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Feedback Control Principles for Biological Control of Dengue Vectors*

Pierre-Alexandre Bliman*

Abstract—Controlling diseases such as dengue fever, chikungunya and zika fever by introduction of the intracellular parasitic bacterium *Wolbachia* in mosquito populations which are their vectors, is presently quite a promising tool to reduce their spread. While description of the conditions of such experiments has received ample attention from biologists, entomologists and applied mathematicians, the issue of effective scheduling of the releases remains an interesting problem for Control theory. Having in mind the important uncertainties present in the dynamics of the two populations in interaction, we attempt here to identify general ideas for building release strategies, which should apply to several models and situations. These principles are exemplified by two interval observer-based feedback control laws whose stabilizing properties are demonstrated when applied to a model retrieved from [1]. Crucial use is made of the theory of monotone dynamical systems.

I. INTRODUCTION

Already a major issue in southern countries since decades, the control of vector-borne diseases transmitted by mosquitoes recently became an important concern for northern countries too, due to the geographical dissemination of the vectors favored by climate change, urbanization and increasing international travel. When no vaccine or curative treatment exists, traditional control measures focus on reducing the vector population in order to reduce the pathogen transmission. Mechanical control methods by preventive actions and removal of breeding sites are invaluable, but costly and difficult to implement efficiently. Chemical control by insecticides has been quite popular, but on top of its negative impacts on humans and animals, it experiences decreasing efficiency due to resistance generation. Recently, various biological control methods have been proposed and tested as alternative or complementary strategies, typically by the release of transgenic or sterile mosquitoes [2], [3]. A new promising strategy based on the use of the bacterium *Wolbachia*, is being developed to control the spread of dengue fever and other diseases transmitted by species of the genus *Aedes* (chikungunya, zika fever, yellow fever). It is grounded in the fact that *Wolbachia* severely reduces the insect vectorial ability, either indirectly by reducing lifespan

and fertility, or directly by reducing the virus ability to proliferate within the organism [4], [5], [6], [7].

The dynamics resulting from the introduction of *Wolbachia*-infected mosquitoes in wild populations has been abundantly considered, even in the absence of spatial aspects; see [8], [9], [10], [11], [12], [13], [14], [15], [1], [16], and [17], [18], [19] for the effects induced on the dengue epidemics. Field sampling methods allow to evaluate population density [20], [21], and such operations are commonly performed during experimental campaigns. Also, the presence of the bacterium in the captured sample may be investigated by polymerase chain reaction (PCR) method [6]. Theoretically, this opens up the possibility to assess the released quantities on the basis of the observed population, and to benefit from the multiple advantages of closed-loop methods. Most papers analyze only the effect of a unique, initial, release. By contrast, [11] considers continuous releases and [12] impulsive releases, both with constant release amplitude, while [1] provides linear control-law and [14], [15] optimal control. However these stabilization results are highly dependent upon the setting, and their generalization is in no way straightforward. Our aim here is to identify simple control principles, based on the understanding of the biological phenomena involved, and to test them on the model introduced in [1]. More specifically, we propose two control laws achieving complete infestation, respectively through the introduction of infected adults and larvae. Their implementation necessitates the construction of an interval observer [22], [23], [24] for the considered system.

The content of the paper is as follows. The characteristics of the compartmental model developed in [1] are recalled in Section II, together with some analysis results. Section III proposes a class of interval observers for this model. The main results (Theorems 3 and 4) are exposed and proved in Section IV. Numerical simulations are shown in Section V, and some concluding remarks are given in Section VI.

Notations. The following notations are used for the positive, resp. negative, parts of a real number z : $|z|_+ := \max\{z, 0\}$, $|z|_- := -\min\{z, 0\}$. Both are nonnegative, and

$$\forall z \in \mathbb{R}, \quad z = |z|_+ - |z|_- . \quad (1)$$

The usual order relation \geq in \mathbb{R} is employed, and the same notation is extended to vectors and matrices by the product order: $(x_1, x_2) \geq 0$ iff $x_1 \geq 0$ and $x_2 \geq 0$. It is similarly extended to locally integrable functions taking on values in one of these ordered spaces, with the evident meaning. In all cases, the symbol $>$ is used as usual to mean ‘at most equal to, but not equal’. As an example, for locally integrable functions f, g defined on a common domain, ‘ $f > g$ ’ is

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equivalent to: ‘ $f \geq g$ and $f > g$ on a nonzero-measured set’. Also, we use the notation \ll for ‘much less than’. Whenever the sign \pm is used, it means that the relevant formula is valid for $+$ and for $-$. Last, usual matrix notations are employed: $I_n, 0_n$ denote respectively the identity and null square matrices of order n , $n \in \mathbb{N}$, $^\top$ denotes transposition.

II. MODELING

A. Model equations

The compartmental model in [1] focuses on the main effects pertinent for control purposes. It contains two life phases: a preliminary phase which gathers the early, aquatic, stages (egg, larva and pupa), subject to competition; and an adult, aerial, mature phase. The corresponding state variables are respectively denoted L (‘larvae’) and A (‘adults’), and the uninfected and *Wolbachia*-infected populations are distinguished by indices U and W . Assuming in first approximation that the sex ratio is stationary and the mortality is sex-independent, these variables represent indifferently the quantities of males or females, up to constant ratio. After normalization, the 4-dimensional population model used in the present paper is the following [1]:

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

$$\dot{A}_U = L_U - \gamma_U A_U \quad (2b)$$

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

$$\dot{A}_W = L_W - \gamma_W A_W + u_A(t) \quad (2d)$$

The term u_L (resp. u_A) represents the infected larvae (resp. adults) released per time unit to steer the system towards the desired complete *Wolbachia*-infection equilibrium. By construction both signals have nonnegative values. Using $x := (L_U, A_U, L_W, A_W)$, $u := (u_L, u_A)$ as state and input variables, the previous controlled system writes compactly:

$$\dot{x} = f(x) + Bu, \quad y = Cx, \quad (3)$$

where the function f is easily expressed from (2) and the input matrix B is given by

$$B := \begin{pmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}^\top.$$

The output matrix C is used to define which are the available measurements, it is specified in Section III.

Well-posedness of the Cauchy problem for system (2) does not present specific difficulty, e.g. for locally integrable input u with nonnegative values almost everywhere. As a result of this and of the fact that $(f(x))_i \geq 0$ whenever $x \geq 0$ and $x_i = 0$, $i = 1, \dots, 4$, the set \mathbb{R}_+^4 is invariant for the flow.

B. Phenomenological hypotheses on the infection dynamics

The main phenomenological assumptions contained in the previous infection model are the following.

◦ 1. The *Wolbachia* infection in *Aedes* mosquito leads to lifespan shortening through adult mortality increase [4], [25]

and fecundity rate reduction [26]. This is accounted for by the following inequalities between normalized constants:

$$0 < \gamma_U < \gamma_W, \quad \mathcal{R}_0^U > \mathcal{R}_0^W > 1. \quad (4)$$

The variations of larval development time and mortality are regarded as limited and are not modeled here.

◦ 2. The density-dependent mortality is a major component of larval dynamics [27], [28], rendered here by quadratic competition terms in the immature phase dynamics. Accounting for restricted food and space in the breeding sites, it acts evenly on the immature infected and uninfected population, with a rate proportional to its global size $L_U + L_W$.

◦ 3. The *Wolbachia* transmission occurs only vertically, from mother to offspring. It is accompanied by a phenomenon called *cytoplasmic incompatibility*, which provides a reproduction advantage to infected females against uninfected ones and facilitates the spread of the bacterium. Cytoplasmic incompatibility is characterized by the fact that an uninfected female only produces offspring when mating with an uninfected male [29], [4], [25], [30]. On the contrary when an infected female mates, the outcome is infected independently of whether the male is infected or not. The probability of a male being uninfected is $\frac{A_U}{A_U + A_W}$, and the nonlinear birth term $\frac{A_U}{A_U + A_W} A_U$ in (2a) accounts for such encounters. By contrast, the birth term for infected in (2c) is simply proportional to the corresponding population A_W .

C. Analysis of the uncontrolled model [1]

The quantities $\mathcal{R}_0^U, \mathcal{R}_0^W$ present in (2) are the *basic offspring numbers* [31], [32] associated, respectively, to each population. They represent the average number of mosquitoes born to each adult (female) mosquito during its entire lifespan. To understand their meaning, let us introduce the following auxiliary system:

$$\dot{L} = \gamma \mathcal{R} A - (1 + L) L, \quad \dot{A} = L - \gamma A, \quad (5)$$

with $\gamma > 0, \mathcal{R} > 0$. One checks easily that when initially one of the two populations (infected or uninfected) is absent from (2), then the other population evolves alone according to system (5). The zero (extinction) equilibrium of the latter is the unique equilibrium and is globally asymptotically stable when $\mathcal{R} < 1$; while when $\mathcal{R} > 1$ it is unstable, and a nonzero equilibrium $(\mathcal{R} - 1, \frac{\mathcal{R}-1}{\gamma})$ appears, which is asymptotically stable and limit point of every nonzero trajectory.

Transposing this remark discloses immediately the existence, under hypothesis (4), of two equilibria for system (2) with zero input u , characterized by the state values $(L_U^*, A_U^*, 0, 0)$ and $(0, 0, L_W^*, A_W^*)$, where:

$$L_\eta^* := \mathcal{R}_0^\eta - 1, \quad A_\eta^* := \frac{L_\eta^*}{\gamma_\eta}, \quad \eta = U, W.$$

They correspond respectively to *disease-free* and *complete infestation* situations. Under hypothesis (4), both are locally asymptotically stable: 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* globally reduces the fitness of the infected mosquitoes.

Two other equilibria exist, which correspond to *extinction* and *coexistence*, and are both unstable. System (2) presents *bistability*, and the control purpose is typically to pass from the disease-free situation to the complete infestation.

A structural property, central to analyze the behavior of system (2), is *monotonicity* [33]. It will be instrumental in the sequel.

Theorem 1: [1] System (2) with zero input u is strongly order-preserving [33, p. 2] in \mathbb{R}_+^4 for the order induced by the cone $\mathbb{R}_- \times \mathbb{R}_- \times \mathbb{R}_+ \times \mathbb{R}_+$, defined by:

$$x \succeq x' \Leftrightarrow x_i \leq x'_i, i = 1, 2 \text{ and } x_i \geq x'_i, i = 3, 4 \quad (6)$$

III. UPPER AND LOWER STATE ESTIMATES

In order to study control synthesis in Section IV, upper and lower estimates of the state variables will be needed. Notice that using monotonicity and the fact that the input variable u takes on nonnegative values, one may show e.g. that the solutions of (2) fulfill, for any initial condition, the properties: $0 \leq \liminf_{t \rightarrow +\infty} L_U(t) \leq \limsup_{t \rightarrow +\infty} L_U(t) \leq L_U^*$, $0 \leq \liminf_{t \rightarrow +\infty} A_U(t) \leq \limsup_{t \rightarrow +\infty} A_U(t) \leq A_U^*$. The use of such rough estimates is possible, but yields uselessly costly control laws.

We assume the availability of, say, p measurements, and introduce the output variable $y = Cx$ for some fixed matrix $C \in \mathbb{R}^{p \times 4}$. Typically y contains measurement on the values of $L_U(t)$, $L_W(t)$ and/or $A_U(t)$, $A_W(t)$, depending upon the information monitored in the field.

In order to take into account measurement uncertainties, one assumes that are available two (locally integrable, nonnegative-valued) auxiliary signals $y_-(t)$, $y_+(t)$ bounding the exact, but unknown, value $y(t)$: for (almost) any $t \geq 0$, $0 \leq y_-(t) \leq y(t) \leq y_+(t)$.

Theorem 2: (Interval observer design). For x evolving according to (3), let the evolution of the variables

$$x_- := \begin{pmatrix} L_U^+ \\ A_U^+ \\ L_W^- \\ A_W^- \end{pmatrix}, \quad x_+ := \begin{pmatrix} L_U^- \\ A_U^- \\ L_W^+ \\ A_W^+ \end{pmatrix} \quad (7)$$

be defined by

$$\dot{x}_- = f(x_-(t)) + Bu + K_-(x_-(t))(y_-(t) - Cx_-(t)) \quad (8a)$$

$$\dot{x}_+ = f(x_+(t)) + Bu + K_+(x_+(t))(y_+(t) - Cx_+(t)) \quad (8b)$$

for gain matrices $K_-(\cdot)$, $K_+(\cdot) \in \mathbb{R}^{4 \times p}$ depending continuously upon the state. Assume that

$$\text{diag}\{-I_2; I_2\}K_{\pm}(\cdot) \geq 0 \quad (9a)$$

$$\text{diag}\{-I_2; I_2\}K_{\pm}(\cdot)C \text{diag}\{-I_2; I_2\} \leq 0 \quad (9b)$$

and that the i -th line of $K_-(\cdot)$ (resp. $K_+(\cdot)$) is null whenever the i -th component of its argument is null, $i = 3, 4$ (resp. $i = 1, 2$). If

$$x_-(t) \preceq x(t) \preceq x_+(t) \text{ and } 0 \leq x_-(t), x(t), x_+(t) \quad (10)$$

for $t = 0$, then the same holds true for any $t \geq 0$.

Recall that f in the previous statement is the function that allows to write (2) as (3). Theorem 2 provides sufficient conditions under which, if $0 \leq L_{\eta}^-(t) \leq L_{\eta}(t) \leq L_{\eta}^+(t)$, $0 \leq A_{\eta}^-(t) \leq A_{\eta}(t) \leq A_{\eta}^+(t)$, $\eta = U, W$, for $t = 0$, then the same holds true for any $t \geq 0$. In other words, system (8) constitutes an *interval observer* [22], [23], [24] for (2).

Coming back to the definition of the order \preceq in (6), conditions (9a)-(9b) appear as rephrasing of the conditions:

$$\forall y, y' \in \mathbb{R}^p, y \preceq y' \Rightarrow K_-(\cdot)y \preceq K_-(\cdot)y', K_+(\cdot)y \preceq K_+(\cdot)y' \quad (11a)$$

$$\forall x, x' \in \mathbb{R}^4, x \preceq x' \Rightarrow K_-(\cdot)Cx \succeq K_-(\cdot)Cx', K_+(\cdot)Cx \succeq K_+(\cdot)Cx' \quad (11b)$$

Remark 1: Notice that (9b) comes as a consequence of (9a) when e.g.

$$C \text{diag}\{-I_2; I_2\} \leq 0. \quad (9c)$$

When for example measurements of the two larval populations $L_U(t)$, $L_W(t)$ are available, then $p = 2$ and one may take $C = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 \end{pmatrix}$, in accordance with (9c). According to (9a), the first two rows of the admissible gain matrices $K_-(\cdot)$, $K_+(\cdot)$ must then be nonpositive, and their last two rows nonnegative. \square

Remark 2: A simple way to fulfill the last technical assumption on the matrix gain lines is to introduce a smoothed Heaviside function for the corresponding components; namely to take the i -th line of $K_{\pm}(x)$ equal to the i -th line of fixed matrix M_{\pm} fulfilling (11), multiplied by the function $\max\{\min\{x_i, \varepsilon\}, 0\}$, for some $0 < \varepsilon \ll 1$. \square

Proof of Theorem 2. For simplicity, we omit in the sequel the argument of the matrix-valued functions K_{\pm} .

When $x_- \preceq x$ and $y_- \leq y = Cx$, one has, using (11): $K_-(y_- - Cx_-) = K_-(y_- - y) + K_-C(x - x_-) \leq 0$; and similarly, when $x_+ \succeq x$ and $y_+ \geq y$: $K_+(y_+ - Cx_+) = K_+(y_+ - y) + K_+C(x - x_+) \geq 0$. Therefore, for system (3)-(8) one has $\dot{x}_- \preceq f(x_-(t))$, $\dot{x}_+ \succeq f(x_+(t))$.

Use of Kamke's theorem [34] then allows to show that when the 1st property in (10) holds for $t = 0$, it holds also for any $t \geq 0$, provided that all components of the three vectors x , x_- , x_+ remain nonnegative — otherwise the composition by f is not licit, and the solution is not defined.

The nonnegativity of x , whose evolution does not depend upon x_- , x_+ , has already been established [1]. We now show that the values of x_- , x_+ effectively remain nonnegative along time. First, one verifies easily that the indexes mentioned in the statement are exactly those related to the evolution of L_U^- , A_U^- , L_W^- , A_W^- . On the other hand, when $(x_{\pm})_i = 0$ for some $i = 1, \dots, 4$, the i -th component $(f(x_{\pm}))_i$ is nonnegative. Thus, for any matrix line concerned by the condition imposed in the statement, $(\dot{x}_{\pm})_i \geq 0$ whenever $(x_{\pm})_i = 0$, and for this reason the values of the corresponding signals never leave the interval $[0, +\infty)$. With an initialization done in accordance with (10), the lower estimates are thus nonnegative, which forces in turn the components L_U^+ , A_U^+ , L_W^+ , A_W^+ to be nonnegative. Therefore

the 2nd inequality in (10) also holds, and this achieves the proof of Theorem 2. \blacksquare

IV. FEEDBACK CONTROL PRINCIPLES AND OBSERVER-BASED STABILIZATION

Due to the uncertainty inherent to the models of population dynamics, it seems valuable to propose feedback control strategies obeying *general* principles, ‘independent of the model’. We propose in the sequel two such approaches, related to control by release of adult mosquitoes and of larvae.

A. Control by release of adult mosquitoes

First, it is clear that, if the inter-species competition induced by the presence of infected mosquitoes is sufficient to make unviable the uninfected population, then the latter disappears. Adults do not directly interact, as shown by equations (2b) and (2d). However, they participate centrally to the natality. With this in mind, assume that, due to releases of adults through the input u_A in (2d), the fractional term responsible in (2b) for the cytoplasmic incompatibility, is kept smaller than $\frac{1}{\mathcal{R}_0^U}$, where \mathcal{R}_0^U is the basic offspring number of the uninfected population. Under such conditions, the uninfected population evolves sensibly as in equation (5) — however with a *subcritical* ‘apparent’ basic offspring number, as $\mathcal{R}_0^U \times \frac{1}{\mathcal{R}_0^U} = 1$. This suggests that targeting the cytoplasmic incompatibility term may be a way to realize eradication of the uninfected population. This general principle underpins the following result.

Theorem 3: (Sufficient conditions for successful introduction via release of adults). Assume available upper and lower state estimates for the solution of (2), according to (10) and (7). Assume that for some $T \geq 0$, (A) holds for given constants $k > 0$, $k_U > \mathcal{R}_0^U - 1$. Then

$$\lim_{t \rightarrow +\infty} \begin{pmatrix} L_U(t) \\ A_U(t) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \quad \liminf_{t \rightarrow +\infty} \begin{pmatrix} L_W(t) \\ A_W(t) \end{pmatrix} \geq \begin{pmatrix} L_W^* \\ A_W^* \end{pmatrix} \quad (12)$$

The goal of the control is to steer the system to the complete infestation equilibrium $(0, 0, L_W^*, A_W^*)$. Notice that when it succeeds, the lower bound of u_A in (A) may vanish asymptotically *only if* $k = \gamma_W$. In view of (4), the 2nd inequality in (A) then becomes

$$u_A \geq (k_U \quad k_U(\gamma_W - \gamma_U) \quad -1) \begin{pmatrix} L_U^+ \\ A_U^+ \\ L_W^- \end{pmatrix} \quad \text{on } [T, +\infty) \quad (13)$$

expression in which the three useful components of the estimator pertain to x_- , see (7).

Proof of Theorem 3.

• 1. We have $\dot{A}_W - k_U \dot{A}_U = L_W - \gamma_W A_W + u_A - k_U(L_U - \gamma_U A_U)$. By assumption, one has on $[T, +\infty)$: $u_A \geq -L_W^- + k_U L_U^+ + |\gamma_W - k|_+ A_W^+ - |\gamma_W - k|_- A_W^- + k_U |k - \gamma_U|_+ A_U^+ - k_U |k - \gamma_U|_- A_U^-$. Thus

$$\begin{aligned} & \dot{A}_W - k_U \dot{A}_U \\ & \geq L_W - L_W^- + k_U(L_U^+ - L_U) \\ & \quad - \gamma_W A_W + |\gamma_W - k|_+ A_W^+ - |\gamma_W - k|_- A_W^- \\ & \quad + k_U(\gamma_U A_U + |k - \gamma_U|_+ A_U^+ - |k - \gamma_U|_- A_U^-) \\ & \geq -\gamma_W A_W + |\gamma_W - k|_+ A_W^+ - |\gamma_W - k|_- A_W^- \\ & \quad + k_U(\gamma_U A_U + |k - \gamma_U|_+ A_U^+ - |k - \gamma_U|_- A_U^-) \end{aligned}$$

Now, using (1), one verifies that $-\gamma_W A_W + |\gamma_W - k|_+ A_W^+ - |\gamma_W - k|_- A_W^- \geq -k A_W$, and similarly $\gamma_U A_U + |k - \gamma_U|_+ A_U^+ - |k - \gamma_U|_- A_U^- \geq k A_U$. One thus deduces from these two inequalities that $\dot{A}_W - k_U \dot{A}_U \geq -k(A_W - k_U A_U)$. Integrating this differential inequality yields, for any $t \geq T$, $A_W(t) - k_U A_U(t) \geq e^{-k(t-T)}(A_W(T) - k_U A_U(T))$. Thus

$$\liminf_{t \rightarrow +\infty} (A_W(t) - k_U A_U(t)) \geq 0. \quad (14)$$

• 2. As $k_U > \mathcal{R}_0^U - 1$, there exists $\varepsilon > 0$ such that $k_U > \mathcal{R}_0^U(1 + \varepsilon) - 1$. Due to (14), there exist $T' \geq T$ such that, for any $t \geq T'$, $A_W(t) \geq (\mathcal{R}_0^U(1 + \varepsilon) - 1)A_U(t)$, and, due to the fact that the function $\mathbb{R}_+ \rightarrow \mathbb{R}_+$, $z \mapsto \frac{1}{1+z}$ is decreasing, $\frac{A_U(t)}{A_U(t) + A_W(t)} \leq \frac{1}{1 + \mathcal{R}_0^U(1 + \varepsilon) - 1} = \frac{1}{\mathcal{R}_0^U(1 + \varepsilon)}$. For $t \geq T'$, the evolution of the uninfected therefore obeys the following inequalities: $\dot{L}_U \leq \frac{\gamma_U}{1 + \varepsilon} A_U - (1 + L_W + L_U)L_U \leq \frac{\gamma_U}{1 + \varepsilon} A_U - (1 + L_U)L_U$, $\dot{A}_U = L_U - \gamma_U A_U$. As system (5) with $\gamma := \gamma_U$, $\mathcal{R} := \frac{1}{1 + \varepsilon} < 1$ is monotone, it may serve as a comparison system: denoting (L, A) the solution of system (5) such that $L(T') = L_U(T')$, $A(T') = A_U(T')$, one has, for any $t \geq T'$, $0 \leq L_U(t) \leq L(t)$, $0 \leq A_U(t) \leq A(t)$. On the other hand, as $\mathcal{R} < 1$, $(L(t), A(t))$ vanishes when $t \rightarrow +\infty$. One thus gets:

$$\lim_{t \rightarrow +\infty} L_U(t) = \lim_{t \rightarrow +\infty} A_U(t) = 0, \quad (15)$$

which is the 1st inequality of (12).

• 3. We now deduce lower bounds on L_W, A_W from the identities in (15). For any $\varepsilon > 0$, there exists $T'' > T$ such that, for any $t \geq T''$, $0 \leq L_U(t) \leq \varepsilon$. Using the fact that u_A, u_L have nonnegative values, one gets: $\dot{L}_W \geq \gamma_W \mathcal{R}_0^W A_W - (1 + \varepsilon + L_W)L_W$, $\dot{A}_W \geq L_W - \gamma_W A_W$. The underlying system

$$\dot{L}' = \gamma_W \mathcal{R}_0^W A' - (1 + \varepsilon + L')L', \quad \dot{A}' = L' - \gamma_W A' \quad (16)$$

is monotone. Applying again comparison result [34], one gets that, for any $t \geq T''$,

$$L_W(t) \geq L'(t), \quad A_W(t) \geq A'(t) \quad (17)$$

for the trajectory of (16) initialized by $L'(T'') = L_W(T'')$, $A'(T'') = A_W(T'')$.

Now, (16) is a variant of (5), and may be analyzed in the same way. It is not difficult to show that when $1 + \varepsilon < \mathcal{R}_0^W$, every nonzero trajectory of (16) converges towards the positive equilibrium $(\mathcal{R}_0^W - 1 - \varepsilon, \frac{\mathcal{R}_0^W - 1 - \varepsilon}{\gamma_W})$. For $\varepsilon > 0$ such that $\varepsilon < \mathcal{R}_0^W - 1$, one thus has $\lim_{t \rightarrow +\infty} L'(t) = \mathcal{R}_0^W - 1 - \varepsilon$, $\lim_{t \rightarrow +\infty} A'(t) = \frac{\mathcal{R}_0^W - 1 - \varepsilon}{\gamma_W}$. Deducing from (17) that $\liminf_{t \rightarrow +\infty} L_W(t) \geq \lim_{t \rightarrow +\infty} L'(t) = \mathcal{R}_0^W - 1 - \varepsilon$, $\liminf_{t \rightarrow +\infty} A_W(t) \geq \lim_{t \rightarrow +\infty} A'(t) = \frac{\mathcal{R}_0^W - 1 - \varepsilon}{\gamma_W}$.

$$u_L \geq 0, u_A \geq K \begin{pmatrix} L_U^+ \\ A_U^+ \\ A_U^- \\ L_W^- \\ A_W^+ \\ A_W^- \end{pmatrix} \text{ on } [T, +\infty), \quad K := (k_U \quad k_U|k - \gamma_U|_+ \quad k_U|k - \gamma_U|_- \quad -1 \quad |\gamma_W - k|_+ \quad |\gamma_W - k|_-) \quad (\mathbf{A})$$

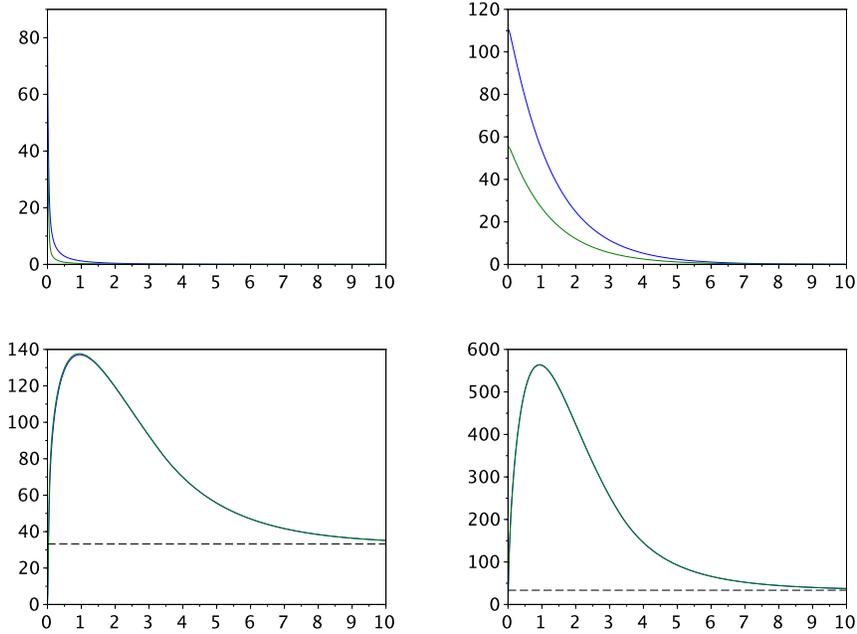


Fig. 1. **Release of adult mosquitoes:** evolution of the uninfected (top) and *Wolbachia*-infected (bottom), as function of time. The larvae appear on the left column, the adults on the right one. The components of the state x (resp. of the estimate x_-) appear in **green** (resp. in **blue**).

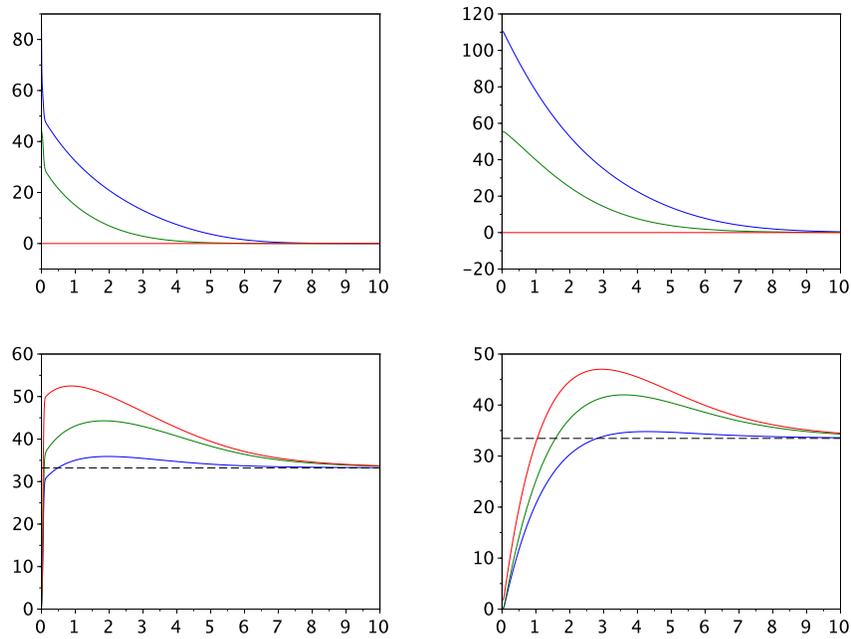


Fig. 2. **Release of larvae:** evolution of the uninfected (top) and *Wolbachia*-infected (bottom), as function of time. The larvae appear on the left column, the adults on the right one. The components of the state x (resp. of the estimates x_-, x^+) appear in **green** (resp. in **blue**, in **red**).

$\lim_{t \rightarrow +\infty} A'(t) = \frac{\mathcal{R}_0^W - 1 - \varepsilon}{\gamma_W}$ and passing to the limit $\varepsilon \rightarrow 0$, yields the 2nd inequality in (12). This completes the proof of Theorem 3. ■

B. Control by release of larvae

We now examine control approaches based on release of larvae. This method amounts to acting on the input term u_L in (2c). The only hindrance to the growth of the infected population lies on the competition term in the previous equation. Therefore, if the rate of introduction of infected larvae is sufficient to compensate for the competition effect, then the infected population should reach the complete infestation equilibrium and induce collapse of the uninfected population, through the competitive pressure term in (2b). This is evidenced by the following result.

Theorem 4: (Sufficient conditions for successful introduction via release of larvae). Assume available upper and lower state estimates for the solution of (2), according to (10) and (7). Assume that for some $T \geq 0$,

$$u_L > L_U^+ L_W^+, \quad u_A \geq 0 \quad \text{on } [T, +\infty). \quad (\mathbf{L})$$

Then (12) holds.

Proof of Theorem 4.

• 1. When **(L)** is fulfilled, then the infected population obeys the following differential inequalities: $\dot{L}_W > \gamma_W \mathcal{R}_0^W A_W - (1 + L_W + L_U) L_W + L_U^+ L_W^+ \geq \gamma_W \mathcal{R}_0^W A_W - (1 + L_W) L_W$ and $\dot{A}_W \geq L_W - \gamma_W A_W$. One may thus bound from below each of its solutions by a solution (L, A) of system (5) with $\gamma := \gamma_W$ and $\mathcal{R} := \mathcal{R}_0^W$, initialized with the same valor than (L_W, A_W) in any $T' \geq T$. This solution of (5) tends to the positive equilibrium, or to the zero equilibrium *only if the initial condition is precisely the zero equilibrium*.

• 2. We now use the 1st inequality in **(L)**. Due to its *strict* character¹, any trajectory of (2) takes on some *nonzero* value on $[T, +\infty)$, say at time T' . As $(0, 0) < (L(T'), A(T'))$, convergence of (L, A) to the zero equilibrium of (5) is excluded, and this solution is forced to converge towards the positive equilibrium. Using this property one deduces that the 2nd inequality in (12) is fulfilled.

• 3. In turn, we deduce from the preceding inference, that the evolution of the non-infected population fulfills asymptotically the inequalities:

$$\begin{aligned} \dot{L}_U &\leq \gamma_U \mathcal{R}_0^U \frac{A_U}{A_U + A_W^*} A_U - (1 + L_W^* + L_U) L_U, \\ \dot{A}_U &\leq L_U - \gamma_U A_U \end{aligned} \quad (18)$$

The underlying differential system

$$\dot{L} = \gamma_U \mathcal{R}_0^U \frac{A}{A + A_W^*} A - (1 + L_W^* + L) L, \quad \dot{A} = L - \gamma_U A \quad (19)$$

is monotone, admits only bounded trajectories and possesses $(0, 0)$ as unique equilibrium (otherwise, a supplementary equilibrium would exist for the initial system (2)). Therefore [33, Theorem 3.1, p. 18], every trajectory of system (19) converges towards the unique equilibrium $(0, 0)$. The system

¹ The use of $>$ in this context is defined in the Notations, see Section I.

of differential inequalities (18) has nonnegative solutions that are at most equal to those of (19). One infers the 1st inequality of (12), and the proof of Theorem 4 is done. ■

V. NUMERICAL SIMULATIONS

Numerical simulations of the controlled system (3)-(8) have been achieved for the control laws designed in Theorems 3 and 4 (using the `stiff` option of the `ode` function of the free open-source software Scilab). The following numerical values, extracted from [1], have been adopted: $\gamma_U = 0.79365$, $\gamma_W = 0.99207$, $\mathcal{R}_0^U = 45$, $\mathcal{R}_0^W = 34.2$, so that $L_U^* = 44.0$, $A_U^* = 55.4$, $L_W^* = 33.2$, $A_W^* = 33.5$.

The initial state is systematically taken at the disease-free equilibrium $(L_U^*, A_U^*, 0, 0)$. For all simulations, observer initialization is done with quite conservative estimates: $(L_U^-(0), A_U^-(0), L_W^-(0), A_W^-(0)) = (0, 0, 0, 0)$ and $(L_U^+(0), A_U^+(0), L_W^+(0), A_W^+(0)) = (2L_U^*, 2A_U^*, 0.05L_W^*, 0.05A_W^*)$. For each type of release, noisy measurement is considered, with $y_- = 80\%y$, $y_+ = 120\%y$. The output gain C is taken as the example in Remark 1, while the observer gains $K_{\pm}(\cdot)$ are chosen as explained in Remark 2, with

$$\varepsilon = 10^{-5}, \quad M_- = M_+ = 0.1 \begin{pmatrix} -1 & -1 & 1 & 1 \\ -1 & -1 & 1 & 1 \end{pmatrix}^T.$$

In these conditions, all assumptions of Theorem 2 are fulfilled. The simulations show, as expected and in spite of imprecise initial state estimation, the convergence of the controlled system towards the complete infestation equilibrium $(0, 0, L_W^*, A_W^*)$, in dashed line in the two Figures.

a) *Release of adult mosquitos (Theorem 3):* The control $u := (u_L, u_A)$ is defined by taking equalities in the formulas in **(A)**. One chooses $k_U = 1.1(\mathcal{R}_0^U - 1)$ and $k = \gamma_W$. The control u_A is then linear², equal to the right-hand side of (13). As noticed after the statement of Theorem 3, only x_- is used for the control synthesis. The results are shown in Figure 1. The green curves represent the ‘true’ values (components of x), while the blue ones show the evolution of the components $L_U^+, A_U^+, L_W^-, A_W^-$ of x_- .

b) *Release of larvae (Theorem 4):* The control $u := (u_L, u_A)$ is defined here by taking equalities in **(L)**. Notice that the strict inequality in **(L)** is obtained thanks to a nonzero initialization of L_W^+ . The results are shown in Figure 2. The green curves represent the components of x , while the blue (resp. red) ones show the components of x_- (resp. x^+).

VI. CONCLUDING REMARKS

Two release strategies have been proposed, allowing to realize complete infestation of a population of *Aedes* mosquitoes by a population artificially infected by the bacterium *Wolbachia*, which reduces their ability as vectors of several important diseases. The efficiency of the approach has been demonstrated analytically and tested numerically. Its main force is to be expressed in general terms, giving rise to

² More precisely: $u_A = \left| \begin{pmatrix} k_U & k_U(\gamma_W - \gamma_U) & -1 \\ L_U^+ \\ A_U^+ \\ L_W^- \end{pmatrix} \right|_+$.

extensions to other models in the literature, e.g. those in [8], [9], [17], [10], [18], [19], [11], [12], [13], [16], due to their monotonicity³. Being based on monotone system properties, it is believed to be a good way to ensure robust behavior with respect to unmodeled dynamics and parameter uncertainties, with no need of precise knowledge of the boundary between the basins of attraction of the two locally asymptotically stable equilibria. Future works include the consideration of measurement delays. Also, further study is needed in order to reduce the peaking effect apparent with the 1st method. Last, extensions to non monotone systems should be considered, as well as more realistic impulsive periodic releases, much in the spirit of [35] in the context of Sterile Insect Techniques.

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³ One may check that the underlying entomological models are all monotone, assuming where appropriate complete cytoplasmic incompatibility, zero delay and possibly after merging of some compartments.