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Bifurcation analysis and Optimal Control Problem of a Theoretical Dengue Model with Delay

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Abstract

A mathematical model with controls and discrete delays is formulated utilizing ordinary nonlinear differential equations, which interpret the dynamics of dengue transmission by coupling the dynamics of the human population to the dynamics of *Aedes aegypti*. Firstly, the presence of a bifurcation is analyzed in the case where the basic reproduction number is equal to one without including delays; subsequently, an optimal control problem is formulated with delay times in one state and in a control, for which a cost functional is established contemplating the direct and indirect costs of two control forms: adulticides and prevention of people at bites. Finally, a contour problem is determined utilizing the extension of the Pontryagin Maximum Principle to dynamic systems with delay and is solved by numerical methods.

Keywords: Mathematical model, delay, optimal control, bifurcation, numerical simulation.

I. INTRODUCTION

The diseases that are transmitted by vectors are generated by parasites, viruses or bacteria and among the vectors that propagate them are: mosquitoes, phlebotomes, triatomine bugs, blackfly, ticks, tsetse flies, mites, snails and lice; worldwide, there are more than 700000 deaths due to diseases transmitted by these vectors. Approximately 17% of infectious diseases are transmitted by vectors, whose distribution is determined by complex demographic, environmental and social factors; many of the diseases can be prevented by implementing fundamental protection measures, although there are other factors that help their dispersion such as: travel, commerce, unplanned urbanization and environmental problems that have an impact on the transmission of pathogens, generating the seasons of transmission are longer or more intense [14], [15].

Among the diseases transmitted by vectors is dengue (DENV), whose virus is an arbovirus that constitutes a threat to world public health, since it is divided into five serotypes (DENV 1-5) with related genetics but differ in its antigenicity. Dengue is transmitted through mosquitoes; the virus replicates inside the mosquitoes and after the bite, they are transmitted to the vertebrate (host) [16], [17]. *Aedes aegypti* is the main vector responsible for transmitting the dengue virus, dispersing through ships, airplanes and land transport, and establishing itself in homes or the human peridomyil. It has a biological cycle characterized by two phases: the aquatic phase and the adult phase; its development from egg to adult is completed under favorable feeding conditions and temperature in approximately 10 days [13], [6].

At present there is no effective therapy for dengue, its treatment is symptomatic and requires a high level of patient care; In general, hospitalized patients are treated with blood and liquid transfusion. Serious cases of the disease occur at 500000 per year for approximately. The absence of a vaccine that confers immunity to this virus has led the World Health Organization to promote control measures on the mosquito and the interruption of its interaction with humans, this approach is known as Integrated Vector Control, a decision-making process to optimize resources in vector control [15].

The control mechanisms focused on reducing vector transmission are divided into:

- The mechanical control or environmental management, is focused on the elimination of sites where the mosquito reproduces, so this control seeks the modification of the environment, environmental manipulation and the change of behavior of people, generating the decrease of places where mosquitoes can complete their biological cycle [16].
- The biological control focuses on mainly eliminating the mosquito larvae, using different biological agents, one of them is the bacterium *Bacillus thuringiensis israelensis* (Bti) that kills the mosquito larvae when they ingest this bacterium; Another biological agent that is used regularly is larvivorous fish, which feed on mosquito larvae and therefore decrease the population density of the vector (this practice is common in India) [16].
- The chemical control consists of the use of chemical compounds that usually affect the larval or adult stages of the mosquito; the most common chemical compounds used in mosquito control are pyrethroids, organochlorines and organophosphates, however this type of control affects other species and contaminates the soils, due to this, an alternative is sought in the use of chemicals consisting of application of botanical insecticides such as *Apium graveolens*, *Persea americana*, *Cipadessa baccifera* and *Callistemon rigidus* that are sustainable and less toxic [16].

Dengue virus has been a research center because it is a systematic disease and its dynamics have a broad clinical spectrum present in its serious and not serious clinical manifestations. The infection develops in phases: a febrile and critical phase, known as dengue hemorrhagic fever and dengue shock syndrome. The dynamics produced by the dengue virus both pathogen-host and vector-host have been studied in different research areas; one of them is the Mathematical Epidemiology, which studies the dynamics of infectious diseases with the purpose of understanding the spread of the disease and under what conditions it could eradicate or diminish its impact; Often these conditions are characterized by the basic reproduction number (denoted by R_0). R_0. expresses

the average number of secondary cases generated by an infected type individual when introduced into an entirely susceptible population. If $R_0 < 1$, indicates that a small number of infected individuals do not cause large outbreaks, and therefore the disease disappears over time (in this case, the disease-free equilibrium is asymptotically stable), in contrast, if $R_0 > 1$ the disease persists over time (in this case, there is an endemic equilibrium, asymptotically stable). The phenomenon that occurs when the disease-free balance loses its stability and a stable endemic equilibrium arises, it is known as forward bifurcation [2], [3], [12].

Mathematical modelling plays a highly relevant role in Epidemiology by generating a deep insight into the mechanisms or factors involved in the spread of emerging and remerging infectious diseases and by suggesting effective control strategies. When establishing these control strategies, the optimal control theory intervenes; Optimal control has been implemented to control epidemic outbreaks, mainly consists of seeking, among the possible strategies, the most effective strategy that allows reducing the infection rate to a minimum level and at the same time optimizing the cost generated by a therapy or a preventive vaccine or any form of control in disease progression [22].

In this paper, a mathematical model of nonlinear differential equations is considered in order to describe the host-vector dynamics produced by dengue virus transmission; in the model the underlying dynamics in the human are coupled and in the vector *Aedes aegypti*. The exhibition of a forward fork is analyzed, a phenomenon that happens when the basic reproduction number is equal to one. Finally, two delay times are introduced to the proposed dynamics, in order to formulate and solve an optimal control problem with delays. The delays introduced represent the period of intrinsic incubation of the virus in the human and the delay at the time of application of the adulticide.

The structure of this paper is as follows: In section 2, the mathematical model that describes the dynamics considered is established. The bifurcation analysis is found in section 3. In Section 4, the optimal control problem with delay is formulated. The numerical simulations are presented in Section 5. Finally, in Section 6 some conclusions are presented.

II. MODEL FORMULATION

A mathematical type host-vector model is proposed, based on nonlinear ordinary differential equations for the dynamics of dengue transmission in endemic regions, coupling the dynamics of the human population to the dynamics of the *Aedes aegypti* mosquito population; it includes prevention of people from mosquito bites and adult mosquito control through the use of adulticides.

The variables of the model are: x_1: average number of people susceptible to acquiring dengue by the bite of a mosquito carrying a dengue virus serotype at a time t, x_2: average number of people infected by a dengue virus serotype and confirmed at a time t, x_3: average number of people infected by a dengue virus serotype and not confirmed at a time t, x_4: average number of people recovered by dengue virus at a time t, y_1: average number of female mosquitoes not carrying a dengue virus serotype at a time t, and y_2: average number of female mosquitoes carrying a dengue virus serotype at a time t, N: total number of people at a time t, M: total mosquito population at a time t.

The parameters are: ϕ: increase in mosquitoes, f: fraction of eggs that give rise to female mosquitoes, σ: probability of transmission of the virus from an infected person (confirmed or unconfirmed) to a non-carrying mosquito, α: mosquito bite rate, ϵ: death rate of mosquitoes due to environmental factors, μ: constant mortality rate equal to the natural death rate in people, β: probability of transmission of the virus to susceptible people due to mosquito bites, p: fraction of infected cases not confirmed, δ: rate of infected unconfirmed cases that become confirmed infected cases, and ω: rate of confirmed and unconfirmed infected cases that acquire immunity to a dengue virus serotype.

The controls are: u_1: use of adulticides that impact mosquito mortality, and u_2: fraction of susceptible people who take prevention measures (mosquito nets, repellents, etc.).

The system of ordinary differential equations that describes the dynamics is:

$$\frac{dx_1}{dt} = \mu N - \beta\alpha\frac{y_2}{M}(1-u_2)x_1 - \mu x_1 \quad (1)$$

$$\frac{dx_2}{dt} = p\beta\alpha\frac{y_2}{M}(1-u_2)x_1 + \delta x_3 - (\mu + \omega)x_2 \quad (2)$$

$$\frac{dx_3}{dt} = (1-p)\beta\alpha\frac{y_2}{M}(1-u_2)x_1 - (\omega + \delta + \mu)x_3 \quad (3)$$

$$\frac{dx_4}{dt} = \omega(x_2 + x_3) - \mu x_4 \quad (4)$$

$$\frac{dy_1}{dt} = f\phi - \sigma\alpha\frac{x_2+x_3}{N}y_1 - (\epsilon + u_1)y_1 \quad (5)$$

$$\frac{dy_2}{dt} = \sigma\alpha\frac{x_2+x_3}{N}y_1 - (\epsilon + u_1)y_2, \quad (6)$$

with initial conditions: $x_1(0) = x_{10} > 0$, $x_2(0) = x_{20} > 0$, $x_3(0) = x_{30} > 0, x_4(0) = x_{40} > 0$, $y_1(0) = y_{10} > 0$, $y_2(0) = y_{20} > 0$ and conditions for non-negative parameters: $\alpha, \epsilon, \phi, \mu, \delta, \omega \geq 0$; $f, p, u_1, u_2, \beta, \sigma, \eta \in [0,1]$.

The epidemiological sense region is given by:

$$\Omega = \left\{ (x_1, x_2, x_3, x_4, y_1, y_2) \in \mathbb{R}_+^6 : x_1 + x_2 + x_3 + x_4 > 0, 0 < y_1 + y_2 \leq \frac{f\phi}{\epsilon + u\_2} \right\}$$

Considering that the variation of the total population of humans is constant, the equation (4) can be omitted from the system, so the reduced model will consist of the equations (1), (2), (3), (5) and (6). The basic reproduction number as a function of (u_1, u_2), calculated using the technique of the next generation matrix [23], [24], is given by:

$$R_0(u_1, u_2) = \frac{p\alpha^2\beta\sigma(1-u_2)}{(\epsilon+u_1)(\omega+\mu)} + \frac{(1-p)\alpha^2\beta\sigma\delta(1-u_2)}{(\epsilon+u_1)(\omega+\mu)(\mu+\omega+\delta)} + \frac{(1-p)\alpha^2\beta\sigma(1-u_2)}{(\epsilon+u_1)(\mu+\omega+\delta)}$$

R_0 is considered the most important epidemic threshold in the epidemiology of infectious diseases, because it establishes the conditions so that there is no epidemic risk; biologically the R_0 is the average number of people who contract the infection in a population of susceptible people [8], [10]. Mathematically, R_0 contributes to analyse the behaviour of a disease, since if

$R_0 < 1$, the disease does not exist or the disease in the population is extinct; if $R_0 = 1$, the infection is endemic; and if $R_0 > 1$, there is an epidemic [10]. Extensive research has been done on intrusion detection system.

III. TRANSCRITICAL BIFURCATION ANALYSIS

The theorem that is applied to demonstrate the appearance of the transcritical bifurcation, which is based on the theory of the central variety, is stated below.

Theorem (Castillo-Chavez et al., 2004) [5]: Consider the following general system of ordinary differential equations with a parameter ϕ.

$$\frac{dx}{dt} = f(x,\phi),\ \ f: \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}\ \ and\ f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}) \qquad (7)$$

where 0 is an equilibrium point of the system (that is, $f(0,\phi)$ for all ϕ) and assume

A1: $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ is the linearization matrix of the system (7) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue ofand other eigenvalues of A have negative real parts;

A2: Matrix A has a right eigenvector v and a left eigenvector w (each corresponding to the zero eigenvalue).

Let f_k be the kth component of f and

$$a = \sum_{k,i,j=1}^{n} w_k v_i v_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j}\ , b = \sum_{k,i=1}^{n} w_k v_i \frac{\partial^2 f_k(0,0)}{\partial x_i \partial \phi}.$$

The local dynamics of (7) around 0 are totally determined by a and b.

i. $a > 0,\ b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;
ii. $a < 0,\ b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;
iii. $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears;
iv. $a < 0,\ b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

The items i. and ii. indicate a backwards bifurcation, items iii. and iv. they refer to a forward bifurcation.

Now, considering that $y_1 + y_2 \to \frac{f\phi}{\epsilon + u_1}$ as $t \to \infty$, whereby $y_1 \to \left(\frac{f\phi}{\epsilon+u_1} - y_2\right)$, the system described previously approaches asymptomatically the following system:

$$\begin{aligned}
\frac{dx_1}{dt} &= \mu N - \beta\alpha \frac{\epsilon+u_1}{f\phi}(1-u_2)x_1 y_2 - \mu x_1 \\
\frac{dx_2}{dt} &= p\beta\alpha \frac{\epsilon+u_1}{f\phi}(1-u_2)x_1 y_2 + \delta x_3 - (\mu + \omega)x_2 \\
\frac{dx_3}{dt} &= (1-p)\beta\alpha \frac{\epsilon+u_1}{f\phi}(1-u_2)y_2 - (\omega + \delta + \mu)x_3 \\
\frac{dy_2}{dt} &= \sigma\alpha \frac{x_2+x_3}{N}\left(\frac{f\phi}{\epsilon+u_1} - y_2\right) - (\epsilon + u_1)y_2,
\end{aligned} \qquad (8)$$

Proposition: Let $\beta^* = \frac{(\epsilon+u_1)(\omega+\mu)}{\sigma\alpha^2(1-u_2)}$. If $R_0(u_1,u_2) = 1$ then the system (8) exhibits a transcritical bifurcation.

Proof: Firstly, considering the bifurcation equation given by

$$R_0(u_1,u_2) - 1 = 0$$

it follows that

$$\beta^* = \beta = \frac{(\epsilon+u_1)(\omega+\mu)}{\sigma\alpha^2(1-u_2)}$$

Now it is verified that the system (8) satisfies the hypotheses given in Theorem **(Castillo-Chavez et al., 2004)**:

Hypothesis 1.

Considering $\beta = \beta^*$ and the system (8), whose Jacobian matrix evaluated at $E_0 = (N,0,0,0)$ (disease-free equilibrium) is given by

$$J(E_0,\beta^*) = \begin{pmatrix} -\mu & 0 & 0 & -\frac{\beta^*\alpha(\epsilon+u_1)(1-u_2)N}{f\phi} \\ 0 & -(\mu+\omega) & \delta & \frac{p\beta^*\alpha(\epsilon+u_1)(1-u_2)N}{f\phi} \\ 0 & 0 & -(\mu+\omega+\delta) & \frac{(1-p)\beta^*\alpha(\epsilon+u_1)(1-u_2)N}{f\phi} \\ 0 & \frac{\alpha\sigma f\phi}{N(\epsilon+u_1)} & \frac{\alpha\sigma f\phi}{N(\epsilon+u_1)} & -(\epsilon+u_1) \end{pmatrix}$$

The characteristic equation corresponding to $J(E_0,\beta^*)$ is:

$$\lambda(\lambda+\mu)(\lambda^2 + a_1\lambda + a\_2) = 0$$

where $a_1 = 2(\mu+\omega) + \delta + \epsilon + u_1$ and $a_2 = (\omega+\mu+\delta)(\omega+\mu+\epsilon+u_1)$. Hence, the eigenvalues of $J(E_0,\beta^*)$ correspond to $\lambda_1 = -\mu, \lambda_2 = 0$ and $\lambda^2 + a_1\lambda + a_2 = 0$; because $a_1 > 0$ and $a_2 > 0$ and according to the Routh-Hurwitz Criteria [11], the real parts of the eigenvalues λ_3 and λ_4 are negative, concluding that two eigenvalues have negative real part and one has zero real part.

Hypothesis 2.

The eigenvector is determined by right corresponding to the null eigenvalue, for which the following system is considered:

$$J(E_0,\beta^*)\,\boldsymbol{V} = \mathbf{0}$$

Explicitly,

$$-\mu v_1 - \frac{(\epsilon + u_1)^2(\omega + \mu)N}{f\phi\alpha\sigma} v_4 = 0$$

$$-(\omega + \mu)v_2 + \delta\, v_3 + \frac{(\epsilon + u_1)^2(\omega + \mu)N}{f\phi\alpha\sigma} v_4 = 0$$

$$-(\omega + \mu + \delta)v_3 + \frac{(\epsilon + u_1)^2(\omega + \mu)N}{f\phi\alpha\sigma} v_4 = 0,$$

whose solution corresponds to:

$$\boldsymbol{V} = \begin{pmatrix} -\dfrac{(\epsilon + \mathrm{u}_1)^2(\omega + \mu)\mathrm{N}}{\mathrm{f}\phi\alpha\sigma\mu}\mathrm{v}_4 \\ \dfrac{(\epsilon + \mathrm{u}_1)^2\mathrm{N}}{\mathrm{f}\phi\alpha\sigma(\omega + \mu + \delta)}\big(\delta + \mathrm{p}(\omega + \mu)\big)\mathrm{v}_4 \\ \dfrac{(1 - \mathrm{p})(\epsilon + \mathrm{u}_1)^2(\omega + \mu)\mathrm{N}}{\mathrm{f}\phi\alpha\sigma(\omega + \mu + \delta)} v_4 \\ v_4 \end{pmatrix}$$

On the other hand, the eigenvector on the left corresponding to the null eigenvalue is determined by:

$$J(E_0, \beta^*)^T\, \boldsymbol{W} = \boldsymbol{0}.$$

Explicitly,

$$-\mu\, w_1 = 0$$

$$-(\omega + \mu)w_2 + \frac{f\phi\alpha\sigma}{(\epsilon + u_1)N} w_4 = 0$$

$$\delta w_2 - (\omega + \mu + \delta)w_3 + \frac{f\phi\alpha\sigma}{(\epsilon + u_1)N} w_4 = 0$$

Thus,

$$\boldsymbol{W} = \begin{pmatrix} 0 \\ \dfrac{f\phi\alpha\sigma}{(\epsilon + u_1)(\omega + \mu)N} w_4 \\ \dfrac{f\phi\alpha\sigma}{(\epsilon + u_1)(\omega + \mu)N} w_4 \\ w_4 \end{pmatrix}$$

The values v_4 and w_4 are such that $\boldsymbol{V} \cdot \boldsymbol{W} = 1$, obtaining from it:

$$v_4 = \frac{1}{\omega + \mu + \epsilon + u_1} \quad y \quad w_4 = \omega + \mu$$

The eigenvectors by left and by right corresponding to the null eigenvalue are:

$$\boldsymbol{V} = \begin{pmatrix} -\dfrac{(\epsilon + \mathrm{u}_1)^2(\omega + \mu)\mathrm{N}}{\mathrm{f}\phi\alpha\sigma\mu(\omega + \mu + \epsilon + u_1)} \\ \dfrac{(\epsilon + \mathrm{u}_1)^2\mathrm{N}}{\mathrm{f}\phi\alpha\sigma(\omega + \mu + \delta)(\omega + \mu + \epsilon + u_1)}\big(\delta + \mathrm{p}(\omega + \mu)\big) \\ \dfrac{(1 - \mathrm{p})(\epsilon + \mathrm{u}_1)^2(\omega + \mu)\mathrm{N}}{\mathrm{f}\phi\alpha\sigma(\omega + \mu + \delta)(\omega + \mu + \epsilon + u_1)} \\ \dfrac{1}{\omega + \mu + \epsilon + u_1} \end{pmatrix}$$

y

$$\boldsymbol{W} = \begin{pmatrix} 0 \\ \dfrac{f\phi\alpha\sigma}{(\epsilon + u_1)N} w_4 \\ \dfrac{f\phi\alpha\sigma}{(\epsilon + u_1)N} w_4 \\ w_4 \end{pmatrix}$$

Finally, the values of the coefficients a and b are calculated; for this and in order to preserve the notation of **Theorem (Castillo-Chavez et al., 2004)**, it is considered $x_4 = y_2$. Now consider the following non-null partial second-order derivatives evaluated at $(E_0, \beta^*) = (E_0, 0)$.

$$\frac{\partial^2 f_4}{\partial x_2 \partial x_4} = \frac{\partial^2 f_1}{\partial x_4 \partial x_2} = -\frac{\alpha\sigma}{N},$$

$$\frac{\partial^2 f_4}{\partial x_3 \partial x_4} = \frac{\partial^2 f_1}{\partial x_4 \partial x_3} = -\frac{\alpha\sigma}{N},$$

$$\frac{\partial^2 f_1}{\partial x_1 \partial \beta^*} = \frac{\partial^2 f_1}{\partial \beta^* \partial x_1} = -\frac{(\epsilon + u_1)(1 - u_2)N}{f\phi},$$

$$\frac{\partial^2 f_2}{\partial x_2 \partial \beta^*} = \frac{\partial^2 f_2}{\partial \beta^* \partial x_2} = -\frac{p(\epsilon + u_1)(1 - u_2)N}{f\phi},$$

$$\frac{\partial^2 f_3}{\partial x_3 \partial \beta^*} = \frac{\partial^2 f_3}{\partial \beta^* \partial x_3} = -\frac{(1 - p)(\epsilon + u_1)(1 - u_2)N}{f\phi},$$

Whereby,

$$a = \sum_{k,i,j=1}^{n} w_k v_i v_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j} = -\frac{2(1-p)(\epsilon+u_1)^2(\omega+\mu)^2 N}{f^2\theta^2\alpha\sigma(\omega+\mu+\delta)(\omega+\mu+\epsilon+u_1)^2}$$

and

$$b = \sum_{k,i=1}^{n} w_k v_i \frac{\partial^2 f_k(0,0)}{\partial x_i \partial \phi} = \frac{(\epsilon+u_1)^2(1-u_2)[p(\delta+p\omega+p\mu)+(1-p)^2]}{f\theta\alpha\sigma(\omega+\mu+\delta)(\omega+\mu+\epsilon+u_1)}$$

Concluding: since $a < 0$ and $b > 0$ and according to **Theorem (Castillo-Chavez et al., 2004)**, the system (8) exhibits at $R_0(u_1, u_2) = 1$ a forward bifurcation.

■

The bifurcation diagram for infected human populations is shown in Figure 1.

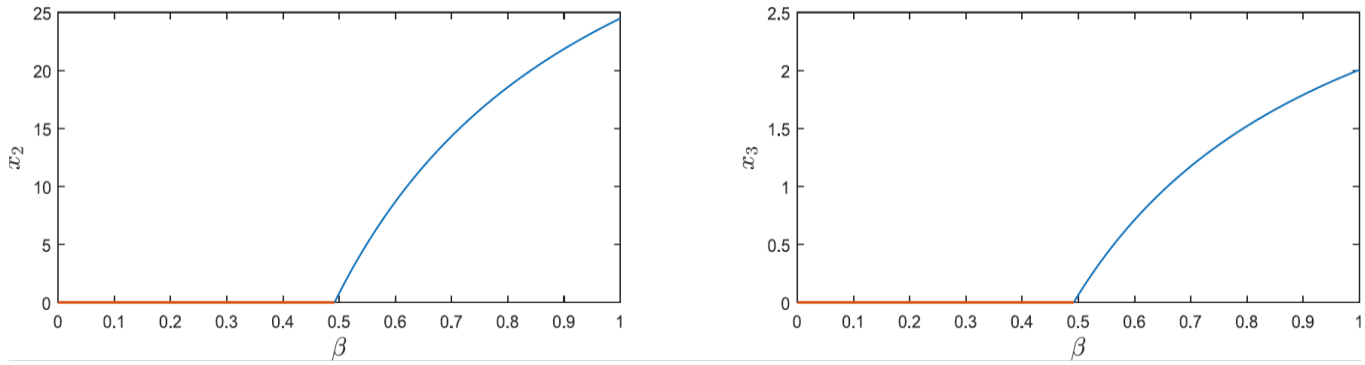

Fig. 1. Bifurcation diagram for infected human populations, that is, x_2 and x_3; the red line indicates the stability of E_0, while the blue line expresses the stability of E_1 (equilibrium solution representing infection populations), the bifurcation is given at $\beta^* = 0.49$.

IV. FORMULATION OF THE OPTIMAL CONTROL PROBLEM WITH DELAY

In the dynamics of dengue disease, there is a period where the vector cannot yet transmit the virus despite having it in its organism, this period is known as the extrinsic incubation period, denoted by ; on the other hand, adulticide control applications are made for certain time ranges, which is why it is considered a delay in the control for the use of adulticide, the delay for this case is given by ξ [8].

The system of nonlinear differential equations with delay corresponds to:

$$\frac{dx_1}{dt} = \mu N - \beta\alpha\frac{x_5}{M}\big(1-u_2(t)\big)x_1 - \mu x_1 \equiv f_1 \quad (9)$$

$$\frac{dx_2}{dt} = p\beta\alpha\frac{x_5}{M}(1-u_2(t))x_1 + \delta x_3 - (\mu + \omega)x_2 \equiv f_2 \quad (10)$$

$$\frac{dx_3}{dt} = (1-p)\beta\alpha\frac{x_5}{M}(1-u_2(t))x_1 - (\omega+\delta+\mu)x_3 \equiv f_3 \quad (11)$$

$$\frac{dx_4}{dt} = f\phi - \sigma\alpha\frac{x_2+x_3}{N}x_4 - (\epsilon + u_1(t-\xi))x_4 \equiv f_4 \quad (12)$$

$$\frac{dx_5}{dt} = \sigma\alpha\frac{x_2+x_3}{N}x_4(t-\tau) - (\epsilon + u_1(t-\xi))x_5 \equiv f_5, \quad (13)$$

with conditions:

$$x_1(0) = x_{10};\ x_{10} \geq 0;\ t \in [0, t_f]$$
$$x_2(0) = x_{20};\ x_{20} \geq 0;\ t \in [0, t_f]$$
$$x_3(0) = x_{30};\ x_{30} \geq 0;\ t \in [0, t_f]$$
$$x_4(t) = x_{40};\ x_{40} \geq 0;\ t \in [-\tau, 0]$$
$$x_5(0) = x_{50};\ x_{50} \geq 0;\ t \in [0, t_f]$$
$$u_1(t) = u_{01};\ u_{01} \geq 0;\ 0 \leq u_{01} \leq 1;\ t \in [-\xi, 0]$$

With the functional of costs objective:

$$J(\boldsymbol{x}, \boldsymbol{u}, \boldsymbol{t}) = \int_0^{t_f}\left[\rho_2 x_2(t) + \rho_3 x_3(t) + \frac{\eta_1}{2}u_1^2(t) + \frac{\eta_2}{2}u_2^2(t)\right]dt \to min_\Gamma$$

where ρ_2, ρ_3, η_1, and η_2 are positive constants that represent the weights of the costs of decreasing the populations of infected unconfirmed and confirmed, the prevention and control by adulticides. It is about finding an optimal control $\$\bar{u}\,(t) = (\bar{u}_1(t), \bar{u}_2(t))$ such that

$$J(\bar{u}_1(t), \bar{u}_2(t)) = \min_\Gamma J(u_{1(t)}, u_2(t))$$

where Γ is the region of admissible controls, which is given by:

$$\Gamma = \{(u_1(t), u_2(t)) \in L^2(0, t_f): 0 \leq u_1, u_2 \leq 1\}$$

There will be applied the optimality conditions given by the Pontryagin Maximum Principle for multiple delayed optimal control problems of Göllmann and Maurer (2009). The state variable $\varphi(t) = x_4(t-\tau)$ and the control variable $\varrho(t) = u_1(t-\xi)$ are introduced. The Hamiltonian for the optimal control problem is given by

$$H(\boldsymbol{x}(t), \boldsymbol{\lambda}(t), \boldsymbol{u}(t))\& = L(\boldsymbol{x}, \boldsymbol{u}) + \sum_{k=1}^{5} f_k \cdot \lambda\_k$$
$$= \rho_2 x_2(t) + \rho_3 x_3(t) + \frac{\eta_1}{2}u_1^2(t) + \frac{\eta_2}{2}u_2^2(t)$$
$$+\lambda_1\left[\mu N - \beta\alpha\frac{x_5}{M}\big(1-u_2(t)\big)x_1 - \mu x_1\right]$$
$$+\lambda_2\left[p\beta\alpha\frac{x_5}{M}\big(1-u_2(t)\big)x_1 + \delta x_3 - (\mu+\omega)x_2\right]$$
$$+\lambda_3\left[(1-p)\beta\alpha\frac{x_5}{M}\big(1-u_2(t)\big)x_1 - (\omega+\delta+\mu)x_3\right]$$
$$+\lambda_4\left[f\phi - \sigma\alpha\frac{x_2+x_3}{N}x_4 - (\epsilon + \varrho(t))x_4\right]$$
$$+\lambda_5\left[\sigma\alpha\frac{x_2+x_3}{N}\varphi(t) - (\epsilon+\varrho(t))x_5\right],$$

where $\lambda_i\,(t)$ with $i = 1, \ldots, 5$, represent the conjugate variables (adjoint variables). By the principle of maximum Pontryagin for the optimal delayed control problem, the optimal control $\boldsymbol{u}^*$ can be one that minimizes at every moment **t**, according to the Hamiltonian function

$$H(\boldsymbol{x}^*(t), \boldsymbol{\lambda}^*(t), \boldsymbol{u}^*(t)) = \min_{u\in[0,1]} H\big(\boldsymbol{x}^*(t), \boldsymbol{\lambda}^*(t), \boldsymbol{u}(t)\big)$$

The system of differential equations for the state variables is given by:

$$\dot{\lambda}_1(t) = -H_{x_1} \equiv g_1$$

$$\dot{\lambda}_2(t) = -H_{x_2} \equiv g_2$$

$$\dot{\lambda}_3(t) = -H_{x_3} \equiv g_3$$

$$\dot{\lambda}_4(t) = -H_{x_4} - \chi_{\{[0,t_f-\tau]\}} H_{\varphi(t+\tau)} \equiv g_4$$

$$\dot{\lambda}_5(t) = -H_{x_5} \equiv g_5$$

with the transversality conditions $\lambda_i(t_f) = 0$. Now to characterize the optimal controls, the first order conditions are utilized, that is, $H\_u_1(t) = 0$ and $H\_u_2(t) = 0$, so

$$H_{u_1}(t) + \chi_{\{[0,t_f-\xi]\}} H_{\varrho(t+\xi)} = 0$$

$$H\_u_2(t) = 0.$$

Also, considering that $0 \leq u_1(t) < 1$ and $0 \leq u_2(t) < 1$, it is obtained that:

$$u_1^*(t) = \begin{cases} min\left\{max\left\{0, \lambda_4(t+\xi)x_4(t+\xi) + \frac{\lambda_5(t+\xi)x_5(t+\xi)}{\eta_1}\right\}, 1\right\} & si \quad t \in [0, t_f - \xi]] \\ 0 & si \quad t \in [t_f - \xi, t_f]] \end{cases}$$

$$u_2^* = \min\left\{max\left\{0, \frac{(\lambda_2 p + \lambda_3(1-p) - \lambda_2)\beta\alpha\frac{x_5}{M}x_1}{\eta_2}\right\}, 1\right\}$$

The above results in an optimality system (or contour problem).

V. RESULT

The numerical simulations of the optimal control problem are executed using the MATLAB software and taking into account the values given in the Table 1 these values were retrieved from the literature; as for the weights η_1 and η_2, η_2 was considered fixed and η_1 was varied, that is, the value due to prevention was fixed while the adulticide application value varies; also $\tau = 5$ and $\xi = 12$ were considered fixed.

In the Figure 2 the dynamics of the optimum couple for the delay control problem is shown; the variation of the amount of application of the control u_1 is observed, which goes from being 100 % to not exceeding 30%, an event produced by the variation of the application cost of the control; on the other hand it is evident that the control applied for u_2, although it is given in low quantities, is indispensable throughout the simulation time, reflecting that the prevention control must be complementary to the application of the adulticide.

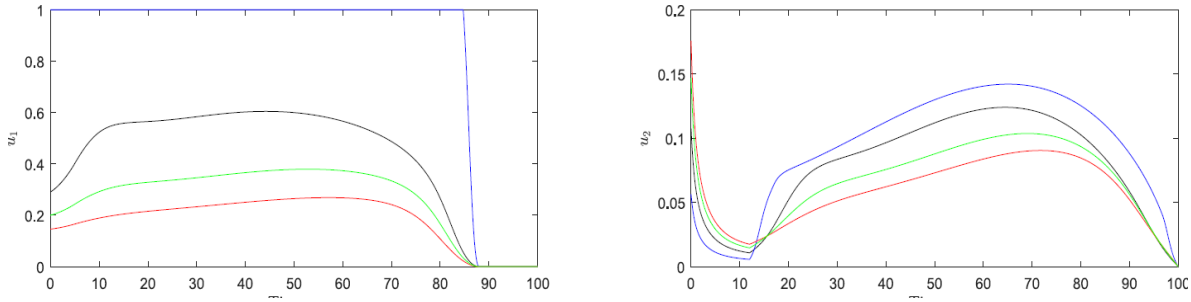

Fig. 2. Mechanics of the controls u_1 and u_2 using for different values of η_1 and considering $\tau = 5$ and $\xi = 12$.

Below is the table with the parameters used in the simulations

Table 1. Summary of the performance of ML algorithms

Parameter	Value	Reference
ϕ	$400 - 5000$	[1], [7], [20]
f	0.5	[21]
σ	0.845	[18]
α	$0.3 - 1$	[19], [20]
ϵ	0.03387	[18]
μ	3.65×10^{-5}	[4]
β	0.853	[18]
p	*Hypothetical*	-
δ	*Hypothetical*	-
ω	$0.071 - 0.33$	[1], [9]

VI. CONCLUSION

The formulation of a mathematical model based on nonlinear ordinary differential equations that represents the dynamics generated by the transmission of dengue virus, coupling the human population and that of the population of the vector, allows to describe the evolution of the disease in a given time and in a context delimited under certain assumptions. In question of this article, the exhibition of a transcritical bifurcation was studied, which biologically expresses that the efforts to control the infection must be such that the basic reproduction number is equivalent to one. On the other hand, delay times were included in the dynamic system in order to solve an optimal control problem, previously considering a cost functional and indicating the costs that directly and indirectly intervene in the application of the control measures (u_1, u_2). With respect to the numerical resolution of said control problem, it is concluded the most effective strategy that allows to reduce the infection rate to a minimum level and at the same

time optimize the cost for the control, it was obtained that the use of adulticides is an indispensable control when controlling an epidemic caused by the dengue virus but must be integrated with the mechanical control (prevention).

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