A Within-host Model of Dengue Infection with a Non-constant Monocyte Production Rate

Jeremy J. Thibodeaux * and Michael Hennessey †

Department of Mathematical Sciences,
Loyola University New Orleans,
New Orleans, LA 70118, USA.

Abstract: In this paper we modify previous models to develop a new model of within-host dengue infection without the assumption that monocyte production is constant. We then proceed by obtaining an expression for the net reproductive rate of the virus and thus establish a stability result. We also perform a sensitivity analysis to test various treatment strategies and find that treatments that reduce the number of new viruses per infected monocyte are the most efficient.

Keywords: Within-host model, Net reproductive rate, Treatment scenarios

1 Introduction

Dengue is a virus belonging to the Flavivirus genus. The Flavivirus genus includes mostly mosquito-borne viruses such as West Nile virus and yellow fever virus. The dengue virus exists in four different serotypes. A serotype is a distinct variation within a species of viruses that may present a different configuration or slightly different kind of antigen. All serotypes of the dengue virus can cause the full spectrum of disease symptoms.[3]

It is estimated that nearly 50 million infections occur annually in over 100 countries. Most dengue infections, however, do not present any symptoms. According to [8, 11, 13] this is due to the phenomena that primary infections are largely asymptomatic while secondary and tertiary infections account for up to 90% of symptomatic dengue infections. As there are no specific antiviral treatments for dengue infection, supportive care is the usual treatment. This may include bed rest, antipyretics and analgesics. A small subset of infections result in dengue hemorrhagic fever which can be fatal.

The incubation period of the virus in an infected host ranges from 5 to 10 days[9]. At the end of the incubation period, viral particles enter the bloodstream and cause the onset of symptomatic fever. Viremia, the presence of virus in the blood stream, occurs roughly two days before the onset of symptoms and lasts 5 to 6 days [14]. Viremia tends to peak at the time of or shortly after the onset of illness. The clearance of virus is performed by the immune system.

There have been many mathematical studies of dengue infection. Of those, relatively few [6, 7, 10] are concerned with within-host dynamics. In these, it is assumed that the production

*Corresponding author email: thibodea@loyno.edu
†Email address: mphennes@loyno.edu
of target cells is constant. This assumption is adequate in healthy individuals but the production of monocytes can vary [8]. In general, the production is controlled by the Macrophage Colony Stimulating Factor (M-CSF). We account for this additional aspect in our model.

The remainder of the paper is organized as follows: in Section 2 we formulate the homogeneous viral infection model. Section 3 is the analysis of the model’s equilibria. Section 4 contains the parameter sensitivity analysis. Section 5 is the conclusion.

2 The Model

Within this section, we formulate a model of population growth of dengue virus in the human body based on the model in [10]. The model starts with the beginning of the detectable viremia period. It is assumed that one serotype of dengue virus circulates within the infected host and that the virus infects the monocyte cell population of the host.

In [10], the authors studied the following model:

\[
\begin{align*}
\frac{dS}{dt} & = \mu - \alpha S - aSV \\
\frac{dI}{dt} & = aSV - \beta I - \nu IZ \\
\frac{dV}{dt} & = k\beta I - \gamma V - aSV \\
\frac{dZ}{dt} & = \eta + \gamma I + dIZ - \delta Z,
\end{align*}
\]

(2.1)

Where \(S(t), I(t), V(t), \) and \(Z(t)\) represent the density of susceptible monocytes, infected monocytes, free virus particles and immune cells in 1 \(\mu\)L blood at time \(t\), respectively. The production of susceptible monocytes is assumed to be a constant \(\mu\) and they also have a constant death rate \(\alpha\). Since the monocyte population can actually be more numerous during infection [8], we have chosen to model the production of monocytes dynamically. First, we account for the fact that the primary catalyst for monocyte production is a hormone called the Macrophage Colony Stimulating Factor (M-CSF). This is also true for other components of the blood. For example, the production of erythrocytes is controlled by the hormone erythropoietin. In several previous works including [1, 4, 5], it was assumed that the rate of production was proportional to the hormone concentration. We will make the same assumption here and will require that in the absence of infection, the rate of production is indeed the constant \(\mu\). This changes the first equation in 2.1 into

\[
\frac{dS}{dt} = \frac{\mu C}{C^*} - \alpha S - aSV,
\]

where \(C^*\) is the normal concentration of M-CSF. We are now required to model the dynamics of the M-CSF production. First, we will model how the body regulates its control under normal conditions, i.e., no infection. In this case, the production’s purpose is to maintain a normal monocyte count [15], which we will call \(S^*\). We want a function that increases when \(S < S^*\) and decreases when \(S > S^*\). To achieve this, we have chosen the function \(k_3 S \exp\left(\frac{S - S^*}{100}\right)\).

It is also known that M-CSF production increases as a result of susceptible cells being infected [2, 11]. Therefore, we will assume that the rate of increased production is proportional to the rate of infection, \(aSV\). Thus we will have the term \(k_2 aSV\), where \(k_2\) is the constant of proportionality. Finally, M-CSF has a natural decay rate which we will call \(k_3\). This results in the equation

\[
\frac{dC}{dt} = k_1 S e^{\frac{S - S^*}{100}} + k_2 aSV - k_3 C.
\]
The infection of susceptible monocytes depends on the successful invasion rate $a$ of virus into susceptible cells per unit time. The infection period of infected monocytes is assumed constant as $1/\beta$. Upon infected cell death, $k$ free virus particles are released into the blood. The free virus particles are assumed to be cleared at a rate of $\gamma$.

It is assumed that the immune cells are produced at a constant rate $\eta$ and they have a lifespan of $1/\delta$. Additionally, we assume immune cell production is stimulated by the infection of susceptible cells at a constant rate $c$, as well as from contacts with infected cell at constant rate $d$. Lastly, we assume that immune cells will eliminate the infected monocytes at a constant rate $v$.

With these assumptions, we formulate the model for within-host dengue viral infection with immune response and variable production rate, as the following.

\[
\begin{align*}
\frac{dC}{dt} &= k_1S e^{\frac{s^*-s}{100}} + k_2aSV - k_3C \\
\frac{dS}{dt} &= \mu C - \alpha S - aSV \\
\frac{dI}{dt} &= aSV - \beta I - \nu IZ \\
\frac{dV}{dt} &= k\beta I - \gamma V - aSV \\
\frac{dZ}{dt} &= \eta + cI + dIZ - \delta Z.
\end{align*}
\]

(2.2)

We were able to find the values for normal susceptible counts and the normal M-CSF concentration, $S^*$ and $C^*$ in the literature. The same is true for the decay rate of M-CSF, $k_3[12]$. The value of $k_1$ was chosen so that in the absence of infection, $C = C^*$ and $S = S^*$. This results in $k_1 = \frac{k_3C^*}{\mu}$. The value of $k_2$ was determined by a statistical analysis based on data found in [8], which we will discuss in detail in the numerical section. Since we can express $S^*$ and $C^*$ in terms of the other parameters, we decided to do so and work with the following version of the model:

\[
\begin{align*}
\frac{dC}{dt} &= k_1\mu S e^{\frac{s^*-s}{100}} + k_2aSV - k_3C \\
\frac{dS}{dt} &= k_3\alpha C - \alpha S - aSV \\
\frac{dI}{dt} &= aSV - \beta I - \nu IZ \\
\frac{dV}{dt} &= k\beta I - \gamma V - aSV \\
\frac{dZ}{dt} &= \eta + cI + dIZ - \delta Z.
\end{align*}
\]

(2.3)

All model parameters are assumed to be positive.

3 Model Equilibria and Analysis

We will focus on the disease-free equilibrium $[C^*, S^*, 0, 0, Z^*]$, where $C^* = \frac{k_1\mu}{k_3\alpha}$, $S^* = \frac{\mu}{\alpha}$, and $Z^* = \frac{\eta}{\delta}$, and the death equilibrium $[0, 0, 0, 0, \frac{\eta}{\delta}]$.

The Jacobian of the model is expressed below.
Substituting the disease-free equilibrium into the Jacobian matrix results in

\[
J(C, S, I, V, Z) = \begin{pmatrix}
-k_3 & k_1 e^{-\frac{S}{100}} (1 - \frac{S}{100}) + k_2 aV & 0 & k_2 aS & 0 \\
\frac{k_3 \alpha}{k_1} & -\alpha - aV & 0 & -aS & 0 \\
0 & aV & -\beta - \nu Z & aS & -\nu I \\
0 & -aV & k\beta & -\gamma - aS & 0 \\
0 & 0 & c + dZ & 0 & dI - \delta
\end{pmatrix}
\]

And the tedious calculation of \( \det[J(C^*, S^*, 0, 0, Z^*) - \lambda I] \) gives the characteristic polynomial:

\[
p(\lambda) = -\frac{1}{100\alpha \delta} \left( \lambda + \delta \right) (100k_3 \lambda + 100\alpha \lambda + 100\lambda^2 + k_3 \mu)(\alpha \beta \gamma \delta + \alpha \beta \delta \lambda + \alpha \gamma \delta \lambda + \alpha \delta \lambda^2 + a \beta \delta \mu + a \delta \lambda \mu + a \gamma \eta \nu + a \eta \lambda \nu + a \eta \mu \nu),
\]

which, conveniently, is a product of a linear polynomial and two quadratics. Solving these three equations gives us the expressions for the eigenvalues given below.

\[
\begin{align*}
\lambda_1 &= -\delta \\
\lambda_2 &= -\frac{5k_3 - 5\alpha + \sqrt{(5k_3 + 5\alpha)^2 - k_3 \mu}}{2\alpha \delta} \\
\lambda_3 &= -\frac{5k_3 - 5\alpha - \sqrt{(5k_3 + 5\alpha)^2 - k_3 \mu}}{2\alpha \delta} \\
\lambda_4 &= \frac{-\Gamma + \sqrt{\Gamma^2 - 4\alpha \delta (\alpha \beta \gamma \delta - a \beta \delta \mu + a \beta \delta \mu + a \gamma \eta \nu + a \eta \lambda \nu + a \eta \mu \nu)}}{2\alpha \delta} \\
\lambda_5 &= \frac{-\Gamma - \sqrt{\Gamma^2 - 4\alpha \delta (\alpha \beta \gamma \delta - a \beta \delta \mu + a \beta \delta \mu + a \gamma \eta \nu + a \eta \lambda \nu + a \eta \mu \nu)}}{2\alpha \delta}
\end{align*}
\]

where \( \Gamma = \alpha \beta \delta + \alpha \gamma \delta + a \delta \mu + a \eta \nu \).

This allows us to formulate the following theorem:

**Theorem 1.** If \( R_0 = \frac{ak \beta \delta \mu}{(\beta \delta + \eta \nu)(\alpha \gamma + a \mu)} < 1 \), then the disease-free equilibrium, \([C^*, S^*, 0, 0, Z^*]\), is locally asymptotically stable.
**Proof.** Recall that all parameter values are nonnegative. Upon inspection, we can clearly see that all \( \lambda_i \) aside from \( \lambda_4 \) are either negative or will have real parts that are negative. In order to ensure that \( \lambda_4 \) has a negative real part we must require

\[
\alpha \beta \gamma \delta - ak \beta \delta \mu + a \beta \delta \mu + a \gamma \eta \nu + a \eta \mu \nu > 0,
\]

which leads to the result.

By substituting \([C, S, I, V] = [0, 0, 0, \eta/\delta] \) the model reaches the equilibrium \([0, 0, 0, \eta/\delta] \). We refer to this as the “death” equilibrium even though the immune cells are still present. The resulting Jacobian in this case is:

\[
J(0, 0, 0, 0, \eta/\delta) = \begin{pmatrix}
-k_3 & k_1 e^{\mu/100\alpha} & 0 & 0 & 0 \\
\frac{k_1 e^{\mu/100\alpha}}{k_3} & -\alpha & 0 & 0 & 0 \\
0 & 0 & -\beta - \frac{\eta \nu}{\delta} & 0 & 0 \\
0 & 0 & k \beta & -\gamma - 0 & 0 \\
0 & 0 & c + \frac{d \eta}{\delta} & 0 & -\delta.
\end{pmatrix}
\]

Here the resulting characteristic polynomial is:

\[
p(\lambda) = (\gamma + \lambda)(\delta + \lambda)(k_3 \alpha - k_3 \alpha e^{\mu/100\alpha} + k_3 \lambda + \alpha \lambda + \lambda^2) \left(-\beta - \lambda - \frac{\eta \nu}{\delta}\right).
\]

In this case also we can get expressions for eigenvalues, which are given below:

\[
\begin{align*}
\lambda_1 &= \frac{-k_3 - \alpha - \sqrt{(k_3 + \alpha)^2 + 4k_3 \alpha e^{\mu/100\alpha}}}{2} \\
\lambda_2 &= \frac{-k_3 - \alpha + \sqrt{(k_3 + \alpha)^2 + 4k_3 \alpha e^{\mu/100\alpha}}}{2} \\
\lambda_3 &= -\gamma \\
\lambda_4 &= -\delta \\
\lambda_5 &= -\frac{\beta \delta + \eta \nu}{\delta}
\end{align*}
\]  

Since \( \lambda_2 > 0 \) for all sets of positive parameters, we see that this equilibrium is always unstable. This is in line with the biology since dengue infection is rarely fatal. We have also seen an interior persistence equilibrium in numerical simulations where \( R_0 > 1 \).

### 4 Parameter Values and Simulations

In this section we provide numerical simulations of different treatment techniques. We were able to find all parameters in the model in literature \([10, 12]\) except the parameters \( k_1 \) and \( k_2 \). The parameter \( k_1 \) was calculated as mentioned in Section 2. To calculate this parameter \( k_2 \), we used the data provided in \([8]\), which gave monocyte counts in individuals infected with dengue. It was found that the individuals had a mean monocyte count of \( 660 \times 10^6/L \) with a standard deviation...
of 370. We used MATLAB’S “randn” function to generate 200 random data sets (each with 15 points) from a normal distribution with that same mean and standard deviation. The 15 points were used as data values measured every 12 hours during a one week period. For each data set, we used MATLAB’S “fminsearch” function to find the value of $k_2$ that minimized the function

$$f(k_2) = \sum_{n=1}^{15} (S(t_n) - s_n)^2,$$

where $t_0 = 0, t_1 = 1/2, t_2 = 1, \ldots$. After these 200 values of $k_2$ were found, we calculated their mean. We repeated this process many times and consistently got values in the upper-fifties, and we finally settled on the value $k_2 = 58.6$.

The rest of the parameter values are given in Table 1. We should also mention that this parameter set and all of the modified ones that follow result in $R_0 < 1$.

### 4.1 Treatment Scenarios

There are several theoretical approaches to treating the disease. For example, the illness might be less severe if the death rate of the viruses, $\beta$, were increased. Another approach might be to reduce the infection rate, $a$, so that fewer monocytes are infected. We will present this case first. We held all other parameters fixed and examined theoretical treatments that could reduce $a$ by 10 %, 25 %, and then 50 %. We then plotted the results along with the results from no treatment at all. The results are presented in Figure 1.

We see that while this type of treatment appears successful in reducing the viral and infected cell loads, it also prolongs the infection. We can now compare this scenario with the previously mentioned increase in $\beta$. In this simulation we increase the value of $\beta$ by 10 %, 25 %, and then 50 % and then plotted the results along with the case without treatment. The results are shown in Figure 2.

We see here that the model has nearly no sensitivity to the parameter $\beta$ and is predicting that treatments of this type are likely not worth exploring. Another approach might be to increase the death rate, $\gamma$, of free viruses. In Figure 3 we present the resulting plots from increasing $\gamma$ by 10 %, 25 %, and 50 %.
Figure 1: Infected cell and virus populations measured with varying $a$ values.

Figure 2: Infected cell and virus populations measured using varying $\beta$ values.
We see again that the model reacts very little to adjusting this parameter suggesting that increasing the free viral death rate is not a useful strategy. Another logical approach is the reduce the number if new viruses produced by an infected monocyte, $k$. In Figure 4 we present plots resulting from reducing $k$ by 10\%, 25\%, and 50\%.

We see the most drastic reaction in this case. By reducing $k$ by 50\% we see a more than 50\% reduction in the viral load. Therefore we conclude that treatments that reduce the number of new viruses produced by infected monocytes are the most efficient.
5 Conclusion

In this paper we have presented a new model for within-host dengue infection. We were able to find the net reproductive rate $R_0$ and thus obtain a stability result for the disease-free equilibrium. We have also shown that the death equilibrium is always unstable, in line with the fact the dengue infection is rarely fatal. Further, through simulations we have seen that the most effective theoretical treatment strategy is to reduce the number of new viruses produced by each infected monocyte.

Acknowledgements: This work was partially funded by the Marquette Fellowship at Loyola University New Orleans.

References


