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A With-In Host Dengue Infection Model with Immune Response and Beddington-DeAngelis Incidence Rate

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ABSTRACT

A model of viral infection of monocytes population by dengue virus is formulated in a system of four ordinary differential equations. The model takes into account the immune response and the incidence rate of susceptible and free virus particle as Beddington-DeAngelis functional response. By constructing a block, the global stability of the uninfected steady state is investigated. This steady state always exists. If this is the only steady state, then it is globally asymptotically stable. If any infected steady state exists, then 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 the other parameters.

Keywords: With-In Host Model; Dengue Viral Infection; Basic Reproduction Ratio; Beddington-DeAngelis Immune Response

1. Introduction

Dengue is an infections mosquito-borne viral disease. It is estimated that about 50 million infections occur annually in over 100 countries [1]. There is no specific treatment for curingdengue patients. Hospital treatment in general is given as supportive care which includes bed rest, antipyretics, and analgesics. Most dengue infections are asymptomatic. Few of them suffer dengue fever and dengue haemorrhagic fever, which may end up in fatality.

Dengue virus is one of the most difficult arboviruses to isolate. There are four serotypes of the dengue virus and each of the serotype 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 serotype, [2]. Identification of the primary target cells of dengue virus replication in infected human body has proven to be extremely difficult. It is generally believed that the target cells of dengue virus are monocytes or its differentiated cells the macrophages [3].

It is usually believed that dengue virus is quickly cleared in human body within approximately 7 days after the day of sudden onset of fever [1]. Naturally this clearing process is done by the immune system which is a result of complex dynamic reactions. Following [4], in this paper we try to understand the process using a mathematical model.

Mathematical modeling of dengue disease transmission in human and mosquito populations has been done since the beginning of last century. Some of the recent models could be seen in [2-5]. Several studies on infection model within human body have been done for various cases [2,3] and [5-11]. Meanwhile, mathematical modeling for with-in host dengue viral disease is quite new.

The model for with-in host dengue viral infection with Beddington-DeAngelis incidence rate and immune response is as following.

$$\begin{cases} \dfrac{\mathrm{d}S}{\mathrm{d}t} = \mu - \alpha S - \dfrac{aSV}{1+\rho S+\omega V}, \\ \dfrac{\mathrm{d}I}{\mathrm{d}t} = \dfrac{aSV}{1+\rho S+\omega V} - \beta_1 I - \nu IZ, \\ \dfrac{\mathrm{d}V}{\mathrm{d}t} = kI - \gamma V - \dfrac{aSV}{1+\rho S+\omega V}, \\ \dfrac{\mathrm{d}Z}{\mathrm{d}t} = c_1 I + dIZ - \delta Z \end{cases} \tag{1}$$

where, $\beta_1 = \beta + \dfrac{\eta\nu}{\delta}$ and $c_1 = c + \dfrac{d\eta}{\delta}$.

The constant $a > 0$, is the rate constant characterizing infection of the cells. The constants ρ, ω are positive.

In the above $S(t), I(t), V(t)$ and $Z(t) + \dfrac{\eta}{\delta}$ represent the density of susceptible monocytes, infected monocytes, free virus particles and immune cells in 1 μl

blood at time *t*, respective. The production of susceptible monocytes by bone marrow is assumed at a constant rate μ and the life span of susceptible monocytes is $\frac{1}{\alpha}$. The flow from susceptible monocytes to the infected monocytes depends on the incidence rate of susceptible monocytes and free virus particle. This rate is shown by $\frac{SV}{1+\rho S+\omega V}$ where $\frac{aS}{1+\rho S+\omega V}$ is the incidence response of susceptible monocytes to free virus particles. The period of infected monocytes is assumed constant as $\frac{1}{\beta}$. We assumed virus multiplication is at constant rate *k* and the virus clearance rate is at constant rate γ. We also assumed the immune cells are produced at constant rate η and their life span is $\frac{1}{\delta}$. Moreover we assumed there is stimulation of immune cells production due to the increase of infected cell which is proportional to the density infected monocytes at a constant rate *c* as well as from the contacts with infected cells at the rate *d* and the immune cells will eliminate the infected monocytes at a constant rate *v*. Finally, the positive constants ρ and ω have some biological meanings.

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

For more detail the reader is referred to [4] and references therein.

The local stability of the equilibrium points of the system (1) for Lotka-Voltera functional response *i.e.* $\varphi(S)=aS$, has been discussed in [4]. The model (1) 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 in chapter 6 of [5].

In this paper, we will analyze the global of stability of the viral free equilibrium for Beddington-DeAngelis incidence response, $\frac{aS}{1+\rho S+\omega V}$. In fact we will show that if this equilibrium is the only rest point of the system (1), then it is globally asymptotically stable. If there are some other equilibria, then the local stability of them depends on the values of the parameters.

2. Global Stability of the Uninfected Equilibrium

In this section, at first we will find the equilibrium points of the system (1) and the eigenvalues of this system at these points. This information leads us to prove the locally asymptotical stability of the equilibrium points.

At an equilibrium point of the system (1) we must have

$$\begin{cases} \mu-\alpha S-\dfrac{aSV}{1+\rho S+\omega V}=0, \\ \dfrac{aSV}{1+\rho S+\omega V}-\beta_1 I-\nu IZ=0, \\ kI-\gamma V-\dfrac{aSV}{1+\rho S+\omega V}=0, \\ c_1 I+dIZ-\delta Z=0 \end{cases} \tag{2}$$

From the first equation we obtain, $=\dfrac{(\mu-\alpha S)(1+\rho S)}{(a+\omega\alpha)S-\omega\mu}$. Substituting this value of *V* into the third equation yields, $=\dfrac{(\mu-\alpha S)}{k}\left[\dfrac{\gamma(1+\rho S)}{(a+\omega\alpha)S-\omega\mu}+1\right]$. From the fourth equation we obtain $Z=\dfrac{C_1 I}{\delta-dI}$. Substituting these values of V, I and Z into the second equation yields,

$$(\mu-\alpha S)\left[1-\frac{\beta_1}{k}\left(\frac{\gamma(1+\rho S)}{aS-\omega(\mu-\alpha S)}+1\right)\right.$$

$$\left.+\frac{\nu c_1\beta_1^2}{k^2}\frac{(\mu-\alpha S)\left(\dfrac{\gamma(1+\rho S)}{aS-\omega(\mu-\alpha S)}+1\right)^2}{\delta-\dfrac{d\beta_1}{k}(\mu-\alpha S)\left(\dfrac{\gamma(1+\rho S)}{aS-\omega(\mu-\alpha S)}+1\right)}\right]=0.$$

If, $\mu-\alpha S=0$, then from this, we have $S=\frac{\mu}{\alpha}$. Thus $y_0=\left(\frac{\mu}{\alpha},0,0,0\right)$ is one of the equilibrium points of the system (1). If,

$$1-\frac{\beta_1}{k}\left(\frac{\gamma(1+\rho S)}{aS-\omega(\mu-\alpha S)}+1\right)$$

$$+\frac{\nu c_1\beta_1^2}{k^2}\frac{(\mu-\alpha S)\left(\dfrac{\gamma(1+\rho S)}{aS-\omega(\mu-\alpha S)}+1\right)^2}{\delta-\dfrac{d\beta_1}{k}(\mu-\alpha S)\left(\dfrac{\gamma(1+\rho S)}{aS-\omega(\mu-\alpha S)}+1\right)}=0,$$

then

$$q_3S^3+q_2S^2+q_1S+q_0=0, \tag{3}$$

where,

$$q_3=-dk\alpha\beta_1(e\alpha+a)(\gamma b+e\alpha+a),$$

$$q_2 = \delta k^2 (a+e\alpha)^2 + dk\alpha\beta_1(\gamma - e\mu)(a+e\alpha) + \left[-e\mu dk\alpha\beta_1 + \alpha\nu c_1\beta_1^2 - d\alpha\beta_1^2 - (a+\alpha e)(dk\mu\beta_1 + \beta_1\delta k)\right](\gamma b + e\alpha + a),$$

$$q_1 = -2e\mu\delta k^2(a+e\alpha) + \left(-adk\mu\beta_1 - a\delta k\beta_1 - e\alpha k\delta\beta_1 - d\alpha\beta_1 + \alpha\nu c_1\beta_1^2\right)(\gamma - e\mu) + \left(edk\mu^2\beta_1^2 + e\mu k\delta\beta_1 + d\mu\beta_1^2 - \mu\nu c_1\beta_1^2\right)(\gamma b + e\alpha + a)$$

and

$$q_0 = e^2\mu^2k^2\delta - (dk\mu\beta_1 + k\delta\beta_1)(a+e\alpha)(\gamma - e\mu) + (\gamma - e\mu)\left(d\mu\beta_1^2 - \mu\nu c_1\beta_1^2\right)$$

In the following we consider the stability property of the equilibrium point y_0. In order to do this we check the sign of the eigenvalues of Jacobi matrix of (1) at y_0. The Jacobi matrix is

$$\boldsymbol{J} = \begin{bmatrix} -\alpha - \dfrac{aV(1+\omega V)}{(1+\rho S+\omega V)^2} & 0 & \dfrac{-aS(1+\rho S)}{(1+\rho S+\omega V)^2} & 0 \\ \dfrac{aV(1+\omega V)}{(1+\rho S+\omega V)^2} & -\beta_1 - \nu Z & \dfrac{aS(1+\rho S)}{(1+\rho S+\omega V)^2} & -\nu I \\ \dfrac{-aV(1+\omega V)}{(1+\rho S+\omega V)^2} & k & -\dfrac{aS(1+\rho S)}{(1+\rho S+\omega V)^2} & 0 \\ 0 & c_1 + dZ & 0 & dI - \delta \end{bmatrix} \tag{4}$$

So the value of $\boldsymbol{J}$ at y_0 is

$$\boldsymbol{J}(y_0) = \begin{bmatrix} -\alpha & 0 & \dfrac{-a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}} & 0 \\ 0 & -\beta_1 & \dfrac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}} & 0 \\ 0 & k & -\gamma - \dfrac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}} & 0 \\ 0 & c_1 & 0 & -\delta \end{bmatrix}$$

The eigenvalues of $\boldsymbol{J}(y_0)$ are the roots of the characteristic polynomial

$$(x+\alpha)(x+\delta)\left(x^2 + \left(\beta_1 + \gamma + \frac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}}\right)x - (k-\beta_1)\left(\frac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}}\right) + \beta_1\gamma\right) = 0.$$

Thus, $x_1 = -\alpha$ and $x_2 = -\delta$ are two of the eigenvalues and the other two are the roots of

$$x^2 + \left(\beta_1 + \gamma + \frac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}}\right)x - (k-\beta_1)\left(\frac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}}\right) + \beta_1\gamma = 0.$$

These roots are

$$x_3 = \frac{-\left(\beta_1 + \gamma + \dfrac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}}\right) - \sqrt{\Delta}}{2},$$

$$x_4 = \frac{-\left(\beta_1 + \gamma + \dfrac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}}\right) + \sqrt{\Delta}}{2},$$

where, $\Delta = \left(\beta_1 - \gamma - \dfrac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}}\right)^2 + 4k\dfrac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}}$.

Clearly, x_1, x_2 and x_3 have negative real part. If x_4 has negative real part, then the equilibrium y_0 is locally asymptotically stable. But x_4 is negative if and only if, $\sqrt{\Delta} < \left(\beta_1 + \gamma + \dfrac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}}\right)$. This condition equals

to, $\sqrt{\frac{k}{\beta_1}\frac{a\frac{\mu}{\alpha}}{\gamma+(\gamma\rho+a)\frac{\mu}{\alpha}}}<1$.

Set, $R_0=\sqrt{\frac{k}{\beta_1}\frac{a\frac{\mu}{\alpha}}{\gamma+(\gamma\rho+a)\frac{\mu}{\alpha}}}$. This number is called the basic reproduction ratio [7].

Therefore we have the following theorem.

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

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

$$D_a=\{(S,I,V,Z):0<S<a,I>0,V>0,Z>0\},\ a\geq\frac{\mu}{\alpha}.$$

It follows that the flow generated by that system (1.1) gets into D_a on the boundary of D_a. Let $D=D_a$ for, $a=\frac{\mu}{\alpha}$. Thus $\bar{D}$ is a global attractor. Now in $\bar{D}$ consider the following set for $C>0$:

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

where, $K(S,I,V,Z)=A_1\left(\frac{\mu}{\alpha}-S\right)+A_2I+A_3V+A_4Z$

and

$$A_1=\beta_1(\gamma+\varphi^*)(1-R_0{}^2)$$

$$A_2=\frac{dk\varphi^*A_1}{\left[(\gamma+\varphi^*+1)(\beta d-\nu c)-dk\varphi^*\right]}$$

$$A_3=\frac{\varphi^*(\beta d-\nu c)A_1}{\left[(\gamma+\varphi^*+1)(\beta d-\nu c)-dk\varphi^*\right]}$$

$$A_4=\frac{\nu k\varphi^*A_1}{\left[(\gamma+\varphi^*+1)(\beta d-\nu c)-dk\varphi^*\right]}$$

and $\varphi^*:=\frac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}}$.

If we differentiate $K(S,I,V,Z)$ along the orbits of the system (1), we obtain:

$$\begin{aligned}\frac{dK}{dt}&=-A_1\dot{S}+A_2\dot{I}+A_3\dot{V}+A_4\dot{Z}\\&=-A_1(\mu-\alpha S-V\varphi(S,V))\\&\quad+A_2(V\varphi(S,V)-\beta_1I-\nu IZ)\\&\quad+A_3(kI-\gamma V-V\varphi(S,V))\\&\quad+A_4(c_1I+dIZ-\delta Z)\\&=-A_1(\mu-\alpha S)+(-\beta_1A_2+kA_3+c_1A_4)I\\&\quad+(\varphi A_1+\varphi A_2-(\gamma+\varphi)A_3)V\\&\quad-\delta A_4Z+(dA_4-iA_2)IZ\end{aligned}$$

Here, $\varphi:=\varphi(S,V)=\frac{aS}{1+\rho S+\omega V}$. 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 $\beta_1(\gamma+\varphi^*)(1-R_0{}^2)>0$, therefore $\frac{dK}{dt}<0$. 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 $C\geq0$. But $y_0=\bigcap_{C\geq0}Q_C$. Thus y_0 is a global attractor. Thus we have proved the following theorem.

Theorem 2.2. If, $R_0<1$, then y_0 ,the uninfected equilibrium is the only equilibrium of the system (1). Moreover this equilibrium is globally asymptotically stable.

Since y_0 is globally asymptotically stable for $R_0<1$, any other equilibrium points of the system (1) cannot exist for $R_0<1$. Therefore, y_0 is the unique equilibrium point for $R_0<1$.

3. Stability of the Other Equilibrium Points

In this section, we consider the stability of the other rest point of the system (1). In order to this, we consider the Equation (3). First, we consider this equation for $c_1=0$ and then for $c_1\neq0$.

There are two cases for $c_1=0$ as follows.

Case 1. $c=d=0$

In this case, the system (1) has two equilibrium points, y_0 and another one. To see this, from the first equation of (2) we obtain, $-\alpha S=\frac{aSV}{1+\rho S+\omega V}$. Since $c=d=0$ from the fourth equation we get $Z=0$. Substituting these values of V and Z into the second equation yields, $I=\frac{\mu-\alpha S}{\beta_1}$. By using the value of I and the third equation we get $V=\frac{(k-\beta_1)(\mu-\alpha S)}{\beta_1\gamma}$. Using these values into the Equation (3), we obtain,

$$S=\frac{\gamma\beta_1+\omega\mu(k-\beta_1)}{(k-\beta_1)(a+\alpha\omega)-\rho\gamma\beta_1}.$$

Therefore, we obtain

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

$S_0=\frac{\gamma\beta_1+\omega\mu(k-\beta_1)}{(k-\beta_1)(a+\alpha\omega)-\rho\gamma\beta_1}$ as the second rest point of the system (1).

Notice that this rest point exists if $\mu-\alpha S_0\geq 0$, or $S_0\leq\frac{\mu}{\alpha}$. If $S_0=\frac{\mu}{\alpha}$, this rest point is the same as $y_0=\left(\frac{\mu}{\alpha},0,0,0\right)$. If $S_0<\frac{\mu}{\alpha}$, then

$$\frac{aS_0}{1+\rho S_0+\omega V_0}<\frac{a\frac{\mu}{\alpha}}{1+\rho\frac{\mu}{\alpha}},$$

or

$$R_0=\sqrt{\frac{k}{\beta_1}\frac{a\frac{\mu}{\alpha}}{\gamma+(\gamma\rho+a)\frac{\mu}{\alpha}}}>1.$$

Now, we consider the local stability of the equilibrium y_1. By using the formula (4), the value of Jacobi matrix at y_1 is

$$J(y_1)=\begin{bmatrix}-\alpha-A & 0 & -B & 0\\ A & -\beta_1 & B & -\nu I_0\\ -A & k & -\gamma-B & 0\\ 0 & 0 & 0 & -\delta\end{bmatrix},$$

where $I_0=\frac{(\mu-\alpha S_0)}{\beta_1}$, $A=\frac{aV_0(1+\omega V_0)}{(1+\rho S_0+\omega V_0)^2}$,

$B=\frac{aS_0(1+\rho S_0)}{(1+\rho S_0+\omega V_0)^2}$ and $V_o=\frac{(k-\beta_1)(\mu-\alpha S_0)}{\beta_1\gamma}$.

We calculate the eigenvalues of $J(y_1)$ as follow:

$$\begin{aligned}&\det\left(xI_{4\times4}-J(y_1)\right)\\ &=\begin{vmatrix}x+\alpha+A & 0 & B & 0\\ -A & x+\beta_1 & -B & \nu I_0\\ A & -k & x+\gamma+B & 0\\ 0 & 0 & 0 & x+\delta\end{vmatrix}\\ &=(x+\delta)\left(x^3+\left[\alpha+\gamma+\beta_1+A+B\right]x^2\right.\\ &\quad+\left[\beta_1\gamma+(\beta_1-k+\alpha)B+(\beta_1+\gamma)(\alpha+A)\right]x\\ &\quad\left.+\left[\beta_1\alpha\gamma+(\beta_1\alpha-k\alpha)B+\beta_1\gamma A\right]\right)=0.\end{aligned}$$

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

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

Here $q_2=\alpha+\gamma+\beta_1+A+B$,
$q_1=\beta_1\gamma+(\beta_1-k+\alpha)B+(\beta_1+\gamma)(\alpha+A)$ and
$q_0=\beta_1\alpha\gamma+(\beta_1\alpha-k\alpha)B+\beta_1\gamma A$.

By substituting the value of A,B and V_o in q_2,q_1 and q_0 we see that q_2,q_1 and q_0 are positive. Moreover, it is easy to check that, $q_2q_1>q_0$. By the Rouths Hurwitz Criteria, all roots of the cubic polynomial have negative real part. 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 y_0 exists and is unstable.

Remark 3.1. Since, the rest points and the eigenvalues depend continuously on the parameters, thus for small values of $c>0$ and >0, y_1 exists and is locally asymptotically stable.

Case 2. $c=\eta=0, d\neq 0$

In this case, the system (1) has three equilibrium points and y_0 is one of them. Since $c=\eta=0$, the fourth equation of the system (1) gives $dIZ-\delta Z=0$. Therefore, $Z=0$ or $I=\frac{\delta}{d}$. For $Z=0$, substituting the value of Z into the second equation yields, $I=\frac{\mu-\alpha S}{\beta}$. By using the value of I and the third equation we get, $V=\frac{(k-\beta)(\mu-\alpha S)}{\beta\gamma}$. Substituting values of c and η into the Equation (3), we obtain,

$S_*=\frac{\gamma\beta+\omega\mu(k-\beta)}{(k-\beta)(a+\alpha\omega)-\rho\gamma\beta}$. Thus, we get

$y_1'=\left(S_*,\frac{(\mu-\alpha S_*)}{\beta},\frac{(k-\beta)(\mu-\alpha S_*)}{\beta\gamma},0\right)$ as another rest point of the system (1).

For $I=\frac{\delta}{d}$, by substituting this value of I in the second equation of the system (1), 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 third equation we get, $V=\frac{k\delta-d(\mu-\alpha S)}{d\gamma}$. By using this value of V into the first equation of the system (1), we obtain the following quadratic equation.

$$\begin{aligned}&\left(\alpha\rho\gamma+a\alpha+\omega\alpha^2\right)S^2\\ &+\left(\frac{k\delta}{d}(a+\alpha\omega)+\alpha\gamma-\rho\mu\gamma-\alpha\mu-2\mu\omega\alpha\right)S\\ &+\left(\omega\mu^2-\gamma\mu-\frac{\mu\omega k\delta}{d}\right)=0.\end{aligned}$$

If $k\delta - d(\mu - \alpha S) > 0$ and $d(\mu - \alpha S) - \beta\delta > 0$, 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) where S_{**} is the positive root of the above quadratic equation.

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

At first consider it for y_1'. Here we check the sign of the eigenvalues of Jacobi matrix of the system (1) at y_1'. From the formula (4) we have

$$J(y_1') = \begin{bmatrix} -\alpha - A & 0 & -B & 0 \\ A & -\beta & B & -\nu I_* \\ -A & k & -\gamma - B & 0 \\ 0 & 0 & 0 & dI_* - \delta \end{bmatrix}$$

where $I_* = \frac{(\mu - \alpha S_*)}{\beta}$, $A = \frac{aV_*(1+\omega S_*)}{(1+\rho S_* + \omega V_*)^2}$, $B = \frac{aS_*(1+\rho S_*)}{(1+\rho S_* + \omega V_*)^2}$ and $V_* = \frac{(k-\beta)(\mu - \alpha S_*)}{\beta\gamma}$.

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

$$\begin{aligned} &\det\left(xI_{4\times 4} - J(y_1')\right) \\ &= \begin{vmatrix} x+\alpha+A & 0 & B & 0 \\ -A & x+\beta & -B & \nu I_0 \\ A & -k & x+\gamma+B & 0 \\ 0 & 0 & 0 & x+\delta-dI_* \end{vmatrix} \\ &= (x+\delta-dI_*)\{x^3 + [\alpha+\gamma+\beta+A+B]x^2 \\ &\quad + [\beta\gamma + (\beta-k+\alpha)B + (\beta+\gamma)(\alpha+A)]x \\ &\quad + [\beta\alpha\gamma + (\beta\alpha - k\alpha)B + \beta\gamma A]\} = 0. \end{aligned}$$

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

$$x^3 + q_2 x^2 + q_1 x + q_0 = 0.$$

Here $q_2 = \alpha+\gamma+\beta+A+B$, $q_1 = \beta\gamma + (\beta - k + \alpha)B + (\beta+\gamma)(\alpha+A)$ and $q_0 = \beta\alpha\gamma + \beta\gamma A + (\beta\alpha - k\alpha)B$.

By substituting the value of A, B and V_o in q_2, q_1 and q_0 we will see that q_2, q_1 and q_0 are positive. Moreover, it is easy to see that, $q_2 q_1 > q_0$. By the Rouths Hurwitz Criteria, all roots of the cubic polynomial have negative real part. If $I_* < \frac{\delta}{d}$ or $(d\mu - \beta\delta) - \alpha d S_* < 0$, then real part of all of the eigenvalues are negative. Therefore the point y_1' is locally asymptotically stable.

Now we consider the stability property of the other equilibrium point, y_2. From the formula (4) we have

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

where $I_* = \frac{\delta}{d}$, $Z_{**} = \frac{d(\mu - \alpha S_{**}) - \beta\delta}{\nu\delta}$, $A = \frac{aV_{**}(1+\omega V_{**})}{(1+\rho S_{**} + \omega V_{**})^2}$, $V_{**} = \frac{k\delta - d(\mu - \alpha S_{**})}{\gamma d}$ and $B = \frac{aS_{**}(1+\_S_{**})}{(1+\rho S_{**} + \omega V_{**})^2}$.

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

$$\begin{aligned} &\det\left(xI_{4\times 4} - J(y_2)\right) \\ &= \begin{vmatrix} x+\alpha+A & 0 & B & 0 \\ -A & x+\beta+\nu Z_{**} & -B & \frac{\nu\delta}{d} \\ A & -k & x+\gamma+B & 0 \\ 0 & -dZ_{**} & 0 & x \end{vmatrix} = 0, \end{aligned}$$

or

$$\begin{aligned} &x\Big[(x+\alpha+A)\big((x+\beta+\nu Z_{**})(x+\gamma+B) - kB\big) \\ &+ B\big(kA - A(x+\beta+\nu Z_{**})\big)\Big] \\ &- dZ_{**}\left[\frac{\nu\delta}{d}AB - \frac{\nu\delta}{d}(x+\alpha+A)(x+\gamma+B)\right] = 0. \end{aligned}$$

Then from the above equation we get

$$\begin{aligned} &x^4 + [\alpha+\beta+\gamma+B+\nu Z_{**}+A]x^3 \\ &+ [\beta(\alpha+\gamma) + \alpha\gamma + (\alpha+\gamma+\delta)\nu Z_{**} + \nu B Z_{**} \\ &+ (\alpha+\beta-k)B + \nu Z_{**}A + (\beta+\gamma)A]x^2 \\ &+ [\alpha\beta\gamma + \alpha\delta\nu + \gamma\delta\nu + \nu\gamma\alpha Z_{**} + \alpha\nu B Z_{**} \\ &+ (\alpha\beta - \alpha k + \delta\nu)B + (\gamma\nu Z_{**} + \beta\gamma + \delta\nu)A]x \\ &+ [\nu\delta(\alpha\gamma + \alpha B + \gamma A] = 0. \end{aligned}$$

By considering the value of Z_{**} it follows that all of the coefficients of the above equation are positive, then from Routh Hourwitz Criteria we see that all of the roots have negative real parts. Therefore we have the following theorem.

Theorem 3.2. 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), then y_0 is unstable and y_1' is locally asymptotically stable.

2) If $d\mu - \beta\delta > 0$, then for $S_* > \frac{d\mu - \beta\delta}{\alpha d}$, the equi-

librium y_1', is locally asymptotically stable and for $S_* < \frac{d\mu - \beta\delta}{\alpha d}$, it becomes unstable. If $k\delta - d\mu < 0$, y_0 and y_1' are the only two rest points of the system (1) and y_2 does not exist.

3) If $d\mu - \beta\delta > 0$ and $\frac{d\mu - k\delta}{\alpha d} < S_* < \frac{d\mu - \beta\delta}{\alpha d}$, then the equilibrium y_2 exists and is locally asymptotically stable. Moreover the equilibrium points y_0 and y_1' are unstable.

Remark 3.2. If $d\mu - \beta\delta \le 0$, the point y_2 does not exist, therefore the point y_1' is the only endemic equilibrium point of the system (1). Also, for $d\mu - \beta\delta > 0$ and $S_* > \frac{d\mu - \beta\delta}{\alpha d}$, the point y_1' is the only endemic equilibrium point.

Remark 3.3. 1) From continuous dependent of the equilibrium points and eigenvalues to the parameters, Theorem 3.1 and 3.2 must be valued for $c_1 > 0$ and small.

2) For the case, $c_1 \neq 0$ and large, if $R_0 < 1$, the point $y_0 = \left(\frac{\mu}{\alpha}, 0, 0, 0\right)$ is the unique equilibrium of the system (1) which is globally asymptotically stable. If $R_0 > 1$, the system (1) has a unique endemic equilibrium point, $\left(S^*, I^*, V^*, Z^*\right)$ satisfying in the equations

$$V = \frac{(\mu - \alpha S)(1 + \rho S)}{(a + \omega\alpha)S - \omega\mu},$$

$$I = \frac{(\mu - \alpha S)}{k}\left[\frac{\gamma(1 + \rho S)}{(a + \omega\alpha)S - \omega\mu} + 1\right], \quad Z = \frac{c_1 I}{\delta - dI}$$ and the Equation (3). Here stability property of this point is not shown.

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·μl), $\alpha = \frac{1}{3}$ days. 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 toward incoming viruses. The larger the invasion rate a, the chance is higher to catch the disease. On the contrary the increase of the elimination rate ν of infected cell, the risk of infection is lower.

For $\rho = \omega = 1, \frac{1}{\delta} = 1y, \quad \eta = 0.265$ cell/(day·μl), $\beta = 0.5, \gamma = 0.8, c = 0.01, k = 20, \nu = 0.001, d = 0.03$, we have

For $\rho = 1, \omega = 0$ we obtain the same result in the above table.

If $\rho = 0, \omega = 1$ then for the same value of parameters we have the following table.

5. Conclusions

In order to understand the main characteristic of Dengue mystery, the author in [4] assumed that this virus can be eliminated by immune response which is described by the last equation of the system (1).

By using linear incidence rate of susceptible and free virus particle, they analyzed the existence of the endemic virus equilibria.

In this paper, from the analysis of the endemic equilibria it is found that, for Beddington DeAngelis incidence rate of susceptible and free virus particle, the same results are valid.

The reson for this correspondence is that in both models, the feature of the immune response is described by the term $\eta + cI + dIZ$. However, the parameter ρ in Beddington DeAngles makes the elimination of dengue virus by immune response in a shorter time. This fact can be seen by comparing **Tables 1** and **2**.

Table 1. Status of equilibrium points of system (1) in the case $\rho = \omega = 1$.

a	Status of system (1)		
	R_0	Equiliburia points	Statuse of 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

Table 2. Status of equilibrium points of system (1) in the case $\rho = 0$, $\omega = 1$.

a	Status of system (1)		
	R_0	Equiliburia points	Statuse of stability
0.001	2.7811	$y_0 = (240, 0, 0, 0)$	Un stable
		$y_1 = (239.3557, 0.3599, 0.7292, 0)$	Unstable
		y_2	Not exist
0.002	3.5452	$y_0 = (240, 0, 0, 0)$	Un stable
		$y_1 = (238.6419, 0.7586, 18.400, 0)$	Unstable
		y_2	Not exist
0.003	3.9844	$y_0 = (240, 0, 0, 0)$	Un stable
		$y_1 = (237.9324, 1.1549, 28.0127, 0)$	Unstable
		y_2	Not exist

By Theorem 2.2, if the basic reproduction number, R_0 is less than one, then uninfected equilibrium point, y_0 is the only steady state point of system (1) and it is globally asymptotically state. This means that the virus is eliminated by immune response. For larger values of η and ρ, R_0 is more attractor and the virus is cleared much faster.

If the basic reproduction number, R_0 is more than one; for $c_1 = 0$, besides of the uninfected steady state y_0 which is uninfected, there are some infected steady state. Here we consider two cases of endemic virus.

Fist, for $c = d = 0$, we have only one infected endemic y_1. If $\eta = 0$, there is no immune response, so the density of susceptible moncytes equal zero. In $\eta \neq 0$, this density equals $\frac{\eta}{\delta}$, so it does not depend on the other parameters for virus load of infected cell. For lager values of β and ρ, the infected endemic y_1 is closer to the uninfected endemic y_0 and it is more controllable.

Second, for $c = \eta = 0$ and $d \neq 0$, from Theorem 3.2 we see that if $d\mu - \beta\delta$ is negative or positive small, then there is only one infected endemic equilibrium y_0' which is stable. However if $d\mu - \beta\delta$ is positive and large, then the endemic virus equilibrium y_2 exists and is stable. This means that we found α new threshold for R_0. For condition R_0 is less than this threshold the dynamic of the model is qualitatively same as the case $c = d = 0$. When R_0 is greater than this threshold, we have a new endemic virus equilibrium, y_2 which is stable and the equilibrium points y_0 and y_1' are unstable. From the components of the endemic equilibrium y_2 we see that after the onset of the symptom, if d increases, the V and I components of equilibria decrease and the S and Z-components of equilibria will increase. Conversely, if a and ρ increase, the V and I-components of equilibria will decrease but the virus load increases at the initial viral infection.

For case $c_1 \neq 0$ and large and $R_0 > 1$, the model has a unique endemic virus. The V and I components of this equilibrium point decrease as a increases and the S and Z-components of it increase as d increases.

Therefore, d, a and ρ are the important parameters to capture the phenomena that dengue virus is quickly cleared in a shorter time.

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