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Modelling the dynamics of CD4+ T cells with and without delay

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ABSTRACT

Acquired immunodeficiency syndrome (AIDS) is one of the most serious public health problems in the world, which greatly affects the socio-economic growth. Mathematical models can serve as tools for understanding the epidemiology of human immunodeficiency virus (HIV) and AIDS. In this paper, we consider a mathematical model having three compartments. Uninfected and infected states are proposed and analysed. It is found that the uninfected state is locally stable when the reproduction number $R_o < 1$ and the infected state is locally stable when $R_o \geq 1$ and globally stable when $R_o > 1$. The model is analysed with and without delay. Numerical simulations are carried out to illustrate the results.

Key words: AIDS; HIV; CD4+ T cells; stability; delay.

INTRODUCTION

AIDS is medically devastating to its victims, and causes financial and emotional havoc on the infected person and his/her relatives. The purpose of this paper is to model and understand the behaviour of the causative agent of AIDS that is HIV. HIV targets, among others, the CD4+ T lymphocytes, which are the most abundant white blood cells of the immune system (referred to as helper T-cells or CD4+ T cells). Helper T-cells play a key role in the process of gaining immunity to specific pathogens; in fact, if one's helper T-cells are destroyed, the entire specific immune response fails. HIV kills the very cells that are required by our bodies to defend us from pathogens, including HIV itself.[1]

Several models have been developed in an attempt to understand the dynamics of infectious diseases.[2-13] In particular, Murray *et. al.*[14] determined the viral level after the initial peak, by the rate of reactivation of memory cells. Perelson *et. al.*[15] observed that the model exhibits many of the symptoms of AIDS seen clinically; the long latency period, low levels of free virus in the body, and the depletion of CD4+ T-cells. They defined the model by considering four compartments: uninfected cells, latently infected cells, actively infected cells and free virus. They described the dynamics of these populations by a system of four ordinary differential equations.

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Mathematical analysis of the global dynamics of a model of HIV infection has also been studied by many authors.[16-18] Elaiw[16] has constructed Lyapunov functions[19] to establish the global stability of the uninfected and infected steady states.

In this paper, we consider three compartments: the uninfected CD4+ T-cells, the infected CD4+ T-cells and the free virus. The existence and stability of the uninfected and infected states are considered. Time-delay model is also proposed and analysed, considering the delay between the infection of CD4+ T cell and emission of virus particles on a cellular level.[20-23]

Mathematical Model

A basic model to study HIV dynamics can be described by the following equations:

$$\begin{aligned}\frac{dT(t)}{dt} &= \lambda - dT(t) - kV(t)T(t)\\ \frac{dT^*(t)}{dt} &= kV(t-\tau)T(t-\tau) - \delta T^*(t)\\ \frac{dV(t)}{dt} &= N\delta T^*(t) - cV(t)\end{aligned} \tag{2.1}$$

In the above model, T, I and V are the concentrations of uninfected CD4+ T cells at time t, concentrations of infected cells at time t and concentrations of free virus at time t respectively, λ is the recruitment rate of uninfected T cells, d is the per capita death rate of uninfected cells, k is the rate constant at which uninfected cells are infected by free virus, δ is the per capita death rate of infected cells, N is the total number of virus particles produced by productively infected cells during its lifetime (burst size), c is the clearance rate of virus, kVT gives the mass action and $N\delta$ gives the per capita viral production. Here, τ is the time delay between infection of the CD+T cells to the cells becoming actively infected.

Model without delay

When τ = 0, the model (1)-(3) reduces to the following model

$$\begin{aligned}\frac{dT(t)}{dt} &= \lambda - dT - kVT\\ \frac{dT^*(t)}{dt} &= kVT - \delta T^*\\ \frac{dV(t)}{dt} &= N\delta T^* - cV\end{aligned} \tag{3.1}$$

The above system has two non-negative steady states, $E_1\left(\frac{\lambda}{d},0,0\right)$ and $E_2(\bar{T},\bar{T^*},\bar{V})$.

E_2 exists when $\lambda > \frac{cd}{kN}$. That is, $R_0 > 1$, where $R_0 = \frac{\lambda kN}{cd}$, the reproductive ratio, that is, the number of secondary infections in a healthy host caused by a single infected cell.

Stability Analysis

Theorem 1. The non-infected state E_1 is locally asymptotically stable when $R_0 < 1$

Proof. The Jacobian matrix of the system at the non-infected state E_1 is

$$J_1 = \begin{bmatrix} -d & 0 & -\frac{k\lambda}{d} \\ 0 & -\delta & \frac{k\lambda}{d} \\ 0 & N\delta & -c \end{bmatrix}$$

All eigenvalues of J_1 have negative real parts. Hence E_1 is locally asymptotically stable.

Theorem 2. The infected state E_2 is locally asymptotically stable when $R_0 \geq 1$.

The detailed proof is shown in appendix A.

Lemma 1. The bounded set

$$S = \left\{ (T(t), T^*(t), V(t)) \in R_+^{\,3} : 0 \leq T + T^* \leq \frac{\lambda}{d}, V \leq K \right\}$$

is positively invariant with respect to the system (3.1).

The proof of the lemma is given in Appendix B.

Theorem 3. The infected steady state E_2 is globally asymptotically stable when $R_0 > 1$. In the bounded set

$$S = \left\{ (T(t), T^*(t), V(t)) \in R_+^3 : 0 \le T + T^* \le \frac{\lambda}{d}, V \le K \right\}$$

The proof is *shown in Appendix C.*

Model with Delay

Here we introduce a time delay into the basic model to describe the time between infection of the CD4+ T cells to the cells becoming actively infected. The model is

$$\begin{aligned} \frac{dT(t)}{dt} &= \lambda - dT(t) - kV(t)T(t) \\ \frac{dT^*(t)}{dt} &= kV(t-\tau)T(t-\tau) - \delta T^*(t) \\ \frac{dV(t)}{dt} &= N\delta T^*(t) - cV(t) \end{aligned} \qquad (5.1)$$

Again we find the uninfected steady state $E_3(T,0,0)$ and $E_4(\bar{T},\bar{T^*},\bar{V})$.

At $E_3(T,0,0)$, from equation (4), we get $T = \frac{\lambda}{d}$. Thus $E_3\left(\frac{\lambda}{d},0,0\right)$ is the uninfected steady state.

At $E_4(\bar{T},\bar{T^*},\bar{V})$, from equation (3), $\bar{V} = \frac{N\delta\bar{T^*}}{c}$

Putting this value of $\bar{V}$ in equation (2), we obtain $\bar{T} = \frac{c}{kN}$

Again putting $\bar{V} = \frac{N\delta\bar{T^*}}{c}$ in equation (1), we get $\bar{T^*} = \frac{1}{\delta}\left(\lambda - \frac{cd}{kN}\right)$

Thus $E_4\left(\frac{c}{kN}, \frac{1}{\delta}\left(\lambda - \frac{cd}{kN}\right), \frac{N\delta\bar{T^*}}{c}\right)$, that is, $E_4\left(\frac{c}{kN}, \frac{1}{\delta}\left(\lambda - \frac{cd}{kN}\right), \frac{k\lambda N - dc}{kc}\right)$ is the infected steady state.

Theorem 4. Suppose

(i) $\alpha > 0, \quad \beta > 0$ and $\alpha\beta - \gamma > 0$

(ii) $\delta > d$

Then the infected steady state $E_4(\bar{T},\bar{T^*},\bar{V})$ of the delay model is asymptotically stable when $R_0 > 1$ for all $\tau \ge 0$.

The proof is given in Appendix D.

Numerical Simulations

We choose the following parameters in the model:

$\lambda = 1, \quad d = 0.3, \quad k = 0.4, \quad \delta = 0.75,$

$c = 0.95, \quad N = 0.8$

With the above values of parameters, the positive equilibrium E_2 exists and it is given by

$\bar{T} = 2.968, \quad \bar{T^*} = 0.147, \quad \bar{V} = 0.094$

Also, with the above values of parameters, $R_0 = 1.122 > 1$

Hence the condition in theorem 2 is satisfied.

Also, the three inequalities in Theorem 3 are satisfied with $C_1 = 0.1$, $C_2 = 5$, $K = 5000$.

With the above parameters,

$\alpha = 1.5790 > 0, \quad \gamma = 0.0577 > 0, \quad \alpha\beta - \gamma = 0.9354 > 0$

Hence conditions (i) and (ii) of Theorem 4 are also satisfied.

a) Behaviour of uninfected cells for different values of k

Behaviour of uninfected cells with respect to time for different values of the rate constant at which uninfected cells are infected by free virus.

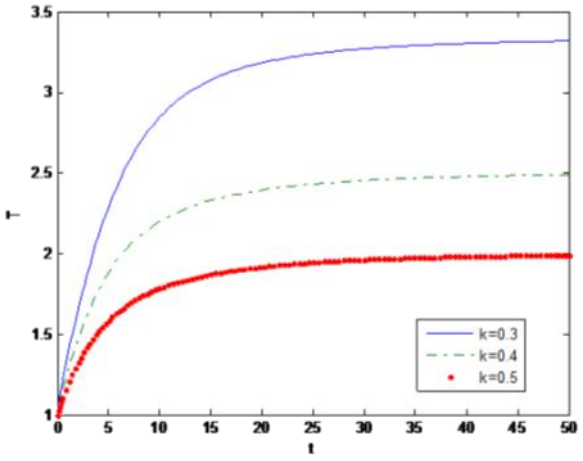

Figure 1

It is noted here that the density of uninfected cells increases as k decreases. It is also observed that T increases rapidly and gradually reaches a steady state.

b) Behaviour of uninfected cells for different values of lambda

Behaviour of uninfected cells with respect to time for different values of the recruitment rate of uninfected T cells.

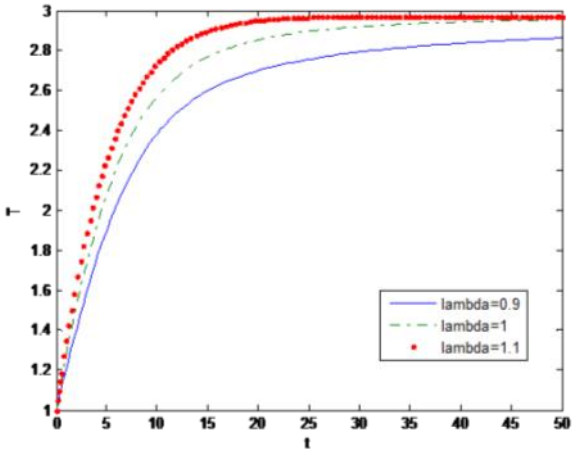

Figure 2

It is noted here that the density of uninfected cells increases as lambda increases. It is also observed that T increases rapidly and then reaches a steady state.

c) Behaviour of infected cells for different values of lambda

Behaviour of infected cells with respect to time for different values of the rate constant at which uninfected cells are infected by free virus.

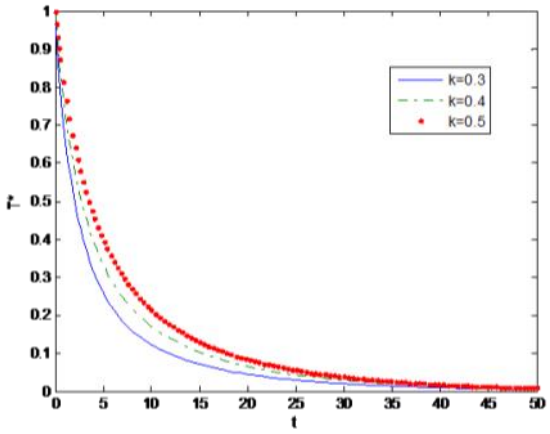

Figure 3

It is noted here that the density of infected cells increases as k increases. It is also observed that T* decreases rapidly and then reaches a steady state.

d) Behaviour of free virus for different values of N

Behaviour of free virus with respect to time for different values of the total number of virus particles produced by productively infected cells during its lifetime (burst size).

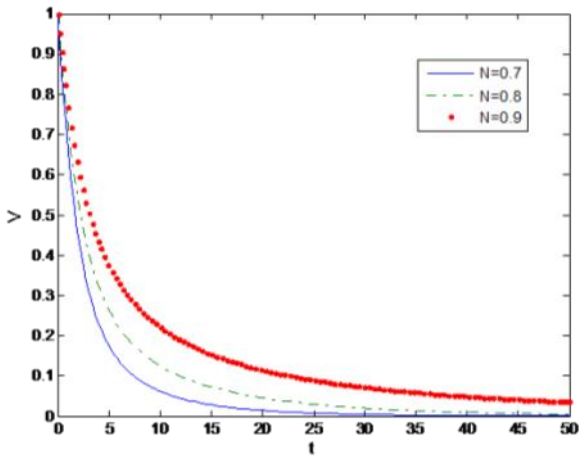

Figure 4

It is noted here that the density of free virus increases as N increases. It is also observed that the population of free virus decreases rapidly and gradually reaches a steady state.

e) Behaviour of uninfected cells, infected cells and virus with respect to time with $\tau = 1$

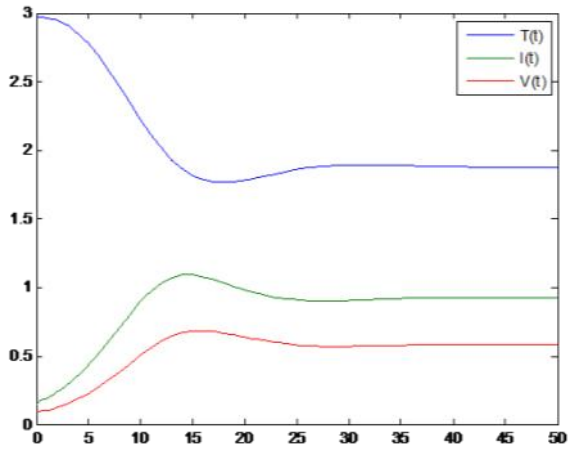

Figure 5

f) Behaviour of uninfected cells, infected cells and virus with respect to time with $\tau \approx 0$

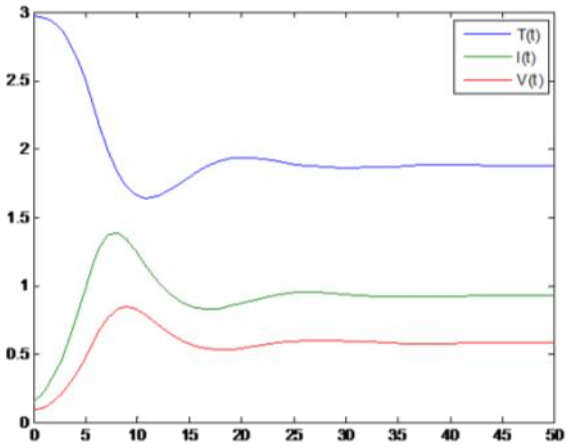

Figure 6

From Figure. 5 and Figure. 6, it is seen that in the presence of delay, the population of infected cells and the population of virus increases at a slower rate.

Conclusions

In this paper, we have studied the basic dynamic model of CD4+ T-cells. The model has three differential equations dealing with the interactions between the uninfected cells, infected cells and free virus. A decrease in density of uninfected cells has been observed upon interaction with virus. The density of infection increases with viral interaction. Existence of equilibrium points and the conditions for local and global stability have been obtained. The basic reproduction number R_0 is obtained and it determines the dynamics of the HIV models. It is seen that the infection is cleared out when $R_0 < 1$ whereas the infection persists when $R_0 \geq 1$. A time delay τ i.e. the time delay between the infection of CD4+T cell and the emission of virus particles on a cellular level, has been incorporated. It is found that the solution of the delay system converges to the disease free equilibria if $R_0 \leq 1$. The infected steady state is asymptotically stable for all $\tau \geq 0$ when $R_0 > 1$.

Appendix A: Proof of Theorem 2

The Jacobian matrix of the system at the infected state E_2 is

$$J_2 = \begin{bmatrix} -d - k\overline{V} & 0 & -k\overline{T} \\ k\overline{V} & -\delta & k\overline{T} \\ 0 & N\delta & -c \end{bmatrix}$$

The characteristic equation is

$$\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 = 0 \quad (1)$$

By using the transformations

$$t_1 = T_1 + \overline{T}$$

$$t_2 = T_2 + \overline{T^*}$$

$$v_1 = V_1 + \overline{V}$$

We linearize the system

$$\begin{bmatrix} \dot{T}_1 \\ \dot{T}_2 \\ \dot{V}_1 \end{bmatrix} = J_2 \begin{bmatrix} T_1 \\ T_2 \\ V_1 \end{bmatrix}$$

and get

$$\begin{bmatrix} \dot{T}_1 \\ \dot{T}_2 \\ \dot{V}_1 \end{bmatrix} = \begin{bmatrix} -\left(d + k\overline{V}\right)T_1 - k\overline{T}V_1 \\ k\overline{V}T_1 - \delta T_2 + k\overline{T}V_1 \\ N\delta T_2 - cV_1 \end{bmatrix}$$

Consider the following positive definite function

$$X = \frac{1}{2}\left[T_1^2 + C_1T_2^2 + C_2V_1^2\right]$$

Then

$$\dot{X} = -\frac{1}{2}\left(d + k\overline{V}\right)T_1^2 + C_1k\overline{V}T_1T_2 - \frac{1}{2}C_1\delta T_2^2 - \frac{1}{2}\left(d + k\overline{V}\right)T_1^2$$

$$+\left(-k\overline{T}\right)T_1V_1 - \frac{1}{2}cC_2V_1^2 - \frac{1}{2}C_1\delta T_2^2 + \left(C_2N\delta + C_1k\overline{T}\right)T_2V_1$$

$$-\frac{1}{2}cC_2V_1^2$$

i.e.

$$\dot{X} = -\frac{1}{2}A_{11}T_1^2 + A_{12}T_1T_2 - \frac{1}{2}A_{22}T_2^2 - \frac{1}{2}A_{11}T_1^2 +$$

$$A_{13}T_1V_1 - \frac{1}{2}A_{33}V_1^2 - \frac{1}{2}A_{22}T_2^2 + A_{23}T_2V_1 - \frac{1}{2}A_{33}V_1^2$$

where

$$A_{11} = d + k\overline{V}$$

$$A_{22} = c_1\delta$$

$$A_{33} = cC_2$$

$$A_{12} = C_1k\overline{V}$$

$$A_{13} = -k\overline{T}$$

$$A_{23} = C_2N\delta + C_1k\overline{T}$$

Sufficient conditions for $\dot{X}$ to be negative definite are that the following inequalities hold

$$A_{12}^2 < A_{11}A_{22}$$

$$A_{13}^2 < A_{11}A_{33}$$

$$A_{23}^2 < A_{22}A_{33}$$

The last inequality is satisfied if $R_0 \geq 1$.

Appendix B: Proof of Lemma 1

Adding the first and the second equations of system (3.1),

$$\dot{T} + \dot{T^*} = \lambda - dT - \delta T^* \leq \lambda - d\left(T + T^*\right) \geq 0$$

(since $d \leq \lambda$)

So both the uninfected and infected T-cell populations are always bounded.

Also from the third equation,

$$V = \frac{N\delta T^*}{c}$$

Therefore, $V \leq K$, for some $K \geq 0$.

Thus we have a bounded set

$$S = \left\{\left(T(t), T^*(t), V(t)\right) \in R_+^3 : 0 \leq T + T^* \leq \frac{\lambda}{d}, V \leq K\right\}$$

that is positively invariant with respect to system (3.1).

Appendix C: Proof of Theorem 3

Let

$$V_1(\overline{T}, \overline{T^*}, \overline{V}) = T - \overline{T} - \overline{T}\ln\left(\frac{T}{\overline{T}}\right) + C\left(T^* - \overline{T^*} - \overline{T^*}\ln\left(\frac{T^*}{\overline{T^*}}\right)\right) + \frac{C_2}{2}\left(V - \overline{V}\right)^2$$

Then

$$\dot{V}_1 = -\frac{1}{2}\frac{\lambda}{T\overline{T}}\left(T-\overline{T}\right)^2 + C_1\frac{kV}{T^*}\left(T-\overline{T}\right)\left(T^*-\overline{T^*}\right) - \frac{1}{2}\frac{2C_1k\overline{V}T}{T^*\overline{T^*}}\left(T^*-\overline{T^*}\right)^2 - \frac{1}{2}\frac{\lambda}{T\overline{T}}\left(T-\overline{T}\right)^2 - + (-k)\left(T-\overline{T}\right)\left(V-\overline{V}\right) - \frac{1}{2}\frac{2}{3}C_2c\left(V-\overline{V}\right)^2 - \frac{1}{2}\frac{2C_1k\overline{V}T}{T^*\overline{T^*}}\left(T^*-\overline{T^*}\right)^2 + \left(C_2N\delta - C_1\frac{k\overline{T}}{\overline{T^*}}\right)\left(T^*-\overline{T^*}\right)\left(V-\overline{V}\right) - \frac{1}{2}\frac{2}{3}C_2c\left(V-\overline{V}\right)^2$$

i.e.

$$\dot{V}_1 = -\frac{1}{2}a_{11}\left(T-\overline{T}\right)^2 + a_{12}\left(T-\overline{T}\right)\left(T^*-\overline{T^*}\right) - \frac{1}{2}a_{22}\left(T^*-\overline{T^*}\right)^2 - \frac{1}{2}a_{11}\left(T-\overline{T}\right)^2 + a_{13}\left(T-\overline{T}\right)\left(V-\overline{V}\right) - \frac{1}{2}a_{33}\left(V-\overline{V}\right)^2 - \frac{1}{2}a_{22}\left(T^*-\overline{T^*}\right)^2 + a_{23}\left(T^*-\overline{T^*}\right)\left(V-\overline{V}\right) - \frac{1}{2}a_{33}\left(V-\overline{V}\right)^2 \quad (2)$$

where

$$a_{11} = \frac{\lambda}{T\overline{T}}$$

$$a_{22} = \frac{2C_1k\overline{V}T}{T^*\overline{T^*}}$$

$$a_{33} = \frac{2}{3}C_2c$$

$$a_{12} = C_1\frac{kV}{T^*}$$

$$a_{13} = -k$$

$$a_{23} = C_2N\delta - C_1\frac{k\overline{T}}{\overline{T^*}}$$

$\dot{V}_1$ will be negative definite if

$a_{12}^2 < a_{11}a_{22}$

$a_{13}^2 < a_{11}a_{33}$

$a_{23}^2 < a_{22}a_{33}$

The last inequality is satisfied if $R_0 > 1$.

Appendix D: Proof of Theorem 4

At the infected steady state $E_4(\overline{T}, \overline{T^*}, \overline{V})$, the linearized system is given by

$$\frac{dY(t)}{dt} = J_1Y(t) + J_2Y(t-\tau) \quad (3)$$

where

$$Y(.) = \left[T(.),\quad T^*(.),\quad V(.)\right]^T$$

The characteristic equation of eqn. (3) is

$$\gamma^3 + A_2\gamma^2 + A_1\gamma + A_0 + \left(B_1\gamma + B_0\right)e^{-\gamma\tau} = 0 \quad (4)$$

where

$$A_2 = c + d + \delta + k\overline{V}$$

$$A_1 = \left(d + k\overline{V}\right)\left(c + \delta\right) + c\delta$$

$$A_0 = c\delta\left(d + k\overline{V}\right)$$

$$B_1 = -kN\delta\overline{T}$$

$$B_0 = -kdN\delta\overline{T}$$

When $\tau = 0$, all the roots of eqn.(4) have negative real part and for $\tau \neq 0$, it has infinitely many roots. By Rouche's theorem and the continuity in τ, eqn.(4) has roots with positive real parts if and only if it has purely imaginary roots.

Taking $\gamma = \eta(\tau) - i\omega(\tau),\quad \omega > 0$, as the eigenvalue of eqn.(4), where $\eta(\tau)$ and $\omega(\tau)$ depend on the delay τ. Since the infected steady state $E_4(\overline{T}, \overline{T^*}, \overline{V})$ of the ODE model is stable, it follows that $\eta(\tau) < 0$ when $\tau = 0$. By continuity, if $\tau > 0$ is sufficiently small, we still

have $\eta(\tau) < 0$ and $E_4(\bar{T}, \overline{T^*}, \bar{V})$ is still stable. If $\eta(\tau_0) = 0$ for certain value $\tau_0 > 0$ so that $\gamma = i\omega(\tau_0)$ is a root of eqn.(4), then the steady state $E_4(\bar{T}, \overline{T^*}, \bar{V})$ loses its stability and becomes unstable when $\eta(\tau)$ becomes positive. If such an $\omega(\tau_0)$ does not exist, that is, if the characteristic eqn.(4) does not have purely imaginary roots for all delay, then the steady state $E_4(\bar{T}, \overline{T^*}, \bar{V})$ is always stable.

Putting $\gamma = i\omega$ in eqn.(4), we get

$$-i\omega^3 - A_2\omega^2 + A_1 i\omega + A_0 + B_1 i\omega Cos\omega\tau + B_1 i^2 \omega Sin\omega\tau + B_0 Cos\omega\tau + B_0 i Sin\omega\tau = 0$$

Separating the real and imaginary parts, we get

$$-A_2\omega^2 + A_0 = B_1\omega Sin\omega\tau - B_0 Cos\omega\tau \quad (5)$$

and

$$\omega^3 - A_1\omega = B_1\omega Cos\omega\tau + B_0 Sin\omega\tau \quad (6)$$

Squaring and adding eqn. (5) and eqn. (6), we obtain

$$\left(\omega^2\right)^3 + \left(-2A_1 + A_2^2\right)\left(\omega^2\right)^2 + \left(A_1^2 - 2A_0A_2 - B_1^2\right)\omega^2 + A_0^2 - B_0^2 = 0$$

Putting $\omega^2 = m$ in the above equation, we get

$$m^3 + \alpha m^2 + \beta m + \gamma = 0 \quad (7)$$

where

$$\alpha = -2A_1 + A_2^2$$

$$\beta = A_1^2 - 2A_0A_2 - B_1^2$$

$$\gamma = A_0^2 - B_0^2$$

Eqn. (7) may be written as

$$h(m) = m^3 + \alpha m^2 + \beta m + \gamma = 0$$

Now, $\frac{dh(m)}{dm} = 3m^2 + 2\alpha m + \beta$

Set $3m^2 + 2\alpha m + \beta = 0 \quad (8)$

Then the roots of eqn. (8) can be expressed as

$$z_1 = \frac{-\alpha + \sqrt{\alpha^2 - 3\beta}}{3} \quad (9)$$

$$z_2 = \frac{-\alpha - \sqrt{\alpha^2 - 3\beta}}{3} \quad (10)$$

If $\beta > 0$, then $\alpha^2 - 3\beta < \alpha^2$, hence $z_1 < 0$ and $z_2 < 0$. Thus eqn. (8) does not have positive roots. Since $h(0) = \gamma \geq 0$, it follows that eqn. (7) has no positive roots. Thus if $\gamma \geq 0$ and $\beta > 0$, then there is no ω such that $i\omega$ is an eigenvalue of the characteristic eqn. (4). Therefore, the real parts of all eigenvalues of eqn. (4) are negative for all delay $\tau \geq 0$.

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