Effect of incubation period of virus for the mathematical model of dengue disease

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Abstract:- The transmission of dengue disease is studied through mathematical model. This disease is transmitted between two people by biting of infectious Aedes aegypti mosquitoes. After infected with dengue virus, both human and vector populations become to be infected class before to be infectious class. Only infectious class can transmit dengue virus to susceptible class. The original \textbf{SIR} (Susceptible-Infected-Recovered) model can not describe the difference between infected and infectious classes. Thus the modified model is considered in this study. This model is formulated by separating the human population into susceptible, infected, infectious and recovered classes. The vector population is divided into susceptible, infected and infectious classes. The dynamical analysis method is used for analyzing this modified model. We confirm these results by using numerical results. We found that the infected class reduces the periods of oscillations in the population.

Key-Words: dengue disease, mathematical model, incubation period, basic reproductive number, equilibrium points, local stability.

1 Introduction
Dengue disease is found in tropical and subtropical regions around the world. This disease is transmitted to the human by biting of the infectious mosquitoes. The primary vector for this disease is Aedes aegypti mosquito. DEN-1, DEN-2, DEN-3 and DEN-4 are four serotypes of dengue virus. Infection with one of these four serotypes apparently produces permanent immunity to it, but only temporary cross immunity to the others. The symptom of this disease is classified into three forms: Dengue Fever (DF), Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS). The symptoms of DF patients are headaches, bone or joint and muscular pains, rash and leukopenia. A more virulent manifestation of this disease is Dengue hemorrhagic fever (DHF). DHF is characterized by four major clinical manifestations: high fever, hemorrhagic phenomena, often with hepatomegaly and, in severe cases, signs of circulatory failure. These patients may develop hypovolemic shock resulting from the plasma leakage, this is called dengue shock syndrome (DSS) and can be fatal [1].

This disease has become a major public health concern in recent year. Two-fifth of the world’s population is now at risk from dengue disease. DF was recognized for at least several hundred years since Benjamin Rush from Philadelphia first described it as “breakbone fever” in 1780. This disease is occurring as an epidemic in tropical and subtropical regions of Asia and Africa, transmission has been geographically increasing during the past few decades. Successive introduction and circulation of all four serotypes into Central, South America and the Caribbean have occurred since 1977. DHF epidemic was first reported in the Caribbean in 1981. Evolving transmission patterns are probably the results of a combination of changing human demographics, expanding vector populations, and alterations in viral virulence. Dengue disease can be found wherever the mosquito vector is introduced. One hundred million cases of this disease are reported yearly by WHO, making it one of the most important viral diseases in the world. Cases seen in the US are imported from the Caribbean region, the others arriving from South America, Africa or
Asia. Transmission of dengue virus is often seasonal, with rates increasing during hot, humid months. The vector *Aedes aegypti* breeds in peridomestic fresh water as might be stored in natural and artificial containers in and around human dwellings (e.g., old tires, flowerpots, water storage containers). This day-biting species is most active in the early morning and late afternoon. The transmission cycle of dengue virus by the mosquito *Aedes aegypti* begins with a dengue infectious person. Most of these people will have virus circulating in the blood (viremia) that lasts for about four to seven days [2]. During this viremic period, an uninfected female *Aedes aegypti* mosquito bites the person and ingests blood that contains dengue virus. Although there is some evidence of transovarial transmission of dengue virus in *Aedes aegypti*, but usually mosquitoes are only infected by biting a viremic person. Then, within the mosquito, the viruses replicate during an extrinsic incubation period of eight to twelve days. After an extrinsic incubation period of the mosquito, its salivary glands become infected and the virus is transmitted when the infectious mosquito bites and injects the salivary fluid into the wound of the human. The mosquito can bite a susceptible person and could transmit the virus to him or her, as well as to every other susceptible person, it bites for the rest of its lifetime. The virus then replicates in the person during an intrinsic incubation period [3-6].

Esteva and Vargas [7] did not include the intrinsic and extrinsic incubation periods of dengue virus in human and vector populations. Their model considered for human and vector populations. The human population is separated into susceptible, infectious and recovered classes. The vector population is divided into susceptible and infectious classes. In our study, length of time during the circulation of dengue virus in the blood of human and vector populations are considered. The infected human and infected vector classes are introduced into our model. There are the difference between the infected and infectious classes for both human and vector populations. The infected class can not transmit dengue virus until it is introduced into infectious class. The comparisons between two models are considered in this study.

## 2 Mathematical model

The mathematical model is formulated by considering the human and vector populations. The length of incubation for dengue virus is involved in this study. The variables in our model are defined as follows:

- $S'(t)$ denotes the number of susceptible human population at time $t$,
- $X'(t)$ denotes the number of infected human population at time $t$,
- $I'(t)$ denotes the number of infectious human population at time $t$,
- $R'(t)$ denotes the number of recovered human population at time $t$,
- $S'_v(t)$ denotes the number of susceptible vector population at time $t$,
- $X'_v(t)$ denotes the number of infected vector population at time $t$,
- $I'_v(t)$ denotes the number of infectious vector population at time $t$.

The rate of change for each population can be described by the following equations:

\[
\frac{dS'}{dt} = \delta N_T - \lambda_h S'T'_v - \theta_h S'
\]

\[
\frac{dX'}{dt} = \lambda_h S'T'_v - (\tau_h + \theta_h)X'
\]

\[
\frac{dI'}{dt} = \tau_h X' - (r + \theta_h)I'
\]

\[
\frac{dR'}{dt} = rI' - \theta_h R'
\]

\[
\frac{dS'_v}{dt} = H - \lambda_v I'S'_v - \theta_v S'_v
\]

\[
\frac{dX'_v}{dt} = \lambda_v I'S'_v - (\tau_v + \theta_v)X'_v
\]

\[
\frac{dI'_v}{dt} = \tau_v X'_v - \theta_v I'_v
\]

with the conditions

$N_T = S + X + I + R$ and $N_V = S'_v + X'_v + I'_v$

where

$N_T$ is the total human population,

$N_V$ is the total vector population,

$\delta$ is the birth rate of the human population,

$\lambda_h$ is the infectious rate of dengue virus from vector to human population,
\( \tau_h \) is the rate at which the infected human becomes to be infectious human,
\( \lambda_v \) is the infectious rate of dengue virus from human to vector population,
\( \theta_h \) is the death rate of human population,
\( r \) is the recovery rate of human population,
\( H \) is the constant recruitment rate of the vector population,
\( \tau_v \) is the rate at which the infected vector becomes to be infectious vector population,
\( \theta_v \) is the death rate of vector population.

The total human and vector populations are constant, thus the rate of change for both populations equal to zero. These give
\[
0 = \frac{d}{dt} N_T = 0 \quad \text{and} \quad 0 = \frac{d}{dt} N_V = 0 . \tag{2}
\]
From (2), we obtain \( \delta = \theta_h \) for human population and \( N_V = \frac{H}{\theta_v} \) for vector population.

We normalize (1) by letting
\[
S^* = \frac{S}{N_T}, \quad X^* = \frac{X}{N_T}, \quad I^* = \frac{I}{N_T}, \quad R^* = \frac{R}{N_T}, \quad S_v^* = \frac{S_v}{N_v}, \quad X_v^* = \frac{X_v}{N_v}, \quad I_v^* = \frac{I_v}{N_v}
\]
then the reduced equations become
\[
\frac{d}{dt} S^* = \theta_h \frac{S^*}{N_T} \lambda_v \frac{I^*}{N_T} - \theta_h S^* + \lambda_v S \frac{I^*}{N_T} - (r + \theta_h) S^* \\
\frac{d}{dt} X^* = \frac{\lambda_v}{\theta_v} S^* \lambda_v \frac{I^*}{N_T} - (r + \theta_h) X^* \\
\frac{d}{dt} I^* = \tau_h \frac{X^*}{N_T} (1 - \frac{X^*}{N_T} - I^*) - (r + \theta_h) X^* \\
\frac{d}{dt} I_v^* = \tau_v \frac{X_v^*}{N_v} - \theta_v I_v^*
\]
with the conditions
\( S^* + X^* + I^* + R^* = 1 \) and \( S_v^* + X_v^* + I_v^* = 1 \).

3 Analysis of the mathematical Model

3.1 Analytical results

We find equilibrium points by setting right hand side of all equations in (3) equal to zero, then two equilibrium points are

i) disease free equilibrium point:
\[
\bar{U}_0 = (1, 0, 0, 0, 0, 0) \tag{4}
\]
ii) endemic equilibrium point:
\[
\bar{U}_1 = (S, X, I, X_v, I_v) \tag{5}
\]
where
\[
S = \frac{(\tau_v + \theta_v)(\tau_h \eta_v \theta_h + AB \theta_h^2 \theta_v)}{\tau_h \eta_v \theta_h (\tau_v + \theta_v) + \tau_v \eta_h}, \quad
X = \frac{AB \theta_h^2 \theta_v (\tau_v + \theta_v) (D_0 - 1) - AB \theta_h^2 \theta_v}{\tau_h \eta_v \theta_h (\tau_v + \theta_v) + \tau_v \eta_h}, \quad
I = \frac{\theta_h \theta_v (\tau_v + \theta_v) (D_0 - 1) - \eta_v \theta_v \theta_h (\tau_v + \theta_v) + \tau_v \eta_h}{\eta_v \theta_v \theta_h (\tau_v + \theta_v) + \tau_v \eta_h}, \quad
X_v = \frac{AB \theta_h^2 \theta_v (D_0 - 1)}{\eta_v \theta_v \theta_h + AB \theta_h^2 \theta_v}, \quad
I_v = \frac{AB \theta_h^3 \theta_v (D_0 - 1)}{\eta_v \theta_v \theta_h + AB \theta_h^2 \theta_v}
\]
and \( \eta_h = \lambda_h (H / \theta_h), \eta_v = \lambda_v N_T, \quad A = \frac{\theta_h + r}{\theta_h} \).

For the equilibrium point \( \bar{U}_0 \), the characteristic equation is
\[
(\psi + \theta_h)(\psi^4 + c_3 \psi^3 + c_2 \psi^2 + c_1 \psi + c_0) = 0 \tag{7}
\]
where
\[
c_3 = \tau_v + (A + B) \theta_h + 2 \theta_v, \quad c_2 = AB \theta_h^2 + 2(A + B) \theta_h \theta_v + \theta_v^2 + \tau_v (A + B) \theta_h + \theta_v, \quad c_1 = \theta_h (\tau_v (AB \theta_h + (A + B) \theta_v) + \theta_v (2AB \theta_h + (A + B) \theta_v)) \quad c_0 = AB \theta_h^2 \theta_v (1 - (D_0)(\tau_v + \theta_v)) \cdot \tag{8}
\]
There are five eigenvalues corresponding to (7). We denote these five eigenvalues by \( \psi_1, \psi_2, \psi_3, \psi_4 \) and \( \psi_5 \). \( \psi_1 \) has negative real part. Other four eigenvalues are obtained by solving
\[ y^4 + c_2 y^3 + c_2 y^2 + c_4 y + c_0 = 0. \]

These four eigenvalues have negative real parts if they satisfy Routh-Hurwitz criteria [8]

\[ c_3 > 0 \quad (9) \]
\[ c_1 > 0 \quad (10) \]
\[ c_0 > 0 \quad (11) \]
\[ c_1 c_2 c_3 > c_1^2 + c_3 c_0. \quad (12) \]

It can be easily seen that coefficients \( c_3, c_1 \) and \( c_0 \) satisfy (9), (10) and (11) when \( D_0 < 1 \). We evaluate

\[
c_1 c_2 c_3 - (c_1^2 + c_3 c_0) = (A + B)\theta_h (A\theta_h + \theta_v)(\tau_v + A\theta_h + \theta_v) + (B\theta_h + \theta_v)(\tau_v + B\theta_h + \theta_v) + \tau_v \eta_h \eta_v (\tau_v + (A + B) \theta_h + 2 \theta_v)^2.
\]

\[ c_1 c_2 c_3 - (c_1^2 + c_3 c_0) \]

is always positive. Therefore the disease free equilibrium point is locally stable for \( D_0 < 1 \).

For the equilibrium point \( U_1 \), the characteristic equation is

\[ y^5 + a_1 y^4 + a_2 y^3 + a_3 y^2 + a_4 y + a_5 = 0 \quad (13) \]

where

\[
a_1 = \tau_v + (1 + A + B) \theta_h + 2 \theta_v + (D_0 - 1) \theta_h \theta_v (\tau_v + \theta_v) + (D_0 - 1) AB \theta_h^2 \theta_v \frac{\tau_v \eta_h \theta_v + 2 \theta_v}{\tau_v \eta_h \eta_v \theta_v + 2 \theta_v}
\]

\[ a_2 = \theta_h^2 \left( (1 + A + B) + \frac{(D_0 - 1) \theta_h \theta_v (\tau_v + \theta_v)}{\tau_v \eta_h \theta_v + 2 \theta_v} \right) \]

\[ a_3 = \theta_h \left( \frac{(D_0 - 1) \theta_h \theta_v (\tau_v + \theta_v)}{\tau_v \eta_h \theta_v + 2 \theta_v} + \frac{(D_0 - 1) AB \theta_h^2 \theta_v}{\tau_v \eta_h \theta_v + 2 \theta_v} \right) \]

\[ a_4 = \theta_h \left( (A + B + AB + (A + B)(D_0 - 1) \theta_h \theta_v (\tau_v + \theta_v)) \right) \]

\[ a_5 = \theta_h \theta_v (\tau_v + \theta_v) \left( AB \theta_h (A + B) \theta_v \right) \]

Five eigenvalues correspond to (13). These five eigenvalues are represented by \( \psi_1, \psi_2, \psi_3, \psi_4 \) and \( \psi_5 \). These eigenvalues
have negative real parts if they satisfy Routh-Hurwitz criteria [8]:
\[ a_i > 0; \quad \text{for } i = 1, 2, 3, 4, 5 \]  
(14)
\[ a_1a_2a_3 - a_3^2 - a_1^2a_4 > 0 \]  
(15)
\[ (a_1a_4 - a_5)(a_1a_2a_3 - a_3^2 - a_1^2a_4) \]
\[ - a_5(a_1a_2 - a_3)^2 - a_1a_5^2 > 0 \]  
(16)
It can be seen that the coefficients \( a_i \) for \( i = 1, 2, 3, 4, 5 \) satisfy (14) for \( D_0 > 1 \). Using program MATHEMATICA, (Wolfram Research, Champaign, IL) to evaluate conditions (15) and (16), we found that these two conditions are satisfied for \( D_0 > 1 \) also.

Thus the endemic equilibrium point is locally stable for \( D_0 > 1 \).

3.2 Numerical results
In this section, the numerical results for the two models are compared. The incubation period of dengue virus is introduced into the first model. The second model is the SIR model [7]. This model is obtained from system model (1) by setting \( h_\tau \) and \( v_\tau \) to zero. The infected and infectious classes are included into one class. In the first model, we are interested in the incubation period of dengue virus in human and vector populations. After each susceptible person is bitten by infectious vector, that person can not transmit dengue virus immediately. We call this person in this period as an infected human. Intrinsic incubation period of dengue virus in human is about 5 days [2]. When a susceptible vector bites an infectious person, it will be an infected vector before it becomes to be an infectious vector. Extrinsic incubation period of dengue virus in vector population is about 10 days [2]. The susceptible person is the person who has no immunity and not infected. The recovered person is the person who has immunity after be infected with dengue virus. The parameters are determined by real life observations. \( \theta_h = 0.0000391 \) corresponds to the real life expectancy of 70 years for human. \( \lambda_h \) and \( \lambda_v \) are arbitrarily chosen. \( \tau_h = 1/5 \) corresponds to the extrinsic incubation period of 5 days. \( \tau_v = 1/10 \) corresponds to the intrinsic incubation period of 10 days. \( r = 1/14 \) corresponds to the length of 14 days for illness. \( \theta_v = 1/14 \) corresponds to the mean life of 14 days for vector population. H is the constant recruitment rate of vector population; this parameter is arbitrarily chosen. The values of parameters for the second model are determined same as the first model. But \( \tau_h \) and \( \tau_v \) are not appeared in the second model [7].

1a) 
Fig.1. Time series of susceptible human.
1a) The solutions for the first model, values of parameters are \( \theta_h = 0.0000391, \lambda_h = 0.00005, \tau_h = 0.2, \)
\( r = 0.0714, N_T = 5,000, \lambda_v = 0.00008, \)
\( \theta_v = 0.0714, \tau_v = 0.1, H = 1,000. \)
1b) The solutions for the second model, values of parameters are same as 1a).

2a) 
Fig.2. Time series of infectious human.
2a) The solutions for the first model, values of parameters are \( \theta_h = 0.0000391, \lambda_h = 0.00005, \tau_h = 0.2, \)
\( r = 0.0714, N_T = 5,000, \lambda_v = 0.00008, \)
\( \theta_v = 0.0714, \tau_v = 0.1, H = 1,000. \)
2b) The solutions for the second model, values of parameters are same as 2a).

3a) 
Fig.3. Time series of infectious vector.
3a) The solutions for the first model, values of parameters are \( \theta_h = 0.0000391, \lambda_h = 0.00005, \tau_h = 0.2, \)
\( r = 0.0714, N_T = 5,000, \lambda_v = 0.00008, \)
\( \theta_v = 0.0714, \tau_v = 0.1, H = 1,000. \)
3b) The solutions for the second model, values of parameters are same as 3a).
4a) The solutions for the first model, values of parameters are
\[ \theta_h = 0.0000391, \lambda_h = 0.00005, \tau_h = 0.2, \]
\[ r = 0.0714, N_I = 5,000, \lambda_v = 0.00008, \]
\[ \theta_v = 0.0714, \tau_v = 0.1, H = 1,000. \]

4b) The solutions for the second model, values of parameters are same as 4a).

4 Discussion and conclusion

The number of secondary infections, which can result from one primary infection, is defined from the square root of the basic reproduction number (D0):
\[ D_0 = \frac{r\theta_v\eta_h\eta_v}{(r + \theta_h)(\tau_h + \theta_h)\theta_v(\tau_v + \theta_v)} \]  (17)

This disease will be capable of invading and establishing itself when this number is more than one. If this number is less than one, then every successive generation will diminish in size until its number approaches zero. Esteva and Vargas [7] did not include the infected human and infected vector populations into their model. They evaluated the basic reproduction number (E0):
\[ E_0 = \frac{\eta_h\eta_v}{(r + \theta_h)\theta_v} \]  (18)

It can be seen that the terms \( \frac{\tau_h}{(r + \theta_h)} \) and \( \frac{\tau_v}{(\tau_v + \theta_v)} \) are canceled. This due to intrinsic and extrinsic incubation periods of dengue virus are not considered in their model.

The numerical comparisons of solutions for the two models are shown in fig.1 to fig.4. The parameters are similar for two models. The time developments of the susceptible human, infectious human and infectious vector for two models are shown in fig.1 to fig.3. In fig. 4, we plot the proportion of infectious human versus the proportion of susceptible human for both models. The equilibrium point is the endemic state which is the stable spiral state. After we substitute parameters in (17) and (18), the basic reproduction numbers are obtained. The basic reproduction number for the first model equals to 31.98. The basic reproduction number for the second model equals to 54.85.

As we see, the periods of fluctuations for the proportion in each class are shorter in the absence of the incubation period of dengue virus. The spiraling in is more severe in the absence of the incubation period of dengue virus. The incubation period of dengue virus appears to calm down the fluctuations.

References: