Dengue disease model with the effect of extrinsic incubation period

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Abstract: Seasonality has been observed in the long-term behavior of the incidence of dengue disease as well as of many other infectious arboviral diseases. It has been hypothesized that these effects are due to the seasonal climate changes which intern induces a seasonal variation in the incubation period of the virus while it is in the mosquito. Applying standard dynamic analysis to a modified Susceptible Infected-Recovered (SIR) model that includes an annual variation in the length of the extrinsic incubation period (EIP), we found that dynamic behavior of the endemic state changes as the influence of the seasonal variation of the EIP becomes stronger. As the influence is further increased, the trajectory when it leaves the chaotic region exhibits sustained oscillations.

Key-Words: transmission model, seasonality, dengue disease, SIR model, extrinsic incubation period and chaotic behavior.

1 Introduction

Dengue disease is the arboviral disease which can be found in tropical region of the world. There are three forms such that Dengue fever (DF), Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS). DF is marked by an onset of sudden high fever, pain behind the eyes and in the muscles and joints. DHF is characterized by fever during the initial phase and other symptoms like headache, pain in the eye, joint pain and muscle pain, followed by signs of bleeding such as petechiae, nosebleed and gum bleed. If there is blood in the stools or blood in the vomit and accompanied by shock, this is called DSS and is often fatal. Dengue disease is transmitted to the human by biting of infected Aedes Aegypti. The mosquito obtains the virus by biting an infectious human. There are four serotypes of dengue virus, denoted as DEN-1, DEN-2, DEN-3 and DEN-4. For the arboviral diseases, climatic factors are very important since the development of the mosquito and of the virus is affected by these factors. For instance, the temperature must be above 20° C, the threshold temperature below which the virus can not reproduce in the mosquitoes [1]. Many people have also noted that the mosquito population increases drastically with the onset of heavy rainfalls. It has even been suggested that El Nino or La Nina may be responsible [2] for the variation of some diseases. Dowell [3] points out that the seasonal variations should be distinguished from periodic large epidemics as observed every two years for measles.

In this paper, we are interested in the transmission of dengue disease taking into account the seasonal change in the length of the extrinsic incubation period (EIP) of the dengue virus when it is in the mosquito. EIP becomes longer as the mean daily temperature is lowered. The temperature dependence of the incubation period $\tau$ versus $T$ looks like a hyperbola with $\tau = 3$ days at $T = 32^\circ C$ and $\tau = 14$ days at $T = 20^\circ C$ [4].

The infection by any dengue virus in the human begins when an infectious mosquito bites a human and injects a large number of the dengue virus of one serotype into the blood of the human. There, the virus causes either a
symptomatic or an asymptomatic infection in the person. The latter type of infections is more common than the former infection. The illness resulting from the former infection last for about one to two weeks. During this time, the infected person is immune to further infection by any of the four dengue virus serotypes. After the person recovers, he keeps his immunity to the infecting serotype but loses the temporary immunity he had to the other serotypes. If a susceptible mosquito bites a person while he has a high count of virus in the blood, the susceptible mosquito can become infected. It takes from three to fourteen days (the incubation period) for the virus to develop inside the mosquito before it becomes infectious, i.e., able to transmit the disease to a human by its bite.

Whether the epidemic can sustain itself and become endemic depends on a number called the basic reproduction number. It is the number of secondary infections, which can results from primary infection. Calling the number \( R_0 \), the disease will be self sustaining if \( R_0 > 1 \) and will die out if \( R_0 \leq 1 \). This number can be determined as follows: If \( b \) is the biting rate (per day) of the mosquito and \( I_v \) is the number of infected mosquitoes, then \( b I_v \) is the total number of bites made by the infected mosquitoes per day. \( \frac{S}{N_T + c} \) is the fraction of these bites which are delivered to susceptible humans (with \( S' \) being the number of susceptible humans, \( c \), number of other animals which the mosquitoes can bite and \( N_T \), the total number of humans). Multiplying the product of the two terms by \( \beta_h \), the probability that the virus survives in the human, we have the number of bites by all mosquitoes that will lead to infectious in the mosquitoes. Dividing this by the total number of mosquitoes, we get for the probability that a bite by a mosquito on an infected human result in the mosquito becomes infected is \( b \beta_v IS' \). Multiplying the product of these two probabilities by the mean life times of the humans and mosquitoes, we get the total number of secondary infections arising from a single primary infection, or basic reproduction number

\[
R_0 = \frac{b^2 \beta_h \beta_v m (1 - a)}{\mu_v (\mu_h + r)}
\]

### 2 Mathematical model

To represent the transmission process, we divide the human populations into three classes, susceptible, infected and recovered human. The vector populations are separated into two classes, susceptible and infected vector populations. Susceptible person is the person who both not immune and not infected. Infected person is the person who is transmitted dengue virus from the infected vector. Recovered person is the infected person after the viremia stage until after they recover from dengue virus infection.

Let

- \( S(t) \) denotes the number of susceptible human population at time \( t \),
- \( I'(t) \) denotes the number of infected human population at time \( t \),
- \( R'(t) \) denotes the number of recovered human population at time \( t \),
S′(t) denotes the number of susceptible vector population at time t, 
I′(t) denotes the number of infected vector population at time t.
The time rate of change in the number of subjects in each class is equal to the number of subjects entering into the group per unit time minus the number leaving the group per unit time. This gives
\[
\frac{dS}{dt} = \lambda N_T - b \frac{h}{N_T} (1-a) S I - \mu_h S,
\]
\[
\frac{dI}{dt} = b \frac{h}{N_T} (1-a) S I - (\mu_h + r) I, \tag{2}
\]
\[
\frac{dR}{dt} = r I - \mu_h R.
\]

We note that the susceptible humans become infected only if they are bitten by an infectious mosquito. \((1-a) I_v\) is the number of infectious mosquitoes. For the vector population, we have
\[
\frac{dS_v}{dt} = A - b \beta_v S_v I_v - \mu_v S_v, \tag{3}
\]
\[
\frac{dI_v}{dt} = b \beta_v S_v I_v - \mu_v I_v.
\]
with the conditions
\[
N_T = S + I + R \quad \text{and} \quad N_v = S_v + I_v \tag{4}
\]
where
\(N_T\) is the total number of the human population,
\(\lambda\) is the birth rate of the human population,
\(b\) is the biting rate of the vector population,
\(\beta_h\) is the transmission probability of dengue virus from the vector population to the human population,
\(\beta_v\) is the transmission probability of dengue virus from the human population to the vector population,
\(a\) is the percentage of the infected vector population which are not infectious,
\(\mu_h\) is the death rate of the human population,
\(r\) is the recover rate of the human population,
\(A\) is the constant recruitment rate of the vector population,
\(\mu_v\) is the death rate of the vector population.

We assume that the total numbers of human and vector populations are constant. Thus the rates of change for the total human and vector populations are equal to zero. This gives \(\lambda = \mu_h\) for the human population. The total number of vector is \(N_v = \Lambda / \mu_v\). We now normalize (2) and (3) by letting
\[
S = \frac{S'}{N_T}, I = \frac{I'}{N_T}, R = \frac{R'}{N_T}, S_v = \frac{S_v'}{N_v}, I_v = \frac{I_v'}{N_v}.
\]
This gives
\[
\frac{dS}{dt} = \lambda - \gamma_h S I_v - \mu_h S,
\]
\[
\frac{dI}{dt} = \gamma_h S I_v - (\mu_h + r) I, \tag{5}
\]
\[
\frac{dI_v}{dt} = \gamma_v (1-I_v) I - \mu_v I_v,
\]
where
\[
\gamma_v = b \beta_v \quad \text{and} \quad \gamma_h = b \beta_h (1-a)
\]
with \(m = (A / \mu_v) / N_T\) \tag{6}
with the two conditions
\[
S + I + R = 1 \quad \text{and} \quad S_v + I_v = 1. \tag{7}
\]

3 Analysis of the mathematical model

3.1 Analytical results
The equilibrium points are found by setting the right hand side of (5) equal to zero. We obtain
1) The disease free equilibrium point,
\(E_0 = (1,0,0)\) and
2) The endemic disease equilibrium point,
\(E_1 = (S^*, I^*, I_v^*)\) where
\[
S^* = \frac{\beta + M}{\beta + MR_0}, \tag{8}
\]
\[
I^* = \frac{R_0 - 1}{\beta + MR_0}, \tag{9}
\]
\[
I_v^* = \frac{\beta (R_0 - 1)}{R_0 (\beta + M)}, \tag{10}
\]
where
\[
\beta = \frac{b \beta_v}{\mu_v}, \quad M = \frac{\mu_h + r}{\mu_h}. \tag{11}
\]
The local stability of an equilibrium point is determined from the Jacobian matrix of the right hand side of (5) evaluated at the equilibrium point. If all eigenvalues (obtained by diagonalizing the Jacobian matrix) have negative real parts then the equilibrium point is local stability. Diagonalizing the Jacobian for the endemic equilibrium point, we obtain the characteristic equation
\[
\lambda^3 + a_2 \lambda^2 + a_1 \lambda + a_0 = 0 \tag{12}
\]
where
\[
a_2 = \mu_h \left( \frac{\beta + MR_0}{\beta + M} \right) + \mu_h M + \mu_v R_0 \left( \frac{\beta + M}{\beta + MR_0} \right),
\]
\[
a_1 = \mu_h^2 M \left( \frac{\beta + MR_0}{\beta + M} \right) + \mu_h \mu_v R_0 + (R_0 - 1) \left( \frac{\mu_h \beta}{\beta + MR_0} \right),
\]
\[
a_0 = \mu_v^2 \mu_h^2 M (R_0 - 1). \tag{13}
\]
It can be seen that the coefficients \(a_2, a_1\) and \(a_0\) satisfy the Routh-Hurwitz criteria for local stability [5]
\[
a_2 > 0, a_1 > 0 \quad \text{and} \quad a_2a_1 > a_0 \tag{14}
\]
when \(R_0 > 1\).

Therefore the endemic equilibrium point is local stability for \(R_0 > 1\) where \(R_0 = \frac{b^2 \mu_h \mu_v (1-a)}{\mu_v (\mu_h + r)}\).

### 3.2 Numerical results

Since we are interested in the transmission of diseases, we should only be interested in whether a person is infectious or not and is immune or not, not whether he is sick. The susceptible class is made up of people who have no immunity and are not infectious. A person infected with the dengue virus is only infectious during the viremia period, which lasts around three days. After that, the person remains sick for one or two weeks. Once the person becomes well, he enters into the recovery class with lifelong immunity to the virus. While the person is infected with the virus, he also has immunity to further infection by a new virus. Accordingly, a recovered person is the same as an infected person after the viremia period. Since the viremia period lasts three days [6], the recovery rate should be equal to \(1/3\) per day and not the inverse of the length of the illness.

The values of most of the other parameters are determined by the real life observations. They are \(\mu_h = 0.0000456\) per day, corresponding to a life expectancy of 60 years; \(\mu_v = 0.071\) per day, corresponding to a mosquito mean life of 14 days; \(b = 0.33\), one bite providing enough blood meal for three days; \(\beta_h = 0.5\) and \(\beta_v = 0.75\), which were chosen arbitrarily. The ratio \(m\) can be adjusted to give a desired value of \(R_0\). Setting \(m\) to be 2 and ignoring the effect of the time delay (EIP), we find that \(R_0 = 3.50\). The equilibrium point would be the endemic equilibrium point \((0.286, 0.0000838, 0.000293)\) and according to the conditions established in the previous section, it would be a stable spiral node. Looking at figure 1a, we see that the trajectory in the S-I phase space is spiraling into the equilibrium point. In Fig 1b, we find that the time evolution of infected human population shows a damped oscillation with a period of 8 years approaching the equilibrium point. If we adjust the parameters (i.e., change \(m\) to 10) so that \(R_0 = 17.50\), the period of oscillation is reduced to 2.72 years. We have plotted on figure 2, the time evolution of the infected human population when the new set of values is used.

**Fig.1** (1a) Spiral Trajectory in the Susceptible-Infected plane. Using the numerical values given in the text, the trajectory spirals into the equilibrium point \((S^*, I^*) = (0.286, 0.0000838)\) since the values of the parameters satisfy the Routh-Hurwitz criterions.

(1b) Time Evolution of the infected human population. The period of oscillation is about 8 years.

**Fig.2** Time evolution of the infected human population for a new set of values for the parameters. The change in time evolution of the infected human population when \(R_0 = 17.5\). The period of oscillation is reduced to 2.72 years.
In general, small $R_0$'s result in long periods while large $R_0$'s result in short periods. A similar trend was seen in a study of the transmission of *Plasmodium falciparum* based on a SEIS model of transmission [7]. In that study, the period of the damped oscillation predicted by the model dropped from about 40 years to about 20 years when the set of parameter values which yielded a value $R_0$ equal 1.3 was changed to the set of values which yielded a value of 3.34. For our model to generate oscillation of one-year period, the value of $R_0$ would have to be much greater than the values observed in nature. Next section, we will show by including a seasonal variation in one of the probability factors, both the annual and multiple year cycles can be predicted.

### 3.3 Seasonality in the incidence of dengue disease

It was suggested long time ago, [8] that the variation in the extrinsic incubation period (EIP) caused by changes in the (lowest daily) temperature changes was the cause of the seasonality in the transmission of dengue disease. In this study, the EIP enters into the model through the dependence of $\alpha$ (the fraction of the infected mosquitoes existing in the EIP) on $\tau$. The fraction is given by

$$ a = \int_0^\tau e^{-\mu_v t} dt $n$$

$$ a = \frac{1 - e^{-\mu_v \tau}}{\mu_v} \tag{15} $$

where $\tau$ is the length of incubation period (day) of dengue virus in mosquitoes. Substituting this into the probability $\beta_h' = \beta_h (1-a)$ and then expanding the exponential, we get

$$ \beta_h' = \beta_h \left( 1 - \frac{1 - e^{-\mu_v \tau}}{\mu_v} \right) $$

$$ \beta_h' = \beta_h \left( \frac{\mu_v \tau + 1 + \mu_v \tau}{2!} + \frac{\mu_v^3 \tau^3}{3!} + \cdots \right) $$

$$ \beta_h' = \beta_h \left( 1 + \frac{\mu_v \tau}{2!} + \frac{\mu_v^3 \tau^3}{3!} + \cdots \right) $$

As we have already point out, the dependence of $\beta_h$ on $T$ appears because the dependence of the latent period depends on $T$. Though the dependence looks like a hyperbola, with $\tau = 13$ days at $T = 24^\circ C$ and $\tau = 25$ days at $T = 18^\circ C$, we have modeled the variation as a sinusoidal variation such that

$$ \beta_h' = \beta_h (1 + \delta \sin \omega t) $$

where $\delta$ is a measure of the influence of the seasonality on the transmission process.

Depending on the values of $\delta$ and the other parameters, the basic reproduction number could remain above $R_0 = 1$ throughout the year or it could drop below 1 during part of the year, resulting in some complicated behaviors. To see what could happen, we have plotted on figure 3, a bifurcation plot using $\delta$ as an index parameter. We see in figure 3, the first period doubling bifurcation at $\delta = 0.24$, the second at 0.62, the third at 0.77. At $\delta = 0.8$, a chaotic band appears. As $\delta$ is further increased, a non-chaotic interval appears at $\delta = 0.88$ and enters into another chaotic band as $\delta$ is increased to 0.92. We have changed some values, which were used to get the curves in figure 1. The changed values are $m = 11$, $\mu_v = 1/17$, $\beta_v = 1.0$ and $\beta_h = 1.0$. These and the other values used yield a $R_0 = 62$. In figure 4, we plot the time evolution of the infected human population after a long passage of time. We observe that the chaotic behavior occur as the time is passed.

![Fig. 3 Bifurcation diagram showing the Maximum value of I for the range of values of the index parameter $\delta$. The values of the parameters are given in the text. We see a series of period doubling bifurcation occurring at $\delta = 0.24, 0.62$ and 0.77. When $\delta$ reaches 0.80, a bifurcation into a chaotic band occurs. A non-chaotic band emerges at $\delta = 0.88$ and a new chaotic band appears as $\delta$ is increased to 0.92.](image-url)
Fig. 4 Long time incidence rate where a seasonal variation in the EIP occurs. The values of the parameters are given in the text. The value of the index parameter $\delta$ is set at 0.90, a value putting $I_{\text{max}}$ in the non-chaotic band emerging from the first chaotic band.

4 Discussion and conclusion
The generation of chaotic behavior by a seasonally forcing term should not be surprising. In addition to Ferguson et al. [9] study on measles, Olsen et al., [10] have also noted the possibility of oscillations and chaos in six childhood diseases in Copenhagen, Denmark. Recently, Gakkhar and Naji [11] have studied the effects of seasonality on a prey-predator model where in the absence of the seasonality, the system has a globally stable limit cycle. They detected an abundance of steady state chaotic solutions. Their results support the conjecture that seasons can give rise to complex population dynamics. In a later study, [12] they considered the cases where the seasonality appears in two places in their model. They obtained extremely rich bifurcation diagrams, which showed long periodic regions emerging from chaotic bands as various parameters in their predator-dependent functional response term in a Lotka-Volterra like model of a predator-prey system. In present study, the seasonality appears in one place.

References: