Sigma J Eng & Nat Sci 10 (3), 2019, 325-342

Publications Prepared for the Sigma Journal of Engineering and Natural Sciences
2019 International Conference on Applied Analysis and Mathematical Modeling
Special Issue was published by reviewing extended papers

Research Article

GLOBAL STABILITY IN A PATHOGEN-SPECIFIC CD8 IMMUNE RESPONSE PREDICTION MODEL

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Received: 13.04.2019 Revised: 10.09.2019 Accepted: 29.09.2019

ABSTRACT

In this study, a system of ordinary differential equations used for modeling pathogen-specific CD8 cell immune response is studied. The positivity and the limitation of the model solutions are proven. The equilibrium points in the cases with the presence and the absence of the pathogen are determined and their stabilities are investigated. Furthermore, the essential reproduction number is obtained for the system. The conditions of the reproduction number for the stability of the equilibrium are shown and numerical examples are given for supporting the analytical results.
Keywords: CD8 T-Cell immunity response, local stability, global stability, equilibrium, persistence.
2010 Mathematics Classification: 34D23, 34D05.

1. INTRODUCTION

Mathematical modeling in epidemiology, medicine and engineering is a popular research field and has been gaining increasing attention in the last several decades. The emergence of mathematical software, powerful computation hardware and numerical techniques with increasing accuracy has gained mathematical modeling a prominent position within the disciplines of applied mathematics. Differential equation systems with fractional derivation [1], random inputs [2-4], stochastic noise [5] and various other components now has wide application areas in numerous fields of science.

One of these application areas includes the analysis of human immune system through systems of differential equations. Understanding CD8 T cell dynamics is a vital part of analyzing immune response. In this context, this study concentrates on a mathematical model that considers the multiple stages of pathogen-specific CD8 T-cell immune response. The T-cell immune response is a process that begins with infection by a virus or bacteria and ends in the production of memory T-cells which play an important part for the defense mechanism of the body against the same pathogen. The progression of the cells from Naïve T-cells to Effector T-cells and Memory T-cells constitutes the response dynamics of immunity.

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We use the deterministic model of Crauste et al. to investigate the global stability of a CD8 T-cell immune system response problem [6]. The analysis of the stability and equilibrium conditions is important in a mathematical modeling study since, for instance in an epidemiological model, it provides crucial information for the solutions of the systems and the persistence or eradication of the disease. The stability of the system in the persistence and eradication of pathogens will be investigated in an effort to provide a deeper understanding of the immune system response.

There are various T-cell immune system response modeling studies in the literature along with various infection studies [7-10]. For instance, Dasbasi has recently used a system of fractional-order differential equations to model the pathogen-specific response [1] whereas Barroux et al. have given a multiscale model structured by intracellular content for CD8 T cell immune system response [11]. The equation system used by Crauste et al. models the case in which infection by multiple pathogens is present. The equation system is given as

$$\frac{dN(t)}{dt} = -\mu_N N - \delta_{NE} PN, \tag{1}$$

$$\frac{dE(t)}{dt} = \delta_{NE} PN + \rho_E PE - \mu_E E^2 - \delta_{EM} E, \tag{2}$$

$$\frac{dM(t)}{dt} = -\mu_M M + \delta_{EM} E, \tag{3}$$

$$\frac{dP(t)}{dt} = \rho_P P^2 - \mu_P EP - \mu_P^0 P. \tag{4}$$

where the variables $N(t), E(t), M(t)$ and $P(t)$ denote the numbers of naïve T cells, effector T cells, memory T cells and pathogens, respectively [6]. The parameters of the model (1)-(4) are given as:

Table 1. Parameters of system (1)-(4)

Parameter	Description	Value
μ_N	Death rate of naïve cells	(0.01)
δ_{NE}	Rate of change of naïve cells	10^{-3}
ρ_E	The rate of proliferation of effector cells	1
μ_E	Death rate of effector cells	10^{-8}
δ_{EM}	Rate of change of effector cells	10^{-5}
μ_M	Mortality rate of memory cells	0
ρ_P	The rate of formation of pathogens	10^{-4}
μ_P	Natural mortality rate of pathogens	10^{-4}
μ_P^0	Measure-related mortality rate of pathogens	10^{-8}

The parameters have been determined for their daily values except μ_P^0 whose value is given with the unit $1/(cells \times day)$. The initial values of the system are

$$N(0) = N_0, E(0) = 0, M(0) = 0, P(0) = 1. \tag{5}$$

All of the values have been obtained from the original modeling study [6]. The equilibria of the system (1)-(4) are obtained through the analysis of points where no changes are seen in compartment populations.

The disease free equilibrium of the model is denoted by x_0 where $x_0 = (0,0,0,0)$. The equilibrium points in the existence of the disease are given as $x_1 = \left(0,0,0,\frac{\mu_P^0}{\rho_P}\right)$, $x_2 = \left(0,\frac{-\delta_{EM}}{\mu_E},\frac{-\delta_{EM}^2}{\mu_M\mu_E},0\right)$ and $x_3 = (N^*, E^*, M^*, P^*)$ where

$$N^* = \frac{\left(\frac{\mu_N\ \rho_P}{\delta_{NE}} + \mu_P^0\right)}{\mu_P\mu_N}\left[\frac{\mu_N\ \rho_E}{\delta_{NE}} - \frac{\mu_E}{\mu_P}\left(\frac{\mu_N\ \rho_P}{\delta_{NE}} + \mu_P^0\right) + \delta_{EM}\right],$$
$$E^* = -\frac{1}{\mu_P}\left[\frac{\mu_N\ \rho_P}{\delta_{NE}} + \mu_P^0\right]$$
$$M^* = -\frac{\delta_{EM}}{\mu_P\mu_M}\left[\frac{\mu_N\ \rho_P}{\delta_{NE}} + \mu_P^0\right], \qquad P^* = -\frac{\mu_N}{\delta_{NE}}.$$

2. THE BASIC RE PRODUCTION NUMBER

Using the next generation matrix method [2], we analyze the basic reproduction number of the model. Consider the equilibrium point $x_1 = (N_1, E_1, M_1, P_1) = \left(0,0,0,\frac{\mu_P^0}{\rho_P}\right)$. If $z = (E, M, P)^T$, then the model can be rewritten as

$$z' = F(z) - V(z),$$

Where

$$F(z) = \begin{bmatrix} \rho_E PE \\ 0 \\ 0 \end{bmatrix}, V(z) = \begin{bmatrix} -\delta_{NE}PN + \mu_E E^2 + \delta_{EM}E \\ -\rho_P P^2 + \mu_P EP + \mu_P^0 P \\ \mu_M M - \delta_{EM}E \end{bmatrix}.$$

The Jacobian matrices of $F(z)$ and $V(z)$ at x_1

$$DF(x_1) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, DV(x_1) = \begin{bmatrix} V & 0 \\ -\delta_{EM} & 0 \end{bmatrix}$$

for

$$F = \begin{bmatrix} \frac{\rho_E\mu_P^0}{\rho_P} & 0 \\ 0 & 0 \end{bmatrix}, V = \begin{bmatrix} \delta_{EM} & 0 \\ \frac{\mu_P\mu_P^0}{\rho_P} & -\mu_P^0 \end{bmatrix}.$$

The basic reproduction number, given by the spectral radius of FV^{-1}, is given as $R_0 = \frac{\rho_E\mu_P^0}{\rho_P\delta_{EM}}$.

3. QUALITATIVE ANALYSIS

In this section, the positivity of the solutions are shown and the stability of the equilibrium points are investigated.

3.1. Positivity and Boundedness

Theorem 1. Under the initial conditions (5), each of the solutions for the model given by (1)-(4), is positive and bounded for every $t > 0$.

Proof. The model given by (1)-(4), is locally lipschitz at $t = 0$ [12]. Hence, a unique solution to the model under the initial conditions (5), exists on $[0, a)$ for some $a > 0$. Let $(N(t), E(t), M(t), P(t))$ be a solution of the model (1)-(4).

For some $t_1 > 0$, using (1), we see that if $N(t_1) = 0$ and t_1 is the first moment satisfying this condition, then $\frac{dN(t_1)}{dt1} \le 0$. Then $\frac{dN(t)}{dt} = -\mu_N N$ for $t \in [0, t_2) \Rightarrow N(t_2) \ge N(0)e^{-\mu_N t_2} > 0$, which is a contradiction. Hence, $N(t) > 0$ for all $t \in [0, a)$.

Using (2), we get $\frac{dE(t)}{dt} = -\delta_{EM}E$ for $t \in [0, t_3) \Rightarrow E(t_3) \ge E(0)e^{-\delta_{EM}t_3} > 0$, which is a contradiction. Therefore $E(t) > 0$ for all $t \in [0, a)$.

A similar approach can be used to show that $N(t), E(t), M(t), P(t) > 0$ for all $t \epsilon [0, a)$. This means

$$\begin{aligned}\frac{dN}{dt} + \frac{dE}{dt} &= -\mu_N N + \rho_E PE - \mu_E E^2 - \delta_{EM} E \\ &= \frac{P^2 \rho_E^2}{4\mu_E} - \left(\sqrt{\mu_E} E - \frac{P\rho_E}{2\sqrt{\mu_E}}\right)^2 - \mu_N N - \delta_{EM} E \\ &\leq \frac{P^2 \rho_E^2}{4\mu_E} - A(E + N)\end{aligned}$$

for $A = \min(\mu_N, \delta_{EM})$. Hence, $\lim_{t\to\infty} \sup(N + E)(t) \leq \frac{P^2\rho_E^2}{4A\mu_E} = K^*(say)$ [12]. Therefore, positive constants $K_T > K^*$ and $T_1 > 0$ exist such that if $t \geq T_1$, then $N(t) + E(t) < K_T$. Since $N(t), I(t) > 0$, for $t \in [0, a)$, we see that $N(t) < K_T, E(t) < K_T$. Using (3), we see $\frac{dM(t)}{dt} = -\mu_M M + \delta_{EM} E \leq -\mu_M M + \delta_{EM} K_T$,

$$\lim_{t\to\infty} \sup M(t) \leq \frac{\delta_{EM} K_T}{\mu_M} = K_M^*.$$

Hence, positive constants $K_M > K_M^*$ and $T_2 > 0$ exist such that if $t \geq T_2$, then $M(t) < K_M$. Similarly, using (4)

$$\begin{aligned}\frac{dP(t)}{dt} &= \rho_P P^2 - \mu_P EP - \mu_P^0 P \leq \rho_P P^2 - \mu_P^0 P \Rightarrow P(t) \\ &\leq \frac{P(0)\mu_p^0}{P(0)\rho_P + \left(\mu_p^0 - P(0)\rho_P\right)e^{\mu_p^0 t}}\end{aligned}$$

and $\lim_{t\to\infty} \sup P(t) \leq 0$ which gives the uniformly boundedness of the solutions of the model (1)-(4). This means that if the positivity of the solutions of (1)-(4) for all $t \in [0, a)$ is considered with the uniform boundedness, then $a = \infty$.

■

Theorem 2. The equilibrium point x_0 of the model,

i. is locally asymptotically stable if $R_0 \geq 1$,
ii. is unstable if $R_0 < 1$.

Proof. (i) The Jacobian matrix of the model at x_0 is

$$J(x_0) = J_0 = \begin{bmatrix} -\mu_N & 0 & 0 & 0 \\ 0 & -\delta_{EM} & 0 & 0 \\ 0 & \delta_{EM} & -\mu_M & 0 \\ 0 & 0 & 0 & -\mu_P^0 \end{bmatrix}.$$

The characteristic equation of J_0 is found as $\lambda^4 + A_3\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 = 0$ for

$$\begin{aligned}A_3 &= \mu_M + \mu_P^0 + \mu_N + \delta_{EM} > 0, \\ A_2 &= (\mu_N + \mu_P^0)(\mu_M + \delta_{EM}) + (\mu_P^0\mu_N + \delta_{EM}\mu_M) > 0, \\ A_1 &= \delta_{EM}\mu_M(\mu_N + \mu_P^0) + (\mu_N + \delta_{EM})\mu_P^0\mu_N > 0, \\ A_0 &= \mu_P^0\mu_M\delta_{EM}\mu_N > 0.\end{aligned}$$

Hence,

$$Q_1 = A_3A_2 - A_1 > 0. \text{ (See Appendix A)}$$

and

$Q_2 > 0$. (See Appendix B)

Thus, the model is locally asymptotically stable around x_0 if $R_0 \geq 1$.

(ii) For $R_0 < 1$, it is seen that $Q_2 < 0$ and $Q_3 < 0$ which fails the Routh-Hurwitz criterion. Thus, the pathogen free equilibrium point x_0 is unstable for $R_0 < 1$.

It is known that for $x_0 = (0,0,0,0)$, the equilibrium is locally asymptotically stable if all eigenvalues have negative real parts and unstable for eigenvalues with positive real parts [13]. All of the eigenvalues are real since

$$\lambda_1 = -\mu_N, \lambda_2 = -\mu_M, \lambda_3 = -\mu_P^0, \lambda_4 = -\delta_{EM}.$$

Through the assumption $\mu_N > 0, \mu_M > 0, \mu_P^0 > 0, \delta_{EM} > 0$ for the parameters, it is seen that $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ are negative for this model. Thus, the equilibrium point $x_0 = (0,0,0,0)$ is locally asymptotically stable.

■

Theorem 3. The equilibrium point $x_1 = \left(0,0,0,\frac{\mu_P^0}{\rho_P}\right)$ of model (1) is locally asymptotically stable for $R_0 < 1$ and unstable for $R_0 \geq 1$.

Proof. The Jacobian matrix of the model at the equilibrium point x_1 is obtained as

$$J(x_1) = J_1$$

$$= \begin{bmatrix} -\mu_N - \delta_{NE}P & 0 & 0 & -\delta_{NE}N \\ \delta_{NE}P & -\delta_{EM} - 2\mu_E E + \rho_E P & 0 & \delta_{NE}N + \rho_E E \\ 0 & \delta_{EM} & -\mu_M & 0 \\ 0 & -\mu_P P & 0 & -\mu_P^0 + 2\rho_P - \mu_P E \end{bmatrix}_{x_1\left(0,0,0,\frac{\mu_P^0}{\rho_P}\right)}$$

$$= \begin{bmatrix} -\mu_N - \frac{\delta_{NE}\mu_P^0}{\rho_P} & 0 & 0 & 0 \\ \frac{\delta_{NE}\mu_P^0}{\rho_P} & -\delta_{EM} + \frac{\rho_E\mu_P^0}{\rho_P} & 0 & 0 \\ 0 & \delta_{EM} & -\mu_M & 0 \\ 0 & -\frac{\mu_P\mu_P^0}{\rho_P} & 0 & -\mu_P^0 + 2\rho_P \end{bmatrix}$$

The characteristic equation of J_1 is

$$\lambda^4 + B_3\lambda^3 + B_2\lambda^2 + B_1\lambda + B_0 = 0,$$

Where

$$B_3 = \mu_M + \mu_N + \mu_P^0 - 2\rho_P + \frac{\delta_{NE}\mu_P^0}{\rho_P} - \frac{\mu_P^0\rho_E}{\rho_P} < 0,$$

$$B_2 = -2\delta_{EM}\rho_P + \mu_M\mu_N + \mu_M\mu_P^0 + \mu_N\mu_P^0 - 2\mu_M\rho_P - 2\mu_N\rho_P + 2\mu_P^0\rho_E + \delta_{EM}\mu_M + \delta_{EM}\mu_N + \delta_{EM}\mu_P^0 - 2\delta_{NE}\mu_P^0 + \frac{\delta_{NE}{\mu_P^0}^2}{\rho_P} - \frac{{\mu_P^0}^2\rho_E}{\rho_P} + \frac{\delta_{EM}\delta_{NE}\mu_P^0}{\rho_P} + \frac{\delta_{NE}\mu_M\mu_P^0}{\rho_P} - \frac{\mu_M\mu_P^0\rho_E}{\rho_P} - \frac{\mu_N\mu_P^0\rho_E}{\rho_P} + \frac{\left(\delta_{NE}{\mu_P^0}^2\rho_E\right)}{\rho_P^2} < 0,$$

$$B_1 = 2\delta_{EM}\delta_{NE}\mu_P^0 + \delta_{EM}\mu_M\mu_N + \delta_{EM}\mu_M\mu_P^0 - 2\delta_{NE}\mu_M\mu_P^0 + \delta_{EM}\mu_N\mu_P^0 - 2\delta_{EM}\mu_M\rho_P - 2\delta_{EM}\mu_N\rho_P + \frac{\delta_{NE}\mu_M{\mu_P^0}^2}{\rho_P} + \frac{\delta_{EM}\delta_{NE}{\mu_P^0}^2}{\rho_P} + \frac{2\delta_{NE}{\mu_P^0}^2\rho_E}{\rho_P} - \frac{\delta_{NE}{\mu_P^0}^3\rho_E}{\rho_P^2} - \frac{\mu_M{\mu_P^0}^2\rho_E}{\rho_P} - \frac{\mu_N{\mu_P^0}^2\rho_E}{\rho_P} + \frac{\delta_{EM}\delta_{NE}\mu_M\mu_P^0}{\rho_P} - \frac{\mu_M\mu_N\mu_P^0\rho_E}{\rho_P} - \frac{\delta_{NE}\mu_M{\mu_P^0}^2\rho_E}{\rho_P^2} > 0$$

$$B_0 = -2\delta_{EM}\delta_{NE}\mu_M\mu_P^0 + \delta_{EM}\mu_M\mu_N\mu_P^0 - 2\delta_{EM}\mu_M\mu_N\rho_P - 2\lambda\mu_M\mu_N\rho_P + 2\mu_M\mu_N\mu_P^0\rho_E + \frac{2\delta_{NE}\mu_M{\mu_P^0}^2\rho_E}{\rho_P} - \frac{\mu_M\mu_N{\mu_P^0}^2\rho_E}{\rho_P} - \frac{\delta_{NE}\mu_M{\mu_P^0}^3\rho_E}{\rho_P^2} + \frac{\delta_{EM}\delta_{NE}\mu_M{\mu_P^0}^2}{\rho_P} = 0$$

Thus,

$$Q_1 = B_3B_2 - B_1 > 0, \text{ (See Appendix C)}$$
$$Q_2 = B_3B_2B_1 - B_1^2 - B_3^2B_0 > 0. \text{ (See Appendix D)}$$

If $R_0 > 1$, then $B_3 < 0$ and $B_2 < 0$ which means the Routh-Hurwitz criterion fails and the equilibrium point is unstable. The equilibrium point $x_1 = \left(0,0,0,\frac{\mu_P^0}{\rho_P}\right)$ is locally asymptotically stable if all eigenvalues have negative real parts and is unstable if there are eigenvalues with positive real parts. All eigenvalues are real since

$$\lambda_1 = -\frac{\mu_P^0\delta_{NE}}{\rho_P} - \mu_N, \lambda_2 = -\mu_M, \lambda_3 = 2\rho_P - \mu_P^0, \lambda_4 = \frac{\mu_P^0\rho_E}{\rho_P} - \delta_{EM}.$$

The parameters were assumed to be $\mu_N > 0, \mu_M > 0, \mu_P^0 > 0, \rho_P > 0$. Hence $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ gives eigenvalues with positive real parts and for this selection of variables and the equilibrium point $x_1 = \left(0,0,0,\frac{\mu_P^0}{\rho_P}\right)$ is locally unstable.

■

Theorem 4. The equilibrium point $x_2 = \left(0,\frac{-\delta_{EM}}{\mu_E},\frac{-\delta_{EM}^2}{\mu_M\mu_E},0\right)$ of model (1) is locally asymptotically stable for $R_0 < 1$ and unstable for $R_0 \geq 1$.

Proof. The Jacobian matrix of the model at x_2 is

$$J(x_2) = J_2$$
$$= \begin{bmatrix} -\mu_N - \delta_{NE}P & 0 & 0 & -\delta_{NE}N \\ \delta_{NE}P & -\delta_{EM} - 2\mu_E E + \rho_E P & 0 & \delta_{NE}N + \rho_E E \\ 0 & \delta_{EM} & -\mu_M & 0 \\ 0 & -\mu_P P & 0 & -\mu_P^0 + 2\rho_P - \mu_P E \end{bmatrix}_{x_2\left(0,\frac{-\delta_{EM}}{\mu_E},\frac{-\delta_{EM}^2}{\mu_M\mu_E},0\right)}$$
$$= \begin{bmatrix} -\mu_N & 0 & 0 & 0 \\ 0 & \delta_{EM} & 0 & -\frac{\rho_E\delta_{EM}}{\mu_E} \\ 0 & \delta_{EM} & -\mu_M & 0 \\ 0 & 0 & 0 & -\mu_P^0 + 2\rho_P - \frac{\mu_P\delta_{EM}}{\mu_E} \end{bmatrix}.$$

The characteristic equation of J_2 is found as

$$\lambda^4 + D_3\lambda^3 + D_2\lambda^2 + D_1\lambda + D_0 = 0,$$

where

$$D_3 = \mu_M - \delta_{EM} + \mu_N + \mu_P^0 - 2\rho_P + \frac{\delta_{EM}\mu_P}{\mu_E} > 0,$$
$$D_2 = 2\delta_{EM}\rho_P + \mu_M\mu_N + \mu_M\mu_P^0 + \mu_N\mu_P^0 - 2\mu_M\rho_P - 2\mu_N\rho_P - \delta_{EM}\mu_M - \delta_{EM}\mu_N - \delta_{EM}\mu_P^0 - \frac{\delta_{EM}^2\mu_P}{\mu_E} + \frac{\delta_{EM}\mu_M\mu_P}{\mu_E} < 0,$$
$$D_1 = -\delta_{EM}\mu_M\mu_N - \delta_{EM}\mu_M\mu_P^0 - \delta_{EM}\mu_N\mu_P^0 + 2\delta_{EM}\mu_M\rho_P + 2\delta_{EM}\mu_N\rho_P + \mu_M\mu_N\mu_P^0 - 2\mu_M\mu_N\rho_P - \frac{\delta_{EM}^2\mu_M\mu_P}{\mu_E} - \frac{\delta_{EM}^2\mu_N\mu_P}{\mu_E} + \frac{\delta_{EM}\mu_M\mu_N\mu_P}{\mu_E} > 0,$$
$$D_0 = 2\delta_{EM}\mu_M\mu_N\rho_P - \frac{\delta_{EM}^2\mu_M\mu_N\mu_P}{\mu_E} - \delta_{EM}\mu_M\mu_N\mu_P^0 = 0.$$

Hence,

$$Q_1 = D_3D_2 - D_1 < 0, \text{ (See Appendix E)}$$

and

$$Q_2 = D_3 D_2 D_1 - D_1^2 - D_3^2 D_0 < 0 \text{ (See Appendix F)}$$

for the case $R_0 < 1$, $D_2 < 0$ and $Q_1 < 0, Q_2 < 0$ which means the Routh-Hurwitz criterion fails and the equilibrium point is unstable.

The equilibrium point $x_2 = \left(0, \frac{-\delta_{EM}}{\mu_E}, \frac{-\delta_{EM}^2}{\mu_M \mu_E}, 0\right)$ is locally asymptotically stable if all eigenvalues have negative real parts and is unstable if there are eigenvalues with positive real parts. All eigenvalues are real since

$$\lambda_1 = \delta_{EM}, \lambda_2 = -\mu_M, \lambda_3 = -\mu_N, \lambda_4 = -\mu_P^0 + 2\rho_P - \frac{\delta_{EM}\mu_P}{\mu_E}.$$

Through the assumption

$$\mu_N > 0, \mu_M > 0, \mu_P^0 > 0, \delta_{EM} > 0, \rho_P > 0$$

for the parameters, it is seen that the eigenvalues have positive real parts and the equilibrium point $x_2 = \left(0, \frac{-\delta_{EM}}{\mu_E}, \frac{-\delta_{EM}^2}{\mu_M \mu_E}, 0\right)$ is locally unstable.

■

Theorem 5. If $R_0 < 1$, then the equilibrium point $x_3 = (N^*, E^*, M^*, P^*)$ of the model is locally asymptotically stable. Elsewhere, x_3 is unstable.

Proof. (i) The Jacobian matrix of the model at x_3 is

$$J(x_3) = J_3 = \begin{bmatrix} -\mu_N - \delta_{NE}P & 0 & 0 & -\delta_{NE}N \\ \delta_{NE}P & -\delta_{EM} - 2\mu_E E + \rho_E P & 0 & \delta_{NE}N + \rho_E E \\ 0 & \delta_{EM} & -\mu_M & 0 \\ 0 & -\mu_P P & 0 & -\mu_P^0 + 2\rho_P - \mu_P E \end{bmatrix}_{x_3(N^*,E^*,M^*,P^*)}$$

$$= \begin{bmatrix} -\mu_N - \delta_{NE}P^* & 0 & 0 & -\delta_{NE}N^* \\ \delta_{NE}P^* & -\delta_{EM} - 2\mu_E E^* + \rho_E P^* & 0 & \delta_{NE}N^* + \rho_E E^* \\ 0 & \delta_{EM} & -\mu_M & 0 \\ 0 & -\mu_P P^* & 0 & -\mu_P^0 + 2\rho_P - \mu_P E^* \end{bmatrix}$$

and the characteristic equation of J_3 is found as

$$\lambda^4 + E_3\lambda^3 + E_2\lambda^2 + E_1\lambda + E_0 = 0,$$

where

$$\begin{aligned} E_3 &= \delta_{EM} + \mu_M + \mu_N + \mu_P^0 - 2\rho P^* + 2E^*\mu_E + E^*\mu_P + P^*\delta_{NE} - P^*\rho_E > 0, \\ E_2 &= -2\delta_{EM}\rho P^* + \mu_M\mu_N + \mu_M\mu_P^0 + \lambda^2\mu_N\mu_P^0 - 2\mu_M\rho_P - 2\mu_N\rho_P + \delta_{EM}\mu_M + \delta_{EM}\mu_N \\ &\quad + \delta_{EM}\mu_P^0 + \; + E^*\delta_{EM}\mu_P + P^*\delta_{NE} + 2E^*\mu_E\mu_M + 2E^*\mu_E\mu_N \\ &\quad + 2E^*\mu_E\mu_P^0 + E^*\mu_M\mu_P + E^*\mu_N\mu_P + P^*\delta_{NE}\mu_M + P^*\delta_{NE}\mu_P^0 \\ &\quad - 4E^*\mu_E\rho_P - 2P^*\delta_{NE}\rho_P - P^*\mu_M\rho_E - P^*\mu_N\rho_E - P^*\mu_P^0\rho_E \\ &\quad + 2P^*\rho_E\rho_P + 2E^{*2}\mu_E\mu_P - P^{*2}\delta_{NE}\rho_E + 2E^*P^*\delta_{NE}\mu_E \\ &\quad + E^*P^*\delta_{NE}\mu_P + N^*P^*\delta_{NE}\mu_P < 0, \end{aligned}$$

$$E_1 = \delta_{EM}\mu_M\mu_N + \delta_{EM}\mu_M\mu_P^0 + \delta_{EM}\mu_N\mu_P^0 - 2\delta_{EM}\mu_M\rho_P - 2\delta_{EM}\mu_N\rho_P + \mu_M\mu_N\mu_P^0 - 2\mu_M\mu_N\rho_P + E^*\delta_{EM}\mu_M\mu_P + E^*\delta_{EM}\mu_N\mu_P + P^*\delta_{EM}\delta_{NE}\mu_M + P^*\delta_{EM}\delta_{NE}\mu_P^0 - 2P^*\delta_{EM}\delta_{NE}\rho_P + 2E^*\mu_E\mu_M\mu_N + 2E^*\mu_E\mu_M\mu_P^0 + 2E^*\mu_E\mu_N\mu_P^0 + E^*\mu_M\mu_N\mu_P + P^*\delta_{NE}\mu_M\mu_P^0 - 4E^*\mu_E\mu_M\rho_P - 4E^*\mu_E\mu_N\rho_P - 2P^*\delta_{NE}\mu_M\rho_P - P^*\mu_M\mu_N\rho_E - P^*\mu_M\mu_P^0\rho_E - P^*\mu_N\mu_P^0\rho_E + 2P^*\mu_M\rho_E\rho_P + 2P^*\mu_N\rho_E\rho_P + 2E^{*2}\mu_E\mu_M\mu_P + 2E^{*2}\mu_E\mu_N\mu_P - P^{*2}\delta_{NE}\mu_M\rho_E - P^{*2}\delta_{NE}\mu_P^0\rho_E + 2P^{*2}\delta_{NE}\rho_E\rho_P + E^*P^*\delta_{EM}\delta_{NE}\mu_P + 2E^*P^*\delta_{NE}\mu_E\mu_M + 2E^*P^*\delta_{NE}\mu_E\mu_P^0 + E^*P^*\delta_{NE}\mu_M\mu_P - 4E^*P^*\delta_{NE}\mu_E\rho_P + N^*P^*\delta_{NE}\mu_M\mu_P + N^*P^*\delta_{NE}\mu_N\mu_P + 2E^{*2}P^*\delta_{NE}\mu_E\mu_P < 0,$$

$$\begin{aligned} E_0 = {} & \delta_{EM}\mu_M\mu_N\mu_P^0 - 2\delta_{EM}\mu_M\mu_N\rho_P + E^*\delta_{EM}\mu_M\mu_N\mu_P + P^*\delta_{EM}\delta_{NE}\lambda\mu_P^0 \\ & + P^*\delta_{EM}\delta_{NE}\mu_M\mu_P^0 - 2P^*\delta_{EM}\delta_{NE}\mu_M\rho_P + 2E^*\mu_E\mu_M\mu_P\mu_P^0 \\ & - 4E^*\mu_E\mu_M\mu_N\rho_P - P^*\mu_M\mu_N\mu_P^0\rho_E + 2P^*\mu_N\mu_N\rho_E\rho_P \\ & + 2E^{*2}\mu_E\mu_M\mu_N\mu_P - P^{*2}\delta_{NE}\mu_M\mu_P^0\rho_E + 2P^{*2}\delta_{NE}\mu_M\rho_E\rho_P \\ & + 2E^{*2}P^*\delta_{NE}\mu_E\mu_M\mu_P + E^*P^*\delta_{NE}\delta_{NE}\mu_M\mu_P + 2E^*P^*\delta_{NE}\mu_E\mu_M\mu_P^0 \\ & - 4E^*P^*\delta_{NE}\mu_E\mu_M\rho_P + N^*P^*\delta_{NE}\mu_M\mu_N\mu_P = 0. \end{aligned}$$

Hence,

$$Q_1 = E_3E_2 - E_1 < 0, \text{ (See Appendix G)}$$
$$Q_2 = E_3E_2E_1 - E_1^2 - E_3^2E_0 > 0.$$

(ii) If $R_0 > 1$ then $E_2 < 0, E_3 < 0$ and $Q_1 < 0$ which means the Routh-Hurwitz criterion is not satisfied and the equilibrium point is unstable for this case.

The equilibrium point $x_3 = (N^*, E^*, M^*, P^*)$ is locally asymptotically stable if all eigenvalues have negative real parts and is unstable if there are eigenvalues with positive real parts. Through the assumption

$$\mu_N > 0, \mu_M > 0, \mu_P^0 > 0, \delta_{EM} > 0, \rho_P > 0$$

for the parameters, it is seen that the eigenvalues have positive real parts and the equilibrium point $x_3 = (N^*, E^*, M^*, P^*)$ is locally unstable.

3.2.Model Permanence

Definition 1. A system is said to be permanent if the positive constants $0 < \delta \leq \Delta$ exist such that

$$\min\left\{\underline{N} = \lim_{t\to\infty} inf N(t), \underline{E} = \lim_{t\to\infty} inf E(t), \underline{M} = \lim_{t\to\infty} inf M(t), \underline{P} = \lim_{t\to\infty} inf P(t)\right\} \geq \delta,$$
$$\max\left\{\overline{N} = \lim_{t\to\infty} sup N(t), \overline{E} = \lim_{t\to\infty} sup E(t), \overline{M} = \lim_{t\to\infty} sup M(t), \overline{P} = \lim_{t\to\infty} sup P(t)\right\} \leq \Delta$$

for all solutions of the system.

Theorem 6. The model (1)-(4) is permanent $\frac{\rho_E\underline{P}-\delta_{EM}}{\mu_E} > 0$, for the limit superiors $\overline{M}$ and $\overline{P}$ of the variables $M(t)$ and $P(t)$, respectively.

Proof. Using (1) and (2), we see that

$$\begin{aligned} \frac{dN}{dt} + \frac{dE}{dt} &= -\mu_N N + \rho_E PE - \mu_E E^2 - \delta_{EM} E \\ &= \frac{P^2\rho_E^2}{4\mu_E} - \left(\sqrt{\mu_E}E - \frac{P\rho_E}{2\sqrt{\mu_E}}\right)^2 - \mu_N N - \delta_{EM} E \leq \frac{P^2\rho_E^2}{4\mu_E} - A(E+N) \end{aligned} \quad (6)$$

where $A = \min(\mu_N, \delta_{EM})$. From (6), we see that

$$\lim_{t\to\infty} \sup(N+E)(t) \leq \frac{P^2\rho_E^2}{4A\mu_E} \Rightarrow \overline{N} = \lim_{t\to\infty} sup N(t) \leq \frac{P^2\rho_E^2}{4A\mu_E}$$

and

$$\overline{E} = \lim_{t\to\infty} supE(t) \le \frac{P^2\rho_E^2}{4A\mu_E}.$$

Through the limit superior definition, a time T' exists for $\epsilon > 0$ such that $E(t) \ge (\overline{E} - \epsilon)$ for $t > T'$. It can be found that

$$E(t) \ge E(0)e^{-\delta_{EM}t} \Rightarrow \lim_{t\to\infty} E(t) = 0$$

and hence, the limit of $E(t)$ exists.

$$\frac{d}{dt}(M+P) = -\mu_M M + \delta_{EM}E + \rho_P P^2 - \mu_P EP - \mu_P^0 P \le \rho_P \overline{P}^2$$

$$\Rightarrow \lim_{t\to\infty} \sup(M+P)(t) \le \rho_P \overline{P}^2$$

$$\Rightarrow \overline{M} = \lim_{t\to\infty} supM(t) \le \rho_P \overline{P}^2, \overline{P} = \lim_{t\to\infty} supP(t) \le \rho_P \overline{P}^2$$

Once again from (3), we find

$$\frac{dM(t)}{dt} = -\mu_M M + \delta_{EM}E \ge -\mu_M M + \delta_{EM}(\overline{E} - \epsilon) = \mu_M \left(\frac{\delta_{EM}}{\mu_M}(\overline{E} - \epsilon) - M\right).$$

Using the equality, it is seen that $\lim_{t\to\infty} infM(t) \ge \frac{\delta_{EM}}{\mu_M}(\overline{E} - \epsilon)$. Since $\epsilon > 0$ is small, we see that

$$\underline{M} = \lim_{t\to\infty} infM(t) \ge \frac{\delta_{EM}}{\mu_M}(\overline{E} - \epsilon)$$

From (4), we find

$$\frac{dP(t)}{dt} = \rho_P P^2 - \mu_P EP - \mu_P^0 P = P[\rho_P P - \mu_P E - \mu_P^0] \ge P[\rho_P P - \mu_P \overline{E} - \mu_P^0]$$

$$= \rho_P P\left[P - \frac{(\mu_P \overline{E} - \mu_P^0)}{\rho_P}\right]$$

and hence

$$\underline{P} = \lim_{t\to\infty} infP(t) \ge -\frac{(\mu_P \overline{E} - \mu_P^0)}{\rho_P}.$$

From (1),

$$\frac{dN(t)}{dt} = -\mu_N N - \delta_{NE}PN \ge -\mu_N N - \overline{N}\delta_{NE}\overline{P} = \mu_N \left(\overline{N}\frac{\delta_{NE}}{\mu_N}\overline{P} - N\right)$$

which gives

$$\underline{N} = \lim_{t\to\infty} infN(t) \ge \overline{N}\frac{\delta_{NE}}{\mu_N}\overline{P}.$$

From (2),

$$\frac{dE(t)}{dt} = \delta_{NE}PN + \rho_E PE - \mu_E E^2 - \delta_{EM}E \ge \rho_E \underline{P}E - \mu_E E^2 - \delta_{EM}E$$

$$= E(\rho_E \underline{P} - \mu_E E - \delta_{EM}) = \mu_E E\left(\frac{\rho_E \underline{P} - \delta_{EM}}{\mu_E} - E\right).$$

Hence,

$$\underline{E} = \lim_{t\to\infty} infE(t) \ge \left[\frac{\rho_E \underline{P} - \delta_{EM}}{\mu_E} - E\right]$$

for $\frac{\rho_E P - \delta_{EM}}{\mu_E} > 0$.

■

3.3. Global Stability

In this section, the global stability of the equilibrium point x_3 will be analyzed through the geometric approach in [14-15].

Theorem 7. Let $y \rightarrow f(y) \in R^4$ be a C^1 function for a y in a simply connected domain $\subset R^4$, meaning it has a continuous derivative, where

$$y = \begin{pmatrix} N \\ E \\ M \\ P \end{pmatrix}, \qquad f(y) = \begin{pmatrix} -\mu_N N - \delta_{NE} PN \\ \delta_{NE} PN + \rho_E PE - \mu_E E^2 - \delta_{EM} E \\ -\mu_M M + \delta_{EM} E \\ \rho_P P^2 - \mu_P EP - \mu_P^0 P \end{pmatrix}.$$

Consider the equation system $\dot{y} = f(y)$ with the initial conditions $(N_0, E_0, M_0, P_0)^T = y_0\ (say)$ satisfying the following properties:

i. Assume that a solution of the system $\dot{y} = f(y)$ is shown as $y(t, y_0)$.
ii. The system has a unique endemic equilibrium $x_3^* \subset D$.
iii. There exists a compact absorbing set $K \subset D$.
iv. The system satisfies the Bendixson criterion, meaning it is robust under C^1 for local perturbations of f at all non-equilibrium non-wandering points of the system [14].
v. Let $y \rightarrow M(y)$ be a 6×6 matrix valued function with a continuous first derivative for $y \in D$, such that $M^{-1}(y)$ exists and is continuous for $y \in K$.

In this case, the endemic equilibrium x_3^* is globally stable in D if

$$\overline{q_2} = \lim_{t\rightarrow\infty} supsup_{x_0 \in K} \frac{1}{t} \int_0^t \mu(B(x(s, x_0)))\, ds < 0 \tag{7}$$

where $B = M_f M^{-1} + M \frac{\partial f^{[2]}}{\partial x} M^{-1}$ and M_f is obtained by replacing each component m_{ij} of M with its directional derivative in the direction of $f, \nabla m_{ij}^* f$ and $\mu(B)$ is the Lozinskii measure of B with respect to the vector norm $|\cdot|$ in R^4, defined by [16]

$$\mu(B) = \lim_{h\rightarrow 0^+} \frac{|I + hB| - 1}{h}. \tag{8}$$

Proof. The model (1)-(4) is persistent since it is permanent, as shown above. Hence, since the endemic equilibrium x_3^* exists, system persistence and boundedness of solutions give the existence of a compact absorbing set $K \subset D$ [17]. The Jacobian matrix of the model is given as

$$J = \begin{pmatrix} -\mu_N - \delta_{NE} P & 0 & 0 & -\delta_{NE} N \\ \delta_{NE} P & -\delta_{EM} - 2\mu_E E + \rho_E P & 0 & \delta_{NE} N + \rho_E E \\ 0 & \delta_{EM} & -\mu_M & 0 \\ 0 & -\mu_P P & 0 & -\mu_P^0 + 2\rho_P - \mu_P E \end{pmatrix}$$

and the corresponding associated second compound matrix $J^{[2]}$ is given as [15,18]

$$J^{[2]} = \begin{pmatrix} a_{11} & 0 & \delta_{NE} N + \rho_E E & 0 & \delta_{NE} N & 0 \\ \delta_{EM} & a_{22} & 0 & 0 & 0 & \delta_{NE} N \\ -\mu_P P & 0 & a_{33} & 0 & 0 & 0 \\ 0 & \delta_{NE} P & 0 & a_{44} & 0 & -\delta_{NE} N - \rho_E E \\ 0 & 0 & \delta_{NE} P & 0 & a_{55} & 0 \\ 0 & 0 & 0 & \mu_P P & \delta_{EM} & a_{66} \end{pmatrix}.$$

Setting $Q = Q(N,E,M,P) \equiv diag\left(1,1,1,1,\frac{E}{M},\frac{E}{M}\right)$, we see that $Q_f Q^{-1} = diag\left(0,0,0,0,\frac{\dot{E}}{E} - \frac{\dot{M}}{M},\frac{\dot{E}}{E} - \frac{\dot{M}}{M}\right)$ and hence $B = Q_f Q^{-1} + QJ^{[2]}Q^{-1}$. Therefore

$$B = \begin{pmatrix} a_{11} & 0 & \delta_{NE}N + \rho_E E & 0 & \delta_{NE}N & 0 \\ \delta_{EM} & a_{22} & 0 & 0 & 0 & \delta_{NE}N \\ -\mu_P P & 0 & a_{33} & 0 & 0 & 0 \\ 0 & \delta_{NE}P & 0 & a_{44} & 0 & -\delta_{NE}N - \rho_E E \\ 0 & 0 & \delta_{NE}P & 0 & b_{55} & 0 \\ 0 & 0 & 0 & \mu_P P & \delta_{EM} & b_{66} \end{pmatrix} \equiv \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix},$$

Where

$$a_{11} = -\mu_N - \delta_{NE}P - \delta_{EM} - 2\mu_E E + \rho_E P,$$
$$a_{22} = -\mu_N - \delta_{NE}P - \mu_M,$$
$$a_{33} = -\mu_N - \delta_{NE}P - \mu_P^0 + 2\rho_P - \mu_P E,$$
$$a_{44} = -\delta_{EM} - 2\mu_E E + \rho_E P - \mu_M,$$
$$b_{55} = -\delta_{EM} - 2\mu_E E + \rho_E P - \mu_P^0 + 2\rho_P - \mu_P E + \frac{\dot{E}}{E} - \frac{\dot{M}}{M},$$
$$b_{66} = -\mu_M - \mu_P^0 + 2\rho_P - \mu_P E + \frac{\dot{E}}{E} - \frac{\dot{M}}{M},$$
$$B_{11} = [a_{11}] = [-\mu_N - \delta_{NE}P - \delta_{EM} - 2\mu_E E + \rho_E P],$$
$$B_{12} = [0 \quad \delta_{NE}N + \rho_E E \quad 0 \quad \delta_{NE}N \quad 0],$$
$$B_{21} = [\delta_{EM} \quad -\mu_P P \quad 0 \quad 0 \quad 0]^T$$

and

$$B_{22} = \begin{pmatrix} a_{22} & 0 & 0 & 0 & \delta_{NE}N \\ 0 & a_{33} & 0 & 0 & 0 \\ \delta_{NE}P & 0 & a_{44} & 0 & -\delta_{NE}N - \rho_E E \\ 0 & \delta_{NE}P & 0 & b_{55} & 0 \\ 0 & 0 & \mu_P P & \delta_{EM} & b_{66} \end{pmatrix}.$$

The Lozinskii measure of B is defined as

$$\mu(B) \le max\{g_1, g_2\}$$

where $g_1 = \mu(B_{11}) + \|B_{12}\|$ and $g_2 = \mu(B_{22}) + \|B_{21}\|$ for the vector norm $\|.\|$.
It can be seen that (see Appendix I)

$$\mu(B) \le \frac{\dot{E}}{E} - \overline{b} \tag{9}$$

where

$$\overline{b} = \frac{\delta_{NE}PN}{E} + \mu_N + \delta_{NE}P + \mu_E E - \delta_{NE}N \tag{10}$$

for sufficiently large t. Then, for $t > \overline{t}$ it is seen that

$$\frac{1}{t}\int_0^t \mu(B)ds \le \frac{1}{t}\int_0^{\overline{t}} \mu(B)ds + \frac{1}{t}\ln\left(\frac{E(t)}{E(\overline{t})}\right) - \frac{(t-\overline{t})}{t}\overline{b} \tag{11}$$

for each solution $(N(t),E(t),M(t),P(t))$ such that $\big(N(0),E(0),M(0),P(0)\big) \in K$. The definition of $\overline{q_2}$ and the boundedness of $E(t)$ imply $\overline{q_2} < 0$. Hence, the equilibrium $x_3 = (N^*,E^*,M^*,P^*)$ is globally stable.

■

4. CONCLUSION

In this study, the deterministic mathematical model of Crauste et al., which consists of four differential equations modeling pathogen-specific CD8 T cell immunity response, has been analyzed. The equation system is original since it models infections by multiple pathogens and a stability analysis has been performed for the system. The steady states, basic reproduction number and the local stability conditions of the equilibrium points have been investigated. The positivity and limitation of the model were analyzed and persistence and global stability of endemic equilibrium were studied. This analysis provides useful information for the dynamics of CD8 T cell immune responses and can be applied to similar models in the area.

5. Acknowledgment

This work was supported by the Gümüşhane University Scientific Research Project under the Grant No. 17.F5121.02.01

6. APPENDICES

Appendix A: **Calculation of Q_1 for the characteristic equation of J_0**

$$Q_1 = A_3A_2 - A_1 = (\mu_M + \mu_P^0 + \mu_N + \delta_{EM})[(\mu_N + \mu_P^0)(\mu_M + \delta_{EM}) + (\mu_P^0\mu_N + \delta_{EM}\mu_M)] - [\delta_{EM}\mu_M(\mu_N + \mu_P^0) + (\mu_N + \delta_{EM})\mu_P^0\mu_N] > 0$$

Appendix B: **Calculation of Q_2 for the characteristic equation of J_0**

$$Q_2 = A_3A_2A_1 - A_1^2 - A_3^2A_0 = (\mu_M + \mu_P^0 + \mu_N + \delta_{EM})[(\mu_N + \mu_P^0)(\mu_M + \delta_{EM}) + (\mu_P^0\mu_N + \delta_{EM}\mu_M)][\delta_{EM}\mu_M(\mu_N + \mu_P^0) + (\mu_N + \delta_{EM})\mu_P^0\mu_N] - [\delta_{EM}\mu_M(\mu_N + \mu_P^0) + (\mu_N + \delta_{EM})\mu_P^0\mu_N]^2 - [\mu_M + \mu_P^0 + \mu_N + \delta_{EM}]^2\mu_P^0\mu_M\delta_{EM}\mu_N > 0.$$

Appendix C: **Calculation of Q_1 for the characteristic equation of J_1**

$$Q_1 = B_3B_2 - B_1 = \left(\mu_M + \mu_N + \mu_P^0 - 2\rho_P + \frac{\delta_{NE}\mu_P^0}{\rho_P} - \frac{\mu_P^0\rho_E}{\rho_P}\right)\Big[-2\delta_{EM}\rho_P + \mu_M\mu_N + \mu_M\mu_P^0 + \mu_N\mu_P^0 - 2\mu_M\rho_P - 2\mu_N\rho_P + 2\mu_P^0\rho_E + \delta_{EM}\mu_M + \delta_{EM}\mu_N + \delta_{EM}\mu_P^0 - 2\delta_{NE}\mu_P^0 + \frac{\delta_{NE}{\mu_P^0}^2}{\rho_P} - \frac{{\mu_P^0}^2\rho_E}{\rho_P} + \frac{\delta_{EM}\delta_{NE}\mu_P^0}{\rho_P} + \frac{\delta_{NE}\mu_M\mu_P^0}{\rho_P} - \frac{\mu_M\mu_P^0\rho_E}{\rho_P} - \frac{\mu_N\mu_P^0\rho_E}{\rho_P} + \frac{(\delta_{NE}{\mu_P^0}^2\rho_E)}{\rho_P^2}(\mu_N + \mu_P^0)(\mu_M + \delta_{EM}) + (\mu_P^0\mu_N + \delta_{EM}\mu_M)\Big] - \Big[2\delta_{EM}\delta_{NE}\mu_P^0 + \delta_{EM}\mu_M\mu_N + \delta_{EM}\mu_M\mu_P^0 - 2\delta_{NE}\mu_M\mu_P^0 + \delta_{EM}\mu_N\mu_P^0 - 2\delta_{EM}\mu_M\rho_P - 2\delta_{EM}\mu_N\rho_P + \frac{\delta_{NE}\mu_M{\mu_P^0}^2}{\rho_P} + \frac{\delta_{EM}\delta_{NE}{\mu_P^0}^2}{\rho_P} + \frac{2\delta_{NE}{\mu_P^0}^2\rho_E}{\rho_P} - \frac{\delta_{NE}{\mu_P^0}^3\rho_E}{\rho_P^2} - (\mu_M{\mu_P^0}^2\rho_E)/\rho_P - (\mu_N{\mu_P^0}^2\rho_E)/\rho_P + (\delta_{EM}\delta_{NE}\mu_M\mu_P^0)/\rho_P - (\mu_M\mu_N\mu_P^0\rho_E)/\rho_P - (\delta_{NE}\mu_M{\mu_P^0}^2\rho_E)/\rho_P^2\Big] > 0.$$

Appendix D: **Calculation of Q_2 for the characteristic equation of J_1**

$$Q_2 = B_3B_2B_1 - B_1^2 - B_3^2B_0 = \left(\mu_M + \mu_N + \mu_P^0 - 2\rho_P + \frac{\delta_{NE}\mu_P^0}{\rho_P} - \frac{\mu_P^0\rho_E}{\rho_P}\right)\Big[-2\delta_{EM}\rho_P + \mu_M\mu_N + \mu_M\mu_P^0 + \mu_N\mu_P^0 - 2\mu_M\rho_P - 2\mu_N\rho_P + 2\mu_P^0\rho_E + \delta_{EM}\mu_M + \delta_{EM}\mu_N + \delta_{EM}\mu_P^0 - 2\delta_{NE}\mu_P^0 + \frac{\delta_{NE}{\mu_P^0}^2}{\rho_P} - \frac{{\mu_P^0}^2\rho_E}{\rho_P} + \frac{\delta_{EM}\delta_{NE}\mu_P^0}{\rho_P} + \frac{\delta_{NE}\mu_M\mu_P^0}{\rho_P} - \frac{\mu_M\mu_P^0\rho_E}{\rho_P} - \frac{\mu_N\mu_P^0\rho_E}{\rho_P} +$$

$\frac{(\delta_{NE}\mu_P^{0^2}\rho_E)}{\rho_P^2}(\mu_N + \mu_P^0)(\mu_M + \delta_{EM}) + (\mu_P^0\mu_N + \delta_{EM}\mu_M)\Big]\Big[2\delta_{EM}\delta_{NE}\mu_P^0 + \delta_{EM}\mu_M\mu_N + \delta_{EM}\mu_M\mu_P^0 - 2\delta_{NE}\mu_M\mu_P^0 + \delta_{EM}\mu_N\mu_P^0 - 2\delta_{EM}\mu_M\rho_P - 2\delta_{EM}\mu_N\rho_P + \frac{\delta_{NE}\mu_M\mu_P^{0^2}}{\rho_P} + \frac{\delta_{EM}\delta_{NE}\mu_P^{0^2}}{\rho_P} + \frac{2\delta_{NE}\mu_P^{0^2}\rho_E}{\rho_P} - \frac{\delta_{NE}\mu_P^{0^3}\rho_E}{\rho_P^2} - (\mu_M\mu_P^{0^2}\rho_E)/\rho_P - (\mu_N\mu_P^{0^2}\rho_E)/\rho_P + \delta_{EM}\delta_{NE}\mu_M\mu_P^0)/\rho_P - (\mu_M\mu_N\mu_P^0\rho_E)/\rho_P - (\delta_{NE}\mu_M\mu_P^{0^2}\rho_E)/\rho_P^2\Big] - \Big[2\delta_{EM}\delta_{NE}\mu_P^0 + \delta_{EM}\mu_M\mu_N + \delta_{EM}\mu_M\mu_P^0 - 2\delta_{NE}\mu_M\mu_P^0 + \delta_{EM}\mu_N\mu_P^0 - 2\delta_{EM}\mu_M\rho_P - 2\delta_{EM}\mu_N\rho_P + \frac{\delta_{NE}\mu_M\mu_P^{0^2}}{\rho_P} + \frac{\delta_{EM}\delta_{NE}\mu_P^{0^2}}{\rho_P} + \frac{2\delta_{NE}\mu_P^{0^2}\rho_E}{\rho_P} - \frac{\delta_{NE}\mu_P^{0^3}\rho_E}{\rho_P^2} - (\mu_M\mu_P^{0^2}\rho_E)/\rho_P - (\mu_N\mu_P^{0^2}\rho_E)/\rho_P + (\delta_{EM}\delta_{NE}\mu_M\mu_P^0)/\rho_P - (\mu_M\mu_N\mu_P^0\rho_E)/\rho_P - (\delta_{NE}\mu_M\mu_P^{0^2}\rho_E)/\rho_P^2\Big]^2 - \Big[\mu_M + \mu_N + \mu_P^0 - 2\rho_P + \frac{\delta_{NE}\mu_P^0}{\rho_P} - \frac{\mu_P^0\rho_E}{\rho_P}\Big]^2\Big[-2\delta_{EM}\delta_{NE}\mu_M\mu_P^0 + \delta_{EM}\mu_M\mu_N\mu_P^0 - 2\delta_{EM}\mu_M\mu_N\rho_P - 2\lambda\mu_M\mu_N\rho_P + 2\mu_M\mu_N\mu_P^0\rho_E + \frac{2\delta_{NE}\mu_M\mu_P^{0^2}\rho_E}{\rho_P} - \frac{\mu_M\mu_N\mu_P^{0^2}\rho_E}{\rho_P} - \frac{\delta_{NE}\mu_M\mu_P^{0^3}\rho_E}{\rho_P^2} + (\delta_{EM}\delta_{NE}\mu_M\mu_P^{0^2})/\rho_P\Big] > 0.$

Appendix E: **Calculation of Q_1 for the characteristic equation of J_2**

$$Q_1 = D_3D_2 - D_1 = \Big(\mu_M - \delta_{EM} + \mu_N + \mu_P^0 - 2\rho_P + \frac{\delta_{EM}\mu_P}{\mu_E}\Big)\Big[2\delta_{EM}\rho_P + \mu_M\mu_N + \mu_M\mu_P^0 + \mu_N\mu_P^0 - 2\mu_M\rho_P - 2\mu_N\rho_P - \delta_{EM}\mu_M - \delta_{EM}\mu_N - \delta_{EM}\mu_P^0 - \frac{\delta_{EM}^2\mu_P}{\mu_E} + \frac{\delta_{EM}\mu_M\mu_P}{\mu_E}\Big] - \Big[-\delta_{EM}\mu_M\mu_N - \delta_{EM}\mu_M\mu_P^0 - \delta_{EM}\mu_N\mu_P^0 + 2\delta_{EM}\mu_M\rho_P + 2\delta_{EM}\mu_N\rho_P + \mu_M\mu_N\mu_P^0 - 2\mu_M\mu_N\rho_P - \frac{\delta_{EM}^2\mu_M\mu_P}{\mu_E} - \frac{\delta_{EM}^2\mu_N\mu_P}{\mu_E} + \frac{\delta_{EM}\mu_M\mu_N\mu_P}{\mu_E}\Big] < 0.$$

Appendix F: **Calculation of Q_2 for the characteristic equation of J_2**

$$Q_2 = D_3D_2D_1 - D_1^2 - D_3^2D_0 = \Big(\mu_M - \delta_{EM} + \mu_N + \mu_P^0 - 2\rho_P + \frac{\delta_{EM}\mu_P}{\mu_E}\Big)\Big[2\delta_{EM}\rho_P + \mu_M\mu_N + \mu_M\mu_P^0 + \mu_N\mu_P^0 - 2\mu_M\rho_P - 2\mu_N\rho_P - \delta_{EM}\mu_M - \delta_{EM}\mu_N - \delta_{EM}\mu_P^0 - \frac{\delta_{EM}^2\mu_P}{\mu_E} + \frac{\delta_{EM}\mu_M\mu_P}{\mu_E}\Big]\Big[-\delta_{EM}\mu_M\mu_N - \delta_{EM}\mu_M\mu_P^0 - \delta_{EM}\mu_N\mu_P^0 + 2\delta_{EM}\mu_M\rho_P + 2\delta_{EM}\mu_N\rho_P + \mu_M\mu_N\mu_P^0 - 2\mu_M\mu_N\rho_P - \frac{\delta_{EM}^2\mu_M\mu_P}{\mu_E} - \frac{\delta_{EM}^2\mu_N\mu_P}{\mu_E} + \frac{\delta_{EM}\mu_M\mu_N\mu_P}{\mu_E}\Big] - \Big[-\delta_{EM}\mu_M\mu_N - \delta_{EM}\mu_M\mu_P^0 - \delta_{EM}\mu_N\mu_P^0 + 2\delta_{EM}\mu_M\rho_P + 2\delta_{EM}\mu_N\rho_P + \mu_M\mu_N\mu_P^0 - 2\mu_M\mu_N\rho_P - \frac{\delta_{EM}^2\mu_M\mu_P}{\mu_E} - \frac{\delta_{EM}^2\mu_N\mu_P}{\mu_E} + \frac{\delta_{EM}\mu_M\mu_N\mu_P}{\mu_E}\Big]^2 - \Big[\mu_M - \delta_{EM} + \mu_N + \mu_P^0 - 2\rho_P + \frac{\delta_{EM}\mu_P}{\mu_E}\Big]^2\Big[2\delta_{EM}\mu_M\mu_N\rho_P - \frac{\delta_{EM}^2\mu_M\mu_N\mu_P}{\mu_E} - \delta_{EM}\mu_M\mu_N\mu_P^0\Big] < 0.$$

Appendix G: **Calculation of Q_1 for the characteristic equation of J_3**

$$\begin{aligned}Q_1 = E_3E_2 - E_1 = (&\delta_{EM} + \mu_M + \mu_N + \mu_P^0 - 2\rho P^* + 2E^*\mu_E + E^*\mu_P + P^*\delta_{NE} \\ &- P^*\rho_E)\big[-2\delta_{EM}\rho P^* + \mu_M\mu_N + \mu_M\mu_P^0 + \lambda^2\mu_N\mu_P^0 - 2\mu_M\rho_P \\ &- 2\mu_N\rho_P + \delta_{EM}\mu_M + \delta_{EM}\mu_N + \delta_{EM}\mu_P^0 + + E^*\delta_{EM}\mu_P + P^*\delta_{NE} \\ &+ 2E^*\mu_E\mu_M + 2E^*\mu_E\mu_N + 2E^*\mu_E\mu_P^0 + E^*\mu_M\mu_P + E^*\mu_N\mu_P \\ &+ P^*\delta_{NE}\mu_M + P^*\delta_{NE}\mu_P^0 - 4E^*\mu_E\rho_P - 2P^*\delta_{NE}\rho_P - P^*\mu_M\rho_E \\ &- P^*\mu_N\rho_E - P^*\mu_P^0\rho_E + 2P^*\rho_E\rho_P + 2E^{*2}\mu_E\mu_P - P^{*2}\delta_{NE}\rho_E \\ &+ 2E^*P^*\delta_{NE}\mu_E + E^*P^*\delta_{NE}\mu_P + N^*P^*\delta_{NE}\mu_P\big] \\ &- \big[\delta_{EM}\mu_M\mu_N + \delta_{EM}\mu_M\mu_P^0 + \delta_{EM}\mu_N\mu_P^0 - 2\delta_{EM}\mu_M\rho_P - 2\delta_{EM}\mu_N\rho_P \\ &+ \mu_M\mu_N\mu_P^0 - 2\mu_M\mu_N\rho_P + E^*\delta_{EM}\mu_M\mu_P + E^*\delta_{EM}\mu_N\mu_P \\ &+ P^*\delta_{EM}\delta_{NE}\mu_M + P^*\delta_{EM}\delta_{NE}\mu_P^0 - 2P^*\delta_{EM}\delta_{NE}\rho_P + 2E^*\mu_E\mu_M\mu_N \\ &+ 2E^*\mu_E\mu_M\mu_P^0 + 2E^*\mu_E\mu_N\mu_P^0 + E^*\mu_M\mu_N\mu_P + P^*\delta_{NE}\mu_M\mu_P^0 \\ &- 4E^*\mu_E\mu_M\rho_P - 4E^*\mu_E\mu_N\rho_P - 2P^*\delta_{NE}\mu_M\rho_P - P^*\mu_M\mu_N\rho_E \\ &- P^*\mu_M\mu_P^0\rho_E - P^*\mu_N\mu_P^0\rho_E + 2P^*\mu_M\rho_E\rho_P + 2P^*\mu_N\rho_E\rho_P \\ &+ 2E^{*2}\mu_E\mu_M\mu_P + 2E^{*2}\mu_E\mu_N\mu_P - P^{*2}\delta_{NE}\mu_M\rho_E - P^{*2}\delta_{NE}\mu_P^0\rho_E \\ &+ 2P^{*2}\delta_{NE}\rho_E\rho_P + E^*P^*\delta_{EM}\delta_{NE}\mu_P + 2E^*P^*\delta_{NE}\mu_E\mu_M \\ &+ 2E^*P^*\delta_{NE}\mu_E\mu_P^0 + E^*P^*\delta_{NE}\mu_M\mu_P - 4E^*P^*\delta_{NE}\mu_E\rho_P \\ &+ N^*P^*\delta_{NE}\mu_M\mu_P + N^*P^*\delta_{NE}\mu_N\mu_P + 2E^{*2}P^*\delta_{NE}\mu_E\mu_P\big] < 0.\end{aligned}$$

Appendix H: **Computation of the Variational Matrix**

Let

$$f_1 = -\mu_N N - \delta_{NE}PN,$$
$$f_2 = \delta_{NE}PN + \rho_E PE - \mu_E E^2 - \delta_{EM}E,$$
$$f_3 = -\mu_M M + \delta_{EM}E,$$
$$f_4 = \rho_P P^2 - \mu_P EP - \mu_P^0 P.$$

Hence, the general variational matrix is given as

$$V = \begin{pmatrix} \frac{\partial f_1}{\partial N} & \frac{\partial f_1}{\partial E} & \frac{\partial f_1}{\partial M} & \frac{\partial f_1}{\partial P} \\ \frac{\partial f_2}{\partial N} & \frac{\partial f_2}{\partial E} & \frac{\partial f_2}{\partial M} & \frac{\partial f_2}{\partial P} \\ \frac{\partial f_3}{\partial N} & \frac{\partial f_3}{\partial E} & \frac{\partial f_3}{\partial M} & \frac{\partial f_3}{\partial P} \\ \frac{\partial f_4}{\partial N} & \frac{\partial f_4}{\partial E} & \frac{\partial f_4}{\partial M} & \frac{\partial f_4}{\partial P} \end{pmatrix}_{(N^*,E^*,M^*,P^*)}$$

where (N^*, E^*, M^*, P^*) is the equilibrium point for $f_1 = f_2 = f_3 = f_4 = 0$. Then the general variational matrix for the model (1)-(4) is given by

$$V = \begin{bmatrix} -\mu_N - \delta_{NE}P^* & 0 & 0 & -\delta_{NE}N^* \\ \delta_{NE}P^* & -\delta_{EM} - 2\mu_E E^* + \rho_E P^* & 0 & \delta_{NE}N^* + \rho_E E^* \\ 0 & \delta_{EM} & -\mu_M & 0 \\ 0 & -\mu_P P^* & 0 & -\mu_P^0 + 2\rho_P - \mu_P E^* \end{bmatrix}.$$

Note that a different variational matrix can also be given for the system.

Appendix I: **Calculation of the Lozinskii Measure of the Matrix B.**

The Lozinskii measure of B is given as

$$\mu(B) \leq max\{g_1, g_2\} \tag{12}$$

for $g_1 = \mu(B_{11}) + \|B_{12}\|$ and $g_2 = \mu(B_{22}) + \|B_{21}\|$. Thus, we obtain

$$\mu(B_{11}) = -\mu_N - \delta_{NE}P - \delta_{EM} - 2\mu_E E + \rho_E P,$$
$$\|B_{12}\| = \delta_{NE}N,$$
$$\|B_{12}\| = \|B_{12}\| = \delta_{NE}N.$$

Then,

$$g_1 = -\mu_N - \delta_{NE}P - \delta_{EM} - 2\mu_E E + \rho_E P + \delta_{NE}N, \tag{13}$$
$$g_2 = \delta_{NE}N + \mu(B_{22} = C). \tag{14}$$

$[B_{22}]_{5\times 5}$ can be denoted as $B_{22} = C' = \begin{bmatrix} C_{11} & C_{12} \\ C_{21} & C_{22} \end{bmatrix}$, where

$$C_{11} = [a_{22}] = [-\mu_N - \delta_{NE}P - \mu_M],$$
$$C_{12} = [0 \quad 0 \quad 0 \quad \delta_{NE}N],$$
$$C_{21} = [0 \quad \delta_{NE}P \quad 0 \quad 0]^T,$$
$$C_{22} = \begin{pmatrix} & a_{33} & 0 & 0 & 0 \\ 0 & a_{44} & 0 & -\delta_{NE}N - \rho_E E \\ & \delta_{NE}P & 0 & b_{55} & 0 \\ & 0 & \mu_P P & \delta_{EM} & b_{66} \end{pmatrix}.$$

Hence,

$$\mu(C') \leq max\{g_3, g_4\} \tag{15}$$

is obtained for

$$g_3 = \mu(C_{11}) + \|C_{12}\| = -\mu_N - \delta_{NE}P - \mu_M + \delta_{NE}N, \tag{16}$$
$$g_4 = \delta_{NE}P + \mu(C_{22}). \tag{17}$$

$[C_{22}]_{4\times 4}$ is partitioned to calculate $\mu(C_{22})$

$$C_{22} = D' = \begin{bmatrix} D_{11} & D_{12} \\ D_{21} & D_{22} \end{bmatrix}$$
$$D_{11} = [a_{33}] = [-\mu_N - \delta_{NE}P - \mu_P^0 + 2\rho_P - \mu_P E],$$
$$D_{12} = [0 \quad 0 \quad 0],$$
$$D_{21} = [0 \quad \delta_{NE}P \quad 0]^T,$$

and

$$D_{22} = \begin{pmatrix} a_{44} & 0 & -\delta_{NE}N - \rho_E E \\ & 0 & b_{55} & 0 \\ & \mu_P P & \delta_{EM} & b_{66} \end{pmatrix}.$$

If we denote

$$\mu(D) \leq max\{g_5, g_6\} \tag{18}$$

for $g_5 = \mu(D_{11}) + \|D_{12}\|$ and $g_6 = \mu(D_{22}) + \|D_{21}\|$, we have $\mu(D_{11}) = -\mu_N - \delta_{NE}P - \mu_P^0 + 2\rho_P - \mu_P E$, $\|D_{12}\| = 0$ and $\|D_{21}\| = \delta_{NE}P$.

Let $D_{22} = E = \begin{bmatrix} E_{11} & E_{12} \\ E_{21} & E_{22} \end{bmatrix}$, then

$$g_5 = -\mu_N - \delta_{NE}P - \mu_P^0 + 2\rho_P - \mu_P E, \tag{19}$$
$$g_6 = \delta_{NE}P + \mu(D_{22} = E). \tag{20}$$

and

$$E_{11} = [a_{44}] = [-\delta_{EM} - 2\mu_E E + \rho_E P - \mu_M],$$
$$E_{12} = [0 \quad -\delta_{NE} N - \rho_E E],$$
$$E_{21} = [0 \quad \mu_P P]^T,$$
$$E_{22} = \begin{bmatrix} b_{55} & 0 \\ \delta_{EM} & b_{66} \end{bmatrix}.$$

Once again, the Lozinskii measure of E is defined as

$$\mu(E) \le max\{g_7, g_8\}, \tag{21}$$

where $g_7 = \mu(E_{11}) + \|E_{12}\|$, $g_8 = \mu(E_{22}) + \|E_{21}\|$, $\mu(E_{11}) = -\delta_{EM} - 2\mu_E E + \rho_E P - \mu_M$, $\|E_{12}\| = -\delta_{NE} N - \rho_E E$, $\|E_{21}\| = \mu_P P$ and $\mu(E_{22}) = max[b_{55} + \delta_{EM}, b_{66}] = -\mu_P^0 + 2\rho_P - \mu_P E + \frac{\dot{E}}{E} - \frac{\dot{M}}{M} + max\{-2\mu_E E + \rho_E P, -\mu_M\}$. Therefore,

$$g_7 = -\delta_{EM} - 2\mu_E E + \rho_E P - \mu_M - \delta_{NE} N - \rho_E E, \tag{22}$$

$$g_8 = \mu_P P - \mu_P^0 + 2\rho_P - \mu_P E + \frac{\dot{E}}{E} - \frac{\dot{M}}{M} + max\{-2\mu_E E + \rho_E P, -\mu_M\}. \tag{23}$$

Using (22) and (23), (21) becomes

$$\mu(E) \le \mu_P P - \mu_P^0 + 2\rho_P - \mu_P E + \frac{\dot{E}}{E} - \frac{\dot{M}}{M} + max\{-2\mu_E E + \rho_E P, -\mu_M\}. \tag{24}$$

(20) and (24) give,

$$g_6 \le \delta_{NE} P + \mu_P P - \mu_P^0 + 2\rho_P - \mu_P E + \frac{\dot{E}}{E} - \frac{\dot{M}}{M} + max\{-2\mu_E E + \rho_E P, -\mu_M\}. \tag{25}$$

Hence,

$$\frac{\dot{E}}{E} = \frac{\delta_{NE} PN}{E} + \rho_E P - \mu_E E - \delta_{EM}, \tag{26}$$

$$\frac{\dot{M}}{M} = -\mu_M + \frac{\delta_{EM} E}{M}. \tag{27}$$

Using, (25) and (27) we obtain

$$g_6 \le \frac{\dot{E}}{E} + \mu_M - \frac{\delta_{EM} E}{M} + \delta_{NE} P + \mu_P P - \mu_P^0 + 2\rho_P - \mu_P E + max\{-2\mu_E E + \rho_E P, -\mu_M\}. \tag{28}$$

(19) and (26) give

$$g_5 = \frac{\dot{E}}{E} - \mu_N - \delta_{NE} P - \mu_P^0 + 2\rho_P - \mu_P E - \frac{\delta_{NE} PN}{E} - \rho_E P + \mu_E E + \delta_{EM}. \tag{29}$$

(18), (28) and (29) give

$$\mu(D) \le \frac{\dot{E}}{E} + \mu_M - \frac{\delta_{EM} E}{M} + \delta_{NE} P + \mu_P P - \mu_P^0 + 2\rho_P - \mu_P E + max\{-2\mu_E E + \rho_E P, -\mu_M\}. \tag{30}$$

(17) and (30) give,

$$g_4 \le \frac{\dot{E}}{E} + \mu_M - \frac{\delta_{EM} E}{M} + 2\delta_{NE} P + \mu_P P - \mu_P^0 + 2\rho_P - \mu_P E + max\{-2\mu_E E + \rho_E P, -\mu_M\} \tag{31}$$

(16), (17) and (31) give

$$\mu(C') \le \frac{\dot{E}}{E} + \mu_M - \frac{\delta_{EM} E}{M} + 2\delta_{NE} P + \mu_P P - \mu_P^0 + 2\rho_P - \mu_P E + max\{-2\mu_E E + \rho_E P, -\mu_M\} \tag{32}$$

(14) and (32) give

$$g_2 \leq \frac{\dot{E}}{E} + \delta_{NE}N + \mu_M - \frac{\delta_{EM}E}{M} + 2\delta_{NE}P + \mu_P P - \mu_P^0 + 2\rho_P - \mu_P E + max\{-2\mu_E E + \rho_E P, -\mu_M\}. \quad (33)$$

Using (13) and (26)

$$g_1 = \frac{\dot{E}}{E} - \frac{\delta_{NE}PN}{E} - \mu_N - \delta_{NE}P - \mu_E E + \delta_{NE}N \quad (34)$$

Hence, we get

$$\mu(B) \leq \frac{\dot{E}}{E} - \overline{b}$$

for sufficiently large t, where

$$\overline{b} = \frac{\delta_{NE}PN}{E} + \mu_N + \delta_{NE}P + \mu_E E - \delta_{NE}N \quad (35)$$

■

REFERENCES

[1] Daşbaşı, B. (2018). Stability Analysis of Mathematical Model including Pathogen-Specific Immune System Response with Fractional-Order Differential Equations. Computational and mathematical methods in medicine, 2018.

[2] Merdan, M., Bekiryazici, Z., Kesemen, T., & Khaniyev, T. (2017). Deterministic stability and random behavior of a Hepatitis C model. PloS one, 12(7), e0181571.

[3] Bekiryazici, Z., Merdan, M., Kesemen, T., & Najmuldeen, M. (2016). Mathematical modeling of dengue disease under random effects. Math. Sci. Appl. E-Notes, 4(2), 58-70.

[4] Merdan, M., & Khaniyev, T. (2008). On the Behaviour of Solutions under the Influence of Stochastic Effect of Avian-Human Influenza Epidemic Model. International Journal of Biotechnology and Biochemistry, 4 (1), 75-100.

[5] Bekiryazici, Z., Kesemen, T., & Merdan, M. (2017) Stochastic and random models of Malaria Disease with vertical transmission. New Trends in Mathematical Sciences, 5(1), 269-277.

[6] Crauste, F., Terry, E., Le Mercier, I., Mafille, J., Djebali, S., Andrieu, T., ... & Gandrillon, O. (2015). Predicting pathogen-specific CD8 T cell immune responses from a modeling approach. Journal of theoretical biology, 374, 66-82.

[7] Gökdoğan, A., Merdan, M., & Yildirim, A. (2012). A multistage differential transformation method for approximate solution of Hantavirus infection model. *Communications in Nonlinear Science and Numerical Simulation*, *17*(1), 1-8.

[8] Callaway, D. S., & Perelson, A. S. (2002). HIV-1 infection and low steady state viral loads. Bulletin of mathematical biology, 64(1), 29-64.

[9] Antia, R., Bergstrom, C. T., Pilyugin, S. S., Kaech, S. M., & Ahmed, R. (2003). Models of CD8+ responses: 1. What is the antigen-independent proliferation program. Journal of theoretical biology, 221(4), 585-598.

[10] Antia, R., Ganusov, V. V., & Ahmed, R. (2005). The role of models in understanding CD8+ T-cell memory. Nature Reviews Immunology, 5(2), 101.

[11] Barbarroux, L., Michel, P., Adimy, M., & Crauste, F. (2018). A multiscale model of the CD8 T cell immune response structured by intracellular content. Discrete & Continuous Dynamical Systems-B, 23(9), 3969-4002.

[12] Banerjee, S., Keval, R., & Gakkhar, S. (2013). Modeling the dynamics of Hepatitis C virus with combined antiviral drug therapy: Interferon and Ribavirin. Mathematical biosciences, 245(2), 235-248.

[13] Hale, J. K., & Lunel, S. M. V. (1993). Properties of the solution map. In Introduction to

functional differential equations (pp. 67-99). Springer, New York, NY.
[14] Li, M. Y., & Muldowney, J. S. (1996). A geometric approach to global-stability problems. SIAM Journal on Mathematical Analysis, 27(4), 1070-1083.
[15] Muldowney, J. S. (1990). Compound matrices and ordinary differential equations. Rocky Mountain Journal of Mathematics, 20(4).
[16] Coppel, W. A. (1965). Stability and asymptotic behavior of differential equation. Boston: Health.
[17] Butler, G., & Waltman, P. (1986). Persistence in dynamical systems. Journal of Differential Equations, 63(2), 255-263.
[18] Fiedler, M. (1974). Additive compound matrices and an inequality for eigenvalues of symmetric stochastic matrices. Czechoslovak Mathematical Journal, 24(3), 392-402.