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Mathematical Modelling of Enfuvirtide and Protease Inhibitors as Combination Therapy for HIV

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Abstract: Enfuvirtide (formerly T20) is an injectable fusion inhibitor that has established effective antiretroviral activity and excellent tolerability in extensively pretreated patients. This fusion inhibitor does not affect the metabolism of other co-administrated drugs for metabolic drug interactions involving enfuvirtide. Few mathematical models have considered co-administration of antiretroviral drugs. We develop a mathematical model to study the effect of enfuvirtide upon this process in combination with protease inhibitors (PIs) using impulsive differential equations. We divide the T cells into several classes to describe the drug activity. Analytical results show that a combination of enfuvirtide and PIs gives a better outcome than single drug activity; furthermore, use of enfuvirtide clearly outranks PIs if only one class of drugs were to be used. We determine the threshold value for the dosage and dosing intervals to ensure the stability of the disease-free state and illustrate our results with numerical simulations. We recommend that use of enfuvirtide, in combination with PIs, be expanded beyond salvage therapy.

Keywords: HIV, enfuvirtide, $CD4^+$ T cells, protease inhibitors, chemokine co-receptors, antiretroviral therapy

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1 Introduction

Acquired immunodeficiency syndrome (AIDS) is a lethal disease that suppresses the effectivity of the immune system and curbs the body's ability to fight against any infection. Human immune deficiency virus (HIV) causes AIDS through infecting and damaging the $CD4^+$ T cells. The T cells are able to fight this attack for a certain period of time, but, due to lack of helper T cells, the immune system eventually fails. As a result, the immune system becomes less effective in fighting against opportunistic infections such as pneumonia. In a healthy human's peripheral blood, the level of $CD4^+$ T cells is between 800 and 1200 per mm^3; once this number falls below 200, the patient is classified as having AIDS [1].

Like most of the other viruses, HIV-1 is a simple RNA virus. It binds to $CD4^+$ T molecules on the surface of T cells. The virus then invades the cytoplasm of the T cell. From a therapeutic perspective, viral entry is one of the most striking points for intervention in the viral life cycle. The first step in the entry process involves binding of the viral envelope glycoprotein (gp120) to the CD4 cell surface receptor on helper T cells [2–5]. The gp120 protein that undergoes a conformational change results in its binding to chemokine co-receptors CCR5 and CXCR4 [6, 7]. The binding of both CD4 and the chemokine co-receptors by gp120 is the first two steps of viral entry. The third and final step in the viral entry process is fusion. Fusion of the viral and cellular membranes is a highly complex process that results in the discharge of the viral RNA and HIV enzymes such as reverse transcriptase, integrase and protease into the cytoplasm of the host cell. By means of its reverse transcriptase enzyme, HIV virus produces a homologous DNA copy and inserts itself into the host cell's DNA by integrase (another virally encoded enzyme). In the final stage of the viral life cycle, with the help of protease enzyme, the viral assembly process is complete.

There are more than 20 FDA-approved anti-HIV drugs currently available; most fall into 1 of the 2 categories: reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) [8–10]. The most widespread treatment strategy for acutely infected HIV patients is highly active antiretroviral therapy (HAART), which uses two or more drugs. Typically, these drug cocktails consist of one or more RTIs as well as a PI. RTIs prevent the conversion of

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HIV RNA into DNA, blocking integration of the viral code into the target cell. On the other hand, PIs effectively reduce the number of infectious virus particles, preventing the proper structure of the viral proteins before their release from the host cell.

Many patients have benefited from these drug regimens, which successfully reduce and maintain viral load below detectable levels [11]. Regardless of the success of these drug regimens, their long-term use comes with substantial complications. Many first-time HAART patients discontinue treatment within 8 months, often due to virological failure, poor adherence to treatment schedules or excessive toxicity [12]. In addition, high drug costs and complicated pill schedules make adherence troublesome for some patients and impossible for those who have limited access to anti-HIV drugs [13].

Major progress has been made in the treatment of HIV-infected patients; as a result, patients can achieve improved quality of life and greater longevity. Due to advances in available drug treatments and their combination in "drug cocktails", many patients successfully maintain low viral load and high T-cell counts for months or even years. The fusion inhibitor T20 (generic name: enfuvirtide; brand name: Fuzeon) is the most clinically advanced drug of a new class of antiretrovirals designed to inhibit viral entry [14]. Enfuvirtide is a synthetic 36 amino acid peptide, derived from the C-terminal region of HR2 [15]. Clinical data show that T20 is effective as salvage therapy for HIV/AIDS patients who have failed to respond to current antiretroviral therapeutics [16]. Enfuvirtide has a unique mechanism of action and has high viral target specificity; in clinical trials, it has been shown to exhibit both high efficacy and low toxicity. However, many patients are now failing to respond to T20 because the viruses develop T20 resistance [17–20].

A number of mathematical models have been developed to describe various treatment strategies and the effects of different drug therapies. The effect of perfect adherence to antiretroviral therapy has been studied using impulsive differential equations [6,7,21–25]. Using this method, the dosing period and threshold values of dosage can be obtained more precisely, as well as the effect of maximal acceptable drug holidays (short breaks taken from medication to alleviate side effects) [13]. Several mathematical models have been developed to describe the interaction of the human immune system with HIV, the decline in $CD4^+$ T cell count and the effects of different drug therapies [1, 26–35]. Here, we consider a combination of enfuvirtide and PIs to examine the effects of combination therapy on viral dynamics. A handful of mathematical models have examined combination therapy [36]. However, none have examined enfuvirtide in combination with PIs. Song et al. examined two different therapy strategies for enfuvirtide, but not in combination [25]. To the best of our knowledge, this is the first mathematical model for combination therapy with enfuvirtide.

We consider a mathematical model in which two classes of drugs are taken: the fusion inhibitor enfuvirtide, which is effective early in the viral life cycle and prevents viral entry into host cells, and a PI, which efficiently reduces the number of infectious virus particles. Using impulsive differential equations, we also evaluate the dosage and dosing period of both drugs.

2 The model

Here, we would like to enlighten the study of different achievable outcomes of $CD4^+$ T cell in a broader sense [6].

We consider two classes of virus populations: V_I denotes infectious virus populations that can infect susceptible $CD4^+$ T cells, and V_{NI} denotes noninfectious virus populations. Let T_S be the population of susceptible $CD4^+$ T cells and T_I denote the population of infected $CD4^+$ T cells. The latter produce both infectious and noninfectious virus. These cells may absorb either enfuvirtide or the PI. Since virus has already entered into $CD4^+$ T cells, absorbing enfuvirtide has no effect on infected cells. At any time, four possible actions may occur.

1. A $CD4^+$ T cell may come into contact with an infectious virion.
2. The cell may absorb enfuvirtide.
3. The cell may absorb the PI.
4. The cell may absorb both drugs.

T_F denotes fusion-inhibited T cells. Fusion-inhibited T cells are noninfected T cells that have absorbed sufficient quantity of fusion inhibitor (enfuvirtide) so that the probability of viral entry into this cell is negligible. If the PI is subsequently absorbed by these cells, then they will become noninfected doubly inhibited cells. T_{PNI} denotes noninfected protease-inhibited T cells. These cells may subsequently be infected by virus or they may absorb enfuvirtide. In the former case, they will become infected protease-inhibited cells; in the latter case, they will become noninfected doubly

inhibited cells. T_{PI} denotes infected cells that have absorbed PI. Due to presence of the PI, these cells release only noninfectious virus. Furthermore, absorption of enfuvirtide has no effect on these cells. Lastly, T_{FP} denotes cells that have absorbed both enfuvirtide and a PI, called doubly infected cells. These cells cannot be infected.

We use F and P to denote the intracellular concentration of enfuvirtide and the PI, respectively. Here, we have considered that the drugs are given at t_k for enfuvirtide and at s_k for PI. Furthermore, we have assumed that the effect of drug is instantaneous. The solutions of the ordinary differential equations (1) are continuous for $t \neq t_k$ and $t \neq s_k$ and go through an instantaneous change when $t = t_k$ or $t = s_k$. According to impulsive theory [37–39], we can describe the nature of the impulse at time t_m via the difference equation,

$$\Delta Z \equiv Z\left(t_m^+\right) - Z\left(t_m^-\right) = f\left(t_m, Z\left(t_m^-\right)\right).$$

The model takes the following form:

$$\begin{aligned}
\frac{dV_I}{dt} &= n_I\omega T_I - d_V V_I - r_I T_S V_I - r_I T_{PNI} V_I \\
\frac{dV_{NI}}{dt} &= n_I T_{PI} + n_I(1-\omega) T_I - d_V V_{NI} \\
\frac{dT_S}{dt} &= \lambda - r_I T_S V_I - d_S T_S - r_P T_S P + m_P T_{PNI} - r_F T_S F + m_F T_F \\
\frac{dT_I}{dt} &= r_I T_S V_I - d_I T_I - r_P T_I P + m_P T_{PI} \\
\frac{dT_F}{dt} &= r_F T_S F - d_S T_F - m_F T_F + m_P T_{FP} - r_P T_F P \\
\frac{dT_{PNI}}{dt} &= r_P T_S P - d_S T_{PNI} - r_I T_{PNI} V_I - m_P T_{PNI} - r_F T_{PNI} F + m_F T_{FP} \\
\frac{dT_{PI}}{dt} &= r_I T_{PNI} V_I - d_I T_{PI} + r_P T_I P - m_P T_{PI} \\
\frac{dT_{FP}}{dt} &= r_F T_{PNI} F - d_s T_{FP} - m_P T_{FP} - m_F T_{FP} + r_P T_F P \\
\frac{dF}{dt} &= -d_F F \\
\frac{dP}{dt} &= -d_P P,
\end{aligned} \tag{1}$$

for $t \neq t_k$ and $t \neq s_k$.

The impulsive conditions are

$$\begin{aligned}
\Delta F &= F^i \quad t = t_k \\
\Delta P &= P^i \quad t = s_k.
\end{aligned} \tag{2}$$

Here, n_I is the number of virions produced per infected cell per day and ω is the fraction of infectious virus produced by an infected T cell. d_V, d_S and d_I are the natural death rates of free virus, noninfected $CD4^+$ T cells and infected $CD4^+$ T cells, respectively. r_I is the infection rate of noninfected T cells, while r_F and r_P are the rates at which enfuvirtide and the PI are absorbed into the T cells. The rates at which enfuvirtide and the PI are cleared from the intracellular compartment are m_R and m_P, respectively. λ represents a source of susceptible cells. All the parameters are assumed to be positive, and we assume that $0 \ll \omega \leq 1$. We have $d_S < d_I < d_V$ [40]. We shall also assume that $n_I\omega > d_I$, as there are significantly more infectious virions produced from a T cell than the death rate of said cells.

Furthermore, we assume that each drug has an effect on the relevant T cells for a certain period of time, after which the T cells will revert to their appropriate state. Here, d_F and d_P are the clearance rates of enfuvirtide and PIs, while F^i and P^i are the dosages.

3 The system without drugs

In absence of both drugs, we set $P = F = 0$ in eq. (1) and ignore the impulsive equations. The system thus becomes a set of ordinary differential equations, for which we can perform standard stability analysis.

3.1 Equilibria

The system has two non-negative steady states: the disease-free equilibrium,

$$\begin{aligned}
&E^0\left(\bar{V}_I, \bar{V}_{NI}, \bar{T}_S, \bar{T}_I, \bar{T}_F, \bar{T}_{PNI}, \bar{T}_{PI}, \bar{T}_{FP}\right) \\
&= \left(0, 0, \frac{\lambda}{d_S}, 0, 0, 0, 0, 0\right),
\end{aligned}$$

and the endemic equilibrium, $E^+\left(\hat{V}_I, \hat{V}_{NI}, \hat{T}_S, \hat{T}_I, \hat{T}_F, \hat{T}_{PNI}, \hat{T}_{\mathrm{PI}}, \hat{T}_{FP}\right) = \left(\frac{\lambda(n_I\omega - d_I)}{d_I d_V} - \frac{d_S}{r_I}, n_I(1-\omega)\left[\frac{\lambda}{d_I d_V} - \frac{d_S}{r_I(n_I\omega - d_I)}\right], \frac{d_I d_V}{r_I(n_I\omega - d_I)}, \frac{\lambda}{d_I} + \frac{d_S d_V}{r_I(n_I\omega - d_I)}, 0, 0, 0, 0\right)$, which only exists if $(\lambda/d_I d_V) > (d_S/r_I(n_I\omega - d_I))$.

3.2 The basic reproductive ratio

Linearisation of the infective differential equations of the drug-free system at E^0 takes the following form:

$$\frac{dZ}{dt} = (F_{E^0} - V_{E^0})Z,$$

where

$$Z = [V_I, V_{NI}, T_I, T_{PI}]^T$$

$$F_{E^0} = \begin{bmatrix} 0 & 0 & n_I\omega & 0 \\ 0 & 0 & n_I(1-\omega) & n_I \\ \frac{r_I\lambda}{d_S} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V_{E^0} = \begin{bmatrix} d_V + \frac{r_I\lambda}{d_S} & 0 & 0 & 0 \\ 0 & d_V & 0 & 0 \\ 0 & 0 & d_I & -m_P \\ 0 & 0 & 0 & d_I + m_P \end{bmatrix}.$$

Deriving the spectral radius of the next-generation matrix, we have the threshold

$$R_0 = \rho\left(F_{E^0}V_{E^0}^{-1}\right)$$

$$= \max_{|\xi|} \det \begin{pmatrix} \xi & 0 & -\frac{n_I\omega}{d_I} & -\frac{n_I\omega m_P}{d_I(d_I+m_P)} \\ 0 & \xi & -\frac{n_I(1-\omega)}{d_I} & -\frac{n_I(1-\omega)m_P}{d_I(d_I+m_P)} - \frac{n_I}{d_I+m_P} \\ -\frac{r_I\lambda}{r_I\lambda + d_V d_S} & 0 & \xi & 0 \\ 0 & 0 & 0 & \xi \end{pmatrix}$$

The characteristic equation of $F_{E^0}V_{E^0}^{-1}$ satisfies

$$\xi^2\left[\xi^2 - \frac{\lambda r_I n_I \omega}{d_I(d_V d_S + \lambda r_I)}\right] = 0.$$

Therefore, the disease-free equilibrium (DFE) is unstable if

$$R_0 = \sqrt{\frac{\lambda r_I n_I \omega}{d_I(d_V d_S + \lambda r_I)}} > 1.$$

Note that this has appropriate threshold properties, although it is not the average number of secondary infections [41].

3.3 Stability analysis

Theorem 3.1: *The disease-free equilibrium E^0 of the drug-free system is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof: The Jacobian matrix J_0 for the drug-free system at E^0 is

$$J_0 = \begin{pmatrix} -d_V - r_I\bar{T}_S & 0 & 0 & n_I\omega & 0 & 0 & 0 & 0 \\ 0 & -d_V & 0 & n_I(1-\omega) & 0 & 0 & n_I & 0 \\ -r_I\bar{T}_S & 0 & -d_S & 0 & m_F & m_P & 0 & 0 \\ r_I\bar{T}_S & 0 & 0 & -d_I & 0 & 0 & m_P & 0 \\ 0 & 0 & 0 & 0 & -d_S - m_F & 0 & 0 & m_P \\ 0 & 0 & 0 & 0 & 0 & -d_S - m_P & 0 & m_F \\ 0 & 0 & 0 & 0 & 0 & 0 & -d_I - m_P & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -d_s - m_P - m_F \end{pmatrix}.$$

J_0 has negative eigenvalues $-d_s - m_P - m_F$, $-d_V$, $-d_S - m_F$, $-d_S - m_P$, $-d_I - m_P$ and $-d_S$, with nontrivial eigenvalues ξ expressed as the roots of the quadratic equation

$$f(\xi) = \xi^2 + a_1\xi + a_2,$$

with

$$a_1 = r_I\bar{T}_S + d_V + d_I$$
$$a_2 = d_I d_V + r_I\bar{T}_S d_I - r_I\bar{T}_S n_I\omega.$$

Here, a_1 is always positive, while $a_2 > 0$ iff $R_0 < 1$. □

Theorem 3.2: *The endemic equilibrium E^+ of the drug-free system exists and is locally asymptotically stable if $R_0 > 1$.*

Proof: The endemic equilibrium E^+ of the drug-free system clearly exists if $R_0 > 1$ and $n_I\omega > d_I$. The characteristic equation at the endemic equilibrium E^+ is

$$(\xi + d_S + m_P + m_F)(\xi + d_V)(\xi + d_S + m_F)(\xi + d_S + m_P + r_I V_I)$$
$$(\xi + d_I + m_P)(d_S + \xi)g(\xi) = 0$$

where

$$g(\xi) = \xi^3 + b_1\xi^2 + b_2\xi + b_3,$$

with

$$b_1 = d_S + r_I\hat{T}_S + r_I\hat{V}_I + d_V + d_I$$
$$b_2 = d_I d_V + r_I\hat{T}_S d_I + r_I\hat{V}_I d_I + d_S d_I + r_I\hat{V}_I d_V + d_S d_V + r_I\hat{T}_S d_S - r_I\hat{T}_S n_I\omega$$
$$b_3 = r_I\hat{V}_I d_V d_I + d_I d_S d_V + d_I r_I\hat{T}_S d_S - r_I\hat{T}_S d_S n_I\omega.$$

Here, b_2 and $b_3 > 0$ if $R_0 > 1$. We have

$$b_1 b_2 - b_3 = \frac{1}{d_V^2}\left[d_I d_S d_V^3 - \lambda d_I^2 d_V r_I + \lambda r_I d_S d_V^2 + \lambda^2 d_I r_I^2 + \lambda^2 d_V r_I^2 + \frac{\lambda\omega r_I n_I}{d_I}\left\{d_V\left(d_I^2 + d_I d_V + d_V^2\right) - 2\lambda r_I(d_I + d_V)\right\} + \frac{\lambda^2\omega^2 r_I^2 n_I^2(d_I + d_V)}{d_I^2} + \frac{d_I^2 d_S^2 d_V^4}{(n_I\omega - d_I)^2} + \frac{d_I d_S d_V^3(d_I + d_V)}{n_I\omega - d_I}\right].$$

We have numerically examined the positivity of $b_1b_2 - b_3$ along with $R_0 > 1$. Hence, E^+ is locally asymptotically stable if $R_0 > 1$.

4 The system in the presence of drugs

Including the dynamics of drugs via impulsive differential equations will obviously perturb the steady states. Instead of equilibria, the solutions will vary in periodic orbits. To apply our stability analysis, we fix $F^\star$ and $P^\star$ as constants representing the appropriate drug levels. Thus, equilibria denoted $X^\star$ will depend on drug levels, while those denoted $\tilde{X}$ will not.

The disease-free equilibrium is

$$E_D^0(\tilde{V}_I, \tilde{V}_{NI}, T_S^\star, \tilde{T}_I, T_F^\star, T_{PNI}^\star, \tilde{T}_{PI}, T_{FP}^\star) = (0, 0, T_S^\star, 0, T_F^\star, T_{PNI}^\star, 0, T_{FP}^\star).$$

where

$$T_S^\star = \frac{\lambda(d_S+m_F)(d_S+m_P)(d_S+m_F+m_P+F^\star r_F)+\lambda P^\star r_P((d_S+m_F)(d_S+m_P)+F^\star r_F d_S)}{d_S(d_S+m_F+F^\star r_F)(d_S+m_P+P^\star r_P)(d_S+m_F+m_P+F^\star r_F+P^\star r_P)}$$

$$T_F^\star = \frac{\lambda F^\star r_F((d_S+m_P)(d_S+m_F+m_P+F^\star r_F)+P^\star r_P m_P)}{d_S(d_S+m_F+F^\star r_F)(d_S+m_P+P^\star r_P)(d_S+m_F+m_P+F^\star r_F+P^\star r_P)}$$

$$T_{PNI}^\star = \frac{\lambda P^\star r_P(d_S^2+d_S(2m_F+m_P+P^\star r_P)+m_F(m_F+m_P+F^\star r_F+P^\star r_P))}{d_S(d_S+m_F+F^\star r_F)(d_S+m_P+P^\star r_P)(d_S+m_F+m_P+F^\star r_F+P^\star r_P)}$$

$$T_{FP}^\star = \frac{\lambda F^\star r_F P^\star r_P(2d_S+m_F+m_P+F^\star r_F+P^\star r_P)}{d_S(d_S+m_F+F^\star r_F)(d_S+m_P+P^\star r_P)(d_S+m_F+m_P+F^\star r_F+P^\star r_P)}. \quad (3)$$

The endemic equilibrium is

$$E_D^+(V_I^\star, V_{NI}^\star, T_S^\star, T_I^\star, T_F^\star, T_{PNI}^\star, T_{PI}^\star, T_{FP}^\star),$$

where

$$V_I^\star = \frac{n_I\omega T_I^\star}{d_V + r_I(T_S^\star + T_{PNI}^\star)} \quad V_{NI}^\star = \frac{n_I T_{PI}^\star + n_I(1-\omega)T_I^\star}{d_V}$$

$$T_S^\star = \frac{\lambda + m_P T_{PNI}^\star + m_F T_F^\star}{r_I V_I^\star + d_S + r_P P^\star + r_F F^\star} \quad T_I^\star = \frac{r_I T_S^\star V_I^\star + m_P T_{\mathrm{PI}}^\star}{d_I + r_P P^\star}$$

$$T_F^\star = \frac{r_F T_S^\star F^\star + m_P T_{FP}^\star}{d_S + m_F + r_P P^\star} \quad T_{PNI}^\star = \frac{r_P T_S^\star P^\star + m_F T_{FP}^\star}{d_S + r_I V_I^\star + m_P + r_F F^\star}$$

$$T_{PI}^\star = \frac{r_I T_{PNI}^\star V_I^\star + r_P T_I^\star P^\star}{d_I + m_P} \quad T_{FP}^\star = \frac{r_F T_{PNI}^\star F^\star + r_P T_F^\star P^\star}{d_S + m_P + m_F}.$$

4.1 Basic reproductive ratio

Linearisation of the infective differential equations of the model (1) at the disease-free state E_D^0 takes the following form:

$$\frac{dZ}{dt} = \left(F_{E_D^0} - V_{E_D^0}\right)Z,$$

where

$$Z = [V_I, V_{NI}, T_I, T_{PI}]^T$$

$$F_{E_D^0} = \begin{bmatrix} 0 & 0 & n_I\omega & 0 \\ 0 & 0 & n_I(1-\omega) & n_I \\ r_I T_S^\star & 0 & 0 & 0 \\ r_I T_{PNI}^\star & 0 & 0 & 0 \end{bmatrix}$$

$$V_{E_D^0} = \begin{bmatrix} d_V + r_I T_S^\star + r_I T_{PNI}^\star & 0 & 0 & 0 \\ 0 & d_V & 0 & 0 \\ 0 & 0 & d_I + P^\star r_P & -m_P \\ 0 & 0 & -P^\star r_P & d_I + m_P \end{bmatrix}.$$

Therefore,

$$R_0^D = \rho\left(F_{E_D^0}V_{E_D^0}^{-1}\right) = \max_{|\zeta|} \det \begin{pmatrix} \zeta & 0 & -\frac{n_I\omega(d_I+m_P)}{d_I(d_I+m_P+P^\star r_P)} & -\frac{n_I\omega m_P}{d_I(d_I+m_P+P^\star r_P)} \\ 0 & \zeta & -\frac{n_I(1-\omega)(d_I+m_P)}{d_I(d_I+m_P+P^\star r_P)} & -\frac{n_I(1-\omega)m_P}{d_I(d_I+m_P+P^\star r_P)} \\ & & -\frac{n_I P^\star r_P}{d_I(d_I+m_P+P^\star r_P)} & -\frac{n_I(d_I+P^\star r_P)}{d_I(d_I+m_P+P^\star r_P)} \\ -\frac{r_I T_S^\star}{d_V + r_I T_S^\star + r_I T_{PNI}^\star} & 0 & \zeta & 0 \\ -\frac{r_I T_{PNI}^\star}{d_V + r_I T_S^\star + r_I T_{PNI}^\star} & 0 & 0 & \zeta \end{pmatrix}.$$

The characteristic equation of $F_{E_D^0}V_{E_D^0}^{-1}$ is

$$\zeta^4 - \zeta^2\left[\frac{r_I T_S^\star n_I\omega(d_I+m_P)}{d_I(d_I+m_P+P^\star r_P)(d_V+r_I T_S^\star + r_I T_{PNI}^\star)} + \frac{n_I\omega m_P r_I T_{PNI}^\star}{d_I(d_I+m_P+P^\star r_P)(d_V+r_I T_S^\star + r_I T_{PNI}^\star)}\right] = 0.$$

Therefore,

$$R_0^D = \sqrt{\frac{r_I T_S^\star n_I\omega(d_I+m_P)}{d_I(d_I+m_P+P^\star r_P)(d_V+r_I T_S^\star + r_I T_{PNI}^\star)} + \frac{n_I\omega m_P r_I T_{PNI}^\star}{d_I(d_I+m_P+P^\star r_P)(d_V+r_I T_S^\star + r_I T_{PNI}^\star)}}, \quad (4)$$

where $T_S^\star$ and $T_{PNI}^\star$ are as in eq. (3).

4.2 Dynamics of drugs

Here, we examine the relationship between drug dosage and dosing interval of combination therapy for a better treatment strategy to effectively reduce viral load and also prevent viral entry into host cell.

The dynamics of the drugs are

$$\begin{aligned}\frac{dF}{dt} &= -d_F F \qquad t \neq t_k\\ \frac{dP}{dt} &= -d_P P \qquad t \neq s_k\\ \Delta F &= F^i \qquad t = t_k\\ \Delta P &= P^i \qquad t = s_k.\end{aligned}$$

Let $\tau = t_{k+1} - t_k$ be the period of enfuvirtide and $\sigma = s_{k+1} - s_k$ be the period of the PI (for $k \geq 1$).

The solution of the system (4) is

$$\begin{aligned}F(t) &= F(t_k^+)e^{-d_F(t-t_k)} \quad \text{for} \quad t_k < t \leq t_{k+1}\\ P(t) &= P(s_k^+)e^{-d_P(t-s_k)} \quad \text{for} \quad s_k < t \leq s_{k+1}.\end{aligned}$$

In the presence of an impulsive effect, we have a recursion relation at the moments of impulse, given by

$$F(t_k^+) = F(t_k^-) + F^i.$$

Thus, the drug concentrations before and after the drug is taken are

$$F(t_k^+) = \frac{F^i(1-e^{-km_F\tau})}{1-e^{-m_F\tau}}$$

and

$$F(t_{k+1}^-) = \frac{F^i(1-e^{-km_F\tau})e^{-m_F\tau}}{1-e^{-m_F\tau}}.$$

Hence, for the limiting case, the drug concentration before and after one dosage is

$$\begin{aligned}\lim_{k\to\infty} F(t_k^+) &= \frac{F^i}{1-e^{-m_F\tau}}\\ \lim_{k\to\infty} F(t_{k+1}^-) &= \frac{F^i e^{-m_F\tau}}{1-e^{-m_F\tau}}\end{aligned}$$

and

$$F(t_{k+1}^+) = \frac{F^i e^{-m_F\tau}}{1-e^{-m_F\tau}} + F^i = \frac{F^i}{1-e^{-m_F\tau}}.$$

We thus have

$$\begin{aligned}F(t_k^+) - \frac{F^i}{1-e^{-m_F\tau}} &= F^i\frac{1-e^{-km_F\tau}}{1-e^{-m_F\tau}} - \frac{F^i}{1-e^{-m_F\tau}}\\ &= -F^i\frac{e^{-km_F\tau}}{1-e^{-m_F\tau}} < 0.\end{aligned}$$

We can conclude that the positive impulsive orbit for enfuvirtide starts at $\frac{F^i e^{-d_F\tau}}{(1-e^{-d_F\tau})}$ and ends at $\frac{F^i}{(1-e^{-d_F\tau})}$.

Similarly, the positive impulsive orbit of the PI starts at $\frac{P^i e^{-d_P\sigma}}{(1-e^{-d_P\sigma})}$ and ends at $\frac{P^i}{(1-e^{-d_P\sigma})}$.

Theorem 4.1: *Let* $F_1 = \frac{X}{\phi}$ *and* $F_2 = \frac{X}{\psi}$, *where* $\phi = \frac{e^{-d_F\tau}}{(1-e^{-d_F\tau})}$ *and* $\psi = \frac{1}{(1-e^{-d_F\tau})}$. *Keeping the PI at a constant dose, we consider the following two cases*:

i. If $F^i > F_1$, the disease-free periodic orbit (E_D^0) exists and the endemic periodic orbit (E_D^*) does not exist.

ii. When the dosage satisfies $0 \leq F^i < F_2$, E_D^0 is unstable and E_D^* exists.

Proof: We have

$$F^i\phi \leq F^* \leq F^i\psi. \tag{5}$$

The disease-free equilibrium point E_D^0 exists if $R_0^D < 1$. Therefore,

$$S_1F^{i2} + S_2F^i + S_3 > 0, \tag{6}$$

where

$$\begin{aligned}S_1 &= d_I d_S d_V r_F^2\phi^2(d_I + m_P + P^*r_P)(d_S + m_P + P^*r_P),\\ S_2 &= d_I(d_S + m_F)(d_S d_V + \lambda r_I)r_F\phi(d_I + m_P + P^*r_P)\\ &\quad (d_S + m_P + P^*r_P)\\ &\quad + d_I d_S d_V r_F\phi(d_I + m_P + P^*r_P)(d_S + m_P + m_F + P^*r_P + F^*r_F)\\ &\quad \times (d_S + m_P + P^*r_P) - n_I\omega\lambda r_I r_F\phi P^*r_P d_S d_I\\ &\quad - n_I\omega\lambda r_I d_I r_F\phi(d_S + m_F)\\ &\quad \times (d_S + m_P) - n_I\omega\lambda r_I P^*r_P m_P r_F\phi(d_S + m_F) - n_I\omega\lambda r_I m_P r_F\phi\\ &\quad \times (d_S + m_F)(d_S + m_P),\\ S_3 &= (d_S + m_P + P^*r_P)(d_S + m_P + m_F + P^*r_P + F^*r_F)\\ &\quad (d_I + m_P + P^*r_P)\\ &\quad \times d_I(d_s + m_F)(d_S d_V + \lambda r_I) - n_I\omega\lambda r_I P^*r_P d_I(d_S + m_F)\\ &\quad (d_S + m_P)\\ &\quad - n_I\omega\lambda r_I d_I(d_S + m_F)(d_S + m_P)(d_S + m_F + m_P)\\ &\quad - n_I\omega\lambda r_I P^*r_P m_P\\ &\quad \times (d_S + m_F)(d_S + m_P + m_F + P^*r_P + F^*r_F)\\ &\quad - n_I\omega\lambda r_I m_P(d_S + m_F)\\ &\quad \times (d_S + m_P + m_F + P^*r_P + F^*r_F)(d_S + m_P).\end{aligned}$$

Using eq. (5), for $R_0^D > 1$, we can find

$$T_1F^{i2} + T_2F^i + T_3 < 0, \tag{7}$$

where

$$T_1 = d_I d_S d_V r_F^2 \psi^2 (d_I + m_P + P^* r_P)(d_S + m_P + P^* r_P),$$

$$T_2 = d_I (d_S + m_F)(d_S d_V + \lambda r_I) r_F \psi (d_I + m_P + P^* r_P)(d_S + m_P + P^* r_P) + d_I d_S d_V r_F \psi (d_I + m_P + P^* r_P)(d_S + m_P + m_F + P^* r_P + F^* r_F) \times (d_S + m_P + P^* r_P) - n_I \omega \lambda r_I r_F \psi P^* r_P d_S d_I - n_I \omega \lambda r_I d_I r_F \psi (d_S + m_F) \times (d_S + m_P) - n_I \omega \lambda r_I P^* r_P m_P r_F \psi (d_S + m_F) - n_I \omega \lambda r_I m_P r_F \psi \times (d_S + m_F)(d_S + m_P)$$

$$T_3 = (d_S + m_P + P^* r_P)(d_S + m_P + m_F + P^* r_P + F^* r_F)(d_I + m_P + P^* r_P) \times d_I (d_s + m_F)(d_S d_V + \lambda r_I) - n_I \omega \lambda r_I P^* r_P d_I (d_S + m_F)(d_S + m_P) - n_I \omega \lambda r_I d_I (d_S + m_F)(d_S + m_P)(d_S + m_F + m_P) - n_I \omega \lambda r_I P^* r_P m_P \times (d_S + m_F)(d_S + m_P + m_F + P^* r_P + F^* r_F) - n_I \omega \lambda r_I m_P (d_S + m_F) \times (d_S + m_P + m_F + P^* r_P + F^* r_F)(d_S + m_P).$$

Here, eqs. (6) and (7) both have a unique positive root if $S_3 > 0$ and $T_0 > 0$. Let F_1 and F_2 be the unique positive roots of eqs. (6) and (7), respectively. So, $F^i > F_1$ holds whenever $R_0^D < 1$ and $F^i > F_2$ holds for $R_0^D > 1$.

Whenever $R_0^D < 1$, we have a threshold value of drug dose F_1 such that

$$F^i > F_1 \Rightarrow \tau < \frac{1}{d_F} \ln\left(1 + \frac{F^i}{X}\right) \equiv \tau_1.$$

If $R_0^D > 1$, we have found a threshold value of drug dose F_2 such that

$$F^i < F_2 \Rightarrow \tau > -\frac{1}{d_F} \ln\left(1 - \frac{F^i}{X}\right) \equiv \tau_2.$$

Keeping the dosages of PI fixed, the disease-free periodic orbit will be stable if the drug regimen satisfies the condition $F^i > F_1$, i.e. when the drug dose is sufficiently high. Conversely, the infection persists and reaches an endemic state if the drug dose satisfies the condition $F^i < F_2$. If we can control the dosing interval τ satisfying the condition $0 \le \tau < \tau_1$ for a fixed dosage, then the disease-free periodic orbit will be stable. If $\tau > \tau_2$ (i.e. if the dosing interval is sufficiently high), then the endemic periodic orbit will be stable in the presence of drug.

It should be noted that prediction is impossible in the interval $\tau_1 < \tau < \tau_2$ (or $F_2 < F^i < F_1$), for ongoing treatment of an individual, because in this situation, R_0^D fluctuates around one.

Theorem 4.2: *Let* $P_1 = \frac{K}{\delta}$, $P_2 = \frac{K}{\theta}$, *where* $\delta = \frac{e^{-d_P \sigma}}{(1 - e^{-d_P \sigma})}$ *and* $\theta = \frac{1}{(1 - e^{-d_P \sigma})}$.

(i) If $P^i > P_1$, the disease-free periodic orbit (E_D^0) exists and the endemic periodic orbit (E_D^*) does not exist.

(ii) When the dosage satisfies $0 \le P^i < P_2$, E_D^0 is unstable and E_D^* exists.

Proof: From the endpoints of the impulsive periodic orbit, we have

$$P^i \delta \le F^* \le P^i \theta. \tag{8}$$

The disease-free equilibrium point E_D^0 exists if $R_0^D < 1$. Therefore,

$$Q_1 P^{i3} + Q_2 P^{i2} + Q_3 P^i + Q_4 > 0, \tag{9}$$

where

$$Q_1 = \delta^3 r_P^3 \{ d_I d_S d_V (d_S + m_F + m_P + F^* r_F) - m_P d_I d_S d_V + \lambda d_I r_I (d_S + m_F) \},$$

$$Q_2 = \delta^2 r_P^2 [\{ d_I d_S d_V (d_S + m_F + m_P + F^* r_F) - m_P d_I d_S d_V + \lambda d_I r_I (d_S + m_F) \} \times (2d_S + d_I + 3m_P + m_F + F^* r_F) - n_I \omega \lambda r_I m_P (d_S + m_F)]$$

$$Q_3 = \delta^2 r_P^2 [\{ d_I d_S d_V (d_S + m_F + m_P + F^* r_F) - m_P d_I d_S d_V + \lambda d_I r_I (d_S + m_F) \} \times \{ (d_I + m_P)(d_S + m_P) + (d_S + m_P)(d_S + m_F + m_P + F^* r_F) + \times (d_S + m_F + m_P + F^* r_F)(d_I + m_P) \} - n_I \omega \lambda r_I d_I d_S F^* r_F + (d_I + m_P). \times (d_S + m_F)(d_S + m_P) + m_P (d_S + m_F)(d_S + m_F + m_P + F^* r_F) \}]$$

$$Q_4 = \{ d_I d_S d_V (d_S + m_F + m_P + F^* r_F) - m_P d_I d_S d_V + \lambda d_I r_I (d_S + m_F) \} \times (d_I + m_P)(d_S + m_P)(d_s + m_F + m_P + F^* r_F) - n_I \omega \lambda r_I (d_S + m_F) \times (d_S + m_P) \{ m_P (d_S + m_F + m_P + F^* r_F) + d_I (d_S + m_F + m_P) + d_I F^* r_F \}.$$

Using eq. (8), for $R_0^D > 1$, we can find

$$R_1 P^{i3} + R_2 P^{i2} + R_3 P^i + R_4 < 0, \tag{10}$$

where

$$R_1 = \theta^3 r_P^3 \{ d_I d_S d_V (d_S + m_F + m_P + F^* r_F) - m_P d_I d_S d_V + \lambda d_I r_I (d_S + m_F) \}$$

$$R_2 = \theta^2 r_P^2 [\{ d_I d_S d_V (d_S + m_F + m_P + F^* r_F) - m_P d_I d_S d_V + \lambda d_I r_I (d_S + m_F) \} \times (2d_S + d_I + 3m_P + m_F + F^* r_F) - n_I \omega \lambda r_I m_P (d_S + m_F)]$$

$$R_3 = \theta r_P [\{ d_I d_S d_V (d_S + m_F + m_P + F^* r_F) - m_P d_I d_S d_V + \lambda d_I r_I (d_S + m_F) \} \times \{ (d_I + m_P)(d_S + m_P) + (d_S + m_P)(d_S + m_F + m_P + F^* r_F) + \times (d_S + m_F + m_P + F^* r_F)(d_I + m_P) \} - n_I \omega \lambda r_I \{ d_I d_S F^* r_F + (d_I + m_P) \times (d_S + m_F)(d_S + m_P) + m_P (d_S + m_F)(d_S + m_F + m_P + F^* r_F) \}]$$

$$R_4 = \{ d_I d_S d_V (d_S + m_F + m_P + F^* r_F) - m_P d_I d_S d_V + \lambda d_I r_I (d_S + m_F) \} \times (d_I + m_P)(d_S + m_P)(d_s + m_F + m_P + F^* r_F) - n_I \omega \lambda r_I (d_S + m_F) \times (d_S + m_P) \{ m_P (d_S + m_F + m_P + F^* r_F) + d_I (d_S + m_F + m_P) + d_I F^* r_F \}.$$

Here, eqs. (9) and (10) can both have positive roots (possibly with multiple roots) if and only if the following inequalities hold:

(i) $Q_1 Q_2 < 0$,

(ii) $Q_1 Q_3 > 0$,

(iii) $Q_1 Q_4 < 0$ and

(iv) $27 Q_1^2 Q_4^2 + 4 Q_1 Q_3^3 + 4 Q_2^3 Q_4 \le 18 Q_1 Q_2 Q_3 Q_4 + Q_2^2 Q_3^2$.

From eqs. (9) and (10), we see that $Q_1 > 0$, $Q_2 > 0$, $R_1 > 0$ and $R_2 > 0$, so inequality (i) cannot be true. Thus, both of the two equations cannot have three positive roots. If $Q_4 < 0$ and $R_4 < 0$, then (9) and (10) must have only one positive root. Let P_1 and P_2 be the unique positive roots of eqs. (9) and (10). So, $P^i > P_1$ holds whenever $R_0^D < 1$ and $P^i > P_2$ holds for $R_0^D > 1$.

Whenever $R_0^D < 1$, we have a threshold value of drug dose P_1 such that

$$P^i > P_1 \Rightarrow \sigma < \frac{1}{d_P} \ln\left(1 + \frac{P^i}{K}\right) \equiv \sigma_1.$$

When $R_0^D > 1$, we have a threshold value of drug dose P_2 such that

$$P^i < P_2 \Rightarrow \sigma > -\frac{1}{d_P} \ln\left(1 - \frac{P^i}{K}\right) \equiv \sigma_2.$$

Keeping the dosages of enfuvirtide fixed, the disease-free periodic orbit will be stable if the drug regimen satisfies the condition $P^i > P_1$, i.e. when the drug dose is sufficiently high. However, the infection persists and reaches an endemic state if drug dose satisfies the condition $P^i < P_2$. If we can control the dosing interval σ satisfying the condition $0 \le \sigma < \sigma_1$ for a fixed dosage, then the disease-free periodic orbit will be stable. If $\sigma > \sigma_2$ (i.e. if the dosing interval is sufficiently high), then the endemic periodic orbit will be stable in the presence of drug.

As before, prediction is impossible in the interval $\sigma_1 < \sigma < \sigma_2$ (or $P_2 < P^i < P_1$), because R_0^D fluctuates around one.

5 Numerical analysis

5.1 Sensitivity analysis

We now perform a sensitivity analysis to explore the robustness of the basic reproductive number to fluctuations in the parameters. From this, we can identify the parameters that have a high impact on the basic reproductive ratio, as well as on the disease transmission. The normalised forward sensitivity index of R_0 with respect to a parameter n_I is defined as follows [42]:

$$\Pi_{n_I}^{R_0} = \frac{\partial R_0}{\partial n_I} \times \frac{n_I}{R_0}. \tag{11}$$

We calculate the sensitivity of R_0 with respect to other parameters similarly (see Table 1). The sensitivity index measures the normalised effect that each parameter has on the outcome (R_0 in our case). For example, in Table 1, a value of $\Pi_{\omega}^{R_0} = 0.5$ indicates that increasing ω by 10% will increase R_0 by 5%. Conversely, since $\Pi_{d_V}^{R_0} = -0.5$,

Table 1: 1 Parameter values in the absence of drugs.

Parameter	Parameter description	Value	Sensitivity
n_I	Number of virions produced per infected cell per day	62.5	0.5
ω	Fraction of infectious virions produced by an infected cell	0.05	0.5
λ	Source of susceptible cells	100	0.1596
r_I	Infection rate of noninfected T cells	0.0032	0.1596
d_S	Death rate of noninfected T cells	0.05	−0.1596
d_I	Death rate of infected T cells	0.5	−0.5
d_V	Death rate of virus	3	−0.1596

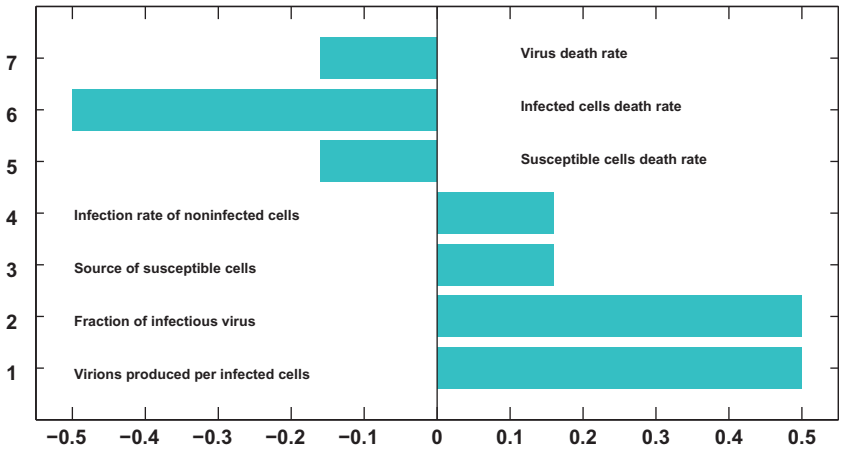

Figure 1: Tornado plots of sensitivity of R_0 for each of the parameters.

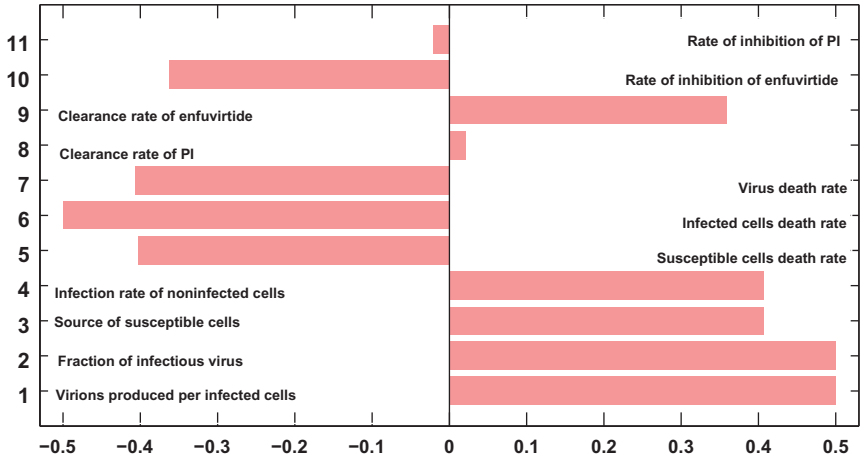

Figure 2: Tornado plots of sensitivity of R_0^D for each of the parameters.

increasing d_V by 10% will decrease R_0 by 5%. The results are plotted in Figures 1 and 2.

The most sensitive parameters are number of virions produced per infected cell per day (n_I) and fraction of virions produced by an infected cell that are infectious (ω). We perform the same analysis for the basic reproductive ratio in the presence of drugs (R_0^D) (see Table 2).

Here, the most sensitive parameters are the number of virions produced per infected cell per day (n_I) and the fraction of virions produced by an infected cell that are infectious (ω).

5.2 Time-dependent solutions

We performed numerical simulations for enfuvirtide and the PI under conditions of perfect drug adherence. The values of the parameters used are $\lambda = 100$, $n_I = 62.5$, $\omega = 0.05$, $r_I = 0.0032$, $r_P = 0.2$, $r_F = 50$, $m_P = 8.522$, $m_F = 4.16$, $d_S = 0.05$, $d_I = 0.5$, $d_V = 3$, $d_P = 1$, $d_F = 1$ [21, 22, 6, 7]. Initial conditions are taken as $V_I(0) = 100$, $V_{NI} = 0$, $T_S(0) = 1000$, $T_I(0) = 20$, $T_F(0) = 0$, $T_{PNI}(0) = 0$, $T_{PI}(0) = 0$, $T_{FP}(0) = 0$ and the unit of the concentration is mm^{-3}.

Figure 3 shows the contour plot of the basic reproductive ratio in the absence (R_0) and presence (R_0^D) of drug therapy as a function of r_I and λ, respectively. From both plots, we observe that if r_I and λ are small, then both R_0 and R_0^D can be below unity. However, if r_I and λ are both very large, then R_0 and R_0^D exceed 1. Comparing both plots, we see that, for most choices of λ and r_I, the disease-free state becomes stable once both drugs are present.

We summarise the four different cases of drug regimen that predict the best therapy strategy.

Table 2: 2 Parameter values in the presence of drugs.

Parameter	Parameter description	Value	Sensitivity
n_I	Number of virions produced per infected cell per day	62.5	0.5
ω	Fraction of infectious virions produced by an infected cell	0.05	0.5
λ	Source of susceptible cells	100	0.4068
r_I	Infection rate of noninfected T cells	0.0032	0.4068
d_S	Death rate of noninfected T cells	0.05	−0.4025
d_I	Death rate of infected T cells	0.5	−0.499
d_V	Death rate of virus	3	−0.4068
m_P	Rate of clearance of PI	8.522	0.0213
m_F	Rate of clearance of enfuvirtide	4.16	0.3588
r_F	Rate of inhibition of T cell by enfuvirtide	50	−0.3631
r_P	Rate of inhibition of T cell by PI	0.2	−0.0213

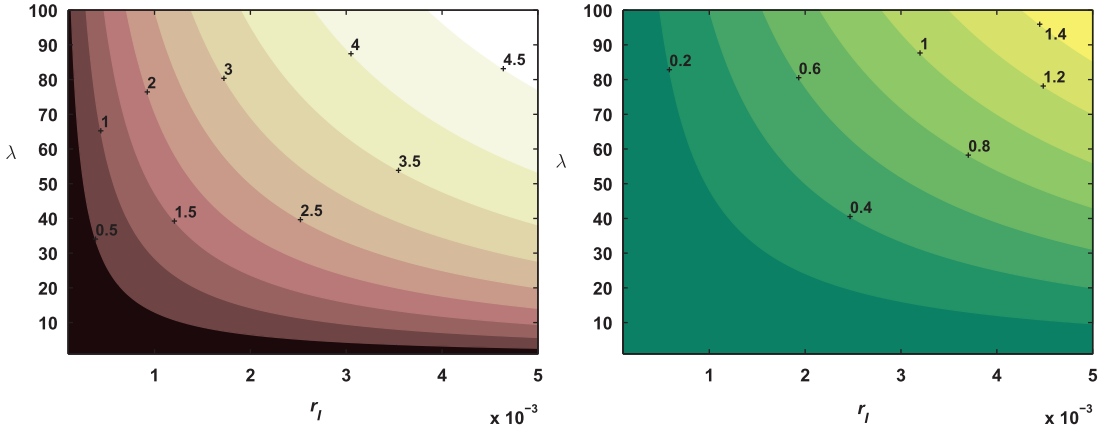

Figure 3: Left panel: Contour plot of R_0 as a function of λ and r_I. Right panel: Contour plot of R_0^D as a function of λ and r_I.

5.2.1 Both drugs with safe dosages and frequent dosing

In this case, we have considered the dosages of enfuvirtide and the PI to be $F^i = 0.7 > F_1$ and $P^i = 1.9 > P_1$ with dosing intervals $\tau = 0.5$ and $\sigma = 0.25$, respectively. Figure 4 illustrates the outcome for this drug regimen. We observe that the virus is under control, due to the high dosage of both drugs. In this case, the T-cell count is maintained close to healthy equilibrium, and the total viral and infected populations are in a lower density. Clearly, sufficient dosing of both drugs can maintain the level of noninfected T cells, thus controlling the virus. Figure 5 shows time-dependent changes of the drug concentration in plasma of both drugs.

5.2.2 Both drugs with unsafe dosages and infrequent dosing

Next, we considered the dosages of enfuvirtide and PI, $F^i = 0.01 < F_2$ and $P^i = 0.1 < P_2$ with dosing intervals $\tau = \sigma = 3$. Figure 6 illustrates the outcome for this drug schedule. Insufficient and infrequent dosing of both drugs leads to a high viral load and a large population of infected T cells. In this case, it is impossible to maintain sufficient noninfected T-cell counts for a healthy immune system.

5.2.3 The protease inhibitor without enfuvirtide

Frequent dosing of the PI alone, even with a relatively high dosage of $P^i = 15$ and high frequency of $\sigma = 0.5$, may be insufficient to maintain T cell counts at a level comparable to the healthy immune system. Figure 7 shows that even large and frequent dosing of the PI may lead to a high viral load and a large population of infected T cells. We conclude that the PI alone, even at an extremely high dose, may not be a good strategy.

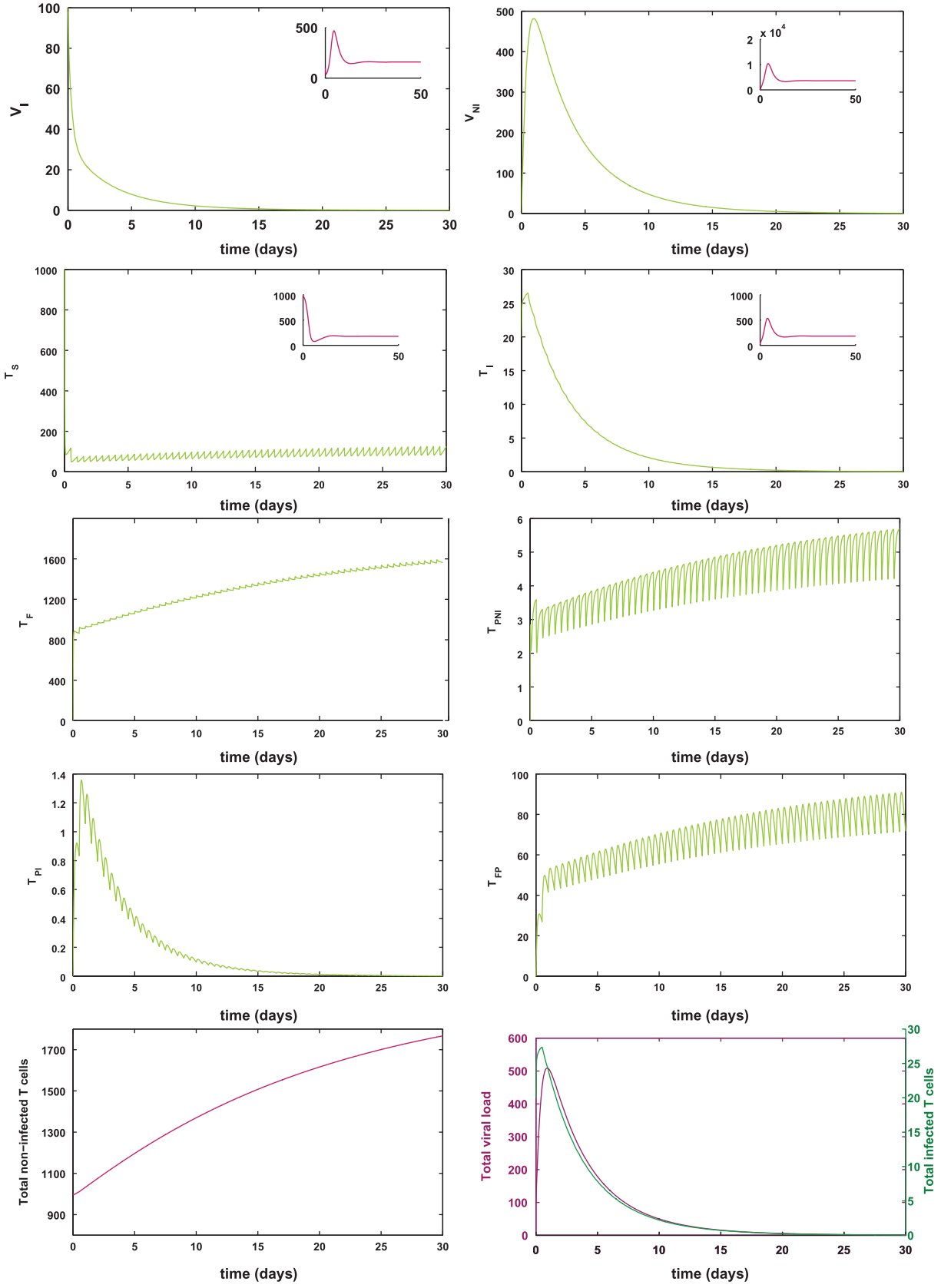

Figure 4: System behaviour for perfect adherence with $F^i = 0.7$, $P^i = 1.9$ and $\tau = 0.5$, $\sigma = 0.25$. Inset: Trajectories of the system in the absence of therapy.

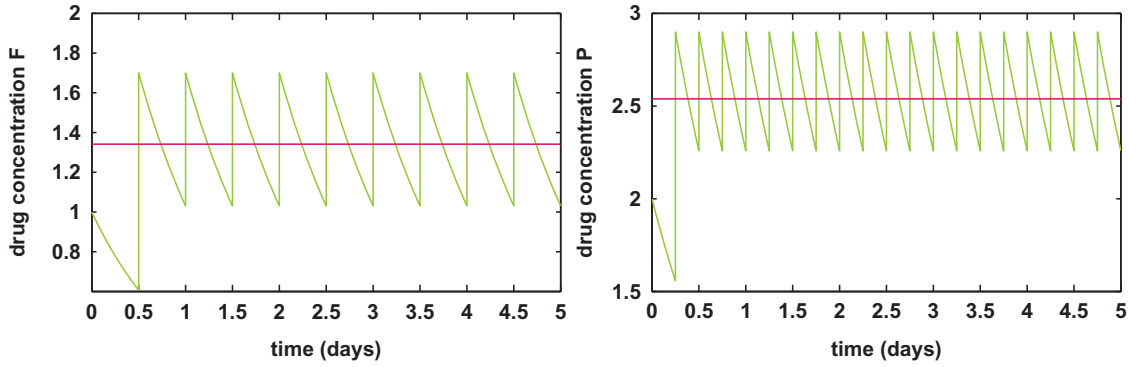

Figure 5: Left panel: Time-dependent changes of concentration of enfuvirtide with $F^i = 0.7$. Right panel: Time-dependent changes of concentration of the PI with $P^i = 1.9$.

5.2.4 Enfuvirtide without the protease inhibitor

Conversely, consider enfuvirtide used alone, with a moderate dosage $F^i = 0.8$ and dosing interval $\tau = 0.5$. Figure 8 shows that the noninfected T-cell count is close to healthy equilibrium and viral population and infected T cells are in a lower density than the previous two cases. Comparing Figures 4 and 8, we observe that, although enfuvirtide monotherapy may effectively control the viral infection, combination therapy can successfully reduce viral load and infected T cells below detectable level and also adequately maintain a healthy immune system by sustaining noninfected T cells at or near the disease-free equilibrium.

6 Discussion

We considered a mathematical model of HIV-1 infection with combination drug therapy of enfuvirtide together with a PI. We incorporated impulsive differential equations to model the dynamics of drug action, and we also formulated a therapy strategy for perfect adherence, which plays an important role in clinical trials. In the absence of drug therapy, the disease-free equilibrium persists whenever R_0 lies below 1, but the system changes its stability whenever the value of R_0 exceeds unity. We found threshold values and the relationship between drug dosage and dosing interval for existence and stability of the disease-free and endemic equilibria for both drugs.

There are some limitations of our modelling, which should be acknowledged. First, we assumed that the two drugs acted independently and had no cumulative contribution when acting together. Since the effect of enfuvirtide occurs at the beginning of the viral life cycle and PIs affect the end of the viral life cycle, this may be a reasonable assumption in this case, but it may not carry over to general modelling of combination therapy. For example, if enfuvirtide and RTIs are taken together, the effects on the virus may be stronger than the sum of their parts. We will investigate such effects in future work. Second, we assumed that the effect of each drug was instantaneous; in reality, there is a small delay as the mechanism of drug reaction reaches its time to peak. Such delays will not affect our results, as long as time between dosages is significantly larger than the instantaneous approximation. Finally, we assumed that the decay of drugs was unaffected by their uptake into cells; this has the effect of overestimating the amount of available drug in the body.

A surprising result from our analysis is that enfuvirtide is significantly more effective at controlling the virus than PIs are. This is likely because enfuvirtide is a "preventative" drug, whereas PIs act after infection has occurred. That is, if enfuvirtide inhibits a cell, then that cell is long lived and impervious to infection; conversely, if PIs inhibit a cell, then such cells do not live long, even if they are only producing noninfectious virus. Clearly, using both drugs is the best case scenario, but we recommend that PIs not be used alone.

In summary, modelling combination therapy allows us to gain insights into disease dynamics that

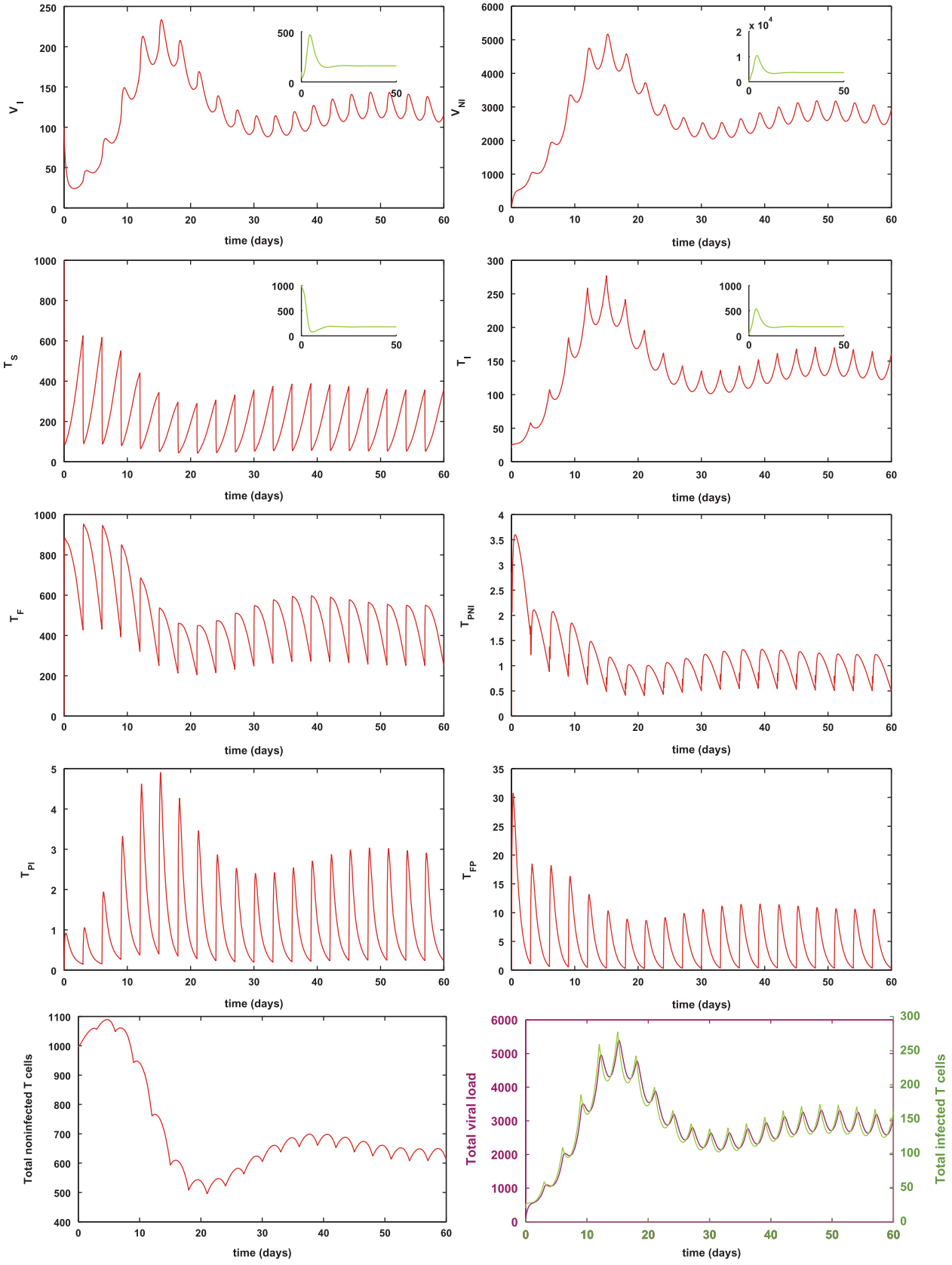

Figure 6: System behaviour for perfect adherence with $F^i = 0.01$, $P^i = 0.1$ and $\tau = 3, \sigma = 3$. Inset: Trajectories of the system in the absence of therapy.

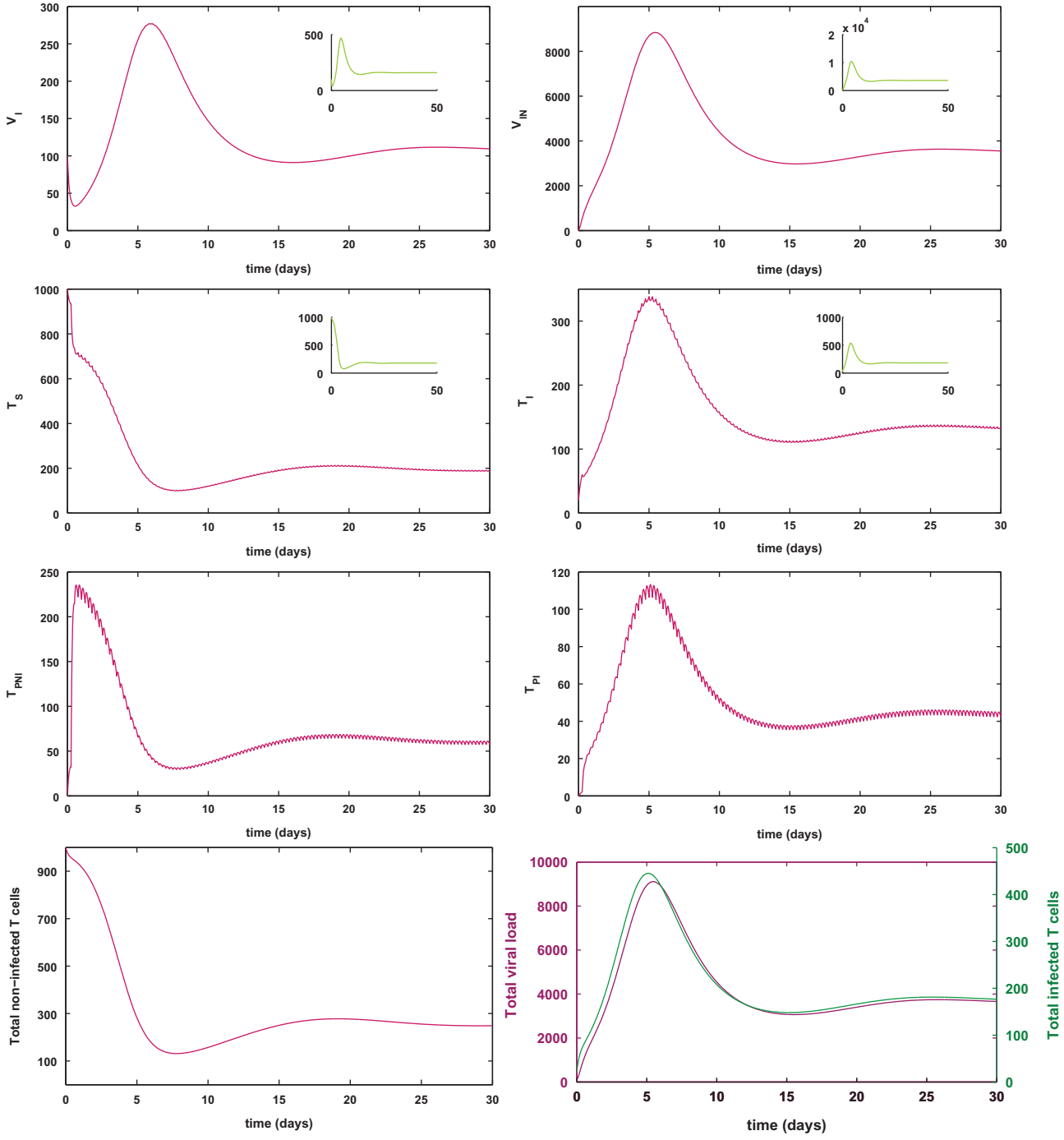

Figure 7: System behaviour for perfect adherence with $F^i = 0$, $P^i = 0.1$ and $\tau = 0$, $\sigma = 0.25$. Inset: Trajectories of the system in the absence of therapy.

monotherapy does not. Furthermore, impulsive differential equations are a useful mathematical tool for elucidating insights into regular drug dosing. The advantages of enfuvirtide over PIs indicate that it may be worthwhile expanding treatment options to patients belonging to salvage therapy.

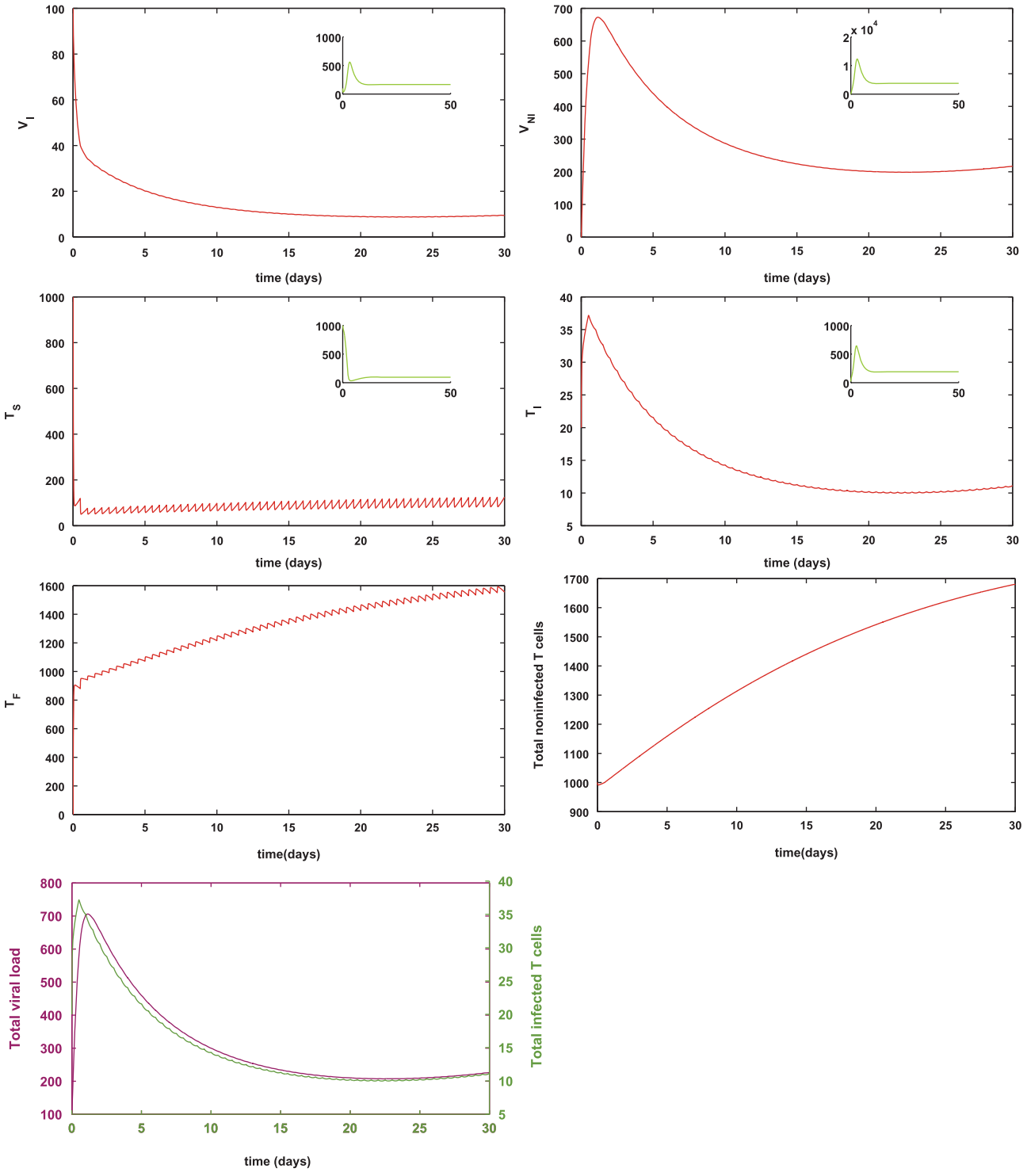

Figure 8: System behaviour for perfect adherence with $F^i = 0.01$, $P^i = 0$ and $\tau = 0.5$, $\sigma = 0$. Inset: Trajectories of the system in the absence of therapy.

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References

[1] A. S. Perelson and P. W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, SIAM Rev. 41(1) (1999), 3–44.

[2] P. L. Earl, R. W. Doms and B. Moss, Oligomeric structure of the human immunodeficiency virus type 1 envelope glycoprotein, Proc. Natl. Acad. Sci. 87(2) (1990), 648–652.

[3] W. R. Gallaher, J. M. Ball, R. F. Garry, A. M. Martin-Amedee and R. C. Montelaro, A general model for the surface glycoproteins of HIV and other retroviruses, AIDS Res. Hum. Retroviruses 11(2) (1995), 191–202.

[4] M. Kowalski, J. Potz, L. Basiripour, T. Dorfman, W. C. Goh, E. Terwilliger, A. Dayton, C. Rosen, W. Haseltine and J. Sodroski, Functional regions of the envelope glycoprotein of human immunodeficiency virus type 1, Science 237(4820) (1987), 1351–1355.

[5] L. A. Lasky, G. Nakamura, D. H. Smith, C. Fennie, C. Shimasaki, E. Patzer, P. Berman, T. Gregory and J. Capon, Delineation of a region of the human immunodeficiency virus type 1 gp120 glycoprotein critical for interaction with the CD4 receptor, Cell 50(6) (1987), 975–985.

[6] R. Smith and L. Wahl, Distinct effects of protease and reverse transcriptase inhibition in an immunological model of HIV-1 infection with impulsive drug effects, Bull. Math. Biol. 66(5) (2004), 1259–1283.

[7] R. Smith and L. Wahl, Drug resistance in an immunological model of HIV-1 infection with impulsive drug effects, Bull. Math. Biol. 67(4) (2005), 783–813.

[8] A. Carr, Toxicity of antiretroviral therapy and implications for drug development, Nat. Rev. Drug Discovery 2(8) (2003), 624–634.

[9] G. K. Robbins, V. De Gruttola, R. W. Shafer, L. M. Smeaton, S. W. Snyder, C. Pettinelli, M. P. Dubé, M. A. Fischl, R. B. Pollard, R. Delapenha, et al., Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection, N. Engl. J. Med. 349(24) (2003), 2293–2303.

[10] S. Staszewski, J. Morales-Ramirez, K. T. Tashima, A. Rachlis, D. Skiest, J. Stanford, R. Stryker, P. Johnson, D. F. Labriola, D. Farina, et al., Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults, N. Engl. J. Med. 341(25) (1999), 1865–1873.

[11] T.-W. Chun and A. S. Fauci, Latent reservoirs of HIV: obstacles to the eradication of virus, Proc. Natl. Acad. Sci. 96(20) (1999), 10958–10961.

[12] A. D. Monforte, A. C. Lepri, G. Rezza, P. Pezzotti, A. Antinori, A. N. Phillips, G. Angarano, V. Colangeli, A. De Luca, G. Ippolito, et al., Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients, AIDS 14(5) (2000), 499–507.

[13] R. E. Miron and R. J. Smith?, Modelling imperfect adherence to HIV induction therapy, BMC Infect. Dis. 10(1) (2010), 6.

[14] A. Lazzarin, B. Clotet, D. Cooper, J. Reynes, K. Arastéh, M. Nelson, C. Katlama, H.-J. Stellbrink, J.-F. Delfraissy, J. Lange, et al., Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia, N. Engl. J. Med. 348(22) (2003), 2186–2195.

[15] C. T. Wild, D. C. Shugars, T. K. Greenwell, C. B. McDanal and T. J. Matthews, Peptides corresponding to a predictive alpha-helical domain of human immunodeficiency virus type 1 gp41 are potent inhibitors of virus infection, Proc. Natl. Acad. Sci. 91 (21) (1994), 9770–9774.

[16] J. M. Kilby and J. J. Eron, Novel therapies based on mechanisms of HIV-1 cell entry, N. Engl. J. Med. 348(22) (2003), 2228–2238.

[17] J. Lu, S. G. Deeks, R. Hoh, G. Beatty, B. A. Kuritzkes, J. N. Martin and D. R. Kuritzkes, Rapid emergence of enfuvirtide resistance in HIV-1-infected patients: results of a clonal analysis, JAIDS 43 (1) (2006), 60–64.

[18] P. R. Sista, T. Melby, D. Davison, L. Jin, S. Mosier, M. Mink, E. L. Nelson, R. DeMasi, N. Cammack, M. P. Salgo, et al., Characterization of determinants of genotypic and phenotypic resistance to enfuvirtide in baseline and on-treatment HIV-1 isolates, AIDS 18(13) (2004), 1787–1794.

[19] X. Wei, J. M. Decker, H. Liu, Z. Zhang, R. B. Arani, J. M. Kilby, M. S. Saag, X. Wu, G. M. Shaw and J. C. Kappes, Emergence of resistant human immunodeficiency virus type 1 in patients receiving fusion inhibitor (T-20) monotherapy, Antimicrob. Agents Chemother. 46(6) (2002), 1896–1905.

[20] L. Xu, S. Hué, S. Taylor, D. Ratcliffe, J. A. Workman, S. Jackson, P. A. Cane and D. Pillay, Minimal variation in T-20 binding domain of different HIV-1 subtypes from antiretroviral-naive and -experienced patients, AIDS 16(12) (2002), 1684–1686.

[21] J. Lou and R. J. Smith?, Modelling the effects of adherence to the HIV fusion inhibitor enfuvirtide, J. Theor. Biol. 268(1) (2011), 1–13.

[22] R. J. Smith?, Explicitly accounting for antiretroviral drug uptake in theoretical HIV models predicts long-term failure of protease-only therapy, J. Theor. Biol. 251(2) (2008), 227–237.

[23] R. J. Smith? and B. Aggarwala, Can the viral reservoir of latently infected CD4+ T cells be eradicated with antiretroviral HIV drugs?, J. Math. Biol. 59(5) (2009), 697–715.

[24] R. J. Smith?, J. T. Okano, J. S. Kahn, E. N. Bodine and S. Blower, Evolutionary dynamics of complex networks of HIV drug-resistant strains: the case of San Francisco, Science 327(5966) (2010), 697–701.

[25] B.-J. Song, J. Lou and Q.-Z. Wen, Modelling two different therapy strategies for drug T-20 on HIV-1 patients, Appl. Math. Mech. 32 (2011), 419–436.

[26] S. Bonhoeffer, J. M. Coffin and M. A. Nowak, Human immunodeficiency virus drug therapy and virus load, J. Virol. 71(4) (1997), 3275–3278.

[27] A. N. Chatterjee and P. K. Roy, Anti-viral drug treatment along with immune activator IL-2: a control-based mathematical approach for HIV infection, Int. J. Control 85(2) (2012), 220–237.

[28] S. Chowdhury and P. K. Roy, CTL response suppression in chronic phase of infection: a mathematical study, 应用泛函分析学报 1 (2012), 007.

[29] A. Gumel, X.-W. Zhang, P. Shivakumar, M. Garba and B. Sahai, A new mathematical model for assessing therapeutic strategies for HIV infection, J. Theor. Med. 4(2) (2002), 147–155.

[30] T. B. Kepler and A. S. Perelson, Drug concentration heterogeneity facilitates the evolution of drug resistance, Proc. Natl. Acad. Sci. 95(20) (1998), 11514–11519.

[31] M. Nowak and R. May, Viral dynamics, Oxford University Press, Oxford, 2000.

[32] A. S. Perelson, Modelling viral and immune system dynamics, Nat. Rev. Immunol. 2(1) (2002), 28–36.
[33] P. K. Roy and A. N. Chatterjee, Effect of haart on CTL mediated immune cells: an optimal control theoretic approach, Electr. Eng. Appl. Comput., Springer (2011), 595–607.
[34] P. K. Roy, S. Chowdhury, A. N. Chatterjee, J. Chattopadhyay, and R. Norman, A mathematical model on CTL mediated control of HIV infection in a long-term drug therapy, J. Biol. Syst. 21(03) (2013), 1350019.
[35] P. K. Roy, S. Chowdhury, and X.-Z. Li, Saturation effects for CTL mediated control of HIV-1 infection: a mathematical study, Int. J. Biomath. 6(03) (2013), 1350013.
[36] J. Velasco-Hernandez, H. Gershengorn, and S. Blower, Could widespread use of combination antiretroviral therapy eradicate HIV epidemics?, Lancet Infect. Dis. 2(8) (2002), 487–493.
[37] D. Bainov and P. Simeonov, Systems with impulsive effect, Ellis Horwood Ltd, Chichester, 1989.
[38] D. Bainov and P. Simeonov, Impulsive differential equations: periodic solutions and applications, Longman Scientific, Burnt Mill, Harlow, Essex, England and New York, NY, 1993.
[39] D. Bainov and P. S. Simeonov, Impulsive differential equations: asymptotic properties of the solutions, World Scientific, Singapore, 1995.
[40] D. D. Ho, A. U. Neumann, A. S. Perelson, W. Chen, J. M. Leonard, M. Markowitz, et al., Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection, Nature 373(6510) (1995), 123–126.
[41] J. Li, D. Blakeley, and R. J. Smith?, The failure of R_0, Comput. Math. Methods Med. (2011), 527610.
[42] G. J. Abiodun, N. Marcus, K. O. Okosun, and P. J. Witbooi, A model for control of HIV/AIDS with parental care, Int. J. Biomath. 6 (2013), 02.