JOURNAL OF MATHEMATICAL ANALYSIS AND APPLICATIONS 170, 276–290 (1992)

On the Model of a Virus Disease with Mutual Interference

N. C. SRINIVAS AND N. CH. PATTABHI RAMACHARYULU

Department of Mathematics and Humanities, Regional Engineering College, Warangal-506 004, India

Submitted by Kenneth L. Cooke

Received September 5, 1990

A mathematical model for a virus disease with mutual interference between the viruses attacking the organ and the organ's immune system is investigated. The non-negativity of the solutions and the conditions for asymptotic stability of the diseased chronic equilibrium state have been established.

1. INTRODUCTION

The mathematical study of the growth, spread, and stability/control of the infectious disease with/without interaction between diverse biological species has become a subject of extensive study in recent times. Bailey [1] gave a detailed account of mathematical theories of infectious diseases. The simplest mathematical model for a virus disease was proposed by Marchuk *et al.* [7, 8] in the form of a set of first order ordinary coupled differential equations with delayed arguments. In their work, the existence-uniqueness and the non-negativity of the solutions of the model are established. Further, the stability analysis of the equilibrium states and the analytical and numerical illustrations of the clinical forms of the disease noted from the model have been examined at length.

In the present work, a mathematical model for a virus disease with due importance to the mutual interference among the viruses attacking the organ, the antibodies fighting with viruses, and the plasma-cells producing the immunocompetent-cells is proposed in Section 2. Further, time-delay in the immune response is taken care of to make the model more general. In Section 3, the non-negativity of the solutions of the model under prescribed initial conditions is established. Section 4 presents the derivation of the characteristic equation of the diseased chronic equilibrium state. Section 5 deals with the derivations of conditions for asymptotic stability of the diseased state, namely, the time-delay interval in which the stable state cannot

0022-247X/92 $5.00

get destabilized and also the realisation of the criterion for no change in stability. These criteria are illustrated by a numerical example. Final conclusions are presented in Section 6.

2. The Model

Motivated by the investigations of Marchuk *et al.* [7, 8] on virus diseases and those of Beddington, Erbe, Freedman, and others [2, 4–6, 9] on food-chains with mutual interference, the model for a virus disease with mutual interference between the viruses attacking the organ and the organ's immune system proposed in this investigation is characterized by the following set of first order ordinary coupled differential equations with delayed arguments:

$$\begin{aligned} V'(t) &= \{\beta(V(t)) - \gamma(V(t), F(t))\} V(t) \\ F'(t) &= \rho(F(t)) C(t) - \eta\gamma(V(t), F(t)) V(t) - \mu_f F(t) \\ C'(t) &= \xi(m)\alpha(V(t), F(t-T)) V(t-T) - \mu_c(C(t) - \tilde{C}) \\ m'(t) &= \sigma(V(t), F(t)) V(t) - \mu_m m(t), \end{aligned}$$

with initial conditions

$$\begin{aligned} V(t)|_{t\in[-T,t_0]} &= V_0(t) \geqslant 0, \qquad F(t)|_{t\in[-T,t_0]} = F_0(t) \geqslant 0, \\ C(t_0) &= C_0 \geqslant 0, \qquad m(t_0) = m_0 \geqslant 0. \end{aligned} \tag{2.1}$$

In the above equations, $V(t)$, $F(t)$, and $C(t)$ are the concentrations of the viruses attacking the organ, antibodies resisting viruses, and the plasma-cells present in the organ, respectively, at the instant t of the observation. Further, $m(t)$ is the relative characteristic at time t of the damaged organ, defined as

$$m = 1 - (M_2/M_1),$$

where

M_1 = a characteristic (say, mass or area, etc.) of a normal, i.e., perfectly healthy organ,

and

M_2 = the corresponding characteristic of the damaged part of the organ.

For a perfectly healthy organ, $m=0$ and when it is completely damaged, $m=1$. Evidently, $0 \leqslant m \leqslant 1$. Also $'$ indicates derivative with respect to time t.

The functions occurring in the model are assumed to be positive and are at least continuously differentiable for non-negative values of their arguments. Further, the following restrictions on the fuctions have been made:

(H_1) $\beta(V)$ is the virus multiplication function, characteristic of the damage to the organ, such that

$$\beta(0)=0, \qquad \frac{\partial \beta(V)}{\partial V}>0.$$

(H_2) $\gamma(V, F)$ is the probability functional response to neutralise the viruses, such that

$$\gamma(0, F)>0, \qquad \gamma(V, 0) \leqslant 0, \qquad \frac{\partial \gamma(V, F)}{\partial V} \leqslant 0,$$

$$\frac{\partial \gamma(V, F)}{\partial F} \geqslant 0.$$

(H_3) $\rho(F)$ is the growth function of the production rate of antibodies by a plasma-cell, such that

$$\rho(0)=0, \qquad \frac{\partial \rho(F)}{\partial F}>0.$$

(H_4) η is a positive constant, indicating the fraction/number of antibodies, involved in the virus multiplication.

(H_5) μ_f is the coefficient, inversely proportional to the time-decay of an antibody.

(H_6) $\alpha(V, F)$ is the function characterizing the propability of an encounter of "antigen-antibody," the stimulation of the Cascade reaction, and the number of newly generated cells, such that

$$\alpha(0, F)>0.$$

(H_7) $\xi(m)$ is the general aggravation of symptoms of the disease and describes the dysfunction of the immune system due to considerable organ-damage, such that

$$0 \leqslant \xi(m) \leqslant 1.$$

(H_8) T is the time-delay and describes the time duration of a Cascade formation of the plasma-cells.

(H_9) μ_c is the coefficient equal to the inverse of the plasma-cell life time.

(H_{10}) $\tilde{C}$ is the normal level of the immuno-competent plasma-cells, before the attack of viruses.

(H_{11}) $\sigma(V, F)$ is a special function of the disease and acts as a multiplication function to the growth of the relative characteristic of the damaged organ, such that

$$\sigma(0, F) = 0, \qquad \frac{\partial \sigma(V, F)}{\partial V} > 0, \qquad \frac{\partial \sigma(V, F)}{\partial F} < 0.$$

(H_{12}) μ_m is the inverse of the recuperation period of the organ multiplied by e times (i.e., the organ-damage time-constant).

3. Non-negativity of the Solutions

From the first equation of the system (2.1), it follows that

$$V(t) = V(t_0) \exp\left[\int_0^t \{\beta(V(\tau)) - \gamma(V(\tau), F(\tau))\}\, d\tau\right] \tag{3.1}$$

which is non-negative for all t.

If possible, let there exist a negative solution for $F(t)$. From the continuity of $F(t)$, there exists a moment t_1, for which, $F(t_1) = 0$ and $F'(t_1) < 0$. But from the second equation of (2.1),

$$\begin{aligned} F'(t_1) &= \rho(F(t_1))\, C(t_1) - \eta\gamma(V(t_1), F(t_1))\, V(t_1) - \mu_f F(t_1) \\ &= -\eta\gamma(V(t_1), 0)\, V(t_1) \geqslant 0. \end{aligned} \tag{3.2}$$

This is a contradiction. Further, t_1 is non-negative. Hence $F(t) \geqslant 0$ for all $t \geqslant 0$.

To establish the non-negativity of $C(t)$, consider an instant $t \in I_0$, where $I_n = [nT, (n+1)T]$, $n = 0, 1, 2, 3, \ldots$, the gestation interval. Then the third equation in (2.1) reduces to

$$C'(t) = -\mu_c(C(t) - \tilde{C}). \tag{3.3}$$

Let this equation possess a negative solution. Then there exists a moment t_1, for which $C(t_1)=0$ and $C'(t_1)<0$. But from (3.3)

$$\begin{aligned} C'(t_1) &= -\mu_c(C(t_1)-\tilde{C}) \\ &= \mu_c\tilde{C} > 0, \end{aligned} \tag{3.4}$$

which is a contradiction. So $t_1 \notin I_0$ and $C(t) \geqslant 0$ for all $t \in I_0$. Also $V(t-T) \geqslant 0$, $F(t-T) \geqslant 0$, and $\alpha(V, F) > 0$. Proceeding in a similar way and noting the non-negativity of $C(t)$ in each previous interval, the non-negativity of $C(t)$ for $t \in I_n$, $\forall n$ can be established. Hence $C(t) \geqslant 0$ for all $t \geqslant 0$.

For realizing the non-negativity of $m(t)$, let there be, if possible, a moment t_1, for which $m(t_1)=0$ and $m'(t_1)<0$. But from (3.3),

$$\begin{aligned} m'(t_1) &= -\mu_m m(t_1) + \sigma(V(t_1), F(t_1))V(t_1) \\ &= \sigma(V(t_1), F(t_1))V(t_1) \geqslant 0, \end{aligned} \tag{3.5}$$

gives the contradiction. So $m(t) \geqslant 0$ for all $t \geqslant 0$.

4. Characteristic Equation of the Diseased Chronic State

Marchuk [7] noted four different states of a virus disease: (i) subclinical, (ii) acute with recovery, (iii) chronic, and (iv) lethal outcome. Some salient features of these are given in the Appendix, for an immediate reference. Of these four states, it is the state (iii), the diseased chronic state, when it is in equilibrium, that is investigated for stability.

Let $E^*(V^*, F^*, C^*, m^*)$ represent the diseased chronic equilibrium state, where V^*, F^*, C^*, and m^* are the equilibrium values of $V(t)$, $F(t)$, $C(t)$, and $m(t)$, respectively.

Let $V_1(t)$, $F_1(t)$, $C_1(t)$, and $m_1(t)$ be small deviations in $V(t)$, $F(t)$, $C(t)$, and $m(t)$ from their equilibrium values V^*, F^*, C^*, and m^*, respectively, with $\xi(m) \equiv 1$ (following Marchuk [7]). Then the linearised version of the system (2.1) can be obtained as

$$\begin{aligned} V_1'(t) &= A_1 V_1(t) + A_2 F_1(t) \\ F_1'(t) &= B_1 V_1(t) + B_2 F_1(t) + \rho(F^*)C_1(t) \\ C_1'(t) &= D_1 V_1(t-T) + \alpha(V^*, F^*)F_1(t) + D_2 F_1(t-T) - \mu_c C_1(t) \\ m_1'(t) &= E_1 V_1(t) + E_2 F_1(t) - \mu_m m_1(t), \end{aligned} \tag{4.1}$$

where

$$A_1 = \beta(V^*) + V^* \frac{\partial \beta(V^*)}{\partial V} - \frac{\partial \gamma(V^*, F^*)}{\partial V} - \gamma(V^*, F^*)$$

$$A_2 = -V^* \frac{\partial \gamma(V^*, F^*)}{\partial F} < 0$$

$$B_1 = -\eta \left(\gamma(V^*, F^*) + V^* \frac{\partial \gamma(V^*, F^*)}{\partial V} \right),$$

$$B_2 = C^* \frac{\partial \rho(F^*)}{\partial F} - \eta V^* \frac{\partial \gamma(V^*, F^*)}{\partial F} - \mu_f$$

$$D_1 = V^* \frac{\partial \alpha(V^*, F^*)}{\partial V}$$

$$D_2 = V^* \frac{\partial \alpha(V^*, F^*)}{\partial F}$$

$$E_1 = \sigma(V^*, F^*) + \frac{\partial \sigma(V^*, F^*)}{\partial V} > 0$$

and

$$E_2 = V^* \frac{\partial \sigma(V^*, F^*)}{\partial F} < 0. \tag{4.2}$$

Consider

$$\begin{bmatrix} V_1(t) \\ F_1(t) \\ C_1(t) \\ m_1(t) \end{bmatrix} = \begin{bmatrix} V_1(t_0) \\ F_1(t_0) \\ C_1(t_0) \\ m_1(t_0) \end{bmatrix} e^{\lambda t} \tag{4.3}$$

as a trial solution for the system (4.1). Then λ satisfies the characteristic equation

$$f(\lambda) = (\lambda + \mu_m)\, \mathscr{F}(\lambda) = 0, \tag{4.4}$$

where

$$\mathscr{F}(\lambda) = \lambda^3 + \delta\lambda^2 + \varepsilon\lambda + \theta + (\chi\lambda + \phi)e^{-\tau\lambda} \tag{4.5(a)}$$

with the coefficients

$$\begin{aligned}
\delta &= (\mu_c - A_1 - B_2) \\
\varepsilon &= A_1 B_2 - A_2 B_1 - \mu_c (A_1 + B_2) \\
\theta &= -\mu_c (A_2 B_1 - A_1 B_2 - \rho(F^*) A_2) \\
\chi &= -\rho(F^*) D_2 \\
\phi &= \rho(F^*)(A_1 D_2 - \alpha(V^*, F^*) A_2).
\end{aligned} \tag{4.5(b)}$$

If all the roots of (4.4) are negative real or complex with negative real parts, then $E^*(V^*, F^*, C^*, m^*)$ would be asymptotically stable. From (4.4), one root $\lambda = -\mu_m$ is real and negative. So it is enough to discuss the roots of the quasicharacteristic equation $\mathscr{F}(\lambda) = 0$. Further, the Routh–Hurwitz conditions checked in (4.4) yield $\delta > 0$, $(\theta + \phi) > 0$, $(\varepsilon + \chi) > 0$, and $\delta(\varepsilon + \chi) - (\theta + \phi) > 0$, which confirms the asymptotic stability of $E^*(V^*, F^*, C^*, m^*)$ in the absence of time-delay ($T = 0$). These inequalities continue to hold even in the presence of delay, throughout our discussion.

Setting

$$\lambda(T) = \mu(T) + iv(T) \tag{4.6}$$

in $\mathscr{F}(\lambda) = 0$ and separating real and imaginary parts, we get

$$\begin{aligned}
&\mu^3 - 3\mu v^2 + \delta(\mu^2 - v^2) + \varepsilon\mu + \theta \\
&\quad + \{(\chi\mu + \phi) \cos vT + \chi v \sin vT\} e^{-T\mu} = 0
\end{aligned}$$

and

$$\begin{aligned}
&-v^3 + 3\mu^2 v + 2\delta\mu v + \varepsilon v \\
&\quad + \{\chi v \cos vT - (\chi\mu + \phi) \sin vT\} e^{-T\mu} = 0.
\end{aligned} \tag{4.7}$$

Defining the space of all real-valued continuous functions on $[-T, \infty)$, such that $V_1(t) \geqslant 0$, $F_1(t) \geqslant 0$, $C_1(t) \geqslant 0$, and $m_1(t) \geqslant 0$ on $[-T, t_0]$ and applying the Laplace transforms to the system (4.1), we obtain

$$\begin{aligned}
(s - A_1)\bar{V}_1(s) &= A_2 \bar{F}_1(s) + V_1(t_0) \\
(s - B_2)\bar{F}_1(s) &= B_1 \bar{V}_1(s) + \rho(F^*)\bar{C}_1(s) + F_1(t_0) \\
(s + \mu_c)\bar{C}_1(s) &= D_1 e^{-Ts}\bar{V}_1(s) + (\alpha(V^*, F^*) + D_2 e^{-Ts})\bar{F}_1(s) \\
&\quad + D_1 e^{-Ts} V_{1int} + D_2 e^{-Ts} V_{1int} + C_1(t_0) \\
(s + \mu_m)\bar{m}_1(s) &= E_1 \bar{V}_1(s) + E_2 \bar{F}_1(s) + m_1(t_0),
\end{aligned} \tag{4.8}$$

where $\bar{V}_1(s)$, $\bar{F}_1(s)$, $\bar{C}_1(s)$, and $\bar{m}_1(s)$ are the Laplace transforms of $V(t)$, $F(t)$, $C(t)$, and $m(t)$, respectively. Further, $V_1(t_0)$, $F_1(t_0)$, $C_1(t_0)$, $m_1(t_0)$ are non-negative. Also

$$V_{1int} = \int_{-T}^{0} e^{-ts} V_1(t)\, dt \qquad \text{and} \qquad F_{1int} = \int_{-T}^{0} e^{-ts} F_1(t)\, dt.$$

Solving the system (4.8), for any one of the variables, say $\bar{m}_1(s)$, we obtain

$$\bar{m}_1(s) = \frac{g(s)}{(s+\mu_m)\mathscr{F}(s)}, \tag{4.9}$$

where $\mathscr{F}(\cdot)$ is the quasicharacteristic polynomial given by (4.5(a)) and

$$\begin{aligned} g(s) = E_1[&A_2\rho(F^*)(D_1 e^{-Ts} V_{1int} + \alpha(V^*, F^*)e^{-Ts} F_{1int} + C_1(t_0)) \\ &+ V_1(t_0)\{(s-B_2)(s+\mu_c) - (\rho(F^*)\alpha(V^*, F^*) + D_2 e^{-Ts})\} \\ &+ (E_2\bar{F}_1(s) + m_1(t_0))\mathscr{F}(s)]. \end{aligned} \tag{4.10}$$

For the state $E^*(V^*, F^*, C^*, m^*)$ to be locally asymptotically stable, $\bar{m}_1(s)$ should have the poles with terms that exponentially decrease with time so that their real parts are negative. This can be achieved by employing the Nyquist's criterion, which states that, if s is the arc length along a curve encircling the right half plane, then the curve $\bar{m}_1(s)$ will encircle the origin a number of times equal to the difference between the number of poles and the number of zeros of $\bar{m}_1(s)$ in the right half plane. Following [4–6], the conditions for asymptotic stability of $E^*(V^*, F^*, C^*, m^*)$ are given by

$$\operatorname{Im} \mathscr{F}(iv_0) > 0$$

and

$$\operatorname{Re} \mathscr{F}(iv_0) = 0. \tag{4.11}$$

In the present case, these conditions reduce to

$$-v_0^3 + \varepsilon v_0 + \chi v_0 \operatorname{Cos} v_0 T - \phi \operatorname{Sin} v_0 T > 0$$

and

$$-\delta v_0^2 + \theta + \phi \operatorname{Cos} v_0 T + \chi v_0 \operatorname{Sin} v_0 T = 0. \tag{4.12}$$

5. Conditions for Stability of the Diseased State

In this section, we derive two conditions for the asymptotic stability of $E^*(V^*, F^*, C^*, m^*)$ by using the results of the above section. The first condition gives an estimate for the length of time-delay to preserve the stability in an interval $[0, T^+)$ where T^+ is the maximum value of T and the second one yields a criterion for no stability change in an interval $[0, v^+]$ where v^+ is the maximum value of v. A numerical example is identified to illustrate the analysis carried out in this section.

From the equality of (4.12),

$$\delta v_0^2 = \theta + \phi \operatorname{Cos} v_0 T + \chi v_0 \operatorname{Sin} v_0 T \leqslant |\theta| + |\phi| + |\chi|\, v_0. \tag{5.1}$$

So if

$$v^+ \equiv \frac{|\chi| + \sqrt{|\chi|^2 + 4\delta(|\theta| + |\phi|)}}{2\delta} \tag{5.2}$$

then $v_0 \leqslant v^+$. From the inequality of (4.12),

$$v_0^2 < \varepsilon + \chi \operatorname{Cos} v_0 T - \frac{\phi \operatorname{Sin} v_0 T}{v_0}. \tag{5.3}$$

Substituting the equality of (4.12) in (5.3) and simplifying,

$$P(T, v_0) < Z, \tag{5.4}$$

where

$$P(T, v_0) = (\chi\delta - \phi)(1 - \operatorname{Cos} v_0 T) + \left(\chi v_0 + \frac{\phi\delta}{v_0}\right) \operatorname{Sin} v_0 T$$

and

$$Z = \delta(\varepsilon + \chi) - (\theta + \phi) > 0. \tag{5.5}$$

Using the inequalities

$$\begin{aligned} (\chi\delta - \phi)(1 - \operatorname{Cos} v_0 T) &= 2(\chi\delta - \phi) \operatorname{Sin}^2 \frac{v_0 T}{2} \\ &\leqslant \frac{(v^+ T)^2}{2} |\chi\delta - \phi|; \\ \left(\chi v_0 + \frac{\phi\delta}{v_0}\right) \operatorname{Sin} v_0 T &\leqslant (|\chi|\,(v^+)^2 + |\phi|\,\delta) T, \end{aligned} \tag{5.6}$$

the inequality (5.4) reduces to

$$XT^2 + YT < Z, \tag{5.7}$$

where

$$X = \tfrac{1}{2} |\delta\chi - \phi| \, (v^+)^2,$$

and

$$Y = |\chi| \, (v^+)^2 + |\phi| \, \delta. \tag{5.8}$$

From the inequality (5.7), we notice the maximum time-delay to be

$$T^+ \equiv \frac{1}{2X}(-Y + \sqrt{Y^2 + 4ZX}). \tag{5.9}$$

The diseased state E^* maintains its stability if (5.9) is satisfied in the interval of time-delay $0 \leqslant T < T^+$.

Further, the stability of E^* can change only when $\mu = 0$. This is true because the equations (4.7) will have purely imaginary roots, i.e., the perturbed system is oscillatory with finite amplitude. In what follows we derive a criterion under which this cannot happen for an arbitrary time-delay.

Let $\hat{T}$ and $\hat{v}$ satisfy the equations (4.7) with $\mu = 0$, i.e.,

$$-\delta\hat{v}^2 + \theta + \phi \operatorname{Cos} \hat{v}\hat{T} + \chi \operatorname{Sin} \hat{v}\hat{T} = 0$$

and

$$-\hat{v}^3 + \varepsilon\hat{v} + \chi\hat{v} \operatorname{Cos} \hat{v}\hat{T} - \phi \operatorname{Sin} \hat{v}\hat{T} = 0. \tag{5.10}$$

We rewrite these equations as

$$\phi \operatorname{Cos} \hat{v}\hat{T} + \chi\hat{v} \operatorname{Sin} \hat{v}\hat{T} = \delta\hat{v}^2 - \theta$$

and

$$\phi \operatorname{Sin} \hat{v}\hat{T} - \chi\hat{v} \operatorname{Cos} \hat{v}\hat{T} = \varepsilon\hat{v} - \hat{v}^3. \tag{5.11}$$

Choosing R and Ψ, such that,

$$\phi = R \operatorname{Cos} \Psi \quad \text{and} \quad \chi\hat{v} = R \operatorname{Sin} \Psi, \tag{5.12}$$

then

$$R = \sqrt{\phi^2 + \chi^2\hat{v}^2} \quad \text{and} \quad \Psi = \tan^{-1}\left(\frac{\chi\hat{v}}{\phi}\right). \tag{5.13}$$

Substituting (5.12) into (5.11), we get

$$\mathrm{Cos}(\hat{\nu}\hat{T} - \Psi) = \frac{\delta\hat{\nu}^2 - \theta}{R}$$

and

$$\mathrm{Sin}(\hat{\nu}\hat{T} - \Psi) = \frac{\varepsilon\hat{\nu} - \hat{\nu}^3}{R}. \tag{5.14}$$

From (5.14), we can write

$$R \geqslant \mathrm{Max}\{|\delta\hat{\nu}^2 - \theta|,\ \hat{\nu}\,|\varepsilon - \hat{\nu}^2|\}, \tag{5.15}$$

i.e.,

$$\sqrt{\phi^2 + \chi^2\hat{\nu}^2} \geqslant \mathrm{Max}\{|\delta\hat{\nu}^2 - \theta|,\ \hat{\nu}\,|\varepsilon - \hat{\nu}^2|\}. \tag{5.16}$$

There can be no change in stability if (5.16) is satisfied for $0 \leqslant \hat{\nu} \leqslant \nu^+$.

EXAMPLE. Consider the system

$$\begin{aligned}
V'(t) &= \{V(t) - (F(t) - V(t))\}\,V(t)\\
F'(t) &= \tfrac{1}{16}F(t)C(t) - 3(F(t) - V(t))\,V(t) - \mu_f F(t)\\
C'(t) &= (-2V(t) + 8F(t-T))\,V(t-T) - \mu_c(C(t) - \tilde{C})\\
m'(t) &= (V(t)/F(t))\,V(t) - \mu_m m(t).
\end{aligned}$$

For the above set, $E^*(V^*, 2V^*, 24V^* + 16\mu_f,\ V^*/2\mu_m)$ is an interior equilibrium point. Let the following inequality hold:

$$\mathrm{Max}\left\{\frac{12}{7}, \sqrt{\frac{12}{7}\mu_c}\right\} < V^* < \mathrm{Min}\left\{\frac{\mu_c}{7}, -\frac{2}{7}\mu_c + \frac{1}{7}\sqrt{\frac{2}{3}\mu_c(13\mu_c + 42)}\right\}.$$

Now

$$A_1 = 2V^*, \qquad A_2 = -V^*, \qquad B_1 = 0, \qquad B_2 = -3V^*, \qquad D_1 = -2V^*,$$

$$D_2 = 8V^*, \qquad E_1 = \frac{1}{2}\left(1 + \frac{1}{V^*}\right), \qquad E_2 = -\frac{1}{4}.$$

Further,

$$\delta = (\mu_c + V^*), \qquad \varepsilon = (\mu_c V^* - 6V^{*2}), \qquad \theta = -\left(6\mu_c V^* + \frac{V^{*3}}{4}\right),$$

$$\chi = -V^{*2}, \qquad \phi = \frac{15}{4}V^{*3}.$$

So

$$v^+ = \frac{1}{2(\mu_c + V^*)}\{V^{*2} + \sqrt{V^{*4} + 8V^*(\mu_c + V^*)(3\mu_c + 2V^{*2})}\}.$$

Also

$$X = \frac{1}{2} V^{*2}\left(\mu_c + \frac{19}{4} V^*\right)(v^+)^2 > 0$$

$$Y = \frac{15}{4} V^{*3}(\mu_c + V^*) + V^{*2}(v^+)^2 > 0$$

and

$$Z = \mu_c(6 + \mu_c) V^* - 6\mu_c V^{*2} - \frac{21}{2} V^{*3} > 0.$$

Hence

$$T^+ = \frac{1}{(4\mu_c + 19V^*)(v^+)^2} \times \left[\begin{array}{l} -15(\mu_c + V^*) V^* - 4(v^+)^2 \\ \quad + \Big(\{15(\mu_c + V^*) V^* + 4(v^+)^2\}^2 \\ \qquad + 4(\mu_c + 19V^*) \left\{ -21V^* - 12\mu_c + \dfrac{2\mu_c}{V^*}(6 + \mu_c) \right\} \Big)^{1/2} \end{array} \right].$$

The state E^* cannot get destabilized for $0 \leqslant T < T^+$ and there can be no change in stability if

$$\frac{1}{4}\sqrt{225V^{*2} + 16\hat{v}^2} \geqslant \text{Max}\left\{ |-(6V^{*2} - \hat{v}^2 + \mu_c V^*)|\, \hat{v};\right.$$
$$\left. 6\mu_c V^* + \frac{V^{*3}}{4} + (\mu_c + V^*)\hat{v}^2 \right\},$$

for $0 \leqslant \hat{v} \leqslant v^+$.

6. Conclusions

In this work, a generalization of Marchuk's model for a virus disease has been proposed giving due importance to the mutual interference among the viruses attacking the organ and the organ's immune system. The solutions

are observed to be non-negative, by inspection. The stability analysis of the diseased equilibrium state has been carried out by deriving its characteristic equation as the function of time-delay. It is observed that the state cannot get destabilized in the time-delay interval $[0, T^+)$, where the estimated T^+ is given by (5.9). Further, there can be no change in stability if (5.16) is satisfied for $[0, v^+]$, where v^+ is given by (5.2). An explicit numerical example satisfying these criteria is presented.

More realistic models with multiple delays can be proposed with more generalised, yet reasonable, restrictions such as (H_1)–(H_{12}) on the mutual interference functions and the stability analysis of the diseased state can be carried out on similar lines.

APPENDIX: MARCHUK'S CLASSIFICATION ON THE MODEL OF A VIRUS DISEASE

The well-known four forms of a disease are (i) subclinical, (ii) acute with recovery, (iii) chronic, and (iv) lethal outcome.

(i) The subclinical form. In this case, the viruses attacking the organ cannot break the immunologic barrier. The virus concentration tends to zero with time, regardless of the dose of viruses, which could cause infection or the extent of the organ-damage or the delay as well as the degree of immune response. In this state, there may be a bleak chance of having a considerable damage to the organ attacked by viruses.

(ii) Acute with recovery. This is a case in which the growth of virus concentration with time would be followed by a sharp drop of the concentration. This may sometimes result in complete elimination of viruses from the organ. Hence it may be possible to have a recovery from an acute state of the disease.

(iii) Chronic. It is this form of the disease which is more important and needs more attention in the analysis. In this case, the virus concentration tends to a constant nonzero level. The viruses, while attacking the organ, break the immunologic barrier to offer resistance to antibodies. The antibodies improve their population, with immunocompetent cells, supplied by plasma-cells. There could also be a continued growth, which may not be rapid, in the relative characteristic of the damaged organ. It would result in the existence of a non-washed-out equilibrium state, i.e., a state in which the viruses and antibodies can coexist in the damaged organ. The stability of this state depends very much upon the strength of the immune system contained in the organ. The destability of this state may result as the lethal outcome.

TABLE I

Form of the disease	Condition for occurrence	Special features
Subclinical	$\beta < \gamma\tilde{F}$	$V(t) \to 0$ as $t \to \infty$
Acute with recovery	$\beta > \gamma\tilde{F}$, $\rho > \beta\gamma\eta$, $\tilde{\beta} > (0, 33)$ days^{-1}	Rapid reduction of $V(t)$ after increase
Chronic	$\beta > \gamma\tilde{F}$, $\alpha\rho > \mu_c\eta\gamma$, $\beta < (0, 33)$ days^{-1}	$V(t) \to V^*$ as $t \to \infty$
Lethal	$\beta > \gamma\tilde{F}$, $\rho < \beta\gamma\eta$	$V(t) \to \infty$ as $t \to \infty$

Note. $\tilde{\beta} = \beta - \gamma\tilde{F}$, $\tilde{F} = \rho\tilde{C}/\mu_f$, where $\tilde{}$ stands for the value at normal level.

(iv) Lethal outcome. This occurs when the stimulation coefficient is small or the time-delay is large. This results in further weakening of the immune system and the unlimited growth of the viruses in the organ.

From a qualitative analysis of the basic model proposed by Marchuk [7] for constant values of β, γ, η, α, ρ, σ, it is possible to distinguish the above four forms of the development of the disease, when the organ is slightly damaged. The results of the analysis are given in Table I.

ACKNOWLEDGMENT

One of the authors, N. C. Srinivas, acknowledges the Council of Scientific and Industrial Research (CSIR), India for providing financial support.

REFERENCES

1. N. T. J. BAILEY, "The Mathematical Theory of Infectious Diseases," Griffin, London, 1975.
2. J. R. BEDDINGTON, Mutual interference between parasites and predators and its effect on searching efficiency, *J. Animal Ecol.* **44** (1975), 331–340.
3. J. M. CUSHING, Integrodifferential equations and delay models in population dynamics, *in* "Lecture Notes in Biomathematics," Vol. 20, Springer, Heidelberg, 1977.
4. L. H. ERBE, H. I. FREEDMAN, AND V. SREE HARI RAO, Three-species food-chain models with mutual interference and time-delays, *Math. Biosci.* **80** (1986), 57–80.
5. H. I. FREEDMAN AND V. SREE HARI RAO, The trade-off between mutual interference and time-delays in predator-prey systems, *Bull. Math. Biol.* **45** (1983), 991–1004.
6. H. I. FREEDMAN AND V. SREE HARI RAO, Stability criteria for a system involving two time-delays, *SIAM J. Appl. Math.* **46**, No. 4 (1986), 552–560.

7. G. I. MARCHUK, "Mathematical Models in Immunology," Optimization Software Inc., New York, 1983.
8. G.I. MARCHUK, A. L. ASACHENOV, L. N. BELYKH, AND S. M. ZUEV, Mathematical modelling of infectious diseases, *in* "Immunology and Epidemiology Proceedings, Poland" (G. W. Hoffman and T. Hraba, Eds.), pp. 64–81, Lecture Notes in Biomathematics, Vol. 65, Springer, Heidelberg, 1985.
9. V. SREE HARI RAO AND H. I. FREEDMAN, A model predator-prey system with mutual interference and time-delay, *in* "Population Biology Proceedings, Edminton, 1982" (H. I. Freedman and C. Strobeck, Eds.), pp. 317–319, Lecture Notes in Biomathematics, Vol. 52, Springer, Heidelberg, 1983.