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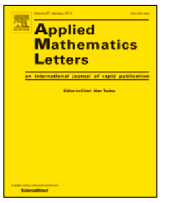

Stochastic HIV model coupled with pharmacokinetics and drug adherence may explain intermittent viral blips

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ABSTRACT

We develop a stochastic HIV model by integrating drug adherence into a pharmacokinetic model and by coupling a pharmacodynamic model with a viral dynamic model. Numerical simulations show that the proposed model can generate viral blips, which have been observed in HIV patients receiving suppressive antiretroviral therapy. We calculate the probability density function of infected $CD4^+$ T cells by developing the generalized density evolution equation. We fit the model to the clinical data of four HIV patients exhibiting viral blips. The results demonstrate that poor drug adherence can be a reason explaining the occurrence of viral blips in treated HIV patients. We also find that viral dynamics are sensitive to drug-adherence parameters, which have a significant impact on the frequency and amplitude of viral blips. The modeling and methods can be applied to the study of long-term therapy of other chronic diseases in which drug adherence might also be an issue.

1. Introduction

In the absence of effective vaccines, human immunodeficiency virus (HIV) infection is still high. About 37.7 million people worldwide were infected with HIV in 2020 based on the Global Progress Report on AIDS 2021 [1]. The commonly used treatment for HIV infection is highly active antiretroviral therapy (HAART), a cocktail of at least three drugs that fall into at least two classes of antiretroviral drugs. The classic combination of HAART is two nucleoside reverse transcriptase inhibitors plus a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor [2]. HAART has been proven to be highly effective in suppressing viral infection and replication and can control the virus below undetectable levels (below 50 RNA copies/mL) [3]. With the treatment of HAART, most infected people in developed countries greatly

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improved their health status and quality of life, and HAART has also significantly reduced HIV-related morbidity and mortality.

However, HAART cannot cure HIV patients, as it cannot eliminate the virus. Viral RNA can be detected by ultra-sensitive assays in plasma [4,5]. Many clinical studies also showed that viral blips occasionally happen in HIV patients [6–9]. Viral blips refer to the occasional viral-load measurements above the detection level in patients who have sustained undetectable viremia under HAART. A number of studies have been used to explain the occurrence of viral blips. Rong et al. [10] demonstrated that asymmetric division of activated latently infected cells may explain the intermittent viral blips by considering an antigen-dependent activation function. Other explanations for the appearance of blips were put forward [11], including the transient increases in viral production due to fluctuations in adherence [12,13], concurrent illnesses or vaccinations [14]. Based on clinical data of 228 subjects, Podsadecki et al. found that blips were associated with decreased adherence to antiretroviral therapy [12]. A recent study, aiming at revealing the safety and efficacy of HIV-1 seroconversion among women during the clinical trial based on the drug adherence data collected from the dapivirine vaginal ring, has demonstrated that improved drug adherence can significantly affect the outcomes of treatment [13]. The underlying etiology for viral blips is still unclear and is worth further investigation [11].

Drug adherence concerns whether patients take drugs at the prescribed time. Poor adherence means that patients miss doses. Drug adherence plays an important role in the success of disease treatment, especially for chronic illnesses, which often require long-term therapy. Using pharmacodynamics (PD) as a bridge, an individual-based treatment regime can be linked to the suppression of the virus in patients. This helps couple the viral kinetics and pharmacokinetics (PK), consequently making it feasible to analyze the impact of different drug administration regimens on HIV therapy [15,16]. Huang et al. [16] developed a viral dynamic model using time-varying drug efficacies to describe the antiretroviral responses. They studied how the time-varying treatment effect, induced by adherence, plasma drug concentrations and phenotypic sensitivities, affects antiretroviral response in terms of the viral load and T-cell counts. The authors extended the previous model in [16] and proposed a dynamic Bayesian nonlinear model of HIV infection with mixed effects, including drug compliance, drug resistance and covariates, and fitted the model to clinical data [17]. However, there are very few, if any, modeling studies that investigate the phenomenon of viral blips from the perspective of drug adherence.

In our previous work [18], we modeled drug adherence in an one-compartment statistical pharmacokinetic model and conducted a thorough analysis of the existence and uniqueness of the limit distribution of drug concentration and its higher order moments after multiple doses. The main purpose of this study is to develop a stochastic model that embeds the stochastic drug-adherence equation to a pharmacokinetic model and that also couples the stochastic PK-PD model with a viral dynamic model. We will examine whether the missed medication due to drug adherence is the potential driver in generating viral blips and provide quantitative guidance for treating HIV infection.

2. Stochastic HIV model and main results

2.1. Model formulation

We start with the assumptions used in the previous model [18]. We assume that each patient would either take full doses or miss doses with a certain probability at the drug-administration time, due to poor drug adherence. The drug adherence is assumed to follow a binomial distribution with parameter a_n. If we take A_n as the quantitative index to indicate whether the patient takes the drug at the nth drug administration time, then it can take two values: 1 when an individual takes the drug with probability a_n at the exact prescribed time, and 0 when the individual misses the drug with probability $1 - a_n$.

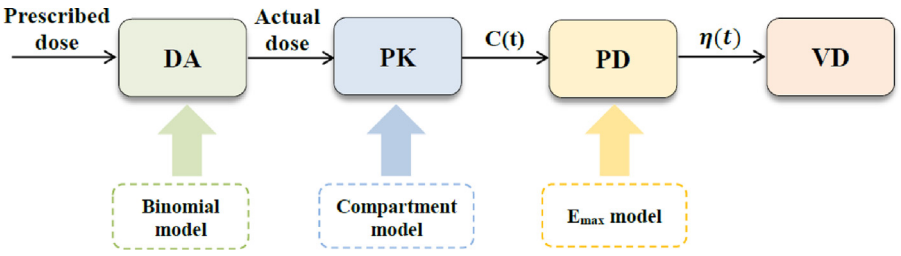

Fig. 1. Diagram for coupling drug adherence (DA), pharmacokinetics (PK), pharmacodynamics (PD) and viral dynamics (VD).

Based on the above assumptions of multiple drug administration in the presence of drug adherence, we can reformulate the one-compartment classical pharmacokinetic model using the stochastic structure. The administration time sequence $\{t_n, n \in N^+\}$ with $t_0 = 0$ is assumed to be a Poisson process with certain intensity λ. This means that the random intervals $\tau_n \overset{\triangle}{=} t_n - t_{n-1}$ between two intakes are independent and identically distributed (i.i.d.) with exponential distribution of parameter λ; i.e., $\tau_n \sim \text{Exp}(\lambda)$ [19]. If t_n is a random variable, then there are two types of randomness: random dose amount and random dosing time. As HIV patients need life-long treatment, we do not consider the random dosing time in this study.

We incorporate drug adherence into a PK model, and consequently into a PD model [18,20]. We also couple the PD model with the VD model of HIV infection. The embedding and coupling diagram is shown in Fig. 1. We propose the following stochastic viral dynamic model of HIV by including pharmacokinetics and drug adherence

$$\begin{cases} \text{Viral dynamics} \Rightarrow \begin{cases} \frac{dT}{dt} = \lambda - dT - (1-\eta_{RA}(t))kTV_I, \\ \frac{dT^*}{dt} = (1-\eta_{RA}(t))kTV_I - \delta T^*, \\ \frac{dV_I}{dt} = (1-\eta_{PI}(t))N\delta T^* - cV_I, \\ \frac{dV_{NI}}{dt} = \eta_{PI}(t)N\delta T^* - cV_{NI}. \end{cases} \\ \text{Pharmacodynamics} \Rightarrow \eta_j(t) = \frac{C(t)}{IC_{50}(t)+C(t)}, \quad j = RA, PI. \\ \text{Pharmacokinetics} \Rightarrow \begin{cases} \frac{dA_a(t)}{dt} = -k_a A_a(t), \quad t \neq t_n, \\ \frac{dC(t)}{dt} = \frac{Fk_a A_a(t)}{V} - k_{el}C(t), \quad t > 0, \\ A_a(t_n^+) = A_a(t_n) + A_n D, \quad t = t_n. \end{cases} \\ \text{Drug adherence} \Rightarrow \begin{cases} a_n = \beta a_{n-1} + (1-\gamma)(1-a_{n-1}), \\ A_n \sim b(1,\ a_n). \end{cases} \end{cases} \tag{1}$$

$T(t)$, $T^*(t)$, $V_I(t)$ and $V_{NI}(t)$ denote the concentrations of CD4$^+$ T cells that are susceptible to HIV, productively infected cells, infectious virus and noninfectious virus at time t, respectively. $A_a(t)$ represents the drug amount at the absorption chamber, $C(t)$ represents the drug concentration of the central compartment, and $\eta(t)$ is the effectiveness of drugs at time t. A summary of the parameters used in model (1) is listed in Table 1. For consistency, we use the following values of parameters in numerical experiments, where the parameters related to PK model can be found in [21], and parameters related to VD model can be found in [22,23]. In model (1), we use the E_{max} model to describe PD. Note that different drugs usually have different treatment effects, so there are two functions, $\eta_{RA}(t)$ and $\eta_{PI}(t)$, denoting the efficacy of reverse transcriptase inhibitors and protease inhibitors, respectively. Using occupation theory [20], E_{max} model converts the concentration to the effect of the drug, generating a dose–effect relationship. Under different elimination and absorption rate constants, $\eta_{RA}(t)$ and $\eta_{PI}(t)$ can be calculated by $\eta_j(t)$.

System (1) is high-dimensional, highly nonlinear, and non-autonomous so it is difficult to directly study its dynamical behavior and viral blips analytically. We start with a numerical simulation of model (1) in

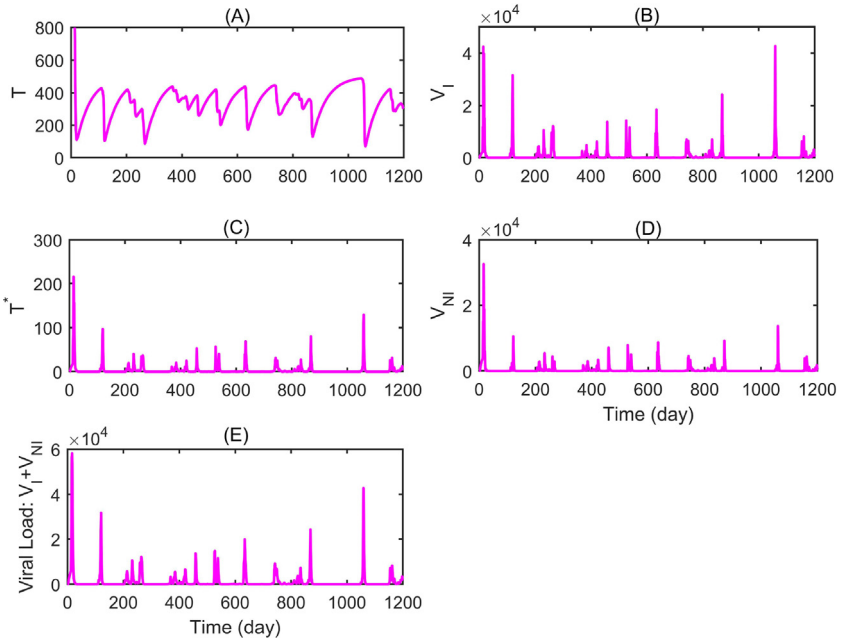

Fig. 2. Numerical simulations of model (1). (A): CD4$^+$ T cells T; (B): infectious virus V_I; (C): infected CD4$^+$ T cells T^*; (D): noninfectious virus V_{NI}; (E): viral load $V_I + V_{NI}$. Subplots (A–D) show model stochastic solutions and (E) is used to compare total viral load $V_I + V_{NI}$ with infected CD4$^+$ T cells T^* shown in (C).

Table 1
Descriptions and values of the parameters in model (1). The PK parameters (Nevirapine is used as an example drug) can be found in [21]. The VD parameters are chosen from [22,23].

Parameter	Description	Value	Range
β	The conditional probability of dose taking at current time under the condition that it is taken at the previous time	Variable	[0, 1]
γ	The conditional probability of no dose taking at current time if no dose is also taken at the previous time	Variable	[0, 1]
a_n	The probability of dose taking at the nth event	Variable	[0, 1]
D	Drug amount (mg)	200	–
k_{el}	First-order elimination rate constant (/h)	0.0614	–
k_a	First-order absorption rate constant (/h)	0.23	–
V	Volume of distribution (L)	60	–
τ	Fixed dosing interval for multi-dose administration (h)	24	–
IC_{50}	Drug concentration necessary to inhibit viral replication by 50% (mg/L)	0.8	–
λ	Recruitment rate of uninfected cells (/mL/day)	10	$[10^{-2},\ 50]$
d	Death rate of uninfected cells (/day)	0.02	$[10^{-4},\ 0.2]$
k	Infection rate of target cells by virus (mL/day)	1.3×10^{-5}	$[10^{-7},\ 10^{-3}]$
δ	Death rate of infected cells (/day)	1	$[10^{-1},\ 1]$
N	Total number of virus particles released by a productively infected cell	1000	[1, 2000]
c	Clearance rate of virus (/day)	3	$[10^{-1},\ 10]$
η_{RA}	Effectiveness of reverse transcriptase inhibitors	Variable	See text
η_{PI}	Effectiveness of protease inhibitors	Variable	See text
A_n	Random variable accounting for the random drug intake behavior	Variable	{0, 1}
$A_a(t)$	Drug amount at time t at the absorption chamber	Variable	–
$C(t)$	Drug concentration of the central compartment	Variable	–

Fig. 2 that illustrates whether poor drug adherence can produce viral blips in HIV patients. It follows from Fig. 2 (A–D) that missed drugs can indeed generate viral blips. It should be noted that pharmacodynamics is stochastic in our model, so the solution of the HIV viral dynamic model is a four-dimensional stochastic process. Instead of finding the solution directly, we will obtain the probability density functions in next section, which can help study the existence of viral blips.

2.2. Generalized density evolution equation of T^*

As depicted in Fig. 2 (C) and (E), the solution of infected CD4$^+$ T cells T^* has a very similar trajectory as the solution of the total viral load $V_I + V_{NI}$. Therefore, given that the large magnitude of viral load could affect the division of finite difference mesh, we choose T^* as the substitution variable to study the evolution of its probability density function (PDF) over time in the presence of drug adherence. For simplicity, we assume $\eta_{RA} = \eta_{PI} = \Theta$. Denoting $X \triangleq (X_1, X_2, X_3, X_4) = (T, T^*, V_I, V_{NI})$, we can reformulate the equations of viral dynamic model (1) as follows

$$\begin{cases} X_1'(t) = \lambda - dX_1 - (1-\Theta)kX_1X_3, \\ X_2'(t) = (1-\Theta)kX_1X_3 - \delta X_2, \\ X_3'(t) = (1-\Theta)N\delta X_2 - cX_3, \\ X_4'(t) = \Theta N\delta X_2 - cX_4. \end{cases} \tag{2}$$

Assume that $X = H(\Theta, t)$ is the solution of model (2) (a four dimensional stochastic process), with $H(\Theta, t) = (H_1(\Theta, t), H_2(\Theta, t), H_3(\Theta, t), H_4(\Theta, t))$. When $\Theta = \theta$, we have $X_2(t) = H_2(\theta, t)$ with probability 1. Hence,

$$p_{X_2|\Theta}(x, t|\theta) = \delta\big(x - H_2(\theta, t)\big), \tag{3}$$

where $\delta(\cdot)$ is Dirac delta function with

$$\delta(y) = \begin{cases} 1, & y = 0, \\ 0, & y \neq 0. \end{cases}$$

Taking the derivative of Eq. (3) with respect to t, we have

$$\begin{aligned} \frac{\partial p_{X_2|\Theta}(x, t|\theta)}{\partial t} &= \frac{\partial \delta\big(x - H_2(\theta, t)\big)}{\partial t} = \frac{\partial \delta\big(x - H_2(\theta, t)\big)}{\partial x} \cdot \frac{\partial\big(x - H_2(\theta, t)\big)}{\partial t} \\ &= -\dot{H}_2(\theta, t)\frac{\partial p_{X_2|\Theta}(x, t|\theta)}{\partial x}. \end{aligned}$$

According to the multiplication formula $p_{X_2\Theta}(x, \theta, t) = p_{X_2|\Theta}(x, t|\theta) \cdot p_\Theta(\theta)$ and setting x_0 as the initial value of X_2, we obtain

$$\begin{cases} \dfrac{p_{X_2\Theta}(x, \theta, t)}{\partial t} + X_2'(\theta, t)\dfrac{p_{X_2\Theta}(x, \theta, t)}{\partial x} = 0, \\ p_{X_2\Theta}(x, \theta, t)|_{t=0} = p_\Theta(\theta) \cdot \delta(x - x_0). \end{cases} \tag{4}$$

Next, we use the finite difference method to solve the above partial differential equation (i.e., model (4)), and then calculate $p_{X_2}(x, t)$ by

$$p_{X_2}(x, t) = \int_{\Omega_\Theta} p_{X_2\Theta}(x, \theta, t)\mathrm{d}\theta.$$

Here, the finite difference method refers to an algorithm that is easy to implement and has good precision. In the difference scheme, Lax–Wendroff has second-order accuracy but it is often not guaranteed that the density function is nonnegative [24]. Under such circumstances, applying a flux limiter to Lax–Wendroff constitutes the total variation diminishing (TVD) difference scheme, which can guarantee the nonnegativity and normality of the density function [25,26].

Note that Eq. (4) does not involve θ, so θ can be taken as a parameter. Consequently, we first calculate the value of θ, then use the value of θ to obtain $X_2'(\theta, t)$ by solving model (2), and finally solve Eq. (4). The algorithm implementation process is summarized as follows:

1. Based on the PK-PD model, the distribution of Θ is approximated by the expectation and variance of the limiting distribution $U(U_{min}, U_{max})$ using 3σ guidelines;

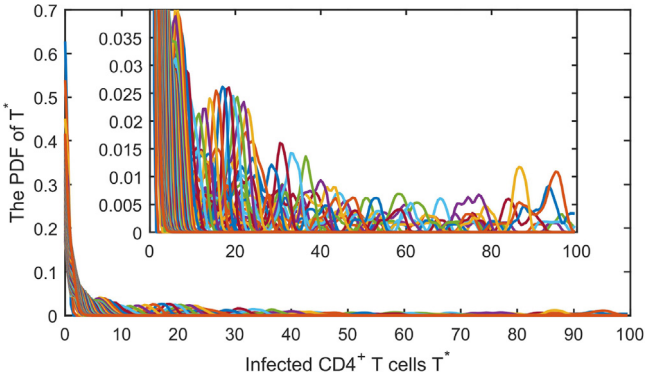

Fig. 3. Solutions of the probability density function of T^* from 0 to 100 days.

2. Randomly generate N discrete points from the distribution of Θ: $\theta_1, \theta_2, \ldots, \theta_N$, which is actually the discretization of initial condition;
3. Substitute θ_i into the model to obtain the discrete $X_2'(\theta_i, t_m)$, where $t_m = m \cdot \triangle t$ and $\triangle t$ is the time step;
4. Substitute $X_2'(\theta_i, t_m)$ into Eq. (4), and use the finite difference method with TVD scheme to solve the equation $p_{X_2\Theta}(x_j, \theta_i, t_m)$, where $x_j = x_0 + j \cdot \triangle x$, $\triangle x$ is the space step;
5. Integrate $p_{X_2\Theta}(x_j, \theta_i, t_m)$ numerically, and obtain $p_{X_2}(x_j, t_m)$.

In what follows, we provide a numerical example (shown in Fig. 3) for solving the PDF of T^* using the algorithm introduced above, where we also focus on presenting viral blips. In the simulation, we used the parameter values listed in Table 1; specifically, $\beta = 0.5$ and $\gamma = 0.6$. Following the analysis of extravascular administration in our previous work [18], we can calculate that the expectation and variance of the limiting distribution are $\mu = 0.5925$ and $\sigma^2 = 0.2730$, respectively. We cannot obtain the expression of the limit distribution, which uses the uniform distribution $U(0.0700,\ 1.1150)$ to approximate based on 3σ guidelines. It is natural that the PDF of Θ is

$$p_\Theta(\theta) = \begin{cases} \frac{IC_{50}}{U_{max}-U_{min}} \cdot \frac{1}{(1-\theta)^2}, & \frac{U_{min}}{IC_{50}+U_{min}} < \theta < \frac{U_{max}}{IC_{50}+U_{max}}, \\ 0, & \text{otherwise.} \end{cases}$$

Here $N = 100,\ \triangle t = 0.01,\ \triangle x = 0.5$. We can calculate the PDF of T^* at typical time following the above algorithm. With the evolution of time, T^* should be stable at 0 if the patient has perfect drug adherence. However, as seen in Fig. 3, under poor drug adherence, T^* can randomly blip within the considered time interval. This further supports the fact that drug adherence can explain the phenomenon of viral blips in HIV patients, which is also a cross-validation of the previous simulation results in terms of the existence of viral blips.

2.3. Data fitting and sensitivity analysis

We obtained the data of four HIV patients from a follow-up database [27], which includes some individual information, follow-up times, $CD4^+$ T cell counts every 3 months and viral loads every 6 months, observed from July 2004 until July 2010. Due to expensive cost, poor compliance or other reasons, some viral loads data are missing actually. We fit the model to these data sets for each of four HIV patients. The fitting results are shown in Fig. 4, where the best-fitting curves of $CD4^+$ T cells and viral loads are shown in red and blue, respectively. The model can capture the characteristics of the data, especially the moments when viral blips happen. It should be mentioned that the fitting curves presented more time points with viral

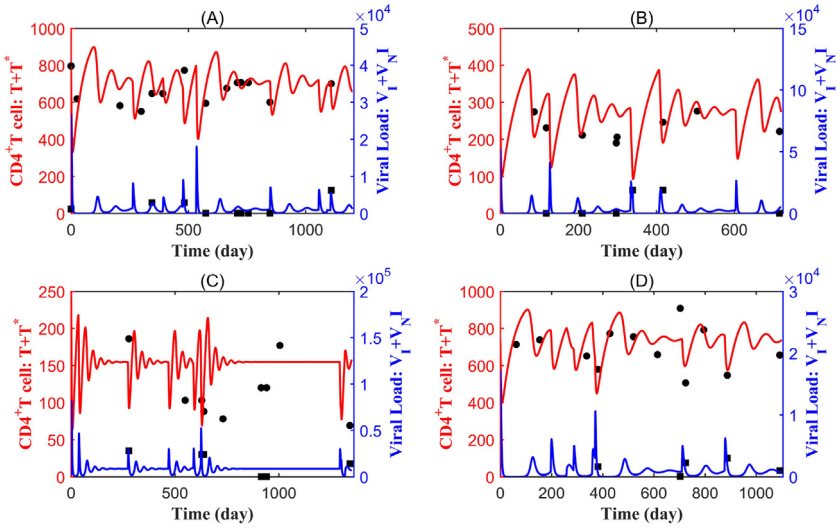

Fig. 4. Data fitting of model (1) to four subjects, where the solid dots and squares denote the data of $CD4^+$ T cells and viral loads, respectively. The best fitting curves of $CD4^+$ T cells and viral loads are shown in red and blue, respectively.

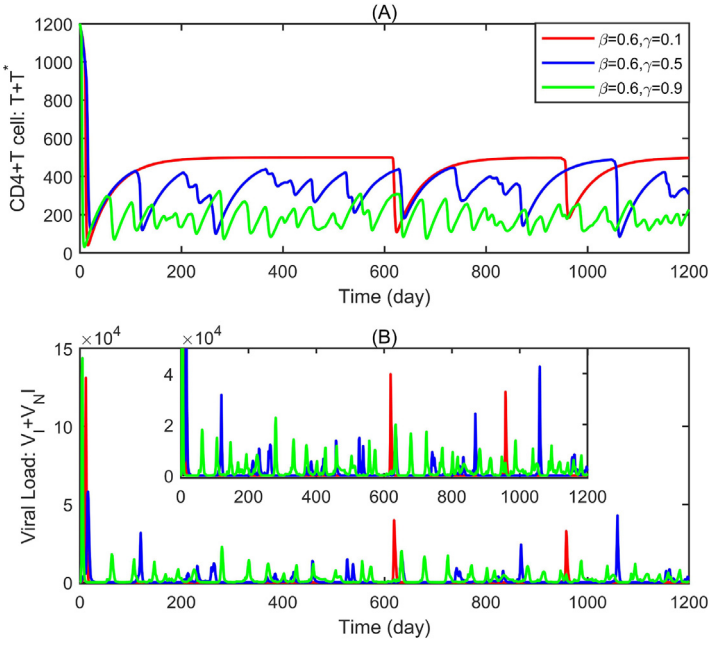

Fig. 5. $CD4^+$ T cells and viral load simulated by model (1) with different values of γ. Parameters related to drug adherence are fixed as $\alpha = 0.5$, $\beta = 0.6$, initial values are $C_0 = 0$, $A_{a_0} = D$, $T_0 = 1200$, $T_0^* = 0$, $V_{I0} = 100$, $V_{NI0} = 100$, and other values are as listed in Table 1.

blips compared to the real data. The most possible reason is that viral loads are measured every 6 months making some blips undetected.

Based on the fitting results, we conducted a scenario analysis by solving model (1) with different values of β and γ. The solutions were shown in Figs. 5 and 6. When β (or γ) was fixed, a larger γ (or a smaller β) means worse adherence. From these simulations, we found that the frequency and amplitude of viral blips can be significantly different as drug adherence varies (i.e., different values of β or γ). The worse drug adherence sets, the lower $CD4^+$ T cells and the more frequent viral blips.

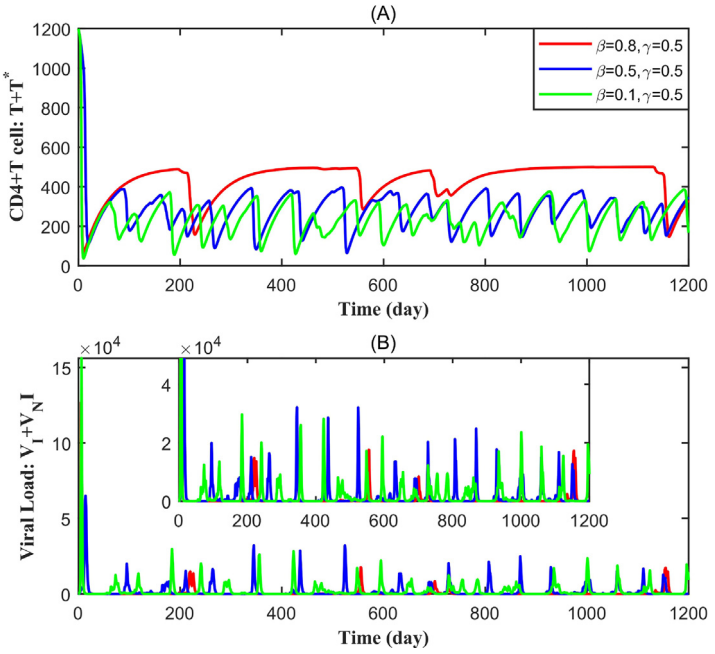

Fig. 6. CD4$^+$ T cells and viral load simulated by model (1) with different values of β. Parameters related to drug adherence are fixed as $\alpha = 0.5$, $\gamma = 0.5$, initial values are $C_0 = 0$, $A_{a_0} = D$, $T_0 = 1200$, $T_0^* = 0$, $V_{I0} = 100$, $V_{NI0} = 100$, and other values are as listed in Table 1.

We further conducted a sensitivity analysis by evaluating the time-dependent partial rank correlation coefficients (PRCCs) [28] of the variables in the viral dynamic model with respect to the drug adherence related parameters β and γ. We used the Latin hypercube sampling (LHS) to sample the parameters from the distributions $\beta \sim U(0.01,\ 1)$, $\gamma \sim U(0.01,\ 1)$. The result is shown in Fig. 7, from which we can see that the PRCC of β is always positive and the value of γ is almost negative for CD4$^+$ T cells $T(t)$. This means that β is positive related to $T(t)$ while γ is negative related to $T(t)$ [29].

In comparison, we found that the PRCCs of $T^*(t)$, $V_I(t)$ and $V_{NI}(t)$ related to β and γ switch their signs in the early phase, while the signs of the PRCC values (except those of V_{NI} related to γ) remain unchanged later. This indicates that drug adherence can bring uncertainty to the viral load dynamics in the early stage of treatment. In addition, the PRCCs related to β are larger than those related to γ most of the time, which means that the results are more sensitive to β in our coupled model.

3. Conclusion and discussion

We investigated whether and how the drug adherence can generate viral blips by mathematical modeling. We developed a novel stochastic HIV model by coupling the stochastic drug uptakes under the imperfect adherence with PK-PD models and the viral dynamic model. The formulated coupled model is a high dimensional non-autonomous stochastic system where the drug effect is a random variable. The approaches in the current study also differ from previous works, which usually considered specific drugs and quantitatively studied blip frequency, viral amplitude and duration of occurrence [30,31].

By solving the model numerically and calculating the probability density function of infected CD4$^+$ T cells, we found that the random dosage uptake assuming binomial distribution in our model can generate viral blips. This shows that poor drug adherence can explain the occurrence of viral blips during the treatment of HIV infection. We fit the model to the clinical data of four HIV patients. The best-fitting curves captured viral blips in the four patients. Drug adherence can have significant influence on the frequency and

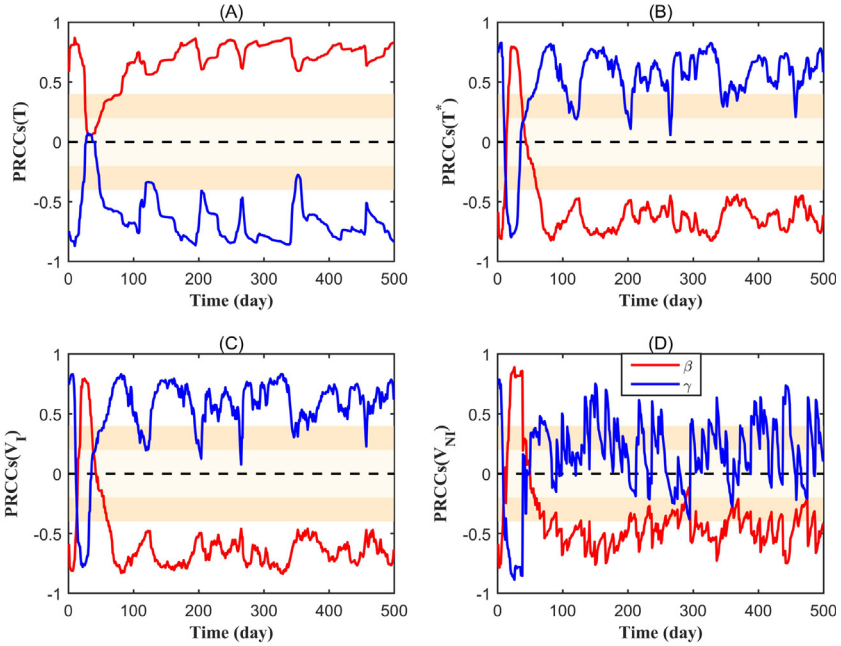

Fig. 7. Partial rank correlation coefficients (PRCCs) of variables in model (1) with respect to β and γ. Latin Hypercube Sampling was performed with 1000 bins. Subplots (A)–(D) are for T, T^*, V_I and V_{NI}, respectively.

amplitude of viral blips. Thus, with different drug adherence, the treatment outcome can be different, even though patients are taking the same drugs under the same treatment protocol.

There are a few limitations in this study. First, we did not conduct a thorough mathematical analysis of the stochastic model because of its high dimensionality and highly nonlinearity. The model may have more complex dynamical behaviors than we observed, but the analysis is challenging. Second, drug adherence considered in this model is individual-based. How to model the population-based drug adherence and integrate it to virus dynamics remains to be investigated. Lastly, we did not include the latent reservoir in the model, which is considered as a significant obstacle to viral elimination with the current antiretroviral treatment. Despite these limitations, the model and methods developed in this study can allow us to better understand the dependence of $CD4^+$ T cells and viral load on individual-based drug adherence. This may provide theoretical guidance for evaluating the relationship between drug adherence and the occurrence of viral blips. The model and methods may be applied to the study of long-term treatment for other chronic diseases in which drug adherence might also be an issue.

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