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COMAP

Module 791

Immunological and Epidemiological HIV/AIDS Modeling

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Differential Equations
Public Health, immunology, epidemiology

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TITLE:	Immunological and Epidemiological HIV/AIDS Modeling
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MATHEMATICAL FIELD:	Differential Equations
APPLICATION FIELD:	Public Health, immunology, epidemiology
TARGET AUDIENCE:	Students in second-term calculus or in differential equations.
ABSTRACT:	This Module applies ordinary differential equations to both immunological and epidemiological aspects of HIV/AIDS modeling. For each aspect, we introduce a basic system that describes the growth of HIV/AIDS in the absence of countermeasures. We then explain how the basic model can be modified to predict the effectiveness of intervention programs to counter the spread of HIV/AIDS.
PREREQUISITES:	A primer (**Section 3**) on equilibrium analysis of systems of ordinary differential equations is included for those who have not had a course in ordinary differential equations.

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Modules and Monographs in Undergraduate Mathematics and its Applications (UMAP) Project

The goal of UMAP is to develop, through a community of users and developers, a system of instructional modules in undergraduate mathematics and its applications, to be used to supplement existing courses and from which complete courses may eventually be built.

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Paul J. Campbell, Editor
Solomon Garfunkel, Executive Director, COMAP

1. Introduction

HIV/AIDS is arguably the number one epidemic today. The United Nations organization UNAIDS [2004] reported these staggering estimates for 2004:

- 39.4 million people have HIV/AIDS;
- 2.3 million children under the age of 15 have HIV/AIDS;
- 4.9 million new cases of HIV were reported;
- 640,000 children under 15 were newly infected with HIV (the vast majority from their mothers); and
- over 3 million people died of AIDS (an average of more than 8,000 per day).

Sub-Saharan Africa, where over 30 million people have HIV, is the current hotbed of the HIV/AIDS epidemic. Officials warn that major epidemics may arise in Eastern Europe, China, and India. Through a nationwide campaign, Uganda, once regarded as the epicenter of the HIV/AIDS epidemic, has now become a model of successful intervention in reducing its HIV/AIDS population from over 30% in some urban centers to under 10% of its total population. We do well to heed these words of the Ugandan Aids Commission [2001]: "Everyone is called to individually or collectively fight the epidemic within their capacities and mandates."

Mathematical models have been used by immunologists and epidemiologists to help understand and combat HIV/AIDS:

- *Immunological models* describe how the HIV virus attacks the body's defense against disease.
- *Epidemiological models* describe the spread of the HIV/AIDS disease throughout a population.

In the years since the first immunological model was proposed by Leon Cooper [1986], a wide variety of deterministic and stochastic models have contributed insight into either the immunology or epidemiology, while failing to capture the full scope of either aspect of the viral behavior.

Model assumptions must remain speculative whenever the underlying mechanisms are not well understood. For example, there is no decisive experimental evidence favoring one of several different proposed mechanisms explaining the various stages occurring in critical T-cell decrease in HIV-infected individuals [Covert and Kirschner 2000]. Even so, assuming the validity of their assumptions, HIV/AIDS models can be useful in predicting the effectiveness of different intervention strategies such as chemotherapy treatments or vaccination programs.

In this Module, after presenting a description of the human immune system (**Section 2**) and summary of the necessary background in ordinary differential equations (**Section 3**), we describe two systems of ordinary differential equations that have been used in HIV/AIDS research:

- *Perelson's immunological model* (**Section 4**) describes the dynamics of the HIV virus in attacking T-cells in the human immune system. Perelson's model can be used to explore how these dynamics are affected by chemotherapy (**Section 4.4**).
- *Blower's epidemiological model* (**Section 5**) describes the spread of the HIV/AIDS disease in a population. Blower's model can be extended to explore the long-range effect of vaccination programs (**Section 5.4**).

The global magnitude of the HIV/AIDS problem and the role of mathematics in predicting effects of chemotherapy treatments and vaccination programs should compel every undergraduate math major to become familiar with the basic background information and modeling described in this Module. For those not already involved, this study can serve as a starting point for greater involvement in the struggle against HIV/AIDS.

2. The Human Immune System

The immune system is a group of cells, molecules, and organs that act together to protect our bodies from foreign invaders. There are two main strategies employed by the immune system:

- *innate*, i.e., act in a general way against all invaders; and
- *acquired*, i.e., target a specific invader.

The immune system also employs two basic lines of defense:

- a front-line defense seeks to keep invaders from entering the body or bloodstream; and
- a second-line defense helps the body to fight off invaders that have passed through the front-line.

The innate immune system is involved in both lines of defense, while the acquired immune system acts only in the second-line defense. The front-line innate immune system includes such things as our skin, stomach acid, mucus, and cough reflex, which do not require previous exposure to the invader to be effective defenses. The second-line innate immune system includes an army of cells called *phagocytes* that seek to destroy invading microbes. Phagocytes are of two main types:

- *microphages*, which are short-lived and constantly circulating through the bloodstream; and
- *macrophages*, which are longer-lived and stationed strategically in places such as the top skin layer, lungs, and intestines.

Complementary to the innate immune system's use of phagocytes, the acquired immune system employs cells known as *lymphocytes* to destroy foreign invaders. Lymphocytes hone in on targets by identifying *antigens*, i.e., large molecules on the surfaces of cells, viruses, fungi, or bacteria. Antigens are usually proteins that uniquely identify the invader. *Antibodies* can attach themselves to a particular antigen making it an easier target for phagocytes.

Lymphocytes are divided into *B-cells* and *T-cells*. B-cells, produced by bone marrow, can either be "antibody-factories" that produce as many antibodies as they can, or "B-cell factories" that make clones of themselves. T-cells are produced by the marrow and matured in the thymus; there are two main types:

- $CD4^+$ T-cells are "helper" T-cells that normally average about 1000 per cubic mm of blood and serve as the command center for the immune system, directing the activity of B-cells;
- $CD8^+$ T-cells are "killer/suppressor" T-cells that destroy infected cells and subsequently dampen the level of activity of the immune system.

$CD4^+$ T-cells can also direct the activity of NK ("natural killer") cells that work in a manner similar to $CD8^+$ cells in destroying tumor cells.

For more information on the immune system, see Linnemeyer [1993]. In what follows, we are particularly interested in the dynamics of healthy and HIV-infected T-cells as we model the immunological aspects of HIV/AIDS.

3. Background in Differential Equations

In the differential equations that we consider in this Module, the independent variable t represents time, and that is the only variable that we differentiate with respect to. Because partial derivatives are not involved, our differential equations are called *ordinary* differential equations (ODEs). We begin this brief tutorial on ODEs by discussing several important *scalar equations*, i.e., equations involving a single function of time t. We then proceed to *ODE systems*, which involve two or more functions of t. (This section can be skipped by those conversant with ordinary differential equations including stability analysis of equilibria in nonlinear systems.)

3.1 Exponential and Logistic Growth

3.1.1 Exponential Growth

In modeling the dynamics of some population $x = x(t)$, it may be reasonable to assume that the rate of increase in population is proportional to the size of the population. In this case,

$$x' = kx,$$

where k is a positive constant. The solution to this differential equation (obtainable by inspection or by separation of variables) is

$$x(t) = x_0 e^{kt},$$

where x_0 is the value of x at time $t = 0$.

This model of population growth implicitly assumes unrestricted growth, since for all positive values of x_0 and k, the model predicts that the population $x(t)$ increases to infinity.

3.1.2 Logistic Growth

A more realistic assumption is that the environment has a finite capacity M, meaning that the population can increase up to but not exceed M. This assumption is incorporated into the *logistic growth model* specified by the equation

$$x' = kx - \frac{k}{M}\,x^2. \qquad \textbf{(1)}$$

If kx^2 is very small in comparison with M, the linear term kx dominates, so the model behavior is essentially the same as exponential growth. When x becomes larger, the negative quadratic term $-kx^2/M$ becomes more important and slows down the growth.

3.1.3 Equilibrium

An *equilibrium* or *steady-state* solution is a solution that does not change with time; that is, a solution such that $x(t)$ is a constant function. To find an equilibrium state for the logistic growth equation **(1)**, set the derivative $x' = kx - kx^2/M$ equal to zero and solve for x. The result is two equilibrium solutions (or "points"), $x_{\text{eq}_1} = 0$ and $x_{\text{eq}_2} = M$.

3.1.4 Stability of an Equilibrium

An equilibrium $x = x_{\text{eq}}$ is *stable* if all solutions initially close to the equilibrium value approach the equilibrium as time increases without bound. More technically, an equilibrium $x = x_{\text{eq}}$ is stable if there is an open interval I containing x_{eq} such that all solutions $x(t)$ with initial value $x_0 \in I$ satisfy

$$\lim_{t\to\infty} x(t) = x_{\text{eq}}.$$

If an equilibrium is not stable, it is *unstable*: Given any open interval containing x_{eq}, there is at least one solution with initial point in I that does not approach x_{eq} as $t \to \infty$.

In the case of the logistic growth equation **(1)**, we can qualitatively analyze the stability of each equilibrium point:

- For the equilibrium $x_{\text{eq}_1} = 0$, let $x_0 = \epsilon$, with ϵ an arbitrarily small positive value. Since the quadratic term is negligible, the derivative $x'(t)$ will initially be positive, so that $x(t)$ must increase. As long as $x(t) < M$, the derivative will remain positive. Hence, as $t \to \infty$, $x(t)$ cannot approach zero, so the equilibrium point $x_{\text{eq}_1} = 0$ is unstable.
- On the other hand, the equilibrium $x_{\text{eq}_2} = M$ is stable. If $x(t) > M$, then the value of $x'(t)$ will be negative and $x(t)$ will decrease towards the equilibrium value M; if $x(t) < M$, then the derivative remains positive and so $x(t)$ must increase towards M.

This qualitative reasoning can be checked by obtaining an exact solution. (See **Exercise 1.**)

3.2 Linear and Bernoulli Equations

3.2.1 The Bernoulli Equation

The logistic growth equation is a special case of the *Bernoulli equation*

$$x' + h(t)x = q(t)x^n. \tag{2}$$

In the logistic equation **(1)**, the coefficient functions $h(t)$ and $q(t)$ are both constant functions, $h(t) \equiv -k$ and $q(t) \equiv -k/M$.

To solve a Bernoulli equation, we use a change of variables $y = x^{1-n}$ to transform the equation into a basic *linear differential equation*, that is, one with the general form

$$y' + p(t)y = q(t). \tag{3}$$

For the Bernoulli equation **(2)**, $p(t) = (1-n)h(t)$. (See **Exercise 1a** for a specific example of how to transform a Bernoulli equation into a linear equation.)

3.2.2 Solving the General Linear Equation

The general linear equation **(3)** is solved by means of an *integrating factor*

$$\mu(t) = e^{\int p(t)\,dt},$$

where for simplicity, the constant of integration is zero. Multiplying both sides of **(3)** by the integrating factor $\mu(t)$, we have

$$y'\mu(t) + p(t)\mu(t)y = q(t)\mu(t). \tag{4}$$

The integrating factor is defined so that the left side of **(4)** is exactly the derivative of $\mu(t)y$. By integrating both sides with respect to t, we obtain

$$y\mu(t) = \int q(t)\mu(t)\,dt + C,$$

and hence

$$y = \frac{1}{\mu(t)} \left(\int q(t)\mu(t)\, dt + C \right).$$

Finally, the solution to the Bernoulli equation **(2)** is obtained from the relation

$$x(t) = y(t)^{\frac{1}{1-n}}.$$

Exercises

1. **a)** Use the Bernoulli change of variable $y = x^{1-n}$ to transform the logistic growth equation $x' = kx - kx^2/M$, which is quadratic in x, into a linear differential equation of the form **(3)** which is linear in y.
   b) Find the integrating factor for the linear equation obtained in part **a)** and find the solution that satisfies $y(0) = y_0$.
   c) Use your answer to part **b)** to find an explicit formula for $x(t)$.
   d) Use your answer to **c)** to prove that the equilibrium $x_{\text{eq}_1} = 0$ is unstable and the equilibrium $x_{\text{eq}_2} = M$ is stable.
2. Consider the modified logistic equation

$$y' = s + ry\left(1 - \frac{y}{y_{\max}}\right) - \mu y, \qquad \textbf{(5)}$$

in which s is a nonnegative real constant and μ, $y_{\max}$, and r are positive constants. (In **Section 4**, we use an equation of this form when developing an immunological model describing the spread of the HIV virus.)

   a) Solve **(5)** for the case $s = 0$.
   b) Solve **(5)** for the case $s > 0$ by making a change of variables $x = y - y_{\text{eq}}$, where y_{eq} is the positive equilibrium solution to **(5)**.
   c) Make a plot that shows how the value of y_{eq} varies with s.

3.3 Linear Systems

3.3.1 Autonomous Linear Systems

As we will see in **Section 5**, in modeling the spread of HIV/AIDS throughout a population, the number of healthy people, the number of HIV infected people, and the number of those who have contracted AIDS are represented by three different functions of time t; we have a *system* of differential equations, rather than a single scalar equation.

Consider the simple system

$$x' = x, \qquad \textbf{(6)}$$

$$y' = x + 2y, \qquad \textbf{(7)}$$

with initial conditions $x(0) = x_0$ and $y(0) = y_0$. This is a two-dimensional system, meaning that two functions $x(t)$ and $y(t)$ are under consideration. This system is *autonomous* because the independent variable t does not appear explicitly on the right side of either differential equation.

A solution to this system is a vector-valued function of the form

$$\gamma(t) = \big(f_1(t), f_2(t)\big),$$

meaning that both of the equations **(6)** and **(7)** are satisfied when x is replaced by $f_1(t)$ and y is replaced by $f_2(t)$. If both f_1 and f_2 are constant, the solution is called an *equilibrium* or *steady-state* solution.

3.3.2 Equilibrium

An equilibrium solution is obtained by setting equal to zero the right-hand sides of all the differential equations in the system, yielding a system of simultaneous algebraic equations. In our example, the algebraic system is

$$\begin{aligned} x &= 0, \\ x + 2y &= 0. \end{aligned}$$

Since in this case $x = y = 0$, the equilibrium solution is the vector-valued function $\gamma(t) = (0, 0)$, meaning that f_1 and f_2 are both the zero function. We refer to $(0, 0)$ as an *equilibrium point* for the system. Each solution $\gamma(t) = \big(f_1(t), f_2(t)\big)$ to a two-dimensional system can be graphed as a parametric curve in the xy plane (with t as the parameter). The graph of an equilibrium solution is a single point.

An n-dimensional system of ordinary differential equations has the form

$$\begin{aligned} x_1' &= F_1(x_1, x_2, \ldots, x_n; t), \\ x_2' &= F_2(x_1, x_2, \ldots, x_n; t), \\ \vdots &= \vdots \\ x_n' &= F_n(x_1, x_2, \ldots, x_n; t), \end{aligned}$$

where $x_1, x_2, \ldots, x_n$ are functions of time t. If each of the F_i is a function only of $x_1, x_2, \ldots, x_n$ so that the independent variable t does not appear explicitly on the right-hand side of any equation, the system is *autonomous*. A solution to this system is a vector-valued function

$$\gamma(t) = \big(f_1(t), f_2(t), \ldots, f_n(t)\big).$$

If each f_i is constant, the solution is an *equilibrium* or *steady-state solution*. Equilibrium solutions can be obtained by solving simultaneously for $x_1, \cdots, x_n$ the system of n algebraic equations specified by $F_i = 0$ $(i = 1, \ldots, n)$.

3.3.3 Stability

Just as for scalar equations, it is important to determine the stability of an equilibrium solution to a system of ODEs. Roughly speaking, if all solutions with initial points sufficiently close to the equilibrium converge to the equilibrium as $t \to \infty$, the equilibrium point is stable; otherwise, it is unstable.

For our example **(6)–(7)**, the solution with initial point (x_0, y_0) is given by (see **Exercise 3**)

$$x(t) = x_0 e^t, \tag{8}$$

$$y(t) = -x_0 e^t + (x_0 + y_0)e^{2t}. \tag{9}$$

The explicit form of $x(t)$ indicates that for any choice of $x_0 \neq 0$, the solution $\big(x(t), y(t)\big)$ cannot converge to the equilibrium $(0, 0)$. Hence, the equilibrium is unstable.

3.3.4 The Method of Eigenvalues

In the theory of differential equations, a method involving eigenvalues and eigenvectors is developed to determine the stability of equilibrium points. We illustrate this method for our example, indicating why the method works, without going into any details of the general proof.

First, we rewrite the system in the matrix form

$$\begin{pmatrix} x' \\ y' \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 1 & 2 \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix},$$

where the matrix $A = \begin{pmatrix} 1 & 0 \\ 1 & 2 \end{pmatrix}$ is called the *coefficient matrix* of the system.

Given a square matrix A, an *eigenvector* is a nonzero vector $\vec{v}$ that is transformed by A into a multiple of itself. That is,

$$A\,\vec{v} = \lambda\,\vec{v},$$

where λ is a scalar (number). Observe that

$$A\,\vec{v} = \lambda\,\vec{v} \quad \Longrightarrow \quad A\,\vec{v} - \lambda\,\vec{v} = 0 \quad \Longrightarrow \quad (A - \lambda I)\,\vec{v} = 0. \tag{10}$$

One solution is the trivial solution $\vec{v} = \vec{0}$. For a nonzero solution to exist, we require that λ satisfy the *characteristic equation*

$$\det(A - \lambda I) = 0.$$

Solutions to the characteristic equation are called *eigenvalues.*

In our example, the eigenvalues of the coefficient matrix A are obtained from the equation

$$\det \begin{pmatrix} 1-\lambda & 0 \\ 1 & 2-\lambda \end{pmatrix} = (1-\lambda)(2-\lambda) = 0.$$

From this, we obtain two positive eigenvalues: $\lambda_1 = 1$, $\lambda_2 = 2$.

Using back-substitution, we can determine eigenvectors $\vec{v}_{\lambda_1}$ and $\vec{v}_{\lambda_2}$ corresponding to the eigenvalues λ_1 and λ_2. First, to find $\vec{v}_{\lambda_1}$, note that the matrix equation

$$\begin{pmatrix} 0 & 0 \\ 1 & 1 \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

is equivalent to the system

$$\begin{aligned} 0v_1 + 0v_2 &= 0, \\ v_1 + \quad v_2 &= 0. \end{aligned}$$

From the relation $v_1 = -v_2$, we take as our eigenvector

$$\vec{v}_{\lambda_1} = \begin{pmatrix} 1 \\ -1 \end{pmatrix}.$$

In the same way, we find $\vec{v}_{\lambda_2}$:

$$\begin{pmatrix} -1 & 0 \\ 1 & 0 \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix};$$

$$\begin{aligned} -v_1 + 0v_2 &= 0, \\ v_1 + 0v_2 &= 0; \end{aligned}$$

$$v_1 = 0 \quad \Longrightarrow \quad \vec{v}_{\lambda_2} = \begin{pmatrix} 0 \\ 1 \end{pmatrix}.$$

There is an important relationship between these eigenvectors and eigenvalues and the solution $\big(x(t), y(t)\big)$ to the system given by **(8)** and **(9)**. Letting $c_1 = x_0$ and $c_2 = (x_0 + y_0)$, we rewrite the solution in matrix form as

$$\begin{aligned} \begin{pmatrix} x(t) \\ y(t) \end{pmatrix} &= \begin{pmatrix} c_1 e^t \\ -c_1 e^t + c_2 e^{2t} \end{pmatrix} \\ &= c_1 e^t \begin{pmatrix} 1 \\ -1 \end{pmatrix} + c_2 e^{2t} \begin{pmatrix} 0 \\ 1 \end{pmatrix}. \end{aligned}$$

It follows that

$$\begin{pmatrix} x(t) \\ y(t) \end{pmatrix} = c_1 e^{\lambda_1 t}\, \vec{v}_{\lambda_1} + c_2 e^{\lambda_2 t}\, \vec{v}_{\lambda_2}\,.$$

This example suggests that

the stability of the equilibrium point $(0, 0)$ *is related to the* signs *of the eigenvalues of the coefficient matrix:*

- If all the eigenvalues are negative, this equilibrium is stable.
- If any of the eigenvalues is positive, the equilibrium is unstable.

Exercises

3. Solve the system

$$x' = x, \tag{11}$$
$$y' = x + 2y \tag{12}$$

by using **(11)** to obtain $x(t)$ explicitly and then substituting your answer into **(12)** and solving the resulting linear equation for $y(t)$.

4. Use eigenvalues to determine the stability of the equilibrium solution $(0, 0)$ for the system

$$x' = -x,$$
$$y' = -x - 2y.$$

3.4 Nonlinear Systems

3.4.1 Equilibrium in Nonlinear Systems

An n-dimensional ODE system is *nonlinear* if at least one of the functions $F_1, \ldots, F_n$ on the right-hand side is nonlinear. For example, the system

$$x' = -x - x^2, \tag{13}$$
$$y' = -x - 2y \tag{14}$$

is nonlinear since the function $F_1(x, y) = -x - x^2$ is nonlinear in x.

To find the equilibrium points of this nonlinear system of differential equations, we begin as we would for a linear system:

$$0 = -x - x^2,$$
$$0 = -x - 2y.$$

Solving this algebraic system simultaneously, we obtain two equilibrium points, namely $(0, 0)$ and $(-1, 1/2)$.

3.4.2 Stability

Stability of an equilibrium point for a nonlinear system can be determined from the stability of a corresponding equilibrium point in a closely-related linear system, which we call the *linearized* system.

For example, the stability of $(0, 0)$ in the nonlinear system **(13),(14)** is related to the stability of the equilibrium $(0, 0)$ for the linearized system

$$x' = -x, \tag{15}$$
$$y' = -x - 2y. \tag{16}$$

Intuitively, in approximating the behavior of solutions to the nonlinear system **(13)–(14)** near $(0,0)$, the nonlinear term x^2 can be omitted since x is small. Using the result of **Exercise 4**, we know that $(0,0)$ is stable for the linearized system **(15)–(16)**. Hence, $(0,0)$ is also stable for the nonlinear system **(13)–(14)**.

Determining the stability of the equilibrium point $(-1,1/2)$ for the system **(13)–(14)** can be accomplished by first making a simple change of coordinates

$$\begin{aligned} u &= x-(-1),\\ v &= y-1/2. \end{aligned}$$

Observe that if (x,y) is near the equilibrium point $(-1,1/2)$, then (u,v) will be near $(0,0)$. The system of differential equations satisfied by u and v is

$$u' = -(u-1)-(u-1)^2 \quad = u-u^2, \tag{17}$$
$$v' = -(u-1)-2(v+1/2) = -u-2v. \tag{18}$$

Once again, when u is small, we can neglect the $-u^2$ term and thereby obtain a linearized system

$$u' = u, \tag{19}$$
$$v' = -u-2v. \tag{20}$$

For this linearized system, the coefficient matrix is

$$\begin{pmatrix} 1 & 0 \\ -1 & -2 \end{pmatrix}.$$

The eigenvalues $\lambda_1 = 1$, $\lambda_2 = -2$ of this coefficient matrix indicate the instability of the equilibrium $(u,v)=(0,0)$ for both the linearized system **(19)–(20)** and the nonlinear system **(17)–(18)**. It follows that the equilibrium $(x,y)=(-1,1/2)$ in the nonlinear system **(13)–(14)** is also unstable.

For a system of the form

$$\begin{aligned} x' &= F_1(x,y),\\ y' &= F_2(x,y), \end{aligned}$$

where F_1 and F_2 are both polynomials in x and y, we can determine the stability of an equilibrium point using the *Jacobian matrix*

$$J(x,y) = \begin{pmatrix} \dfrac{\partial F_1(x,y)}{\partial x} & \dfrac{\partial F_1(x,y)}{\partial y} \\ \\ \dfrac{\partial F_2(x,y)}{\partial x} & \dfrac{\partial F_2(x,y)}{\partial y} \end{pmatrix}.$$

If both eigenvalues of the matrix $J(x_{\text{eq}}, y_{\text{eq}})$ are negative, the equilibrium point $(x_{\text{eq}}, y_{\text{eq}})$ is stable; if either (or both) of the eigenvalues is positive, the equilibrium is unstable.

Exercise

5. Compute the Jacobian matrix $J(x, y)$ for the system

$$x' = -x - x^2,$$
$$y' = -x - 2y$$

and then use $J(0, 0)$ and $J(-1, 1/2)$ to determine the stability of the two equilibrium points for this system.

4. T-Cell and HIV Viral Dynamics

In **Section 2**, we described the importance of T-cells within the acquired immune system. Perelson's immunological model describes the dynamics of healthy $CD4^+$ T-cells as they become infected with the HIV virus. Clinically, after the primary infection with the HIV virus, a variable latency period of between 2 and 18 years has been observed, during which time T-cells are infected but the healthy T-cell count remains at a high enough level so that the immune system is not critically impaired. The onset of AIDS is signalled by a decrease in healthy T-cell concentration to a dangerously low level and rapid increase in free HIV viral concentration, thereby crippling the acquired immune system.

Figure 1 shows qualitatively the three stages observed in clinical data: primary infection, latency period, and destruction of the immune system that occurs after the onset of AIDS. Stochastic models of the primary infection period have been developed (see Murray [2002]), but we do not consider them in this Module. The Perelson model describes only the latency period and destruction of the immune system following onset of AIDS. Microbiological mechanisms for the transitions between the three stages are not completely understood.

4.1 Basic Model Formulation and Assumptions

Perelson's immunological model is a nonlinear system of four ordinary differential equations in which $T(t)$, $T^*(t)$, $T^{**}(t)$, and $V(t)$ represent respectively the number of healthy T-cells, latently infected T-cells, actively infected T-cells and free viral cells:

$$\frac{dT}{dt} = s + rT\left(1 - \frac{T + T^* + T^{**}}{T_{\max}}\right) - \mu_T T - k_1 TV, \tag{21}$$

$$\frac{dT^*}{dt} = k_1 TV - \mu_{T^*} T^* - k_2 T^*, \tag{22}$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_{T^{**}} T^{**}, \tag{23}$$

$$\frac{dV}{dt} = N\mu_{T^{**}} T^{**} - k_1 TV - \mu_V V. \tag{24}$$

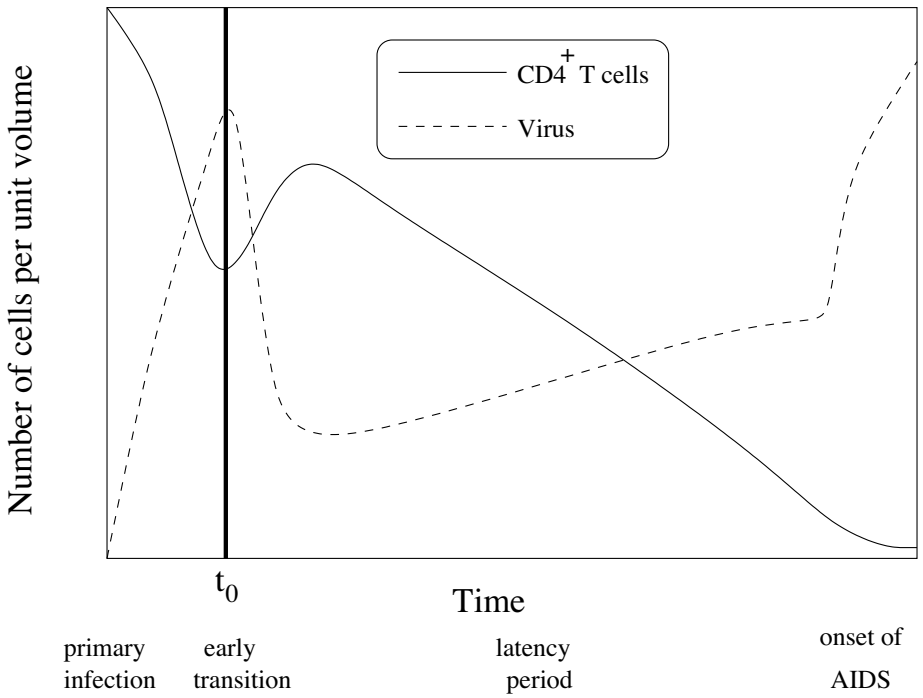

Figure 1. Qualitative dynamics of the healthy T-cell and HIV-viral concentrations based on clinical data. The Perelson immunological model simulates the dynamics beginning at $t = t_0$.

Immunologically, it is important to differentiate between latently infected T-cells and actively infected T-cells because only the latter are utilized by the virus to replicate new free viral cells.

Clinically, flow cytometry is the most commonly used method of evaluating T-cell counts and differentiating between healthy, latently infected, and actively infected T-cells. Cells are suspended in a solution that passes through the flow cytometer in front of a laser. Light from the laser refracts off each cell, and the device measures these angles. The angles depend on the enzymes coating the cell, which are slightly different for healthy, latently infected, and actively infected T- cells.

Referring to **Figure 2** and **Table 1**, we now outline explicit assumptions used in formulating the four equations of Perelson's system:

Equation (21), giving the rate of change dT/dt in the concentration $T(t)$ of healthy T-cells:

$$\frac{dT}{dt} = s + rT\left(1 - \frac{T + T^* + T^{**}}{T_{\max}}\right) - \mu_T T - k_1 TV.$$

- New, healthy T-cells enter into the blood stream at a constant rate s. (This is an oversimplification, since the rate is expected to decrease during the course of the HIV infection. See Kirschner and Webb [1996].)
- In the absence of free virus ($V = 0$), the entire right-hand side of the

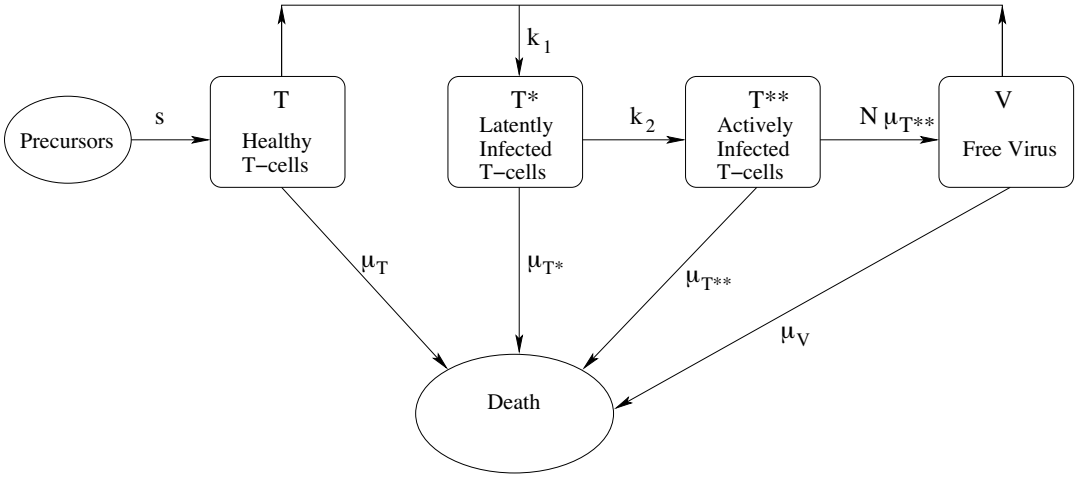

Figure 2. Rates of increase/decrease in concentrations described by Perelson's immunological model **(21)–(24)**.

Table 1.
Variables and parameters in Perelson's immunological model **(21)–(24)**.

		Initial or default value
Independent Variable		
t	time	days
Dependent Variables		
T	Uninfected CD4$^+$ cell concentration	500 mm^{-3}
T^*	Latently infected CD4$^+$ helper cell concentration	0 mm^{-3}
T^{**}	Actively infected CD4$^+$ helper cell concentration	0 mm^{-3}
V	Free HIV viral concentration	10^{-3} mm^{-3}
Parameters and constants		
s	Rate of supply of CD4$^+$ T cells from precursors	10 mm^{-3} day^{-1}
r	Growth rate constant for the CD4$^+$ T cells	0.03 day^{-1}
$T_{\max}$	Maximum CD4$^+$ T cell concentration	1500 mm^{-3}
μ_T, μ_{T^*}	Death rates of uninfected and latently infected CD4$^+$ T cells	0.02 day^{-1}
$\mu_{T^{**}}$	Death rate of actively infected CD4$^+$ T cell population	0.24 day^{-1}
μ_V	Death rate of free virus	2.4 day^{-1}
k_1	Rate constant for infection of CD4$^+$ T cells with free virus	2.4×10^{-5} mm^3 day^{-1}
k_2	Rate latently infected CD4$^+$ T cells convert to actively infected CD4$^+$ T cells	3×10^{-3} day^{-1}
N	Number of free virus produced by lysing a CD4$^+$ T cell	varies
Derived quantities		
$T_{\text{uninfected}}$	Steady-state concentration of CD4$^+$ T cells in uninfected individuals	1000 mm^{-3}
N_{crit}	Critical number of viral progeny needed for endemic infection	774

equation reduces to

$$s + rT\left(1 - \frac{T}{T_{\max}}\right) - \mu_T T,$$

which implies that healthy T-cell dynamics is described by the modified logistic equation presented in **Exercise 2**.

- The $-k_1TV$ term assumes that the rate of infection of T-cells by free viral cells is jointly proportional to the concentration of T-cells and the concentration of free virus.

Equation (22), giving the rate of change dT^*/dt in the concentration $T^*(t)$ of latently infected T-cells:

$$\frac{dT^*}{dt} = k_1TV - \mu_{T^*}T^* - k_2T^*.$$

- Growth is due to the infection of healthy T-cells with free viral cells (k_1TV).
- Decreases are due to death ($-\mu_{T^*}T$) (the death rates may be different for healthy, latently infected, and actively infected T-cells), and by progression from latent to active infection ($-k_2T^*$).

Equation (23), giving the rate of change dT^{**}/dt in the concentration $T^{**}(t)$ of actively infected T-cells:

$$\frac{dT^{**}}{dt} = k_2T^* - \mu_{T^{**}}T^{**}.$$

- Growth is due to latently infected cells becoming actively infected (k_2T^*).
- Decrease in concentration is due only to death ($\mu_{T^{**}}T^{**}$).

Equation (24), giving the rate of change dV/dt in the concentration $V(t)$ of the free virus:

$$\frac{dV}{dt} = N\mu_{T^{**}}T^{**} - k_1TV - \mu_V V.$$

- Growth occurs when an actively infected T-cell *lyses* (i.e., explodes). It is assumed that N copies of the free viral cell are created upon lysing ($N\mu_{T^{**}}T^{**}$).
- The free viral concentration decreases as the free virus becomes attached to healthy T-cells ($-k_1TV$) and also through death ($-\mu_V V$).

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.

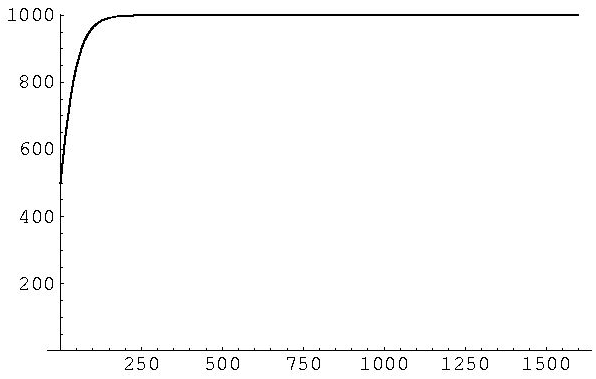

Figure 3. $T(t)$ converges to the stable equilibrium value $T_{\text{uninfected}} = 1000$ when $N = 500$.

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**).

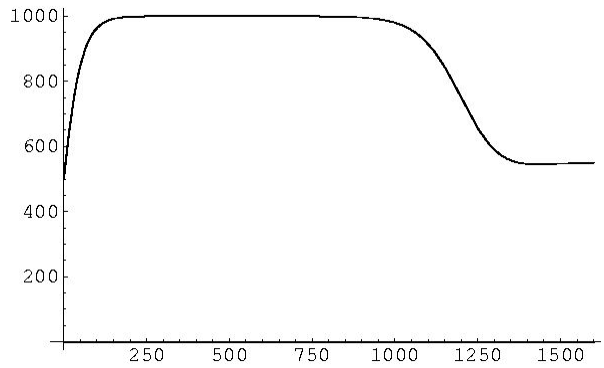

Figure 4. When $N = 1400$, the equilibrium value $T_{\text{uninfected}} = 1000$ is unstable but the equilibrium value $T_{\text{uninfected}} = 580$ is stable.

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**).

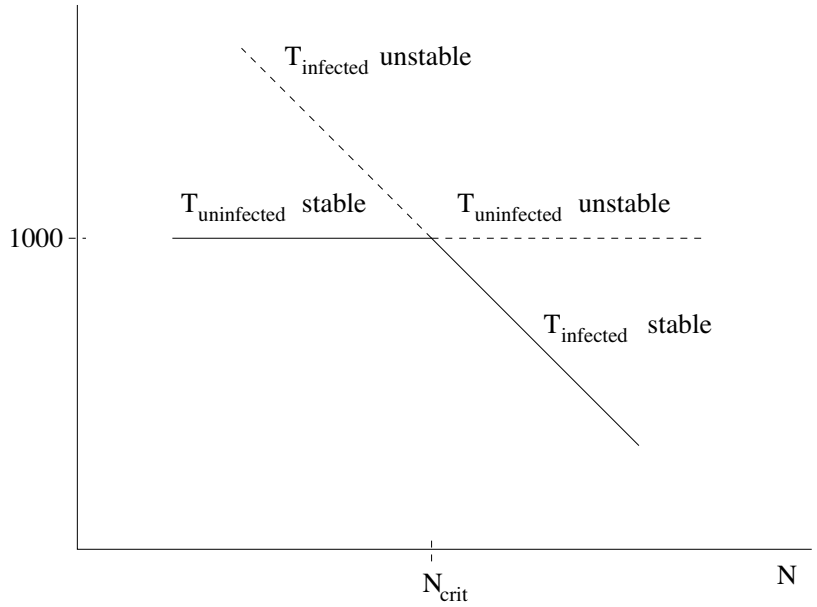

Figure 5. In the Perelson immunological model, a transcritical bifurcation occurs in which the two equilibrium solutions with $T = T_{\text{uninfected}}$ and $T = T_{\text{infected}}$ exchange stability as the parameter N crosses a critical value $N_{\text{crit}} \approx 774$.

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**).

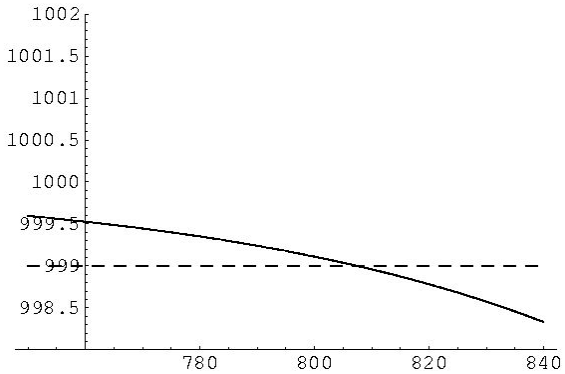

Figure 6. We define the onset of AIDS to be the time t_{onset} when T falls to 999. In this case, $t_{\text{onset}} \approx 806$.

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**).

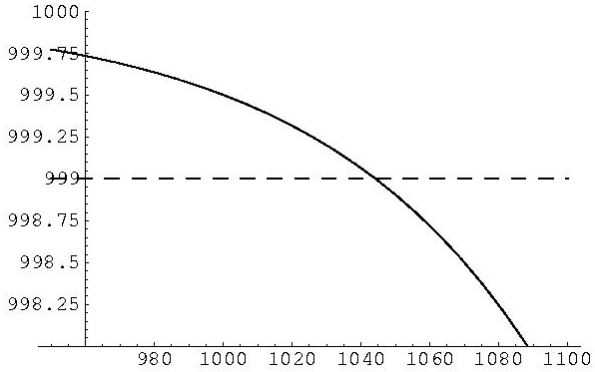

Figure 7. An effective chemotherapy treatment, as modeled by Perelson **(21′,22′,24′)** with $p = .4$, $t_1 = 500$, and $t_2 = 680$, delays the onset of AIDS by about 8 months (239 days) to $t_{\text{onset}} \approx 1045$.

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

Perelson's model to study the efficacy of chemotherapy treatment. In this section, we begin our epidemiological modeling by introducing another system of ordinary differential equations in which the dynamics of the spread of HIV within a population is analyzed, at first without public health intervention. We then use sensitivity analysis to investigate abstinence intervention (**Section 5.3**). Finally, by extending the basic model using additional variables and equations, we study the efficacy of vaccination intervention programs (**Section 5.4**).

Our ODE systems approach to epidemiological modeling parallels closely the approach of our study of immunological modeling. We delegate a greater part of the parallel analysis to the exercises, to maximize active learning. (Most solutions are provided.)

5.1 Basic Model Formulation and Assumptions

To model the spread of HIV/AIDS throughout a sexually active population, we follow Blower et al. [2001] and divide the population into three groups. Let

$X(t)$ denote the number of susceptible individuals at time t measured in years,

$Y_W(t)$ the number of individuals infected with wild-type HIV (as opposed to a weakened strain of HIV used in certain vaccines), and

$A(t)$ the number of individuals with AIDS.

The population dynamics is described by the following third-order linear system of differential equations, which we call *Blower's epidemiological model*:

$$\frac{dX}{dt} = \pi - X(c\lambda_W + \mu_X), \tag{31}$$

$$\frac{dY_W}{dt} = Xc\lambda_W - Y_W(\nu_W + \mu_W), \tag{32}$$

$$\frac{dA}{dt} = Y_W\nu_W - A(\mu_A + \delta_A). \tag{33}$$

The meaning of the constants and their values are displayed in **Table 2**, with a diagram showing the transition rates displayed in **Figure 8**. (Realistic initial and constant values can be obtained by statistical study and would vary by country; we use hypothetical values.)

In **Exercise 9a**, you are asked to explain the assumptions employed in formulating the three equations of Blower's epidemiological model **(31)–(33)** in a manner similar to the explanation that we gave immediately for the equations in Perelson's immunological model **(21)–(24)**.

5.2 Analysis

The Mathematica plot of the sexually active wild-strain HIV population $Y_W(t)$ shown in **Figure 9** indicates that this population will rise from the hypothesized initial value of 3 million to roughly 12 million after five years before

Table 2.
Variables and constants used in Blower's epidemiological model **(31)–(33)**.

		Initial or default value
Independent Variable		
t	time	years
Dependent Variables		
X	Number of susceptible individuals	15×10^6 people
Y_W	Number of individuals infected with wild-type HIV	3×10^6 people
A	Number of individuals with AIDS	0.05×10^6 people
Constants		
π	Rate new susceptibles join the population	1×10^6 people yr^{-1}
λ_W	Probability that sexual partner is infected with wild-type HIV	.2
c	Average rate of acquiring new partners	2 yr^{-1}
ν_W	Proportion of wild strain infected HIV population that progress to AIDS	.1 yr^{-1}
μ_X	Proportion of total healthy population that becomes sexually inactive	.025 yr^{-1}
μ_W	Proportion of total HIV population that becomes sexually inactive	.025 yr^{-1}
μ_A	Proportion of total Aids population that becomes sexually inactive	.025 yr^{-1}
δ_A	Proportion of AIDS population that will die	.95 yr^{-1}

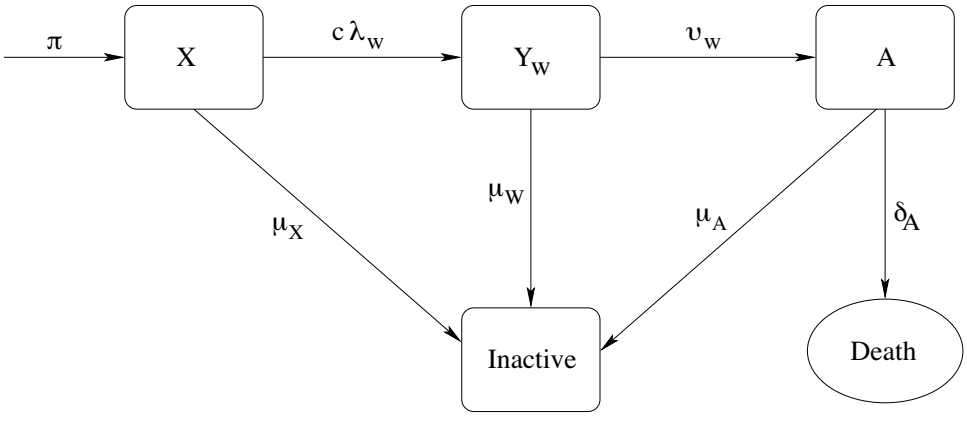

Figure 8. Transition rates for Blower's epidemiological model **(31)–(33)**.

decreasing towards an equilibrium level of about 7.5 million (see **Exercise 9b**). The epidemic rise in the HIV population is accompanied by a fall in the susceptible population $X(t)$ from an initial value of 15 million to an equilibrium level of about 2.3 million. The sexually active AIDS population $A(t)$, initially 50,000, climbs to an equilibrium level of about 772,000.

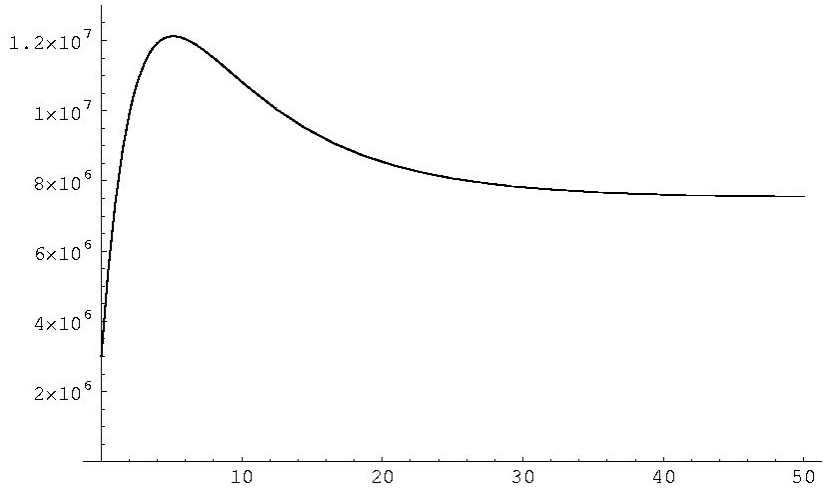

Figure 9. Plot of $Y_W(t)$ over a 50-year time span using the initial and constant values in **Table 2**. Blower's epidemiological model **(31)–(33)** predicts an equilibrium HIV population of about 7.5 million.

A simple yet important sensitivity analysis that can be performed for this model determines how an increase in each of the parameters affects the equilibrium levels (see **Table 3**).

Table 3.
The effect of parameter changes on the equilibrium values of Blower's epidemiological model.

Parameter increased	X	Y_w	A
π	$\uparrow$	$\uparrow$	$\uparrow$
λ_w	$\downarrow$	$\uparrow$	$\uparrow$
c	$\downarrow$	$\uparrow$	$\uparrow$
ν_w	no change	$\downarrow$	$\uparrow$
μ_X	$\downarrow$	$\downarrow$	$\downarrow$
μ_W	no change	$\downarrow$	$\downarrow$
μ_A	no change	no change	$\downarrow$
δ_A	no change	no change	$\downarrow$

The unique equilibrium point for Blower's linear model **(31)–(33)**:

- is globally stable (the eigenvalues determining stability are all negative ($-\delta_A - \mu_A$, $-c\lambda_W - \mu_X$, and $-\mu_W - \nu_W$), so all solutions converge to the equilibrium values regardless of initial conditions); and
- does not depend explicitly on the initial conditions.

If a country has equilibrium HIV/AIDS populations exhibiting these two characteristics (global stability and independence from initial conditions), any intervention that moves one or more of the parameter values in the right direction (i.e., toward a decrease in the equilibrium HIV and AIDS populations) will in the long run be effective regardless of the current magnitude of the problem (i.e., initial conditions). In this case, we say that the country exhibits *fundamental hope of intervention.*

Exercises

9. a) With the help of the transition diagram shown in **Figure 8** and **Table 2** explain the assumptions used in formulating Blower's epidemiological model **(31)–(33)**.

b) Find the equilibrium values for Blower's epidemiological model, and then show that the system's equilibrium point is stable. (For the latter, you need to compute the eigenvalues of a 3×3 Jacobian matrix.)

c) Use the values determined in part **b)** to find the equilibrium percentage of the total sexually active population ($X + Y_W + A$) that has HIV. (In **Exercise 10**, we investigate how this percentage is affected as we model the introduction of a vaccination program into this population.)

5.3 Intervention Strategies

Comprehensive intervention programs can make a significant difference in mitigating the deadly consequences of an HIV/AIDS epidemic. Practical methods to combat the deadly spread of HIV/AIDS include:

- advocating the highest standards of sexual morality, including abstinence outside of marriage as foolproof protection, above and beyond so-called "safe sex" (using the limited protection of condoms);
- identifying HIV-positive individuals and informing the public about best practices;
- making chemotherapy and vaccination programs widely available;
- providing job-training for young women as an alternative to prostitution;
- curbing needle-sharing by drug users (in some countries, the largest group of the HIV/AIDS infected population);
- proper discarding of used syringes in hospitals and clinics;
- reducing the transmission of HIV/AIDS from mother to child during pregnancy via antiretroviral drugs; and
- replacing breastfeeding by HIV-positive mothers with formula feeding.

An important type of sensitivity analysis relates to sexual abstinence as an intervention strategy. (This was a major factor in Uganda's successful HIV/AIDS intervention.) Intuitively, an abstinence campaign should increase the value of μ_X, μ_W, and μ_A (the proportions of the populations becoming sexually inactive) while decreasing the value of c (the average rate of acquiring new partners). If we let $\mu_X = \mu_W = \mu_A = \mu$, even a modest increase in μ— say, from $\mu = .025$ to $\mu = .03$— along with a decrease in the rate of acquiring sexual partners—say, to $c = 1.75$—results in a decrease in the equilibrium HIV population $Y_W(t)$ by almost half a million, to 7.1 milllion (see **Figure 10**).

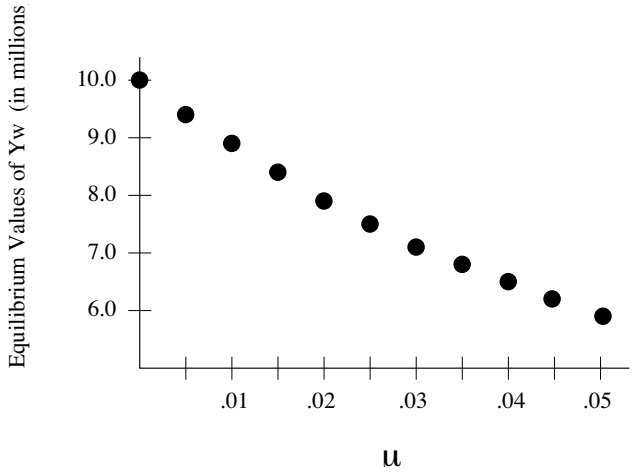

Figure 10. Equilibrium values of Y_W vs. μ.

5.4 Vaccination Model

Similar to vaccines used to control smallpox, polio, and measles, HIV vaccines have been developed that employ a weakened "vaccine-strain" of HIV to help the body build immunity to the wild-strain virus. However, it is possible for a vaccinated individual to contract the wild-strain virus; even worse, there is the possibility that the vaccine strain will cause AIDS.

Unlike abstinence intervention, vaccination intervention requires a more substantial change in the model, in particular, an increase by two in the number of functions under consideration—that is, the dimension of the system increases from three to five. In particular, we extend Blower's epidemiological model to include a variable Y_V that gives the number of sexually active individuals that have received the vaccination, and a variable Y_{VW} that indicates the number of sexually active, vaccinated individuals that have contracted the wild-strain HIV virus. The resulting fifth-order system, which we call the *extended Blower epidemiological model*, is

$$\frac{dX}{dt} = (1-p)\pi - X(c\lambda_V + c\lambda_W + \mu_X), \tag{34}$$

$$\frac{dY_V}{dt} = p\pi + Xc\lambda_V - (1-\psi)Y_V c\lambda_W - Y_V(\nu_V + \mu_V), \tag{35}$$

$$\frac{dY_W}{dt} = Xc\lambda_W - Y_W(\nu_W + \mu_W), \tag{36}$$

$$\frac{dY_{VW}}{dt} = (1-\psi)Y_V c\lambda_W - Y_{VW}(\nu_{VW+}\mu_{VW}), \tag{37}$$

$$\frac{dA}{dt} = Y_W\nu_W + Y_{VW}\nu_{VW} + Y_V\nu_V - A(\mu_A + \delta_A). \tag{38}$$

With the help of **Table 2** and **4**, which explain the meaning of the dependent variables and constants, you are asked in **Exercise 10** to construct a transition diagram for equations **(34)–(38)** similar to **Figures 2** and **8**, and also to explain the assumptions behind formulation of the extended five-dimensional system.

Table 4.
Additional variables and parameters used to study vaccination programs.

		Initial or default value
Dependent Variables		
Y_V	Number of vaccinated individuals	1000 people
Y_{VW}	Number of vaccinated individuals infected with wild-type HIV	0 people
Parameters and constants		
p	Proportion of entering sexually active population that is vaccinated	.4
λ_V	Probability that sexual partner is vaccinated	.5
ψ	Degree of protection provided by the vaccine	.93
ν_V	Proportion of vaccinated pop. that progress to AIDS	.005 year^{-1}
ν_{VW}	Proportion of vaccinated wild-strain pop. that progress to AIDS	.95 year^{-1}
μ_V	Proportion of vaccinated pop. that becomes sexually inactive	.025 year^{-1}
μ_{VW}	Proportion of vaccinated HIV pop. that becomes sexually inactive	.025 year^{-1}

Many HIV vaccine trials are controlled by the HVTN, a network of research and medical institutions that oversee and unify different approaches to HIV vaccination. Current research involves HIV vaccinations which do not employ weakened strain HIV, but rather, tiny pieces of bacterium that produce HIV proteins, chemically synthesized replicas of HIV proteins, or direct injection of the DNA that creates coding for HIV proteins. Vaccines have succeeded in reducing the viral load, which significantly decreases the probability of transmission from an infected individual to a healthy one.

Vaccines have not yet been able to prevent primary HIV infection, but we can do a simple simulation experiment to predict the effect if such a vaccine could be developed. The Mathematica plot in **Figure 11** indicates that under the assumptions that 40% of the entering sexual population has been vaccinated ($p = .4$) and that the vaccine reduces the rate of infection with HIV by 93% ($\psi = .93$), the growth of the wild-strain HIV population $Y_W(t)$ is curbed, so that the equilibrium value is under 2 million. This is a dramatic improvement over the HIV population equilibrium level (7.5 million) in the absence of a vaccination program (**Figure 9**, p. 25).

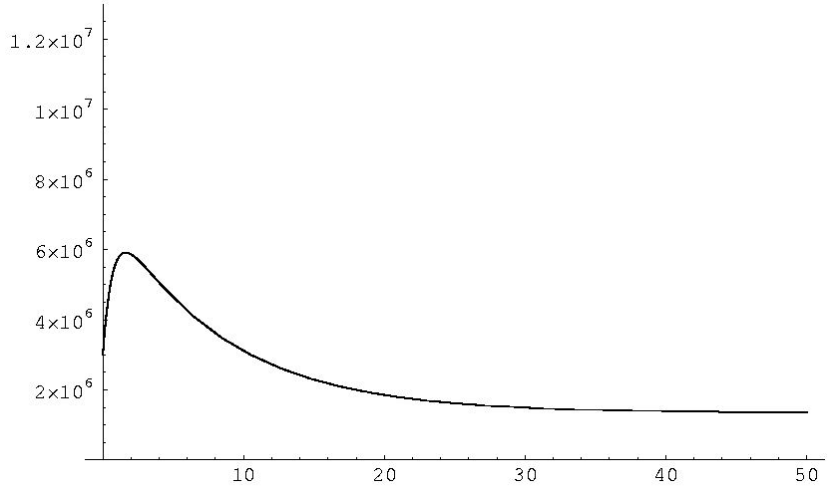

Figure 11. Using the initial and constant values in **Tables 2** and **4**, Blower's extended epidemiological model **(34)–(38)** predicts that the vaccination program will curb the growth of the HIV population $Y_W(t)$ to an equilibrium value under 2 million. (Compare this with the growth without vaccination shown in **Figure 9**, p. 25.)

Exercises

10. a) Construct a transition diagram for the dependent variables in Blower's epidemiological model extended for the study of vaccination programs **(34)–(38)**.

b) Explain the role and makeup of the equations in Blower's extended epidemiological model.

c) Find the equilibrium values for Blower's extended epidemiological model using the constant values given in **Tables 2** and **4**, and then determine the stability of the equilibrium point.

d) How effective is the vaccination program in reducing the percentage of the total sexually active equilibrium population $(X+Y_V+Y_{VW}+Y_W+A)$ that has AIDS? (Compare your answer with the answer to **Exercise 9c)**.

11. Does Blower's extended epidemiological model **(34)–(38)**

a) allow for the fact that vaccinated individuals may contract AIDS as a result of receiving the vaccine?

b) model a population with *fundamental hope of intervention* in the sense defined at the end of **Section 5.2**?

5.5 Discussion

Blower's epidemiological models are based on a simple conceptual framework. The inclusion of a large number of parameter values allows considerable flexibility in the specific assumptions being made about the population. A major difficulty arises in trying to determine specific parameters that are

applicable to a particular country. Though extensive statistical studies have been performed in a country such as Uganda, the studies were not designed to determine the relevant parameters needed to apply Blower's model.

Determination of T-cell counts by flow cytometry is an expensive procedure. Hence, to differentiate the population that has progressed to AIDS, clinical diagnosis based on characteristic symptoms are employed. In other words, it is difficult to obtain accurate values for $Y_W(t)$ and $A(t)$.

Once parameter and initial values are established, predictions can be obtained by numerical simulation under a wide variety of hypothesized interventions. This information may provide some guidance as to effective policy.

6. The Ongoing Challenge

We have attempted to make accessible to calculus students two differential equation models of the immunological and epidemiological aspects of HIV/AIDS. We have also suggested how the assumptions of the basic models introduced can be revised to obtain a more complete description of the disease dynamics.

Those far removed from the epicenter of the HIV/AIDS pandemic all too easily dismiss the enormous magnitude of the present-day global crisis. At the 13th International Conference on AIDS and STIs in Africa, held in September 2003, Pres. Kibaki of the host country Kenya put the ongoing challenge in no uncertain terms: "the pandemic cannot only be fought sometimes, but must be fought all the time, every moment, every day" [Piot 2003].

7. Solutions to Selected Exercises

1. a) Since $n = 2$, letting $y = x^{1-n}$ we have that $y = 1/x$ and $x = 1/y$, so

$$\frac{dx}{dt} = -\frac{1}{y^2}\frac{dy}{dt}.$$

Substituting these expressions for dx/dt and x into the logistic equation gives

$$-\frac{1}{y^2}\frac{dy}{dt} = \frac{k}{y} - \frac{k}{My^2}.$$

Simplifying, we obtain

$$y' + ky = \frac{k}{M}, \tag{39}$$

which is linear in y.

b) In **(39)**, the integrating factor is $\mu(t) = e^{\int k dt} = e^{kt}$. Multiplying both sides of **(39)** by $\mu(t)$, we obtain

$$y'e^{kt} + kye^{kt} = \frac{ke^{kt}}{M}.$$

Integrating both sides with respect to t gives

$$ye^{kt} = \frac{e^{kt}}{M} + C, \qquad \text{or} \qquad y = \frac{1}{M} + \frac{C}{e^{kt}}.$$

Using the initial condition $y(0) = y_0$, we obtain $C = y_0 - 1/M$. Hence,

$$y = \frac{e^{kt} + My_0 - 1}{Me^{kt}} \tag{40}$$

is a solution to **(39)**.

c) Recalling that $y = 1/x$, the solution **(40)** expressed in terms of x is

$$x = \frac{Me^{kt}}{e^{kt} + My_0 - 1}. \tag{41}$$

Substituting $y_0 = 1/x_0$, we obtain an explicit solution to the logistic growth equation:

$$x = \frac{Me^{kt}}{e^{kt} + \frac{M}{x_0} - 1}.$$

d) The explicit form of x obtained in **c)** can be written

$$x = \frac{M}{1 + \left(\frac{M}{x_0} - 1\right) e^{-kt}}.$$

For any $x_0 > 0$, $\lim_{t\to\infty} x(t) = M$, which proves the stability of M. It also demonstrates the instability of the 0 equilibrium, because positive initial conditions arbitrarily close to 0 converge to M rather than 0.

2. a) We need to solve the equation $y' = ay - dy^2$, where $a = r - \mu$ and $d = r/y_{\max}$. The change of variables $v = 1/y$ leads to the equation

$$-\frac{1}{v^2}\, v' = \frac{a}{v} - \frac{d}{v^2} \quad \Longrightarrow \quad v' + av = d.$$

Multiplying through by the integrating factor e^{at} gives

$$v'e^{at} + ave^{at} = de^{at}.$$

Integrating both sides, we find

$$ve^{at} = \frac{de^{at}}{a} + C \quad \Longrightarrow \quad v(t) = \frac{d}{a} + \frac{C}{e^{at}}.$$

The initial condition $v(0) = v_0$ is used to find C:

$$v(0) = v_0 = \frac{d}{a} + C \quad \Longrightarrow \quad C = v_0 - \frac{d}{a} \quad \Longrightarrow \quad v(t) = \frac{d}{a} + \frac{v_0 - \frac{d}{a}}{e^{at}}$$
$$\Longrightarrow \quad v(t) = \frac{av_0 - d + de^{at}}{ae^{at}}.$$

It follows that

$$y(t) \quad = \quad \frac{ae^{at}}{\frac{a}{y_0} - d + de^{at}}.$$

b) We again let $a = r - \mu$ and $d = r/y_{\max}$ and now seek to solve the differential equation

$$y' = s + ay - dy^2.$$

By making the change of variables $u = y - y_{\text{eq}}$, where

$$y_{\text{eq}} = \frac{a + \sqrt{a^2 + 4ds}}{2d},$$

we obtain $u' = -du^2 - u\sqrt{a^2 + 4ds}$. If we let $q = \sqrt{a^2 + 4ds}$, then $u' + qu = -du^2$, which is a Bernoulli differential equation in u. Letting $v = 1/u$, we obtain $v' - qv = d$. Multiplying through by the integrating factor e^{-qt}, and then integrating both sides with respect to t, we reach

$$ve^{-qt} = \frac{-d}{q}e^{-qt} + C, \qquad v = \frac{-d}{q} + Ce^{qt}.$$

Back substitution gives

$$y = \frac{q}{-d + qCe^{qt}} + y_{\text{eq}}.$$

If $y_0 \neq y_{\text{eq}}$, then we have

$$qC = \frac{q}{y_0 - y_{\text{eq}}} + d,$$

and so obtain the following formula for nonequilibrium solutions:

$$y = \frac{qe^{-qt}}{\frac{q}{y_0 - y_{\text{eq}}} + d - de^{-qt}} + y_{\text{eq}}.$$

3. From the first equation, we see that $x' = x \implies x = x_0 e^t$. Substituting this expression for $x(t)$ into the second equation yields

$$y' = x_0 e^t + 2y \implies y' - 2y = x_0 e^t.$$

Letting $\mu(t) = e^{\int -2dt} = e^{-2t}$ gives

$$\begin{aligned} y'e^{-2t} - 2ye^{-2t} = x_0 e^{-t} &\implies (ye^{-2t})' = x_0 e^{-t} \\ &\implies ye^{-2t} = -x_0 e^{-t} + c \implies y(t) = -x_0 e^t + ce^{2t}. \end{aligned}$$

Since $y(0) = y_0$, then

$$y_0 = -x_0 + c \implies c = x_0 + y_0 \implies y(t) = -x_0 e^t + (x_0 + y_0)e^{2t}.$$

4. The system

$$\begin{aligned} x' &= -x \\ y' &= -x - 2y \end{aligned}$$

can be expressed in matrix form as

$$\begin{pmatrix} x' \\ y' \end{pmatrix} = \begin{pmatrix} -1 & 0 \\ -1 & -2 \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}.$$

The eigenvalues of the coefficient matrix are obtained as follows:

$$\begin{aligned} \det \begin{pmatrix} -1-\lambda & 0 \\ -1 & -2-\lambda \end{pmatrix} = 0 &\implies (-1-\lambda)(-2-\lambda) = 0 \\ &\implies \lambda_1 = -1,\ \lambda_2 = -2. \end{aligned}$$

Since both eigenvalues for this system are negative, the equilibrium point $(0, 0)$ must be stable.

5. The Jacobian matrix is

$$J(x, y) = \begin{pmatrix} -1-2x & 0 \\ -1 & -2 \end{pmatrix}, \quad \text{so} \quad J(0, 0) = \begin{pmatrix} -1 & 0 \\ -1 & -2 \end{pmatrix},$$

giving $(-1-\lambda)(-2-\lambda) = 0$ and $\lambda = -1, -2$. Since both of the eigenvalues are negative, this system has a stable equilibrium at $(0, 0)$.

$$J(-1, 1/2) = \begin{pmatrix} 1 & 0 \\ -1 & -2 \end{pmatrix} \quad \text{gives} \quad (1-\lambda)(-2-\lambda) = 0 \quad \text{and} \quad \lambda = 1,\ -2.$$

Since one of the eigenvalues is positive, this system has an unstable equilibrium at $(-1, 1/2)$.

6. The matrix is

$$\begin{pmatrix} r - \frac{2rT+rT^*+rT^{**}}{T_{\max}} - \mu_T - k_1 V & -rT/T_{\max} & -rT/T_{max} & -k_1 T \\ k_1 V & -\mu_{T^*} - k_2 & 0 & k_1 T \\ 0 & k_2 & -\mu_{T^{**}} & 0 \\ -k_1 V & 0 & N\mu_{T^{**}} & -k_1 T - \mu_V \end{pmatrix}.$$

7. Substituting in the parameter values given in **Table 1**, using the value $T = T_{\text{unifected}} = 1000$, we obtain the matrix

$$\begin{pmatrix} -0.03 & -0.02 & -0.02 & -0.024 \\ 0 & -0.023 & 0 & .024 \\ 0 & 0.003 & -0.24 & 0 \\ 0 & 0 & N(0.24) & -2.424 \end{pmatrix}.$$

Using a symbolic manipulator such as Maple, we find that when $N = 500$, the eigenvalues are all negative reals ($\approx -0.03,\ -0.257,\ -0.008,\ -2.422$), and when $N = 1400$, three eigenvalues are negative ($-0.03,\ -0.283\ -2.419$) and one of the eigenvalues is positive (0.016).

8. A simulation using Mathematica indicates that Perelson **(30)** predicts a similar delay in the onset of AIDS as Perelson **(21',22',24')**. Can the similarity in effect be investigated analytically?

9. a)

- Equation **(31)** gives the rate of change dX/dt for the susceptible population $X(t)$. Growth is due to new susceptibles joining the population at a constant rate (π), while decreases are due to infection with wild-strain HIV ($-c\lambda_W X$) and transition to sexual inactivity ($-\mu_X X$).
- Equation **(32)** gives the rate of change dY_W/dt of the sexually active wild-strain HIV population ($Y_W(t)$). Growth is due to infection of susceptible individuals ($c\lambda_W X$) while decreases are due to transition to AIDS ($-Y_W \nu_W$) and transition to sexual inactivity ($-\mu_W Y_W$).
- Equation **(33)** gives the rate of change dA/dt of the sexually active AIDS population $A(t)$. Growth is due to progression to AIDS in the population infected with HIV ($Y_W \nu_W$) and decreases are due to transition to sexual inactivity ($-A\mu_A$) and AIDS-related death ($-A\delta_A$).

b) Setting the right-hand side of each equation in Blower's epidemiological model equal to zero, we find the following equilibrium values:

$$X = \frac{\pi}{c\lambda_W + \mu_X} \approx 2{,}353{,}000,$$

$$Y_W = \frac{\pi c \lambda_W}{(c\lambda_W + \mu_X)(\nu_W + \mu_W)} \approx 7{,}530{,}000,$$

$$A = \frac{\pi c \lambda_W \nu_W}{(c\lambda_W + \mu_X)(\nu_W + \mu_W)(\mu_A + \delta_A)} \approx 772{,}000.$$

The stability of this equilibrium can be determined by finding the eigenvalues of the matrix

$$\begin{pmatrix} -(c\lambda_W + \mu_X) & 0 & 0 \\ c\lambda_W & -(\nu_W + \mu_W) & 0 \\ 0 & \nu_W & -(\mu_A + \delta_A) \end{pmatrix}.$$

For the parameter values given in **Table 2**, the equilibrium must be stable, since the eigenvalues are all negative ($-.425$, $-.125$ and $-.975$).

c) In equilibrium, roughly 71% of the total sexually active population have HIV.

10. a) See **Figure S1**.

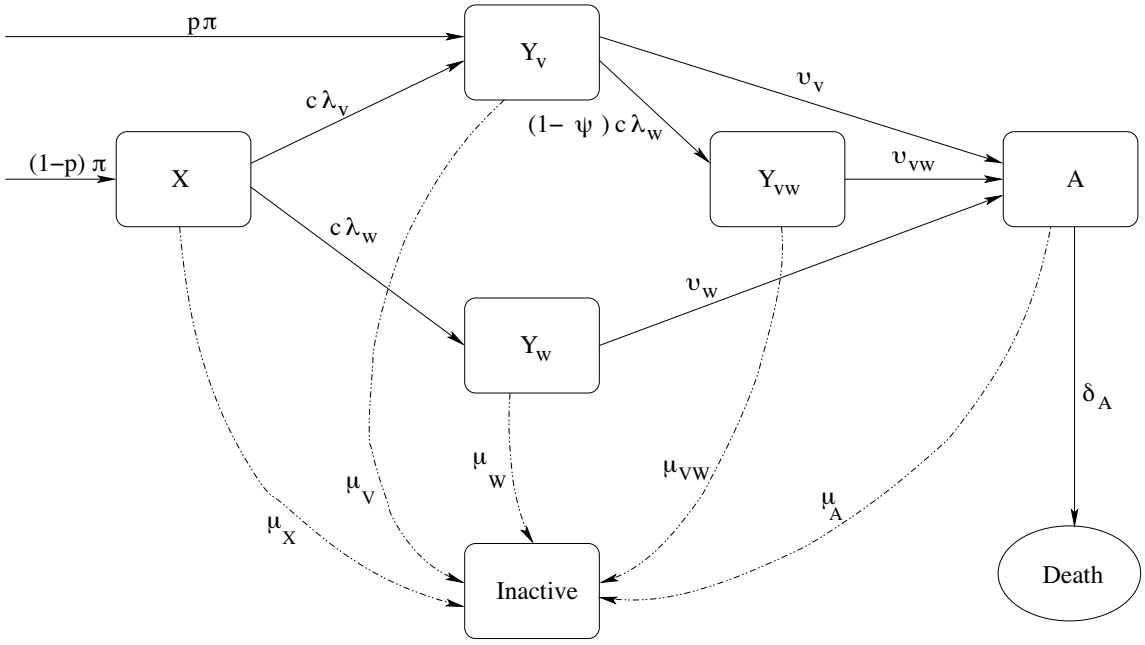

Figure S1. Solution to **Exercise 10a** showing the transition rates for the modification of Blower's epidemiological model used to study the efficacy of HIV vaccination programs.

11. Yes. This is built into the model as the term $Y_V \nu_V$ in **(35)** and **(38)** and by the arrow from Y_V to A in **Figure S1**.

Appendix: Mathematica Program

The following Mathematica commands

- solve Perelson's immunological model **(21)–(24)** numerically, using the initial values and parameter values given in **Table 1**; and

- generate the graph show in **Figure 3**.

In addition to several other minor notational modifications, we have used n, $T1$, and $T2$ in place of N, T^*, and T^{**} respectively.

```
%% Assignment of Parameter Values
s    = 10
r    = .03
Tmax = 1500
muT  = .02
mub  = .24
muV  = 2.4
k1   = .000024
k2   = .003
n    = 500

%% Obtaining the Numerical Solution
sol =  NDSolve[{T'[t]
    == s + r*T[t]*(1-(T[t]+T1[t]+T2[t])/Tmax)
         - muT*T[t]-k1*T[t]*V[t],
       T1'[t] == k1*T[t]*V[t] - muT*T1[t]-k2*T1[t],
       T2'[t] == k2*T1[t] - mub*T2[t],
       V'[t]  == n*mub*T2[t] - k1*T[t]*V[t] - muV*V[t],
       T[0] == 500, T1[0] == 0, T2[0] == 0, V[0] == .001},
       {T,T1,T2,V}, {t,0,2000}]

%% Generating the Graph of T(t)
Plot[{0,Evaluate[T[t].sol]}, {t,0,1600}, PlotRange -> {0,1001}]
```

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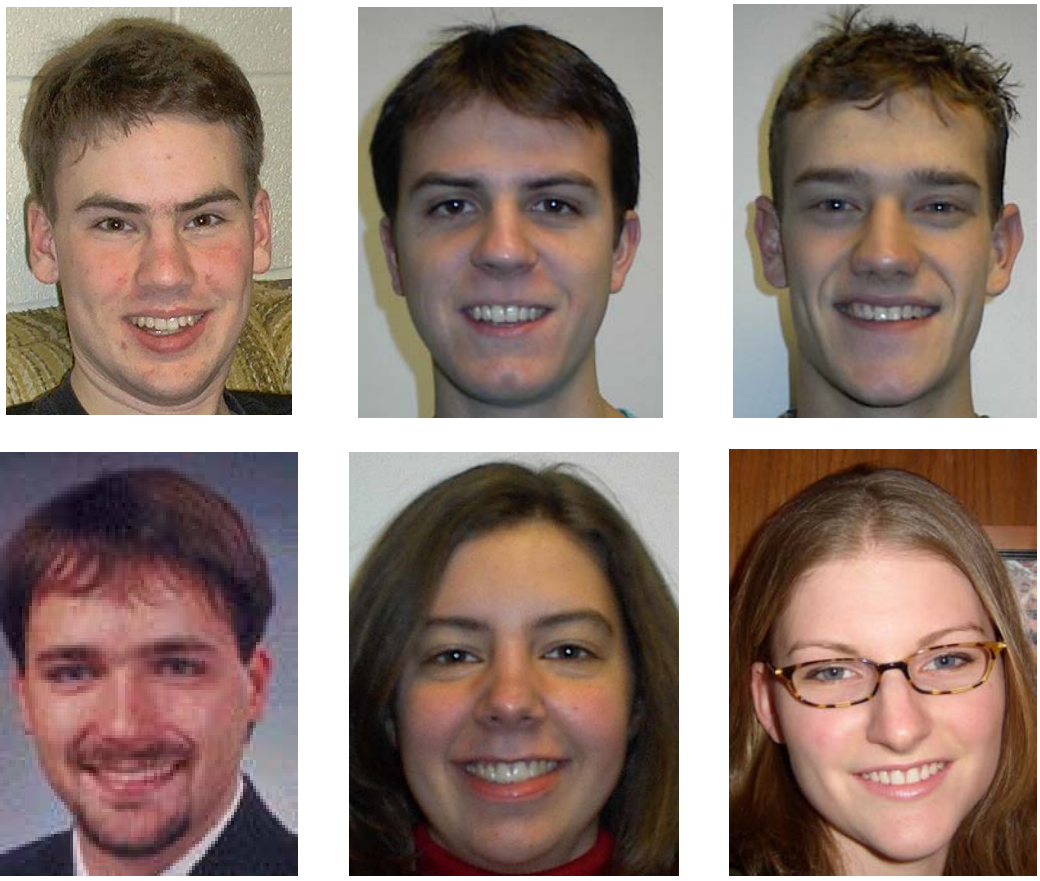
About the Authors

Paul Isihara, a mathematics professor at Wheaton College, was inspired to write this Module by his involvement at Mekelle Institute of Technology (MIT), a new engineering college in Ethiopia with a strategic vision for development of some of the most impoverished areas of the country. He was interviewed about MIT on Chicago Public Radio on 27 January 2005: `http://www.chicagopublicradio.org/programs/worldview/series/globalactivism.asp` .



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