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Stability Analysis of Within Host Dengue Model Incorporating the Impact of Cell-Mediated and Innate Immune Reactions

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ABSTRACT: Dengue a globally prevalent mosquito-borne disease affects millions each year. Developing a model to understand its dynamics within hosts is crucial for effective prevention and control. Mathematical models considering vector-host interactions, innate immunity, and IFN levels shed light on the interplay between host defences and viral spread. This paper deals with the analysis of a within-host dengue infection model with innate and adaptive immunity. In this context, a nonlinear mathematical model is developed and analyzed to reveal the growth of infection within host along with innate and adaptive immunity. The model has two equilibria: infection-free and endemic equilibrium. The infection-free equilibrium is locally and globally stable for $R_0 < 1$, while numerically it is found that endemic equilibrium is locally and globally asymptotically stable for $R_0 > 1$. Further, all the analytical results are verified through numerical simulations using MATLAB.

Keywords: Dengue infection, Antibodies, Basic reproduction number, Innate immunity, T immune cells.

INTRODUCTION

Dengue is a mosquito-borne disease that has spread globally and it is of significant international health concern. According to a World Health Organization (WHO) report, dengue cases are estimated to reach 50-100 million annually. Female mosquitoes bearing the Aedes aegypti and Aedes albopictus virus are the primary carriers of the dengue virus. However, the growth of Aedes aegypti is affected by several factors of society, e.g., agriculture, economy, living status, religion, etc (Priyanka Spring *et al.,* 2022; Singh and Rahman 2013). A healthy person can become infected by these mosquitoes after being bitten by an infected person. As the symptoms begin to emerge, such as high fever, headache, pain behind the eyes, joint pains, nausea, and vomiting, many of the typical symptoms will appear (Halstead, 2007). The dengue virus has four distinct serotypes, DEN-I, DEN-II, DEN-III, and DEN-IV. The immune response against a dengue virus is activated when a person contracts it for the first time (Gibbons and Vaughn 2002). There are currently no effective vaccines for all strains of dengue (Kinney and Huangs 2001), so many countries employ protection and prevention strategies to prevent this disease (Gubler, 2011). Mosquitoes are most commonly controlled using chemical or biological methods.

An understanding of the cellular dynamics inside the host is required to model the dengue infection phenomenon within a host. Dengue virions attack macrophages, monocytes, dendritic cells, endothelial cells, and epithelial cells in the body (Jindadamrongwech *et al.,* 2004; Nowak and May 2000). They are antigen-presenting cells (APC) for dengue. Once these cells are infected with the virus, the virions multiply in huge numbers and burst out. When virions are in abundance, the adaptive immune response becomes active. These responses to viruses have more specificity and longer-lasting immunity and memory. T cells and B cells are released in response to an activated cellular immune response and a humoral immune response (Murphy and Whitehead 2011). The immune response of the cellular system releases cytotoxic T cells as well as T helper cells. T helper cells activate long-lived and antigen-specific memory T cells. B cells are also activated by T helper cells. Hence, humoral responses must be activated by the cellular immune response. A humoral immune response is further induced as the naive B cells recognize the antigens. And these cells expand and differentiate, they become clonal. As the B cells mature, they become plasma cells that secrete antibodies. Antibodies bind to virions and neutralize them (Clapham *et al.,* 2014). Consequently, antibodies take time to secrete. Even when humoral responses begin to decline, memory cells remain in the system. This memory cell recognizes the same antigen when the body is re-infected with it, allowing it to respond more quickly and efficiently when the body gets re-infected by it. Therefore, a particular strain has developed lifelong immunity. The humoral response provides long-term protection from viruses, a part of our adaptive immune system. Therefore, disease dynamics should incorporate both responses (Janeway *et al.,* 2001). Without vaccine, the biological process of the virus clearance within-host need only understanding its

spread mechanism. The immune response for clearing dengue infection has been examined (Nuraini *et al.,* 2009). There has been no differentiation between cellular and humoral immune responses in their analysis of immune response dynamics. Type I interferon (Primarily IFN-α/β) is one of the most important cytokines involved in the innate immune response. Many IFN-stimulated gene products, including antiviral proteins like protein kinase R and PKR, are expressed in the neighboring cells when IFN-α/β is engaged during infection resistance (Julkunen *et al.*, 2001). The IFN also triggers the activation of immune system cells in the early stages of infection, such as natural killer cells (NK), which can destroy the infected cells (Gazit *et al.,* 2006).

In last two decades, it has been proven that the coupled system of ordinary differential are able to model the different real world problems (Khare *et al.,* 2022; Mathur 2016; Narayan *et al.,* 2023). To study the dynamics of diseases at the population level, many mathematical models have been developed to describe vector-host interactions (Adams and Boots 2010; Alera *et al.,* 2016; Esteva and Vargas 2003; Lutambi *et al.,*2013; Mathur and Kumar 2022; Supriatna *et al.,* 2008). (Ben-Shachar and Koelle 2015), describe the role of innate immunity in dengue infection. They assumed that several activated NK cells are proportional to the level of IFN and the similar assumption is also used by Pawelek *et al.* (2012). This paper aims to develop and analyze a nonlinear model of the biological process of primary dengue infection to reveal how the infection proceeds. During the primary dengue infection, both T immune cells and antibodies are included in the model.

MATERIAL AND METHOD

A. Model development

We develop a mathematical model to study dengue infection which incorporates both innate and adaptive immune responses. We assume that only one serotype of the dengue virus circulates in an infected host and the dengue virus infects monocytes, macrophages, etc in the bloodstream. Let S be the susceptible cells (monocytes, macrophages, dendritic cells, hepatocytes, or mast cells), I be the infected cells, V be the dengue virus particles, and let Z be the density of T immune cells due to cellular immune response activation. T cells activate B cells that again differentiate into plasma cells to produce antibodies. Here B and A represent the density of B cells and neutralizing antibodies, respectively. Let F be the interferon, Λ be the rate at which susceptible cells are produced (monocytes, macrophages, dendritic cells, etc.), a be the rate at which susceptible cells become infected, μ_1, β and γ be the death rates of infected cells, susceptible cells, and virus particles, respectively. Further, assume that b is the infected cells, which may be killed by NK cells at a rate proportional to b, k burst rate of virus particles. p represents virion neutralizing rate of antibodies, μ_2 represents the rate at which infected cells activate their immune response, d, d_1, and d_3 are the death rates of immune cells, B cells, and antibodies, respectively. Moreover, η represents a constant rate at which B-cells are produced, β_1 represents the rate at which T immune responses activate B cells, f is a rate of produce antibodies (A), q is rate of Antibodies are destroyed by a virus. It is assumed that IFN(F) is produced by infected cells at a rate β_2 and decays at a rate d_2.

$$\frac{dS}{dt} = \Lambda - \mu_1 S - aSV, \frac{dI}{dt} = aSV - \beta I - bIF,$$
$$\frac{dV}{dt} = \mathrm{kI} - \gamma V - pAV, \frac{dZ}{dt} = \mu_2 ZI - dZ, \qquad (2.1)$$
$$\frac{dB}{dt} = \eta + \beta_1 BZ - d_1 B, \frac{dA}{dt} = \mathrm{fB} - qAV - d_3 A,$$
$$\frac{dF}{dt} = \beta_2 I - d_2 F.$$

The model possesses the following non-negative initial conditions:

$$S(0) \geq 0, I(0) \geq 0, V(0) \geq 0, Z(0) \geq 0, B(0) \geq 0, A(0) \geq 0, F(0) \geq 0.$$

Model Analysis

Existence of Equilibria. The equilibria of the system can be calculated by substituting all the model equations to zero. Hence, the infection-free equilibrium point is given as

$$E_0 = (\tilde{S}, \tilde{I}, \tilde{V}, \tilde{Z}, \tilde{B}, \tilde{A}, \tilde{F}) = \left(\frac{\Lambda}{\mu_1}, 0, 0, 0, \frac{\eta}{d_1}, \frac{f\eta}{d_1 d_3}, 0\right).$$

And the endemic equilibrium $E^* = (S^*, I^*, V^*, Z^*, B^*, A^*, F^*)$ exists provided following conditions are satisfied: $kd\Lambda a d_2 \mu_2^2 > kd\eta + \mu_2\gamma\mu_1 d_2\beta d\mu_2 + \mu_2\gamma\mu_1 bqd^2$, $d_1 B^* > \eta$, where,

$$S^* = \frac{\Lambda\left(\Lambda a d_2\mu_2^2 - (ad_2\beta d\mu_2 + ab\beta_2 d^2)\right)}{\mu_1\Lambda a d_2\mu_2^2 - \mu_1(ad_2\beta d\mu_2 + ab\beta_2 d^2) + a\mu_1(d_2\beta d\mu_2 + b\beta_2 d^2)};$$
$$I^* = \frac{d}{\mu_2}; V^* = \frac{\mu_1(d_2\beta d\mu_2 + b\beta d^2)}{\Lambda \mathrm{a} d_2\mu_2^2 - (ad_2\beta d\mu_2 + ab\beta_2 d^2)}; Z^* = \frac{d_1 B^* - \eta}{B^*\beta_1};$$
$$B^* = \frac{\left(kd(\Lambda a d_2\mu_2^2 - r + 1) - \mu_2\gamma\mu_1(d_2\beta d\mu_2 + b\beta_2 d^2)\right)}{\mu_1\mu_2 pf(d_2\beta d\mu_2 + b\beta_2 d^2)} X$$
$$\frac{q\mu_1(d_2\beta d\mu_2 + b\beta_2 d^2)d_3\Lambda a d_2\mu_2^2 - d_3(ad_2\beta d\mu_2 + ab\beta_2 d^2)}{\left(\Lambda \mathrm{a} d_2\mu_2^2 - (ad_2\beta d\mu_2 + ab\beta_2 d^2)\right)};$$
$$A^* = \frac{kd(\Lambda a d_2\mu_2^2 - r + 1) - \mu_2\gamma\mu_1(d_2\beta d\mu_2 + b\beta_2 d^2)}{\mu_1\mu_2 p(d_2\beta d\mu_2 + b\beta_2 d^2)}; F^* = \frac{\beta_2 d}{d_2\mu_2}.$$

This ensures the existence of endemic equilibrium point (E^*).

Basic Reproduction Number. The basic reproduction number (R_0) is defined as the average number of infected cells produced by each infected cell when almost all cells are uninfected (Jones, 2007). It can be calculated by the next-generation method as follows:

$$F = \begin{pmatrix} 0 & a\tilde{S} \\ k & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} \beta + b\tilde{F} & 0 \\ 0 & \gamma + p\tilde{A} \end{pmatrix}.$$

At E_0 the next generation matrix is

$FV^{-1} = \begin{pmatrix} 0 & \frac{a\Lambda d_1 d_3}{\mu_1(\gamma d_1 d_3 + pfn)} \\ \frac{k}{\beta} & 0 \end{pmatrix}$. It is known that largest eigenvalue of FV^{-1} is the basic reproduction number (R_0), which is computed as $R_0 = \frac{ak\Lambda d_1 d_3}{\mu_1\beta(\gamma d_1 d_3 + pfn)}$.

$$\text{J[E]} = \begin{pmatrix} -(\mu_1 + aV) & 0 & -aS & 0 & 0 & 0 & 0 \\ aV & -(\beta + bF) & aS & 0 & 0 & 0 & -bI \\ 0 & k & -(\gamma + pA) & 0 & 0 & -pV & 0 \\ 0 & \mu_2 Z & 0 & \mu_2 I - d & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta_1 B & \beta_1 Z - d_1 & 0 & 0 \\ 0 & 0 & -qA & 0 & f & -qV - d_3 & 0 \\ 0 & \beta_2 & 0 & 0 & 0 & 0 & -d_2 \end{pmatrix}.$$

At E_0, we get

$$\text{J[E}_0\text{]} = \begin{pmatrix} -\mu_1 & 0 & -\frac{a\Lambda}{\mu_1} & 0 & 0 & 0 & 0 \\ aV & -(\beta + bF) & \frac{a\Lambda}{\mu_1} & 0 & 0 & 0 & -bI \\ 0 & k & -\left(\gamma + \frac{pf\eta}{d_1 d_3}\right) & 0 & 0 & -pV & 0 \\ 0 & \mu_2 Z & 0 & -d & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_1 \eta}{d_1} & -d_1 & 0 & 0 \\ 0 & 0 & -\frac{qf\eta}{d_1 d_3} & 0 & f & -d_3 & 0 \\ 0 & \beta_2 & 0 & 0 & 0 & 0 & -d_2 \end{pmatrix}.$$

The eigenvalue of J[E_0] are $-\mu_1, -d, -d_1, -d_2, -d_3$ and remaining two eigenvalues can be obtained as follows from the quadratic equation $p_2\lambda^2 + p_1\lambda + p_0 = 0$,

$$\lambda = \frac{-p_1 \pm \sqrt{p_1^2 - 4d_1 d_3\beta(\gamma d_1 k + pf\eta)(R_0 - 1)}}{2d_1 d_3},$$

where $p_0 = \beta(\gamma d_1 d_3 + pf\eta)(R_0 - 1)$,

$$p_1 = (\beta + \gamma)d_1 d_3 + pf\eta, p_2 = d_1 d_3.$$

Since, $p_1 > 0$, $p_2 > 0$ the above eigenvalues are negative provided $R_0 < 1$. Thus, the disease-free equilibrium E_0 is locally asymptotically stable for $R_0 < 1$ and unstable for $R_0 > 1$. Besides, for $R_0 > 1$, the endemic equilibrium exits.

B. Global Stability of Equilibria

This section devoted to the global stability of disease-free equilibrium using the method given (Castillo-Chavez *et al.*, 2002).

Let $X = (S, Z, B, A, F)$ *and* $Z = (I, V)$. Here $U^0 = (X^0, Z^0)$, with $X^0 = (S_0, Z_0, B_0, A_0, F_0)$ and $Z^0 = (0, 0)$. At $Z = Z^0$, $G(X, 0) = (S_0, Z_0, B_0, A_0, F_0)$, then we have

$$\begin{aligned} &\frac{dS}{dt} = \Lambda - \mu_1 S - aSV, \\ &\frac{dZ}{dt} = \mu_2 ZI - dZ, \frac{dB}{dt} = \eta + \beta_1 BZ - d_1 B, \\ &\frac{dA}{dt} = \text{fB} - qAV - d_3 A, \\ &\frac{dF}{dt} = \beta_2 I - d_2 F. \end{aligned} \qquad (2.2)$$

RESULTS AND DISCUSSION

A. Local Stability of Equilibria

Theorem 1. The disease-free state is locally and globally asymptotically stable for $R_0 < 1$ and unstable for $R_0 > 1$.

Proof. The Jacobian for the system (2.1) has been computed as:

It is easy to show that $S(t) \to S_0, Z(t) \to Z_0, B(t) \to B_0$ and $F(t) \to F_0$ as $t \to \infty$. Now, form the system (2.2), we have $\frac{dA}{dt} = \text{fB} - qAV - d_3 A$ which implies that $\frac{dA}{dt} \leq \frac{\text{f}\eta}{\text{d}_1} - qAV - d_3 A$. The solution of the above equation is given by $A(t) = \frac{f\eta}{d_1 d_3} + ce^{-d_3 t}$, where c is any non-zero arbitrary constant. Clearly, $A(t) \to A_0$ as $t \to \infty$.

Hence $X^0 = (S_0, Z_0, B_0, A_0, F_0)$ is globally asymptotically stable, which shows that the condition (H1) of (Castillo-Chavez *et al.*, 2002), is satisfied. Again, from equation (2.2), it is obtained that $\frac{dZ}{dt} = \text{G(X, Z)} = BZ - \tilde{Q}(X, Z)$,

where $B = \begin{pmatrix} -(\beta + bF) & aS \\ k & -(\gamma + pA) \end{pmatrix}$,

and $\tilde{Q}(X, Z) = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$.

Hence, B is an M-matrix, which satisfied the condition (H2) of (Castillo-Chavez *et al.*, 2002). Finally, it concludes that the DFE is globally asymptotically stable provided $R_0 \leq 1$.

Theorem 2. The endemic equilibrium E^* of system (2.1) is locally and globally asymptotically stable for $R_0 > 1$.

Proof. Here, the local and global stability of endemic equilibrium is proven using numerical computation approach. Let us assume that $\Lambda = 10$, $a = 0.01$,

$\mu_2 = 0.005$, $\mu_1 = 0.05$, $\beta = 0.5$, $\gamma = 0.5$, $d = 0.049$, $d_1 = 0.05$, $d_2 = 1$, $d_3 = 0.051$, $p = 0.001$, $\beta_1 = 0.001$, $\eta = 50$, $k = 1.909$, $q = 0.6$, $f = 1$, $b = 1$, $\beta_2 = 1$. Clearly, $R_0 = 3.7975 > 1$, which is larger than unity. Therefore, endemic state exists and its value is $E^*(S^*, I^*, V^*, Z^*, B^*, A^*, F^*) = (0.0219, 0.0067, 0.0224, 0.0009, 1.0248, 0.0761, 0.0067)$ is locally asymptotically stable (Fig. 5).

Now for the global stability, we consider the system (2.1) with following choice of arbitrary initial conditions:

$$P_1 = (500, 40.1, 20.8, 9.5, 10, 5.0, 2.0),$$
$$P_2 = (250, 30.9, 12, 9.0, 110, 5.0, 3.0),$$
$$P_3 = (350, 25.1, 35, 8.5, 130, 6.0, 4.0),$$
$$P_4 = (150, 20.1, 43, 8.0, 100, 2.0, 3.5).$$

In the hyperplanes of Figs. 3 and 4 respectively, the phase plots of Z − B − F and I − V − A show that solutions converge towards the state E*. Thus, endemic equilibrium states are verified to be globally stable.

D. Numerical Simulation

In this section, we will verify the local dynamics of the system (2.1). If we choose $\eta = 10$ and $k = 1$. Then, the basic reproduction number is $R_0 = 0.9065 < 1$, which is less than unity. Therefore, disease free equilibrium state exists, and its value is $E_0(\tilde{S}, \tilde{I}, \tilde{V}, \tilde{Z}, \tilde{B}, \tilde{A}, \tilde{F}) = (0.0200, 0, 0, 0, 0.1000, 1.9567, 0)$. Using the same initial conditions, we will determine the stability of DFE of the system (2.1) by performing numerical simulations. In the hyperplanes of Figs. 1 and 2 respectively, the phase plots of I − V − Z and S − A − V show that solutions converge towards the state E_0. Thus, disease free equilibrium states are verified to be globally stable.

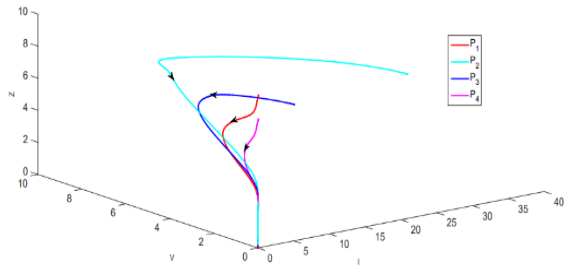

Fig. 1. A 3D $I - V - Z$ phase plot showing the convergence to E_0.

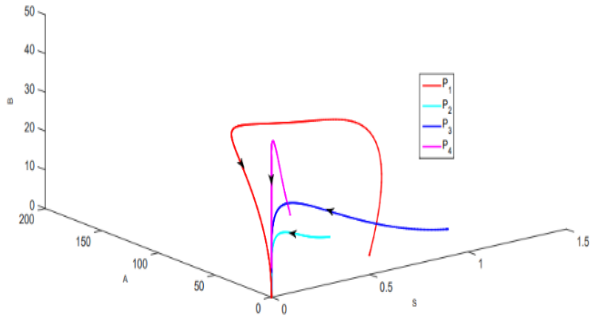

Fig. 2. A 3D $S - A - V$ phase plot showing the convergence to E_0.

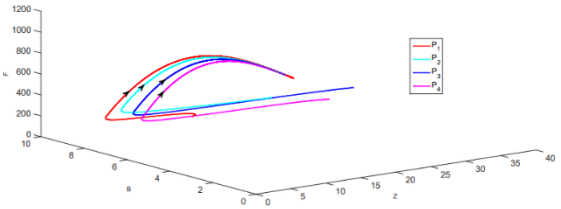

Fig. 3. A 3D $Z - B - F$ phase plot showing the convergence to E*

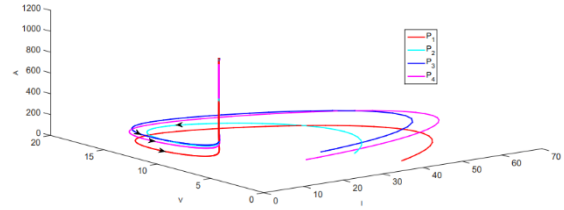

Fig. 4. A 3D $I - V - A$ phase plot showing the convergence to E*.

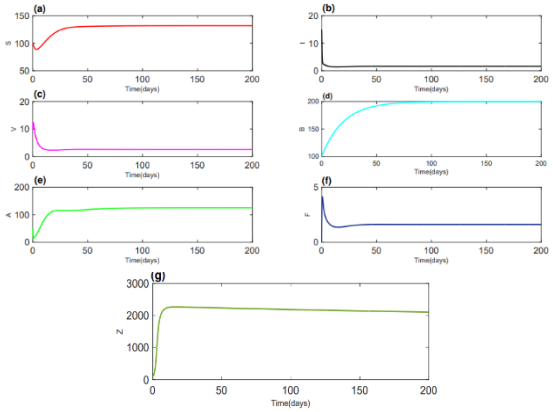

Fig. 5. Endemic Equilibrium E*.

CONCLUSIONS

In this paper, a non-linear dynamical model is proposed to analyze the dynamics of dengue infection within a host and to understand the effect of innate immune response in the form of type I interferon as well as adaptive immune response in the form of B cells, T helper cells, antibodies. We have studied the model analytically and numerically to capture the qualitative behaviour of virus dynamics within the host. The disease-free and endemic equilibria are obtained and studied, which depends upon a basic reproduction number (R_0). The disease-free equilibrium point is locally and globally asymptotically stable when basic reproduction number $R_0 < 1$ and unstable when $R_0 > 1$. Based on numerical simulation, the endemic equilibrium point appears to be locally and globally stable. All analytical results were also verified through numerical simulations.

Further, since the infected cells activate the immune system and its rate is inversely proportional to the basic reproduction number, the higher rate is more beneficial in killing the virus. Similarly, T cell activates the B cells and B cells, which further differentiates into plasma cells through antibodies. These plasma cells can kill the virus.

Hence, the rate **f** to produce antibodies here is also inversely proportional to R_0, which depicts an adverse effect on the virus. Finally, it is concluded that the basic reproduction number is crucial for controlling disease outbreaks in the study of disease dynamics.

FUTURE SCOPE

The future scope involves utilizing the proposed non-linear dynamical model to develop effective strategies for controlling dengue infection outbreaks by targeting the innate and adaptive immune responses. This includes exploring interventions that increase the rate of immune response activation and antibody production, considering the influence of the basic reproduction number (R_0) as a crucial factor in disease dynamics.

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Conflict of interest. None.

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