12-1-2005

The Stochastic Dance of Early HIV Infection

Stephen J. Merrill
Marquette University, stephen.merrill@marquette.edu

Accepted version. *Journal of Computational and Applied Mathematics*, Vol. 184, No. 1 (December 1, 2005): 242-257. DOI.

Journal of Computational and Applied Mathematics, Vol. 184, No. 1 (2005): 242-257. DOI.

The Stochastic Dance of Early HIV Infection

Stephen J. Merrill
Marquette University, Milwaukee WI

Abstract

The stochastic nature of early HIV infection is described in a series of models, each of which captures aspects of the dance of HIV during the early stages of infection. It is to this highly variable target that the immune response must respond. The adaptability of the various components of the immune response is an important aspect of the system's operation, as the nature of the pathogens that the response will be required to respond to and the order in which those responses must be made cannot be known beforehand. As HIV infection has direct influence over cells responsible for the immune response, the dance predicts that the immune response will be also in a variable state of readiness and capability for this task of adaptation. The description of the stochastic dance of HIV here will use the tools of stochastic models, and for the most part, simulation. The justification for this approach is that the early stages and the development of HIV diversity require that the model to be able to describe both individual sample path and patient-to-patient variability. In addition, as early viral dynamics are best described using branching processes, the explosive growth of these models both predicts high variability and rapid response of HIV to changes in system parameters.

In this paper, a basic viral growth model based on a time dependent continuous-time branching process is used to describe the growth of HIV infected cells in the macrophage and lymphocyte populations. Immigration from the reservoir population is added to the basic model to describe the incubation time distribution. This distribution is deduced directly from the modeling assumptions and the model of viral growth. A system of two branching processes, one in the infected macrophage population and one in the infected lymphocyte population is used to provide a description of the relationship between the development of HIV diversity as it relates to tropism (host cell preference). The role of the immune response to HIV and HIV infected cells is used to describe the movement of the infection from a few infected macrophages to a disease of infected $CD4^+$ T lymphocytes.

Keywords
Stochastic model, HIV, Branching process, Branching process simulation

1. Introduction
The immune system consists of cells, tissues, organs and specialized structures, secreted molecules, receptors, and the mechanisms by which the system can communicate with itself. The system also communicates with other systems in the body, for instance the signals from our hormones and nerves, the process of blood clotting, and the production of cells of the blood by the marrow. The immune system communicates with the outside world as well and serves as our sentry against those things that might harm us in what we eat, breathe, and touch. In this role, the system must both identify those agents (pathogens) that have the potential to harm and devise a response to neutralize that danger.

The correct responses to specific recognized form of attack, such as bacteria, yeast, and viruses have been devised over evolutionary time. Those individuals that did it right reproduced, and those that did not, were not able to pass their genes (and their defective responses) to as many offspring. As such, the immune system represents the “intelligence” from what was learned over these eons of time in how to deal with various classes of pathogens. More recent diseases, such as those caused by prions, the system is relatively silent, having no past successful responses to fall back on. Somewhat in this later category is HIV, the hepatitis viruses (HBV, HCV), cytomegalovirus (CMV), *Plasmodium falciparum* (which causes malaria), and others pathogens in which the system is unable to clear the infection by following the learned response, often resulting in chronic infection. Modeling and describing the “unsuccessful” responses to those pathogens is for the purpose of describing why the response may not be effective and suggesting avenues of immune modulation. It is in that vein that we present these simulation studies.

The goal of this paper is to illustrate modeling HIV growth in early stages of the infection using branching process models. The parameters for growth depend on the state and nature of the virus, the condition of the immune system, and the environment in which the interaction takes place—the body. The environment of the body is determined by the overall health of the individual. This overall health affects the condition and readiness of the immune system. Other pathogens and factors that affect the immune system can also play a role. These “cofactors” include vaccinations, malnutrition, and herpes viruses.[27] The dance that results from the growth of HIV with the immune system is a microcosm of the evolution of pathogens and the response over evolutionary time.

Using branching processes to model the growth of HIV began with Merrill,[19] while other stochastic approaches were used in Merrill.[18] The necessity of using stochastic models to describe viral growth

was suggested by Bartoszynski[1,2,3] in a series of papers describing rabies growth. The ability to answer questions in a context of the innate randomness of the process makes a strong statement for using stochastic models—especially in the early stages of a viral infection. Since that time, there have been many stochastic models in the context of HIV and HIV epidemiology, most notably Tan et al.,[29] Tan and Wu,[30] Tuckwell and Le Corfec,[32] Wick and Self,[34] Tan and Ye,[31] Fraser et al.6 and Kousignian et al.[14] Tuckwell and Le Corfec[32] (see also Kamina et al.[11]) used stochastic differential equations to model the process of early HIV growth when the immune response is intact and its effect on HIV growth more predictable. Kousignian et al.[14] employed a continuous-time Markov model for the CTL responses to seven HIV proteins over time as well as the effect of viral load on the CTL recognition. They used Markov Chain Monte Carlo (MCMC) to estimate parameters fitting clinical results with 152 HIV-infected patients.

Deterministic models and deterministic/stochastic hybrid models are often used to describe the dynamics of viral production from infected cells with growth limited by aspects of the immune response. These models are used for the period after the infection has been seeded (at the "set point"). In this setting, populations are large and variability is generally due to parameter differences between individuals and different initial conditions due to the variable result of the early stage. Examples of this approach can be found in Perelson et al.,[23] McLean et al.,[16] Grossman et al.,[8] and Perelson and Nelson.[24] Recent reviews can be found in Perelson[22] and Wodarz & Nowak.[35] Fraser et al.[6] and Root-Bernstein and Merrill[26] and Merrill and Root-Bernstein[20] have examined the role of antigenic stimulation. Fraser et al. employed a deterministic/stochastic hybrid while the work by Root-Bernstein and Merrill used deterministic methods. Perelson et al.,[25] used a simple deterministic model of viral growth to establish important parameters of viral growth. A recent review of the immune response to HIV can be found in Gandhi and Walker.[7] Excellent reviews of branching processes in biology can be found in the monographs of Jagers[10] and Kimmel and Axelrod.[13]

In general, choice of a model type depends on the nature of the process to be described. If the process has many particles and a description of their aggregate behavior is desired, models with deterministic aspects often allow one to employ analytic methods and obtain sharp results. In cases where the number of particles are small and/or the range of behavior of the particles is being studied, then stochastic or hybrid models are often chosen. For these models (which usually have nonlinear aspects), generally only simulation-based results are available. The context and outlook of this work is best stated in Tuckwell and Le Corfec:[32]

"Here we include these hitherto neglected but significant chance mechanisms. If these are introduced in a biological meaningful fashion, one should be able to estimate their contributions to the variability in the early time course of the viral load, which has not been possible with deterministic models."

This paper differs with Tuckwell and Le Corfec[32] in the nature and scope of stochastic models employed and the range of questions examined. For instance, branching models can only be approximated by diffusion processes (solutions of stochastic differential equations) after limits are applied. Diffusion processes are continuous (with probability 1) while branching processes are not. This relationship was explored in Merrill.[17]

2. Section 1. Viral growth described a continuous-time branching process

Consider an initial number of HIV infected cells, $I(0)$. Although cells other than $\mathrm{CD4^+T}$ lymphocytes are infected, we will use that population in this section as an indicator of the level of the infection. The effect of other types of infected cells will be discussed below. The history of each infected cell will be considered to be independent of the others, thus one may take $I(0) = 1$ without loss of generality. (If $I(0) = n > 1$, the process is equivalent to *n* independent processes and the sample path is the sum of *n* processes, each starting at 1.) For that reason, let $I(t)$ be the number of infected T cells given that $I(0) = 1$. When an infected cell is stimulated, the process of viral production in the infected cell begins resulting in the release of virions which "bud" from the host cell membrane. So many virions are released from an infected cell, each taking a piece of the cell membrane, that the viability of the cell can be eventually compromised. In the time scale of the disease, the process of virion production will be assumed to involve two independent processes, host cell death and batch release. In addition, this batch release will result in some number of new infected cells, stimulated $\mathrm{CD4^+T}$ cells being the prime target. The time of the death events, the number of infected virions released, and the number of T lymphocytes infected by those virions are all random variables. One should note that cell death need not result from the process if the release of virions is slow enough. This can happen, apparently, with infected cells of monocyte lineage (e.g. macrophages and dendritic cells).

The nature of the batch release makes the modeling of this process by a differential equation, or the stochastic analog, a birth and death process, problematic at the early stages (at least on this time scale) when the infected cell numbers are relatively small. On the other hand, a continuous-time branching process is able to describe both the kinetics of the cell death and the creation of a random number of new infected cells from a single death event.

A continuous time branching process involves an exponentially distributed time to the next event (a cell death and a batch of newly infected cells) and a specification of the pdf for the batch size. Declaring the infinitesimal probabilities, $a_0, a_1, a_2, \ldots$, specifies the branching process. These take the form[12]

$$P(k,h) = \delta_{1k} + a_k h + o(h), k = 0,1,2, \ldots,$$

where

$$\delta_{1k} = \begin{cases} 1 & \text{if } k = 1, \\ 0, & \text{otherwise.} \end{cases}$$

$P(k,h)$ is the probability that an infected $\mathrm{CD4^+T}$ cell will die in the interval $(t, t+h)$, having given rise to *k* infected daughters. It is assumed that

$$a_1 \leqslant 0 \text{ and } a_k \geqslant 0 \text{ for } k = 0,2,3, \ldots$$

and that

$$\sum_{k=0}^{\infty} a_k = 0\,.$$

One modeling assumption is that the process of the infected cell death and the resulting infection of new cells happen on a much shorter time scale than the time scale of the overall infection, hours and years, respectively. Also, as $P(k,h)$ is independent of t, this model carries the assumption of time

homogeneity. While usually a technical convenience, here it is an assumption that the environment for the HIV growth process does not change in time. This aspect will be addressed below.

Simulation of this process is straightforward, once the a_k are specified. The first parameter to describe is the rate of events, α, the parameter for the exponential distribution. The form of the pdf for the number of new infected cells once an event has occurred is often taken to be Poisson,

$$\mathrm{e}^{-\lambda}\frac{\lambda^k}{k!} \text{ for } k = 0,1,2,\ldots.$$

In our setting, this is an assumption that each virion released has a very small probability of finding a receptive (i.e. stimulated) cell. In that case, the number of successfully infected cells is binomial with a small probability *p* of success—approximated by a Poisson. In this light, the mean of the Poisson distribution $\lambda = Np$, where *N* is the (fixed) number of virions released. However, in this application, *N* is also a random variable, so the Poisson assumption is taken to be a reasonable form for an averaged description. With the exponential parameter and the distribution specified, the parameters are determined

$$a_k = \alpha\mathrm{e}^{-\lambda}\frac{\lambda^k}{k!} \quad \text{for} \quad k = 0,2,3,\ldots$$

and

$$a_1 = \alpha(-1 + \lambda\mathrm{e}^{-\lambda}) < 0. \tag{1}$$

There are only 2 parameters that specify this process, α and λ. The first parameter specifies the rate of events (usually on the order of a day) while λ, the branching number, is assumed to be slightly larger than 1. This assumption is based on the kinetics of these processes on this time scale if λ was bigger than one. Note that the number of virions in the blood is much larger than the number of infected cells.

Simulation proceeds through finding the time of the first cell to die, then determining how many new infected cells result. The memoryless property of the exponential distribution can be used to simplify the process. Fig. 1, shows a series of sample paths that illustrate both the extreme variability in the process and the possibility of extinction. These aspects cannot be described in the deterministic models.

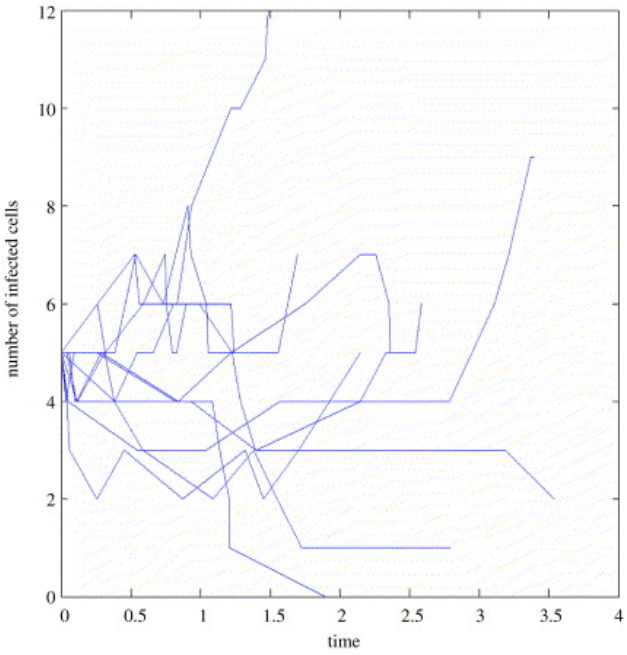

Fig. 1. Simulation of 10 sample paths of the branching process (1) through the first 10 transitions. Parameters are $\alpha = 1$ and $\lambda = 1.1$, with all simulations starting at $I(0) = 5$. Note that extinction is a possibility in this model. Time is in units of days. All simulations using MATLAB 6.5 (The Mathworks, Natick, MA) with the Statistics Toolbox.

3. Section 2. The effect of cofactors

In Root-Bernstein and Merrill[26] and Merrill and Root-Bernstein,[20] the role of infectious cofactors were studied in the context of a system of differential equations. It was discovered that the increase in the number of stimulated $\mathrm{CD4}^+$ cells due to the presence of another infection could play a role in the establishment of a long-term HIV infection. Here we examine an analogous question in the context of the branching process model, where HIV infection and the associated production of viral proteins and products serve as the source of the additional stimulation in the system.

In general, the presence of infectious cofactors increase the number of stimulated $\mathrm{CD4}^+$ cells which are viable targets of HIV (increasing parameter λ) and increase the rate at which infected cells are stimulated (parameter α), reviewed in Wahl and Orenstein.[33] One of the hallmarks of an HIV infection is an early decrease in numbers and activity of HIV-reactive $\mathrm{CD4}^+$ T cells.[7] It may be the case that the increased stimulation rate of HIV-reactive cells makes them high probability targets for infection, resulting in early elimination of that population. A similar result is suggested in long-term trends by Fraser et al.[6] To study this process, we adjust the parameter λ to

$$\lambda = baselinevalue + param^{*}I(t). \qquad (2)$$

The baseline corresponds to the normal fraction of $\mathrm{CD4}^+$ T cells stimulated at any one time (usually 5–10%) while the second term allows for the increase in the stimulation in the host population due to the level of HIV infection. Although α also increases in this context, in branching models that parameter controls only the timing of the evens, not the nature of the events. For that reason, we can describe the result of this increased stimulation by only changing λ. The results of these simulations are seen in Fig. 2. In that figure, the fraction of 50 simulations becoming extinct as a function of the initial lambda value at $t = 0$ with $I(0) = 3$ was plotted for two different values of *baselinevalue* and 20 values of *param*. This result strongly suggests that only this initial value of λ, $\lambda_0 = baselinevalue +$

$param^{*}I(0)$, determines the probability of extinction of the process (an abortive HIV infection). Note that the probability of extinction is approximately .5 when $\lambda = 1$. This empirical result suggests that if $\lambda_0 > 1$, the probability of extinction is less than .5. The probability of an abortive infection is greater than .5 if $\lambda_0 < 1$. Using this empirical result, we can plot level curves that represent the effect of initial dose on the probability of extinction in Fig. 3. This argument may explain why so few needlestick HIV exposures (low HIV initial dose) resulted in an infection due to extinction of the infected cell process. Also, for any one value of *param*, an increased level of baseline stimulation lowers the probability of extinction thus raising the probability of HIV infection becoming established.

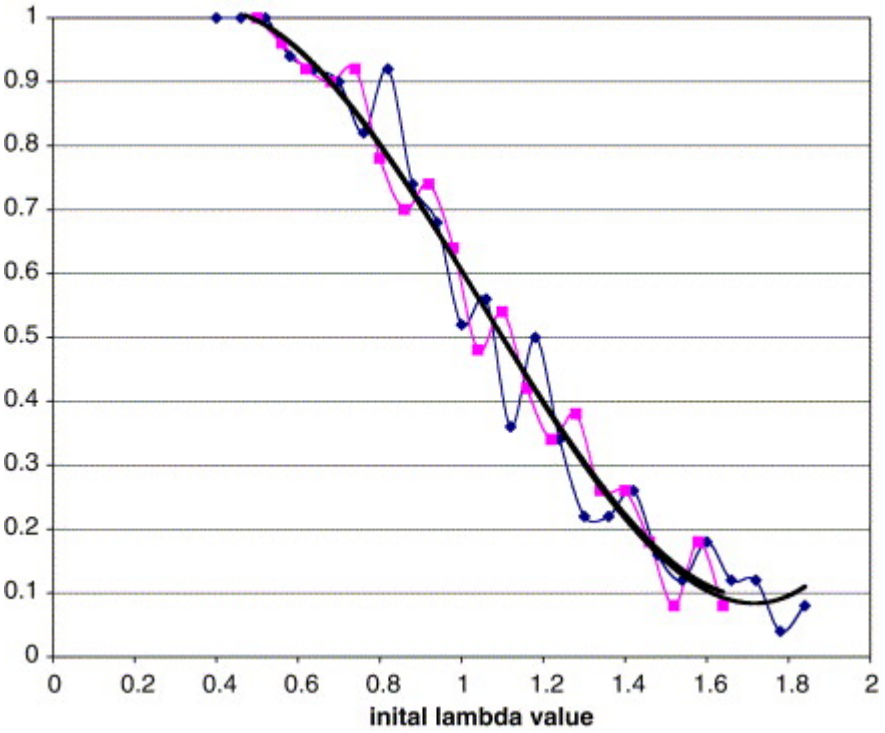

Fig. 2. With $baselinevalue = .4$ and .5, and *param* ranging from .4 to 1.85, the result of 50 simulations at each of 20 values, essentially identical curves resulted. Solid curves represent a cubic fit for each of the two simulations.

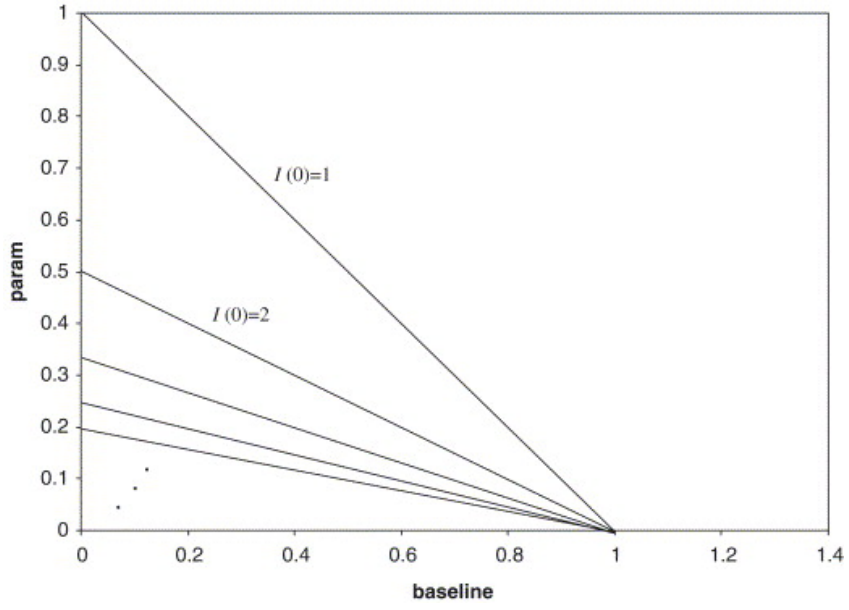

Fig. 3. Level curves of the probability of extinction being .5 for the branching process with the mean number of newly infected cells λ given by (2).

4. Section 3. The incubation time distribution

One aspect of the process of HIV growth not described in this model is the introduction of infected cells due to a reservoir of infected cells that are not T lymphocytes. The first aspect of the immune system encountered by most pathogens is the mucosal immune system. This part of immune system although specifically responding to an assault is not capable of "immunity." This means that memory of the response is not recorded for a rapid and large result if and when that pathogen is met again. This is why children can repeatedly get *streptococci* infections, for instance. HIV generally also first encounters the immune system in the mucosal immune system. The fact that HIV can infect the macrophages and T lymphocytes found there provides the initial reservoir for the infection. Characteristic of virus production in these cells include that they have a lower rate of virion production, there are fewer of these cells infected than the $\mathrm{CD4}^+$ T lymphocytes (in later stages), and their tropism (preferred host) may be different than those released by the infected T cells. We will model the newly infected lymphocytes due to virions released from the reservoir cells by adding an immigration term to the basic model (1). It will be assumed that early stages create this reservoir and that its size stays relatively constant throughout the period of the infection being described. If the number of infected T lymphocytes is large, then the effect of this small immigration term is negligible. On the other hand, when the infection is near extinction, this immigration prevents it. The situation is similar to that observed when HAART (highly active antiretrovial therapy) drives the presence of the virus below detectable levels but cannot promise a cure. A review of the role of dendritic cells and their interplay with stimulated T cells is Frank and Pope.[5]

Immigration is also described by specifying the infinitesimal probabilities, b_k of the process. These are defined by describing $R(k,h)$, the probability that *k* newly infected $\mathrm{CD4}^+$ T lymphocytes are added during the interval t to $t+h$. For a (time-homogeneous) process, these take the form

$$R(k,h) = \delta_{0k} + b_k h + o(h), k = 0,1,2,\ldots. \quad (3)$$

The b_k must satisfy $b_0 \leqslant 0$ and $b_k \geqslant 0$ for all other *k* with $\sum_{k=0}^{\infty} b_k = 0$. These processes were introduced by Jagers [9] (see also Jagers[10]). In Merrill,[19] these parameters were taken as $b_1 = \beta, b_0 = -\beta$, and all other $\beta_k = 0$, resulting in a pure birth process. If this is added to the original branching process (1), we have the results in Table 1. The parameter β is the rate at which newly infected cells are added due to infection by virions from the reservoir population. In all simulations, we take β to be .1 of the value of α. The fact that β is nonzero (preventing extinction) is more important than its actual value.

Table 1. Summary of analytic results of the branching model (1) with immigration as in Merrill [19]

Value of the branching parameter	Result	Reference
$\boldsymbol{\lambda < 1}$**(subcritical)**	$E(I(t)) \to \frac{\beta}{\alpha(1-\lambda)}$	[19]
$\boldsymbol{\lambda > 1}$**(supercritical)**	$\frac{E(I(t))}{\mathrm{e}^{\alpha(\lambda-1)t}} \to \frac{\beta}{a(\lambda-1)}$	[19]
$\boldsymbol{\lambda = 1}$**(critical)**	$\frac{I(t)}{t} \xrightarrow{d}$ gamma distribution	[21]

$E(I(t))$ refers to the expected value of the random variable $I(t)$, In the subcritical case (branching number less than 1, the immigration in the process ensures that the expected value approaches a positive number. In the

supercritical case, the expected value grows exponentially while in the critical case, $I(t)$ generally has linear growth.

Using the results in Table 1 allows us to create a picture of the shape of the incubation time distribution. This distribution can be seen as the time from infection to some identifiable clinical milestone, such as seroconversion (the detection of anti-HIV antibodies). The basic shape of the distribution will be the same for any of the milestones, only the time axis and the parameters being adjusted. Simulating as before, randomly adding in an infected cell due to virus produced by the reservoir, and recording the time each simulation first reaches an arbitrary level, we have Fig. 4. Biologically, this arbitrary level is the size of infection needed before the threshold for the initiation of the immune response is met.

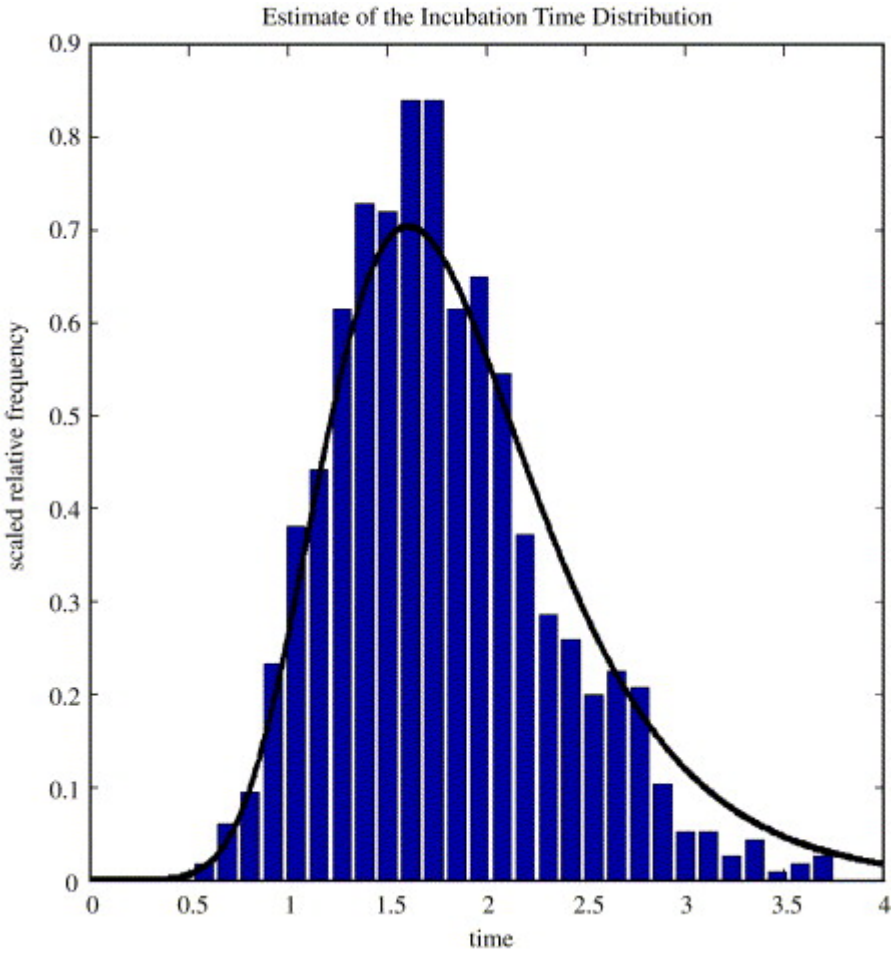

Fig. 4. The result of 1000 simulations of the branching process with immigration. Parameters are $\alpha = 1$, $\lambda = 1.1$, and $\beta = .1$. Solid curve of the form (5) is the pdf $g(t) = 53.1\mathrm{e}^{-2t-20\exp(-1.8t)}$.

The shape of this distribution is very characteristic of a class of distributions containing the log-gamma distribution. These distributions tend to have very heavy tails resulting in large and possibly infinite means. Using the results above in Table 1, an approximate form for this incubation time distribution can be derived. From the critical case,

(4)

$$\frac{I(t)}{t} \xrightarrow{d} \frac{\left(\frac{x}{\tau}\right)^{z-1} \mathrm{e}^{-\frac{x}{\tau}}}{\tau\Gamma(z)}$$

and for the supercritical case, with λ only slightly bigger than 1, the distribution of

$$\frac{I(t)}{\mathrm{e}^{\alpha(\lambda-1)t}}$$

should also have a limit distribution that is approximated by a gamma. The fact that it has a limit distribution was demonstrated by Levinson.[15] With many simulations in this supercritical case, looking at the distribution of $I(t)/\mathrm{e}^{\alpha(\lambda-1)t}$ at a sequence of fixed times gives a sequence of distributions not significantly different from a gamma (data not shown). It is a conjecture that as $\lambda \to 1^{+}$, the limit distribution of the ratio will approach a gamma.

Assuming that the process $I(t)/\mathrm{e}^{\alpha(\lambda-1)t}$ is approximately a gamma, we can establish Theorem 1.

Theorem 1

If $\lambda > 1$ for the branching process with immigration $I(t)$ specified by (1), (3),

$$\frac{I(t)}{\mathrm{e}^{\alpha(\lambda-1)t}} \sim Gamma(\tau, z),$$

then the incubation time distribution has a pdf, $g(t)$, with the form

$$g(t) \approx \alpha(\lambda-1)\hat{I}\mathrm{e}^{-\alpha(\lambda-1)t}\left(\frac{\left(\frac{\hat{I}\mathrm{e}^{-\alpha(\lambda-1)t}}{\tau}\right)^{z-1}\mathrm{e}^{-\frac{\hat{I}\mathrm{e}^{-\alpha(\lambda-1)t}}{\tau}}}{\tau\Gamma(z)}\right).$$

Proof

As $\lambda > 1$, the first time a sample path crosses $\hat{I}$ and the last time that happens are close, thus if we compute that probability that a sample path satisfies $I(t) > \hat{I}$ at time t, it approximates the probability that a sample path have passed $\hat{I}$ at least once by time t. Let $a(t) = \hat{I}/\mathrm{e}^{\alpha(\lambda-1)t}$. Then

$$h(t) = P(I(t) \geqslant \hat{I}) = P\left(\frac{I(t)}{\mathrm{e}^{\alpha(\lambda-1)t}} \geqslant \frac{\hat{I}}{\mathrm{e}^{\alpha(\lambda-1)t}}\right) = \int_{a(t)}^{\infty} f(x)\mathrm{d}x = 1 - \int_{0}^{a(t)} f(x)\mathrm{d}x,$$

where $f(x)$ (a general gamma pdf) is given by

$$f(x) = \frac{\left(\frac{x}{\tau}\right)^{z-1}\mathrm{e}^{-\frac{x}{\tau}}}{\tau\Gamma(z)}$$

for some τ and z. Differentiating $h(t)$ with respect to *t* provides an approximate pdf for the incubation time distribution,

(5)

$$h'(t) = (\alpha(\lambda-1)\hat{I}e^{-\alpha(\lambda-1)t})(f(\hat{I}e^{-\alpha(\lambda-1)t})) = \alpha(\lambda-1)\hat{I}e^{-\alpha(\lambda-1)t}\left(\frac{\left(\frac{\hat{I}e^{-\alpha(\lambda-1)t}}{\tau}\right)^{z-1} e^{-\frac{\hat{I}e^{-\alpha(\lambda-1)t}}{\tau}}}{\tau\Gamma(z)}\right).$$

The form (5) belongs to a family of heavy-tailed distributions that includes the log-gamma distribution. The typical shape is given in Fig. 5.

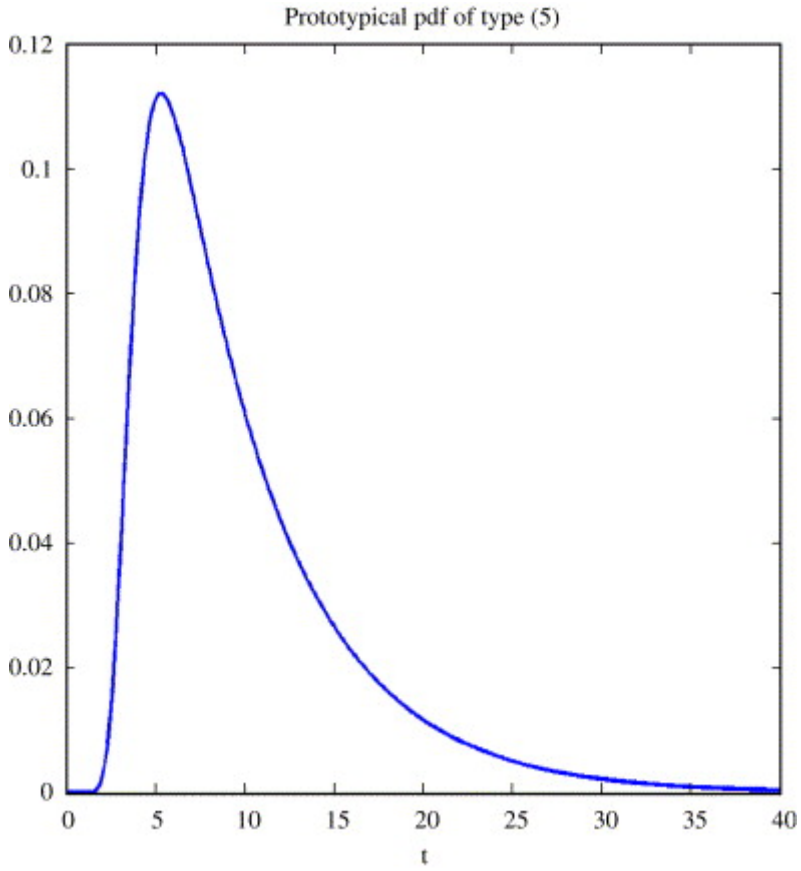

Fig. 5. Typical shape of pdf given by the form in (5). This is a plot of $.31665e^{-.165t-33e^{-t}}$

This characteristic shape can also be seen in Tan and Ye[31] and by N.I. Stilianakis (private communication) based on work in Stilianakis et al.[28] Both of the other approaches used epidemiological data instead of the variability in the infectious process within individuals.

5. Section 4. Modeling the generation of tropism diversity of HIV response to the immune defense

A feature of HIV that makes both the virus difficult to control with an immune response and a difficult target for vaccine development is the rapid generation of viral diversity due to errors in the reverse transcription (RNA to DNA) after cells have been infected. This diversity generates clouds of quasispecies, each differing with respect to their viral envelopes seen by cells of the immune system, drug resistance, and tropism (host cell preference). Although the generation of the diversity is naturally modeled as a branching process, the “pruning” of the resulting tree by the immune response is more difficult as the response is changing in time. In this section, we examine the change in tropism, the HIV infection being initially in macrophages and other monocyte lineage cells (with macrophage tropic

strains), then gradually moving to $\mathrm{CD4}^+$ T lymphocytes as the disease develops. Initially, cytotoxic T cells effectively remove infected cells, and that process becomes less efficient as time goes on and the disease progresses. The first model examines the drift of tropism, the average tropism over time, and the division of the infection between the two populations. A more complete model with the development of diversity in the envelope as well as tropism was created by Radke in 1994. This effort is described in documents and MATLAB code available through ftp at jim.mscs.mu.edu/pub/Radke. A current review of tropism and its relationship chemokine receptors can be found in Clapham and McKnight.[4]

The simulation begins with 2 branching models, one applied to the growth in macrophages and the other in T lymphocytes. In this simulation, a *tropism* of 0 indicates a macrophage tropic strain while a *tropism* of 1 indicates a T tropic strain. Tropism is thought of as the probability of that virus infecting a T cell. We assume that the virus does not kill these cells but virions produced can infect other cells, depending on the tropism of the virus. It is assumed that the tropism is altered slightly in a random way when a cell is infected. Fig. 6 describes the distribution of tropism after 1000 transitions. The increase in the variable *tropism* brings with it an increase in the number of T lymphocytes infected and the fraction of infected cells that are lymphocytes as seen in Fig. 7. In Fig. 8, the change in the average tropism is described.

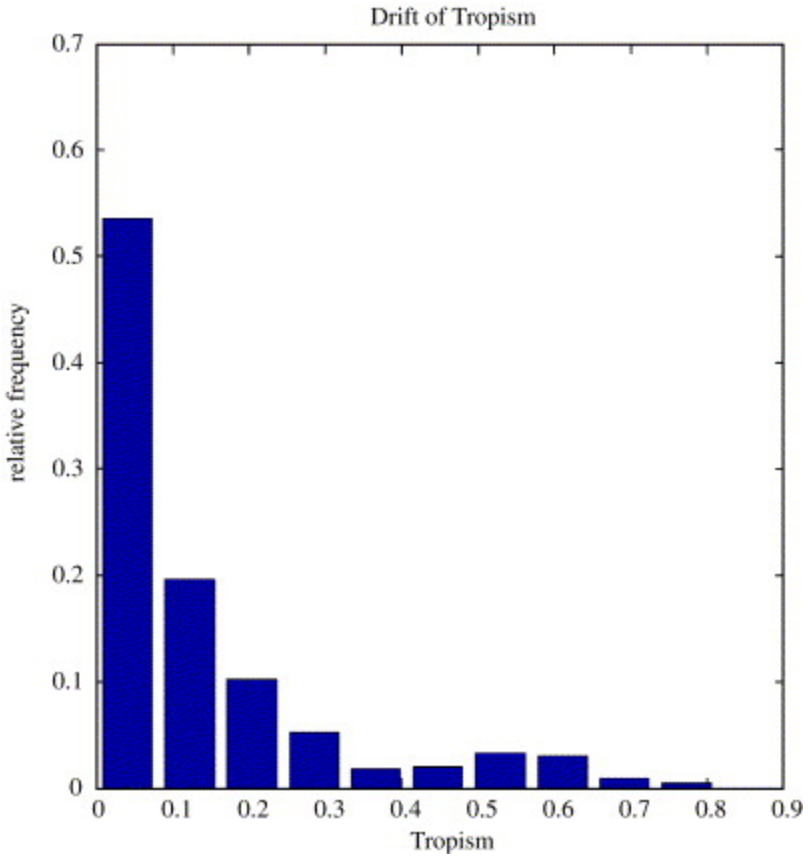

Fig. 6. Tropism distribution after 500 events (roughly 2 years) starting with 1 infected macrophage with tropism 0. Parameter values were $\alpha_{\mathrm{mac}} = 10$, $\alpha_{\mathrm{T}} = 1, \lambda_{\mathrm{mac}} = .7$, $\lambda_{\mathrm{T}} = 1.1$. The tropism of a daughter cell was assumed to be normally distributed about that of the parent.

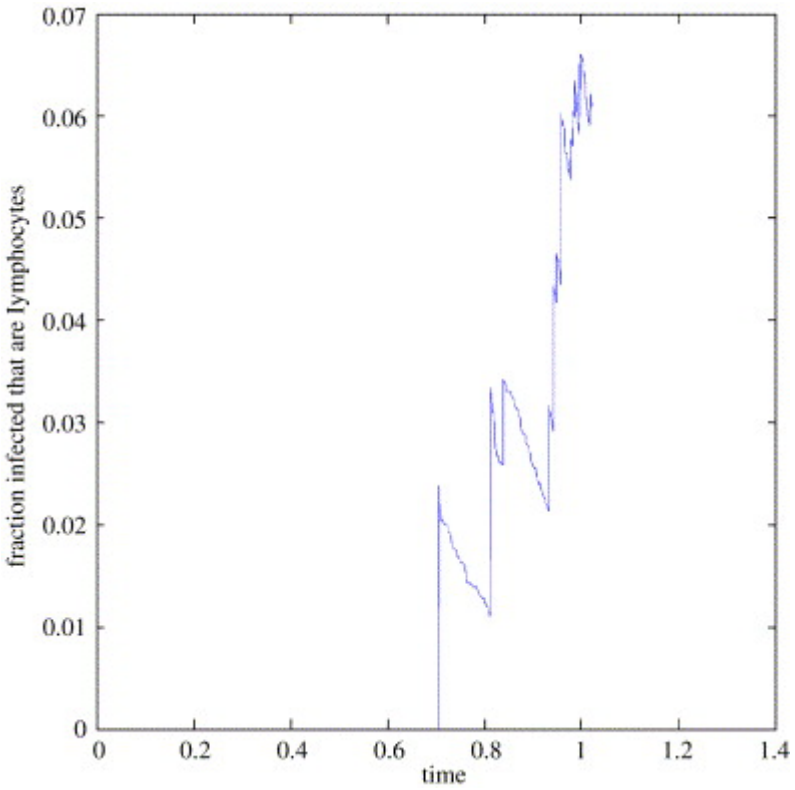

Fig. 7. The fraction of infected cells that are lymphocytes as a function of time. This graph represents 1000 events in a single sample path. Parameter values as in Fig. 6 (time is in units of 10 year intervals).

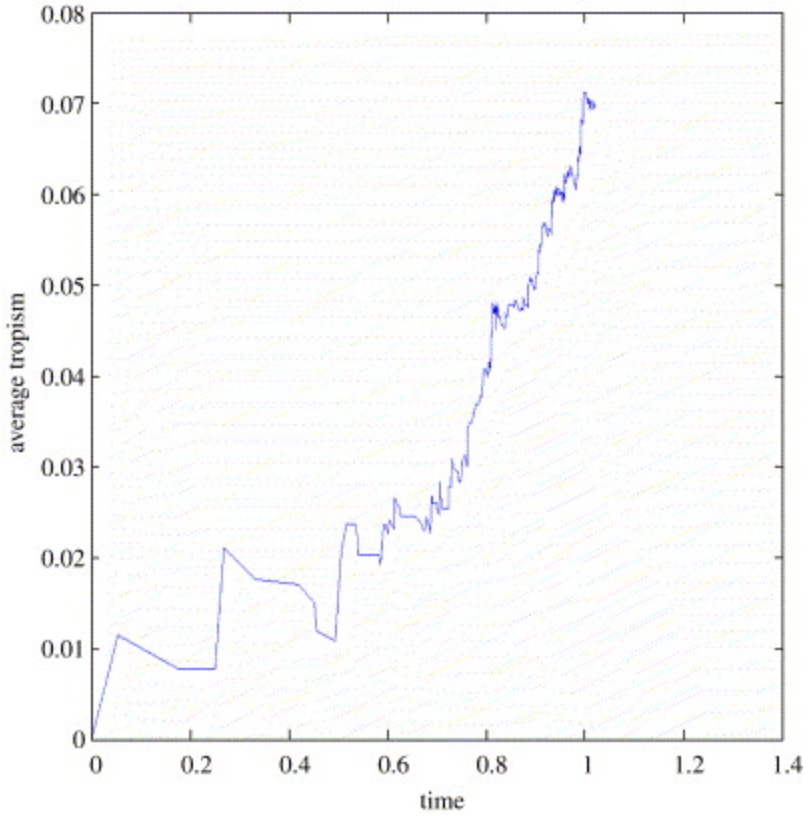

Fig. 8. Average tropism as a function of time for a single sample path. Parameter values as in Fig. 6. Time is in 10 year units.

As a simulation progresses, not only is the average tropism changing, but the distributions of tropism in the two infected populations. This is demonstrated in Figs. 9a and b. Note that virus with higher tropism (more T tropic) had more offspring.

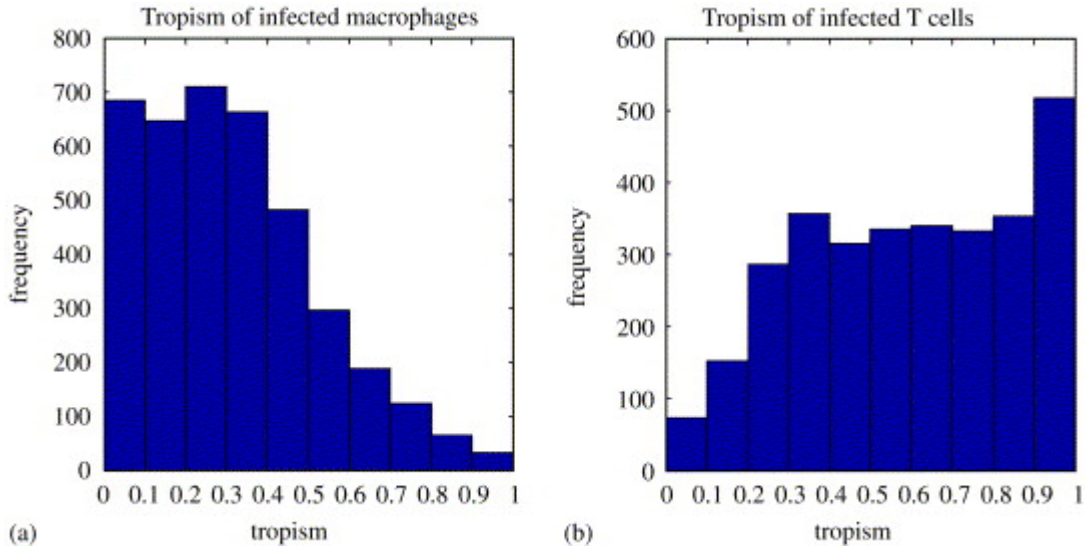

Fig. 9. a,b Tropism after 1000 events in the macrophage and T lymphocyte population.

The story told by these simulations points to a gradual change of tropism towards more T topic strains. As the virus grows more readily in the T host, the infection explodes once it is seeded there and the tropism of the virus allows it. This is clearly seen in Fig. 10.

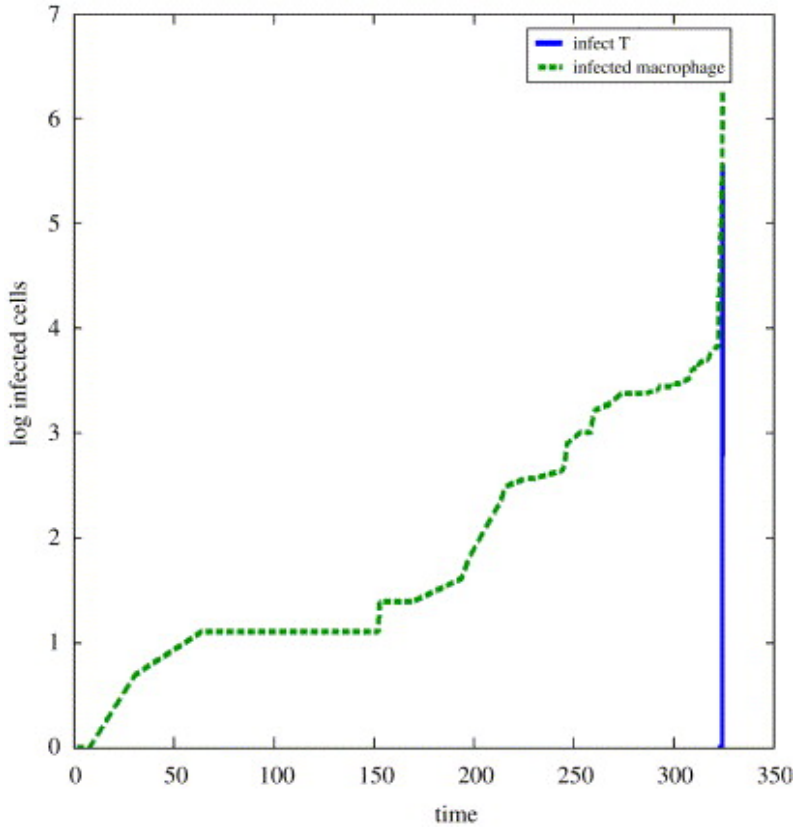

Fig. 10. Explosion of infected T lymphocytes once tropism has changed sufficiently to allow it. Parameter values $\alpha_{\mathrm{mac}} = .02, \alpha_{\mathrm{T}} = 10, \lambda_{\mathrm{mac}} = .7, \lambda_{\mathrm{T}} = 9$. This is a single sample path.

The immune response slows this change of tropism, keeping the disease in the macrophage (and other) reservoirs. A result from this approach is the ability to see the importance of the parameter λ_T in the time it takes the growth in the lymphocyte population to occur. The parameter λ_T is reduced by both neutralizing antibody and cytotoxic T cells specific for the virus.

6. Discussion

The goal of this paper was to illustrate the use of a number of stochastic models of viral growth of early HIV infection all based on continuous-time branching processes. The use of these models, to demonstrate the variability in the early stages of HIV infection, the effect of "immigration" from a reservoir population, the role of stimulation in the early infection, the shape of the incubation time distribution, and the dynamic changes in tropism of the viral strains points to the flexibility of this approach and the power of obtaining distributional information directly from the distributions. Parameter estimates for these parameters can be difficult. Although the work of Perelson and coworkers have obtained estimates for viral production rates from various infected populations of cells, the number of new infected cells from these virions is not known. However, dynamic behavior and shapes of distributions is not changed greatly by most parameter choices. These models allow a new look at what governs the dynamic behavior of HIV.

References

[1] R. Bartoszynski. On the risk of rabies. *Math. Biosci*., 24 (1975), pp. 355-377.

[2] R. Bartoszynski, A model for risk of rabies, With discussion, Proceedings of the 40th Session of the International Statistical Institute, vol. 1, Warsaw, 1975, Invited papers; *Bull. Inst. Internat. Statist*. 46 (1975) 545–552 and 569–574.

[3] R. Bartoszynski, A stochastic model of development of rabies, Proceedings of the Symposium to honour Jerzy Neyman, Warsaw, 1974, Pastwowe Wydawn Nauk Warsaw, 1977, pp. 19–28.

[4] P.R. Clapham, A. McKnight. Cell surface receptors, virus entry and tropism of primate lentiviruses. *J. Gen. Virol*., 83 (2002), pp. 1809-1829

[5] I. Frank, M. Pope. The enigma of dendritic cell-immunodeficiency virus interplay. *Curr. Mol. Med*., 2 (2002), pp. 229-248.

[6] C. Fraser, N.M. Ferguson, F. deWolf, R.M. Anderson. The role of antigenic stimulation and cytotoxic T cell activity in regulating the long-term immunopathogenesis of HIV: mechanisms and clinical implications. *Proc. Roy. Soc. London Ser. B: Biol. Sci*., 268 (2001), pp. 2085-2095.

[7] R.T. Gandhi, B.D. Walker. Immunological control of HIV-1. *Annu. Rev. Med*., 53 (2002), pp. 149-172.

[8] Z. Grossman, M.B. Feinberg, W.E. Paul. Multiple modes of cellular activation and virus transmission in HIV infection: a role for chronically and latently infected cells in sustaining viral replication. *Proc. Natl. Acad. Sci*. USA, 95 (1998), pp. 6314-6319.

[9] P. Jagers. Age dependent branching processes allowing immigration. *Theory Probab. Appl*., 13 (1968), pp. 225-236.

[10] P. Jagers. Branching Processes with Biological Applications. Wiley-Interscience, New York (1975)

[11] A. Kamina, R.W. Makuch, H. Zhao. A stochastic modeling of early HIV-1 population dynamics. *Math. Biosci*., 170 (1975), pp. 187-198.

[12] S. Karlin, H.M. Taylor. *A First Course in Stochastic* Processes (second ed.), Academic Press, New York (1975).

[13] M. Kimmel, D.E. Axelrod. *Branching Processes in Biology*. Springer, Berlin (2002)

[14] I. Kousignian, B. Autran, C. Chouquet, V. Calvez, E. Gormand, C. Katlama, Y. Rivière, D. Costaglioa. IMMUNOCO Study group, Markov modeling of the changes in HIV-specific cytotoxic T-

lymphocyte responses with time in untreated HIV-1 infected patients. *Statist. Med*., 22 (2003), pp. 1675-1690.

[15] N. Levinson. Limiting theorem for age dependent branching process. *Ill. J. Math*., 4 (1960), pp. 100-118.

[16] A.R. McLean, V.C. Emery, A. Webster, P.D. Griffiths. Population dynamics of HIV within an individual after treatment with zidovudine**.** *AIDS*, 5 (1991), pp. 485-489.

[17] S.J. Merrill. Stochastic models of tumor growth and the probability of elimination by cytotoxic cells. *J. Math. Biol*., 20 (1984), pp. 305-320.

[18] S.J. Merrill. AIDS: background and the dynamics of the decline of immunocompetence. A.S. Perelson (Ed.), Theoretical Immunology, part II, Addison-Wesley, Reading, MA (1988), pp. 59-75

[19] S.J. Merrill. Modeling the interaction of HIV with cells of the immune system. C. Castillo-Chavez (Ed.), Mathematical and Statistical Approaches to AIDS Epidemiology, Springer, Berlin (1989), pp. 371-385.

[20] S.J. Merrill, R.S. Root-Bernstein. A model of the role of cofactors in the initiation and development of AIDS**.** *Canad. Appl. Math. Quart*., 6 (1998), pp. 173-185.

[21] A.G. Pakes. Limit theorems for an age-dependent branching process with immigration. *Math. Biosci.,* 14 (1972), pp. 221-234.

[22] A.S. Perelson. Modeling viral and immune system dynamics. *Nat. Rev. Immunol*., 2 (2002), pp. 28-36.

[23] A.S. Perelson, D.E. Kirschner, R.J. DeBoer. Dynamics of HIV infection of T cells. *Math. Biosci*., 114 (1993), pp. 81-125.

[24] A.S. Perelson, P.W. Nelson. Mathematical analysis of HIV-1 dynamics in vivo. *SIAM Rev*., 41 (1999), pp. 3-44.

[25] A.S. Perelson, A.U. Neumann, M. Markowitz, J.M. Leonard, D.D. Ho. HIV-1 dynamics in vivo: viral clearance rate, infected cell life-span, and viral generation time. *Science*, 271 (1996), pp. 1582-1586.

[26] R.S. Root-Bernstein, S.J. Merrill. The necessity of cofactors in the pathogenesis of AIDS: a mathematical model. *J. Theoret. Biol*., 187 (1997), pp. 135-146.

[27] R.S. Root-Bernstein, S.J. Merrill. Etiology and pathology of AIDS. L.J. Standish, C. Calabrese, M.L. Galantino (Eds.), AIDS and Complementary & Alternative Medicine, Churchill Livingstone (2002), pp. 31-50.

[28] N.I. Stilianakis, K. Dietz, D. Schenzle. Analysis of a model for the pathogenesis of AIDS. *Math. Biosci*., 145 (1997), pp. 27-46.

[29] W.-Y. Tan, S.R. Lee, S.C. Tang. Characterization of HIV infection and seroconversion by a stochastic model of the HIV epidemic. *Math. Biosci*., 126 (1995), pp. 81-123.

[30] W.-Y. Tan, H. Wu. Stochastic modeling of the dynamics of T-cell infection by HIV and some Monte Carlo studies**.** *Math. Biosci*., 147 (1998), pp. 173-205.

[31] W.-Y. Tan, Z. Ye. Estimation of HIV infection and incubation via state space models. *Math. Biosci*., 167 (2000), pp. 31-50.

[32] H.C. Tuckwell, E. LeCorfec. A stochastic model for early HIV-1 population dynamics. *J. Theoret. Biol*., 195 (1998), pp. 451-463.

[33] S.M. Wahl, J.M. Orenstein. Immune stimulation and HIV-1 viral replication. *J. Leukocyte Biol*., 62 (1997), pp. 67-71.

[34] D. Wick, S.G. Self. Early HIV infection in vivo: branching-process model for studying timing of immune responses and drug therapy. *Math. Biosci*., 165 (2000), pp. 115-134.

[35] D. Wodarz, M.A. Nowak. Mathematical models of HIV pathogenesis and treatment. *Bioessays*, 24 (2002), pp. 1178-1187.