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EFFECT OF TIME DELAY ON THE TRANSMISSION OF DENGUE FEVER

[1]I-Ming Tang, [2]Klot Patanarapelert
[1]Department of Physics, Faculty of Science, Mahidol University, Bangkok 10400, Thailand
[2] Department of Mathematics, Faculty of Science, Silpakorn University, Nakhon Pathom, Thailand
e-mail: [1]scimt@mahidol.ac.th

Abstract. *The effect of a time delay on the transmission on dengue fever is studied. The time delay is due to the presence of an incubation period during which the virus replicates enough in the mosquito so that the viruses can be transmitted by the mosquito to a human. The conditions for the existence of a Hopf bifurcation to limit cycle behavior are established. A theorem for determining whether for a given set of parameter values which satisfies the mathematical conditions, the system will actually undergo a transition from a stable state into a limit cycle state is established. It is found that for a set of realistic values of the parameters in the model, a Hopf bifurcation will not occur even when it is mathematically possible. For a set of unrealistic values of some of the parameters, it is shown that a Hopf bifurcation can occur. Numerical solutions using this set of values show the trajectory of two of the variables making a transition from a spiraling orbit to a limit cycle orbit.*

1 Introduction

This paper is concerned with the transmission of diseases among humans. These diseases fall in three categories: I. Those transmitted directly from one human to another without the need of a third party. II. Those transmitted from one person to other through a third party, called a vector. III. Zoonotic diseases are those which are transmitted from an animal to a human. Within this category, the animal-to-human can be direct (III.a) or indirect (III.b), i.e., through a third party. Common examples of diseases belong-in to category I are SARS, HIV/AID, common flu, measles, TB, small pox, etc. Examples of category II are malaria and dengue fever. Among sub-category III.a, the examples are rabies and chicken flu while among the sub-category III.b are Japanese encephalitis and West Nile Fever.

Insights into the behavior of systems can often be achieved through a mathematical modeling of the system. The models are usually expressed as a set of differential equations obtained by noting that the time rate change of the number of members of any population group is equal to the numbers entering minus the numbers leaving. The models are based on separating the population into different groups. Then each group is then divided into susceptible members (S), infected members (I) and recovered (R). The infected members may be sometimes divided in two groups; exposed (E), exposed to the disease but who are not infectious and infected members (I) who are infectious, i.e., they can transmit the disease. Depending on the disease, the recovered individuals may revert back to the susceptible.

Mathematical modeling has undergone a renaissance in recent years. This has occurred in part to the availability of very powerful computers which can numerically simulate the solutions a model no matter how complicated the models must be in order to take into account all the different population groups which play a role in the transmission process. For instance, the model introduced by Barth-Jones and Longini [1] to simulate the progress of HIV/AID over a 40 year period contains about 48 population groups. The model being used to develop a public health strategy to contain a possible H5N1 pandemic contains 8 population groups based on age and their risk conditions. The need for this arises from the realization by mathematicians that many factors in the transmission of diseases are age dependent and sex dependent. Medical doctors and epidemiologist have long recognized this.

In this paper, we are interested in the effects of a time delay caused by an incubation period in the virus development in the mosquitoes on the transmission of dengue fever. Dengue fever (DF) is an illness, which is characterized by a moderately high fever, extreme pain and stiffness in the joints, a rash and a reduction in the white blood cells [2]. These symptoms are caused by the toxins produced by one of the four serotypes of a virus belonging to the genus Flavirus, in the family Flavicidae. In many cases, the illness is asymptomatic and an infection can only be determined through serologic tests. A second infection by different strain of this virus can result in a more virulent form of the disease, dengue hemorrhagic fever (DHF). From its first appearance in the Philippines in 1953, DHF has become the most important arthropod-borne viral diseases of human's [3]. It has

been estimated that there are between 50 and 100 million cases of dengue fever (DF) a year, over 250,000 cases of dengue haemorrhagic fever (DHF) with approximately 10,000 infant deaths due to the latter form of this disease.

2 Mathematical model of dengue fever transmission

To formulate a model for dengue fever transmission, one needs to know what the transmission cycle of this disease is. The infection in the human begins when an infectious mosquito bites a human and injects a large number of dengue viruses of one strain into the blood of the human. There, the virus develops and causes either a symptomatic or asymptomatic infection in the person. The illness resulting from the infection lasts for about one to two weeks. During this time, the infected person is immune to further infection by all of the four dengue virus strains. After the person recovers, he keeps his immunity to the infecting strain but losses the temporary immunity (after three or so months) he had to the other strains. To simply matters, we have assumed in our model there is only one strain present. If a susceptible mosquito bites a person while he has a high count of virus in his blood, the virus could enter into the mosquito and mosquito is then said to be infected. It then takes from 3 to 14 days (the incubation period) for the virus to develop inside the mosquito before the mosquito is able to transmit the disease to a human by a subsequent bite.

To represent the transmission process, we divide the human population into three classes, susceptible, infectious and recovered (S', I' and R') and the mosquito population into two classes, susceptible and infectious, S'_v and I'_v. The time rate of change in the number of subjects in each class is equal to the number of subjects entering into the group minus the number leaving the group. This gives for the different human population classes

$$\frac{dS'(t)}{dt} = \lambda N_T - \frac{b\beta_h}{N+c} S'(t) I_v(t) - \mu_h S'(t) \quad , \tag{1a}$$

$$\frac{dI'(t)}{dt} = \frac{b\beta_h}{N_T+c} S'(t) I'_v(t) - (\mu_h + r) I'(t) \tag{1b}$$

and

$$\frac{dR'(t)}{dt} = rI'(t) - \mu_h R'(t) \quad . \tag{1c}$$

The time rate of change of the number of susceptible mosquitoes S'_v is

$$\frac{dS'_v(t)}{dt} = A - \frac{b\beta_v}{N_T+m} S'_v(t) I'(t) - \mu_v S'_v(t) \quad . \tag{1d}$$

In the above, N_T is the total host population; A, the recruitment rate of female mosquitoes; λ, the human birth rate; μ_h (μ_v), the death rate of the humans (mosquitoes); β_h (β_v), the probability that a bite by an infected mosquito (human) on a susceptible human (mosquito) will result in a new infection; r, the rate at which the infected human recovers; b, the biting rate of the mosquito and c is the number of other animals the mosquitoes can fed on. The derivation of the contact term is given in ref. 9.

Since we are interested in the time rate of change of the **infectious** mosquitoes at time t and since it takes τ number of days for the infected mosquitoes to become infectious, we should be interested in the number of susceptible mosquitoes who bit an infected human at the time $t - \tau$. not at the time t. Between the times t and $t - \tau$, a portion of these infected mosquitoes would have died. Taking into account all of these additional considerations, we get

$$\frac{dI'_v(t)}{dt} = \frac{b\beta_v}{N_T+c} S'_v(t-\tau) I'(t-\tau) e^{-\mu_v \tau} - \mu_v I'_v(t) \, . \tag{1e}$$

In this approach, the presence of an exposed class is taken care of by including a time delay and the inclusion of the exponential factor, $\exp\{-\mu_v\tau\}$. If we assume that the total human and mosquito population remains constant,

we have $\lambda = \mu_h$ and $N_V = A/\mu_v$. Dividing the human classes by the total human population and the mosquito classes by the total mosquito populations, we get the densities for each class. We also have $S + I + R = 1$ and $S_v + I_v = 1$ where the absence of the prime denotes a density. Because of these two constraints, only three equations are needed to define the model which is described by three variables only, e.g.

$$\frac{dS}{dt} = \mu_h - \gamma_h S I_V - \mu_h S, \tag{2a}$$

$$\frac{dI}{dt} = \gamma_h S I_v - (\mu_h + r) I \tag{2b}$$

and

$$\frac{dI_V(t)}{dt} = \gamma_V S_V(t-\tau) I(t) e^{-\mu_V \tau} - \mu_V I_V(t) \tag{2c}$$

where $\gamma_h = b\beta_h m$, $\gamma_v = b\beta_v$ and where m is the ratio between the total number of mosquitoes and total number of humans. In eqn. (2c), we have replaced $I(t-\tau)$ by $I(t)$ since the density of infectious humans is not expected to vary much over the period τ which is much less then the life time of a human.

The equilibrium states are obtained by setting the RHS of eqns. (2a) to (2c) to zero. Doing this, we get two equilibrium states, the disease free state, $E_o = (0, 1, 0)$ and the endemic equilibrium state, $E_1 = (I_v^*, S^*, I^*)$ where

$$I_v^* = \frac{I^* \dfrac{\gamma_v}{\mu_v}}{I^* \dfrac{\gamma_v}{\mu_v} e^{-\mu_V \tau} + 1} e^{-\mu_V \tau}, \tag{3a}$$

$$S^* = \frac{I^* \dfrac{\gamma_v}{\mu_v} e^{-\mu_V \tau} + 1}{1 + \left[\dfrac{\gamma_v}{\mu_v} + \dfrac{\mu_h + r}{\mu_h} R_o \right] I^* e^{-\mu_V \tau}} \tag{3b}$$

and

$$I^* = \frac{R_o e^{-\mu_V \tau} - 1}{\left[\dfrac{\gamma_v}{\mu_v} + \dfrac{\beta\mu_h + r}{\beta\mu_h} R_o \right] e^{-\alpha\mu_V \tau}}, \tag{3c}$$

where

$$R_o = \frac{b^2 \beta_v \beta_h m}{\mu_v (\mu_h + r)} \tag{4}$$

is the basic reproduction number in the absence of any time delay. As we see, S^*, I^* and I_v^* are functions of the time delay, τ. Since $I^* \geq 0$, we need

$$R_o \exp\{-\mu_v \tau\} \geq 1 \tag{5}$$

For the equilibrium point E_1 to exist, τ must lie in the range $0 \leq \tau \leq \tau^* = \{\ln R_o\}/\mu_v$. The factor $R = R_o \exp\{-\mu_v \tau\}$ is called the basic reproduction number and it is the number of secondary infections which could result from a single primary infection. When it is less than one, the disease-free state is the equilibrium state; if it is greater one, then the endemic state is the equilibrium state.

3 Bifurcation conditions for the endemic equilibrium state

The stability of the equilibrium point is established by studying the properties of the eigenvalues of the Jacobian of the systems of equations Eqns. (2a) to (2c) and see whether the eigenvalues met the conditions of the Hopf Bifurcation Theorem. Diagonalizing the Jacobian matrix, we get

$$P(\lambda,\tau) + Q(\lambda,\tau)e^{-\mu_v \tau} = 0 \tag{6}$$

where

$$P(\lambda,\tau) = \lambda^3 + a_o(\tau)\lambda^2 + b_o(\tau)\lambda + a_2(\tau) \tag{7a}$$

and

$$Q(\lambda,\tau) = a_1(\tau)\lambda^2 + b_1(\tau)\lambda - a_3(\tau) \tag{7b}$$

with

$$a_o(\tau) = 2\mu_h + \mu_v + r + \gamma_h I_v^* \quad , \tag{8a}$$

$$a_1(\tau) = \gamma_v I^* \exp\{-\mu_v \tau\} \quad , \tag{8b}$$

$$a_2(\tau) = (\mu_h + \gamma_h I_v^*)(\mu_v(\mu_h + r) - \gamma_v\gamma_h S^* \exp\{-\mu_v\tau\}) + \gamma_v\gamma_h^2 S^* I_v^* \exp\{-\mu_v\tau\} \, , \tag{8c}$$

$$a_3(\tau) = -\exp\{-\mu_v\tau\}((\mu_h + \gamma_h I_v^*)(\mu_h + r)\gamma_v I^* + \mu_h\gamma_h\gamma_v S^* I_v^*) \quad , \tag{8d}$$

$$b_o(\tau) = (\mu_h + \gamma_h I_v^*)\exp\{-\mu_v\tau\}(\mu_h + \mu_v + r) + \mu_v(\mu_h + r) - \gamma_v\gamma_h S^* \exp\{-\mu_v\tau\}, \tag{8e}$$

and

$$b_1(\tau) = ((2\mu_h + r + \gamma_h I_v^*)\gamma_v I^* + \gamma_v\gamma_h S^* I_v^*)\exp\{-\mu_v\tau\} \quad . \tag{8f}$$

Whether the equilibrium point of the given system undergoes a Hopf bifurcation to a limit cycle behavior is determined by whether the eigenvalues of the Jacobian for the system of equations satisfy the two theorems. The usual method to find the value of the critical point is to find the value of τ for which the real part of the eigenvalue $u(\tau) = 0$ (condition i. of Hopf's Theorem). Since we do not have an explicit expression for $u(\tau)$, we instead use the method developed by Tam and by Ruan and Wei.

To show the stability of the equilibrium state, we first look at the case where $\tau = 0$. For this case, the characteristic equation for the Jacobian becomes

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0 \tag{9}$$

where

$$A = a_o(\tau = 0) + a_1(\tau = 0) \, ,$$

$$B = b_o(\tau = 0) + b_1(\tau = 0)$$

and

$$C = a_2(\tau = 0) - a_3(\tau = 0) \tag{10}$$

where the definitions of the a's and b's are given by eqns. (8a) to (8f). According the Routh-Hurwitz theorem [10], all the roots of eqn. (9) will have a negative real part if A > 0, AB > C and AB > C. If these conditions are met, then $u(\tau = 0) < 0$ and the equilibrium states, eqns. (3a) to (3c), are stable when $\tau = 0$. By continuity $u(\tau) < 0$ for sufficiently small τ. Therefore the steady state would remain stable for values of τ less than some positive value of τ_0. Suppose $u(\tau) = 0$ for $\tau > \tau_0$, then $u(\tau) < 0$ for $\tau \in [0, \tau_0)$ and the equilibrium states are stable for time delays less than τ_0.

To determine what the critical value τ_c is and then whether $u(\tau)$ and $v(\tau)$, the imaginary part of the eigenvalues, satisfy the conditions of Hopf's Theorem, we substituting $\lambda = u + iv$ into eqn. (6), and then separating the resulting equation into its real and imaginary parts. We get

$$\begin{aligned} 3u(\tau)v(\tau)^2 - u(\tau)^3 - a_o(\tau)(u(\tau)^2 - v(\tau)^2) - b_o(\tau)u(\tau) - a_2(\tau) = \\ [\{a_1(\tau)\,(u(\tau)^2 - v(\tau)^2) + b_1(\tau)u(\tau) - a_3(\tau)\}\cos(v(\tau)\tau) + \\ \{2a_1(\tau)u(\tau)v(\tau) + b_1(\tau)v(\tau)\}\sin(v(\tau)\tau)]e^{-u\tau} \end{aligned} \tag{11}$$

and

$$\begin{aligned} v(\tau)^3 - 3u(\tau)^2v(\tau) - 2a_o(\tau)u(\tau)v(\tau) - b_o(\tau)v(\tau) = \\ [\{2a_1(\tau)u(\tau)v(\tau) + b_1(\tau)v(\tau)\}\cos(v(\tau)\tau) - \\ \{a_1(\tau)\,(u(\tau)^2 - v(\tau)^2) + b_1(\tau)u(\tau) - a_3(\tau)\}\sin(v(\tau)\tau)]e^{-u\tau} \end{aligned} \tag{12}$$

It should be noted that u and v are real numbers or functions. The critical point, τ_c is the point at which $u(\tau_c) = 0$, i.e., $\tau_c = \tau_0$.

To determine whether there is a τ_c, we set $\tau = \tau_c$ and set $u(\tau) = u(\tau_c) = 0$. Denoting $v(\tau_c)$ as v*, eqns (11) and (12) become

$$a_o(\tau_c)v^{*2} - a_2(\tau_c) = b_1(\tau_c)v^*\sin(v^*\tau_c) - (a_1(\tau_c)v^{*2} + a_3(\tau_c))\cos(v^*\tau_c) \tag{13a}$$

$$v^{*3} - b_o(\tau_c)v^* = b_1(\tau_c)v^*\cos(v^*\tau_c) + (a_1(\tau_c)v^{*2} + a_3(\tau_c))\sin(v^*\tau_c) \tag{13b}$$

Squaring both equations and adding them together, we get

$$f(\omega) = \omega^3 + c_1(\tau_c)\omega^2 + c_2(\tau_c)\omega + c_3(\tau_c) = 0 \tag{14}$$

where $\omega = v^{*2}$ and

$$c_1(\tau_c) = a_o(\tau_c)^2 - a_1(\tau_c)^2 - 2b_o(\tau_c)^2 \quad , \tag{15a}$$

$$c_2(\tau_c) = b_o(\tau_c)^2 - 2a_o(\tau_c)a_2(\tau_c) - b_1(\tau_c)^2 - 2a_1(\tau_c)a_3(\tau_c) \tag{15b}$$

and

$$c_3(\tau_c) = a_2(\tau_c)^2 - a_3(\tau_c)^2 \quad . \tag{15c}$$

It should be noted that the coefficients $c_1(\tau_c)$, $c_2(\tau_c)$ and $c_3(\tau_c)$ are real.

The problem is reduced to determining whether eqn. (14) has at least one positive real root. The necessity of root being positive and real comes from the fact the imaginary part of the eigenvalues is the square root of ω, i.e., $\mathrm{Im}\{\lambda\} = v^* = \sqrt{\omega}$. If ω were negative or complex, then $\sqrt{\omega}$ would be imaginary or complex, which would be a contradiction since $\mathrm{Im}\{\lambda\}$ has to be a real number. To determine under what conditions eqn. (12) has at least one positive real solution, we establish the following theorem:

Theorem 1. Let α and β be the two turning points of $f(\omega)$, i.e., the roots of $df(\omega)/d\omega = 3\omega^2 + 2c_1(\tau)\omega + c_2(\tau) = 0$ and let $\Delta = f(\alpha)f(\beta)$.

If either

i. $_3(\tau) < 0$ or

ii. $c_2(\tau) < 0$ and $\Delta(\tau) < 0$, for all $\tau \in [0, (\ln R_o)/\mu_v)$,

then a Hopf bifurcation can arise as τ passes through τ_c where τ_c is the critical time delay that satisfies conditions i, ii, and iii of Theorem 2.

The fact that c_2, c_3 and Δ are functions of τ leads to some new consequences. To see why, we note that it is possible to find a value of τ (τ^{**}) in the interval [0, τ^*) for which either $c_2(\tau^{**}) = 0$ or $c_3(\tau^{**}) = 0$ or $\Delta(\tau^{**}) = 0$. One of these τ^{**} will divide the interval into two sub intervals, [0, τ^{**}) and [τ^{**}, τ^*) in which different conditions can hold. We can then ask, "What are the conditions that we can impose on the two regions which will affect the stability or instability of the endemic state?" This question has been touched on by Xiao and Chen [5]. The answer is given by the following theorem.

Theorem 2 Suppose the interval $[0, (\ln R_o)/\mu_v)$ is divided into two sub intervals by τ^{**}, [0, τ^{**}) and [τ^{**}, τ^*). If in the interval [0, τ^{**}), only conditions i. or ii. (at least one positive real root of eqn. (12) exist) of the *Lemma* is satisfied and in the interval [τ^{**}, τ^*), only condition iii. (there is no positive real root) is satisfied, then there is no critical value of τ in the interval [0, τ^*) at which a bifurcation occurs.

4 Numerical results and conclusions

Our bifurcation analysis begins with picking the values of the parameters in our model. The endemic state will be a stable spiral node if the basic reproduction number $R > 1$ (defined by eqn. (6)). Its actual value can be determined from observations. If T_2 is the observed doubling time during the initial stage of the epidemic, then $R = \{(\ln T_2)/\mu_v + 1\}$. Based on the measured doubling times in the growth of infected people during the 1990-91 dengue fever endemic in Sao Paulo State, Marques *et al.*, [10] determined the basic reproduction numbers for twelve cities in the state to be between 1.6 and 2.5. The values of the parameters picked should be such that if we substitute the values into the expression for the basic reproduction number, eqn. (6), we should obtain a value of R of the same magnitude as the values observed in nature, i.e., in the range $1 < R < 10$.

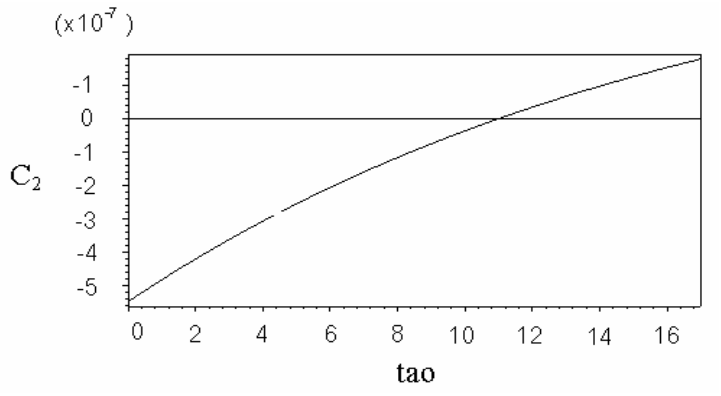
The values of some of the parameters in the model are dictated by reality, e.g. the death rates of the humans and mosquitoes, the duration of the infectious period in the human, etc. As we have pointed out, a person infected with the dengue virus is only infectious during the viremia period, which lasts around three days. The recovery rate should be equal to 1/3 per day and not the inverse of the length of the illness. The values of the parameters determined by nature are $\mu_h = 0.000039$ per day, corresponding to a life expectancy of 70 years; $\mu_v = 0.059$ per day, corresponding to a mosquito mean life of 17 days and b = 1. While one full bite provides enough blood meal for three days, the eating habits of the *Aedes aegypti* and *Ae. albopictus* mosquitoes are such that the meal can be interrupted by the slightest movement of the blood provider. Therefore, it takes more than one bite per three days to get a full meal. We have assumed it takes three bites to get a full meal, giving b = 1. The values of the other parameters must be such their substitution into eqn. (5) yields a R in the desired range. Since we will be treating τ as the bifurcation parameter, we first look at the case of $\tau = 0$. The basic reproduction number would now be given by eqn. (5d), R_o. Using the following values of β_h, β_v and m, 0.5, 0.75 and 0.1, respectively, we get a R = 1.91.

We will now determine whether the system can undergo a Hopf bifurcation to a limit cycle as τ is increased. As we just showed, the endemic state is stable when $\tau = 0$. *Theorem 2* will be used to establish whether a critical value τ_c (the point at which the stable endemic state loses its stability and trajectory becomes a limit cycle) exists in the interval [0, 11.02). The number 11.02 is just the value of $(\ln R_o)/\mu_v$. In Figure 1, we have plotted the values of $c_2(\tau)$, $c_3(\tau)$ and $\Delta(\tau)$ as a function of τ, using the same numerical values for the other parameters. As we see from Figure 1, $c_3(\tau) \geq 0$ for $\tau \in [0, 11.02)$, $c_2(\tau) < 0$ for $\tau \in [0, 11.014)$ and $\Delta(\tau) < 0$ for $\tau \in [0, 4.48)$ and [11.018, 11.02. Looking at Figure 2, we can identify τ^{**} as being 4.48. This will given us two sub intervals $I_1 = [0.4.48)$ and $I_2 = [4.48, 11.02)$. In I_1, $c_2 < 0$ and $\Delta < 0$ while in I_2, condition iii. of the *Lemma* holds, i.e., no positive real root of eqn. (15) exist [Note that for $\tau \in [4.48, 11.018)$, $\Delta > 0$ and $c_2 < 0$ and for $\tau \in [11.018, 11.02)$, $\Delta < 0$ and $c_2 > 0$]. Therefore

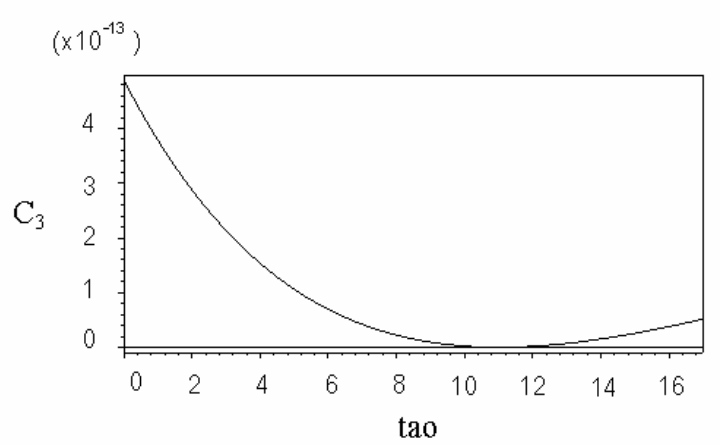
by *Theorem* 2, there is no critical delay time in the interval $[0, (\ln R_o)/\mu_v)$ when the above values of the parameters are used.

5 Discussion

The annual cycle seen in the incidence of dengue fever (dengue Hemorrhagic fever) in Bangkok, Thailand between 1966 and 1998 by Hay *et al.*,[13] is not indicative of a limit cycle. We have shown that the appearance of a limit cycle in the transmission cycle of dengue fever is highly unlikely. The annual cycles arise from the seasonal variations, which occur in many of the parameters in the model.



1a.



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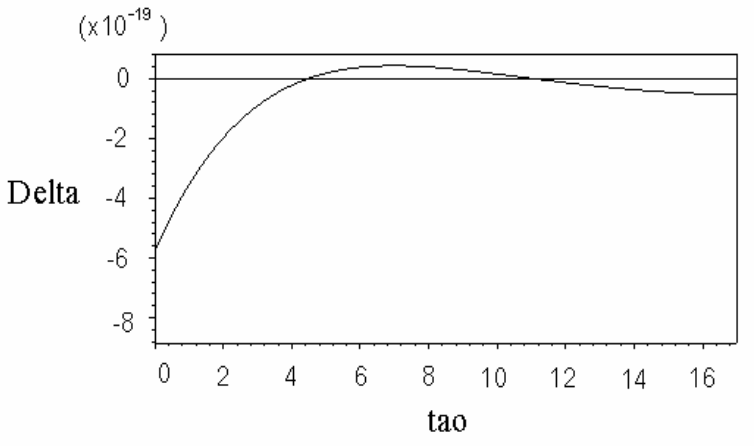

1c.

Dependence of $c_2(\tau)$, $c_3(\tau)$ and $\Delta(\tau)$ on the time delay τ using realistic values of the parameters. The values used are $\{\beta_h = 0.5, \beta_v = 0.75, \mu_h = 0.000039, \mu_v = 0.059, r = 0.33, b = 1$ and $m = 0.1\}$. The incubation period τ is varied between 0 and 11.02 which is the value of $(\ln 1.91)/\mu_v$. As is seen, $c_2(\tau)$ is negative for $\tau < 11.01$, $c_3(\tau)$ is positive over the entire range of τ and $\Delta(\tau)$ is negative in the range [0, 4.48), positive in [4.48, 11. 018) and negative again in [11.018, 11.02). The point τ^* divides the entire interval into two sub intervals, I_1 and I_2. In I_1, the conditions for a positive real root of eqn. (12) while in I_2, the conditions for eqn. (12) to have no positive real roots hold.

Dowell [14] has classified the causes of these cycles into three groups: pathogen appearance and disappearance, environmental changes and host behavior changes. Statistical significant correlation's between epidemic cycles and cycles of temperature, humility, rains or winds have been found. Dowell has pointed out that the seasonal variations should be distinguished from the periodic behaviors, which would be intrinsic to the model. Hay *et al.,* also drew attention to this when they remarked that the focus of future research on mosquito borne diseases should be on combining the extrinsic (climate changes) determinants with the intrinsic determinants.

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