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Optimal control applied in a within-host HIV model

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Abstract. In this paper, we are concerned with a mathematical model of ODEs incorporating cell-to-cell transmission and considering defense cells. Seeking to reduce the population of virus classes, we derive HIV therapeutic strategies for our proposed model by formulating an optimal control using three types of therapies involving reverse transcriptase inhibitors (RTIs), protease inhibitors (PIs) and entry/fusion inhibitors. Using an objective function based on a combination of minimizing virus counts, we solve for the optimal control in the optimality system obtained by our model. At the end of article, the impact of combination of the strategies in the control of our proposed model for HIV are compared by numerical simulation.

Keywords: HIV, reverse transcriptase inhibitor, protease inhibitor, entry inhibitor, optimal control

1 Section heading

HIV attacking the $CD4^+$ T helper T cells is the major cause of years of potential lives lost and the most common cause of death attributed to many infectious diseases. This virus gradually destroys the immune system, which makes it harder for the body to fight infections. Hence, infection with HIV is almost very dangerous and fatal if left untreated and uncontrolled. Further, control is available in the form of antiretroviral drugs, such as reverse transcriptase inhibitors, protease inhibitors and also entry inhibitors.

Mathematical immunology is concerned with the study of disease dynamics in an infected host, where an infectious agent is transmitted from cell to cell within one patient [21]. Within-host models has flourished over the past few decades. Mathematical modeling over the years have been a powerful tool for investigating the dynamics and control of various diseases such as HIV, Malaria and Tuberculosis. Anderson et al. proposed a simple mathematical HIV transmission model to investigate the impacts of various factors on the overall pattern of the AIDS epidemic [2]. Nikolao et al. derived and analyzed a mathematical model describing the dynamics of pathogenesis of HIV infection [17]. Karrakchou et al. considered the fundamental role of chemotherapy treatment in controlling the virus reproduction in an HIV patient [22]. For considering the impact of optimal control in some epidemic models, we refer the reader to [1, 3, 5, 9, 14, 16, 18–20, 22].

The model we consider in this paper is an improved model of which is described in [15] by removing the latently infected class, inclusion of time dependent control parameters and considering defense cells consisting of $CD8^+$ T cells and B cells. In this study, we analyze and apply optimal control to our model to determine the possible impact of control parameters on the spread of HIV. We carry out detailed qualitative optimal control analysis of our model and give the necessary conditions for optimal control of the disease using Pontryagin's maximum principle under which we determine optimal strategies for controlling the spread of HIV in a host. Our objective functional balances the effect of minimizing the cost of implementing the control strategies.

The organization of the remaining part is as follows. In section 2, we propose a model consisting of ordinary differential equations that describes the dynamics of HIV under the assumption that there is no control.

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The distinguishing feature in our proposed model with respect to our former model in the literature is considering defense cells consisting of CD8$^+$ T cells and B cells. Then, the qualitative analysis of the model is studied. In section 3, we incorporate a reverse transcriptase inhibitor, a protease inhibitor and an entry inhibitor to our model. We formulate an optimal control problem with time dependent controls in order to minimize the population of viruses as well as the cost and side effect of the controls. Section 4 is devoted to discussing the effects of combination antiretroviral therapies on the spread of HIV by numerical simulation. Section 5 contains concluding remarks.

2 Mathematical model

In this section, we process with development of a mathematical model for the spread of HIV infection. The infection mechanism is described by the system of ordinary differential equations with five compartments. The state variables are T, the concentration of susceptible CD4$^+$ T cells, T^*, the concentration of infected T cells, V, the concentration of free viruses, Z_1, the concentration of defense cells (CD8$^+$ T and B cells) and Z_2, the concentration of activated defense cells (activated CD8$^+$ T and B cells) consisting of cytotoxic T cells and plasma. The system of ODEs describing the compartmental infection dynamics is represented by

$$\begin{cases} \dfrac{dT}{dt} = s - \mu_T T - k_1 V T - k_2 T T^* \\ \dfrac{dT^*}{dt} = k_1 V T + k_2 T T^* - \delta T^* - p_1 T^* Z_2 \\ \dfrac{dV}{dt} = N\delta T^* - cV - p_2 V Z_2 \\ \dfrac{dZ_1}{dt} = \lambda - \mu_z Z_1 - k_3 Z_1 V \\ \dfrac{dZ_2}{dt} = k_3 Z_1 V - \mu_z Z_2, \end{cases} \tag{1}$$

where s is the recruitment rate of healthy CD4$^+$ T cells, μ_T is the per capita death rate of healthy T cells, k_1 is the rate at which an uninfected cell becomes infected by an infectious virus, k_2 is the rate of infection transmitted from cell to cell, δ is the death rate of infected T cells, p_1 is the rate at which the activated defense cells eliminate the infected T cells, N is the number of virions produced at bursting, c is the death rate of virus, p_2 is the rate of elimination of viruses by means of activated defense cells, λ is the rate at which new defense cells are produced, μ_z is the death rate of defense cells and k_3 is the activation rate of defense cells in the presence of the virus. See Table 1 for a summary of the associated parameters and units of model 1.

2.1 Analysis of the model

In this subsection, we study the dynamical behavior of our system 1.

2.1.1 Boundedness of the system

Lemma 1. *Every solution of Eq. (1) starting in $\mathbb{R}^+_5$ is complete and bounded in $\mathbb{R}^+_5$.*

Proof. Clearly, $\mathbb{R}^+_5$ is positive invariant. Now, to prove the boundedness, let $\epsilon > 0$ be a fixed parameter. By choosing a constant, a, such that $0 < a < \dfrac{1}{N}$ and considering the auxiliary function $U = T + T^* + aV + Z_1 + Z_2$, we have

$$\dot{U} \leq (s + \lambda) - bU,$$

where $b = \min(\mu_T, \delta(1 - aN), c, \mu_z) > 0$. Hence, $U(t) \leq \max\left(U(0), \dfrac{s+\lambda}{b}\right)$ for all $t \geq 0$ which implies that the corresponding solution of Eq. (1) is bounded in $\mathbb{R}^+_5$ and complete.

Table 1: Variables and parameters used for numerical simulations.

	Model parameters and their interpretations	
Parameters	Definition	Data values
s	Healthy T cells concentration	10^4 ml^{-1}day^{-1}
μ_T	Death rate of healthy T cells	0.01 day^{-1}
k_1	Viral infecting rate	2.4×10^{-8} mlday^{-1}
k_2	Infection rate of cell-to-cell transmission	10^{-6} mlday^{-1}
δ	Death rate of infected T cells	1day^{-1}
c	Death rate of virions	23 day^{-1}
N	Number of virions produced by infected cells	2000
λ	Defense cells supply rate	200 ml^{-1}day^{-1}
μ_z	Death rate of defense cells	0.4 day^{-1}
k_3	Activation of immunologic response rate	5×10^{-7} mlday^{-1}
p_1	Infected T cells destruction rate	2×10^{-5} mlday^{-1}
p_2	Virus destruction rate	2×10^{-5} mlday^{-1}

2.2 Equilibria and their stability

In this subsection, we study steady state solutions, the stability of disease-free equilibrium and derive the basic reproduction number for our model.

The disease-free equilibrium is $E_0 = \left(\frac{s}{\mu_T}, 0, 0, \frac{\lambda}{\mu_z}, 0\right)$. In order to discuss the local stability of the disease-free equilibrium, we consider the Jacobian matrix evaluated at E_0

$$J(E_0) = \begin{bmatrix} -\mu_T & -k_2T_0 & -k_1T_0 & 0 & 0 \\ 0 & -k_2T_0 - \delta & k_1T_0 & 0 & 0 \\ 0 & N\delta & -c & 0 & 0 \\ 0 & 0 & -\frac{k_3\lambda}{\mu_z} & -\mu_z & 0 \\ 0 & 0 & \frac{k_3\lambda}{\mu_z} & 0 & -\mu_z \end{bmatrix},$$

where $T_0 = \frac{s}{\mu_T}$. The submatrix of $J(E_0)$ corresponding to the infectious compartments is

$$\begin{aligned} J(E_{01}) &= \begin{bmatrix} k_2T_0 - \delta & k_1T_0 \\ N\delta & -c \end{bmatrix} \\ &= \begin{bmatrix} k_2T_0 & k_1T_0 \\ N\delta & 0 \end{bmatrix} - \begin{bmatrix} \delta & 0 \\ 0 & c \end{bmatrix} =: F - V. \end{aligned}$$

Hence, we obtain the basic reproduction number, $\mathcal{R}_0$, as follows

$$\begin{aligned} \mathcal{R}_0 &= \frac{1}{2}\Big(\frac{k_2T_0}{\delta} + \sqrt{(\frac{k_2T_0}{\delta})^2 + \frac{4k_1NT_0}{c}}\Big), \\ &= \frac{1}{2}\Big(\frac{k_2T_0}{\delta} + \sqrt{(2 - \frac{k_2T_0}{\delta})^2 + 4(\mathcal{T}_0 - 1)}\Big), \end{aligned} \tag{2}$$

in which

$$\mathcal{T}_0 = \frac{k_2T_0}{\delta} + \frac{k_1NT_0}{c}.$$

Hence, we have $\mathcal{R}_0 = 1$ if and only if $\mathcal{T}_0 = 1$. Furthermore, $\mathcal{R}_0 > 1$ ($\mathcal{R}_0 < 1$) if and only if $\mathcal{T}_0 > 1$ ($\mathcal{T}_0 < 1$) since $\mathcal{R}_0$ is increasing respect to $\mathcal{T}_0$.

Theorem 1. *If $\mathcal{R}_0 < 1$, then the disease-free equilibrium, E_0, is locally asymptotically stable. If $\mathcal{R}_0 > 1$, E_0 is an unstable saddle point.*

Proof. After somewhat algebra, we obtain that the eigenvalues of $J(E_0)$ are

$$\begin{aligned}
\lambda_1 =& -\mu_T < 0, \\
\lambda_2 =& \lambda_3 = -\mu_z < 0, \\
\lambda_4 =& -\frac{c+\delta-k_2T_0}{2} + \frac{1}{2}\sqrt{(c+\delta-k_2T_0)^2 + 4c\delta(\mathcal{T}_0-1)}, \\
\lambda_5 =& -\frac{c+\delta-k_2T_0}{2} - \frac{1}{2}\sqrt{(c+\delta-k_2T_0)^2 + 4c\delta(\mathcal{T}_0-1)}.
\end{aligned} \tag{3}$$

λ_1, λ_2 and λ_3 are obviously negative. To prove negativeness of λ_4 and λ_5, we have

$$\mathcal{T}_0 < 1 \Rightarrow \frac{k_2T_0}{\delta} < 1 \Rightarrow \delta - k_2T_0 > 0 \Rightarrow \lambda_4, \lambda_5 < 0,$$

which completes the proof.

Theorem 2. *The disease-free equilibrium, E_0, is globally asymptotically stable if $\mathcal{R}_0 < 1$.*

Proof. We will prove the global stability of disease-free equilibrium, E_0, using a Lyapunov function. We claim that for each $t \geq 0$, we have $T(t) \leq T_0$. Otherwise, there must be $t_1 > 0$ such that $T(t_1) > T_0$ and $\frac{dT}{dt}(t_1) > 0$. The first equation of system 1 implies that

$$\frac{dT}{dt}(t_1) = s - \mu_T T(t_1) - k_1 V(t_1)T(t_1) - k_2 T(t_1)T^*(t_1) \leq 0,$$

which is in contradiction with $\frac{dT}{dt}(t_1) > 0$.

Now, we construct the following Lyapunov function

$$U(t) = cT^* + k_1 V T_0.$$

By estimating the derivative of $U(t)$ along positive solutions of Eq. (1), we get

$$\begin{aligned}
\frac{dU}{dt} =& ck_1VT + ck_2TT^* - c\delta T^* - cp_1T^*Z_2 + k_1N\delta T^*T_0 \\
& - k_1cVT_0 - k_1p_2VZ_2T_0 \\
=& (k_1cV + k_2cT^*)(T-T_0) + c\delta T^*\left(-1 + \frac{k_2T_0}{\delta} + \frac{k_1NT_0}{c}\right) \\
& - cp_1T^*Z_2 - k_1P_2T_0VZ_2 \\
\leq& (k_1cV + k_2cT^*)(T-T_0) - k_1p_2T_0VZ_2.
\end{aligned} \tag{4}$$

$\mathcal{R}_0 < 1$ implies that $\frac{dU}{dt} \leq 0$ for all positive values of T, T^*, V, Z_1 and Z_2. Furthermore, $\frac{dU}{dt} = 0$ if and only if $T = T_0$, $T^* = 0$, $V = 0$, $Z_1 = \frac{\lambda}{\mu_z}$ and $Z_2 = 0$ which results that the maximum invariant set in $\{(T, T^*, V, Z_1, Z_2) : \frac{dU}{dt} = 0\}$ is the singleton E_0. Hence, LaSalles Invariance Principle implies that all solutions in $\mathbb{R}^5_+$ converge to E_0. The local stability of E_0 established in Theorem 1 and its global attractivity derive the global stability of E_0.

In order to find the infected equilibrium of system 1, we equate all the differential equations of system 1 to zero. Hence, we get

$$E_1 = (\bar{T}, \bar{T^*}, \bar{V}, \bar{Z_1}, \bar{Z_2}),$$

where

$$\begin{aligned}
\bar{T} =& \frac{sN - c\bar{V}}{N\mu_T} - \frac{k_3\lambda\bar{V}^2(\delta p_2 + cp_1)}{\mu_z N\delta\mu_T(\mu_z + k_3\bar{V})} - \frac{k_3^2\lambda^2 p_1 p_2\bar{V}^3}{\mu_z^2 N\delta\mu_T(\mu_z + k_3\bar{V})^2}, \\
\bar{T}^* =& \frac{\left(c + \dfrac{p_2\lambda k_3\bar{V}}{\mu_z(\mu_z + k_3\bar{V})}\right)\bar{V}}{N\delta}, \\
\bar{V} =& \bar{V}, \\
\bar{Z}_1 =& \frac{\lambda}{\mu_z + k_3\bar{V}}, \\
\bar{Z}_2 =& \frac{\lambda k_3\bar{V}}{\mu_z(\mu_z + k_3\bar{V})}
\end{aligned} \tag{5}$$

and also $\bar{V}$ satisfies

$$a_4\bar{V}^4 + a_3\bar{V}^3 + a_2\bar{V}^2 + a_1\bar{V} + a_0 = 0, \tag{6}$$

with

$$\begin{aligned}
a_4 =& k_3^3(\mu_z c + \lambda p_2)(\mu_z\delta + \lambda p_1)(k_2\lambda p_2 + k_1 N\delta\mu_z + k_2 c\mu_z), \\
a_3 =& k_3^2\mu_z[k_3\mu_z N\delta^2\mu_T(\mu_z c + \lambda p_2)(1 - \mathcal{T}_0) + k_3 N\delta\lambda\mu_T p_1(\mu_z c + \lambda p_2) \\
&+ \mu_z^2 c(k_1 N\delta + k_2 c)(3\mu_z\delta + 2\lambda p_1) + \mu_z\lambda p_2(k_1 N\delta + 2k_2 c)(2\mu_z\delta + \lambda p_1) \\
&+ k_2\lambda^2\mu_z\delta p_2^2], \\
a_2 =& k_3\mu_z^2[k_3\mu_z N\delta^2\mu_T(3\mu_z c + 2p_2\lambda)(1 - \mathcal{T}_0) + \mu_z^2 c(k_1 N\delta + k_2 c)(p_1\lambda + 3\mu_z\delta) \\
&+ k_3\mu_T N\delta\lambda p_1(2\mu_z c + \lambda p_2) + 2\frac{k_1 k_3}{c}\mu_z N^2\delta^2 s p_2\lambda + 3k_3 N\delta^2 c\mu_T\mu_z^2], \\
a_1 =& \mu_z^4\delta[\mu_z^2 c(k_1 N\delta + k_2 c) + k_3 N\delta\mu_T(3c\mu_z + p_2\lambda)(1 - \mathcal{T}_0) + \frac{k_1 k_3}{c}N^2\delta p_2\lambda s \\
&+ k_3 N c p_1\lambda\mu_T], \\
a_0 =& N\mu_z^6\delta^2 c\mu_T(1 - \mathcal{T}_0).
\end{aligned} \tag{7}$$

The coefficients of Eq. (6) are all positive if $\mathcal{R}_0 < 1$ which implies that there exists no positive solutions. If $\mathcal{R}_0 > 1$, we have $a_0 < 0$ and a_1 becomes negative as $\mathcal{R}_0$ increases, followed by a_2. Therefore, a unique change of sign occurs between successive coefficients for $\mathcal{R}_0 > 1$. Hence, Descartes rule of signs implies that there exists a unique positive solution.

3 Optimal control problem

HIV infection begins when a virus enters CD4$^+$ T helper cells and reproduces. There exist three steps to this process: entry to a target T cell, replication and release of new virus particles.

Recently, a new class of drugs, entry/fusion inhibitors has been introduced for the treatment of HIV [20, 22] which can be capable of blocking the fusion of the viral envelope to the target cell membrane and interfering with continued infection.

Once the viral capsid has entered the cell, an HIV enzyme called reverse transcriptase makes a DNA copy of the virus's RNA genome. The existence of RT inhibitor during this process causes that the viral genome will not be copied into DNA which results that the host cell will not produce new virus particles. A viral protease is required to cleave the polyproteins into individual functional HIV proteins and enzymes. Then the various structural components assemble to produce a mature HIV virion. This step can be inhibited by drugs called protease inhibitors which results that the newly produced virus will be noninfectious.

According to the above description of the roles of various inhibitors in the treatment of HIV, the proposed dynamic system 1 with control can be reformulated as

$$\begin{cases} \dfrac{dT}{dt} = s - \mu_T T - k_1(1-\epsilon_{EN})VT - k_2 TT^* + \epsilon_{RT} T^*_{preRT} \\ \dfrac{dT^*}{dt} = k_1(1-\epsilon_{EN})VT + k_2 TT^* - \delta T^* - p_1 T^* Z_2 - \epsilon_{RT} T^*_{preRT} \\ \dfrac{dV}{dt} = N\delta(1-\epsilon_{PI})T^*_{postRT} - cV - p_2 V Z_2 \\ \dfrac{dZ_1}{dt} = \lambda - \mu_z Z_1 - k_3 Z_1 V \\ \dfrac{dZ_2}{dt} = k_3 Z_1 V - \mu_z Z_2 \end{cases} . \tag{8}$$

In order to consider the efficacy of three drugs mentioned above, we divide the class of infected cells, $T^*(t)$, into two subclasses consisting of $T^*_{preRT}(t)$ and $T^*_{postRT}(t)$. T^*_{prtRT} represents the density of infected cells in which the process of reverse transcription has not been completed. Hence, a RT inhibitor could cause an infected T cell to revert back to an uninfected T cell. Furthermore, $T^*_{postRT}(t)$ represents the density of infected T cells that have progressed to the postRT phase. Let β represent the proportion of infected cells that have not completed reverse transcription. Therefore, we have

$$T^*_{preRT}(t) = \beta T^*(t), \quad T^*_{postRT}(t) = (1-\beta)T^*(t). \tag{9}$$

Furthermore, let ϵ_{RT} denote the rate at which preRT T cells revert back to the uninfected T cells because of the failure of reverse transcription, ϵ_{PI} denote the efficacy of the therapy with protease inhibitors and ϵ_{EN} represent the efficacy of entry inhibitors $(0 \leq \epsilon_{RT},\ \epsilon_{PI},\ \epsilon_{EN} \leq 1)$. The control functions ϵ_{RT}, ϵ_{PI} and ϵ_{EN} are bounded Lebesgue integrable functions. If $\epsilon_{RT} = 0$, $\epsilon_{PI} = 0$ and $\epsilon_{EN} = 0$, there is no inhibition of reverse transcriptase, protease and entry.

Using the relation 9, we derive the following system

$$\begin{cases} \dfrac{dT}{dt} = s - \mu_T T - k_1(1-\epsilon_{EN})VT - k_2 TT^* + \epsilon_{RT}\beta T^* \\ \dfrac{dT^*}{dt} = k_1(1-\epsilon_{EN})VT + k_2 TT^* - \delta T^* - p_1 T^* Z_2 - \epsilon_{RT}\beta T^* \\ \dfrac{dV}{dt} = N\delta(1-\epsilon_{PI})(1-\beta)T^* - cV - p_2 V Z_2 \\ \dfrac{dZ_1}{dt} = \lambda - \mu_z Z_1 - k_3 Z_1 V \\ \dfrac{dZ_2}{dt} = k_3 Z_1 V - \mu_z Z_2 \end{cases} . \tag{10}$$

3.1 Adjoint systems

Below, we formulate an objective functional for our system, with the goal of minimizing free virus particles

$$J(\epsilon_{RT},\ \epsilon_{PI},\ \epsilon_{EN}) = \int_0^{t_f} (A_1 V(t) + A_2\epsilon_{RT}^2 + A_3\epsilon_{PI}^2 + A_4\epsilon_{EN}^2)dt, \tag{11}$$

where A_1, A_2, A_3 and A_4 are positive constants that balance the relative importance of terms in J. In our objective functional, the first term with A_1 represents the total of the free virus particles over time and the other three terms represent costs of implementing the controls. The optimal control formulation of system 10 is

$$\min_{(\epsilon_{RT},\ \epsilon_{PI},\ \epsilon_{EN})\in\Theta} J(\epsilon_{RT},\ \epsilon_{PI},\ \epsilon_{EN}),$$

where the control set Θ is

$$\Theta = \{(\epsilon_{RT},\ \epsilon_{PI},\ \epsilon_{EN}) \text{ such that } \epsilon_{RT},\ \epsilon_{PI} \text{ and } \epsilon_{EN} \text{ measurable with } 0 \leq \epsilon_{RT},\ \epsilon_{PI},\ \epsilon_{EN} \leq 1 \text{ for } t \in [0, t_f]\}. \tag{12}$$

The square of the control variables are taken here to consider the harmness causes due to the side effect and overdoses of reverse transcriptase, protease and entry inhibitors.

In order to find the optimal control variables ϵ^*_{RT}, ϵ^*_{PI} and ϵ^*_{EN}, we use Pontryagin's maximum principle [21]. The Lagrangian of our problem is given by

$$L = A_1 V(t) + A_2 \epsilon^2_{RT} + A_3 \epsilon^2_{PI} + A_4 \epsilon^2_{EN}.$$

Forming the Hamiltonian of the problem to minimize the Lagrangian L, we have

$$H = L + \lambda_1(t)\frac{dT}{dt} + \lambda_2(t)\frac{dT^*}{dt} + \lambda_3(t)\frac{dV}{dt} + \lambda_4(t)\frac{dZ_1}{dt} + \lambda_5(t)\frac{dZ_2}{dt}, \tag{13}$$

where $\lambda_i(t)$, for $i = 1, 2, 3, 4, 5$ are known as the costate variables. Applying Pontryagin's maximum principle and the existence result for optimal control [6] imply the following proposition.

Proposition 1. *For the optimal control triple ϵ^*_{RT}, ϵ^*_{PI} and ϵ^*_{EN} that minimizes $J(\epsilon_{RT},\ \epsilon_{PI},\ \epsilon_{EN})$ over Θ, there exist costate variables λ_1, λ_2, λ_3, λ_4 and λ_5 satisfying*

$$\begin{aligned}
\dot{\lambda_1}(t) &= -\frac{\partial H}{\partial T} = \lambda_1(t)(\mu_T + k_1(1-\epsilon_{EN})V + k_2 T^*) \\
&\quad + \lambda_2(t)(-k_1(1-\epsilon_{EN})V - k_2 T^*), \\
\dot{\lambda_2}(t) &= -\frac{\partial H}{\partial T^*} = \lambda_1(t)(k_2 T - \beta\epsilon_{RT}) + \lambda_2(t)(-k_2 T + \delta + p_1 Z_2 + \beta\epsilon_{RT}) \\
&\quad + \lambda_3(t)(-N\delta(1-\beta)(1-\epsilon_{PI})), \\
\dot{\lambda_3}(t) &= -\frac{\partial H}{\partial V} = -A_1 + \lambda_1(t)(k_1(1-\epsilon_{EN})T) + \lambda_2(t)(-k_1(1-\epsilon_{EN})T) \\
&\quad + \lambda_3(t)(c + p_2 Z_2) + k_3 Z_1 \lambda_4(t) - k_3 Z_1 \lambda_5(t), \\
\dot{\lambda_4}(t) &= -\frac{\partial H}{\partial Z_1} = \lambda_4(t)(\mu_z + k_3 V) - k_3 V \lambda_5(t), \\
\dot{\lambda_5}(t) &= -\frac{\partial H}{\partial Z_2} = p_1 T^* \lambda_2(t) + p_2 V \lambda_3(t) + \mu_z \lambda_5(t)
\end{aligned} \tag{14}$$

and with transversality conditions

$$\lambda_i(t_f) = 0, \quad i = 1, 2, 3, 4, 5. \tag{15}$$

Since there is no dependence on the states at the final time in the objective functional. We assume that $\bar{T}$, $\bar{T^*}$, $\bar{V}$, $\bar{Z_1}$ and $\bar{Z_2}$ are the optimum value of T, T^*, V, Z_1 and Z_2 respectively. Furthermore let $\{\bar{\lambda}_1, \bar{\lambda}_2, \bar{\lambda}_3, \bar{\lambda}_4, \bar{\lambda}_5\}$ be the solutions of the system 14. Using the results in [10, 16, 22], we state and prove the following theorem.

Theorem 3. *There exists an optimal control $(\epsilon^*_{RT},\ \epsilon^*_{PI},\ \epsilon^*_{EN})$ for $t \in [0, t_f]$ such that*

$$J(V(t),\ \epsilon^*_{RT},\ \epsilon^*_{PI},\ \epsilon^*_{EN}) = \min_{\epsilon_{RT}, \epsilon_{PI}, \epsilon_{EN}} J(V(t),\ \epsilon_{RT}(t),\ \epsilon_{PI}(t),\ \epsilon_{EN}(t))$$

subject to system of differential Eq. (10).

Proof. Being non negativeness of all the state and control variables implies that all the control variables $\epsilon_{RT}(t)$, $\epsilon_{PI}(t)$ and $\epsilon_{EN}(t)$ are convex. Furthermore, since the control space Θ is also closed and convex, the optimal control is bounded which gives us the assurance about the existence of an optimal control $(\epsilon^*_{RT},\ \epsilon^*_{PI},\ \epsilon^*_{EN})$ that minimizes Eq. (11) for $t \in [0, t_f]$ with the help of system of differential Eq. (10). Hence, we have the desired result.

Theorem 4. *The optimal control triplet* $(\epsilon^*_{RT},\ \epsilon^*_{PI},\ \epsilon^*_{EN})$ *minimizing* J *over the region* Θ *is characterized by*

$$\begin{aligned}\epsilon^*_{RT} &= \max\{0, \min(\bar{\epsilon}_{RT}, 1)\},\\ \epsilon^*_{PI} &= \max\{0, \min(\bar{\epsilon}_{PI}, 1)\},\\ \epsilon^*_{EN} &= \max\{0, \min(\bar{\epsilon}_{EN}, 1)\},\end{aligned} \tag{16}$$

where

$$\begin{aligned}\bar{\epsilon}_{RT} &= \frac{\beta \bar{T}^*(\bar{\lambda}_2 - \bar{\lambda}_1)}{2A_2},\\ \bar{\epsilon}_{PI} &= \frac{N\delta \bar{T}^*(1-\beta)\bar{\lambda}_3}{2A_3},\\ \bar{\epsilon}_{EN} &= \frac{k_1 \bar{V}\bar{T}(\bar{\lambda}_2 - \bar{\lambda}_1)}{2A_4}.\end{aligned} \tag{17}$$

Proof. With the help of optimality conditions that are $\frac{\partial H}{\partial \epsilon_{RT}} = 0$, $\frac{\partial H}{\partial \epsilon_{PI}} = 0$ and $\frac{\partial H}{\partial \epsilon_{EN}} = 0$, we obtain

$$\begin{aligned}\epsilon_{RT} &= \frac{\beta \bar{T}^*(\bar{\lambda}_2 - \bar{\lambda}_1)}{2A_2} (= \bar{\epsilon}_{RT}),\\ \epsilon_{PI} &= \frac{N\delta \bar{T}^*(1-\beta)\bar{\lambda}_3}{2A_3} (= \bar{\epsilon}_{PI}),\\ \epsilon_{EN} &= \frac{k_1 \bar{V}\bar{T}(\bar{\lambda}_2 - \bar{\lambda}_1)}{2A_4} (= \bar{\epsilon}_{EN}).\end{aligned} \tag{18}$$

By taking bounds into account, we obtain the control characterization for $\bar{\epsilon}_{RT}$, $\bar{\epsilon}_{PI}$ and $\bar{\epsilon}_{EN}$.

The state system of differential equations and the costate system of differential equations together with the control characterization above model the optimality system to be solved numerically. We are not able to solve the optimality system directly by just sweeping forward in time since the state equations have initial conditions and costate equations have final time conditions. Hence, an iterative scheme, "forward-backward sweep method" is used for solving the optimality system. We start to solve the state equations with an initial estimate for the controls over the simulated time using the fourth order Runge-Kutta scheme. Resulting state values are placed in the right-hand sides of the costate equations. Due to the transversality conditions Eq. (15), the costate equations is solved backward in time, again employing a fourth order Runge-Kutta method. Then, the controls are updated by using a convex combination of the previous controls and the value from the characterization using both state and costate values and the process is repeated. This iterative process is stopped if the current state, costate and control values converge sufficiently.

4 Numerical results applied to the optimal control problem

In this section, we examine the modified deterministic HIV model and apply the following eight possible strategies for the control of the disease. The strategies applied are (i) when there is no control that is ϵ_{RT}, ϵ_{PI} and ϵ_{EN} are set to zero, (ii) when control on application of reverse transcriptase inhibitor (ϵ_{RT}) is optimized while the control efforts on application of protease inhibitor (ϵ_{PI}) and entry inhibitor (ϵ_{EN}) are set to zero, (iii) when control on application of protease inhibitor (ϵ_{PI}) is optimized while the control efforts on application of reverse transcriptase inhibitor (ϵ_{RT}) and entry inhibitor (ϵ_{EN}) are set to zero, (vi) when control on application of entry inhibitor (ϵ_{EN}) is optimized while the control efforts on application of reverse transcriptase inhibitor (ϵ_{RT}) and protease inhibitor (ϵ_{PI}) are set to zero, (v) when control efforts on application of both reverse transcriptase inhibitor (ϵ_{RT}) and protease inhibitor (ϵ_{PI}) are optimized while control on application of entry inhibitor (ϵ_{EN}) is set to zero, (vi) when control efforts on application of both reverse transcriptase inhibitor (ϵ_{RT}) and entry inhibitor (ϵ_{EN}) are optimized while control on application of protease inhibitor (ϵ_{PI}) is set

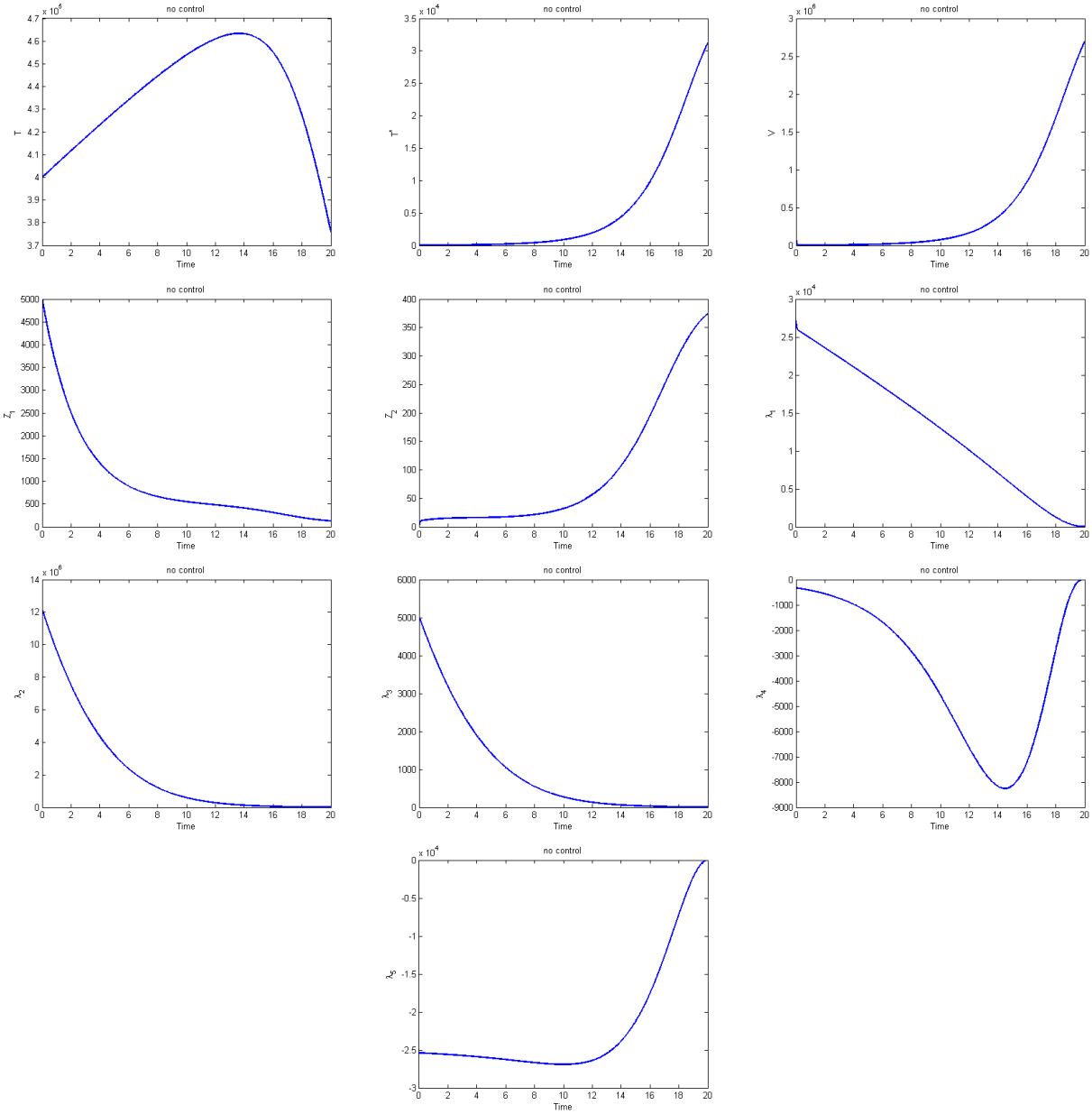

Fig. 1: Simulations of the model with no control

to zero, (vii) when control efforts on application of both protease inhibitor (ϵ_{PI}) and entry inhibitor (ϵ_{EN}) are optimized while control on application of reverse transcriptase inhibitor (ϵ_{RT}) is set to zero, (viii) when all controls are optimized.

For all the simulations, we use the dataset described in Tab. 1. Furthermore, we set that $A_1 = 100$, $A_2 = 10$, $A_3 = 9$ and $A_4 = 8$ with initial state variables $T(0) = 4 \times 10^5$, $T^*(0) = 0$, $V(0) = 10^5$, $Z_1(0) = 5000$ and $Z_2(0) = 0$ to illustrate the impact of different optimal control strategies on the spread of HIV in a body. Here, we suppose that reverse transcriptase inhibitor presents more side effects than protease inhibitor and entry inhibitor. Similarly, we can change the values of A_2, A_3 and A_4 and consider other cases in a similar way.

4.1 No control

Fig. 1 conveys a numerical simulation of the system Eq. (1) when there is no control. The system rapidly approaches the infected steady state. From Fig. 1, we see that the number of susceptible CD4$^+$ T cells, T,

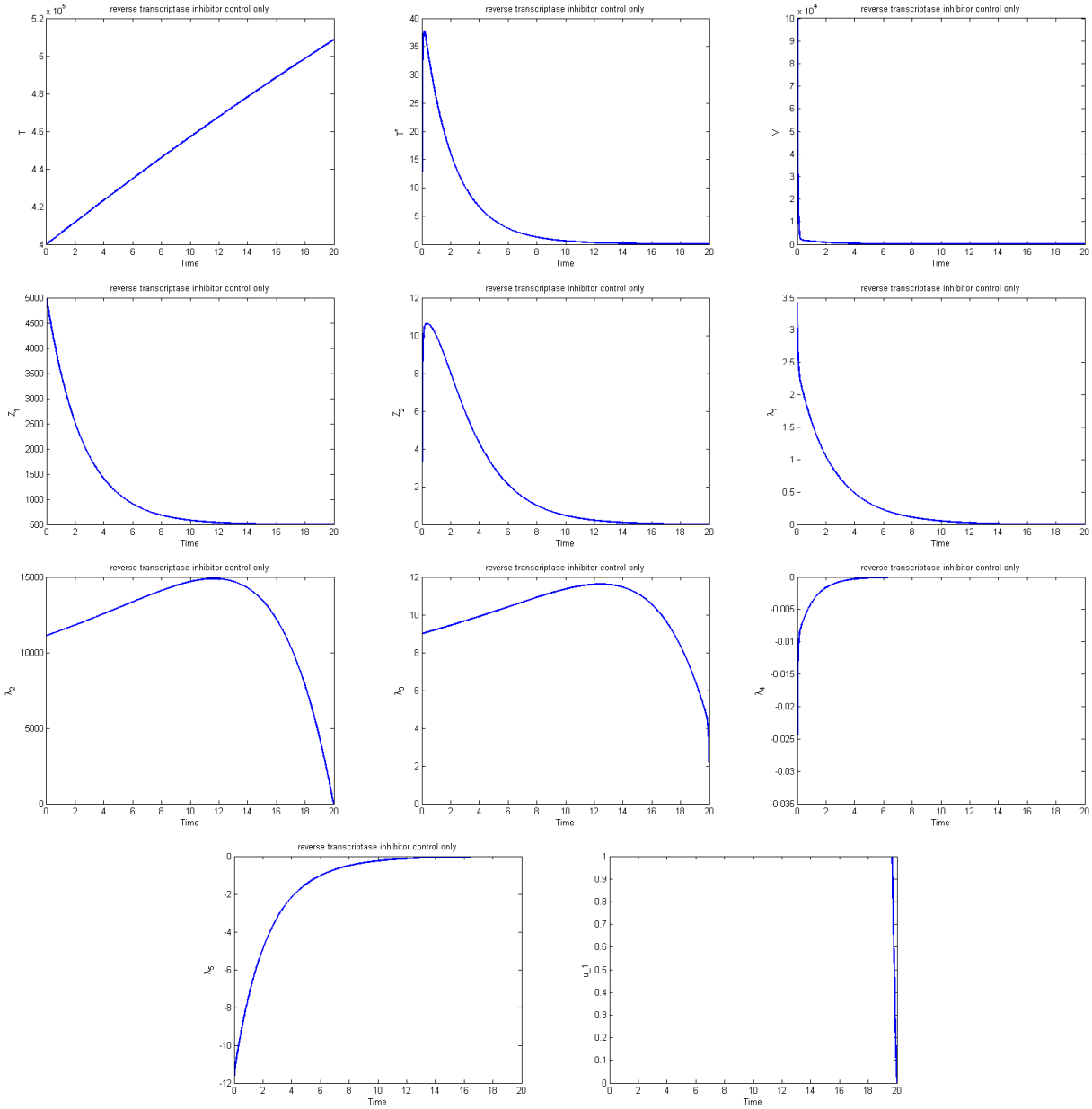

Fig. 2: Simulations of the model showing the effects of reverse transcriptase inhibitor control

decreases more when there is no control. In this case, most of these population goes to the infected class. Furthermore, we can notice a steep increase in the number of viruses. In Fig. 1, one can see a migration of immune cells into the compartment of activated defense cells.

4.2 Optimal reverse transcriptase inhibitor use only

With this strategy, we use reverse transcriptase inhibitor control only, ϵ_{RT}, to optimize the objective function (J) while other controls, ϵ_{PI} and ϵ_{EN}, are set to zero. As Fig. 2 illustrates, this control strategy results in a significant decrease in the number of infected T cells and free viruses compared with the case without control. Furthermore, this control strategy results in the significant increase in the number of uninfected T cells. The control prifile is also shown in Fig. 2.

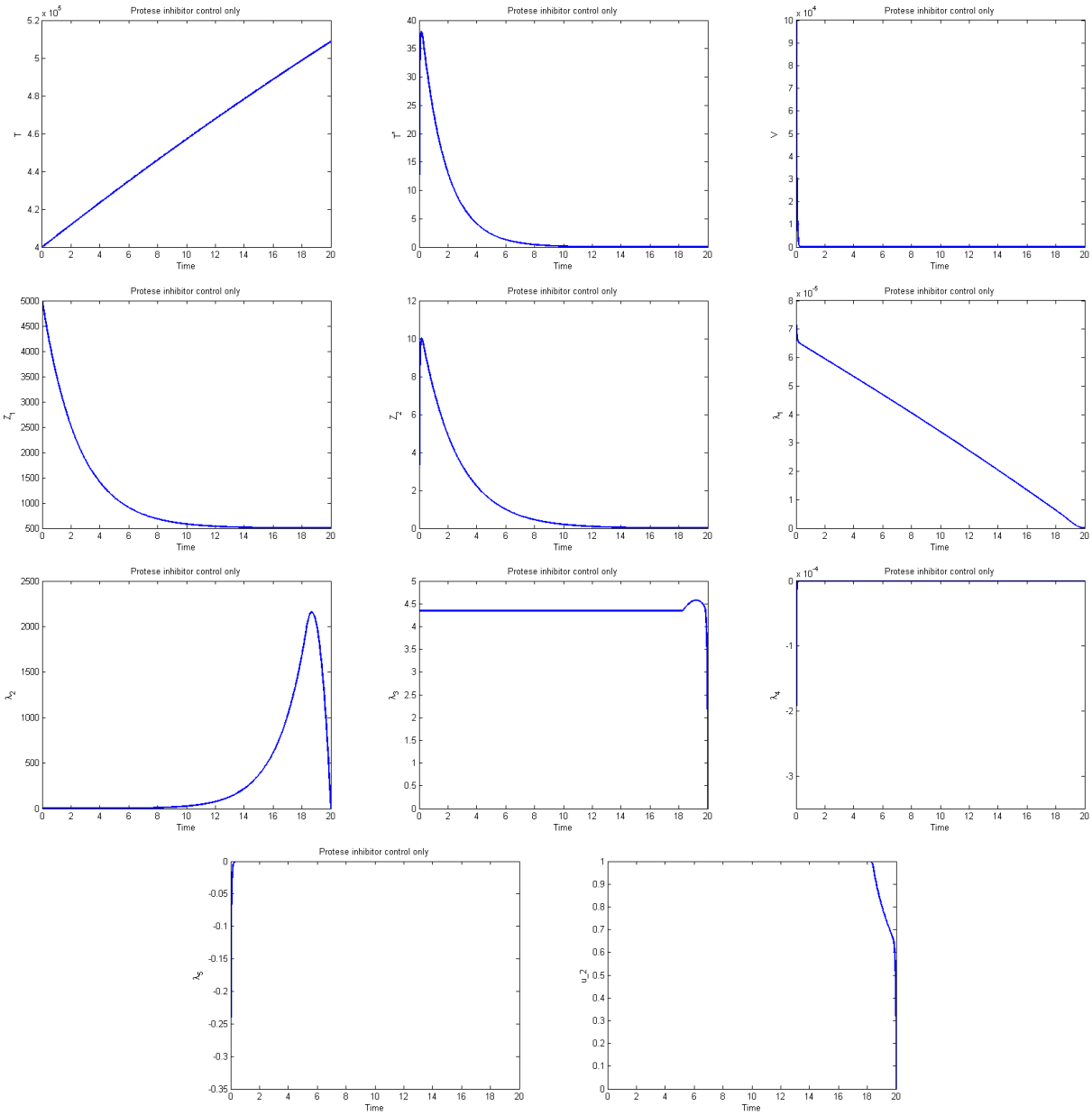

Fig. 3: Simulations of the model showing the effects of protease inhibitor control

4.3 Optimal protease inhibitor application only

With this strategy, we apply only protease inhibitor control, ϵ_{PI}, to optimize J while ϵ_{RT} and ϵ_{EN} are set to zero. In Fig. 3, we observe that this control strategy results in a significant decrease in the population of infected T cells and free viruses and increase in the population of susceptible T cells compared with the case without control.

4.4 Optimal entry inhibitor use only

In this case, we use only entry inhibitor control, ϵ_{EN}, to optimize J while ϵ_{RT} and ϵ_{PI} are set to zero. From Fig. 4, we can see that this control strategy has a very desirable effect upon the population of infected T cells and viruses which decreases while the population of susceptible T cells increases.

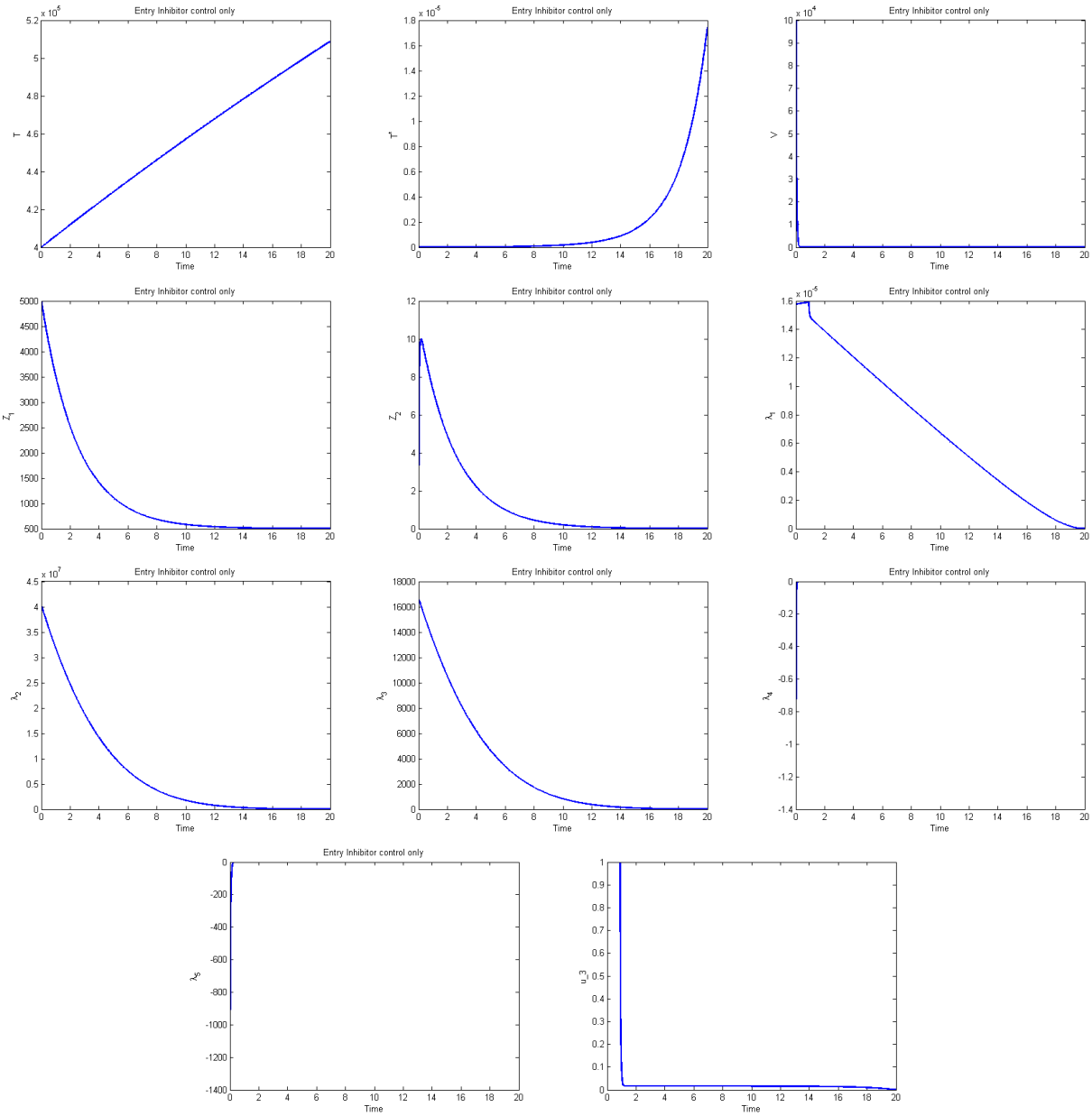

Fig. 4: Simulations of the model showing the effects of entry inhibitor control

4.5 Optimal reverse transcriptase inhibitor use and protease inhibitor use

With this strategy, we apply both reverse transcriptase inhibitor and protease inhibitor to optimize J while ϵ_{EN} is set to zero. Again from Fig. 5, we see that the application of both reverse transcriptase inhibitor and protease inhibitor gives better result than the application of no control. From Fig. 5, it is evident that both the controls take their highest value 1 in starting period and at the end of the time interval they admit the value 0. Also the application of RT inhibitor admits its highest value 1 in longer time period than the application of protease inhibitor.

The results are shown in Fig. 5.

4.6 Optimal reverse transcriptase inhibitor use and entry inhibitor use

In this case, we use both ϵ_{RT} and ϵ_{EN} to optimize J while ϵ_{PI} is set to zero. The results are shown in Fig. 6. In this strategy, one can notice that the number of uninfected T cells increases while the number of

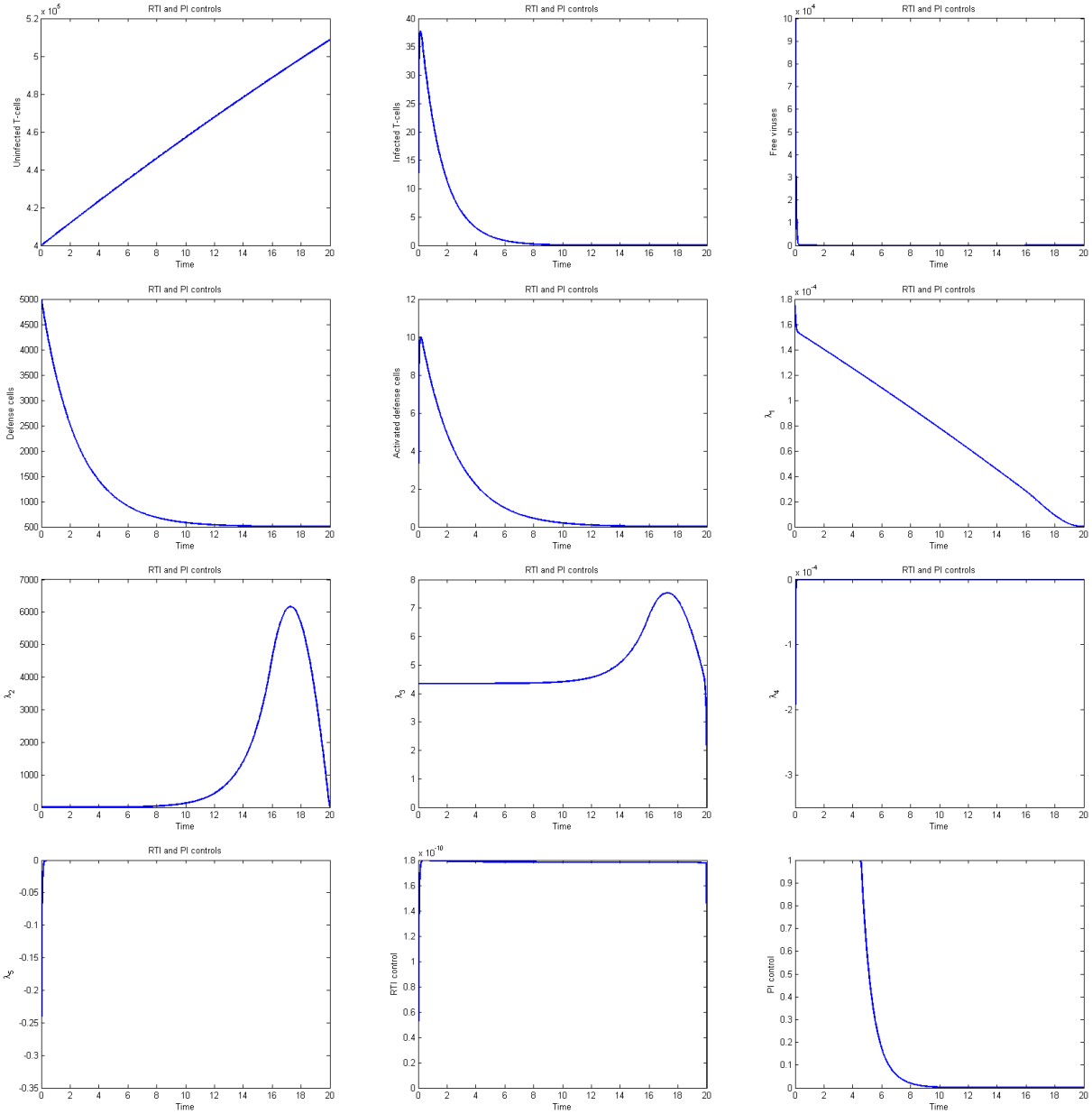

Fig. 5: Simulations of the model showing the effects of both reverse transcriptase inhibitor and protease inhibitor controls

viruses decreases. In Fig. 6, it is noticiable that the number of infected T cells is increased but this increase is not so much that can't be dangerous.

4.7 Optimal use of both protease inhibitor control and entry inhibitor control

With this strategy, we use both ϵ_{PI} and ϵ_{EN} to optimize J while ϵ_{RT} is set to zero. The impact of this strategy is shown in Fig. 7. Again in Fig. 7, we can see the increase in uninfected and infected cells and decrease in the number of viruses. Again the increase in the number of infected cells is not so much that can be harmful.

4.8 Optimal reverse transcriptase inhibitor use, protease inhibitor use and entry inhibitor use

With this strategy, the reverse transcriptase inhibitor use (ϵ_{RT}), protease inhibitor use (ϵ_{PI}) and entry inhibitor use (ϵ_{EN}) are all used to optimize the objective function (J). The effect of using these three controls

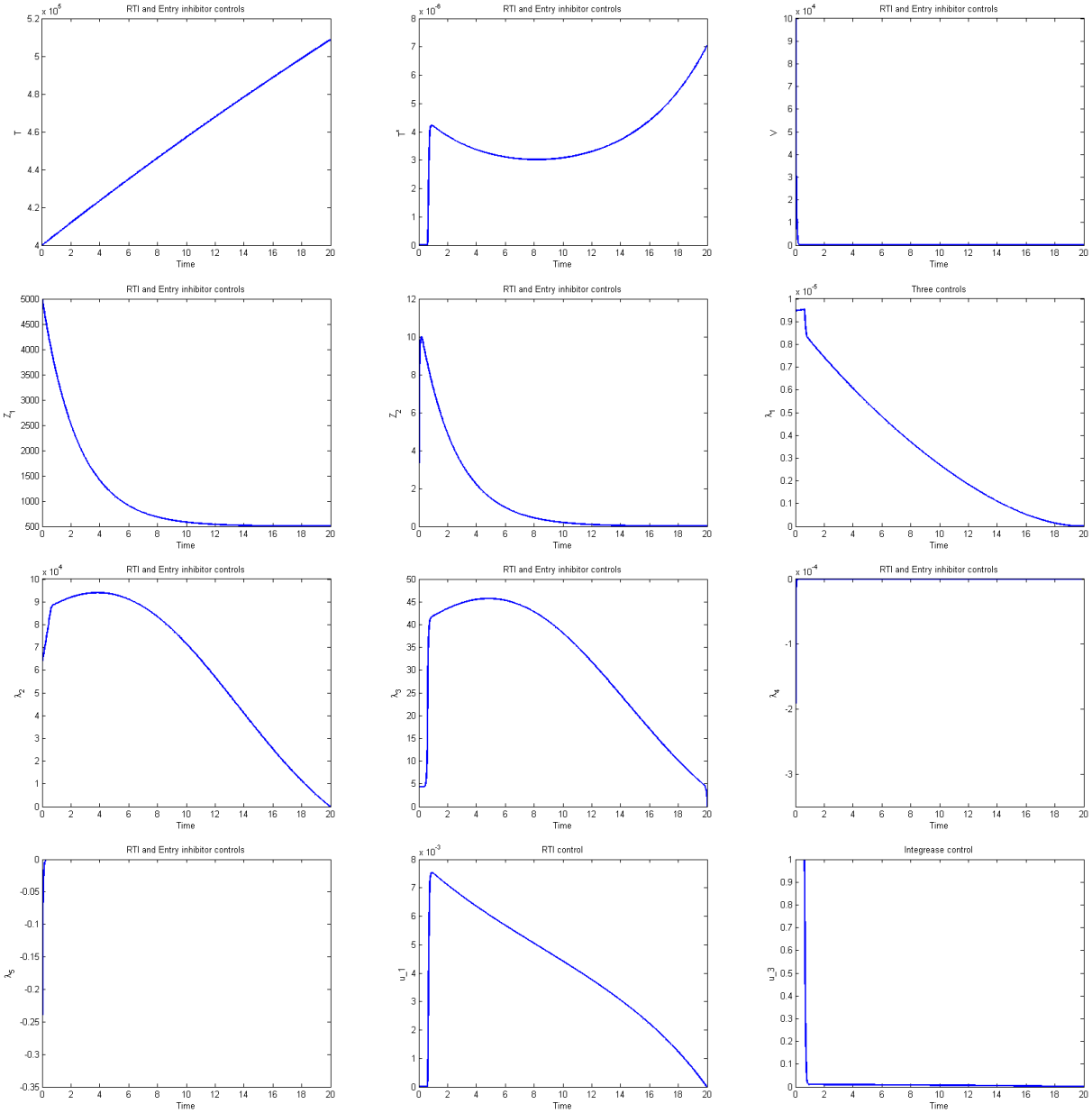

Fig. 6: Simulations of the model showing the effects of both reverse transcriptase inhibitor and entry inhibitor controls

on the state variables and also the control prifile are shown in Fig. 8. From Fig. 8, we can notice that both the controls, ϵ_{PI} and ϵ_{EN}, take their highest value 1 in starting period and to the end of the duration of application of controls they slow down and at the end of the time interval they admit the value 0. But the RTI control, ϵ_{RT} takes approximately 0.18 as highest value and then vanishes.

5 Concluding remarks

In this paper, we have formulated a within-host model of HIV infection with drug treatment to study the impact of antiretroviral therapy on viral dynamics. We have considered three types of drugs consisting of reverse transcriptase inhibitors, protease inhibitors and entry inhibitors. When an RT inhibitor is used, some infected T cells may have already competed reverse transcription that have been called postRT T cells. For these T cells, the RT inhibitor will not be effective. For infected T cells that have not completed reverse transcription, which have

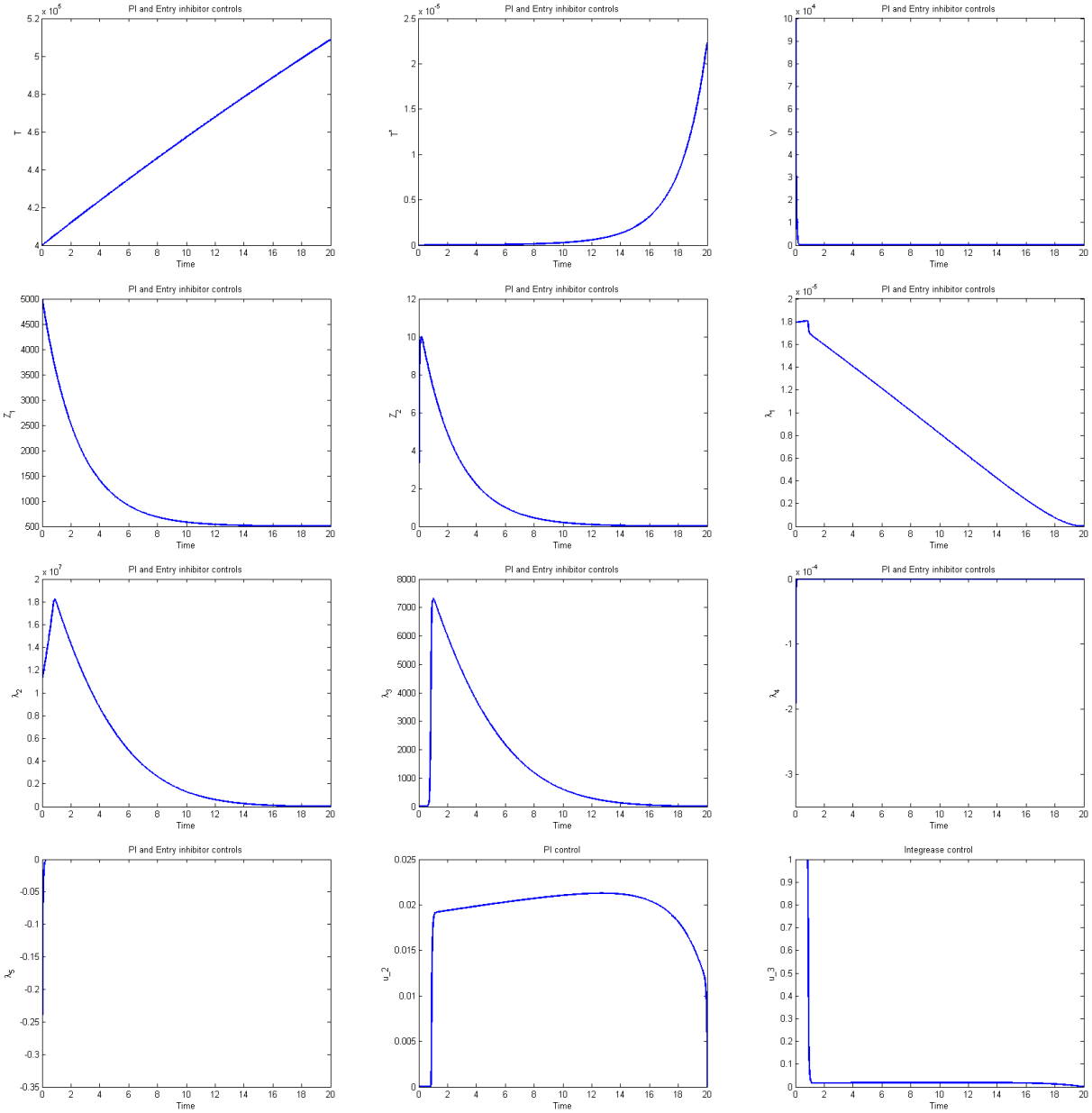

Fig. 7: Simulations of the model showing the effects of both protease inhibitor and entry inhibitor controls

been called preRT T cells, the RT inhibitor will be effective in preventing the process of reverse transcription. A protease inhibitor prevents cleavage of viral polyproteins into functional subunits, thereby inhibiting maturation of the virus. Recently, a new class of drugs called entry inhibitors has been introduced which block the fusion of the viral envelope to the T cell membrane. Using these three types of therapies, we formulate an optimal control problem which aims at minimizing virus counts. In our model, we have included cell-to-cell viral transmission considering defense cells. In the first part of our analysis, having established the basic reproduction number, $\mathcal{R}_0$, the dynamic of disease-free equilibrium is studied.

Using a forward-backward sweep method, we have solved the optimality system numerically for illustration. In the absence of control in our model, numerical simulations have indicated a significant decrease in the number of healthy $CD4^+$ T cells and an increase in the number of infected T cells and free viruses. We have also examined the impact of drug efficacy on viral dynamics by numerical simulations. We have also compared the effects of various treatments on reducing the viral population in plasma.

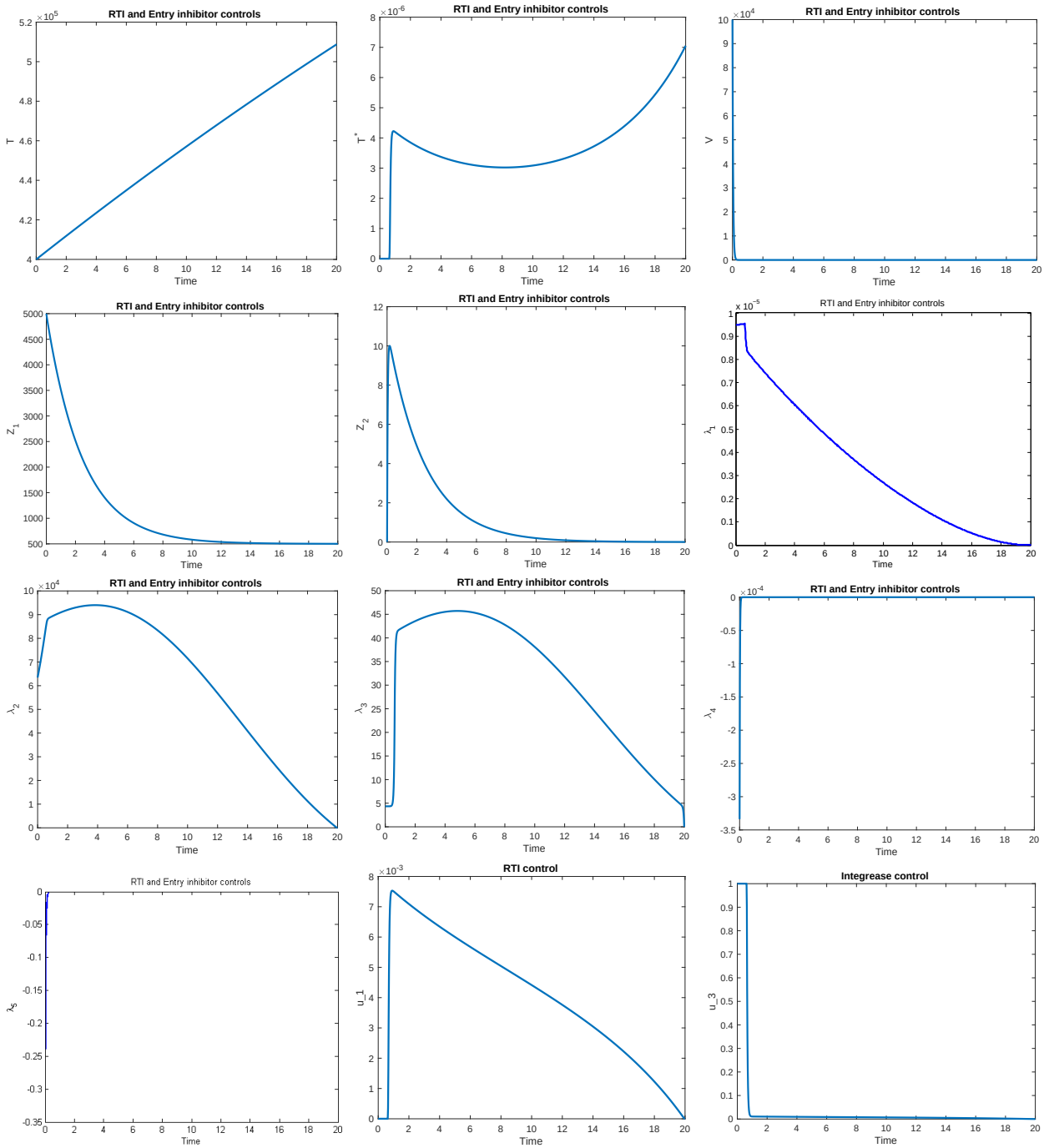

Fig. 8: Simulations of the model showing the effects of both reverse transcriptase inhibitor and entry inhibitor controls

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