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Andronov-Hopf and Neimark-Sacker Bifurcations in Time-Delay Models of HIV Transmission

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Abstract : In this paper, we study the bifurcation properties of one-dimensional, time-delayed disease models for HIV. The models include the effects of vertical HIV transmission from mother to baby, the effects of births and deaths and of treatment by antivirals. We first investigate the properties of differential equation models and establish conditions for the existence and stability of equilibrium points and for the existence of Andronov-Hopf bifurcations at critical values of the time delays. We then investigate the properties of discretized versions of the models and establish conditions for the existence and stability of equilibrium points and for the existence of Neimark-Sacker bifurcations at critical values of the time delays.

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We show that the critical delay times for Neimark-Sacker bifurcations are less than the critical times for Andronov-Hopf bifurcation but converge to them in the limit as the time step of the discretization in the discretized model tends to zero. Numerical simulations are presented for a selected set of parameter values.

Keywords : Andronov-Hopf bifurcation; Neimark-Sacker bifurcation; time delay; asymptotic stablility; limit cycles; HIV.
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1 Introduction

Many researchers have developed mathematical models in an attempt to develop an understanding of HIV transmission at either the cell level (see, e.g. [1–10]) or the population level (see, e.g. [11, 12]).

In the present paper, we consider a generalization of a model at the population level originally proposed by Roberts and Saha [12]. The model is a nonlinear differential equation model for the fraction of a population infected with HIV.

$$\frac{dx(t)}{dt} = (p-1)Bx(t) + (\beta C - \alpha)x(t)(1-x(t)), \tag{1.1}$$

where $x(t)$ is the proportion of the total population that is infected at time t, $p(0 < p < 1)$ is the vertical transmission probability (the fraction of babies born with HIV infection), B is the birth rate for the population, β is the transmission rate on contact between an infected and an uninfected individual, C is the contact rate between infected and uninfected individuals, and α is the increase of the death rate due to the HIV infection.

Although current treatment of HIV patients with antiretroviral therapy can slow the progression of the disease and reduce the level of the virus below detectable levels, it cannot cure the infected patients (see, e.g., [4]–[6], [13]). Antiretroviral therapy can reduce both disability and mortality. There is also recent evidence (see, e.g., [14–16]) that antiretroviral theraphy can depress the HIV level in an HIV+ person sufficiently to effectively stop transmission of HIV from an HIV+ person to an uninfected person. However, in many countries antiretroviral therapy is not available. A further difficulty is that, in the early stages, infection by HIV is asymptomatic. As a result, these asymptomatic infected people may interact normally with people and pass on the disease to uninfected people.

Several authors have studied the effects of time delays in mathematical models of HIV transmission (see, e.g., [8, 17–20]). For example, they separate the HIV populations into susceptible, latently infected, and actively infected populations and then assume a time delay for transition from the latently infected to the actively infected stage. An important property of many time-delay models is that they have bifurcations. Common types of bifurcation for differential equations are the Andronov-Hopf (or Hopf) bifurcations and common types of bifurcation

for difference equations are the Neimark-Sacker bifurcations (see, e.g., [21]). In this paper, we are interested in comparing the Andronov–Hopf bifurcations in differential equation models with the Neimark-Sacker bifurcations in approximating difference equation models.

2 Differential Equation Models

In this paper, we extend the model in equation (1.1) by introducing time delays into the model and by including the effect of treatment by antiretrovirals.

We divide the population into a susceptible (uninfected group) $S(t)$ and an infected group $I(t)$ and consider a basic model of the following form

$$\begin{aligned} \frac{dS}{dt} &= BS(t) + (1-p)BI(t) - \beta CS(t)I(t) - \mu S(t), \\ \frac{dI}{dt} &= pBI(t) + \beta CS(t)I(t) - (\mu+\alpha)I(t), \end{aligned} \tag{2.1}$$

where B is the birth rate, p is the probability that an infected mother gives birth to an infected baby (the vertical transmission probability), β is the rate of infection on contact between a susceptible and an infected person, C is the contact rate of a susceptible and an infected person, μ is the natural death rate and α is the increase in death rate of an infected person. We assume that this extra death rate of an infected person includes a possible transition to AIDS as well as actual death.

Two commonly used antivirals are the reverse transcriptase inhibitors (RTI) and the protease inhibitors (PI) (see, e.g., [22–24]). The main effect of the RTI appears to be to reduce the rate of transmission from latent infection to active infectiousness and the main effect of the PI appears to be to reduce the level of active free virus in the blood (see, e.g., [2, 4–6, 10]). In the present model, we assume that the effects of both the RTI and the PI can be included in the model in (2.1) as factors reducing the value of β (the rate of infection on contact) and p (the vertical transmission probability). We assume that

$$\beta = (1-n_{av})\beta_0, \qquad p = (1-n_{av})p_0, \tag{2.2}$$

where n_{av} is an antiretroviral therapy factor ($0 \le n_{av} < 1$) and β_0 and p_0 are, respectively, the infection rate of a susceptible person and the vertical transmission probability in the absence of antiretroviral therapy.

We transform the 2-population model in (2.1) into a single equation model by letting $x(t) = \frac{I(t)}{S(t)+I(t)}$ be the fraction of the total population that is infected (see, e.g., [12]). For the rate of change of the total population, we obtain an equation of the form ($N = S + I$)

$$\frac{dN}{dt} = \frac{d(S+I)}{dt} = (B-\mu)N - \alpha I,$$

and then

$$\frac{dx}{dt} = \frac{1}{N}\frac{dI}{dt} - \frac{x}{N}\frac{dN}{dt} = -\delta x(t) + \varepsilon x(t)(1-x(t)), \tag{2.3}$$

where $\delta = (1-p)B$ and $\varepsilon = \beta C - \alpha$. We can assume that $\delta > 0$ and $\varepsilon > 0$.

As there are 3 different positions to include a single time delay τ into model (2.3), there are a total of 7 different time delay versions of the model. We have studied the behaviour of these 7 versions and found that their bifurcation properties can be very different, with 5 of the versions having bifurcations under certain conditions on the parameter values and 2 of the versions not having bifurcations. In this paper, we will discuss only two of these versions that have bifurcations, namely, the two versions shown in (2.4). It is interesting to compare the different bifurcation properties of these HIV models for the differential equation models, which have Andronov-Hopf bifurcations, and equivalent difference equation models, which have Neimark-Sacker bifurcations.

$$\begin{aligned} \text{HIV1} \quad \frac{dx(t)}{dt} &= -\delta x(t) + \varepsilon x(t)[1 - x(t-\tau)], \\ \text{HIV2} \quad \frac{dx(t)}{dt} &= -\delta x(t-\tau) + \varepsilon x(t-\tau)[1 - x(t-\tau)]. \end{aligned} \tag{2.4}$$

3 Difference Equation Models

As the growth rate of diseases (such as HIV/AIDS) or other kinds of populations (such as fish) can be a slow process or the collection of data can often only be carried out at regular intervals such as a month or a year, it is often only possible to construct difference equation models. One method that is often used to construct a difference equation model is to use a first-order Euler method to approximate the differential equation model (see, e.g., [19,25,26]) This method is also often used to solve Itó stochastic differential equations (see, e.g., Euler-Mayurama method [27]).

For time-delay models it is useful to rescale the time variable in units of the time delay, i.e., we define $T = t/\tau$ (see, e.g., [11]) and then make the substitutions

$$x(t) = x(T\tau) = w(T), \quad \frac{dx(t)}{dt} = \frac{1}{\tau}\frac{dw(T)}{dT}, \quad w(T-1) = x(T\tau - \tau). \tag{3.1}$$

Applying the rescaling in (3.1) to (2.4), we obtain the 2 equations in (3.2).

$$\begin{aligned} \text{HIV1} \quad \frac{dw(T)}{dT} &= -\delta\tau w(T) + \varepsilon\tau w(T)[1 - w(T-1)], \\ \text{HIV2} \quad \frac{dw(T)}{dT} &= -\delta\tau w(T-1) + \varepsilon\tau w(T-1)[1 - w(T-1)]. \end{aligned} \tag{3.2}$$

Next, we transform the equations into difference equations by using the forward Euler scheme with step size given by $h = \frac{1}{m}$, where m is the number of time steps in the delay time. Then, we let

$$T_n = nh, \quad w(T_n) = w_n, \quad w(T_n - 1) = w(nh - mh) = w_{n-m}, \tag{3.3}$$

and use the finite difference approximation

$$\frac{dw(T_n)}{dT_n} = \frac{1}{h}(w(T_{n+1}) - w(T_n)) = \frac{1}{h}(w_{n+1} - w_n). \tag{3.4}$$

and obtain the two Euler difference equations in (3.5).

$$\begin{array}{lrcl} \text{HIV1} & w_{n+1} & = & w_n - \delta h\tau w_n + \varepsilon h\tau w_n(1 - w_{n-m}), \\ \text{HIV2} & w_{n+1} & = & w_n - \delta h\tau w_{n-m} + \varepsilon h\tau w_{n-m}(1 - w_{n-m}). \end{array} \tag{3.5}$$

It can be seen that each of these Euler approximation equations are difference equations of order $m + 1$.

4 Equilibrium Points, Stability and Andronov-Hopf Bifurcations of Differential Equation Models

4.1 Equilibrium Points and Basic Reproduction Numbers

The equilibrium points x^* for the differential equation models are obtained by setting $\frac{dx}{dt} = 0$ in the differential equation (2.4). We obtain a trivial equilibrium point $x^* = 0$ and an endemic equilibrium point which exists only if $x^* > 0$. The two equilibrium points are:

$$\text{Disease-free} \quad x^* = 0, \qquad \text{Endemic} \quad x^* = 1 - \frac{\delta}{\varepsilon}. \tag{4.1}$$

The endemic equilbrium exists only if $\varepsilon > \delta$. Using a standard approach, such as the next-generation method [28], or by checking the eigenvalues of the linearized system at the disease-free equilibrium (see section 4.2), we can show that the basic reproduction number R_0 for the HIV model is $R_0 = \frac{\varepsilon}{\delta}$ for both differential and difference equation models. Therefore, the disease-free equilibrium points are stable for $R_0 < 1$ and the endemic equilibrium points exist only if $R_0 > 1$.

4.2 Conditions for Stability and Andronov-Hopf Bifurcations

Using the standard methods, we derive the conditions for local asympotic stability (see, e.g., [29, 30]) and Andronov-Hopf bifurcations (see, e.g., [21]) by linearizing the nonlinear equations about equilibrium points.

We can obtain the linearized time-delayed versions of the nonlinear equations by defining perturbations $y(t) = x(t) - x^*$ and $y(t - \tau) = x(t - \tau) - x^*$. Then the linearized versions for the two HIV model delay equations in (2.4) are:

$$\text{Disease-free} \quad \frac{dy}{dt} = (\varepsilon - \delta)y(t - \tau), \quad \text{Endemic} \quad \frac{dy}{dt} = (\delta - \varepsilon)y(t - \tau). \tag{4.2}$$

As usual, we assume a trial solution $y(t) = e^{\lambda t}$. The characteristic equations from the trial solution are then:

$$\text{Disease-free} \quad \lambda = (\varepsilon - \delta)e^{-\lambda\tau}, \quad \text{Endemic} \quad \lambda = (\delta - \varepsilon)e^{-\lambda\tau}. \tag{4.3}$$

Then, the general solution $y(t) \to 0$ as $t \to \infty$ and the equilibrium point x^* is locally asymptotically stable if the real parts of all eigenvalues λ of (4.3) are negative.

For the disease-free equilibrium and zero time delay, the characteristic equation has negative eigenvalues for $\varepsilon - \delta < 0$. Therefore the disease-free equilibrium is locally stable if $R_0 = \frac{\varepsilon}{\delta} < 1$ and unstable if $R_0 > 1$. These values for R_0 agree with the values obtained in section (4.1) from the condition for existence of the endemic equilibrium points.

For $R_0 > 1$, the possibilities are that the endemic equilibrium is locally stable or that a bifurcation, for example, an Andronov–Hopf (or Hopf) bifurcation, might occur. From bifurcation theory (see, e.g., [21]), Andronov–Hopf bifurcations exist in an equilibrium solution if the eigenvalues λ of the linearized equation about this equilibrium solution have the following properties:

1. There exists a critical value of $\tau = \tau_c$ for which an eigenvalue $\lambda_c = i\omega_c$ is purely imaginary.
2. At the critical value, all other eigenvalues have negative real parts.
3. The derivative $\left.\dfrac{d(\text{Real}(\lambda))}{d\tau}\right|_{\tau=\tau_c} \neq 0.$

We first look for possible bifurcation points for the endemic equilbrium $\varepsilon > \delta$ by looking for a purely imaginary solution $\lambda_c = i\omega_c$ of (4.3) for $\omega_c \in (-\pi, \pi)$, $\omega_c \neq 0$.

Theorem 4.1. *A necessary condition for existence of purely imaginary solutions $\lambda = i\omega$ of the characteristic equation $\lambda = (\delta - \varepsilon)e^{-\lambda\tau}$ for $\tau > 0$ and $\omega \in (-\pi, \pi)$, $\omega \neq 0$ is $\varepsilon - \delta > 0$. Then, a possible critical delay time for an Andronov-Hopf bifurcation is*

$$\tau_c = \frac{\pi}{2\omega_c}, \qquad \textit{where} \;\; \omega_c = \varepsilon - \delta. \tag{4.4}$$

Proof. Substituting $\lambda_c = i\omega_c$ into (4.3) and separating real and imaginary parts, we obtain

$$\omega_c = (\varepsilon - \delta)\sin(\omega_c\tau_c), \qquad 0 = (\varepsilon - \delta)\cos(\omega_c\tau_c). \tag{4.5}$$

Therefore, if $\varepsilon - \delta > 0$, the critical omega value ω_c and delay time τ_c in (4.4) satisfies condition 1 for the existence of an Andronov-Hopf bifurcation point. Note that this value of τ_c is also the minimum value of τ for which purely imaginary eigenvalues of (4.3) exist. □

Lemma 4.2. *If the necessary condition $\varepsilon - \delta > 0$ is satisfied and $\tau \geq 0$, then all real eigenvalues of* (4.3) *are negative. Therefore, the endemic equilibrium can only become unstable if a complex conjugate pair of solutions of* (4.3) *with zero or positive real parts exist.*

Proof. If $\lambda = \mu$ is real, then the characteristic equation is $\mu = -(\varepsilon - \delta)e^{-\mu\tau}$. For $\varepsilon - \delta > 0$ and $\tau \geq 0$, all solutions are negative. □

We can now prove condition 2.

Theorem 4.3. *For $0 \leq \tau < \tau_c$ all eigenvalues of (4.3) have negative real parts.*

Proof. For $\tau = 0$, the solution of the characteristic equation (4.3) is $\lambda = \mu = -(\varepsilon - \delta)$ and $\omega = 0$. From Lemma 4.2, if eigenvalues of (4.3) exist with zero or positive real parts then they must be a complex conjugate pair. Then, since the solutions of (4.3) are continuous functions of τ and $\mu < 0$ for $\tau = 0$, solutions can only have positive real parts if there exists a critical value of τ at which $\mu = 0$. As shown in Theorem 4.1 the minimum value of τ for a zero real part is τ_c. □

We now prove that condition 3 for the existence of an Andronov-Hopf bifurcation point is satisfied by τ_c.

Theorem 4.4. *If the necessary condition of Theorem 4.1 is satisfied, then the critical delay time $\tau_c > 0$ in (4.4) also satisfies condition 3 for the existence of an Andronov-Hopf bifurcation.*

Proof. Let $\lambda = \mu + i\omega$. Then differentiating the characteristic equation (4.3) with respect to τ and separating real and imaginary parts, we obtain

$$\frac{d\mu}{d\tau} = \frac{1}{\Delta}(\varepsilon - \delta)e^{-\mu\tau}[\mu\cos(\omega\tau) + \omega\sin(\omega\tau) - \mu\tau(\varepsilon - \delta)e^{-\mu\tau}], \tag{4.6}$$

where

$$\Delta = (1 - \tau(\varepsilon - \delta)e^{-\mu\tau})^2 + 2\tau(\mu + (\varepsilon - \delta)e^{-\mu\tau}). \tag{4.7}$$

Then substituting $\mu = 0$, $\omega = \omega_c$ and $\tau = \tau_c$ into (4.6) and (4.7), we obtain

$$\left.\frac{d\mu}{d\tau}\right|_{\tau=\tau_c} = \frac{1}{\Delta_c}(\varepsilon - \delta)\omega_c\sin(\omega_c\tau_c) = \frac{\omega_c^2}{(1 - \tau_c(\varepsilon - \delta))^2 + 2\tau_c(\varepsilon - \delta)}. \tag{4.8}$$

Since $\varepsilon - \delta > 0$, the denominator is always positive and therefore condition 3 is satisfied. Also, since $\left.\frac{d\mu}{d\tau}\right|_{\tau=\tau_c} > 0$, the bifurcation occurs as τ increases to τ_c. □

5 Equilibrium Points, Stability and Neimack-Sacker Bifurcations of Difference Equation Models

5.1 Equilibrium Points and Basic Reproductive Numbers

The equilibrium points w^* for the difference equation models are obtained by setting $w_{n+1} = w_n = w_{n-m} = w^*$ in the difference equations (3.5). For each model, we obtain a trivial equilibrium point $w^* = 0$ and an endemic equilibrium

point which exists only if $w^* > 0$. The two equilibrium points for each model are the same as for the differential equation models, i.e.,

$$\text{Disease-free} \quad w^* = 0, \qquad \text{Endemic} \quad w^* = 1 - \frac{\delta}{\varepsilon}. \tag{5.1}$$

The endemic equilbrium exists only if $\varepsilon > \delta$. As for the differential equation case, this condition can be written as $R_0 = \frac{\varepsilon}{\delta} > 1$, where R_0 is the basic reproduction number for the model.

5.2 Stability and Conditions for Neimark-Sacker Bifurcations

The local stability of the difference equation models (3.5) can be obtained by looking at the linearized equations about the equilibrium points. Setting $y_n = w_n - w^*$, where y_n is a perturbation, the linearized versions of the two models are:

$$\begin{aligned} \text{Disease-free} \qquad & y_{n+1} = y_n + (\varepsilon - \delta)h\tau y_{n-m}, \\ \text{Endemic} \qquad & y_{n+1} = y_n + (\delta - \varepsilon)h\tau y_{n-m}. \end{aligned} \tag{5.2}$$

Assuming a trial solution of the form $y_n = \lambda^n$ for (5.2) gives the characteristic equations:

$$\begin{aligned} \text{Disease-free} \qquad & P_0(\lambda) = \lambda^m(\lambda - 1) - (\varepsilon - \delta)h\tau = 0, \\ \text{Endemic} \qquad & P_1(\lambda) = \lambda^m(\lambda - 1) - (\delta - \varepsilon)h\tau = 0. \end{aligned} \tag{5.3}$$

For the disease-free equilibrium, we have $|\lambda| \leq 1$ for $\varepsilon \leq \delta$, and therefore it is locally stable for $R_0 = \frac{\varepsilon}{\delta} \leq 1$ and unstable for $R_0 > 1$.

For $R_0 > 1$, the possibilities are that the endemic equilibrium is locally stable or that a bifurcation, for example, a Neimark-Sacker bifurcation, might occur. We now consider the conditions for Neimarker-Sacker bifurcations, which are as follows (see, e.g., [21]):

Theorem 5.1. *A Neimark-Sacker bifurcation point occurs if there exists a complex conjugate pair of eigenvalues $\lambda_{1,2} = r(\tau_c)\, e^{\pm i\omega(\tau_c)}$ of a linearized system of nonlinear difference equations and if the following four conditions are satisfied*
(C1) $\lambda(\tau_c) = r(\tau_c)\, e^{i\omega(\tau_c)}$, where $r(\tau_c) = 1, r'(\tau_c) \neq 0$ and $\omega(\tau_c) = \omega_c$;
(C2) All other eigenvalues are inside the unit circle;
(C3) $e^{ik\omega_c} \neq 1$, for $k = 1, 2, 3, 4$;
(C4) $Re\left[e^{-i\omega_c} c_1(\tau_c)\right] \neq 0$, where $c_1(\tau_c)$ is a critical function for determining the direction and stability of Neimark-Sacker bifurcations.

If the condition (C4) of the Neimark-Sacker theorem is satisfied, then an invariant closed curve, topologically equivalent to a circle, will occur for τ in a one sided neighborhood of τ_c. The radius of the invariant curve will grow like $O\left(\sqrt{|\tau - \tau_c|}\right)$. One of the four cases below applies:
(1) $r'(\tau_c) > 0$, $Re\left[e^{-i\omega_c} c_1(\tau_c)\right] < 0$. The origin is asymptotically stable for

$\tau < \tau_c$ and unstable for $\tau > \tau_c$. An attracting invariant closed curve exists for $\tau > \tau_c$.
(2) $r'(\tau_c) > 0$, $Re\left[e^{-i\omega_c}c_1(\tau_c)\right] > 0$. The origin is asymptotically stable for $\tau < \tau_c$ and unstable for $\tau > \tau_c$. A repelling invariant closed curve exists for $\tau < \tau_c$.
(3) $r'(\tau_c) < 0$, $Re\left[e^{-i\omega_c}c_1(\tau_c)\right] < 0$. The origin is asymptotically stable for $\tau > \tau_c$ and unstable for $\tau < \tau_c$. An attracting invariant closed curve exists for $\tau < \tau_c$.
(4) $r'(\tau_c) > 0$, $Re\left[e^{-i\omega_c}c_1(\tau_c)\right] > 0$. The origin is asymptotically stable for $\tau > \tau_c$ and unstable for $\tau < \tau_c$. A repelling invariant closed curve exists for $\tau > \tau_c$.

From condition (C1), we know that a Neimark-Sacker bifurcation might occur if there exists a complex conjugate pair of eigenvalues of (5.3) on the unit circle. We now check if there are critical values of $\omega = \omega_c$ and $\tau = \tau_c$ such that a solution of (5.3) is of the form $\lambda = e^{\pm i\omega_c}, \omega_c \in (0, \pi)$.

Theorem 5.2. *A necessary condition for the existence of a complex conjugate pair of eigenvalues $\lambda = e^{\pm i\omega_c}$ of the characteristic equation $\lambda^m(\lambda - 1) + (\varepsilon - \delta)h\tau_c = 0$ for $\tau > 0$ and $0 < \omega < \pi$ is $\varepsilon - \delta > 0$. Then, possible critical values of $\omega = \omega_c$ and delay time $\tau = \tau_c$ for a Neimark-Sacker bifurcation are:*

$$\omega_c = \frac{\pi}{2m+1}, \qquad \tau_c = \frac{2}{(\varepsilon-\delta)h}\sin(\frac{\pi}{4m+2}). \tag{5.4}$$

Proof. We note that $\varepsilon - \delta > 0$ for the endemic equilibrium and that an alternative form of (5.3) is

$$\lambda^{m+\frac{1}{2}}(\lambda^{\frac{1}{2}} - \lambda^{-\frac{1}{2}}) = -(\varepsilon - \delta)h\tau. \tag{5.5}$$

Substituting $\lambda = e^{i\omega}$ into equation (5.5) and separating real and imaginary parts, we obtain

$$-2\sin((m+\frac{1}{2})\omega)\sin(\frac{1}{2}\omega) = -(\varepsilon-\delta)h\tau, \quad 2\cos((m+\frac{1}{2})\omega)\sin(\frac{1}{2}\omega) = 0. \tag{5.6}$$

Then, a real nonzero solution exists for $\omega = \omega_c$ and $\tau = \tau_c$ in (5.6) if and only if $\varepsilon - \delta > 0$ and $\cos((m + \frac{1}{2})\omega_c) = 0$. Then possible solutions are:

$$\omega_c = \frac{(2j+1)\pi}{2m+1}, \qquad \tau_c = \frac{2}{(\varepsilon-\delta)h}\sin(\frac{1}{2}\omega_c) \quad \text{for} \quad j = 0, 1, 2, \ldots. \tag{5.7}$$

The minimum values for τ_c are for $j = 0$, and then ω_c and τ_c are as given in (5.4). □

We now prove the second part of condition (C1).

Theorem 5.3. *For the critical values ω_c and τ_c defined in Theorem 5.2, we have $\frac{dr(\tau)}{d\tau}\Big|_{\tau=\tau_c} \neq 0$, where $\lambda(\tau) = r(\tau)e^{i\omega(\tau)}$ is the eigenvalue of maximum modulus of the endemic characteristic equation* (5.3).

Proof. Since $\lambda(\tau) = r(\tau)e^{i\omega(\tau)}$, we have

$$\frac{1}{r}\frac{dr}{d\tau} + i\frac{d\omega}{d\tau} = \frac{1}{\lambda}\frac{d\lambda}{d\tau} = -\frac{(\varepsilon-\delta)h}{\lambda^m((m+1)\lambda - m)}. \tag{5.8}$$

After some straightforward algebra, we obtain

$$\frac{dr}{d\tau} = -\frac{(\varepsilon-\delta)hr^{m+1}\left((m+1)\cos((m+1)\omega) - m\cos(m\omega)\right)}{r^{2m}\left((m+1)^2r^2 - 2m(m+1)r\cos(\omega) + m^2\right)}. \tag{5.9}$$

Then, on substituting $r(\tau_c) = 1$, $\omega = \omega_c$, $\tau = \tau_c$ into (5.9), we have

$$\left.\frac{dr}{d\tau}\right|_{\tau=\tau_c} = \frac{\tau_c(\varepsilon-\delta)^2h^2(m+\frac{1}{2})}{1 + m(m+1)(\varepsilon-\delta)^2h^2\tau_c^2} > 0. \tag{5.10}$$

□

In Theorem 5.4, we prove that a real solution of the characteristic equation cannot be the cause of the endemic equilibrium point becoming unstable.

Theorem 5.4.

1. *If λ is a real positive solution of the characteristic equation $\lambda^m(\lambda-1) = -(\varepsilon-\delta)h\tau$ then $\lambda < 1$, i.e., it is inside the unit circle.*
2. *If a real negative solution of the characteristic equation exists on the unit circle for a time delay τ_{-1}, then a Neimark-Sacker bifurcation has occurred for $\tau = \tau_c < \tau_{-1}$.*

Proof. 1. Since $\varepsilon - \delta > 0$, condition 1 is obviously true for $\tau > 0$.

2. For $\lambda = re^{i\omega}$, we have on taking the absolute value of the characteristic equation $\lambda^m(\lambda-1) = -(\varepsilon-\delta)h\tau$ that

$$|\lambda|^m|1-\lambda| = (\varepsilon-\delta)h\tau, \qquad r^m\sqrt{1-2r\cos(\omega)+r^2} = (\varepsilon-\delta)h\tau. \tag{5.11}$$

Then, for $\lambda = -1$, (5.11) gives $\quad 2 = (\varepsilon-\delta)h\tau, \quad \tau_{-1} = \dfrac{2}{(\varepsilon-\delta)h}$.

However, $\tau_c = \dfrac{2}{(\varepsilon-\delta)h}\sin(\dfrac{\pi}{4m+2}) < \dfrac{2}{(\varepsilon-\delta)h} = \tau_{-1}$.

□

Theorem 5.5. *If $\varepsilon - \delta > 0$, then the endemic equilibrium can only become unstable for a complex conjugate pair of solutions of the characteristic equation* (5.3) *and the minimum values of τ and ω giving solutions on the unit circle are the critical values τ_c and ω_c given in Theorem 5.2.*

Proof. In Theorem 5.4, we proved that the endemic equilibrium cannot become unstable due to a real solution of the characteristic equation (5.3) crossing the unit circle, i.e., instability can only be caused by a complex conjugate pair of solutions crossing the unit circle. In Theorem 5.2, we showed that the τ_c and ω_c give a complex conjugate pair of solutions on the unit circle and that τ_c is the minimum value of τ at which the solution crosses the unit circle. The proof of condition (C2) of the Neimark-Sacker theorem is complete. □

We now prove condition (C3).

Theorem 5.6. *For ω_c defined in Theorem 5.2, $e^{ik\omega_c} \neq 1$, for $k = 1, 2, 3, 4$.*

Proof. From Theorem 5.2, we have $\omega_c = \frac{\pi}{2m+1}$. Clearly, for $m \geq 1$,

$$k\omega_c = \frac{k\pi}{2m+1} \neq 2\pi, \quad \text{for} \quad k = 1, 2, 3, 4 \tag{5.12}$$

and therefore condition (C3) is satisfied. □

6 Direction and Stability of the Neimark-Sacker Bifurcations

In the previous section, we obtained a complex conjugate pair of solutions of the characteristic equation (5.3) that satisfied conditions (C1), (C2) and (C3) of the Neimark-Sacker theorem 5.1. In this section, we consider condition (C4) and find the direction, stability and the period of the solution of the nonlinear system (3.5) near the critical time delay τ_c.

We use a method given in Kuznetsov [21] and Li [26]. We first convert the two difference equations (3.5) into the systems for the perturbations $y_n = w_n - w^*$ given in equations (6.1).

$$\begin{aligned} &\text{HIV1} \qquad y_{n+1} = y_n - (\varepsilon - \delta)h\tau y_{n-m} - \varepsilon h\tau y_n y_{n-m}, \\ &\text{HIV2} \qquad y_{n+1} = y_n - (\varepsilon - \delta)h\tau y_{n-m} - \varepsilon h\tau y_{n-m}^2. \end{aligned} \tag{6.1}$$

Then following [21] and [26], we convert the two equations in (6.1) into the systems of first-order equations given in (6.2).

$$Y_{n+1} = AY_n + \frac{1}{2}B(X_n, Y_n) + \frac{1}{6}C(X_n, Y_n, Z_n), \tag{6.2}$$

where $Y_{n+1} = (y_{n+1}, y_n, y_{n-1}, \ldots, y_{n-m+1})^T$, $Y_n = (y_n, y_{n-1}, y_{n-2}, \ldots, y_{n-m})^T$ and for both the HIV1 and HIV2 models, we have

$$A = \begin{pmatrix} 1 & 0 & \cdots & 0 & -h\tau(\varepsilon - \delta) \\ 1 & 0 & \cdots & 0 & 0 \\ 0 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 1 & 0 \end{pmatrix}. \tag{6.3}$$

The values of B in (6.2) for the two models are

$$\begin{aligned} B\left(X_n, Y_n\right) &= \left(b_0\left(X_n, Y_n\right), 0, \ldots, 0\right)^T, \\ \text{HIV1}\quad b_0\left(X_n, Y_n\right) &= -h\tau\varepsilon\left(x_n y_{n-m} + y_{n-m} x_n\right), \\ \text{HIV2}\quad b_0\left(X_n, Y_n\right) &= -2h\tau\varepsilon x_{n-m} y_{n-m}. \end{aligned} \tag{6.4}$$

Also, for both models $C = 0$. The matrix A corresponds to the companion matrix (see, for example, [31]) of the characteristic polynomial $P_1(\lambda)$ in (5.3) and therefore the eigenvalues of A and the solutions of (5.3) are the same.

Let $q = q\left(\tau_c\right) \in C^{m+1}$ be an eigenvector of A corresponding to the critical eigenvalue solution $\lambda = e^{i\omega_c}$ of the characteristic equation (5.3). Then q is a solution of:

$$\begin{pmatrix} 1 & 0 & \cdots & 0 & -h\tau_c(\varepsilon-\delta) \\ 1 & 0 & \cdots & 0 & 0 \\ 0 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 1 & 0 \end{pmatrix} \begin{pmatrix} q_0 \\ q_1 \\ q_2 \\ \vdots \\ q_m \end{pmatrix} = \begin{pmatrix} e^{i\omega_c} q_0 \\ e^{i\omega_c} q_1 \\ e^{i\omega_c} q_2 \\ \vdots \\ e^{i\omega_c} q_m \end{pmatrix}. \tag{6.5}$$

The solution from rows 2 to m of (6.5) is $q_0 = e^{i\omega_c} q_1 = e^{i2\omega_c} q_2 = \ldots = e^{im\omega_c} q_m$. Then, substituting $q_0 = e^{im\omega_c} q_m$ into the first row, we obtain the equation for q_m as

$$\left(e^{i(m+1)\omega_c} - e^{i(m)\omega_c} + h\tau_c(\varepsilon-\delta)\right) q_m = 0. \tag{6.6}$$

Since $e^{i\omega_c}$ is a solution of the characteristic equation (5.3), we have that $P_1(e^{i\omega_c}) = e^{i(m+1)\omega_c} - e^{im\omega_c} + h\tau_c(\varepsilon-\delta) = 0$. Therefore, we can choose $q_m \neq 0$ and then $q = q\left(\tau_c\right) \in C^{m+1}$ is an eigenvector of A. If we choose $q_m = 1$ the eigenvector can be written in the form

$$q = q\left(e^{i\omega_c}\right) = \left(e^{im\omega_c}, e^{i(m-1)\omega_c}, \ldots, e^{i\omega_c}, 1\right)^T. \tag{6.7}$$

We also introduce an eigenvector $r = r\left(\tau_c\right) \in C^{m+1}$ of the adjoint matrix $\bar{A}^T$ corresponding to the eigenvalue $e^{-i\omega_c}$. Note that $e^{-i\omega_c}$ is also a solution of the characteristic equation (5.3). Then, following the same procedure as above, we find that the eigenvector of $\bar{A}^T$ can be written in the form

$$r = r\left(e^{i\omega_c}\right) = \left(1, \gamma e^{im\omega_c}, \gamma e^{i(m-1)\omega_c}, \ldots, \gamma e^{i2\omega_c}, \gamma e^{i\omega_c}\right)^T, \text{ where } \gamma = -h\tau_c(\varepsilon-\delta). \tag{6.8}$$

If we define an inner product by $\langle u, v\rangle = \sum_{i=0}^{m} \overline{u}_i v_i$, then the inner product of the adjoint eigenvector r in (6.8) and the eigenvector q of A in (6.7) is $\langle r, q\rangle = e^{im\omega_c} + m\gamma e^{-i\omega_c}$. If we define $D = \left(e^{-im\omega_c} + m\gamma e^{i\omega_c}\right)^{-1}$ and let $q^* = Dr$, then q^* is an adjoint eigenvector with the normalization $\langle q^*, q\rangle = 1$. In the following, we use the notation $\lambda_c = e^{i\omega_c}$ and $\overline{\lambda_c} = e^{-i\omega_c}$ for the eigenvalues of A and note

that the polynomial $P_1(\lambda)$ in (5.3) is the characteristic polynomial of A. Then, following the algorithms in Kuznetsov [21] and Li [26], we consider the following expression for the critical coefficient $c_1(\tau_c)$ in condition (C4) of the Neimark–Sacker theorem 5.1.

$$c_1(\tau_c) = \frac{g_{20}g_{11}(1-2\lambda_c)}{2(\lambda_c^2-\lambda_c)} + \frac{|g_{11}|^2}{1-\overline{\lambda_c}} + \frac{|g_{02}|^2}{2(\lambda_c^2-\overline{\lambda_c})} + \frac{g_{21}}{2}, \tag{6.9}$$

where

$$\begin{aligned}
&g_{02} = \langle q^*, B(\overline{q},\overline{q})\rangle, \quad g_{11} = \langle q^*, B(q,\overline{q})\rangle, \quad g_{20} = \langle q^*, B(q,q)\rangle,\\
&g_{21} = \langle q^*, B(\overline{q},\omega_{20})\rangle + 2\langle g^*, B(q,\omega_{11})\rangle + \langle q^*, C(q,q,\overline{q})\rangle,\\
&\omega_{11} = \frac{b_0(q,\overline{q})}{P_1(1)}p(1) - \frac{\langle q^*, B(q,\overline{q})\rangle}{1-\lambda_c}q - \frac{\langle \overline{q^*}, B(q,\overline{q})\rangle}{1-\overline{\lambda_c}}\overline{q},\\
&\omega_{20} = \frac{b_0(q,q)}{P_1(\lambda_c^2)}p(\lambda_c^2) - \frac{\langle q^*, B(q,q)\rangle}{\lambda_c^2-\lambda_c}q - \frac{\langle \overline{q^*}, B(q,q)\rangle}{\lambda_c^2-\overline{\lambda_c}}\overline{q},
\end{aligned} \tag{6.10}$$

and where

$$p(\lambda) = (\lambda^m, \lambda^{m-1}, \ldots, \lambda, 1)^T. \tag{6.11}$$

The formulas for the b_0 and inner products required to compute the terms in (6.10) are shown in Table 1. The values of the characteristic polynomial required in (6.10) are $P_1(1) = h\tau_c(\varepsilon-\delta)$ and $P_1\left(e^{i2m\omega_c}\right) = e^{i2(m+1)\omega_c} - e^{i2m\omega_c} + h\tau_c(\varepsilon-\delta)$. The values of $p(1)$ and $p(\lambda_c^2)$ can be obtained from (6.11).

	HIV 1	HIV 2
$b_0(q,q)$	$-2h\tau_c\varepsilon e^{im\omega_c}$	$-2h\tau_c\varepsilon$
$b_0(q,\overline{q})$	$-h\tau_c\varepsilon\left(e^{im\omega_c}+e^{-im\omega_c}\right)$	$-2h\tau_c\varepsilon$
$\langle q^*, B(\overline{q},\overline{q})\rangle = g_{02}$	$-2h\tau_c\varepsilon\overline{D}e^{-im\omega_c}$	$-2h\tau_c\varepsilon\overline{D}$
$\langle q^*, B(q,\overline{q})\rangle = g_{11}$	$-h\tau_c\varepsilon\overline{D}\left(e^{im\omega_c}+e^{-im\omega_c}\right)$	$-2h\tau_c\varepsilon\overline{D}$
$\langle q^*, B(q,q)\rangle = g_{20}$	$-2h\tau_c\varepsilon\overline{D}e^{im\omega_c}$	$-2h\tau_c\varepsilon\overline{D}$
$\langle \overline{q^*}, B(q,q)\rangle$	$-2h\tau_c\varepsilon De^{im\omega_c}$	$-2h\tau_c\varepsilon D$
$\langle \overline{q^*}, B(q,\overline{q})\rangle$	$-h\tau_c\varepsilon D\left(e^{im\omega_c}+e^{-im\omega_c}\right)$	$-2h\tau_c\varepsilon D$

Table 1: Formulas for the b_0 and inner products in the terms of the critical constant $c_1(\tau_c)$

On substituting the expressions in Table 1 into (6.9), we can obtain a formula for $c_1(\tau_c)$. Unfortunately, it is difficult to prove analytically that $c_1(\tau_c) \neq 0$, and therefore that condition (C4) is satisfied. However, as shown in section 7, the value of $Re\left[e^{-i\omega_c}c_1(\tau_c)\right]$ can easily be computed numerically for any given parameter values.

7 Numerical Results

In this section, we present results of numerical simulations to illustrate the analytical results obtained in previous sections. For the numerical simulations we use the set of parameter values shown in Table 2. These values have been adapted from parameter values published by Cai et al. [32].

Parameter name	B	α	p	β	C	δ	ε
Used Values	0.05	0.05	0.01	0.5	0.5	0.0495	0.2

Table 2: Values of parameters used for numerical simulation [32]

We first compute the values of the disease-free and endemic points for the differential equation and difference equations and compare the stability. We then compute and compare the critical values for the time delays for the Andronov-Hopf and Neimark-Sacker bifurcations. We also check numerically that condition (C4) of the Neimark-Sacker theorem is satisfied. Finally, we analyze the effect of antiretroviral therapy and give conditions for the antiretroviral therapy to reduce the value of R_0 to less than 1.

7.1 Equilibrium Points and Stability

From sections 4.1 and 5.1, we have that the equilibrium populations and values of R_0 for the differential equation and difference equation models are the same and are given by

$$\begin{aligned} &\text{Disease free } \; x_0^* = w_0^* = 0, \quad \text{Endemic } \; x_1^* = w_1^* = 1 - \frac{\delta}{\varepsilon} = 0.7525, \\ &\text{and } \quad R_0 = \frac{\varepsilon}{\delta} = 4.0404 > 1. \end{aligned} \tag{7.1}$$

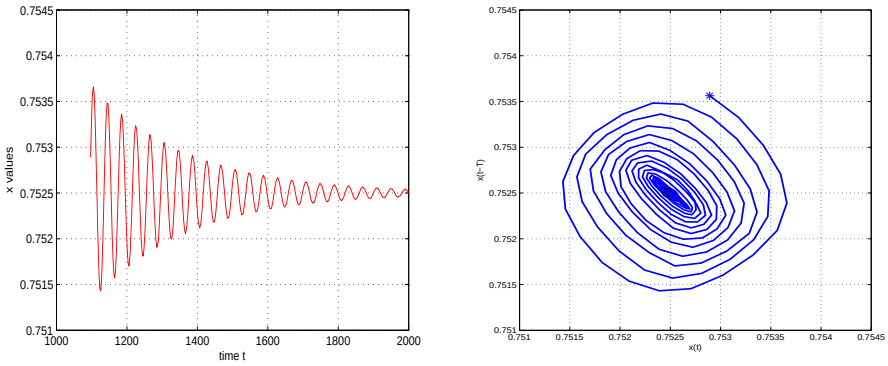
7.2 Andronov-Hopf Bifurcations

For the parameter values in Table 2, the Andronov-Hopf bifurcation occurs at the critical time delay $\tau_c = \frac{\pi}{2\omega_c} = 10.4372$ and angle $\omega_c = \varepsilon - \delta = 0.1505$. From equation (4.8), we have for condition 3 of the Andronov-Hopf conditions that the value for derivative of the real part of the eigenvalue at the critical point is:

$$\frac{d\mu}{d\tau} = 0.0065 > 0. \tag{7.2}$$

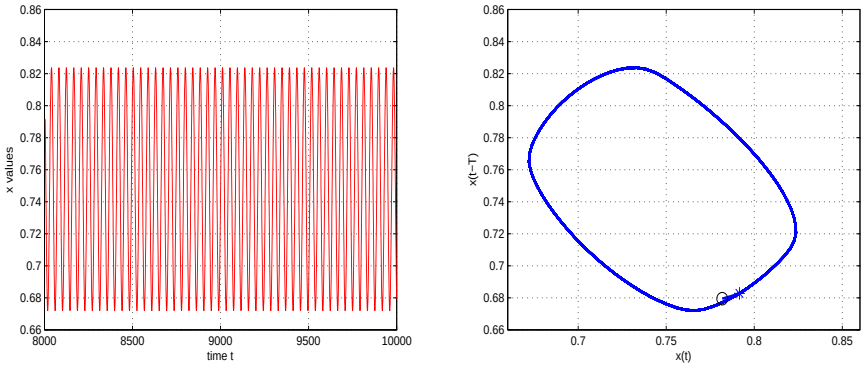
Therefore, the bifurcation will occur as τ increases through τ_c.

Examples of plots of the time dependence and phase plane plots of the solutions of the differential equations (2.4) are shown in Figures 1 and 2 for time delays below and above the critical value, respectively. The figures show plots for model HIV2. The plots for model HIV1 are qualitatively similar but slightly different in detail.



(a) Plot of population vs time (b) Phase plane plot

Figure 1: Time dependence and phase plane plots for differential equation model for delay less than critical point ($\tau = 9.91532 < \tau_c = 10.43718$).



(a) Plot of population vs time (b) Phase plane plot

Figure 2: Time dependence and phase plane plots for differential equation model for delay greater than critical point ($\tau = 10.54156 > \tau_c = 10.43718$).

7.3 Neimark-Sacker Bifurcations

For the parameter values in Table 2, the Neimark-Sacker bifurcation occurs at the critical time delay $\tau_c = \frac{2}{(\varepsilon-\delta)h}\sin(\frac{\pi}{4m+2}) = 10.3355$ and angle $\omega_c = \frac{\pi}{2m+1} = 0.0305$. From equation (5.10), we have for condition (C1) part 2 of the Neimark-Sacker conditions that the value for derivative of the modulus (r) of the eigenvalue

at the critical point is:

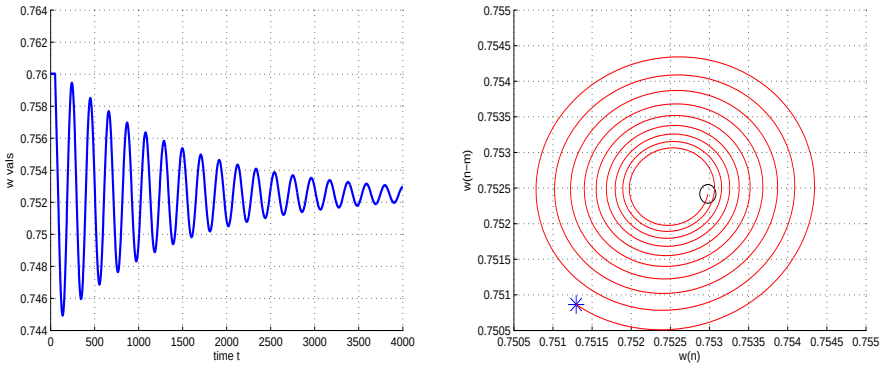
$$\frac{dr}{d\tau} = 0.0013369 > 0. \tag{7.3}$$

For condition (C4), we compute the values of $\mathrm{Re}(e^{-i\omega_c}c_1(\tau_c))$ from the formulas in section 6 and obtain the value

$$\mathrm{Re}(e^{-i\omega_c}c_1(\tau_c)) = -0.09494 < 0. \tag{7.4}$$

Therefore, the parameters in Table 2 correspond to case 1 for condition (C4). The bifurcation should occur as τ increases through τ_c and an attracting invariant closed curve should exist for $\tau > \tau_c$.

Examples of plots of the time dependence and phase plane plots of the solutions of the difference equations (3.5) are shown in Figures 3 and 4 for time delays below and above the critical value, respectively. The figures show plots for model HIV2. The plots for model HIV1 are qualitatively similar but slightly different in detail. These figures show that the endemic equilibrium is stable for $\tau < \tau_c$ and passes through a Neimark-Sacker bifurcation point as τ increases through τ_c. The plots in Figure 4 show the convergence to a stable limit cycle as time increases.

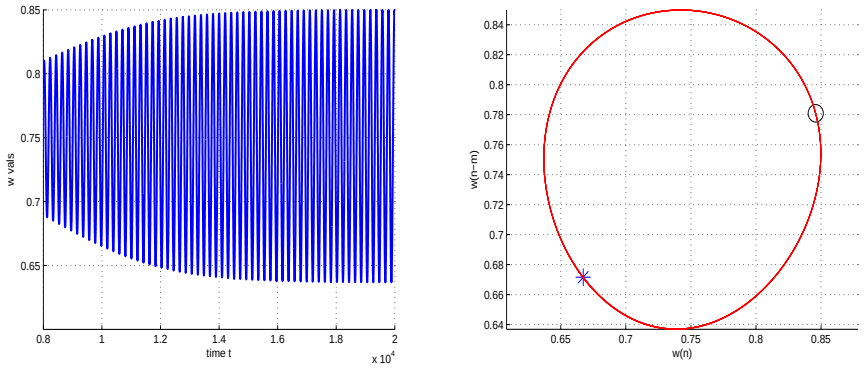


(a) Plot of population vs time (b) Phase plane plot

Figure 3: Time dependence and phase plane plots for difference equation model for delay less than critical point ($m = 51,\ \tau = 9.8187 < \tau_c = 10.33545$).

7.4 Comparison of Critical Values for Andronov-Hopf and Neimark-Sacker Bifurcations

A comparison of the critical delay values τ_c for the Andronov-Hopf and Neimark-Sacker bifurcations are shown in Figure 5. It can be seen that the Neimark-Sacker values tend to the Andronov-Hopf values as the value of m increases, i.e., as the



(a) Plot of population vs time (b) Phase plane plot

Figure 4: Time dependence and phase plane plots for difference equation model for delay greater than critical point ($m = 51,\ \tau = 10.542 > \tau_c = 10.33545$).

step size $h = 1/m$ in the Euler difference equation approximation for the differential equation is reduced. These results suggest that difference equation models based on the Euler approximation can be used to obtain good estimates for critical delay values for models of the type studied in this paper.

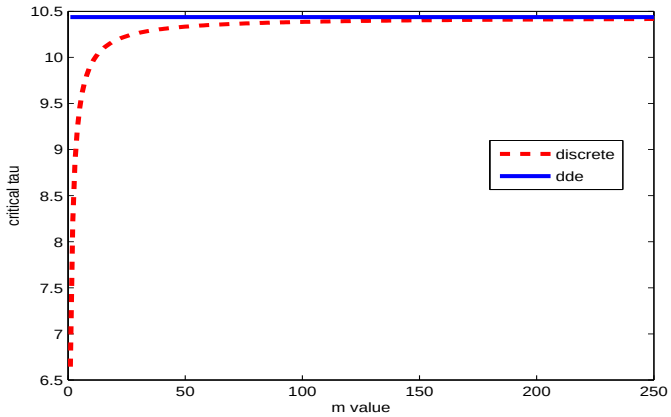
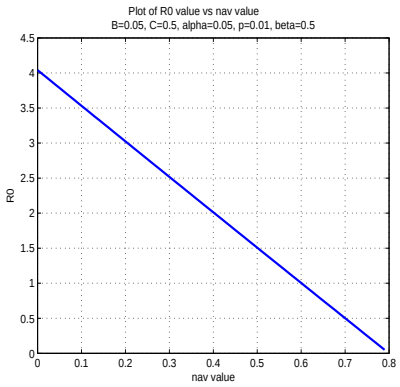


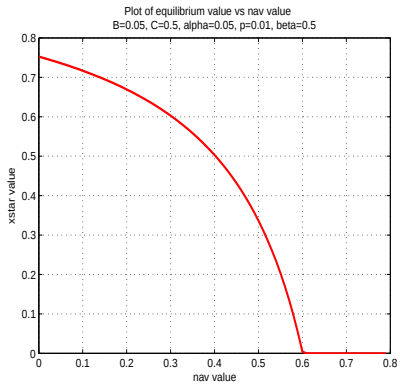
Figure 5: Comparison of critical values τ_c for difference equation and differential equation models.

7.5 Effect of Antiviral Therapy

The effects of increasing the antiretroviral therapy factor n_{av} in (2.2) are shown in Figure 6. Figure 6(a) shows the reduction in the basic reproduction number and Figure 6(b) shows the effect on the equilibrium infected population. In practise, as stated in the introduction, it is known (see, e.g., [4]– [6], [13]) that antiretroviral therapy cannot completely eliminate the virus. However, recent studies (see, e.g., [14–16]) have suggested that the therapy can reduce the virus sufficiently that HIV transmission from an HIV+ to an uninfected person will not occur.



(a) Plot of R_0 vs antiviral infectiousness factor



(b) Plot of equilibrium population vs antiviral infectiousness factor

Figure 6: Effect of antiretroviral therapy on R_0 and endemic equilibrium population.

8 Conclusions

The bifurcation properties of time-delayed one-dimensional differential equation and approximating difference equation models for HIV transmission have been studied. The models include the effects of vertical HIV transmission from mother to baby, the effects of births and deaths and of treatment by antivirals. For the differential equation models, the existence of Andronov-Hopf bifurcations at critical values of the time delays has been proved analytically. For the difference equation models, the existence of Neimark–Sacker bifurcations has also been proved analytically. The direction and stability of the Neimark-Sacker bifurcations has been analyzed, and it has been shown that stable limit cycles exist for time delays greater than the critical value. Numerical simulations have been presented for a set of reasonable parameter values to illustrate the analytical results. The numerical results verify the analytical results. The numerical results also show that the critical delay times for Neimark-Sacker bifurcations of approximating difference

equation models are less than the critical times for Andronov-Hopf bifurcations in a differential equation model but converge to them in the limit as the time step of the discretization in the difference equation model tends to zero. The effect of antiretroviral treatment in the model has been shown by plotting the reduction in the basic reproductive number R_0 and the equilibrium fraction of the infected population as the antiretroviral treatment is increased.

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