4.2 Numerical Analysis

Perelson's model is sufficiently complex to allow extended analysis well beyond the scope of this Module. Rather than seeking exact solutions analytically, we follow Perelson et al. [1993] and use Mathematica to obtain approximate numerical solutions to this system.

Table 1 gives the initial and constant values (based on experimental data) used in our numerical simulations. We focus on how the value of N (the number of infectious virus particles produced per actively infected cell) affects the long-term T-cell concentration.

In **Figure 3** (see the **Appendix** for the Mathematica commands to generate this figure), with $N = 500$, we see that the uninfected T-cell level approaches a steady-state concentration of $T_{\text{uninfected}}$= 1000 cells mm^{-3} after about 150 days.

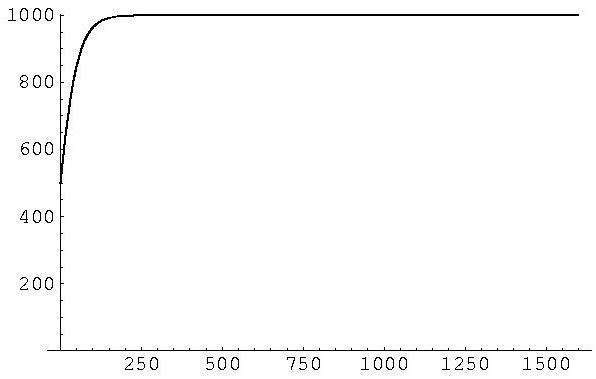

Figure 3. $T(t)$ converges to the stable equilibrium value $T_{\text{uninfected}} = 1000$ when $N = 500$.

Investigating sensitivity of the system to changes in the parameter N, we find that a small increase in N does not affect this steady-state concentration. However, if we increase N to 1400, the stable steady-state concentration decreases dramatically to about 580 cells mm^{-3} (**Figure 4**).

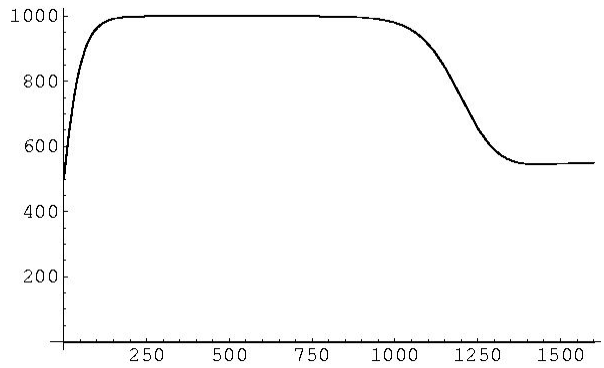

Figure 4. When $N = 1400$, the equilibrium value $T_{\text{uninfected}} = 1000$ is unstable but the equilibrium value $T_{\text{uninfected}} = 580$ is stable.

If we continue to increase the value of N, the steady-state concentration will continue to decrease. This suggests that there is a critical value of N

beyond which there is an important change in the stable steady-state values of T. We now gain insight into this numerical observation by means of equilibrium stability analysis.

4.3 Equilibrium Analysis

Analytical methods are helpful to clarify these numerical observations about the steady-state concentration of T in relationship to N. In the computations that follow, we observe the coexistence of two different steady-state values of T:

- $T_{\text{uninfected}}$, corresponding to $V = 0$ and having a constant value of 1000 independent of N; and
- T_{infected}, corresponding to $V \neq 0$, and having a value inversely related to N.

Furthermore, there is a critical value N_{crit} (called a *bifurcation point*) such that for $N < N_{\text{crit}}$, the steady-state value $T_{\text{uninfected}}$ is stable, and for $N > N_{\text{crit}}$, the steady-state value T_{infected} is stable.

The steady states $T_{\text{uninfected}}$ and T_{infected} are obtained from Perelson's immunological model as follows:

$$\frac{dT}{dt} = 0 \quad \Longrightarrow \quad s + rT\left(1 - \frac{T + T^* + T^{**}}{T_{\max}}\right) - \mu_T T - k_1 TV = 0, \qquad \textbf{(25)}$$

$$\frac{dT^*}{dt} = 0 \quad \Longrightarrow \quad T^* = \frac{k_1}{\mu_{T^*} + k_2}\, TV, \qquad \textbf{(26)}$$

$$\frac{dT^{**}}{dt} = 0 \quad \Longrightarrow \quad T^{**} = \frac{k_2}{\mu_{T^{**}}}\, T^* = \frac{k_2 k_1}{\mu_{T^{**}}(\mu_{T^*} + k_2)}\, TV, \qquad \textbf{(27)}$$

$$\frac{dV}{dt} = 0 \quad \Longrightarrow \quad N\mu_{T^{**}} T^{**} - k_1 TV - \mu_V V = 0, \qquad \textbf{(28)}$$

$$\Longrightarrow \quad \left[\left(\frac{Nk_2k_1}{\mu_{T^*} + k_2} - k_1\right) T - \mu_V\right] V = 0. \qquad \textbf{(29)}$$

The uninfected steady state $T_{\text{uninfected}}$ is obtained by taking $V = 0$ in **(29)**, in which case from **(26)** and **(27)** we have $T^* = T^{**} = 0$; and from **(25)**, we have

$$s + (r - \mu_T)T - \frac{r}{T_{\max}}\, T^2 = 0.$$

Solving the quadratic equation gives

$$T_{\text{uninfected}} = \frac{T_{\max}}{2r}\left(r - \mu_T + \left[(r - \mu_T)^2 + \frac{4sr}{T_{\max}}\right]^{1/2}\right).$$

Using the parameter values given in **Table 1**, we have $T_{\text{uninfected}} = 1000$.

The infected steady state T_{infected} is obtained from **(29)** with $V \neq 0$, so that

$$T_{\text{infected}} = \frac{\mu_V}{\frac{Nk_2k_1}{\mu_{T^*} + k_2} - k_1}.$$

In this case, we find that T_{infected} is a decreasing function of N.

To determine the stability of $T_{\text{uninfected}}$ and T_{infected}, we must extend slightly the method introduced for a two-dimensional nonlinear system at the end of **Section 3.4**. Observe that the Perelson model is a four-dimensional system:

$$\begin{aligned}
\frac{dT}{dt} &= f_1(T, T^*, T^{**}, V),\\
\frac{dT^*}{dt} &= f_2(T, T^*, T^{**}, V),\\
\frac{dT^{**}}{dt} &= f_3(T, T^*, T^{**}, V),\\
\frac{dV}{dt} &= f_4(T, T^*, T^{**}, V).
\end{aligned}$$

Let $\Gamma_{\text{eq}} = (T_{\text{eq}}, T^*_{\text{eq}}, T^{**}_{\text{eq}}, V_{\text{eq}})$ be an equilibrium point satisfying $f_1(\Gamma_{\text{eq}}) = f_2(\Gamma_{\text{eq}}) = f_3(\Gamma_{\text{eq}}) = f_4(\Gamma_{\text{eq}}) = 0$. The equilibrium point Γ_{eq} is stable if all nearby solutions (i.e., those with $\big(T(0), T^*(0), T^{**}(0), V(0)\big)$ sufficiently close to Γ_{eq}) approach Γ_{eq} as $t \Longrightarrow \infty$. To determine whether Γ_{eq} is stable, we compute the Jacobian matrix

$$\begin{pmatrix}
\dfrac{\partial f_1}{\partial T} & \dfrac{\partial f_1}{\partial T^*} & \dfrac{\partial f_1}{\partial T^{**}} & \dfrac{\partial f_1}{\partial V}\\[2ex]
\dfrac{\partial f_2}{\partial T} & \dfrac{\partial f_2}{\partial T^*} & \dfrac{\partial f_2}{\partial T^{**}} & \dfrac{\partial f_2}{\partial V}\\[2ex]
\dfrac{\partial f_3}{\partial T} & \dfrac{\partial f_3}{\partial T^*} & \dfrac{\partial f_3}{\partial T^{**}} & \dfrac{\partial f_3}{\partial V}\\[2ex]
\dfrac{\partial f_4}{\partial T} & \dfrac{\partial f_4}{\partial T^*} & \dfrac{\partial f_4}{\partial T**} & \dfrac{\partial f_4}{\partial V}
\end{pmatrix},$$

where all the partials are evaluated at Γ_{eq}. If all the eigenvalues have a negative real part, then the equilibrium Γ_{eq} is stable; if any of the eigenvalues have a positive real part, the equilibrium is unstable. In **Exercises 6** and **7**, you are asked to use this method to verify that the stability of the uninfected equilibrium solution changes for the values of N corresponding to **Figure 3** and **Figure 4**. (For the latter, it turns out that two of the eigenvalues are negative and one positive. This explains why the plot of $T(t)$ in **Figure 4** first rises and remains near the equilibrium level of 1000 before dropping sharply.)

Perelson et al. [1993] prove that the coexisting steady states exchange stability as N crosses the bifurcation value $N_{\text{crit}} \approx 774$. Perelson's model provides a nice example of the exchange of stability of equilibria known as a *transcritical bifurcation* (see **Figure 5**).

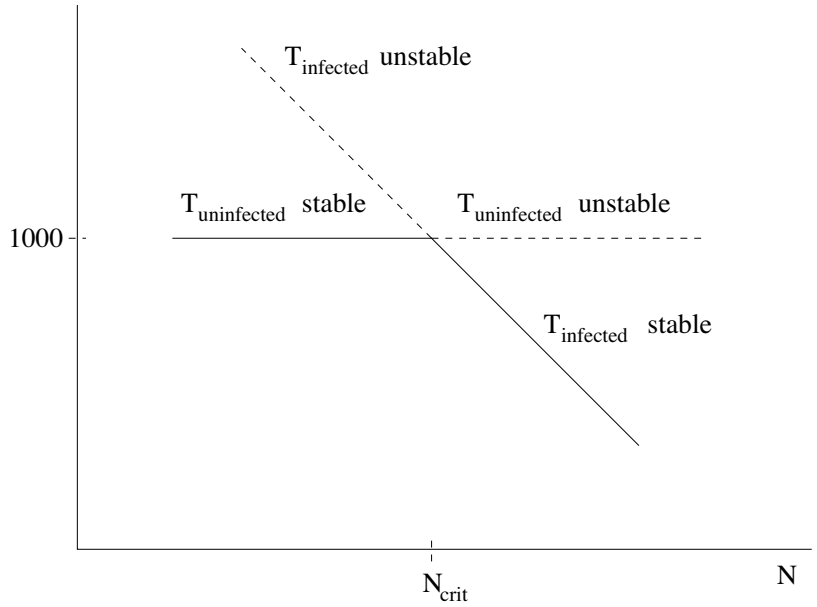

Figure 5. In the Perelson immunological model, a transcritical bifurcation occurs in which the two equilibrium solutions with $T = T_{\text{uninfected}}$ and $T = T_{\text{infected}}$ exchange stability as the parameter N crosses a critical value $N_{\text{crit}} \approx 774$.

Exercises

6. Compute the Jacobian matrix for the functions f_1, f_2, f_3, f_4 given by the Perelson model **(21)–(24)**.

7. Show that the equilibrium $T_{\text{uninfected}} = (1000, 0, 0, 0)$ is stable when $N = 500$ and unstable when $N = 1400$.

4.4 Chemotherapy Treatment

An important part of mathematical modeling is *sensitivity analysis*, which investigates how the system behavior is affected by a change in one or more of the model parameters or initial conditions. We have already seen one example of this type of analysis related to the transcritical bifurcation value for the parameter N.

Modeling the possible efficacy of chemotherapy treatment with antiretroviral drugs can be regarded as an extended form of sensitivity analysis. We would like to study changes in parameters that effectively delay or perhaps even eliminate altogether the onset of AIDS:

Drug Target What are the key parameters with greatest effect on the onset of AIDS? Can drugs be designed to alter those parameters favorably?

Drug Potency How much does a key parameter need to be changed in order to make a substantial difference in patient history? Can a drug accomplish this degree of parameter change?

Treatment Duration How long does a key parameter need to be changed in order to make a significant difference in patient history?

Two of the key parameters that might be targeted by chemotherapy are:

- the rate k_1 at which healthy T-cells become latently infected T-cells; and/or
- the number N of free viral cells created upon lysing of a healthy T-cell.

Four main classes of antiretroviral drugs are in use. All affect either the value of N or that of k_1.

- NRTIs, NNRTIs, and PIs all reduce N. NRTIs and NNRTIs do so by preventing the virus from reproducing inside infected T-cells. (AZT is an example of an NRTI, a nucleotide reverse transcriptase inhibitor.) PIs still allow new viruses to be produced when an infected cell lyses, but the PIs bond to the viral enzymes in such a way that these new viruses are ineffective and cannot actively infect new cells.
- *Fusion inhibitors* reduce k_1 by bonding to the viral cells so that those cells can no longer couple with healthy T-cells.

These drugs, taken separately or in combinations, can significantly delay the onset of AIDS. Current research seeks to perfect the drugs, enhancing their effect on the key parameters.

We illustrate how Perelson's model can predict the effect produced by a change in the parameter k_1. We delegate a similar investigation of the parameter N to **Exercise 8**. (In addition, we encourage readers to design their own simulations on the possible effectiveness of combination drug treatments.)

Let $z_{p,t_1,t_2}(t)$ be the step function defined by

$$z_{p,t_1,t_2} = \begin{cases} p, & \text{if } t_1 \le t \le t_2; \\ 1, & \text{otherwise.} \end{cases}$$

Here p is a positive constant, $0 \le p \le 1$, and the values of t_1 and t_2 specify the time interval during which the drug treatment has a direct effect. We assume that a chemotherapy treatment by a fusion inhibitor multiplies by a factor p the rate at which healthy T-cells become latently infected during the time interval $t_1 \le t \le t_2$. In other words, the smaller the value of p, the more effective the treatment. This effect is incorporated by modifying **(21)**, **(22)**, and **(24)** of the Perelson model (p. 12):

$$\frac{dT}{dt} = s + rT\left(1 - \frac{T + T^* + T^{**}}{T_{\max}}\right) - \mu_1 T - z_{p,t_1,t_2} k_1 TV, \qquad \textbf{(21')}$$

$$\frac{dT^*}{dt} = z_{p,t_1,t_2} k_1 TV - \mu_{T^*} T^* - k_2 T^*, \qquad \textbf{(22')}$$

$$\frac{dV}{dt} = N\mu_{T^{**}} T^{**} - z_{p,t_1,t_2} k_1 TV - \mu_V V. \qquad \textbf{(24')}$$

We designate Perelson's model with equations **(21)**, **(22)**, and **(24)** revised in this way as Perelson **(21′, 22′, 24′)**.

To study the effect of chemotherapy numerically, we must define what is meant by the onset of AIDS. In what follows, we fix $N = 1400$ and use the initial and constant values given in **Table 1**. Referring back to **Figure 4**, we see that the T-cell concentration eventually drops dramatically from the healthy equilibrium concentration of 1000 mm^{-3}. We therefore define the onset of AIDS to be the time t_{onset} at which the value of T falls to 999 (**Figure 6**).

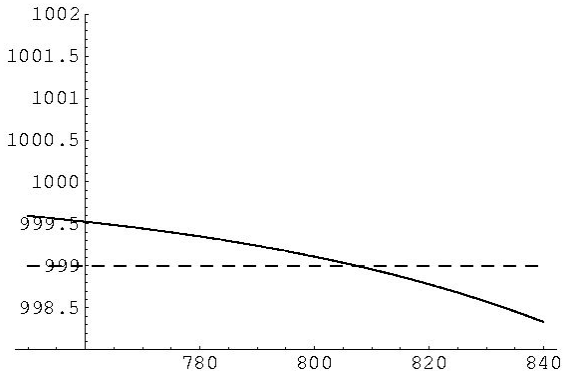

Figure 6. We define the onset of AIDS to be the time t_{onset} when T falls to 999. In this case, $t_{\text{onset}} \approx 806$.

Without chemotherapy (i.e., taking $p = 1$), $t_{\text{onset}} \approx 806$ days. For a six-month chemotherapy treatment modeled by taking $p = .4$, $t_1 = 500$, $t_2 = 680$, Perelson **(21′, 22′, 24′)** predicts that the progression to AIDS will be delayed by about eight months (**Figure 7**).

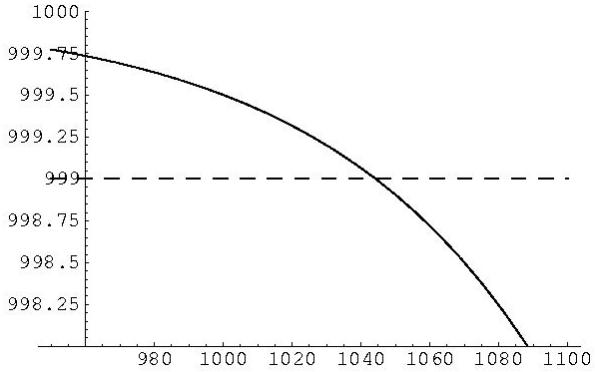

Figure 7. An effective chemotherapy treatment, as modeled by Perelson **(21′,22′,24′)** with $p = .4$, $t_1 = 500$, and $t_2 = 680$, delays the onset of AIDS by about 8 months (239 days) to $t_{\text{onset}} \approx 1045$.

Exercise

8. This exercise suggests a second way to modify the Perelson model to study the efficacy of chemotherapy treatment. If, during the time interval $t_1 \leq$

$t \le t_2$, a chemotherapy treatment using a drug such as AZT reduces the parameter N by a factor p, equation **(24)** of Perelson's model must be modified to

$$\frac{dV}{dt} = z_{p,t_1,t_2} N \mu_{T^{**}} T^{**} - k_1 TV - \mu_V V. \qquad \textbf{(30)}$$

Call the resulting system Perelson **(30)**. Using the same values ($p = .4$, $t_1 = 500$, and $t_2 = 680$) that we employed above for Perelson **(21', 22', 24')**, what does Perelson **(30)** predict will happen to the value of t_{onset}, the time marking the onset of AIDS?

4.5 Discussion

Immunological aspects of HIV/AIDS are sufficiently varied and complex to elude hope of a complete description by means of a single deterministic model. Three major stages of this disease—primary infection, latency, and AIDS—have been clinically identified, but the biological mechanisms responsible for transitions between stages are not well understood. Perelson's model only seeks to capture the transition from the latency period to AIDS. The dramatic decrease in the $CD4^+$ T-cell concentration associated with the onset of AIDS is explained mathematically by a transcritical bifurcation. The healthy T-cell equilibrium level loses its stability, and the T-cell concentration is attracted towards a much lower infected equilibrium level.

One reason why Perelson's model does not capture qualitatively the dynamics of all three stages of the disease is that viral mutations are not taken into account. If the viral cell population $V(t)$ is viewed in a nonhomogeneous way, taking into account viral mutations that counter T-cells in absence of chemotherapy, plus viral mutations that develop resistance to chemotherapy, all three stages (primary infection, latency, AIDS) can be captured, as seen, for example, in the models discussed by Kirschner and Webb [1996] and Hersberger et al. [2002].

Since there is considerable variability in the length of the latency period (2 to 18 years), the numerically generated graphs of the $CD4^+$ concentration in Perelson's system give qualitative agreement with clinical data (as shown in **Figure 1.**). Perelson's model is elegant in its simplicity of conception and flexible because of the large number of parameters. A strength of the model is its ability to predict effects due to changes in parameters, as we have demonstrated in discussing the possible effect of antiretroviral drugs in delaying the onset of AIDS.

5. The HIV/AIDS Epidemic

We used Perelson's immunological model **(21)–(24)** to show how the HIV virus affects the immune system without drug intervention. We then modified