

Optimal control of *Aedes aegypti* mosquitoes by the sterile insect technique and insecticide

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ABSTRACT

We present a mathematical model to describe the dynamics of mosquito population when sterile male mosquitoes (produced by irradiation) are introduced as a biological control, besides the application of insecticide. In order to analyze the minimal effort to reduce the fertile female mosquitoes, we search for the optimal control considering the cost of insecticide application, the cost of the production of irradiated mosquitoes and their delivery as well as the social cost (proportional to the number of fertilized females mosquitoes). The optimal control is obtained by applying the Pontryagin's Maximum Principle.

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1. Introduction

Dengue disease is actually an important problem of public health in the tropical regions of the world. The infective agent is the *Dengue virus* of the family *Flaviviridae*. Four serotypes have been recognized, denoted by DEN-I, DEN-II, DEN-III, and DEN-IV. Infection for any Dengue serotype produces permanent immunity to it, but apparently only temporary cross immunity to other serotypes [1]. Therefore, individuals that live in dengue endemic areas can have the disease more than one time. The virus is transmitted to humans by the bite of *Aedes* female mosquitoes, being *Aedes aegypti* its principal transmissor [2].

Dengue infection by any of the four serotypes causes a spectrum of illness in humans, ranging from clinically inapparent, to severe and fatal hemorrhagic disease [1]. Due to the geographical expansion of the vector and virus [3], the incidence of dengue infection in all of its manifestations has been increasing in the last decades. In 2005, dengue was considered the more important viral vector borne disease. Its world distribution is compared to malaria, and it is estimated that more than 2.5 billion of persons live in transmission risk areas.

Since there is not vaccine to control dengue disease, all efforts are directed to avoid the proliferation of the mosquito population. The control mechanisms include

- (1) Chemical control of adult population by dichloro-diphenyl-trichloroethane (DDT) spraying, and ultra low volume (ULV) spraying.
- (2) Chemical control of larvae by larvicides.
- (3) Reduction of mosquito breeding sites by elimination of discarded tires, and litter, draining of unnecessary containers, etc.
- (4) Biological control by using parasites or/and predators of mosquitoes.
- (5) Genetic manipulation of mosquitoes to produce mosquitoes refractory to infection of transmission, or sterile insects.

The sterile insect technique (SIT) is a biological control in which the natural reproductive process of insects is disrupted by the use of mutagens such as gamma radiation thus rendering the insects sterile. These sterile insects are then released into the environment in very large numbers in order to mate with the native insects that are present in the environment. A native female that mates with a sterile male will produce eggs, but the eggs will not hatch (the same effect will occur for the reciprocal cross). If there is a sufficiently high number of sterile insects, most of the crosses are sterile, and as time goes on, the number of native insects decreases and

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the ratio of sterile to normal insects increases, thus driving the native population to extinction.

The SIT was first conceived by Knipling [4], and used successfully in 1958 in Florida to control Screwworm fly (*Cochliomya omnivorax*) [5,6]. Since then, the release of sterile insects have been used with varying success. Some examples are screwworm fly in USA, Mexico and Libya; Mediterranean Fruit Fly (*Ceratitidis capitata Wiedemann*) in USA and Mexico; Melon Fly (*Dacus cucurbitae Coquillett*) in Japan and Taiwan; Pink Bollworm (*Pectinophora gossypiella Saunders*) in USA; Tsetse Fly (*Glossina species*) in Tanzania, Zimbabwe and Upper Volta; Boll Weevil (*Anthonomus grandis Boheman*) in Southeastern USA; Mexican Fruit Fly (*Anastrepha ludens Loew*) in USA and Mexico; Gypsy Moth (*Lymantria dispar Linnaeus*) in USA and Canada [7].

Mathematical models have been done to assist the effectiveness of the SIT (see, e.g., [4,8–13]). Some of them contemplate combination of SIT with other control measures as pesticides [14], or release of parasitoids [15].

The goal of this paper is to use optimal control theory to evaluate the effectiveness of the application of both SIT and insecticide to mosquito population. We want to find the minimal effort necessary to reduce the fertile female mosquitoes considering the cost of insecticide application, the cost of the production of irradiated mosquitoes, and the social cost. By social cost we mean all the expenses related to the disease like infectives treatment, hospital care, and even eventual death. This work is a continuation of [16] where the authors formulated a model to analyze the application of the SIT for the control of *Aedes aegypti* mosquitoes.

2. The basic model

The basic model is taken from [16] where a system of nonlinear differential equations was formulated to assess the effectiveness of the SIT technique applied to mosquito population. In this section we present the model and a summary of the results.

We denote by A the population size of the immature phase of the insect (eggs, larvae and pupae) at time t . For the adult form we consider the following compartments: females before mating (singles), I ; mating fertilized females, F ; mating unfertilized females, U ; and male insects, M . The population size of sterile (irradiated or transgenic) insects at time t is denoted by M_T . The model is given by the following system of ODE:

$$\begin{aligned} A' &= \phi \left(1 - \frac{A}{C} \right) F - (\gamma + \mu_A) A \\ I' &= r\gamma A - \frac{\beta MI}{M + M_T} - \frac{\beta_T M_T I}{M + M_T} - \mu_I I \\ F' &= \frac{\beta MI}{M + M_T} - \mu_F F \\ M' &= (1 - r)\gamma A - \mu_M M \\ M_T' &= \alpha - \mu_T M_T, \end{aligned} \tag{1}$$

and the remaining decoupled equation for the mating unfertilized females

$$U' = \frac{\beta_T M_T I}{M + M_T} - \mu_U U.$$

In the equations above, $\mu_A, \mu_I, \mu_F, \mu_U, \mu_M$ and μ_T denote the mortality rates of the immature form, unmating females, mating fertilized females, mating unfertilized females, natural (or wild) males, and sterile male insects, respectively; ϕ is the oviposition rate per female mosquito which is proportional to female density, but it is also regulated by a carrying capacity effect, C , related to the amount of available nutrients and space.

The aquatic population becomes winged mosquitoes at a rate γ , and a proportion $1-r$ transforms in female, and $1-r$, in male.

A female mosquito mates once in its life, and oviposits its eggs in different places during its entire life [17]. We assume that the per capita mating rate of a unmating female with a natural male mosquito is given by $\frac{\beta M}{M + M_T}$. Since irradiated insects are placed artificially, and the effective mating rate could be diminished due to the sterilization, we assume that the per capita mating rate of a female with an irradiated male is given by $\frac{\beta_T M_T}{M + M_T}$, where $\beta_T = pq\beta$, and $0 \leq p, q \leq 1$. In some extend, the parameter p is related to the effectiveness of sterile male introduction regarded to the spatial distribution of female insects, and q can be thought of as physiological modifications induced by the sterilization technique.

Finally α is the rate at which sterile males are recluded and sprayed.

System (1) has a trivial equilibrium $P_2 = (0, 0, 0, 0, \frac{\alpha}{\mu_T})$ corresponding to the state where natural insects are absent, and there is only a constant population of sterile insects. The non-trivial steady states $(\bar{A}, \bar{I}, \bar{F}, \bar{M}, \frac{\alpha}{\mu_T})$ satisfy the following relations

$$\begin{aligned} \bar{I} &= \frac{r\gamma\bar{A} \left(\bar{M} + \frac{\alpha}{\mu_T} \right)}{(\mu_I + \beta)\bar{M} + (\mu_I + \beta_T)\frac{\alpha}{\mu_T}} \\ \bar{F} &= \frac{(\gamma + \mu_A)\bar{C}\bar{A}}{\phi(C - \bar{A})} \\ \bar{M} &= \frac{(1 - r)\gamma\bar{A}}{\mu_M}, \end{aligned} \tag{2}$$

where \bar{A} is a solution of the second degree equation

$$p(A) = aA^2 + bA + c = 0, \tag{3}$$

with coefficients

$$\begin{aligned} a &= \frac{1}{C} \frac{\phi r \gamma \beta}{(\gamma + \mu_A)(\beta + \mu_I)\mu_F} \\ b &= 1 - \frac{\phi r \gamma \beta}{(\gamma + \mu_A)(\beta + \mu_I)\mu_F} \\ c &= \frac{(\beta_T + \mu_I)\mu_M \alpha}{(\beta + \mu_I)(1 - r)\gamma \mu_T}. \end{aligned}$$

We define the average number of secondary female insects produced by a single female insect by

$$R = \frac{\phi r \gamma \beta}{(\mu_A + \gamma)(\beta + \mu_I)\mu_F}, \tag{4}$$

and the ratio of mated but not fertilized female insects with respect to the fertilized ones by

$$S = \frac{(\beta_T + \mu_I)\mu_M \alpha}{(\beta + \mu_I)(1 - r)\gamma C \mu_T}. \tag{5}$$

In [16] it is proved that under the conditions

$$R > 1 \tag{6}$$

and

$$S \leq \frac{(R - 1)^2}{4R} \equiv S^c, \tag{7}$$

system (1) has two positive equilibria P_{3_-} and P_{3_+} corresponding to \bar{A}_- and \bar{A}_+ given by

$$\bar{A}_- = \frac{(R - 1)}{2R} C \left[1 - \sqrt{1 - \frac{4RS}{(R - 1)^2}} \right] \tag{8}$$

and

$$\bar{A}_+ = \frac{(R - 1)}{2R} C \left[1 + \sqrt{1 - \frac{4RS}{(R - 1)^2}} \right]. \tag{9}$$

Notice that if equality holds in (7), P_{3-} and P_{3+} collapse to an equilibrium P_3 with $\bar{A} = \frac{(R-1)}{2R}C$, which provides the minimum threshold condition

$$R^* = (1 + 2S) \left[1 + \sqrt{1 - \frac{1}{(1 + 2S)^2}} \right] \geq 1 \tag{10}$$

for the existence of the non-trivial equilibria.

The above results show that for natural (or wild) mosquitoes to maintain in nature, condition $R > 1$ is necessary. However, in the presence of sterile individuals, this could not be a sufficient condition since a proportion of the females would not actually being fertilized. If S is sufficiently high ($S \geq S^*$), the next generation of wild mosquitoes would be lower than the actual one since a proportion of eggs would not hatch. Spraying sterile males for a sufficiently long period of time would drive the natural insect population to zero.

The stability properties of the equilibrium points are summarized in the following theorem.

Theorem 1. *The equilibrium $P_2 = (0, 0, 0, 0, \frac{\alpha}{\mu_T})$ of system (1) is always stable. When $R > 1$ and $\frac{(R-1)^2}{4RS} > 1$, the non-trivial equilibria, P_{3-} and P_{3+} , are feasible. In this case P_{3-} is always unstable and P_{3+} , stable.*

According to Theorem 1, for a fixed $R > 1$, if S is above $S^c = \frac{(R-1)^2}{4R}$ it is possible to control insects by sterile male release, independently of their initial population size.

Fig. 1 represents the bifurcation diagram with respect to R . In the diagram, the trivial equilibrium P_2 is represented by the R -axis. In [16] it is shown that the stability of this point is global for $0 \leq R < R^*$, and local for $R > R^*$, where R^* is given by Eq. (10). When $R = R^*$, the turning equilibrium point P_3 appears, and for $R > R^*$ and $\alpha > 0$, P_3 bifurcates to the non-trivial equilibrium points P_{3-} and P_{3+} , which are represented in the figure by the lower and upper branch of the parabola, respectively. We call R^* the threshold value since it separates the region where we have only sterile insects ($R < R^*$) from the region where natural and sterile mosquitoes coexist at two different levels ($R > R^*$). For $R > R^*$ the decreasing branch of the parabola separates two attracting regions containing one of the equilibrium points P_2 and P_{3+} . In other words, we have a hyper-surface generated by the coordinates of the equilibrium point P_{3-} , e.g., $f(\bar{A}, \bar{I}, \bar{F}, \bar{M}, \frac{\alpha}{\mu_T}) = 0$, such that one of the equilibrium points P_2 and P_{3+} is attractor depending on the relative position of the initial conditions supplied to the dynamical system (1) with respect to the hyper-surface.

It is interesting to notice that, from the ecological point of view, the introduction of sterile mosquitoes could create an Allee effect

in the natural mosquito population due to the difficulty of a female to find a fertile male in order to mate. This Allee effect either limits small population to a small area, or the population dies off.

3. The optimal control problem

In this section we formulate the optimal control problem applied to model (1). We want to minimize the insecticide cost, as well as the cost of production and release of sterile mosquitoes. For this end we consider as control variables:

1. The insecticide investment denoted by $u_1(t)$, and
2. The investment in production and release of sterile mosquitoes denoted by $u_2(t)$.

The control variable u_1 gives information about the quantity of insecticide that should be applied, meanwhile u_2 is related to the number of sterile mosquitoes, M_T , that should be released at time t .

Further, we want to minimize the number of fertilized females. For this end, we consider the following performance index

$$J[u_1, u_2] = \frac{1}{2} \int_0^T (c_1 u_1^2 + c_2 u_2^2 + c_3 F^2 - c_4 M_T^2) dt \tag{11}$$

where c_1, c_2 , and c_3 are the cost of insecticide application, cost of production and release of sterile mosquitoes, and social cost, respectively, and c_4 is the penalty.

Social cost depends on the number of dengue infections which are related directly with the number of mosquito bites. As other mosquito species, fertilized females of *A. aegypti* are the only ones that are hematophagous (that feed with blood), because they need human or animal blood to mature their eggs. For this reason, we assume that social cost is proportional to the density of fertilized female mosquitoes.

In the control problem, we assume fixed final time, and free dynamical variables at this time. Further, we assume a quadratic functional cost [18–20] since we believe that the performance index is a nonlinear function. The quadratic terms act as a penalization [21,22], amplifying the effects of great variations of the variables. Each quadratic term is multiplied by a coefficient, $c_i, i = 1, \dots, 4$, which establishes the relative importance of the term on dengue control cost. Notice that when we minimize the performance index, J , the sterile mosquito population is maximized. This is because we want that the insecticide u_1 does not reduce the population of released sterile males u_2 .

Mathematically, the optimal control problem is formulated as the minimization of the functional (11) subject to the system

$$\begin{aligned} A' &= \phi \left(1 - \frac{A}{C} \right) F - (\gamma + \mu_A) A, \\ I' &= r\gamma A - \frac{\beta M I}{M + M_T} - \frac{\beta_T M_T I}{M + M_T} - (\mu_I + u_1) I \\ F' &= \frac{\beta_M M I}{M + M_T} - (\mu_F + u_1) F \\ M' &= (1 - r)\gamma A - (\mu_M + u_1) M \\ M_T' &= u_2 - (\mu_T + u_1) M_T, \end{aligned} \tag{12}$$

where the initial conditions are the coordinates of the non-trivial equilibrium of system (1) letting $\alpha = 0$, which are

$$\begin{aligned} A(0) &= A_0 = \frac{C(R-1)}{R} \\ I(0) &= I_0 = \frac{r\gamma A_0}{(\mu_I + \beta)} \\ F(0) &= F_0 = \frac{(\gamma + \mu_A) C A_0}{\phi(C - A_0)} \end{aligned}$$

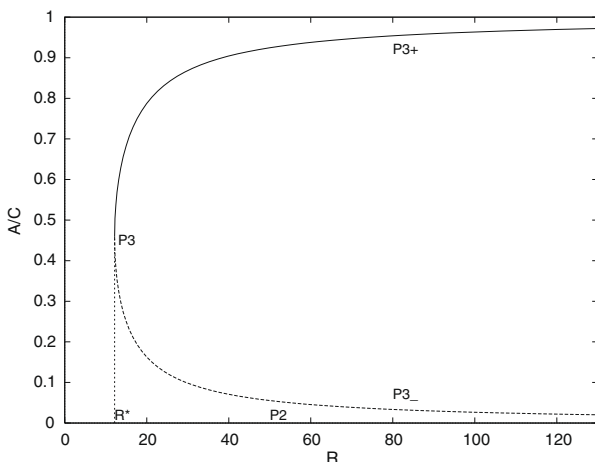


Fig. 1. Bifurcation diagram of system (1) with respect to R .

$$M(0) = M_0 = \frac{(1-r)\gamma A_0}{\mu_M}$$

$$M_T(0) = M_{T_0} = 0, \tag{13}$$

and the control variables u_1 , and u_2 are non-negatives. This scenario assumes that control mechanisms are introduced in a steady state of the mosquito population at time $t=0$.

Since one of our objectives is to control the introduction of sterile mosquitoes, M_T , the constant rate α in (1) is replaced by the control function u_2 . The insecticide control u_1 in (12) appears as an extra mortality only in the equations corresponding to the adult form of mosquitoes since it is assumed that insecticide is effective only in the adult stage and not in the aquatic phase.

3.1. Characterization of the optimal control problem

We use the Pontryaguin Maximum Principle [23] to determine the formulation of our optimal control u_1^* and u_2^* . To this end, we note that the Hamiltonian for our problem is given by

$$H = \frac{1}{2} [c_1 u_1^2 + c_2 u_2^2 + c_3 F^2 - c_4 M_T^2] + \lambda_1 \left[\phi \left(1 - \frac{A}{C} \right) F - (\gamma + \mu_A) A \right] + \lambda_2 \left[r\gamma A - \frac{\beta MI}{M + M_T} - \frac{\beta_T M_T I}{M + M_T} - (\mu_I + u_1) I \right] + \lambda_3 \left[\frac{\beta MI}{M + M_T} - (\mu_F + u_1) F \right] + \lambda_4 [(1-r)\gamma A - (\mu_M + u_1) M] + \lambda_5 [u_2 - (\mu_T + u_1) M_T]. \tag{14}$$

In (14), λ_j , $j = 1, \dots, 5$, are the adjoint variables; they determine the adjoint system which, together with the state system (12), gives the optimality system. We shall consider all possible non-negative values for the control variables, including the case $u_1 = u_2 = 0$.

Pontryaguin Maximum Principle [23] states that the unconstrained optimal variables u_1^* , and u_2^* satisfy

$$\frac{\partial H}{\partial u_1^*} = \frac{\partial H}{\partial u_2^*} = 0.$$

We find $\frac{\partial H}{\partial u_i^*}$ and solve for u_i^* , $i = 1, 2$, by setting the partial derivatives of H equal to zero. Thus, from

$$\frac{\partial H}{\partial u_1^*} = c_1 u_1^* - \lambda_2 I - \lambda_3 F - \lambda_4 M - \lambda_5 M_T = 0$$

$$\frac{\partial H}{\partial u_2^*} = c_2 u_2^* + \lambda_5 = 0,$$

we obtain

$$u_1^* = \frac{\lambda_2 I + \lambda_3 F + \lambda_4 M + \lambda_5 M_T}{c_1} \tag{15}$$

$$u_2^* = -\frac{\lambda_5}{c_2}.$$

The Pontryagin Maximum Principle establishes that the following equations

$$\frac{d\lambda}{dt} = -\frac{\partial H}{\partial x} \tag{16}$$

$$H(x(t), u^*(t), \lambda(t), t) \equiv \max_{u \in U} H(x(t), u(t), \lambda(t), t) \tag{17}$$

are necessary conditions that must be satisfied by the optimal control $u(t)$ and the state variable $x(t)$ [24]. System (16) is referred as the adjoint system. In our problem it becomes

$$\lambda_1' = -\frac{\partial H}{\partial A}, \lambda_2' = -\frac{\partial H}{\partial I}, \lambda_3' = -\frac{\partial H}{\partial F}, \lambda_4' = -\frac{\partial H}{\partial M}, \text{ and } \lambda_5' = -\frac{\partial H}{\partial M_T}.$$

Taking the partial derivatives of H in (14) and substituting them above we obtain

$$\lambda_1' = \left(\phi \frac{F}{C} + \gamma + \mu_A \right) \lambda_1 - r\gamma \lambda_2 - (1-r)\gamma \lambda_4$$

$$\lambda_2' = \left(\frac{\beta M}{M + M_T} + \frac{\beta_T M_T}{M + M_T} + \mu_I + u_1 \right) \lambda_2 - \frac{\beta M}{M + M_T} \lambda_3$$

$$\lambda_3' = -c_3 F - \phi \left(1 - \frac{A}{C} \right) \lambda_1 + (\mu_F + u_1) \lambda_3 \tag{18}$$

$$\lambda_4' = [(\beta - \beta_T) \lambda_2 - \beta \lambda_3] \frac{M_T I}{(M + M_T)^2} + (\mu_M + u_1) \lambda_4$$

$$\lambda_5' = c_4 M_T - [(\beta - \beta_T) \lambda_2 - \beta \lambda_3] \frac{MI}{(M + M_T)^2} + (\mu_T + u_1) \lambda_5.$$

Finally we analyze the transversality conditions for the adjoint variables. Since in our problem there are not terminal values for the state variables, these conditions are given at the final time T by

$$\lambda_i(T) = 0, \quad i = 1, \dots, 5. \tag{19}$$

3.2. The optimality system

The optimality system describes how the system behaves under the application of the controls that minimize J . It is obtained taking the state system (12), with the adjoint system (18), the optimal control u_1^* , and u_2^* (15), the initial conditions (13), and the transversality conditions (19), which gives:

$$A' = \phi \left(1 - \frac{A}{C} \right) F - (\gamma + \mu_A) A$$

$$I' = r\gamma A - \frac{\beta MI}{M + M_T} - \frac{\beta_T M_T I}{M + M_T} - (\mu_I + u_1) I$$

$$F' = \frac{\beta MI}{M + M_T} - (\mu_F + u_1) F$$

$$M' = (1-r)\gamma A - (\mu_M + u_1) M$$

$$M_T' = u_2 - (\mu_T + u_1) M_T$$

$$\lambda_1' = \left(\phi \frac{F}{C} + \gamma + \mu_A \right) \lambda_1 - r\gamma \lambda_2 - (1-r)\gamma \lambda_4$$

$$\lambda_2' = \left(\frac{\beta M}{M + M_T} + \frac{\beta_T M_T}{M + M_T} + \mu_I + u_1 \right) \lambda_2 - \frac{\beta M}{M + M_T} \lambda_3$$

$$\lambda_3' = -c_3 F - \phi \left(1 - \frac{A}{C} \right) \lambda_1 + (\mu_F + u_1) \lambda_3$$

$$\lambda_4' = [(\beta - \beta_T) \lambda_2 - \beta \lambda_3] \frac{M_T I}{(M + M_T)^2} + (\mu_M + u_1) \lambda_4$$

$$\lambda_5' = c_4 M_T - [(\beta - \beta_T) \lambda_2 - \beta \lambda_3] \frac{MI}{(M + M_T)^2} + (\mu_T + u_1) \lambda_5$$

$$u_1^* = \frac{\lambda_2 I + \lambda_3 F + \lambda_4 M + \lambda_5 M_T}{c_1}$$

$$u_2^* = -\frac{\lambda_5}{c_2}$$

$$A(0) = A_0 = \frac{C(R-1)}{2R}$$

$$I(0) = I_0 = \frac{r\gamma A_0}{(\mu_I + \beta)}$$

$$F(0) = F_0 = \frac{(\gamma + \mu_A) C A_0}{\phi(C - A_0)}$$

$$M(0) = M_0 = \frac{(1-r)\gamma A_0}{\mu_M}$$

$$M_T(0) = M_{T_0} = 0$$

$$\lambda_i(T) = 0, i = 1, \dots, 5. \tag{20}$$

4. Numerical results

In this section we discuss the method to solve numerically the optimality system (20), and we present the obtained results.

4.1. Methodology

The numerical method deals with a two-point boundary-value problem with separated boundary conditions at time $t = 0$ and $t = T$. In our simulations we use a period of $T = 120$ days. This value was chosen to represent the time (in days) at which the release strategy of mosquitoes is applied (around 4 months).

Since the optimality system (20) has fixed conditions at the final time for the adjoint variables, it turns out that it is difficult to solve numerically. One method is to use a finite difference approach. In [19] the authors used the software package COLDAE [25] that solves boundary-value differential and differential-algebraic equations evaluated at Gaussian points. Here, we used the software package *bvp4c* [26] of **Matlab**® that solves ODE systems with two boundary conditions.

An important factor to consider is that the optimality system is in general a nonlinear problem, hence it needs an initial approximation to begin the Newton’s method. It is well known that the convergence of the Newton’s method depends critically on the closeness of the initial approximation to the solution. For our optimality system (20) is practically impossible to guess an initial approximation that guarantees this convergence. One way to solve the problem is to use the method of analytic continuation [27,28]. This is a standard and powerful technique used to solve nonlinear two boundary value problems.

The idea behind the analytical continuation is to transform the problem in a one-parameterized family of related problems. For the optimality system (20), we use the time T as a parameter. When $T = 120$, we recover the original problem. For $T = 1$ the problem is easily solvable, and the solution can be used as an initial approximation for the nearby problem $T = 1 + \Delta T$, with ΔT suffi-

ciently small. This process is continued until the desired problem is solved. The successive values of the parameter chosen are known as a *homotopy path*.

4.2. Results

Our aim is to understand the effect of two conflicting mechanisms of control, named, insecticide application and the release of sterilized male mosquitoes. For the epidemiological and demographic parameters in all simulations, we use the values given in [29] (see Table 1); the initial conditions for the state variables are given by $A_0 = 2.95, I_0 = 0.24, F_0 = 4.99, M_0 = 2.97$ and $M_{T_0} = 0$.

We will determine the optimal strategies obtained for different set of values of the costs defined in the functional (11). As a reference we use the values $c_i = 1, i = 1, \dots, 4$. For this case, the value of $J = 0.6625$. Figs. 2a and 2b illustrate the optimal trajectories u_1^* and u_2^* , showing, respectively, chair (bottom of the chair is almost a constant plateau) and bell (top of bell is almost constant plateau) shapes. Interestingly, Fig. 2 shows that the maximum insecticide induced mortality rate (a measure of insecticide application) is ten times higher than the maximum sterile insects release rate. Another remarking feature is that a great quantity of insecticide must be applied during the first days, while the sterile insects are releasing at almost constant rate.

Figs. 3a–3e present the optimal trajectories of the different stages of the mosquito population. As was expected, the population of the irradiated mosquitoes follows the same pattern than the control u_2 . On the other hand, we observe that the curves corresponding to the aquatic phase, the mating fertilized females, the male insects have similar shape to the inverted graph of the irradiated mosquito investment u_2 , and the trajectory of the unmated females is similar to the inverted trajectory of the insecticide investment u_1 .

Let us define the reduction in the variables (percentage) by $D_X = (X_0 - X^*)100/X_0$, where X_0 stands for the initial values of the state variables A, I, F and M , and X^* is the quasi-constant pla-

Table 1
Parameter values for the optimality system (20). Units are days⁻¹ except for r . The values for $\phi, \mu_A, \mu_I, \mu_F, \mu_U, \mu_M$, and γ are taken from [29] for an average temperature of 25 °C. For irradiated mosquitoes we assume a higher mortality rate, and a reduction of around 27% in the mating rate with respect to the wild population.

ϕ	μ_A	μ_I	μ_F	μ_U	μ_M	μ_T	γ	r	β	β_T	C
6.353	0.0583	0.0337	0.0337	0.0337	0.06	0.07	0.121	0.5	0.7	0.5	3

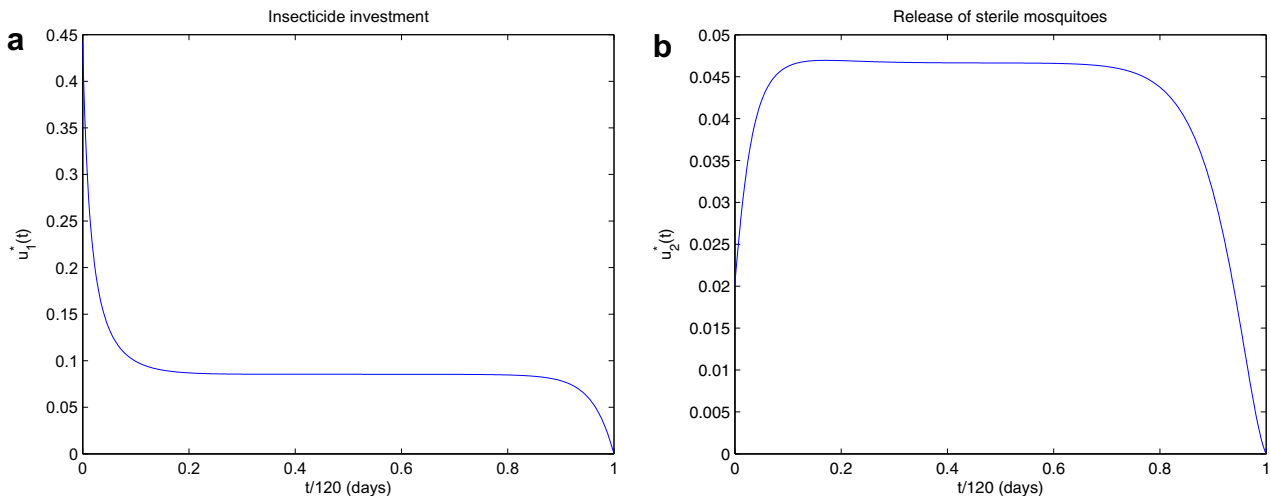


Fig. 2. Optimal control trajectories for insecticide application (a), and release of sterile male mosquitoes (b) when all the costs are proportionally equal ($c_1 = c_2 = c_3 = c_4 = 1$). Both figures are taken as standard case.

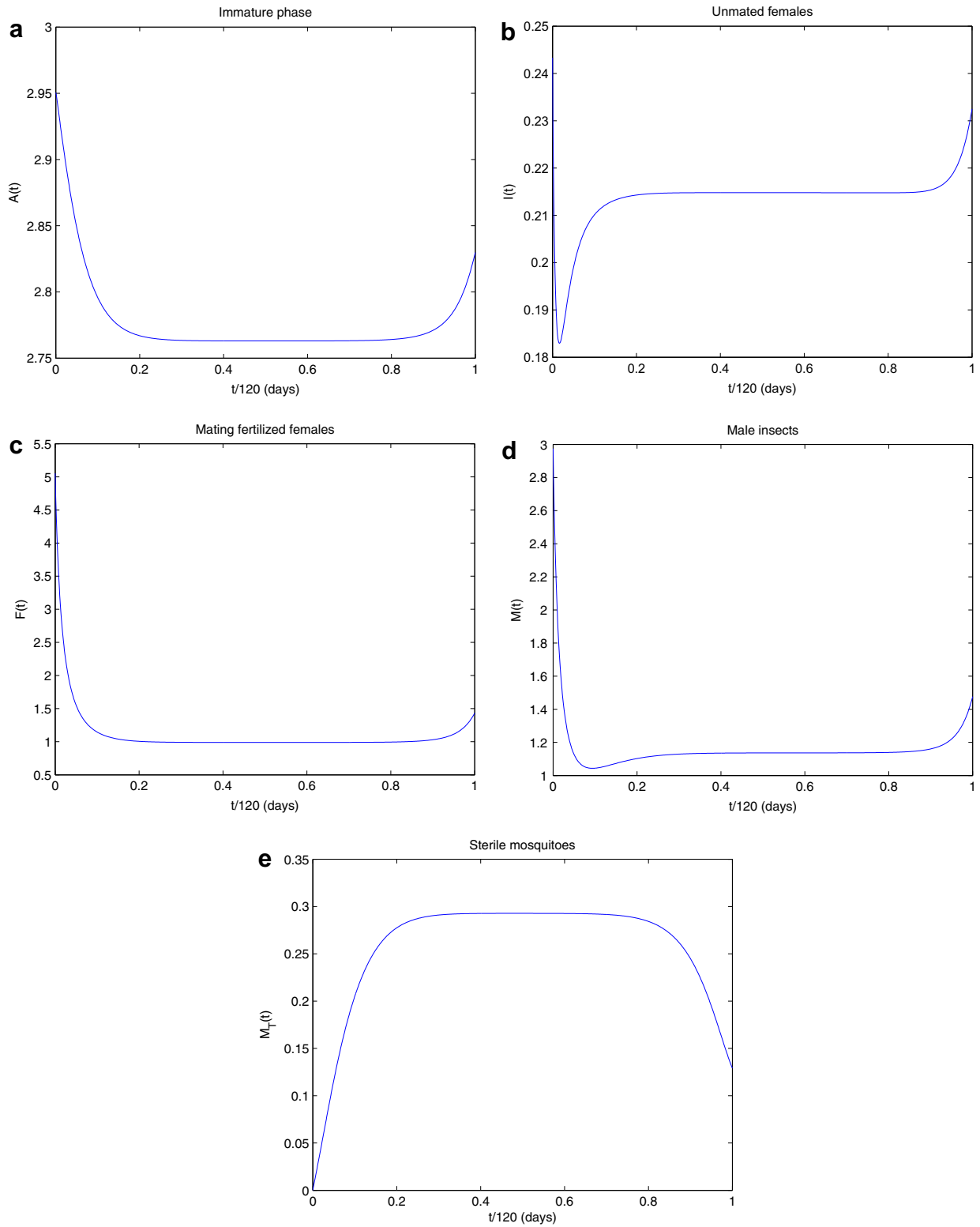


Fig. 3. Optimal trajectories for the state variables corresponding to the optimal control shown in Fig. 2: aquatic phase (a), unmated female mosquitoes (b), fertilized female mosquitoes (c), wild male mosquitoes (d), and sterile male mosquitoes (e).

Table 2

Relative decrease, D_x , for the stages comprising the mosquito population under equal costs. For T, u_1^* and u_2^* we show the values of the plateau. The maximum value of u_1^* from which it decreases is 0.43. Units are omitted.

c_1	c_2	c_3	c_4	J	D_A	D_I	D_F	D_M	T^*	u_1^*	u_2^*
1	1	1	1	0.6625	6.10	11.89	79.96	61.28	0.29	0.09	0.0455

teau reached by these variables. In Table 2 we summarize the findings of the reference case.

Actually, the production and release of sterile insects are more expensive than insecticide application, so we increase in ten times the cost of the biological control ($c_2 = 10$) maintaining the other costs unchanged. In this case, $J = 0.7796$. In Figs. 4a and 4b we show the optimal controls u_1^* , and u_2^* . We observe that insecticide application is practically unchanged, but the insect release decreases ten times from the reference control. The behavior of the mosquito population in the different stages follow the pattern of the optimal controls u_1^* , and u_2^* as in the standard case. The natural

mosquito population classes increase slightly, and the sterile mosquito population decreases in ten times.

In Table 3 we summarize the findings of the high biological cost. The reduction in the number of sterile insects decrease A and F , but increase I and M in comparison with the reference case. This is a result of spraying slightly higher insecticide (u_1^*), but 10 times less delivery of sterile male insects (u_2^*). Reduced number of sterile insects tends to decrease proportionally the number of mated female mosquitoes. The case above only diminish the cost of the control measures, but do not take into account the reduction of the population size of fertilized females, which is related

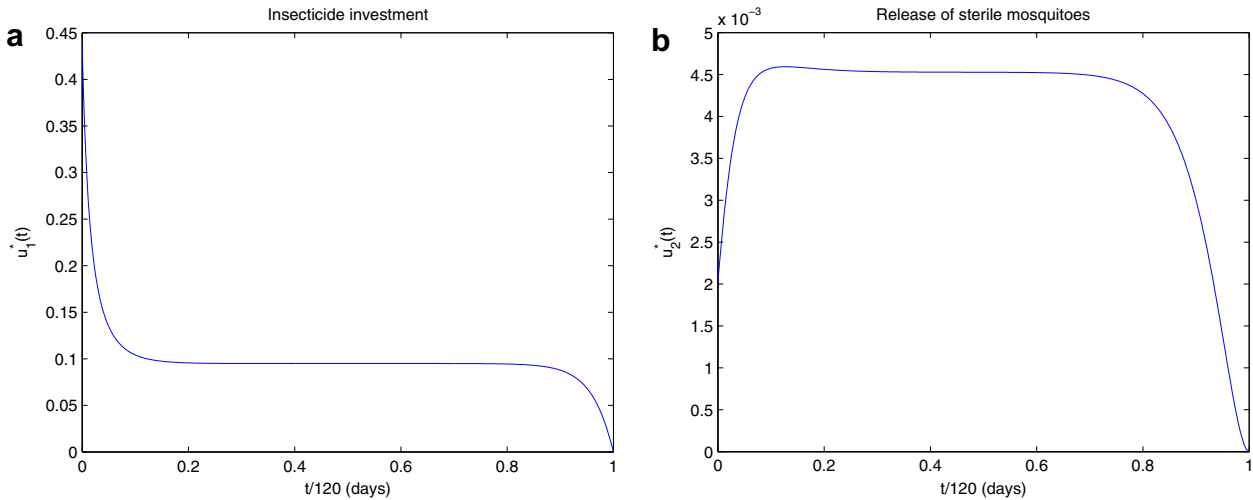


Fig. 4. Optimal control trajectories for insecticide application (a), and release of sterile male mosquitoes (b). In this case the cost of biological control is 10 times higher than the other costs ($c_2 = 10$, and $c_1 = c_3 = c_4 = 1$). The release of sterile mosquitoes is around seven times lower than in the standard case.

Table 3
Relative decrease, D_X , in percentage with respect to the reference case of the stages comprising the mosquito population when c_2 is incremented 10 times. For T, u_1^* and u_2^* we show the values of the plateau. The maximum value of u_1^* from which it decreases is 0.43. Units are omitted.

c_1	c_2	c_3	c_4	J	D_A	D_I	D_F	D_M	T^*	u_1^{**}	u_2^{**}
1	10	1	1	0.7796	5.76	16.39	77.96	63.64	0.027	0.1	0.00451

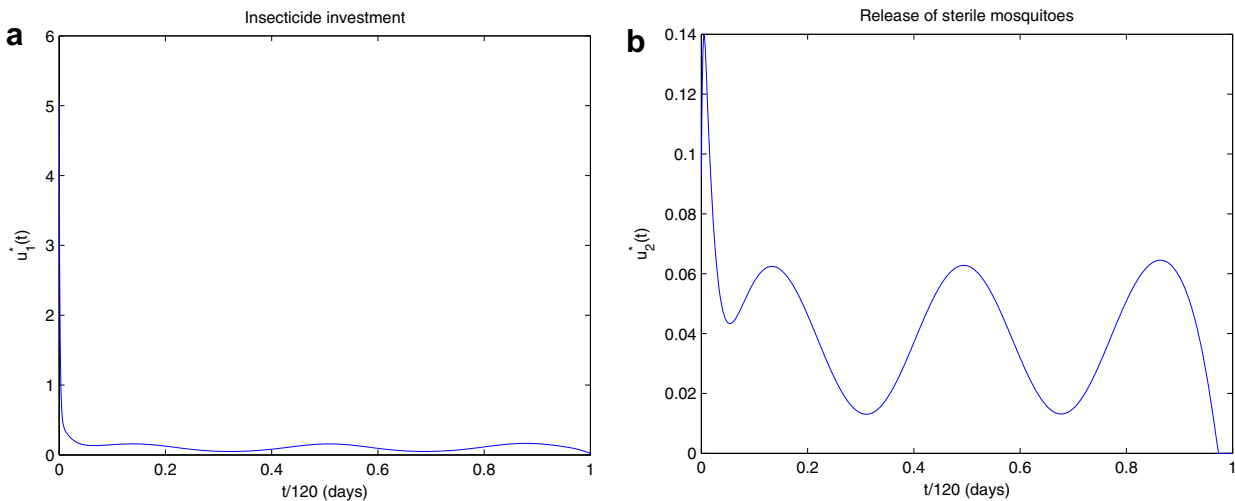


Fig. 5. Optimal control trajectories for insecticide application (a), and release of sterile male mosquitoes (b). Social cost is 100 times higher than the other costs ($c_3 = 100$, and $c_1 = c_2 = c_4 = 1$). In order to decrease the fertilized female mosquitoes, both release of sterile mosquitoes, and insecticide application must be higher (10 times the application of insecticide, and three times the release of sterile insects, in comparison to the standard case). Chemical and biological controls must be applied earlier.

to the social cost. Dengue infection is in general a mild disease, however in some cases it can evolved to dengue haemorrhagic fever. This form of the disease can be fatal if it is not adequately treated, and for this reason, the social cost (hospitalization, treatment) gets very high. We analyze two cases including the social cost.

First, we put $c_3 = 100$ maintaining the other costs as in the reference case. Here, the cost is $J = 1.9427$. It is interesting to notice that huge amount of insecticide must be applied very early, and similar behavior is observed respecting to the release of sterile mosquitoes (see Figs. 5a and 5b). Interestingly, we observe an oscillatory pattern in both controls. The curve corresponding to

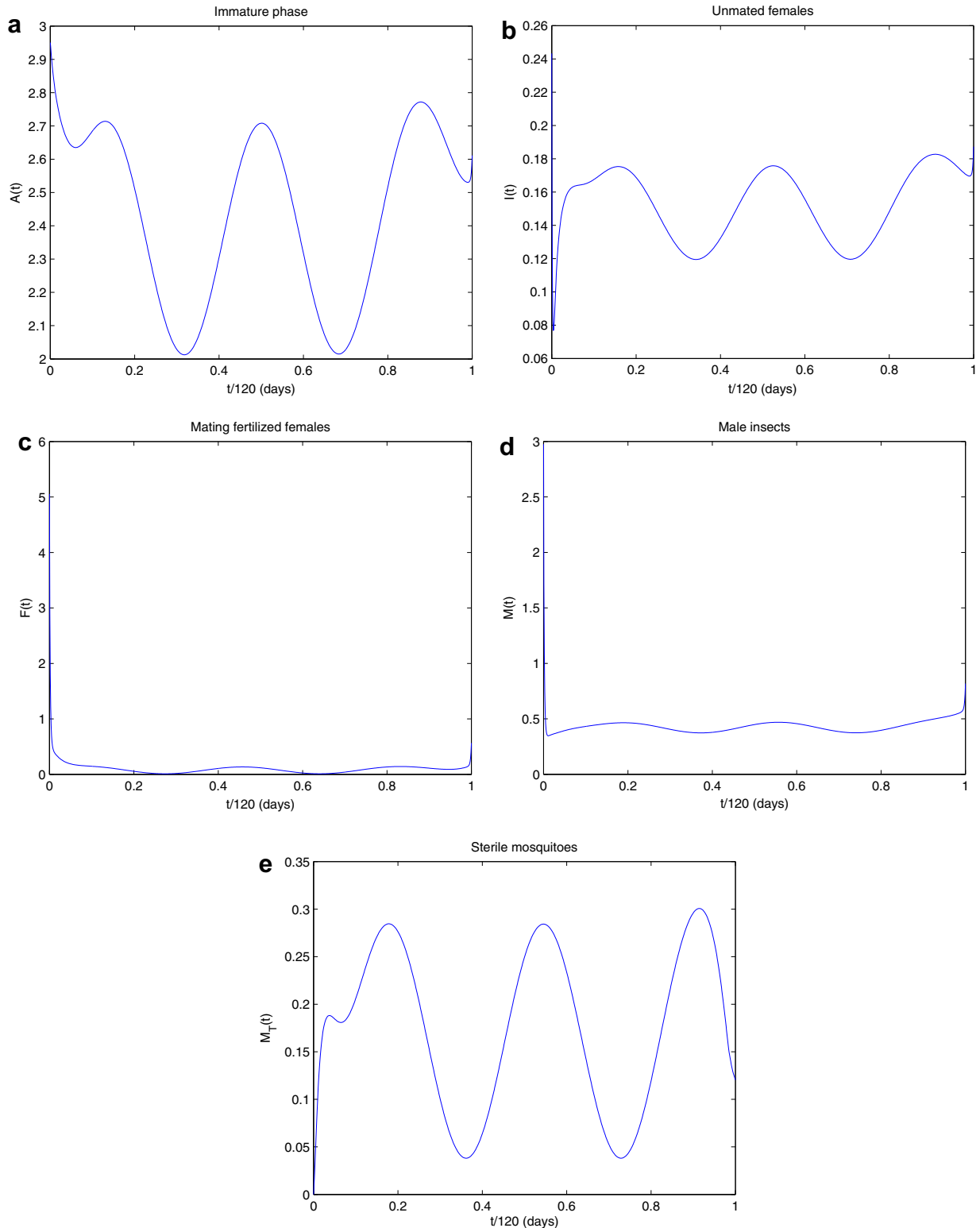


Fig. 6. Optimal trajectories for the state variables corresponding to the optimal control shown in Fig. 5: aquatic phase (a), unmated female mosquitoes (b), fertilized female mosquitoes (c), wild male mosquitoes (d), and sterile male mosquitoes (e).

the mating fertilized female and male mosquitoes are very similar to the insecticide investment graph, meanwhile the behavior of the rest of the mosquito stages is similar to the release of sterile mosquitoes curve (Figs. 6a–6e).

In Table 4 we summarize the findings of the high social cost. We observe a great reduction in the state variables A , F , I and M in comparison with the reference case. In order to avoid dengue cases, high number of fertilized female mosquitoes must be eliminated.

Table 4
Relative decrease, D_X , with respect to the reference case of the stages comprising the mosquito population when c_3 is incremented 100 times. All variables oscillate, for this reason the plateau is the average value around which they oscillate. With respect to T , u_1^* and u_2^* , we show the values of the plateau. The maximum value of u_1^* from which it decreases is 5.5. Units are omitted.

c_1	c_2	c_3	c_4	J	D_A	D_I	D_F	D_M	T^*	u_1^{**}	u_2^{**}
1	1	100	1	1.9427	18.64	38.52	96.99	84.85	0.17	0.1	0.038

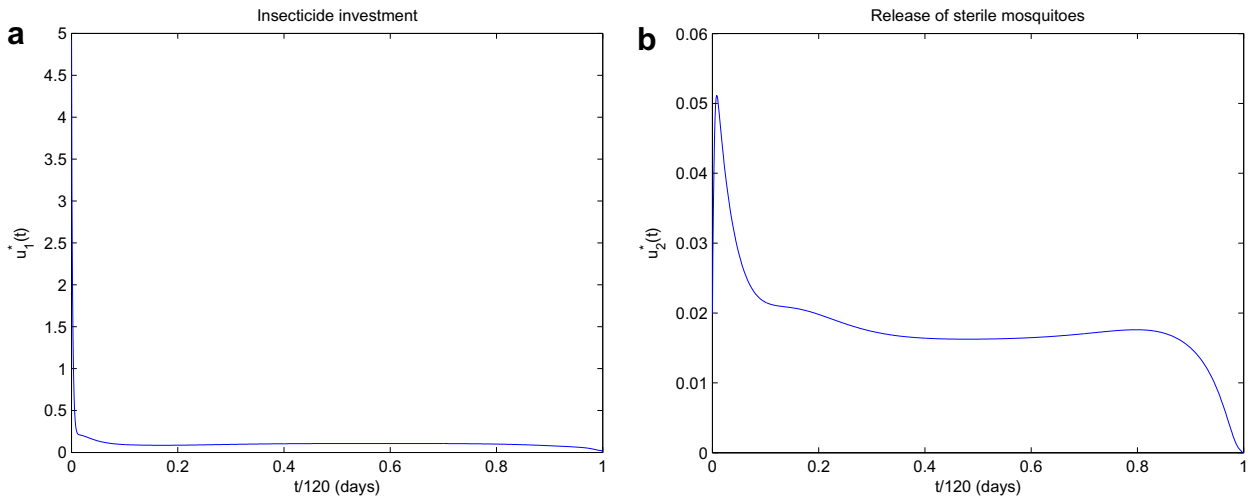


Fig. 7. Optimal control trajectories for insecticide application (a), and release of sterile male mosquitoes (b). Social cost is 100 times higher, and biological control, 10 times, than the other costs ($c_2 = 10, c_3 = 100$, and $c_1 = c_4 = 1$). The increasing cost of the biological control resulted in 2.5 times lower releasing of sterile mosquitoes at the beginning (b).

Table 5
Relative decrease, D_X , with respect to the reference case of the stages comprising the mosquito population when c_2 and c_3 are incremented 10, and 100 times, respectively. All variables oscillate, but less pronounced than the previous case. With respect to T , u_1^* and u_2^* , we show the values of plateau. The maximum value of u_1^* from which it decreases is 5.0. There is an acute increase in u_2^* up to 0.05, following by a chair shape instead of a bell shape. Units are omitted.

c_1	c_2	c_3	c_4	J	D_A	D_I	D_F	D_M	T^*	u_1^{**}	u_2^{**}
1	10	100	1	1.9427	18.64	27.46	99.80	84.85	0.124	0.1	0.018

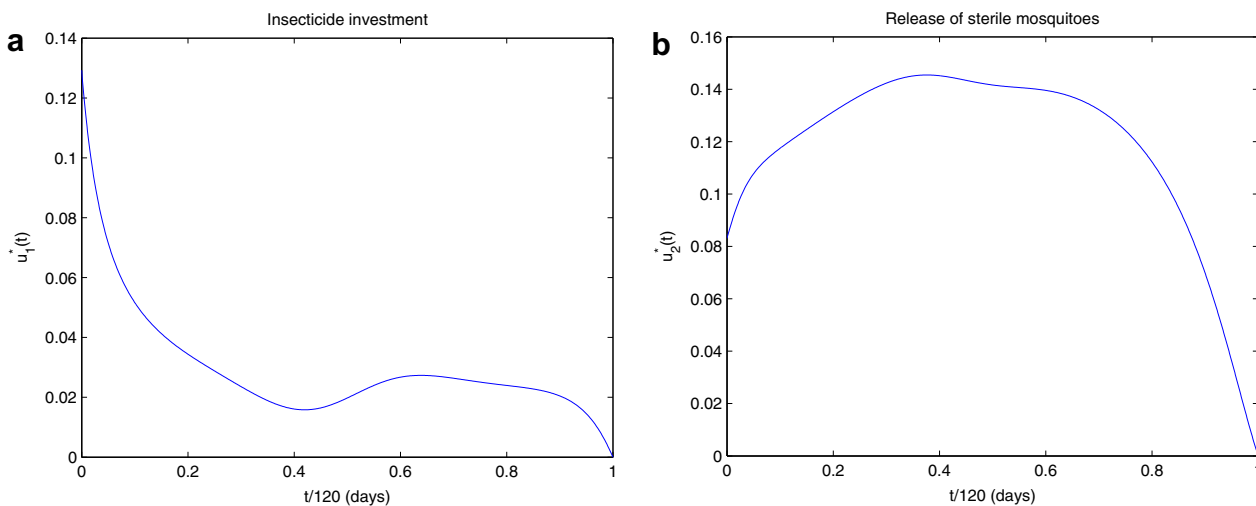


Fig. 8. Optimal control trajectories for insecticide application (a), and release of sterile male mosquitoes (b). In this case the cost of insecticide is 10 times higher than the other costs ($c_1 = 10$, and $c_2 = c_3 = c_4 = 1$). Here, the release of sterile mosquitoes is around three times higher, and insecticide application is around three times lower in comparison to the standard case.

This is a result of higher insecticide application (the peak is thirteen times bigger), and high delivery of sterile male insects (with respect to reference case, three times higher). The number of female mosquitoes is drastically reduced.

Let us discuss the oscillatory behavior of this case analyzing the immature female population trajectory, which has a rapid decay

followed by an increase up to a plateau, and increases at final times. In the previous cases, the smallest values of I did not attain 0.18, but I decreases below 0.08 when social cost is increasing. This means that a very strong perturbation is introduced to the dynamical system producing damped oscillations with high amplitudes in the trajectories returning to the new equilibrium value [30].

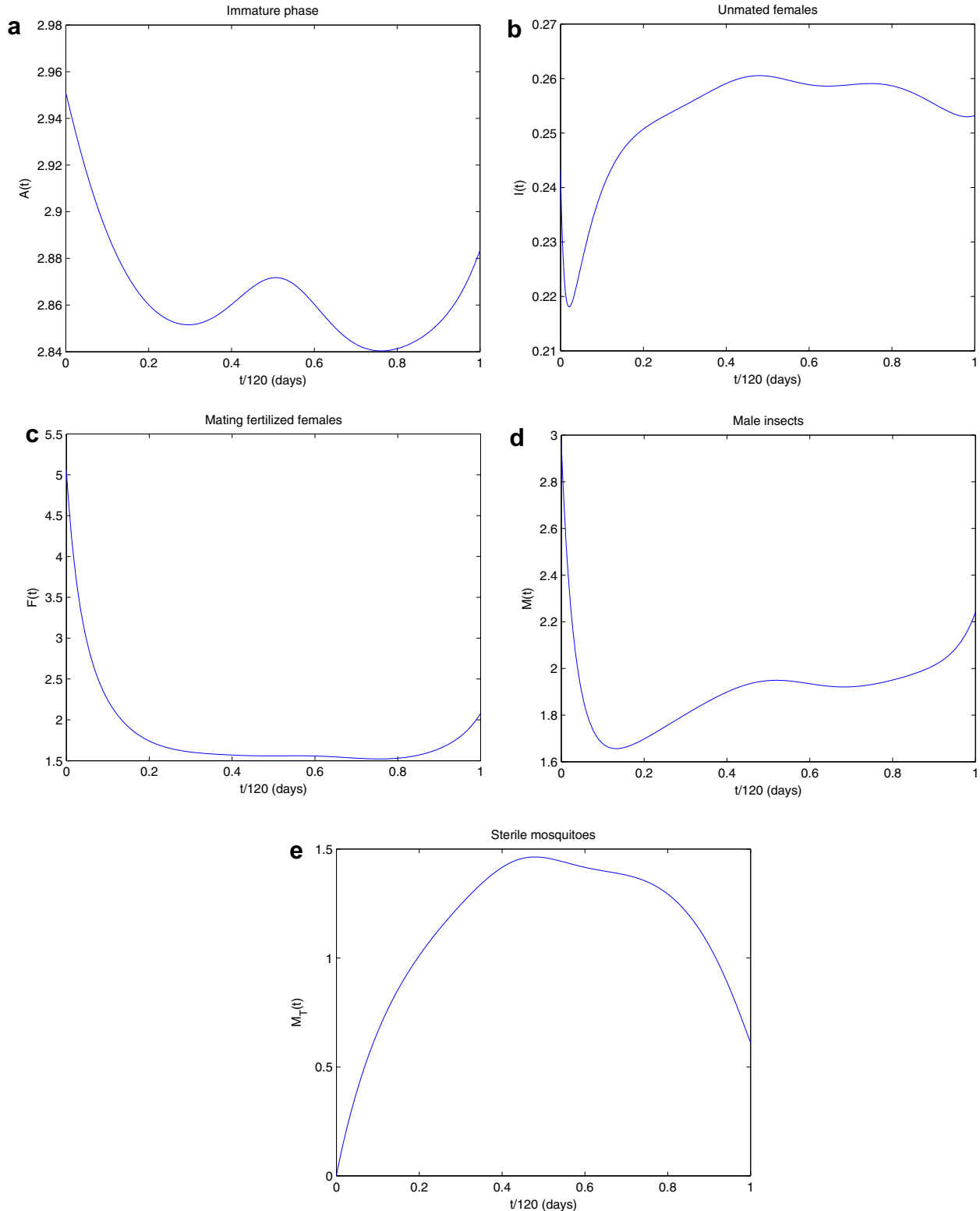


Fig. 9. Optimal trajectories for the state variables corresponding to the optimal control shown in Fig. 8: aquatic phase (a), unmated female mosquitoes (b), fertilized female mosquitoes (c), wild male mosquitoes (d), and sterile male mosquitoes (e).

Table 6

Relative decrease, D_x , with respect to the reference case of the stages comprising the mosquito population when c_1 is incremented 10 times. All variables oscillate, for this reason the plateau is the average value around which they oscillate. With respect to T , u_1^* and u_2^* , we show the values of plateau. The maximum value of u_1^* from which it decreases is 0.13. The oscillations are less regular, and chair and bell shapes are not maintained. Units are omitted.

c_1	c_2	c_3	c_4	J	D_A	D_I	D_F	D_M	T^*	u_1^{**}	u_2^{**}
10	1	1	1	1.5646	3.05	-5.74	68.94	35.35	1.4	0.021	0.138

We present a second case taking into account the current situation, namely, sterile release is more expensive than the available insecticide, and high incidence of the disease requires elevated social cost. We let $c_2 = 10$, and $c_3 = 100$. In Figs. 7a and 7b we illustrate the optimal trajectories u_1^* and u_2^* associated to this situation. In this case, $J = 1.5646$. From Fig. 7a, it is seen that insecticide spraying must be concentrated at the beginning in a very high amount (ten times the reference case) as in the previous case. Increasing in ten times the biological control resulted in proportionally small decreasing in release of mosquitoes at the beginning, but presenting a small peak at the beginning in comparison of the control case. Note that the controls present oscillatory behavior with very small amplitudes comparing with the previous case. The same behavior occurs for the subpopulations of mosquitoes. The reason behind it is that combined intervention produces lower disturbance on the dynamical system than the previous case (note that u_1^* is quite the same, but the first peak of u_2^* is three times lower than the previous case) [30].

In Table 5 we summarize the findings for high social and biological control costs. We observe a reduction in A , F , I and M in comparison with the reference case. The results are similar to the previous case, where A and M are equally reduced, while I is less reduced, and the reduction in F increases a little bit. In this case the insecticide application is slightly diminished, while the delivery of the sterile insects is reduced (in the first peak) three times in comparison with the previous case. In order to avoid dengue cases, high number of fertilized female mosquitoes must be eliminated. This is a result of higher insecticide application (the peak is thirteen times higher) and high delivery of sterile male insects (with respect to reference case, three times higher). It is interesting to notice that the delivery of less number of sterile insects increases the reduction in the fertilized female mosquitoes, and that the cost of this last case is lower than the previous case. The oscillatory behavior can explain this outcome. Hence, if a strong intervention does not eliminate the infection, the amplitudes of the damped oscillations are very intense, which is the reason to assure an intervention that drives the transmission of the infection to eradication [30].

It is observing an increasing trend of resistant mosquitoes to insecticide, which led to the development of new products. Since the cost of research, and development of new insecticides is very expensive, we increase the chemical application cost in ten times ($c_1 = 10$), maintaining all other costs the same as the reference. In this case, $J = 1.0589$. Figs. 8a and 8b illustrate the optimal trajectories u_1^* , and u_2^* , and Figs. 9a–9d the optimal trajectories of the different stages of the mosquito population. We observe that the slope of u_1^* is less stiff than the reference one, and has a minimum followed by a small bump. Although the cost of insecticide increases ten times, the maximum application decreases around three times. With respect to the mosquito releasing, we observe that it increases about three times the reference amount. Further, the decreasing phase begins earlier and the slope is softer. Since insecticide is expensive, more mosquitoes have to be released at the beginning. The quantity of sterile mosquitoes diminishes as time goes on, and the insecticide application has to be increased. This explains the ending bump in Fig. 8a.

Figs. 9a–9e illustrate the behavior of the mosquito population for the last case ($c_1 = 10$). We observe that the aquatic phase de-

creases monotonically, has a small peak, and increases during the last time of the control. The unmated female mosquitoes after an abrupt decrease, increase to a maximum and then decrease monotonically again. On the other hand, the fertilized females F decrease abruptly because the high initial release of sterile males. The natural male population initially follows a similar pattern than unmated females but it grows during the last time of the control. The population of sterile male mosquitoes follows the same pattern of the control u_2^* .

In Table 6 we summarize the findings of the high cost of insecticide application. The stages A and M decreased half with respect to the reference case, but F decreases moderately. However, the amount of I increases with respect to I_0 when a control is introduced. This case presents the lowest insecticide application (u_1^*), but the largest delivery of sterile male insects (u_2^*). Note that the aquatic phase is practically unchanged, and the wild male population decreases in a minor quantity in comparison with the initial value M_0 (observe that D_M is the lowest among all cases). As a result, the unmated female population grows above the initial value, because the intervention changed the new equilibrium. However, the fertilized female mosquitoes are reasonably decreased (in comparison with F_0 , and also the lowest reduction) due to high amount of sterile insects released in the environment.

The cost, J , in the two cases where social cost was considered is higher than the cost in the other cases. This is explained by the increment of the efforts to reduce the fertilized female mosquitoes. For this reason, social cost is a very important factor that should be considered in control strategies, because its incorporation drives to the decreasing in the female mosquito population size.

5. Discussion

We developed an optimal control model to assess the effectivity of two conflicting mosquito control measures. One of them is chemical control which kills both natural and sterile mosquitoes; the other is a biological control consisting in the release of sterile insects. The dynamical model was formulated in [16].

One of the side effects of the chemical control is that it affects ecosystem killing another insects, besides the development of mosquito resistance to it. There is not residual effect and the efficacy is very low, contrarily to the larvicide which has longer residual effect and higher efficacy. On the other side, the biological control is a clean ecological control, but to be effective, a higher proportion of sterile mosquitoes relative to the natural mosquitoes should be released [16]. Additionally, the sterile mosquitoes must be able to find the randomly distributed breeding sites where female mosquitoes emerged [31].

In this paper we analyzed the optimal control using the functional J in terms of quadratic forms. Minimizing the cost we obtained the optimal controls u_1^* and u_2^* where F was minimized and M_T maximized. Additionally, we let the variables to be free at the final time. Then, we compared the dynamical trajectories under optimal controls, in order to assess the effects of relative costs c_1 , c_2 , c_3 , and c_4 .

Possible control scenarios were assessed adjusting the control parameters. We defined a reference scenario in order to compare the different control strategies. First, we studied the effect of the

sterile insect release cost, and for this end, we increased this cost 10 times. Further, the social cost was increased 100 times, and then we analyzed the case when the sterile insect release increases 10 times, and the social cost, one hundred times. Finally, we analyzed what happens if the insecticide cost increases 10 times.

One interesting result is that minimizing only the cost of the control measures without considering social cost could lead to incorrect strategies to minimize the occurrence of the disease. For this reason, social cost should be considered in the control strategies.

When an intervention is introduced in a population at endemic equilibrium, oscillations can result depending on the strength of intervention, even if the overall incidence of infection is always lower than the endemic situation. The main trouble is the huge number of infected individuals resulting in the next peak of epidemics (the inter epidemic period is large [30]), which is much more pronounced under a strong intervention that not attain the eradication condition. In general, there are limited resources (eg, the number of beds in hospitals, specialized physicians and nursery) leading to poor health care, and treatable haemorrhagic fever can result in death. Hence, interventions that avoid large oscillations must be chosen.

All the cases shown in this paper did not achieve the eradication of dengue disease. Hence, the implementation of all optimal controls analyzed in this paper is doomed to failure the task of eliminating dengue transmission. However, optimal control as mathematical results at least showed the relative amount of insecticide and release of sterile insects must be introduced at different costs. We can deal with optimal control problem by introducing a strong constraint, that is, letting to the state variables assume fixed values at the final time (should be fixed or not). By constraining the values of the variables at the final time with the coordinates of the small non-trivial equilibrium P_{3-} , in such a way that the final values are moved to the attracting region of the trivial equilibrium point, then the dengue disease can be controlled. This situation illustrates the optimal control forecasted mathematically that is biologically acceptable as feasible implementation in order to cease the dengue epidemics, which will be analyzed in a future paper.

The main conclusion based on the results furnished by all the strategies is that high application of insecticide is needed at the beginning of the control, with an exponential decay. Furthermore, the release of insects in general follows a bell shape distribution with an abrupt increasing and decreasing at the extremes, and a plateau at the middle, except in the case when social cost is increasing one hundred times. In a further work we will analyze constant application of insecticide restricted to the first few days followed by a constant release of sterile insects for the remaining days. The reason behind this is that the application of discontinuous control strategies by the health authorities are more feasible than the optimal control u_1^* and u_2^* which vary continuously with time.

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