# SUMMARY of PhD THESIS

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Title:"**Qualitative Analysis of Delay Differential Equations Modelling Tropical Diseases**"

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A delay differential equation is a differential equation where the time derivatives of the state at the current time depends on the state and possibly its derivatives at previous times (see [36]). Models including delay differential equations are relatively new in studying diverse kinds of diseases such as Malaria, Chikungunya and Dengue Fever. To predict the future behavior of the disease, it is necessary to have some knowledge of the earlier behavior of this disease. In this case, we use differential equations with delays since simple initial conditions or boundary conditions are not satisfactory. The thesis includes three mathematical models based on delay differential equations modelling tropical diseases. The thesis is divided into five chapters.

**Chapter 1. Mathematical Framework.** In this chapter we present the basic definitions related to delay differential equations and we recall the main theorems related to the stability of delay differential equations using the characteristic equation and Lyapunov-Krasovskii functional.

**Chapter 2. Biological and Epidemiological Aspects.** In this chapter we present the role of the immune system and the biological aspects of Malaria and Chikungunya diseases which are used in constructing the physiological models. Also, we present the epidemiological aspects of Chikungunya-Dengue co-infection which are used in the framework of a SIR model.

**Chapter 3. Critical Case Theorem with Application to a Model of Cell Evolution in Malaria.** In this chapter we start by presenting and proving a theorem for the stability of the zero solution of a DDEs system in a critical case, for a particular class of systems with time delays. This type of systems, for ordinary differential equations, were studied by Malkin in [40] where a theorem for the stability in a critical case is proved. We extend this theorem to the case of DDE systems. Forced by the models under investigation, we had to generalize the result proved in the thesis of Ragheb Mghames. The main tool is the use of a complete Lyapunov-Krasovskii functional using some results from [31]. For general results on stability for delay differential equation we refer to [10],[18],[24], [26].

In what follows, the euclidean norm in the corresponding spaces will be denoted by $||\cdot||$.

Consider the following system with time-delay:

$$\begin{aligned} \dot{z}(t) &= A_0 z(t) + \sum_{j=1}^{m} A_j z(t-\tau_j) + B[z(t), z(t-\tau_1), ..., z(t-\tau_m), y(t)] \\ \dot{y}_i(t) &= D_i[z(t), z(t-\tau_1), ..., z(t-\tau_m), y(t)],\ 1 \leq i \leq p, \end{aligned} \tag{1}$$

where $A_j \in M_n(\mathbb{R})$, $0 \leq j \leq m$, $\tau_j > 0$ for all $1 \leq j \leq m$, $z(t) \in \mathbb{R}^n$, $y(t) \in \mathbb{R}^p$, $D_i(0,0,...,0,y) = 0, 1 \leq i \leq p$ and $B(0,0,...,0,y) = 0$, $\forall y \in \mathbb{R}^p$. $B$ takes values in $\mathbb{R}^n$ and the domain of $D$ is $\mathbb{R}^{mn+p}$. Denote $D = (D_1, \ldots, D_p)$. Suppose that $B$ and $D$ are real-analytic and their Taylor expansions around zero contain only powers of the variables with sum greater or equal to two (i.e.terms of the form $z_i(t)^r z_j(t)^s$, $z_i(t)^r z_j(t-\tau_k)^s$, $z_i(t)^r y_j(t)^s$, $z_i(t-\tau_k)^r z_j(t)^s$, $r+s \geq 2$). Then, for every $\rho > 0$, there exist $M_1(\rho)$ and $M_2(\rho)$ with

$\underset{\rho\to 0}{lim} M_1(\rho) = \underset{\rho\to 0}{lim} M_2(\rho) = 0$ so that, whenever $||z(t)|| \leq \rho, ||z(t-\tau_j)|| \leq \rho$, $1 \leq j \leq m$, $||y|| \leq \rho$,

$$\begin{aligned}
&\|B\left(z(t), z(t-\tau_1), \ldots, z(t-\tau_m), y(t)\right)\| \leq \\
&\leq M_1(\rho)\left(\|z(t)\| + \|z(t-\tau_1)\| + \cdots + ||z(t-\tau_m)||\right) \\
&\|D\left(z(t), z(t-\tau_1), \ldots, z(t-\tau_m), y(t)\right)\| \leq \\
&\leq M_2(\rho)\left(\|z(t)\| + \|z(t-\tau_1)\| + \cdots + ||z(t-\tau_m)||\right).
\end{aligned} \tag{2}$$

In what follows the norms in $\mathbb{R}^m$ will be the euclidean norms, $||z||_2 = \sqrt{z_1^2 + \cdots + z_m^2}$ and for $\delta \in C\left([-\tau, 0]\,; \mathbb{R}^{n+p}\right)$ the uniform norm will be

$$||\delta||_\infty = \sup_{t\in[-\tau,0]} ||\delta(t)||_2,\ \tau = \max_{1\leq j\leq m} \tau_j$$

**Lemma 0.0.1.** *Suppose that the linear system*

$$\dot{z}(t) = A_0 z(t) + \sum_{j=1}^{m} A_j z(t-\tau_j) \tag{3}$$

*is uniformly asymptotically stable. Then the Lyapunov matrix $U(t)$ is bounded for $t \geq 0$ and verifies*

$$||U(t)|| \leq C_1$$

**Remark 1.** *Uniformly asymptotically stable is equivalent to being exponentially stable (by [24], Ch.4, Th.4.5).*

**Theorem 0.0.1.** *Suppose that the linear system (3) is uniformly asymptotically stable. Then the zero solution of (1) is stable. Moreover, if $\delta$ is the initial data of (1) in $C\left([-\tau, 0]\,; \mathbb{R}^{n+p}\right)$ such that, if* $\sup\left\{||\delta(t)||_2 \mid t \in [-\tau, 0]\right\} <$

$\rho$, *then*

$$\lim_{t \longrightarrow \infty} z_i(t) = 0, i = 1, ..., n \textit{ and a finite} \lim_{t \longrightarrow \infty} y_i(t) = \tilde{y}_i \textit{ exists}, 1 \leq i \leq p,$$
$$\textit{with } |\tilde{y}_i| < \epsilon \textit{ if } ||\delta||_\infty < \rho(\epsilon).$$

**Model formulation**

After that, we apply the theorem for an original biological model that depicts cell evolution in Malaria under treatment, with the action of the immune system taken into consideration. Malaria is an infectious disease which spreads through mosquito bites. It is commonly found in tropical regions. The parasites enter the bloodstream and infect erythrocytes. Our model, extending those introduced in [11] and [39], includes the process of erythropoiesis, the evolution of the parasites, the action of the immune system and the effect of the treatment. We will concentrate only on the evolution of merozoites during Malaria, since their number considerably overcomes that of gametocytes and their influence is responsible for the damaging effects of the disease. Recent studies ([28]) show that Plasmodium falciparum acts on both young and mature erythrocytes. The following equations describe the evolution of the disease induced by Plasmodium falciparum (under treatment with Artemisinin).

$$
\begin{aligned}
\dot{z}_1= & -\tfrac{\gamma_0}{1+z_3^\alpha} z_1-(\eta_1+\eta_2)k(z_3)z_1-(1-\eta_1-\eta_2)\beta(z_1,z_3)z_1+\\
& +2z_4(1-\eta_1-\eta_2)\beta(z_{1\tau_1},z_{3\tau_1})z_{1\tau_1}+\eta_1 z_4 k(z_{3\tau_1})z_{1\tau_1}\\
\dot{z}_2= & -\gamma_2 z_2+\tilde{A}k(z_{3\tau_2})z_{1\tau_2}-pz_2z_6\\
\dot{z}_3= & -kz_3+\tfrac{a_1}{1+z_2^r}\\
\dot{z}_4= & z_4\left(-\tfrac{\gamma_0}{1+z_3^\alpha}+\tfrac{\gamma_0}{1+z_{3\tau_1}^\alpha}\right)\\
\dot{z}_5= & pz_2z_6-\gamma_3 z_5-pz_{2\tau_3}z_{6\tau_3}S\\
\dot{z}_6= & (1-c)\beta p z_{2\tau_3}z_{6\tau_3}S-pz_2z_6 l_1(z_{12})-\mu_M z_6-b_1 z_6 z_{12}\\
\dot{z}_7= & d_1-c_2z_7-b_2z_7l_2(z_6)\\
\dot{z}_8= & -c_3z_8+b_2z_7l_2(z_6)\\
\dot{z}_9= & d_2-c_4z_9-b_3z_8z_9\\
\dot{z}_{10}= & -c_5z_{10}-e_1\zeta(z_{10})z_{10}l_2(z_6)+2e^{-c_5\tau_4}e_1\zeta(z_{10\tau_4})z_{10\tau_4}l_2(z_{6\tau_4})+\\
& +2^{m_1}b_{41}z_{8\tau_6}z_{9\tau_6}l_2(z_{6\tau_6})\\
\dot{z}_{11}= & -c_6z_{11}-e_2z_{10}z_{11}\zeta(z_{10})+2e^{-c_6\tau_5}e_2z_{10\tau_5}z_{11\tau_5}\zeta(z_{10\tau_5})+\\
& +2^{m_2}b_{42}z_{8\tau_7}z_{9\tau_7}l_2(z_{6\tau_7})\\
\dot{z}_{12}= & -c_7z_{12}z_6+e_3z_{11}\tfrac{z_6}{a_4+z_6}
\end{aligned}
$$

For more details on the model, please see [8] and [11].

**Remark 2.** *If the initial condition is positive then the solution will be positive on all the interval on which exists due to the presence of delayed terms.*

### Equilibrium Points

We conclude that the Malaria Model has the following possible types of equilibrium points. $E_1 = (0, 0, \hat{z}_3, \hat{z}_4, 0, 0, \hat{z}_7, 0, \hat{z}_9, 0, 0, 0)$ is an equilibrium point, that can be interpreted as the equilibrium representing the last stage of the disease (i.e. close to the death of the patient). The equilibrium point $E_2 = (\tilde{z}_1, \tilde{z}_2, \tilde{z}_3, \tilde{z}_4, 0, 0, \tilde{z}_7, 0, \tilde{z}_9, 0, 0, 0)$ can be interpreted as the disease free equilibrium and $E_3 = (z_1^*, z_2^*, z_3^*, z_4^*, z_5^*, z_6^*, z_7^*, z_8^*, z_9^*, z_{10}^*, z_{11}^*, z_{12}^*)$ which corresponds to a chronic phase of the disease.

### Stability Analysis

Let $A = [a_{i,j}]$ be the matrix in the linear approximation around $E_1$ corresponding to undelayed terms, $B = [b_{i,j}]$ the matrix corresponding to terms with the delay $\tau_1$, $C = [c_{i,j}]$ the matrix that corresponds to the terms with the delay $\tau_2$, $D = [d_{i,j}]$ the matrix that corresponds to the terms with the delay $\tau_3$, $E = [e_{i,j}]$ the matrix that corresponds to the terms with the delay $\tau_4$, $F = [f_{i,j}]$ the matrix that corresponds to the terms with the delay $\tau_5$, $G = [g_{i,j}]$ the matrix that corresponds to the terms with the delay $\tau_6$ and $H = [h_{i,j}]$ the matrix that corresponds to the terms with the delay $\tau_7$.

The characteristic equation corresponding to $E_1$ has the following form:

$$(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22})(\lambda - a_{33})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})(\lambda - a_{88})$$
$$(\lambda - a_{99})(\lambda - a_{10,10})(\lambda - a_{11,11})\lambda^2 = 0.$$

$\lambda = 0$ is a root, so we are in a critical case for the stability of the nonlinear system. Suppose the transcendental equations have only roots with negative real parts, then the critical case is completely investigated in theorem (0.0.1). Since we do not have the linear part equal to zero then this theorem is not directly applicable, so we will proceed to bring the system to the canonical form to which this theorem can be applied. We perform a translation to zero by $p_i = z_i - \hat{z}_i$, for $i = 3, 4, 7, 9$.

The new system becomes

$$\dot{p} = \tilde{f}_i(p, p_{\tau_j}), i = \overline{1,12}, j = \overline{1,7} \tag{4}$$

After some calculations we conclude that Theorem (0.0.1) can be applied to study the stability of the zero solution of system (4). Since $a_{22} < 0, a_{33} < 0, a_{55} < 0, a_{66} < 0, a_{77} < 0, a_{88} < 0, a_{99} < 0, a_{10,10} < 0, a_{11,11} < 0$, then the stability depends on the study of the following transcendental term in the characteristic equation

$$\lambda - a_{11} - b_{11}e^{-\lambda\tau_1} = 0 \tag{5}$$

The stability of equation (5) is completely investigated in [10] and [15].

The characteristic equation for $E_2$ has the following form:

$$d_1(\lambda)d_2(\lambda) = 0$$

$$d_1(\lambda) = \lambda(\lambda - a_{22})(\lambda - a_{33})(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1}) - \lambda a_{32}(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})$$

$$c_{23}e^{-\lambda\tau_2} - \lambda a_{32}c_{21}e^{-\lambda\tau_2}(a_{13} + b_{13}e^{-\lambda\tau_1}) - a_{32}a_{14}c_{21}e^{-\lambda\tau_2}(a_{43} + b_{43}e^{-\lambda\tau_1})$$

$$d_2(\lambda) = (\lambda - a_{66} - d_{66}e^{-\lambda\tau_3})(\lambda - a_{55})(\lambda - a_{77})(\lambda - a_{88})(\lambda - a_{99})$$

$$(\lambda - a_{10,10})(\lambda - a_{11,11})\lambda$$

Since $a_{43} = -b_{43}$ it follows that $\lambda = 0$ is also a root of $d_1(\lambda) = 0$ , so, once again, the critical case of a double zero eigenvalue must be discussed as in the case of $E_1$.

Since the characteristic equations corresponding to $E_3$ is complicated the stability of $E_3$ will be investigated using numerical procedures.

**Numerical Calculations**

The numerical calculations show that the analyzed equilibrium points exhibit partial stability, i.e. stability with respect to some of the variables (see [13], [56]).

As $E_1(0, 0, 1.6667, 0.77452, 0, 10, 0, 66.6667, 0, 0, 0)$ represents the death equilibrium, small disturbances from it will stand for an aggravated state of the disease. The numerical calculations show that $E_1$ has only partial stability with respect to state variables $z_5, z_8, z_{10}$ and $z_{11}$.

From a medical point of view, this is the desired progress, as the optimal evolution of the state variables trajectories is towards a healthy state, mainly involving the vanishing of the merozoites and of the infected erythrocytes and the recovering of the healthy erythrocyte population. From a mathematical perspective, this translates into the following dynamical behavior of trajectories starting near $E_1$: a stable state for the variables $z_5$ (the infected RBC population) and $z_6$ (free merozoites population) and an unstable state for the variables $z_1$ and $z_2$ (healthy erythrocyte population and precursors).

One can notice also that the equilibrium $E_2(0.0012, 0.9412, 1.0075, 0.7268, 0, 10, 0, 66.6667, 0, 0, 0)$ exhibits partial stability with respect to state variables $z_1, z_8$, $z_{10}$ and $z_{11}$. As this stationary point represents the disease-free state of the disease, here the stability of $z_1$ and $z_2$ together with stability of $z_5$ and $z_6$ is the awaited outcome.

These calculations establish that the dynamics of the components of the immune system might have different behaviors: the antibodies cell population might remain high for a long period, while some other components of the immune response will die out. From an immunological perspective this is also the expected evolution.

**Chapter 4. Model of Cell Evolution in Chikungunya.** In this chapter we introduce a new model for Chikungunya evolution within host under treatment and considering the action of the immune response. It was demonstrated that CHIKVAs could be detected in vivo in the monocytes of acutely infected patients, so infected and uninfected monocytes are also considered in the model. The model consists of 12 equations with 10 delays, the following equations describe the evolution of the disease under treatment with Ribavirin.

$$\begin{aligned}
\dot{y}_1 = & -\gamma_1 y_1 - (\eta_1+\eta_2)k(y_2+y_5)y_1 - (1-\eta_1-\eta_2)\beta(y_1)y_1 \\
& +2e^{-\gamma_1\tau_1}(1-\eta_1-\eta_2)\beta(y_{1\tau_1})y_{1\tau_1} + \eta_1 e^{-\gamma_1\tau_1}k(y_{2\tau_1}+y_{5\tau_1})y_{1\tau_1}
\end{aligned}$$

$$\dot{y}_2 = -\gamma_2 y_2 + A(2\eta_2+\eta_1)k(y_{2\tau_2}+y_{5\tau_2})y_{1\tau_2} - r_1 e^{-\gamma_2\tau_3}P_1(y_{4\tau_3})y_{2\tau_3} - py_2$$

$$\dot{y}_3 = R - \left(\frac{C}{V}\right)y_3$$

$$\dot{y}_4 = k_t y_4 \left(1 - \left[\frac{(\frac{y_3}{V})^h}{E+(\frac{y_3}{V})^h}\right]\right)\left(1-\frac{y_4}{p_m}\right) - k_d y_4 - r_1 P_1(y_4)y_2 - r_2 P_2(y_4)y_{12}$$

$$\dot{y}_5 = r_1 P_1(y_4)y_2 - \gamma_3 y_5 - k_1\delta y_{11}y_5 - py_5$$

$$\dot{y}_6 = d_1 - c_2 y_6 - b_2 y_6 l(y_4)$$

$$\dot{y}_7 = -c_3 y_7 + b_2 y_6 l(y_4)$$

$$\dot{y}_8 = d_2 - c_4 y_8 - b_3 y_7 y_8$$

$$\dot{y}_9 = -c_5 y_9 - e_1 \zeta(y_9) y_9 l(y_4) + 2e^{-c_5\tau_4} e_1 \zeta(y_{9\tau_4}) y_{9\tau_4} l(y_{4\tau_4}) + 2^{m_1} b_{41} y_{7\tau_6} y_{8\tau_6} l(y_{4\tau_6})$$

$$\dot{y}_{10} = -c_6 y_{10} - e_2 y_9 y_{10} \zeta(y_9) + 2e^{-c_6\tau_5} e_2 y_{9\tau_5} y_{10\tau_5} \zeta(y_{9\tau_5}) + 2^{m_2} b_{42} y_{7\tau_7} y_{8\tau_7} l(y_{4\tau_7})$$

$$\dot{y}_{11} = -c_7 y_{11} - e_3 y_9 y_{11} \zeta(y_9) + 2e^{-c_7\tau_8} e_3 y_{9\tau_8} y_{11\tau_8} \zeta(y_{9\tau_8}) + 2^{m_3} b_{43} y_{7\tau_9} y_{8\tau_9} l(y_{4\tau_9}) - e_4 \zeta_1(y_9) y_{11} - b_4 y_{11} l_1(y_4) + 2^n e_5 y_{11\tau_{10}} l_1(y_{4\tau_{10}})$$

$$\dot{y}_{12} = -c_8 y_{12} y_4 + e_6 y_{10} \frac{y_4}{a_5 + y_4}$$

**Equilibrium Points**

We conclude that the Chikungunya Model has the following possible types of equilibrium points:

$$E_1 = (0, 0, \hat{y}_3, 0, 0, \hat{y}_6, 0, \hat{y}_8, 0, 0, 0, 0)$$

$$E_2 = (\hat{y}_1, \hat{y}_2, \hat{y}_3, 0, 0, \hat{y}_6, 0, \hat{y}_8, 0, 0, 0, 0)$$

$$E_3 = (0, 0, y_3^*, 0, y_5^*, y_6^*, y_7^*, y_8^*, y_9^*, y_{10}^*, y_{11}^*, 0)$$

When linearizing the system the following matrices are to be used in the study of the stability of equilibria.

$$\begin{aligned} A &= \frac{\partial f}{\partial y} = [a_{i,j}], B = \frac{\partial f}{\partial y_{\tau_1}} = [b_{i,j}], C = \frac{\partial f}{\partial y_{\tau_2}} = [c_{i,j}], D = \frac{\partial f}{\partial y_{\tau_3}} = [d_{i,j}], \\ E &= \frac{\partial f}{\partial y_{\tau_4}} = [e_{i,j}], F = \frac{\partial f}{\partial y_{\tau_5}} = [f_{i,j}], G = \frac{\partial f}{\partial y_{\tau_6}} = [g_{i,j}], H = \frac{\partial f}{\partial y_{\tau_7}} = [h_{i,j}], \\ I &= \frac{\partial f}{\partial y_{\tau_8}} = [i_{i,j}], J = \frac{\partial f}{\partial y_{\tau_9}} = [j_{i,j}], K = \frac{\partial f}{\partial y_{\tau_{10}}} = [k_{i,j}] \end{aligned}$$

**Stability Analysis of $E_1$**

The characteristic equation corresponding to $E_1$ is:

$$(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22})(\lambda - a_{33})(\lambda - a_{44})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})$$
$$(\lambda - a_{88})(\lambda - a_{99})(\lambda - a_{10,10})(\lambda - a_{11,11})\lambda = 0$$

$\lambda = 0$ is a root, so we are in a critical case for the stability of the nonlinear system. Since we do not have the linear part equal to zero then this theorem is not directly applicable, so we will proceed to bring the system to the canonical form to which this theorem can be applied. We perform a translation to zero by $x_i = y_i - \hat{y}_i$. The new system becomes:

$$\dot{x} = \bar{f}_i(x, x_{\tau_j}), i = \overline{1, 12}, j = \overline{1, 10} \qquad (6)$$

After some calculations we conclude that theorem (0.0.1) can be applied to study the stability of the zero solution of system (6). Since $a_{22}, a_{33}, a_{44}, a_{55}, a_{66}, a_{77}, a_{88}, a_{99}$, $a_{10,10}, a_{11,11}$ are all negative, the stability depends on the study of the transcendental term in the characteristic equation. This term has the following form:

$$\lambda - a_{11} - b_{11}e^{-\lambda\tau_1} = 0 \qquad (7)$$

The stability of equation (7) is completely investigated in [10] and [15].

**Stability Analysis of $E_2$**

The characteristic equation corresponding to $E_2$ is:

$$\lambda(\lambda - \bar{a}_{33})(\lambda - \bar{a}_{44})(\lambda - \bar{a}_{55})(\lambda - \bar{a}_{66})(\lambda - \bar{a}_{77})(\lambda - \bar{a}_{88})(\lambda - \bar{a}_{99})(\lambda - \bar{a}_{10,10})(\lambda - \bar{a}_{11,11})$$
$$[(\lambda - \bar{a}_{11} - \bar{b}_{11}e^{-\lambda\tau_1})(\lambda - \bar{a}_{22} - \bar{c}_{22}e^{-\lambda\tau_2}) - \bar{c}_{21}e^{-\lambda\tau_2}(\bar{a}_{12} + \bar{b}_{12}e^{-\lambda\tau_1})] = 0$$

Since $\lambda = 0$ is also a root so, once again, the critical case of a zero eigenvalue must be discussed as in the case of $E_1$. Since $\bar{a}_{33}, \bar{a}_{44}, \bar{a}_{55}, \bar{a}_{66}, \bar{a}_{77}, \bar{a}_{88}, \bar{a}_{99}, \bar{a}_{10,10}, \bar{a}_{11,11}$

are all negative, the stability depends on the study of the transcendental terms in the characteristic equation:

$$(\lambda - \bar{a}_{11} - \bar{b}_{11}e^{-\lambda\tau_1})(\lambda - \bar{a}_{22} - \bar{c}_{22}e^{-\lambda\tau_2}) - \bar{c}_{21}e^{-\lambda\tau_2}(\bar{a}_{12} + \bar{b}_{12}e^{-\lambda\tau_1}) = 0 \quad (8)$$

The study of equation (8) follow the approach of theorem (1) in [16].

**Stability Analysis of $E_3$**

The characteristic equation corresponding to $E_3$ is:

$$(\lambda - \tilde{a}_{22})(\lambda - \tilde{a}_{33})(\lambda - \tilde{a}_{44})(\lambda - \tilde{a}_{55})(\lambda - \tilde{a}_{66})(\lambda - \tilde{a}_{77})(\lambda - \tilde{a}_{88})(\lambda - \tilde{a}_{99})$$
$$(\lambda - \tilde{a}_{11} - \tilde{b}_{11}e^{-\lambda\tau_1})(\lambda - \tilde{a}_{10,10} - \tilde{f}_{10,10}e^{-\lambda\tau_5})(\lambda - \tilde{a}_{11,11} - \tilde{i}_{11,11}e^{-\lambda\tau_8})\lambda = 0$$

The stability depends on the study of the following transcendental terms in the characteristic equation

$$\lambda - \tilde{a}_{11} - \tilde{b}_{11}e^{-\lambda\tau_1} = 0$$

$$\lambda - \tilde{a}_{10,10} - \tilde{f}_{10,10}e^{-\lambda\tau_5} = 0$$

$$\lambda - \tilde{a}_{11,11} - \tilde{i}_{11,11}e^{-\lambda\tau_8} = 0$$

The stability of the above equations is completely investigated in [10] and [15].

**Chapter5. Epidemiological Model of Chikungunya-Dengue Co-Infection.** In this chapter we introduce a new epidemiological model for the Dengue fever and Chikungunya co-infection with 2 delays. Many epidemiological models have been developed to understand Chikungunya infection [22] and Dengue infection [47], and also some models of co-infection between Dengue and Chikungunya [43],[48]. The model describing the Dengue-Chikungunya co-infection is given below:

$$\dot{s}_1 = a_1 - b_1 e^{-c_1\tau_1}(s_8 + s_{10})s_1 - b_2 e^{-c_1\tau_1}(s_9 + s_{10})s_1 - c_1 s_1$$

$$\dot{s}_2 = b_1 e^{-c_1\tau_1} s_{8_{\tau_1}} s_1 - (c_1 + d_1 + e_1)s_2$$

$$\dot{s}_3 = b_2 e^{-c_1\tau_1} s_{9_{\tau_1}} s_1 - (c_1 + d_2 + e_2)s_3$$

$$\dot{s}_4 = (b_1 + b_2) e^{-c_1\tau_1} s_{10_{\tau_1}} s_1 - (c_1 + d_1 + d_2 + e_3)s_4$$

$$\dot{s}_5 = d_1(s_2 + s_4) - c_1 s_5$$

$$\dot{s}_6 = d_2(s_3 + s_4) - c_1 s_6$$

$$\dot{s}_7 = a_2 - b_3 e^{-c_2\tau_2}(s_2 + s_4)s_7 - b_4 e^{-c_2\tau_2}(s_3 + s_4)s_7 - c_2 s_7$$

$$\dot{s}_8 = b_3 e^{-c_2\tau_2} s_{2_{\tau_2}} s_7 - c_2 s_8$$

$$\dot{s}_9 = b_4 e^{-c_2\tau_2} s_{3_{\tau_2}} s_7 - c_2 s_9$$

$$\dot{s}_{10} = (b_3 + b_4) e^{-c_2\tau_2} s_{4\tau_2} s_7 - c_2 s_{10}$$

**Equilibrium Points**

The model has a non trivial disease-free equilibrium $E_1 = (\hat{s}_1, 0, 0, 0, 0, 0, \hat{s}_7, 0, 0, 0)$, the equilibrium point $E_2 = (\tilde{s}_1, \tilde{s}_2, 0, 0, \tilde{s}_5, 0, \hat{s}_7, \tilde{s}_8, 0, 0)$ can be interpreted as "CHIKV endemic equilibrium point" and the equilibrium point $E_3 = (\bar{s}_1, 0, \bar{s}_3, 0, 0, \bar{s}_6, \bar{s}_7, 0, \bar{s}_9, 0)$ can be interpreted as "DENV endemic equilibrium point".

**Stability Analysis**

When linearizing the system the following matrices are to be used in the study of the stability of equilibria.

$$A = \frac{\partial f}{\partial s} = [a_{i,j}], B = \frac{\partial f}{\partial s_{\tau_1}} = [b_{i,j}], C = \frac{\partial f}{\partial s_{\tau_2}} = [c_{i,j}]$$

For the particular case of the equilibrium point $E_1$, the characteristic equation will be:

$$(\lambda - a_{11})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})[(\lambda - a_{44})(\lambda - a_{10,10}) - b_{4,10}e^{-\lambda\tau_3}c_{10,4}]$$
$$[(\lambda - a_{33})(\lambda - a_{99}) - b_{39}e^{-\lambda\tau_3}c_{93}][(\lambda - a_{22})(\lambda - a_{88}) - b_{28}e^{-\lambda\tau_3}c_{82}] = 0 \quad (9)$$

where $\tau_3 = \tau_1 + \tau_2$.

The real solutions of equation (9) are $a_{11}, a_{55}, a_{66}, a_{77} < 0$. Therefore the stability analysis of the characteristic equation corresponding to $E_1$ depends on the stability of the following equations:

$$(\lambda - a_{44})(\lambda - a_{10,10}) - c_{10,4}b_{4,10}e^{-\lambda\tau_3} = 0 \quad (10)$$

$$(\lambda - a_{33})(\lambda - a_{99}) - b_{39}c_{93}e^{-\lambda\tau_3} = 0 \quad (11)$$

$$(\lambda - a_{22})(\lambda - a_{88}) - b_{28}e^{-\lambda\tau_3} = 0 \quad (12)$$

The stability analysis of equations (10), (11) and (12) follows the approach of theorem (1) in [16].

Since the characteristic equations corresponding to $E_2$ and $E_3$ are complicated, the stability of $E_2$ and $E_3$ will be investigated using numerical procedures.

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