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Research Article

Optimization of the *Aedes aegypti* Control Strategies for Integrated Vector Management

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We formulate an infinite-time quadratic functional minimization problem of *Aedes aegypti* mosquito population. Three techniques of mosquito population management, chemical insecticide control, sterile insect technique control, and environmental carrying capacity reduction, are combined in order to obtain the most sustainable strategy to reduce mosquito population and consequently dengue disease. The solution of the optimization control problem is based on the ideas of the Dynamic Programming and Lyapunov Stability using State-Dependent Riccati Equation (SDRE) control method. Different scenarios are analyzed combining three mentioned population management efforts in order to assess the most sustainable policy to reduce the mosquito population.

1. Introduction

According to World Health Organization, dengue is reported to be the most rapidly spreading mosquito-borne disease in the world [1]. Recent estimates are that 50 million dengue infections occur each year, with 2.5 billion people at risk of infection in dengue endemic countries. *Aedes aegypti* is a domesticated urban mosquito and is the vector responsible for the transmission of some infectious diseases. The most common of them is dengue disease-virus infection caused by four distinct but related single-strand RNA viruses of the family Flaviviridae. Each of them causes a different type of clinical manifestation of dengue disease, varying from classic form to severe dengue shock syndrome and the fatal hemorrhagic dengue form.

Integrated vector management (IVM) is a strategy which aims to achieve a maximum impact on vector borne diseases like dengue. The emphasis of IVM is on examining and analyzing the local situation, making decisions at decentralized levels, and utilizing the appropriate mosquito control tools [1]. One of the features of IVM is the use of a range of interventions, often in combination and simultaneously, that work together to reduce dengue transmission. For dengue control, there are three main categories of intervention: biological control, the use of chemicals to kill the adult and immature mosquito stages, and the physical (mechanical) control, eliminating possible breeding sites.

The biological control includes the well-known sterile insect technique (SIT). The SIT is a biological control, firstly presented by Knipling [2], and was used in 1958 to control Screwworm fly (*Cochliomyia hominivorax* [3, 4]). SIT control is a technique in which natural male insects are exposed to radiations that eliminate their ability to fertilize eggs. The sterile males are released in the environment to mate with natural female population. Once irradiated, the sperms of sterile male mosquitoes fertilize the eggs of female mosquitoes producing unviable eggs, which do not hatch and disrupt the natural reproductive process of the population.

Ultra low volume (ULV) method consists of aerial sprays of insecticide for adult mosquitoes control. Chemical insecticides are sprayed using portable or truck-mounted machines in order to kill adult insects. Although studies have been shown that space spraying alone is relatively ineffective as a routine control strategy [5], it should be reserved for use only during epidemics.

Aedes aegypti mosquitoes lay their eggs in containers such as bottles, tires, fountains, barrels, and pots. By removing these habitats, mosquitoes have fewer opportunities to lay eggs. This strategy is called mechanical control. The mechanical control must be done both by public health officials and by residents in affected areas [1].

Mathematical modeling of mosquito population in order to assist SIT can be found in [6]. In [7] an optimal control of the *A. aegypti* population problem was formulated in terms of Pontryagin Maximum Principle, where a quadratic functional was minimized in finite time interval. It is known that in many cases the application of the Pontryagin Maximum Principle does not guarantee the long time stability of the controlled system.

In this paper we formulate an infinite-time quadratic functional minimization problem of *A. aegypti* mosquito population. The solution of this problem is based on the ideas of the Dynamic Programming and Lyapunov Stability using State-Dependent Riccati Equation (SDRE) control method [8, 9]. The reduction in the mosquito population is achieved by applying three control mechanisms: chemical insecticides control, biological control by release of the sterilized male insects, and mechanical control based on the reduction of the breeding sites.

2. Population Dynamics Model

The mosquito population dynamics model, proposed in [6], represents the interaction among four different stages of the natural mosquito population, and a sterile male mosquito group artificially was introduced into the environment as a control strategy.

The population size of the immature phase of the insect (eggs, larvae and pupae) is considered as one compartment denoted by A. The natural adult or mature insects are divided into three compartments, which are denoted as I-unmated female population (before copulation), F-fertilized female adult population (after copulation with natural male mosquito), and M-natural male population.

The remaining two compartments are S-sterile male population and U-females mated with sterile males resulting in unviable insects with dynamics uncoupled from the rest of the population. The dynamics of the population described above is represented by the following mathematical model:

$$\begin{aligned}\frac{dA}{dt} &= \phi\left(1-\frac{A}{C}\right)F-(\gamma+\mu_A)A,\\ \frac{dI}{dt} &= r\gamma A-\frac{\beta MI}{M+S}-\frac{\beta_S SI}{M+S}-\mu_I I,\\ \frac{dF}{dt} &= \frac{\beta MI}{M+S}-\mu_F F,\\ \frac{dM}{dt} &= (1-r)\gamma A-\mu_M M,\\ \frac{dS}{dt} &= \alpha-\mu_S S,\end{aligned} \tag{1}$$

plus one equation uncoupled from the rest

$$\frac{dU}{dt} = \frac{\beta_S SI}{M+S}-\mu_U U. \tag{2}$$

In (1) the mortality rates of aquatic phase, immature female adults, fertilized female adults, male adults, sterile male adults, and unmated female adults are represented by μ_A, μ_I, μ_F, μ_M, μ_S, and μ_u, respectively.

An adult female mosquito mates only once during its lifespan and lays eggs in different places every three days (gonadotrophic cycle) during entire life. Therefore, the aquatic population growth is regulated by the parameter ϕ, which represents the oviposition rate per female mosquito and depends on the environmental carrying capacity C. The term $\phi(1-A/C)$ is the per capita oviposition rate. The aquatic population becomes winged adult mosquitoes at rate γ. The female portion of these winged adults is represented by coefficient r, while the male portion is represented by coefficient $(1-r)$. Unmated female mosquitoes I transform into fertilized female F or fertilized but unviable female U mosquitoes only after mating a natural male or a sterile male, respectively. It is assumed that the probability of the female I and natural male M encounter is given by $M/(M+S)$. Therefore the per capita mating rate is given by $\beta M/(M+S)$, where β represents the intrinsic mating rate of natural mosquitoes. For sterile male, this intrinsic rate could be diminished by physiological modification of the sterilization technique. So another β_s is considered and the per capita mating rate of female I and sterile male is given by $\beta_S SI/(M+S)$. The rate α represents the artificial release of the sterile male population S in the environment.

The dynamics of system (1) was considered in [6]. According to Esteva and Yang [6] the trivial equilibrium point $P_0=(0,0,0,0,0)$ of system (1) without SIT control is stable if $R=\phi r\gamma\beta/(\mu_A+\gamma)(\mu_I+\beta)\mu_F<1$; that is, in the absence of sterile insects ($\alpha=0$), the condition for existence of natural insects is $R>1$. In affected areas the last inequality is satisfied, and an application of IVM is necessary.

In next section, the integrated vector management of the mosquito population is formulated as an optimal control problem.

3. Formulation of the Optimal Control Problem of *Aedes aegypti* Mosquitoes

Now, it is possible to formulate a control problem where the main goal is to minimize the fertile female mosquito population, and, consequently, all other mosquito populations are reduced by the action of three different control techniques: mechanical, chemical (insecticide spraying), and biological (sterile insect introduction).

The mechanical control is related to educational campaigns, and it is essential to remove water from domestic recipients, eliminating possible breeding sites (such as bottles, tires, fountains, barrels, and pots). This control decreases the environmental carrying capacity C in the initial time of the educational campaign, and it can be considered constant for some periods of time.

Let the insecticide control effort be denoted by u_1, and it affects only adult phase of mosquito population. The sterile male insects release is represented by u_2. Then the control model is given by

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

Table 1: Parameter values (units are days^{-1}, except for r and C).

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

$$\frac{dI}{dt} = r\gamma A - \frac{\beta MI}{M+S} - \frac{\beta_S SI}{M+S} - (\mu_I + u_1) I,$$
$$\frac{dF}{dt} = \frac{\beta MI}{M+S} - (\mu_F + u_1) F,$$
$$\frac{dM}{dt} = (1-r)\gamma A - (\mu_M + u_1) M,$$
$$\frac{dS}{dt} = u_2 - (\mu_S + u_1) S. \quad (3)$$

For this system, the functional to be minimized can be represented as

$$J = \frac{1}{2}\int_0^\infty \left[q_1 {x_1}^2 + q_2 {x_2}^2 + q_3 {x_3}^2 + q_4 {x_4}^2 + q_5 {x_5}^2 + r_1 {u_1}^2 + r_2 {u_2}^2\right] dt, \quad (4)$$

where q_1, q_2, q_3, q_4, and q_5 represent the cost of control effort to minimize specific population compartment. The parameters r_1 and r_2 are the cost of insecticide application and cost of production and release of sterile mosquitoes, respectively. We assume a quadratic functional cost [7, 8] since we believe that the performance index is a nonlinear function. The quadratic terms act as a penalization [9, 10], amplifying the effects of great variations of the variables. Each quadratic term is multiplied by a coefficient, which establishes the relative importance of the term on dengue control cost.

The optimization problem of the control of the *Aedes aegypti* mosquito population by the sterile insect technique and insecticide can be formulated as determination of the strategy u which leads nonlinear system (3) from a given initial to a final state:

$$x(\infty) = 0, \quad (5)$$

minimizing cost functional (4) and satisfying constraints:

$$0 \le u_1 \le u_{\text{mas}}, \quad 0 \le u_{\text{mas}} \le 1. \quad (6)$$

The formulated control problem can be solved by State-Dependent Riccati Equation (SDRE) method [11, 12]. SDRE approach is explained in more detail in the Appendix.

Defining the vectors x and u as

$$x = [A \;\; I \;\; F \;\; M \;\; S]^T,$$
$$u = [u_1 \;\; u_2]^T, \quad (7)$$

this results in the following system:

$$\dot{x} = A(x)\, x + B(x)\, u, \quad (8)$$

where

$$A(x) = \begin{bmatrix} -\gamma - \mu_A & 0 & \phi\left(1 - \frac{x_1}{C}\right) & 0 & 0 \\ r\gamma & -\mu_I & 0 & -\frac{\beta x_2}{x_4 + x_5} & -\frac{\beta_s x_2}{x_4 + x_5} \\ 0 & \frac{\beta_s x_4}{x_4 + x_5} & -\mu_F & 0 & 0 \\ (1-r)\gamma & 0 & 0 & -\mu_M & 0 \\ 0 & 0 & 0 & 0 & -\mu_S \end{bmatrix}, \quad (9)$$

$$B(x) = \begin{bmatrix} 0 & 0 \\ -x_2 & 0 \\ -x_3 & 0 \\ -x_4 & 0 \\ -x_5 & 1 \end{bmatrix}.$$

According to SDRE method the control u was determined by

$$u = -R^{-1} B^T P(x)\, x, \quad (10)$$

where a matrix P is a solution of the following State-Dependent Riccati Equation:

$$P(x) A(x) + A^T(x) P(x) - P(x) B(x) R^{-1}(x) B^T(x) P(x) + Q(x) = 0. \quad (11)$$

4. Numerical Simulation Results

For the solution of the control problem and attainment of control u determined by (10), it is necessary to solve State-Dependent Riccati Equation (11). For this purpose the MATLAB software intrinsic *lqr* function was used. Once obtaining control u, system (5) is solved as initial value problem using numeric, fourth-order Runge-Kutta integrator in MATLAB.

The parameter values of system (5) are shown in Table 1. The values for ϕ, μ_A, μ_I, μ_M, and γ are taken from [7].

The numerical simulations showed that SIT control alone cannot be a sustainable control strategy due to the lack of effectiveness in reducing mosquito population and high costs. In the same manner, the application of insecticide spraying alone cannot be seen as such an alternative because of its high ecological toxicity and mainly because it demands every day application at, almost, the maximum level of insecticide, which is obviously difficult for many reasons (weather conditions, restricted access of houses, lack of personal, and machinery).

Figures 1 and 2 present a scenario where both chemical (insecticide) and biological (sterile male insect release) controls are considered. The environmental carrying capacity has the original value, $C = 3$, as in scenario 1.

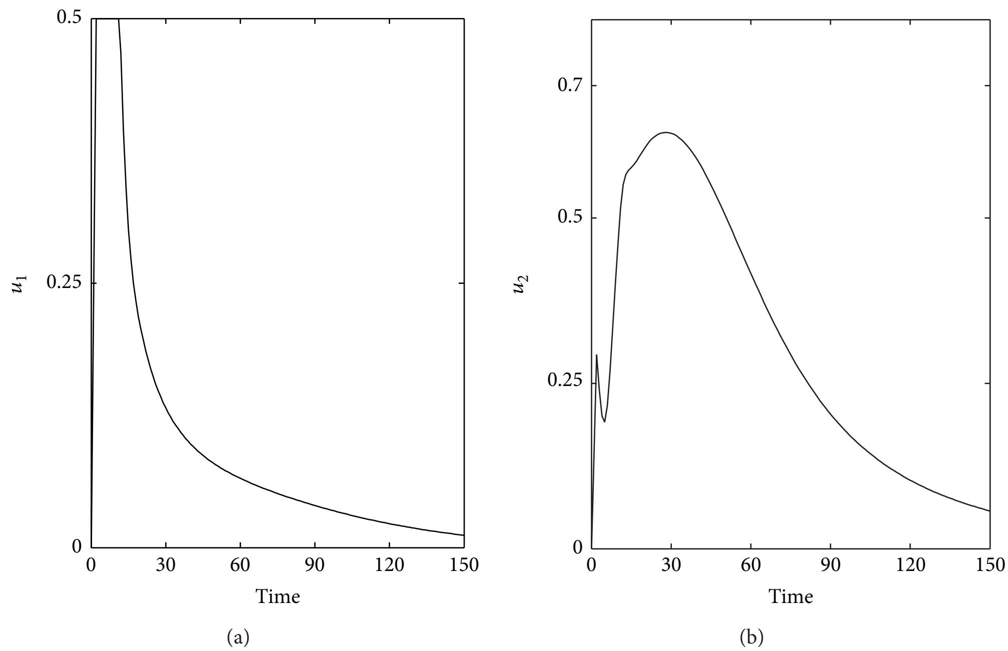

FIGURE 1: Insecticide control (a) and SIT control (b).

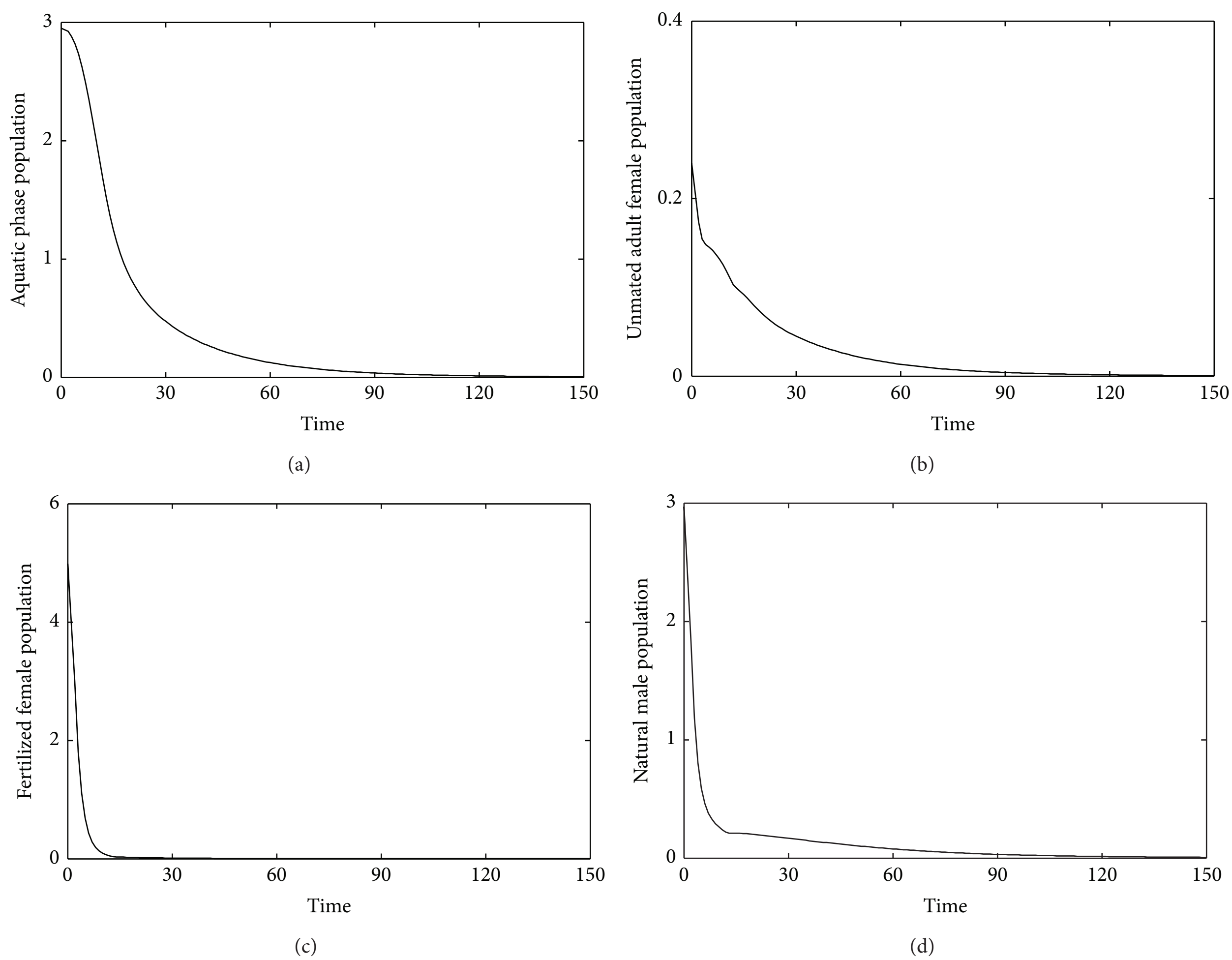

FIGURE 2: Aquatic population (a), adult immature female population (b), adult female fertilized population (c), and natural male population (d).

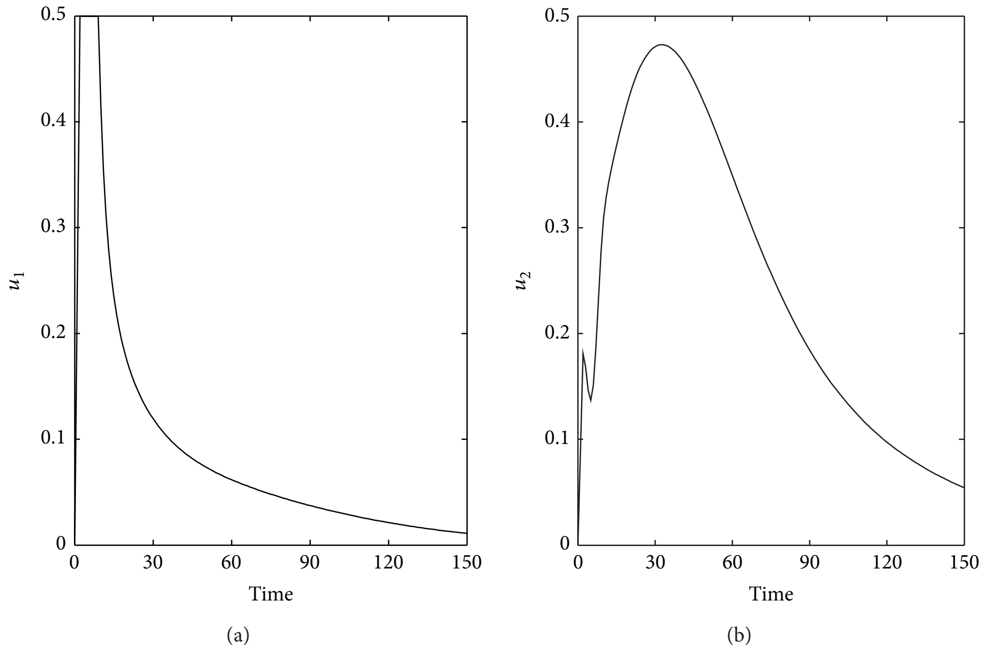

Figure 3: Insecticide control (a) and SIT control (b).

As it is seen from Figure 1, the control u_1 grows to its limit at the beginning of the period, acting at its maximum for approximately 10 days, and then asymptotically decreases. The total effort of u_1 control is 14.91. The u_2 control increases when u_1 starts to decrease, forming the bell shaped pattern. The total cost of this control is 46.24.

All four compartments of the mosquito population asymptotically tend to zero (Figure 2). The aquatic population and the unmated female population decrease more slowly than fertilized female and natural male population. It means that a practically similar investment in SIT control (compared to previous scenario) plus a little more investment in insecticide reduced significantly the mosquito population.

Next scenario illustrates the combination of insecticide control, SIT control, and reduction of the environmental carrying capacity to $C = 1.5$ (Figures 3 and 4). This mainly affects aquatic phase and unmated female population, reducing them more efficiently than in previous scenario (Figures 4(a) and 4(b)). The sum of efforts of the insecticide control and SIT control are 13.51 and 36.9, respectively (Figure 3). These costs are lower than in previous scenario pointing out that the combination of three types of mosquito population management increases the efficacy of mosquito population control and reduces its costs.

5. Discussion and Conclusion

This paper considers optimization control problem regarding *Aedes aegypti* that combines three techniques of mosquito population management, chemical insecticide control, sterile insect technique control, and environmental carrying capacity reduction, in order to obtain the most sustainable strategy to reduce mosquito population and consequent dengue disease reduction.

When one seeks a control mechanism or a strategy that combines different but sometimes antagonistic mechanisms aiming at the mosquito population control, some criteria should be considered and some concerns arise. First of them is to find a control strategy that significantly and immediately reduces the adult mosquito population in order to reduce the disease propagation. Second concern is the use of the minimum chemical insecticide spraying due to its toxicity. And the last concern is to find a strategy that can be feasible, or easily employable by the government, which implies minimization of costs.

In general, optimal control problems are addressed in specific situations, for instance, when public policy authorities have limited budget or when one type of controls is dangerous to public health (as insecticide, which presents another inconvenience of generating resistant strains). Discussions are presented bearing these features in mind.

The numerical simulations in this paper showed that SIT control alone and the application of insecticide spraying alone cannot be sustainable control strategies due to many reasons noted in Section 4.

The combination of SIT control and insecticide spraying is an alternative to a sustainable mosquito population control. The numerical simulation of this scenario showed that all four compartments of natural population are minimized (Figure 2). With respect to the optimal control, the insecticide application is active during only few days (which is attractive in terms of implementation) and the SIT control is also optimized.

Scenario, presented in Figures 3 and 4, reflects the combination of three kinds of effort in controlling the mosquito population: the insecticide control, the SIT control, and reduction of environmental carrying capacity. All the population compartments are minimized in the first week

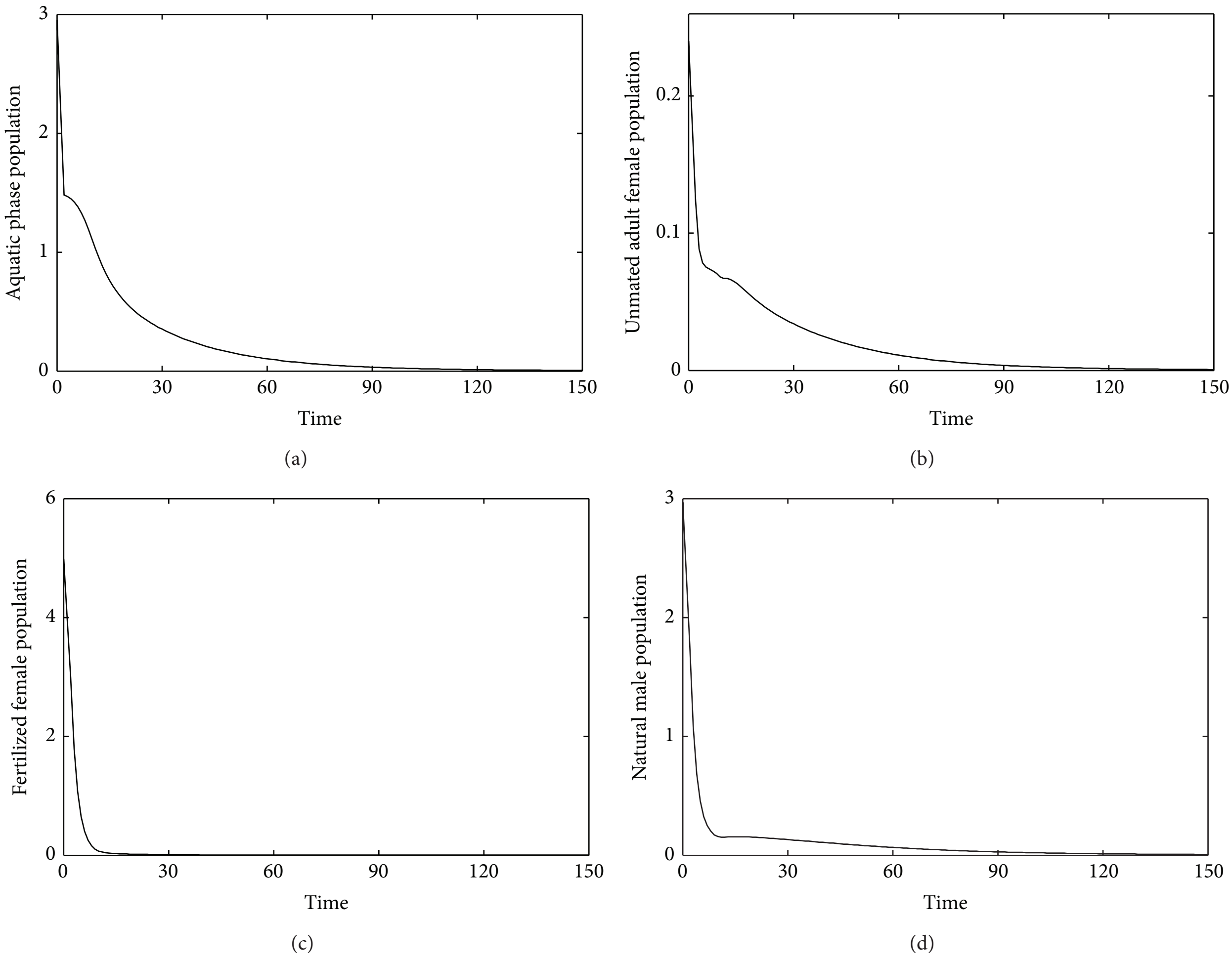

FIGURE 4: Aquatic phase population (a), immature female population (b), fertilized female population (c), and normal male population (d).

and the cost of insecticide and SIT controls is lower than in all previous scenarios. This strategy can be seen as the ideal control strategy of mosquito population in this optimization problem.

In the case of presence of antagonistic control mechanism such as the combined release of sterile male insects and the application of the insecticide, optimal control problem provides management strategies for both interventions. The considered scenarios show that insecticide application must take place in early times with the maximum amount, but should be soon decreased. Meanwhile, sterile insect must be released in small amounts at the early times when insecticide is applied (as the insecticide also kills sterile insects) and must increase while insecticide application decreases. Then the release of sterile insects should decrease with the reduction in total mosquito population.

Appendix

SDRE Nonlinear Control Method

We consider the nonlinear dynamical system given by

$$\dot{x} = f(x) + B(x)u, \quad f(0) = 0, \tag{A.1}$$

where $x \in R^n$ denotes the state, $u \in R^m$ denotes the control, and $f(x) : R^n \to R^n$ and $B(x) : R^n \to R^{n\times m}$ are differentiable in all arguments.

Our goal is to determine the optimal control u that drives system (A.1) from an initial state to 0 minimizing the following functional:

$$J[u] = \int_0^\infty \left[q(x) + u^T Ru\right] dt \tag{A.2}$$

for $q(y)$ continuously differentiable and positive definite. The desired solution is a state-feedback control law. Applying a standard dynamic programming argument, the above optimal control problem reduces to the Hamilton-Jacobi-Bellman (HJB) partial differential equation [13]:

$$\min_{u\in U}\left(\frac{dS}{dt} + w\right) = \left(\frac{dS}{dt} + w\right)_{u=u^o} = 0, \tag{A.3}$$

where U is a set of control functions, u^o are the optimal functions, $w = q(x) + u^T Ru$, and S (commonly referred to as the *value function*) specifies the minimum cost in shifting from the current state $x(t)$; that is,

$$S(x(t)) = \min_{u\in U}\int_t^\infty \left[q(x) + u^T Ru\right] dt. \tag{A.4}$$

The optimal control u is given by

$$u = -R^{-1}B(x)^T \operatorname{grad} S, \tag{A.5}$$

where

$$\operatorname{grad} S = \begin{bmatrix} \frac{\partial S}{\partial x_1} & \frac{\partial S}{\partial x_2} & \cdots & \frac{\partial S}{\partial x_n} \end{bmatrix} \tag{A.6}$$

and the function S is the solution of the Hamilton-Jacobi-Bellman (HJB) partial differential equation (A.3). Generally, HJB equation (A.3) is extremely difficult to solve.

In particular case, $f(x) = Ax$, $q(x) = x^TQx$, and $B(x) = B$ (matrices A, B, Q, and R are constant), problem (A.1)–(A.5) is called Linear Quadratic Regulator (LQR) technique, and the HJB equation becomes the following Riccati Equation:

$$PA + A^TP - PBR^{-1}B^TP + Q = 0. \tag{A.7}$$

The LQR control law is given by

$$u = -R^{-1}B^TPx, \tag{A.8}$$

where a matrix P is a solution of Riccati Equation (A.7).

The SDRE approach can be regarded as an extension of the LQR. It produces a suboptimal nonlinear controller. This is because of the approximations required in parametrization of the nonlinear system, as well as using a Riccati Equation to approximate the solution to the optimal control problem rather than solving the corresponding Hamilton-Jacobi equation [12].

Instead of using a linear model, the SDRE starts with the following nonlinear model [12]:

$$\dot{x} = f(x) + B(x)u, \quad f(0) = 0. \tag{A.9}$$

Problem (A.1)-(A.2) can now be formulated as a minimization of the following functional:

$$J[u] = \int_0^\infty \left[x^TQ(x)x + u^TRu\right] dt. \tag{A.10}$$

According to [12], the solution of problem (A.9)-(A.10) is equivalent to solving associated Hamilton-Jacobi equation (A.3). However, because solving the Hamilton-Jacobi-Bellman equation is very difficult, the HJB equation is approximated using a State-Dependent Riccati Equation:

$$\begin{aligned} &P(x)A(x) + A^T(x)P(x) \\ &\quad - P(x)B(x)R^{-1}(x)B^T(x)P(x) + Q(x) = 0. \end{aligned} \tag{A.11}$$

This makes the problem feasible, although it leads to a suboptimal controller.

The control law in this problem, like the LQR, is also a state-feedback law:

$$u = -R^{-1}B^TP(x)x \tag{A.12}$$

which depends on the solution to the State-Dependent Riccati Equation.

This can be seen by rewriting system (A.9) as

$$\dot{x} = f(x) + B(x)u, \quad f(0) = 0, \tag{A.13}$$

where $f(x) = A(x)x$. This is known as the State-Dependent Coefficient form. Note that the matrices $A(x)$ and $B(x)$ are functions of the states of the system, and they become coefficients in Riccati Equation (A.11). It is important to notice that the State-Dependent Coefficient form is not unique. There are many possible $A(x)$ and $B(x)$ matrices. Once a State-Dependent Coefficient form has been found the SDRE approach is reduced to solving a LQR problem at each sampling instant. For a controller to exist, the conditions in the following definition must be satisfied [12].

Definition A.1. $A(x)$ is a controllable (stabilizable) parametrization of the nonlinear system for a given region if $[A(x), B(x)]$ are pointwise controllable (stabilizable) for all x in that region.

Given this standing assumption, the SDRE design proceeds as follows [12]:

(1) Start with a State-Dependent Coefficient form of the system to be controlled.

(2) Solve State-Dependent Riccati Equation (A.11) to obtain a positive, semidefinite matrix $P(x)$.

(3) Construct the controller in form (A.12).

It is important to stress that the existence of the optimal control for a particular parametrization of the system is not guaranteed. Furthermore, there may be an infinite number of parameterizations of the system, so the choice of parametrization is very important. The other factor which may determine the existence of a solution to the Riccati Equation is the selection of the Q and R weighing matrices in Riccati Equation (A.11).

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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