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Honors Thesis

A Mathematical Model Describing the Dynamics of HIV Virions and CD4$^+$ T Cells in the
Human Immune System

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Abstract

Human Immunodeficiency Virus (HIV) is an intracellular parasite that attacks cells of the immune system called $CD4^+$ T cells. In ecology the Lotka-Volterra models, a classical set of differential equations, describe three interactions between species in ecosystems: predator/prey, mutualism, and competition. The human body is also an ecosystem with HIV and T cells exhibiting the three Lotka-Volterra interactions with each other. I pose a mathematical model that predicts T cell/HIV dynamics by incorporating the three Lotka-Volterra interactions and other salient biological phenomena that influence the dynamics, such as T cell senescence and the presence of viral reservoirs.

Introduction

Human Immunodeficiency Virus (HIV) is an intracellular parasite that specifically attacks cells of the immune system. Viruses are parasites unable to replicate without a host. The host for HIV is the $CD4^+$ T cell, a lymphocyte (a type of white blood cell) that specializes in the detection of pathogens in the body. Infected T cells eventually die by apoptosis, a programed cellular death or suicide (Alimonti et al., 2003). When sufficient numbers of $CD4^+$ T cells are depleted, the disease has reached the stage of Acute Immunodeficiency Syndrome (AIDS) and the body eventually dies from opportunistic infections (Freeman, 2004).

In-host dynamics refers the temporal effects two species have on each other *in vivo*. Many studies have been done on the in-host dynamics of various microorganisms and viruses in the body. One model suggests the importance of concealed infected cells in the maintenance of HIV infection when the delay models show Hopf bifurcations (Culshaw et al., 2003). Another model demonstrates a feedback that occurs between $CD4^+$ lymphocytes and $CD8^+$ lymphocytes, which is critical during HIV infection, but the model fails to take into account lymphoid cells that are not involved in anti-HIV immune reactions (Dolezal & Hraba, 1996). Other studies have been done on non-specific viral infections, where two variables, the mitosis rate of target cells and the intracellular delay in the viral replication inside a target cell, influence viral infections. The results suggest that mitosis plays a larger role in target-cell dynamics than delays (Li and Shu, 2011). Feng et al. (2008) discuss the contributions of mathematical models to the understanding of HIV dynamics, but note that a further understanding of residual replication, viral latency, and sanctuary sites are necessary to design models that provide better treatment regimen protocols.

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Ecologists use mathematical models depicting the interactions between species to describe the temporal dynamics of biological communities. A classical set of differential equations called the Lotka-Volterra models describe three types of interactions between species: 1) predator/prey, in which the interaction is positive for one species and negative for the other, 2) competition, in which the interaction is negative for both species, and 3) mutualism, in which the interaction is positive for both species (Henson, 2012).

If one considers the term "species" in its broader sense, the human body is an ecological system in which all three types of interactions exist between human cells and pathologic (or beneficial) agents, in this case $CD4^+$ T cells and HIV virions. In particular, T cells and virions have both positive and negative effects on each other. An increase in virion numbers bolsters the immune system's response and consequently increases the number of $CD4^+$ T cells; at the same time, virions kill their host T cells, so an increase in virions also has a negative effect on the number of T cells. An increase in T cells has a negative effect on virions because the increased lymphocytes bolster detection and destruction of the pathogens. An increase in T cells also has a positive effect on virions because virions must replicate in the T cells. Thus, by pairing various types of positive and negative effects, one can consider the $CD4^+$ T cell/HIV virion dynamics to be characterized by predator/prey (both directions), competition, and mutualism.

For example, the Lotka-Volterra model for a predator/prey system is

- $\frac{dx}{dt} = ax - bxy$

- $\frac{dy}{dt} = cxy - dy$

The first equation represents the dynamics of the prey in relation to the predator, where x is the number of prey, y is the number of predators, and a is the intrinsic growth rate of prey. The term ax represents the growth of the prey in the absence of predators. The negative term $-bxy$ denotes

the predation of the prey, where *b* is the predation rate. The second equation illustrates the

dynamics of the predator in relation to the prey. The term *–dy* represents the decrease in the

predator population in the absence of prey. The positive term *cxy* is the growth rate of the

predator in the presence of prey. The fact that the two interaction terms (*–bxy* and *cxy*) have

opposite signs indicates that this is a predator/prey system.

The Lotka-Volterra models for competition and mutualism are similar. In each case,

positive interaction terms increase the focal species and negative terms decrease it. Thus, terms

due to competition are negative whereas terms due to mutualism are positive.

Figure 1A shows the Lotka-Volterra graph of predator/prey dynamics. An increase in

prey eventually leads to an increase in the predators and there is a lag between the two rising

peaks. As the predator numbers increase, the prey population falls. When the prey population has

fallen to a point where there is not an adequate food supply, the predator population falls. With

lowered predator numbers, the prey rebounds and the cycle repeats.

Figure 1B shows typical observed dynamics of HIV virions and CD4$^+$ T cells (ref). Two

features of note in Figure 1B are 1) the time lag between the initial fall of the CD4$^+$ T cells (solid

vertical line) and the peak in the HIV population (dashed vertical line) in the Acute phase of the

diagram and the lag between the fall of the HIV population and rise of the CD4$^+$ T cells as it

progresses to the Chronic phase, and 2) the difference in time scales on the x-axis, with time

initially measured in weeks and then switching to years.

The dynamics shown in Figure 1B are similar to the predator/prey dynamics in Figure

1A. Initially, the T cells act as the predators and the virions act as the prey: note the T cell trough

followed quickly by the virion peak in the acute phase of the graph. In the beginning of the

chronic phase, however, at about week 10-12, the roles are reversed: the virion trough occurs

before the T cell peak, indicating that the virions are the predators and the T cells are the prey. The classical predator/prey dynamics break down in the chronic phase as the virions slowly overwhelm the immune system, causing a terminal depletion of the $CD4^+$ T cells.

The goal of this project was to construct a Lotka-Volterra-type mathematical model for the T cell/HIV system that includes all three ecological interactions as well as other salient biological mechanisms and predicts the observed dynamics in Figure 1B.

Methodology

Model Construction

There are two ways to model a biological system: phenomenologically and mechanistically. A phenomenological model simply reproduces the observed dynamics of a given system. It does not take into account the mechanisms that drive the system and has little or no explanatory power or predictive ability. I have constructed a Lotka-Volterra-type mechanistic model, one that deals directly with the biological mechanisms that influence the system. This model both reproduces the observed dynamics in Figure 1B and conveys significant information on how different variables affect the dynamics between the $CD4^+$ T cells and the HIV virions.

When constructing a successful model, the modeler must ensure the model is both tractable and realistic. A model that focuses too heavily on tractability sacrifices the intended reality of the model. However, a model that is too realistic is not tractable and defeats the purpose of modeling. When modeling, the goal is to construct a model just complicated enough to capture the main dynamics of the system, while ignoring higher order processes. Thus, there are many known details of the T cell/HIV story that I have left out of the model, adding them only as necessary.

Model Analysis and Testing

Initially, I completed an in-depth study of the Lotka-Volterra models, analyzing their graphical properties using phase plane analysis. This classical technique involves the plotting of two species against each other to determine equilibria and stability (Henson, 2012). To graphically analyze the properties of the Lotka-Volterra models, I used the programs "dfield and pplane" (Polking, 2005, Rice University). I then completed a comprehensive literature search for relevant articles that gave information about the in-host dynamics of HIV and T cells. After relevant information had been collected, I created a Lotka-Volterra type mechanistic model that incorporated the three interactions (predator-prey, mutualism, and competition). The model is comprised of two differential equations, one that describes the population of the T cells over time and one that describes the population of the virions over time. The model also describes how these two populations influence each other. Once the model was created, I used the computer program Matlab to numerically simulate the model and study the effect of the parameters on the model. During the modeling process, I searched the literature for salient biological mechanisms that occur in the dynamics and incorporated those in the model as new parameters. I also incorporated temporal submodels for certain parameters. If the given parameters and their values did not reproduce the dynamics, I modified the model by changing the parameters and/or their values.

Results

I initially considered the model

$$
\begin{aligned}
\frac{dT}{dt} &= aT - bTV - eT^2 + fTV \\
\frac{dV}{dt} &= cTV - dV - gTV,
\end{aligned}
\tag{1}
$$

Here dT/dt represents the change in the T cell population (T) in relation to time (t) and dV/dt is the change in virion population (V) in relation to time (t). Parameter a is the intrinsic growth rate of the T cell population, b is the predation rate of HIV on the T cells, c is the HIV/predator growth rate, e is the self-limiting rate of the T cells on themselves, f is the immune response growth rate of the T cells, and g is the immune system related death rate of the virions.

Figure 2A shows the dynamics of model (1) when $a = 0.4$, $b = 0.001$, $c = 0.005$, $d = 0.3$, $e = 0.002$,

$$f = \begin{cases} 0 \ if \ t < 12 \\ 0.008 \ if \ t \geq 12, \end{cases} \tag{2}$$

and

$$g = \begin{cases} 0 \ if \ t < 7.1 \\ 0.0025 \ if \ t \geq 7.1. \end{cases} \tag{3}$$

Figure 2A and Figure 1B show similar dynamics during the acute stage of the infection but different dynamics during the chronic stage. In particular, both show an initial decline in the T cell population and increase in the virion population with the T cell trough occurring before the virion peak. Both figures show the T cell population then increasing to a peak while the virion population decreases to a trough that occurs before the T cell peak. During the chronic stage, Figure 1B shows the T cell population becoming extinct and the virion population growing. Figure 2A, however, shows both populations approaching a positive equilibrium.

Figure 2B shows the dynamics of model (1) with

$$a = \begin{cases} 0.4 \ if \ t < 12 \\ 0.2 \ if \ t \geq 12, \end{cases} \tag{4}$$

$b = 0.001$, $c = 0.005$, $d = 0.3$, $e = 0.002$, and f and g as in equations (2)-(3). Figure 2B and Figure 1B are similar in that the first T cell trough occurs before the virion peak. In Figure 2B, however,

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there is a decline to extinction in the virion population, whereas in Figure 1B the virion

population increases and persists indefinitely.

I next considered the model

$$\frac{dT}{dt} = aT - bTV - eT^2 + fTV$$
$$\frac{dV}{dt} = cTV - dV - gTV + hVR$$

(5)

in which h represents the viral growth rate due to the presence of a reservoir R.

Figure 2C shows the dynamics of model (5) with $a = 0.4$, $b = 0.001$, $c = 0.005$, $d = 0.3$, e

$= 0.002$, $h = 0.001$, $R = 100$, and f and g as in equations (2)-(3). Figure 2C and Figure 1B show

similar dynamics during the acute stage of the infection but different dynamics during the

chronic stage. In particular, both show an initial decline in the T cell population and an increase

in the virion population with the T cell trough occurring before the virion peak. Both figures

show the T cell population then increasing to a peak while the virion population decreases to a

trough that occurs before the T cell peak. However, in Figure 2C the virion trough never dips

below the T cell peak. During the chronic stage, Figure 1B shows the T cell population becoming

extinct and the virion population growing indefinitely, whereas Figure 2C shows both

populations approaching positive equilibria.

I finally considered the model

$$\frac{dT}{dt} = aT - bTV - eT^2 + fTV - iTV$$
$$\frac{dV}{dt} = cTV - dV - gTV + hVR$$

(6)

in which i represents the T cell senescence rate.

Figure 2D shows the dynamics of model (1) when $a = 0.4$, $b = 0.001$, $c = 0.005$, $d = 0.3$, e

$= 0.002$, $h = 0.001$, $i = 0.001$, $R = 100$, and f and g as in equations (2)-(3). Figure 2D and Figure

1B show similar dynamics during the acute stage of the infection but different dynamics during

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the chronic stage. In particular, both show an initial decline in the T cell population and increase in the virion population with the T cell trough occurring before the virion peak. Both figures show the T cell population then increasing to a peak while the virion population decreases to a trough that occurs before the T cell peak. In Figure 2D the virion trough dips below the T cell peak, although not to the same extent as in Figure 2A. During the chronic stage, Figure 1B shows the T cell population becoming extinct and the virion population growing indefinitely, whereas Figure 2A shows both populations approaching positive equilibria.

Discussion

Simulations of model (1) yielded the most realistic dynamics (compare Figures 1B and 2A), suggesting that all three ecological interaction terms play a role in the observed in-host dynamics of HIV and T cells.

Figure 2B illustrates that diminishing the intrinsic growth rate of T cells caused extinction of the virion population. This counterintuitive but intriguing result may be due to the attendant decrease in virion reproductive sites. In this early stage, the immune system is able to mount a strong immune defense on virions circulating in the plasma. Furthermore, with fewer viral replication sites, HIV cannot mutate as rapidly and may not have time to evolve the novel surface proteins which normally impede immune response. Thus, HIV may be subject to effective immune system detection and eradication.

The incorporation of a reservoir term (Figure 2C) produced less realistic model simulations, although the additional incorporation of a T cell senescence term (Figure 2D) improved the simulation results. Although I investigated many parameter combinations, it is important to note that I did not fit the model to data, and hence it is possible that some optimal parameter set may produce more realistic results than those shown in Figure 2D.

Further improvements in model accuracy likely will require refinements in mechanisms related to end-stage dynamics and initial dynamics. For example, to improve accuracy in the initial dynamics one might consider two additional mechanisms: 1) the eclipse phase and 2) immunosuppression. The eclipse phase is the time between initial infection and the first detection of viral RNA in the plasma. The virus population grows exponentially, peaks 21-28 days after infection begins, and viral reservoirs form (Borrow et al., 2010). Immunosuppression is when HIV-produced microparticles have immunosuppressant effects on T cells and macrophages. This causes suppression of the immune system and establishes the chronic phase of infection (Crossman & Gasper-Smith, 2008). A model that incorporates the eclipse phase, immunosuppression, and salient end-stage mechanisms may yield more accurate dynamics.

Conclusion

Lotka-Volterra-type differential equation models incorporating the three ecological interactions of predator/prey, competition, and mutualism can reproduce the in-host dynamics of the HIV/T cell system. Such models can serve as templates for constructing testable hypotheses regarding the effects of various biological mechanisms and interventions on the HIV/T cell system, and may assist in the determination of better treatment options.

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Figure Captions

Figure 1. A. Lotka-Volterra simulation of predator/prey interactions. After Huffaker (1958). B. Observed dynamics of CD4$^+$ T cells and HIV (Bartlett & Moore, 1998).

Figure 2. A. Model (1) with submodels (2)-(3) and $a = 0.4$; $b = 0.01$; $c = 0.005$; $d = 0.3$; $e = 0.002$. B. Model (1) with submodels (2)-(4). A reduction in a, the intrinsic growth rate of the T cells, after 12 weeks leads to an extinction in the virion population. C. Model (5) with submodels (2)-(3) and $a = 0.4$; $b = 0.01$; $c = 0.005$; $d = 0.3$; $e = 0.002$; R = 100. D. Model (6) with submodels (2)-(3) and $a = 0.4$; $b = 0.01$; $c = 0.005$; $d = 0.3$; $e = 0.002$; $h = 0.001$; $i = 0.001$; $R = 100$.
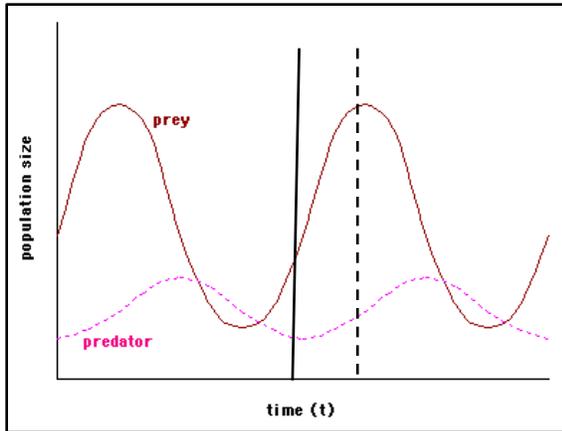
Figure 1A

Figure 1B

SOURCE: Anthony Fauci et al. in Annals of Internal Medicine, Vol. 124; 1996

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Figure 2A

Figure 2B

Figure 2C

Figure 2D