Available online at www.sciencedirect.com
ScienceDirect
J. Math. Anal. Appl. 341 (2008) 1084–1101
Journal of MATHEMATICAL ANALYSIS AND APPLICATIONS
www.elsevier.com/locate/jmaa

A stochastic model for internal HIV dynamics

Nirav Dalal, David Greenhalgh *, Xuerong Mao

Department of Statistics and Modelling Science, University of Strathclyde, Glasgow G1 1XH, UK

Received 20 October 2006

Available online 12 November 2007

Submitted by J.J. Nieto

Abstract

In this paper we analyse a stochastic model representing HIV internal virus dynamics. The stochasticity in the model is introduced by parameter perturbation which is a standard technique in stochastic population modelling. We show that the model established in this paper possesses non-negative solutions as this is essential in any population dynamics model. We also carry out analysis on the asymptotic behaviour of the model. We approximate one of the variables by a mean reverting process and find out the mean and variance of this process. Numerical simulations conclude the paper.
© 2007 Elsevier Inc. All rights reserved.

Keywords: HIV virus dynamics; Brownian motion; Stochastic differential equation; Itô's formula; Asymptotic behaviour; Mean reverting process

1. Introduction

Since its discovery in 1981, HIV has spread relentlessly throughout the world and now is a major epidemic worldwide. HIV spreads by attacking the immune system, in particular by depleting the CD4 cells. The pathogenesis of HIV infection is a function of the virus life cycle, the host cellular environment, and quantity of virus in the infected individual. Factors such as age or genetic differences among individuals, the level of virulence of an individual strain of virus, and co-infection with other microbes may influence the rate and severity of disease progression.

Cells with CD4 receptors at the site of HIV entry become infected and viral replication begins within them. The infected cells can then release virions or infected cells can undergo lysis to release new virions, which can then infect additional cells. CD4 cells, the primary targets of HIV, become infected as they encounter HIV. Active replication of HIV occurs at all stages of the infection. Over a period of years, even when little virus is detectable in the blood, significant amounts of virus accumulate within infected cells. This interaction between the virus and the immune system is called HIV internal viral dynamics. In this paper we will formulate a stochastic model for this host virus interaction.

Modelling the interaction between HIV-1 virus and CD4 cells has been a major area of research for many years [4,10,11]. Mathematical models have come to play an important part in biological systems. Mathematics makes it possible to make predictions about the behaviour of the system. We try to obtain some analytical results for the

* Corresponding author.
E-mail address: david@stams.strath.ac.uk (D. Greenhalgh).

0022-247X/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.jmaa.2007.11.005

stochastic model posed in this paper. In particular we derive expressions for the expected value and the variance of the limit process.

There are real benefits to be gained in using stochastic rather than deterministic models. Real life is stochastic rather than deterministic, particularly when modelling biological phenomena such as internal HIV viral dynamics. This is because different cells and infective virus particles reacting in the same environment can often give different results. In this paper we model the effect of environmental stochasticity on some of the model parameters. Stochastic models produce more useful output than deterministic models as by running a stochastic model many times we can build up a distribution of the predicted outcomes, for example the number of infected cells at time t, whilst a deterministic model will just give a single predicted value. Having a distribution for the predicted outcomes is more versatile as it helps us examine practically important essentially stochastic quantities, for example the variance of the number of infective virus particles at a given time and the probability that the infective virus particles have died out at a given time, which cannot be examined using deterministic models. Even quantities such as the expected values of the number of cells can be more accurately modelled using stochastic models because they include the effect of random variation on these quantities which deterministic models cannot.

Other work by Dalal, Greenhalgh and Mao [9] introduces stochasticity into a model of AIDS and condom use via the technique of parameter perturbation which is standard in stochastic population modelling. They show that the model established in the paper possesses non-negative solutions as desired in any population dynamics. They also carried out a detailed analysis on asymptotic stability both in probability one and in pth moment. Our results reveal that a certain type of stochastic perturbation may help stabilise the system.

Abell, Braselton and Braselton [1] incorporate basic genetics into an AIDS model. They illustrate that if a homozygote is immune to the disease or resistant to the disease, the corresponding allele goes to fixation. On the other hand if the heterozygote is immune to the disease or is resistant to the effects of the disease, polymorphism usually occurs. Li and Ma [16] study asymptotic properties of an HIV-1 infection model with a time delay. Based on some important biological meanings, a class of more general HIV-1 infection models with a time delay is proposed in the paper. In the HIV-1 infection model a time delay is used to describe the time between infection of uninfected target cells and the emission of viral particles as proposed by Herz et al. [14]. Then the effect of time delay on the stability of the equilibria of the HIV-1 infection model has been studied and sufficient criteria for the local asymptotic stability of the infected equilibrium and global asymptotic stability of the viral-free equilibrium are given.

Many mathematical models have been developed to describe the viral dynamics of HIV-1, mostly using a system of ordinary differential equations. Perelson et al. [24] tried to estimate the length of the life cycle of the virus. Korthals Altes et al. [15] concentrated on the question of whether it was advisable to stimulate CD4 cell response. They found that only when the virus has a low basic reproductive number does the number of CD4 cells at the moment of infection influence the outcome of infection. Di Mascio et al. [10] provided a statistical characterisation of transient viraemia observed in 123 patients, suggesting that patients have different tendencies to show transient viraemia during the period of viral load suppression. Ding and Wu [11] modelled the effect of Reverse Transcriptase Inhibitor drugs as inhibition rates of cell infection and Protease Inhibitor drugs as inhibition rates of infectious virus production based on the biological mechanisms of these two different types of drugs. They showed that the two viral decay rates are monotone functions of the treatment effects of these antiviral therapies.

We start the paper by proving the positivity of the solutions which is a very important property for any model on population dynamics which uses stochastic differential equations. We then focus on the stability aspect of the three variables in question. We show that under certain conditions the number of infected cells and virus particles will both almost surely tend to zero (their disease free equilibrium value). We introduce a mean reverting process and show that the number of healthy cells tends in probability to this mean reverting process. Hence the number of healthy cells is stable in distribution. We then give details of the parameters of the mean reverting process. Finally we present a section on simulations of the system and end the paper with our conclusions.

2. Deterministic model

This process of HIV-1 pathogenesis can be slowed down or reversed to a certain extent by Highly Active Antiretroviral Treatment (HAART). Primarily HAART inhibits the process of virus particle formation. This keeps the viral load down and in turn increases the quantity of CD4 cells. The model we are going to study is a stochastic model of viral dynamics including the effect of HAART.

Verotta and Schaedeli [27] used nonlinear models to present the virus dynamics of HIV-1 which can incorporate different factors associated with resurgence. They first gave a nonlinear model of HIV-1 dynamics, then included drug exposure, compliance to treatment and insurgence of resistant HIV-1 strains. They also showed the application of the models using real AIDS clinical trial data involving patients treated with a combination of antiretroviral drugs.

Nelson and Perelson [21] were of the opinion that models that include intracellular delays are more accurate representations of the biology and change the estimated values of kinetic parameters when compared to models without delays. They developed and analysed a set of models that included intracellular delays, combination antiretroviral therapy, and the dynamics of both infected and uninfected T cells. They showed that for less than perfect drug effect, the value of the death rate of productively infected cells is increased when data is fitted with delay models compared to the values estimated with a non-delay model. They also provided some general results on the stability of the system.

Very recently Ciupe et al. [7] discussed the dynamics of HIV-1 infection consisting of three distinct phases starting with primary infection, then latency and finally AIDS or drug therapy. In this paper the dynamics of primary infection and the beginning of latency was modelled. They showed that allowing for time delays in the model better predicts viral load data when compared to models with no time delays. They also found that the model of primary infection predicts the turnover rates for productively infected T cells and viral totals to be much longer than those observed from patients receiving antiviral drug therapy. However, they also showed that with the data available the results are highly sensitive to the chosen model. They compared the results using analysis and Monte Carlo techniques for three different models and showed how each predicts rather dramatic differences between the fitted parameters.

We propose the following three-dimensional model to describe the viral dynamics in the presence of HIV-1 infection and HAART:

$$\frac{dx_1(t)}{dt} = \lambda - \delta x_1(t) - (1-\gamma)\beta x_1(t)x_3(t),$$

$$\frac{dx_2(t)}{dt} = (1-\gamma)\beta x_1(t)x_3(t) - ax_2(t),$$

and

$$\frac{dx_3(t)}{dt} = (1-\eta)Nax_2(t) - ux_3(t) - (1-\gamma)\beta x_1(t)x_3(t)$$

with suitable initial conditions. This model captures mathematically the viral dynamics of HIV-1 virus interacting with CD4 cells. The model is represented diagrammatically by Fig. 1.

HAART is generally a combination of reverse transcriptase inhibitor (RTI) drugs and protease inhibitor (PI) drugs. RTI drugs are designed to prevent the conversion of HIV RNA to DNA in early stages of HIV replication. Thus RTI drugs block conversion of uninfected cells to infected cells. PI drugs are designed to intervene in the last stage of the virus replication cycle to prevent HIV from being properly assembled, and thus cause the newly produced virus to be noninfectious [11]. The variables and parameters in the model are described as follows:

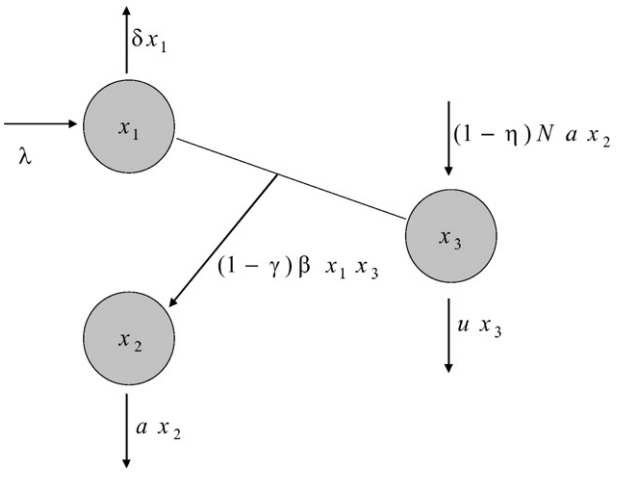


Fig. 1. Box diagram representing cell and virus dynamics.

$x_1(t)$	is the concentration of uninfected cells;
$x_2(t)$	is the concentration of infected cells;
$x_3(t)$	is the concentration of virus particles;
$(1-\gamma)$	is the reverse transcriptase inhibitor drug effect;
$(1-\eta)$	is the protease inhibitor drug effect;
λ	is the total rate of production of healthy cells per unit time;
δ	is the per capita death rate of healthy cells;
β	is the transmission coefficient between uninfected cells and infective virus particles;
a	is the per capita death rate of infected cells;
N	is the average number of infective virus particles produced by an infected cell in the absence of HAART during its entire infectious lifetime;
u	is the per capita death rate of infective virus particles.

Note that when a single infective virus particle infects a single uninfected cell the virus particle is absorbed into the uninfected cell and effectively dies. Hence the term $(1-\gamma)\beta x_1 x_3$ appears in all the three equations. It is clear that the above model has a unique disease-free equilibrium given by $(\lambda/\delta_1, 0, 0)$. Each newly infected cell entering the disease-free equilibrium remains infected for time $(1/a)$ and during this time produces $(1-\eta)N$ infective virus particles. As an approximation assuming that the system is still near the disease-free equilibrium each infective virus particle survives for time $(u + (1-\gamma)\beta\lambda/\delta)$ and during this time infects

$$\frac{(1-\gamma)\beta\frac{\lambda}{\delta}}{(u+(1-\gamma)\beta\frac{\lambda}{\delta})} = \frac{(1-\gamma)\beta\lambda}{\delta u + (1-\gamma)\beta\lambda}$$

cells. R_0, the basic reproduction number, is defined as the expected number of secondary infected cells caused by a single infected cell entering the disease-free population at equilibrium. Here a secondary infected cell is a cell which is infected by an infective virus particle which is produced by the initial infected cell. Hence

$$R_0 = \frac{(1-\gamma)\beta\lambda N(1-\eta)}{(\delta u + \beta\lambda(1-\gamma))}.$$

R_0 can also be interpreted as the expected number of secondary infected virus particles caused by a single infected virus particle entering the disease-free population at equilibrium. Here a secondary infective virus particle is an infective virus particle produced by an infected cell which was infected by the original infective virus particle. We obtain the same expression for R_0.

The deterministic model has been analysed by Tuckwell and Wan [26]. They show that if $R_0 \leqslant 1$ then the disease-free equilibrium is the unique equilibrium and if $R_0 > 1$ then as well as the disease-free equilibrium there is a unique endemic equilibrium given by

$$x_1^* = \frac{u}{\beta(1-\gamma)[N(1-\eta)-1]},$$
$$x_2^* = \frac{\beta\lambda(1-\gamma)N(1-\eta) - \beta\lambda(1-\gamma) - \delta u}{a\beta(1-\gamma)(N(1-\eta)-1)},$$
$$x_3^* = \frac{\beta\lambda(1-\gamma)N(1-\eta) - \beta\lambda(1-\gamma) - \delta u}{(1-\gamma)\beta u}.$$

Moreover if $R_0 < 1$ the disease-free equilibrium is locally asymptotically stable, whilst if $R_0 > 1$ then the disease-free equilibrium is unstable whilst the unique endemic equilibrium is locally asymptotically stable. Thus if $R_0 < 1$ we expect the number of infected cells and infected virus particles to die out and the number of uninfected cells to approach λ/δ, whilst if $R_0 > 1$ we expect the number of uninfected cells, infected cells and infective virus particles to approach their unique endemic equilibrium values.

Perelson et al. [24] studied a simplified version of our deterministic model. They assume that the number of uninfected cells is constant. They later introduce drug treatment and fit the model to data. Bonhoeffer et al. [4] analyse a simplified version of our deterministic model where the term $(1-\gamma)\beta x_1(t)x_3(t)$ is neglected as an approximation.

They do not include any stochastic effects. They show that there is a basic reproduction number R_0 which determines the behaviour of the system. For $R_0 \leqslant 1$ there is a unique disease-free equilibrium which is locally asymptotically stable but for $R_0 > 1$ there is a unique endemic equilibrium. They later modify the basic model to include the effect of resistance. Di Mascio et al. [10] take the simple deterministic model of Bonhoeffer et al. and modify it to introduce the effect of HAART in a similar way as we have done. They later discuss another model and fitting their models to data. Nelson and Perelson [21] outline the basic model discussed by Bonhoeffer et al. [4]. They discuss modification of this basic model to summarize the effects of drug therapy on virus concentration and introduce a time delay into the model. The model is then fitted to data.

All of the above models are deterministic models and do not introduce stochastic effects. The other models discussed in our literature review such as Ding and Wu [11], Korthals Altes et al. [15], Ciupe et al. [7] and Verotta and Schaedeli [27] have similarities with our model but introduce extra or different variables such as two types of infected cells, two types of infective virus particles or CD8 cells.

3. Stochastic model derivation

There are a range of mechanisms through which CD4 cell death takes place. This includes syncytium formation and apoptosis among other things [20]. The clearance rate of virions can be caused by a variety of factors including binding and entry into cells and immune elimination [24]. Since both the death rates of the cells and the virus are affected by many complicated biological phenomena we think that there is randomness involved in these death rates.

For a number of years, many scientists have believed that HIV depletes its primary target, CD4+ T cells, by blocking new T-cell production. On the other hand some studies have challenged that point of view, showing that HIV does not block such production but instead accelerates the division of existing T cells. Following the initiation of highly active antiretroviral therapy, or HAART, there is an immediate drop in the rate of T-cell production accompanied by an even greater decrease in the rate of CD4 T-cell death. Thus, the increases in CD4+ T-cell counts seen following HAART are not due to a boost in the production of new T cells. Rather, they are caused by a slowdown in the loss of existing T cells. This contradictory view gives us reason to believe that we can input randomness in the death rates of CD4 cells.

Taking these factors into account we introduce randomness into the model by replacing the parameters δ, a and u by $\delta \to \delta + \sigma_1 \dot{B}_1(t)$, $a \to a + \sigma_1 \dot{B}_1(t)$ and $u \to u + \sigma_2 \dot{B}_2(t)$. This is only a first step in introducing stochasticity into the model. Ideally we would also like to introduce stochastic environmental variation into the other parameters such as the transmission coefficient β and λ, the total rate of production of healthy cells per unit time, but to do this would make the analysis much too difficult.

Hence we get the following system of stochastic differential equations:

$$dx_1(t) = \big(\lambda - \delta x_1(t) - (1-\gamma)\beta x_1(t)x_3(t)\big)\,dt - \sigma_1 x_1(t)\,dB_1(t), \tag{1}$$

$$dx_2(t) = \big((1-\gamma)\beta x_1(t)x_3(t) - a x_2(t)\big)\,dt - \sigma_1 x_2(t)\,dB_1(t), \tag{2}$$

and

$$dx_3(t) = \big((1-\eta)N a x_2(t) - u x_3(t) - (1-\gamma)\beta x_1(t)x_3(t)\big)\,dt - \sigma_2 x_3(t)\,dB_2(t) \tag{3}$$

with suitable initial conditions.

Here $B_1(t)$ and $B_2(t)$ are independent standard Brownian motions. When there is randomness in parameters such as the disease death rate it is a standard technique to introduce environmental noise into the parameters in this way [3,5,13,18,19]. Note that the intensity of the noise σ and the Brownian motion $B(t)$ are the same for uninfected and infected CD4 cells, but different for CD4 cells and virus particles. This is because whilst the biological factors affecting the death rates of infected and uninfected CD4 cells can be expected to be very similar, different biological factors affect CD4 cells and virus particles.

Hence although in the absence of detailed biological data it is possible that the intensity of the noise σ and the Brownian motion $B(t)$ are different for uninfected and infected CD4 cells it is plausible as a first simplifying approximation to assume that these are the same. As CD4 cells and virus particles are much more different biological entities it seems much more possible that both σ and $B(t)$ are different between CD4 cells and infective virus particles.

Note that the situation with no infected cells and no infective virus particles present

$$(x_1, x_2, x_3) = (\lambda/\delta, 0, 0)$$

is an equilibrium point in the deterministic model but not for the stochastic model. In the stochastic model the last two co-ordinates $(x_2, x_3) = (0, 0)$ are still a stochastic equilibrium, but the situation is changed for the first co-ordinate of the process which we shall see later varies stochastically around the value λ/δ.

4. Non-negative solutions

It is important that we do not have to worry about negative values when dealing with a model of population dynamics is concerned. Hence we first prove the positivity of the solutions.

In this paper, unless otherwise specified, we let $(\Omega, \mathcal{F}, P)$ be a complete probability space with a filtration $\{\mathcal{F}_t\}_{t\geqslant 0}$ satisfying the usual conditions (i.e. it is increasing and right continuous while $\mathcal{F}_0$ contains all P-null sets). Let $B(t)$ be the one-dimensional Brownian motion defined on this probability space. Also let $R^3_{++} = \{x \in R^3\colon\ x_i > 0 \text{ for all } 1 \leqslant i \leqslant 3\}$ and let $x(t) = (x_1(t), x_2(t), x_3(t))$.

Before proving the main theorem we put forward a lemma.

Lemma 4.1. *The following inequality holds*

$$u \leqslant 2\big(u + 1 - \log(u)\big) - (4 - 2\log 2), \quad \forall u > 0.$$

Proof. Define, for $u > 0$,

$$f(u) = u + 2 - 2\log(u).$$

$f(u)$ has a minimum at $u = 2$. The result follows. □

We now prove the main theorem.

Theorem 4.1. *Assume that $0 < \gamma$, $\eta < 1$ and that δ, λ, a, u, N and β are positive real numbers. Then for any initial value $x_0 \in R^3_{++}$, there is a unique solution $x(t)$ to Eqs.* (1)–(3) *on $t \geqslant 0$ and the solution will remain in R^3_{++} with probability* 1, *namely $x(t) \in R^3_{++}$ for all $t \geqslant 0$ almost surely.*

Proof. Since the coefficients of the equation are locally Lipschitz continuous, for any given initial value $x_0 \in R^3_{++}$ there is a unique local solution $x(t)$ on $t \in [0, \tau_e)$, where τ_e is the explosion time [2,12]. To show this solution is global, we need to show that $\tau_e = \infty$ a.s. Let $k_0 \geqslant 0$ be sufficiently large so that every component of x_0 lies within the interval $[1/k_0, k_0]$. For each integer $k \geqslant k_0$, define the stopping time

$$\tau_k = \inf\big\{t \in [0, \tau_e)\colon\ x_i(t) \notin (1/k, k) \text{ for some } i,\ 1 \leqslant i \leqslant 3\big\},$$

where throughout this paper we set $\inf \emptyset = \infty$ (as usual $\emptyset$ denotes the empty set). Clearly, τ_k is increasing as $k \to \infty$. Set $\tau_\infty = \lim_{k\to\infty} \tau_k$, whence $\tau_\infty \leqslant \tau_e$ a.s. If we can show that $\tau_\infty = \infty$ a.s. then $\tau_e = \infty$ and $x(t) \in R^3_{++}$ a.s. for all $t \geqslant 0$. In other words, to complete the proof all we need to show is that $\tau_\infty = \infty$ a.s. For if this statement is false, then there is a pair of constants $T > 0$ and $\epsilon \in (0, 1)$ such that

$$P\{\tau_\infty \leqslant T\} > \epsilon.$$

Hence there is an integer $k_1 \geqslant k_0$ such that

$$P\{\tau_k \leqslant T\} \geqslant \epsilon \quad \text{for all } k \geqslant k_1. \tag{4}$$

Define a C^2-function $V : R^3_{++} \to R_{++}$ by

$$V(x) = \sum_{i=1}^{3} \big[x_i + 1 - \log(x_i)\big].$$

The non-negativity of this function can be seen from $u + 1 - \log(u) \geqslant 0$, $\forall u > 0$. Using Itô's formula we get

$$
\begin{aligned}
dV\big(x(t)\big) &= \bigg[\bigg(1-\frac{1}{x_1(t)}\bigg)\big(\lambda-\delta x_1(t)-(1-\gamma)\beta x_1(t)x_3(t)\big)+\bigg(1-\frac{1}{x_2(t)}\bigg)\big((1-\gamma)\beta x_1(t)x_3(t)-ax_2(t)\big)\\
&\quad+\bigg(1-\frac{1}{x_3(t)}\bigg)\big((1-\eta)Nax_2(t)-ux_3(t)-(1-\gamma)\beta x_1(t)x_3(t)\big)+\sigma_1^2+\frac{\sigma_2^2}{2}\bigg]dt\\
&\quad+\sigma_1\big(2-x_1(t)-x_2(t)\big)\,dB_1(t)+\sigma_2\big(1-x_3(t)\big)\,dB_2(t)\\
&=\bigg[\lambda-\delta x_1(t)-(1-\gamma)\beta x_1(t)x_3(t)+(1-\gamma)\beta x_1(t)x_3(t)-ax_2(t)+(1-\eta)Nax_2(t)-ux_3(t)\\
&\quad-(1-\gamma)\beta x_1(t)x_3(t)-\frac{\lambda}{x_1(t)}+\delta+(1-\gamma)\beta x_3(t)-\frac{(1-\gamma)}{x_2(t)}\beta x_1(t)x_3(t)+a\\
&\quad-\frac{(1-\eta)Nax_2(t)}{x_3(t)}+u+(1-\gamma)\beta x_1(t)+\sigma_1^2+\frac{\sigma_2^2}{2}\bigg]dt+\sigma_1\big(2-x_1(t)-x_2(t)\big)\,dB_1(t)\\
&\quad+\sigma_2\big(1-x_3(t)\big)\,dB_2(t).
\end{aligned}
$$

Hence

$$
\begin{aligned}
dV\big(x(t)\big) &\leqslant \bigg[\lambda+\delta+a+u+\sigma_1^2+\frac{\sigma_2^2}{2}+(1-\eta)Nax_2(t)+(1-\gamma)\beta x_3(t)+(1-\gamma)\beta x_1(t)\bigg]dt\\
&\quad+\sigma_1\big(2-x_1(t)-x_2(t)\big)\,dB_1(t)+\sigma_2\big(1-x_3(t)\big)\,dB_2(t).
\end{aligned}
$$

Write

$$
c_1=\lambda+\delta+a+u+\sigma_1^2+\frac{\sigma_2^2}{2}\quad\text{and}\quad c_2=2(1-\eta)Na+2(1-\gamma)\beta.
$$

By Lemma 4.1, $x_i\leqslant 2(x_i+1-\log(x_i))$ so $(1-\eta)Nax_2(t)+(1-\gamma)\beta x_3(t)+(1-\gamma)\beta x_2(t)\leqslant c_2V(x)$. Therefore

$$
dV\big(x(t)\big)\leqslant\big(c_1+c_2V(x)\big)\,dt+\sigma_1\big(2-x_1(t)-x_2(t)\big)\,dB_1(t)+\sigma_2\big(1-x_3(t)\big)\,dB_2(t).
$$

Hence

$$
dV\big(x(t)\big)\leqslant c_3\big(1+V(x)\big)+\sigma_1\big(2-x_1(t)-x_2(t)\big)\,dB_1(t)+\sigma_2\big(1-x_3(t)\big)\,dB_2(t)
$$

where $c_3=\max(c_1,c_2)$. Therefore if $t_1\leqslant T$,

$$
\int_0^{\tau_k\wedge t_1}dV\big(x(t)\big)\leqslant\int_0^{\tau_k\wedge t_1}c_3\big(1+V\big(x(t)\big)\big)\,dt+\int_0^{\tau_k\wedge t_1}\sigma_1\big(2-x_1(t)-x_2(t)\big)\,dB_1(t)+\int_0^{\tau_k\wedge t_1}\sigma_2\big(1-x_3(t)\big)\,dB_2(t).
$$

This implies that

$$
\begin{aligned}
EV\big(x(\tau_k\wedge t_1)\big)&\leqslant V(x_0)+E\int_0^{\tau_k\wedge t_1}c_3\big(1+V\big(x(t)\big)\big)\,dt\leqslant V(x_0)+c_3t_1+c_3E\int_0^{\tau_k\wedge t_1}V\big(x(t)\big)\,dt\\
&\leqslant V(x_0)+c_3T+c_3E\int_0^{t_1}V\big(x(\tau_k\wedge t)\big)\,dt=V(x_0)+c_3T+c_3\int_0^{t_1}EV\big(x(\tau_k\wedge t)\big)\,dt.
\end{aligned}
$$

By the Gronwall inequality,

$$
EV\big(x(\tau_k\wedge T)\big)\leqslant c_4 \tag{5}
$$

where $c_4=(V(x_0)+c_3T)e^{c_3T}$. □

Set $\Omega_k=\{\tau_k\leqslant T\}$ for $k\geqslant k_1$ and by (4), $P(\Omega_k)\geqslant\epsilon$. Note that for every $\omega\in\Omega_k$, there is some i $(1\leqslant i\leqslant 3)$ such that $x_i(\tau_k,\omega)$ equals either k or $1/k$, and hence $V(x(\tau_k,\omega))$ is no less than the smallest of

$$
k+1-\log(k)\quad\text{and}\quad(1/k)+1-\log(1/k)=(1/k)+1+\log(k).
$$

Consequently,

$$V\big(x(\tau_k,\omega)\big) \geqslant \big[k+1-\log(k)\big] \wedge \big[(1/k)+1+\log(k)\big].$$

It then follows from (4) and (5) that

$$c_4 \geqslant E\big[1_{\Omega_k}(\omega)V\big(x(\tau_k,\omega)\big)\big] \geqslant \epsilon\big(\big[k+1-\log(k)\big] \wedge \big[(1/k)+1+\log(k)\big]\big),$$

where 1_{Ω_k} is the indicator function of Ω_k. Letting $k \to \infty$ leads to the contradiction $\infty > c_4 = \infty$. So we must therefore have $\tau_\infty = \infty$ a.s.

In the next section we look at the asymptotic behaviour of the system and try to obtain some more analytical results.

5. Asymptotic behaviour

For the deterministic system the disease free equilibrium is $(\lambda/\delta, 0, 0)$. Recall that this is not an equilibrium point for the stochastic model where $(x_2, x_3) = (0, 0)$ is still a stochastic equilibrium but the first co-ordinate instead of being fixed at λ/δ follows a stochastic process which varies around the value λ/δ. First we consider $x_2(t)$, $x_3(t)$ and find the conditions for exponential stability. Then we obtain the stability in distribution of $x_1(t)$.

Definition 5.1. (See [17, p. 119].) Let $(\Omega, \mathcal{F}, P)$ be a complete probability space with a filtration $\{\mathcal{F}_t\}_{t\geqslant 0}$ which is right continuous and $\mathcal{F}_0$ contains all P-null sets.

Suppose that $0 \leqslant t_0 < T < \infty$. Let x_0 be an $\mathcal{F}_{t_0}$-measurable R^d-valued random variable such that $E|x_0|^2 < \infty$. Let $f : R^d \times [t_0, T] \to R^d$ and $g : R^d \times [t_0, T] \to R^{d\times m}$ be both Borel measurable with $f(0,t) = 0$ and $g(0,t) = 0$ for all $t \geqslant t_0$. Consider the d-dimensional stochastic differential equation of Itô-type

$$dx(t) = f\big(x(t),t\big)\,dt + g\big(x(t),t\big)\,dB(t) \tag{6}$$

on $t_0 \leqslant t \leqslant T$, with initial value $x(t_0) = x_0$. Write $x(t; t_0, x_0)$ for the value of the solution to this equation at time t.

The trivial solution of Eq. (6) is said to be almost surely exponentially stable if

$$\lim_{t\to\infty} \sup \frac{1}{t} \log\big|x(t; t_0, x_0)\big| < 0 \quad \text{a.s.}$$

for all $x_0 \in R^d$.

Theorem 5.1. *Under the following two conditions*:

(i) $2[(1-\eta)Na - a] - \sigma_1^2 < 0$;
(ii) $[((1-\eta)Na - a) - u]^2 < (\sigma_2^2 + 2u)(\sigma_1^2 - 2[(1-\eta)Na - a])$;

$x_2(t)$ and $x_3(t)$ are almost surely exponentially stable in the sense that $x_2(t)$ and $x_3(t)$ will tend to their equilibrium value 0 *exponentially with probability* 1.

Proof. From Eqs. (2) and (3) consider $d(x_2(t) + x_3(t))$,

$$\begin{aligned} d\big(x_2(t)+x_3(t)\big) = {} & \big((1-\gamma)\beta x_1(t)x_3(t) - ax_2(t) + (1-\eta)Nax_2(t) - ux_3(t) - (1-\gamma)\beta x_1(t)x_3(t)\big)\,dt \\ & - \sigma_1 x_2(t)\,dB_1(t) - \sigma_2 x_3(t)\,dB_2(t). \end{aligned}$$

Let $x = (x_2, x_3)$ and $V(x) = \log(x_2 + x_3)$ for $x_2, x_3 \in (0, \infty)$. Using Itô's formula we get

$$\begin{aligned} dV\big(x(t)\big) = {} & \left(\frac{(1-\eta)Nax_2(t)}{x_2(t)+x_3(t)} - \frac{ax_2(t)}{x_2(t)+x_3(t)} - \frac{ux_3(t)}{x_2(t)+x_3(t)} - \frac{1}{2}\frac{\sigma_1^2 x_2^2(t)}{(x_2(t)+x_3(t))^2} - \frac{1}{2}\frac{\sigma_2^2 x_3^2(t)}{(x_2(t)+x_3(t))^2}\right)dt \\ & - \frac{\sigma_1 x_2(t)}{(x_2(t)+x_3(t))}\,dB_1(t) - \frac{\sigma_2 x_3(t)}{(x_2(t)+x_3(t))}\,dB_2(t). \end{aligned}$$

Simplifying we get

$$dV\big(x(t)\big) = \frac{1}{2(x_2(t)+x_3(t))^2}\big(2\big(x_2(t)+x_3(t)\big)\big((1-\eta)Nax_2(t) - ax_2(t) - ux_3(t)\big) - \sigma_1^2x_2^2(t) - \sigma_2^2x_3^2(t)\big)\,dt$$
$$- \frac{\sigma_1x_2(t)}{(x_2(t)+x_3(t))}\,dB_1(t) - \frac{\sigma_2x_3(t)}{(x_2(t)+x_3(t))}\,dB_2(t).$$

We can write the term

$$\big(2\big(x_2(t)+x_3(t)\big)\big((1-\eta)Nax_2(t) - ax_2(t) - ux_3(t)\big) - \sigma_1^2x_2^2(t) - \sigma_2^2x_3^2(t)\big)$$

in the following way

$$\begin{pmatrix} x_2(t) & x_3(t)\end{pmatrix}\begin{pmatrix} 2((1-\eta)Na-a)-\sigma_1^2 & ((1-\eta)Na-a)-u \\ ((1-\eta)Na-a)-u & -2u-\sigma_2^2\end{pmatrix}\begin{pmatrix} x_2(t)\\ x_3(t)\end{pmatrix}.$$

Hence we can write $dV(x(t))$ as

$$dV\big(x(t)\big)$$
$$= \frac{1}{2(x_2(t)+x_3(t))^2}\left\{\begin{pmatrix} x_2(t) & x_3(t)\end{pmatrix}\begin{pmatrix} 2((1-\eta)Na-a)-\sigma_1^2 & ((1-\eta)Na-a)-u \\ ((1-\eta)Na-a)-u & -2u-\sigma_2^2\end{pmatrix}\begin{pmatrix} x_2(t)\\ x_3(t)\end{pmatrix}\right\}dt$$
$$- \frac{\sigma_1x_2(t)}{(x_2(t)+x_3(t))}\,dB_1(t) - \frac{\sigma_2x_3(t)}{(x_2(t)+x_3(t))}\,dB_2(t).$$

Now consider the matrix

$$\begin{pmatrix} 2((1-\eta)Na-a)-\sigma_1^2 & ((1-\eta)Na-a)-u \\ ((1-\eta)Na-a)-u & -2u-\sigma_2^2\end{pmatrix}.$$

As the above matrix is negative-definite with largest (negative) eigenvalue $\lambda_{\max}$ then

$$\begin{pmatrix} x_2(t) & x_3(t)\end{pmatrix}\begin{pmatrix} 2((1-\eta)Na-a)-\sigma_1^2 & 2((1-\eta)Na-a)-u \\ 2((1-\eta)Na-a)-u & -2u-\sigma_2^2\end{pmatrix}\begin{pmatrix} x_2(t)\\ x_3(t)\end{pmatrix}$$
$$\leqslant \lambda_{\max}\big(x_2^2(t)+x_3^2(t)\big) = -|\lambda_{\max}|\big(x_2^2(t)+x_3^2(t)\big).$$

Therefore

$$dV\big(x(t)\big) \leqslant \left(-|\lambda_{\max}|\frac{1}{2(x_2(t)+x_3(t))^2}\big(x_2^2(t)+x_3^2(t)\big)\right)dt$$
$$- \frac{\sigma_1x_2(t)}{(x_2(t)+x_3(t))}\,dB_1(t) - \frac{\sigma_2x_3(t)}{(x_2(t)+x_3(t))}\,dB_2(t). \tag{7}$$

As $0.5(x_2^2+x_3^2) \geqslant x_2x_3$ we can write $-(x_2^2+x_3^2) \leqslant -0.5(x_2+x_3)^2$.

Substituting this in inequality (7) we get

$$dV\big(x(t)\big) \leqslant -\frac{1}{4}|\lambda_{\max}|\,dt - \frac{\sigma_1x_2(t)}{(x_2(t)+x_3(t))}\,dB_1(t) - \frac{\sigma_2x_3(t)}{(x_2(t)+x_3(t))}\,dB_2(t),$$

$$d\big(\log\big(x_2(t)+x_3(t)\big)\big) \leqslant -\frac{1}{4}|\lambda_{\max}|\,dt - \frac{\sigma_1x_2(t)}{(x_2(t)+x_3(t))}\,dB_1(t) - \frac{\sigma_2x_3(t)}{(x_2(t)+x_3(t))}\,dB_2(t).$$

Integrating the above inequality and using the fact that

$$\limsup_{t\to\infty}\frac{1}{t}\big|B_i(t)\big| = 0 \quad \text{for } i = 1,2 \quad \text{(Mao [17])},$$

we get

$$\limsup_{t\to\infty}\frac{1}{t}\log\big(x_2(t)+x_3(t)\big) \leqslant -\frac{1}{4}|\lambda_{\max}| < 0 \quad \text{a.s.}$$

Hence $x_2(t)\to 0$ and $x_3(t)\to 0$ a.s. as $t\to\infty$. This completes the proof of Theorem 5.1. □

Note that Theorem 5.1 does not assume anything about R_0, in particular it does not assume that $R_0 < 1$. Note also that the conditions of Theorem 5.1 cannot possibly be satisfied in the deterministic model when $\sigma_1 = \sigma_2 = 0$.

The constraints on the variances in Theorem 5.1(i) and (ii) have no obvious biological meaning in themselves. However note that the expression $(1-\eta)Na$ is the per capita rate at which an infected cell produces virus particles in the presence of HAART. Under the condition $(1-\eta)N < 1$, i.e. an infected cell produces on average less than one infective virus particle during its entire infectious lifetime, which implies that $R_0 < 1$, the first condition in Theorem 5.1 will always be true. If the variances σ_1^2 and σ_2^2 are large enough these conditions will always be satisfied. This is an interesting result as it says that if the noise variances are large enough then the populations of infected cells and infective virus particles will always die out, whatever the other parameter values, even if $R_0 > 1$. Thus the behaviour of the stochastic system with added environmental noise can be very different than the behaviour of the basic deterministic system.

We now concentrate on $x_1(t)$. We shall eventually show that $x_1(t)$ is stable in distribution in the sense that it stabilises around the mean value λ/δ. To do this we introduce a new stochastic process $z(t)$ which is defined by its initial condition $z(0) = x_1(0)$ and the stochastic differential equation

$$dz(t) = \big(\lambda - \delta z(t)\big)\,dt - \sigma_1 z(t)\,dB_1(t).$$

We shall show that in the limit as t becomes large $x_1(t)$ can be approximated by $z(t)$ so

$$\lim_{t\to\infty}\big(z(t) - x_1(t)\big) = 0 \quad \text{in probability.}$$

To help with the proof we introduce another function $y_\epsilon(t)$ which is defined by the initial condition $y_\epsilon(0) = x_1(0)$ and the stochastic differential equation

$$dy_\epsilon(t) = \big(\lambda - (\delta+\epsilon)y_\epsilon(t)\big)\,dt - \sigma_1 y_\epsilon(t)\,dB_1(t). \tag{8}$$

Theorem 5.2. *Under the conditions of Theorem* 5.1*,*

$$\lim_{t\to\infty}\big(z(t) - x_1(t)\big) = 0 \quad \textit{in probability.}$$

Proof. The original equation is

$$dx_1(t) = \big(\lambda - \delta x_1(t) - (1-\gamma)\beta x_1(t)x_3(t)\big)\,dt - \sigma_1 x_1(t)\,dB_1(t).$$

First we prove that

$$\liminf_{t\to\infty}\big(x_1(t) - y_\epsilon(t)\big) \geqslant 0 \quad \text{a.s.}$$

Therefore consider

$$\begin{aligned} d\big(x_1(t) - y_\epsilon(t)\big) &= \big(-\delta\big(x_1(t) - y_\epsilon(t)\big) + \epsilon y_\epsilon(t) - (1-\gamma)\beta x_1(t)x_3(t)\big)\,dt - \sigma_1\big(x_1(t) - y_\epsilon(t)\big)\,dB_1(t) \\ &= \big(-(\delta+\epsilon)\big(x_1(t) - y_\epsilon(t)\big) + \big(\epsilon - (1-\gamma)\beta x_3(t)\big)x_1(t)\big)\,dt - \sigma_1\big(x_1(t) - y_\epsilon(t)\big)\,dB_1(t). \end{aligned}$$

The solution is given by

$$x_1(t) - y_\epsilon(t) = \psi(t)\int_0^t \psi^{-1}(s)\big(\epsilon - (1-\gamma)\beta x_3(s)\big)x_1(s)\,ds$$

where

$$\psi(t) = \exp\left\{-\left(\delta + \epsilon + \frac{\sigma_1^2}{2}\right)t - \sigma_1 B_1(t)\right\}.$$

Using the result of Theorem 5.1 where it has been shown that $x_3(t) \to 0$ a.s. as $t \to \infty$ we can write, for almost all $\omega \in \Omega$, $\exists T = T(\omega)$ such that

$$x_3(t) < \frac{\epsilon}{(1-\gamma)\beta}, \quad \forall t \geqslant T.$$

Hence for all $\omega \in \Omega$, if $t > T$, then

$$x_1(t) - y_\epsilon(t) = \psi(t)\left(\int_0^T \psi^{-1}(s)\big(\epsilon - (1-\gamma)\beta x_3(s)\big)x_1(s)\,ds + \int_T^t \psi^{-1}(s)\big(\epsilon - (1-\gamma)\beta x_3(s)\big)x_1(s)\,ds\right).$$

Hence $x_1(t) - y_\epsilon(t) \geqslant \psi(t)\kappa(T)$ where

$$\kappa(T) = \int_0^T \psi^{-1}(s)\big(\epsilon - (1-\gamma)\beta x_3(s)\big)x_1(s)\,ds.$$

Clearly $|\kappa(T)| < \infty$ and $\psi(t) \to 0$ a.s.

Therefore

$$\liminf_{t\to\infty}\big(x_1(t) - y_\epsilon(t)\big) \geqslant 0 \quad \text{a.s.} \tag{9}$$

Next we prove $\liminf_{t\to\infty}(z(t) - x_1(t)) \geqslant 0$ a.s. For this consider

$$d\big(z(t) - x_1(t)\big) = \big(-\delta\big(z(t) - x_1(t)\big) + (1-\gamma)\beta x_1(t)x_3(t)\big)\,dt - \sigma_1\big(z(t) - x_1(t)\big)\,dB_1(t).$$

This implies that

$$d\big(z(t) - x_1(t)\big) \geqslant -\delta\big(z(t) - x_1(t)\big)\,dt - \sigma_1\big(z(t) - x_1(t)\big)\,dB_1(t).$$

Let $\xi = z - x_1$. Hence

$$d\xi(t) \geqslant -\delta\xi(t)\,dt - \sigma_1\xi(t)\,dB_1(t).$$

For any $\omega \in \Omega$ either

$$\omega \in \Omega_1 = \big\{\omega\colon\ \xi(t_0) > 0 \text{ for some } t_0 \geqslant 0\big\}$$

or

$$\omega \in \Omega_2 = \big\{\omega\colon\ \xi(t) \leqslant 0 \text{ for all } t \geqslant 0\big\}.$$

For $\omega \in \Omega_1$ then let $t_1 = \sup\{t\colon\ t \geqslant t_0 \text{ and } \xi(t) > 0\}$. If $t_1 < \infty$ then in $[t_0, t_1]$

$$d\xi(t) = \big(-\delta + f(t)\big)\xi(t)\,dt - \sigma_1\xi(t)\,dB_1(t) \tag{10}$$

where $f(t) \geqslant 0$ is a random variable. The solution of (10) is given by

$$\xi(t) = \xi(t_0)\exp\left\{\int_0^t \left(-\delta + f(s) - \frac{\sigma_1^2}{2}\right)ds - \sigma_1 B_1(t)\right\} > 0.$$

Hence

$$\xi(t_1) = \xi(t_0)\exp\left\{\int_{t_0}^{t_1} \left(-\delta + f(s) - \frac{\sigma_1^2}{2}\right)ds - \sigma_1 B_1(s)\right\} > 0.$$

Thus $\xi(t) > 0$ in $[t_1, t_1 + \delta_1]$ for some $\delta_1 > 0$. This is a contradiction. Hence $t_1 = \infty$ and $\xi(t) \geqslant 0$ for all $t \geqslant t_0$. So $\liminf_{t\to\infty}\xi(t) \geqslant 0$ a.s.

It remains to consider the case $\omega \in \Omega_2$ where $\xi(t) \leqslant 0$ for all $t \geqslant 0$. Then

$$d\xi(t) = \big(-\delta - f(t)\big)\xi(t)\,dt - \sigma_1\xi(t)\,dB_1(t) \tag{11}$$

where $f(t) \geqslant 0$ is a random variable. The solution of (11) is given by

$$\xi(t) = \xi(0)\exp\left\{\int_0^t \left(-\delta - f(s) - \frac{\sigma_1^2}{2}\right) ds - \sigma_1 B_1(t)\right\} = 0.$$

Hence $\liminf_{t\to\infty} \xi(t) \geqslant 0$ a.s. That is

$$\liminf_{t\to\infty} \big(z(t) - x_1(t)\big) \geqslant 0 \quad \text{a.s.} \tag{12}$$

Next consider $d(y_\epsilon(t) - z(t))$,

$$d\big(y_\epsilon(t) - z(t)\big) = \big(-\delta\big(y_\epsilon(t) - z(t)\big) - \epsilon y_\epsilon(t)\big)\,dt - \sigma_1\big(y_\epsilon(t) - z(t)\big)\,dB_1(t).$$

The solution is written as

$$y_\epsilon(t) - z(t) = -\epsilon \exp\left\{-\left(\delta + \frac{\sigma_1^2}{2}\right)t - \sigma_1 B_1(t)\right\} \int_0^t \exp\left\{\left(\delta + \frac{\sigma_1^2}{2}\right)s + \sigma_1 B_1(s)\right\} y_\epsilon(s)\,ds.$$

Note that $y_\epsilon(s) \geqslant 0$ as it is a solution of a linear stochastic differential equation (8) which can be solved explicitly to give

$$y_\epsilon(t) = \lambda \int_0^t \exp\left\{-\left(\delta + \epsilon + \frac{\sigma_1^2}{2}\right)(t-s) - \sigma_1\big(B_1(t) - B_1(s)\big)\right\} ds. \tag{13}$$

Therefore

$$\big|y_\epsilon(t) - z(t)\big| = \epsilon \int_0^t y_\epsilon(s) \exp\left\{-\left(\delta + \frac{\sigma_1^2}{2}\right)(t-s) - \sigma_1\big(B_1(t) - B_1(s)\big)\right\} ds.$$

Since $B_1(t) - B_1(s) \sim N(0, t-s)$ we write

$$\begin{aligned} E\big[\exp\big[-\sigma_1\big(B_1(t) - B_1(s)\big)\big]\big] &= \int_{-\infty}^{\infty} e^{-\sigma_1 u} \frac{1}{\sqrt{2\pi(t-s)}} e^{-u^2/2(t-s)}\,du \\ &= \frac{1}{\sqrt{2\pi(t-s)}} \int_{-\infty}^{\infty} \exp\left\{\frac{-1}{2(t-s)}\big(u^2 + 2(t-s)\sigma_1 u\big)\right\} du \\ &= \frac{1}{\sqrt{2\pi(t-s)}} \exp\left\{\frac{\sigma_1^2(t-s)}{2}\right\} \int_{-\infty}^{\infty} \exp\left\{\frac{-1}{2(t-s)}\big\{u + (t-s)\sigma_1\big\}^2\right\} du. \end{aligned}$$

Hence

$$E\big[\exp\big[-\sigma_1\big(B_1(t) - B_1(s)\big)\big]\big] = \exp\left\{\frac{\sigma_1^2(t-s)}{2}\right\}. \tag{14}$$

Therefore

$$\begin{aligned} E\big|y_\epsilon(t) - z(t)\big| &= \epsilon E\left[\int_0^t y_\epsilon(s) \exp\left\{-\left(\delta + \frac{\sigma_1^2}{2}\right)(t-s) - \sigma_1\big(B_1(t) - B_1(s)\big)\right\} ds\right] \\ &= \epsilon \int_0^t E\left[y_\epsilon(s) \exp\left\{-\left(\delta + \frac{\sigma_1^2}{2}\right)(t-s) - \sigma_1\big(B_1(t) - B_1(s)\big)\right\} ds\right] \\ &= \epsilon \int_0^t E\left[y_\epsilon(s) \exp\left\{-\left(\delta + \frac{\sigma_1^2}{2}\right)(t-s)\right\}\right] E\big[\exp\big[-\sigma_1\big(B_1(t) - B_1(s)\big)\big]\big]\,ds \end{aligned}$$

as $y_\epsilon(s)$ is independent of $B_1(t) - B_1(s)$,

$$= \epsilon \int_0^t \exp\{-\delta(t-s)\} E y_\epsilon(s)\, ds, \quad \text{using (14).} \tag{15}$$

Taking the expectation of (13) and using (14) we see that

$$E y_\epsilon(t) = \lambda \int_0^t \exp\{-(\delta+\epsilon)(t-s)\}\, ds \leqslant \frac{\lambda}{\delta+\epsilon}.$$

Substituting this result in (15) we get

$$E\big|y_\epsilon(t) - z(t)\big| \leqslant \frac{\lambda\epsilon}{\delta+\epsilon} \int_0^t \exp\{-\delta(t-s)\}\, ds \leqslant \frac{\lambda\epsilon e^{-\delta t}}{(\delta+\epsilon)\delta}\big(e^{\delta t} - 1\big).$$

Hence we can write

$$\lim_{\epsilon\to 0} \lim_{t\to\infty} E\big|y_\epsilon(t) - z(t)\big| = 0.$$

This implies that

$$\lim_{\epsilon\to 0} \lim_{t\to\infty} \big|y_\epsilon(t) - z(t)\big| = 0 \quad \text{in probability.} \tag{16}$$

Combining (9), (12) and (16) we obtain the required assertion. This completes the proof of Theorem 5.2. □

In the next section we try and obtain some more information about the mean reverting process.

6. Mean reverting process

As we are approximating the process $x_1(t)$ by $z(t)$ we wish to find some information about the process $z(t)$. We try and do that here by finding the parameters of the process such as the mean and the variance.

The mean reverting process is given by

$$dz(t) = \big(\lambda - \delta z(t)\big)\, dt - \sigma_1 z(t)\, dB_1(t).$$

The explicit solution of the above equation is given by

$$z(t) = z(0) \exp\left\{-\left(\delta + \frac{\sigma_1^2}{2}\right)t - \sigma_1 B_1(t)\right\} + \lambda \int_0^t \exp\left\{-\left(\delta + \frac{\sigma_1^2}{2}\right)(t-s) - \sigma_1\big(B_1(t) - B_1(s)\big)\right\} ds.$$

Taking the expectation and using (14) we get

$$E\big(z(t)\big) = z(0)e^{-\delta t} + \frac{\lambda}{\delta}\big(1 - e^{-\delta t}\big).$$

Hence taking the limit we get

$$\lim_{t\to\infty} E\big(z(t)\big) = \frac{\lambda}{\delta}.$$

To find the second moment consider $V(z(t)) = z^2$. Using Itô's formula we get

$$d\big(z^2(t)\big) = \big(\sigma_1^2 - 2\delta\big)z^2(t)\, dt + 2\lambda z(t)\, dt - 2\sigma_1 z^2(t)\, dB_1(t).$$

Therefore

$$z^2(t) = z^2(0) + \int_0^t \big(\sigma_1^2 - 2\delta\big) z^2(s)\,ds + 2\lambda \int_0^t z(s)\,ds - 2\sigma_1 \int_0^t z^2(s)\,dB_1(s).$$

Taking expectation we get

$$E\big(z^2(t)\big) = E\big(z^2(0)\big) + \int_0^t \big(\sigma_1^2 - 2\delta\big) E\big(z^2(s)\big)\,ds + 2\lambda \int_0^t E\big(z(s)\big)\,ds.$$

Differentiating with respect to t we deduce that

$$\frac{d}{dt} E\big(z^2(t)\big) = \big(\sigma_1^2 - 2\delta\big) E\big(z^2(t)\big) + 2\lambda E\big(z(t)\big), \qquad \frac{d}{dt}\big\{E\big(z^2(t)e^{-(\sigma_1^2-2\delta)t}\big)\big\} = 2\lambda E\big(z(t)\big)e^{-(\sigma_1^2-2\delta)t}.$$

Integrating and multiplying by $e^{(\sigma_1^2-2\delta)t}$ we deduce that

$$E\big(z^2(t)\big) = E\big(z^2(0)\big)e^{(\sigma_1^2-2\delta)t} + 2\lambda e^{(\sigma_1^2-2\delta)t} \int_0^t e^{-(\sigma_1^2-2\delta)s} E\big(z(s)\big)\,ds.$$

Now substituting the value of $E(z(s))$ in the above equation we see that

$$E\big(z^2(t)\big) = E\big(z^2(0)\big)e^{(\sigma_1^2-2\delta)t} + 2\lambda e^{(\sigma_1^2-2\delta)t} \left\{ \int_0^t e^{-(\sigma_1^2-2\delta)s} \left(z(0)e^{-\delta s} + \frac{\lambda}{\delta}\big(1 - e^{-\delta s}\big)\right)\right\} ds.$$

Simplifying we get

$$\begin{aligned} E\big(z^2(t)\big) &= E\big(z^2(0)\big)e^{(\sigma_1^2-2\delta)t} + 2\lambda e^{(\sigma_1^2-2\delta)t} \left\{ z(0) \int_0^t e^{-(\sigma_1^2-2\delta)s} e^{-\delta s}\,ds \quad + \frac{\lambda}{\delta} \int_0^t e^{-(\sigma_1^2-2\delta)s}\big(1 - e^{-\delta s}\big)\,ds \right\} \\ &= E\big(z^2(0)\big)e^{(\sigma_1^2-2\delta)t} + 2\lambda e^{(\sigma_1^2-2\delta)t} \left\{ -\left(\frac{z(0) - \frac{\lambda}{\delta}}{\sigma_1^2 - \delta}\right)\big(e^{-(\sigma_1^2-\delta)t} - 1\big) - \frac{\lambda}{\delta(\sigma_1^2 - 2\delta)}\big(e^{-(\sigma_1^2-2\delta)t} - 1\big)\right\}, \end{aligned}$$

provided that $\sigma_1^2 \neq \delta, 2\delta$,

$$\begin{aligned} &= E\big(z^2(0)\big)e^{(\sigma_1^2-2\delta)t} - 2\lambda\left(\frac{z(0) - \frac{\lambda}{\delta}}{\sigma_1^2 - \delta}\right)e^{-\delta t} + 2\lambda\left(\frac{z(0) - \frac{\lambda}{\delta}}{\sigma_1^2 - \delta}\right)e^{(\sigma_1^2-2\delta)t} - \frac{2\lambda^2}{\delta(\sigma_1^2 - 2\delta)} \\ &\quad + \frac{2\lambda^2}{\delta(\sigma_1^2 - 2\delta)} e^{(\sigma_1^2-2\delta)t}. \end{aligned}$$

Taking the limit we need $\sigma_1^2 < 2\delta$ for $\lim_{t\to\infty} E(z^2(t)) < \infty$, when we obtain

$$\lim_{t\to\infty} E\big(z^2(t)\big) = \frac{2\lambda^2}{\delta(2\delta - \sigma_1^2)}.$$

The above term is positive since $\sigma_1^2 - 2\delta < 0$. Hence the asymptotic variance of the mean reverting process is

$$\lim_{t\to\infty} V\big(z(t)\big) = \frac{2\lambda^2}{\delta(2\delta - \sigma_1^2)} - \frac{\lambda^2}{\delta^2} = \frac{\lambda^2\sigma_1^2}{\delta^2(2\delta - \sigma_1^2)}.$$

A similar argument shows that if $\sigma_1^2 = \delta$ then

$$\lim_{t\to\infty} V\big(z(t)\big) = \frac{\lambda^2}{\delta^2},$$

and if $\sigma_1^2 \geqslant 2\delta$ then $\lim_{t\to\infty} V(z(t)) = \infty$.

Hence if $\sigma_1^2 < 2\delta$ then the limit process has finite variance σ_1^2 given by

$$\frac{\lambda^2\sigma_1^2}{\delta^2(2\delta - \sigma_1^2)}$$

whereas if $\sigma_1^2 \geqslant 2\delta$ then the limit process has infinite variance.

7. Simulations

According to our analytical results the infected cells and the virus particles are both exponentially stable and tend to zero under conditions specified in Theorem 5.1. Also we see that we can asymptotically approximate $x_1(t)$ by $z(t)$ where $z(t)$ is the mean reverting process. We now try and support our analytical results by simulations. Our simulation programs have been written in FORTRAN and the results were verified by running them repeatedly and extensively checking the results.

To illustrate the stochastic effects clearly we performed simulations first for the deterministic case (Fig. 2) and then for a corresponding stochastic simulation (Fig. 3). The parameter values used have all been taken from published literature. δ, u, a have been taken from [4], N from [6], β from [23] and λ from [22]. The parameter values for Fig. 2 are $\beta = 1 \times 10^{-8}$ day^{-1} dm^3, $\lambda = 10^6$ day^{-1} dm^{-3}, $N = 100$ per cell, $\gamma = 0.5$, $\eta = 0.5$, $a = 0.5$ day^{-1}, $\delta = 0.1$ day^{-1} and $u = 5$ day^{-1}. The initial values were $x_1(0) = 10000$ dm^{-3}, $x_2(0) = 10000$ dm^{-3} and $x_3(0) = 10000$ dm^{-3}. The corresponding stochastic simulation (Fig. 3) uses the same parameter and initial values but additionally has $\sigma_1 = 0.1$ and $\sigma_2 = 0.1$. It is straightforward to verify that with these parameter values $R_0 = 0.495 < 1$ and that the conditions of Theorem 5.1 are not satisfied.

As can be clearly seen from Figs. 2 and 3 both $x_2(t)$ and $x_3(t)$ tend to zero exponentially in both the deterministic and stochastic models. These simulations and others suggest that when R_0 for the deterministic model is less than one, in the stochastic model both $x_2(t)$ and $x_3(t)$ tend to zero exponentially even if the conditions of Theorem 5.1 are not satisfied. Comparing Figs. 2 and 3 one can also see the stochastic effects very clearly.

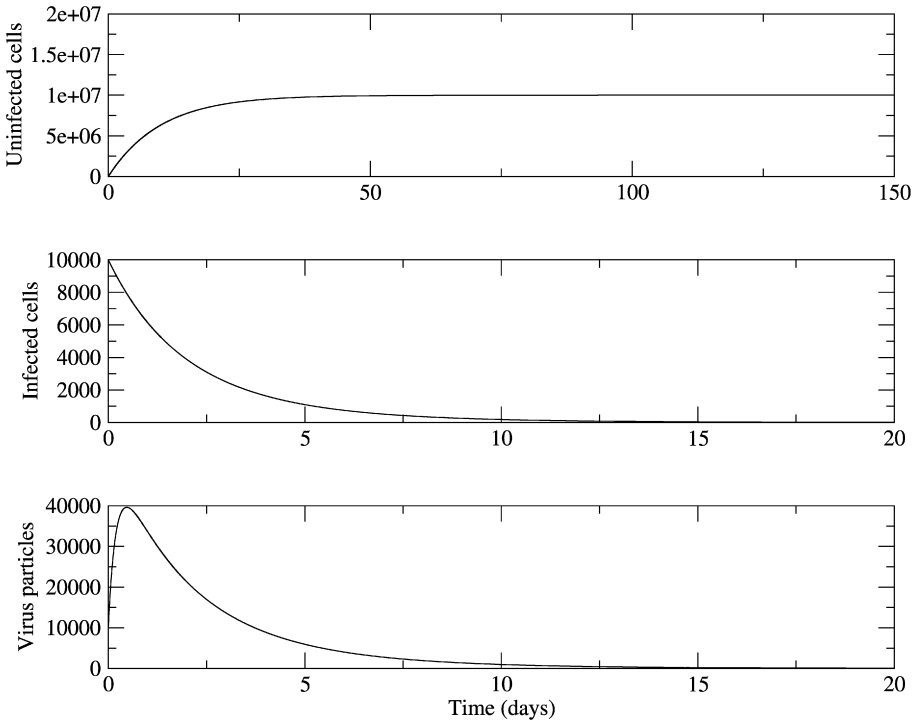


Fig. 2. HIV in vivo virus dynamics deterministic differential equation model approaches the disease free equilibrium for $R_0 < 1$.

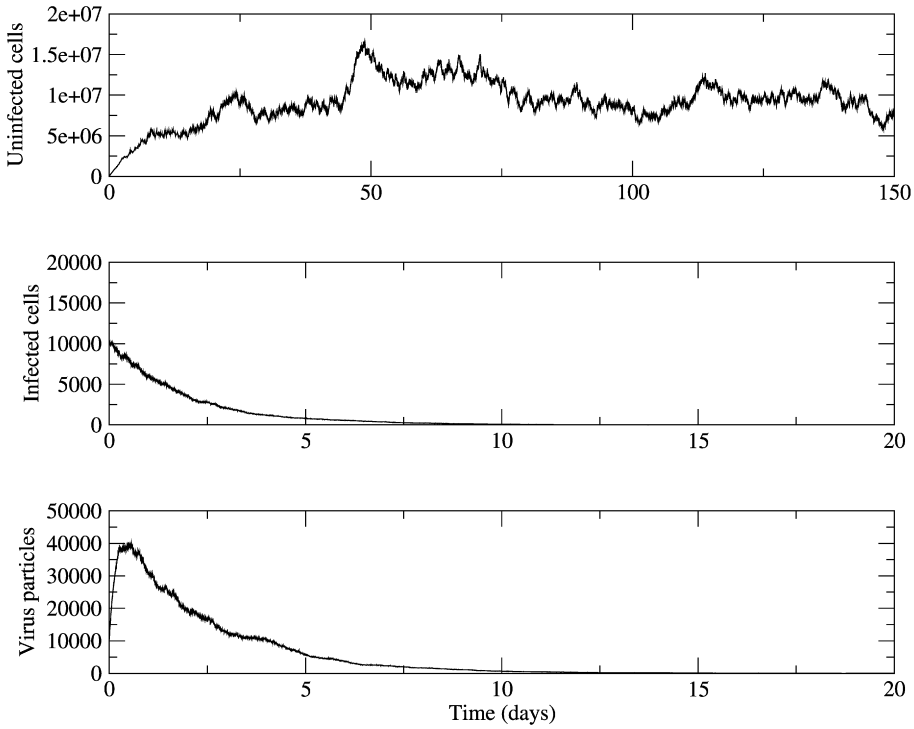


Fig. 3. Stochastic simulation corresponding to Fig. 2.

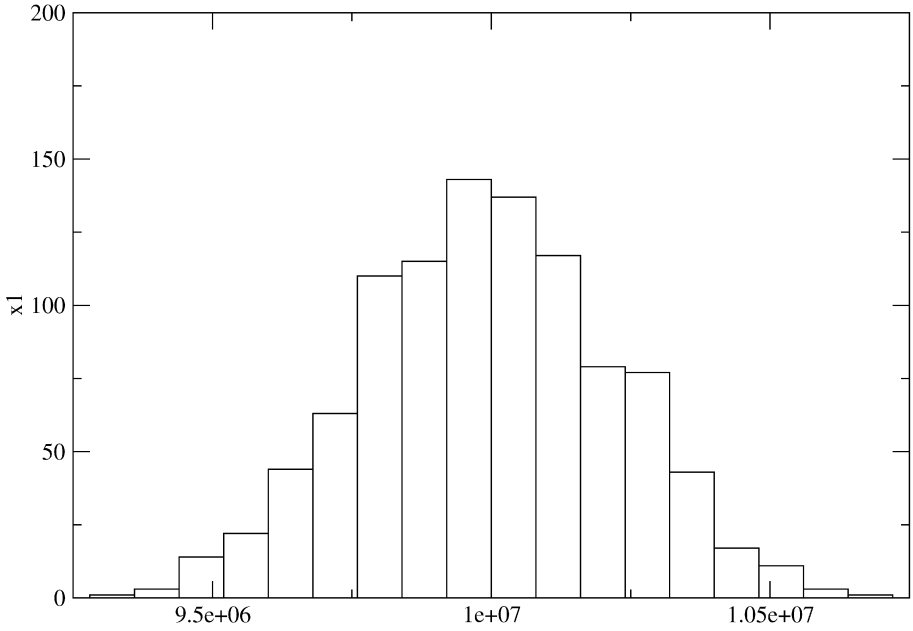


Fig. 4. Distribution of $x_1(t)$ at large time t.

Figures 4 and 5 represent the histograms of the values of $x_1(t)$ and $z(t)$, respectively. The parameter values and the initial values are the same as in Fig. 2 but this time we took $\sigma_1 = \sigma_2 = 0.01$. These values were recorded at a single large time $t = 9000$ days from one thousand different realisations of each of the two stochastic processes. Comparing these figures we see that the distribution of both the variables $x_1(t)$ and $z(t)$ at large times look very similar. The vari-

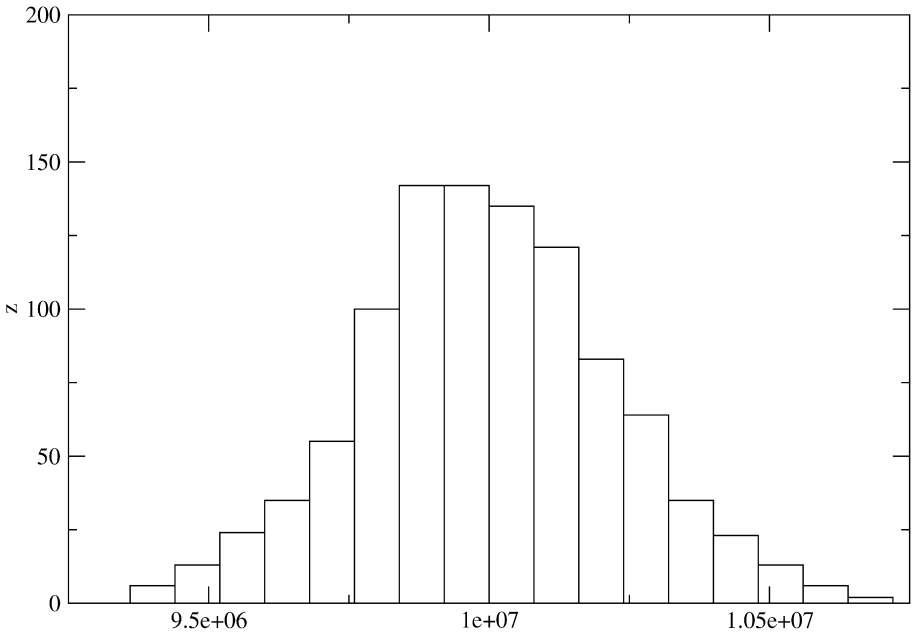


Fig. 5. Distribution of $z(t)$ at large time t.

ables are distributed around the mean value of λ/δ, the actual value being 10^7. A two sample Kolmogorov–Smirnov test for equality of distribution was performed using a 5% significance level and showed that the two distributions could not be distinguished statistically (test statistic $D = 0.033$, p-value $= 0.6476$). We see that if t is large then $z(t)$ is a good approximation to $x_1(t)$ in the situation where $x_2(t)$ and $x_3(t)$ tend to zero.

8. Conclusions

In this paper, we have considered a stochastic model describing the viral dynamics of HIV-1 infection. We first proved the positivity of the solutions. Then we looked at the stability aspect of the model. We proved that the numbers of infected cells and virus particles tended asymptotically to zero exponentially almost surely. We also showed that $x_1(t)$ approached a mean reverting process $z(t)$ in probability. We then supported our analytical results with the help of simulations.

Most previously studied models of internal HIV dynamics in the literature have used deterministic differential equation models, ignoring stochastic effects. Perelson et al. [24] assumed that the number of uninfected cells was a constant and modelled the dynamics of infected cells and infective virus particles. Bonhoeffer et al. [4], Di Mascio et al. [10] and Nelson and Perelson [21] discuss models similar to our deterministic model, neglecting the term $(1-\gamma)\beta x_1(t)x_3(t)$ as an approximation. Di Mascio et al. introduce HAART and Nelson and Perelson introduce protease inhibitor drug therapy. Tuckwell and Wan [26] discuss and analyse our deterministic model including the term $(1-\gamma)\beta x_1(t)x_3(t)$ and obtain equilibrium and stability results.

The only stochastic differential equation model which we are aware of for HIV internal viral dynamics is due to Tuckwell and Le Corfec [25] who use a stochastic differential equation model. Their model has similarities with ours but they use two types of infected cells, latently infected cells and actively infected cells. The variance terms are also different being functionally dependent on the variables. They explore the model using simulation only and do not give any analytical results.

Our work shows that stochastic differential equations give another option to model viral dynamics. By replicating the results from the deterministic case [8] and improving some we have shown that the stochastic model as discussed here adds another dimension to model viral dynamics. It adds a different perspective to this particular problem and gives researchers a different route which they can take in the future. As most real world problems are not deterministic including stochastic effects into the model gives us a more realistic way of modelling viral dynamics.

For example using a stochastic model we were able to examine the limiting asymptotic distribution of the number of uninfected cells, infected cells and infective virus particles and derive an expression for the limiting asymptotic variance of the distribution of the number of uninfected cells. Stochastic models are more versatile than deterministic models because they incorporate random effects such as environmental stochasticity and enable us to model quantities such as probability distributions of variables, probabilities of extinction and variances which are features which cannot be included in a deterministic model.

References

[1] M. Abell, J. Braselton, L. Braselton, The effects of immunity and resistance on the development of AIDS, J. Math. Anal. Appl. 333 (2007) 8–23.
[2] L. Arnold, Stochastic Differential Equations: Theory and Applications, Wiley, New York, 1972.
[3] A. Bahar, X. Mao, Stochastic delay Lotka–Volterra model, J. Math. Anal. Appl. 292 (2004) 364–380.
[4] S. Bonhoeffer, G. Shaw, R. May, M. Nowak, Virus dynamics and drug therapy, Proc. Natl. Acad. Sci. USA 94 (1997) 6971–6976.
[5] C.A. Braumann, Variable effort harvesting models in random environments: Generalisation to density-dependent noise intensities, Math. Biosci. 177–178 (2002) 229–245.
[6] D. Callaway, A. Perelson, HIV-1 infection and low steady state viral loads, Bull. Math. Biol. 64 (2002) 29–64.
[7] M. Ciupe, B. Bivort, D. Bortz, P. Nelson, Estimating kinetic parameters from HIV primary infection data through the eyes of three different mathematical models, Math. Biosci. 200 (2006) 1–27.
[8] N. Dalal, Applications of stochastic and ordinary differential equations to HIV dynamics, Unpublished PhD thesis, University of Strathclyde, 2006.
[9] N. Dalal, D. Greenhalgh, X. Mao, A stochastic model of AIDS and condom use, J. Math. Anal. Appl. 325 (2007) 36–53.
[10] M. Di Mascio, R. Ribeiro, M. Markowitz, D. Ho, A. Perelson, Modelling the long-term control of viraemia in HIV-1 infected patients treated with antiretroviral therapy, Math. Biosci. 188 (2004) 47–62.
[11] A. Ding, H. Wu, Relationships between antiviral treatment effects and biphasic viral decay rates in modelling HIV dynamics, Math. Biosci. 160 (1999) 63–82.
[12] A. Friedman, Stochastic Differential Equations and Their Applications, Academic Press, New York, 1976.
[13] T.C. Gard, Introduction to Stochastic Differential Equations, Marcel Dekker, New York, 1988.
[14] A.V.M. Herz, S. Bonhoeffer, R.M. Anderson, R.M. May, M.A. Nowak, Viral dynamics in vivo: Limitations on estimates of intracellular delay and virus decay, Proc. Natl. Acad. Sci. USA 93 (1996) 7247–7251.
[15] H. Korthals Altes, D. Wodarz, V. Jansen, The dual role of CD4 T helper cells in the infection dynamics of HIV and their importance for vaccination, J. Theoret. Biol. 214 (2002) 633–646.
[16] D. Li, W. Ma, Asymptotic properties of a HIV-1 infection model with time delay, J. Math. Anal. Appl. 335 (2007) 683–691.
[17] X. Mao, Stochastic Differential Equations and Applications, Horwood Publishing Limited, Chichester, 1997.
[18] X. Mao, G. Marion, E. Renshaw, Environmental Brownian noise suppresses explosions in population dynamics, Stochastic Process. Appl. 97 (2002) 95–110.
[19] X. Mao, C. Yuan, J. Zou, Stochastic differential delay equations of population dynamics, J. Math. Anal. Appl. 304 (2005) 296–320.
[20] Mechanisms of CD4 cell destruction, www.aidsmap.com, 2006.
[21] P. Nelson, A. Perelson, Mathematical analysis of delay differential equation models of HIV-1 infection, Math. Biosci. 179 (2002) 73–94.
[22] P. Nelson, J. Murray, A. Perelson, A model of HIV-1 pathogenesis that includes an intracellular delay, Math. Biosci. 163 (2000) 201–215.
[23] M. Nowak, S. Bonhoeffer, G. Shaw, R. May, Antiviral drug treatment: Dynamics of resistance in free virus and infected cell populations, J. Theoret. Biol. 184 (1997) 203–217.
[24] A. Perelson, A. Neumann, M. Markowitz, J. Leonard, D. Ho, HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time, Science 271 (1996) 1582–1586.
[25] H.C. Tuckwell, E. Le Corfec, A stochastic model for early HIV-1 population dynamics, J. Theoret. Biol. 195 (1998) 451–463.
[26] H.C. Tuckwell, F.Y.M. Wan, Nature of equilibria and effects of drug treatments in some simple viral population dynamical models, IMA J. Math. Appl. Med. Biol. 17 (2000) 311–327.
[27] D. Verotta, F. Schaedeli, Non-linear dynamics models characterising long-term virological data from AIDS clinical trials, Math. Biosci. 176 (2002) 163–183.