A DELAY DIFFERENTIAL EQUATION MODEL FOR CELL EVOLUTION IN CHIKUNGUNYA

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In this paper, we introduce a new delay differential equation model of Chikungunya that describes the evolution of the disease under treatment with Ribavirin. A physiological model representing the hematopoietic cells, healthy and infected monocytes, is considered together with the action of the immune system, such as the concentrations of APC, T cells, B lymphocytes and antibodies produced by the B cells. The stability properties of the equilibrium point representing the most aggravated phase of the disease are investigated: a critical case theorem is applied, followed by the study of a transcendental equation. Finally, the numerical simulations show the estimated favorable evolution from a medical point of view.

Keywords

Delay Differential Equations, Stability, Critical Case, Chikungunya, Immune Response, Ribavirin.

1. Introduction

Chikungunya disease (CHIKD) is caused by the Chikungunya arbovirus. CHIKD is transmitted to humans through the bite of Aedes mosquitoes that initially started its outbreak in Africa in 1952 and then spreads to Asia, Europe and recently, in 2015, a major outbreak occurred in America (see [14]). Individuals infected with Chikungunya virus (CHIKV) show primarily fever and joint pain that last from 3 to 12 days after exposure to virus. In addition, some individuals show varied degrees of myalgia, rash and joint swelling. In severe cases, a molecule of viral RNA remains circulating in the synovial monocytes for years and triggering joint inflammation associated arthralgia (see [13]).

Aedes aegypti and Aedes albopictus are the main types of mosquitoes that host the replication of CHIKV. Aedes then transmit the virus to continue its replication cycle in a human host and then it can be picked up back by other CHIKV free mosquitoes after feeding on an infected human host. After a blood meal from an infected host the virus takes 2 to 3 days to inhabit the salivary glands of Aedes mosquitoes. It is a relatively fast cycle that makes the transmission of CHIKV back to human hosts quicker than other mosquito- borne virus (see [9]).

After the bite of an infected mosquito, CHIKV from the saliva of mosquito escapes to the blood stream of the human host. The pathogenesis of CHIKV infection is still poorly understood. Invitro analysis showed that CHIKV is capable of infecting fibroblast, endothelial cells and monocytes. In 10 % of infected patients, a copy of the viral genome circulates within the perivascular synovial monocytes which might be the cause of the persistence of CHIKD related chronic symptoms of arthralgia and joint inflammation (see [22]).

The primary immune cells involved in targeting CHIKV infection are the macrophages, natural killer cells and dendritic cells that are the first line in confronting the virus and activating the specific immune response of lymphocytes. B and T lymphocytes of the specific immune defense then attack the viruses released into the blood stream and the infected host cells respectively. After triggering an immune response and clearing the virus, it is believed

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that infected individuals become immune against CHIKV the disease being controlled by the host memory cells, when the virus next infects the same host (see [16]).

The development of a vaccine against CHIKV is still in clinical trials.

While supportive anti-inflammatory drugs and analgesic were prominently used to relieve joint pain and fever, the antiviral activity of Ribavirin (RBV) was evaluated as monotherapy against CHIKV. In the absence of drug, CHIKV rapidly replicates, reaching a peak of $10^{8.5}$ PFU/ml at day 2 after infection. The 100 $\mu g/ml$ and 1000 $\mu g/ml$ concentrations of RBV were effective at suppressing CHIKV at day 1, resulting in a $2-\log_{10}$ PFU/ml decrease in CHIKV level for the 100 $\mu g/ml$ concentration and a $4-\log_{10}$ PFU/ml decrease for the 1000 $\mu g/ml$ concentration (see [13]).

The paper is organized as follows. In Section 2 we introduce a new and complex DDE model of Chikungunya under treatment incorporating the action of the immune system. In Section 3, the equilibrium point E_1 representing the most aggravated phase of the disease is found. In section 4 the stability analysis of E_1 is investigated, using a critical case theorem that represents the Lyapunov-Malkin approach for delay differential equations. The numerical simulations are presented in section 5 and conclusions are drawn in Section 6.

2. **The Model**

Denote $y_\tau(t) = y(t-\tau)$.The following 12 equations describe the evolution of the Chikungunya disease considering the action of the immune system and under treatment with Ribavirin.

$$
\begin{aligned}
\dot{y}_1 &= -\gamma_1 y_1 - (\eta_1+\eta_2)k(y_2+y_5)y_1 - (1-\eta_1-\eta_2)\beta(y_1)y_1 \\
&\quad + 2e^{-\gamma_1\tau_1}(1-\eta_1-\eta_2)\beta(y_{1\tau_1})y_{1\tau_1} + +\eta_1 e^{-\gamma_1\tau_1}k(y_{2\tau_1}+y_{5\tau_1})y_{1\tau_1} \\
\dot{y}_2 &= -\gamma_2 y_2 + A(2\eta_2+\eta_1)k(y_{2\tau_2}+y_{5\tau_2})y_{1\tau_2} - r_1 e^{-\gamma_2\tau_3}P_1(y_{4\tau_3})y_{2\tau_3} - py_2 \\
\dot{y}_3 &= R - (\tfrac{C}{V})y_3 \\
\dot{y}_4 &= k_t y_4\left(1-\left[\tfrac{(\frac{y_3}{V})^h}{E+(\frac{y_3}{V})^h}\right]\right)\left(1-\tfrac{y_4}{p_m}\right) - k_d y_4 - r_1 P_1(y_4)y_2 - r_2 P_2(y_4)y_{12} \\
\dot{y}_5 &= r_1 P_1(y_4)y_2 - \gamma_3 y_5 - k_1\delta y_{11}y_5 - py_5 \\
\dot{y}_6 &= d_1 - c_2 y_6 - b_2 y_6 l(y_4) \\
\dot{y}_7 &= -c_3 y_7 + b_2 y_6 l(y_4) \\
\dot{y}_8 &= d_2 - c_4 y_8 - b_3 y_7 y_8 \\
\dot{y}_9 &= -c_5 y_9 - e_1\zeta(y_9)y_9 l(y_4) + 2e^{-c_5\tau_4}e_1\zeta(y_{9\tau_4})y_{9\tau_4}l(y)_{4\tau_4} \\
&\quad + 2^{m_1}b_{41}y_{7\tau_6}y_{8\tau_6}l(y_{4\tau_6}) \\
\dot{y}_{10} &= -c_6 y_{10} - e_2 y_9 y_{10}\zeta(y_9) + 2e^{-c_6\tau_5}e_2 y_{9\tau_5}y_{10\tau_5}\zeta(y_{9\tau_5}) \\
&\quad + 2^{m_2}b_{42}y_{7\tau_7}y_{8\tau_7}l(y_{4\tau_7}) \\
\dot{y}_{11} &= -c_7 y_{11} - e_3 y_9 y_{11}\zeta(y_9) + 2e^{-c_7\tau_8}e_3 y_{9\tau_8}y_{11\tau_8}\zeta(y_{9\tau_8}) \\
&\quad + 2^{m_3}b_{43}y_{7\tau_9}y_{8\tau_9}l(y_{4\tau_9}) - e_4\zeta_1(y_9)y_{11} - b_4 y_{11}l_1(y_4) + 2^n e_5 y_{11\tau_{10}}l_1(y_{4\tau_{10}}) \\
\dot{y}_{12} &= -c_8 y_{12}y_4 + e_6 y_{10}\tfrac{y_4}{a_5+y_4}
\end{aligned}
$$

The first equation represents the stem-like healthy cell population. This population increases by $\eta_1 e^{-\gamma_1\tau_1}$, with the cells that go through asymmetric division and by $2e^{-\gamma_1\tau_1}(1-\eta_1-\eta_2)$, with the cells that go through self-renewal. These cells return to the stem-like cell population after a time period τ_1 (see [6]). Following [7] the rate of self-renewel is

$$\beta(y) = \beta_0\frac{\theta_1^m}{\theta_1^m + y^m}.$$

and the rate of differentiation is

$$k(y) = k_0\frac{\theta^n}{\theta^n + y^n}.$$

Equation 2 represents the dynamics of healthy monocytes governed by the amplification of $2\eta_2 + \eta_1$ stem-like cells that went through differentiation. A is an multiplication (amplification) factor. τ_2 is the time for the stem-like cells to become mature. The third term represents the infection process (see [12]). τ_3 is the time necessary for an uninfected monocyte to become actively infected monocyte after the CHIKV entry (such monocyte produces new CHIKV particles). The mortality of non-infected monocytes to the age τ_3 is represented by $e^{-\gamma_2\tau_3}$. The fourth term is the description of monocyte migration to other tissues, though the Lymph nodes (LNs).

Equation 3 describes the pharmacokinetic (PK) of the antiviral Ribavirin in the tissue. Since static drug concentrations were used, a rapid fusion rate was used in R, the infusion-rate constant. Additionally, the clearance rate (C), and the volume (V) parameters were set to simulate a continuous infusion (see [13]).

Equation 4 describes the viral burden, where y_4 represents CHIKV titers (measured in log10 PFU per milliliter). k_t is the first-order viral production rate, constant for CHIKV and E is the concentration of drug at which viral production rate constants are reduced by half. h represents the Hill constant, and p_m is the mayimal amount of total viral burden and is part of the logistic carrying function. k_d is the first order rate of disintegration of infectious viral particles (see [13]). The Hill-type function:

$$P_1(y_4) = \frac{y_4^r}{y_4^r + k_2^r}$$

represents receptor-ligand binding kinetics between the virus and activated monocytes. r_1 is the rate at which the virus are killed by inflammatory monocytes. Antibodies can opsonize the virus and contribute to further virus clearance at the late stage of inflammation, as represented by the fourth term, $r_2P_2(y_4)y_{12}$, where:

$$P_2(y_4) = \frac{y_4^r}{y_4^r + k_3^r}.$$

Equation 5 describes the dynamics of infected monocytes. The first term represents the infection process. A natural mortality with rate γ_3 is present through the second term. Infected monocytes can be recognized and removed by $CD8+$ T-cells. This process is described by the third term. The fourth term represents the migration of infected monocytes to other tissues and this term is important since infected monocytes are apparently the main cellular reservoirs during the late stages of CHIKV infection in vivo. Infected blood monocytes may therefore disseminate the virus to sanctuaries sites supporting persistent viral replication in the chronic phase of the disease (see [22]).

The following feedback functions regulate the evolution of the immune system and its interaction with infected cells (see [17] and [18]):

$$l(y) = \frac{y}{a_1 + y^2}, l_1(y) = \frac{y}{a_2 + y^2}, \zeta(y) = \frac{1}{1+y}, \zeta_1(y) = \frac{a_3 + y^2}{a_4 + y^2}.$$

Equation 6 represents the concentration of immature APCs, equation 7 the concentration of mature APCs, equation 8 the concentration of naive T cells of both CD4+ and CD8+ phenotype, equation 9 the concentration of active CD4+ T-helper cells, equation 10 the concentration of active B lymphocytes, equation 11 the active CD8+ cytotoxic T-cells that play a role in removing the infected cells and equation 12 the concentration of antibodies produced by the B cells.

3. **Equilibrium Points**

We introduce the following notation for the previous system:

$$\dot{y}_i = f_i(y, y_{\tau_j}),\ i = \overline{1,12},\ j = \overline{1,10},\ y = (y_1, ..., y_{12}).$$

The equilibrium points are obtained solving the equations $f_i(y,y)=0$, $i=\overline{1,12}$.
We notice first that, from $f_3=0, f_6=0$ and $f_8=0$ it follows that:

$$\begin{aligned}\hat{y}_3 &= \tfrac{VR}{C},\\ \hat{y}_6 &= \tfrac{d_1}{c_2},\\ \hat{y}_8 &= \tfrac{d_2}{c_4}.\end{aligned}$$

The lanscape of equilibrium points is varied but, in order to keep the number of pages in a reasonable margin and due to its medical implications, we will analyse in this paper only the equilibrium point E_1 obtained for:
$y_1=y_2=y_4=y_5=y_7=y_9=y_{10}=y_{11}=y_{12}=0$,

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

that can be interpreted as the equilibrium representing the last stage of the disease. We leave for future work the analysis of other equilibrium points.

4. **Stability Analysis**

When linearizing the system around E_1, the following matrices are to be used in the study of the stability of equilibrium point E_1.

$$A=\frac{\partial f}{\partial y}$$

$$\begin{aligned}
a_{11} &= -\gamma_1-(\eta_1+\eta_2)k(y_2+y_5)-(1-\eta_1-\eta_2)\left[\beta(y_1)+y_1\beta'(y_1)\right],\\
a_{12} &= -(\eta_1+\eta_2)k^{'}(y_2+y_5)y_1,\\
a_{15} &= -(\eta_1+\eta_2)k^{'}(y_2+y_5)y_1,\\
a_{22} &= -\gamma_2-p,\\
a_{33} &= -\tfrac{C}{V},\\
a_{42} &= -r_1P_1(y_4),\\
a_{43} &= -\tfrac{E.h(\frac{y_3}{V})^{h-1}}{\left(E+(\frac{y_3}{V})^h\right)^2}k_ty_4\left(1-\tfrac{y_4}{p_m}\right),\\
a_{4,12} &= -r_2P_2(y_4),\\
a_{44} &= k_t\left(1-\left[\tfrac{(\frac{y_3}{V})^h}{E+(\frac{y_3}{V})^h}\right]\right)\left(1-\tfrac{2}{p_m}y_4\right)\\
&\quad -k_d-r_1P_1^{'}(y_4)y_2-r_2P_2^{'}(y_4)y_{12},\\
a_{52} &= r_1P_1(y_4), a_{54}=r_1P_1^{'}(y_4)y_2,\\
a_{55} &= -\gamma_3-k_1\delta y_{11}-p,\\
a_{5,11} &= -k_1\delta y_5, a_{64}=-b_2y_6l^{'}(y_4),\\
a_{66} &= -c_2-b_2l(y_4),\\
a_{74} &= b_2y_6l^{'}(y_4),\\
a_{76} &= b_2l(y_4), a_{77}=-c_3,\\
a_{87} &= -b_3y_8, a_{88}=-c_4-b_3y_7,\\
a_{94} &= -e_1\zeta(y_9)y_9l^{'}(y_4),\\
a_{99} &= -c_5-e_1\zeta^{'}(y_9)y_9l(y_4)-e_1\zeta(y_9)l(y_4),\\
a_{10,9} &= -e_2y_{10}\zeta(y_9)-e_2y_9y_{10}\zeta^{'}(y_9),\\
a_{10,10} &= -c_6-e_2y_9\zeta(y_9),\\
a_{11,4} &= -b_4y_{11}l_1^{'}(y_4),\\
a_{11,9} &= -e_3y_{11}[\zeta(y_9)+y_9\zeta'(y_9)]-e_4\zeta_1'(y_9)y_{11},\\
a_{11,11} &= -c_7-e_3y_9\zeta(y_9)-e_4\zeta_1(y_9)-b_4l_1(y_4),\\
a_{12,4} &= -c_8y_{12}+e_6y_{10}\tfrac{a_4}{(a_4+y_4)^2},\\
a_{12,10} &= e_6\tfrac{y_4}{a_4+y_4}, a_{12,12}=-c_8y_4.
\end{aligned}$$

$$B = \frac{\partial f}{\partial y_{\tau_1}}$$

$b_{11} = +2e^{-\gamma_1\tau_1}(1-\eta_1-\eta_2)\,[\beta(y_1)+y_1\beta'(y_1)]$
$+\eta_1 e^{-\gamma_1\tau_1}k(y_2+y_5)$,
$b_{12} = \eta_1 e^{-\gamma_1\tau_1}k^{'}(y_2+y_5)y_1$,
$b_{15} = \eta_1 e^{-\gamma_1\tau_1}k^{'}(y_2+y_5)y_1$.

$$C = \frac{\partial f}{\partial y_{\tau_2}}$$

$c_{21} = A(2\eta_2+\eta_1)k(y_2+y_5)$,
$c_{22} = A(2\eta_2+\eta_1)k^{'}(y_2+y_5)y_1$,
$c_{25} = A(2\eta_2+\eta_1)k^{'}(y_2+y_5)y_1$.

$$D = \frac{\partial f}{\partial y_{\tau_3}}$$

$d_{2,2} = -r_1 e^{-\gamma_2\tau_3}P_1(y_4)$,
$d_{2,4} = -r_1 e^{-\gamma_2\tau_3}P_1^{'}(y_4)y_2$.

$$E = \frac{\partial f}{\partial y_{\tau_4}}$$

$e_{9,4} = 2e^{-c_5\tau_4}e_1\zeta(y_9)y_9 l^{'}(y_4)$,
$e_{9,9} = 2e^{-c_5\tau_4}e_1 l(y_4)[\zeta(y_9)+y_9\zeta'(y_9)]$.

$$F = \frac{\partial f}{\partial y_{\tau_5}}$$

$f_{10,9} = 2e^{-c_6\tau_5}e_2 y_{10}[\zeta(y_9)+y_9\zeta'(y_9)]$,
$f_{10,10} = 2e^{-c_6\tau_5}e_2 y_9\zeta(y_9)$.

$$G = \frac{\partial f}{\partial y_{\tau_6}}$$

$g_{9,4} = 2^{m_1}b_{41}y_7y_8 l^{'}(y_4)$,
$g_{9,7} = 2^{m_1}b_{41}y_8 l(y_4)$,
$g_{9,8} = 2^{m_1}b_{41}y_7 l(y_4)$.

$$H = \frac{\partial f}{\partial y_{\tau_7}}$$

$h_{10,4} = 2^{m_2}b_{42}y_7y_8 l^{'}(y_4)$,
$h_{10,7} = 2^{m_2}b_{42}y_8 l(y_4)$,
$h_{10,8} = 2^{m_2}b_{42}y_7 l(y_4)$.

$$I = \frac{\partial f}{\partial y_{\tau_8}}$$

$i_{11,9} = 2e^{-c_7\tau_8}e_3 y_{11}[\zeta(y_9)+y_9\zeta'(y_9)]$,
$i_{11,11} = 2e^{-c_7\tau_8}e_3 y_9\zeta(y_9)$.

$$J = \frac{\partial f}{\partial y_{\tau_9}}$$

$j_{10,4} = 2^{m_3}b_{43}y_7y_8 l^{'}(y_4)$,
$j_{10,7} = 2^{m_3}b_{43}y_8 l(y_4)$, $j_{10,8}$
$= 2^{m_3}b_{43}y_7 l(y_4)$.

$$K = \frac{\partial f}{\partial y_{\tau_{10}}}$$

$k_{11\,4} = 2^n e_5 y_{11} l'(y_4)$ $k_{11\,11} = 2^n e_5 l_1(y_4)$.

The general form of the characteristic equation is:

$det(\lambda I - A - e^{-\lambda\tau_1}B - e^{-\lambda\tau_2}C - e^{-\lambda\tau_3}D - e^{-\lambda\tau_4}E - e^{-\lambda\tau_5}F$
$-e^{-\lambda\tau_6}G - e^{-\lambda\tau_7}H - e^{-\lambda\tau_8}I - e^{-\lambda\tau_9}J - e^{-\lambda\tau_{10}}K) = 0.$

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. Suppose the transcendental equation have only roots with negative real parts.Then the critical case is completely investigated in [4] where we have the following theorem.

Consider the nonlinear system with time delays :

$$\begin{aligned} \dot{x}(t) &= A_0 x(t) + \sum_{j=1}^{m} A_j x(t-\tau_j) + F[x(t), x(t-\tau_1), ..., x(t-\tau_m), y(t)] \\ \dot{y}(t) &= G[x(t), x(t-\tau_1), ..., x(t-\tau_m), y(t)], \end{aligned} \tag{1}$$

where $A_j \in M_n(\mathbb{R})$, $\tau_j > 0$ for all $1 \leq j \leq m$, $G(0,0,...,0,y) = F(0,0,...,0,y) = 0$, $\forall y \in \mathbb{R}$, F takes values in $\mathbb{R}^n$ and G is scalar. F and G contain only powers of the variables with sum greater or equal to two. Then, for every $\delta > 0$, there exist $M_1(\delta)$ and $M_2(\delta)$ with $\lim\limits_{\delta\to 0} M_1(\delta) = \lim\limits_{\delta\to 0} M_2(\delta) = 0$ so that, whenever $||x(t)|| \leq \delta, ||x(t-\tau_j)|| \leq \delta, 1 \leq j \leq m, |y| \leq \delta$,

$$\begin{aligned} &\|F(x(t), x(t-\tau_1), \ldots, x(t-\tau_m), y(t))\| \leq \\ &\leq M_1(\delta)\left(\|x(t)\| + \|x(t-\tau_1)\| + \cdots + ||x(t-\tau_m)||\right) \\ &\|G(x(t), x(t-\tau_1), \ldots, x(t-\tau_m), y(t))\| \leq \\ &\leq M_2(\delta)\left(\|x(t)\| + \|x(t-\tau_1)\| + \cdots + ||x(t-\tau_m)||\right). \end{aligned} \tag{2}$$

Theorem 4.1. *(see [4]) Consider the previous system (1). Suppose that the linear system:*

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

is asymptotically stable, that is, if λ is a root of the characteristic equation, then $Re(\lambda) < 0$. Then the zero solution of (1) is simple stable and, if φ is the initial data of (1) in $C\left([-\tau, 0]; \mathbb{R}^{n+1}\right)$ with $\tau = \max\limits_{1\leq j\leq m} \tau_j$, there exist $\delta > 0$ so that, if $\sup\{||\varphi(t)||_2 / t \in [-\tau, 0]\} < \delta$,then

$$\lim_{t\longrightarrow\infty} x_i(t) = 0, i = 1, ..., n \text{ and } \exists \lim_{t\longrightarrow\infty} y(t) = \tilde{y}.$$

Since we do not have the linear part of some equation 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 first a translation to zero by $x_i = y_i - \hat{y}_i$.

The new system becomes:

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

We take $\eta = \alpha_1 x_1 + \alpha_2 x_2 + \cdots + \alpha_{12} x_{12}$
where $\dot{x} = Ax$ and $A = \frac{\partial \bar{f}}{\partial x}(0) = [a_{ij}]_{i,j}$

Then

$$\dot{\eta} = \alpha_1 x_1 + \alpha_2 x_2 + \cdots + \alpha_{12} x_{12}.$$

So

$$\begin{aligned}\dot{\eta} &= \alpha_1 a_{11}x_1 + \alpha_2 a_{22}x_2 + \alpha_3 a_{33}x_3 + (\alpha_4 a_{44} + \alpha_6 a_{64} + \alpha_7 a_{74} \\ &\quad +\alpha_{12}a_{12,4})x_4 + \alpha_5 a_{55}x_5 + \alpha_6 a_{66}x_6 + (\alpha_7 a_{77} + \alpha_8 a_{87})x_7 \\ &\quad +\alpha_8 a_{88}x_8 + \alpha_9 a_{99}x_9 + \alpha_{10}a_{10,10}x_{10} + \alpha_{11}a_{11,11}x_{11}.\end{aligned}$$

Now if one imposes $\dot{\eta} = 0$, it follows that

$$\alpha_4 a_{44} + \alpha_6 a_{64} + \alpha_7 a_{74} + \alpha_{12}a_{12,4} = 0$$

$$\alpha_7 a_{77} + \alpha_8 a_{87} = 0.$$

Since $\alpha_6 = \alpha_8 = 0$, then $\alpha_7 = 0$.
For $\alpha_{12} = 1$ we have $\alpha_4 = -\frac{a_{12,4}}{a_{44}}$, thus

$$\eta = \alpha_4 x_4 + x_{12},$$

and the equation of η has no linear part, that is

$$\dot{\eta} = Q_4^{(2)},$$

with $Q_4^{(2)}$ containing only terms of order greater or equal to two. Take,

$$x_{12} = \eta - \alpha_4 x_4,$$

Replace the twelfth equation by the equation of $\dot{\eta}$ so this equation has a zero linear term. Substitute x_{12} in the equations of the system and define:

$$\begin{aligned}&g_4(x_2, x_3, x_4, \eta) = k_t x_4 \left(1 - \left[\frac{(\frac{x_3}{V})^h}{E+(\frac{x_3}{V})^h}\right]\right)\left(1 - \frac{x_4}{p_m}\right) \\ &-k_d x_4 - r_1 P_1(x_4)x_2 - r_2 P_2(x_4)(\eta - \alpha_4 x_4).\end{aligned}$$

Remark that the linear part of g_4 does not contain η and the other equations do not contain η at all. From the previous calculations we conclude that the general theorem on the critical case can be applied to the system. 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:

$$\lambda - a - be^{-\lambda\tau} = 0 \tag{4}$$

and is completely investigated in many places. For example, from [8], we have the following theorem:

Theorem 4.2. *All the roots of equation (4) have negative real parts if and only:*

(1) $a\tau < 1$
(2) $a + b < 0$
(3) $-b\tau < \sqrt{\theta^2 + a^2\tau^2}$ where θ is the unique root of $\theta = a\tau\tan\theta$, $0 < \theta < \pi$ or $\theta = \frac{\pi}{2}$ if $a = 0$

Remark 4.1. *If $b > 0$, then the conditions reduce to $a\tau < 1$ and $a + b < 0$.*

As shown also in [8], if equation (4) is stable for $\tau = 0$, then either it is stable for all $\tau \geq 0$, or there is a value τ^*such that it is stable for $\tau < \tau^*$ and unstable for $\tau > \tau^*$, without the possibility of restabilization for larger τ.

In our case the equation is:

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

Proposition 4.1. *Assume that the following condition holds true:*

$$(1 - \eta_1 - \eta_2)\beta_0 < \gamma_1 + \eta_2 k_0. \tag{6}$$

Then equation (5) is stable for $\tau_1 = 0$ and remains stable for $\tau_1 > 0$.

Proof: For the equilibrium point E_1 we have $x_1 = x_2 = 0$, and $k(0) = k_0$, $\beta(0) = \beta_0$, so

$$a_{11} = -\gamma_1 - (\eta_1 + \eta_2)k_0 - (1 - \eta_1 - \eta_2)\beta_0 < 0,$$
$$b_{11} = 2e^{-\gamma_1\tau_1}(1 - \eta_1 - \eta_2)\beta_0 + \eta_1 e^{-\gamma_1\tau_1}k_0 > 0.$$

For $\tau_1 = 0$ equation (5) becomes:

$$\lambda + \gamma_1 + \eta_2 k_0 - (1 - \eta_1 - \eta_2)\beta_0 = 0.$$

Equation (5) is stable for $\tau_1 = 0$ if:

$$(1 - \eta_1 - \eta_2)\beta_0 < \gamma_1 + \eta_2 k_0.$$

When $\tau_1 > 0$, since $b_{11} > 0$, using Theorem (4.2) and Remark (4.1) the following conditions must hold for stability:

(1) $a_{11} < \frac{1}{\tau_1}$
(2) $a_{11} + b_{11} < 0$

Since we have,

$$a_{11} = -\gamma_1 - (\eta_1 + \eta_2)k_0 - (1 - \eta_1 - \eta_2)\beta_0 < 0 < \frac{1}{\tau_1},$$

the first condition holds true. For the second condition to hold we must have :

$$e^{-\gamma_1\tau_1} < \frac{\gamma_1 + (\eta_1 + \eta_2)k_0 + (1 - \eta_1 - \eta_2)\beta_0}{2(1 - \eta_1 - \eta_2)\beta_0 + \eta_1 k_0}. \tag{7}$$

We notice that condition (7) follows from (6) and the Proposition is proved.

5. **Numerical Simulations**

In figure 1, the trajectories starting in a neighborhood of equilibrium E_1, representing the most aggravated phase of the disease, are plotted. The values and the interpretation of the parameters are given in Table 1. In this case, the left hand side of the inequality giving the stability of E_1 is equal to 0.345, while the right hand side is 0.11, hence the inequality is not satisfied. Moreover, one can easily notice that y_1 and y_2 representing the healthy monocyte population and precursors are unstable while y_4 and y_5 representing the Chikungunya virus population and the infected monocytes population are stable. From a medical point of view, this might translate into the recovery of the patient, since the Chikungunya virus and the infected monocytes are vanishing while the healthy monocytes are recovering.

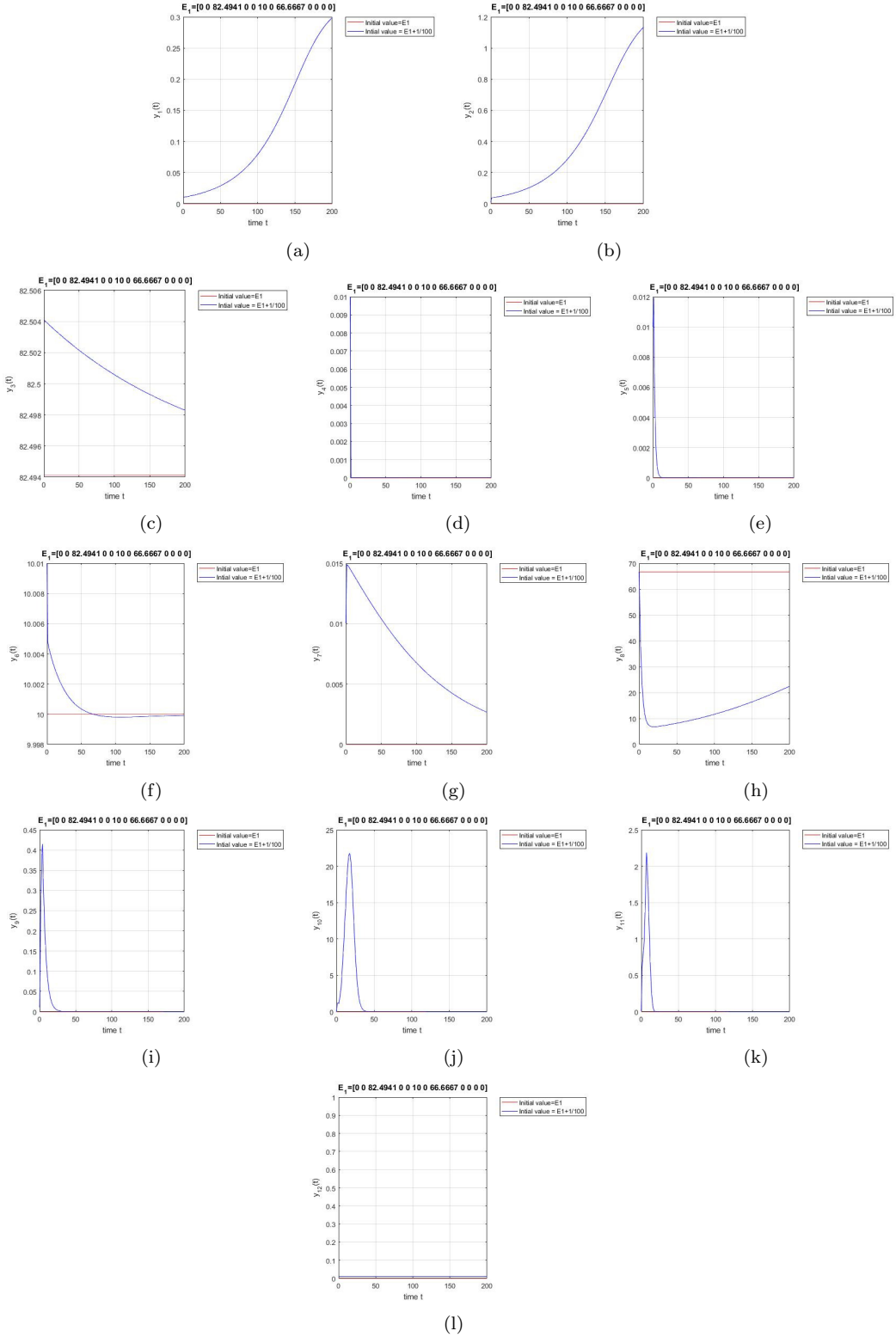

FIGURE 1. Small disturbances in initial conditions near E_1.

Maximal value of the β function [7], [1]	β_0	1.77
Maximal value of the function k [1]	k_0	0.1
Parameter for the β function [7]	θ_1	0.5
Parameter for the function k [5]	θ	36
Parameter in the Hill function β [6]	m	2
Parameter in the Hill function k [6]	n	2
Loss of stem cells due to mortality [1]	γ_1	0.1
Rate of asymmetric division for healthy cells [5]	η_1	0.7
Rate of symmetric division for healthy cells [5]	η_2	0.1
Instant mortality of mature monocytes [12]	γ_2	2.4
Amplification factor of healthy cells [7]	A	120
The extent of ligands binding to receptors (*estimated)*	r	2
Concentration of monocytes which phagocytose half of the virus (*estimated)*	k_2	0.002
Concentration of antibody which kills half of the virus (*estimated)*	k_3	0.035
Rapid fusion rate of the virus [13]	R	0.36
clearence rate of the virus [13]	C	15.3
volume [13]	V	3506
viral production rate [13]	k_t	0.85
Drug concentration [13]	E	142.7
Hill constant [13]	h	4.28
maximum amount of total viral burden [13]	p_m	8.54
Rate of disintegration of infictious viral particles [13]	k_d	0.37
Rate at which the virus are killed by monocytes (*estimated)*	r_1	7
Rate at which the virus are killed by antibodies (*estimated)*	r_2	1
Instant mortality of infected monocytes (*estimated)*	γ_3	0.15
Fraction of monocytes migrating to LNs (*estimated)*	p	0.4
A fraction of actively infected monocytes (*estimated)*	p_1	0.5
Rate of CD8+ removes infected cells (*estimated)*	k_1	2.5
Recognition rate of infected moncytes (*estimated)*	δ	0.001
Supply daily rate of immature APCs [5]	d_1	0.3
Death/turnover dayly rate of immature APCs [5]	c_2	0.03
Coefficient of the feedback function l [6]	a_1	1.5
Coefficient of the feedback function l_1 [6]	a_2	5
Coefficient of the "regulatory process" function ζ_1 [6]	a_3	0.2
Coefficient of the "regulatory process" function ζ_1 [6]	a_4	3.48
Coefficient of feedback maturation of immature APCs (*estimated)*	b_2	1
Death/turnover dayly rate of mature APCs [18]	c_3	0.01
Supply rate of naive T cells of both fenotypes [18]	d_2	2
Death/turnover dayly rate of naive CD4+ and CD8+ T cells [18]	c_4	0.03
Kinetic coefficient [17]	b_3	20
Kinetic coefficients [17]	b_{41}, b_{42}, b_{43}	10, 10,10
Death/turnover dayly rate of effector CD4+ T helper cells [5]	c_5	0.23
Death/turnover rate of effector B lymphocytes (*estimated)*	c_6	0.4/day
Number of divisions in minimal CD4+ developmental program (*estimated)*	m_1	2
Number of divisions in minimal B lymphocytes developmental program (*estimated)*	m_2	7
Coefficient of the autocrine loop function (*estimated)*	e_1	0.2
Coefficient of the positive growth signal function (*estimated)*	e_2	40
Maximum reproduction rate [20]	e_6	0.6
Decay rate of antibodies [20]	c_8	$5 * 10^{-2}$
Population when the antibodies grow half of its maximum growth rate [20]	a_5	150
Death/turnover rate of effector CD8+ T cytotoxic cells [18]	c_7	0.4
Coefficient of the "positive growth signal" function ζ [18]	e_3	40
Coefficient of the regulatory process function ζ_1 [18]	e_4	60
Coefficient of the "regulatory process" function ζ_1 [18]	e_5	0.2
Number of divisions in minimal CD8+ developmental program (*estimated)*	m_3	7
Coefficient for apopthosis rate and regulatory mechanism (*estimated)*	b_4	0.8
The number of antigen depending divisions (*estimated)*	n	2
Duration of stem cells' cycle of self-renewall [7]	τ_1	2.8
Duration of stem cells' cycle of differentiation [7]	τ_2	3.5
Time between CHIKV entry monocytes to become actively infected [12]	τ_3	2.3086
Duration of one $CD4^+T$ cell division (*estimated)*	τ_4	2.6
Duration of one B lymphocyte cell division (*estimated)*	τ_5	1.4
Duration of minimal developmental program [6]	τ_6	$1 + (m_1 - 1)\tau_4$
Duration of minimal developmental program [6]	τ_7	$1 + (m_2 - 1)\tau_5$
Duration of one $CD8^+$ T cell division [6]	τ_8	1
Duration of minimal developmental program [6]	τ_9	$1 + (m_3 - 1)\tau_8$
Duration of minimal developmental program [6]	τ_{10}	$n\tau_8$

TABLE 1. Parameters of the model.

6. Conclusion

The Chikungunya virus is a re-emerging mosquito-borne virus that causes a broad range of severe clinical symptoms in humans. In this paper a complex model of DDEs for the evolution of Chikungunya under treatment is introduced. A critical case appears in the characteristic equation of one equilibrium point, representing an aggravated stage of the disease . The critical case theorem from [4] is applied, followed by the study of a transcendental equations. The numerical results complete the study, emphasizing that the mathematical model is in line with medical evidence.

Acknowledgment

The authors wish to thank the referees for their careful reading of the article and useful comments

Author's contributions

All the authors have equal contributions in this paper.

REFERENCES

[1] *M. Adimy, Y. Bourfia, M. L. Hbid, C. Marquet*, Age-structured model of hematopoiesis dynamics with growth factor-dependent coefficients. Electr. J. of Diff. Eq., vol. 2016 (2016), no. 140, pp. 1-20.
[2] *M. Adimy, F. Crauste, S. Ruan*, A mathematical study of the hematopoiesis process with application to chronic myelogenous leukemia. SIAM J. Appl. Math., 2005, 65(4), 1328–1352.
[3] *M. Adimy, F. Crauste, S. Ruan*, Periodic oscillations in leukopoiesis models with two delays. J. Theor. Biol., 2006, 242, 288-299.
[4] *K. Amin, I. Badralexi, A. Halanay, R. Mghames*, A stability theorem for equilibria of delay differential equations in a critical case with application to a model of cell evolution, Math. Model. Nat. Phenom. 16 (2021) 36.
[5] *S. Balea, A. Halanay, D. Jardan, M. Neamtu, C. A. Safta*, Stability Analysis of a Feedback Model for the Action of the Immune System in Leukemia, Math. Model. Nat.Phenom. 2014, Vol. 9, No. 1, pp. 108-132.
[6] *I. Badralexi, S. Balea, A. Halanay, D. Jardan, R. Radulescu*, A complex model of cell evolution in leukemia including competition and the action of the immune system, Ann. Acad. Rom. Sci. Ser. Math. Appl. Vol. 12, No. 1-2/ (2020).
[7] *C. Colijn, M. C. Mackey*, A Mathematical Model for Hematopoiesis: I. Periodic Chronic Myelogenous Leukemia. J. Theor. Biol. 237, 2005, pp. 117-132.
[8] *K.L. Cooke, Z. Grossmann*, Discrete delay, distributed delay and stability switches. J. Math. Analy. and Applic. 1982, 86(2), 592-627.
[9] *M. Dubrulle, et al.*, Chikungunya virus and Aedes mosquitoes: Saliva is infectious as soon as two days after oral infection, PLOS ONE, (2009), 4(6): p. e5895.
[10] *K. Cooke, P. van den Driessche*, On Zeroes of Some Transcendental Equations. Funkcialaj Ekvacioj. (1986), 29, 77-90.
[11] *Parashar D, Cherian S,* Antiviral perspectives for chikungunya virus. BioMed ResInt 2014; 2014:1–11.
[12] *A. Elaiw, T. Alade & S. Alsulami*, Analysis of latent CHIKV dynamics models with general incidence rate and time delays. Journal of Biological Dynamics, 2018, VOL. 12, NO. 1, 700–730.
[13] *K. M. Gallegos, G. L. Drusano, D. Z. D'Argenio*, Chikungunya Virux: In vitro Response to Combination Therapy With Ribavirin and Interferon Alfa 2. The journal of infictious disease, 2016, pp. 1192-1197.
[14] *L. Goffart I, A. Nougairede, S. Cassadou*, Chikungunya in the Americas. Lancet. 2014, 383-514.
[15] *A. Halanay, D. Candea, I.R. Radulescu*, Existence and Stability of Limit Cycles in a Two Delays Model of Hematopoietis Including Asymmetric Division. Math. Model. Nat. Phen. 9, 2014, no.1, 58-78.
[16] *Z. Her, B. Malleret, M. Chan*, Active Infection of Human Blood Monocytes by Chikungunya Virus Triggers an Innate Immune Response. The journal of Immunology, 2020, 5903-5913.
[17] *P. Kim, P. Lee, D. Levy*, Emergent Group Dynamics Governed by Regulatory Cells Produce a Robust Primary T Cell Response, Bull. Math. Biol.,72: (2010).
[18] *P. Kim, P.Lee, D. Levy*, A theory of immunodominance and adaptive regulation. Bull.Math. Biol., 2010.

[19] *I. G. Malkin*, Theory of stability of motion (in Russian)Nauka, Moskow (English translation: Atomic Energy Comm. Translation AEC–TR–3352), 1966.
[20] *B. Ma, C. Li, J. Warner*, Structured mathematical models to investigate the interactions between Plasmodium falciparum malaria parasites and host immune response. Mathematical Biosciences, 2019, 310, 65-75.
[21] *I. Radulescu, D. Candea, A. Halanay*, A study on stability and medical implicationsor a complex delay model for CML with cell competition and treatment. Journal of Theoretical Biology, 2014, 363, 30-40.
[22] *I.Tanabe, E. Tanabe, E. Santos, W. Martins, I. Araújo*, Cellular and Molecular Immune Response to Chikungunya Virus Infection, Frontiers in cellular and infection microbiology, v.8, (2018).