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Nature of equilibria and effects of drug treatments in some simple viral population dynamical models

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We examine some simple mathematical models which have been recently employed to predict the evolution of population dynamical systems involving virus particles. They include: (1) A general two-component antibody-viral system; (2) A simplified two-component model for HIV-1 dynamics (3) An HIV-1 three-component model including virions and (4) A four-component HIV-1 dynamical model which includes both latently and actively infected cells. For each system we find equilibrium points and analyse their local stability properties in order to obtain a global phase portrait. Analytical methods are complemented with numerical solutions. In all four models there are at most two equilibrium points for physically meaningful values of the variables. As the viral growth rate parameter increases through a critical value, a transcritical bifurcation occurs. One critical point (P_1) is always found at zero viral or infected cell levels and non-zero antibody or uninfected cell levels. For parameter values in their usual ranges, P_1 is either an asymptotically stable node or a saddle point. When the critical point P_2 occurs at biologically meaningful values, it is either an asymptotically stable node or an asymptotically stable spiral point. For all three HIV-1 models, the values of the parameters at which P_2 makes a transition to physically meaningful values are precisely those at which P_1 changes from an asymptotically stable node to an unstable saddle point. The global pictures for all four models are similar and examples are represented graphically. No limit-cycle solutions were found in any of the models for parameter values in their usual ranges. In the four-component HIV-1 model, the effects of varying each parameter are found and conditions under which P_2 changes from spiral point to node are investigated numerically. The effects of reverse transcriptase inhibitors and protease inhibitors, two classes of drugs used to treat HIV-1 infection, are examined in the three-component model for early HIV-1 dynamics.

1. Introduction

The importance of dynamical mathematical models of viral-antibody systems has been emphasized recently in many theoretical studies of the growth of HIV-1 populations in infected hosts. The models employed vary from reduced two-component models such as

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those employed by Bonhoeffer *et al.* (1997), to more complete three-component models (Herz *et al.*, 1996) and four-component models (McLean *et al.*, 1991; Phillips, 1996; Nowak & Bangham, 1996; Perelson *et al.*, 1996, 1997; Tuckwell & Le Corfec, 1998). One important application (see Section 6 of this article) has been to ascertain the effects of various drug treatments, such as reverse transcriptase inhibitors and protease inhibitors (Kirschner & Webb, 1996; Wein *et al.*, 1997, 1998).

Most of the above studies involve the numerical solution of systems of non-linear ordinary differential equations. However, a useful supplement to such a numerical approach is the analysis of the nature of the various equilibrium points for various ranges of values of the parameters. Such analysis provides insight into the nature of solutions without numerical solution. In this note we summarize the results of such an analysis for some simple models of viral-immune system population dynamics. These results are also useful in the synthesis and analysis of spatial epidemic network models in which viral or other noxious particles are transmitted between individuals within a population (Tuckwell *et al.*, 1998, 2000).

We shall perform a partly analytical investigation of models with up to four components, deemed by some authors appropriate for early dynamics. However, despite the above and more recent mathematical models, there is still uncertainty as to the mechanisms underlying the time course of the variable of primary interest, namely the viral load. During the initial stages of HIV infection, the viral load in plasma increases, reaches a maximum, and then decresaes. Phillips (1996) supposed that the decline is due to a limited number of cells susceptible to HIV infection. However, Stafford *et al.* (2000) developed models of primary HIV-1 infection, and compared the results with data on infected patients. The data were consistent with a target-cell-limited model until shortly after the peak in viremia, but in some patients, not during the subsequent fall and recovery in virus concentration. It was suggested that some additional process, perhaps mediated by CD8+ T cells, is important in at least some patients. Cogent mathematical investigations of the effects of drug treatments, especially in the long term, require models which can satisfactorily predict the time course of both viral load and CD4+ T-cell numbers in the absence of treatment. Such models seem to require more variables than those considered in the present article. For example, Wein *et al.* (1997, 1998), in their quest for optimal drug regimes, introduced extra variables for wild-type and mutant virus strains and for long-lived infected CD4+ T-cells. In our analysis of the three-component HIV-1 model under chemotherapy we only consider one viral strain and only have one compartment for uninfected cells. With this restricted model we are able to find exact outcomes for various combinations of reverse transcriptase and protease inhibitors. We do not include (cf. Fraser *et al.*, 2000) any drug that produces T-cell activation, such as interleukin-2; these authors have demonstrated that greater doses of such a drug may sometimes give rise to a negative result.

2. General two-component effector-virus system

The following is a very simple model (Anderson & May, 1991) which may be considered to be a paradigm system for many virus-effector populations. Although it omits details of the immune response, it captures the essence of immune system attack on disease-causing particles, thus providing some insight into the properties of more complicated realistic

models. Let $a(t)$ and $v(t)$ be the numbers or densities of effectors and virus, respectively, at time t. In this model, effectors (here defined as any agent which acts to eliminate a virus) are produced at a rate s, assumed constant, die at a per capita rate μ, and are produced at a rate ϵav by interaction with the viral population. Hence

$$\frac{da}{dt} = s - \mu a + \epsilon av. \tag{1}$$

Viral particles have an intrinsic per virion production rate r and are removed at rate γav by effectors so that

$$\frac{dv}{dt} = rv - \gamma av. \tag{2}$$

All the parameters are non-negative as are the variables a and v. In the system (1) and (2), for any value of s, there are two critical points (steady state solutions) at $P_1 = \left(\frac{s}{\mu}, 0\right)$ and $P_2 = \left(\frac{r}{\gamma}, \frac{\mu r - s\gamma}{\epsilon r}\right)$.

The nature of P_1

The eigenvalues associated with P_1 are $\lambda_1 = -\mu$ and $\lambda_2 = r - \frac{s\gamma}{\mu}$. If $s = 0$, then $\lambda_1 = -\mu$ and $\lambda_2 = r$ so that the critical point is an unstable saddle point. If $s \neq 0$, then P_1 is an unstable saddle point if $s\gamma \leqslant r\mu$ and an asymptotically stable node if $s\gamma > r\mu$.

The nature of P_2

The eigenvalues associated with P_2 are

$$\lambda_{1,2} = -\frac{1}{2r}\left\{\gamma s \pm \sqrt{(\gamma s)^2 + 4r^2(\gamma s) - 4\mu r^3}\right\}.$$

If $s = 0$ the eigenvalues are $\lambda_1 = -i\sqrt{\mu r}$ and $\lambda_2 = i\sqrt{\mu r}$, so that P_2 is a center.
If $s\gamma > \mu r$, then $\lambda_1 < 0 < \lambda_2$ so that P_2 is an unstable saddle point.
If $s\gamma < \mu r$, then there are two distinct possibilities.

(a) $\frac{4r^2}{(s\gamma)^2}[\mu r - \gamma s] \leqslant 1$. In this case, the eigenvalues are distinct and negative, which makes P_2 an asymptotically stable node.

(b) $\frac{4r^2}{(s\gamma)^2}[\mu r - \gamma s] > 1$. The eigenvalues are then a complex conjugate pair with a negative real part. Hence P_2 is an asymptotically stable spiral point.

Note that for the singular case, in which $\mu r = \gamma s$, the nature of P_2 will have to be determined by consideration of non-linear effects of the system.

Discussion and phase portrait

CASE 1 Firstly we observe that if $s\gamma > \mu r$, the point P_2 occurs at negative v and is hence is not at a biologically relevant value. There is then just one meaningful critical point P_1 on the a-axis and this is an asymptotically stable node. Thus no matter where solutions start in the non-negative quadrant, they approach P_1 with zero virions and with $a(\infty) = \frac{s}{\mu}$ effectors.

CASE 2 When $s\gamma < \mu r$, there is an unstable saddle point on the a-axis at P_1 together with an equilibrium point P_2 in the positive quadrant which is either an asymptotically stable node or an asymptotically stable spiral point. Then whenever the initial value $v(0)$ is positive, regardless of whether $a(0)$ is positive or zero, the system ends up at P_2. Thus in such cases it is impossible to end up with zero virions; an equilibrium is approached with $\frac{r}{\gamma}$ effectors and $\frac{\mu r - s\gamma}{\epsilon r}$ virions. If s is relatively small, the solutions undergo damped oscillations on their approach to P_2; if s is large enough solutions show no oscillatory behavior and proceed directly to P_2.

Note that at the critical value $s\gamma = r\mu$ where there is a change of stability of P_1 and P_2, the two critical points coincide, both being located at $\left(\frac{s}{\mu}, 0\right)$ with P_2 emerging as the asymptotically stable steady state for $\frac{s}{\mu} < \frac{r}{\gamma}$. Thus, there is a transcritical bifurcation, with P_2 emerging as $\frac{s}{\mu}$ decreases below $\frac{r}{\gamma}$. The distinction between the two cases of either one or two equilibria can be most clearly understood by noting that they arise when $s/\mu > r/\gamma$ and $s/\mu < r/\gamma$ respectively. These are relations between the relative strength of effector persistence (s/μ) and the corresponding quantity for virions (r/γ). If s is very small and positive the predator-prey case of periodic solutions is manifest by the oscillatory nature of the solutions. However, as is expanded on elsewhere (Tuckwell & Wan, 2000), in no case for the two-component virus–antibody model for one individual, are there limit cycle solutions.

The various possibilities for this model are sketched in Figure 1. In the top part, with $s\gamma > \mu r$, the paths all end up at the asymptotically stable node on the a-axis. In the middle and bottom figures we have $s\gamma < \mu r$, and solutions either spiral towards the positive critical point (middle part) or approach the critical point, now a node, along a line parallel to the v-axis.

3. Two-component model for HIV-1 dynamics

We will consider more complete models for HIV-1 population dynamics below but first analyse a simplified model introduced by Bonhoeffer *et al.* (1997). Here there are two components: x, the number of uninfected CD4+ T-cells and y, the number of infected such cells. Then the following two equations describe the evolution of the system:

$$\frac{dx}{dt} = s - \mu x - kxy, \tag{3}$$

$$\frac{dy}{dt} = kxy - \alpha y, \tag{4}$$

where again all parameters and variables are non-negative. Again s is the assumed constant rate of production of CD4+ T-cells, μ is their per capita death rate, kxy is the rate of infection of CD4+ T-cells by virus, and αy is the rate of disappearance of infected cells. The viral variable has been omitted for simplicity as it is here assumed to be linearly related to y.

It can be seen that (3) and (4) are of the same form as (1) and (2) but with sign changes which alter the character of the solutions. The critical points are $P_1 = \left(\frac{s}{\mu}, 0\right)$ and $P_2 = \left(\frac{\alpha}{k}, \frac{sk - \alpha\mu}{\alpha k}\right)$. For all meaningful parameter values ($s \geqslant 0$), the first point P_1 always occurs at biologically meaningful values. However, P_2 is only at meaningful values if $sk \geqslant \alpha\mu$.

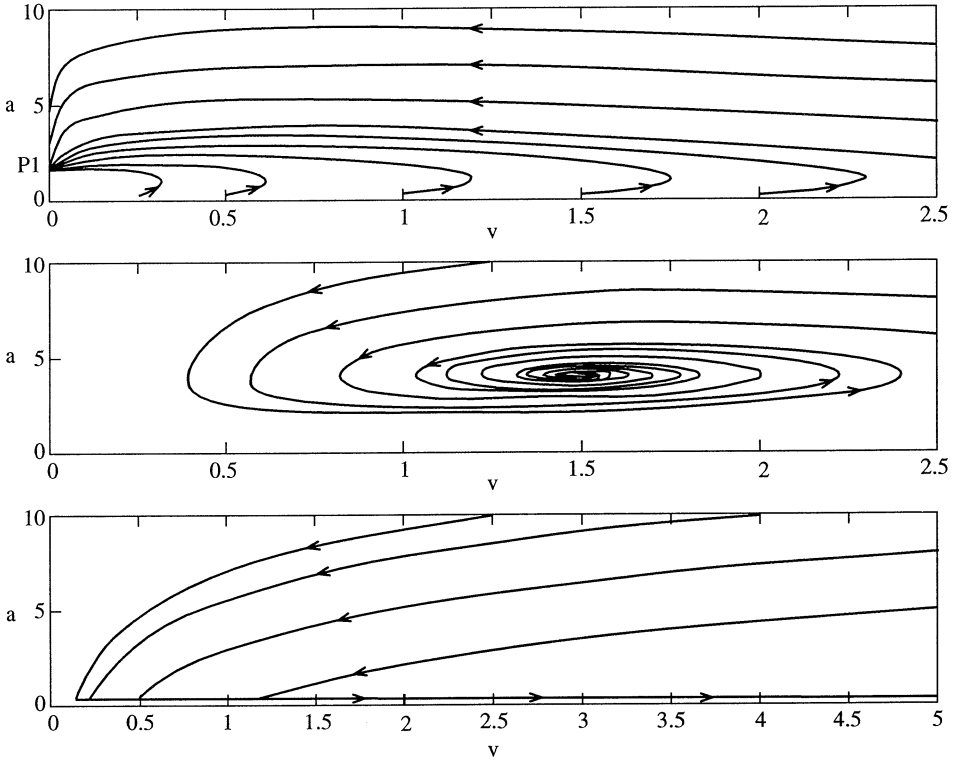

FIG. 1. Examples of phase portraits for the Anderson–May two-component model for viral–antibody dynamics. Top part. Here there is just one critical point—a stable node P_1. All solutions end up at P_1 regardless of the initial values. The viral population is driven to extinction. Parameter values: $\lambda = 1{\cdot}5, \mu = 1, \epsilon = 1, r = 1, \gamma = 1$, which puts P_1 at $(0, 3/2)$. Middle part. There are two critical points but only the one in the positive quadrant is stable and this is a spiral point. Parameter values: $\lambda = 2, \mu = 2, \epsilon = 1, r = 2, \gamma = 0{\cdot}5$, putting the two critical points at $(0, 1)$ and $(3/2, 4)$. Bottom figure. There are two critical points, but again only one is asymptotically stable and a node. Parameter values: $\lambda = 3, \mu = 10, \epsilon = 0{\cdot}2, r = 1, \gamma = 3$ with equilibrium points $(0, 0{\cdot}3)$ and $(5, 1/3)$.

The nature of P_1

The associated eigenvalues are $-\mu$ and $\frac{sk-\mu\alpha}{\mu}$. Thus if $s = 0$, both eigenvalues are negative and $P_1 = (0, 0)$ is an asymptotically stable node.

If $s > 0$ there are the following cases. If $sk < \mu\alpha$, both eigenvalues are negative and P_1 is an asymptotically stable node. If $sk > \mu\alpha$, one eigenvalue is negative and the other is positive so that P_1 is a saddle point (unstable). At the critical value $sk = \alpha\mu$ when a change of stability of the uninfected state P_1 as well as the endemically infected state P_2 occurs, we have $P_2 = \left(\frac{\alpha}{k}, \frac{sk-\alpha\mu}{\alpha k}\right) = \left(\frac{s}{\mu}, 0\right) = P_1$ so that the two states coincide. Hence, at the critical value $sk = \mu\alpha$, there is a transcritical bifurcation with the endemically infected state P_2 emerging for $sk > \alpha\mu$. (This is the two-component counterpart of the four component case analysed by Perelson *et al.* (1993) where he coined the term endemically infected state for P_2.) With $\mathrm{d}y/\mathrm{d}t = 0$ for $y = 0$, the unrealistic state P_2 (when $sk < \alpha\mu$) cannot be reached

from any initial state in the first quadrant. Hence, we only need to be concerned with the stability of P_2 for $sk > \alpha\mu$.

The nature of P_2

For P_2 the associated eigenvalues are

$$\lambda_{1,2} = \frac{ks}{2\alpha}\left[-1 \pm \sqrt{1 - \frac{4\alpha^2}{ks}\left(1 - \frac{\alpha\mu}{ks}\right)}\right].$$

In those cases where P_2 is biologically meaningful ($sk \geqslant \alpha\mu$), we have $0 \leqslant 1 - \frac{\alpha\mu}{ks} < 1$ and there are two possibilities.

(a) $\frac{4\alpha^2}{(ks)^2}[ks - \alpha\mu] > 1$. Then the eigenvalues are complex conjugates with negative real part, making P_2 an asymptotically stable spiral point

(b) $\frac{4\alpha^2}{(ks)^2}[ks - \alpha\mu] \leqslant 1$. In this case the eigenvalues are both real and negative so that P_2 is an asymptotically stable node.

Discussion and phase portrait

CASE 1 $sk < \alpha\mu$. Here there is one biologically meaningful critical point P_1 on the x-axis (since y cannot be negative). Then for any non-negative s this critical point is an asymptotically stable node. Trajectory analysis shows that solutions which start in the positive quadrant must remain there. Thus for any combination of initial numbers of uninfected (x) and infected CD4+ T-cells, the infected cell population is eventually totally eliminated.

CASE 2 $sk \geqslant \alpha\mu$. There are two critical points. P_1 is on the x-axis and P_2 is in the non-negative quadrant. When $sk > \alpha\mu$, P_1 is always an unstable saddle point and P_2 is either an asymptotically stable spiral point (case (a) above), or an asymptotically stable node (case (b)). For any initial values the solution eventually approaches the equilibrium point P_2, either with damped oscillatory motion or by direct approach; thus eventually there is present an equilibrium mixture of both uninfected and infected cells. The various possibilities are similar in qualitative detail to those shown in Figure 1.

4. Three-component early HIV-1 model with virions

A more complete model of human immunodeficiency virus type 1 (HIV-1) dynamics considers in addition to the uninfected and infected CD4+ T-cells, x and y respectively, the number of virions in plasma, v. The following three equations are a slightly modified version of those in Herz *et al.* (1996):

$$\frac{dx}{dt} = s - \mu x - kvx \tag{5}$$

$$\frac{dy}{dt} = kvx - ay \tag{6}$$

$$\frac{dv}{dt} = cy - \gamma v - kvx. \tag{7}$$

The third equation in the last mentioned reference does not contain the term $-kvx$ to account for the fact that when a virus infects a CD4+ T-cell, v decreases at the same time as x decreases. Without this we have just

$$\frac{dv}{dt} = cy - \gamma v \tag{7A}$$

Here c is the rate at which infected cells emit virions.

For (5),(6) and either (7) or (7A) we find a critical point at $P_1 = \left(\frac{s}{\mu}, 0, 0\right)$. For the model with (7) we find a second critical point at $P_2 = \left(\frac{a\gamma}{k(c-a)}, \frac{s}{a} - \frac{\gamma\mu}{k(c-a)}, \frac{s(c-a)}{a\gamma} - \frac{\mu}{k}\right)$. On the other hand for the model with (7A), the second critical point is at $P_2' = \left(\frac{a\gamma}{ck}, \frac{s}{a} - \frac{\gamma\mu}{ck}, \frac{cs}{a\gamma} - \frac{\mu}{k}\right)$. To see how great a difference there is between the model with (7) and that with (7A), we compute the coordinates of the critical points with the following representative parameter values which we refer to as standard. These values and those of the next section are taken from Phillips (1996):

$s = 0{\cdot}272$ /day/mm^3,
$\mu = 0{\cdot}00136$ /day/mm^3,
$k = 0{\cdot}00027$ /day /(virion/mm^3),
$a = 0{\cdot}33$ /day/mm^3,
$c = 50$ virion/CD4/day and
$\gamma = 2{\cdot}0$ /day.

This gives $P_2 = (49{\cdot}21, 0{\cdot}6214, 15{\cdot}43)$ and $P_2' = (48{\cdot}89, 0{\cdot}6228, 15{\cdot}57)$. Thus omission of the term kvx in the viral equation leads to only very small changes in the coordinates of the critical point P_2 in the vicinity of standard parameter values. For certain parameter values, however, the position of P_2 can be physically meaningful for one choice and not for the other.

The nature of P_1

If $s = 0$, the equilibrium point P_1 is at the origin and is an asymptotically stable node. In general the associated eigenvalues for (7) are $\lambda_1 = -\mu$ and

$$\lambda_{2,3} = \frac{1}{2}\left\{-(a + \gamma + kx_1) \pm \sqrt{(a + \gamma + kx_1)^2 - 4[a\gamma + kx_1(a - c)]}\right\}$$

where $x_1 = s/\mu$. The nature of this critical point varies as follows. It is a saddle point if $a\gamma < \frac{ks(c-a)}{\mu}$. When the latter inequality is reversed, it is an asymptotically stable node. It cannot be a spiral point as the quantity under the square root sign can be rewritten $\frac{4ksc}{\mu} + \left[\left(\gamma + \frac{ks}{\mu} - a\right]^2\right.$, making the eigenvalues always real. For the typical parameter values given in the previous paragraph, $a\gamma = 0{\cdot}66$ and $\frac{ks(c-a)}{\mu} = 2{\cdot}68$, so $P_1 = (200, 0, 0)$ is then a saddle point.

The nature of P_2

Linearizing about $P_2 = (x_2, y_2, v_2)$ by putting $x' = x - x_2$, $y' = y - y_2$, $v' = v - v_2$, we obtain the following system:

$$\frac{dx'}{dt} = -(\mu + kv_2)x' - kx_2v'$$
$$\frac{dy'}{dt} = kv_2x' - ay + kx_2v'$$
$$\frac{dv'}{dt} = -kv_2x' + cy' - (\gamma + kx_2)v'.$$

The eigenvalues satisfy the following cubic:

$$\lambda^3 + \sigma\lambda^2 + \delta\lambda + \epsilon^2 = 0$$

where

$$\sigma = a + \gamma + \mu + k(x_2 + v_2)$$
$$\delta = a(\mu + kv_2) + \mu(\gamma + kx_2) + k\gamma v_2 = (a + \gamma)(\mu + kv_2) + \mu kx_2$$
$$\epsilon^2 = a\gamma kv_2$$

so that the eigenvalues may be accurately found by numerical solution. For the standard set of parameters given above, it is found that the eigenvalues are $\lambda_1 = -2{\cdot}3438$, $\lambda_{2,3} = -0{\cdot}0025 \pm 0{\cdot}0342i$ so that P_2 is an asymptotically stable spiral point. More generally, for any given set of positive input parameter values, the coefficients σ, δ and ϵ^2 are all positive. In addition it is straightforward to verify that $\sigma\delta - \epsilon^2$ is always positive. The Routh-Hurwitz necessary and sufficient criteria (of $\sigma > 0$, $\epsilon^2 > 0$ and $\sigma\delta - \epsilon^2 > 0$) for all three roots of the cubic equation for λ to have a negative real part are satisfied. Hence P_2 is always asymptotically stable.

Effects of variations in s

When s is varied from 50% below the standard value to 50% above it, and the other parameters are kept at their standard values, the equilibrium point P_2 remains an asymptotically stable spiral point. This is also the case when s is decreased to the critical value

$$s_c = \frac{a\gamma\mu}{k(c - a)}$$

at which P_2 becomes unphysical and when s is increased by as much as a factor of 10. When s is decreased below s_c, solutions approach the asymptotically stable node at P_1 where there are zero virions and zero infected cells.

Effects of variations in the remaining parameters

On varying the remaining five parameters (a, c, γ, k, μ) one at a time to 50% above and below their standard values, while keeping all the remaining parameters at their standard values, the nature of P_2 remained unchanged as an asymptotically stable spiral point.

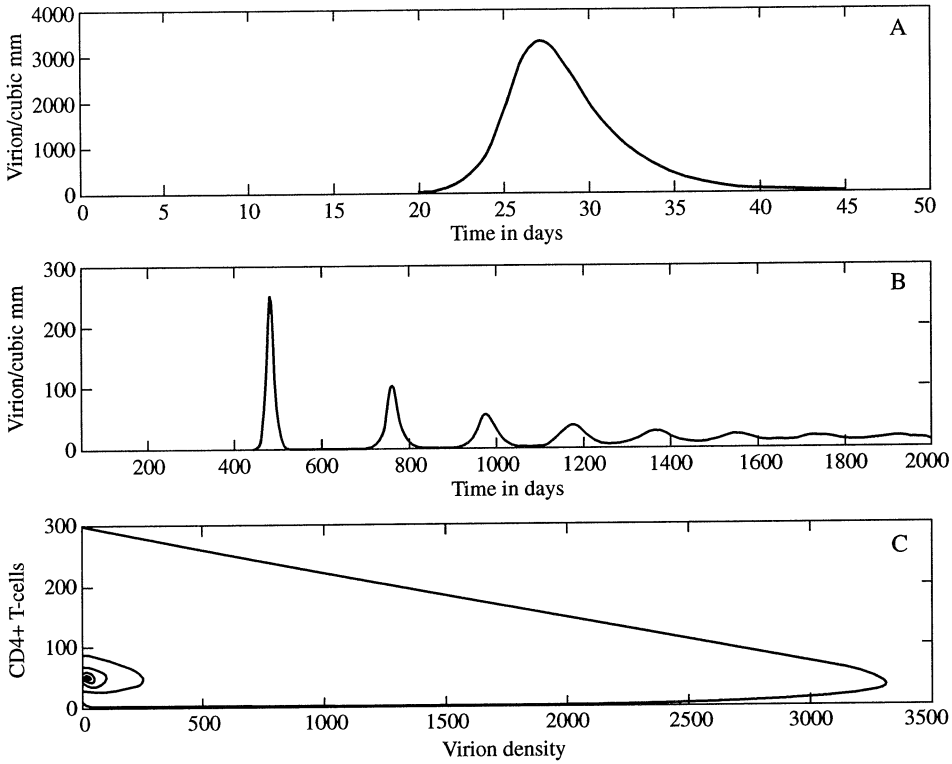

FIG. 2. Computed solutions for the 3-component HIV-1 model using the standard parameter set, $a = 0{\cdot}33$, $\lambda = 0{\cdot}272$, $\mu = 0{\cdot}00136$, $k = 0{\cdot}00027$, $\gamma = 2$, $c = 50$ and $x(0) = 200$, $y(0) = 0$ and $v(0) = 4 \times 10^{-7}$, where x, y, v are in mm^{-3}. a. The virion density for the first 50 days, showing a primary peak of about 3000 mm^{-3} at about 27 days after initial infection. b. The time course of the virion density over days 50–2000, showing peaks of diminishing amplitude as solutions approach the asymptotically spiral point P_2. c. Phase diagram of the solution in which uninfected CD4+ T-cell density is plotted against virion density for the first 2000 days.

Discussion and phase portrait

The behavior of solutions in the three-component HIV-1 model is similar to that for the two-component model. There are at most two critical points and one of these (P_2) may occur at unphysical values of the variables y and v. We note that the condition that P_2 occurs at physical values, i.e. $a\gamma < \frac{ks(c-a)}{\mu}$, is precisely the necessary and sufficient condition for P_1 to be an unstable saddle point; otherwise P_2 is at physically unmeaningful values and P_1 is an asymptotically stable node. The computed solution for the standard parameter values given above is shown in Figure 2. Part a of this figure shows the virion density for the first 50 days after infection whereas part b shows the behavior for later times. The damped oscillations of virion density are apparent as P_2 is approached, although it is pointed out that the model is only designed to represent the early response period.

For parameter values varying over considerable ranges about the standard values, numerical computations indicate that there are two main types of behavior for the solutions.

CASE (1). P_1 is an asymptotically stable node and P_2 is at unphysical values with y and v both negative. Analysis of direction fields shows that solutions which start in the positive octant remain there. Thus, no matter where solutions start in the (x, y, v) positive octant, they approach the equilibrium point P_1 with zero infected cells, zero virions and $\frac{s}{\mu}$ uninfected activated CD4+ T-cells.

CASE (2). P_1 is an unstable saddle point and P_2, at physical values is an asymptotically stable spiral point. The latter may be ascertained by using perturbation analysis and is the case for the standard set of parameters and all variations of them which put P_2 at physical values. In this case all solutions show damped oscillations as they approach P_2. For any given set of positive input parameter values, the two critical points coalesce at $\left(\frac{s}{\mu}, 0, 0\right)$ at the critical value $a\gamma\mu = ks(c - a)$ (that is, $s = s_c$). As $ks(c - a)$ increases above $a\gamma\mu$, P_2 emerges as the asymptotically stable steady state for $ks(c - a) > a\gamma\mu$, and P_1 becomes unstable. Thus there is a transcritical bifurcation with the endemically infected state emerging for $s > s_c$.

5. Four-component HIV-1 dynamical model with latently infected CD4+ T-cells

The following system has been employed (Tuckwell & Le Corfec, 1998) as the basis for a stochastic differential equation model for early HIV-1 dynamics. It differs from the system employed by Phillips (1996), which was in turn adopted from McLean *et al.* (1991), only in that it includes in the virus equation a term for the interaction of virus and uninfected CD4+ T-cells. We have

$$\frac{dx}{dt} = s - \mu x - kvx \tag{8}$$

$$\frac{dy}{dt} = (1 - p)kvx + \alpha z - ay \tag{9}$$

$$\frac{dz}{dt} = pkvx - (\alpha + \mu)z \tag{10}$$

$$\frac{dv}{dt} = cy - \gamma v - kvx. \tag{11}$$

The variables are: x, the number of (activated) uninfected CD4+ T-cells; y, the number of actively infected (i.e. virus-producing) such cells; z, the number of latently (i.e. not yet producing virus) infected cells; and v, the number of virions. These quantities may refer to whole blood (about 5×10^6 mm^3) or be given for 1 mm^3 of plasma. The parameters are as follows:

s is the rate of arrival (or production) of uninfected CD4+ T-cells in plasma;
μ is their death rate per cell;
k is the interaction parameter for virus-activated CD4+ T-cell reactions;
p is the fraction of uninfected cells that upon infection become latent;
α is the rate per cell at which latently infected cells become actively infected;
a is the death rate per cell of actively infected CD4+ T-cells;
c is the net rate of virion production per actively infected cell; and
γ is the death rate of free virus particles.

Standard parameters, in addition to those given for the three-component model, are $\alpha = 0{\cdot}036$ /day/mm^3, and $p = 0{\cdot}1$, these also being taken from Phillips (1996).

Setting the four derivatives (8)–(11) to zero, we obtain two equilibrium points. The first is $P_1 = \left(\frac{s}{\mu}, 0, 0, 0\right)$ and we let the second be $P_2 = (x_2, y_2, z_2, v_2)$. Then,

$$x_2 = \frac{1}{k}\left[\frac{\gamma a(\alpha+\mu)}{(c-a)(\alpha+\mu) - cp\mu}\right]$$

$$z_2 = \frac{p(s-\mu x_2)}{(\alpha+\mu)}$$

$$y_2 = (\alpha+\mu-p\mu)\frac{z_2}{ap}$$

$$v_2 = \frac{s-\mu x_2}{kx_2}.$$

With the standard parameter values, we have $P_1 = (200, 0, 0, 0)$ and $P_2 = (49{\cdot}3947, 0{\cdot}6184, 0{\cdot}5482, 15{\cdot}3580)$. These values agree with those obtained for very large t by numerical solution of (8)–(11).

When linearized about P_1, the system (8)–(11) yields

$$\frac{dx}{dt} = -\mu x - k_1 v$$

$$\frac{dy}{dt} = -ay + \alpha z + (1-p)k_1 v$$

$$\frac{dz}{dt} = -(\alpha+\mu)z + pk_1 v$$

$$\frac{dv}{dt} = cy - (\gamma + k_1)v,$$

where $k_1 = ks/\mu$. The first of the four eigenvalues is $\lambda_1 = -\mu$ and the remaining three are the roots of

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0,$$

where,

$$A = \alpha + \mu + a + \gamma + k_1$$

$$B = (\alpha+\mu)(a+\gamma+k_1) + a(\gamma+k_1) - (1-p)ck_1$$

$$C = a(\alpha+\mu)(\gamma+k_1) - [\alpha+\mu(1-p)]ck_1].$$

For the standard values of the parameters this gives $\lambda_1 = -0{\cdot}00136$, $\lambda_2 = -2{\cdot}165$, $\lambda_3 = 0{\cdot}7645$, $\lambda_4 = 1{\cdot}4007$ and P_1 is a saddle point. It has been found by numerical solution that the remaining equilibrium point P_2 is an asymptotically stable spiral point. This is illustrated in Figure 3. In the upper part of the figure, virion density is shown as a function of time for various values of the initial density ($x(0)$) of uninfected CD4+ T-cells. In the lower part is shown a phase portrait for the variables $x(t)$ and $v(t)$, showing clearly how solutions spiral towards the critical point P_2.

More generally, for any set of positive input parameter values, $P_1 = \left(\frac{s}{\mu}, 0, 0, 0\right)$ is the only realizable critical point if

$$k_1 < kx_2 = \frac{\gamma a(\alpha+a)}{(c-a)(\alpha+\mu) - cp\mu}$$

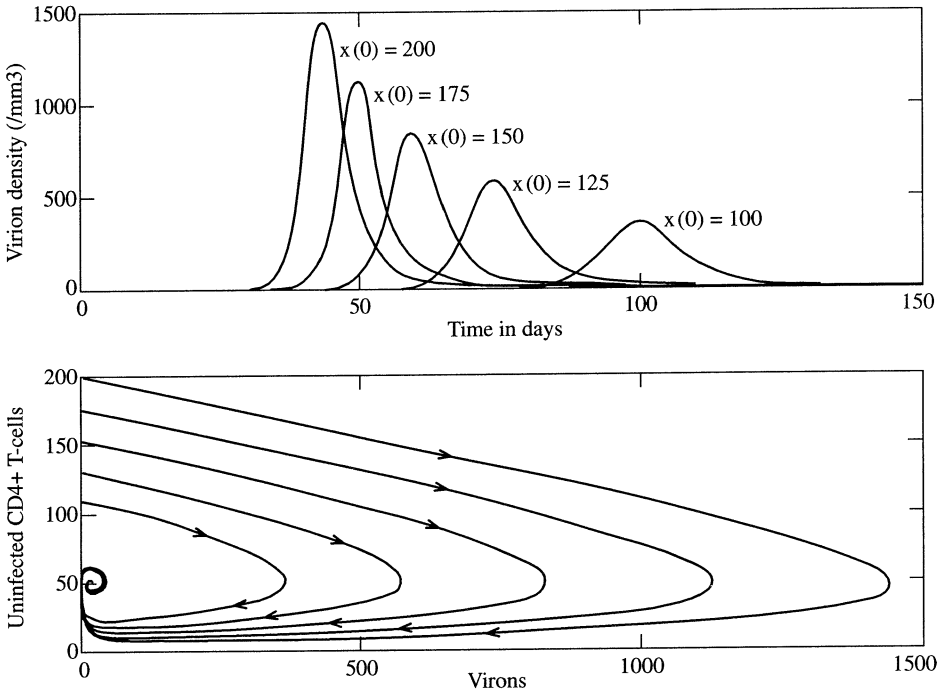

FIG. 3. In the top part are shown virion density versus time curves in the four-component HIV-1 model for various initial densities of CD4+ T-cells as indicated alongside the corresponding solutions. Parameter values are given in the text. In the lower part, a phase portrait is shown for the variables (x, v), namely uninfected activated CD4+ T-cell density versus HIV-1 virion density. Solutions travel towards the spiral point P_2 giving rise to small secondary peaks of viral load.

since y_2, z_2 and v_2 are all negative in this range of values of k_1. By rewriting $k_1 < kx_2$ as

$$[\alpha + \mu(1-p)]ck_1 < a(\alpha+\mu)(\gamma+k_1),$$

the coefficient C in the cubic equation for λ is seen to be positive for this range of k_1. At the same time the identity

$$(\mu+\alpha)[a(\gamma+k_1)-(1-p)ck_1] = a(\mu+\alpha)(\gamma+k_1)-[\alpha+\mu(1-p)]ck_1+(1-p)\alpha ck_1$$

implies

$$\begin{aligned} AB - C =& (a+\gamma+k_1)[(\alpha+\mu)^2+(\alpha+\mu)(a+\gamma+k_1) \\ &+ a(\gamma+k_1)-(1-p)ck_1]+(\mu+\alpha)pck_1 > 0. \end{aligned}$$

Since A is always positive (for any set of positive parameter values), it follows from the Routh-Hurwitz criteria ($A > 0$, $C > 0$ and $AB - C > 0$), that the three roots of the cubic equation for λ all have negative real parts (with the remaining eigenvalue λ_1 already having been found to be $-\mu$). Hence the critical point P_1 is asymptotically stable whenever it is the only physically realizable critical point.

At the critical value, $\frac{s}{\mu} = x_2$, the two critical points P_1 and P_2 coincide at $\left(\frac{s}{\mu}, 0, 0, 0\right)$. It is deduced from numerical solutions for the fourth order system of ODEs (8)–(12) that if $\frac{s}{\mu} > x_2$, then P_2 is either an asymptotically stable node or an asymptotically stable spiral point. In that case we again have a transcritical bifurcation at $\frac{s}{\mu} = x_2$ with P_2 emerging as the asymptotically stable steady state as $\frac{s}{\mu}$ increases beyond x_2. The situation is similar to that of another four-component model considered by Perelson *et al.* (1993). That model corresponds to the present one with $p = 1$ but with the additional feature of logistic growth of the uninfected CD4+ T-cells. In that model P_2 was found to be unstable in some parameter regimes. We expect that the stability of P_2 is similar in our model and report the results of numerical experiments for different ranges of values of the various parameters.

Effects of varying the parameters

Setting the parameters at the above standard values but putting $c = 100$ as in Phillips (1996), P_1 is unchanged and $P_2 = (24{\cdot}615, 0{\cdot}7202, 0{\cdot}638, 35{\cdot}889)$.The natures of P_1 and P_2 are unchanged, but the peak virion density is about 4500/mm^3 at about 23 days after exposure to the virus. This may be compared with the maximum value of v of about 1440/mm^3 at about 44 days when $c = 50$.

Relative to this standard set, i.e. $s = 0{\cdot}272$, $\mu = 0{\cdot}00136$, $k = 0{\cdot}00027$, $a = 0{\cdot}33$, $c = 100$, $\gamma = 2{\cdot}0$, $\alpha = 0{\cdot}036$, $p = 0{\cdot}1$ we have varied each parameter in turn to 50% above and below its standard values. These ranges may be conservative for some parameters—see Perelson *et al.* (1996) for the standard deviations of some. The results of varying each parameter are as follows.

Increases in s, k and c and decreases in μ, a and γ increased the magnitude of the peak virion level dramatically and shifted the time of peak to smaller values (with converse effects for changes in the opposite direction). For such changes, the smallest time to peak of 14 days occurred with μ reduced to 50% of standard value, the maximum being about 10 600 virus particles per mm^3. With the changed values of s, μ, k or c, whether up or down by 50%, the point P_2 remained a spiral point. However, when either a or γ were decreased by 50%, the nature of P_2 changed to an asymptotically stable node. Furthermore, as k was increased to several times its standard value, the peak for v grew and occurred faster until at five times the standard value, P_2 became an asymptotically stable node; the peak then occurred at 7·5 days.

Changes in the parameters α and p had less significant effects with P_2 remaining a spiral point. Changes in α to 50% above or below the standard value resulted in practically no change in either the maximum virion level nor its time of occurence; corresponding changes in p had similar, but slightly greater, effects.

6. Effects of certain drug treatments

Mathematical models for viral population dynamics can be used to analyse the effects of drug treatments through the changes in parameters induced by the drugs. In the treatment of HIV-1 infected patients, we will concentrate attention on the effects of reverse transcriptase inhibitors and of protease inhibitors. The first class of drugs, typified by AZT (zidovudine), disables the process of infection of CD4+ T-cells by the virus; the second class block the

production of new infectious virus by already infected cells so that only non-infectious virions are generated. These same two drug treatments were considered in a 10-component model by Wein *et al.* (1997). Subsequently, Wein *et al.* (1998) analysed the transient and steady-state behaviors of a mathematical model of HIV-1 dynamics *in vivo* in order to predict whether combinations of antiretroviral agents could eradicate HIV-1 or maintain viral loads at low levels. They included two cell types (CD4+ T cells and a long-lived pool of cells), two strains of virus (drug-sensitive wild type and drug-resistant mutant) and two types of antiretroviral agents (reverse transcriptase and protease inhibitors). The present mathematical model is similar but only includes one viral and only a plasma compartment, resulting in a more straightforward analysis which complements that of Wein *et al.* (1998) and of Ferguson *et al.* (1999). Thus we will only consider the effects of the same combination treatment in the three-component model of HIV-1 dynamics given by equations (5)–(7). The reverse transcriptase inhibitor changes the infection rate from k to $(1-r)k$, where r is the effciency of the drug, being the fraction of infections that are blocked. The value of r will generally depend upon the dose schedule and hence be a function of time. Here we assume that r is constant. The protease inhibitor divides the viral population into infectious virions, whose density we let be v_I and non-infectious particles, with density v_{NI}. Suppose now that the drug treatment commences at $t = t_0$. Then for $t < t_0$ the model equations are simply (5)–(7) with v replaced by v_I. For $t \geqslant t_0$ we have, letting the fraction of newly produced virus particles rendered non-infectious by the protease inhibitor be q,

$$\frac{dx}{dt} = s - \mu x - (1-r)kv_I x \tag{12}$$

$$\frac{dy}{dt} = (1-r)kv_I x - ay \tag{13}$$

$$\frac{dv_I}{dt} = (1-q)cy - \gamma v_I - (1-r)kv_I x \tag{14}$$

$$\frac{dv_{NI}}{dt} = qcy - \gamma v_{NI}. \tag{15}$$

The first three equations are independent of the fourth so it suffices to consider the reduced three-component system (x, y, v_I). At any equilibrium point we will always have

$$v_{NI}^* = \frac{qcy^*}{\gamma},$$

where asterisks denote equilibrium values.

The critical point P_1 is still at $\left(\frac{\lambda}{\mu}, 0, 0\right)$ and this is an attractor if

$$(1-r)[(1-q)c - a] < \frac{a\gamma\mu}{k\lambda} \tag{16}$$

TABLE 1
Critical values of the efficiency q, of the protease inhibitor, for various values of the efficiency r of the reverse transcriptase inhibitor

$r = 0{\cdot}00$	$q = 0{\cdot}7490$
$r = 0{\cdot}25$	$q = 0{\cdot}6675$
$r = 0{\cdot}50$	$q = 0{\cdot}5045$
$r = 0{\cdot}75$	$q = 0{\cdot}0156$
$r = 1{\cdot}0$	$q = 0$

whereas it is a saddle point if this inequality is reversed. The point P_2 has coordinates

$$x_2^* = \frac{a\gamma}{(1-r)k(1-q)(c-a)}$$
$$y_2^* = \frac{\lambda}{a} - \frac{\gamma\mu}{(1-r)k[(1-q)c-a]}$$
$$v_{I,2}^* = \frac{\lambda[(1-q)c-a]}{a\gamma} - \frac{\mu}{(1-r)k}.$$

As before, the condition that P_2 be at unphysical values coincides with that for P_1 to be an attractor. Relative to the non-treatment values, x^* is increased, whereas y^* and v_I^* are decreased, which are desired outcomes. However, one may make the viral load vanish with treatments which are less than 100% efficient—it is sufficient that the inequality (16) be satisfied because then solutions tend to P_1 where $v_I = 0$, no matter what the values of $(x(t_0), y(t_0), v_I(t_0))$. It is useful to rearrange (16) to give a critical value of q (efficiency of the protease inhibitor) for extinction of the virus for a given value of r (efficiency of the reverse transcriptase inhibitor). This gives

$$q_c = 1 - \frac{a}{c}\left[1 + \frac{\gamma\mu}{k\lambda(1-r)}\right],$$

so that if q is greater than q_c the virus will be extinguished. These critical values are listed in Table 1 for the standard parameter set.

Thus one can see that even in the absence of a reverse transcriptase inhibitor ($r = 0$), the virus is extinguished if $q > 0{\cdot}75$, and that even if both of the drugs are only 50% efficient, the virus may be eliminated. Of course these remarks only apply if the three-component model employed here is valid.

7. Conclusions and discussion

We have investigated a general two-component virus-antibody dynamical system and models for early HIV-1 population dynamics which incorporate either two, three or four components. Such models have proven useful in understanding the clinical time course of

HIV-1 infection and with modifications have been used to investigate various regimes of drug therapy. In each model there are always two critical (equilibrium) points, one of which may not be at biologically meaningful values of the dynamical variables. The behavior of solutions is broadly only of two types; either the critical point P_1 at zero virion density is an attractor and all solutions end up at P_1; or P_1 is an unstable saddle point and all solutions end up at the other critical point, P_2, which may be a spiral point or a node, at non-zero virion levels. There is in fact a transcritical bifurcation as parameters pass through critical values. For the three-component HIV-1 model, which includes uninfected CD4+ T-cells, infected cells and virions, the parameter values which divide the two kinds of behavior are found analytically. If $a\gamma < \frac{ks(c-a)}{\mu}$, then P_1 is an unstable saddle point and P_2 is either a node or spiral point. Otherwise, P_2 is at unphysical values and P_1 is an asymptotically stable node or spiral point. In these systems, which are only weakly non-linear, we have not found any periodic solutions in the absence of additional forcing terms. Perelson *et al.* (1993) had also found an absence of periodic solutions for the usual parameter ranges, but demonstrated the occurrence of a Hopf bifurcation at parameter values beyond such ranges. For the 4-component HIV-1 dynamical model, which includes both latently and actively infected CD4+ T-cells, we have obtained expressions for the positions of the critical points and investigated solution properties for various parameter values. The properties of the solutions of the more complicated 4-component model are not very qualitatively different from those of the simpler 2- and 3-component models, despite the fact that the additional parameters in the 4-component model have clear biological interpretations. We have illustrated the effects of treatment with certain classes of drugs, in particular reverse transcriptase inhibitors and protease inhibitors, by using the three-component HIV-1 model. We have seen that in this framework the virus could be eliminated with various values for the efficiencies of the two treatments. However, it is again pointed out that the model is only supposed to be a reasonable representation for the early period after HIV-1 infection. As pointed out by Ferguson *et al.* (1999), additional factors need to be accounted for in the quest for satisfactory long-term therapy.

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