PERGAMON

Applied Mathematics Letters 13 (2000) 79–83

Applied Mathematics Letters

www.elsevier.nl/locate/aml

First Passage Time to Detection in Stochastic Population Dynamical Models for HIV-1

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(Received October 1998; revised and accepted June 1999)

Abstract—The detection of HIV-1 levels in human hosts is cast as a first exit time problem for a multidimensional diffusion process. We consider a four-component model for early HIV-1 dynamics including uninfected CD4+ T-cells, latently infected cells, actively infected cells, and HIV-1 virions. An analytical framework is presented for the distribution of the time at which a given virion level is attained. A one-dimensional diffusion approximation for a branching process leads to an estimate for the distribution of the virion density and an expression for the mean detection time for any given detection threshold.

Keywords—HIV-1, Virus detection, Diffusion process.

1. INTRODUCTION

The dynamics of HIV-1 (human immunodeficiency virus-1) populations in infected hosts have been modeled mathematically by various systems of deterministic ordinary differential equations, as for example in [1–3]. These have been used to ascertain the effects of various drug therapies through alterations in the parameters of the model [1,4,5]. However, the growth of HIV-1 populations is not deterministic in nature and more accurately described by stochastic models [6–9].

In a recent communication, a mathematical model for early HIV-1 population dynamics in plasma has been presented as a four-dimensional diffusion process which may be described by a system of stochastic differential equations [9]. This is a stochastic version of the models developed in [1,2]. Letting the components be X_k, $k = 1, 2, 3, 4$, we have that at time t (days) since initial

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0893-9659/00/$ - see front matter Typeset by AMS-TEX
PII: S0893-9659(00)00037-9

infection, for one cubic millimeter of plasma, $X_1(t)$ is the number of activated uninfected CD4+ T-cells, $X_2(t)$ 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 model has the following parameters:

λ appearance rate of uninfected CD4+ T-cells,
μ net death rate of uninfected CD4+ T-cells,
k_1 infection rate per virion,
k_2 infection rate per uninfected CD4+ T-cell,
p proportion of infected cells which are latent,
α activation rate of latently infected cells,
a death rate of actively infected cells,
c rate of virion emission by infected CD4+ T-cells,
γ death or clearance rate of virions, and
τ the fraction of activated uninfected CD4+ T-cells.

However, because in the model equations we restrict attention to activated cells, the constant τ does not appear explicitly.

For the four-component diffusion model [9], the transition probability density function $P(\mathbf{y}, t; \mathbf{x}, s)$, $s < t$, where $\mathbf{y}$ is a four-vector of forward variables and $\mathbf{x}$ is a four-vector of corresponding backward variables, satisfies the following backward Kolmogorov equation [10]:

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

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

$$\begin{aligned} L_{\mathbf{x}} = {} & [\lambda - \mu x_1 - k_1 x_1 x_4] \frac{\partial}{\partial x_1} + [k_1 p x_1 x_4 - (\mu + \alpha) x_2] \frac{\partial}{\partial x_2} \\ & + [k_1(1-p) x_1 x_4 + \alpha x_2 - a x_3] \frac{\partial}{\partial x_3} + [c x_3 - \gamma x_4 - k_2 x_1 x_4] \frac{\partial}{\partial x_4} \\ & + x_1 x_4 \left[\frac{1}{2} \left\{ k_1 \frac{\partial^2}{\partial x_1^2} + k_1 p \frac{\partial^2}{\partial x_2^2} + k_1(1-p) \frac{\partial^2}{\partial x_3^2} + k_2 \frac{\partial^2}{\partial x_4^2} \right\} \right. \\ & - k_1 \sqrt{p} \frac{\partial^2}{\partial x_1 \partial x_2} - k_1 \sqrt{1-p} \frac{\partial^2}{\partial x_1 \partial x_3} + \sqrt{k_1 k_2} \frac{\partial^2}{\partial x_1 \partial x_4} \\ & \left. + k_1 \sqrt{p(1-p)} \frac{\partial^2}{\partial x_2 \partial x_3} - \sqrt{k_1 k_2 p} \frac{\partial^2}{\partial x_2 \partial x_4} - \sqrt{k_1 k_2 (1-p)} \frac{\partial^2}{\partial x_3 \partial x_4} \right]. \end{aligned}$$

There are extra terms here involving k_2, relative to the deterministic models [1,2], in the equation for the virion density, as in [9], to allow for a decrease in viral numbers when a virus attaches to a CD4-cell. Simulations showed that solutions of the system of stochastic differential equations are little changed when these extra terms are ignored.

In [9], sample paths of the diffusion process were simulated and were found to give good agreement with the time course and variability of the acute phase of HIV-1 infection. 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.

It is possible to find the properties of the distribution of the time to detection by the using first passage time theory [10,11] 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 $\mu_n = E[T_\theta^n(\mathbf{x})]$, $n=1,2,\ldots$, 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. The accuracy of this approximation can also be determined using first exit time theory.

2. APPROXIMATIONS

The above four-component framework can be simplified to a two-component one at early times by not distinguishing between latently and actively infected CD4+ T-cells, as in [12], and by considering the number of uninfected CD4+ T-cells as constant. This approach is vindicated by observations on the sample paths in the four-component model. Neglecting also the interaction term in the viral dynamical equation, which has been shown to only have a small effect, one obtains a simplified stochastic model for the very early (less than 15 days) period of HIV-1 dynamics. Putting the numbers of infected cells and of free virions as $Y(t)$ and $V(t)$, respectively, we find

$$\begin{aligned} dY &= (k_1'V - aY)\,dt + \sqrt{k_1'V}\,dW, \\ dV &= (cY - \gamma V)\,dt - \sqrt{k_2'V}\,dW, \end{aligned}$$

where $k_1' = X_0k_1$, $k_2' = X_0k_2$, X_0 being the initial number of actively infected CD4+ T-cells, and where W is a standard Wiener process. The operator $L_{\mathbf{x}}$ then simplifies to

$$L^* = (k_1'v - ay)\frac{\partial}{\partial y} + (cy-\gamma v)\frac{\partial}{\partial v} + v\left[\frac{1}{2}\left(k_1'\frac{\partial^2}{\partial y^2} + k_2'\frac{\partial^2}{\partial v^2}\right) - \sqrt{k_1'k_2'}\frac{\partial^2}{\partial y\partial v}\right].$$

Further simplification is possible by means of a one-dimensional diffusion approximation to a branching process. Here the viral population is modeled as follows. At time t there are $V(t)=v$ virions and in $(t,t+\delta t]$ each has probability $p\delta t$ of being replaced by $m+1$ virions and probability $1-p\delta t$ of being unchanged. Then the number of virions at $t+\delta t$ is $v+mB(v,p\delta t)$ where B denotes a binomial random variable. Determining the first and second infinitesimal moments of this continuous time branching process leads to the diffusion approximation

$$dV = mpV\,dt + m\sqrt{pV}\,dW.$$

For this diffusion process it is known that the origin is an exit boundary and it is possible to obtain the transition probability density as a solution of the forward Kolmogorov equation

$$\frac{\partial Q}{\partial t} = -mp\frac{\partial}{\partial v}(vQ) + m^2p\frac{\partial^2}{\partial v^2}(vQ).$$

The explicit solution for an initial number v_0 of virions is [13]

$$Q(v,t;v_0) = \rho\left(\frac{M}{v}\right)^{1/2}\exp\left[-\rho(v+M)\right]I_1\left(2\rho\sqrt{vM}\right), \qquad 0<v<\infty,$$

where $M(t)=v_0e^{mpt}$,

$$\rho(t) = \frac{1}{m\left(e^{mpt}-1\right)},$$

and

$$I_1(z) = \sum_{n=0}^{\infty} \frac{(z/2)^{2n+1}}{n!(n+1)!}$$

is a Bessel function. The mean of the number of virions at time t is $M(t)$ and the variance is $2e^{mpt}m(e^{mpt}-1)$.

If we put T_θ as the time to reach level θ, and assume that the paths of $V(t)$ are almost surely monotonically increasing, then we may use the fact that

$$\Pr\{T_\theta > t\} = \Pr\{V(t) < \theta\},$$

to find the approximation for the distribution function of T_θ as

$$F_{T_\theta}(t) = 1 - \rho\sqrt{M}e^{-\rho M}\int_0^\theta \frac{e^{-\rho v}}{\sqrt{v}} I_1\left(2\rho\sqrt{Mv}\right)\, dv.$$

Note that here the t-dependence is contained within ρ and M.

We can also apply first passage time theory to this approximation to estimate the mean time at which the virion level first reaches a threshold level of detection, again ignoring the small fraction of paths which attain zero virion level in the early period. Letting the mean first exit time be $\mu_1(x) = f(x)$, with $x = V(0) = v_0$, we have as a particular case of the theory outlined above, that

$$mpx\frac{d^2f}{dx^2} + m^2px\frac{df}{dx} = -1, \qquad 0 < x < \theta.$$

There is a necessary exit condition $f(0) = 0$ at zero and we require $f(\theta) = 0$. Then the solution is found by quadratures to be

$$f(x) = \frac{\kappa}{m}\left[1 - e^{-mx}\right] - \frac{1}{mp}\int_0^x \int_0^z \frac{e^{-m(z-t)}}{t}\, dt\, dz,$$

where

$$\kappa = \frac{1}{p\left[1 - e^{-m\theta}\right]}\int_0^\theta \int_0^z \frac{e^{-m(z-t)}}{t}\, dt\, dz.$$

These expressions can also be extended to the case where the death rate, γ, of virions is included so that

$$dV = (\gamma - mp)V\, dt + m\sqrt{pV}\, dW.$$

The results of the numerical evaluation of the quantities relating to the time to detection and comparisons with simulations and experimental results will require considerable journal space and be reported elsewhere. We may remark that there is no question concerning the validity of the theory outlined for the first-passage time to detection in the four-component model, as this theory is exact. The two-component approximation will be valid in the early phase of virion growth where there has been little change in the numbers of uninfected CD4+ T-cells. The branching-process approximation or one-component approximation is only expected to provide a crude estimate of the virion density, but is considered worthy of inclusion since no other analytical results are available.

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