedness of the trajectories

We denote the WFE by $X_{\text{wfe}} = (X_U^*, 0)$, the CWIE by $W_{\text{cwie}} = (0, X_W^*)$ and the coexis-
tence equilibrium by

$$X_{\text{coex}} = (E_{U,\text{coex}}, L_{U,\text{coex}}, P_{U,\text{coex}}, Y_{U,\text{coex}}, F_{UU,\text{coex}}, M_{U,\text{coex}}, \dots$$

$$E_{W,\text{coex}}, E_{W,\text{coex}}, L_{W,\text{coex}}, P_{W,\text{coex}}, F_{W,\text{coex}}, M_{W,\text{coex}})^T.$$

We will prove that

$$X_{\text{coex}} <_K \ X_{\text{cwie}} <_K \ X_{\text{wfe}}.$$

Since $X_{\text{cwie}} \gg 0$, this is equivalent to $X_W^* > X_{W,\text{coex}}$ and $X_{U,\text{coex}} < X_U^*$.

Since $f(X_{\text{cwie}}) = f(X_{\text{coex}}) = f(X_{\text{cwie}}) = 0$, this proves, by the argument already used in the proof of Proposition 2.1, that for the order $\leq_K$ the order intervals

$$[X_{\text{cwie}} , \ X_{\text{coex}}]_K \quad \text{and} \quad [X_{\text{coex}} , \ X_{\text{wfe}}]_K$$

are positively compact invariant sets contained in $\mathcal{D}$.

We have also proved that for any $\rho > 1$, then $f_2(\rho\, X_W^*) < 0$ and $f_1(\rho\, W_U^*) < 0$. Using again monotonicity, this proves that the order intervals

$$[\rho_1\, X_{\text{cwie}} , \ X_{\text{coex}}]_K \quad \text{and} \quad [X_{\text{cwie}} , \ \rho_2\, X_{\text{wfe}}]_K$$

are positively invariant compact sets, as far as $1 \leq \rho_1 \leq \dfrac{C}{L_W^*}$ and $1 \leq \rho_2 \leq \dfrac{C}{L_U^*}$ (we need monotonicity and then we are restricted to $\mathcal{D}$). Using the relation for L_W^* and L_U^* this gives

$$\rho_2 \leq 1 + \frac{1}{\mathcal{R}_{0,\text{offsp},W}}, \quad \rho_1 \leq 1 + \frac{1}{\mathcal{R}_{0,\text{offsp},U}}.$$

For completeness we prove now our claims on comparisons of the 3 equilibria.
We have

$$P_{U,\text{coex}} + P_{X,\text{coex}} = P_W^*.$$

Now, with relation (14) and $\mathcal{R}_{0,W} < 1$, we have

$$\frac{P_W^*}{P_U^*} = \frac{\mathcal{R}_{0,W}\,(\mathcal{R}_{0,\text{offsp},U} - 1)}{R_{0,W}\,\mathcal{R}_{0,\text{offsp},U} - R_{0,W})} < 1$$

Using these two inequalities, it is now not difficult, using relations (10) to (21), to prove the desired inequalities for the equilibria. As a consequence the 3 equilibria are in the domain $\mathcal{D}$.

We can find by an argument similar to Proposition 2.1 a vector $X_k \in \overline{\mathcal{D}}$ such that $f(X_k) \ll 0$. We begin to choose $L_U + L_k = C$ and we continue as in the Proposition. Since f is monotone in $\overline{\mathcal{D}}$, the order set $[0, X_k]$ is a positively invariant absorbing set. This proves that all the trajectories are bounded.

3.4. Stability Analysis of the equilibria

In this section we will prove the following Theorem

Theorem 3.1
Trajectories of system (7) are forward bounded.

 – If $\mathcal{R}_{0,W}\,\mathcal{R}_{0,offsp,U} = \mathcal{R}_{0,offsp,W} > 1$,

 three equilibria exist. A disease free equilibria (WFE), an equilibrium with the total population infected (CWIE) and a coexistence equilibrium in the positive orthant. The WFE and CWIE are asymptotically stable, the coexistence equilibrium is unstable;

 – If $\mathcal{R}_{0,offsp,U} > 1$,

 there exists an equilibrium without infection (WFE) which is asymptotically stable. When $\mathcal{R}_{0,W} < \dfrac{1}{\mathcal{R}_{0,offsp,U}}$ only the WFE exists and is globally asymptotically stable on the nonnegative orthant minus the manifold $M_W = 0$.

3.4.1. Stability of the *Wolbachia* Free Equilibrium

To study the stability of the infection free equilibrium WFE we compute the basic reproduction ratio for the infection by *Wolbachia*. The variable corresponding to uninfected compartments

$$X_U = (E_U, L_U, P_U, Y_U, F_{UU}, M_U),$$

and the other variables for infected compartments

$$X_W = (E_W, L_W, P_W, Y_W, F_W, M_W).$$

We use the technique of [60] to compute the basic reproduction ratio for *Wolbachia*.

Since we are dealing with 12 equations, the verification of the hypothesis (A5) [60] is not completely straightforward. Namely we have to prove (hypothesis A5) that, when the transmission is set to zero, then the Jacobian of the resulting system, computed at the WFE, is a stable matrix (by stable we mean Hurwitz). Setting the transmission to zero amounts to set $\theta = 0$. It is well known that the Jacobian computed at the WFE is a diagonal block upper triangular matrix :

$$\mathrm{Jac}(WFE) = \begin{bmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{bmatrix}.$$

In the present case A_{11} and A_{22} are 6×6 matrices.

The matrix A_{22} when $\theta = 0$ is equal to

$$A_{22} = \begin{bmatrix} -(\eta_E + \mu_E) & 0 & 0 & 0 & 0 & 0 \\ \dfrac{\eta_E}{\mathcal{R}_{0,\text{offsp},U}} & -(\mu_L + \eta_L) & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P + \mu_P) & 0 & 0 & 0 \\ 0 & 0 & \nu\eta_P & -(\beta + \mu_Y) & 0 & 0 \\ 0 & 0 & 0 & \beta & -\mu_{\text{FW}} & 0 \\ 0 & 0 & (1-\nu)\eta_P & 0 & 0 & -\mu_{\text{MW}} \end{bmatrix}, \quad (25)$$

and is clearly stable.

We now consider A_{11} :

$$A_{11} = \begin{bmatrix} -(\eta_E + \mu_E) & 0 & 0 & 0 & \phi & 0 \\ \dfrac{\eta_E}{\mathcal{R}_{0,\text{offsp},U}} & -\dfrac{\mu_L + \eta_L}{\mathcal{R}_{0,\text{offsp},U}} & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P + \mu_P) & 0 & 0 & 0 \\ 0 & 0 & \nu\eta_P & -(\beta + \mu_Y) & 0 & 0 \\ 0 & 0 & 0 & \beta & -\mu_{\text{FU}} & 0 \\ 0 & 0 & (1-\nu)\,\eta_P & 0 & 0 & -\mu_{\text{MU}} \end{bmatrix}.$$

The matrix A_{11} is a Metzler matrix. We can apply a lemma from [35], which we recall for the convenience of the reader

Lemma 3.1
Let $\mathbf{M}$ be a Metzler matrix, which is block decomposed :

$$\mathbf{M} = \begin{bmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{C} & \mathbf{D} \end{bmatrix}.$$

Where $\mathbf{A}$ and $\mathbf{D}$ are square matrices.
Then $\mathbf{M}$ is Hurwitz if and only if $\mathbf{A}$ and $\mathbf{D} - \mathbf{C}\mathbf{A}^{-1}\mathbf{B}$ are Metzler stable.

We can now prove that A_{11} is Hurwitz. Since we have an evident eigenvalue $-\mu_{\text{MW}}$ in position $(6,6)$; we can reduce the stability to the stability of the 5×5 principal upper block.

$$V5 = \begin{bmatrix} -(\eta_E + \mu_E) & 0 & 0 & 0 & \phi \\ \dfrac{\eta_E}{\mathcal{R}_{0,\text{offsp},U}} & -\dfrac{\mu_L + \eta_L}{\mathcal{R}_{0,\text{offsp},U}} & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P + \mu_P) & 0 & 0 \\ 0 & 0 & \nu\eta_P & -(\beta + \mu_Y) & 0 \\ 0 & 0 & 0 & \beta & -\mu_{\text{FU}} \end{bmatrix}.$$

If we define $A = V5(1:4, 1:4)$, the first upper 4×4 block of $V5$ and the other blocks accordingly. Since the block A is lower triangular with a negative diagonal, we have the

stability of this block. A computation of $D - C A^{-1} B$, with this block decomposition, yields after some simplifications

$$D - C A^{-1} B = -\mu_{FU} \left(1 - \frac{1}{\mathcal{R}_{0,\text{offsp},U}} \right) < 0.$$

That proves that A_{11} is Hurwitz and finally that the hypothesis (A5) is satisfied.
We can now compute the basic reproduction ratio for *Wolbachia* infection. We denote by F the Jacobian of all the transmission term in the infected compartments.

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 & \theta\,\phi & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

We denote by V the remaining part of the Jacobian A_{22} computed at the WFE.
Using the results of [60], we know that the reproduction number for *Wolbachia* is given by $\mathcal{R}_{0,W} = \rho(-F\,V^1)$. An immediate computation gives

$$-F\,V^{-1} = \begin{bmatrix} \frac{\theta\,\mu_{FU}}{\mu_{FW}} & \mathcal{R}_{0,\text{offsp},W}\,\frac{\mu_E + \eta_E}{\eta_E} & \frac{\theta\,\phi\,\beta\,\nu\,\eta_P}{\mu_{FW}\,(\mu_P + \eta_P)\,(\beta + \mu_Y)} & \frac{\theta\,\phi\,\beta}{\mu_{FW}\,(\beta + \mu_Y)} & \frac{\theta\,\phi}{\mu_{FW}} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

Finally we obtain what we have already denoted as $\mathcal{R}_{0,W}$.

$$\mathcal{R}_{0,W} = \frac{\theta\,\mu_{\text{FU}}}{\mu_{\text{FW}}} < 1.$$

This proves that the WFE is locally asymptotically stable.

3.4.2. Stability of the Completely *Wolbachia*-Infected Equilibrium

In this section, for the existence of the CWIE, we assume

$$1 < \mathcal{R}_{0,\text{offsp},W} = \mathcal{R}_{0,W}\,\mathcal{R}_{0,\text{offsp},U} < \mathcal{R}_{0,\text{offsp},U}.$$

The Jacobian computed at the CWIE is a block diagonal lower triangular matrix

$$\mathrm{Jac}(CWIE) = \begin{bmatrix} A_{11} & 0 \\ A_{21} & A_{22} \end{bmatrix}.$$

We have

$$A_{11} = \begin{bmatrix} -(\eta_E + \mu_E) & 0 & 0 & 0 & \phi & 0 \\ \dfrac{\eta_E}{\mathcal{R}_{0,\mathrm{offsp},W}} & -(\mu_L + \eta_L) & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P + \mu_P) & 0 & 0 & 0 \\ 0 & 0 & \nu\eta_P & -(\beta + \mu_Y) & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_{\mathrm{FU}} & 0 \\ 0 & 0 & (1-\nu)\eta_P & 0 & 0 & -\mu_{\mathrm{MU}} \end{bmatrix}.$$

the last term $-\mu_{\mathrm{MU}}$ is clearly an eigenvalue of A_{11}. Considering the other 5×5 remaining principal subblock we see that the elements of the diagonal are also eigenvalues of A_{11}, hence this block is Hurwitz.

We consider now A_{22}

$$A_{22} = \begin{bmatrix} -(\eta_E + \mu_E) & 0 & 0 & 0 & \theta\phi & 0 \\ \dfrac{\eta_E}{\mathcal{R}_{0,\mathrm{offsp},W}} & -(\mu_L + \eta_L)\,\mathcal{R}_{0,\mathrm{offsp},W} & 0 & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P + \mu_P) & 0 & 0 & 0 \\ 0 & 0 & \nu\eta_P & -(\beta + \mu_Y) & 0 & 0 \\ 0 & 0 & 0 & \beta & -\mu_{\mathrm{FW}} & 0 \\ 0 & 0 & -(\nu-1)\eta_P & 0 & 0 & -\mu_{\mathrm{MW}} \end{bmatrix}.$$

The matrix A_{22} is Hurwitz if and only if the upper principal 5×5 block A_{111} is stable.

$$A_{111} = \begin{bmatrix} -(\eta_E + \mu_E) & 0 & 0 & 0 & \theta\phi \\ \dfrac{\eta_E}{\mathcal{R}_{0,\mathrm{offsp},W}} & -(\mu_L + \eta_L)\,\mathcal{R}_{0,\mathrm{offsp},W} & 0 & 0 & 0 \\ 0 & \eta_L & -(\eta_P + \mu_P) & 0 & 0 \\ 0 & 0 & \nu\eta_P & -(\beta + \mu_Y) & 0 \\ 0 & 0 & 0 & \beta & -\mu_{\mathrm{FW}} \end{bmatrix}.$$

We will use again lemma (3.1) for the stability of Metzler matrices. With the notation of the lemma, we choose for A the upper principal 4×4 block. This block is a lower triangular matrix with negative diagonal elements, hence stable.

A straightforward computation gives

$$D - C\,A^{-1}\,B = -\mu_{FW}\left(1 - \frac{1}{\mathcal{R}_{0,\mathrm{offsp},W}}\right)$$

This proves finally the asymptotic stability of the CWIE.

3.4.3. Stability of the coexistence equilibrium

We will prove, in this section, that any trajectory in $[X_{\mathrm{coex}}, X_{\mathrm{wfe}}]_K \setminus \{X_{\mathrm{coex}}\}$ tends to X_{wfe} and any trajectory in $[X_{\mathrm{coex}}, X_{\mathrm{cwie}}]_K \setminus \{X_{\mathrm{coex}}\}$ tends to X_{cwie}.

Then we will prove that the coexistence equilibrium is always unstable. Based on the monotonicity properties, this can be done without any computation. If we consider, for example, the closed order interval $[X_{\mathrm{coex}}, X_{\mathrm{wfe}}]_K$, this interval is a compact positively invariant and contain only two equilibria. This is almost a situation encountered in [28].

However we cannot apply Theorem 10.5 of Hirsch [28] which would give the desired result. To use this Theorem we need that our system is strongly monotone on our closed order interval. This is not true since the face of this interval, contained in $\mathbb{R}_+^6 \times \{0\}$, is invariant. A key result for the proof of the Theorem of Hirsch is that the set of quasiconvergent points, in a totally ordered arc for a strongly monotone system, is at most countable. A common difficulty in applying the Theorem of density, often overlooked in applications, arises from the fact that irreducibility is an open condition. It commonly occurs that irreducibility holds only in the interior of the domain while some parts of the boundary are invariant sets. In this case, strong monotonicity (and even the strong order preserving property) may fail to hold on the boundary. This is exactly our case.

For proving the result we need to tailor Hirsch's Theorem to our situation. We will prove a general result applicable to our situation.

Then we consider on $\mathbb{R}_+^n$, strongly ordered by a cone K, a $\mathcal{C}^1$ monotone system $\dot{x} = f(x)$ with semiflow ϕ.

We need to define what is a face of a closed order interval $[p, q]$.

Definition 3.1
The closed order interval $[p, q]$ is a convex polytope, i.e, the finite intersection of half-spaces. A hyperplane H of R^n is supporting $[p, q]$, at a point $x \in [p, q]$, if one of the two closed halfspaces of H contains $[p, q]$.
A subset F of $[p, q]$ is called a face of $[p, q]$ if it is either $\emptyset$, $[p, q]$ itself or the intersection of $[p, q]$ with a supporting hyperplane.

Theorem 3.2
We consider a $\mathcal{C}^1$ monotone system $\dot{x} = f(x)$, whose flow ϕ preserves $\mathbb{R}_+^n$ for $t \geq 0$.
Let p, q be equilibria with $p \ll q$, with no other equilibria in $[p, q]$.
We assume that p is asymptotically stable for ϕ and that there exists a positively invariant face F of $[p, q]$ containing p which is in the basin of p. We also assume that some other faces $F_1, F_2, \cdots, F_K$ are positively invariant, and for any point x of each F_i, the omega-limit set satisfies $\omega(x) \cap F \neq \emptyset$.
We assume that the system is strongly monotone on the complement

$$[p, q] \setminus (F \cup F_1 \cup \cdots \cup F_k).$$

Then any trajectory of $[p, q] \setminus \{q\}$ converges to p. Hence the equilibrium q is unstable.

Proof

By monotonicity $[p, q]$ is a compact positively invariant set. Consequently any trajectory in $[p, q]$ is bounded.

Consider the totally ordered arc in $[p, q]$, $J = \{x = (1 - t) p + t q \mid 0 \leq t \leq 1\}$. If a point $x \in I$ converges to p then by monotonicity $[x, p]$ is in the basin of p. Since p is asymptotically stable there exists $x \neq p$ in J converging to p. Let $a = \sup\{x \in J \mid x$ converges to $p\}$. Similarly let $b = \inf\{x \in J \mid x$ converges to $q\}$. The order interval $[[a, b]]$ is composed of points converging neither to p, neither to q.

The ordered interval $[p, a]]$ is an open subset of $[p, q]$, containing p in the basin of p.

We will show that $a = b = q$ which will prove the Theorem.

Before this we show that any face F_i is in the basin of p. We know that for any x in F_i, $\omega(x) \cap F \neq \emptyset$. Since any point of F converges to p, by invariance of the omega limit set, we have $p \in \omega(x)$, which implies that the trajectory from x enters $[p, a]]$ proving that x converges to p.

To prove $a = b$, we proceed by contradiction assuming $a \ll b$. By definition of a and b, any point of $[[a, b]]$ does not converge to an equilibrium. Moreover a cannot be in the basin of p. Otherwise, since p is asymptotically stable, the basin is open, which contradicts the definition of a. Let

$$W = \overline{\phi_{\mathbb{R}_+}([a, b]] \cup J)}.$$

Continuity of ϕ implies that W is a separable compact metric space positively invariant under ϕ. Moreover $W \cap (F \cup F_1 \cup \cdots \cup F_k) = \emptyset$, otherwise this will implies that a point of $[[a, b]]$ converges to p, a contradiction. It follows that W is an ordered space, with a strongly monotone semiflow ϕ.

The set W is a positively invariant compact ordered set with a strongly monotone semiflow ϕ without equilibrium. By lemma 1.1 of [29], W has a maximal element z. By monotonicity $\phi_t(z)$ is an upper bound of W for any $t \geq 0$. Hence $z \leq \phi_t(z)$. If for a $t > 0$ we have $z < \phi_t(z)$ by strong monotonicity, we can apply the convergence crtiterion (Theorem 1.4 [29]), z converges to an equilibrium. Otherwise z is an equilibrium. In any case we have an equilibrium in W, which is a contradiction. This proves $a = b$.

It remains to prove $a = b = q$. If $b \ll q$, $[b, q]$ is a neighborhood of q, then q is asymptotically stable, hence the basin of q is open, which contradicts the definition of b. Hence $a = b = q$ which ends the proof of the Theorem.

∎

To prove our results we have only to consider the invariant faces where our system is not strongly monotone. The face $[X_{\text{coex}}, X_{\text{cwie}}]_K \bigcap \{0\} \times \mathbb{R}_+^6$ is contained in the basin of X_{cwie}

and is positively invariant. The positively invariant set, in which the system is not strongly monotone, is exactly the two faces $[X_{\text{coex}}, X_{\text{cwie}}]_K \bigcap \{0\} \times \mathbb{R}_+^6$ and $[X_{\text{wfe}}, X_{\text{coex}}]_K \bigcap \mathbb{R}_+^6 \times \{0\}$ which are respectively in the basin of X_{cwie} and X_{wfe}. All the hypotheses of our Theorem are satisfied.

This proves that any trajectory in $[X_{\text{coex}}, X_{\text{cwie}}]_K \setminus \{X_{\text{coex}}\}$ tends X_{cwie}. This proves that the coexistence equilibrium X_{coex} is unstable. We have a similar result for the other ordered interval.

This result can be obtain directly : we compute the determinant of the Jacobian at the coexistence equilibrium. We obtain after rearrangement and simplifications

$$
\det(\text{Jac}(Coex)) = (\theta\,\mu_{FU} - \mu_{FW})\,\mu_{FU}\,\mu_{MU}\,\mu_{MW}\,(\mu_E + \eta_E)^2\,(\mu_L + \eta_L)^2
$$
$$
(\mu_P + \eta_P)^2\,(\beta + \mu_Y)^2\,(\mathcal{R}_{0,\text{offsp},W} - 1)\;<0 \quad (26)
$$

The negativity comes from $(\theta\,\mu_{FU} - \mu_{FW}) < 0$ and, since we are in dimension 12, this proves the instability of the coexistence equilibrium.

3.4.4. More invariant set

We know that our system is strongly monotone on the interior of $\mathcal{D}$ for the order relative to the cone $\leq_K$.

The coexistence equilibrium $X_{\text{coex}} = (X_{U,\text{coex}}, X_{W,\text{coex}})$ is in the interior of $\mathcal{D}$. Then the matrix $P.Jac(Coex).P$ computed at this equilibrium is an irreducible unstable Metzler matrix, where P is the diagonal matrix defined in section 3.2. By Perron-Frobenius the stability modulus $s(Jac(Coex)) > 0$ is an eigenvalue of the Jacobian and there exists a positive vector $v \gg 0$ such that

$$
P.Jac(Coex)\,.P.v = s(Jac(Coex))\,v
$$

Hence $P\,v = (v_U, -v_W)$ is an eigenvalue of the Jacobian. By Theorem 3.3 (p 62) and Remark 3.2 (p 63) of [53] we obtain that, for any $\varepsilon > 0$, following the order intervals

$$
[(X_U^* - \rho_1\,v_1, 0)\;,\;\; X_{\text{coex}} - \varepsilon(v_U, -v_W)]\,_K
$$

and

$$
[X_{\text{coex}} + \varepsilon(v_U, -v_W)\,,\;\; (0, X_W^* + \rho_2\,v_2)]\,_K
$$

are positively compact invariant sets. Since each of these set contains an unique equilibrium, this proves that this unique equilibrium is globally asymptotically stable on the considered set.

We have proven, using section 3.3, that $[\rho_1\,X_{\text{cwie}}\;,\;\; X_{\text{coex}}]_K$ is in the basin of attraction of the CWIE $(0, X_W^*)$. An analogous result for the WFE.
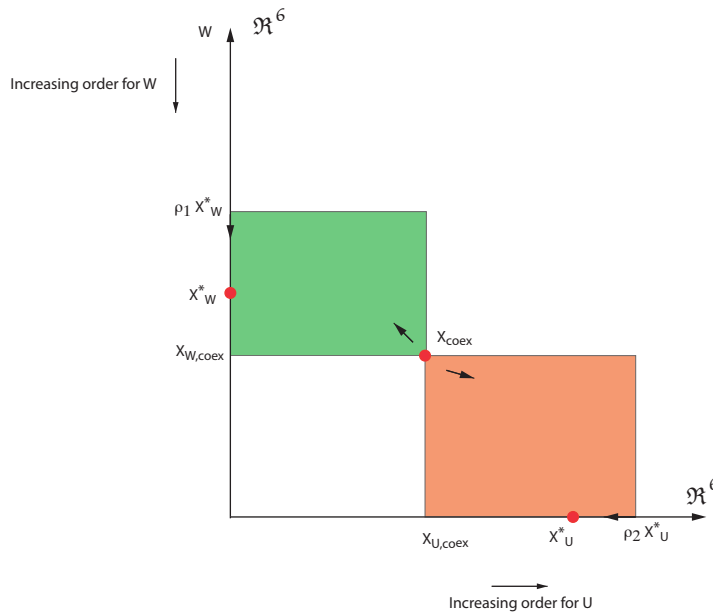
Figure 3. *Compact invariant sets for system (1), ρ_1 and ρ_2 defined in 3.3*

We have obtained a lower bound for the basin of attraction of X_{cwie}. It is determined by X_{coex} and finally by the basic offspring number $\mathcal{R}_{0,\text{offsp},W}$.

3.5. What happens when $\mathcal{R}_{0,\textbf{offsp},W} \leq 1$?

We can have upper bounds for the matrices $A_U(X)$ and $A_W(X)$. Using notations of section (3) we get

$$A_U(X) \leq A(X, \theta, \mu_{FU}, \mu_{MU}) \quad A_W(X) \leq A(X, \theta \phi, \mu_{FW}, \mu_{MW})$$

With the hypotheses $\mathcal{R}_{0,\text{offsp},U} > 1$ and $\mathcal{R}_{0,\text{offsp},W} \leq 1$ we have already proved that

$$\dot{X}_U = A(X, \theta, \mu_{FU}, \mu_{MU}) \, X_U$$

is globally asymptotically stable at a positive equilibrium $X_U^* \in \mathbb{R}_+^6$ and

$$\dot{X}_W = A(X, \theta \phi, \mu_{FW}, \mu_{MW}) \, X_W$$

has the origin for globally asymptotically stable equilibrium. Then by comparison Theorems of ODE for positive systems (all our matrices are Metzler) this proves that our system (7) converges to X_{wfe}.

4. Conclusion

The phenomenon described above is now well known in epidemiological models, this is the so-called backward bifurcation. See [2, 8, 59, 21] and references therein. Usually in epidemiological model when $\mathcal{R}_0 < 1$ the disease free equilibrium is stable and there are no other "infected" equilibria. At $\mathcal{R}_0 = 1$ an infected equilibrium bifurcates. In backward bifurcation there are infected equilibrium points in the domain $\mathcal{R}_0 < 1$. To quote [21] a general mechanism leading to backward bifurcations in epidemic models seems unlikely. Backward bifurcations is known to occur in models with group structure and large differences between groups or models with interacting mechanisms (e.g. Vaccination models or reinfection). Our model does not enter in these categories. We can reduce our model, by lumping variables, to a very simple four dimensional system which also exhibits backward bifurcation. This result adds a new situation to the known ones.

From the biological point of view, we have considered a complete model. We choose not to lump some compartments and instead to distinguish those considered by biologists. This is for two reasons. Firstly it is easier for a biologist to understand our model and then the data we have are related to biological compartments. Consideration of lumped compartments makes difficult and problematic data integration. Moreover this integration needs complex modeling assumptions. The objective of this paper was to check if, some different modeling assumptions would modify previous results [37]. We observe that this model predicts that the successful establishment of *Wolbachia* in a population of *Aedes aegyptii* is possible. This has been observed in the field [30] for certain strain of *Wolbachia*. Our model also predicts that the strain must not be too effective in the reduction of the death rate. If $\mathcal{R}_{0,W} = \dfrac{\theta\,\mu_{FU}}{\mu_{FW}}$ is too small, then $\mathcal{R}_{0,\text{offsp},W} = \mathcal{R}_{0,W}\,\mathcal{R}_{0,\text{offsp},U}$ will be less than 1 preventing the successful establishment of *Wolbachia*. Unpublished data seems to confirm that prediction.

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5. References

[1] R. ANGUELOV, Y. DUMONT, AND J. LUBUMA, " Mathematical modeling of sterile insect technology for control of *anopheles* mosquito.", *Comput. Math. Appl.*, vol. 64, (2012), pp. 374–389.

[2] J. ARINO, C. C. MCCLUSKEY, AND P. VAN DEN DRIESSCHE, "Global results for an epidemic model with vaccination that exhibits backward bifurcation.", *SIAM J. Appl. Math.*, vol. 64 (2003), pp. 260–276.

[3] R. BARRERA, M. AMADOR, AND G. G. CLARK, "Ecological factors influencing aedes ae-

gypti (diptera: Culicidae) productivity in artificial containers in salinas, puerto rico.", *J Med Entomol*, vol. 43 (2006), pp. 484–492.

[3] N. H. BARTON AND M. TURELLI, "Spatial waves of advance with bistable dynamics: cytoplasmic and genetic analogues of allee effects.", *Am Nat*, vol. 178 (2011), pp. E48–75.

[4] G. BIAN, Y. XU, P. LU, Y. XIE, AND Z. XI, "The endosymbiotic bacterium wolbachia induces resistance to dengue virus in aedes aegypti.", *PLoS Pathog*, vol. 6 (2010), p. e1000833.

[5] M. S. C. BLAGROVE, C. ARIAS-GOETA, A.-B. FAILLOUX, AND S. P. SINKINS, "Wolbachia strain wmel induces cytoplasmic incompatibility and blocks dengue transmission in aedes albopictus", *Proc Natl Acad Sci U S A*, vol. 109 (2012), pp. 255–260.

[6] B. BOSSAN, A. KOEHNCKE, AND P. HAMMERSTEIN, "A new model and method for understanding wolbachia-induced cytoplasmic incompatibility", *PLoS One*, vol. 6 (2011), p. e19757.

[7] M. A. H. BRAKS, S. A. JULIANO, AND L. P. LOUNIBOS, "Superior reproductive success on human blood without sugar is not limited to highly anthropophilic mosquito species", *Med Vet Entomol*, vol. 20 (2006), pp. 53–59.

[8] F. BRAUER, "Backward bifurcations in simple vaccination models", *J. Math Anal Appl*, vol. 298 (2004), pp. 418–431.

[9] J. S. BROWNSTEIN, E. HETT, AND S. L. O'NEILL, "The potential of virulent wolbachia to modulate disease transmission by insects", *J Invertebr Pathol*, vol. 84 (2003), pp. 24–29.

[10] M. H. T. CHAN AND P. S. KIM, "Modelling a wolbachia invasion using a slow-fast dispersal reaction-diffusion approach", *Bull Math Biol*, vol. 75 (2013), pp. 1501–1523.

[11] N. CHITNIS, J. M. HYMAN, AND J. CUSHING, "Determining Important Parameters in the Spread of Malaria Through the Sensitivity Analysis of a Mathematical Model", *Bull. Math. Biol*, vol. 70 (2008), pp. 1272–1296.

[12] P. R. CRAIN, J. W. MAINS, E. SUH, Y. HUANG, P. H. CROWLEY, AND S. L. DOBSON, "Wolbachia infections that reduce immature insect survival: Predicted impacts on population replacement", *BMC Evol Biol*, vol. 11 (2011), p. 290.

[13] M. R. DAVID, R. LOURENCO-DE OLIVEIRA, AND R. M. D. FREITAS, " Container productivity, daily survival rates and dispersal of aedes aegypti mosquitoes in a high income dengue epidemic neighbourhood of rio de janeiro: presumed influence of differential urban structure on mosquito biology.", *Mem Inst Oswaldo Cruz*, vol. 104 (2009), pp. 927–932.

[14] Y. DUMONT, F. CHIROLEU, AND C. DOMERG, "On a temporal model for the Chikungunya disease: modeling, theory and numerics.", *Math Biosci*, vol. 213 (2008), pp. 80–91.

[15] Y. DUMONT AND J. M. TCHUENCHE, "Mathematical studies on the sterile insect technique for the chikungunya disease and aedes albopictus", *J Math Biol*, vol. 65 (2012), pp. 809–854.

[16] J. ENGELSTADTER, A. TELSCHOW, AND P. HAMMERSTEIN, "Infection dynamics of different wolbachia-types within one host population", *J Theor Biol*, vol. 231 (2004), pp. 345–355.

[17] J. E. FADER AND S. A. JULIANO, "Oviposition habitat selection by container-dwelling mosquitoes: responses to cues of larval and detritus abundances in the field", *Ecol Entomol*, vol. 39 (2014), pp. 245–252.

[18] J. Z. FARKAS AND P. HINOW, "Structured and unstructured continuous models for wolbachia infections", *Bull Math Biol*, vol. 72 (2010), pp. 2067–2088.

[19] D. A. FOCKS, D. G. HAILE, E. DANIELS, AND G. A. MOUNT, "Dynamic life table model for aedes aegypti (diptera: Culicidae): simulation results and validation.", *J Med Entomol*, vol. 30 (1993), pp. 1018–1028.

[20] F. D. FRENTIU, J. ROBINSON, P. R. YOUNG, E. A. MCGRAW, AND S. L. O'NEILL, "Wolbachia-mediated resistance to dengue virus infection and death at the cellular level.", *PLoS One*, vol. 5 (2010), p. e13398.

[21] K. HADELER AND P. VAN DEN DRIESSCHE, "Backward bifurcation in epidemic control.", *Math Biosci*, vol. 146 (1997), pp. 15–35.

[22] P. A. HANCOCK AND H. C. J. GODFRAY, "Modelling the spread of wolbachia in spatially heterogeneous environments.", *J R Soc Interface*, vol. 9 (2012), pp. 3045–3054.

[23] P. A. HANCOCK AND H. C. J. GODFRAY, "Modelling the spread of wolbachia in spatially heterogeneous environments.supplement online information.", *J R Soc Interface*, vol. 9 (2012), pp. 3045–3054.

[24] P. A. HANCOCK, S. P. SINKINS, AND H. C. J. GODFRAY, "Population dynamic models of the spread of Wolbachia.", *Am Nat*, vol. 177 (2011), pp. 323–333.

[25] P. A. HANCOCK, S. P. SINKINS, AND H. C. J. GODFRAY , "Strategies for introducing wolbachia to reduce transmission of mosquito-borne diseases.", *PLoS Negl Trop Dis*, vol. 5 (2011), p. e1024.

[26] M. HERTIG AND S. B. WOLBACH, "Studies on rickettsia-like micro-organisms in insects.", *J Med Res*, vol. 44 (1924), pp. 329–374.

[27] M. HIRSCH, "The dynamical system approach to differential equations.", *Bull AMS*, vol. 11 (1984), pp. 1–64.

[28] M. W. HIRSCH, "Stability and convergence in strongly monotone dynamical systems.", *J Reine Angew. Math*, vol. 383 (1988), pp. 1–53.

[29] M. W. HIRSCH AND H. L. SMITH, "Monotone dynamical systems.", in *Handbook of differential equations: ordinary differential equations.* vol. Vol. II, (2005), pp. 239–357.

[30] HOFFMANN, A A AND MONTGOMERY, B L AND POPOVICI, J AND ITURBE-ORMAETXE, I AND JOHNSON, P H AND MUZZI, F AND GREENFIELD, M AND DURKAN, M AND LEONG, Y S AND DONG, Y AND COOK, H AND AXFORD, J AND CALLAHAN, A G AND KENNY, N AND OMODEI, C AND MCGRAW, E A AND RYAN, P A AND RITCHIE, S A AND TURELLI, M AND O'NEILL, S L, "Successful establishment of wolbachia in aedes populations to suppress dengue transmission.", *Nature*, vol. 476 (2011), pp. 454–457.

[31] P. I. HOWELL AND B. G. J. KNOLS, "Male mating biology.", *Malar J*, vol. 8 Suppl 2 (2009), p. S8.

[32] G. L. HUGHES, R. KOGA, P. XUE, T. FUKATSU, AND J. L. RASGON, " Wolbachia infections are virulent and inhibit the human malaria parasite plasmodium falciparum in anopheles gambiae.", *PLoS Pathog*, vol. 7 (2011), p. e1002043.

[33] H. HUGHES AND N. F. BRITTON, "Modelling the use of wolbachia to control dengue fever transmission.", *Bull Math Biol*, vol. 75 (2013), pp. 796–818.

[34] I. ITURBE-ORMAETXE, T. WALKER, AND S. L. O' NEILL, "Wolbachia and the biological control of mosquito-borne disease.", *EMBO Rep*, vol. 12 (2011), pp. 508–518.

[35] J. KAMGANG AND G. SALLET, "Computation of threshold conditions for epidemiological models and global stability of the disease free equilibrium(DFE).", *Math Biosci*, vol. 213 (2008), pp. 1–12.

[36] M. J. KEELING, F. M. JIGGINS, AND J. M. READ, "The invasion and coexistence of competing wolbachia strains.", *Heredity (Edinb)*, vol. 91 (2003), pp. 382–388.

[37] J. KOILLER, M. DA SILVA, M. SOUZA, C. CODEÇO, A. IGGIDR, AND G. SALLET, "Aedes, Wolbachia and Dengue.", *Research Report RR-8462, INRIA*, vol. Jan. 2014.

[38] P. M. LUZ, C. T. CODECO, J. MEDLOCK, C. J. STRUCHINER, D. VALLE, AND A. P. GALVANI, "Impact of insecticide interventions on the abundance and resistance profile of aedes aegypti.", *Epidemiol Infect*, vol. 137 (2009), pp. 1203–1215.

[39] A. MACIA, "Differences in performance of aedes aegypti larvae raised at different densities in tires and ovitraps under field conditions in argentina.", *J Vector Ecol*, vol. 31 (2006), pp. 371–377.

[40] R. MACIEL-DE FREITAS, C. T. CODECO, AND R. LOURENCO-DE OLIVEIRA, " Daily survival rates and dispersal of aedes aegypti females in rio de janeiro, brazil.", *Am J Trop Med Hyg*, vol. 76 (2007), pp. 659–665.

[41] C. J. MCMENIMAN, R. V. LANE, B. N. CASS, A. W. C. FONG, M. SIDHU, Y.-F. WANG, AND S. L. O'NEILL, "Stable introduction of a life-shortening wolbachia infection into the mosquito aedes aegypti.", *Science*, vol. 323 (2009), pp. 141–144.

[42] C. J. MCMENIMAN AND S. L. O'NEILL, "A virulent wolbachia infection decreases the viability of the dengue vector aedes aegypti during periods of embryonic quiescence.", *PLoS Negl Trop Dis*, vol. 4 (2010), p. e748.

[43] L. A. MOREIRA, I. ITURBE-ORMAETXE, J. A. JEFFERY, G. LU, A. T. PYKE, L. M. HEDGES, B. C. ROCHA, S. HALL-MENDELIN, A. DAY, M. RIEGLER, L. E. HUGO, K. N. JOHNSON, B. H. KAY, E. A. MCGRAW, A. F. VAN DEN HURK, P. A. RYAN, AND S. L. O'NEILL, "A wolbachia symbiont in aedes aegypti limits infection with dengue, chikungunya, and plasmodium.", *Cell*, vol. 139 (2009), pp. 1268–1278.

[44] M. Z. NDII, R. I. HICKSON, D. ALLINGHAM, AND G. N. MERCER, "Modelling the transmission dynamics of dengue in the presence of wolbachia.", *Math Biosci*, vol. 262 (2015), pp. 157–166.

[45] M. OTERO, H. G. SOLARI, AND N. SCHWEIGMANN, "A stochastic population dynamics model for aedes aegypti: formulation and application to a city with temperate climate.", *Bull Math Biol*, vol. 68 (2006), pp. 1945–1974.

[46] J. POPOVICI, L. A. MOREIRA, A. POINSIGNON, I. ITURBE-ORMAETXE, D. MC-NAUGHTON, AND S. L. O'NEILL, "Assessing key safety concerns of a wolbachia-based strategy to control dengue transmission by aedes mosquitoes.", *Mem Inst Oswaldo Cruz*, vol. 105 (2010), pp. 957–964.

[47] J. L. RASGON, "Using predictive models to optimize wolbachia-based strategies for vector-borne disease control.", *Adv Exp Med Biol*, 627 (2008), pp. 114–125.

[48] J. L. RASGON AND T. W. SCOTT, "Impact of population age structure on wolbachia transgene driver efficacy: ecologically complex factors and release of genetically modified mosquitoes.", *Insect Biochem Mol Biol*, vol. 34 (2004), pp. 707–713.

[49] J. L. RASGON, L. M. STYER, AND T. W. SCOTT, "Wolbachia-induced mortality as a mechanism to modulate pathogen transmission by vector arthropods.", *J Med Entomol*, vol. 40 (2003), pp. 125–132.

[50] J. R. REY AND S. M. O'CONNELL, "Oviposition by aedes aegypti and aedes albopictus: influence of congeners and of oviposition site characteristics.", *J Vector Ecol*, vol. 39 (2014), pp. 190–196.

[51] S. A. RITCHIE, B. L. MONTGOMERY, AND A. A. HOFFMANN, "Novel estimates of aedes aegypti (diptera: Culicidae) population size and adult survival based on wolbachia releases.", *J Med Entomol*, vol. 50 (2013), pp. 624–631.

[52] P. SCHOFIELD, "Spatially explicit models of turelli-hoffmann wolbachia invasive wave fronts.", *J Theor Biol*, vol. (215 (2002), pp. 121–131.

[53] H. L. SMITH, "Monotone dynamical systems: an introduction to the theory of competitive and cooperative systems..", *Mathematical Surveys and Monographs.*, vol. 41, (1995).

[54] M. O. SOUZA, "Multiscale analysis for a vector-borne epidemic model.", *J Math Biol*, vol. 68 (2014), pp. 1269–1293.

[55] A. S. SPIELMAN, M. G. LEAHY, AND V. SKAFF, "Failure of effective insemination of young female aedes aegypti mosquitoes.", *J Insect Physiol*, vol. 15 (1969), pp. 1471–1479.

[56] L. M. STYER, S. L. MINNICK, A. K. SUN, AND T. W. SCOTT, "Mortality and reproductive dynamics of aedes aegypti (diptera: Culicidae) fed human blood.", *Vector Borne Zoonotic Dis*, vol. 7 (2007), pp. 86–98.

[57] M. TURELLI, "Cytoplasmic incompatibility in populations with overlapping generations.", *Evolution*, vol. 64 (2010), pp. 232–241.

[58] A. P. TURLEY, L. A. MOREIRA, S. L. O'NEILL, AND E. A. MCGRAW, " Wolbachia infection reduces blood-feeding success in the dengue fever mosquito, aedes aegypti.", *PLoS Negl Trop Dis*, vol. 3 (2009), p. e516.

[59] P. VAN DEN DRIESSCHE AND J. WATMOUGH, "A simple SIS epidemic model with a backward bifurcation .", *J Math Biol*, vol. 40 (2000), pp. 525–540.

[60] P. VAN DEN DRIESSCHE AND J. WATMOUGH, "reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission.", *Math Biosci*, vol. 180 (2002), pp. 29–48.

[61] T. WALKER, P. H. JOHNSON, L. A. MOREIRA, I. ITURBE-ORMAETXE, F. D. FRENTIU, C. J. MCMENIMAN, Y. S. LEONG, Y. DONG, J. AXFORD, P. KRIESNER, A. L. LLOYD, S. A. RITCHIE, S. L. O'NEILL, AND A. A. HOFFMANN, "supplement to : The wmel wolbachia strain blocks dengue and invades caged aedes aegypti populations.", *Nature*, vol. 476 (2011).

[62] ———, "The wmel wolbachia strain blocks dengue and invades caged aedes aegypti populations.", *Nature*, vol. 476 (2011), pp. 450–453.

[63] R. K. WALSH, L. FACCHINELLI, J. M. RAMSEY, J. G. BOND, AND F. GOULD, " Assessing the impact of density dependence in field populations of aedes aegypti.", *J Vector Ecol*, vol. 36 (2011), pp. 300–307.

[64] C. R. WILLIAMS, P. H. JOHNSON, T. S. BALL, AND S. A. RITCHIE, " Productivity and population density estimates of the dengue vector mosquito aedes aegypti (stegomyia aegypti)

in australia.", *Med Vet Entomol*, vol. 27 (2013), pp. 313–322.

[65] J. WONG, S. T. STODDARD, H. ASTETE, A. C. MORRISON, AND T. W. SCOTT, " Oviposition site selection by the dengue vector aedes aegypti and its implications for dengue control.", *PLoS Negl Trop Dis*, vol. 5 (2011), p. e1015.

[66] H. M. YANG, M. D. L. D. G. MACORIS, K. C. GALVANI, AND M. T. M. ANDRIGHETTI, "Follow up estimation of aedes aegypti entomological parameters and mathematical modellings.", *Biosystems*, vol. 103 (2011), pp. 360–371.

[67] H. L. YEAP, P. MEE, T. WALKER, A. R. WEEKS, S. L. O'NEILL, P. JOHNSON, S. A. RITCHIE, K. M. RICHARDSON, C. DOIG, N. M. ENDERSBY, AND A. A. HOFFMANN, "Dynamics of the "popcorn" wolbachia infection in outbred aedes aegypti informs prospects for mosquito vector control.", *Genetics*, vol. 187 (2011), pp. 583–595.