



# On the behavior of solutions in viral dynamical models

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## Abstract

We consider simple mathematical models for the early population dynamics of the human immunodeficiency type 1 virus (HIV-1). Although these systems of differential equations may be solved by numerical methods, few general theoretical results are available due to nonlinearities. We analyze a model whose components are plasma densities of uninfected CD4+ T-cells and infected cells (assumed in this model to be proportional to virion density). In addition to analyzing the nature of the equilibrium points, we show that there are no periodic or limit-cycle solutions. Depending on the values of the parameters, solutions either tend without oscillation to an equilibrium point with zero virion density or to an equilibrium point in which there are a nonzero number of virions. In the latter case the approach to equilibrium may be through damped oscillations or without oscillation.

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## 1. Introduction

There has been much interest recently in mathematical models of viral population dynamics in host cells (Nowak and May, 2000), with most attention focussed on HIV (Perelson and Nelson, 2000). The aim of such modeling is not only to understand the nature of various diseases and their time courses, but also to develop efficient regimes for drug treatments, including the highly successful combination therapies (Callaway and Perelson, 2002; Perelson et al., 1997; Phillips et al., 1997; Wein et al., 1997). Stochastic models have also proven to be useful, especially in determining probabilities of detection of the virus (Le Corfec et al., 1999; Tan and Wu, 1998; Kamina et al., 2001; Tuckwell, 2004).

### 1.1. The elements of viral reproduction

Viral reproduction always involves host cells. The sequence of steps after the virus has penetrated the body's initial physical barriers (skin, mucosal lining) is

- (a) the virus attaches to a host cell at a receptor on the cell surface;
- (b) penetration occurs;
- (c) the virus sheds its protein coat and releases its nucleic acid (RNA or DNA) into the cell;
- (d) transcription occurs followed by replication of the virus genetic material and the production of proteins for new coats;
- (e) virus particles are assembled and released and may infect new host cells; the original host cell may die.

These processes have been translated into a basic model for viral population growth, consisting of

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three differential equations which govern the evolution of the numbers or densities of uninfected host cells, infected cells and virus particles. The elementary properties of such systems of equations are well understood and numerical solution proceeds routinely with software such as Matlab. Constituting a special case because the infected cells are those of the immune system itself, dynamical models for HIV-1 usually consist of systems of differential equations which range from the simple two-component models (Bonhoeffer et al., 1997), to three-component (Herz et al., 1996) and four-component models (McLean et al., 1991; Phillips, 1996; Le Corfec and Tuckwell, 1998) and possibly as many as ten components (Essunger and Perelson, 1994). The basic components consist of the densities (in units, for example, of numbers per cubic mm of plasma) of uninfected (activated) CD4+ T-cells, infected such cells and HIV-1 virions.

In a previous communication (Tuckwell and Wan, 2000) we have investigated the nature of equilibrium points in models with two, three or four components and included certain drug treatments in the four-component case. The solutions of such systems of differential equations exhibit similar overall behavior. For example, all three models have just two equilibrium points. One of these at a zero level of infection and is either an asymptotically stable node or a saddle point. The other equilibrium point is at nonnegative values of infection and uninfected CD4+ T-cells, and for standard parameter values is an asymptotically stable spiral point. Phase portraits were given in Tuckwell and Wan (2000), where we complemented an analytical approach with numerical methods to ascertain the general classes of behaviors of solutions.

In this paper we report some further basic results concerning the properties of solutions in the two-component model. In particular, we are interested in addressing the question of the occurrence of solutions with periodic behavior, corresponding to a continually recurring disease process. Such investigations have previously been carried out for classical competition models of the Lotka–Volterra type (Van den Driessche and Zeeman, 1998). The results we obtain may also apply qualitatively to the models with three or four components where the analysis is algebraically more complicated.

## 2. Model description and results

The components of the basic three-component model are uninfected CD4+ T-cells, infected such cells and free virus, whose densities at time  $t$  are denoted respectively by  $x(t)$ ,  $y(t)$  and  $v(t)$ . These quantities satisfy

$$\frac{dx}{dt} = s - \mu x - \beta xv$$

$$\frac{dy}{dt} = \beta xv - \alpha y$$

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

Here  $s$  is the (assumed constant) rate of production of CD4+ T-cells,  $\mu$  is their per capita death rate,  $\beta xy$  is the rate of infection of CD4+ T-cells by virus,  $\alpha$  is the per capita rate of disappearance of infected cells,  $c$  is the rate of production of virions by infected cells and  $\gamma$  is the death rate of virus particles. Typical parameter values are, with time in days and particle (cell) densities in numbers per cubic millimeter:  $s = 0.272$ ,  $\mu = 0.00136$ ,  $\beta = 0.00027$ ,  $\alpha = 0.33$ ,  $c = 50$  and  $\gamma = 2.0$ .

In the simplified model employed by Bonhoeffer et al. (1997) there are two components:  $x$ , the number of uninfected CD4+ T-cells and  $y$ , the number of infected such cells. Here it is assumed that the viral density is at the equilibrium value with  $\dot{v} = 0$ , so that  $v$  can be eliminated by putting  $v = cy/\gamma$ . Then, with  $k = \beta c/\gamma$ ,  $x$  and  $y$  satisfy

$$\frac{dx}{dt} = s - \mu x - kxy \quad (1)$$

$$\frac{dy}{dt} = kxy - \alpha y \quad (2)$$

where all parameters and variables are nonnegative.

The investigation of the equilibria is straightforward and is given for completeness. The critical points are  $P_1 = ((s/\mu), 0)$  and  $P_2 = ((\alpha/k), ((sk - \alpha\mu)/\alpha k))$ . For all meaningful parameter values ( $s \geq 0$ ), the first point  $P_1$  always occurs at biologically meaningful (nonnegative) values. However,  $P_2$  is only at meaningful values if  $sk \geq \alpha\mu$ . For  $P_1$  the associated eigenvalues are  $-\mu$  and  $((sk - \mu\alpha)/\mu)$ . 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 possibilities. 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). In the event that  $sk = \mu\alpha$  special consideration must be given to nonlinear effects.

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 ( $sk \geq \alpha\mu$ ), we have  $0 \leq 1 - (\alpha\mu/ks) < 1$  and there are two possibilities.

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

(B)  $(4\alpha^2/(ks)^2)(ks - \alpha\mu) \leq 1$ . In this case the eigenvalues are both real and negative so that  $P_2$  is an asymptotically stable node.

2.1. 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 nonnegative  $s$  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** ( $sk \geq \alpha\mu$ ). There are two critical points.  $P_1$  is on the  $x$ -axis and  $P_2$  is in the nonnegative quadrant. When  $sk > \alpha\mu$ ,  $P_1$  is always an unstable saddle point and  $P_2$  is either an asymptotically stable spi-

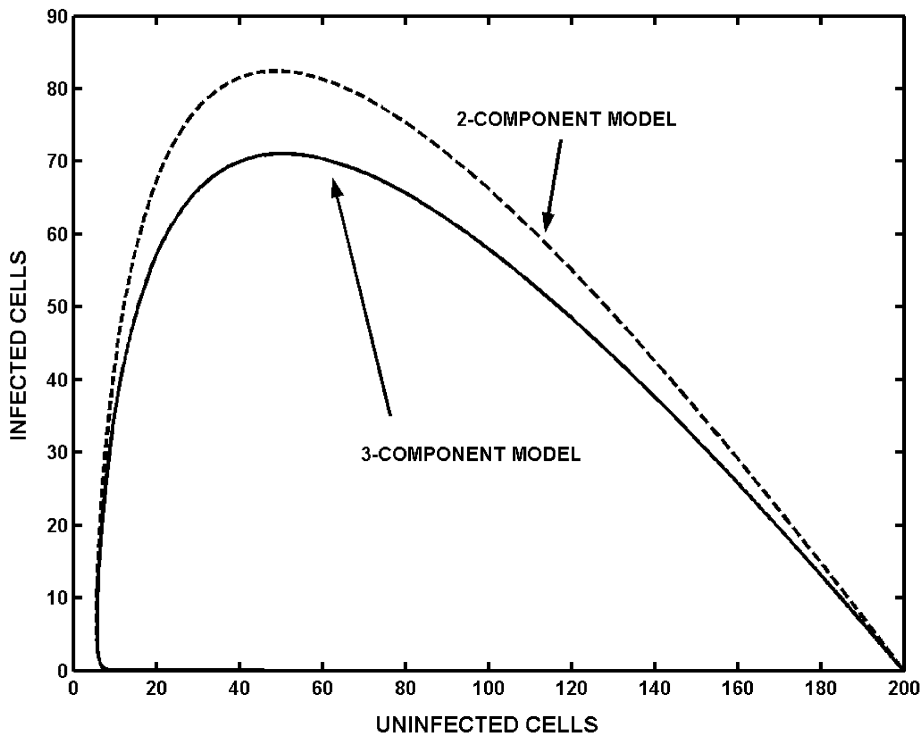


Fig. 1. Showing trajectories in the two- and three-component HIV models. The density of infected cells is plotted against that of uninfected cells. Parameter and initial values are given in the text.

ral 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.

To show that solutions of the two and three component models are essentially similar, we have computed the solutions of both models using Runge–Kutta methods. This was done with the standard parameter values given above and initial values  $x(0) = 200$ ,  $y(0) = 0$  and  $v(0) = 1$  for the three-component model and corresponding values  $x(0) = 200$ ,  $y(0) = \gamma/c$  for the two-component model. The phase portraits are shown in Fig. 1 for a time period of 200 days and it can be seen that the orbits are quite close. Computed solutions for the four-component model were similar and have been described in Tuckwell and Wan (2000).

## 2.2. Periodic solutions

We will show that there are no periodic solutions, including limit cycles. This is done by using the following generalization of Bendixson's criterion, called Dulac's criterion (see, for example, Hale and Kocak, 1991, Chapter 12). To carry this out, the system of Eqs. (1) and (2) is put in the following form, with  $(x, y) \in D$ , a simply connected open set in  $R^2$ :

$$\frac{dx}{dt} = f(x, y) \quad (3)$$

$$\frac{dy}{dt} = g(x, y) \quad (4)$$

Dulac's result states that if there exists a continuously differentiable real-valued function  $B(x, y)$  in  $D$  such that

$$G(x, y) = \frac{\partial(Bf)}{\partial x} + \frac{\partial(Bg)}{\partial y}$$

is of constant sign and not identically zero in  $D$ , then the system (3) and (4) has no periodic orbit in  $D$ .

For the present problem a suitable Dulac function is found to be  $B(x, y) = 1/y$ . Then with  $f = s - \mu x - kxy$  and  $g = kxy - \alpha y$ , we find that  $G(x, y) = -(\mu/y) - k$ . Thus,  $G = 0$  on  $y = -(\mu/k)$  and  $G < 0$  for  $y > -(\mu/k)$  and  $G > 0$  for  $y < -(\mu/k)$ . Since  $G$  satisfies Dulac's criterion for  $y > 0$  we may conclude

there are no periodic solutions including limit cycles for the two-component HIV-1 model described by Eqs. (1) and (2).

## 3. Conclusions

The classical Lotka–Volterra system for predator–prey interactions is well known to have periodic solutions (Freedman, 1980) whereas competitive Lotka–Volterra systems of standard form do not (Van den Driessche and Zeeman, 1998). The model (1), (2) for HIV-1 is not in the standard form but is nevertheless similar to the classical Lotka–Volterra system. We have demonstrated there is an important difference in that the HIV-1 system has no periodic solutions. In light of the analysis of the equilibrium points given above, we see that HIV-1 densities cannot recurrently reach the same level as at the primary peak. There are only the two possibilities of an approach to zero or an approach, either monotonically or by damped oscillation, to some positive equilibrium value. Although our analysis has considered a simplified two-component HIV-1 model, the similarity between the numerically computed solutions for this model and those for the three- and four-component models, indicates that the results obtained above probably apply to the more complicated models of HIV-1 population dynamics and hence to the evolution of the virus in human hosts.

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