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A WITHIN-HOST DENGUE INFECTION MODEL WITH IMMUNE RESPONSE AND NONLINEAR INCIDENCE RATE

Abstract. A model of viral infection of monocytes population by the dengue virus is formulated as a system of four ordinary differential equations. The model takes into account the immune response and nonlinear incidence rate of susceptible and free virus particles.

Global stability of the uninfected steady state is investigated. Such a steady state always exists. If it is the only steady state, then it is globally asymptotically stable. If any infected steady state exists, then the uninfected steady state is unstable and one of the infected steady states is locally asymptotically stable. These different cases depend on the values of the basic reproduction ratio and other parameters.

1. Introduction. Dengue is an infectious mosquito-borne viral disease. The dengue virus is one of the most difficult arboviruses to isolate. There are four serotypes of the dengue virus and each of them has numerous virus strains. Infection with one dengue serotype may provide lifelong immunity to that serotype, but there is no cross-protective immunity to other serotypes, [G]. Identification of the primary target cells of the dengue virus replication in infected human body has proven to be extremely difficult. It is generally believed that the target cells of the dengue virus are monocytes or their differentiated cells macrophages [HP].

It is usually believed that the dengue virus is quickly cleared in human body within approximately seven days after the day of sudden onset of fever [TDR]. Naturally this clearing process is done by the immune system and is a result of complex dynamic reactions. Following [NTSS], in this paper we try to understand the process using a mathematical model.

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Mathematical modeling of dengue disease transmission in human and mosquito populations has been done since the beginning of the last century. Some of the recent models could be seen in [G, HP, NM, NTSS]. Several studies of infection models within human body have been done for various cases [BLM, NM]. Meanwhile, mathematical modeling for within-host dengue viral disease is a quite new topic.

A model for within-host dengue viral infection with nonlinear incidence rate and immune response is as follows:

$$\begin{cases} \dfrac{dS}{dt} = \mu - \alpha S - V\varphi(S), \\ \dfrac{dI}{dt} = V\varphi(S) - \beta I - \nu IZ, \\ \dfrac{dV}{dt} = kI - \gamma V - V\varphi(S), \\ \dfrac{dZ}{dt} = \eta + cI + dIZ - \delta Z. \end{cases} \tag{1.1}$$

Here $S(t)$, $I(t)$, $V(t)$ and $Z(t)$ represent the density of susceptible monocytes, infected monocytes, free virus particles and immune cells in 1 μl of blood at time t, respectively. The production of susceptible monocytes by bone marrow is assumed to occur at constant rate μ and the life span of susceptible monocytes is $1/\alpha$. The flow from susceptible monocytes to infected monocytes depends on the incidence rate of susceptible monocytes and free virus particles. This rate is expressed by $V\varphi(S)$, where $\varphi(S)$ is the incidence response of susceptible monocytes to free virus particles. The period of infected monocytes is assumed to be constant and equal to $1/\beta$. We assume virus multiplication is at constant rate k and virus clearance is at constant rate γ. We also assume that immune cells are produced at constant rate η and their life span is $1/\delta$. Moreover we assume there is stimulation of immune cells production due to the increase of infected cells, which is proportional to the density of infected monocytes, at constant rate c, as well as from contacts with infected cells at rate d, and immune cells eliminate infected monocytes at constant rate ν.

Before we analyze model (1.1) further, we reduce the number of parameters by introducing $Z_1 = Z - \eta\delta$. After renaming Z_1 as Z, we get

$$\begin{cases} \dfrac{dS}{dt} = \mu - \alpha S - V\varphi(S), \\ \dfrac{dI}{dt} = V\varphi(S) - \beta_1 I - \nu IZ, \\ \dfrac{dV}{dt} = kI - \gamma V - V\varphi(S), \\ \dfrac{dZ}{dt} = c_1 I + dIZ - \delta Z, \end{cases} \tag{1.2}$$

where $\beta_1 = \beta + \eta\nu/\delta$ and $c_1 = c + d\eta/\delta$.

The above model is valid for only one serotype of dengue virus circulating in an infected host and dengue infects monocytes in blood stream.

For more details the reader is referred to [NTSS] and references therein. Here we assume that $k > \beta_1$ and the function $\varphi(S)$ satisfies the following natural hypotheses:

(H_1) $\varphi(0) = 0$,
(H_2) $\varphi(S) > 0$ for all $S > 0$,
(H_3) $\varphi_S(S) > 0$ for all $S \geq 0$.

Notice that most of famous functional responses such as: Lotka–Volterra, Michaelis–Menten, Holling type II and III, Sigmoidal and Ivlev satisfy the above hypotheses. For more details about this functional response the reader is referred to [FH] and references therein.

The local stability of the equilibrium points of the system (1.2) for Lotka–Volterra functional response, i.e. $\varphi(S) = aS$, has been discussed in [NTSS]. The model (1.2) is a generalization of the self-regulating cytotoxic T lymphocytes (CTL) response model. The predator-prey like CTL response model and the linear immune response model are discussed in Chapter 6 of [NM].

In this paper, we will analyze global stability of the viral free equilibrium point for general incidence response, $\varphi(S)$. In fact we will show that if this equilibrium point is the only rest point of the system (1.2), then it is globally asymptotically stable. If there are some other equilibria, then their local stability depends on the values of the parameters.

2. Global stability of the uninfected equilibrium point. In this section, first we will find the equilibrium points of the system (1.2) and the eigenvalues of this system at these points. This information leads us to prove the locally asymptotic stability of the equilibrium points.

At an equilibrium point of the system (1.2) we must have

$$\begin{cases} \mu - \alpha S - V\varphi(S) = 0, \\ V\varphi(S) - \beta_1 I - \nu IZ = 0, \\ kI - \gamma V - V\varphi(S) = 0, \\ c_1 I + dIZ - \delta Z = 0. \end{cases} \tag{2.1}$$

From the first equation we obtain $V = (\mu - \alpha S)/\varphi(S)$. Substituting this into the third equation yields $I = (\mu - \alpha S)(\gamma + \varphi(S))/(k\varphi(S))$. From the fourth equation we obtain $Z = c_1 I/(\delta - dI)$. Substituting these values of V, I and Z into the second equation yields

$$(\mu - \alpha S)\left(1 - \frac{\beta_1(\gamma + \varphi)}{k\varphi} - \frac{\nu c_1}{k\varphi}\,\frac{(\mu - \alpha S)(\gamma + \varphi)^2}{\delta k\varphi - d(\mu - \alpha S)(\gamma + \varphi)}\right) = 0, \tag{2.2}$$

where $\varphi = \varphi(S)$.

If $\mu - \alpha S = 0$, then $S = \mu/\alpha$. Thus $y_0 = (\mu\ \alpha, 0, 0, 0)$ is one of the equilibrium points of the system (1.2). If

$$1 - \frac{\beta_1(\gamma+\varphi)}{k\varphi} - \frac{\nu c_1}{k\varphi}\,\frac{(\mu-\alpha S)(\gamma+\varphi)^2}{\delta k\varphi - d(\mu-\alpha S)(\gamma+\varphi)} = 0,$$

then

$$\begin{aligned}&\big[\delta k(k-\beta_1) + (d\beta_1 - \nu c_1 - kd)(\mu-\alpha S)\big]\varphi^2\\ &\quad + \big[2\gamma(\beta_1 d - \nu c_1 - kd)(\mu-\alpha S) - \beta_1\gamma\delta\big]\varphi + \gamma^2(\beta_1 d - c_1\nu)(\mu-\alpha S) = 0.\end{aligned}$$

Solving this equation for φ yields

$$\varphi = \frac{(-2\gamma(\beta_1 d - \nu c_1) - 2kd\gamma)(\mu-\alpha S) + \beta_1\gamma\delta k + \sqrt{\Delta}}{2(\delta k(k-\beta_1) + (\beta_1 d - \nu c_1 - kd)(\mu-\alpha S))} \tag{2.3}$$

where $\Delta = 4k\gamma^2(\beta_1 d - \nu c_1)(\mu-\alpha S)(d(\mu-\alpha S) - k\delta) + k^2\gamma^2\delta^2$.

The other equilibrium points are obtained from (2.3), which will be considered in the next section.

In the following we consider the stability of the equilibrium point y_0. To do this we check the signs of the real parts of the eigenvalues of the Jacobi matrix of (1.2) at y_0. This matrix is

$$J = \begin{bmatrix} -\alpha - V\varphi_S & 0 & -\varphi & 0\\ V\varphi_S & -\beta_1 - \nu Z & \varphi & -\nu I\\ -V\varphi_S & k & -\gamma-\varphi & 0\\ 0 & c_1 + dZ & 0 & dI - \delta \end{bmatrix}. \tag{2.4}$$

So the value of J at y_0 is

$$J(y_0) = \begin{bmatrix} -\alpha & 0 & -\varphi(\mu/\alpha) & 0\\ 0 & -\beta_1 & \varphi(\mu/\alpha) & 0\\ 0 & k & -\gamma - \varphi(\mu/\alpha) & 0\\ 0 & c_1 & 0 & -\delta \end{bmatrix}.$$

The eigenvalues of $J(y_0)$ are the roots of the characteristic polynomial

$$(x+\alpha)(x+\delta)\big(x^2 + (\beta_1 + \varphi(\mu/\alpha) + \gamma)x - (k-\beta_1)\varphi(\mu/\alpha) + \beta_1\gamma\big) = 0.$$

Thus, $x_1 = -\alpha$ and $x_2 = -\delta$ are two of the eigenvalues, and the other two are roots of $x^2 + (\beta_1 + \varphi(\mu/\alpha) + \gamma)x - (k-\beta_1)\varphi(\mu/\alpha) + \beta_1\gamma = 0$. These roots are

$$x_3 = \frac{-(\beta_1 + \varphi(\mu/\alpha) + \gamma) - \sqrt{\Delta}}{2}, \quad x_4 = \frac{-(\beta_1 + \varphi(\mu/\alpha) + \gamma) + \sqrt{\Delta}}{2}$$

where $\Delta = (\beta_1 + \varphi(\mu/\alpha) + \gamma)^2 + 4(k - \beta_1)\varphi(\mu/\alpha) - 4\beta_1\gamma$. Notice that Δ is always positive.

Clearly, x_1, x_2 and x_3 are negative real. If x_4 is negative too, then the equilibrium point y_0 is locally asymptotically stable. But x_4 is negative if and only if $\sqrt{\Delta} < \beta_1 + \varphi(\mu/\alpha) + \gamma$. This condition is equivalent to

$$R_0 := \frac{k}{\beta_1} \frac{\varphi(\mu/\alpha)}{\gamma + \varphi(\mu/\alpha)} < 1.$$

The number R_0 is called the basic reproduction ratio [CFH].

Thus we have the following theorem.

THEOREM 2.1. *If $R_0 < 1$, the equilibrium point y_0 is locally asymptotically stable, and if $R_0 > 1$, then y_0 is unstable.*

From now on in this section we assume that $\nu c_1 < d(\beta_1 + k\varphi(\mu/\alpha))$.

Now we will show that if $R_0 < 1$, then the equilibrium point y_0 is globally asymptotically stable. To see this, first consider the following domain in the (S, I, V, Z) space:

$$D_m = \{(S, I, V, Z) : 0 < S < m,\ I > 0,\ V > 0,\ Z > 0\}, \quad m \geq \mu/\alpha.$$

It follows from the hypotheses (H_1) and (H_2) that the flow generated by the system (1.2) gets into D_m on the boundary of D_m. Let $D = D_m$ for $m = \mu/\alpha$. Thus $\bar{D}$ is a global attractor. Now in $\bar{D}$ consider the following set for $C > 0$:

$$Q_C = \{(S, I, V, Z) : 0 < S < \mu/\alpha,\ I > 0,\ V > 0,\ Z > 0 \text{ and } K(S, I, V, Z) \leq C\},$$

where

$$\begin{aligned}
K(S, I, V, Z) &= A_1(\mu/\alpha - S) + A_2 I + A_3 V + A_4 Z,\\
A_1 &= \beta_1(\gamma + \varphi^*)(1 - R_0),\\
A_2 &= \frac{dk\varphi^*(\beta_1(\gamma + \varphi^*) - k\varphi^*)}{(\gamma + \varphi^* + 1)(\beta_1 d - \nu c_1) - dk\varphi^*},\\
A_3 &= \frac{\varphi^*(\beta_1 d - \nu c_1)(\beta_1(\gamma + \varphi^*) - k\varphi^*)}{(\gamma + \varphi^* + 1)(\beta_1 d - \nu c_1) - dk\varphi^*},\\
A_4 &= \frac{\nu k\varphi^*(\beta_1\gamma + \varphi^*) - k\varphi^*}{(\gamma + \varphi^* + 1)(\beta_1 d - \nu c_1) - dk\varphi^*} \quad \text{and} \quad \varphi^* = \varphi\left(\frac{\mu}{\alpha}\right).
\end{aligned}$$

From $R_0 < 1$ and $d\beta_1 - \nu c_1 - dk\varphi^* > 0$, it follows that A_1, A_2 and A_4 are positive. Also from $\beta_1 d - \nu c_1 > 0$, it follows that A_3 is positive too. If we differentiate $K(S, I, V, Z)$ along the orbits of the system (1.2), we obtain

$$\begin{aligned}\frac{dK}{dt} &= -A_1\dot{S} + A_2\dot{I} + A_3\dot{V} + A_4\dot{Z}\\ &= -A_1(\mu - \alpha S - V\varphi(S)) + A_2(V\varphi(S) - \beta_1 I - \nu IZ)\\ &\quad + A_3(kI - \gamma V - V\varphi(S)) + A_4(c_1 I + dIZ - \delta Z)\\ &= -A_1(\mu - \alpha S) + (-\beta_1 A_2 + kA_3 + c_1 A_4)I\\ &\quad + (\varphi A_1 + \varphi A_2 - (\gamma + \varphi)A_3)V - \delta A_4 Z + (dA_4 - \nu A_2)IZ,\end{aligned}$$

where $\varphi := \varphi(S)$. Since on the surface $K(S, I, Z, V) = C$ of the boundary of Q_C, we have $\mu - \alpha S > 0$ and $\varphi - \varphi^* < 0$ and $\beta(\gamma + \varphi^*) - k\varphi^* = \beta(\gamma + \varphi^*)(1 - R_0) > 0$, it follows that $dK/dt < 0$. Thus the flow gets into Q_C on $K(S, I, Z, V) = C$. Hence the flow gets into Q_C from its boundary. Therefore Q_C is an attractor in D for all $C \geq 0$. But $\{y_0\} = \bigcap_{C\geq 0} \bar{Q}_C$. Since the coefficients in the definition of K are positive, Q_C is a corner domain, thus y_0 is a global attractor.

Thus we have proven the following theorem.

THEOREM 2.2. *If $R_0 < 1$, then y_0, the uninfected equilibrium point, is the only equilibrium of the system* (1.2)*. Moreover, it is globally asymptotically stable.*

Since y_0 is globally asymptotically stable for $R_0 < 1$, no other equilibrium points of the system (1.2) can exist for $R_0 < 1$. Therefore, y_0 is the unique equilibrium point for $R_0 < 1$.

3. Stability of other equilibrium points. Throughout this section we assume that $R_0 > 1$. We consider the stability of the other rest points of the system (1.2). To do this, we consider the equation (2.2). First, we consider this equation for $c_1 = 0$ and then for $c_1 \neq 0$ where $c_1 = c + d\eta/\delta$.

Here we consider the following two cases for $c_1 = 0$.

CASE 1: $c_1 = d = 0$. In this case, the system (1.2) has two equilibrium points, y_0 and another one. To see this, from the first equation of (2.1) we obtain $V = (\mu - \alpha S)/\varphi(S)$. Since $c_1 = d = 0$, from the fourth equation we get $Z = 0$. Substituting these values of V and Z into the second equation yields $I = (\mu - \alpha S)/\beta_1$. Using these in (2.2), we obtain $\varphi = \gamma\beta_1/(k - \beta_1)$. Since $k > \beta_1$ and φ is a nonnegative increasing function, there exists a unique point $S_0 > 0$ such that $\varphi(S_0) = \gamma\beta_1/(k - \beta_1)$. Thus

$$y_1 = \left(S_0, \frac{\mu - \alpha S_0}{\beta_1}, \frac{(k - \beta_1)(\mu - \alpha S_0)}{\gamma\beta_1}, 0\right)$$

is the second rest point of (1.2). Notice that this rest point exists if $\mu - \alpha S_0 \geq 0$, or $S_0 \leq \mu/\alpha$. If $S_0 = \mu/\alpha$, this rest point is the same as $y_0 =$

$(\mu/\alpha, 0, 0, 0)$. If $S_0 < \mu/\alpha$, then

$$\varphi(S_0) < \varphi\left(\frac{\mu}{\alpha}\right) \;\Leftrightarrow\; \varphi\left(\frac{\mu}{\alpha}\right) > \frac{\gamma\beta_1}{\alpha(k-\beta_1)} \;\Leftrightarrow\; R_0 = \frac{k}{\beta_1}\,\frac{\varphi(\mu/\alpha)}{\gamma+\varphi(\mu/\alpha)} > 1.$$

Now, we consider the local stability of y_1. By using (2.4), the Jacobi matrix at y_1 is

$$J(y_1) = \begin{bmatrix} -\alpha - V_0\varphi_S(S_0) & 0 & -\varphi(S_0) & 0 \\ V_0\varphi_S(S_0) & -\beta_1 & \varphi(S_0) & -\nu I_0 \\ -V_0\varphi_S(S_0) & k & -\gamma-\varphi(S_0) & 0 \\ 0 & 0 & 0 & -\delta \end{bmatrix}$$

where $V_0 = (k-\beta_1)(\mu-\alpha S_0)/(\gamma\beta_1), I_0 = (\mu-\alpha S_0)/\beta_1$ and $\varphi(S_0) = \gamma\beta_1/(k-\beta_1)$. We calculate the eigenvalues of $J(y_1)$:

$$\det(xI_{4\times4} - J(y_1)) = \begin{vmatrix} -\alpha - V_0\varphi_S(S_0) & 0 & -\varphi(S_0) & 0 \\ V_0\varphi_S(S_0) & -\beta_1 & \varphi(S_0) & -\nu I_0 \\ -V_0\varphi_S(S_0) & k & -\gamma-\varphi(S_0) & 0 \\ 0 & 0 & 0 & -\delta \end{vmatrix} = 0,$$

yielding

$$\begin{aligned}(x+\delta)\Big(&x^3 + \big(\alpha+\gamma+\beta_1+\varphi(S_0)+V_0\varphi_S(S_0)\big)x^2 \\ &+ \big(\alpha\beta_1+\gamma\beta_1+\alpha\gamma+(\beta_1 k+\alpha)\varphi(S_0)+(\beta_1+\gamma)V_0\varphi_S(S_0)\big)x \\ &+ \big(\alpha\gamma\beta_1+(\alpha\beta_1-k\alpha)\varphi(S_0)+\gamma\beta_1 V_0\varphi_S(S_0)\big)\Big) = 0.\end{aligned}$$

Substituting the value of $\varphi(S_0)$ into the above equation we get

$$\begin{aligned}(x+\delta)\Bigg(&x^3 + \left(\alpha+\beta_1+\frac{\gamma k}{k-\beta_1}+V_0\varphi_S(S_0)\right)x^2 \\ &+ \left(\frac{\alpha\gamma\beta_1}{k-\beta_1}+(\beta_1+\gamma)(\alpha+V_0\varphi_S(S_0))\right)x + \gamma\beta_1 V_0\varphi_S(S_0)\Bigg) = 0.\end{aligned}$$

Thus one of the roots is $x = -\delta$. The other roots are given by

$$x^3 + q_2x^2 + q_1x + q_0 = 0,$$

where

$$\begin{aligned} q_2 &= \alpha+\beta_1+\frac{\gamma k}{k-\beta_1}+V_0\varphi_S(S_0), \\ q_1 &= \frac{\alpha\gamma\beta_1}{k-\beta_1}+(\beta_1+\gamma)(\alpha+V_0\varphi_S(S_0)), \\ q_0 &= \beta_1\gamma V_0\varphi_S(S_0). \end{aligned}$$

Since $k > \beta_1$, q_2, q_1 and q_0 are positive. Moreover, it is easy to see that $q_2 q_1 > q_0$. By the Routh–Hurwitz Criterion, all roots of the cubic polynomial have negative real parts. Therefore we have the following theorem.

THEOREM 3.1. *If $R_0 > 1$, then the equilibrium point y_1 exists and is locally asymptotically stable. Moreover, the equilibrium point y_0 exists and is unstable.*

REMARK 3.2. Since the rest points and the eigenvalues depend continuously on the parameters, for small values of $c_1 > 0$ and $d > 0$, y_1 exists and is locally asymptotically stable.

CASE 2: $c_1 = \eta = 0$, $d \neq 0$. When $c_1 = \eta = 0$, in the system (1.2), we have $\beta_1 = \beta$ and $c_1 = c = 0$. In this case, (1.2) has three equilibrium points and y_0 is one of them. From the first equation of (1.2) we obtain $V = (\mu - \alpha S)/\varphi(S)$. Since $c_1 = \eta = 0$, the fourth equation of (1.2) gives $dIZ - \delta Z = 0$. Therefore, $Z = 0$ or $I = \delta/d$. For $Z = 0$, substituting the values of V and Z into the second equation yields $I = (\mu - \alpha S)/\beta$. Substituting the values of c_1 and η into (2.2), we obtain $\varphi = \gamma\beta/(k - \beta)$. Since $k > \beta$ and φ is a nonnegative increasing function, there exists a unique point $S_* > 0$ such that $\varphi(S_*) = \gamma\beta/(k - \beta)$. Thus,

$$y_1' = \left(S_*, \frac{\mu - \alpha S_*}{\beta}, \frac{(k - \beta)(\mu - \alpha S_*)}{\beta\gamma}, 0 \right)$$

is another rest point of the system (1.2).

For $I = \delta/d$, by substituting this value in the second equation of (1.2), we obtain

$$Z = \frac{d(\mu - \alpha S)}{\nu\delta} - \frac{\beta}{\nu} = \frac{d(\mu - \alpha S) - \beta\delta}{\nu\delta}.$$

Then from the first equation we get $V = (\mu - \alpha S)/\varphi(S)$. By using these values of I and V in the third equation of (1.2), we obtain

$$\varphi(S) = \frac{\gamma d(\mu - \alpha S)}{k\delta - d(\mu - \alpha S)}.$$

If $\frac{d}{k}(\mu - \alpha S_{**}) < \delta < \frac{d}{\beta}(\mu - \alpha S_{**})$, then

$$y_2 = \left(S_{**}, \frac{\delta}{d}, \frac{k\delta - d(\mu - \alpha S_{**})}{\gamma d}, \frac{d(\mu - \alpha S_{**}) - \beta\delta}{\nu\delta} \right)$$

is another equilibrium point of the system (1.2).

In the following, we consider the stability of these points.

First, for y_1', we check the signs of the real parts of the eigenvalues of the Jacobi matrix of (1.2) at y_1'. From (2.4) we have

$$J(y_1') = \begin{bmatrix} -\alpha - V_*\varphi_S(S_*) & 0 & -\varphi(S_*) & 0 \\ V_*\varphi_S(S_*) & -\beta_1 & \varphi(S_*) & -\nu I_* \\ -V_*\varphi_S(S_*) & k & -\gamma - \varphi(S_*) & 0 \\ 0 & 0 & 0 & -\delta \end{bmatrix},$$

where $V_* = (k-\beta)(\mu - \alpha S_*)/(\beta\gamma)$, $I_* = (\mu - \alpha S_*)/\beta$.

We calculate the eigenvalues of $J(y_1')$:

$$\det(xI_{4\times 4} - J(y_1')) = \begin{vmatrix} x + \alpha + V_*\varphi_S(S_*) & 0 & \varphi(S_*) & 0 \\ -V_*\varphi_S(S_*) & x + \beta_1 & -\varphi(S_*) & \nu I_* \\ V_*\varphi_S(S_*) & -k & x + \gamma + \varphi(S_*) & 0 \\ 0 & 0 & 0 & x + \delta \end{vmatrix} = 0,$$

yielding

$$\begin{aligned}(x + \delta - dI_*)\Big(&x^3 + \big(\alpha + \gamma + \beta + \varphi(S_*) + V_*\varphi_S(S_*)\big)x^2 \\ &+ \big(\beta\alpha + \beta\gamma + \alpha\gamma + (\beta - k + \alpha)\varphi(S_*) + (\beta + \gamma)V_*\varphi_S(S_*)\big)x \\ &+ \big(\beta\alpha\gamma + (\beta\alpha - k\alpha)\varphi(S_*) + \beta\gamma V_*\varphi_S(S_*)\big)\Big) = 0.\end{aligned}$$

Substituting the value of $\varphi(S_*)$ into the above equation we get

$$\begin{aligned}(x + \delta - dI_*)\Bigg(&x^3 + \left(\alpha + \beta + \frac{\gamma k}{k-\beta} + V_*\varphi_S(S_*)\right)x^2 \\ &+ \left(\frac{\alpha\gamma\beta}{k-\beta} + (\beta + \gamma)(\alpha + V_*\varphi_S(S_*))\right)x + \beta\gamma V_*\varphi_S(S_*)\Bigg) = 0.\end{aligned}$$

Thus one of the roots is $x = -\delta + dI_*$ and the other roots are given by

$$x^3 + q_2x^2 + q_1x + q_0 = 0,$$

where

$$\begin{aligned} q_2 &= \alpha + \beta + \frac{\gamma k}{k-\beta} + V_*\varphi_S(S_*), \\ q_1 &= \frac{\alpha\gamma\beta}{k-\beta} + (\beta + \gamma)(\alpha + V_*\varphi_S(S_*)), \\ q_0 &= \beta\gamma V_*\varphi_S(S_*). \end{aligned}$$

Clearly, q_2, q_1 and q_0 are positive and $q_2q_1 > q_0$. By the Routh–Hurwitz Criterion, all roots of the cubic polynomial must have negative real parts. If $I_* < \delta/d$, that is, $\delta > d(\mu - \alpha S_*)/\beta$, then the real parts of all the eigenvalues are negative and so y_1' is locally asymptotically stable. Notice that y_1' is stable when y_2 does not exist.

Now we consider the stability property of the other equilibrium point, y_2. From (2.4) we have

$$J(y_2) = \begin{bmatrix} -\alpha - V_{**}\varphi_S(S_{**}) & 0 & -\varphi(S_{**}) & 0 \\ V_{**}\varphi_S(S_{**}) & -\beta - \nu Z_{**} & \varphi(S_{**}) & \frac{-\nu\delta}{d} \\ -V_{**}\varphi_S(S_{**}) & k & -\gamma - \varphi(S_{**}) & 0 \\ 0 & dZ_{**} & 0 & 0 \end{bmatrix},$$

where

$$V_{**} = \frac{k\delta - d(\mu - \alpha S_{**})}{\gamma d} = \frac{(k\delta - d\mu) + d\alpha S_{**}}{\gamma d},$$
$$Z_{**} = \frac{d(\mu - \alpha S{**}) - \beta\delta}{\nu\delta} = \frac{(d\mu - \beta\delta) - \alpha S_{**}}{\nu\delta}.$$

The eigenvalues of $J(y_2)$ are given by the algebraic equation

$$\det(xI_{4\times 4} - J(y_2)) = \begin{vmatrix} x + \alpha + V_{**}\varphi_S(S_{**}) & 0 & \varphi(S_{**}) & 0 \\ -V_{**}\varphi_S(S_{**}) & x + \beta + \nu Z_{**} & -\varphi(S_{**}) & \frac{\nu\delta}{d} \\ V_{**}\varphi_S(S_{**}) & -k & x + \gamma + \varphi(S_{**}) & 0 \\ 0 & -dZ_{**} & 0 & x \end{vmatrix} = 0$$

or

$$\begin{aligned} &x\big[(x + \alpha + V_{**}\varphi_S(S_{**}))\big((x + \beta + \nu Z_{**})\big(x + \gamma + \varphi(S_{**})\big) \\ &\quad - k\varphi(S_{**})\big) + \varphi(S_{**})\big(kV_{**}\varphi_S(y_{**}) - V_{**}\varphi_S(S_{**})(x + \beta + \nu Z_{**})\big)\big] \\ &\quad - dZ_{**}\left[\frac{\nu\delta}{d}V_{**}\varphi(S_{**})\varphi_S(S_{**}) - \frac{\nu\delta}{d}\big(x+\alpha+V_{**}\varphi_S(S_{**})\big)\big(x+\gamma+\varphi(S_{**})\big)\right] = 0. \end{aligned}$$

Hence we get

$$\begin{aligned} &x^4 + [\alpha + \beta + \gamma + \varphi(S_{**}) + \nu Z_{**} + V_{**}\varphi_S(S_{**})]x^3 \\ &\quad + \big[\beta(\alpha + \gamma) + \alpha\gamma + (\alpha + \gamma + \delta)\nu Z_{**} + (\alpha + \beta - k)\varphi(S_{**}) + \nu\varphi(S_{**})Z_{**} \\ &\quad + \nu Z_{**}V_{**}\varphi_S(S_{**})(\beta + \gamma)V_{**}\varphi_S(S_{**})\big]x^2 \\ &\quad + \big[\alpha\beta\gamma + \alpha\delta\nu + \gamma\delta\nu + \nu\gamma\alpha Z_{**} + (\alpha\beta - \alpha k + \delta\nu)\varphi(S_{**}) + \alpha\nu\varphi(S_{**})Z_{**} \\ &\quad + (\gamma\nu Z_{**} + \beta\gamma + \delta\nu)V_{**}\varphi_S(S_{**})\big]x \\ &\quad + [\nu\delta(\alpha\gamma + \alpha\varphi(S_{**}) + \gamma V_{**}\varphi_S(S_{**})]Z_{**} = 0. \end{aligned}$$

Here we assume that $\alpha > k - \beta$ and $\nu\delta > \alpha(k - \beta)$. It is easy to check that all the coefficients of the above equation are positive, so from the Routh–Hurwitz Criterion we see that all roots have negative real parts. Therefore we have the following theorem.

THEOREM 3.3. *For $c = \eta = 0$, $d \neq 0$ and $R_0 > 1$, we have the following results.*

(1) *If $d\mu - \beta\delta \leq 0$, the equilibrium points y_0 and y_1' are the only rest points of the system* (1.2)*. Moreover, y_0 is unstable and y_1' is locally asymptotically stable.*
(2) *If $d\mu - \beta\delta > 0$, then for $S_* > (d\mu - \beta\delta)/(\alpha d)$, the equilibrium y_1' is locally asymptotically stable and for $S_* < (d\mu - \beta\delta)/(\alpha d)$, it becomes unstable. If $k\delta - d\mu < 0$, then y_0 and y_1' are the only two rest points of* (1.2) *and y_2 does not exist.*
(3) *If $d\mu - \beta\delta > 0$, $\alpha > k - \beta$, $\nu\delta > \alpha(k - \beta)$ and $(d\mu - k\delta)/(\alpha d) < S_{**} < (d\mu - \beta\delta)/(\alpha d)$, then the equilibrium y_2 exists and is locally asymptotically stable. Moreover, the equilibrium points y_0 and y_1' are unstable.*

REMARK 3.4. If $d\mu - \beta\delta \leq 0$, the point y_2 does not exist, so y_1' is the only endemic equilibrium point of the system (1.2). Also, for $d\mu - \beta\delta > 0$ and $S_* > (d\mu - \beta\delta)/(\alpha d)$, the point y_1' is the only endemic equilibrium point.

REMARK 3.5. (a) From continuous dependence of the equilibrium points and eigenvalues on parameters, Theorems 3.1 and 3.3 are valid for $c_1 > 0$ and small.

(b) For $c_1 \neq 0$ large, if $R_0 < 1$, the point $y_0 = (\mu/\alpha, 0, 0, 0)$ is the unique equilibrium of the system (1.2) which is globally asymptotically stable. If $R_0 > 1$ and S_* is the unique solution of the equation (2.3) satisfying $0 < S_* < \mu/\alpha$, the system (1.2) has a unique endemic equilibrium point, (S^*, I^*, V^*, Z^*), satisfying the equations $V = (\mu - \alpha S)/\varphi(S)$, $I = (\mu - \alpha S)(\gamma + \varphi(S)/(k\varphi)$, $Z = cI/(\delta - dI)$ and (2.3). Here stability of this point is not known.

4. Numerical simulation. For the following numerical simulations, we use parameters of T-cells as the parameters of immune cells, those are $\mu = 80$ cell/(day $\cdot$ μl), $\alpha = 1/3$ days. These parameter values are taken from [NTSS]. The estimated value of η is obtained by assuming that the equilibrium value of the density of immune cells in the absence of infection is 2000 cells. In this model the endemic status of the disease depends on the individual response to incoming viruses. The larger the invasion rate a, the higher the chance to catch the disease. In contrast, with the increase of the elimination rate ν of infected cells, the risk of infection is lower.

For $\varphi(S) = aS$, $1/\delta = 1$ year, $\eta = 0.265$ cell/(day $\cdot$ μl), $\beta = 0.5$, $\gamma = 0.8$, $c = 0.01$, $k = 20$, $\nu = 0.001$, $d = 0.03$, we have

Table 1

a	R_0	Equilibria	Stability
0.001	2.7811	$y_0 = (240, 0, 0, 0)$	unstable
	2.7811	$y_1 = (24.603, 120.3217, 2918.2943, 0)$	unstable
	2.7811	y_2	non-existing
0.002	3.5452	$y_0 = (240, 0, 0, 0)$	unstable
	3.5452	$y_1 = (24.603, 120.3217, 2918.2943, 0)$	unstable
	3.5452	y_2	non-existing
0.003	3.9844	$y_0 = (240, 0, 0, 0)$	unstable
	3.9844	$y_1 = (24.603, 120.3217, 2918.2943, 0)$	unstable
	3.9844	y_2	non-existing

For $\varphi(S) = aS/(1 + \rho S)$, $\rho = 1$, $1/\delta = 1$ year, $\eta = 0.265$ cell/(day $\cdot$ μl), $\beta = 0.5$, $\gamma = 0.8$, $c = 0.01$, $k = 20$, $\nu = 0.001$, $d = 0.03$, we have

Table 2

a	R_0	Equilibria	Stability
0.001	0.2041	$y_0 = (240, 0, 0, 0)$	globally stable
0.002	0.2885	$y_0 = (240, 0, 0, 0)$	globally stable
0.003	0.3531	$y_0 = (240, 0, 0, 0)$	globally stable

For $\varphi(S) = aS/(1 + \rho S)$, $\rho = 0.5$, $1/\delta = 1$ year, $\eta = 0.265$ cell/(day $\cdot$ μl), $\beta = 0.5$, $\gamma = 0.8$, $c = 0.01$, $k = 20$, $\nu = 0.001$, $d = 0.03$, we have

Table 3

a	R_0	Equilibria	Stability
0.001	0.2879	$y_0 = (240, 0, 0, 0)$	globally stable
0.002	0.4066	$y_0 = (240, 0, 0, 0)$	globally stable
0.003	0.4974	$y_0 = (240, 0, 0, 0)$	globally stable

For $\varphi(S) = aS^2/(1 + \rho S^2)$, $\rho = 1$, $1/\delta = 1$ year, $\eta = 0.265$ cell/(day $\cdot$ μl), $\beta = 0.5$, $\gamma = 0.8$, $c = 0.01$, $k = 20$, $\nu = 0.001$, $d = 0.03$, we have

Table 4

a	R_0	Equilibria	Stability
0.001	0.2045	$y_0 = (240, 0, 0, 0)$	globally stable
0.002	0.2891	$y_0 = (240, 0, 0, 0)$	globally stable
0.003	0.3538	$y_0 = (240, 0, 0, 0)$	globally stable

and for $\varphi(S) = aS^2/(1 + \rho S^2)$, $\rho = 0.5$ or $\varphi(S) = aS^2/(1 + \frac{1}{2}S^2)$, we have

Table 5

a	R_0	Equilibria	Stability
0.001	0.2891	$y_0 = (240, 0, 0, 0)$	globally stable
0.002	0.4083	$y_0 = (240, 0, 0, 0)$	globally stable
0.003	0.4995	$y_0 = (240, 0, 0, 0)$	globally stable

In Figure 1, the simulation of the model (1.1) is shown. The parameters are $1/\delta = 1$ year, $\eta = 0.265$ cell/(day $\cdot$ μl), $\beta = 0.5$, $\gamma = 0.8$, $c = 0.01$, $k = 20$, $\nu = 0.001$, $d = 0.03$, $\rho = 0.5$ and $a = 0.001$, $a = 0.002$, $a = 0.003$. These data are taken from [NTSS].

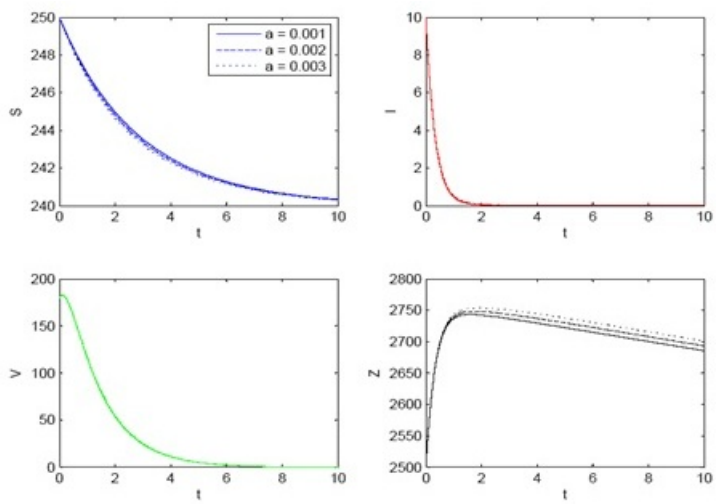

Fig. 1. The vertical lines indicate the day of the onset of the symptom. The horizontal axis has time unit a day.

5. Conclusion. In order to understand the main characteristic of dengue mystery, the authors in [NTSS] assumed that this virus can be eliminated by immune response which is described by the last equation of the system (1.2). By using linear incidence rate of susceptible and free virus particle, i.e. $\varphi(S) = aS$, they analyzed the existence of endemic virus equilibria. In [AH] by using the Beddington–DeAngelis incidence rate of susceptible and free virus particles the authors showed that the elimination of the dengue virus can be achieved in shorter time.

In this paper, from the analysis of endemic equilibria it is found that, for most of the famous nonlinear incidence rates of susceptible and free virus particle, the above results are valid.

The reason for this correspondence is that in both models, the feature of immune response is described by the term $\eta + cI + dIZ$. However, the shape

of the function $\varphi(S)$ enables the elimination of the dengue virus by immune response in a shorter or longer time. This fact can be seen by comparing Tables 1–5.

In fact, by Theorem 2.2, if the basic reproduction number is less than one, then the uninfected equilibrium point is the only steady state point and it is globally asymptotically stable.

If the basic reproduction rate is more than one, for $c_1 = 0$, besides the uninfected steady state which is unstable, there are some infected steady states.

For $c = d = 0$, by Theorem 3.1 there exists only one infected endemic. If $\eta = 0$, there is no immune response, and the density of immune cells is zero. If $\eta \neq 0$, then the density of immune cells equals η/δ, which is independent of the other parameters.

For $c = \eta = 0$ and $d \neq 0$, and some values of the other parameters, by Theorem 3.3, besides the above two equilibria we have a new infected endemic equilibrium point, which is the only stable equilibrium point. This means that we found a new threshold for R_0.

For $c_1 \neq 0$ and small, the above results are valid, too.

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