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Continuous and discrete modeling of HIV-1 decline on therapy

Elvan Akın[1] · Gülşah Yeni[1] · Alan S. Perelson[2]

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Abstract

Mathematical models have shed light on the dynamics of HIV- 1 infection in vivo. In this paper, we generalize continuous mathematical models of drug therapy for HIV-1 by Perelson et al. (Science 271:1582–1586, 1996) and Perelson and Nelson (SIAM Rev 41:3–44, 1999) on time scales, i.e., a nonempty closed subset of real numbers in order to derive new discrete models that predict the total concentration of plasma virus as a function of time. One of our main goals is to compare discrete mathematical models with the continuous model in Perelson et al. (1996) where HIV infected patients were given protease inhibitors and sampled frequently thereafter. For the comparison, we use experimental data collected in Perelson et al. (1996) and estimate the parameters such as the virion clearance rate and the rate of loss of infected cells by fitting the total concentration of plasma virus to this data set. Our results show that discrete systems describe the best fit. In the previous models of this study, the efficacy of protease inhibitor is assumed to be perfect. Motivated by Perelson and Nelson (1999), we end the paper with a mathematical model of imperfect protease inhibitor and reverse transcriptase (RT) inhibitor combination therapy of HIV-1 infection on time scales with its stability analysis.

Keywords Time scales · HIV · Dynamic equations · Difference equations · Differential equations · Systems · Mathematical modeling

Mathematics Subject Classification P34N05 · 93A30 · 39A10 · 35F16 · 35G46 · 65Q10

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Extended author information available on the last page of the article

1 Introduction

The human immunodeficiency virus (HIV) infects a host's $CD4^+$ T cells which play an essential role in the immune system. HIV-1 infection leads to reduction of T cells over time. Therefore, the count of T cells is used to measure advancement of HIV-1 infection. The population dynamics of $CD4^+$ T cells is modeled in Perelson and Nelson (1999) as follows

$$\frac{dT}{dt} = s + pT\left(1 - \frac{T}{T_{max}}\right) - d_T T,$$

where T is the concentration of $CD4^+$ T cells, s is the source of new T cells from the thymus, p is the maximum $CD4^+$ T cells proliferation rate, T_{max} is the maximum level of $CD4^+$ T concentration when T_{max} is chosen such that $d_T T_{max} > s$ and d_T is the death rate per T cell. When HIV-1 infects $CD4^+$ T cells, they become infected cells, I. Hence, the model of dynamics between the immune system and HIV-1 is given in Perelson and Nelson (1999) by

$$\begin{cases} \dfrac{dT}{dt} = s + pT\left(1 - \dfrac{T}{T_{max}}\right) - d_T T - kVT \\ \dfrac{dI}{dt} = kVT - \delta I \\ \dfrac{dV}{dt} = N\delta I - cV, \end{cases} \tag{1}$$

where I and V are the concentrations of infected $CD4^+$ T cells and viral particles in plasma, respectively. The term kVT denotes the infection of $CD4^+$ T cells by HIV-1 with the infection rate constant k. In this model, δ represents the death rate of infected cells, c is the virus clearance rate constant, and N is the number of new virus particles produced per infected cell.

Perelson et al. (1996) developed a mathematical model from a clinical trial where five HIV-1 infected patients were given the protease inhibitor ritonavir. After treatment, HIV-1 RNA concentrations in plasma, viral load of genetic material, were measured every 2 h until the 6 h, every 6 h until day 2, and every day until day 7. In this clinical trial, 15 data points were obtained from each patient where the unit of time was in days. System (1) is assumed to be at quasi-steady state before treatment, that is, V and I are relatively constant yielding $I' = 0$ and $V' = 0$. Hence, $kV_0T_0 = \delta I_0$ and $N\delta I_0 = cV_0$, and so $c = NkT_0$ and $I_0 = \frac{kV_0T_0}{\delta}$, where the subscript 0 denotes a pretreatment quasi-steady state value.

After treatment, newly created virions are noninfectious while infectious virions from prior to the treatment still remain. Therefore, the total virus concentration is

$$V = V_I + V_{NI}, \tag{2}$$

where V_I and V_{NI} are the concentrations of infectious and noninfectious virions, respectively. Drug efficacy is assumed 100% and (1) becomes

$$\begin{cases} \dfrac{dT}{dt} = s + pT\left(1 - \dfrac{T}{T_{max}}\right) - d_T T - kVT \\ \dfrac{dI}{dt} = kV_I T - \delta I \\ \dfrac{dV_I}{dt} = -cV_I \\ \dfrac{dV_{NI}}{dt} = N\delta I - cV_{NI}. \end{cases} \tag{3}$$

Assuming that system (1) is at quasi-steady state before drug treatment and T remains at approximately its steady state value T_0, that is $T = constant = T_0$ for 1 week after drug treatment, (3) leads to the following system

$$\begin{cases} \dfrac{dI}{dt} = kV_I T_0 - \delta I \\ \dfrac{dV_I}{dt} = -cV_I \\ \dfrac{dV_{NI}}{dt} = N\delta I - cV_{NI} \end{cases} \tag{4}$$

with the initial conditions

$$\begin{cases} I(0) = \frac{kV_0 T_0}{\delta} \\ V_I(0) = V_0 \\ V_{NI}(0) = 0. \end{cases} \tag{5}$$

Perelson and Nelson (1999) also develop a mathematical model for the effects of combination therapy with both RT and protease inhibitors

$$\begin{cases} \dfrac{dI}{dt} = (1 - \eta_{RT})kV_I T_0 - \delta I \\ \dfrac{dV_I}{dt} = (1 - \eta_{PI})N\delta I - cV_I \\ \dfrac{dV_{NI}}{dt} = \eta_{PI} N\delta I - cV_{NI} \end{cases} \tag{6}$$

with the initial conditions (5), where η_{RT} and η_{PI} are the efficacy of the RT and protease inhibitors, respectively, on anti-HIV treatment. In particular, $\eta_{PI}, \eta_{RT} = 0$ denote a null therapy, while $\eta_{PI}, \eta_{RT} = 1$ denotes a 100% effective therapy.

The systems above are continuous models of HIV-1 dynamics in vivo. According to our knowledge, there hasn't been any study of the discrete cases of these models. Instead of considering a discrete model itself, we prefer unifying the continuous and discrete analysis in one comprehensive theory, a so called time scales theory. A time

scale, denoted by $\mathbb{T}$, is an arbitrary nonempty closed subset of the real numbers. The theory of time scales was first initiated by Stefan Hilger in his PhD thesis (Hilger 1988). The set of all real numbers $\mathbb{R}$, which gives rise to differential equations, the set of all integers $\mathbb{Z}$, which gives rise to difference equations, and the set of all integer powers of a number $q > 1$, including 0, which gives rise to q-difference equations, are the well known examples of time scales, see Elaydi (2005), Kelley and Peterson (2001) and Kac and Cheung (2002).

In this paper, we first consider a mathematical model of perfect protease inhibitor monotherapy of HIV-1 infection on time scales. One of our main purposes is to analyze patient data presented in Perelson et al. (1996) on continuous and discrete cases. The outline of this paper is as follows: In Sect. 2, time scales calculus is introduced briefly including essentials. In Sect. 3, we formulate an initial value problem (IVP) modeling the dynamics of HIV-1 on time scales generalizing the IVP (4), (5) and calculate the total concentration of plasma virions on different time scales. In addition to these models, we also introduce an alternative discrete model in Sect. 4. We compare all these models by using nonlinear least squares fitting in Sect. 5. It turns out that the alternative discrete model gives the best fit in hours. This motivates us to consider another discrete model with the step-size $h > 0$ and this model has the best fit in days. In the last section, we present a mathematical model of imperfect RT and protease inhibitors combination therapy of HIV-1 infection on time scales, and analyze the stability of the zero solution.

2 Essentials

In this section, we first include some preliminary concepts regarding the calculus on time scales without proofs. The proofs can be found in the books written by Bohner and Peterson (2001, 2003).

Definition 1 For $t \in \mathbb{T}$, the *forward jump operator* $\sigma : \mathbb{T} \to \mathbb{T}$ is

$$\sigma(t) := \inf\{s \in \mathbb{T} : s > t\}$$

while the *backward jump operator* $\rho : \mathbb{T} \to \mathbb{T}$

$$\rho(t) := \sup\{s \in \mathbb{T} : s < t\},$$

and the *graininess function* $\mu : \mathbb{T} \to [0, \infty)$, defined as $\mu(t) := \sigma(t) - t$.

If $\sigma(t) > t$, we say that t is *right-scattered*, while if $\rho(t) < t$ we say that t is *left-scattered*. Points that are right-scattered and left-scattered at the same time are called *isolated*. Besides, if $t < \sup \mathbb{T}$ and $\sigma(t) = t$, then t is called *right-dense*, and if $t > \inf \mathbb{T}$ and $\rho(t) = t$, then t is called *left-dense*. Points that are right-dense and left-dense at the same time are called *dense*. The function $f^\sigma : \mathbb{T} \to \mathbb{R}$ is defined by $f^\sigma(t) = f(\sigma(t))$ for all $t \in \mathbb{T}$, i.e., $f^\sigma = f \circ \sigma$ and $[t_0, \infty)_{\mathbb{T}} := [t_0, \infty) \cap \mathbb{T}$. If $\mathbb{T}$ has a left-scattered maximum m, then $\mathbb{T}^\kappa = \mathbb{T} - \{m\}$. Otherwise, $\mathbb{T}^\kappa = \mathbb{T}$.

Definition 2 Assume $f : \mathbb{T} \to \mathbb{R}$ is a function and let $t \in \mathbb{T}^\kappa$. Then, the *delta* (or Hilger) *derivative* of f, denoted by f^Δ, on $\mathbb{T}^\kappa$ is defined to be the number (provided it exists) such that for given any $\epsilon > 0$, there is a neighborhood $U = (t - \delta, t + \delta)$ for some $\delta > 0$ such that

$$|[f^\sigma(t) - f(s)] - f^\Delta(t)[\sigma(t) - s]| \leq \epsilon|\sigma(t) - s|$$

for all $s \in U$.

If $\mathbb{T} = \mathbb{R}$, then $f^\Delta = f'$, i.e., the delta derivative coincides with the usual derivative. If $\mathbb{T} = \mathbb{Z}$, then $f^\Delta(t) = \Delta f(t) = f(t + 1) - f(t)$, where Δ is the usual forward difference operator.

Theorem 1 *Assume $f : \mathbb{T} \to \mathbb{R}$ is a function and let $t \in \mathbb{T}^\kappa$. Then we have the following:*

(i) *If f is differentiable at t, then f is continuous at t.*
(ii) *If f is continuous at t and t is right-scattered, then f is differentiable at t with*

$$f^\Delta(t) = \frac{f^\sigma(t) - f(t)}{\mu(t)}.$$

(iii) *If t is right-dense, then f is differentiable at t iff the limit*

$$\lim_{s \to t} \frac{f(t) - f(s)}{t - s}$$

exists as a finite number. In this case

$$f^\Delta(t) = \lim_{s \to t} \frac{f(t) - f(s)}{t - s}.$$

(iv) *If f is differentiable at t, then $f^\sigma(t) = f(t) + \mu(t) f^\Delta(t)$.*

Theorem 2 *Assume $f, g : \mathbb{T} \to \mathbb{R}$ are differentiable at $t \in \mathbb{T}^\kappa$. Then:*

(i) *The sum $f + g : \mathbb{T} \to \mathbb{R}$ is differentiable at t with*

$$(f + g)^\Delta(t) = f^\Delta(t) + g^\Delta(t).$$

(ii) *The product $fg : \mathbb{T} \to \mathbb{R}$ is differentiable at t with*

$$(fg)^\Delta(t) = f^\Delta(t)g(t) + f^\sigma(t)g^\Delta(t) = f(t)g^\Delta(t) + f^\Delta(t)g^\sigma(t).$$

(iii) *If $g(t)g^\sigma(t) \neq 0$, then $\frac{f}{g}$ is differentiable at t and*

$$\left(\frac{f}{g}\right)^\Delta(t) = \frac{f^\Delta(t)g(t) - f(t)g^\Delta(t)}{g(t)g^\sigma(t)}.$$

Definition 3 A function $f : \mathbb{T} \to \mathbb{R}$ is called *rd-continuous* provided it is continuous at right-dense points in $\mathbb{T}$ and its left-sided limit exists (finite) at left dense points in $\mathbb{T}$. The set of rd-continuous $f : \mathbb{T} \to \mathbb{R}$ is denoted by $C_{rd} = C_{rd}(\mathbb{T}) = C_{rd}(\mathbb{T}, \mathbb{R})$.

Every rd-continuous function has an antiderivative. In particular, if $t_0 \in \mathbb{T}$, then for $t \in T$

$$F := \int_{t_0}^{t} f(\tau)\Delta\tau$$

is an antiderivative of f.

Definition 4 A function $f : \mathbb{T} \to \mathbb{R}$ is called *regressive* provided

$$1 + \mu(t) f(t) \neq 0$$

for all $t \in \mathbb{T}^{\kappa}$. The set of all regressive and rd-continuous functions $f : \mathbb{T} \to \mathbb{R}$ is denoted by $\mathscr{R} = \mathscr{R}(\mathbb{T}) = \mathscr{R}(\mathbb{T}, \mathbb{R})$.

Definition 5 If $p, q \in \mathscr{R}$, then the function $\ominus p$ *circle minus* is defined by

$$(\ominus p)(t) := -\frac{p(t)}{1 + \mu(t)p(t)}$$

while the function *circle minus substraction* is defined by

$$(p \ominus q)(t) := \frac{p(t) - q(t)}{1 + \mu(t)q(t)}$$

for all $t \in \mathbb{T}^{\kappa}$.

Theorem 3 *Suppose $p \in \mathscr{R}$ and fix $t_0 \in \mathbb{T}$. Then the initial value problem*

$$y^{\Delta} = p(t)y, \quad y(t_0) = 1$$

has a unique solution $e_p(\cdot, t_0)$, the so called the exponential function on time scales.

Let $a, b \in \mathbb{T}$ with $a < b$, $f \in C_{rd}$ and $\alpha \in \mathscr{R}$. Then, if $\mathbb{T} = \mathbb{R}$

$$\int_a^b f(t)\Delta t = \int_a^b f(t)dt, \quad e_\alpha(t, t_0) = e^{\alpha(t-t_0)} \quad \text{and} \quad e_{\ominus\alpha} = e^{-\alpha(t-t_0)}.$$

If $\mathbb{T} = h\mathbb{Z} = \{hk : k \in \mathbb{Z}\}$, where $h > 0$ then

$$\int_a^b f(t)\Delta t = \sum_{k=a/h}^{b/h-1} f(kh)h, \quad e_\alpha(t, t_0) = (1 + \alpha h)^{(t-t_0)/h} \quad \text{and}$$
$$e_{\ominus\alpha} = (1 + \alpha h)^{-(t-t_0)/h}.$$

We use the following properties of exponential functions on time scales in our proofs, see Theorems 2.36 and 2.38 in Bohner and Peterson (2001).

Theorem 4 *If $p, q \in \mathscr{R}$, then*

(i) $e_0(t,s) = 1$ *and* $e_p(t,t) = 1$
(ii) $e_p(\sigma(t),s) = (1+\mu(t)p(t))e_p(t,s)$
(iii) $e_p(t,s) = \dfrac{1}{e_p(s,t)} = e_{\ominus p}(s,t)$
(iv) $e_p(t,s)e_p(s,r) = e_p(t,r)$
(v) $e^{\Delta}_{p\ominus q}(\cdot,t_0) = (p-q)\dfrac{e_p(\cdot,t_0)}{e^{\sigma}_q(\cdot,t_0)}$.

We need the following Variation of Constants Formulas on time scales.

Theorem 5 (Bohner and Peterson (2001), Theorem 2.74) *Suppose $p \in \mathscr{R}$ and $f \in C_{rd}$. Let t_0 and $y_0 \in \mathbb{R}$. The unique solution of the initial value problem*

$$y^{\Delta} = -p(t)y^{\sigma} + f(t), \quad y(t_0) = y_0$$

is given by

$$y(t) = e_{\ominus p}(t,t_0)y_0 + \int_{t_0}^{t} e_{\ominus p}(t,\tau)f(\tau)\Delta\tau.$$

Theorem 6 (Bohner and Peterson (2001), Theorem 2.77) *Suppose $p \in \mathscr{R}$ and $f \in C_{rd}$. Let t_0 and $y_0 \in \mathbb{R}$. The unique solution of the initial value problem*

$$y^{\Delta} = -p(t)y + f(t), \quad y(t_0) = y_0$$

is given by

$$y(t) = e_p(t,t_0)y_0 + \int_{t_0}^{t} e_p(t,\sigma(\tau))f(\tau)\Delta\tau.$$

An $n \times n$ -matrix-valued function A on a time scale $\mathbb{T}$ is called regressive provided $I + \mu(t)A(t)$ is invertible for all $t \in \mathbb{T}^{\kappa}$.

Theorem 7 (Bohner and Peterson (2001), Exercise 5.6) *An $n \times n$ -matrix-valued function A is regressive iff the eigenvalues $\lambda_i(t)$ of $A(t)$ are regressive for all $1 \le i \le n$.*

The vector dynamic equation

$$x^{\Delta} = Ax,$$

where $A \in \mathscr{R}$ is a real constant $n \times n$-matrix is considered.

Theorem 8 (Bohner and Peterson (2001), Theorem 5.30) *If λ_0, ξ is an eigenpair for the constant $n \times n - matrix$ A, then $x(t) = e_{\lambda_0}(t,t_0)\xi$ is a solution of the vector dynamic equation above on $\mathbb{T}$.*

To have an alternative discrete model to the IVP (3), (5), we need the following results.

Theorem 9 (Kelley and Peterson (2001), Theorem 3.1) *Let $p(t) \neq 0$ and $r(t)$ be given for $t = a, a+1, \ldots$. Then,*

(i) *The solutions of $u(t+1) = p(t)u(t)$ are*

$$u(t) = u(a)\prod_{s=a}^{t-1} p(s), \quad (t = a, a+1, \cdots)$$

(ii) *All solutions of $y(t+1) - p(t)y(t) = r(t)$ are given by*

$$y(t) = u(t)\left[\sum \frac{r(t)}{Eu(t)} + C\right],$$

where E is the shift operator defined by $Eu(t) = u(t+1)$, C is a constant, and $u(t)$ is any nonzero function from part (i).

Here, an "indefinite sum" (or "antidifference") of $y(t)$, denoted $\sum y(t)$, is any function so that $\Delta\left(\sum y(t)\right) = y(t)$ for all t in the domain of y.

The following system of n linear equations:

$$\begin{array}{rcl} u_1(t+1) &=& a_{11}u_1(t) + a_{12}u_2(t) + \cdots + a_{1n}u_n(t) \\ u_2(t+1) &=& a_{21}u_1(t) + a_{22}u_2(t) + \cdots + a_{2n}u_n(t) \\ \vdots & & \vdots \\ u_n(t+1) &=& a_{n1}u_1(t) + a_{n2}u_2(t) + \cdots + a_{nn}u_n(t) \end{array}$$

may be written in the vector form

$$u(t+1) = Au(t) \tag{7}$$

where $u(t) = (u_1(t), u_2(t), \cdots, u_n(t))^T \in \mathbb{R}^n$, and $A = (a_{ij})$ is an $n \times n$ real nonsingular matrix. Here T indicates the transpose of a vector. System (7) is considered autonomous, or time-invariant, since the values of A are all constants. The *spectral radius* of A is defined as

$$r(A) = max\left\{|\xi| : \xi \text{ is an eigenvalue of A}\right\}.$$

The next theorem summarizes the main stability results for the linear autonomous (time-invariant) systems (7).

Theorem 10 (Elaydi (2005), Theorem 4.13) *The following statements hold:*

(i) *The zero solution of (7) is stable if and only if $r(A) \leq 1$ and the eigenvalues of unit modulus are semisimple, i.e., if the corresponding Jordan block is diagonal.*
(ii) *The zero solution of (7) is asymptotically stable if and only if $r(A) < 1$.*

3 Dynamics of HIV-1 decline during 100% effective protease inhibitor monotherapy

We consider one of the generalization of the IVP (4), (5)

$$\begin{cases} I^{\Delta} = kV_I^{\sigma} T_0 - \delta I^{\sigma} \\ V_I^{\Delta} = -cV_I^{\sigma} \\ V_{NI}^{\Delta} = N\delta I^{\sigma} - cV_{NI}^{\sigma} \end{cases} \tag{8}$$

on $[0, \infty)_{\mathbb{T}}$ subject to the initial conditions (5), where all parameters are positive constants such that $\delta \neq c$. Here, the forward jump operator appears in the system. In this section, our purpose is to find the total concentration of plasma virions on different time scales. To do this, we first solve the IVP (8), (5).

Theorem 11 *The unique solution (I, V_I, V_{NI}) of the IVP (8), (5) is given by*

$$\begin{cases} I(t) = e_{\ominus\delta}(t,0)kV_0T_0\left\{\frac{1}{\delta} + \frac{1}{\delta - c}\left[e_{\delta\ominus c}(t,0) - 1\right]\right\} \\ V_I(t) = e_{\ominus c}(t,0)V_0 \\ V_{NI}(t) = \frac{cV_0}{c-\delta}\left\{\frac{c}{c-\delta}\left[e_{\ominus\delta}(t,0) - e_{\ominus c}(t,0)\right] - \delta e_{\ominus c}(t,0)\int_0^t \frac{1}{1+\mu(\tau)c}\Delta\tau\right\}, \end{cases}$$

where all parameters are positive constants such that $\delta \neq c$.

Proof We start with the second equation of (8) with $V_I(0) = V_0$ to solve the system. From Theorem 5, we obtain

$$V_I(t) = e_{\ominus c}(t,0)V_0. \tag{9}$$

Substituting V_I into the first equation of (8) yields

$$I^{\Delta}(t) = ke_{\ominus c}^{\sigma}(t,0)V_0T_0 - \delta I^{\sigma}(t). \tag{10}$$

From Theorem 5, the IVP (10) with $I(0) = \frac{kV_0T_0}{\delta}$ has a unique solution

$$I(t) = e_{\ominus\delta}(t,0)I(0) + kV_0T_0\int_0^t e_{\ominus\delta}(t,\tau)e_{\ominus c}^{\sigma}(\tau,0)\Delta\tau, \quad t \geq 0.$$

Since we assume that I is in quasi-steady state before initiation of theraphy, after plugging $I(0)$ into I above and using the properties of exponential functions given in

Theorem 4, we get

$$
\begin{aligned}
I(t) &= e_{\ominus\delta}(t,0)\frac{kV_0T_0}{\delta} + kV_0T_0\int_0^t e_{\ominus\delta}(t,\tau)e^{\sigma}_{\ominus c}(\tau,0)\Delta\tau \qquad (11)\\
&= e_{\ominus\delta}(t,0)\frac{kV_0T_0}{\delta} + kV_0T_0e_{\ominus\delta}(t,0)\int_0^t e_{\ominus\delta}(0,\tau)\frac{1}{e^{\sigma}_c(\tau,0)}\Delta\tau\\
&= e_{\ominus\delta}(t,0)\frac{kV_0T_0}{\delta} + kV_0T_0\frac{e_{\ominus\delta}(t,0)}{\delta-c}\int_0^t e^{\Delta}_{\delta\ominus c}(\tau,0)\Delta\tau\\
&= e_{\ominus\delta}(t,0)\frac{kV_0T_0}{\delta} + kV_0T_0\frac{e_{\ominus\delta}(t,0)}{\delta-c}\left[e_{\delta\ominus c}(t,0)-1\right].
\end{aligned}
$$

Therefore,

$$
I(t) = e_{\ominus\delta}(t,0)kV_0T_0\left\{\frac{1}{\delta}+\frac{1}{\delta-c}\left[e_{\delta\ominus c}(t,0)-1\right]\right\}. \qquad (12)
$$

To solve V_{NI}, we substitute (12) into the third equation of system (8) and obtain

$$
V^{\Delta}_{NI}(t) = N\delta kV_0T_0e^{\sigma}_{\ominus\delta}(t,0)\left\{\frac{1}{\delta}+\frac{1}{\delta-c}\left[e^{\sigma}_{\delta\ominus c}(t,0)-1\right]\right\} - cV^{\sigma}_{NI}(t). \qquad (13)
$$

From Theorem 5 and $c = NkT_0$, the IVP (13) with $V_{NI}(0) = 0$ has a unique solution

$$
\begin{aligned}
V_{NI}(t) &= e_{\ominus c}(t,0)V_{NI}(0) + cV_0\delta\int_0^t e_{\ominus c}(t,\tau)e^{\sigma}_{\ominus\delta}(\tau,0)\\
&\quad\times\left\{\frac{1}{\delta}+\frac{1}{\delta-c}\left[e^{\sigma}_{\delta\ominus c}(\tau,0)-1\right]\right\}\Delta\tau.
\end{aligned}
$$

Using $V_{NI}(0) = 0$ and properties of exponential functions on time scales yield

$$
\begin{aligned}
&V_{NI}(t)\\
&= cV_0\left\{\frac{c}{c-\delta}\int_0^t e_{\ominus c}(t,\tau)e^{\sigma}_{\ominus\delta}(\tau,0)\Delta\tau + \frac{\delta}{\delta-c}\int_0^t e_{\ominus c}(t,\tau)e^{\sigma}_{\ominus\delta}(\tau,0)e^{\sigma}_{\delta\ominus c}(\tau,0)\Delta\tau\right\}\\
&= cV_0\left\{\frac{c}{c-\delta}\left[\frac{e_{\ominus c}(t,0)}{c-\delta}\left(e_{c\ominus\delta}(t,0)-1\right)\right] + \frac{\delta}{\delta-c}\int_0^t e_{\ominus c}(t,\tau)\frac{1}{e^{\sigma}_{\delta}(\tau,0)}\frac{e^{\sigma}_{\delta}(\tau,0)}{e^{\sigma}_{c}(\tau,0)}\Delta\tau\right\}\\
&= cV_0\left\{\frac{c}{(c-\delta)^2}\left[e_{\ominus\delta}(t,0)-e_{\ominus c}(t,0)\right] + \frac{\delta}{\delta-c}e_{\ominus c}(t,0)\int_0^t e_{\ominus c}(0,\tau)\frac{1}{e^{\sigma}_{c}(\tau,0)}\Delta\tau\right\}\\
&= cV_0\left\{\frac{c}{(c-\delta)^2}\left[e_{\ominus\delta}(t,0)-e_{\ominus c}(t,0)\right] + \frac{\delta}{\delta-c}e_{\ominus c}(t,0)\int_0^t \frac{1}{1+\mu(\tau)c}\Delta\tau\right\},
\end{aligned}
$$

where the first integration above is computed as in (11). Hence,

$$
V_{NI}(t) = \frac{cV_0}{c-\delta}\left\{\frac{c}{c-\delta}\left[e_{\ominus\delta}(t,0)-e_{\ominus c}(t,0)\right] - \delta e_{\ominus c}(t,0)\int_0^t \frac{1}{1+\mu(\tau)c}\Delta\tau\right\}. \qquad (14)
$$

This completes the proof. □

Note that (9) and (14) imply that the total concentration of plasma virions (2) is

$$V(t) = e_{\ominus c}(t,0)V_0 + \frac{cV_0}{c-\delta}\left\{\frac{c}{c-\delta}\left[e_{\ominus\delta}(t,0) - e_{\ominus c}(t,0)\right] - \delta e_{\ominus c}(t,0)\int_0^t \frac{1}{1+\mu(\tau)c}\Delta\tau\right\}. \tag{15}$$

In the next examples, we calculate (15) on different time scales for data analysis.

Example 1 The total viral concentration (15) turns out to be

$$V(t) = e^{-ct}V_0 + \frac{cV_0}{c-\delta}\left\{\frac{c[e^{-\delta t} - e^{-ct}]}{c-\delta} - \delta t e^{-ct}\right\} \tag{16}$$

on $[0,\infty)$ which is consistent with the total viral load in Perelson et al. (1996).

Example 2 Now consider the isolated time scales $[0,\infty)_{h\mathbb{Z}}$, $h > 0$. In this case, the total concentration of plasma virions is

$$V(t) = \frac{1}{(1+ch)^{\frac{t}{h}}}V_0 + \frac{cV_0}{c-\delta}\left\{\frac{c[(1+ch)^{\frac{t}{h}} - (1+\delta h)^{\frac{t}{h}}]}{(c-\delta)(1+\delta h)^{\frac{t}{h}}(1+ch)^{\frac{t}{h}}} - \frac{\delta t}{(1+ch)^{\frac{t}{h}+1}}\right\}. \tag{17}$$

In the special case of $h = 1$ in (17), that is on $[0,\infty)_{\mathbb{Z}}$, we have

$$V(t) = \frac{1}{(1+c)^t}V_0 + \frac{cV_0}{c-\delta}\left\{\frac{c[(1+c)^t - (1+\delta)^t]}{(c-\delta)(1+\delta)^t(1+c)^t} - \frac{\delta t}{(1+c)^{t+1}}\right\}. \tag{18}$$

4 An alternative discrete HIV-1 model

Note that system (8) turns out to be the following advanced system of first order difference equations:

$$\begin{cases} \Delta I(t) = kV_I(t+1)T_0 - \delta I(t+1) \\ \Delta V_I(t) = -cV_I(t+1) \\ \Delta V_{NI}(t) = N\delta I(t+1) - cV_{NI}(t+1) \end{cases} \tag{19}$$

on $[0,\infty)_{\mathbb{Z}}$ and the related total concentration of plasma virions of system (19) is given by (18). In this section, we now consider an alternative discrete model that is not advanced in order to determine which system models the dynamics of HIV-1 decline in ART-treated patients better. In particular, we study

$$\begin{cases} \Delta I(t) = kV_I(t)T_0 - \delta I(t) \\ \Delta V_I(t) = -cV_I(t) \\ \Delta V_{NI}(t) = N\delta I(t) - cV_{NI}(t) \end{cases} \tag{20}$$

on $[0, \infty)_{\mathbb{Z}}$ with initial conditions (5) and the related total concentration of plasma virions of system (20) is given by (25). A comparison of fits to patients data using models (19) and (20) will be given in Tables 1 and 2 below after we establish some properties of model (20).

We have the following theorem where we assume $c \neq \delta$ and $c, \delta \neq 1$ in order to solve (20).

Theorem 12 *The unique solution (I, V_I, V_{NI}) of the IVP (20), (5) is given by*

$$\begin{cases} I(t) = \frac{kV_0T_0}{\delta - c}\left\{(1-c)^t - \frac{c(1-\delta)^t}{\delta}\right\} \\ V_I(t) = V_0(1-c)^t \\ V_{NI}(t) = \frac{cV_0}{c-\delta}\left\{\frac{c}{c-\delta}\left[(1-\delta)^t - (1-c)^t\right] - \delta t(1-c)^{t-1}\right\}, \end{cases}$$

where all parameters are positive constants such that $\delta \neq c$ and $c, \delta \neq 1$.

Proof System (20) can be written as a recurrence relation

$$\begin{cases} I(t+1) = kV_I(t)T_0 + (1-\delta)I(t) \\ V_I(t+1) = (1-c)V_I(t) \\ V_{NI}(t+1) = N\delta I(t) + (1-c)V_{NI}(t). \end{cases} \tag{21}$$

Solving the second equation with $V_I(0) = V_0$ and using Theorem 9 (i), we obtain

$$V_I(t) = V_I(0)\prod_{s=0}^{t-1}(1-c) = V_0(1-c)^t. \tag{22}$$

Substituting (22) into the first equation of (21), one can obtain

$$I(t+1) = kV_0T_0(1-c)^t + (1-\delta)I(t).$$

By Theorem 9 (i), the solution of $u^*(t+1) = (1-\delta)u^*(t)$ is

$$u^*(t) = u^*(0)\prod_{s=0}^{t-1}(1-\delta) = (1-\delta)^t,$$

where $u^*(0) = 1$. Then by Theorem 9 (ii), we have

$$\begin{aligned} I(t) &= u^*(t)\left[\sum \frac{kV_0T_0(1-c)^t}{u^*(t+1)} + C\right] \\ &= (1-\delta)^t\left[\sum \frac{kV_0T_0(1-c)^t}{(1-\delta)^{t+1}} + C\right] \\ &= (1-\delta)^t\left[\frac{kV_0T_0(1-c)^t}{(\delta-c)(1-\delta)^t} + C\right], \end{aligned}$$

where C is an arbitrary constant. Therefore,

$$I(t) = \frac{kV_0T_0(1-c)^t}{\delta - c} + (1-\delta)^t C, \tag{23}$$

and $I(0) = \frac{kV_0T_0}{\delta}$ implies $C = -\frac{ckV_0T_0}{\delta(\delta-c)}$. Substituting C into (23), we obtain

$$I(t) = \frac{kV_0T_0}{\delta - c}\left[(1-c)^t - \frac{c(1-\delta)^t}{\delta}\right].$$

To solve V_{NI}, we first plug I into the third equation of (20) and then use the fact $NkT_0 = c$ and obtain

$$V_{NI}(t+1) = \frac{cV_0\delta}{\delta - c}\left[(1-c)^t - \frac{c}{\delta}(1-\delta)^t\right] + (1-c)V_{NI}(t).$$

By Theorem 9 (i), the solution of $u(t+1) = (1-c)u(t)$ is

$$u(t) = u(0)\prod_{s=0}^{t-1}(1-c) = (1-c)^t,$$

where $u(0) = 1$. Then, we have

$$\begin{aligned}
V_{NI}(t) &= u(t)\left\{\sum \frac{\frac{cV_0\delta}{\delta-c}\left[(1-c)^t - \frac{c(1-\delta)^t}{\delta}\right]}{u(t+1)} + D\right\} \\
&= (1-c)^t\left\{\sum \frac{\frac{cV_0\delta}{\delta-c}\left[(1-c)^t - \frac{c(1-\delta)^t}{\delta}\right]}{(1-c)^{t+1}} + D\right\} \\
&= (1-c)^t\left\{\frac{cV_0\delta}{(\delta-c)(1-c)}\sum\left[1 - \frac{c}{\delta}\left(\frac{1-\delta}{1-c}\right)^t\right] + D\right\} \\
&= (1-c)^t\left\{\frac{cV_0\delta}{(\delta-c)(1-c)}\left[t - \frac{c}{\delta}\left(\frac{1-\delta}{1-c}\right)^t\frac{1-c}{c-\delta}\right] + D\right\},
\end{aligned}$$

where D is an arbitrary constant and we use Theorem 9 (ii). Hence,

$$V_{NI}(t) = -\frac{cV_0\delta t(1-c)^{t-1}}{c-\delta} + \frac{c^2V_0(1-\delta)^t}{(c-\delta)^2} + (1-c)^t D.$$

To evaluate D, we use $V_{NI}(0) = 0$ yielding $D = -\frac{c^2V_0}{(c-\delta)^2}$, and that

$$V_{NI}(t) = \frac{cV_0}{c-\delta}\left\{\frac{c}{c-\delta}\left[(1-\delta)^t - (1-c)^t\right] - \delta t(1-c)^{t-1}\right\}, \tag{24}$$

and hence the proof is completed. □

In this discrete case, the total concentration of plasma virions of the IVP (20), (5) that follows from (22) and (24) is given by

$$V(t) = V_0(1-c)^t + \frac{cV_0}{c-\delta}\left\{\frac{c}{c-\delta}\left[(1-\delta)^t - (1-c)^t\right] - \delta t(1-c)^{t-1}\right\}, \quad (25)$$

which is not equivalent to (18).

Note that $\delta > c > 1$ and chosing t to be even guarantee the positiveness of V_I as in (22) and V_{NI} as in (24).

5 Data analysis

In this section, we determine how well the total viral concentrations obtained from our models fit the HIV-1 RNA measurements from one reprensentative patient, namely patient 104 in Perelson et al. (1996). Here, we use MATLAB with nonlinear least squares fitting of data to estimate the parameters of our models.

In the previous sections, we model the dynamics of HIV-1 decline in patients on protease inhibitor monotherapy by the IVPs (8), (5) and (20), (5). From the IVP (8), (5), we obtain the total viral concentrations (16), (17), (18) on $[0, \infty)_{\mathbb{T}}$ when $\mathbb{T}$ is equal to $\mathbb{R}$, $h\mathbb{Z}$ and $\mathbb{Z}$, respectively. From the alternative discrete model (20), (5), we obtain (25) on $[0, \infty)_{\mathbb{Z}}$.

In Tables 1 and 2, these total viral concentrations are represented in the second row when $\mathbb{T}$ is equal to $\mathbb{R}$, $h\mathbb{Z}$ and $\mathbb{Z}$. Estimated parameters and evaluated R^2_{adj}, SSE and $RMSE$ values from the fit of (16), (17), (18) and (25) to the HIV-1 RNA data are listed in these tables as well.

In the following two subsections, we discuss the results from the fit of the total viral concentrations when the unit of time is in days and in hours.

5.1 Time in days

In Perelson et al. (1996), HIV-1 RNA data was measured every 2 h until the 6 h, every 6 h until day 2, and every day until day 7 and the unit of the original data is in days.

Note that the IVP (8), (5) when $\mathbb{T} = \mathbb{R}$ is known as the continuous case and (16) is the corresponding total viral load introducing in Perelson et al. (1996). From Table 1, we conclude that the discrete cases (17) and (18) fit to the data as well as the continuous case (16) except for the alternative discrete case (25). (17) has the best fit when h gets very close to zero. In fact, the continuous case is obtained when $h \to 0$. In Perelson et al. (1996), the lower and upper 68% confidence intervals are calculated and the virion clearance rate is estimated as $c = 3.68$ day^{-1} that lies between 2.53 and 6.19 day^{-1} while the rate of loss of infected cells is estimated as $\delta = 0.50$ day^{-1} that lies between 0.47 and 0.54 day^{-1}. Note that c and δ obtained from the nonlinear regression analysis for the continuous case in our study are estimated as 3.11 day^{-1} and 0.51 day^{-1}, and within those confidence intervals, respectively, see Table 1.

Table 1 Data analysis when time is in days results

IVP		(8), (5)		(20), (5)
V	(16)	(17)	(18)	(25)
$\mathbb{T}$	$\mathbb{R}$	$h\mathbb{Z}$	$\mathbb{Z}$	$\mathbb{Z}$
R^2_{adj}	0.88916	0.87808	0.87955	0.52586
SSE	3079703800	3079703900	3346799500	13174681000
$RMSE$	14328.768	14328.768	14937.201	29636.33
V_0	133956.89	133958.03	138869.87	110124.12
c	3.11582	3.11637	2.54322	0.62332867
δ	0.51553	0.51549	0.83074	0.62332868
h		0.00000007		

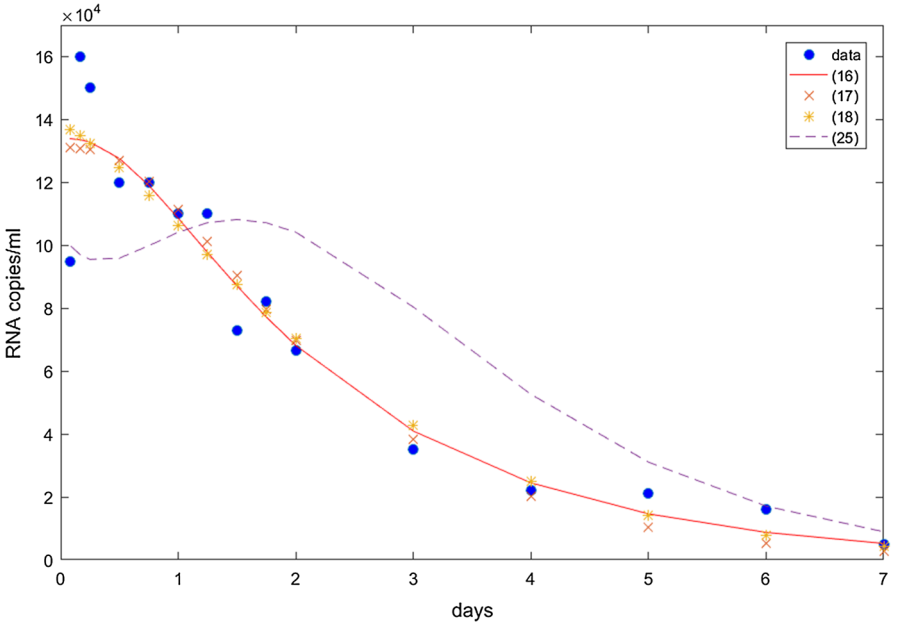

Fig. 1 Fitted models in days

Since (25) results a bad fit in days, see Fig. 1, this urges us to investigate a different time domain for (25). Therefore, we attempt scaling the input data by changing the unit from days to hours.

5.2 Time in hours

When changing the unit from days to hours, we note that all data was collected at times that are even when expressed in hours, i.e. t is even. We also observe that curve

Table 2 Data analysis when time is in hours

IVP		(8), (5)		(20), (5)
V	(16)	(17)	(18)	(25)
$\mathbb{T}$	$\mathbb{R}$	$h\mathbb{Z}$	$\mathbb{Z}$	$\mathbb{Z}$
R^2_{adj}	0.88916	0.87808	0.88859	0.97198
SSE	3079703800	3079703800	3095595300	778626850
$RMSE$	14328.768	14328.768	14365.689	7204.7524
V_0	133957	133956.79	134261.42	95708.735
c	0.12983	0.12982	0.12861	1.13006
δ	0.02148	0.02148	0.02189	1.98095
h		0.00000059		

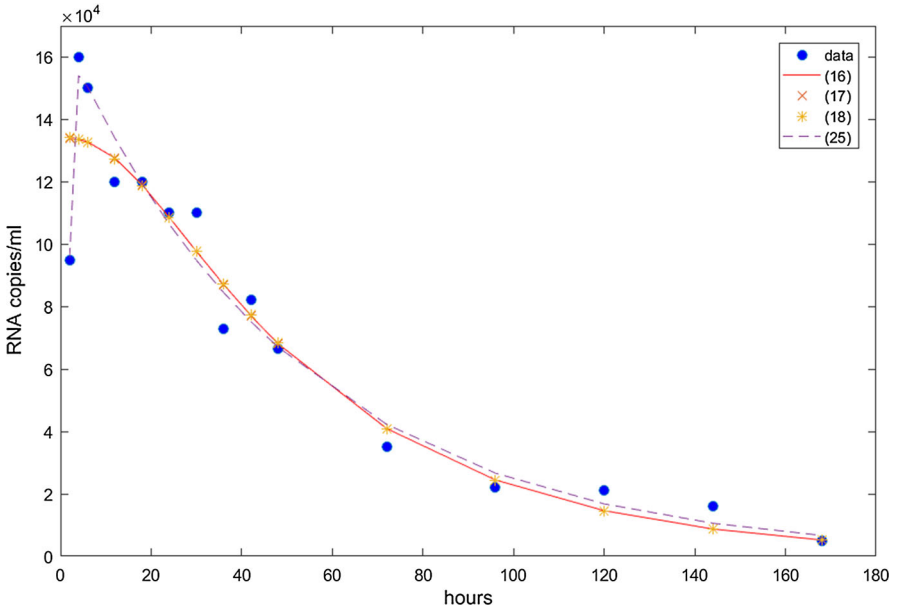

Fig. 2 Fitted models in hours

fittings of (16) and (17) to the data predict the same virion concentrations, see Tables 1 and 2. On the other hand, fittings of (18) and (25) to the data are improved. Indeed, fitting (25) to the data is not only improved significantly but also results in by far the highest R^2_{adj} value and smaller errors.

For all the patients in Perelson et al. (1996), HIV-1 RNA levels increase at the beginning of therapy, then drop down and keep decreasing. As seen in Fig. 2, (25) is the only model capturing this behavior in hours. For t even and $1 < c < 2$, the last term in (25), $-\delta t(1-c)^{t-1}$, is positive and initially increases and then decreases for the estimated parameters. Hence, this causes the initially increasing behavior of (25).

We observe that by changing the unit from days to hours the alternative discrete curve (25) has the best fit. This leads to the important point of whether one should discuss more discrete models for HIV-1 dynamics. Therefore, we now want to unify and extend the continuous IVP (4), (5) and the discrete IVP (20), (5) in order to obtain the total viral load on more discrete time settings. The model is formulated as follows:

$$\begin{cases} I^{\Delta} = kV_I T_0 - \delta I \\ V_I^{\Delta} = -cV_I \\ V_{NI}^{\Delta} = N\delta I - cV_{NI} \end{cases} \tag{26}$$

subject to the initial conditions (5), where all parameters are positive constants such that $\delta \neq c$, and $-c, -\delta \in \mathscr{R}$, i.e., $1 + \mu(-c) \neq 0$ and $1 + \mu(-\delta) \neq 0$.

Note that system (26) is equivalent to systems (4) and (8) on $[0, \infty)$ whereas it is equivalent to system (20) on $[0, \infty)_{\mathbb{Z}}$.

To find the total concentrations of virions, we follow similar steps of the proof of Theorem 13. By Theorems 4 and 6, we first obtain

$$V_I(t) = e_{-c}(t, 0)V_0$$

and

$$I(t) = kV_0T_0 \left\{ \frac{ce_{-\delta}(t, 0) - \delta e_{-c}(t, 0)}{\delta(c - \delta)} \right\}. \tag{27}$$

Substituting (27) in the third equation of system (26) and solving for V_{NI} yield

$$V_{NI}(t) = \frac{cV_0}{c - \delta} \left\{ \frac{c\left[e_{-\delta}(t, 0) - e_{-c}(t, 0)\right]}{c - \delta} - \delta e_{-c}(t, 0) \int_0^t \frac{1}{1 - \mu(\tau)c} \Delta\tau \right\}.$$

Hence, the total concentration of plasma virions is

$$V(t) = e_{-c}(t, 0)V_0 + \frac{cV_0}{c - \delta} \left\{ \frac{c\left[e_{-\delta}(t, 0) - e_{-c}(t, 0)\right]}{c - \delta} - \delta e_{-c}(t, 0) \int_0^t \frac{1}{1 - \mu(\tau)c} \Delta\tau \right\}. \tag{28}$$

As a result, (28) yields the same total concentration of plasma virions (16) on $[0, \infty)$ and (25) obtained on $[0, \infty)_{\mathbb{Z}}$. One can also calculate the total concentration of plasma virions (28) on $h\mathbb{Z}$ as

$$V(t) = (1 - ch)^{\frac{t}{h}} V_0 + \frac{cV_0}{c - \delta} \left\{ \frac{c\left[(1 - \delta h)^{\frac{t}{h}} - (1 - ch)^{\frac{t}{h}}\right]}{c - \delta} - \delta t(1 - ch)^{\frac{t}{h} - 1} \right\}, \tag{29}$$

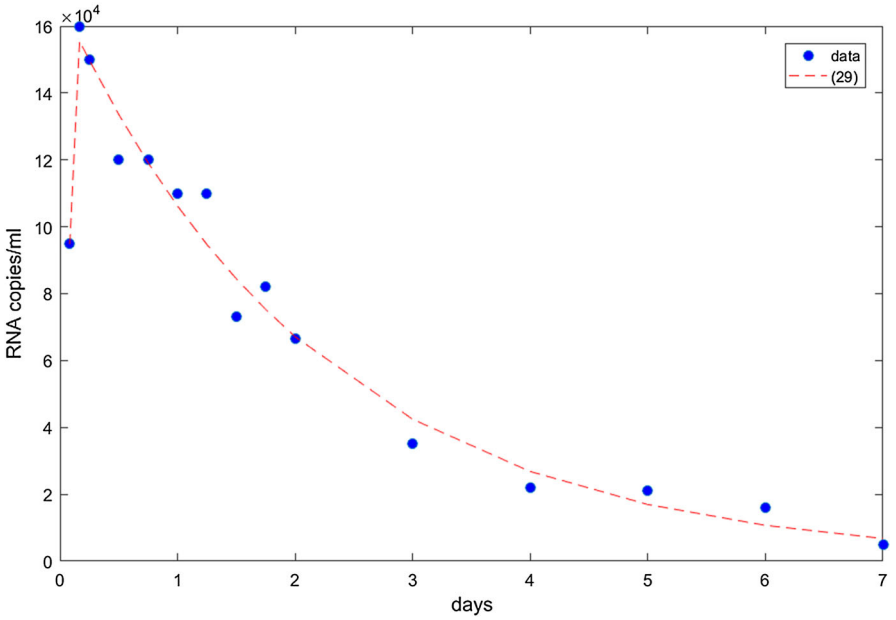

Fig. 3 Fitted model in days obtained from $h\mathbb{Z}$

which is not same as (17). Tables 1 and 2 show data fitting of (16), (17), (18) and (25). Now we compare (17) obtained from the system with forward jump operator and (29) obtained from the system without forward jump operator.

The data fitting of (29) is done with MATLAB fmincon and results 0.97004 R^2_{adj} value, where $SSE = 756676980$, $RMSE = 7102.4736$ and estimated initial value of virus concentration $V_0 = 151569.87$ in days. Figure 3 shows that (29) fits to the data better than other models with $c = 8.93828$, $\delta = 0.44710944$ day^{-1}, and $h = 0.11186$ in days. Note that the fittings of (29) in days and in hours result the same curve. Estimated parameters are $c = 0.35556$, $\delta = 0.01863$ hours^{-1}, $V_0 = 151082.19$, and $h = 2.81180$ in hours with 0.96996 hours^{-1} R^2_{adj} value, where $SSE = 758649430$, $RMSE = 7111.7247$.

When we compare all these models with MATLAB fmincon, we conclude that they yield consistent curve fittings as before.

6 Dynamics of HIV-1 decline on combination therapy

In the previous sections, we formulate the models of interaction of the immune system with HIV-1 when the patients were given only protease inhibitors under the assumption of efficacy of the protease inhibitor is 100%, i.e. $\eta_{PI} = 1$. Mathematical model (6) of HIV-1 infection is studied in Perelson and Nelson (1999) when patients were given combination of imperfect protease inhibitor and RT inhibitors. Hence, under the assumption of $\eta_{PI} \neq 0, 1$ and $\eta_{RT} \neq 0, 1$ we generalize this model on time scales as follows:

$$\begin{cases} I^{\Delta} = (1-\eta_{RT})kV_I T_0 - \delta I \\ V_I^{\Delta} = (1-\eta_{PI})N\delta I - cV_I \\ V_{NI}^{\Delta} = \eta_{PI} N\delta I - cV_{NI} \end{cases} \tag{30}$$

subject to the initial conditions (5) and find the total concentration of plasma virions on different time scales by solving the IVP (30), (5).

Theorem 13 *The unique solution* (I, V_I, V_{NI}) *of the IVP* (30), (5) *is given by*

$$\begin{cases} I(t) = \dfrac{kT_0V_0(1-\eta_{RT})}{\lambda_2-\lambda_1}\left\{\dfrac{\lambda_2+c\eta_{PI}}{\lambda_1+\delta}e_{\lambda_1}(t,0) - \dfrac{\lambda_1+c\eta_{PI}}{\lambda_2+\delta}e_{\lambda_2}(t,0)\right\} \\ V_I(t) = \dfrac{V_0}{\lambda_2-\lambda_1}\left\{(\lambda_2+c\eta_{PI})e_{\lambda_1}(t,0) - (\lambda_1+c\eta_{PI})e_{\lambda_2}(t,0)\right\} \\ V_{NI}(t) = \dfrac{V_0\eta_{PI}}{\lambda_2-\lambda_1}\left\{\dfrac{(\lambda_2+c\eta_{PI})e_{\lambda_1}(t,0) - (\lambda_1+c\eta_{PI})e_{\lambda_2}(t,0)}{\lambda_2-\lambda_1} - e_{-c}(t,0)\right\}, \end{cases}$$

where all parameters are positive constants and

$$\lambda_{1,2} = \frac{-(c+\delta) \pm \sqrt{(c+\delta)^2 - 4\delta c(1-(1-\eta_{RT})(1-\eta_{PI}))}}{2}. \tag{31}$$

Proof We first rewrite the first two equations as a vector dynamic equation and solve the obtained the two dimensional linear system of I and V_I. The vector dynamic equation is as follows

$$\begin{bmatrix} I^{\Delta} \\ V_I^{\Delta} \end{bmatrix} = \begin{bmatrix} -\delta & (1-\eta_{RT})kT_0 \\ (1-\eta_{PI})N\delta & -c \end{bmatrix} \begin{bmatrix} I \\ V_I \end{bmatrix},$$

where the characteristic equation is $\lambda^2 + (c+\delta)\lambda + \delta c(1-(1-\eta_{RT})(1-\eta_{PI})) = 0$. Here, since we assume the patient was in quasi-steady state before treatment began, then $c = NkT_0$. Hence, the eigenvalues of the coefficient matrix are given as (31). By the fact that $(\delta - c)^2 > 0$, one can get that $(\delta + c)^2 > 4\delta c$. Also, since $0 < \eta_{RT} < 1$ and $0 < \eta_{PI} < 1$, then

$$(\delta + c)^2 > 4\delta c > 4\delta c(1-(1-\eta_{RT})(1-\eta_{PI}))$$

and this shows that these two eigenvalues are real. Furthermore,

$$0 < (c+\delta)^2 - 4\delta c(1-(1-\eta_{RT})(1-\eta_{PI})) < (c+\delta)^2, \tag{32}$$

which implies that $-(c+\delta) + \sqrt{(c+\delta)^2 - 4\delta c(1-(1-\eta_{RT})(1-\eta_{PI}))} < 0$. Hence, $\lambda_1 < 0$. Note that $\lambda_2 < 0$ is negative by the definition. We have shown that λ_1 and λ_2 are real, negative and distinct eigenvalues. The vector equation is regressive for any time scale such that $1 + \lambda_{1,2}\mu(t) \neq 0$ for all $t \in \mathbb{T}^{\kappa}$ by Theorem 7. From the

characteristic equation for the two dimensional I and V_I system, we have for i=1, 2

$$(1-\eta_{RT})(1-\eta_{PI}) = \frac{(\lambda_i+\delta)(\lambda_i+c)}{c\delta}. \tag{33}$$

Eigenvectors corresponding to λ_1 and λ_2 are

$$\xi_1 = \begin{bmatrix} c+\lambda_1 \\ (1-\eta_{PI})N\delta \end{bmatrix}, \quad \xi_2 = \begin{bmatrix} c+\lambda_2 \\ (1-\eta_{PI})N\delta \end{bmatrix}$$

respectively. By Theorem 8, it follows that

$$\begin{bmatrix} I \\ V_I \end{bmatrix} = c_1 e_{\lambda_1}(t,0)\begin{bmatrix} c+\lambda_1 \\ (1-\eta_{PI})N\delta \end{bmatrix} + c_2 e_{\lambda_2}(t,0)\begin{bmatrix} c+\lambda_2 \\ (1-\eta_{PI})N\delta \end{bmatrix}, \tag{34}$$

where c_1 and c_2 are arbitrary constants. To find c_1 and c_2, we use the initial conditions $I(0) = \frac{kV_0T_0}{\delta}$ and $V_I(0) = V_0$ with the properties of exponential functions on time scales. Hence, we get the following equations

$$\begin{aligned} kV_0T_0 &= c_1\delta(c+\lambda_1) + c_2\delta(c+\lambda_2) \\ V_0 &= c_1(1-\eta_{PI})N\delta + c_1(1-\eta_{PI})N\delta \end{aligned}$$

with the constants

$$c_1 = \frac{V_0(\lambda_2 + c\eta_{PI})}{N\delta(1-\eta_{PI})(\lambda_2-\lambda_1)} = \frac{kV_0T_0(\lambda_2+c\eta_{PI})(1-\eta_{RT})}{(\lambda_1+\delta)(\lambda_1+c)(\lambda_2-\lambda_1)}$$

and

$$c_2 = -\frac{V_0(\lambda_1 + c\eta_{PI})}{N\delta(1-\eta_{PI})(\lambda_2-\lambda_1)} = -\frac{kV_0T_0(\lambda_1+c\eta_{PI})(1-\eta_{RT})}{(\lambda_2+\delta)(\lambda_2+c)(\lambda_2-\lambda_1)},$$

where we use (33) to get equivalent relations for c_1 and c_2. Now, substituting c_1 and c_2 into I of (34) yields

$$\begin{aligned} I(t) &= c_1 e_{\lambda_1}(t,0)(1-\eta_{PI})N\delta + c_2 e_{\lambda_2}(t,0)(1-\eta_{PI})N\delta \\ &= e_{\lambda_1}(t,0) - \frac{kV_0T_0(\lambda_1+c\eta_{PI})(1-\eta_{RT})}{(\lambda_2+\delta)(\lambda_2-\lambda_1)} e_{\lambda_2}(t,0). \end{aligned}$$

Therefore,

$$I(t) = \frac{kT_0V_0(1-\eta_{RT})}{\lambda_2-\lambda_1}\left\{\frac{\lambda_2+c\eta_{PI}}{\lambda_1+\delta}e_{\lambda_1}(t,0) - \frac{\lambda_1+c\eta_{PI}}{\lambda_2+\delta}e_{\lambda_2}(t,0)\right\}. \tag{35}$$

Similarly, substituting c_1 and c_2 into V_I of (34) yields

$$V_I(t) = \frac{V_0(\lambda_2+c\eta_{PI})}{\lambda_2-\lambda_1}e_{\lambda_1}(t,0) - \frac{V_0(\lambda_1+c\eta_{PI})}{\lambda_2-\lambda_1}e_{\lambda_2}(t,0).$$

Hence,

$$V_I(t) = \frac{V_0}{\lambda_2 - \lambda_1}\left\{(\lambda_2 + c\eta_{PI})e_{\lambda_1}(t,0) - (\lambda_1 + c\eta_{PI})e_{\lambda_2}(t,0)\right\}.$$

Substituting (35) into the third equation of (30) results

$$V_{NI}^{\Delta}(t) = \frac{V_0\delta c\eta_{PI}(1-\eta_{RT})}{\lambda_2-\lambda_1}\left\{\frac{\lambda_2+c\eta_{PI}}{\lambda_1+\delta}e_{\lambda_1}(t,0) - \frac{\lambda_1+c\eta_{PI}}{\lambda_2+\delta}e_{\lambda_2}(t,0)\right\} - cV_{NI}. \tag{36}$$

From Theorem 6, (36) with $V_{NI}(0) = 0$ has a unique solution

$$\begin{aligned}
V_{NI}(t) &= \int_0^t e_{-c}(t,\sigma(\tau))\frac{V_0\delta c\eta_{PI}(1-\eta_{RT})}{\lambda_2-\lambda_1}\left\{\frac{\lambda_2+c\eta_{PI}}{\lambda_1+\delta}e_{\lambda_1}(\tau,0) - \frac{\lambda_1+c\eta_{PI}}{\lambda_2+\delta}e_{\lambda_2}(\tau,0)\right\}\Delta\tau \\
&= \frac{V_0\delta c\eta_{PI}(1-\eta_{RT})}{\lambda_2-\lambda_1}\left\{\frac{\lambda_2+c\eta_{PI}}{\lambda_1+\delta}\int_0^t e_{-c}(t,\sigma(\tau))e_{\lambda_1}(\tau,0)\Delta\tau\right. \\
&\quad \left. - \frac{\lambda_1+c\eta_{PI}}{\lambda_2+\delta}\int_0^t e_{-c}(t,\sigma(\tau))e_{\lambda_2}(\tau,0)\Delta\tau\right\} \\
&= \frac{V_0\delta c\eta_{PI}(1-\eta_{RT})}{\lambda_2-\lambda_1}\left\{\frac{\lambda_2+c\eta_{PI}}{\lambda_1+\delta}\frac{e_{-c}(t,0)}{\lambda_1+c}\int_0^t e^{\Delta}_{\lambda_1\ominus(-c)}(\tau,0)\Delta\tau\right. \\
&\quad \left. - \frac{\lambda_1+c\eta_{PI}}{\lambda_2+\delta}\frac{e_{-c}(t,0)}{\lambda_2+c}\int_0^t e^{\Delta}_{\lambda_2\ominus(-c)}(\tau,0)\Delta\tau\right\} \\
&= \frac{V_0\delta c\eta_{PI}(1-\eta_{RT})}{\lambda_2-\lambda_1}\left\{\frac{\lambda_2+c\eta_{PI}}{\lambda_1+\delta}\frac{e_{-c}(t,0)}{\lambda_1+c}\left[e_{\lambda_1\ominus(-c)}(t,0)-1\right]\right. \\
&\quad \left. - \frac{\lambda_1+c\eta_{PI}}{\lambda_2+\delta}\frac{e_{-c}(t,0)}{\lambda_2+c}\left[e_{\lambda_2\ominus(-c)}(t,0)-1\right]\right\}.
\end{aligned}$$

Therefore,

$$\begin{aligned}
V_{NI}(t) &= \frac{V_0\delta c\eta_{PI}(1-\eta_{RT})}{\lambda_2-\lambda_1}\left\{\frac{\lambda_2+c\eta_{PI}}{(\lambda_1+\delta)(\lambda_1+c)}e_{\lambda_1}(t,0) - \frac{\lambda_2+c\eta_{PI}}{(\lambda_1+\delta)(\lambda_1+c)}e_{-c}(t,0)\right\} \\
&\quad - \frac{V_0\delta c\eta_{PI}(1-\eta_{RT})}{\lambda_2-\lambda_1}\left\{\frac{\lambda_1+c\eta_{PI}}{(\lambda_2+\delta)(\lambda_2+c)}e_{\lambda_2}(t,0) + \frac{\lambda_1+c\eta_{PI}}{(\lambda_1+\delta)(\lambda_1+c)}e_{-c}(t,0)\right\}.
\end{aligned}$$

Substituting (33) into the above equation and then simplifying the resulting equation, one can get

$$V_{NI} = \frac{V_0\eta_{PI}}{\lambda_2-\lambda_1}\left\{\frac{(\lambda_2+c\eta_{PI})e_{\lambda_1}(t,0) - (\lambda_1+c\eta_{PI})e_{\lambda_2}(t,0)}{\lambda_2-\lambda_1} - e_{-c}(t,0)\right\}.$$

This completes the proof. □

Hence, the total concentration of plasma virions is given by

$$V(t) = \frac{V_0}{1-\eta_{PI}} \left\{ \frac{(\lambda_2 + c\eta_{PI})e_{\lambda_1}(t,0) - (\lambda_1 + c\eta_{PI})e_{\lambda_2}(t,0)}{\lambda_2 - \lambda_1} - \eta_{PI} e_{-c}(t,0) \right\}. \tag{37}$$

System (30) with $\eta_{RT} = 0$ and $\eta_{PI} = 1$ reduces to (26). Note that corresponding total viral load (37) does not reduce to (28) due to the singularity.

System (30) on $[0, \infty)$ has eigenvalues $-c$ and (31) that are real, negative and distinct. Hence, the zero solution of system (30) on $[0, \infty)$ is asymptotically stable. One can also consider system (30) on $[0, \infty)_{\mathbb{Z}}$ and write it as

$$\begin{cases} I(t+1) = (1-\delta)I(t) + (1-\eta_{RT})kT_0 V_I(t) \\ V_I(t+1) = (1-\eta_{PI})N\delta I(t) + (1-c)V_I(t) \\ V_{NI}(t+1) = \eta_{PI} N\delta I(t) + (1-c)V_{NI}(t). \end{cases} \tag{38}$$

In the following theorem, we discuss the behavior of the zero solution of system (38).

Theorem 14 *If $c + \delta < 2$, the zero solution of system (38) is asymptotically stable.*

Proof Assume $c + \delta < 2$. An equivalent vector equation of system (38) has the companion matrix

$$A = \begin{bmatrix} 1-\delta & (1-\eta_{RT})kT_0 & 0 \\ (1-\eta_{PI})N\delta & 1-c & 0 \\ \eta_{PI}N\delta & 0 & 1-c \end{bmatrix}$$

whose characteristic equation is

$$(1-c-\xi)\big[(1-\delta-\xi)(1-c-\xi) - \delta c(1-\eta_{RT})(1-\eta_{PI})\big] = 0,$$

and the eigenvalues are $\xi_1 = 1-c, \xi_{2,3} = \frac{-(c+\delta-2) \pm \sqrt{(c+\delta-2)^2 - 4\delta c(1-(1-\eta_{RT})(1-\eta_{PI}))}}{2}$. Note that ξ_i for $i = 1, 2, 3$ are real. Since $0 < c < 2$, $|\xi_1| < 1$. From (32) and the assumption, we have

$$0 < \frac{-(c+\delta-2)}{2} < \frac{-(c+\delta-2) + \sqrt{(c+\delta)^2 - 4\delta c(1-(1-\eta_{RT})(1-\eta_{PI}))}}{2} < 1.$$

Hence, $|\xi_2| < 1$. Furthermore, since $2(\delta + c) - \delta c(1-(1-\eta_{RT})(1-\eta_{PI})) < 4$ and $4\delta c(1-(1-\eta_{RT})(1-\eta_{PI})) < 4\delta c$, we have

$$c + \delta - 4 < -\sqrt{(c+\delta)^2 - 4\delta c(1-(1-\eta_{RT})(1-\eta_{PI}))} < \delta - c$$

and so $-1 < -\delta - c + 2\sqrt{(c+\delta)^2 - 4\delta c(1-(1-\eta_{RT})(1-\eta_{PI}))} < 1 - c$. The positivity of c implies that $|\xi_3| < 1$. Therefore, from Theorem 10 the zero solution of system (38) is asymptotically stable. This completes the proof. □

7 Conclusion

In this study, one of our goals was to call attention to discrete models of the HIV-1 infection and make a comparison with the existing continuous model in Perelson et al. (1996).

We obtain the total concentration of plasma virus as a function of time for each model. Then, we test the new discrete models (17), (18) and (25) with data from a clinical trial and find the fitted new models to be as accurate as the continuous model (16) and in some cases much better.

Based on the findings, the discrete model (25) on $\mathbb{Z}$ is found to yield the best fit in hours. This motivated us to study other discrete models which have the best fit in days. It turns out that the latest proposed discrete model (29) on $h\mathbb{Z}$ achieves an almost equally good fit in both units. Moreover, in the continuous model (16) the clearance rate c and the rate of loss δ are estimated as 3.11 day^{-1} and 0.51 day^{-1}, respectively, while the clearance rate c and the rate of loss δ are estimated as 8.93 day^{-1} and 0.44 day^{-1} in the discrete model (29).

In these models, the patients were given protease inhibitor monotherapy under the assumption of the efficacy of the protease inhibitor is perfect. In addition, we consider a mathematical model of imperfect protease inhibitor and RT inhibitor combination therapy of HIV-1 infection on time scales and show that the zero solution is asymptotically stable.

By considering mathematical models on time scales, i.e. dynamic models, one can derive solutions of corresponding continuous and discrete models directly from dynamic models. This helps to avoid solving models individually on their own domain. This has shown to be significant when considering the model of HIV-1 dynamics. It is also worth to mention that not only one continuous model can be obtained from a mathematical model on time scales, but also many discrete models. In this work, one of the models on $h\mathbb{Z}$, namely (29), has an excellent fit to the data, captures the behavior of the data perfectly no matter what the unit of time and has a better fit compared to the existing continuous model in literature. Therefore, one can consider modeling on other discrete time scales such as disjoint closed intervals, the set of all integer powers of a number $q > 0$, including zero etc. which may result in better fitting.

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Affiliations

Elvan Akın[1] · Gülşah Yeni[1] · Alan S. Perelson[2]

✉ Alan S. Perelson
asp@lanl.gov

Elvan Akın
akine@mst.edu

Gülşah Yeni
gyq3f@mst.edu

1 Department of Mathematics and Statistics, Missouri S & T, Rolla, MO 65409, USA

2 Theoretical Biology and Biophysics, Los Alamos National Laboratory, Los Alamos, NM 87545, USA