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Research Article

Stochastic Model for Langerhans Cells and HIV Dynamics *In Vivo*

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Many aspects of the complex interaction between HIV and the human immune system remain elusive. Our objective is to study these interactions, focusing on the specific roles of Langerhans cells (LCs) in HIV infection. In patients infected with HIV, a large amount of virus is associated with LCs in lymphoid tissue. To assess the influence of LCs on HIV viral dynamics during antiretroviral therapy, we present and analyse a stochastic model describing the dynamics of HIV, CD_4^+ T cells, and LCs interactions under therapeutic intervention *in vivo* and show that LCs play an important role in enhancing and spreading initial HIV infection. We perform sensitivity analyses on the model to determine which parameters and/or which interaction mechanisms strongly affect infection dynamics.

1. Introduction

HIV is a devastating human pathogen that causes serious immunological diseases in humans around the world. The virus is able to remain latent in an infected host for many years, allowing for the long-term survival of the virus and inevitably prolonging the infection process [1]. The location and mechanisms of HIV latency are under investigation and remain important topics in the study of viral pathogenesis. Given that HIV is a blood-borne pathogen, a number of cell types have been proposed to be the sites of latency, including resting memory CD_4^+ + T cells, peripheral blood monocytes, dendritic cells (including Langerhans cells) and macrophages in the lymph nodes, and haematopoietic stem cells in the bone marrow [2]. This study updates the latest advances in the study of HIV interactions with Langerhans cells and highlights the potential role of these cells as viral reservoirs and the effects of the HIV-host-cell interactions on viral pathogenesis.

Despite advances in our understanding of HIV and the human immune response in the last 25 years, much of this complex interaction remains elusive. CD_4^+ T cells are targets of HIV and are also important for the establishment and maintenance of an adaptive immune response [3]. The skin and mucosa are the first line of defense of the organism against external agents, not only as a physical barrier between the body and the environment but also as the site of initiation of immune reactions. The immunocompetent cells which act as antigen-presenting cells are Langerhans cells (LCs). Infection of LCs by HIV is relevant to several reasons. Firstly, LCs of mucosal epithelia may be among the first cells to be infected following mucosal HIV exposure and, secondly, LCs may serve as a reservoir for continued infection of CD_4^+ T cells, especially in lymph nodes where epidermal LCs migrate following antigenic activation [4].

Many indirect and/or direct experimental data have shown that LCs may be a privileged target, reservoir, and vector of dissemination for the HIV from the inoculation sites (mucosa) to lymph nodes where the emigrated infected LCs could infect T lymphocytes [5]. Originated from the bone marrow, LCs migrate to the peripheral epithelia (skin, mucous membranes) where they play a primordial role in the induction of an immune response and are especially active in stimulating naive T lymphocytes in the primary response through a specific cooperation with CD_4^+-positive lymphocytes after migration to proximal lymph nodes [6]. Apart from many plasma membrane determinants, LCs also express CD_4^+ molecules which make them susceptible targets and reservoirs for HIV [7]. Once infected, these cells due to their localization in areas at risk (skin, mucous membranes), their capacity to migrate from the epidermal compartment to lymph nodes, and their ability to support viral replication without major cytopathic effects could play a role of vector in the dissemination of virus from the site of inoculation to the lymph nodes and thereby contribute to the infection of T lymphocytes [7].

Langerhans cells (LCs), which are members of the dendritic cells family and are professional antigen-presenting cells, reside in epithelial surfaces such as the skin and act as one of the primary, initial targets for HIV infection [8]. They specialize in antigen presentation and belong to the skin immune system (SIS) and play a major role in HIV pathogenesis. As part of the normal immune response, LCs capture virions at the site of transmission in the mucosa (peripheral tissues) and migrate to the lymphoid tissue where they present to naive T cells and hence are responsible for large-scale infection of CD_4^+ T lymphocytes [8]. These cells play an important role in the transmission of HIV to CD_4^+ cells [9]; thus, LC-CD_4^+ cell interactions in lymphoid tissue, which are critical in the generation of immune responses, are also a major catalyst for HIV replication and expansion. This replication independent mode of HIV transmission, known as *trans*-infection, greatly increases T cell infection *in vitro* and is thought to contribute to viral dissemination *in vivo* [10].

The Langerhans cell is named after Paul Langerhans, a German physician and anatomist, who discovered the cells at the age of 21 in 1868 while he was a medical student [11]. The uptake of HIV by professional antigen-presenting cells (APCs) and subsequent transfer of virus to CD_4^+ T cells can result in explosive levels of virus replication in the T cells. This could be a major pathogenic process in HIV infection and development of AIDS. This process of *trans*- (Latin; to the other side) infection of virus going across from the APC to the T cell is in contrast to direct, *cis*- (Latin; on this side) infection of T cells by HIV [12]. Langerhans cell results in a burst of virus replication in the T cells that is much greater than that resulting from direct, cis infection of either APC or T cells, or *trans*-infection between T cells. This consequently shows that Langerhans cells may be responsible for the quick spread of HIV infection.

The individual cells of the immune system are highly interactive, and the overall function of the system is a product of this multitude of interactions. The interplay between HIV and the immune system is particularly complicated, as HIV directly interacts with many immune cells, altering their functions, ultimately subverting the system at its core [3]. Because of this complexity, the immune response and its interaction with HIV are naturally suited to a mathematical modelling approach. Elucidating the mechanisms of LC-HIV-CD_4^+ T cells interactions is crucial in uncovering more details about host-HIV dynamics during HIV infection. To explore the role of LCs in HIV infection, we first develop a stochastic model of HIV dynamics *in vivo* before therapy. Next, we introduce therapeutic intervention and finally investigate which parameters and/or which interaction mechanisms strongly affect the infection dynamics.

Table 1: Variables for the stochastic model.

Variable	Description
$T(t)$	The concentration of healthy (susceptible) CD_4^+ cells at time t
$T_I(t)$	The concentration of infected CD_4^+ cells at time t
$L(t)$	The concentration of healthy (susceptible) Langerhans cells at time t
$L_T(t)$	The concentration of latently infected Langerhans cells at time t
$L_I(t)$	The concentration of infected Langerhans cells at time t
$V(t)$	The concentration of virus particles at time t

The organization of this paper is as follows. In Section 2, we formulate our stochastic model describing the interaction of HIV and the immune system and obtain a partial differential equation for the joint probability generating function of the numbers of healthy immune cells, the HIV infected immune cells, and the free HIV particles at any time t. The marginal probability distributions for the variables and the population measures which include the expectation of the variables are also derived in Section 2. HIV dynamic model incorporating therapy is derived and model analysis is discussed in Section 3. Some concluding remarks follow in Section 4.

2. The Role of LC in HIV Infection *In Vivo*

In HIV infection, LCs play a dual role in promoting immunity while also facilitating infection. During antigen presentation, LC-associated viruses migrate to the lymphoid tissue where they present to naive T cells and hence facilitate infection of CD_4^+ T cells [15]. Taken together, these interactions suggest that LC dynamics are particularly important to HIV infection. Several mechanisms have been proposed to trigger progression from the chronic phase of infection to AIDS. Many have hypothesized that progressive alteration of the immune system results in the transition to AIDS [16, 17].

To study the roles of LCs during HIV infection, we present a mathematical model of HIV infection and accompanying immune response. Specifically, we develop a stochastic model focusing on the HIV-LC-CD_4^+ cell dynamics *in vivo*. Our model analysis allows us to predict the importance of LC mechanisms and their role in triggering progression to AIDS. In particular, our model predicts which mechanisms of LC dysfunction are most significant in the transition to AIDS. A typical life cycle of HIV virus and immune system interaction is shown in Figure 1.

2.1. Variables and Parameters for the Model.

The variables and parameters in the model are described as in Tables 1 and 2.

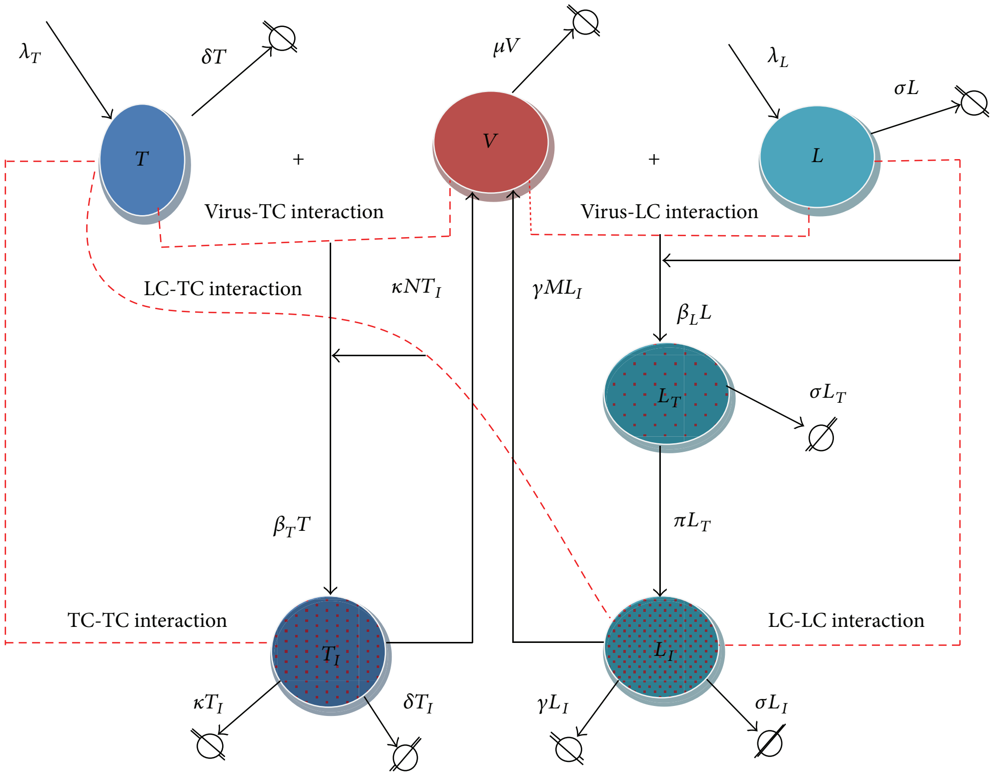


FIGURE 1: The interaction of HIV virus and the immune system.

TABLE 2: Parameters for the stochastic model.

Parameter	Description
λ_T	The total rate of production of healthy CD_4^+ cells per unit time
λ_L	The total rate of production of Langerhans cells per unit time
δ	The per capita death rate of healthy CD_4^+ cells
σ	The per capita death rate of healthy Langerhans cells
β_1	The transmission coefficient between uninfected CD_4^+ cells and infective virus particles
β_2	The transmission coefficient between uninfected CD_4^+ cells and IV infected Langerhans cells
β_3	The transmission coefficient between uninfected Langerhans cells and infective virus particles
β_4	The transmission coefficient between uninfected Langerhans cells and HIV infected Langerhans cells
κ	Per capita death rate of infected CD_4^+ cells
τ	Intracellular delay time
γ	Per capita death rate of infected Langerhans cells
μ	The per capita death rate of infective virus particles
N	The average number of infective virus particles produced by an infected CD_4^+ cell in the absence of treatment during its entire infectious lifetime
M	The average number of infective virus particles produced by an infected Langerhans cell in the absence of treatment during its entire infectious lifetime

From Table 1 and by using the population change scenarios and parameters in Table 2 and applying probability arguments, we now summarize the events that occur during the interval $(t, t + \Delta t)$ together with their transition probabilities in Table 3.

The change in population size during the time interval Δt, which is assumed to be sufficiently small to guarantee that only one such event can occur in $(t, t + \Delta t)$, is governed by the following conditional probabilities:

$$\begin{aligned}
&P_{x,x_I,y,y_I,v}(t+\Delta t) \\
&= \{1 - (\lambda_T \Delta t + \lambda_L \Delta t + \delta x \Delta t + \sigma y \Delta t \\
&\qquad + \beta_1 x v \Delta t + \beta_2 x y_I \Delta t + \beta_3 y v \Delta t \\
&\qquad + \beta_4 y y_I \Delta t + \kappa x_I \Delta t + \gamma y_I \Delta t + \mu v \Delta t) + o(\Delta t)\} \\
&\quad \times P_{x,x_I,y,y_I,v}(t) \\
&\quad + \{\lambda_T \Delta t + o(\Delta t)\} P_{x-1,x_I,y,y_I,v}(t) \\
&\quad + \{\lambda_L \Delta t + o(\Delta t)\} P_{x,x_I,y-1,y_I,v}(t) \\
&\quad + \{\delta(x+1)\Delta t + o(\Delta t)\} P_{x+1,x_I,y,y_I,v}(t) \\
&\quad + \{\sigma(y+1)\Delta t + o(\Delta t)\} P_{x,x_I,y+1,y_I,v}(t) \\
&\quad + \{[\beta_1 (x+1)(v+1) + \beta_2 (x+1)(y_I)]
\end{aligned}$$

$$\begin{aligned}
&\times e^{-\rho\tau}\Delta t + o(\Delta t)\} P_{x+1,x_I-1,y,y_I,v+1}(t) \\
&+ \{[\beta_3 (y+1)(v+1) + \beta_4 (y+1)(y_I)]\Delta t + o(\Delta t)\} \\
&\times P_{x,x_I,y+1,y_I-1,v+1}(t) \\
&+ \{\kappa N (x_I+1)\Delta t + o(\Delta t)\} P_{x,x_I+1,y,y_I,v-1}(t) \\
&+ \{\gamma M (y_I+1)\Delta t + o(\Delta t)\} P_{x,x_I,y,y_I+1,v-1}(t) \\
&+ \{\mu (v+1)\Delta t + o(\Delta t)\} P_{x,x_I,y,y_I,v+1}(t).
\end{aligned} \tag{1}$$

Rearranging (1), then dividing through by Δt, and taking the limit as $\Delta t \Rightarrow 0$ we have the following difference differential equation:

$$\begin{aligned}
&P'_{x,x_I,y,y_I,v}(t) \\
&\quad = -\{\lambda_T + \lambda_L + \delta x + \sigma y + \beta_1 x v + \beta_2 x y_I \\
&\qquad + \beta_3 y v + \beta_4 y y_I + \kappa x_I + \gamma y_I + \mu v\} P_{x,x_I,y,y_I,v}(t) \\
&\qquad + \lambda_T P_{x-1,x_I,y,y_I,v}(t) + \lambda_L P_{x,x_I,y-1,y_I,v}(t) \\
&\qquad + \delta (x+1) P_{x+1,x_I,y,y_I,v}(t) + \sigma (y+1) P_{x,x_I,y+1,y_I,v}(t) \\
&\qquad + \{\beta_1 (x+1)(v+1) + \beta_2 (x+1)(y_I)\} \\
&\qquad \times e^{-\rho\tau} P_{x+1,x_I-1,y,y_I,v+1}(t) \\
&\qquad + \{\beta_3 (y+1)(v+1) + \beta_4 (y+1)(y_I)\} \\
&\qquad \times P_{x,x_I,y+1,y_I-1,v+1}(t) \\
&\qquad + \kappa N (x_I+1) P_{x,x_I+1,y,y_I,v-1}(t) \\
&\qquad + \gamma M (y_I+1) P_{x,x_I,y,y_I+1,v-1}(t) \\
&\qquad + \mu (v+1) P_{x,x_I,y,y_I,v+1}(t).
\end{aligned} \tag{2}$$

This is also called the Master equation or the forward Kolmogorov partial differential equation for $P_{x,x_I,y,y_I,v}(t)$, with initial condition

$$\begin{aligned}
P'_{0,0,0,0,0}(t) &= -(\lambda_T + \lambda_L) P_{0,0,0,0,0}(t) \\
&\quad + \delta P_{1,0,0,0,0}(t) + \sigma P_{0,0,1,0,0}(t) + \mu P_{0,0,0,0,1}(t).
\end{aligned} \tag{3}$$

For detailed description and derivation of the model we refer the reader to [18].

2.2. The Probability Generating Function. Now we apply the generating function method. Multiplying (2) by $z_1^x z_2^y z_3^{x_I} z_4^{y_I} z_5^v$ and summing over x, y, x_I, y_I, and v, then applying the properties of generating function, we obtain

$$\begin{aligned}
\frac{\partial G}{\partial t} &= -(\lambda_T + \lambda_L) G - \delta z_1 \frac{\partial G}{\partial z_1} - \sigma z_2 \frac{\partial G}{\partial z_2} - \kappa z_3 \frac{\partial G}{\partial z_3} \\
&\quad - \gamma z_4 \frac{\partial G}{\partial z_4} - \mu z_5 \frac{\partial G}{\partial z_5} - \beta_1 z_1 z_5 \frac{\partial^2 G}{\partial z_1 \partial z_5} \\
&\quad - \beta_2 z_1 z_4 \frac{\partial^2 G}{\partial z_1 \partial z_4} - \beta_3 z_2 z_5 \frac{\partial^2 G}{\partial z_2 \partial z_5} \\
&\quad - \beta_4 z_2 z_4 \frac{\partial^2 G}{\partial z_2 \partial z_4} + \lambda_T z_1 G + \lambda_L z_2 G + \delta \frac{\partial G}{\partial z_1} \\
&\quad + \sigma \frac{\partial G}{\partial z_2} + z_5 N \kappa \frac{\partial G}{\partial z_3} + z_5 M \gamma \frac{\partial G}{\partial z_4} + \mu \frac{\partial G}{\partial z_5} \\
&\quad + z_3 \beta_1 e^{-\rho\tau} \frac{\partial^2 G}{\partial z_1 \partial z_5} + z_3 \beta_2 e^{-\rho\tau} \frac{\partial^2 G}{\partial z_1 \partial z_4} \\
&\quad + z_4 \beta_3 \frac{\partial^2 G}{\partial z_2 \partial z_5} + z_4 \beta_4 \frac{\partial^2 G}{\partial z_2 \partial z_4}.
\end{aligned} \tag{4}$$

On simplification we have

$$\begin{aligned}
\frac{\partial G}{\partial t} &= \{(z_1 - 1)\lambda_T + (z_2 - 1)\lambda_L\} G + (1 - z_1)\delta \frac{\partial G}{\partial z_1} \\
&\quad + (1 - z_2)\sigma \frac{\partial G}{\partial z_2} + (N z_5 - z_3)\kappa \frac{\partial G}{\partial z_3} \\
&\quad + (M z_5 - z_4)\gamma \frac{\partial G}{\partial z_4} + (1 - z_5)\mu \frac{\partial G}{\partial z_5} \\
&\quad + \beta_1 (z_3 e^{-\rho\tau} - z_1 z_5) \frac{\partial^2 G}{\partial z_1 \partial z_5} \\
&\quad + \beta_2 (z_3 e^{-\rho\tau} - z_1 z_4) \frac{\partial^2 G}{\partial z_1 \partial z_4} \\
&\quad + \beta_3 (z_4 - z_2 z_5) \frac{\partial^2 G}{\partial z_2 \partial z_5} + \beta_4 (z_4 - z_2 z_4) \frac{\partial^2 G}{\partial z_2 \partial z_4}.
\end{aligned} \tag{5}$$

This is called Lagrange partial differential equation for the probability generating function (pgf) G.

2.3. The Marginal Generating Functions. Recall that

$$G(z_1, 1, 1, t) = \sum_{x=0}^{\infty} \sum_{y=0}^{\infty} \sum_{v=0}^{\infty} P_{x,y,v}(t) z_1^x. \tag{6}$$

Table 3: In-host interaction of HIV.

Possible transitions in-host interaction of HIV and immune system cells and corresponding probabilities			
Event	Population components (T, T_I, L, L_I, V) at t	Population components (T, T_I, L, L_I, V) at $(t, t+\Delta t)$	Probability of transition
Production of healthy CD_4^+ cell	$(x-1, x_I, y, y_I, v)$	(x, x_I, y, y_I, v)	$\lambda_T \Delta t$
Death of healthy CD_4^+ cell	$(x+1, x_I, y, y_I, v)$	(x, x_I, y, y_I, v)	$\delta(x+1)\Delta t$
Infection of healthy CD_4^+ cell	$(x+1, x_I-1, y, y_I, v+1)$	(x, x_I, y, y_I, v)	$\beta_1(x+1)(v+1)e^{-\rho\tau}\Delta t + \beta_2(x+1)(y_I)e^{-\rho\tau}\Delta t$
Production of Langerhans cell	$(x, x_I, y-1, y_I, v)$	(x, x_I, y, y_I, v)	$\lambda_L \Delta t$
Death of Langerhans cell	$(x, x_I, y+1, y_I, v)$	(x, x_I, y, y_I, v)	$\sigma(y+1)\Delta t$
Infection of Langerhans cell	$(x, x_I, y+1, y_I-1, v+1)$	(x, x_I, y, y_I, v)	$\beta_3(y+1)(v+1)\Delta t + \beta_4(y+1)(y_I)\Delta t$
Production of virions from the infected cell	$(x, x_I+1, y, y_I+1, v-1)$	(x, x_I, y, y_I, v)	$\kappa N(x_I+1)\Delta t + \gamma M(y_I+1)\Delta t$
Death of virions	$(x, x_I, y, y_I, v+1)$	(x, x_I, y, y_I, v)	$\mu(v+1)\Delta t$

Assuming $z_2 = z_3 = z_4 = z_5 = 1$ and solving (5), we obtain the marginal partial generating function for healthy CD_4^+ cells:

$$\frac{\partial G(z_1, 1, 1, 1, 1; t)}{\partial t} = (z_1 - 1)\lambda_T G + (1 - z_1)\delta \frac{\partial G}{\partial z_1} + \beta_1 (e^{-\rho\tau} - z_1)\frac{\partial^2 G}{\partial z_1 \partial z_5} + \beta_2 (e^{-\rho\tau} - z_1)\frac{\partial^2 G}{\partial z_1 \partial z_4}. \quad (7)$$

Assuming $z_1 = z_3 = z_4 = z_5 = 1$ and solving (5), we obtain the marginal partial generating function for healthy Langerhans cells:

$$\frac{\partial G(1, z_2, 1, 1, 1; t)}{\partial t} = (z_2 - 1)\lambda_L G + (1 - z_2)\sigma \frac{\partial G}{\partial z_2} + \beta_3 (1 - z_2)\frac{\partial^2 G}{\partial z_2 \partial z_5} + \beta_4 (1 - z_2)\frac{\partial^2 G}{\partial z_2 \partial z_4}. \quad (8)$$

Assuming $z_1 = z_2 = z_4 = z_5 = 1$ and solving (5), we obtain the marginal partial generating function for infected CD_4^+ cells:

$$\frac{\partial G(1, 1, z_3, 1, 1; t)}{\partial t} = (N - z_3)\kappa \frac{\partial G}{\partial z_3} + \beta_1 (z_3 e^{-\rho\tau} - 1)\frac{\partial^2 G}{\partial z_1 \partial z_5} + \beta_2 (z_3 e^{-\rho\tau} - 1)\frac{\partial^2 G}{\partial z_1 \partial z_4}. \quad (9)$$

Assuming $z_1 = z_2 = z_3 = z_5 = 1$ and solving (5), we obtain the marginal partial generating function for infected Langerhans cells:

$$\frac{\partial G(1, 1, 1, z_4, 1; t)}{\partial t} = (M - z_4)\gamma \frac{\partial G}{\partial z_4} + \beta_3 (z_4 - 1)\frac{\partial^2 G}{\partial z_2 \partial z_5}. \quad (10)$$

Assuming $z_1 = z_2 = z_3 = z_4 = 1$ and solving (5), we obtain the marginal partial generating function for virus population:

$$\frac{\partial G(1, 1, 1, 1, z_5; t)}{\partial t} = (N z_5 - 1)\kappa \frac{\partial G}{\partial z_3} + (M z_5 - 1)\gamma \frac{\partial G}{\partial z_4} + (1 - z_5)\mu \frac{\partial G}{\partial z_5} + \beta_1 (e^{-\rho\tau} - z_5)\frac{\partial^2 G}{\partial z_1 \partial z_5} + \beta_3 (1 - z_5)\frac{\partial^2 G}{\partial z_2 \partial z_5}. \quad (11)$$

2.4. Numbers of Cells and the Virions.

As we know from probability generating function,

$$\frac{\partial G_x}{\partial z} = \sum_{x=0}^{\infty} x P_x(t) z^{x-1}. \quad (12)$$

Letting $z = 1$, we have

$$\left.\frac{\partial G_x}{\partial z}\right|_{z=1} = \sum_{x=0}^{\infty} x P_x(t) z^{x-1} = E[X]. \quad (13)$$

Differentiating the partial differential equation of the pgf G, we get the moments of $T(t)$, $L(t)$, $T_I(t)$, $L_I(t)$, and $V(t)$.

Differentiating (5) with respect to z_1 and setting $z = 1$, we have

$$\frac{\partial}{\partial t}E[T(t)] = \lambda_T - \delta E[T(t)] - \beta_1 E[T(t)V(t)] - \beta_2 E[T(t)L_I(t)]. \tag{14}$$

Differentiating (5) with respect to z_2 and setting $z = 1$, we have

$$\frac{\partial}{\partial t}E[L(t)] = \lambda_L - \sigma E[L(t)] - \beta_3 E[L(t)V(t)] - \beta_4 E[L(t)L_I(t)]. \tag{15}$$

Differentiating (5) with respect to z_3 and setting $z = 1$, we have

$$\frac{\partial}{\partial t}E[T_I(t)] = -\kappa E[T_I(t)] + \beta_1 e^{-\rho\tau}E[T(t)V(t)] + \beta_2 e^{-\rho\tau}E[T(t)L_I(t)]. \tag{16}$$

Differentiating (5) with respect to z_4 and setting $z = 1$, we have

$$\frac{\partial}{\partial t}E[L_I(t)] = -\gamma E[L_I(t)] + \beta_3 E[L(t)V(t)]. \tag{17}$$

Differentiating (5) with respect to z_5 and setting $z = 1$, we have

$$\frac{\partial}{\partial t}E[V(t)] = N\kappa E[T_I(t)] + M\gamma E[L_I(t)] - \mu E[V(t)] - \beta_1 E[T(t)V(t)] - \beta_3 E[L(t)V(t)]. \tag{18}$$

Therefore the moments of $T(t), L(t), T_I(t), L_I(t)$, and $V(t)$ from the pgf before introduction of treatment are

$$\begin{aligned}
\frac{d}{dt}E[T(t)] &= \lambda_T - \delta E[T(t)] - \beta_1 E[T(t)V(t)] - \beta_2 E[T(t)L_I(t)],\\
\frac{d}{dt}E[L(t)] &= \lambda_L - \sigma E[L(t)] - \beta_3 E[L(t)V(t)] - \beta_4 E[L(t)L_I(t)],\\
\frac{d}{dt}E[T_I(t)] &= -\kappa E[T_I(t)] + \beta_1 e^{-\rho\tau}E[T(t)V(t)] + \beta_2 e^{-\rho\tau}E[T(t)L_I(t)],\\
\frac{d}{dt}E[L_I(t)] &= -\gamma E[L_I(t)] + \beta_3 E[L(t)V(t)],\\
\frac{d}{dt}E[V(t)] &= N\kappa E[T_I(t)] + M\gamma E[L_I(t)] - \mu E[V(t)] - \beta_1 E[T(t)V(t)] - \beta_3 E[L(t)V(t)].
\end{aligned} \tag{19}$$

3. HIV Dynamics under Therapeutic Intervention

Now we introduce the treatment effect on the HIV-immune cell interaction. If we let $1-\alpha$ be the reverse transcriptase inhibitor and let $1-\omega$ be the protease inhibitor drug effects, then introducing these treatment effects on our model, we have the following forward Kolmogorov partial differential equations (Master equation) for $P_{x,x_I,y,y_I,v}(t)$:

$$\begin{aligned}
P'_{x,x_I,y,y_I,v}(t) &= -\{\lambda_T + \lambda_L + \delta x + \sigma y + (1-\alpha)\beta_1 x v + (1-\alpha)\beta_2 x y_I + (1-\alpha)\beta_3 y v + (1-\alpha)\beta_4 y y_I\\
&\quad + (1-\omega)\kappa x_I + (1-\omega)\gamma y_I + \mu v\} P_{x,x_I,y,y_I,v}(t)\\
&\quad + \lambda_T P_{x-1,x_I,y,y_I,v}(t) + \lambda_L P_{x,x_I,y-1,y_I,v}(t)\\
&\quad + \delta(x+1)P_{x+1,x_I,y,y_I,v}(t) + \sigma(y+1)P_{x,x_I,y+1,y_I,v}(t)\\
&\quad + \{\beta_1(x+1)(v+1) + \beta_2(x+1)(y_I)\}\\
&\quad \times (1-\alpha)e^{-\rho\tau}P_{x+1,x_I-1,y,y_I,v+1}(t)\\
&\quad + \{\beta_3(y+1)(v+1) + \beta_4(y+1)(y_I)\}\\
&\quad \times (1-\alpha)P_{x,x_I,y+1,y_I-1,v+1}(t)\\
&\quad + (1-\omega)\kappa N(x_I+1)P_{x,x_I+1,y,y_I,v-1}(t)\\
&\quad + (1-\omega)\gamma M(y_I+1)P_{x,x_I,y,y_I+1,v-1}(t)\\
&\quad + \mu(v+1)P_{x,x_I,y,y_I,v+1}(t),
\end{aligned} \tag{20}$$

with initial condition

$$P'_{0,0,0,0,0}(t) = -(\lambda_T + \lambda_L)P_{0,0,0,0,0}(t) + \delta P_{1,0,0,0,0}(t) + \sigma P_{0,0,1,0,0}(t) + \mu P_{0,0,0,0,1}(t). \tag{21}$$

Solving the Master equation using generating function, the Lagrange partial differential equation becomes

$$\begin{aligned}
\frac{\partial G}{\partial t} &= \{(z_1-1)\lambda_T + (z_2-1)\lambda_L\}G\\
&\quad + (1-z_1)\delta\frac{\partial G}{\partial z_1} + (1-z_2)\sigma\frac{\partial G}{\partial z_2}\\
&\quad + (Nz_5 - z_3)(1-\omega)\kappa\frac{\partial G}{\partial z_3}\\
&\quad + (Mz_5 - z_4)(1-\omega)\gamma\frac{\partial G}{\partial z_4}\\
&\quad + (1-z_5)\mu\frac{\partial G}{\partial z_5} + (1-\alpha)\beta_1(z_3 e^{-\rho\tau} - z_1 z_5)\frac{\partial^2 G}{\partial z_1 \partial z_5}
\end{aligned}$$

Table 4: Parameters for the stochastic model.

Parameter	Parameter description	Estimate
$(1-\alpha)$	The reverse transcriptase inhibitor drug effect	0.5
$(1-\omega)$	The protease inhibitor drug effect	0.5
λ_T	Rate of production of healthy CD_4^+ cells per unit time	1.5 $\text{day}^{-1}\text{mm}^{-3}$
λ_L	Rate of production of LCs per unit time	5 $\text{day}^{-1}\text{mm}^{-3}$
δ	Death rate of healthy CD_4^+ cells	0.001 day^{-1}
σ	Death rate of healthy LCs	0.005 day^{-1}
β_1	Infection between uninfected CD_4^+ cells and free virus particles	0.00024 $\text{day}^{-1}\text{mm}^{-3}$
β_2	Infection between uninfected CD_4^+ cells and HIV infected LCs	0.00004 $\text{day}^{-1}\text{mm}^{-3}$
β_3	Infection between uninfected LCs and free virus particles	0.00045 $\text{day}^{-1}\text{mm}^{-3}$
β_4	Infection between uninfected LCs and HIV infected LCs	0.000015 $\text{day}^{-1}\text{mm}^{-3}$
κ	Death rate of infected CD_4^+ cells	0.24 day^{-1}
κ^*	Viral induced death of infected CD_4^+ cells	0.239 day^{-1}
ρ	Death rate of infected but not yet virus producing cell	0.24 day^{-1}
τ	Intracellular delay time	0.5
γ	Death rate of infected LCs	0.03 day^{-1}
γ^*	Viral induced death rate of infected LCs	0.025 day^{-1}
μ	Death rate of infective virus particles	2.4 day^{-1}
N	Viral production rate by infected CD_4^+ cells	90 day^{-1}
M	Viral production rate by infected LCs	62.5 day^{-1}

Where $\kappa = \kappa^* + \delta$ and $\gamma = \gamma^* + \sigma$, values adapted from [13, 14].

Table 5: Variables for the stochastic model.

Variable	Description	Initial condition
$T(t)$	The concentration of healthy (susceptible) CD_4^+ cells at time t	1000 cells mm^{-3}
$T_I(t)$	The concentration of infected CD_4^+ cells at time t	0 cells mm^{-3}
$L(t)$	The concentration of healthy (susceptible) Langerhans cells at time t	1000 cells mm^{-3}
$L_I(t)$	The concentration of infected Langerhans cells at time t	0 cells mm^{-3}
$V(t)$	The concentration of virus particles at time t	0.001 virion mm^{-3}

$$
\begin{aligned}
&+ (1-\alpha)\beta_2\left(z_3 e^{-\rho\tau} - z_1 z_4\right)\frac{\partial^2 G}{\partial z_1 \partial z_4} \\
&+ (1-\alpha)\beta_3\left(z_4 - z_2 z_5\right)\frac{\partial^2 G}{\partial z_2 \partial z_5} \\
&+ (1-\alpha)\beta_4\left(z_4 - z_2 z_4\right)\frac{\partial^2 G}{\partial z_2 \partial z_4}.
\end{aligned}
\tag{22}
$$

Solving the pgf of the in-host HIV dynamics with therapeutic intervention, we have the moments of $T(t), L(t), T_I(t), L_I(t)$, and $V(t)$:

$$
\begin{aligned}
\frac{d}{dt}E[T(t)] &= \lambda_T - \delta E[T(t)] - (1-\alpha)\beta_1 E[T(t)V(t)] \\
&\quad - (1-\alpha)\beta_2 E[T(t)L_I(t)], \\
\frac{d}{dt}E[L(t)] &= \lambda_L - \sigma E[L(t)] - (1-\alpha)\beta_3 E[L(t)V(t)] \\
&\quad - (1-\alpha)\beta_4 E[L(t)L_I(t)], \\
\frac{d}{dt}E[T_I(t)] &= -\kappa E[T_I(t)] + (1-\alpha)\beta_1 e^{-\rho\tau} E[T(t)V(t)] \\
&\quad + (1-\alpha)\beta_2 e^{-\rho\tau} E[T(t)L_I(t)], \\
\frac{d}{dt}E[L_I(t)] &= -\gamma E[L_I(t)] + (1-\alpha)\beta_3 E[L(t)V(t)], \\
\frac{d}{dt}E[V(t)] &= (1-\omega)N\kappa E[T_I(t)] + (1-\omega)M\gamma E[L_I(t)] \\
&\quad - \mu E[V(t)] - (1-\alpha)\beta_1 E[T(t)V(t)] \\
&\quad - (1-\alpha)\beta_3 E[L(t)V(t)].
\end{aligned}
\tag{23}
$$

3.1. Simulation of the Models

3.1.1. Variables and Parameter Values. The initial variable values and parameter values for the model are described in Tables 4 and 5.

Using the parameter values and initial conditions defined in Tables 4 and 5, we illustrate the general dynamics of the

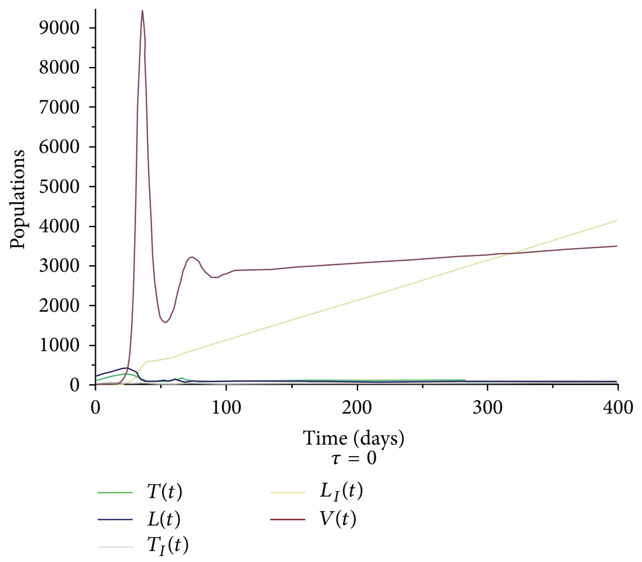


FIGURE 2: Cells and HIV population dynamics before therapeutic intervention. The population dynamics are shown when $\tau = 0$.

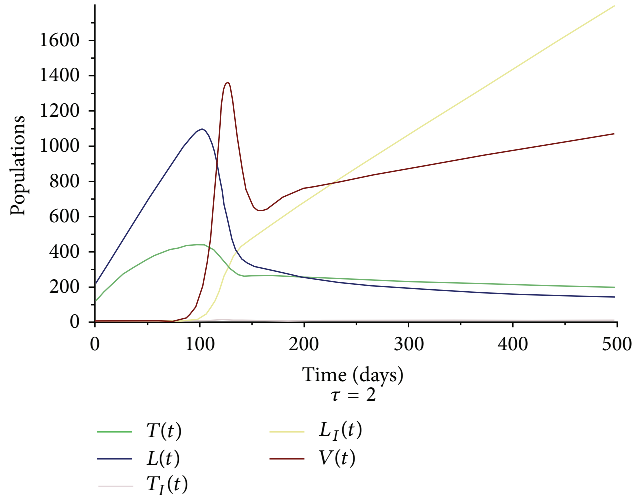


FIGURE 3: Cells and HIV population dynamics before therapeutic intervention. The population dynamics are shown when $\tau = 2$.

CD_4^+ T cells and HIV virus by performing sensitivity analysis on the effect of intracellular delay and drug efficacy.

From the simulations in Figures 2 and 3, it is clear that, in the primary stage of HIV infection, drastic decrease in the levels of healthy immune cells occurs but the number of free virions and infected LCs increases with time.

With 60% drug efficacy, the virus population drops and stabilizes after some time t, but the number of infected LCs increases with time; see Figures 4 and 5.

With an increase in efficacy for the current HIV drugs, a patient will have low, undetectable viral load levels, but the population of infected LCs is still at large; see Figures 6 and 7.

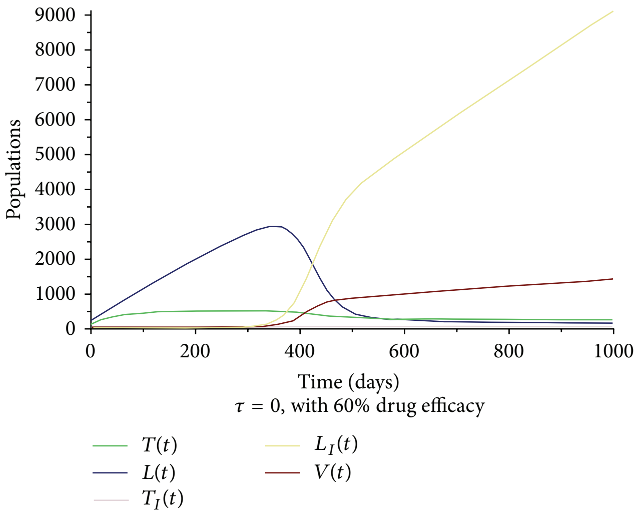


FIGURE 4: Cells and HIV population dynamics under therapeutic intervention. The population dynamics are shown with drug efficacy of 60% and when $\tau = 0$.

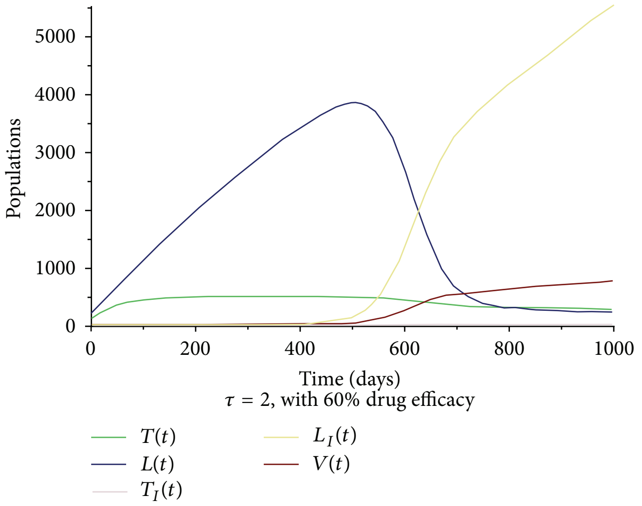


FIGURE 5: Cells and HIV population dynamics under therapeutic intervention. The population dynamics are shown with drug efficacy of 60% and when $\tau = 2$.

4. Discussion

In this study, we derived and analysed a stochastic model describing the dynamics of HIV, CD_4^+ T cells, and LCs interactions under therapeutic intervention *in vivo*. This model included dynamics of five compartments—the number of healthy CD_4^+ cells, the number of infected CD_4^+ cells, the number of healthy Langerhans cells, the number of infected Langerhans cells, and the HIV virions. The model describes HIV infection before and during therapy. We derived equations for the joint probability generating function of the numbers of healthy immune cells, the HIV infected immune cells, and the free HIV particles at any time t and obtained the moment structures of the healthy immune cells, infected immune cells, and the virus particles over time

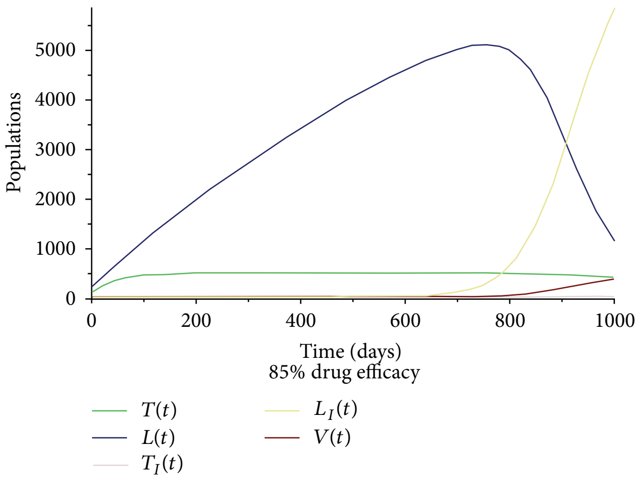


Figure 6: Cells and HIV population dynamics under therapeutic intervention. The population dynamics are shown with drug efficacy of 85%.

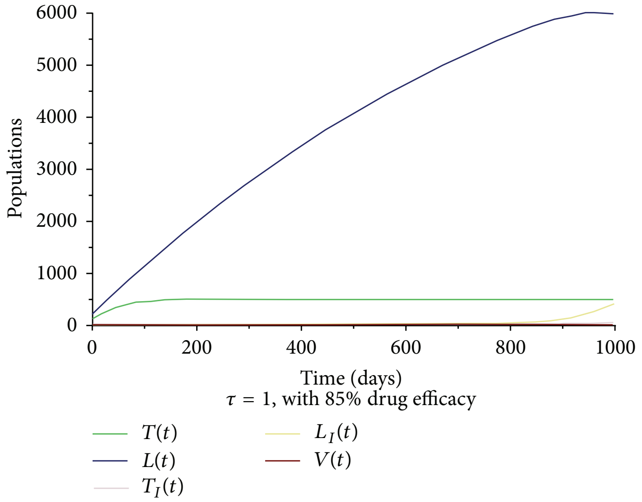


Figure 7: Cells and HIV population dynamics under therapeutic intervention. The population dynamics are shown with drug efficacy of 85% and when $\tau = 1$.

t. We simulated the mean number of the healthy immune cells, the infected immune cells, and the virus particles before and after combined therapeutic treatment at any time t.

Our analysis shows that eradication of HIV is not possible without clearance of latently infected Langerhans cells. Therefore, understanding HIV therapeutic treatment dynamics *in vivo* is critical to eliminate the virus, which shows that LCs are important in determining the disease progression. Our model analysis suggests that therapies should be developed to block the binding of HIV onto Langerhans cells. Such therapies will have the potential to dramatically accelerate viral decay. We conclude that, to control the concentrations of the virus and the infected cells in HIV infected person, a strategy should aim to improve the drug efficacy; hence the efficacy of the protease inhibitor and the reverse transcriptase inhibitor and also the intracellular delay play crucial role in preventing the progression of HIV [13]. These findings illustrate the role of LCs as a central hub of interaction and information exchange during HIV infection. Our model produces interesting feature that classification of HIV disease states should not be based on CD_4^+ cells as the only immune cells infected by the virus, but the most reliable HIV state classification criteria should be classification using clinical signs (the CDC/WHO classification).

In our work, the dynamics of mutant virus were not considered and also our study only included dynamics of only five compartments (healthy immune cells, infected immune cells, and free virus particles ignoring the latency of infected immune cells) of which extensions are recommended for further extensive research. In a follow-up work, we intend to obtain real data in order to test the efficacy of our models as we have done here with parameter values from the literature.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] C. M. Coleman and L. Wu, "HIV interactions with monocytes and dendritic cells: viral latency and reservoirs," *Retrovirology*, vol. 6, no. 1, article 51, 2009.

[2] C. St. Gelais, C. M. Coleman, J.-H. Wang, and L. Wu, "HIV-1 nef enhances dendritic cell-mediated viral transmission to CD4$^+$ T cells and promotes T-cell activation," *PLoS ONE*, vol. 7, no. 3, Article ID e34521, 2012.

[3] I. B. Hogue, S. H. Bajaria, B. A. Fallert, S. Qin, T. A. Reinhart, and D. E. Kirschner, "The dual role of dendritic cells in the immune response to human immunodeficiency virus type 1 infection," *Journal of General Virology*, vol. 89, no. 9, pp. 2228–2239, 2008.

[4] E. Ramazzotti, A. Marconi, M. C. Re et al., "In vitro infection of human epidermal Langerhans' cells with HIV-1," *Immunology*, vol. 85, no. 1, pp. 94–98, 1995.

[5] J. Paul Zoeteweij and A. Blauvelt, "HIV-dendritic cell interactions promote efficient viral infection of T cells," *Journal of Biomedical Science*, vol. 5, no. 4, pp. 253–259, 1998.

[6] D. Schmitt and C. Dezutter-Dambuyant, "Epidermal and mucosal dendritic cells and HIV1 infection," *Pathology Research and Practice*, vol. 190, no. 9-10, pp. 955–959, 1994.

[7] C. Dezutter-Dambuyant, "In vivo and in vitro infection of human langerhans cells by HIV-1," in *Dendritic Cells in Fundamental and Clinical Immunology*, J. Banchereau and D. Schmitt, Eds., vol. 378, pp. 447–452, Springer, New York, NY, USA, 1995.

[8] N. K. Saksena, B. Wang, L. Zhou, M. Soedjono, Y. Shwen Ho, and V. Conceicao, "HIV reservoirs in vivo and new strategies for possible eradication of HIV from the reservoir sites," *HIV/AIDS*, vol. 2, pp. 103–122, 2010.

[9] W. S. Hlavacek, N. I. Stilianakis, and A. S. Perelson, "Influence of follicular dendritic cells on HIV dynamics," *Philosophical Transactions of the Royal Society B*, vol. 355, no. 1400, pp. 1051–1058, 2000.

[10] D. McDonald, "Dendritic cells and HIV-1 trans-infection," *Viruses*, vol. 2, no. 8, pp. 1704–1717, 2010.

[11] N. Romani, P. M. Brunner, and G. Stingl, “Changing views of the role of langerhans cells,” *Journal of Investigative Dermatology*, vol. 132, no. 3, pp. 872–881, 2012.

[12] C. R. Rinaldo, “HIV-1 trans infection of CD4$^+$ t cells by professional antigen presenting cells,” *Scientifica*, vol. 2013, Article ID 164203, 30 pages, 2013.

[13] W. R. Mbogo, L. S. Luboobi, and J. W. Odhiambo, “Stochastic model for in-host HIV dynamics with therapeutic intervention,” *ISRN Biomathematics*, vol. 2013, Article ID 103708, 11 pages, 2013.

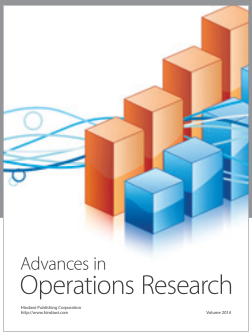
[14] T. Mugwagwa, *Mathematical models of coreceptor usage and a dendritic cell-based vaccine during HIV-1 infection [Ph.D. thesis]*, University of Cape Town, 2005.

[15] J.-F. Arrighi, M. Pion, E. Garcia et al., “DC-SIGN-mediated infectious synapse formation enhances X4 HIV-1 transmission from dendritic cells to T cells,” *Journal of Experimental Medicine*, vol. 200, no. 10, pp. 1279–1288, 2004.

[16] C. Chougnet and S. Gessani, “Role of gp120 in dendritic cell dysfunction in HIV infection,” *Journal of Leukocyte Biology*, vol. 80, no. 5, pp. 994–1000, 2006.

[17] A. Granelli-Piperno, A. Golebiowska, C. Trumpfheller, F. P. Siegal, and R. M. Steinman, “HIV-1-infected monocyte-derived dendritic cells do not undergo maturation but can elicit IL-10 production and T cell regulation,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 20, pp. 7669–7674, 2004.

[18] W. R. Mbogo, L. S. Luboobi, and J. W. Odhiambo, “Mathematical model for HIV and CD4$^+$ cells dynamics in vivo,” *International Electronic Journal of Pure and Applied Mathematics*, vol. 6, no. 2, pp. 83–103, 2013.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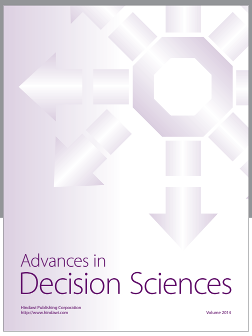
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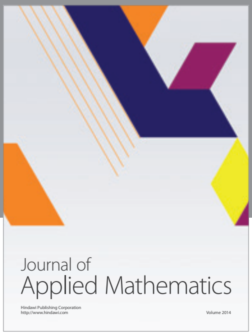
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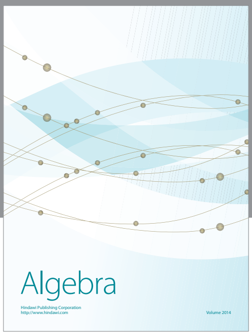
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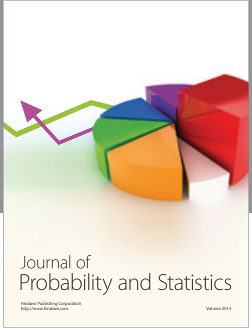
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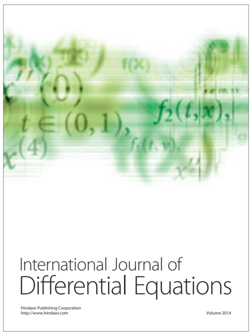
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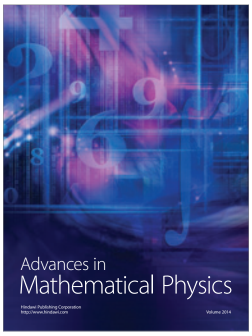
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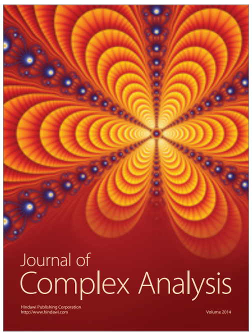
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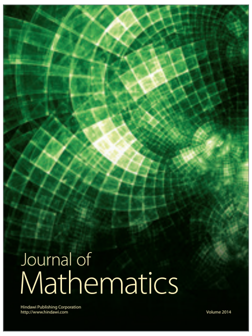
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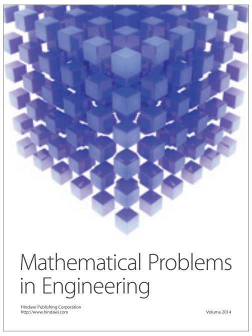
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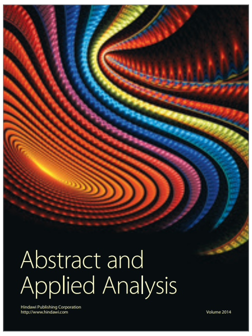
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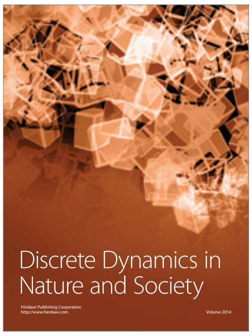
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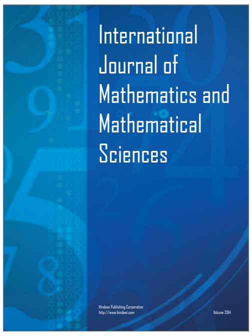
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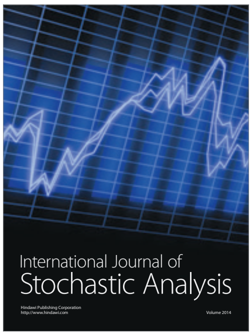
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