Modeling of HIV and CTL Response

Catherine Tran
Diana Lubyanaya

Advisors: Dr. Dominik Wodarz* and Dr. Frederic Wan**

*Department of Ecology and Evolutionary Biology
**Department of Mathematics
University of California, Irvine

August 17, 2013

Abstract

Our research focuses on the study of HIV cell dynamics in healthy bodies and the immune response. Our goal is to create a mathematical system that models the dynamics between the immune system's CTL cells and HIV with the complications of time delay between infection and response. The expansion of the model allows our method to reflect a more realistic biological system. Varying the parameters in the simulations within the system will help us understand and predict the behavior of the CTL response and the potential viral long-term nonprogression.

1 Background

1.1 What is HIV?

HIV, also known as human immunodeficiency virus, is a infectious immune dieases that affects, according to the CDC, "about 1.1 million people in the United States [in 2008]" where "about 50,000 people get infected each year". The HIV disease is a serious health issue worldwide affecting "34.2 million people" (CDC). HIV dynamics with the immune system is different from any other virus in that it affects the immune system directly by attacking the CD4 T cells, also know as Helper T cells. CD4 T cells are cells in the immune system that plays a key role in identifying foreign bodies and infected cells in the body. These virions and infected cells are consumed by a macrophage, which tags itself for distruction. The CD4 T cells identify these protein tags on the macrophage and produce cytokines that stimulates production of beta cells and CTL cells, also known as Killer T cells. Just as it's nickname implies, CTL cells are the actual cells that connect with the macrophages and injects chemicals that denatures the foreign body and exterminates the infection.

1.2 HIV Lifecycle

HIV virons attaches to CD4 T cells through connecting particular co-receptors found on the CD4 T cell membrane, thus allowing them access into the cell. The viron then goes to fuse with the cell releasing its DNA and replication mechanics into the cell. From there, the virus replicates its DNA through reverse transcription where a reverse transcriptase and intergrase proteins regenerates the virus's DNA and incoporates it into the cell's DNA. The cell will unknowingly continue to reproduce it's own DNA along with the virus DNA. This process

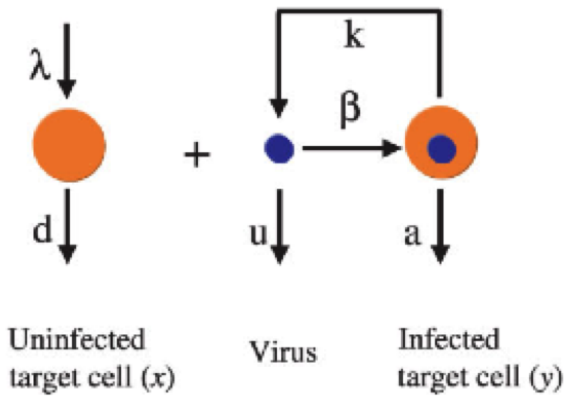

Figure 1: Basic Virus-Cell Dynamics
This diagram illustrates the situation where the uninfected cells are exposed to the virus, resulting in an infection. The infection is based on given parameters that express the life, interaction, and death of the virus-cell components.

may remain asympotmatic for many years, ten year on average, allow the infection to spread and remain undetected. After the virus's DNA has been translated into protein strings, an enzyme known as protease will cut these long HIV protein chains into individual proteins that, combined with the virus's DNA, can assemble into a new virus. The virus will then push itself out of the host cell taking parts of its membrane along with it and go on to infect other cells.

The most intericate part of this cycle for HIV viruses in particular is by infect CD4 T cells, it reduceds the number of CTL stimulators and thus weakens the body's immune response towards fighting off the virus. When the virus become pathogenic and the CD4 T cell count drops, the diagnosis of AIDS is given

2 Introduction

The interactions between the virus and a host cell vary significantly based on fluctuating ingredients and manipulations within the system. These changes and alterations can be best recorded by the method of mathematical modeling. This method allows us to monitor the infection with wavering alterations and analyze the potential characteristics of the virus. The modeling technique exposes diverse states of equilibria that help further investigation of virus-cell dynamics.

3 Modeling

3.1 Basic Virus-Cell Dynamics

As a component of a basic model technique, we begin with a simple construction of a healthy cell and virus interaction that produces an infected cell. First, the development of a normal healthy cell (x) is denoted as 'λ', growth rate, and 'd', for death rate. Second, the growth rate of the virus (v) depends on k, which is the quantity produced by an infected cell, and the death rate 'u'. Finally, the interaction of the two systems results in an infected cell (y) that grows at rate 'β' and dies at rate 'a'. The following is the mathematical representation of the model:

$$\begin{aligned} dx/dt &= \lambda - dx - \beta xv \\ dv/dt &= ky - uv \\ dy/dt &= \beta xv - ay \end{aligned} \tag{1}$$

This mathematical model illustrates only minimal guidelines, far from reality; however, it depicts simple concepts that we can use in our future analysis. For example, one important concept is the Reproductive number (R$\circ$). It allows us to understand and predict the behavior of the system, whether it approaches potential decay or an epidemic. Another aspect is finding the critical points that depict the equilibrium of the system. The new equilibria states will allow us to build and expand on our model for a more realistic point of view.

3.2 Virus-Cell Dynamics with CTL Response

Because the previous model lacks the immune response, we introduce a new variable z, which represents the CTL response that grows at rate c and dies at rate d. A new parameter p represents the kill rate of infected cells that are interacted with CTL. In addition to the new variable, we combine

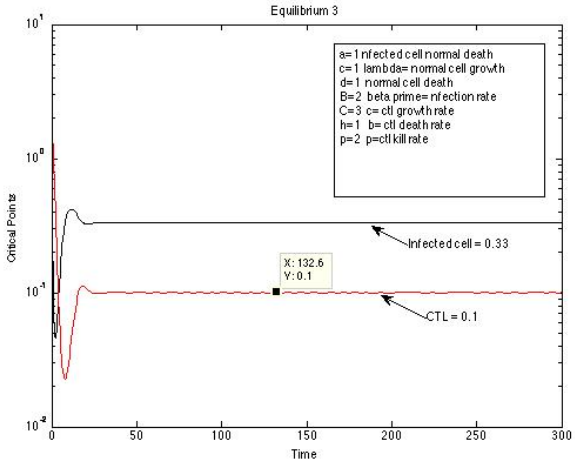

Figure 2: Infected cells and CTL steady states.
These steady states allow us to understand the behavior of the system and expand our model to account for further complexities.

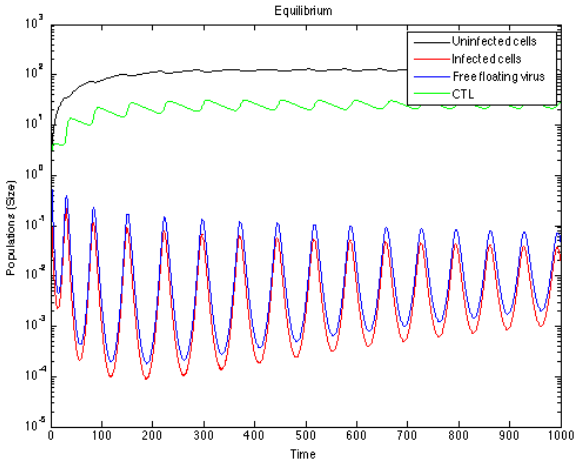

Figure 3: Basic Virus-Cell Dynamics with CTL
This graph portrays the system's oscillatory behavior that resembles the interactions within the process of infection.

the infected cell and virus into one category y because they are directly proportional in terms of the infection process. Hence, we have a new parameter $\tilde{\beta}$ that represents $\beta k/u$ and our new model results in the following:

$$\begin{aligned} dx/dt &= \lambda - dx - \tilde{\beta}x(ky/u) \\ dy/dt &= \tilde{\beta}x(ky/u) - ay - pyz \\ dz/dt &= cyz - bz \end{aligned} \tag{2}$$

Now we have the full system that incorporates both, the viral infection and the immune response. Our next step is to examine the steady states where the system reaches an equilibrium by setting the variable rates equal to zero. The expressions result in constants that we can manipulate by varying the parameters and evaluate the results.

4 Time Delay

4.1 Biological Perspective

In the biological system, the virons and immune system response are not free floating and originate from specific locations. For the most part, weak virons only are located at the site of infection or in the blood system, where leukocytes, also known as white blood cells, fend off the body. With stronger virons, the infected cells and free virons mainly exist in the bloodstream and only after the numbers increae through replication and out numbering the leukocytes do the infected cells travel on to invade the lymphatic system .

CD4 T Cells along with majority of the immune system response originates from the lymph nodes. The CD4 T cells are consistently produced at this site however they are not actively stimulating production of CTL nor beta cells unless they come in contact with an infected cell. This is due to the need for the body to conserve energy and resources, which is used in the production, and as a safety precaution against the denaturing ability of CTL cells. Because these CD4 T cells and its response production is housed in the lymphatic system, the system remains inactive until the infected cell or viron reaches and is identified by CD4 T cells. During intial stages of infection, when the viron is identified by the leukocytes, some are consumed and digested while a small portion is engulfed in macrophages that are sent to the lymph node to help stimulate production of CTL cells. From there, the CTL cells travel down to the site of infec-

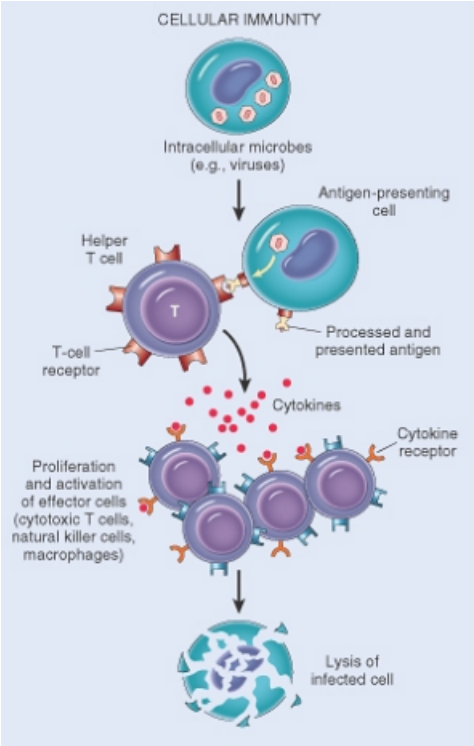

Figure 4: Biological System with CTL Compartments. This illustration shows the process by which the CTL operates when the infection is detected. Understanding the behavior of the CTL response will help generate the model of CTL memory and long-term nonprogression of HIV

tion to fight off the virons. After the CTL cells finish, they travel back to the lymph node and are changed into memory cells. Memory cells are similar to CTL cells, in terms that they are still cells that are used to fight off infection, however these cells are specialized in terms of virons they fight off and remain inactive until it is re-exposed to the viron.

Following the immune dynamic, there are expected time delay that account of spread and travel time between the time of infection and time of immune response and production of CTL cells. In terms of modeling, we seperated the traveling infected cell population and the traveling CTL cells from that of the rest of its population. We based the time delay model off of location, subscripting the traveling infected cell as y_L when they are located in the lymph node and the stationary CTL cells in the lymph node as z_L.

4.2 Basic Time Delay

For a basic time delay model, we began with our basic model with CTL and add the two now seperated population of CTL cells and infected cells that resign in the lymph node. To simply the model, we make the assumption that the rate of population change for the infected cells in the lymph node are proportional to the point where we can assum them to be equal to one another and thus we subsitute the infected cells in the lymph node population, (y_L), with the infected cell at the infection site population, y.

Biologically, this assumption means that we assume the travel time for infected cells from the site of infection to the lymph node to be instantaneous. However, we still include the time delay between the CTL cells from lymph node to site of infection. Because the CTL cells and the HIV-infected cell rely on each other to for in terms of production and there are some time delay in between the two, we can assume this model to resemble the Lotka- Volterra Model. These hypothesis is proven true as the system displays intial ocsillatory behavior prior to reaching equalibrium.

$$\begin{aligned} dx/dt &= \lambda - dx - \tilde{\beta}x(ky/u) \\ dy/dt &= \tilde{\beta}x(ky/u) - ay - pyz \\ dz/dt &= fyz_L - bz - hz \\ dz_L/dt &= cyz_L - b_L z_L - fyz_L + hz \end{aligned} \tag{3}$$

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4.3 Expanded Time Delay

Now that a working time delay model has been established, we reopen the infected cell in lymph node population and assume that the rate of change of infected cell population size at the two seperate locations are not proportional, thus expecting some

delay that accounts for spread and travel time.

$$\begin{aligned} dx/dt &= \lambda - dx - \beta\prime xv \\ dy/dt &= \beta\prime xv - ay - pyz \\ dz/dt &= fyz_L - bz - hz \\ dz_L/dt &= cyz_L - b_L z_L - fyz_L + hz \\ dy_L/dt &= gy - uy_L \end{aligned} \tag{4}$$

5 Revised Time Delay

Because infected cell and virus population change of rate are proportional, we were able to simplify and condense the model in which we ignore the virus population. With this new alteration, we calculated what our intended equilibrium was and ran computer simulations to test this theory. After seeing that both the calculated equilibrium matched the the theoretical computer simulations, we continued to further expand upon this model, changing it to a more spatial location based model with the inclusion of time delay to account for travel time and infection time offsets. In order to establish this model, we broke up the CTL cells and the infected cell population, as both population rates are initially delayed and affected by travel and spread. This model, however, did not reflect that of a realistic biological system as it is not the infected cells that spread the infection but the free virons that do so. In order to account for this we re-included the virus population in the dynamic and expanded upon the CTL population as three main components that are involved with the process: antigens, CTL precursor and CTL effectors. With these new compartments, we were able to establish a mechanism that accounted for sensory activation, attack and memory.

$$\begin{aligned} dx/dt &= \lambda - dx - \beta xv \\ dy/dt &= \beta xv - ay - pyz \\ dv/dt &= ky - uv - \alpha v \\ dz/dt &= \gamma wv - bz - \mu z \\ dv_o/dt &= \alpha v - u_o v_o \\ dw/dt &= cv_o w - b_1 w - \gamma wv + \mu z \end{aligned} \tag{5}$$

After developing this model, we ran a realistic range of parameters found from Alan S Perelson's collection of papers on the estimates of HIV infection parameters.

6 Conclusion

From our research, we were able to find a working model of the HIV and CTL Response dynamic with the inclusion of time delay that is seen in most biological systems. We hope to further expand our research by building upon this model in the future with the inclusion of other biological processes and complications.

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