T-Cells in the Presence of HIV (Part 2 of 2)

Step I – Background

Perelson, Kerschner, and DeBoer [4] have presented a model for the interaction of T-cells and HIV. In the project "Normal T-Cells" we learned how T-cells function in a healthy individual. In this project we will see some of the changes that are needed to model T-cells when the HIV is present in the body. This discussion is more difficult than the previous one. Thinking about the biological interpretation of each term should help you understand the full model. The final qualitative results should be consistent with what you know about T-cells, HIV, and AIDS.

This project has a slightly different structure than most of the others. The general idea is to explain a biological theory. Mathematical problems will be encountered, formulated, solved, and interpreted throughout this investigation. It might be even more informative if you compared this discussion with the discussion found in the original paper.

Step II – The Basic Model

The HIV virus attacks various types of T-cells. The T-cells are able to fight this invasion for a period of time, but eventually cannot withstand the onslaught. As a result, the immune system becomes less effective at fighting diseases (including the spread of HIV). The models presented in this section of the project will incorporate some of the forces involved in this process.

The first difference is that it is now necessary to include v, the amount of HIV, in our analysis. Also, there will be a distinction between T-cells that are not infected, T, T-cells that are latently infected, T_L, and the T-cells that are actively infected, T_A. (Latently infected T-cells are those that are infected with the provirus and are not producing free virus; actively infected T-cells are infected and are producing free virus.)

A different differential equation will be needed for each of v, T, T_L, and T_A. Thus, the complete model will be a system of four differential equations. This system will be assembled by considering each of the four populations separately.

First, the normal T-cells. These cells are produced and die according to the processes identified in the earlier project. In addition, interactions between uninfected T-cells and the virus transfer some normal T-cells into latently infected T-cells. Thus, $\dfrac{dT}{dt} = R_T(t, T, T_L, T_A, v)$ where

$$R_T(t, T, T_L, T_A, v) = s + rT\left(1 - \frac{T + T_L + T_A}{T_{max}}\right) - \mu T - k_1 vT.$$

Explain the change in appearance of the numerator of the logistic term?

Next, the latently infected T-cells population is increased as normal T-cells interact with HIV and decrease due to both natural death and by transfer to actively infected T-cells. The differential equation for T_L is, therefore: $\dfrac{dT_L}{dt} = R_{T_L}(t, T, T_L, T_A, v)$ where

$$R_{T_L}(t, T, T_L, T_A, v) = k_1 vT - \mu T_L - k_2 T_L.$$

The actively infected T-cells population grows due to conversion of latently infected T-cells and decreases due to viral replication. If the rate at which viral replication leads to lysis is denoted by b, then the model for these cells is: $\dfrac{dT_A}{dt} = R_{T_A}(t, T, T_L, T_A, v)$ where

$$R_{T_A}(t, T, T_L, T_A, v) = k_2 T_L - bT_A.$$

The viral population is assumed to grow at a rate proportional to the death rate of the actively infected T-cells (with constant of proportionality N). The only ways in which free virions are removed is by combination with uninfected T-cells or by clearance from the body. The equation for the virus will be: $\dfrac{dv}{dt} = R_v(t, T, T_L, T_A, v)$ where

$$R_v(t, T, T_L, T_A, v) = NbT_A - k_1 vT - av.$$

Step III – Understanding the Parameters and Checking the Model

The biological interpretations of each of the parameters was explained when it was introduced. However, the units of each parameter have not been discussed. Assuming each of the three T-cell populations and the virus population is measured in cells per cubic millimeter and time is measured in days, determine the units of each parameter.

A realistic numerical value for each of the new parameters is: $b = 0.24$, $a = 2.4$, $k_1 = 2.4 \times 10^{-5}$, $k_2 = 3 \times 10^{-3}$, and $N = 1400$.

The appropriateness of the model that has just been constructed would be seriously compromised if any of the populations could become negative (when starting from non-negative initial conditions).

Consider the the uninfected T-cell population. The only way this can ever become negative is for $dTdt < 0$ at some point when $T = 0$. Now, if $T = 0$, then $dTdt = R_T(t, 0, T_L, T_A, v) = s$ and we see that $s > 0$ assures that the uninfected T-cell population can never be negative.

Determine conditions which guarantee that none of T_L, T_A, and v can ever be negative.

Step IV – Steady-State Analysis

The qualitative analysis will focus on two key issues:

- what is the infected steady-state?
- how does an initial infection evolve towards the steady-state solution?

Prior to answering these questions, it is important to understand the importance of these questions. First, it is possible that the onset of AIDS might be avoided if the infected steady-state occurs with a sufficiently high level of uninfected T-cells. The second question is important because even if the steady-state does not provide enough T-cells to balance the virus, it is possible that the evolution to the steady-state would not be completed within the (normal) lifetime of the patient.

Using the given values of the parameters, find all physically realistic steady-state solutions to the system of four ODEs.

One of these steady-state solutions is the steady-state solution for the uninfected case. The other has a reduced T-cell level (well below the normal range) and a fairly high concentration of HIV.

To conclude, let's examine the evolution of the solution to this steady-state solution. Using initial values of $T = 1000$, $T_L = T_A = 0$, and $v = 0.001$, create one plot showing T_L, T_A, and V during the first 150 days of the infection. (Two timesteps per day should provide enough resolution to create a reasonable graph.)

Create a separate plot showing the evolution of T. Why is the uninfected T-cell population not included in the original plot?

Note the dramatic initial decrease in the concentration of the free virus. Which term in the equation for v is responsible for this behavior? What is the biological explanation of this?

Note that the solution is very close to the virus-free steady-state solution. While it is possible that the solution will converge to this solution, unfortunately, this does not occur.

Next, continue the calculations until the solution converges to its steady-state solution. When did the uninfected T-cell population first drop below the normal range for a healthy individual? How much longer does it take for the solution to converge to a steady-state solution. Is it likely that this transition will occur during the patient's lifetime?

<u>Step V</u> – Concluding Remarks

The model developed in this problem is consistent with the current understanding of the transition from infection with HIV to the onset of AIDS. That is, immediately after infection there is an enhanced level of infected T-cells. After only a few days these levels become so low that they are undetectable by the typical testing procedures. During this period, the normal T-cell population is strong enough to combat the virus. However,the level of T-cell production cannot be maintained forever. At this point the T-cell concentration drops to a fraction of the necessary level. AIDS is now very likely to be detected.

While the overall picture presented by this model is rather bleak, there are some bright spots. In particular, this model suggests that the onset of AIDS can be delayed if healthy T-cell production can be extended. This is the idea behind some of the drugs already being tested and used for the "treatment" of AIDS.

Bibliography

[1] Greene, W.C., *AIDS and the Immune System*, Scientific American, September 1993 (Special Issue).

[2] Herod, J.V., *A Model for an HIV Infection*, Maple Technical Newsletter, **10**, 1993, pp. 72–78.

[3] Herod, J.V., E.K. Yeagers, *Mathematics, Biology, and Maple*, Maple Technical Newsletter (Special Issue), 1994, pp. 69–76.

[4] Perelson, A.S., D.E. Kerschner, R. DeBoer, *Dynamics of HIV Infections of* $CD4_+$ *T-Cells*, Mathematical Biosciences, **114**, 1993, pp. 81–125.