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Impact of Innate and Cell mediated Immune Responses on Dengue Virus Dynamics

Sulanie Perera[1] and S.S.N.Perera[1]

[1]*Research and Development Center for Mathematical Modeling, Faculty of Science, University of Colombo, Colombo 3, Sri Lanka*
sulanieperera@gmail.com
ssnp@maths.cmb.ac.lk

Abstract

Dengue infection is one of the most prevalent mosquito-bore illnesses in the world. In order to understand how the infection can be prevented or controlled, we should first understand the dynamics of the dengue virus. The model presented here incorporates innate immune response and Cytotoxic T lymphocytes (CTL) mediated immune response which plays a crucial role in clearing the infection. The basic reproduction number R_0 was computed and a detailed stability analysis was done. It was found that the model has three equilibria, namely, pathogen free equilibrium, no immune equilibrium and the endemic equilibrium. Stability at each equilibrium point is discussed with respect to R_0. The proposed model also shows that introduction of immune response strongly affects the stability of the system.

AMS Subject Classification: 92B05, 34D20, 65L20

Key Words and Phrases: Dengue virus, innate immune response, Cytotoxic T lymphocytes, basic reproduction number, stability.

1 Introduction

Dengue is a mosquito borne viral disease that has rapidly spread all around the world and is mostly found in tropical and subtropical regions. It is transmitted to humans through a mosquito bite, mainly by the peridomestic female mosquito *Aedes aegyptii* [1]. There are four distinct closely related viruses (DEN-1, DEN-2,

DEN-3 and DEN-4) that cause dengue.

Dengue fever is an acute, self-limited febrile illness that resolves on its own within 5-7 days. Symptoms include high fever, headache, retro-orbital pain, muscle or joint pain, nausea and vomiting [2]. Its more severe forms, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) can be fatal if not attended and treated early.

The clearing process of the dengue virus from the human body is done by the immune system. Experimental studies have shown that innate immune response is essential for virus clearance during the first few days of infection [3]. Innate immune response activates Interferon which is responsible for inhibiting viral replication and activation of natural killer cells (NK) cells, which kills infected cells [4, 5]. Also the virus infected cells stimulates and expands cytotoxic T cells which are important for virus clearance as they directly kill the infected cells [6]. Reduction in infected cells reduces the viral load. Nuraini et al. [7] have developed a within-host dengue infection model with cytotoxic T lymphocytes (CTL) response.

In this paper, we extend this model to incorporate both CTL immune response as well as innate immune response which plays a protective role by lysing infected cells. Next we analyze the existence and the stability of different equilibrium states. We obtain the basic reproduction number for this model and examine the parameter values that lead to different equilibrium states.

2 Model Development

We extend the model presented in [7] by introducing CTL immune response and innate immune response for within host primary dengue infection.

The model is given by the nonlinear system of equations described in (1).

$$\begin{aligned}
\frac{dS}{dt} &= \mu - \alpha S - aSV \\
\frac{dI}{dt} &= aSV - \beta I - \nu IT - \phi IF \\
\frac{dV}{dt} &= kI - \gamma V - aSV \\
\frac{dT}{dt} &= \eta + cI + dIT - \delta T \\
\frac{dF}{dt} &= qI - \sigma F
\end{aligned} \tag{1}$$

where S-healthy cells (monocytes, macrophages, dendritic cells, hepatocytes or mast cells), I-infected cells, V-Dengue virus particles, T-T lymphocytes and F-Interferon. The description of the parameters along with the baseline parameter values are given in Table 1.

Table 1: Description of the parameters

Parameter Symbols	Parameter Description	Value
μ	Production rate of healthy cells	10
α	Death rate of healthy cells	0.05
a	Rate at which healthy cells are converted to infected cells due to their interaction with virus particles	0.003
β	Death rate of infected cells	0.7
ν	Rate at which Infected cells are lysed by T-cells	0.001
ϕ	Rate at which infected cells are being killed by NK cells	0.002
k	Burst rate of virus particles	5
γ	Rate at which virus particles degrade	0.7
η	production rate of T lymphocytes	5
c	Density of infected cells	0.01
d	Rate at which T-cells are stimulated by infected cells	0.02
δ	Death rate of antibodies	0.0027
q	Rate of production of interferon	0.8
σ	Death rate of interferon	0.7

3 Results and Discussion

3.1 Basic Reproduction Number

The basic reproduction number, R_0, is defined as the number of secondary infected cells that arise from one infected cell placed in an uninfected population [6, 7]. Using the next generation method, R_0 was computed. The basic reproduction number, R_0, in the absence of immune response is given by equation (2).

$$R_0 = \frac{a\mu k}{\beta(\alpha\gamma + a\mu)} \tag{2}$$

If $R_0 > 1$, an infection can take place and the immune response becomes activated. The basic reproduction number in the presence of CTL immune response is given by equation (3).

$$R_1 = \frac{a\delta\mu k}{(\delta\beta + \nu\eta)(\alpha\gamma + a\mu)} \tag{3}$$

Whether the infection becomes endemic or clears out depends on the basic reproduction number in the presence of immune response.

3.2 Stability Analysis

In this section we first find the equilibrium states of the model (1) and discuss their stability over a long period of time.

Three equilibrium states were obtained for model (1). The infection free equilibrium, no immune equilibrium and the endemic equilibrium. Next, we analyze the stability at each equilibria.

3.3 Infection free equilibrium

This is obtained when $V^* = 0$.

The model (1)'s equilibria are given by,

$$S^* = \frac{\mu}{\alpha + aV^*} \tag{4}$$

$$I^* = \frac{aS^*V^* + \gamma V^*}{k} \tag{5}$$

$$T^* = \frac{\eta k + c(aS^*V^* + \gamma V^*)}{\delta k - d(aS^*V^* + \gamma V^*)} \tag{6}$$

$$F^* = \frac{q(aS^*V^* + \gamma V^*)}{k\sigma} \tag{7}$$

Thus we obtain the infection free equilibrium $E_1 = \left(\frac{\mu}{\alpha}, 0, 0, \frac{\eta}{\delta}, 0\right)$. It is clear that the infection free equilibrium exists for all sets of parameters. It can be also seen that S^* and T^* have non-zero values. This means that the virus gets cleared in a short period of time but T-cells remains in the body for a longer period.

The stability property obtained is summarized in Theorem 1.

Theorem 1. *The infection free equilibrium* $E_1 = \left(\frac{\mu}{\alpha}, 0, 0, \frac{\eta}{\delta}, 0\right)$ *is*

1. *Locally asymptotically stable if* $R_1 < 1$
2. *Unstable if* $R_1 > 1$

Proof. We must first linearize the model about its equilibrium points and the corresponding Jacobian matrix is given by (8).

$$J = \begin{bmatrix} -(\alpha + aV^*) & 0 & -aS^* & 0 & 0 \\ aV^* & (-\beta - \nu T^* - \phi F^*) & aS^* & -\nu I^* & -\phi I^* \\ -aV^* & k & -(\gamma + aS^*) & 0 & 0 \\ 0 & c + dT^* & 0 & (dI^* - \delta) & 0 \\ 0 & q & 0 & 0 & -\sigma \end{bmatrix}. \tag{8}$$

After substituting the equilibrium values for $S^*, I^*, T^*$and F^* obtained from equation (4), (5), (6) and (7) and applying $V^* = 0$ in (8), the characteristic equation for J can be written as,

$$G(\lambda) = (\sigma + \lambda)(\delta + \lambda)(\alpha + \lambda)(\alpha\delta\lambda^2 + (\alpha\delta\gamma + a\delta\mu\lambda + \alpha\beta\delta + \alpha\eta\nu)\lambda + (\alpha\beta\delta\gamma + a\beta\delta\mu + \alpha\eta\gamma\nu - a\delta\mu k + a\eta\nu\mu) \tag{9}$$

The eigenvalues of equation (9) are

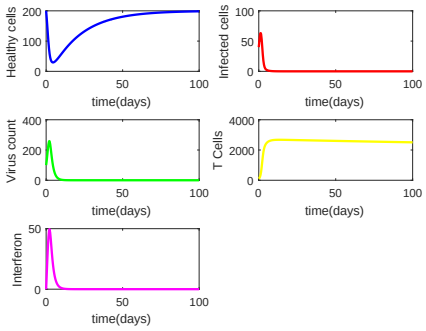
$$\lambda_1 = -\delta \tag{10}$$

$$\lambda_2 = -\alpha \tag{11}$$

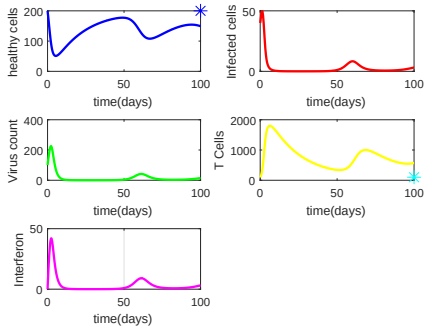
$$\lambda_3 = -\sigma \tag{12}$$

$$\lambda_4 = \frac{-b \pm \sqrt{b^2 - 4\alpha\delta(\alpha\gamma + a\mu)(\beta\delta + \eta\nu)(1 - R_1}}{2\alpha\delta}) \tag{13}$$

$$\text{where} \quad b = (\alpha\delta\gamma + a\delta\mu + \alpha\beta\delta + \alpha\eta\nu) \tag{14}$$



Infection free equilibrium for $R_1 < 1$.The numerical values of the parameters used are $\mu = 10,\ \alpha = 0.05,\ a = 0.003,\ \beta = 0.7,\ \gamma = 0.7,\ k = 5,\ \delta = 0.0027,\ \eta = 5,\ c = 0.01,\ d = 0.02,\ \nu = 0.001,\ q = 0.8,\ \sigma = 0.7 \text{and} \phi = 0.002$. Initial values $S, I, V, T, F = (200, 40, 100, 100, 0)$



Infection free equilibrium for $R_1 > 1$.The numerical values of the parameters used are $\mu = 10,\ \alpha = 0.05,\ a = 0.002,\ \beta = 0.7,\ \gamma = 0.7,\ k = 5,\ \delta = 0.05,\ \eta = 5,\ c = 0.01,\ d = 0.02,\ \nu = 0.001,\ q = 0.8,\ \sigma = 0.7 \text{and} \phi = 0.002$. Initial values $S, I, V, T, F = (200, 40, 100, 100, 0)$

Figure 1: Infection free equilibrium stable and unstable cases

For $R_1 < 1$, $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ are all negative. Thus the equilibrium point E_1 is locally asymptotically stable.

For $R_1 > 1$,
$\lambda_4 > 0$. Thus E_1 is unstable. □

Figure 1a and 1b depicits the stable and unstable cases described in Theorem 1. It is clear from Fig.1a that for $R_1 < 1$, S^* converges to μ/α, I^*, V^* and F^* converges to 0 and T^* converges to η/δ. In Fig.1b , the equilibrium points are marked with an $*$ and we can see that for $R_1 > 1$, the equilibrium becomes unstable.

3.4 No immune equilibrium

If we assume, $T^* = 0$ and $F^* = 0$, we obtain the uninfected steady state, $E_2 = \left(\frac{\mu}{\alpha}, 0, 0, 0, 0\right)$.

If we assume only $F^* = 0$, we get the infection free equilibrium E_1.

If we assume only $T^* = 0$, this equilibrium does not exists which is generally true as an infection would activate both immune responses.

3.5 Endemic equilibrium

Theorem 2. *If $R_1 > 1$, there exists a unique endemic equilibrium $(S^*, I^*, V^*, T^*, F^*)$.*

Proof. Analytical proof of stability of endemic equilibrium is not shown here. Numerical exploration indicates that the endemic equilibrium is locally stable. This phenomenon is shown in Fig. 2 where the virus count settles to some non-zero value. □

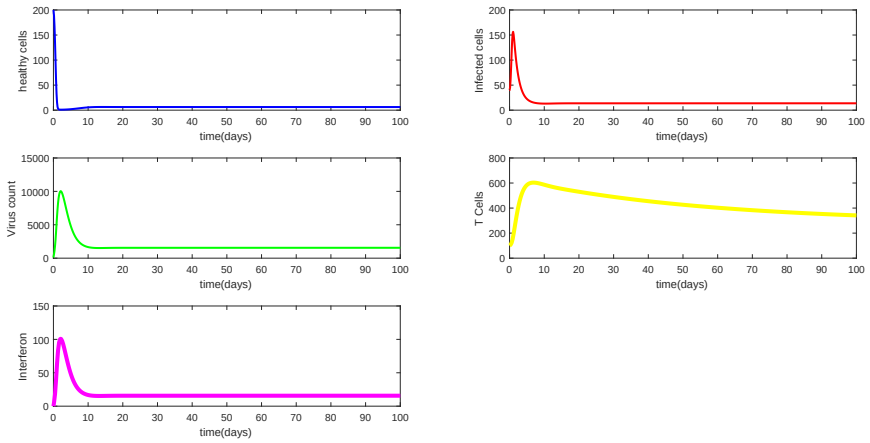


Figure 2: Endemic equilibrium.The numerical values of the parameters used are $\mu = 10,\ \alpha = 0.05,\ a = 0.001,\ \beta = 0.7,\ \gamma = 0.7,\ k = 80,\ \delta = 0.1,\ \eta = 5,\ c = 0.001,\ d = 0.006,\ \nu = 0.00001,\ q = 0.8,\ \sigma = 0.7 \text{and} \phi = 0.002$. Initial values $S, I, V, T, F = (200, 40, 100, 100, 0)$

4 Conclusion

A mathematical model with innate and CTL immune responses was developed to study the dynamics of dengue virus. Three equilibrium states, namely the infection free equilibrium, no immune equilibrium and the endemic equilibrium were identified.

Whether or not a virus can replicate and cause an infection depends on the basic reproduction number R_0. If $R_0 > 1$, then an infection can take place and activate immune response. Whether or not the infection continues, depends on the basic reproduction number in the presence of immune response denoted by R_1.

By establishing the characteristic equation of the model at infection free equilibrium, it was observed that the infection free equilibrium is locally asymptotically stable if $R_1 < 1$ and unstable for $R_1 > 1$. No immune equilibrium was obtained in three ways. If assumed that there's no immune response involved, it leads to the uninfected equilibrium. If we assume only innate immune response is absent, we get the infection free equilibrium and if we assume only CTL immune response is absent, this equilibrium does not exists as an infection would activate both immune responses. For high R_1 values an endemic equilibrium was numerically identified.

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