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# Deterministic and Stochastic Models for HIV-1 Dynamics

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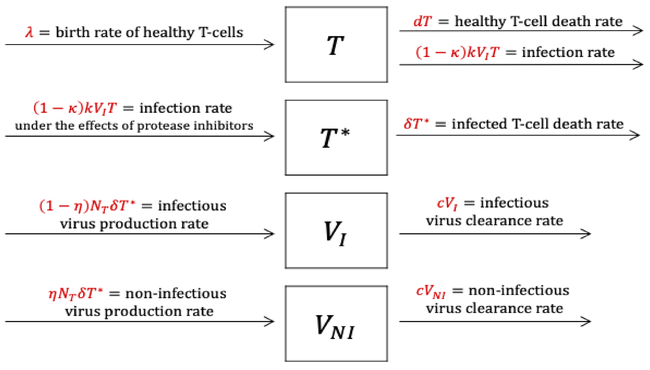
## Abstract

In this research project, I investigated deterministic and stochastic versions of the $T$, $T^*$, $V_I$, $V_{NI}$ model for Human Immunodeficiency Virus Type 1 (HIV-1) dynamics. Numerical techniques are used to obtain an approximate solution to the deterministic model. Patient data is introduced, and numerical methods are used to find an approximate solution to the stochastic system. These results demonstrate the behavior of HIV-1 in an infected patient under the effects of reverse transcriptase and protease inhibitors, and illustrate how the addition of randomness to the constants in the model impact the development of HIV-1 in a given patient.

## Deterministic Model

The model investigated in this project is one that has been a basis for many mathematical studies of HIV-1 Dynamics, and considers four populations: activated CD4+ T cells that are susceptible to infection ($T$), productively infected CD4+ T cells ($T^*$), infectious virus particles ($V_I$) and noninfectious virus particles ($V_{NI}$). The following system of equations represents the change of these populations under the effects of reverse transcriptase (RT) and protease inhibitors:

$$\begin{aligned}\frac{dT}{dt} &= \lambda - dT - (1-\kappa)kV_IT\\ \frac{dT^*}{dt} &= (1-\kappa)kV_IT - \delta T^*\\ \frac{dV_I}{dt} &= (1-\eta)N_T\delta T^* - cV_I\\ \frac{dV_{NI}}{dt} &= \eta N_T\delta T^* - cV_{NI}\end{aligned}$$




Each of the constants in the model ($\lambda$, $d$, $k$, $\delta$, $N_T$, $c$, $\kappa$, and $\eta$) are positive values. The following table contains the values and units of these constants along with their interpretations in the model.

| Parameter | Value | Units | Interpretation |
|---|---|---|---|
| $\lambda$ | 0.1089 | cells per day | Healthy T-cell birth rate. |
| $d$ | 0.01089 | 1 / day | Healthy T-cell death rate. |
| $k$ | $1.179 \times 10^{-3}$ | 1 / (virions · day) | Infection rate of T-cells. |
| $\delta$ | 0.366 | 1 / day | Infected T-cell death rate. |
| $N_T$ | 4246.4 | virions / cell | Virus production rate. |
| $c$ | 3.074 | 1 / day | Viral clearance rate. |
| $\kappa$ | 0.6 | - | RT inhibitor efficacy. |
| $\eta$ | 0.6 | - | Protease inhibitor efficacy. |

## Existence and Uniqueness

Before solving this system, we need to show that a unique system to our initial value problem exists. To do so, we make use of the Picard Lindelöf Theorem.

**Theorem 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 $x(0) = x_0$.

Note that our system of equations is autonomous since it does not explicitly depend on the dependent variable $t$. In our system, let $x$ and $f(x)$ be defined as

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

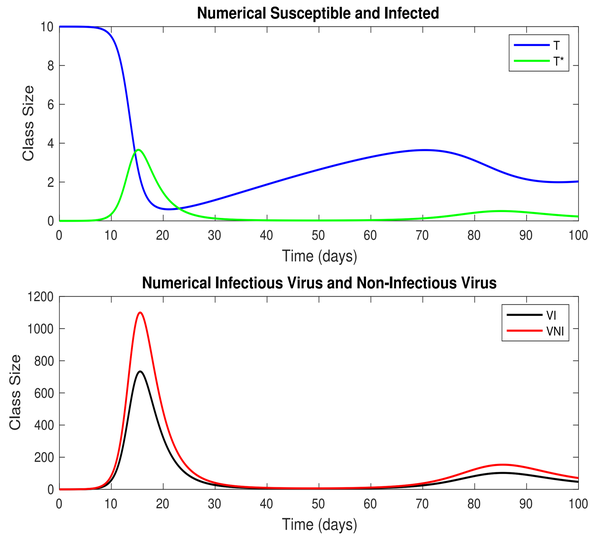
The Jacobian matrix is then given by

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

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 $[0, t^*]$.

## Numerical Solution

Now that we have verified that a unique solution to our system of equation exists, we solve the system using a predictor-corrector method that combines the explicit four-step Adams-Bashforth Method and the implicit three-step Adams-Moulton Method, and uses the Runge-Kutta Method of order four to obtain its starting values.
With initial conditions $T_0 = 10$, $T_0^* = 0$, $V_{I0} = 0.1$, and $V_{NI0} = 0$ and parameter values $\lambda = 0.1089$, $d = 0.01089$, $k = 1.179 \times 10^{-3}$, $\delta = 0.366$, $N_T = 4246.4$, $c = 3.074$, $\kappa = 0.6$, and $\eta = 0.6$, the following approximation was obtained:



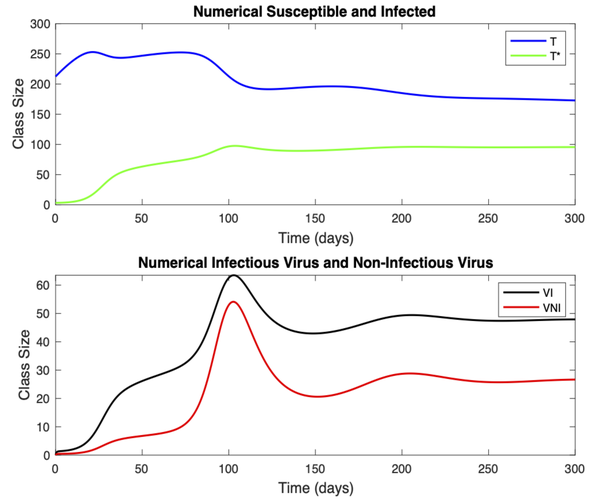

## Stochastic Model

Realistically, the constants and initial values of this model will not have a single, fixed value; they will vary within the population. The use of a stochastic system will take this random variation into account by replacing each of the constants and initial conditions of the model with random variables.
Data for 176 HIV-infected persons was retrospectively collected from medical records of Severance Hospital, South Korea. This data was used to identify the probability distributions of each random variable in the model. The Method of Moments was used to obtain parameter estimates for each of these distributions.

| Random Variable | Estimated Probability Distribution and Parameter Values |
|---|---|
| $T_0$ | Gamma($\alpha = 1.802, \beta = 141.4863$) |
| $T_0^*$ | Exponential($\beta = 0.2413$) |
| $V_{I0}$ | Gamma($\alpha = 0.013898, \beta = 0.26095$) |
| $\lambda$ | Exponential ($\beta = 0.2691$) |
| $d$ | Exponential ($\beta = 135.3297$) |
| $k$ | Gamma ($\alpha = 0.5086, \beta = 0.00796$) |
| $\delta$ | Exponential ($\beta = 51.7362$) |
| $N_T$ | Exponential ($\beta = 0.02015$) |
| $c$ | Gamma ($\alpha = 0.5675, \beta = 29.3465$) |
| $\kappa$ | Uniform ($\alpha = 0.6, \beta = 0.8$) |
| $\eta$ | Uniform ($\alpha = 0, \beta = 0.6$) |

## Monte Carlo Method

For each random variable in the model, $n$ independent random observations $X_1, X_2, \ldots, X_n$ were generated and used to obtain a solution to the model. The expected value of these $n$ solutions is the solution to our stochastic model by the Monte Carlo Method. Below is an example of an approximate solution obtained using the Monte Carlo Method.




| $T_0$ | $T_0^*$ | $V_{I0}$ | $V_{NI0}$ |
|---|---|---|---|
| 82.2732 | 0.1557 | $8.6507 \times 10^{136}$ | 8.7534 |

| $\lambda$ | $d$ | $k$ | $\delta$ | $N_T$ | $c$ | $\kappa$ | $\eta$ |
|---|---|---|---|---|---|---|---|
| 8.7534 | 0.0154 | 0.0016 | 0.1639 | 99.1055 | 3.8313 | 0.7089 | 0.59862 |

This patient has an extremely small amount of infectious virus initially present in the body. However, the high viral production rate ($N_T\delta$) causes the virus concentration to grow fairly quickly. This high viral production rate is then contrasted by a relatively high viral clearance rate ($c$), which causes the virus population to hit a peak and begin to decrease. The behavior of $V_I$ and $V_{NI}$ in this model is similar to the behavior we would expect based on the numerical approximation to the deterministic model seen previously.

## Conclusion

The results of this project display the development of HIV-1 in an infected patient under the effect of reverse transcriptase and protease inhibitors. These results are made more practical with the inclusion of an element of randomness in the stochastic system of equations. Obtaining a solution to the stochastic model using the Monte Carlo Method gives us a better understanding of how HIV-1 Dynamics may change in a given patient due to differences in model parameters caused by the randomness that occurs biologically.

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