

A stochastic modeling of early HIV-1 population dynamics

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Abstract

In a recent paper, Tuckwell and Le Corfec [J. Theor. Biol. 195 (1998) 450–463] applied the multi-dimensional diffusion process to model early human immunodeficiency virus type-1 (HIV-1) population dynamics. The purpose of this paper is to assess certain features and consequences of their model in the context of Tan and Wu's stochastic approach [Math. Biosci. 147 (1998) 173–205]. © 2001 Elsevier Science Inc. All rights reserved.

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1. Introduction

By applying the multi-dimensional diffusion process, Tuckwell and Le Corfec [1] introduced stochastic components into the deterministic model of early human immunodeficiency virus type-1 (HIV-1) population dynamics presented by Phillips [2]. Their model includes four variables: healthy CD4⁺ T-cell population, both latently and actively infected CD4⁺ T-cells, and HIV-1 free particles in plasma. Stochastic effects are introduced into two components of the infection process, namely, infections of healthy CD4⁺ T-cells by HIV-1 and transitions from uninfected to latently or actively infected cells. The other biological events such as supply of healthy CD4⁺ T-cells from precursor cells, death of CD4⁺ T-cells, and clearance of HIV-1 particles are assumed to occur with fixed rates whenever an infection of CD4⁺ T-cell by HIV-1 does not take place (i.e., modelled deterministically).

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Unlike Tuckwell and Le Corfec's mathematical approach, Tan and Wu [3] introduced stochastic processes to a broader spectrum of HIV-1 population dynamics described by Perelson [4]. Their model introduced four random components of the infection process in addition to the two stochastic components modeled in Tuckwell and Le Corfec model. Those four random components are: supply of uninfected CD4⁺ T-cells, death of the infected cells, clearance of HIV-1, and conversion of latently to actively infected cells. Therefore, Tan and Wu's stochastic approach mimics more closely randomness of the HIV-1 infection process.

One of the main contributions of Tan and Wu's stochastic model is that their model allows for positive probability of viral extinction early in the infection process. This possibility of viral extinction can be explained by clinical evidence that disease transmission does not always occur among individuals who are exposed to HIV-1 [5]. This accounts for the fact that modeling the probability of viral extinction is an important end point in modeling early HIV-1 population dynamics. When HIV-1 particles enter into a human body, there is a positive probability that the virus either grows by infecting susceptible CD4⁺ T-cells or is cleared from the human body before further infection takes place. In the latter case, the infection process is terminated before becoming persistent so that disease transmission does not take place. The possibility of viral extinction is an important outcome in stochastic modeling of HIV-1 population dynamics. For example, Merrill's stochastic model calculated the probability of viral extinction using a branching process [6].

The possibility of viral extinction in the early HIV-1 infection period was not explicitly discussed in Tuckwell and Le Corfec [1]. Thus, we chose to examine whether the results are consistent between Tuckwell and Le Corfec's and Tan and Wu's approaches in describing the possibility of viral extinction. The results of our numerical replication of Tuckwell and Le Corfec's multi-dimensional diffusion process show that no viral extinction is observed early in the HIV-1 infection process described by their model.

The next question is whether this difference is caused by the deterministic models upon which the two stochastic processes are based, or by the methods which introduce stochastic processes into the modeling process. In order to answer this question, we developed a new model which incorporates stochastic effects by applying Tan and Wu's stochastic approach to the Phillips's deterministic model used by Tuckwell and Le Corfec. Therefore, our model differs from Tuckwell and Le Corfec's model only in modeling randomness of the process and introduces randomness to the HIV-1 population dynamics in a broader manner. We show that our new model is capable of capturing more variability in HIV-1 population dynamics explained by chance mechanisms: (i) the probability of viral extinction as a function of initial viral population, and (ii) outliers where some sample paths grow to their initial peaks in much delayed timing, caused by the existence of latently infected cell population.

The remainder of the paper is organized as follows: Section 2 briefly reviews Tuckwell and Le Corfec's multi-dimensional diffusion process on early HIV-1 population dynamics and presents the results of our replication of their model. Section 3 provides descriptions of the new model, and shows the results of our Monte-Carlo simulations for the new model. Conclusions and discussions are provided in Section 4.

2. The multi-dimensional diffusion process model

The multi-dimensional diffusion process model presented by Tuckwell and Le Corfec [1] is a system of stochastic differential equations including the following four variables:

- $T(t)$ the number of uninfected and activated CD4⁺ T-cells at time t ,
- $L(t)$ the number of latently infected CD4⁺ T-cells at time t ,
- $I(t)$ the number of actively infected CD4⁺ T-cells at time t , and
- $V(t)$ the number of free HIV-1 particles at time t .

Changes in the number of uninfected CD4⁺ T-cells and virus populations in an arbitrary small interval $(t, t + \delta t]$ are expressed as δT and δV , respectively. Similarly δL and δI are defined for the number of latently infected and actively infected cells, respectively. We assume $\delta T = -1$, with probability $k_1 TV \delta t$, and $\delta T = (\lambda - \mu T) \delta t$, with probability $1 - k_1 TV \delta t$. Similar assumptions can be applied to the random changes for δL , δI , and δV . Thus, the model considers whether an infection by HIV-1 occurs during $[t, t + \delta t)$ only because of chance mechanisms. If infection does not occur, then the model considers whether the system grows or decreases deterministically according to fixed rates of supply of new CD4⁺ T-cells and of death of infected and uninfected CD4⁺ T-cells. The model is described as (Tuckwell and Le Corfec [1]):

$$dT = (\lambda - \mu T - k_1 TV) dt - \sqrt{k_1 TV} dW_1, \tag{1}$$

$$dL = (k_1 p TV - \mu L - \alpha L) dt + \sqrt{k_1 p TV} dW_2, \tag{2}$$

$$dI = [k_1(1 - p)TV + \alpha L - aI] dt + \sqrt{k_1(1 - p)TV} dW_3, \tag{3}$$

$$dV = (cI - \gamma V - k_2 TV) dt - \sqrt{k_2 TV} dW_4, \tag{4}$$

where W_i ($i = 1, \dots, 4$) is a standard Wiener process (i.e. mean 0, variance t at time t) and the W_i s are independent of each other. The descriptions and values of the parameters in the above equations are given in Table 1. The deterministic solutions are obtained by removing the terms of W_i from Eqs. (1)–(4). Fig. 1 shows the deterministic solutions for this model for 60 post-primary-infection days. Soon after primary infection takes place ($t = 0$ days), the viral load quickly grows to the initial peak ($t = 22.49$ days) and then quickly reduces to a lower level.

We replicated Tuckwell and Le Corfec’s stochastic simulations by generating 1000 Monte-Carlo sample paths using parameter values in Table 1 for 60 post-primary-infection days, with a time step (δt) of 0.01 days. Absorbing barriers are inserted in the following manner on all four variables T , L , I , and V in order to prevent them taking unrealistic negative values; if any variable resulted in having a negative value after each iteration, then zero replaces the negative value. Ten sample paths from our stochastic simulations are given in Fig. 2.

Fig. 3 presents the distributions of peak viral volumes per 1 mm³ blood (V_{\max}) and time in days to reach viral initial peaks (T_{\max}) from our Monte-Carlo simulations. Among the 1000 Monte-Carlo samples, \bar{V}_{\max} was 4482.8/mm³ and its standard deviation (S.D.) was 100.5 with a range 4151.6–4767.6. Similarly, \bar{T}_{\max} was 21.5 days and its S.D. was 1.4 days with a range 18.7–30.5. These numbers were similar to those obtained by Tuckwell and Le Corfec’s 200 sample paths: $\bar{V}_{\max} = 4494/\text{mm}^3$ with S.D. = 104/mm³ and $\bar{T}_{\max} = 21.5$ days with S.D. = 1.4 days.

Table 1
The descriptions and values of the parameters used in Eqs. (1)–(4)

Variables	Description of variables	Initial and default values
T	Activated uninfected CD4 ⁺ T-cell concentration	200/mm ³ = 200 × 5 × 10 ⁶ /5 dm ³
L	Latently infected CD4 ⁺ T-cell concentration	0
I	Actively infected CD4 ⁺ T-cell concentration	0
V	HIV-1 density	4 × 10 ⁻⁷ /mm ³ = 2/5 dm ³
λ	Appearance rate of uninfected CD4 ⁺ T-cells	0.272/(day mm ³) = 0.272 × 5 × 10 ⁶ /5 dm ³
μ	Net death rate of T and L	0.00136/day
k_1	Infection rate per virion	0.00027 mm ³ /day = 5.4 × 10 ⁻¹¹ dm ³ /day
k_2	Infection rate per uninfected CD4 ⁺ T-cell	0.00027 mm ³ /day = 5.4 × 10 ⁻¹¹ dm ³ /day
p	Proportion of infected cells which are latent	0.1
α	Activation rate of latently infected cells	0.036/day
a	Death rate of I	0.33/day
c	Rate of infectious virions produced by an actively infected T-cell	100/day
γ	Death rate of V	2/day

Source: [1].

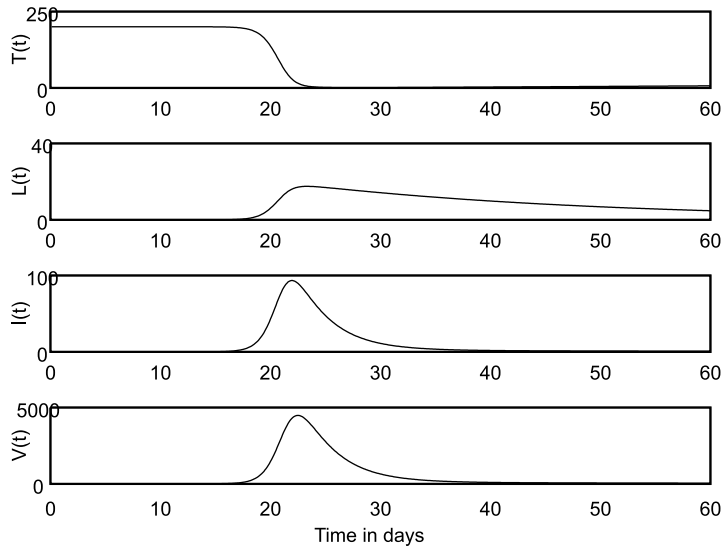


Fig. 1. Deterministic paths of Tuckwell and Le Corfec’s stochastic model of early HIV-1 dynamics described by Eqs. (1)–(4). Variables are uninfected CD4⁺ T-cells (T), latently infected CD4⁺ T-cells (L), actively infected CD4⁺ T-cells (I), and HIV-1 particles (V). All values are given for 1 mm³. Parameter values and initial volumes of the four variables are described in Table 1.

All 1000 viral paths reached their initial peaks around the deterministic peak time. Viral extinction was not observed in our Monte-Carlo simulations using Tuckwell and Le Corfec’s multi-dimensional diffusion process model. This absence of viral extinction may not be

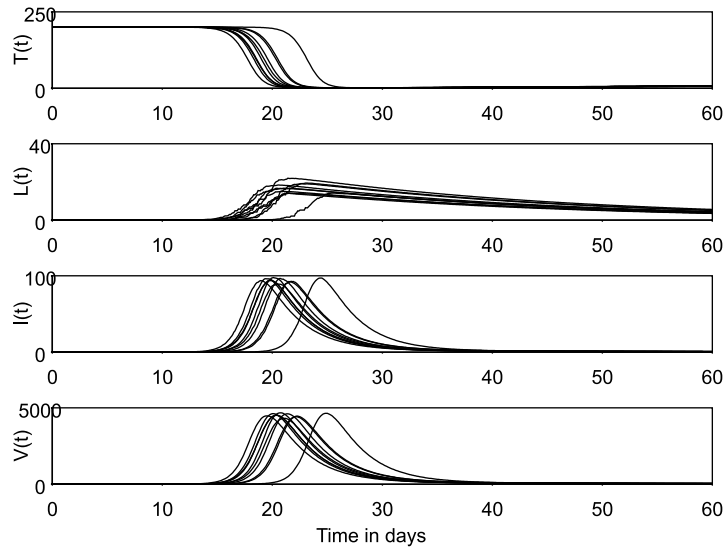


Fig. 2. Ten sample paths from our Monte-Carlo simulation of replicating Tuckwell and Le Corfec’s stochastic model of early HIV-1 dynamics described by Eqs. (1)–(4). Variables are uninfected $CD4^+$ T-cells (T), latently infected $CD4^+$ T-cells (L), actively infected $CD4^+$ T-cells (I), and HIV-1 particles (V). All values are given per one mm^3 . Parameter values and initial volumes of the four variables are described in Table 1.

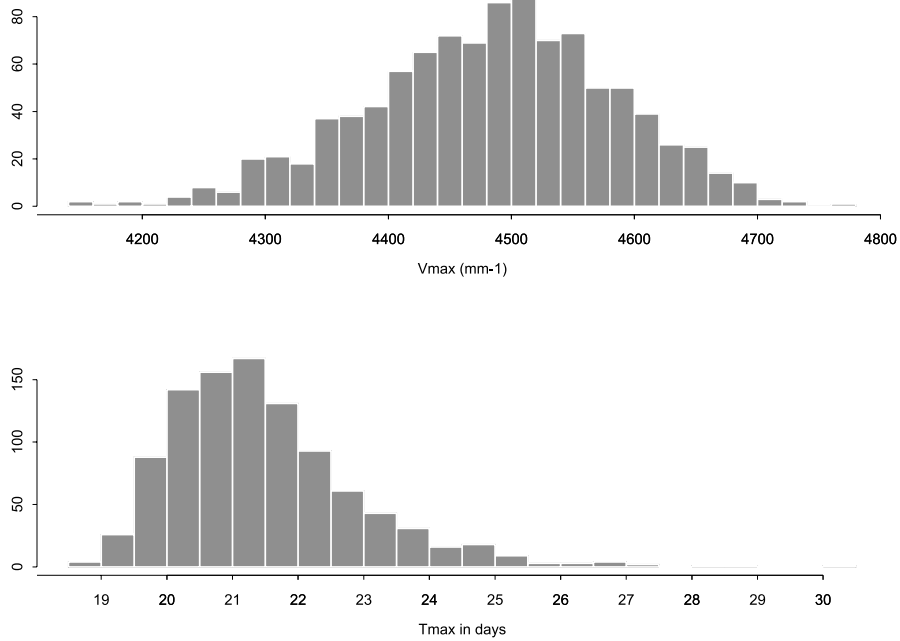


Fig. 3. The upper histogram shows the distribution of the viral peak volumes (V_{max}) of the 1000 sample paths from our simulation of replicating the Tuckwell and Le Corfec model. The lower histogram shows the distribution of time to reach V_{max} , (T_{max}).

intuitively understood and may appear to contradict the fact that absorbing barriers were introduced in the model as described previously. By introducing the absorbing barriers, when the viral load is very close to zero, the value of each variable converges to zero with a probability close to $1/2$. However, in order to cause viral extinction, the three variables, viral load, actively and latently infected cell populations, must become zero simultaneously. Such an event does not occur in our simulations because even when one or two variables become zero during one iteration, the ongoing process always generates positive increments of viral load during the following iterations before all variables could fall to zero simultaneously. For example, when the viral load becomes zero and the number of actively infected cells is still positive, the non-zero actively infected cell population always increases viral population during the subsequent iteration because this component is modeled deterministically. In order to confirm that this absence of viral extinction is not caused by the choice of length of time steps used in our simulations, we repeatedly generated 1000 Monte-Carlo sample paths using smaller step-size, $1/1000$ days and $1/5000$ days. Viral extinction was not observed in any of these sample paths.

3. Tan and Wu's stochastic model

Tan and Wu introduced a stochastic model on the basis of Perelson's deterministic model [4]. Although Perelson's and Phillips' models are similar, their solutions differ because different parameter values are used and different time periods of infection are studied. Therefore, direct comparison of the two stochastic approaches is not possible.

In this section we develop a new model by applying Tan and Wu's stochastic approach [3] to Phillips's deterministic model [2] used by Tuckwell and Le Corfec's multi-dimensional diffusion process [1]. Numerical solutions are obtained in the same manner as that used in the previous model except that we no longer use a multi-dimensional diffusion process method. The new model enables us to compare the two stochastic approaches directly.

3.1. Description of the model

The four variables used in this model are the same as described in the previous section. By applying Tan and Wu's stochastic approach, a four-dimensional stochastic process $X = \{T(t), L(t), I(t), V(t)\}$ is described based on the following set of assumptions:

- (i) New normal $CD4^+$ T-cells are generated stochastically from precursor cells. This is modeled by a Poisson process with rate $\lambda\delta t$.
- (ii) Susceptible $CD4^+$ T-cells can be infected by HIV-1 to become latently or actively infected cells. The conditional probability that an HIV-1 infects a $CD4^+$ T-cell during $[t, t + \delta t)$ is $k_1 T(t)\delta t + o(\delta t)$. A $CD4^+$ T-cell infected by HIV-1 during $[t, t + \delta t)$ becomes latent with probability p .
- (iii) Activation of an $L(t)$ cell during $[t, t + \delta t)$ takes place with probability $\alpha\delta t + o(\delta t)$.
- (iv) The probability of death of a $T(t)$ cell and an $L(t)$ cell is $\mu\delta t + o(\delta t)$. Similarly the probability of death of an $I(t)$ cell and a $V(t)$ during $[t, t + \delta t)$ are $a\delta t + o(\delta t)$ and $\gamma\delta t + o(\delta t)$, respectively.

(v) An $I(t)$ cell releases c HIV-1 particles during $[t, t + \delta t)$. This process is modeled deterministically and the random variation of this quantity is ignored.

Given the above assumptions, the numerical solutions for the $(n + 1)$ th step of the four variables are given by the following algorithm:

$$T_{n+1} = T_n + S_n - F_n - D_{Tn}, \quad (5)$$

$$L_{n+1} = L_n + X_n - F'_n - D_{Ln}, \quad (6)$$

$$I_{n+1} = I_n + F_n - X_n + F'_n - D_{In}, \quad (7)$$

$$V_{n+1} = V_n + cI_n\delta t - F_n - D_{Vn}, \quad (8)$$

where

$S_n \sim$ Poisson with a mean of $\lambda\delta t$,

$F_n, D_{Vn} | [T_n, V_n] \sim$ Multinomial $[V_n; k_1 T_n \delta t, \gamma \delta t]$,

$F'_n, D_{Ln} | L_n \sim$ Multinomial $[L_n, \alpha \delta t, \mu \delta t]$,

$X_n | F_n \sim$ Binomial $[F_n, p]$,

$D_{Tn} | T_n \sim$ Binomial $[T_n, \mu \delta t]$,

$D_{In} | I_n \sim$ Binomial $[I_n, a \delta t]$.

Functions of 'rpois' and 'rbinom' of the statistical package SPLUS are used to generate the Poisson and binomial random variables. The conditional distribution method is used to generate the multinomial random variables [7]. The deterministic solutions are computed by replacing all terms in Eqs. (5)–(8) with expected values of the corresponding distributions.

3.2. The results of Monte-Carlo simulations

Using the model described above, we generated 1000 Monte-Carlo samples for 60 post-primary-infection days with time step of 0.01 days. We repeatedly generated sample paths for the six different initial viral volumes, $V(0) = 2, 5, 10, 50, 100,$ and 300 . Parameter values and initial values for the remaining three variables used in our Monte-Carlo simulations were the same as those used by Tuckwell and Le Corfec shown in Table 1. Initial viral volume of 2 was used by Tuckwell and Le Corfec's simulation, therefore the sample paths with $V(0) = 2$ can be directly compared with the replicated sample paths for Tuckwell and Le Corfec's multi-dimensional diffusion process model.

The individual sample path is categorized into either one of the following three conditions depending on growth pattern observed at the end of the simulation: (i) *infected steady state* where the viral load has grown to the peak and stabilized at a lower level thereafter or is still in process of growth to the peak, (ii) *uninfected steady state* where the infection process is terminated and viral extinction takes place, and (iii) *undetermined state* where either of infected or uninfected steady states has not yet taken place.

Among the 1000 sample paths of the initial viral volume of 2, we observed viral load converged to an infected steady state in 5.3% (53 cases/1000) of the sample paths. In 94.6% of the sample paths (946 cases/1000), the entire process stopped when the condition $L(t) = I(t) = V(t) = 0$ was satisfied for an arbitrary time point $t = t' < 60$, so that no further viral infection is expected (uninfected steady state). One sample path remained without converging to either uninfected or infected steady states at the end of the simulation (undetermined state).

The probability of viral extinction is significantly influenced by initial viral density. When initial viral volume is increased to 5, 10, 50, and 100, the probability of viral extinction decreased to 89.4%, 80.9%, 29.9% and 9.2%, respectively. When initial viral volume is 300, the viral extinction occurred in only 0.2% of sample paths while 99.8% of sample paths grew to their initial peaks.

After the infection process survives during a near-zero random fluctuation period, the viral population soon grows to the initial peak, then quickly reduces to a lower level (infected steady state). No viral extinction was observed after 60 days among the sample paths of infected steady state. The individual sample path of infected steady state is almost identical except that variability exists in time to initiation of growth of the viral population after early random fluctuation periods. Among the 53 sample paths of infected steady state, 49 cases reached their initial peaks close to the deterministic peak time ($t = 22.49$). In the remaining 4 sample paths, the viral population reached their peaks at delayed timings ($t = 35.7, 48.5, 54.0, 56.4$). Fig. 4 shows 10 sample paths among the 53 sample paths of infected steady state. These sample paths are directly comparable with those obtained by our replication of Tuckwell and Le Corfec's model shown in Fig. 2 because they differ only by the way randomness of the process was introduced. The deterministic solutions corresponding to the sample paths in Fig. 4 were identical with those obtained by the Tuckwell and Le Corfec's model shown in Fig. 1.

We found that the delay occurs only among the sample paths where the number of latently infected cells remains non-zero after the populations of HIV-1 and actively infected cells decrease to zero. Mathematically, this is represented by the condition $L(t) \geq 1$, and $I(t) = V(t) = 0$ for arbitrary time point $t = t' < 60$. Once this condition is satisfied, the time to death of the latently

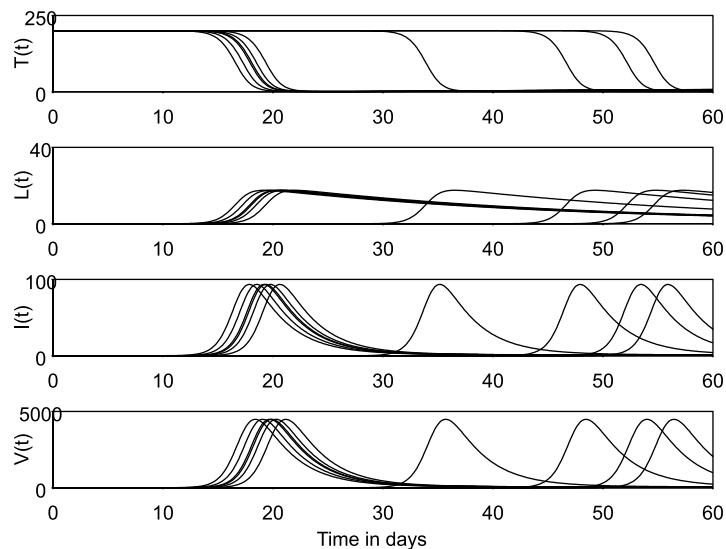


Fig. 4. Ten sample paths of infected steady state from the Monte-Carlo simulation of our new stochastic model of early HIV-1 population dynamics. Only 53 sample paths among 1000 generated paths grew to their initial peaks before 60 days. Among 53 cases, 49 cases grew to their peaks close to the deterministic peak time ($t = 24.5$). The remaining four sample paths grew to their peaks in much delayed timing than others ($t = 35.7, 48.5, 54.0, \text{ and } 56.4$ days). The parameter values and initial volumes of the four variables are the same as those used in Fig. 1. The deterministic paths for this stochastic model were identical with those shown in Fig. 2.

infected cell population or activation for further infection varies widely because the latently infected cell population may live for a long time without being activated.

The factors $L(t)$, $I(t)$ and $V(t)$ can be used to define the two categories of sample paths. If viral loads grow to their peaks without satisfying the condition $L(t) \geq 1$ and $I(t) = V(t) = 0$, viral loads reach their peaks at times close to the deterministic peak time. We define this type of growth as Type 1. Sample paths where the condition $L(t) \geq 1$ and $I(t) = V(t) = 0$ is satisfied at least once before the end of simulation, are defined to be Type 2.

Table 2 shows the numbers of sample paths (among 1000 generated) by growth category for different initial viral volumes. Among the 53 sample paths of infected steady state, 46 were Type 1 and the remaining 7 were Type 2. The proportion of sample paths in Type 2 to total number of infected steady state decreases with increased initial viral volume (Table 2). For sample paths with $V(0) = 300$, only two cases are of Type 2 growth, and 996 cases among 1000 total are Type 1 growth. This is because with higher initial viral volumes, the viral populations are more likely to increase to their initial peak without fluctuating near zero.

Table 3 presents a summary of time to viral peaks of Types 1 and 2 infected steady state for different initial viral volumes. The deterministic viral peak time was reached faster with larger number of $V(0)$. All sample paths of Type 1 grew to the peaks close to the deterministic peak time

Table 2

Number of Monte-Carlo samples by types of growth of HIV-1 among total of 1000 samples for different initial viral populations^a

$V(0)$	Uninfected steady state	Infected steady state		Undetermined state
		Type 1	Type 2	
2	946	46	7	1
5	894	94	11	1
10	809	176	12	3
50	299	656	43	2
100	92	880	25	3
300	2	996	2	0

^a $V(0)$, initial population size of viral particles.

Table 3

Time to viral peaks (days) of sample paths of infected steady state^a

$V(0)$	Deterministic	Type 1			Type 2		
		Min.	Max.	Mean (S.D.)	Min.	Max.	Mean (S.D.)
2	22.5	18.4	22.2	19.9 (0.8)	21.7	56.4	37.5 (15.4) ^b
5	21.7	18.2	23.0	20.1 (0.9)	22.9	55.5	34.1 (12.2)
10	21.1	18.4	22.9	20.1 (0.8)	19.7	60+	43.1 (12.3)
50	19.7	17.9	25.2	19.8 (1.0)	23.0	60+	40.3 (12.8)
100	19.2	17.5	26.4	19.4 (0.9)	22.6	60+	40.2 (11.7)
300	18.2	17.1	23.6	18.4 (0.6)	23.5	35.7	29.6 (8.6) ^b

^a $V(0)$, initial population size of viral particles, Min., minimum volume at viral peak, Max., maximum viral peak volume, S.D., standard deviation.

^b Sample size < 10.

Table 4
Peak viral volumes which grew to the peaks (mm^{-1}) before 60 days^a

$V(0)$	Min.	Max.	Mean (S.D.)	Det.
2	4480.2	4481.9	4481.2 (0.4)	4481.6
5	4479.8	4481.8	4481.1 (0.5)	4481.6
10	4479.9	4482.1	4481.1 (0.5)	4481.6
50	4479.7	4482.0	4481.1 (0.5)	4481.6
100	4479.8	4482.1	4481.1 (0.5)	4481.6
300	4479.6	4482.1	4481.1 (0.5)	4481.6

^a $V(0)$, initial population size of viral particles, Min., minimum volume at viral peak, Max., maximum viral peak volume, S.D., standard deviation, Det., deterministic peak viral volume.

of corresponding $V(0)$. On the other hand, sample paths of Type 2 grew to their peaks at a much delayed time compared to the deterministic peak time, and the durations of the delay range widely.

During the infection period where the condition of $L(t) \geq 1$ and $I(t) = V(t) = 0$ is maintained, no viral particle or virus-producing cell exists in circulated blood; however, viral infection remains possible because activation of latently infected cells can still take place (undetermined state). In Table 2, we observed that for all values of $V(0)$ except for $V(0) = 300$, some sample paths remained at undetermined state at the end of the simulation time ($t = 60$). These sample paths may converge to an infected steady state if the simulation time is extended for a longer period.

Table 4 presents the minimum, maximum, mean and standard deviation of distributions of the viral peak loads which reached the initial peaks before 60 days. The conditional distribution of viral peak volumes is significantly concentrated around the means ($\bar{V}_{\max} = 4481.2/\text{mm}^3$, S.D. = 0.4 for $V(0) = 2$, $\bar{V}_{\max} = 4481.1/\text{mm}^3$, S.D. = 0.5 for $V(0) = 300$). The mean viral peak volumes for all levels of initial viral densities are almost identical with the corresponding deterministic viral peak volume. Initial viral density does not appear to affect the deterministic viral peak volumes. In summary, the distribution of viral peak volumes obtained in Tan and Wu's model is clearly different from what was observed in Tuckwell and Le Corfec's multi-dimensional diffusion model where much larger variability was observed ($\bar{V}_{\max} = 4482.8/\text{mm}^3$, S.D. = 100.5). Finally, computing time was similar for evaluation of both models, and it should not be considered a hindrance to the examination of more complex models.

4. Conclusions and discussions

The probability of viral extinction represents an important outcome in modeling stochastic effects on early HIV-1 population dynamics. Several stochastic models of HIV-1 population dynamics have shown positive probability of viral extinction during early post-primary-infection times [3,6]. Tuckwell and Le Corfec developed a stochastic model for early HIV-1 infection by applying a multi-dimensional diffusion process on the basis of the deterministic model developed by Phillips. The possibility of viral extinction, however, was not clearly discussed in their paper. In our replication of Tuckwell and Le Corfec's numerical simulation, we showed that their multi-dimensional diffusion process model is not capable of predicting viral extinction in an early period

of HIV-1 infection. This occurs because the continuous approximation of the multi-dimensional diffusion process is not adequate when the population of CD4⁺ T-cells and viral particles are close to zero boundary. The boundary conditions in diffusion processes were first investigated in detail by Feller [8] and summarized by Karlin and Taylor [9] for one-dimensional diffusion processes. Because little theoretical work has been done to study boundary behaviors in multi-dimensional diffusion processes similar to the one we studied here, we empirically studied the process by reducing the time steps. Even when the time size was very small, no viral extinction was observed through Tuckwell and Le Corfec's approach.

We further evaluated Tuckwell and Le Corfec's multi-dimensional diffusion process in the context of the stochastic approach developed by Tan and Wu. The results of our simulations using Tan and Wu's stochastic method show that 95% of viral infections were terminated soon after primary infection. The observed difference is only due to methods used to introduce stochastic process to the infection process. Furthermore, varying the initial viral population of the Monte-Carlo simulations for our new model showed that the probability of viral extinction decreased significantly with increased initial viral density. Based on this observation, the threshold viral volume was estimated to fall around 300 virions per 5 liter of blood above which viral extinction may be unlikely. In other words, if a patient is inoculated with more than 300 virions, transmission of disease is highly likely to take place. In such cases, the deterministic model provides a very good description of the true dynamic process. On the other hand, if the inoculated viral load is less, likelihood of successful disease transmission becomes smaller. This is consistent with clinical evidence that patients who are exposed to higher density of HIV-1 have higher probability of disease transmission [10]. Tuckwell and Le Corfec's multi-dimensional diffusion process fails to capture the important characteristic of HIV-1 population dynamics at an early stage of HIV-1 infection, which a deterministic approach alone cannot describe.

With our new model, we also showed that outlier condition exists among sample paths of infected steady state. Such condition was caused because some sample paths were much delayed in growing to the peaks compared with others. This delay can be explained by the existence of latently infected CD4⁺ T-cells. When generation of a latently infected CD4⁺ T-cell occurs, the infected cell can remain in a body without either dying or being activated for a long time. In our simulation, some sample paths remain without any free viral particles in the body but persistent infection is still possible even after 60 days in the post-primary-infection period. The existence of these outliers indicates that more caution is necessary when we estimate false negative results of HIV-1 testing. Clinical evidence also supports the existence of such outliers [11]. Clearly the estimation of the probability of a false negative test based on Tuckwell and Le Corfec's approach does not consider the existence of these outliers.

In regard to variability among viral peak volumes, our model is associated with less variability than the Tuckwell and Le Corfec model. The difference may be explained as follows. In the multi-dimensional diffusion process, random variations of the four variables are modeled at arbitrary time points independently. In Tan and Wu's approach, all variables are dependent, and a change in one variable directly relates to a change in the other variables. As illustrated through our simulation studies, the approach by Tuckwell and Le Corfec unnecessarily inflates the variation of the state variables (T , L , I and V).

In summary, the results of our comparison study in stochastic modeling of early HIV-1 population dynamics suggest the method of Tuckwell and Le Corfec's multi-dimensional diffusion

process may be insufficient to characterize important aspects of the random nature of early HIV-1 population dynamics. The fundamental problem with the Tuckwell and Le Corfec approach is that instead of examining the nature of randomness of the variables, the approach simply adds a Gaussian random noise to the state variables and wrongly assumes that independence for these random noises which are correlated with each other. As a consequence, the state variables have positive probabilities to take negative numbers and the variances of the state variables are unnecessarily inflated. Modifications and extensions of their diffusion model are necessary to better describe the early HIV-1 population dynamics. For example, to incorporate more of the randomness of the HIV-1 infection process through the approach we have described in this paper.

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