

VIRAL POPULATION GROWTH MODELS

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Abstract

The steps involved in viral reproduction are described briefly. Mathematical models for the growth of viral populations without random effects take the form of systems of differential equations and these are reviewed, including the standard HIV equations, with correction terms. The validity of the “mass action” assumption is questioned for low virion levels. Stochastic differential equation models for HIV are described, including those with both discontinuous and diffusion processes. Simulation results are given for early HIV population growth, including the distribution of the time to reach a detection level, for which an analytical theory is also available. The more complicated long-term model of Tan and Wu is discussed briefly as well as mutation and its effect on drug treatments. Although there has been some useful analysis of patient data with respect to simple differential equations, it is concluded that modeling, either deterministic or stochastic, of viral populations requires much further development to give an accurate and useful representation of the underlying biological processes.

1. Introduction

Viruses are amongst the most dangerous and devastating threats to human health. They may invade a human or animal population and spread rapidly amongst its members, sometimes causing a large number of fatalities, possibly on a recurrent basis. A well known case is the influenza virus, a new strain sweeping the globe and causing approximately 25 million deaths in 1919. At the present time there are several countries, particularly in Africa, with up to 35% of their populations between the ages of 15 and 50 years infected by human immunodeficiency virus (HIV). Throughout the world, already over 16 million deaths have been caused by this virus. Renewed interest in the dynamical processes involved in the spread of viruses has arisen recently due to the threat of bioterrorist attacks, especially with such viruses as smallpox Henderson *et al.* (1999), which was eradicated many years ago. We will first briefly describe in a simplified fashion some of the processes which determine the outcome of a viral invasion (Nash, 2001).

Viral reproduction

Viral reproduction depends on 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.

The time taken for some of these steps is extremely variable. For HIV replication is unpredictable but may occur in a few hours; with herpes virus there may be a delay of weeks or up to many years, which seems to be an evolutionary strategy (Stumpf *et al.*, 2002).

Models of viral population growth may be distinguished by whether they consider the within host population, or the total across all individuals. To determine the latter the dynamics of transmission amongst members of the host population are needed and this is usually the domain of classical models such as SIR (susceptible infected, recovered). These are discussed, for example, in Bailey (1975) and Hethcote (2000). Recently we have formulated nonlinear dynamical spatial network models for determining the total viral load (Tuckwell, Toubiana and Vibert, 2001, and references therein). In this work we only consider within host dynamics.

2. Deterministic models

Since the growth of a viral population depends on the ability of the virus to penetrate new host cells, the simplest growth model has the following three components for a given volume of tissue: $x(t)$ = number of uninfected cells; $y(t)$ = number of infected cells; and $v(t)$ = number of free virus particles. Then

$$\frac{dx}{dt} = \lambda - \mu x - \beta vx \tag{1}$$

$$\frac{dy}{dt} = \beta vx - \alpha y \tag{2}$$

$$\frac{dv}{dt} = cy - \gamma v - \beta vx, \tag{3}$$

where uninfected host cells are supplied at rate λ and have a per cell death rate of μ , the parameter β describes the rate at which virus infects host cells, c is the rate at which free virions are produced per infected cell, and α and γ are the ‘‘per capita’’ rates of attrition of infected cells and virions, respectively. Equation (3) is a slightly modified version of the standard model formulated by Herz *et al.*(1996), which is

analyzed in by Nowak and May (2000). The modification, suggested by Tuckwell and Le Corfec (1998) and others consists of the additional term $-\beta vx$ in (3) to allow for the fact that whenever a cell is attacked, a free virus must disappear. The more complete model (1)-(3) is analyzed in detail by Tuckwell and Wan (2000a).

The system (1)-(3) has 2 equilibrium points

$$P_1 = (\lambda/\mu, 0, 0), \quad P_2 = \left(\frac{\alpha\gamma}{\beta c}, \frac{\lambda}{\alpha} - \frac{\gamma\mu}{\beta c}, \frac{c\lambda}{\alpha\gamma} - \frac{\mu}{\beta} \right).$$

For $\lambda > 0$, P_1 is either a saddle point or an asymptotically stable node, but for usual parameter values, the former. P_2 is usually an asymptotically stable spiral point. Note that P_2 is unphysical when $\beta c\lambda < \alpha\gamma\mu$. When P_2 is in the first octant, solutions of the system (1)-(3) approach this point in an oscillatory fashion so that eventually there remain infected cells, virions and uninfected cells in equilibrium. In the less usual case that P_2 is unphysical, the free virus must be extinguished.

The above model does not include an ‘‘immune response’’. The presence of infected cells may stimulate the production of cytotoxic T-cells which attack infected cells. If these have concentration $z(t)$ then a plausible model system is given by (1) and (3) with (2) changed by the addition of a term representing the removal of infected cells

$$\frac{dy}{dt} = \beta vx - \alpha y - \rho yz \tag{2'}$$

and an additional equation for the cytotoxic cells:

$$\frac{dz}{dt} = kyz - \delta z, \tag{4}$$

where δ is their natural death rate. Some dynamical properties of the model (1),(2'),(3) (without the correction term) and (4) are also discussed in Nowak and May (2000).

HIV

The virus which has attracted the most dramatic attention in the previous two decades is HIV (human immunodeficiency virus, usually type 1). A distinguishing feature of this virus is that the infected cells are those of the immune system itself, being CD4+ T-cells (helper cells). After infection there is a rapid initial rise of virion density followed usually by a similarly paced fall, the latter being originally ascribed to an immune response. Modeling indicated that the early dynamics might be reasonably explained without invoking such a response (McLean *et al.*, 1991; Phillips, 1996), and this has been mainly vindicated by subsequent studies. However, fitting the data on viral loads after the primary peak in some patients seemed to require the introduction of more complex dynamics such as the inclusion of cytotoxic T lymphocytes (Stafford *et al.*, 2000). There is a large number of

models which have been posited to describe these phenomena, and they may be distinguished by whether they address only the early phases or the later phases of the disease - Perelson and Nelson (1999) and Nowak and May (2000) can be consulted for numerous references.

The general model of McLean *et al.* (1991) was later used in a different context by Phillips (1996) to explain the decline in viral load in HIV after the initial rise to about 5000 per mm³. Two classes of infected cells are introduced because the insertion of viral genetic material may be followed by a delay before virions emerge. Thus $x(t)$ is the density of uninfected CD4+ T-cells, but now $u(t)$ is the density of latently infected cells and $w(t)$ is the density of infected cells producing virus. With $v(t)$ the density of free virions in the plasma we have, with an added correction term for dv/dt :

$$\frac{dx}{dt} = \lambda - \mu x - \beta vx \quad (5)$$

$$\frac{du}{dt} = \beta p vx - (\mu + \alpha)u \quad (6)$$

$$\frac{dw}{dt} = \beta(1-p)vx + \alpha u - aw \quad (7)$$

$$\frac{dv}{dt} = cw - \gamma v - \beta vx. \quad (8)$$

Here p is the fraction of infected cells which become latent, α is the rate of conversion of latent to actively infected cells, and a is the death rate of actively infected cells. The term λ in (5) gives the rate at which new T cells are created from sources in the body. Another term may be added, such as a logistic, to represent growth due to the proliferation of existing T cells. The parameters are possibly time-varying so that for example, if the immune response is weakening, then γ may decrease. A long term model not dissimilar to the above and which leads to the breakdown of immunity (AIDS) was analyzed in Stilianakis *et al.*(1997).

In all the above dynamical models, not only for HIV but for other viruses, the law of “mass action” is assumed to operate giving a rate of new infections proportional to the product of viral and host cell numbers. However, there are strong grounds for sometimes questioning the validity of this assumption. For such a law to apply, there must be homogeneous mixing and the latter is unlikely if there are only one or two virions and say 10^{11} host cells. The law may nevertheless be accurate for a very restricted volume of tissue or fluid. It is also worth mentioning that the viral density in plasma may be low, or essentially zero, but that due to the continued existence of latently infected host cells, the viral density may increase at a later time, making the disease extremely difficult to eradicate.

Other viruses

There has been a considerable effort to model the invasion and within host growth of influenza virus populations, sometimes with very complex systems (Bocharov and Romanyukha, 1994). Although there have been many epidemiological studies of the spread of such viruses as smallpox, measles, herpes etc, mathematical models for the growth of their within host viral populations have been sparse. Nowak and May (2000) have described simple differential equations for the hepatitis B virus, which presently afflicts about 300 million people, and Neumann *et al.* (1998) have analyzed the dynamics of the hepatitis C virus.

3. Stochastic dynamical models for HIV

As pointed out by Tan and Wu (1998), a stochastic description of viral population growth is more realistic than a deterministic one because of the nature of the subcellular processes. Furthermore, it is expected that a stochastic approach can provide a more accurate quantitative basis for evaluating the efficacy of drug treatments in infected host populations. Nevertheless, relatively little attention has been given to stochastic dynamical viral growth models. From an analytic viewpoint, this is probably due to the complexity of the systems. The general viral growth model (1)-(3) does not have a stochastic counterpart, though one could easily be developed using approaches similar to those described below for HIV. One of the first stochastic models for HIV was a simple branching process (Merrill, 1989).

In general, the following effects are stochastic:

- (a) generation and fluctuations in the rate of appearance of new host cells
- (b) contacts between viruses and the host cell and random attachment
- (c) transition to active or latent infected cell
- (d) time for the emergence of new virions
- (e) number of new virions emerging from a host cell
- (f) death process for infected and uninfected host cells and virions
- (g) mutation to other viral strains
- (h) appearance and action of immune system components which assist in the removal of virions

A. Models for a single viral genotype

Here it is assumed that all virus particles have the same genetic properties. Vector valued Markov process models for the growth of HIV populations have been introduced by Tuckwell and Le Corfec (1998) and Tan and Wu (1998). Both models have the same four biological components. A comparison of these models was made in Kamina *et al.* (2002), but the nature of the boundaries for the diffusions (see for

example, Feller, 1952) needs further investigation. The Tuckwell-Le Corfec model is a 4-dimensional diffusion process and as it is simpler than Tan and Wu's model, it will be described first, after a consideration of a Poisson model.

Stochastic model for early HIV growth

In this work emphasis is on the early period (to several weeks) after infection and not on the later progression to the acquired immune deficiency syndrome which may follow. Letting the components be X_k , $k = 1, 2, 3, 4$, we have that at time t (days) after initial infection, for a fixed and relatively small (in order to enhance the validity of the mass action principle) volume of plasma, $X_1(t)$ is the number of uninfected CD4+ T-cells (called "activated" by Phillips (1996)), $X_2(t)$ is the number of latently infected cells, $X_3(t)$ is the number of actively infected cells and $X_4(t)$ is the number of circulating HIV-1 virions. The attachment of virus to CD4+ T-cells (assumed to be one on one) occurs according to a Poisson process N with rate $\beta X_1 X_4$ so that the system of stochastic differential equations corresponding to the above deterministic model is

$$dX_1 = (\lambda - \mu X_1)dt - dN(\beta X_1 X_4; t) \quad (9)$$

$$dX_2 = p dN(\beta X_1 X_4; t) - (\mu X_2 + \alpha X_2)dt \quad (10)$$

$$dX_3 = (1 - p) dN(\beta X_1 X_4; t) + (\alpha X_2 - a X_3)dt \quad (11)$$

$$dX_4 = (cI - \gamma)dt - dN(\beta X_1 X_4; t). \quad (12)$$

Note that N has different units in, for example (9) and (12), but equal numerical values. In a diffusion approximation (Tuckwell and Le Corfec, 1998) the evolution of the system is described by

$$dX_1 = (\lambda - \mu X_1 - \beta X_1 X_4)dt - \sqrt{\beta X_1 X_4} dW \quad (9A)$$

$$dX_2 = (\beta p X_1 X_4 - \mu X_2 - \alpha X_2)dt + \sqrt{\beta p X_1 X_4} dW \quad (10A)$$

$$dX_3 = [\beta(1 - p) X_1 X_4 + \alpha X_2 - a X_3]dt + \sqrt{\beta(1 - p) X_1 X_4} dW \quad (11A)$$

$$dX_4 = (cI - \gamma X_4 - \beta' X_1 X_4)dt - \sqrt{\beta' X_1 X_4} dW. \quad (12A)$$

The model parameters are as defined above for the deterministic model. There is only one primary Wiener process, not four as portrayed in Kamina *et al.* (2002) as each component carries the same one, derived from the Poisson process N .

For the 4-component diffusion process (9A)-(12A), the transition probability density function $P(\mathbf{y}, t; \mathbf{x}, s)$, $s < t$, where \mathbf{y} is a 4-vector of forward variables and \mathbf{x} is a 4-vector of corresponding backward variables, satisfies the following backward Kolmogorov equation (Gihman and Skorohod, 1972)

$$\frac{\partial P}{\partial s} + L_{\mathbf{x}} P = 0,$$

where the operator $L_{\mathbf{x}}$ is defined through

$$\begin{aligned}
L_{\mathbf{x}} = & [\lambda - \mu x_1 - \beta x_1 x_4] \frac{\partial}{\partial x_1} + [\beta p x_1 x_4 - (\mu + \alpha) x_2] \frac{\partial}{\partial x_2} \\
& + [\beta(1-p)x_1 x_4 + \alpha x_2 - a x_3] \frac{\partial}{\partial x_3} + [c x_3 - \gamma x_4 - \beta' x_1 x_4] \frac{\partial}{\partial x_4} \\
& + x_1 x_4 \left[\frac{1}{2} \left\{ \beta \frac{\partial^2}{\partial x_1^2} + \beta p \frac{\partial^2}{\partial x_2^2} + \beta(1-p) \frac{\partial^2}{\partial x_3^2} + \beta' \frac{\partial^2}{\partial x_4^2} \right\} \right. \\
& \quad \left. + \beta \sqrt{p} \frac{\partial^2}{\partial x_1 \partial x_2} + \beta \sqrt{1-p} \frac{\partial^2}{\partial x_1 \partial x_3} - \sqrt{\beta \beta'} \frac{\partial^2}{\partial x_1 \partial x_4} \right. \\
& \quad \left. + \beta \sqrt{p(1-p)} \frac{\partial^2}{\partial x_2 \partial x_3} - \sqrt{\beta \beta' p} \frac{\partial^2}{\partial x_2 \partial x_4} - \sqrt{\beta \beta' (1-p)} \frac{\partial^2}{\partial x_3 \partial x_4} \right].
\end{aligned}$$

For the diffusion model some simulated sample paths obtained with a strong Euler scheme for X_1 , X_2 and X_4 are shown in Figure 1. Good agreement with the time course and variability of the acute phase of HIV-1 infection is found. In addition it was found useful to find the times at which the virion density attains levels corresponding to the thresholds for detection of the virus in plasma samples; a typical distribution is shown in the bottom part of Figure 1. Such results are useful in ascertaining the risks in tests of blood donations for infection by HIV (Le Corfec *et al.*, 1999).

Figure 1 about here

It is possible to find the properties of the distribution of the time to detection by the using first passage time theory for diffusion processes, which results in the following analytical framework. Let the threshold level of detection of the virus be θ/mm^3 . Let A be a set in R^4 containing the initial value \mathbf{x} of the process such that $x_4 \in (0, \theta)$. Then we consider the time to detection as the first exit time, $T_\theta(\mathbf{x})$, of the process from A . The distribution function of this quantity, $F_\theta(\mathbf{x}; t) = Pr\{T_\theta(\mathbf{x}) \leq t\}$, satisfies

$$\frac{\partial F_\theta}{\partial t} = L_{\mathbf{x}} F_\theta,$$

with initial condition $F_\theta(\mathbf{x}; 0) = 0$, if $\mathbf{x} \in A$ and $F_\theta(\mathbf{x}; 0) = 1$, if $\mathbf{x} \notin A$, with boundary condition $F_\theta(\mathbf{x}; t) = 1$, $\mathbf{x} \notin A, t \geq 0$. Furthermore, the moments $\mu_n = E[T_\theta^n(\mathbf{x})]$, $n = 1, 2, \dots$, satisfy the recursive system

$$L_{\mathbf{x}} \mu_n = -n \mu_{n-1},$$

for $\mathbf{x} \in A$, with boundary conditions $\mu_n(\mathbf{x}) = 0, \mathbf{x} \in \partial A$. Here, $\mu_0 = 1$ is the probability of ever leaving A . There may be some escape of probability mass at zero virion level but this is expected to be insignificant compared to that associated with paths which attain level θ , so $T_\theta(\mathbf{x})$ will be very close to the time to detection.

Approximation for small times

The above 4-component framework can be simplified to a 2-component one at early times by not distinguishing between latently and actively infected CD4+ T-cells, as in Herz et al. (1996), and by considering the number of uninfected CD4+ T-cells as constant. Neglecting also the interaction term in the viral dynamical equation one obtains a simplified stochastic model for the very early (less than 15 days) period of HIV-1 dynamics (Tuckwell and Wan, 2000b).

Long term stochastic HIV model

The mathematical model of Tan and Wu (1998) has the same four components as above, but the dynamics of the uninfected cells are more complicated. These are generated by a means of a (possibly temporally nonhomogeneous) Poisson process with rate $s(t)$ (replacing the constant λ), the rate declining as free virion level increases. Furthermore, these cells are stimulated by HIV and antigen to produce new X_1 by a stochastic logistic birth process with rate $r(t) = r_0 \left[1 - \frac{(X_1 + X_2 + X_3)}{T_{max}} \right]$, where r_0 is a constant and T_{max} is the saturating level of host cells in all stages. The proportion of infected cells which become latent is possibly time dependent and give by $\omega(t)$ and the number of virions released by an actively infected cell is (possibly) random and given by $M(t)$. Furthermore, the three kinds of host cells and free HIV die according to simple death processes with rates μ_1, μ_2, μ_3 and μ_4 , respectively. The stochastic equations take the form

$$dX_1 = s(t)dt + r(t)X_1dt - X_1[\mu_1 + k_1X_4]dt + \epsilon_1(t)dt \quad (13)$$

$$dX_2 = \omega(t)k_1X_1X_4dt - X_2[\mu_2 + k_2]dt + \epsilon_2(t)dt \quad (14)$$

$$dX_3 = [1 - \omega(t)]k_1X_1X_4dt + k_2X_2dt - \mu_3X_3dt + \epsilon_3(t)dt \quad (15)$$

$$dX_4 = M(t)\mu_3X_3dt - k_1X_1X_4dt - \mu_4X_4dt + \epsilon_4(t)dt. \quad (16)$$

The constants k_1 and k_2 are the interaction rate between HIV and uninfected cells and the transition rate from X_2 to X_3 . Note that here virions are released (only) whenever an X_3 cell “dies”. The terms $\epsilon_k, k = 1, \dots, 4$, are “random noises.” The means of the X_k ’s are not the same as the deterministic model. By means of simulation, Tan and Wu were able to distinguish three regimes: (a), an early infection period; (b), a transition period; and (c), a steady state period. Using parameters estimated from patient data, in both their simple and complex models they found there was a positive probability of approaching a non-infected state ($X_3 = X_4 = 0$), even in the absence of drug treatments.

B. Models with mutant virus strains

It is important to address the effects of the appearance of mutant strains of virus, which may lead to ineffective or less effective drug treatments (Nowak, 1992; Abundo and Rossi, 1994; Nowak and May, 2000; Phillips *et al.*, 2001). Abundo and Rossi (1994) consider a multi-component diffusion process model. In addition to distinguishing viral strains, $V_i, i = 1, \dots, n$, each of which has its own unique growth rate r_i , it was assumed that there are associated specialized classes of CD4+ T-cells, X_i . There are also an uninfected cell population Y and a nonspecific class of activated cells, X . A virus of any strain may attack host cells. The drift terms correspond to the deterministic model of Nowak *et al.*(1990). The process of viral mutation does not appear explicitly in the model, which seems undesirable. However, in the simulated solutions of the diffusion model, explosions of viral load eventually occur, accompanied by the collapse of the immune system. For a perspective on the ramifications for strategies of drug treatment, see Phillips *et al.*(2001).

C. Statistical models and drug treatments

Using simple differential equations similar to those in Section 2 modified to incorporate the effects of drug treatments, patient data on CD4 cell counts and HIV loads may be used to estimate model parameters from explicit solutions. For example, using nonlinear regression analysis, the viral clearance rate constant, and the rate of loss of virus-producing cells were estimated for each of a group of patients (Perelson and Nelson, 1999). However, as there is presently no suitable long-term HIV model, Wu and Zhang (2002a) have applied a class of semiparametric nonlinear mixed effects models developed for longitudinal data (Wu and Zhang, 2002b). At the population level, combination antiretroviral therapies (ARV) are widely used to treat HIV but drug-resistant strains have quickly evolved and the overall impact that ARV will have on HIV epidemics remains unclear. Velasco-Hernandez *et al.*(2002) used a mathematical model to determine the effectiveness of current therapies in reducing the severity of HIV epidemics. They found that even a high-prevalence HIV epidemic could be eradicated using current ARV.

4. Conclusions

Mathematical models of viral dynamics are potentially very useful for understanding the progression and treatment of virally induced diseases. Simple statistical models and the incorporation of mutant viral strains can lead to optimized drug treatments for HIV which ameliorate the disease but not eliminate it. The stochastic modeling of viral dynamics is in its infancy and existing models omit many important agents and properties of both virus, host cell and immune response.

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Figure caption

Numerical solutions of the stochastic differential equations (9A)-(12A), showing 20 sample paths for the components X_1 , activated uninfected cells, X_2 , latently infected cells, and X_4 , free plasma virus. For more details, see Tuckwell and Le Corfec (1998). An estimate of the distribution of the time to reach an assumed detection threshold (100 virions/cubic millimeter) is also shown, based on 500 trials.

