ON THE STABILITY OF AN EQUILIBRIUM POINT IN A MODEL OF CELL EVOLUTION IN CHIKUNGUNYA

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This paper continues the study of a delay differential equation model for Chikungunya, begun in [2]*, detailing the disease's progression under Ribavirin treatment. The model incorporates physiological representations of the evolution of hematopoietic cells, both healthy and infected monocytes, alongside the immune system's activities. The stability properties of one equilibrium point, that can be viewed as a healthy state, are examined using a critical case theorem and transcendental equation analysis. Finally, numerical simulations demonstrate a favorable prognosis from a medical perspective.*

Keywords. Chikungunya, Immune Response, Equilibrium Points, Stability Analysis, Critical Case, Numerical Simulations.

1. Introduction

Chikungunya is a viral illness transmitted to humans through the bites of infected mosquitoes, primarily the Aedes aegypti and Aedes albopictus species. The disease is caused by the Chikungunya virus (CHIKV), a member of the Togaviridae family, genus Alphavirus. Chikungunya fever was first identified during an outbreak in Tanzania in 1952, (see [5]).

The name "Chikungunya" originates from the Makonde language, meaning "to become contorted," describing the stooped appearance of individuals afflicted with severe joint pain, a hallmark symptom of the disease. Chikungunya is characterized by abrupt onset of fever, debilitating joint pain, muscle aches, headache, fatigue, and rash. While not usually fatal, the symptoms can be severe and disabling, impacting an individual's quality of life for weeks to months, (see [6]).

Chikungunya has historically been prevalent in Africa and Asia, especially the Indian subcontinent. However, in recent years, the virus has spread to new regions, including the Americas, causing large outbreaks and garnering increased global attention.

The transmission cycle involves mosquitoes biting infected individuals and then transmitting the virus to other humans they subsequently bite. There have also been rare cases of transmission from mother to newborn during childbirth, as well as through blood transfusion, (see [7] and [8]).

Given its potential for rapid spread and significant impact on public health, Chikungunya remains a concern for global health authorities, necessitating ongoing research efforts into prevention, treatment, and control strategies.

The structure of the paper is outlined as follows: In Section 2, we present a Delay Differential Equation (DDE) model of Chikungunya under treatment, integrating the role of the immune system, already introduced in [2]. Section 3 is dedicated to identifying the equilibrium points. The stability analysis of E_2 is explored in Section 4, employing a critical case theorem that utilizes the Lyapunov-Malkin approach specifically tailored

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for delay differential equations. Section 5 showcases the results of numerical simulations conducted, offering insights into the dynamics of the proposed model.

2. The Model

The model comprises 12 equations integrating various biological processes. Equation 1 represents the evolution of healthy stem-like cells. Equation 2 outlines the dynamics of healthy monocytes. Equation 3 illustrates the pharmacokinetics (PK) of the antiviral Ribavirin within tissue. Equation 4 characterizes the viral load. Equation 5 describes the dynamics of infected monocytes. Equation 6 quantifies the concentration of immature antigen-presenting cells (APCs), while equation 7 specifies the concentration of mature APCs. Equation 8 describes the evolution of the concentration of naive T cells, encompassing both CD4+ and CD8+ phenotypes. Equation 9 portrays the concentration of active CD4+ T-helper cells. Equation 10 represents the concentration of active B lymphocytes. Equation 11 accounts for the activity of CD8+ cytotoxic T-cells, instrumental in eliminating infected cells. Lastly, equation 12 captures the concentration of antibodies produced by B cells. All pertinent information regarding the model can be found in (see [2] and [3]).
The model is:

$$
\begin{aligned}
\dot{x}_1 = \; & -\gamma_1 x_1 - (\eta_1+\eta_2)k(x_2+x_5)x_1 - (1-\eta_1-\eta_2)\beta(x_1)x_1 \\
& +2e^{-\gamma_1\tau_1}(1-\eta_1-\eta_2)\beta(x_{1\tau_1})x_{1\tau_1} + \eta_1 e^{-\gamma_1\tau_1}k(x_{2\tau_1}+x_{5\tau_1})x_{1\tau_1} \\
\dot{x}_2 = \; & -\gamma_2 x_2 + A(2\eta_2+\eta_1)k(x_{2\tau_2}+x_{5\tau_2})x_{1\tau_2} \\
& -r_1 e^{-\gamma_2\tau_3}P_1(x_{4\tau_3})x_{2\tau_3} - p x_2 \\
\dot{x}_3 = \; & R - (\tfrac{C}{V})x_3 \\
\dot{x}_4 = \; & k_t x_4 \left(1 - \left[\frac{(\frac{x_3}{V})^h}{E+(\frac{x_3}{V})^h}\right]\right)\left(1-\frac{x_4}{p_m}\right) - k_d x_4 - r_1 P_1(x_4)x_2 \\
& -r_2 P_2(x_4)x_{12} \\
\dot{x}_5 = \; & r_1 P_1(x_4)x_2 - \gamma_3 x_5 - k_1\delta x_{11}x_5 - p x_5 \\
\dot{x}_6 = \; & d_1 - c_2 x_6 - b_2 x_6 l(x_4) \\
\dot{x}_7 = \; & -c_3 x_7 + b_2 x_6 l(x_4) \\
\dot{x}_8 = \; & d_2 - c_4 x_8 - b_3 x_7 x_8 \\
\dot{x}_9 = \; & -c_5 x_9 - e_1\zeta(x_9)x_9 l(x_4) + 2e^{-c_5\tau_4}e_1\zeta(x_{9\tau_4})x_{9\tau_4}l(x_{4\tau_4}) \\
& +2^{m_1}b_{41}x_{7\tau_6}x_{8\tau_6}l(x_{4\tau_6}) \\
\dot{x}_{10} = \; & -c_6 x_{10} - e_2 x_9 x_{10}\zeta(x_9) + 2e^{-c_6\tau_5}e_2 x_{9\tau_5}x_{10\tau_5}\zeta(x_{9\tau_5}) \\
& +2^{m_2}b_{42}x_{7\tau_7}x_{8\tau_7}l(x_{4\tau_7}) \\
\dot{x}_{11} = \; & -c_7 x_{11} - e_3 x_9 x_{11}\zeta(x_9) + 2e^{-c_7\tau_8}e_3 x_{9\tau_8}x_{11\tau_8}\zeta(x_{9\tau_8}) \\
& +2^{m_3}b_{43}x_{7\tau_9}x_{8\tau_9}l(x_{4\tau_9}) - e_4\zeta_1(x_9)x_{11} - b_4 x_{11}l_1(x_4) \\
& +2^n e_5 x_{11\tau_{10}}l_1(x_{4\tau_{10}}) \\
\dot{x}_{12} = \; & -c_8 x_{12}x_4 + e_6 x_{10}\tfrac{x_4}{a_5+x_4}
\end{aligned}
$$

The following notation was used for the delayed variables: $x_\tau = x(t-\tau)$.

3. Equilibrium Points

We introduce the following notation for the previous system:

$$\dot{x}_i = f_i(x, x_\tau), i = \overline{1,12}, x = (x_1, \ldots\ldots, x_{12}), , x_\tau = (x_{\tau_1}, \ldots\ldots, x_{\tau_{12}})$$

We notice first that, from $f_3 = 0, f_6 = 0$ and $f_8 = 0$ it follows that:

$$\hat{x}_3 = \frac{VR}{C}$$
$$\hat{x}_6 = \frac{d_1}{c_2}$$
$$\hat{x}_8 = \frac{d_2}{c_4}$$

For $x_1 = x_2 = x_4 = x_5 = x_7 = x_9 = x_{10} = x_{11} = x_{12} = 0$,

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

is an equilibrium point, which corresponds to the death of the patient. The stability analysis of E_1 is completely studied in ([2]).

For different equilibrium points, we look for $(\hat{x}_1, \hat{x}_2) \neq (0, 0)$, while $\hat{x}_4 = \hat{x}_5 = \hat{x}_7 = \hat{x}_9 = \hat{x}_{10} = \hat{x}_{11} = \hat{x}_{12} = 0$. To find $\hat{x}_1$ and $\hat{x}_2$, the following system must be solved:

$$-\gamma_1 x_1 + (\eta_1 e^{-\gamma_1 \tau_1} - \eta_1 - \eta_2) k(x_2) x_1 + (2e^{-\gamma_1 \tau_1} - 1)(1 - \eta_1 - \eta_2) \beta(x_1) x_1 = 0$$
$$-(\gamma_2 + p) x_2 + A(2\eta_2 + \eta_1) k(x_2) x_1 = 0$$

Then

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

is the second equilibrium point which can be viewed as a healthy state.

The study of stability for equilibria by linear approximation necessitates the calculation of the following matrices. Only the potential nonzero terms within these matrices will be introduced. The values of the state variables should be substituted with the corresponding values of the equilibrium point under examination.

$$A = \frac{\partial f}{\partial x}, B = \frac{\partial f}{\partial x_{\tau_1}}, C = \frac{\partial f}{\partial x_{\tau_2}}, D = \frac{\partial f}{\partial x_{\tau_3}}, E = \frac{\partial f}{\partial x_{\tau_4}}, F = \frac{\partial f}{\partial x_{\tau_5}}, G = \frac{\partial f}{\partial x_{\tau_6}},$$

$$H = \frac{\partial f}{\partial x_{\tau_7}}, I = \frac{\partial f}{\partial x_{\tau_8}}, J = \frac{\partial f}{\partial x_{\tau_9}} I = \frac{\partial f}{\partial x_{\tau_8}}, K = \frac{\partial f}{\partial x_{\tau_{10}}}.$$

4. Stability analysis of the equilibrium point E_2

The characteristic equation corresponding to E_2 is:

$$d = \lambda(\lambda - a_{33})(\lambda - a_{44})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})$$
$$(\lambda - a_{88})(\lambda - a_{99})(\lambda - a_{10,10})(\lambda - a_{11,11}).T$$

with

$$T = \left(\lambda - a_{11} - b_{11} e^{-\lambda\tau_1}\right)\left(\lambda - a_{22} - c_{22} e^{-\lambda\tau_2}\right) - \left(c_{21} e^{-\lambda\tau_2}\right)\left(a_{12} + b_{12} e^{-\lambda\tau_1}\right)$$
$$= \lambda^2 - a_{22}\lambda - c_{22}\lambda e^{-\lambda\tau_2} - a_{11}\lambda + a_{11}a_{22} - a_{11}c_{22}e^{-\lambda\tau_2} - \lambda b_{11} e^{-\lambda\tau_1}$$
$$+ a_{22}b_{11}e^{-\lambda\tau_1} + b_{11}c_{22}e^{-\lambda(\tau_1+\tau_2)} - a_{12}c_{21}e^{-\lambda\tau_2} - b_{12}c_{21}$$

then

$$T = \lambda^2 - (a_{22} + a_{11})\lambda + a_{11}a_{22} + (a_{22}b_{11} - \lambda b_{11}) e^{-\lambda\tau_1}$$
$$+ (-c_{22}\lambda + a_{11}c_{22} - a_{12}c_{21}) e^{-\lambda\tau_2} + (b_{11}c_{22} - b_{12}c_{21}) e^{-\lambda(\tau_1+\tau_2)}.$$

Denote by

$$T_1(\lambda) = \lambda^2 - (a_{22} + a_{11})\lambda + a_{11}a_{22} \quad (4.1)$$
$$T_2(\lambda) = a_{22}b_{11} - \lambda b_{11} \quad (4.2)$$
$$T_3(\lambda) = -c_{22}\lambda + a_{11}c_{22} - a_{12}c_{21} \quad (4.3)$$
$$T_4(\lambda) = b_{11}c_{22} - b_{12}c_{21} \quad (4.4)$$

We get

$$T = T_1(\lambda) + T_2(\lambda) e^{-\lambda\tau_1} + T_3(\lambda) e^{-\lambda\tau_2} + T_4(\lambda) e^{-\lambda(\tau_1+\tau_2)} \qquad (\mathbf{4}.5)$$

Since $\lambda = 0$ is an eigenvalue, the critical case involving the zero eigenvalue arises. The stability analysis can be addressed using a Malkin-type theorem established in [1], similar to the approach in [2].

Since $a_{33}; a_{44}; a_{55}; a_{66}; a_{77}; a_{88}; a_{99}; a_{10;10}; a_{11;11}$ are all negative, the stability is governed by the examination of the transcendental terms in the characteristic equation. As a result, the stability of E_2 relies on the roots of:

$$\Gamma(\lambda) = T_1(\lambda) + T_2(\lambda) e^{-\lambda\tau_1} + T_3(\lambda) e^{-\lambda\tau_2} + T_4(\lambda) e^{-\lambda(\tau_1+\tau_2)} = 0 \qquad (\mathbf{4}.6)$$

We adopt the approach from [9] to analyze the roots of $\Gamma(\lambda)$.

Let $\tau_1 = \tau_2 = 0$, then equation ($\mathbf{4}.6$) will be:

$$T_1(\lambda) + T_2(\lambda) + T_3(\lambda) + T_4(\lambda) = 0$$

then,

$\lambda^2 - (a_{22} + a_{11})\lambda + a_{11}a_{22} + a_{22}b_{11} - \lambda b_{11} - c_{22}\lambda + a_{11}c_{22} - a_{12}c_{21} + b_{11}c_{22} - b_{12}c_{21} = 0$

$\lambda^2 - (a_{22} + a_{11} - c_{22} + b_{11})\lambda + a_{11}a_{22} + a_{22}b_{11} + a_{11}c_{22} - a_{12}c_{21} + b_{11}c_{22} - b_{12}c_{21} = 0$

Let

$$\omega_1 = -(a_{22} + a_{11} - c_{22} + b_{11})$$

and

$$\omega_2 = a_{11}a_{22} + a_{22}b_{11} + a_{11}c_{22} - a_{12}c_{21} + b_{11}c_{22} - b_{12}c_{21}$$

which is stable if and only if $\omega_1 > 0$ and $\omega_2 > 0$.

Stability hinges on whether the roots of equation ($\mathbf{4}.6$) transition across the imaginary axis from left to right as delays change. This shift occurs only if pure imaginary roots can manifest. so it is necessary to consider the equation: $\Gamma(iz) = 0$ where z is a real number, we get

$$\begin{aligned}\Gamma(iz) = &-z^2 - (a_{22} + a_{11})iz + a_{22}a_{11} + a_{22}b_{11}e^{-iz\tau_1} - b_{11}ize^{-iz\tau_1} - c_{22}ize^{-iz\tau_2} \\ &+ a_{11}c_{22}e^{-iz\tau_2} - a_{12}c_{21}e^{-iz\tau_2} + b_{11}c_{22}e^{-iz(\tau_1+\tau_2)} - b_{12}c_{21}e^{-iz(\tau_1+\tau_2)} = 0\end{aligned}$$

Next, we explore the circumstances in which $\Gamma(iz)$ does not possess real roots for z. We will examine the equation to determine if there are particular conditions involving coefficients and parameters that could prevent the presence of real roots.

Convert the exponential terms into trigonometric form to solve equation ($\mathbf{4}.6$)

$$e^{-iz\tau_1} = \cos(z\tau_1) - i\sin(z\tau_1)$$

$$e^{-iz\tau_2} = \cos(z\tau_2) - i\sin(z\tau_2)$$

$$e^{-\lambda(\tau_1+\tau_2)} = \cos(z(\tau_1+\tau_2)) - i\sin(z(\tau_1+\tau_2))$$

Therefore

$$\begin{aligned}\Gamma(iz) = &-z^2 - (a_{22} + a_{11})iz + a_{22}a_{11} + a_{22}b_{11}\cos(z\tau_1) - ia_{22}b_{11}\sin(z\tau_1) \\ &- b_{11}iz\cos(z\tau_1) + b_{11}z\sin(z\tau_1) - c_{22}iz\cos(z\tau_2) - c_{22}z\sin(z\tau_2) \\ &+ a_{11}c_{22}\cos(z\tau_2) - ia_{11}c_{22}\sin(z\tau_2) - a_{12}c_{21}\cos(z\tau_2) + ia_{12}c_{21}\sin(z\tau_2) \\ &+ b_{11}c_{22}\cos(z(\tau_1+\tau_2)) + ib_{11}c_{22}\sin(z(\tau_1+\tau_2)) \\ &- b_{12}c_{21}\cos(z(\tau_1+\tau_2)) - ib_{12}c_{21}\sin(z(\tau_1+\tau_2)) = 0\end{aligned}$$

we know that $\Gamma(iz)$ can be written as:

$$\Gamma(iz) = A(z) + iB(z)$$

where $A(z)$ is the real part and $B(z)$ is the imaginary part, we get:

$$A(z) = -z^2 + a_{22}a_{11} + a_{22}b_{11}\cos(z\tau_1) + b_{11}z\sin(z\tau_1) - c_{22}z\sin(z\tau_2) + a_{11}c_{22}\cos(z\tau_2) - a_{12}c_{21}\cos(z\tau_2) + b_{11}c_{22}\cos(z(\tau_1+\tau_2)) - b_{12}c_{21}\cos(z(\tau_1+\tau_2))$$

then

$$A(z) = -z^2 + a_{22}a_{11} + a_{22}b_{11}\cos(z\tau_1) + b_{11}z\sin(z\tau_1) - c_{22}z\sin(z\tau_2) + (a_{11}c_{22} - a_{12}c_{21})\cos(z\tau_2) + (b_{11}c_{22} - b_{12}c_{21})\cos(z(\tau_1+\tau_2))$$

and,

$$B(z) = -(a_{22}+a_{11})z - a_{22}b_{11}\sin(z\tau_1) - b_{11}z\cos(z\tau_1) - c_{22}z\cos(z\tau_2) - a_{11}c_{22}\sin(z\tau_2) + a_{12}c_{21}\sin(z\tau_2) + b_{11}c_{22}\sin(z(\tau_1+\tau_2)) - b_{12}c_{21}\sin(z(\tau_1+\tau_2))$$

then

$$B(z) = -(a_{22}+a_{11})z - a_{22}b_{11}\sin(z\tau_1) - b_{11}z\cos(z\tau_1) - c_{22}z\cos(z\tau_2) + (a_{12}c_{21} - a_{11}c_{22})\sin(z\tau_2) + (b_{11}c_{22} - b_{12}c_{21})\sin(z(\tau_1+\tau_2))$$

it follows

$$[A(z)]^2 = [-z^2 + a_{22}a_{11} + a_{22}b_{11}\cos(z\tau_1) + b_{11}z\sin(z\tau_1) - c_{22}z\sin(z\tau_2) + (a_{11}c_{22} - a_{12}c_{21})\cos(z\tau_2) + (b_{11}c_{22} - b_{12}c_{21})\cos(z(\tau_1+\tau_2))]^2$$

and

$$[B(z)]^2 = [-(a_{22}+a_{11})z - a_{22}b_{11}\sin(z\tau_1) - b_{11}z\cos(z\tau_1) - c_{22}z\cos(z\tau_2) + (a_{12}c_{21} - a_{11}c_{22})\sin(z\tau_2) + (b_{11}c_{22} - b_{12}c_{21})\sin(z(\tau_1+\tau_2))]^2$$

E_2 is stable if the following equation has no positive roots.

$$[A(z)]^2 + [B(z)]^2 = 0 \qquad (\mathbf{4}.7)$$

Concerning the stability for $\tau_1 = \tau_2 = 0$, one has

$$T_1(\lambda) + T_2(\lambda) + T_3(\lambda) + T_4(\lambda) = \lambda^2 - \lambda(a_{11} + a_{22} + b_{11} + c_{22}) + a_{11}a_{22} + a_{22}b_{11} + a_{11}c_{22} + b_{11}c_{22} - a_{12}c_{21} - b_{12}c_{21} = \lambda^2 + t_1\lambda + t_2$$

and (**4**.6) has, for $\tau_1 = \tau_2 = 0$, only roots with negative real parts, if and only if

$$t_1 > 0 \text{ and } t_2 > 0. \qquad (\mathbf{4}.8)$$

5. Numerical Results and Simulations

In the next figures, the trajectories around the equilibrium point E_2, which represents the healthy state of the system, are illustrated in detail. These trajectories provide insights into how the system behaves when it is near this equilibrium. The specific parameter values used in the model, along with their interpretations, are meticulously detailed in the reference ([2]). These parameters are crucial for understanding the dynamics of the system and how it responds to various conditions.

The analysis shows that x_1 and x_2, which correspond to the population of healthy monocytes and their precursor cells, maintain stability in the vicinity of E_2. This stability implies that, under the current conditions, the hematopoietic system's monocyte production and regulation processes are functioning normally, with no signs of abnormal behavior such as rapid population growth or decline. This is significant because monocytes play a vital role in homeostasis, and their stability suggests a well-regulated behavior.

Similarly, the variables x_4 and x_5, representing the Chikungunya virus population and the infected monocytes, also exhibit stability. This indicates that, even though the virus is present in the system, its population and the number of infected cells are not increasing uncontrollably. The system is able to manage the virus effectively, preventing it from reaching levels that could overwhelm the immune response. This stability is essential for maintaining the overall health of the patient, as it suggests that the infection is under control and not causing significant harm.

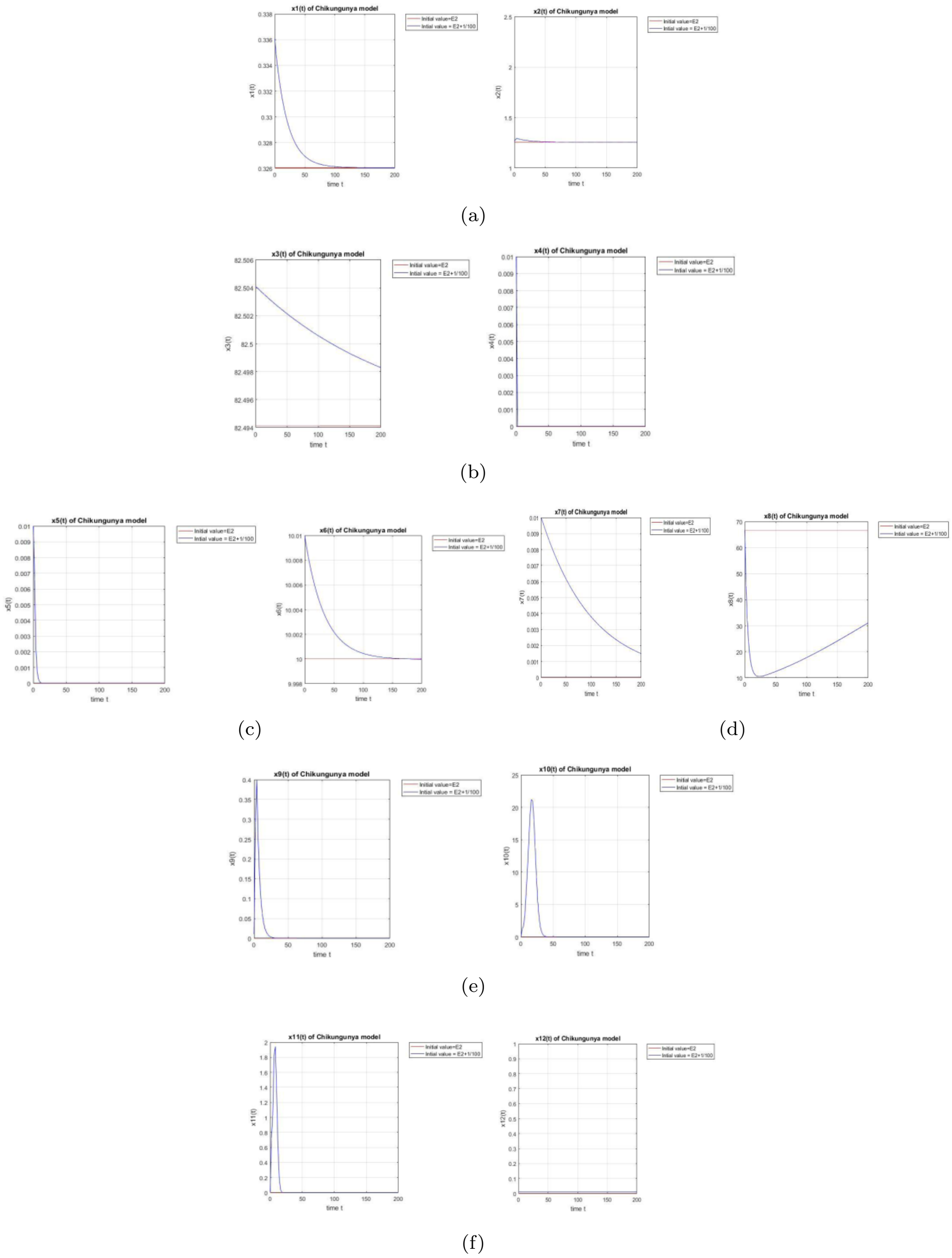

FIGURE 1. Small disturbances in initial conditions near E_2.

Additionally, after running the MATLAB code, we observed that there are no positive roots for equation (7). The absence of positive roots is a strong indicator that the system does not exhibit any unstable behavior within the given range of parameters. In mathematical terms, this means that the system is not prone to exponential growth or decay that could lead to instability. Moreover, the parameters $t_1 = 0.721$ and $t_2 = 1.231$ are both positive, satisfying the stability conditions outlined in (8). These parameters are critical for ensuring that the system remains stable, and their positive values confirm that the conditions for stability are met. This is important because it provides further mathematical validation that the system is robust and resistant to disturbances that could push it out of equilibrium. The system remains in a locally stable equilibrium, with all variables returning to their equilibrium values after small perturbations.

From a medical perspective, these findings are highly encouraging. The stability of the system, as indicated by both the trajectories and the absence of positive roots, suggests that the patient's immune system is functioning effectively and that the infection is being kept under control. The positive values of the stability parameters further reinforce this conclusion, indicating that the system is not only stable but also resilient to changes in the environment or internal conditions.

6. Conclusion

The Chikungunya virus, a re-emerging disease transmitted by mosquitoes, causes a wide range of severe clinical symptoms in humans. This paper develops a complex model utilizing delay differential equations (DDEs) to monitor the progression of Chikungunya under treatment. A critical scenario is identified in the characteristic equation of one equilibrium point, representing a healthy state. The critical case theorem from ([1]) is applied, followed by an analysis of transcendental equations. Numerical results support the study, showing that the patient's condition is stable and indicative of a healthy state. Below are some medical considerations.

Symptom Management: Chikungunya infection often leads to debilitating joint pain and fever. Effective symptom management is crucial, which may include analgesics, anti-inflammatory drugs, and supportive care to improve the patient's quality of life.

Treatment Protocols: While there is no specific antiviral treatment for Chikungunya, understanding the progression of the disease through models like DDEs can help in optimizing treatment protocols and interventions to prevent complications.

Monitoring and Follow-up: Regular monitoring of patients is essential to track their response to treatment and adjust medical care as needed. Long-term follow-up may be required for individuals experiencing chronic symptoms.

Prevention and Control: Given that Chikungunya is mosquito-borne, preventive measures such as vector control, use of insect repellent, and public health campaigns are important to reduce the incidence and spread of the virus.

Public Health Implications: The re-emergence of Chikungunya highlights the need for robust public health infrastructure to respond to outbreaks and protect vulnerable populations, including the elderly and those with pre-existing health conditions.

Research and Development: Continued research is necessary to develop effective vaccines and treatments. The use of complex mathematical models can aid in understanding the disease dynamics and inform future research efforts.

**Authors contribution:
The authors took full responsibility for every aspect of the study, from the conception and design to data collection, analysis, and writing. Their contributions to this article were equal.

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