

Ensuring successful introduction of Wolbachia in natural populations of *Aedes aegypti* by means of feedback control

Pierre-Alexandre Bliman, M. Soledad Aronna, Flávio C. Coelho, Moacyr A. H. B. Da Silva

► **To cite this version:**

Pierre-Alexandre Bliman, M. Soledad Aronna, Flávio C. Coelho, Moacyr A. H. B. Da Silva. Ensuring successful introduction of Wolbachia in natural populations of *Aedes aegypti* by means of feedback control. *Journal of Mathematical Biology*, Springer Verlag (Germany), 2017, <10.1007/s00285-017-1174-x>. <hal-01579477>

HAL Id: hal-01579477

<https://hal.inria.fr/hal-01579477>

Submitted on 31 Aug 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Ensuring successful introduction of *Wolbachia* in natural populations of *Aedes aegypti* by means of feedback control

Pierre-Alexandre Bliman · M. Soledad Aronna · Flávio C. Coelho · Moacyr A.H.B. da Silva

July 19, 2017

Abstract The control of the spread of dengue fever by introduction of the intracellular parasitic bacterium *Wolbachia* in populations of the vector *Aedes aegypti*, is presently one of the most promising tools for eliminating dengue, in the absence of an efficient vaccine. The success of this operation requires locally careful planning to determine the adequate number of individuals carrying the *Wolbachia* parasite that need to be introduced into the natural population. The introduced mosquitoes are expected to eventually replace the *Wolbachia*-free population and guarantee permanent protection against the transmission of dengue to human.

In this study, we propose and analyze a model describing the fundamental aspects of the competition between mosquitoes carrying *Wolbachia* and mosquitoes free of the parasite. We then use feedback control techniques to devise an introduction protocol that is proved to guarantee that the population converges to a stable equilibrium where the totality of mosquitoes carry *Wolbachia*.

Pierre-Alexandre Bliman (✉)
Escola de Matemática Aplicada, Fundação Getulio Vargas, Praia de Botafogo 190, 22250-900 Rio de Janeiro - RJ, Brazil and Sorbonne Universités, Inria, UPMC Univ. Paris 06, Lab. J.-L. Lions UMR CNRS 7598, Paris, France
E-mail: pierre-alexandre.bliman@inria.fr

M. Soledad Aronna
Escola de Matemática Aplicada, Fundação Getulio Vargas, Praia de Botafogo 190, 22250-900 Rio de Janeiro - RJ, Brazil
E-mail: soledad.aronna@fgv.br

Flávio C. Coelho
Escola de Matemática Aplicada, Fundação Getulio Vargas, Praia de Botafogo 190, 22250-900 Rio de Janeiro - RJ, Brazil
E-mail: fccoelho@fgv.br

Moacyr A.H.B. da Silva
Escola de Matemática Aplicada, Fundação Getulio Vargas, Praia de Botafogo 190, 22250-900 Rio de Janeiro - RJ, Brazil
E-mail: moacyr@fgv.br

Keywords Wolbachia · Vector control · Global stabilization · Monotone systems · Input-output characteristic

Mathematics Subject Classification (2000) Primary 92D30; Secondary 34C12, 93D15, 93D25

1 Introduction

1.1 Arboviroses and vector control

Arboviruses (arthropod borne viruses) are viruses transmitted to humans by arthropods, such as the mosquito. They are pathogens of many and important diseases, putting considerable portions of the human population at risk, and infecting millions of people every year. Mosquitoes (*Culicidae* family of the insects) are a huge public health concern as they are vectors of many arboviroses such as yellow fever, dengue, chikungunya and zika.

The control of these diseases can be achieved by acting on the population of mosquitoes, and in absence of vaccine or curative treatment, control turns out to be an important tool in the mission of reducing transmission. Application of insecticides for both adults and larvae and mechanical removal of breeding sites are the most popular strategies to control the population of mosquitoes. The intensive use of insecticides, however, has negative impacts for humans, animals and the environment. Besides, the increase of mosquito resistance to insecticides usually leads to partial or complete decrease of the efficiency of this strategy (Brogdon and McAllister, 1998; Ocampo et al, 2011; de Freitas et al, 2014; de Freitas and Valle, 2014). In addition to chemical control and mechanical removal of the breeding sites, alternative or supplementary vector control strategies have been proposed and implemented, such as the release of transgenic or sterile mosquitoes (Alphey et al, 2010; Alphey, 2014). Notice that an intrinsic weakness of the techniques listed above lies paradoxically in the fact that they aim at the local eradication of the vector, whose disappearance offers no protection against subsequent reinvasions.

Recently the release of *Aedes aegypti* mosquitoes infected by the bacterium *Wolbachia* has been proposed as a promising strategy to control dengue fever and chikungunya, due to the fact that this bacterium severely limits the vectorial competence of *Aedes aegypti* (Ruang-Areerate and Kittayapong, 2006; Moreira et al, 2009b; McMeniman et al, 2009; Bian et al, 2010; Yeap et al, 2011; Hoffmann et al, 2011; Walker et al, 2011). The release of mosquitoes infected with *Wolbachia* is usually believed to be safe both for humans and the environment (see (Murray et al, 2016; O’Neill, 2015) and references therein), and a quite inexpensive control strategy (O’Neill, 2015). The international program “Eliminate Dengue” (Hoffmann et al, 2012) is currently testing this strategy in the field in several locations around the world: Australia, Indonesia, Vietnam, Colombia and Brazil.

1.2 *Wolbachia* sp. as a biological control tool

Wolbachia sp. is a *genus* of bacteria that is a common intracellular parasite of many species of arthropods. It is often found in anthropophilic mosquitoes such as *Aedes albopictus* or *Culex quinquefasciatus* but there is no report of *Aedes aegypti* naturally infected by this bacterium (Rasgon and Scott, 2004).

There is evidence that the spread of certain strains of *Wolbachia* in populations of *Aedes aegypti* drastically reduces the vector competence of the mosquito for dengue and other diseases. Some strains of *Wolbachia* reduce the lifespan of the mosquito (McMeniman et al, 2009; Yeap et al, 2011), consequently limiting the proportion of surviving mosquitoes at the completion of the incubation period. More importantly, *Wolbachia* appears to decrease the virulence of the dengue infection in the mosquitoes (Moreira et al, 2009,b; Bian et al, 2010; Hoffmann et al, 2011; Walker et al, 2011), increasing the incubation period or blocking the virus, which also reduces the overall vector competence.

The infestation of natural *Aedes aegypti* populations by *Wolbachia*-contaminated strains can be achieved by field release of a large number of *Wolbachia*-infected mosquitoes bred in laboratory. Experiments have been conducted successfully in Australia (Hoffmann et al, 2011), Vietnam, Indonesia and are currently being undertaken in Brazil, within the “Eliminate Dengue” Program. In these experiments, the introduction of a number of *Wolbachia*-infected mosquitoes in the population triggered a *Wolbachia* outbreak whose outcome was the fixation of the bacteria in the population, with more than 90% prevalence. The effects of this fixation of *Wolbachia* on the dynamics of dengue in the field are currently under investigation, but preliminary results are encouraging (Frentiu et al, 2014). If tractable in practice, this method has certainly the advantage of offering certain resilience to subsequent invasions of *Wolbachia*-free mosquitoes.

Several mathematical models of the dynamics of invasion of *Wolbachia* in a population of mosquitoes have been proposed, each with distinct objectives. For example, Turelli (2010) describes a simple model with a single differential equation, sufficient to reveal the bistable nature of the *Wolbachia* dynamics. Models for spatial dispersion are analyzed by Barton and Turelli (2011), Hancock and Godfray (2012) and Huang et al (2015). In the latter, a reaction-diffusion model with one infected and one uninfected population of adults is analyzed and the existence of a minimum infection frequency above which *Wolbachia* can spread is investigated. In (Hughes and Britton, 2013; Ndi et al, 2015), models are presented that assess the effect of the *Wolbachia* in dengue dynamics. In a different spirit, Keeling et al (2003) analyze the possibility of coexistence of two different strains of *Wolbachia* in a same population. We do not focus here neither on spatial effects nor with the interaction with dengue epidemics, and we assume that the invasion is done with a unique *Wolbachia*-strain. On the other hand, Zheng et al (2014) consider a delay-differential model describing the evolution of the adult mosquitoes (the delay representing the mean duration of the maturation period). Assuming a single initial

release, sufficient conditions are provided therein that ensure complete infestation. Results of the same nature are established in (Hu et al, 2015) for an ordinary differential model that takes into account random variations of the environment affecting the mosquitoes birth rates. Koiller et al (2014) describes a data-driven model suitable for accurately estimating some biological parameters by fitting the model with field and lab data. The model used therein has state-variable of dimension 13. In the present paper, we introduce a simplified version of the latter, with state variable of dimension 4 (immatures and adults, uninfected and *Wolbachia*-infected) focusing on the main effects pertinent for the purpose of control analysis. This model of mosquito development with a single early stage allows to analyze the effects of *Wolbachia* in the population during continuous release.

1.3 Description of the problem

A key question about the introduction of *Wolbachia* in wild mosquitoes concerns the effective strategies of release of infected mosquitoes in the field that can be applied with limited cost to reach the desired state of 100% of *Wolbachia*-carrying mosquitoes. In this paper we propose and analyze a simple model of the dynamics of *Wolbachia*, that allows to investigate these strategies.

The main features of the natural dynamics of *Wolbachia* that have to be present in the model are the vertical transmission and the peculiar interference on the reproductive outcomes induced by *cytoplasmic incompatibility* (O'Neill et al, 1998; McMeniman et al, 2009; Yeap et al, 2011; Walker et al, 2011). The transmission of *Wolbachia* occurs only vertically (i.e. from mother to the offspring), there is no transmission by contact. Cytoplasmic incompatibility (CI) occurs when a female uninfected by *Wolbachia* is inseminated by an infected male, a mating that leads to sterile eggs. This provides a reproduction advantage to infected females against uninfected ones which facilitates the *Wolbachia* spread (Table 1 schematizes the results of the mating of infected and uninfected mosquitoes, when the CI is 100%). The *Wolbachia* strains *wMel* and *wMelPop* that are being used in the field experiments with *Aedes aegypti* induce almost total CI (Walker et al, 2011). The *wAlbB* strain was also observed to induce total CI in *Aedes aegypti* in (Xi et al, 2005). The model that we introduce below captures all of these features and is simple enough to allow a fairly complete analysis. The corresponding system is shown to possess two unstable equilibria, which correspond to extinction and to coexistence of the two populations; and two locally asymptotically stable equilibria, which correspond to *Wolbachia*-free and complete infestation equilibria.

The release strategy we propose here is based on techniques from Control theory. Several types of traps exist to capture mosquitos at various stages of their development, permitting to evaluate their abundance through statistical methods (Focks , 2003; Silver , 2007), and the presence of the bacterium *Wolbachia* in the captured sample may be checked by polymerase chain reaction (PCR) method (Hoffmann et al, 2011). It is therefore possible, in principle,

| | | |
|----------------------|---------------------|---------------------|
| | Uninfected σ | Infected σ |
| Uninfected φ | Uninfected | Sterile eggs |
| Infected φ | Infected | Infected |

Table 1: Cytoplasmic incompatibility and vertical transmission of *Wolbachia* bacteria. The state of the offspring is indicated, depending on the parents status

to use information on the composition of the population of mosquitoes to determine the volume to be released, seen here as the *control input*. As a main contribution we propose in the present paper a simple, linear, *feedback control law*, and demonstrate its capacity to asymptotically steer the system to the complete *Wolbachia*-infected equilibrium *from arbitrary initial conditions* and, in particular, from the completely *Wolbachia*-free equilibrium. A major advantage of feedback compared to *open-loop approaches* (where the release schedule is computed once for all before the beginning of the experiment), is its ability to cope with the uncertainties in the model dynamics (e.g. in the modeling of the life stages and the population structure), in the parameters (population size, mortality, reproductive rates, etc.), and in the size of the population to be treated.

To our knowledge, the present paper constitutes the first attempt to use feedback approach for introduction of *Wolbachia* within a population of arthropods. We treat here only the case of the release of *Wolbachia*-positive larvae and full information on the quantity of *Wolbachia*-negative larvae. Yet, the same dynamical model offers the ability to study other configurations, both for the control and the observation, and the corresponding issues will be examined in future work.

The paper is organized as follows. The simple model used throughout the article is introduced and commented in Section 2. The analysis of the uncontrolled model is made in Section 3, showing the above-mentioned bistability between the *Wolbachia*-free equilibrium and full infestation. A proportional control law is then proposed in Section 4, and proved to lead to global stability of the full infestation equilibrium (Theorems 13 and 14). Simulations are provided in Section 5. Last, concluding remarks complete the text in Section 6.

Notation. For $n \in \mathbb{N}$, we let \mathbb{R}^n denote the n -dimensional Euclidean real space, \mathbb{R}_+^n the cone of vectors in \mathbb{R}^n with *nonnegative* components and \mathbb{R}_-^n the cone of vectors with *nonpositive* components. We write $\max\{a; b\}$ (resp. $\min\{a; b\}$) for the maximum (resp. minimum) of two real numbers a, b .

2 A simple model of infestation by *Wolbachia*

The simplified compartmental model we introduce includes two life stages: a preliminary one, gathering the early stages (egg, larva and pupa), in which

| Notation | Meaning |
|----------------------|---|
| α_U, α_W | Fecundity rates of uninfected and infected insects |
| ν | Rate of transfer from the early to the adult stage |
| μ | Mortality rate of uninfected and infected insects in early stage |
| μk | Characteristic of the additional mortality rate in early stage |
| μ_U, μ_W | Mortality rates of uninfected and infected insects at adult stage |

Table 2: List of parameters of model (1)

the mosquitoes are subject to space and food competition; and an adult one, representing all the posterior aerial phases (mature adult). Accordingly, we let \mathbf{L} and \mathbf{A} denote the corresponding state variables. The uninfected and *Wolbachia*-infected populations will be distinguished by indices U and W respectively, so we end up with a four state variables model, namely $\mathbf{L}_U, \mathbf{L}_W$ and $\mathbf{A}_U, \mathbf{A}_W$, which represent the numbers of uninfected, resp. infected, vectors in early and adult phases. No distinction between males and females is made in this model. A sexual version of the latter is provided in Appendix A, which comes down to (1) when the sex ratio is constant and the mortality is sex-independent: in such conditions, one may interpret the state variables as representing indifferently the quantities of males and females, up to constant ratio.

We propose the following evolution model:

$$\dot{\mathbf{L}}_U = \alpha_U \frac{\mathbf{A}_U}{\mathbf{A}_U + \mathbf{A}_W} \mathbf{A}_U - \nu \mathbf{L}_U - \mu(1 + k(\mathbf{L}_W + \mathbf{L}_U)) \mathbf{L}_U \quad (1a)$$

$$\dot{\mathbf{A}}_U = \nu \mathbf{L}_U - \mu_U \mathbf{A}_U \quad (1b)$$

$$\dot{\mathbf{L}}_W = \alpha_W \mathbf{A}_W - \nu \mathbf{L}_W - \mu(1 + k(\mathbf{L}_W + \mathbf{L}_U)) \mathbf{L}_W + \mathbf{u} \quad (1c)$$

$$\dot{\mathbf{A}}_W = \nu \mathbf{L}_W - \mu_W \mathbf{A}_W \quad (1d)$$

All the parameters are positive, their meaning is summarized in Table 2.

Note that a quadratic *competition term* is included in the immature phase dynamics. This term, which accounts for the restricted food and space in the breeding sites, acts equally on both infected and uninfected populations, with an effect that is proportional to the size of the immature population. According to (Southwood et al, 1972; Focks et al, 1993), this density-dependent mortality is a major component of larval dynamics. See also (Otero et al, 2006, 2008; Smith et al, 2013). Model (1) indeed extends a model introduced in Smith et al (2013) to describe the spreading of *Wolbachia*. Finally, notice that modeling competition between adults has not been considered necessary in the present context, but could be added without major changes.

The differences between the behaviors of the uninfected and infected populations lie in the different fecundity and mortality rates. First, different mortality rates μ_U and μ_W have been introduced for the adult stages in (1b) and (1d), as infection by *Wolbachia* reduces life duration (McMeniman et al, 2009; Yeap et al, 2011). On the contrary, the variations of larval development time

seems limited (Yeap et al, 2011, Table 2). Accordingly, mortality and phase duration during the early stage are considered here unmodified by the disease: the same density-dependent *per capita* mortality rate $\mu(1 + k(\mathbf{L}_W + \mathbf{L}_U))$ is used in (1a) and (1c), as well as the same *per capita* rate of transfer ν from the immature to the adult stage.

We now turn to the fecundity terms in (1a) and (1c), which incorporates the effect of complete cytoplasmic incompatibility. This reproductive incompatibility is characterized by the fact that an uninfected female only produces offspring when mating with an uninfected male (O'Neill et al, 1998; McMeniman et al, 2009; Yeap et al, 2011; Walker et al, 2011). When she encounters a male and mates, the probability of that male being uninfected is $\frac{\mathbf{A}_U}{\mathbf{A}_U + \mathbf{A}_W}$, giving rise to the birth term $\alpha_U \frac{\mathbf{A}_U}{\mathbf{A}_U + \mathbf{A}_W} \mathbf{A}_U$ in (1a). The situation is different when an infected female mates, as the outcome is independent of whether the male is infected with *Wolbachia* or not. Therefore the birth term in (1c) is simply $\alpha_W \mathbf{A}_W$, proportional to the number of infected adults (that is of infected females, the sex ratio being assumed constant).

The bacterium *Wolbachia* has the effect of globally reducing the fitness of the infected mosquitoes. More precisely, it has been observed that *Wolbachia* infection in *Aedes aegypti* mosquito may lead to lifespan shortening (McMeniman et al, 2009; Yeap et al, 2011) and fecundity rate reduction (Ruang-Areerate and Kittayapong, 2006). This assumption will correspond to the choice of parameters made in (6) below.

Finally, notice the term \mathbf{u} in equation (1c). The latter is an *input variable* representing the infected larvae that are intentionally released to steer the system towards the desired complete *Wolbachia*-infection equilibrium.

2.1 Normalization and general assumption

In order to reduce the number of parameters and to exhibit meaningful quantities, we now normalize model (1). Define

$$\begin{aligned} L_\eta(t) &:= \frac{k\mu}{\nu + \mu} \mathbf{L}_\eta \left(\frac{t}{\nu + \mu} \right), & A_\eta(t) &:= \frac{k\mu}{\nu} \mathbf{A}_\eta \left(\frac{t}{\nu + \mu} \right), & \eta &= U, W \\ u(t) &:= \frac{k\mu}{(\nu + \mu)^2} \mathbf{u} \left(\frac{t}{\nu + \mu} \right) \end{aligned}$$

with the following choice of *dimensionless* parameters

$$\gamma_\eta := \frac{\mu_\eta}{\nu + \mu}, \quad \mathcal{R}_\eta := \frac{\nu \alpha_\eta}{(\nu + \mu) \mu_\eta}, \quad \eta = U, W \quad (2)$$

Notice that in this setting, the new time variable t is *dimensionless*. The following normalized model is deduced, that will be used in the remainder of

the paper.

$$\dot{L}_U = \gamma_U \mathcal{R}_U \frac{A_U}{A_U + A_W} A_U - (1 + L_W + L_U) L_U \quad (3a)$$

$$\dot{A}_U = L_U - \gamma_U A_U \quad (3b)$$

$$\dot{L}_W = \gamma_W \mathcal{R}_W A_W - (1 + L_W + L_U) L_W + u \quad (3c)$$

$$\dot{A}_W = L_W - \gamma_W A_W \quad (3d)$$

The state variable for system (3) will be denoted

$$x := (L_U, A_U, L_W, A_W),$$

and for sake of simplicity, we write (3) as

$$\dot{x} = f(x) + Bu, \quad (4)$$

where f and B are defined as

$$f(x) := \begin{pmatrix} \gamma_U \mathcal{R}_U \frac{A_U}{A_U + A_W} A_U - (1 + L_W + L_U) L_U \\ L_U - \gamma_U A_U \\ \gamma_W \mathcal{R}_W A_W - (1 + L_W + L_U) L_W \\ L_W - \gamma_W A_W \end{pmatrix}, \quad B := \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \end{pmatrix}.$$

Considering situations where only one of the two populations (uninfected and infected) is present, yields the following uncoupled systems:

$$\dot{L}_U = \gamma_U \mathcal{R}_U A_U - (1 + L_U) L_U, \quad \dot{A}_U = L_U - \gamma_U A_U \quad (5a)$$

$$\dot{L}_W = \gamma_W \mathcal{R}_W A_W - (1 + L_W) L_W, \quad \dot{A}_W = L_W - \gamma_W A_W \quad (5b)$$

The quantities denoted \mathcal{R}_U and \mathcal{R}_W are the *basic offspring numbers* (Yang et al, 2009; Ferreira and Godoy, 2014) associated, respectively, to the uninfected and the infected populations. They represent the average number of mosquitoes born to each adult mosquito during its entire lifespan. We assume in the sequel that

$$\mathcal{R}_U > \mathcal{R}_W > 1. \quad (6)$$

This assumption ensures the sustainability of each of the two isolated populations with a greater basic offspring number for the uninfected population, in accordance with the fact that *Wolbachia* reduces the fecundity rate and increases mortality.

3 Analysis of the uncontrolled system

The uncontrolled system is obtained by taking zero input u , that is:

$$\dot{x} = f(x) \quad (7)$$

3.1 Well-posedness, positivity and boundedness

One first shows the well-posedness of the Cauchy problem related to equation (7) for nonnegative initial conditions.

Theorem 1. *For any initial value in \mathbb{R}_+^4 , there exists a unique solution to the initial value problem associated to system (7). The latter is defined on $[0, +\infty)$, depends continuously on the initial conditions and takes on values in \mathbb{R}_+^4 . Moreover, it is uniformly ultimately bounded.*

Remark 2. The previous result shows that system (7) is *positive*. Therefore, when talking about “trajectories”, we will always mean trajectories with initial values in \mathbb{R}_+^4 . The same shortcut will be used for all positive systems considered later.

Let us introduce the following definition of an *order induced by a cone*, that will be instrumental in proving Theorem 1.

Definition 3. *Given a topological vector space X and a convex pointed cone $\mathcal{K} \subset X$ with nonempty interior, we consider the partial order induced by \mathcal{K} in X (see Smith (1995)) in the following way: given $x_1, x_2 \in X$ we write*

- (i) $x_1 \leq_{\mathcal{K}} x_2$ if $x_2 - x_1 \in \mathcal{K}$,
- (ii) $x_1 <_{\mathcal{K}} x_2$ if $x_2 - x_1 \in \mathcal{K}$ and $x_1 \neq x_2$,
- (iii) $x_1 \ll_{\mathcal{K}} x_2$ when $x_2 - x_1$ is in the (topological) interior of the cone \mathcal{K} .

In the next subsection we apply these concepts to define monotonicity of dynamical systems.

Proof of Theorem 1. Function f in (7) is clearly well-defined and continuous in \mathbb{R}_+^4 , except in points where $A_U = A_W = 0$. Due to the fact that $0 \leq \frac{A_U}{A_U + A_W} \leq 1$, the quantity $\frac{A_U}{A_U + A_W} A_U$ tends towards zero when one approaches such points, and $f(x)$ can thus be defined by continuity when $A_U = A_W = 0$. In addition, the right-hand side is clearly locally Lipschitz in \mathbb{R}_+^4 , and a classical result ensures the *local* well-posedness of the initial value problem, as long as the trajectory does not leave this set.

The invariance property of the set \mathbb{R}_+^4 is verified due to the fact that

$$\forall x \in \mathbb{R}_+^4, \forall i \in \{1, 2, 3, 4\} : \quad x_i = 0 \Rightarrow f_i(x) \geq 0 .$$

Let us now show that, for any initial condition in \mathbb{R}_+^4 , the associated trajectory remains bounded for all $t \geq 0$. With this aim, let us define

$$L := L_U + L_W, \quad A := A_U + A_W, \quad (8a)$$

$$\gamma := \min\{\gamma_U; \gamma_W\} > 0, \quad \mathcal{R}_0 := \frac{\max\{\gamma_U \mathcal{R}_U; \gamma_W \mathcal{R}_W\}}{\gamma} . \quad (8b)$$

Notice that, in view of hypothesis (6),

$$\mathcal{R}_0 > 1 . \quad (9)$$

It turns out that

$$\begin{aligned}\dot{L} &= \gamma_U \mathcal{R}_U \frac{A_U}{A_U + A_W} A_U + \gamma_W \mathcal{R}_W A_W - (1 + L_W + L_U)(L_U + L_W) \\ &\leq (\gamma_U \mathcal{R}_U A_U + \gamma_W \mathcal{R}_W A_W) - (1 + L)L \\ &\leq \gamma \mathcal{R}_0 A - (1 + L)L\end{aligned}$$

and

$$\dot{A} \leq L - \gamma A$$

Now, the auxiliary system

$$\dot{L}' = \gamma \mathcal{R}_0 A' - (1 + L')L', \quad \dot{A}' = L' - \gamma A' \quad (11)$$

is evidently *cooperative* (see Hirsch (1988)) for the canonic order induced by the cone \mathbb{R}_+^2 . One may thus use Kamke's theorem, see e.g. (Coppel, 1965, Theorem 10, p. 29) or Smith (1995), and compare the solutions of (7) (with L and A defined by (8)) and (11). One deduces

$$L(t) \leq L'(t), \quad A(t) \leq A'(t), \quad \text{for all } t \geq 0, \quad (12)$$

whenever the solutions are considered with the same initial conditions.

It may be shown without difficulty that system (11) possesses exactly two equilibria, namely

$$x_* := (L_*, A_*) := (0, 0) \quad \text{and} \quad x^* := (L^*, A^*) := \left(\mathcal{R}_0 - 1, \frac{1}{\gamma}(\mathcal{R}_0 - 1) \right).$$

Due to (9), linearization around each point shows that x_* is locally unstable, while x^* is locally asymptotically stable (LAS). On the other hand, notice that $x_* \leq_{\mathbb{R}_+^2} x^*$. Using the local stability information, application of (Hirsch, 1988, Theorem 10.3) then shows that the stability of x^* is *global* in the topological interior of \mathbb{R}_+^2 , and that this point is in fact attractive for any initial point distinct from $x_* = (0, 0)$. In any case, all solutions of (11) converge to the order interval

$$\llbracket x_*; x^* \rrbracket_{\mathbb{R}_+^2} := \{x' \in \mathbb{R}_+^2 : L_* \leq L' \leq L^*, A_* \leq A' \leq A^*\}.$$

Observe that due to the invariance of \mathbb{R}_+^4 in system (7) and the comparison (12) shown above, one can deduce that L and A also converge to the order interval $\llbracket x_*; x^* \rrbracket_{\mathbb{R}_+^2}$. Consequently, also due to the invariance of \mathbb{R}_+^4 , we have that (L_U, A_U) and (L_W, A_W) remain inside $\llbracket x_*; x^* \rrbracket_{\mathbb{R}_+^2}$ for large enough values of time. We conclude that all solutions of (7) are uniformly ultimately bounded, and this yields global existence of solutions, and hence the proof of Theorem 1. □

3.2 Monotonicity

One shows here that the uncontrolled system (7) is *monotone*. Using the concepts and notations from Definition 3, one introduces first some useful notions, borrowed from Smith (1995).

Definition 4. A semiflow $\Phi: \mathbb{R}_+ \times X \rightarrow X$ is called *monotone* if

$$\Phi_t(x) \leq_{\mathcal{K}} \Phi_t(x') \quad \text{whenever } x \leq_{\mathcal{K}} x' \text{ and } t \geq 0 .$$

The semiflow Φ is called *strongly order-preserving* if Φ is monotone and, whenever $x <_{\mathcal{K}} x'$, there exist open subsets Ω, Ω' of X with $x \in \Omega$, $x' \in \Omega'$, and $t > 0$ such that

$$\Phi_t(\Omega) \leq_{\mathcal{K}} \Phi_t(\Omega') ,$$

this meaning $z \leq_{\mathcal{K}} z'$, for all $z \in \Phi_t(\Omega)$, $z' \in \Phi_t(\Omega')$. The semiflow Φ is called *strongly monotone* if Φ is monotone and

$$\Phi_t(x) \ll_{\mathcal{K}} \Phi_t(x') \quad \text{whenever } x <_{\mathcal{K}} x' \text{ and } t > 0 .$$

A dynamical system is said to have one of the properties above if its associated semiflow does.

We now examine system (7) at the light of these properties.

Theorem 5. System (7) is strongly order-preserving in \mathbb{R}_+^4 for the order induced by the cone

$$\mathcal{K} := \mathbb{R}_- \times \mathbb{R}_- \times \mathbb{R}_+ \times \mathbb{R}_+ , \quad (13)$$

where $\mathbb{R}_- := \{y \in \mathbb{R} : y \leq 0\}$. Hence, $x \geq_{\mathcal{K}} x' \Leftrightarrow x_i \leq x'_i$, $i = 1, 2$ and $x_i \geq x'_i$, $i = 3, 4$.

System (7) is therefore monotone in \mathbb{R}_+^4 , but not strongly monotone, due to the fact that the trajectories departing inside the sets $\{x \in \mathbb{R}_+^4 : L_U = 0, A_U = 0\}$ and $\{x \in \mathbb{R}_+^4 : L_W = 0, A_W = 0\}$ remain in these sets and, consequently, do not verify strict ordering property for the two null components.

Before proving Theorem 5, we summarize in the following result the behavior of the trajectories in relation with some parts of the boundaries.

Lemma 6. Let $x_0 \in \mathbb{R}_+^4$ and let $x_{0,0} := (0, 0, 0, 0)$ denote the trivial equilibrium of (7). Then exactly one of the four following properties is verified by the trajectories of (7) departing from x_0 at $t = 0$.

- $x \equiv x_{0,0}$ (that is, $x(t) = x_{0,0}$, $\forall t \geq 0$).
- $A_W \equiv 0$ and $A_U(t) > 0$, $\forall t > 0$.
- $A_U \equiv 0$ and $A_W(t) > 0$, $\forall t > 0$.
- $A_W(t) > 0$ and $A_U(t) > 0$, $\forall t > 0$.

Proof of Lemma 6. Clearly, one sees from (3b) (resp. (3d)) that $A_U \equiv 0$ (resp. $A_W \equiv 0$) if and only if $A_U(0) = 0$ and $L_U \equiv 0$ (resp. $A_W(0) = 0$ and $L_W \equiv 0$). Therefore, if $(A_U(0), L_U(0)) \neq (0, 0)$ (resp. $(A_W(0), L_W(0)) \neq (0, 0)$), then $A_U(t) > 0$ (resp. $A_W(t) > 0$) for all $t > 0$. This proves Lemma 6. \square

Proof of Theorem 5. We now introduce the Jacobian matrix of f . At each point $x = (L_U, A_U, L_W, A_W) \in \mathbb{R}_+^4$ such that $A_U + A_W > 0$, $Df(x)$ is equal to

$$\begin{pmatrix} -1 - 2L_U - L_W \gamma_U \mathcal{R}_U \left(1 - \frac{A_W^2}{(A_U + A_W)^2}\right) & -L_U & -\gamma_U \mathcal{R}_U \frac{A_U^2}{(A_U + A_W)^2} \\ 1 & -\gamma_U & 0 & 0 \\ -L_W & 0 & -1 - L_U - 2L_W & \gamma_W \mathcal{R}_W \\ 0 & 0 & 1 & -\gamma_W \end{pmatrix} \quad (14)$$

Notice that, as a corollary of Lemma 6, either $x \equiv x_{0,0}$, or $A_U(t) + A_W(t) > 0$ for all $t > 0$. Therefore, the Jacobian can be computed at any point of a trajectory, except if the latter is reduced to $x_{0,0}$.

For any $x \in \mathbb{R}_+^4$, one verifies easily that

$$\begin{aligned} \forall (i, j) \in \{1, 2\} \times \{3, 4\}, \quad \frac{\partial f_i}{\partial x_j}(x) &\leq 0, \quad \frac{\partial f_j}{\partial x_i}(x) \leq 0, \\ \forall (i, j) \in \{1, 2\}^2 \cup \{3, 4\}^2, \quad i \neq j, \quad \frac{\partial f_i}{\partial x_j}(x) &\geq 0. \end{aligned}$$

Hence, in view of the characterization of monotonicity given e.g. in Angeli and Sontag (2003) for orders induced by *orthants*, we deduce that system (7) is monotone.

Moreover, except when $A_U = 0$ or $A_W = 0$, the Jacobian matrix in (14) is irreducible, and the semiflow related to system (7) is therefore strongly monotone therein. On the other hand, trajectories confined to one of the sets $\{x \in \mathbb{R}_+^4 : L_U = 0, A_U = 0\}$ and $\{x \in \mathbb{R}_+^4 : L_W = 0, A_W = 0\}$, also verify strong monotonicity, for the order relation restricted to the two non-identically zero components. These two remarks, together with Lemma 6, show that overall the strongly order-preserving property is verified. This completes the proof of Theorem 5. \square

3.3 Equilibrium points and stability

The next result describes the situation of the equilibrium points and their stability. Recall that the cone \mathcal{K} used to order the state space has been defined in (13) (in Theorem 5).

Theorem 7. *System (7) possesses four equilibrium points, denoted $x_{0,0}$, $x_{U,0}$, $x_{0,W}$ and $x_{U,W}$ and corresponding respectively to zero population, disease-free state, complete infestation and coexistence. They have the following values*

$$x_{0,0} = (0, 0, 0, 0), \quad x_{U,0} := \left(\mathcal{R}_U - 1, \frac{\mathcal{R}_U - 1}{\gamma_U}, 0, 0 \right), \quad (16a)$$

$$x_{0,W} := \left(0, 0, \mathcal{R}_W - 1, \frac{\mathcal{R}_W - 1}{\gamma_W} \right), \quad (16b)$$

$$x_{U,W} := \frac{\mathcal{R}_W - 1}{1 + \delta} \left(\delta, \frac{\delta}{\gamma_U}, 1, \frac{1}{\gamma_W} \right), \quad (16c)$$

where

$$\delta := \frac{\gamma_U}{\gamma_W} \frac{\mathcal{R}_W}{\mathcal{R}_U - \mathcal{R}_W}. \quad (16d)$$

Moreover, the equilibria fulfill the following inequalities:

$$x_{U,0} \ll_{\mathcal{K}} x_{U,W} \ll_{\mathcal{K}} x_{0,W} \quad \text{and} \quad x_{U,0} \ll_{\mathcal{K}} x_{0,0} \ll_{\mathcal{K}} x_{0,W}. \quad (17)$$

Last, the equilibrium points $x_{U,0}$ and $x_{0,W}$ are locally asymptotically stable (LAS), while the two other ones are unstable.

For the sake of readability, the proof of Theorem 7 has been put in Appendix B.

3.4 Positively invariant sets and basins of attraction

We further exploit the monotonicity properties of (7) to prove the forward invariance of some given ordered intervals.

Theorem 8. *The order interval*

$$\llbracket x_{U,0}; x_{0,W} \rrbracket_{\mathcal{K}} := \{x \in \mathbb{R}^4 : x_{U,0} \leq_{\mathcal{K}} x \leq_{\mathcal{K}} x_{0,W} \subset \mathbb{R}_+^4\}$$

is positively invariant for system (7). Moreover, the order intervals $\llbracket x_{U,W}; x_{0,W} \rrbracket_{\mathcal{K}}$ and $\llbracket x_{0,0}; x_{0,W} \rrbracket_{\mathcal{K}}$ (resp. $\llbracket x_{U,0}; x_{U,W} \rrbracket_{\mathcal{K}}$ and $\llbracket x_{U,0}; x_{0,0} \rrbracket_{\mathcal{K}}$) are contained in the basin of attraction of $x_{0,W}$ (resp. $x_{U,0}$).

Proof. The positive invariance properties are direct consequences of the monotonicity properties exhibited in Theorem 5. More precisely, endowing the state space with the ordering induced by the cone \mathcal{K} (see (13)), the autonomous system (3) induces a monotone flow in \mathbb{R}^4 , strongly monotone in $\mathbb{R}_+^4 \setminus (\mathbb{R}_+^2 \times \{0\}^2 \cup \{0\}^2 \times \mathbb{R}_+^2)$. As the trajectories are bounded, the set of initial points whose corresponding trajectories do not converge to one of the equilibria is of zero measure (Hirsch, 1988, Theorem 7.8). Among the equilibria, only $x_{U,0}$ and $x_{0,W}$ are locally stable.

The same rationale applies for any trajectory with initial condition in the order interval $\llbracket x_{U,W}; x_{0,W} \rrbracket_{\mathcal{K}} \setminus (\mathbb{R}_+^2 \times \{0\}^2 \cup \{0\}^2 \times \mathbb{R}_+^2)$, and the convergence (for almost every initial condition) in this interval can only occur towards $x_{0,W}$: the latter is therefore included in the basin of attraction. The same argument applies for the other equilibrium $x_{U,0}$.

Last, for initial condition in $\llbracket x_{0,0}; x_{0,W} \rrbracket_{\mathcal{K}}$, monotonicity of the system implies that the L_U and A_U remain identically zero, and the same argument than above applies to the degenerate system that describes the evolution of (L_W, U_W) , showing that all trajectories converge towards $x_{W,0}$ except the unstable equilibrium $x_{0,0}$. The same argument applies for $x_{U,0}$. \square

4 Analysis of the controlled system

In this section we analyze the controlled system (4). We assume that the number of uninfected larvae is continuously measured. Taking advantage of these measurements, we propose a simple *linear feedback law* for the control u , given by $u(x) = KL_U$ for $K > 0$, and analyze the asymptotic behavior of the resulting *closed-loop* system. The control action thus consists in releasing infected larvae, with a rate proportional to the number of non-infected larvae (in particular, no control action is required once the full infestation has been realized). Theorem 13 below states the almost global asymptotic stability of the complete-infestation equilibrium for K greater than a given threshold K^* . Theorem 14 shows that taking large values of this gain provides robustness of this asymptotic stability property with respect to measurement noise.

4.1 A class of static output-feedback control laws

The following feedback law for equation (4) will be considered in the sequel:

$$u = KL_U \quad (18)$$

for adequate (positive) values of the *scalar gain* K .

Writing

$$e := \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

one obtains the closed-loop system:

$$\dot{x} = f(x) + KBe^\top x, \quad (19)$$

or in developed form:

$$\dot{L}_U = \gamma_U \mathcal{R}_U \frac{A_U}{A_U + A_W} A_U - (1 + L_W + L_U)L_U \quad (20a)$$

$$\dot{A}_U = L_U - \gamma_U A_U \quad (20b)$$

$$\dot{L}_W = \gamma_W \mathcal{R}_W A_W - (1 + L_W + L_U)L_W + KL_U \quad (20c)$$

$$\dot{A}_W = L_W - \gamma_W A_W \quad (20d)$$

The basic results gathered in the following theorem can be demonstrated by use of the same arguments than for Theorem 1. The proof presents no difficulty and is left to the reader.

Theorem 9. *For any initial value in \mathbb{R}_+^4 , there exists a unique solution to the initial value problem associated to system (19). The latter is defined on $[0, +\infty)$, depends continuously on the initial conditions and takes on values in \mathbb{R}_+^4 . Moreover, it is uniformly ultimately bounded.*

4.2 Equilibrium points and critical gain

We now turn to the study of the equilibrium points. The following result shows that, for gains larger than certain critical value, the only locally asymptotically stable equilibrium is $x_{0,W}$. Moreover, the explicit value of this critical number depends only upon the basic offspring numbers of the two populations and the ratio between their mortality rates, which are all scale-free information.

Theorem 10. *If the feedback gain K is such that*

$$K > K^* := \frac{\gamma_W}{\gamma_U} \left(\sqrt{\mathcal{R}_U} - \sqrt{\mathcal{R}_W} \right)^2, \quad (21)$$

then the closed-loop system (19) possesses two equilibrium points, namely $x_{0,0}$ and $x_{0,W}$ (given explicitly in (16)), and their local stability properties are not modified (i.e. $x_{0,0}$ is unstable and $x_{0,W}$ is locally stable).

Proof of Theorem 10.

- The equilibrium points of system (19) are the points that verify

$$f(x) + KBe^\top x = 0. \quad (22)$$

Clearly, the points $x_{0,0}$ and $x_{0,W}$ are still equilibria of system (19), as in these points $L_U = 0$; and there are no other equilibria with $L_U = 0$. In fact, fixing $L_U = 0$ one gets, from the third and fourth equations of (22),

$$0 = \gamma_W \mathcal{R}_W A_W - (1 + L_W)L_W = (L_W^* - L_W)L_W,$$

where the second identity follows from the definition of L_W^* in (47).

Let us show that there are no other equilibria than $x_{0,0}$ and $x_{0,W}$. We suppose, on the contrary, that there exists a third equilibrium point. Then, necessarily, it should have $L_U \neq 0$, which yields, in view of (22),

$$0 = \gamma_W \mathcal{R}_W A_W - (1 + L_W + L_U)L_W + KL_U = (\mathcal{R}_W - 1 - L_W - L_U)L_W + KL_U \quad (23)$$

and thus $L_W \neq 0$. Consequently, $A_W \neq 0$. At such supplementary equilibrium point, one should have

$$\mathcal{R}_U \frac{A_U}{A_U + A_W} = \mathcal{R}_W + K \frac{L_U}{L_W} = \mathcal{R}_W + \frac{\gamma_U}{\gamma_W} K \frac{A_U}{A_W}$$

Defining the unknown quantity

$$\theta := \frac{A_U}{A_W},$$

the latter should fulfill

$$\mathcal{R}_U \frac{\theta}{1 + \theta} = \mathcal{R}_W + \frac{\gamma_U}{\gamma_W} K \theta, \quad (24)$$

that is

$$\frac{\gamma_U}{\gamma_W} K \theta^2 + \left(\frac{\gamma_U}{\gamma_W} K + \mathcal{R}_W - \mathcal{R}_U \right) \theta + \mathcal{R}_W = 0$$

The roots of this equation are given by

$$\frac{\gamma_W}{2\gamma_U K} \left(- \left(\frac{\gamma_U}{\gamma_W} K + \mathcal{R}_W - \mathcal{R}_U \right) \pm \sqrt{\left(\frac{\gamma_U}{\gamma_W} K + \mathcal{R}_W - \mathcal{R}_U \right)^2 - 4\mathcal{R}_W \frac{\gamma_U}{\gamma_W} K} \right)$$

For positive values of K , there exist real nonnegative solutions to this equation if, and only if,

$$\frac{\gamma_U}{\gamma_W} K + \mathcal{R}_W - \mathcal{R}_U \leq 0 \quad \text{and} \quad \left(\frac{\gamma_U}{\gamma_W} K + \mathcal{R}_W - \mathcal{R}_U \right)^2 \geq 4\mathcal{R}_W \frac{\gamma_U}{\gamma_W} K ,$$

that is if and only if

$$\frac{\gamma_U}{\gamma_W} K + \mathcal{R}_W - \mathcal{R}_U \leq -2\sqrt{\mathcal{R}_W \frac{\gamma_U}{\gamma_W} K} .$$

This is equivalent to

$$\left(\sqrt{\frac{\gamma_U}{\gamma_W} K} + \sqrt{\mathcal{R}_W} \right)^2 - \mathcal{R}_U \leq 0$$

or again

$$K \leq \frac{\gamma_W}{\gamma_U} \left(\sqrt{\mathcal{R}_U} - \sqrt{\mathcal{R}_W} \right)^2 = K^* .$$

As hypothesis (21) is incompatible with the previous inequality, we deduce that system (19) possess only two equilibrium points.

• We now study the local stability properties of $x_{0,W}$ by applying adequate modifications to the Jacobian exhibited in (14) and used in Section B.2 to study the stability of the uncontrolled model equilibria. In fact, one just has to add to $Df(x_{0,W})$ the term

$$\begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ K & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} .$$

It is clear, due to the form of this additional term, that the characteristic polynomial of the system obtained from linearizing (19) at $x_{0,W}$ is *affine* with respect to K , and that, for $K = 0$, it coincides with the characteristic polynomial of the linearization of (3).

Developing the determinant $\det(\lambda I - Df(x_{0,W}) - KBe^\top)$ (see (53)), the additional term is equal, for the feedback control law defined in (18), to

$$-K \begin{vmatrix} 0 & 0 & 0 \\ \lambda + \gamma_U & 0 & 0 \\ 0 & -1 & \lambda + \gamma_W \end{vmatrix} = 0 .$$

Therefore the local behavior is not perturbed, and the asymptotic stability of the equilibrium $x_{0,W}$ is conserved when the control term $KB e^\top x$ is added. This completes the proof of Theorem 10. \square

Remark 11. From the latter proof it can be deduced that the set of equilibrium points, considered as function of the nonnegative gain K , is constituted by four continuous branches of solutions. Apart from the two equilibria $x_{0,0}$ (unstable) and $x_{0,W}$ (locally asymptotically stable) that do not depend on K , there exist for any $0 < K < K^*$, two branches of solutions. A branch of locally asymptotically stable equilibria starts at $x_{U,0}$ for $K = 0$, and a branch of unstable equilibria begins at $x_{U,W}$, also for $K = 0$. These two branches coalesce when $K = K^*$, and disappear for $K > K^*$. For the parameter value $K = K^*$, a *saddle-node bifurcation* occurs.

Remark 12. It can be checked from the latter proof that the previous result is not true when the effect of cytoplasmic incompatibility is absent. The latter is materialized by the term $\frac{A_U}{A_U + A_W}$ present in the first line in equation (19). When replacing this term by 1, (24) is replaced by

$$\mathcal{R}_U = \mathcal{R}_W + \frac{\gamma_U}{\gamma_W} K \theta ,$$

which possesses the positive solution

$$\theta = \frac{\gamma_W}{\gamma_U K} (\mathcal{R}_U - \mathcal{R}_W) ,$$

leading to a coexistence equilibrium solution, in addition to $x_{0,0}$ and $x_{0,W}$.

4.3 Main results: global stability

We now turn to the most innovative part of this paper, namely the global behavior of the closed-loop system (19). The result we establish first shows that the introduction of infected larvae according to the proportional feedback law (18) yields conclusive infestation when the gain is larger than the critical value. More precisely, we have the following convergence result.

Theorem 13. *If $K > K^*$, all trajectories of system (19) issuing from a point in \mathbb{R}_+^4 distinct from $x_{0,0}$ converge towards the complete infestation equilibrium $x_{0,W}$.*

Notice that strictly speaking, Theorem 13 is an *almost global convergence* result: convergence towards the complete infestation equilibrium is ensured, except for a zero measure set of initial conditions. However, in the present case, this set is reduced to the unstable equilibrium.

The measurement of L_U is likely to be subject to uncertainties, so the analysis of the unnoisy case is certainly not sufficient. The following result extends Theorem 13 in order to cope with this issue.

Theorem 14. *All trajectories of system (4) closed by a control $u \geq K^*L_U$ issuing from a point in \mathbb{R}_+^4 distinct from $x_{0,0}$ result in complete infestation, with *Wolbachia* population levels at least equal to the ones of the equilibrium $x_{0,W}$.*

Estimation of the measurement errors may thus allow to ensure complete infestation, by taking large enough gains: if e.g. the relative error $\frac{|L_U - y|}{L_U}$ is known to be at most equal to certain $\phi \in (0, 1)$ then, using the gain $K > \frac{K^*}{1 - \phi}$ yields $u = Ky \geq \frac{K^*}{1 - \phi}(1 - \phi)L_U$. Theorem 14 is therefore a robustness result.

Technical results necessary for the proof of Theorems 13 and 14 are given in Section 4.4, and proved in Section 4.5, together with the two Theorems.

Remark 15. Formally putting $0 = L_U - \gamma_U A_U$, $0 = L_W - \gamma_W A_W$ in (20) yields the system

$$\dot{L}_U = \mathcal{R}_U \frac{\gamma_W L_U}{\gamma_W L_U + \gamma_U L_W} L_U - (1 + L_W + L_U)L_U \quad (25a)$$

$$\dot{L}_W = \mathcal{R}_W L_W - (1 + L_W + L_U)L_W + KL_U \quad (25b)$$

It is shown in Bliman PA et al (2015) that system (25) possesses two equilibria: an unstable one at $(0, 0)$ and an equilibrium of the form $(0, L_W^*)$ towards which *all the trajectories* (not starting at $(0, 0)$) converge. An interesting point is that the proportion of *Wolbachia*-infected larvae $\frac{L_U}{L_U + L_W}$ is a Lyapunov function for this singularly perturbed system. See details in Bliman PA et al (2015).

4.4 Decomposition of system (19) and statement of technical lemmas

We state in this subsection some technical lemmas that will be used in the proof of Theorem 13. We start by introducing the concept of *monotone input-output system with negative feedback*.

Consider an *input/output system*

$$\begin{aligned} \dot{x} &= F(x, u), \\ y &= H(x), \quad u = y, \end{aligned}$$

where the state and control spaces are endowed with partial orderings defined, as before, by pointed convex cones with nonempty interior (see Definition 3). This system is said to be *monotone with negative feedback* if the input-to-state map $u \mapsto x$ is monotone, while the state-to-output map $x \mapsto H(x) = y$ is anti-monotone. The reader is referred to Angeli and Sontag (2003) for more details on this subject, see also Bliman PA et al (2015).

Set

$$|z|_- := \begin{cases} z & \text{if } z \leq 0 \\ 0 & \text{otherwise} \end{cases} \quad \text{and} \quad |z|_+ := \begin{cases} z & \text{if } z \geq 0 \\ 0 & \text{otherwise} \end{cases}$$

Clearly, one has

$$z = |z|_- + |z|_+, \quad z \in \mathbb{R}. \quad (26)$$

A key step consists in considering the following decomposition that will show convenient in the proof of Theorem 13.

$$\dot{L}_U = \gamma_U \mathcal{R}_U \frac{A_U}{A_U + A_W} A_U - (1 + L_W + L_U) L_U \quad (27a)$$

$$\dot{A}_U = L_U - \gamma_U A_U \quad (27b)$$

$$\dot{L}_W = \gamma_W \mathcal{R}_W A_W - (1 + L_W) L_W + |K - L_W|_- L_U + K u \quad (27c)$$

$$\dot{A}_W = L_W - \gamma_W A_W \quad (27d)$$

$$y = \left| 1 - \frac{L_W}{K} \right|_+ L_U \quad (27e)$$

As a matter of fact, using property (26), one sees easily that the closing of the input-output link (27) by $u = y$ indeed yields system (19).

Next, we state Lemmas 16, 17 and 18, that will be used in the proof of the main result, Theorem 13.

Lemma 16. *For any integrable control u taking on nonnegative values, the set \mathbb{R}_+^4 is positively invariant by system (27).*

Lemma 17. *The input-output system (27) is monotone with negative feedback, when the state space is endowed with the order $\geq_{\mathcal{K}}$ defined in Theorem 5.*

Lemma 18. *For any constant nonnegative input, system (27a)–(27d) possesses a unique LAS equilibrium. The latter yields null value of L_U .*

Moreover, the solution of the input-output system (27a)–(27d) converges towards the corresponding equilibrium when time goes to infinity (and in particular the output L_U converges to zero), except possibly if $u \equiv 0$ and $L_W(0) = 0$, $A_W(0) = 0$.

4.5 Proof of the technical lemmas and of the main results

In this subsection are given the proofs of the Lemmas 16, 17 and 18 and the Theorems 13 and 14. The arguments of these proofs are based on the use of the notion of *I/O characteristic* (Angeli and Sontag, 2003; Angeli et al, 2004; Enciso, 2014). Some additional comments on the use of these arguments in the present context are given in Bliman PA et al (2015).

Proof of Lemma 16. The key point is that $|K - L_W|_- L_U = 0$ when $0 \leq L_W < K$. Therefore, near the border of \mathbb{R}_+^4 where $L_W = 0$, the system (27) behaves locally as $\dot{L}_W = \gamma_W \mathcal{R}_W A_W - (1 + L_W) L_W + K u$. The fact that $\dot{L}_W \geq 0$ whenever $L_W = 0$ then forbids escape from the set \mathbb{R}_+^4 by this side. The same happens for the other three variables: their derivatives are nonnegative at the points where they vanish. Hence, the trajectories can neither escape by the other sides. This establishes the positive invariance of \mathbb{R}_+^4 and achieves the proof of Lemma 16. \square

Proof of Lemma 17. The right-hand sides of (27a), (27b) and (27d) have been studied in Theorem 5. The right-hand side of (27c) is clearly increasing with respect to A_W and u , and non-increasing with respect to L_U . So the input-to-state map is monotone when the state space is endowed with the order defined in Theorem 5.

On the other hand, the state-to-output map defined by (27e) is non-increasing with respect to L_W , and non-decreasing with respect to L_U . Therefore, it is anti-monotone with respect to the ordering used in the state space. This achieves the proof of Lemma 17. \square

Proof of Lemma 18. One first studies the equilibria of system (27a)–(27d), for constant inputs $u : t \mapsto u(t) \equiv \bar{u}$, for $\bar{u} \in \mathbb{R}_+$. Clearly, the set of these equilibria is the union of two sets: the set of equilibria of (27a)+(27b)+(27d) and

$$\dot{L}_W = \gamma_W \mathcal{R}_W A_W - (1 + L_W)L_W + K\bar{u} \quad (28a)$$

such that $K - L_W \geq 0$; and the set of equilibria of (27a)+(27b)+(27d) and

$$\dot{L}_W = \gamma_W \mathcal{R}_W A_W - (1 + L_W + L_U)L_W + KL_U + K\bar{u} \quad (28b)$$

such that $K - L_W \leq 0$.

Consider first the system (27a)+(27b)+(28a)+(27d). As can be seen, the latter is decoupled, since L_U is not anymore present in the right-hand side of (28a). One shows without difficulty that there exists a unique equilibrium in \mathbb{R}_+^4 , which is LAS and characterized by

$$L_W = \frac{1}{2} \left(\mathcal{R}_W - 1 + \sqrt{(\mathcal{R}_W - 1)^2 + 4K\bar{u}} \right), \quad (29)$$

provided that this expression verifies $L_W \leq K$. Another equilibrium exists, which is $x_{0,0}$ if $\bar{u} = 0$, but which has *negative* value of L_W if $\bar{u} > 0$, and is therefore discarded, due to Lemma 16.

Consider now the second case, of system (27a)+(27b)+(28b)+(27d). Arguing as in the proof of Theorem 10, the only equilibria that may exist are such that $L_U = 0$. As a matter of fact, for a solution with nonzero L_U , a term $K\bar{u}$ in the right-hand side of (23) could be written, jointly with KL_U , as $K'L_U$ for some $K' \geq K > K^*$, leading therefore to $L_U = 0$ and a contradiction. Therefore, any potential equilibrium has to fulfill $L_U = 0$, and the only possibility is given by (29) if this expression verifies $L_W \geq K$.

Putting together the two cases, one sees that:

- ★ there exist two equilibria, $x_{0,0}$ and $x_{0,W}$, if $\bar{u} = 0$;
- ★ there exists a unique equilibrium if $\bar{u} > 0$.
- ★ In any case, the corresponding output value is 0.

Now, for any constant input $u(t) \equiv \bar{u}$, system (27) is strongly order-preserving, just as system (7) was shown to be (Theorem 5). Then, the uniqueness of equilibrium in the case where $\bar{u} > 0$ allows to use (Smith, 1995, Theorem 2.3.1, p. 18) and to deduce that all trajectories in \mathbb{R}_+^4 converge to this

unique equilibrium. When $\bar{u} = 0$, applying (Smith, 1995, Theorem 2.2.1, p. 17) shows that every trajectory converges towards one of the two equilibria $x_{0,0}$ and $x_{0,W}$. The behavior of system (27) in the vicinity of $x_{0,0}$ obeys the equations

$$\dot{L}_W = \gamma_W \mathcal{R}_W A_W - (1 + L_W)L_W, \quad \dot{A}_W = L_W - \gamma_W A_W .$$

This system is monotone and the projection of $x_{0,W}$ attracts all trajectories, except if $L_W(0) = 0$ and $A_W(0) = 0$. This achieves the proof of Lemma 18. \square

One is now ready to achieve the proof of Theorem 13.

Proof of Theorem 13. We define $y(t; x_0, u)$ the output of system (27a)–(27d) corresponding to the input signal u and the initial state value x_0 . For any trajectory of the closed-loop system (19), we will denote indifferently u and y , in order to exploit the formalism of the input-output decomposition given in (27).

First of all, recall that, due to Theorem 9, all trajectories of (19) are bounded. Therefore, for any nonnegative initial condition x_0 ,

$$0 \leq \liminf_{t \rightarrow +\infty} y(t; x_0, u) \leq \limsup_{t \rightarrow +\infty} y(t; x_0, u) < +\infty \quad \forall x_0 \in \mathbb{R}_+^4 . \quad (30)$$

Assume first

$$\liminf_{t \rightarrow +\infty} y(t; x_0, u) > 0 . \quad (31)$$

Using monotonicity of the input-output system to compare trajectories with different inputs, one obtains from the fact that

$$\forall \varepsilon > 0, \exists T > 0, t \geq T \Rightarrow u(t) \geq \liminf_{t' \rightarrow +\infty} u(t') - \varepsilon ,$$

that

$$\forall \varepsilon > 0, \limsup_{t \rightarrow +\infty} y(t; x_0, u) \leq \limsup_{t \rightarrow +\infty} y \left(t; x_0, \liminf_{t' \rightarrow +\infty} u(t') - \varepsilon \right) . \quad (32)$$

Using Lemma 18 for $\varepsilon > 0$ smaller than $\liminf_{t' \rightarrow +\infty} y(t'; x_0, u)$ yields

$$\limsup_{t \rightarrow +\infty} y \left(t; x_0, \liminf_{t' \rightarrow +\infty} u(t') - \varepsilon \right) = 0 . \quad (33)$$

By putting together (30), (32) and (33), one gets:

$$0 < \liminf_{t \rightarrow +\infty} y(t; x_0, u) \leq \limsup_{t \rightarrow +\infty} y(t; x_0, u) \leq 0 , \quad (34)$$

which is absurd. This shows consequently that the premise (31) was erroneous.

We thus have

$$\liminf_{t \rightarrow +\infty} y(t; x_0, u) = 0 \quad (35)$$

for all trajectories. Assume

$$(L_W(0), A_W(0)) \neq (0, 0) . \quad (36)$$

As above, one can deduce that

$$0 \leq \liminf_{t \rightarrow +\infty} y(t; x_0, u) \leq \limsup_{t \rightarrow +\infty} y(t; x_0, u) \leq \limsup_{t \rightarrow +\infty} y \left(t; x_0, \liminf_{t' \rightarrow +\infty} u(t') \right) = 0 ,$$

and therefore that

$$\lim_{t \rightarrow +\infty} y(t; x_0, u) = 0 . \quad (37)$$

Now Lemma 18 permits to deduce from (37) and (36) that

$$\lim_{t \rightarrow +\infty} x(t; x_0, u) = x_{0,W} . \quad (38)$$

On the other hand, if (36) is false but $(L_U(0), A_U(0)) \neq (0, 0)$, then it is easy to show that $(L_W(t), A_W(t)) \neq (0, 0)$ for some $t > 0$ (and indeed for *any* $t > 0$). As a matter of fact, due to the presence of the control term (which is continuous and initially positive), L_W is certainly positive on a sufficient small punctured open neighborhood of $t = 0$. This in turn yields the same property for A_W , due to the linearity of its evolution. The analysis previously conducted in the case where (36) is true, can therefore be applied in the present case (where (36) is false but $(L_U(0), A_U(0)) \neq (0, 0)$) from a new, positive, initial time instant. It allows to conclude similarly that (37) and (38) hold.

As a conclusion, the convergence to $x_{0,W}$ occurs in any case, except if $(L_W(0), A_W(0)) = (L_U(0), A_U(0)) = (0, 0)$, that is except if $x(0) = x_{0,0}$. This achieves the proof of Theorem 13. \square

Proof of Theorem 14. The proof of Theorem 14 is an adaptation of the preceding one.

Consider system (27) closed by $u = y + v$ for some nonnegative function v . Reproducing the argument developed in the proof of Theorem 13, one deduces that for all trajectories,

$$\begin{aligned} \limsup_{t \rightarrow +\infty} y(t; x_0, u) &\leq \limsup_{t \rightarrow +\infty} y \left(t; x_0, \liminf_{t' \rightarrow +\infty} (u(t') + v(t')) \right) \\ &\leq \limsup_{t \rightarrow +\infty} y \left(t; x_0, \liminf_{t' \rightarrow +\infty} u(t') \right) \end{aligned} \quad (39)$$

due to the fact that $\liminf_{t' \rightarrow +\infty} (u(t') + v(t')) \geq \liminf_{t' \rightarrow +\infty} u(t')$ (as $v \geq 0$), and that the input/output system is monotone with negative feedback (Lemma 17). One then deduces, as done in the proof of Theorem 13, that $\liminf_{t \rightarrow +\infty} y(t; x_0, u) = 0$, and indeed that $\lim_{t \rightarrow +\infty} y(t; x_0, u) = 0$ when the initial condition is different from the zero equilibrium $x_{0,0}$. Therefore $L_U(t)$ and $A_U(t)$ vanishes for $t \rightarrow +\infty$, and complete infestation is established.

| Parameter | Value |
|------------|-------------------------|
| α_U | 3.5 day^{-1} |
| α_W | $0.95\alpha_U$ |
| ν | $1/20 \text{ day}^{-1}$ |
| μ | 0.02 day^{-1} |
| μ_U | $1/18 \text{ day}^{-1}$ |
| μ_W | $\frac{1}{0.8}\mu_U$ |

Table 3: List of approximated parameter values for unnormalized model (1) (Sources: Farnesi et al (2009); Yang et al (2009); Hancock et al (2011a))

Asymptotically the components L_W, A_W thus behave according to

$$\dot{L}_W = \gamma_W \mathcal{R}_W A_W - (1 + L_W)L_W + Kv, \quad \dot{A}_W = L_W - \gamma_W A_W \quad (40)$$

The previous system is monotone with respect to the order induced by the cone \mathbb{R}_+^2 . When $v \equiv 0$, all trajectories converge towards the complete infestation equilibrium, and we deduce that in the general case $v \geq 0$, $\liminf_{t \rightarrow +\infty} x(t) \geq x_{0,W}$, where the \liminf has to be applied componentwise and the order is also componentwise. This achieves the proof of Theorem 14. \square

5 Numerical simulations

In this section we present some illustrative simulations, with parameters adapted from Farnesi et al (2009); Yang et al (2009); Hancock et al (2011a) and shown in Table 3. Some parameters vary significantly with climate conditions, see for instance Christophers (1960); Southwood et al (1972); Brownstein et al (2003); Dutra et al (2015); Koiller et al (2014) and references therein for other estimates.

With the values given in Table 3 we obtain (from (2))

$$\gamma_U = 0.79365, \quad \gamma_W = 0.99207, \quad \mathcal{R}_U = 45, \quad \mathcal{R}_W = 34.2$$

Notice that, since *Wolbachia* increases the mortality rate (that is, $\mu_W > \mu_U$) and reduces the fecundity ($\alpha_W < \alpha_U$), one has $\gamma_U < \gamma_W$ and $\mathcal{R}_U > \mathcal{R}_W$. The critical gain value (see (21)) can be computed and is equal to

$$K^* \simeq 0.92477$$

Figure 1 shows the evolution of the state variables L_U and L_W as functions of time in different values of K . The initial value is the *Wolbachia*-free equilibrium $x_{U,0} = (44, 55.4, 0, 0)$ (see formulae in (16)), and the gain values are respectively chosen to be 1, 0.95, 0.93 and 0.92. For the first three values of K , the solution converges to the total infestation equilibrium $x_{0,W} = (0, 0, 33.2, 33.5)$. The last value, $K = 0.92$ (see Figure 1d), smaller than the critical value K^* , yields convergence to a coexistence equilibrium.

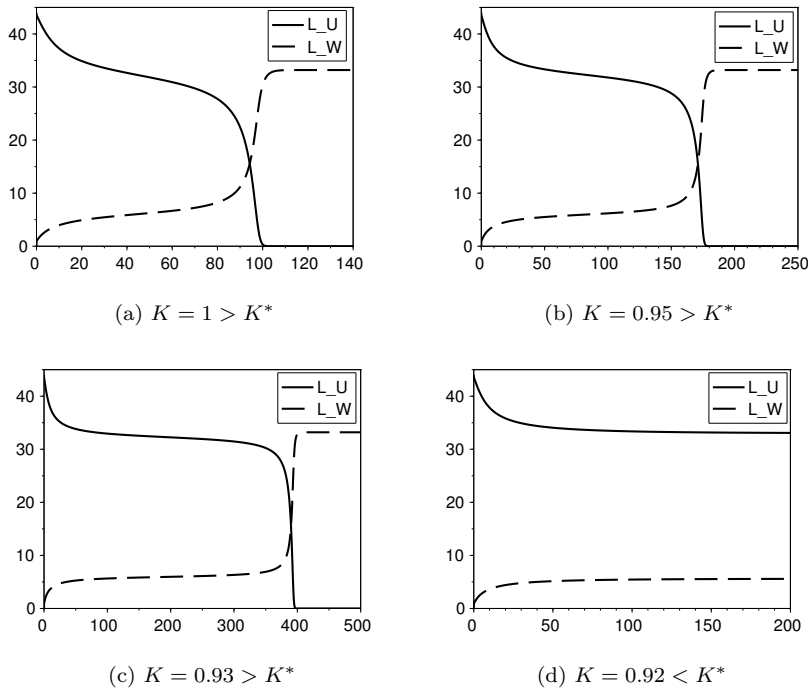


Fig. 1: Evolution of $L_U(t)$ and $L_W(t)$ as functions of time for different values of K

6 Conclusions and further studies

We presented and analyzed a model for the infestation by bacterium *Wolbachia* of a population of mosquitoes — typically *Aedes aegypti* which is involved in the transmission of arboviroses such as yellow fever, dengue, Zika or chikungunya, and is the focus of a large scale dengue control initiative (Hoffmann et al (2011)). A control method based on the introduction of a number of *Wolbachia*-positive insects, proportional to the size of the healthy population was proposed. This method was shown, analytically and through simulations, to be capable to guarantee the invasion of the wild mosquito population by *Wolbachia*-positive ones, provided the gain is sufficiently large. A robustness result has been also shown, which enables one to cope with the measurement uncertainties. This feedback method requires continuous measurement of the population. Fortunately, such monitoring of population size is part of the protocol for the introduction of *Wolbachia* mosquitoes in the field (Jeffery et al (2009)). The main goal of this method is to determine the least number of infected mosquitoes that needs to be introduced in order to guarantee a successful invasion while keeping the control cost to a minimum. To our knowledge, this is the first use of the control theory notion of feedback in such a context.

When considering the application of the proposed model to field experiments, some adaptations are required. First, the model presented here is continuous in time for simplicity, but converting it to discrete-time should not, *a priori*, present difficulties. Also, the present framework assumes measurement of the larval stage of the uninfected population, and as well release of infected larvae. The release of eggs instead of adult mosquitoes may present significant benefits in terms of logistics, and it is presently tested in Colombia¹. However, the practical conditions can be different, and the method can be adapted in consequence (leading though to similar, but different, convergence questions).

An advantage of the present modeling framework is to open the way to comparisons with optimal policies — for example the one that minimizes the total number of released mosquitoes, while succeeding in spreading *Wolbachia*. Some recent publications have started to look at such optimal strategies (Hancock et al (2011a,b); Hoffmann (2014)). Hancock et al (2011a,b) discuss the importance of male-biased introduction to maintain the risk of a temporary increase of disease transmission due to the increased number of females right after introduction. We disagree with this point of view since *Wolbachia*-infected females, are in principle unable to transmit the dengue virus in any significant level. They can however become a nuisance which can lead the population to actively try to reduce the mosquito population by applying more insecticides, which can have a negative effect on the control efforts.

Also, this framework provides a first basis to consider questions related to strategy improvement by mitigating several control principles, or to the complex phenomena of interaction between different vector species and different arboviruses, that may occur in the context of control of different diseases.

From a mathematical point of view, one of the difficulties of the study is that the system presents two stable equilibria, corresponding to *Wolbachia*-free situation and complete infestation. While the key arguments are based on the theory of input-output monotone systems developed after Angeli and Sontag (2003), none of the posterior refinements to multivalued characteristics or quasi-characteristics allowed to establish formally the main convergence result, and adequate adaptation had to be achieved. Extensions in this direction are presently studied.

Acknowledgements We wish to thank the anonymous referees for their valuable advices that helped improve this manuscript. The first author is indebted to T. Gedeon for valuable discussions. The second author thanks H. Solari for useful bibliographical references. This work was done while the second author was a postdoctoral fellow at IMPA, Rio de Janeiro, funded by CAPES-Brazil. The authors also acknowledge CAPES-Brazil for the STIC AmSud funding for the MOSTICAW project, process number 99999.007551/2015-00, and FGV for the Pesquisa Aplicada funding of the project “Controle da Dengue através do uso da bactéria *Wolbachia*”.

¹ See e.g. the page <http://www.eliminatedengue.com/co/progress/article/690/> in the site of the project Eliminate Dengue (Hoffmann et al, 2012).

Appendix A – A sexual version of the infestation model

We here provide a sexual version of model (1). For simplicity, no control input is written. We denote respectively $\mathbf{m}_U, \mathbf{m}_W, \mathbf{M}_U, \mathbf{M}_W$, the numbers of uninfected, resp. *Wolbachia*-infected, *males* in early and adult phases; and similarly $\mathbf{f}_U, \mathbf{f}_W, \mathbf{F}_U, \mathbf{F}_W$ for the *females*. The model is:

$$\dot{\mathbf{m}}_U = \lambda_U \alpha_U \frac{\mathbf{M}_U}{\mathbf{M}_U + \mathbf{M}_W} \mathbf{F}_U - \nu \mathbf{m}_U - \mu(1 + k(\mathbf{m}_W + \mathbf{m}_U + \mathbf{f}_W + \mathbf{f}_U)) \mathbf{m}_U \quad (41a)$$

$$\dot{\mathbf{M}}_U = \nu \mathbf{m}_U - \mu_U \mathbf{M}_U \quad (41b)$$

$$\dot{\mathbf{m}}_W = \lambda_W \alpha_W \mathbf{F}_W - \nu \mathbf{m}_W - \mu(1 + k(\mathbf{m}_W + \mathbf{m}_U + \mathbf{f}_W + \mathbf{f}_U)) \mathbf{m}_W \quad (41c)$$

$$\dot{\mathbf{M}}_W = \nu \mathbf{m}_W - \mu_W \mathbf{M}_W \quad (41d)$$

$$\dot{\mathbf{f}}_U = \alpha_U \frac{\mathbf{M}_U}{\mathbf{M}_U + \mathbf{M}_W} \mathbf{F}_U - \nu \mathbf{f}_U - \mu(1 + k(\mathbf{m}_W + \mathbf{m}_U + \mathbf{f}_W + \mathbf{f}_U)) \mathbf{f}_U \quad (41e)$$

$$\dot{\mathbf{F}}_U = \nu \mathbf{f}_U - \mu_U \mathbf{F}_U \quad (41f)$$

$$\dot{\mathbf{f}}_W = \alpha_W \mathbf{F}_W - \nu \mathbf{f}_W - \mu(1 + k(\mathbf{m}_W + \mathbf{m}_U + \mathbf{f}_W + \mathbf{f}_U)) \mathbf{f}_W \quad (41g)$$

$$\dot{\mathbf{F}}_W = \nu \mathbf{f}_W - \mu_W \mathbf{F}_W \quad (41h)$$

Here λ_U, λ_W are the *sex ratio* (ratio of males to females) of the offspring for the uninfected and infected populations. The other parameters have the same meaning than for model (1) (see Table 2). Here they have been chosen identical for both sex, and in such conditions, it is straightforward to see that the variables defined by

$$\mathbf{L}_U := \mathbf{m}_U + \mathbf{f}_U, \mathbf{L}_W := \mathbf{m}_W + \mathbf{f}_W, \mathbf{A}_U := \mathbf{M}_U + \mathbf{F}_U, \mathbf{A}_W := \mathbf{M}_W + \mathbf{F}_W \quad (42)$$

obey the following equations:

$$\dot{\mathbf{L}}_U = (1 + \lambda_U) \alpha_U \frac{\mathbf{M}_U}{\mathbf{M}_U + \mathbf{M}_W} \mathbf{F}_U - \nu \mathbf{L}_U - \mu(1 + k(\mathbf{L}_W + \mathbf{L}_U)) \mathbf{L}_U \quad (43a)$$

$$\dot{\mathbf{A}}_U = \nu \mathbf{L}_U - \mu_U \mathbf{A}_U \quad (43b)$$

$$\dot{\mathbf{L}}_W = (1 + \lambda_W) \alpha_W \mathbf{F}_W - \nu \mathbf{L}_W - \mu(1 + k(\mathbf{L}_W + \mathbf{L}_U)) \mathbf{L}_W \quad (43c)$$

$$\dot{\mathbf{A}}_W = \nu \mathbf{L}_W - \mu_W \mathbf{A}_W \quad (43d)$$

If moreover $\lambda_U = \lambda_W$ and the sex ratio are initially equal to this common value, that is:

$$\frac{\mathbf{m}_U(0)}{\mathbf{f}_U(0)} = \frac{\mathbf{M}_U(0)}{\mathbf{F}_U(0)} = \lambda_U, \quad \frac{\mathbf{m}_W(0)}{\mathbf{f}_W(0)} = \frac{\mathbf{M}_W(0)}{\mathbf{F}_W(0)} = \lambda_W \quad (44)$$

then the same proportions are conserved along the evolution, and it is possible to replace $\frac{\mathbf{M}_U}{\mathbf{M}_U + \mathbf{M}_W}$ by $\frac{\mathbf{L}_U}{\mathbf{L}_U + \mathbf{L}_W}$, $(1 + \lambda_U) \mathbf{F}_U$ by \mathbf{L}_U and $(1 + \lambda_W) \mathbf{F}_W$ by \mathbf{L}_W in (43a), (43c), showing that (41) boils down to the simpler model (1).

Appendix B – Proof of Theorem 7

B.1 Computation and ordering of the equilibrium points

One here computes the equilibrium points. The latter verify

$$\gamma_U \mathcal{R}_U \frac{A_U}{A_U + A_W} A_U - (1 + L_W + L_U) L_U = 0 \quad (45a)$$

$$\gamma_W \mathcal{R}_W A_W - (1 + L_W + L_U) L_W = 0 \quad (45b)$$

$$L_U = \gamma_U A_U, \quad L_W = \gamma_W A_W \quad (45c)$$

The point $x_{0,0} := (0, 0, 0, 0)$ is clearly an equilibrium. Let us look for an equilibrium $x_{U,0} := (L_U^*, A_U^*, 0, 0)$. The quantities L_U^*, A_U^* then have to satisfy

$$\gamma_U \mathcal{R}_U A_U^* - (1 + L_U^*) L_U^* = 0, \quad L_U^* = \gamma_U A_U^*. \quad (46)$$

Dividing by $L_U^* \neq 0$ yields $1 + L_U^* = \mathcal{R}_U$. One thus gets the unique solution of this form verifying

$$L_U^* = \mathcal{R}_U - 1, \quad A_U^* = \frac{\mathcal{R}_U - 1}{\gamma_U},$$

which is positive due to the sustainability hypothesis (6).

Similarly, one now looks for an equilibrium defined as $x_{0,W} := (0, 0, L_W^*, A_W^*)$. The values of L_W^*, A_W^* must verify

$$\gamma_W \mathcal{R}_W A_W^* - (1 + L_W^*) L_W^* = 0, \quad L_W^* = \gamma_W A_W^*.$$

This is identical to (46), and as for the $x_{U,0}$ case, one gets a unique, positive, solution, namely

$$L_W^* = \mathcal{R}_W - 1, \quad A_W^* = \frac{\mathcal{R}_W - 1}{\gamma_W}. \quad (47)$$

We show now that system (7) also admits a unique coexistence equilibrium with positive components $x_{U,W} = (L_U^{**}, A_U^{**}, L_W^{**}, A_W^{**})$. Coming back to (45) and expressing the value of the factor common to the first and second identity leads to

$$\begin{aligned} 1 + L_U^{**} + L_W^{**} &= \gamma_W \mathcal{R}_W \frac{A_W^{**}}{L_W^{**}} = \mathcal{R}_W \\ &= \gamma_U \mathcal{R}_U \frac{A_U^{**}}{A_U^{**} + A_W^{**}} \frac{A_U^{**}}{L_U^{**}} = \mathcal{R}_U \frac{A_U^{**}}{A_U^{**} + A_W^{**}} \end{aligned}$$

One thus deduces

$$\frac{A_U^{**}}{A_U^{**} + A_W^{**}} = \frac{\mathcal{R}_W}{\mathcal{R}_U},$$

and one can express all three remaining unknowns in function of A_W^{**} :

$$L_W^{**} = \gamma_W A_W^{**}, \quad A_U^{**} = \frac{\mathcal{R}_W}{\mathcal{R}_U - \mathcal{R}_W} A_W^{**}, \quad L_U^{**} = \gamma_U A_U^{**} = \gamma_U \frac{\mathcal{R}_W}{\mathcal{R}_U - \mathcal{R}_W} A_W^{**}.$$

Using the value of L_U^{**} and L_W^{**} now yields the relation

$$\mathcal{R}_W - 1 = L_U^{**} + L_W^{**} = \gamma_W \left(1 + \frac{\gamma_U}{\gamma_W} \frac{\mathcal{R}_W}{\mathcal{R}_U - \mathcal{R}_W} \right) A_W^{**},$$

which has a unique, positive, solution when (6) holds. Hence, the fourth equilibrium is given by

$$\begin{aligned} L_U^{**} &= \frac{\delta}{1+\delta}(\mathcal{R}_W - 1), & A_U^{**} &= \frac{\delta}{(1+\delta)\gamma_U}(\mathcal{R}_W - 1) \\ L_W^{**} &= \frac{1}{1+\delta}(\mathcal{R}_W - 1), & A_W^{**} &= \frac{1}{(1+\delta)\gamma_W}(\mathcal{R}_W - 1) \end{aligned}$$

where δ was given in equation (16d) in the statement of the theorem.

So far we have found all equilibrium points. Actually, it is easy to see that no equilibria is missing: for $L_U = 0$ we necessarily have $A_U = 0$, and this gives us $x_{0,0}$ and $x_{0,W}$, while for $L_U \neq 0$ we get $A_U \neq 0$, and this leads us to $x_{U,0}$ and to $x_{U,W}$.

Notice that the last equilibrium can be expressed alternatively by use of the values of the equilibrium $x_{0,W}$:

$$L_U^{**} = \frac{\delta}{1+\delta} L_W^*, \quad A_U^{**} = \frac{\delta}{1+\delta} \frac{\gamma_W}{\gamma_U} A_W^* \quad (49a)$$

$$L_W^{**} = \frac{1}{1+\delta} L_W^*, \quad A_W^{**} = \frac{1}{1+\delta} A_W^* \quad (49b)$$

and this provides straightforward comparison result:

$$L_U^{**} < L_W^{**} < L_U^* \quad \text{and} \quad L_W^{**} < L_W^* < L_U^* \quad (50a)$$

and thus $A_\eta^{**} = \gamma_\eta L_\eta^{**} < \gamma_\eta L_\eta^* = A_\eta^*$, for $\eta \in \{U, W\}$ and, therefore,

$$A_U^{**} < A_U^* \quad \text{and} \quad A_W^{**} < A_W^*, \quad (50b)$$

the second inequality being directly deduced from (49b). The relations (50) allow us to establish the inequalities (17).

B.2 Local stability analysis

The local stability analysis is conducted through analysis of the eigenvalues of the Jacobian matrices. Recall that the Jacobian has been computed in (14).

Stability of $x_{0,0}$. The value of Df is not defined at $x_{0,0}$. To show the instability of the equilibrium $x_{0,0}$, let the function V be defined on \mathbb{R}_+^4 by

$$V(x) := \rho(L_U + (1 + \varepsilon)A_U) + L_W + (1 + \varepsilon)A_W,$$

for values of ε, ρ still to be defined. Notice that V is positive definite for any positive ε and ρ . We will show that there exists $\rho > 0$ for which the derivative \dot{V} of V along the trajectories is *positive definite* in a sufficiently small relative neighborhood of $x_{0,0}$ in \mathbb{R}_+^4 .

One can check that

$$\begin{aligned} \dot{V}(x) &= (\varepsilon - L_U - L_W)(\rho L_U + L_W) \\ &\quad + \rho\gamma_U \left(\mathcal{R}_U \frac{A_U}{A_U + A_W} - 1 - \varepsilon \right) A_U + \gamma_W(\mathcal{R}_W - 1 - \varepsilon)A_W. \end{aligned} \quad (51)$$

The first term of the last expression is positive for all values of (L_U, L_W) in some relative neighborhood of the origin in \mathbb{R}_+^2 . Assuming from now on that $\varepsilon \in (0, \mathcal{R}_W - 1)$, one verifies easily that the sum of the two remaining terms in the right-hand side of (51) is positive when exactly one of the two numbers A_U, A_W is zero, due to (6). Assume now that e.g. $A_U \neq 0$. Then the sum of the last two terms in (51) is equal to

$$\gamma_W A_U \left(b \left(\mathcal{R}_U \frac{1}{1+a} - 1 - \varepsilon \right) + (\mathcal{R}_W - 1 - \varepsilon)a \right), \quad a := \frac{A_W}{A_U}, \quad b := \frac{\rho\gamma_U}{\gamma_W}.$$

We will now prove that there exists $b > 0$ (and therefore $\rho > 0$) such that the previous expression is positive for any nonnegative a (and therefore for any pair (A_U, A_W) with $A_U > 0, A_W \geq 0$).

The map

$$a \mapsto b \left(\mathcal{R}_U \frac{1}{1+a} - 1 - \varepsilon \right) + (\mathcal{R}_W - 1 - \varepsilon)a \quad (52)$$

is clearly convex. It has a positive value at the origin, where its derivative is equal to $-b\mathcal{R}_U + \mathcal{R}_W - 1 - \varepsilon$. Taking now $0 < b < \frac{\mathcal{R}_W - 1 - \varepsilon}{\mathcal{R}_U}$, this expression is positive, which ensures that the map (52) takes on positive values on \mathbb{R}^+ .

Set $\rho := \frac{b\gamma_W}{\gamma_U}$.

Therefore, positive values of ε and ρ have been exhibited, for which \dot{V} is positive definite in a relative neighborhood of $x_{0,0}$ in \mathbb{R}_+^4 . This demonstrates the instability of $x_{0,0}$.

Stability of $x_{U,0}$. Using (14) and recalling the value of $x_{U,0}$ given in (16), we see that $Df(x_{U,0})$ is the upper block-triangular matrix

$$\begin{pmatrix} 1 - 2\mathcal{R}_U & \gamma_U \mathcal{R}_U & 1 - \mathcal{R}_U & -\gamma_U \mathcal{R}_U \\ 1 & -\gamma_U & 0 & 0 \\ 0 & 0 & -\mathcal{R}_U & \gamma_W \mathcal{R}_W \\ 0 & 0 & 1 & -\gamma_W \end{pmatrix}.$$

The eigenvalues of this block-triangular matrix have negative real parts if and only if

$$\frac{\mathcal{R}_U}{2\mathcal{R}_U - 1} < 1 \quad \text{and} \quad \mathcal{R}_W < \mathcal{R}_U.$$

These conditions are satisfied since the sustainability condition (6) holds. In conclusion, the equilibrium $x_{U,0}$ is locally asymptotically stable.

Stability of $x_{0,W}$. From (14) and (16) we get that the Jacobian $Df(x_{0,W})$ of f at $x_{0,W}$ is the lower block-triangular matrix

$$\begin{pmatrix} -\mathcal{R}_W & 0 & 0 & 0 \\ 1 & -\gamma_U & 0 & 0 \\ 1 - \mathcal{R}_W & 0 & 1 - 2\mathcal{R}_W & \gamma_W \mathcal{R}_W \\ 0 & 0 & 1 & -\gamma_W \end{pmatrix}. \quad (53)$$

The left-upper 2×2 -block is a Hurwitz matrix, while asymptotic stability of the second one is equivalent to the condition

$$2\mathcal{R}_W - 1 > \mathcal{R}_W,$$

that is $\mathcal{R}_W > 1$, which holds true, due to hypothesis (6). The equilibrium $x_{0,W}$ is thus locally asymptotically stable.

Stability of $x_{U,W}$. The instability of $x_{U,W}$ can be proved by showing that the determinant of the Jacobian matrix $Df(x_{U,W})$ is negative, which, together with the fact that the state space has even dimension 4, establishes the existence of a positive real root to the characteristic polynomial; and thus that the Jacobian is not a Hurwitz matrix. This argument yields lengthy computations.

It is more appropriate to use here the monotonicity properties of system (7), established in Theorem 5. As a matter of fact, bringing together the inequalities (17) (already proved in the end of the previous section, see (50)), the asymptotical stability of $x_{U,0}$ and $x_{0,W}$ and the strongly order-preserving property of the reference problem, Theorem 2.2 in Smith (1995) shows that the intermediate point $x_{U,W}$ cannot be stable. This finally achieves the stability analysis, as well as the proof of Theorem 7.

References

- Alphey L (2014) Genetic Control of Mosquitoes. *Annu Rev Entomol* 59(1):205–224
- Alphey L, Benedict M, Bellini R, Clark GG, Dame DA, Service MW, Dobson SL (2010) Sterile-Insect Methods for Control of Mosquito-Borne Diseases: An Analysis. *Vector-Borne and Zoonotic Diseases* 10(3):295–311
- Angeli D, Sontag ED (2003) Monotone control systems. *IEEE Transactions on Automatic Control* 48:1684–1698
- Angeli D, De Leenheer P, Sontag ED (2004) A small-gain theorem for almost global convergence of monotone systems. *Systems & Control Letters* 52(5):407–414
- Barton N, Turelli M (2011) Spatial waves of advance with bistable dynamics: cytoplasmic and genetic analogues of Allee effects. *The American Naturalist* 178(3):E48–E75
- Bian G, Xu Y, Lu P, Xie Y, Xi Z (2010) The endosymbiotic bacterium *Wolbachia* induces resistance to dengue virus in *Aedes aegypti*. *PLoS pathog.* 6(4):e1000833
- Bliman PA, Aronna MS, Coelho FC, and da Silva MAHB (2015) Ensuring successful introduction of *Wolbachia* in natural populations of *Aedes aegypti* by means of feedback control. arXiv Available: <http://arxiv.org/abs/1503.05216>
- Brogdon, WG and McAllister, JC (1998) Insecticide resistance and vector control. *Emerging infectious diseases, Centers for Disease Control and Prevention* 4(4):605–613
- Brownstein JS, Hett E, O’Neill SL (2003) The potential of virulent *Wolbachia* to modulate disease transmission by insects. *Journal of Invertebrate Pathology* 84(1):24–29
- Christophers S (1960) *Aedes aegypti* (*L.*) the yellow fever mosquito: its life history, bionomics and structure. Cambridge University Press
- Coppel WA (1965) Stability and asymptotic behavior of differential equations. Heath mathematical monographs, Heath
- Dutra HLC, Santos LMBd, Caragata EP, Silva JBL, Villela DAM, Maciel-de Freitas R, Moreira LA (2015) From lab to field: The influence of urban landscapes on the invasive potential of *Wolbachia* in Brazilian *Aedes aegypti* mosquitoes. *PLOS Negl Trop Dis* 9(4):e0003,689
- Enciso G (2014) Fixed points and convergence in monotone systems under positive or negative feedback. *International Journal of Control* 87(2):301–311
- Enciso G, Sontag ED (2006) Nonmonotone systems decomposable into monotone systems with negative feedback. *Journal of Differential Equations* 224:205–227
- Farnesi LC, Martins AJ, Valle D, Rezende GL (2009) Embryonic development of *Aedes aegypti* (Diptera: Culicidae): influence of different constant temperatures. *Memórias do Instituto Oswaldo Cruz.* 104(1):124–6

- Ferreira CP, Godoy WA, editors (2014) *Ecological modelling applied to entomology*. Springer
- Focks DA, Haile DG, Daniels E, Mount GA (1993) Dynamic life table model of *Aedes aegypti* (Diptera: Culicidae) - Analysis of the literature and model development. *J Med Entomol* 30:1003–1017.
- Focks, DA (2003) A review of entomological sampling methods and indicators for dengue vectors. Geneva: WHO.
- de Freitas RM, Valle D (2014) Challenges encountered using standard vector control measures for dengue in Boa Vista, Brazil. *Bulletin of the World Health Organization* 92(9):685–689
- de Freitas RM, Avendanho FC, Santos R, Sylvestre G, Araujo SC, Lima JBP, Martins AJ, Coelho GE, Valle D (2014) Undesirable Consequences of Insecticide Resistance following *Aedes aegypti* Control Activities Due to a Dengue Outbreak. *PLOS ONE* 9:1–9
- Frentiu FD, Zakir T, Walker T, Popovici J, Pyke AT, van den Hurk A, McGraw EA, O'Neill SL (2014) Limited Dengue Virus Replication in Field-Collected *Aedes aegypti* Mosquitoes Infected with *Wolbachia*. *PLoS Neglected Tropical Diseases* 8(2):e2688
- Gedeon T, Hines G (2009) Multi-valued characteristics and morse decompositions. *Journal of Differential Equations* 247(4):1013–1042
- Gouzé JL (1988) A criterion of global convergence to equilibrium for differential systems with an application to Lotka-Volterra systems. Research report 0894, Inria, France
- Hancock PA, Godfray HCJ (2012) Modelling the spread of *Wolbachia* in spatially heterogeneous environments. *Journal of The Royal Society Interface* 9(76):3045–3054
- Hancock PA, Sinkins SP, Godfray HCJ (2011a) Population dynamic models of the spread of *Wolbachia*. *The American Naturalist* 177(3):323–333
- Hancock PA, Sinkins SP, Godfray HCJ (2011b) Strategies for introducing *Wolbachia* to reduce transmission of mosquito-borne diseases. *PLoS Negl Trop Dis* 5(4):e1024
- Hirsch MW (1988) Stability and convergence in strongly monotone dynamical systems. *J reine angew Math* 383:1–53
- Hoffmann AA (2014) Facilitating *Wolbachia* invasions. *Austral Entomology* 53(2):125132
- Hoffmann A, Moreira L, O'Neill S, Osorio JE, Ritchie S, Simmons C, Turelli M (2012), Eliminate dengue. <http://www.eliminatedengue.com/>
- Hoffmann AA, Montgomery BL, Popovici J, Iturbe-Ormaetxe I, Johnson PH, Muzzi F, Greenfield M, Durkan M, Leong YS, Dong Y, Cook H, Axford J, Callahan AG, Kenny N, Omodei C, McGraw EA, Ryan PA, Ritchie SA, Turelli M, O'Neill SL (2011) Successful establishment of *Wolbachia* in *Aedes* populations to suppress dengue transmission. *Nature* 476(7361):454–457
- Hu L, Huang M, Tang M, Yu J, Zheng B (2015) *Wolbachia* spread dynamics in stochastic environments. *Theoretical population biology*, 106, 32-44.
- Huang M, Tang M, Yu J (2015) *Wolbachia* infection dynamics by reaction-diffusion equations. *Science China Mathematics* 58(1): 77–96

- Hughes H, Britton NF (2013) Modelling the use of *Wolbachia* to control dengue fever transmission. *Bulletin of mathematical biology* 75(5):796–818
- Jeffery JAL, Yen NT, Nam VS, Nghia LT, Hoffmann AA, Kay BH, Ryan PA (2009) Characterizing the *Aedes aegypti* population in a Vietnamese village in preparation for a *Wolbachia*-based mosquito control strategy to eliminate dengue. *PLOS Negl Trop Dis* 3(11):e552
- Keeling MJ, Jiggins FM, Read JM (2003) The invasion and coexistence of competing *Wolbachia* strains. *Heredity* 91(4): 382–388
- Koiller J, Da Silva M, Souza M, Codeço C, Iggidr A, Sallet G (2014) *Aedes*, *Wolbachia* and Dengue. Research Report RR-8462, Inria, France
- La Salle JP (1976) *The Stability of Dynamical Systems*. SIAM
- Malisoff M, De Leenheer P (2006) A small-gain theorem for monotone systems with multi-valued input-state characteristics. *IEEE Transactions on Automatic Control* 41(2):287–292
- McMeniman CJ, Lane RV, Cass BN, Fong AW, Sidhu M, Wang YF, O’Neill SL (2009) Stable introduction of a life-shortening *Wolbachia* infection into the mosquito *Aedes aegypti*. *Science* 323(5910):141–4.
- Moreira LA, Iturbe-Ormaetxe I, Jeffery JA, Lu G, Pyke AT, Hedges LM, Rocha BC, Hall-Mendelin S, Day A, Riegler M, Hugo LE, Johnson KN, Kay BH, McGraw EA, van den Hurk AF, Ryan PA, O’Neill SL (2009) A *Wolbachia* Symbiont in *Aedes aegypti* Limits Infection with Dengue, Chikungunya, and Plasmodium. *Cell* 139(7):1268–1278
- Moreira LA, Saig, E, Turley AP, Ribeiro JMC, O’Neill SL, McGraw AE (2009) Human Probing Behavior of *Aedes aegypti* when Infected with a Life-Shortening Strain of *Wolbachia* *PLOS Neglected Tropical Diseases* 12(3):1–6
- Murray JV, Jansen CC, De Barro P (2016) Risk associated with the release of *Wolbachia*-infected *Aedes aegypti* Mosquitoes into the environment in an effort to control Dengue. *Frontiers in public health* 4
- Ndii MZ, Hickson R, Allingham D, Mercer G (2015) Modelling the transmission dynamics of dengue in the presence of *Wolbachia*. *Mathematical biosciences* 262:157–166
- O’Neill S (2015) The dengue stopper. *Scientific American*. 312(6):72–7.
- O’Neill SL, Hoffman AA, Werren JH (eds) (1998) *Influential Passengers: Inherited Microorganisms and Arthropod Reproduction*. Oxford University Press
- Ocampo CB and Myriam J. Salazar-Terrerros and Neila J. Mina and Janet McAllister and William Brogdon (2011) Insecticide resistance status of *Aedes aegypti* in 10 localities in Colombia . *Acta Tropica* 118(1):37 - 44
- Otero M, Solari HG, Schweigmann N (2006) A stochastic population dynamics model for *Aedes aegypti*: Formulation and application to a city with temperate climate. *Bull Math Biol* 68: 1945–1974.
- Otero M, Schweigmann N, Solari HG (2008) A stochastic spatial dynamical model for *Aedes aegypti*. *Bull Math Biol* 70: 1297–1325
- Rasgon JL, Scott TW (2004) An initial survey for *Wolbachia* (Rickettsiales: Rickettsiaceae) infections in selected California mosquitoes (Diptera: Culicidae). *Journal of medical entomology* 41(2):255–257

- Ruang-Areerate T, Kittayapong P (2006) *Wolbachia* transinfection in *Aedes aegypti*: a potential gene driver of dengue vectors. Proceedings of the National Academy of Sciences 103(33):12534-9
- Silver JB (2007) *Mosquito ecology: field sampling methods*. Springer Science & Business Media.
- Smith HL (1995) Monotone dynamical systems: an introduction to the theory of competitive and cooperative systems, Mathematical surveys and monographs, vol 41. American Mathematical Society
- Smith DL, Perkins TA, Tusting LS, Scott TW, Lindsay SW (2013) Mosquito population regulation and larval source management in heterogeneous environments. PLoS One 8.8 : e71247
- Southwood TR, Murdie G, Yasuno M, Tonn RJ, Reader PM (1972) Studies on the life budget of *Aedes aegypti* in Wat Samphaya, Bangkok, Thailand. Bulletin of the World Health Organization. 46(2):211
- Turelli M (2010) Cytoplasmic incompatibility in populations with overlapping generations. Evolution 64(1):232–241
- Walker T, Johnson P, Moreira L, Iturbe-Ormaetxe I, Frentiu F, McMeniman C, Leong YS, Dong Y, Axford J, Kriesner P, et al (2011) The *wMel* *Wolbachia* strain blocks dengue and invades caged *Aedes aegypti* populations. Nature 476(7361):450–453
- Xi Z, Khoo CC, Dobson SL (2005) *Wolbachia* establishment and invasion in an *Aedes aegypti* laboratory population. Science (2005) 310(5746):326–8
- Yang HM, Macoris ML, Galvani KC, Andrighetti MT, Wanderley DM (2009) Assessing the effects of temperature on the population of *Aedes aegypti*, the vector of dengue. Epidemiology and infection 137(08):1188–1202
- Yeap HL, Mee P, Walker T, Weeks AR, O'Neill SL, Johnson P, Ritchie SA, Richardson KM, Doig C, Endersby NM, Hoffmann AA (2011) Dynamics of the popcorn *Wolbachia* infection in outbred *Aedes aegypti* informs prospects for mosquito vector control. Genetic 187(2):583-95
- Zheng B, Tang M, Yu J (2014) Modeling *Wolbachia* spread in mosquitoes through delay differential equations. SIAM Journal on Applied Mathematics 74(3):743–770.