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Global stabilizing feedback law for a problem of biological control of mosquito-borne diseases

Pierre-Alexandre Bliman[1,2] and M. Soledad Aronna[1] and Flávio C. Coelho[1] and Moacyr A.H.B. da Silva[1]

***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 mosquitoes carrying the *Wolbachia* parasite that need to be introduced into the natural population. The latter are expected to eventually replace the *Wolbachia*-free population and guarantee permanent protection against the transmission of dengue to human.**

In this paper, 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 introduce a simple feedback control law to synthesize an introduction protocol, and prove that the population is guaranteed to converge to a stable equilibrium where the totality of mosquitoes carry *Wolbachia*. The techniques are based on the theory of monotone control systems, as developed after Angeli and Sontag. Due to bistability, the considered input-output system has multivalued static characteristics, but the existing results are unable to prove almost-global stabilization, and ad hoc analysis has to be conducted.

Keywords: Wolbachia, Global stabilization, Monotone systems, Input-output characteristic

I. INTRODUCTION

A. *Arboviroses and vector control*

Arboviruses (arthropod borne viruses) are viruses transmitted to humans by arthropod, such as the mosquito. They are pathogens of many and important diseases, putting at risk considerable portions of the human population, 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 and chikungunya.

The control of these diseases can be achieved by acting on the population of mosquitoes, and in absence of vaccine or curative treatment, it is essentially the only feasible way. 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 gradual increase of mosquito resistance to insecticides usually leads to partial or complete decrease of the efficiency of this strategy in the long run [1], [2]. Alternative or supplementary vector control strategies have been proposed and implemented, such as the release of transgenic or sterile mosquitoes [3], [4]. 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 and chikungunya, due to the fact that this bacterium limits severely the vectorial competence of *Aedes aegypti*. The international program Eliminate Dengue [5] is currently testing in the field this strategy, in several locations around the world: Australia, Indonesia, Vietnam, Colombia and Brazil. The release of infected mosquitoes with *Wolbachia* has the advantages of being safe for humans and the environment and inexpensive when compared to other control strategies [6].

B. 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 [7].

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 [8], [9], [10]. Some strains of *Wolbachia* reduce the lifespan of the mosquito, 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, 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 releasing in the field a large number of *Wolbachia*-infected mosquitoes bred in laboratory. Experiments have been conducted successfully in Australia [11], Vietnam, Indonesia and are currently being applied 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% of prevalence. The effects of this fixation of *Wolbachia* on the dynamics of dengue in the field is currently under investigation, but

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	Uninfected ♂	Infected ♂
Uninfected ♀	**Uninfected**	**Sterile eggs**
Infected ♀	**Infected**	**Infected**

TABLE I

CYTOPLASMIC INCOMPATIBILITY AND VERTICAL TRANSMISSION OF *Wolbachia* BACTERIA. THE STATE OF THE OFFSPRING IS INDICATED, DEPENDING ON THE PARENTS STATUS

preliminary results are encouraging [12]. If tractable in practice, this method has certainly the advantage of offering certain robustness to subsequent invasion of *Wolbachia*-free mosquitoes.

Several mathematical models of the dynamics of invasion of *Wolbachia* in a population of mosquitoes have been proposed, with distinct objectives. For example, [13] 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 in [14] and [15]. In [16], [17], models are presented that assess the effect of the *Wolbachia* in dengue dynamics. [18] describes a data driven model suitable to estimate accurately some biological parameters by fitting the model with field and lab data. The model presented here is a simplified version of the latter.

C. Description of the problem and contribution

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 [19]. The transmission of *Wolbachia* occurs only maternally (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. It provides a benefit to infected females against uninfected ones and therefore facilitates the *Wolbachia* spread. The strains *w*Mel and *w*MelPop of *Wolbachia* that are being used in the field experiments with *Aedes aegypti* induce almost total CI [20]. Table I schematizes the results of the mating of infected and uninfected mosquitoes when the CI is 100%. The model that we propose below captures all of these features and is simple enough to allow for a fairly complete analysis.

The corresponding system is shown to possess two unstable equilibria, which correspond to extinction of the two populations and a coexistence equilibrium; and two locally asymptotically stable equilibria, which correspond to *Wolbachia*-free and complete infestation equilibria. Using the fact that measurements are achieved and available during the whole release process, we propose a simple feedback control law to compute the released quantity of infected mosquitoes. The key result of the paper (Theorem 7) proves that, in the presence of mosquitoes, this control law has the capacity to asymptotically settle the bacterium from whatever initial conditions, and in particular from the completely *Wolbachia*-free equilibrium. Of course, a major benefit of feedback compared to open-loop approaches is its ability to cope with the uncertainties on the model dynamics (e.g. in the modeling of the life stages and the population structure), on the parameters (population size, mortality, reproductive rates, etc.), and on the conditions of the realization (in particular on the size of the population to be treated).

Up to our knowledge, this constitutes the first attempt to use feedback approach for introduction of *Wolbachia* within a population of arthropods. We only treat here 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 control and observation, and the corresponding issues will be examined in future work.

The paper is organized as follows. The model is introduced in Section II, and normalized. Analysis of the uncontrolled model is made in Section III, showing the announced bistability between *Wolbachia*-free equilibrium and full infestation. A proportional control law is then proposed in Section IV, that leads to global stability of the full infestation equilibrium. Simulations are shown in Section V and concluding remarks achieve the text in Section VI. The reader is referred to [21] for details and complete proofs.

Notation. For $n \in \mathbb{N}$, $\mathbb{R}^n$ denotes the n-dimensional Euclidean real space, and $\mathbb{R}^n_+$ the cone of vectors in $\mathbb{R}^n$ with *nonnegative* components. We write $\max\{a;b\}$ (resp. $\min\{a;b\}$) for maximum (resp. minimum) of two real numbers a, b. Also, for a closed convex cone $\mathcal{K} \subset \mathbb{R}^n$ with nonempty interior $\texttt{int}\ \mathcal{K}$, $x \gg_{\mathcal{K}} x'$ means $x - x' \in \texttt{int}\ \mathcal{K}$. Last, we write LAS (resp. GAS) for locally (resp. globally) asymptotically stable.

II. A SIMPLE MODEL OF INFESTATION BY *Wolbachia*

The simplified compartment model we introduce includes two life stages: a preliminary one, gathering the aquatic phases (egg and larva) where the mosquitoes are subject to space and food competition; and an adult one, representing all the posterior aerial phases (pupae, immature and mature adult). Accordingly, we will denote $\mathbf{L}$ and $\mathbf{A}$ the corresponding state variables. The uninfected and infected (by *Wolbachia*) populations will be distinguished by indexes U and W respectively, so we end up with a four state variables model, namely $\mathbf{L}_U, \mathbf{L}_W$ and $\mathbf{A}_U, \mathbf{A}_W$, that represent the numbers of uninfected, resp. infected, vectors in preliminary and adult phases. The parameters are positive and have the following meaning, α_U, α_W: fecundity rates of uninfected and infected insects; ν: rate of transfer from the preliminary to the adult stage; μ: mortality rate of uninfected and infected insects in preliminary stage; μk: characteristic of the additional competition-induced mortality rate in preliminary stage; μ_U, μ_W: mortality rates of uninfected and infected insects at adult stage. The model is as follows.

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

$$\dot{\mathbf{A}}_U = \nu \mathbf{L}_U - \mu_U \mathbf{A}_U \tag{1b}$$

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

$$\dot{\mathbf{A}}_W = \nu \mathbf{L}_W - \mu_W \mathbf{A}_W \tag{1d}$$

The difference between the two populations lies in the different fecundity and mortality rates. The mortality during the larva stage and the duration of the latter are considered unmodified by the disease. Also, the (quadratic) competition term is assumed to act equally on both populations, with an effect proportional to the global number of larvae.

The first effect of *Wolbachia* is to diminish fertility and life duration, leading to reduced fitness for the infected mosquitoes. This assumption will correspond to the choice of parameters made in (4) below. The second effect, namely the cytoplasmic incompatibility, modeled here as complete, forbids fecund mating between infected males and uninfected females. This is rendered in (1a) by a birth term proportional altogether to the *number* and to the *ratio* of uninfected adults. Last, notice the input variable $\mathbf{u}$ in equation (1c), that models the on-purpose introduction of infected larvae in the system in order to settle *Wolbachia*.

The previous model is now normalized, see [21] for details. The normalized model, used in the sequel, is:

$$\dot{L}_U = \gamma_U \mathcal{R}_0^U \frac{A_U}{A_U + A_W} A_U - (1 + L_W + L_U)L_U \tag{2a}$$

$$\dot{A}_U = L_U - \gamma_U A_U \tag{2b}$$

$$\dot{L}_W = \gamma_W \mathcal{R}_0^W A_W - (1 + L_W + L_U)L_W + u \tag{2c}$$

$$\dot{A}_W = L_W - \gamma_W A_W \tag{2d}$$

with the choice of dimensionless parameters

$$\gamma_\eta := \frac{\mu_\eta}{\nu + \mu}, \quad \mathcal{R}_0^\eta := \frac{\nu \alpha_\eta}{(\nu + \mu)\mu_\eta}, \qquad \eta = U, W \ . \tag{3}$$

The state variable for system (2) is denoted $x := (L_U, A_U, L_W, A_W)$, and for sake of simplicity (2) is written $\dot{x} = f(x) + Bu$, with $B := \begin{pmatrix} 0 & 0 & 1 & 0 \end{pmatrix}^\intercal$ and

$$f(x) := \begin{pmatrix} \gamma_U \mathcal{R}_0^U \frac{A_U}{A_U + A_W} A_U - (1 + L_W + L_U)L_U \\ L_U - \gamma_U A_U \\ \gamma_W \mathcal{R}_0^W A_W - (1 + L_W + L_U)L_W \\ L_W - \gamma_W A_W \end{pmatrix} .$$

We assume in the remainder of the paper

$$\mathcal{R}_0^U > \mathcal{R}_0^W > 1 \ . \tag{4}$$

Ensuring sustainability of each of the two isolated populations, with even better sustainability for the non-infected one, (4) is coherent with the experimental observations.

III. ANALYSIS OF THE UNCONTROLLED SYSTEM

A. Well-posedness, positivity and boundedness

One first shows the well-posedness of the Cauchy problem associated to the uncontrolled (zero-input) system

$$\dot{x} = f(x) \tag{5}$$

Theorem 1: For any initial value in $\mathbb{R}_+^4$, there exists a unique solution to the initial value problem associated to system (5). 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. □

B. Monotonicity

Noticing that the presence of the infected population cripples the growth of the uninfected one and vice versa, yields the following fundamental result [21].

Theorem 2: System (5) is *strongly order-preserving* in $\mathbb{R}_+^4$ for the order induced by the cone $\mathcal{K} := \mathbb{R}_- \times \mathbb{R}_- \times \mathbb{R}_+ \times \mathbb{R}_+$, defined by: $x \geq_\mathcal{K} x' \Leftrightarrow x_i \leq x'_i, \ i = 1, 2$ and $x_i \geq x'_i, \ i = 3, 4$. □

Definitions of monotone and strongly order-preserving semi-flows defined on a topological space X partially ordered by an order relation $\leq_\mathcal{K}$ generated by a cone $\mathcal{K}$, can be found in [22]. System (5) is therefore monotone in $\mathbb{R}_+^4$, but not *strongly* monotone: indeed, the trajectories departing from 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 the strict ordering property for the two null components.

C. Equilibrium points and stability

The next result [21] describes the situation of the equilibrium points and their stability.

Theorem 3: System (5) 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*. Moreover, the latter fulfill the following inequalities: $x_{U,0} \ll_\mathcal{K} x_{U,W} \ll_\mathcal{K} x_{0,W}$, and $x_{U,0} \ll_\mathcal{K} x_{0,0} \ll_\mathcal{K} x_{0,W}$. Last, the equilibria $x_{U,0}$ and $x_{0,W}$ are LAS, while the two other ones are unstable. □

D. Positively invariant sets and basins of attraction

The order relations between the equilibria (see Theorem 3) yield supplementary information on some invariant sets.

Theorem 4: The order interval $\llbracket x_{U,0}; x_{0,W} \rrbracket_\mathcal{K} := \left\{ x \in \mathbb{R}^4 \ : \ x_{U,0} \leq_\mathcal{K} x \leq_\mathcal{K} x_{0,W} \right\} \subset \mathbb{R}_+^4$ is positively invariant for system (5). Moreover, the order interval $\llbracket x_{U,W}; x_{0,W} \rrbracket_\mathcal{K}$ (resp. $\llbracket x_{U,0}; x_{U,W} \rrbracket_\mathcal{K}$) is contained in the basin of attraction of $x_{0,W}$ (resp. $x_{0,U}$). □

IV. ANALYSIS OF THE CONTROLLED SYSTEM

A. A class of static output-feedback control laws

The feedback law $u = KL_U$ is considered in the sequel, for adequate (positive) values of the *scalar gain* K. Writing $e := \begin{pmatrix} 1 & 0 & 0 & 0 \end{pmatrix}^\intercal$, one obtains the closed-loop system:

$$\dot{x} = f(x) + KBe^\intercal x \ , \tag{6}$$

or in developed form:

$$\dot{L}_U = \gamma_U \mathcal{R}_0^U \frac{A_U}{A_U + A_W} A_U - (1 + L_W + L_U) L_U \tag{7a}$$

$$\dot{A}_U = L_U - \gamma_U A_U \tag{7b}$$

$$\dot{L}_W = \gamma_W \mathcal{R}_0^W A_W - (1 + L_W + L_U) L_W + K L_U \tag{7c}$$

$$\dot{A}_W = L_W - \gamma_W A_W \tag{7d}$$

Theorem 5: For any initial value in $\mathbb{R}_+^4$, there exists a unique solution to the initial value problem associated to system (6). 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. □

B. Equilibrium points and critical gain

The next result shows that, for gains larger than certain critical value, the only LAS equilibrium is $x_{0,W}$. Moreover, the value of this critical gain 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 6: If $K > K^* := \frac{\gamma_W}{\gamma_U}\left(\sqrt{\mathcal{R}_0^U} - \sqrt{\mathcal{R}_0^W}\right)^2$, then the closed-loop system (6) possesses two equilibria, namely $x_{0,0}$ and $x_{0,W}$, and their local stability properties are not modified: $x_{0,0}$ is unstable and $x_{0,W}$ is LAS. □

C. Global stability issues

We now turn to the most innovative part of this paper, namely the global behavior of the closed-loop system (6). The result we state here shows that the introduction of infected larvae according to the proposed proportional feedback law yields conclusive infestation when the gain is larger than the critical value. More precisely, we have the following convergence result.

Theorem 7: If $K > K^*$, all trajectories of system (6) issuing from a point in $\mathbb{R}_+^4$ distinct from $x_{0,0}$ converge towards the complete infestation equilibrium $x_{0,W}$. □

Strictly speaking, Theorem 7 is an *almost global convergence* result: complete infestation occurs, except for a zero measure set of initial conditions. However, in the present case, this set is reduced to the unstable equilibrium.

Two attempts to prove Theorem 7 are rapidly presented in Sections IV-C.1 and IV-C.2. Their interest is to show how quite natural approaches fail to provide information on the asymptotic behavior: a new approach is therefore needed. A conclusive method is exposed in Section IV-C.3.

1) Global stability of a singularly perturbed system, by LaSalle's invariance principle: We present a first attempt, based on Lyapunov techniques. Consider the simpler system

$$\dot{L}_U = \mathcal{R}_0^U \frac{\gamma_W L_U}{\gamma_W L_U + \gamma_U L_W} L_U - (1 + L_W + L_U) L_U \tag{8a}$$

$$\dot{L}_W = \mathcal{R}_0^W L_W - (1 + L_W + L_U) L_W + K L_U \tag{8b}$$

System (8) is deduced from (7) by applying singular perturbation, formally putting $0 = L_U - \gamma_U A_U$, $0 = L_W - \gamma_W A_W$. In other words, we assume that (7b) and (7d) are fast dynamics, and (7a) and (7c) are comparatively slower. Well-posedness and positiveness of system (8) present no difficulties, one states directly its asymptotic properties.

Theorem 8: Assume $K > K^*$. Then system (8) possesses two equilibria, which are the projections of $x_{0,0}$ and $x_{0,W}$. The former one is unstable, while the latter one is LAS. Last, all trajectories of system (8) converge towards the LAS one, except the unstable equilibrium itself. □

An interesting point is that stability may be obtained by showing that the derivative of the function $V(L_U, L_W) := \frac{L_U}{L_U + L_W}$ is nonpositive along the trajectories of (8) when $K > K^*$ [21]. While this Lyapunov function is quite appealing, it has not proved possible to extend this idea to the complete controlled system (6).

2) A monotone control system perspective: The second method now explored is an attempt to apply the results on *monotone control systems*, as worked out in particular by [23], see also [24], [25], [26], [27]. The principle of this approach consists in decomposing the system under study as a *monotone input-output system with feedback*. Given the fact (see Theorem 2) that the uncontrolled system is monotone, a most natural way to do this is to write system (6) as

$$\dot{x} = f(x) + KBu, \qquad y = L_U = e^{\intercal} x \tag{9a}$$

$$u = y \tag{9b}$$

Arguing as in Theorem 2, one shows that the input-to-state map $u \mapsto x$ given by (9a) is monotone when the state space is endowed with the ordering $\leq_{\mathcal{K}}$; while the state-to-output map $x \mapsto y = e^{\intercal} x = L_U$ is anti-monotone. We are thus in a configuration of *monotone system with negative feedback*.

In such a case, the study of asymptotics of the system obtained when closing the loop by the unitary feedback (9b) can be done by introducing *static characteristics* [23], [27]. However, things become immediately complicated in the case of system (9): constant input $\bar{u} = 0$ leads to the uncontrolled system (5), which has been proved to possess

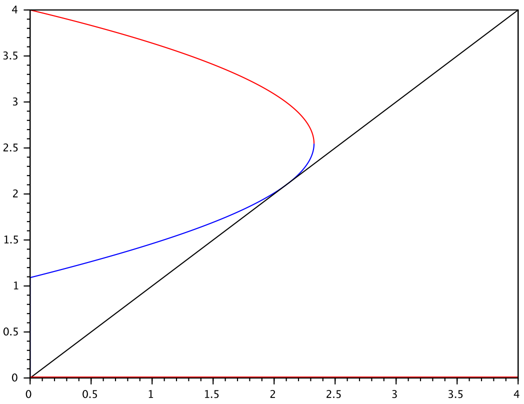

Fig. 1. The multivalued input-output characteristic $\bar{u} \mapsto k(\bar{u})$ corresponding to input-output system (9a) (in red) and the diagonal $\bar{u} \mapsto \bar{u}$ (in black), in the critical case $K^* = K$. See text for explanations

two LAS equilibria (and two unstable ones). In such a case, one can consider *multivalued input-state and input-output characteristics*, as made in [28], [29]. The corresponding input-output characteristic is drawn in red in Figure 1 (for the parameter values given in Section V below) and for the corresponding critical value K^* of K.

As seen in the figure, the input-output characteristic has basically two branches (both drawn in red). The first one merges with the horizontal axis: it corresponds to a branch of equilibria with null value of the output $y = L_U$ that departs from $x_{0,W}$ for $\bar{u} = 0$. The second one is a decreasing curve, defined for values of $\bar{u}$ ranging from zero to a value close to 2.32: it corresponds to the output value of a branch of equilibria departing from $x_{U,0}$. The blue curve, which does *not* pertain to the input-output characteristic, indicates the output values of a branch of unstable equilibria originating from $x_{U,W}$, that vanishes together with the upper curve. The diagonal line (that determines the fixed points of k) is shown, tangent to the blue curve due to the fact that $K = K^*$ here.

For $K > K^*$, the complete infestation equilibrium is therefore the only fixed point of the multivalued map k. But the iterative sequences $\bar{u}_{k+1} = k(\bar{u}_k)$ do *not* converge systematically towards this point, and the only information that can be deduced in case of multivalued input-output characteristic [28], [29] is that all trajectories are bounded and that the output $y = L_U$ fulfills the inequalities: $0 \le \limsup_{t\to+\infty} y(t) \le k^{\sup}\left(\liminf_{t\to+\infty} y(t)\right)$, where $k^{\sup}(\bar{u}) := \max_{y\in k(\bar{u})} y$. As a conclusion, the decomposition (9), that seemed a natural framework to analyze the behavior of the controlled system (6) immediately fails to produce a global vision of the asymptotic behavior.

3) Monotonicity revisited and proof of the global stability: A crucial step in the proof of Theorem 7 is the introduction of a decomposition of system (6) different from (9). Let $|z|_\pm := z$ if $\pm z \ge 0$, 0 otherwise. Clearly, $z = |z|_- + |z|_+$, $z \in \mathbb{R}$. Consider now the input-output system

$$\dot{L}_U = \gamma_U \mathcal{R}_0^U \frac{A_U}{A_U + A_W} A_U - (1 + L_W + L_U) L_U \tag{10a}$$

$$\dot{A}_U = L_U - \gamma_U A_U \tag{10b}$$

$$\dot{L}_W = \gamma_W \mathcal{R}_0^W A_W - (1 + L_W) L_W + |K - L_W|_- L_U + K u \tag{10c}$$

$$\dot{A}_W = L_W - \gamma_W A_W \tag{10d}$$

$$y = \left| 1 - \frac{L_W}{K} \right|_+ L_U \tag{10e}$$

One verifies easily that closing (10) by $u = y$ yields (6). The following result is a key step, see [21] for further details.

Lemma 9: The input-output system (10) is monotone with negative feedback, when the state space is endowed with the order $\geq_{\mathcal{K}}$ defined in Theorem 2. □

V. NUMERICAL SIMULATIONS

Illustrative simulations are presented, with the following realistic parameters: $\gamma_U = 0.8$, $\gamma_W = 1$, $\mathcal{R}_0^U = 5$, $\mathcal{R}_0^W = 3$. Notice that the mortality is higher for the *Wolbachia* infected population ($\gamma_U < \gamma_W$), and its sustainability inferior ($\mathcal{R}_0^U > \mathcal{R}_0^W$). Computation of the critical gain yields $K^* \simeq 0.318$.

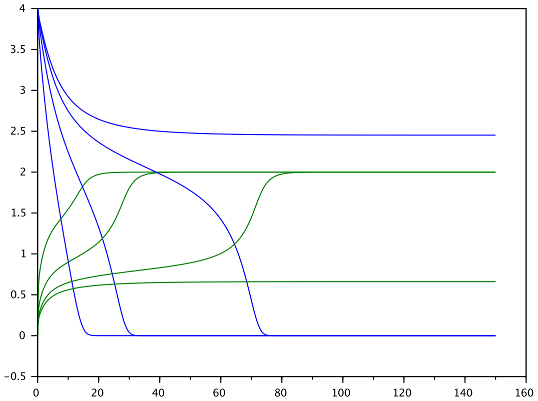

Fig. 2. Evolution of $L_U(t)$ and $L_W(t)$ as functions of time, for $K = 1$, $K = 0.5$, $K = 0.35$ and $K = 0.3$. See the text for details

Figures 2 shows on the same diagram the evolution of the state variables L_U (in blue) and L_W (in green) as functions of time, for different values of the gain. The initial state is the *Wolbachia*-free equilibrium $x_{U,0}$, and K is respectively chosen to be 1, 0.5, 0.35 and 0.3. For the three first values, settling of complete infestation is slower when the gain decreases. For the last value, slightly smaller than the critical value $K^* \simeq 0.318$, a coexistence equilibrium appears asymptotically, indicating that the bound K^* is tight.

VI. CONCLUSIONS AND FURTHER STUDIES

We presented and analyzed a model for the infestation by bacterium *Wolbachia* of a population of mosquitoes — typically one of the *genera Aedes* involved in the transmission of arboviroses such as yellow fever, dengue fever or chikungunya. A method of implementation based on the introduction of a quantity of contaminated insects proportional to the size of the healthy population was proposed and shown, analytically and by simulation, to be capable of successfully spreading the bacteria, provided the gain is sufficiently large. This feedback method requires continuous measurement of the population. Its main interest with respect to the release(s) of a predefined quantity, is the reduction of the number of released mosquitoes, and thus of the treatment cost, without jeopardizing the success of the introduction of the bacteria — something which can happen e.g. in case of underestimation of the initial population size. To our knowledge, this is the first use of the control theory notion of feedback in such a context.

Among other steps leading to application, the adaptation to effective conditions has to be done. First, the model presented here has been chosen continuous in time for simplicity, but passing to discrete-time system seems to present *a priori* no difficulties. Also, the present framework assumes the measurement of a larva stage of the healthy portion of the population, and as well the release of a larva stage of the contaminated one. The practical conditions can be different, and the method can be adapted in consequence (leading though to similar, but different, convergence questions). Last, robustness with respect to parameter uncertainties (or to seasonal variations) has not been tackled here.

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*. This point will be studied in a next future. 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 [23], 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.

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