International Journal of Engineering, Mathematical and Physical Sciences
ISSN: 2517-9934
Vol:1, No:10, 2007

Effect of Time Delay on the Transmission of Dengue Fever

K. Patanarapelert and I.M. Tang

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 for the dengue virus to develop in the mosquito before the mosquito becomes infectious. The conditions for the existence of a Hopf bifurcation to limit cycle behavior are established. The conditions are different from the usual one and they are based on whether a particular third degree polynomial has positive real roots. A theorem for determining whether for a given set of parameter values, a critical delay time exist is given. It is found that for a set of realistic values of the parameters in the model, a Hopf bifurcation can not occur. For a set of unrealistic values of some of the parameters, it is shown that a Hopf bifurcation can occur. Numerical solutions using this last set show the trajectory of two of the variables making a transition from a spiraling orbit to a limit cycle orbit.

Keywords**—**Dengue fever transmission, time delay, Hopf bifurcation, limit cycle behavior

I. Introduction.

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 from physical laws, Newton's second law or from the basic principle that the time rate of change of the number of members in a category is equal to the numbers entering minus the numbers leaving. The last method is the main one used to obtain models for chemical and biochemical reactions. Mathematical modeling has undergone a renaissance in recent years. This has occurred because much of biology and medicine is now discussed in terms of molecular biology processes. The full force of mathematical modeling can now be applied to these processes.

In this paper, we are interested in the effects of a time delay caused by an incubation period in the virus development on the transmission of dengue fever. Dengue fever (DF) is an illness that is characterized by a moderately high fever, extreme pain in and stiffness in the joints, a rash and a reduction in the white blood cells [1]. 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 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 [2]. 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.

Time delays can play a very import role in the dynamics of real systems. Martin and Ruan [3] showed that a time delay in a generalized Gause-type predator-prey model could cause a stable equilibrium to become unstable. Khan and Greenhalgh [4] have studied the consequences of there being a time delay in the effects of vaccination on the spread of diseases in an epidemic. Xiao and Chen [5] have studied a predator-prey model and showed that a time delay can cause in their model, a transition from a stable equilibrium to an unstable one and then a transition back to a stable one. Other recent studies have been done by Ruan and Wei [6] and by Tam [7].

Most of the above studies have used the Hopf bifurcation method [8] to analysis their models. They did not, however, include all the effects of the time delay. By neglecting one term, they obtained equilibrium states, which do not depend on the time delay. In this paper, we included all the effects of the time delay and find that the equilibrium state does depend on the time delay, τ. In Section II, we introduce a model for the transmission of the disease, which takes into account a delay in the mosquito becoming infectious after it is infected with the virus. This delay leads to the factor $\exp\{-\mu_v\tau\}$ (μ_v being the death rate or inverse mean life of the mosquitoes) appearing in the equations describing the evolution of the mosquito populations. Since the mean life and the delay (incubation period) time are of the same magnitude, the product $\mu_v\tau$ does not approach zero and so the exponential factor can not be dropped, i.e. set to unity. We also obtain here the equilibrium states of the system and the conditions for the endemic state to be physically realizable. In Section III, we establish the conditions under which a Hopf bifurcation to a limit cycle behavior is possible. We perform a parameter space analysis in Section IV, and show that the conditions can not be met when realistic values of the

Manuscript received January 23, 2008.

Kot Patanarapelert was with the Department of Mathematics, Faculty of Science, Mahidol University. He is now with the [1]Department of Mathematics, Faculty of Science, Silpakorn University, Sunan Chandra Palace Campus, Nakhon Pathum 73000, Thailand

I-Ming Tang is with the Department of Physics, Faculty of Science, Mahidol University, Bangkok 10400, Thailand. (Corresponding author) Tel: 662 201 5758, email: scimt@mahidol.ac.th.

(biological) parameters are used. Using unrealistic values of the parameters however, we find that the conditions for bifurcation can be met. Solving the equations for these parameter values, we obtain trajectories in phase space which shows a stable spiral node for values of $\tau < \tau_c$ and a limit cycle when $\tau = \tau_c$ (τ_c being the critical delay at which the equilibrium state becomes unstable and bifurcates). Finally in Section V, we discuss some implications of our results.

II. Mathematical Model of Dengue Fever Transmission

II.a Mathematical Model.

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 last 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 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, virus could enter into the mosquito and mosquito is 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 its 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

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

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

and

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

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

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

and of the infected mosquitoes is

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

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 - τ. not at the time t. Between the times t and t - τ, a portion of these infected mosquitoes would have died. Taking into account all of these additional considerations, we get 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.

Adding Eqns. (1a) - (1c) together and Eqns. (1d) to (1e), we obtain

$$\frac{dN_T}{dt} = (\lambda - \mu_h) N_T \ \text{ where } N_T = S' + I' + R' \tag{2a}$$

and

$$\frac{dN_V}{dt} = A - \mu_V N_V \ \text{ where } N_V = S_V' + I_V' \tag{2b}$$

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 we take to be

$$\frac{dS}{dt} = \mu_h - \gamma_h S I_V - \mu_h S \ , \tag{3a}$$

$$\frac{dI}{dt} = \gamma_h S I_v - (\mu_h + r) I \tag{3b}$$

and

$$\frac{dI_V(t)}{dt} = \gamma_V S_V(t-\tau) I(t) e^{-\mu_V \tau} - \mu_V I_V(t) \tag{3c}$$

where

$$\gamma_V = b\beta_V \tag{4a}$$

and

$$\gamma_h = b\beta_h m \tag{4b}$$

with m being the ratio between the total number of mosquitoes and total number of humans and where we have set c = 0. In Eqn. (3c), we have replaced I(t-τ) 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.

II.b Equilibrium States and Their Stabilities.

The equilibrium states are obtained by setting the RHS of Eqns. (3a) to (3c) 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

$$I_v^* = \frac{I^*\frac{\gamma_v}{\mu_v}}{I^*\frac{\gamma_v}{\mu_v}e^{-\mu_v\tau}+1}e^{-\mu_v\tau} \quad , \tag{5a}$$

$$S^* = \frac{I^*\frac{\gamma_v}{\mu_v}e^{-\mu_v\tau}+1}{1+\left[\frac{\gamma_v}{\mu_v}+\frac{\mu_h+r}{\mu_h}R_o\right]I^*e^{-\mu_v\tau}} \tag{5b}$$

where

$$I^* = \frac{R_o e^{-\mu_v\tau}-1}{\left[\frac{\gamma_v}{\mu_v}+\frac{\beta\mu_h+r}{\beta\mu_h}R_o\right]e^{-\alpha\mu_v\tau}} \tag{5c}$$

with

$$R_o = \frac{b^2\beta_v\beta_h m}{\mu_v(\mu_h+r)} \tag{5d}$$

As we see, S*, I* and I_v* are functions of the delay time τ. This would not be true if we had dropped the exponential factor, $\exp\{-\mu_v\tau\}$. Since I* ≥ 0, we need

$$R_o \exp\{-\mu_v\tau\} \geq 1 \tag{6}$$

For the equilibrium point E_1 to exist, τ must lie in the range $0 \leq \tau \leq (\ln R_o)/\mu_v$. The factor $R = R_o \exp\{-\mu_v\tau\}$ is called the basic reproduction number and it is the number of secondary infections resulting from a 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.

III, Bifurcation Conditions for the Endemic Equilibrium State.

III.a Basic Theorems.

To establish the conditions for the stability of the endemic state, we introduce the following two theorems:

Theorem 1. The equilibrium point of Eqns. (3a) –(3c) is stable if and only if every characteristic root of the matrix **J** has a real part not greater than zero, and those with zero real part are zero. It is asymptotically stable if and only if every characteristic root of **J** has nega-tive real part.

Theorem 2. Let **x*** = **x***(a) be an equilibrium point of a system of first order differential equations given by

$$\frac{d\vec{x}}{dt} = F(\{\vec{x}\};a)$$

where F( ) is a column vector and let the Jacobian matrix at an equilibrium point be defined as

$$\mathbf{J}(a) = D_x F(x^*,a) = \frac{\partial F_i}{\partial x_j}(x^*,a) \quad i,j = 1,2,.,n \ ,$$

if **J**(a) has a pair of complex eigenvalues, λ(a) = u(a) ± iv(a) such that

i. $u(a_c) = 0$,

ii. $v(a_c) = v^* > 0$

iii. $\frac{du}{da}(a_c) \neq 0$

where a_c is called a critical value of the bifurca-ion parameter 'a', and no other eigenvalues with zero real part exist, the system undergoes a transition to a limit cycle about the point $(\mathbf{x}^*, a_c)$.

The proofs of these two theorems can be found in ref. [8].

III.b. Application to the Present System.

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 presence of a τ-dependence in the equations requires modifications of the usual conditions for a Hopf bifurcation. To see this, we diagonalizing the Jacobian and obtain the following characteristic equation

$$P(\lambda,\tau) + Q(\lambda,\tau)e^{-\mu_v\tau} = 0 \tag{8}$$

where

$$P(\lambda,\tau) = \lambda^3 + a_o(\tau)\lambda^2 + b_o(\tau)\lambda + a_2(\tau) \tag{9a}$$

and

$$Q(\lambda,\tau) = a_1(\tau)\lambda^2 + b_1(\tau)\lambda - a_3(\tau) \tag{9b}$$

with

$$a_o(\tau) = 2\mu_h + r + \gamma_h I_v^*, \tag{10a}$$

$$a_1(\tau) = \gamma_v I^* \exp\{-\mu_v\tau\} \ , \tag{10b}$$

$$a_2(\tau) = (\mu_h + \gamma_h I_v^*)(\mu_v(\mu_h + r)\gamma_v\gamma_h S^* \exp\{-\mu_v\tau\}) + \gamma_v\gamma_h^2 S^* I_v^* \exp\{-\mu_v\tau\} \quad , \tag{10c}$$

$$a_3(\tau) = -\exp\{-\mu_v\tau\}((\mu_h + \gamma_h I_v^*)(\mu_h + r)\gamma_v I^* + \mu_h\gamma_h\gamma_v S^* I_v^*) \ , \tag{10d}$$

$$b_o(\tau) = (\mu_h + \gamma_h I_v^*)\exp\{-\mu_v\tau\}(\mu_h + \mu_v + r) + \mu_v(\mu_h + r) - \gamma_v\gamma_h S^* \exp\{-\mu_v\tau\}, \tag{10e}$$

and

$$b_1(\tau) = ((2\mu_h + r + \gamma_h I_v^*)\gamma_v I^* + \gamma_v\gamma_h S^* I_v^*)\exp\{-\mu_v\tau\} \ . \tag{10f}$$

The characteristic equations obtained by Ruan and Wei [6] and by Klan and Greenhalgh [4] for their models are of form

$$\lambda^3 + a\lambda^2 + b\lambda + c = de^{-\lambda\tau} \quad , \tag{11a}$$

while the characteristic equation studied by Tam [7] has the form

$$\lambda^3 + a\lambda^2 + (b + ce^{-\lambda\tau})\lambda + d = fe^{-\lambda\tau} \tag{11b}$$

The constants (a, b, c, d, f) in Eqns. (9) and (10) are defined in the respective references. The important thing to note is that none of the constants depend on τ.

To determine the conditions for Hopf bifurcation, we apply the technique used in refs. [4] and [6]. Substituting λ = u + iv (where u and v are real numbers and may be functions of τ) into Eqn. (7) and separating the real and imaginary parts, we get

$$3u(\tau)v(\tau)^2 - u(\tau)^3 - a_o(\tau)(u(\tau)^2 - v(\tau)^2) - b_o(\tau)u(\tau) - a_2(\tau) = [\{a_1(\tau)(u(\tau)^2 - v(\tau)^2) + b_1(\tau)u(\tau) - a_3(\tau)\}\cos(v(\tau)\tau) + \{2a_1(\tau)u(\tau)v(\tau) + b_1(\tau)v(\tau)\}\sin(v(\tau)\tau)]e^{-u\tau} \quad (12)$$

and

$$v(\tau)^3 - 3u(\tau)^2v(\tau) - 2a_o(\tau)u(\tau)v(\tau) - b_o(\tau)v(\tau) = [\{2a_1(\tau)u(\tau)v(\tau)+) + b_1(\tau)v(\tau)\}\cos(v(\tau)\tau) - \{a_1(\tau)(u(\tau)^2 - v(\tau)^2) + b_1(\tau)u(\tau) - a_3(\tau)\}\sin(v(\tau)\tau)]e^{-u\tau} \quad . \quad (13)$$

We now set $\tau = \tau_c$. At this value of τ, $u(\tau_c) = 0$. Denoting $v(\tau_c)$ as v*, Eqns (12) and (13) become

$$a_o(\tau_c)v^{*2} - a_2(\tau_c) = b_1(\tau_c)v^*\sin(v^*\tau_c) - (a_1(\tau_c)v^{*2} + a_3(\tau_c))\cos(v^*\tau_c) \quad (14a)$$

$$v^{*3} - b_o(\tau_c)v^* = b_1(\tau_c)v^*\cos(v^*\tau_c) + (a_1(\tau_c)v^{*2} + a_3(\tau_c))\sin(v^*\tau_c) \quad (14b)$$

Squaring both equations and adding them together, we get

$$f(\omega) = \omega^3 + c_1(\tau_c)\omega^2 + c_2(\tau_c)\omega + c_3(\tau_c) = 0 \quad (15)$$

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

$$c_1(\tau_c) = a_o(\tau_c)^2 - a_1(\tau_c)^2 - 2b_o(\tau_c)^2 \quad , \quad (16a)$$

$$c_2(\tau_c) = b_o(\tau_c)^2 - 2a_o(\tau_c)a_2(\tau_c) - b_1(\tau_c)^2 - 2a_1(\tau_c)a_3(\tau_c) \quad (16b)$$

and

$$c_3(\tau_c) = a_2(\tau_c)^2 - a_3(\tau_c)^2 \quad (16c)$$

It should be noted that the coefficients $c_1(\tau_c)$, $c_2(\tau_c)$ and $c_3(\tau_c)$ are real. The value of the critical point τ_c is usually determined from the requirement that $u(\tau_c) = 0$. In the method used here, the critical point is determined from the requirement that at least one root of Eqn. (15) be real and positive, otherwise $v = \sqrt{\omega_o}$ (ω_o being the root of the equation) would be imaginary. The existence of an imaginary part of the eigenvalues depends on whether equation has a positive real root. We now state the conditions under which Eqn. (15) has a positive real root.

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

i. If $c_3(\tau) < 0$, then f(ω) has at least one positive real root.
ii. If $c_3(\tau) \geq 0$, $c_2(\tau) < 0$ and $\Delta < 0$, then f(ω) has positive simple roots.
iii. If $c_3(\tau) \geq 0$, the necessary conditions for f(ω) to have no positive real roots are either
   a. $c_1(\tau)^2 < 3\,c_2(\tau)$
   b. $c_1(\tau)^2 = 3\,c_2(\tau)$
   c. $c_1(\tau)^2 - 3\,c_2(\tau) > 0$ and $\Delta > 0$ or
   d. $c_1(\tau)^2 - 3\,c_2(\tau) > 0$ and $\Delta < 0$, $c_1(\tau) > 0$ and $c_2(\tau) > 0$.

Proof of the above *Lemma* is given in the Appendix I.

Finally, we have to show that $d\mathbf{u}(\tau=*)/d\tau \neq 0$. This is done by taking the total derivative of Eqns. (12) and (13) with respect to τ and then setting $\tau = \tau_c$. Doing this, we get

$$B\frac{du(\tau = \tau_c)}{d\tau} + C\frac{dv(\tau = \tau_c)}{d\tau} + D = 0 \quad (17)$$

and

$$-C\frac{du(\tau = \tau_c)}{d\tau} + B\frac{dv(\tau = \tau_c)}{d\tau} + E = 0 \quad (18)$$

with

$$B = (2a_1v^* - \tau_c b_1 v^*)\sin(v^*\tau_c\,\tau^*) + (b_1 + \tau^*(a_1v^{*2} + a_3))\cos(v^*\tau_c\,\tau^*) - 3v^{*2} + b_o \quad , \quad (19a)$$

$$C = (b_1 + \tau_c(a_1v^{*2} + a_3))\sin(v^*\tau_c) - (2a_1v^* - \tau_c b_1 v^*)\cos(v^*\tau_c) - 2a_o v^* \quad , \quad (19b)$$

$$D = ((a_1v^{*2} + a_3)v^* + b_1v^*)\sin(v^*\tau_c) + (b_1v^* - a_1'v^{*2} - a_3')\cos(v^*\tau_c) + a_2' - a_o'v^{*2} \quad (19c)$$

and

$$E = (a_1'v^{*2} + a_3' - b_1v^{*2})\sin(v^*\tau_c) + ((a_1v^{*2} + a_3)v^* + b_1'v^*)\cos(v^*\tau_c) + b_o'v^* \quad (19d)$$

where the prime denotes a derivative with respect of τ and a_o, a_1, etc and which are then evaluated at $\tau = \tau_c$. Applying Crammer's rule to Eqns. (17) and (18), we get

$$\frac{du(\tau = \tau_c)}{d\tau} = \frac{EC - BD}{B^2 + C^2} \quad (20)$$

where

$$EC - BD = v^{*2}\{3v^{*4} + 2(a_o^2 - a_1^2 - 2b_o)v^{*2} + (b_o^2 - b_1^2 - 2(a_oa_2 + a_1a_3))\} \quad . \quad (21)$$

For $du(\tau = \tau_c)/d\tau \neq 0$, $EC - BD = v^{*2}g(v^*) \neq 0$ and so

$$g(v^*) = 3v^{*4} + 2(a_o^2 - a_1^2 - 2b_o)v^{*2} + (b_o^2 - b_1^2 - 2(a_oa_2 + a_1a_3)) \neq 0. \quad (22)$$

Looking at the *Lemma*, we see that g(v*) is equal to $df(\omega)/d\omega$, evaluated at $\tau = \tau_c$. The roots of $df(\omega)/d\omega = g(\omega=v^*) = 0$ are the two turning points, α and β with $\tau = \tau_c$. Since one of the requirements we have established for the existence of imaginary part of the eigenvalue is $f(\alpha)f(\beta) < 0$, v* can not be either $\alpha(\tau_c)$ or $\beta(\tau_c)$, otherwise the product would be equal to

zero and not less than zero. Thus, EC - BD ≠ 0 and so for the model described by Eqns. (3a) – (3c), we have $d\mathbf{u}(\tau = \tau_c)/d\tau \neq 0$ provided a critical point exists in the interval of allowed τ.

All of the above discussion can be collected together to form a new theorem;

Theorem 3. Concerning the endemic state of *our system*, Eqns. (3a) – (3b), if either
i. $c_3(\tau) < 0$ 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*. *Theorem 3* differs from *Theorem 2* by the additional requirement that $\tau \in [0, (\ln R_o)/\mu_v)$. This condition insures that the endemic state is an allowed state, one where all the population densities are positive.

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 $[0, (\ln R_o)/\mu_v)$ 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*, $(\ln R_o)/\mu_v$) 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 4. Suppose the interval $[0, (\ln R_o)/\mu_v)$ is divided into two sub intervals by τ*, [0, τ*) and [τ*, $(\ln R_o)/\mu_v$). If in the interval [0, τ*), only conditions i. or ii. (at least one positive real root of Eqn. (15) exist) of the *Lemma* is satisfied and in the interval [τ*, $(\ln R_o)/\mu_v$), only condition iii. (there is no positive real root) is satisfied, then there is no critical value of τ in the interval $[0, (\ln R_o)/\mu_v)$ at which a bifurcation occurs.

The proof of this theorem is given in Appendix II. This *theorem* allows us to determine if a bifurcation is possible for a given set of parameter values.

IV. Numerical Results and Conclusions

IVa Realistic Parameter Values.

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 habbits 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 τ = 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 have numerically solved Eqns. (3a) to (3c) using the values of the parameters given. In Figure 1, we have plotted the trajectory of the solution in the I_v-I phase space and we indeed see a stable spiral node.

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 τ = 0. *Theorem 4* 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 2, 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 2, $c_3(\tau) \geq 0$ 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). Some of the conclusions drawn from Figure 2a. could also be obtained analytically. If we evaluate $c_2(\tau)$, $c_3(\tau)$ and $\Delta(\tau)$ at $\tau = (\ln R_o)/\mu_v$, we find

$$c_2(\tau = (\ln R_o)/\mu_v) = \mu_h^2 (\mu_h + \mu_v + r)^2 > 0 \quad ,$$

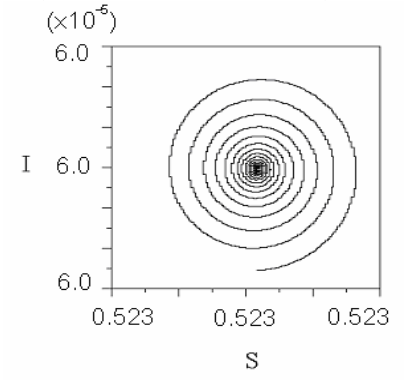
$$c_3(\tau = (\ln R_o)/\mu_v) = 0$$

and

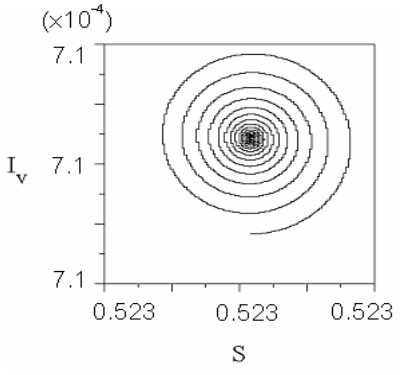
$$\Delta\left(\frac{\ln R_o}{\mu_v}\right) = \frac{-\mu_h^4 (2\mu_h + \mu_v + r)^2 (\mu_h + \mu_v + r)^4 (\mu_v + r)^2}{27} < 0\Delta$$

These are the same results we obtained by looking at Figure 2.

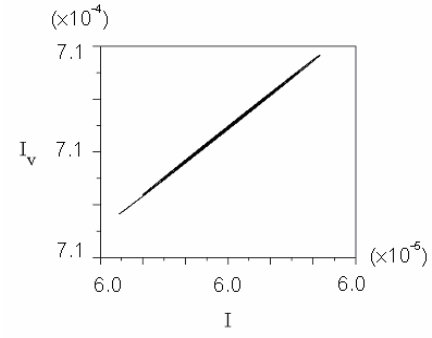
Looking at Figure 2., we can identify $\tau*$ as being 4.48. This will given us two sub intervals I_1 = [0.4.48) and I_2 = [4.48, 11.02). In I_1, $c_2 < 0$ and $\Delta < 0$ while in I_2, condition iii. of the



1.a



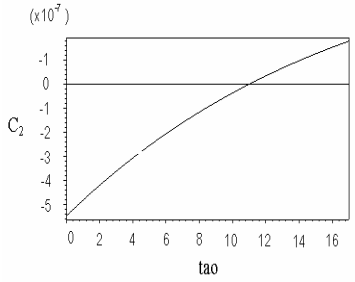
1.b



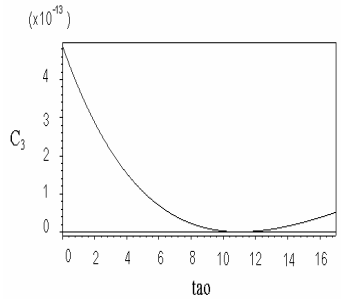
1.c

Fig. 1. Stable Spiral Trajectory. Numeric-ally solving Eqns. (3a) - (3b) for $\tau = 0$ using the following set of parameter values {$\beta_h = 0.5$, $\beta_v = 0.75$,$\mu_h = 0.000039$, $\mu_v = 0.059$, r = 0.33, b = 1 and m = 0.1}. With this set of values, $R_o = 1.91$ which is within the range of biological acceptable values. As we see, the trajectories in the I_v-S and I-S phase plane spirals into the endemic equilibrium state. The trajectory in the I_v-I also spirals in, although this is not clearly evident.

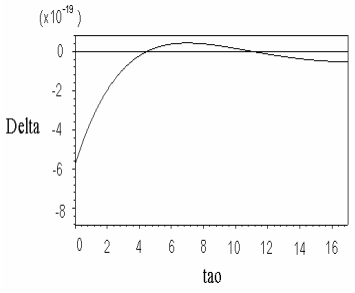
Lemma holds, i.e., no positive real root of eqn. (15) exist [Note that for $\tau \in$ [4.48, 11.018), $\Delta > 0$ and $c_2 < 0$ and for $\tau \in$ interval [0, $(\ln R_o)/\mu_v$) when the above values of the parameters are used. The above conclusion is not surprising. It has been pointed out that the limit cycles predicted by a mathematical



2.a



2.b



2.c

Fig. 2. 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 the same as those used to generate Figure 1, i.e., {$\beta_h = 0.5$, $\beta_v = 0.75$,$\mu_h = 0.000039$, $\mu_v = 0.059$, 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 $\tau*$ 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.

equation does not always occur when biologically relevant values are used. In a seminal paper, Caughley [11] proposed a simple predator-prey model to describe an elephant-tree ecosystem. He found that the elephants and trees could coexist in a stable limit cycle with a frequency of oscillation of approximately 270 years. Duffy *et al.,* [12] has questioned this hypothesis. They found that using realistic parameter values, limit cycles were highly unlikely. Instead, their

parameter analysis showed that an equilibrium state was more likely. In their paper, Khan and Greenhalgh [4] found that while a Hopf bifurcation was theoretically possible in their model, it would not occur under most realistic conditions. For a bifurcation to occur, the disease that they would be vaccinating against would be one for which the chances of dying from the diseases are greater than that of recovering. In addition, the fraction of newborns, who are effectively vaccinated at birth (immunity being passed from the mother) is just below its critical threshold value. Such a disease probably does not exist.

IV.b Unrealistic Parameter Values.

To determine whether it is possible that there are parameter values such that a Hopf bifurcation is possible, we have picked a set of parameter values (β_h,, β_v, μ_h , μ_v ,b ,r ,m) for which the basic reproduction number would be unphysical, i.e., not between 1 and 3. The set chosen (0.00001, 1.0, 0.0000456, 0.058, 170 ,0.02, 0.2) gives a $R_o = 57.67$. We have plotted on Figure 3, the values of $c_3(\tau)$ over the range $0 < \tau < 81.09$, the value of $(\ln R_o)/\mu_v$. While we have varied τ up to 81.09, τ should have been varied up to 17, the life time of the mosquito.

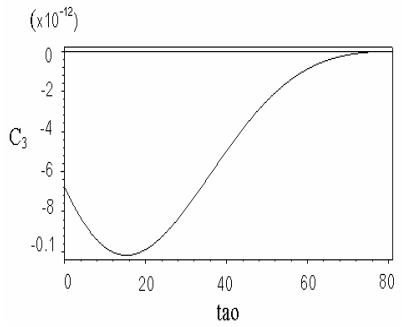


Fig. 3. Dependence of $c_3(\tau)$ on the time delay τ using parameter values which produce an unrealistic R_o. The values of the parameters used are $\beta_h = 0.00005$, $\beta_v = 1$, $\mu_h = 0.000046$, $\mu_v = 0.05$, r = 0.02, b = 170 and m = 0.2. These values give a $R_o = 57.67$. We have varied τ between 0 and 81.09 $(\ln 57.67)/\mu_v$. As we see, $c_3(\tau) < 0$ over the entire range of τ.

.If the mosquito dies before it becomes infectious, the transmission of the disease can not be maintained and the epidemic ceases. As we see, $c_3(\tau)$ is negative over the entire range of τ. According to *Theorem 3*, the critical delay τ_c exist in the interval {0, 81.09]. We then systematically varied τ (keeping the same values for the other parameters) starting from $\tau = 0$ and attempted to solve eqn.(15). Doing this, we found $\tau^* = 9.5$. To truly see whether the system bifurcates, we have solved Eqns. (3a) - (3b) for $\tau = 9.0 < \tau^*$. The trajectory of the solution in the I_v-I phase space is plotted in Figure 4a. As we see, the solution spirals into the equilibrium point (0.809, 0.142, 0.002). Changing τ to the critical value 9.5, we get a stable limit cycle orbit (Figure 4b). Increasing τ to beyond the critical value, i.e., $\tau = 10 > \tau^*$, we get the trajectory shown in Figure 4c. It is an outward spiral going away from an unstable equilibrium point. As we have mentioned, the endemic states depend on the time delay. At $\tau = 9.5$, the equilibrium state is (0.805, 0.143, 0.002). It becomes an unstable point located at (0.801, 0.144, 0.002) when $\tau = 10$.

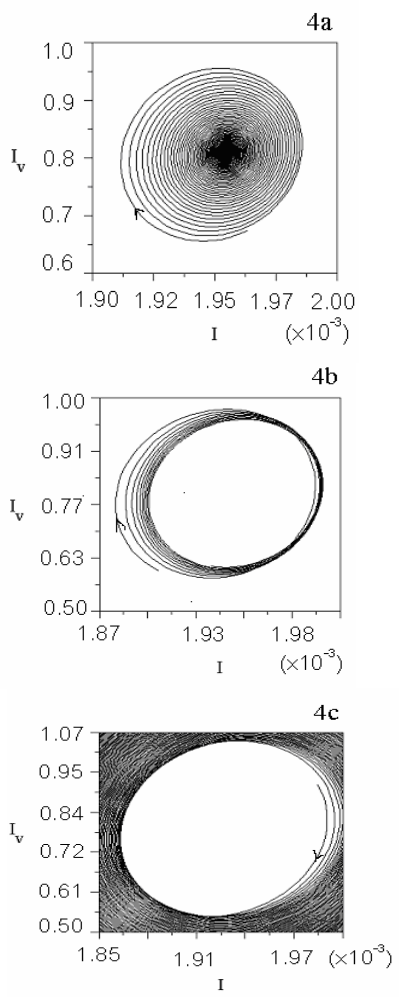


Fig. 4. Trajectories of $(I_v(t), I(t))$ for three values of τ. Numerical solutions of Eqns. (3a) – (3b) using the parameter values used to obtain Figure 3. The critical value of τ was found to be $\tau^* = 9.5$. (4a) Stable spiral trajectory when $\tau = 9.0 < \tau^*$ is used. (4b) Limit cycle orbital is obtained when τ is set to τ^* (9.5). (4c) Unstable spiral trajectory when $\tau = 10.0 > \tau^*$.

The two most obvious unrealistic parameters are the biting rates of the mosquitoes and the recovery rate of the human. For the system to bifurcate, we need a mosquito that would bite 170 times a day. Even though the *Ae. Aegypti* mosquito is a mosquito which will take a new bite if her meal is interrupted, 170 interruptions would be too much to expect. A recovery rate of 0.02 per day requires the viremia stage last for at least fifty days. This is not a characteristic of dengue infection. In addition, the choice of parameters used is unrealistic since they would also lead to an unrealistically large number of secondary infections.

IV. 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. 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.

Acknowledgements

One of the authors (IMT) would like to thank the Thailand Research Fund (TRF) for financial support.

References

[1] D.J. Gubler DJ, Dengue and Dengue Hemorrhagic Fever, *Clin. Mirobiol. Rev.* 11 (1998) 480.
[2] World Health Organization, Dengue hemorrhagic fever: diagnosis, treatment, prevention and control, 2nd Ed. (1997) WHO..
[3] A. Martin and S. Ruan, Predator-prey models with delay and prey harvesting. J. Math. Biol. **43** (2001) 247.
[4] Q.L.A. Khan, D. Greenhalgh, Hopf bifurcation in epidemic models with a time delay in vaccination. IMA J. Math. Appl. Med. Bio. 16 (1998) 113.
[5] Y. Xiao, L. Chen, Modeling and analysis of a predator-prey model with disease in prey. Math. Biosci. 171 (2001) 59.
[6] S. Ruan, J. Wei, On the zeros of a third degree exponential polynomial with application to a delay model for control of testosterone secretion. IMA J. Math. Appl. Med. Biol.18 (2001) 41.
[7] J. Tam, Delay effect in a model for virus replication. IMA J. Math. Appl. Med. Biol. 16 (1999) 29.
[8] J.E. Marsden, M. McCracken, The Hopf Bifurcation and Its Application, (Springer-Verlag, Berlin(1976)).
[9] L. Esteva, C. Vargas C, Analysis of a dengue disease transmission model. M*ath. BioSci. 150* (1998) 131.
[10] C.A. Marques, O.P. Forattini, E. Massad,. The basic reproduction number for dengue fever in Sao Paulo state, Brazil: 1990-1991 epidemic. *Trans. Roy. Soc. Trop. Med Hyg.* 88 (1994), 58.
[11] G Caughley, The elephant problem-an alternative hypothesis. East Aft. Wildl. J. 14 (1976) 265.
[12] K.J. Duffy, B.R. Page, J.H. Swart, V.B. Bajic, Realistic parameter assessment for a well known elephant-tree ecosystem model reveals that limit cycles are unlikely. Ecol. Mod. 121 (1999) 115.
[13] SI Hay, MF Myers, DS Burke, DW Vaughn, T Endy, N Ananda, GD Shanks, RW Snow, DJ Rogers, Etiology of interepidemic periods of mosquito-born disease. PNAS 97 (2000) 9335.
[14] S. Dowell, Seasonal variation in host susceptibility and cycles of certain infectious diseases. Emer. Inf. Dis. 7 (2001) 369.
[15] Y. Kuang, in: Delay differential equations with appli-cation to population dynamics, (Academic Press, New York, 1993) page 66.

Appendix I

Poof of the Lemma:

To establish condition i., we first note that with $c_3(\tau) < 0$, $f(\omega=0)$ would be negative. At $\omega = \infty$, $f(\infty)$ would be positive. $F(\omega)$ would have to cross the $f(\omega) = 0$ axis in the interval $[0,\infty]$, thus showing that at least one of the roots is real and positive. Condition ii. is more complicated to established. If $c_2(\tau) < 0$, one of the turning points (say α) would be positive while the other (say β) would be negative. The condition $\Delta < 0$ means that the sgn $f(\alpha)$ = - sgn $f(\beta)$, i.e., if $f(\alpha)$ is in the upper half plane, then $f(\beta)$ is in the lower half plane or vice versa . The condition $c_3(\tau) > 0$, means that $f(0)$ would now be positive. $f(\infty)$ would remain positive and $f(-\infty)$ would be negative. Since α is the positive valued turning point, the signs of $f(0)$ and $f(\infty)$ requires that $f(\alpha)$ be in the lower half ω-$f(\omega)$ plane. The $f(\omega)$ would have to cross the $f(\omega) = 0$ axis at two points somewhere between 0 and α and between α and ∞.

Since the coefficients $c_1(\tau)$, $c_2(\tau)$ and $c_3(\tau)$ are real numbers, the roots of $f(\omega) = 0$, the roots must be either all real or one real and a pair of complex conjugates. If z_1, z_2 and z_3 are the three roots, then $c_3(\tau) = - z_1z_2z_3$. If $c_1(\tau)^2 < 3\ c_2(\tau)$, then there is only one real root. Calling this root z_1, we get $-z_1\{(\text{Re } z_2)^2 + (\text{Im } z_2)^2\}$. Since this is just $c_3(\tau)$ and $c_3(\tau) \geq 0$, z_1 must be negative. The condition $c_1(\tau)^2 = 3\ c_2(\tau)$ leads to two of the roots being double roots leaving $c_3(\tau) = -z_1z_2^2$. For this to be greater or equal to zero, z_1 must again be negative. The conditions $c_1(\tau)^2 - 3\ c_2(\tau) > 0$ and $\Delta > 0$ means that two turning points exist and that both $f(\alpha)$ and $f(\beta)$ lie in the same (upper or lower half) plane. Now, however, $f(\omega)$ does not cross the $f(\omega) = 0$ axis between α and β, meaning that we do not have a positive real root. The last condition for the non existence of a positive real root, $c_1(\tau)^2 - 3\ c_2(\tau) > 0$ and $\Delta < 0$, $c_1(\tau) > 0$ and $c_2(\tau) > 0$ is established by noting that the two turning points appear in the left half plane. The crossing of $f(\omega)$ with the zero axis occurs between 0 and $-\infty$ at a , leading the root to be negative.

Appendix II

Proof of Theorem 4.

We first introduce three delay times, τ_i^*,τ_j^* and τ_k^* defined by $c_2(\tau_i^*) = 0$, $c_3(\tau_k^*) = 0$ and $\Delta(\tau_j^*) = 0$. There may be more than one value of each of these critical delays since $c_2(\tau_i^*) = 0$, $c_3(\tau_k^*) = 0$ or $\Delta(\tau_j^*) = 0$ could have more than one root. τ^* could be either τ_i^*,τ_j^* or τ_k^*. Picking it to be $\max\{\tau_i^*, \tau_j^*, \tau_k^*\}$ or to be $\min\{\tau_i^*,\tau_j^*, \tau_k^*\}$, we find that it can not be in the region satisfying any of the conditions of the *Lemma* (i.e. all the conditions are expressed as being less than, not equal to zero). I_1 and I_2 are the intervals $[0, \tau^*)$ and $[\tau^*, (\ln R_o)/\mu_v)$, respectively. The roots of Eqn. (8) can be viewed as a continuous function of the time delay τ, i.e., $\lambda = \lambda(\tau)$ [See Lemma 5.1 in ref. 5 or Theorem 1.4 in the textbook of Yuang Kuang [15]]. At $\tau = 0$, we know that the endemic state is asymptotically stable (by *Theorem 1*). Therefore the

$\mathrm{Re}\{\lambda(\tau=0)\}$ would be negative and $\lambda(\tau = 0)$ would lie on the left hand side (LHS) of the complex λ-plane. As τ moves from I_1 to I_2, $\lambda(\tau)$ would enter into the right half plane (RHS) by crossing the imaginary axis. Then the endemic state would be unstable and $\mathrm{Re}\{\lambda(\tau > \tau^*)\}$ would be positive. Now consider what will happen if the critical time delay τ_c lies in I_1. Since the transversality condition holds in I_1, a bifurcation will occur at $\tau = \tau_c$. Therefore, as τ passes τ_c, the endemic state becomes unstable, i.e., $\mathrm{Re}\{\lambda(\tau = \tau_c \in I_1\}$ would be in the RHS of the complex λ-plane. As τ approaches τ^*, $\lambda(\tau)$ should be approaching the boundary from the right

$$\frac{d\lambda(\tau = \tau_c)}{d\tau} > 0 \quad ,$$

it cannot cross the imaginary axis to get into the RHS since it is already in the RHS. This inconsistency requires that there be no τ_c in I_1. If, however, there were two critical time delays in I_1, the present arguments would not apply. Our theorem only applies if there is only one (or an odd number) critical point.

To complete the proof, we consider what would happen if $\tau_c \in I_2$, notwithstanding the fact that the definition of I_2 precludes the presence of τ_c in the interval. But first we look at the stability for τ close to $(\ln R_o)/\mu_v$. For $\tau \in I_2$, $\lambda(\tau)$ is on the RHS of the complex λ-plane. As $\tau \to (\ln R_o)/\mu_v$, the basic reproduction number

$$R_o e^{-\mu_v \tau} \to 1$$

Also in this limit, $S^* \to 1$, $I^* \to 0$ and $I_v^* \to 0$. The characteristic equiation, Eqn. (8) reduces to

$$\lambda(\lambda^2 + a_o\lambda + b_o) = 0$$

where $a_o = 2\mu_h + \mu_v + r$ and $b_o = \mu_h(\mu_h + \mu_v + r)$. It is easily shown that the two non-zero roots of this equation are real and negative. This means that as $\tau \to (\ln R_o)/\mu_v$, $\lambda(\tau)$ must head towards the imaginary axis from the right. We now place τ_c into I_2. As τ passes τ_c, $\lambda(\tau)$ should cross the imaginary axis and move into the LHS of the complex λ-plane. As we have stated before, as $\tau \to (\ln R_o)/\mu_v$, $\lambda(\tau)$ should be moving to the left to get close to the imaginary axis. With τ_c present in I_2, $\lambda(\tau > \tau_c)$ is already on the LHS and there is no need to move towards the imaginary axis. This contradicts the original requirement. To resolve this, we need $\tau_c \notin I_2$. Since $\tau_c \notin I_1$ also, $\tau_c \notin I_1 \cup I_2$ and no bifurcation is possible in the interval $[0, (\ln R_o)/\mu_v)$ if the interval can be divided into two sub intervals, one in which conditions i. and ii. of the *Lemma* hold and the other in which condition iii. holds. (Again we point out that the theorem and proof do not apply if there are two critical time delays in the interval I_1.)