Analytical Solution of the T, T^*, V_I, V_{NI} Model for HIV-1 Dynamics

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Abstract

This paper investigates a model for cellular and viral interactions following Human Immunodeficiency Virus Type 1 (HIV-1) infection. A simplified version of this model, which considers interactions between the populations of susceptible CD4+ T cells, infected CD4+ T cells, infectious virus, and non-infectious virus, under the effects of reverse transcriptase and protease inhibitors, is presented and solved analytically. The solution is obtained through an iterative method after isolating one dependent variable and performing various substitutions. Although an analytical solution is more difficult to obtain than numerical approximations, it produces exact results to the system of equations. As such, the analytical solution can be used to study the behavior of HIV-1 and its interactions with various treatment methods in an infected patient.

1 Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus that infects CD4+ T cells, a class of white blood cells that are central to the immune response [1]. Once infectious virus particles enter a human's immune system, they invade (i.e., infect) susceptible CD4+ T cells and assemble new virus particles within these infected cells. Once these newly produced virus particles are activated, leave their respective cells, and mature, they become infectious and, as such, have the ability to infect other susceptible T cells [2]. Continuation of this process depletes the population of T cells over time, consequently harming the immune system, and eventually resulting in the development of Acquired Immune Deficiency Syndrome (AIDS) [3]. Mathematical models can be used to describe the interactions between the CD4+ T cell and virus populations over time, which is beneficial for understanding the dynamics of HIV infection and predicting the onset of AIDS.

Previous mathematical works have used various models of cellular and viral interactions to study the dynamics of HIV Type 1 (HIV-1) [1, 4, 5, 6, 7]. The model investigated here, which was originally presented in 2002 by Callaway and Perelson [5], considers the behavior of four distinct populations: uninfected CD4+ T cells (denoted T), productively infected CD4+ T cells (denoted T^*), infectious virus particles (denoted V_I), and non-infectious virus particles (denoted V_{NI}). This model also includes the efficacy of two treatment methods: reverse transcriptase (RT) inhibitors and protease inhibitors. RT inhibitors prevent HIV ribonucleic acid (RNA) from being converted to deoxyribonucleic acid (DNA), thus reducing its infectiousness [8]. Protease inhibitors, on the other hand, do not have a direct impact on infectiousness of the virus; rather, they lead to the production of non-infectious (rather than infectious) virus particles by infected CD4+ T cells [9].

Time-dependent changes in the model's cellular and viral populations (T, T^*, V_I, V_{NI}) under the effects of RT and protease inhibitors are described by the following system of ordinary differential equations (ODEs):

$$\frac{dT}{dt} = \lambda - dT - (1-\kappa)kV_I T \tag{1.1}$$

$$\frac{dT^*}{dt} = (1-\kappa)kV_I T - \delta T^* \tag{1.2}$$

$$\frac{dV_I}{dt} = (1-\eta)N_T \delta T^* - cV_I \tag{1.3}$$

$$\frac{dV_{NI}}{dt} = \eta N_T \delta T^* - cV_{NI} \tag{1.4}$$

with parameters λ, d, k, δ, N_T, c, κ, $\eta > 0$.

Equations 1.1 and 1.2 represent the dynamics of the susceptible and infected classes of CD4+ T cells, respectively. The addition of susceptible CD4+ T cells to the population is regulated by birth rate λ, and their removal via cell death is regulated by death rate d. Cells are also removed from this population through infection by virus particles; the term $(1-\kappa)kV_I T$ in equations 1.1 and 1.2 represents this transfer of a CD4+ T cell from a susceptible state to an infected state, taking into account the effects of RT inhibitors with efficacy level κ. Cells are removed from the infected CD4+ T cell population via cell death, regulated by death rate δ.

Equations 1.3 and 1.4 represent the dynamics of infectious and non-infectious virus particles, respectively. Addition of virus particles to these populations is controlled by the viral production rate, $N_T \delta T^*$. This rate is impacted by protease inhibitors with efficacy η, and thus infectious virus particles are produced at rate $(1-\eta)N_T \delta T^*$, while non-infectious virus particles are produced at rate $\eta N_T \delta T^*$. Removal of virus particles from these populations is regulated by the viral clearance rate c.

Table 1 summarizes the model parameters and their interpretations, and presents their baseline values as given in [10].

PARAMETER	VALUE	UNITS	INTERPRETATION	REF.
λ	0.1089	$^{\text{cells}}/_{\text{day}}$	Birth rate of susceptible T cells.	[10]
d	0.01089	$^{1}/_{\text{day}}$	Death rate of susceptible T cells.	[10]
k	1.179×10^{-3}	$^{1}/_{\text{virions} \cdot \text{day}}$	Infection rate of susceptible T cells.	[10]
δ	0.366	$^{1}/_{\text{day}}$	Infected T cell death rate.	[10]
N_T	4246.4	$^{\text{virions}}/_{\text{cell}}$	Virus production rate.	[10]
c	3.074	$^{1}/_{\text{day}}$	Viral clearance rate.	[10]

Table 1: Model parameters, interpretations, and baseline values.

Observe that κ and η are not included in Table 1. These parameters represent efficacy of RT and protease inhibitors, respectively, and thus fall within the range $(0, 1)$ [5]. Their baseline values are derived from data collected for 176 HIV-infected patients from medical records of Severance Hospital, South Korea, which includes values for the initial conditions $T(0) = T_0$, $T^*(0) = T_0^*$, and $V_I(0) = V_{I0}$ and parameters λ, d, k, μ, N_T, c, κ, and η for each patient. The average values of κ and η in this data set are 0.6; therefore their baseline values are defined as $\kappa = 0.6$ and $\eta = 0.6$.

Some shortcomings of the model described by equations 1.1-1.4 are addressed in [5], including its extreme sensitivity to small changes in the drug efficacy parameters (κ and η), suggesting the ability of a patient to clear the virus. This implication conflicts with patient studies, which observe a reduction in (rather than full elimination of) viral population in patients [11, 12, 13, 14, 15, 16].

More recent work in this area has been focused on the introduction of a time delay into the system of ODEs describing HIV-1 dynamics to account for the time between viral entry and latent infection, as well as the time between cellular infection and viral production [17, 18, 19, 20, 21]. There has also been an increase in studies of stochastic models of HIV-1 dynamics in order to account for the earlier stages of infection, where there is a small number of infected cells and fewer virus particles in the body [20, 22, 23, 24].

The work presented within is focused on a model that is relatively simple, including neither a time delay nor an element of stochasticity; however, its simplistic nature presents a more reasonable problem from which an analytical solution can be derived. In [25], an analytical solution was found to the Susceptible-Infected-Virus (SIV) model for HIV dynamics, which does not consider treatment methods and the resultant production of non-infectious virus particles. Inclusion of RT inhibitors, protease inhibitors, and non-infectious virus in the model investigated here allows for expansion of the results produced in [25], and is a useful step in the direction of ultimately deriving analytical solutions to more biologically sound models of HIV-1 dynamics.

2 Solution to the Simplified Model

The system of ODEs given in equations 1.1-1.4 is simplified by removing terms of the model involving the susceptible CD4+ T cell birth and death rates, as well as those involving the viral clearance rate. Although removing these terms makes the model inaccurate in characterizing the development of HIV-1 in later stages of infection, its analytical solution can still provide some useful insight into the behavior of and interaction between the terms of the system. The simplified model is given by:

$$\frac{dT}{dt} = -(1-\kappa)kV_I T \tag{2.1}$$

$$\frac{dT^*}{dt} = (1-\kappa)kV_I T - \delta T^* \tag{2.2}$$

$$\frac{dV_I}{dt} = (1-\eta)N_T \delta T^* \tag{2.3}$$

$$\frac{dV_{NI}}{dt} = \eta N_T \delta T^* \tag{2.4}$$

Observe that the removal of λ, the birth rate of susceptible CD4+ T cells, implies that the population of CD4+ T cells is strictly decreasing. Moreover, removal of the terms involving viral clearance rate c indicates that the levels of infectious and non-infectious virus monotonically increase. Although these behavioral assumptions stemming from removal of the terms λ, dT, cV_I, and cV_{NI} result in a model that is not fully biologically sound, these reductions allow for the system to be sufficiently simplified to the point where an analytical solution is obtainable.

The simplified model presented in equations 2.1-2.4 is considered to satisfy the initial conditions $T(0) = T_0$, $T^*(0) = T_0^*$, $V_I(0) = V_{I0}$, and $V_{NI}(0) = V_{NI0}$. For a discussion of the steady state solutions to the full and simplified systems, see Appendix A.

2.1 Existence and Uniqueness

Prior to solving the system of ODEs in equations (2.1)-(2.4) analytically, we verify that a unique solution exists. To do so, we use the Picard Lindelöf Theorem, adoptiong the approach in [25].

Theorem 2.1. (Picard Lindelöf Theorem) Let $n \in \mathbb{N}$ and $x_0 \in \mathbb{R}^n$ be given. Assume the function $f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n$ is locally Lipschitz in its first argument and continuous in its second argument. Then there exists $t^* > 0$ and a unique function $x : [0, t^*] \to \mathbb{R}^n$ satisfying

$$x'(t) = f(x(t), t)$$

for every $t \in [0, t^*]$ and the initial condition $x(0) = x_0$.

Observe that the system of ODEs given by equations (2.1)-(2.4) is autonomous since it does not explicitly depend on the dependent variable t. In our system, let x and $f(x)$ be defined as

$$x = \begin{bmatrix} T \\ T^* \\ V_I \\ V_{NI} \end{bmatrix} \quad \text{and} \quad f(x) = \begin{bmatrix} -(1-\kappa)kV_I T \\ (1-\kappa)kV_I T - \delta T^* \\ (1-\eta)N_T \delta T^* \\ \eta N_T \delta T^* \end{bmatrix}.$$

The Jacobian matrix is then given by

$$\begin{bmatrix} -(1-\kappa)kV_I & 0 & -(1-\kappa)kT & 0 \\ (1-\kappa)kV_I & -\delta & (1-\kappa)kT & 0 \\ 0 & (1-\eta)N_T\delta & 0 & 0 \\ 0 & \eta N_T \delta & 0 & 0 \end{bmatrix}.$$

Note that the partial derivatives of f exist and are continuous, which implies that f is Lipschitz continuous; therefore, there exists a unique solution to our system on some interval $[0, t^*]$.

2.2 Exact Solution

We now solve the simplified system of ODEs given by equations 2.1)-(2.4. Note that

$$\frac{d}{dt}\left[T + T^* + \frac{1}{N_T}(V_I + V_{NI})\right] = 0 \quad \text{and} \quad \frac{d}{dt}\left[V_I + \left(\frac{\eta - 1}{\eta}\right) V_{NI}\right] = 0.$$

Therefore,

$$T + T^* + \frac{1}{N_T}(V_I + V_{NI}) = P \quad \text{and} \quad V_I + \left(\frac{\eta - 1}{\eta}\right) V_{NI} = P_V,$$

where P and P_V are constants, with P representing total population of white blood cells and virus in the body and P_V representing the total viral population in the body. Then

$$T = P - T^* - \frac{1}{N_T}(V_I + V_{NI}) \quad \text{and} \quad T^* = P - T - \frac{1}{N_T}(V_I + V_{NI}),$$
$$V_I = P_V - \left(\frac{\eta - 1}{\eta}\right) V_{NI} \quad \text{and} \quad V_{NI} = \left(\frac{\eta}{\eta - 1}\right)(P_V - V_I).$$

Additionally, with the previously defined initial conditions, we have

$$P = T_0 + T_0^* + \frac{1}{N_T}(V_{I0} + V_{NI0}) \quad \text{and} \quad P_V = V_{I0} + \left(\frac{\eta - 1}{\eta}\right) V_{NI0}.$$

To obtain an analytical solution for this simplified model, we first use an iterative technique to obtain an implicit solution for V_I, and then use this solution to find V_{NI}, T, and T^*.

We begin by differentiating equation 2.3 with respect to t and applying substitutions for T and V_{NI} to obtain the second derivative of V_I with respect to time. For the sake of simplicity, let $\alpha = (1-\eta)\delta(1-\kappa)k$ and $\omega = \alpha N_T = (1-\eta)N_T\delta(1-\kappa)k$. Then

$$\frac{d^2V_I}{dt^2} = \omega P V_I - \alpha V_I^2 - \alpha\left(\frac{\eta}{\eta-1}\right)P_V V_I + \alpha\left(\frac{\eta}{\eta-1}\right)V_I^2 - (1-\kappa)kV_I\frac{dV_I}{dt} - \delta\frac{dV_I}{dt}.$$

Therefore, the second derivative of V_I with respect to time is given by

$$V_I'' = \left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]V_I^2 + \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I - (1-\kappa)kV_IV_I' - \delta V_I'. \tag{2.5}$$

To make equation 2.5 easier to solve, let

$$u = \frac{dt}{dV_I} = \frac{1}{V_I'},$$

with initial condition

$$u(V_{I0}) = \frac{1}{(1-\eta)N_T\delta T_0^*}.$$

Then

$$\frac{du}{dV_I} = \left[-\left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]V_I^2 - \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right]u^3 + \left[(1-\kappa)kV_I + \delta\right]u^2. \tag{2.6}$$

Equation 2.6 is an Abel equation of the first kind, and can be solved using an iterative method as in [26]. This is done by obtaining a sequence of approximate analytical solutions to equation 2.6, and then taking the limit of this sequence at infinity to acquire the exact solution. Let

$$\phi = \ln(u),$$

so that

$$u = e^{\phi}.$$

The initial condition for ϕ is given by

$$\phi(V_{I0}) = -\ln\left((1-\eta)N_T\delta T_0^*\right).$$

Then the differential equation (equation 2.6) can be rewritten as

$$\frac{d\phi}{dV_I} = \left[(1-\kappa)kV_I + \delta\right]e^{\phi} - \left[\left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]V_I^2 + \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right]e^{2\phi}. \tag{2.7}$$

We can use the Taylor series expansion of e^{ϕ} to rewrite equation 2.7 as

$$\begin{aligned}\frac{d\phi}{dV_I} = {} & \left[(1-\kappa)kV_I + \delta\right]\left[1 + \phi + \frac{\phi^2}{2} + \cdots\right] \\ & - \left[\left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]V_I^2 + \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right]\left[1 + 2\phi + \frac{(2\phi)^n}{2} + \cdots\right].\end{aligned} \tag{2.8}$$

For a first approximation, namely $\phi_1(V_I)$, we use the first two terms of the Taylor series:

$$\begin{aligned}\frac{d\phi_1}{dV_I} &= \big[(1-\kappa)kV_I+\delta\big]\Big[1+\phi_1\Big]-\left[\left[\alpha\left(\frac{\eta}{\eta-1}\right)-\alpha\right]V_I^2+\left[\omega P-\alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right]\Big[1+2\phi_1\Big]\\ &= \left((1-\kappa)kV_I+\delta-\left[\alpha\left(\frac{\eta}{\eta-1}\right)-\alpha\right]V_I^2-\left[\omega P-\alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right) \qquad (2.9)\\ &\quad+\left((1-\kappa)kV_I+\delta-2\left[\left[\alpha\left(\frac{\eta}{\eta-1}\right)-\alpha\right]V_I^2+\left[\omega P-\alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right]\right)\phi_1\end{aligned}$$

Equation 2.9 is a first order linear differential equation of the form $\phi_1(V_I)' = Q(V_I)+R(V_I)\phi_1$, with $Q(V_I)$ and $R(V_I)$ given by

$$Q(V_I) = (1-\kappa)kV_I+\delta-\left[\alpha\left(\frac{\eta}{\eta-1}\right)-\alpha\right]V_I^2-\left[\omega P-\alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I,$$

$$R(V_I) = (1-\kappa)kV_I+\delta-2\left[\left[\alpha\left(\frac{\eta}{\eta-1}\right)-\alpha\right]V_I^2+\left[\omega P-\alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right].$$

As such, we can solve equation 2.9 using an integrating factor. Let

$$F = \exp\left[\frac{2}{3}\left[\alpha\left(\frac{\eta}{\eta-1}\right)-\alpha\right]V_I^3+\left[\omega P-\alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I^2-\frac{1}{2}(1-\kappa)kV_I^2-\delta V_I\right].$$

Applying this integrating factor to solve equation 2.9 above, we obtain the solution to the ϕ_1, the first approximation for ϕ:

$$\begin{aligned}\phi_1(V_I) &= \frac{1}{F(V_I)}\big[-\ln\big((1-\eta)N_T\delta T_0^*\big)F(V_{I0})\big] \qquad (2.10)\\ &\quad+\frac{1}{F(V_I)}\left[\int_{V_{I0}}^{V_I}F(\xi)\left[(1-\kappa)k\xi+\delta-\left[\alpha\left(\frac{\eta}{\eta-1}\right)-\alpha\right]\xi^2-\left[\omega P-\alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]\xi\right]d\xi\right],\end{aligned}$$

where $\phi_1(V_{I0}) = \phi(V_{I0})$.
Observe that equation 2.8 can be rewritten in the following manner:

$$\begin{aligned}\frac{d\phi}{dV_I} &= \left[(1-\kappa)kV_I+\delta\right]\left[1+\phi+\sum_{n=2}^{\infty}\frac{\phi^n}{n!}\right]\\ &\quad-\left[\left[\alpha\left(\frac{\eta}{\eta-1}\right)-\alpha\right]V_I^2+\left[\omega P-\alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right]\left[1+2\phi+\sum_{n=2}^{\infty}\frac{(2\phi)^n}{n!}\right]\\ &= \left[(1-\kappa)kV_I+\delta-\left[\alpha\left(\frac{\eta}{\eta-1}\right)-\alpha\right]V_I^2-\left[\omega P-\alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right] \qquad (2.11)\\ &\quad+\left[(1-\kappa)kV_I+\delta-2\left(\left[\alpha\left(\frac{\eta}{\eta-1}\right)-\alpha\right]V_I^2+\left[\omega P-\alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right)\right]\phi\\ &\quad+\sum_{n=2}^{\infty}\left[(1-\kappa)kV_I+\delta\right]\left[\frac{(\phi)^n}{n!}\right]-\left[\left[\alpha\left(\frac{\eta}{\eta-1}\right)-\alpha\right]V_I^2+\left[\omega P-\alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right]\left[\frac{(2\phi)^n}{n!}\right]\end{aligned}$$

We can obtain a second approximation, $\phi_2(V_{I0})$, by plugging ϕ_1 (our first approximation) into the infinite sum expression in equation 2.11. Then

$$\begin{aligned}\frac{d\phi_2}{dV_I} = &\left[(1-\kappa)kV_I + \delta - \left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]V_I^2 - \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right] \\ &+ \left[(1-\kappa)kV_I + \delta - 2\left(\left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]V_I^2 + \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right)\right]\phi_2 \qquad (2.12) \\ &+ \sum_{n=2}^{\infty}\left[(1-\kappa)kV_I + \delta\right]\left[\frac{(\phi_1)^n}{n!}\right] - \left[\left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]V_I^2 + \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]V_I\right]\left[\frac{(2\phi_1)^n}{n!}\right]\end{aligned}$$

The result given by 2.12 is another first order and linear differential equation, which can again be solved using an integrating factor. Note that the coefficient for ϕ_2 in equation 2.12 is the same as the coefficient for ϕ_1 in equation 2.9, and therefore the same integrating factor will be used. Thus:

$$\begin{aligned}\phi_2(V_I) = &\frac{1}{F(V_I)}\left[-\ln\left((1-\eta)N_T\delta T_0^*\right)F(V_{I0})\right] \\ &+\frac{1}{F(V_I)}\left[\int_{V_{I0}}^{V_I} F(\xi)\left[(1-\kappa)k\xi + \delta - \left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]\xi^2 - \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]\xi\right]d\xi\right] \\ +&\frac{1}{F(V_I)}\int_{V_{I0}}^{V_I} F(\xi)\sum_{n=2}^{\infty}\left[(1-\kappa)k\xi + \delta\right]\left[\frac{(\phi_1)^n}{n!}\right] - \left[\left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]\xi^2 + \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]\xi\right]\left[\frac{(2\phi_1)^n}{n!}\right]d\xi,\end{aligned}$$

with $\phi_2(V_{I0}) = \phi(V_{I0})$.

We can continue this process to get successively more accurate approximations to ϕ. In general, for any integer $m > 1$, we have:

$$\begin{aligned}\phi_{m+1}(V_I) = &\frac{1}{F(V_I)}\left[F(V_{I0})\phi_{m+1}(V_{I0})\right] \\ &+ \frac{1}{F(V_I)}\left[\int_{V_{I0}}^{V_I} F(\xi)\left[(1-\kappa)k\xi + \delta - \left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]\xi^2 - \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]\xi\right]d\xi\right] \\ +&\frac{1}{F(V_I)}\int_{V_{I0}}^{V_I} F(\xi)\sum_{n=2}^{\infty}\left[(1-\kappa)k\xi + \delta\right]\left[\frac{(\phi_m)^n}{n!}\right] - \left[\left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]\xi^2 + \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]\xi\right]\left[\frac{(2\phi_m)^n}{n!}\right]d\xi,\end{aligned}$$

which can be written more compactly as

$$\begin{aligned}\phi_{m+1}(V_I) = \phi_1(V_I) &+ \frac{1}{F(V_I)}\int_{V_{I0}}^{V_I} F(\xi)\left[(1-\kappa)k\xi + \delta\right]\left[e^{\phi_m(\xi)} - 1 - \phi_m(\xi)\right]d\xi \\ &- \frac{1}{F(V_I)}\int_{V_{I0}}^{V_I} F(\xi)\left[\left[\alpha\left(\frac{\eta}{\eta-1}\right) - \alpha\right]\xi^2 + \left[\omega P - \alpha\left(\frac{\eta}{\eta-1}\right)P_V\right]\xi\right]\left[e^{2\phi_m(\xi)} - 1 - 2\phi_m(\xi)\right]d\xi.\end{aligned}$$

Each consecutive approximation of $\phi(V_I)$ becomes closer and closer to the actual solution of $\phi(V_I)$. In other words,

$$\lim_{m\to\infty}\phi_m(V_I) = \phi(V_I).$$

With this limit, we have obtained a solution to $\phi(V_I)$, and can now work backwards to obtain the solution of V_I. Recall that

$$\frac{dt}{dV_I} = e^{\phi(V_I)}.$$

Separating variables and integrating both sides, we have

$$\int_{t_0}^{t} d\xi = \int_{V_{I0}}^{V_I} e^{\phi(\xi)} d\xi.$$

Then, taking $t_0 = 0$, we have $V_I(t)$ given implicitly by

$$t = \int_{V_{I0}}^{V_I} e^{\phi(\xi)} d\xi. \tag{2.13}$$

The implicit solution for V_I can now be used to obtain solutions for T, T^*, and V_{NI}. First, the solution for V_{NI} is found using the following equation:

$$V_{NI} = \left(\frac{\eta}{\eta - 1}\right)(P_V - V_I). \tag{2.14}$$

We will now derive a solution for T. Recall that

$$\frac{dT}{dt} = -(1 - \kappa)kV_I T.$$

Separating variables and integrating,

$$\int_{T_0}^{T} \frac{1}{\xi} d\xi = -(1 - \kappa)k \int_{t_0}^{t} V_I(\xi) d\xi.$$

Taking $t_0 = 0$,

$$T = T_0 e^{-(1-\kappa)k \int_0^t V_I(\xi) d\xi}. \tag{2.15}$$

Finally, we obtain a solution for T^*. Recall that

$$T^* = P - T - \frac{1}{N_T}\left(V_I + V_{NI}\right)$$

Applying the solutions for T^*, V_I, and V_{NI} obtained above, we have

$$T^* = P - T_0 e^{-(1-\kappa)k \int_0^t V_I(\xi) d\xi} - \frac{1}{N_T}\left[V_I + \left(\frac{\eta}{\eta - 1}\right)(P_V - V_I)\right]. \tag{2.16}$$

Equations 2.13-2.16 give the analytical solution to the simplified model.

Figures 1 and 2 display various approximations to ϕ, T, T^*, V_I and V_{NI} obtained using 100, 200, 300, 400, and 500 iterations, along with their exact solutions obtained by numerical methods. The initial conditions $T_0 = 500$ $^{\text{cells}}/_{mm^3}$, $T_0^* = 0.1$ $^{\text{cells}}/_{mm^3}$, $V_{I0} = 1 \times 10^{-7}$ $^{\text{virions}}/_{mm^3}$ and $V_{NI0} = 1 \times 10^{-9}$ $^{\text{virions}}/_{mm^3}$ were used to obtain these results. Observe that as the number of iterations increase, the approximations obtained by the analytical solution get closer to the exact solution. In fact, in Figures 1 and 2, the approximations overlap with the exact solutions once the 400th iteration is reached.

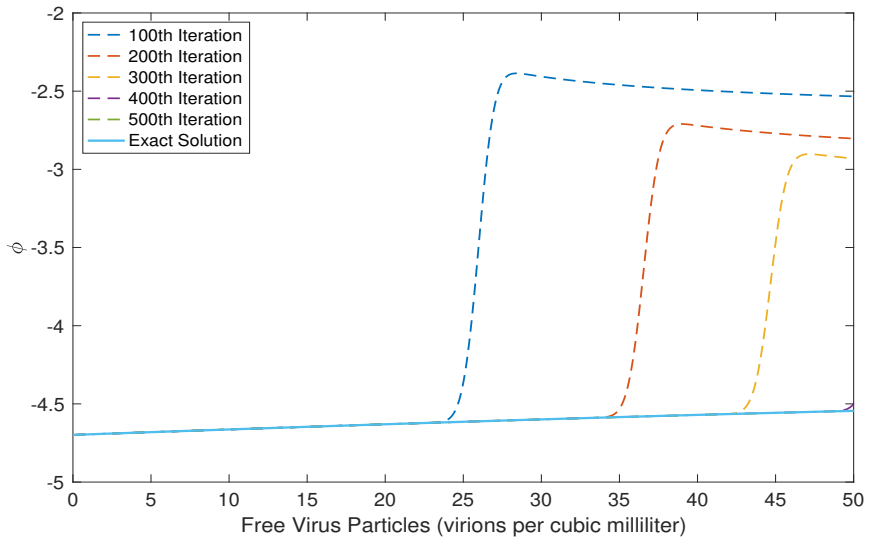

Figure 1: Various approximations of ϕ obtained by the analytical solution, along with the exact solution obtained by numerical methods.

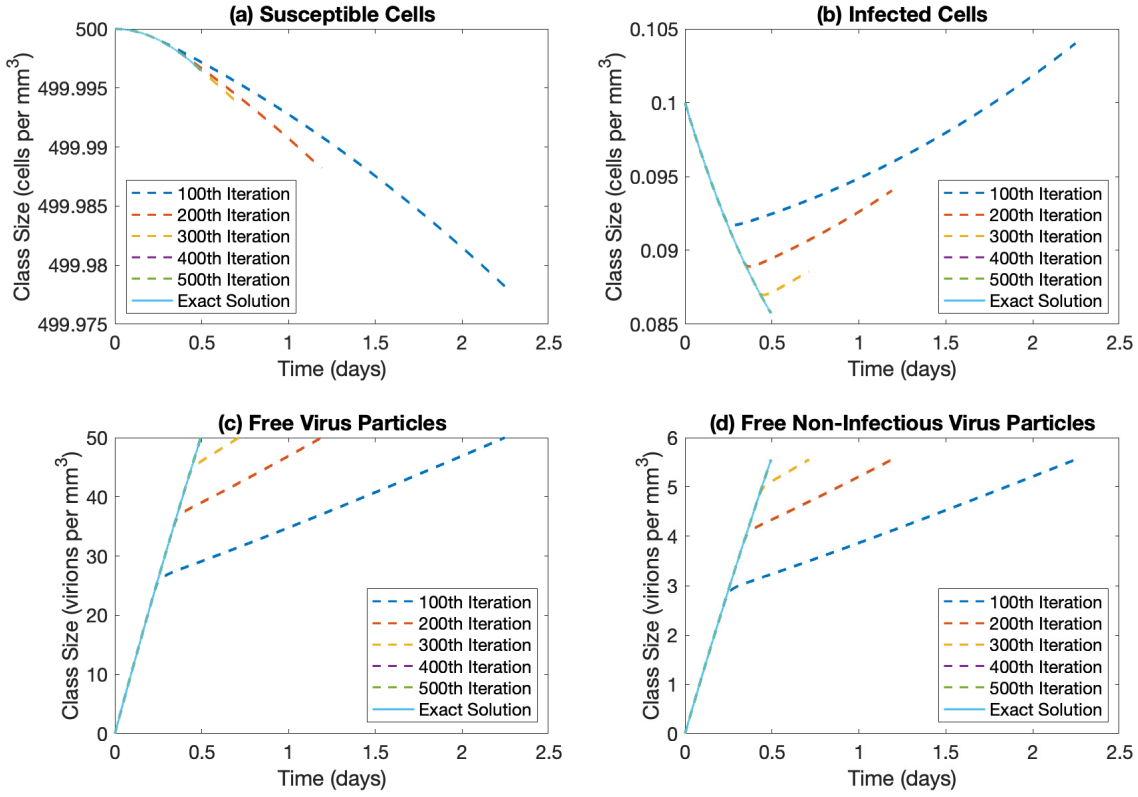

Figure 2: Various approximations of T (2a), T^* (2b), V_I (2c) and V_{NI} (2d) obtained by the analytical solution, along with the exact solution obtained by numerical methods.

3 Discussion

To further understand the dynamics of HIV-1 according to the simplified model described by equations 2.1-2.4, a predictor-corrector method was used to numerically solve the system. The explicit four-step Adams-Bashforth Method and implicit three-step Adams-Moulton Method were used to obtain this solution, and the Runge-Kutta Method of order four was used to find its starting values [27]. The resulting approximation is plotted in Figure 3. Due to the discrepancy in class sizes between virus particles (V_I and V_{NI}) and CD4+ T cells (T and T^*), it is helpful to plot V_I and V_{NI} separately from T and T^*.

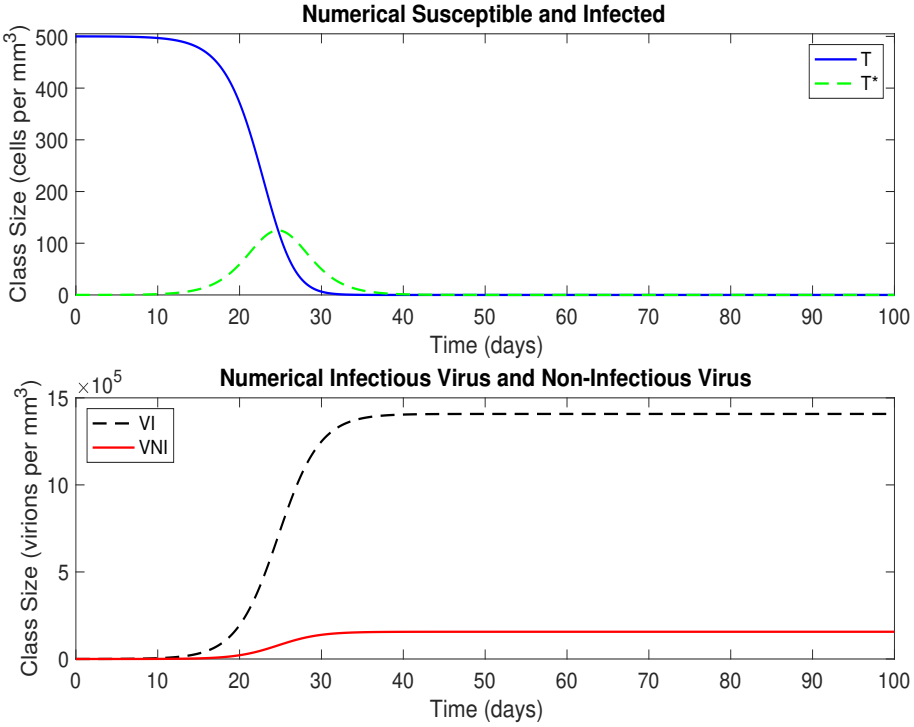

Figure 3: Approximate solution for T, T^*, V_I, and V_{NI} in the simplified model.

As expected, the removal of the CD4+ T cell birth rate results in a continuous decrease in the population density of susceptible cells until it reaches its steady state. Conversely, removal of the viral clearance rate leads to a continuous increase in the density of infectious and non-infectious virus particles until they reach their steady states. Each class reaches its steady state relatively quickly, before $t = 40$ days.

The behavior of the analytical and numerical results provided here are quite similar to those presented in [25], which is anticipated as a similar model was solved. However, the inclusion of protease and RT inhibitors in this work leads to slower growth of the infected T cell population and viral population densities (both infectious and non-infectious).

The full model given in equations 1.1-1.4, which incorporates the CD4+ T cell birth and death rates as well as the viral clearance rate, is a more biologically sound model for the study of HIV-1 dynamics. Figure 4 displays an approximate solution to the full system obtained by the same predictor-corrector multistep method that was used to solve the simplified system.

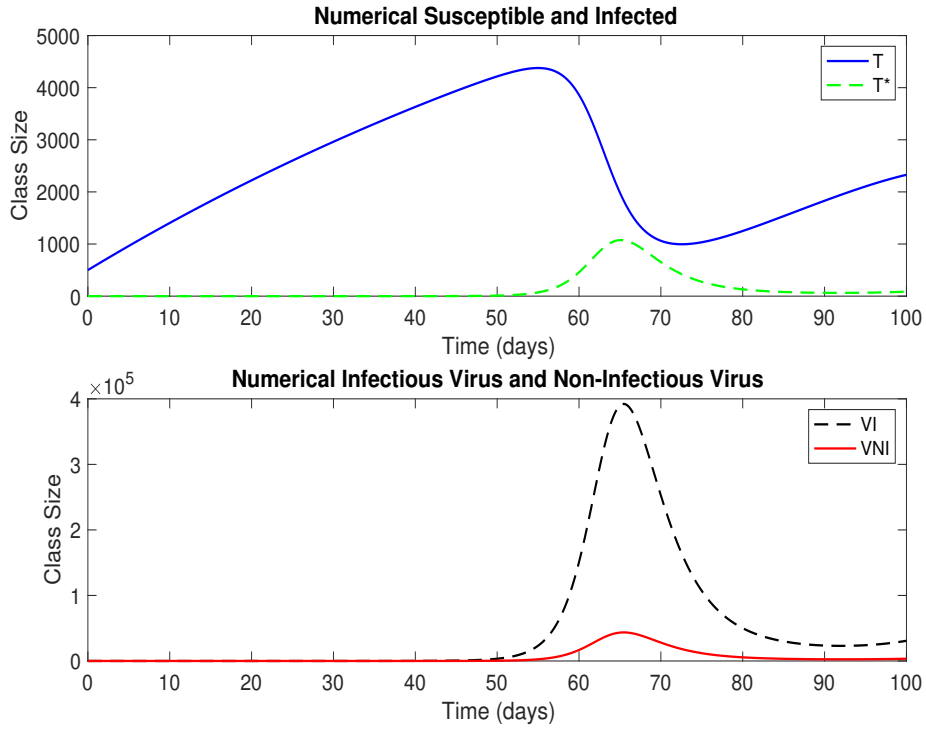

Figure 4: Approximate solution for T, T^*, V_I, and V_{NI} obtained by the Multistep Method.

Figure 4 shows that around $t = 50$ days, the amount of infectious and non-infectious virus present increases, and the population densities of infected and susceptible CD4+ T cells consequently increase and decrease, respectively. Once virus concentration hits its peak and begins to decrease, the number of infected T cells decrease, while the number of susceptible T cells increase. This pattern continues as time progresses, from the beginning of antiretroviral therapy until each class reaches its respective steady state.

Observe in Figure 4 that the inclusion of the CD4+ T cell birth rate in the full model allows the population of susceptible T cells to increase, while in Figure 3, their population is monotonically decreasing. Similarly, the incorporation of viral clearance rate in the full model (Figure 4) allows for a decrease in the populations of infectious and non-infectious virus particles, as opposed to their monotonically increasing behavior predicted by the simplified model (Figure 3).

It is interesting to consider the possibility that one or both of the treatment methods considered in this model could be unsuccessful in reducing the viral load through its respective method of enzyme inhibition. Recall that κ and η represent the efficacy level of RT and protease inhibitors, respectively, with baseline values $\kappa = \eta = 0.6$ (see Section 1). To investigate how efficacy impacts model dynamics, consider results produced by the full model (equations 1.1-1.4) for four cases of varying treatment efficacies: (1) neither treatment method is ineffective, i.e., $\kappa = \eta = 0.6$; (2) only RT inhibitors are ineffective, i.e., $\kappa = 0$ and $= \eta = 0.6$; (3) only protease inhibitors are ineffective, i.e., $\kappa = 0.6$ and $\eta = 0$; and (4) both treatment methods are ineffective, i.e., $\kappa = \eta = 0$.

Figure 5 displays the results produced by the full system in each of the scenario for the population of susceptible CD4+ T cells, T (Fig. 5A); population of infected CD4+ T cells, T^* (Fig. 5k); infectious virus population, V_I (Fig. 5C); and non-infectious virus population, V_{NI} (Fig. 5D).

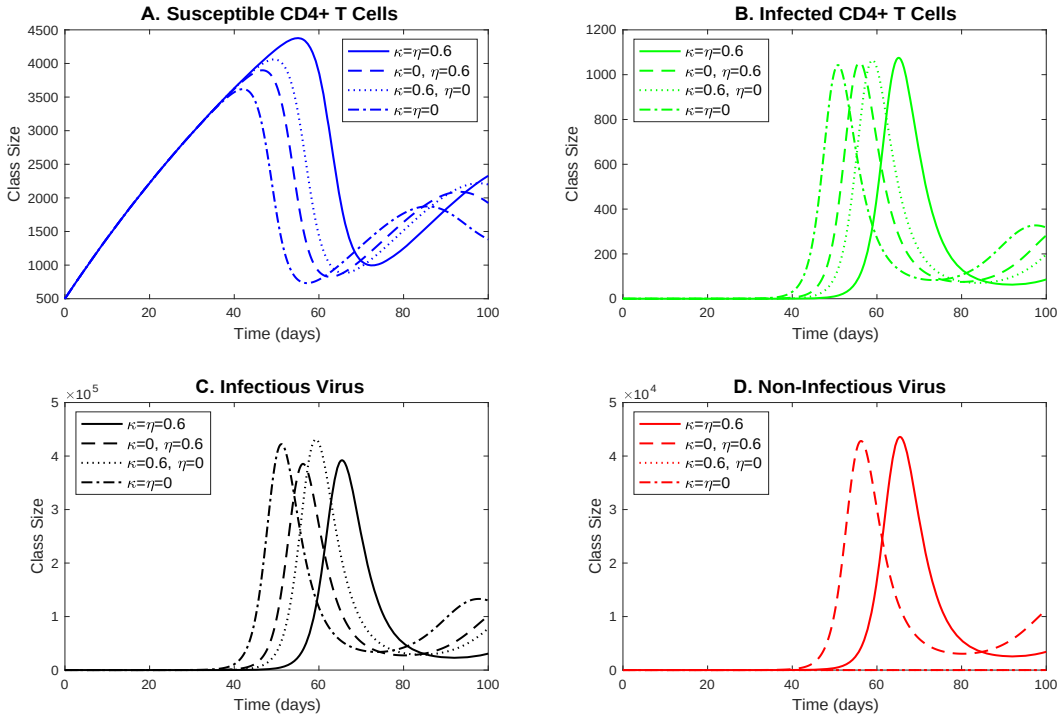

Figure 5: Comparison of results for various levels of efficacy of RT and protease inhibitors (i.e., various values of κ and η, respectively).

RT inhibitors treat HIV-1 infection by preventing HIV RNA from being converted to DNA [5], thus reducing infectiousness of the virus. It follows that an effective RT inhibitor will hinder depletion of the susceptible CD4+ T cell population, as seen in Figure 5A. Moreover, the results presented in Figure 5C show that the peak population levels of infectious virus computed with an RT efficacy level of $\kappa = 0.6$ are lower than those observed with an ineffective RT inhibitor ($\kappa = 0$).

Protease inhibitors, through modification of the viral assembly process, lead to the production of noninfectious virus in place of infectious virus [5]. It follows that an ineffective protease inhibitor ($\eta = 0$) will result in the absence of non-infectious virus, or $V_{NI} = 0$; this is supported by the numerical results presented in Figure 5D. Furthermore, there is a visible increase in the population of V_I when $\eta = 0$ relative to the scenario in which $\eta > 0$, which is expected as the protease inhibitor no longer hinders the ability of an infected cell to produce infectious virus.

Effective RT and protease inhibitors correspond to a less severe depletion of susceptible CD4+ T cells, as seen in Figure 5A. Visually, it appears that the RT inhibitors are slightly more effective at slowing the depletion of CD4+ T cells than protease inhibitors. Additionally, the results in Figure 5C show that the concentration of infectious virus is higher in scenarios where the RT inhibitor is ineffective (i.e., $\kappa = 0$), while the efficacy of the protease inhibitors seems to have less of an effect on the infectious virus population. This is a reasonable implication, as the purpose of RT inhibitors is to reduce infectiousness of the virus, which will ultimately result in a lower viral concentration.

In sum, the results produced by the full model demonstrate that an efficient RT inhibitor will reduce the concentration of infectious virus, while an efficient protease inhibitor will increase the population of non-infectious virus (note that the non-infectious virus population is only introduced if protease inhibitor efficacy $\eta > 0$). Moreover, both treatment methods hinder the depletion of CD4+ T cells during infection, with higher efficacy levels corresponding to lower levels of depletion.

4 Future Work

Limitations of the simplified model presented in this work, including the removal of terms and a lack of time delays and stochastic elements, imply that its solution will not accurately predict the dynamics of HIV-1 in an infected patient. However, the method applied in Section 2.2 to derive an analytical solution from this simplified system may be extended and applied to systems of increasing complexity. Therefore, the work presented within is an advantageous step in the direction of producing more biologically sound results, which will ultimately be obtained by analytically solving more comprehensive models of HIV-1 dynamics.

As discussed in Section 3, removal of the T cell birth rate, susceptible T cell death rate, and viral clearance rate leads to inaccurate model predictions. The reintroduction of these terms will relax the behavioral assumptions outlined in Section 2 (i.e., the monotonically decreasing behavior of uninfected CD4+ T cells and monotonically increasing behavior of infectious and non-infectious virus populations), and consequently improve the accuracy of model predictions.

The introduction of time delays in future work will be essential for establishing changes in model dynamics resulting from the time delays between viral entry and latent infection, cell infection and virus production, and infection and beginning of antiretroviral therapy.

Inclusion of stochasticity (i.e., some element of randomness) within the model will further improve the credibility of results, particularly in the early stages of HIV infection, as the processes being considered are inherently stochastic [24].

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Appendix A: Steady State Solutions

A.1 Full Model Steady State

The full model describing the dynamics of HIV-1 infection is given by the following system of ODEs:

$$\frac{dT}{dt} = \lambda - dT - (1-\kappa)kV_I T \tag{A.1}$$

$$\frac{dT^*}{dt} = (1-\kappa)kV_I T - \delta T^* \tag{A.2}$$

$$\frac{dV_I}{dt} = (1-\eta)N_T \delta T^* - cV_I \tag{A.3}$$

$$\frac{dV_{NI}}{dt} = \eta N_T \delta T^* - cV_{NI} \tag{A.4}$$

To find the steady state(s) of the model described by A.1-A.4, the change in each state variable over time is set to zero:

$$0 = \lambda - dT - (1-\kappa)kV_I T \tag{A.5}$$

$$0 = (1-\kappa)kV_I T - \delta T^* \tag{A.6}$$

$$0 = (1-\eta)N_T \delta T^* - cV_I \tag{A.7}$$

$$0 = \eta N_T \delta T^* - cV_{NI} \tag{A.8}$$

First, observe that rearrangement of equations A.7 and A.8 allow V_I and V_{NI} to be expressed in terms of T^*:

$$V_I = \frac{(1-\eta)N_T \delta T^*}{c} \tag{A.9}$$

$$V_{NI} = \frac{\eta N_T \delta T^*}{c} \tag{A.10}$$

The expression for V_I presented in equation A.9 is substituted into A.6, and T^* is then factored out as follows:

$$\begin{aligned} 0 &= (1-\kappa)k\left[\frac{(1-\eta)N_T \delta T^*}{c}\right] T - \delta T^* \\ 0 &= T^*\left[\frac{(1-\kappa)k(1-\eta)N_T \delta}{c} T - \delta\right] \end{aligned} \tag{A.11}$$

There are two cases for which equation A.11 is true: $T^* = 0$ or $T^* \neq 0$. This implies the existence of two steady state solutions for the full model in equations A.1-A.4.

First consider the case in which $T^* = 0$. Then, by equations A.9 and A.10, $V_I = 0$ and $V_{NI} = 0$; and substituting $V_I = 0$ into equation A.5 results in $T = \lambda/d$. Thus, the first steady state of the full model in equations A.1-A.4 is:

$$\begin{cases} \overline{T} &= \dfrac{\lambda}{d} \\ \overline{T}^* &= 0 \\ \overline{V}_I &= 0 \\ \overline{V}_{NI} &= 0 \end{cases} \tag{A.12}$$

In the second case, for which $T^* \neq 0$, both sides of equation A.11 can be divided by T^*. Doing so and solving for T, we obtain:

$$T = \frac{c}{(1-\kappa)k(1-\eta)N_T\delta} \tag{A.13}$$

Substituting the expression for T in equation A.13 into equation A.5, the corresponding value of V_I is derived, given by:

$$V_I = \frac{(1-\eta)N_T\lambda}{c} - \frac{d}{(1-\kappa)k} \tag{A.14}$$

Then, replacing V_I in equation A.9 with the expression for V_I in A.14 and solving for T^* results in:

$$T^* = \frac{\lambda}{\delta} - \frac{cd}{(1-\eta)N_T\delta(1-\kappa)k} \tag{A.15}$$

Finally, V_{NI} is found by substituting equation A.15 into A.10 and solving for V_{NI}, resulting in:

$$V_{NI} = \frac{\eta N_T\lambda}{c} - \frac{d\eta}{(1-\eta)(1-\kappa)k} \tag{A.16}$$

Thus, the second steady state of the full system in equations A.1-A.4 is:

$$\begin{cases} \overline{T} &= \dfrac{c}{(1-\kappa)k(1-\eta)N_T\delta} \\ \overline{T}^* &= \dfrac{\lambda}{\delta} - \dfrac{cd}{(1-\eta)N_T\delta(1-\kappa)k} \\ \overline{V}_I &= \dfrac{(1-\eta)N_T\lambda}{c} - \dfrac{d}{(1-\kappa)k} \\ \overline{V}_{NI} &= \dfrac{\eta N_T\lambda}{c} - \dfrac{d\eta}{(1-\eta)(1-\kappa)k} \end{cases} \tag{A.17}$$

Note that $\overline{V}_I = \overline{V}_{NI} = 0$ in the first steady state (equation A.12) suggests complete clearance of virus populations within the host. Conversely, the second steady state (equation A.17) requires $\overline{V}_I > 0$ and $\overline{V}_{NI} > 0$, implying that the host will be in a state of perpetual infection. As such, these steady states will be hereinafter referred to as the virus-free and infected steady states of the full model, respectively.

A.2 Simplified Model Steady State

The full model can be reduced by removing the terms involving the birth and death rates of the susceptible CD4+ T-cell population (i.e., λ and dT, respectively) and terms involving the viral clearance rate (i.e., cV_I and cV_{NI}). In doing so, a simplified model of HIV-1 dynamics is obtained, described by the following system of ODEs:

$$\frac{dT}{dt} = -(1-\kappa)kV_IT \tag{A.18}$$

$$\frac{dT^*}{dt} = (1-\kappa)kV_IT - \delta T^* \tag{A.19}$$

$$\frac{dV_I}{dt} = (1-\eta)N_T\delta T^* \tag{A.20}$$

$$\frac{dV_{NI}}{dt} = \eta N_T\delta T^* \tag{A.21}$$

To find the steady state(s) of this reduced model, as in Section A.1, we set the change in each state variable over time (i.e., equations A.18-A.21) to zero as follows:

$$0 = -(1-\kappa)kV_I T \tag{A.22}$$
$$0 = (1-\kappa)kV_I T - \delta T^* \tag{A.23}$$
$$0 = (1-\eta)N_T \delta T^* \tag{A.24}$$
$$0 = \eta N_T \delta T^* \tag{A.25}$$

The steady state of T^* can be obtained directly from equation A.24 or A.25; solving either of these equations for T^* results in $T^* = 0$.

Equation A.22 implies that either $T = 0$ or $V_I = 0$. First, let $T = 0$. Note that V_I and V_{NI} cannot be found directly from equations A.22-A.25. However, note that both V_I and V_{NI} are strictly increasing over time in the simplified model due to the removal of viral clearance rate; it follows that $\overline{V}_I \geq V_{I0}$ and $\overline{V}_{NI} \geq V_{NI0}$. Thus, the first steady state of the reduced model is:

$$\begin{cases} \overline{T} = 0 \\ \overline{T}^* = 0 \\ \overline{V}_I \geq V_{I0} \\ \overline{V}_{NI} \geq V_{NI0} \end{cases} \tag{A.26}$$

Next, let $V_I = 0$. Again, neither T nor V_{NI} can be solved from equations A.22-A.25 directly. As in the first case, since V_{NI} is monotonically increasing, $\overline{V}_{NI} \geq V_{NI0}$. Conversely, note that in the reduced model, T is strictly decreasing over time due to the removal of CD4+ T-cell birth and death rates; it follows that $0 \leq \overline{T} \leq T_0$. Thus, the second steady state of the reduced model is:

$$\begin{cases} 0 \leq \overline{T} \leq T_0 \\ \overline{T}^* = 0 \\ \overline{V}_I = 0 \\ \overline{V}_{NI} \geq V_{NI0} \end{cases} \tag{A.27}$$

The first steady state of the simplified system (equation A.26) suggests that growth in the infectious and non-infectious virus populations slows only as the susceptible T cell population diminishes, eventually resulting in clearance of the susceptible and infected T cell populations with non-zero infectious and non-infectious virus populations at the steady state. This behavior results from the lack of a T cell production rate (i.e., λ, the birth rate of CD4+ T cells) and viral clearance rate (i.e., c) in the simplified model.

Note that the second steady state of the simplified system (equation A.27) is similar to the virus-free steady state of the full model in its clearance of infected CD4+ T cells and infectious virus particles (i.e., $\overline{T}^* = 0$ and $\overline{V}_{NI} = 0$). This implies that the infection has cleared the system, regardless of the non-zero population of non-infectious virus at this steady state. As such, this steady state can be considered the virus-free steady state of the simplified system.