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COMAP

Module 791

Immunological and Epidemiological HIV/AIDS Modeling

Paul A. Isihara, Dept. of Mathematics
with Andrew Barker, Jordan Hostetter, Michael Hubbell, Kyle Hunsberger, Kimberly Waite, Rebecca Wilson,
Wheaton College, Wheaton, IL 60187

Differential Equations
Public Health, immunology, epidemiology

COMAP, Inc., Suite 210, 57 Bedford Street, Lexington, MA 02420 (781) 862-7878

INTERMODULAR DESCRIPTION SHEET:	UMAP Unit 791
TITLE:	Immunological and Epidemiological HIV/AIDS Modeling
AUTHOR:	Paul A. Isihara Department of Mathematics Paul.A.Isihara@wheaton.edu with Andrew Barker Jordan Hostetter Michael Hubbell Kyle Hunsberger Kimberly Waite Rebecca Wilson Wheaton College Wheaton, IL 60187
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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(800) 77-COMAP = (800) 772-6627, or (781) 862-7878; http://www.comap.com

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Paul A. Isihara
Department of Mathematics
Paul.A.Isihara@wheaton.edu

with
Andrew Barker
Jordan Hostetter
Michael Hubbell
Kyle Hunsberger
Kimberly Waite
Rebecca Wilson
Wheaton College
Wheaton, IL 60187

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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:

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

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

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

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

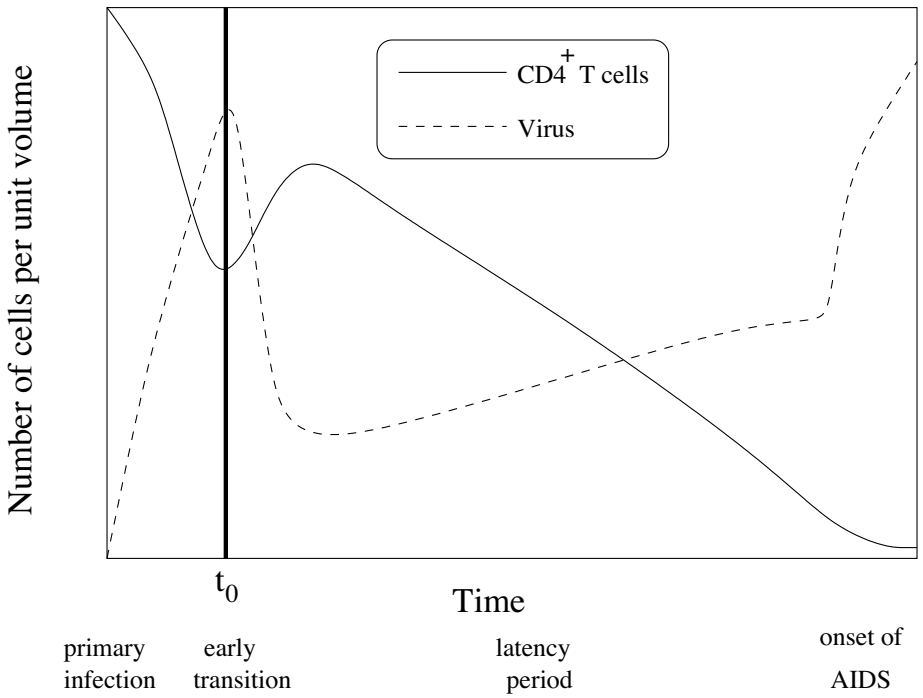

Figure 1. Qualitative dynamics of the healthy T-cell and HIV-viral concentrations based on clinical data. The Perelson immunological model simulates the dynamics beginning at $t = t_0$.

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

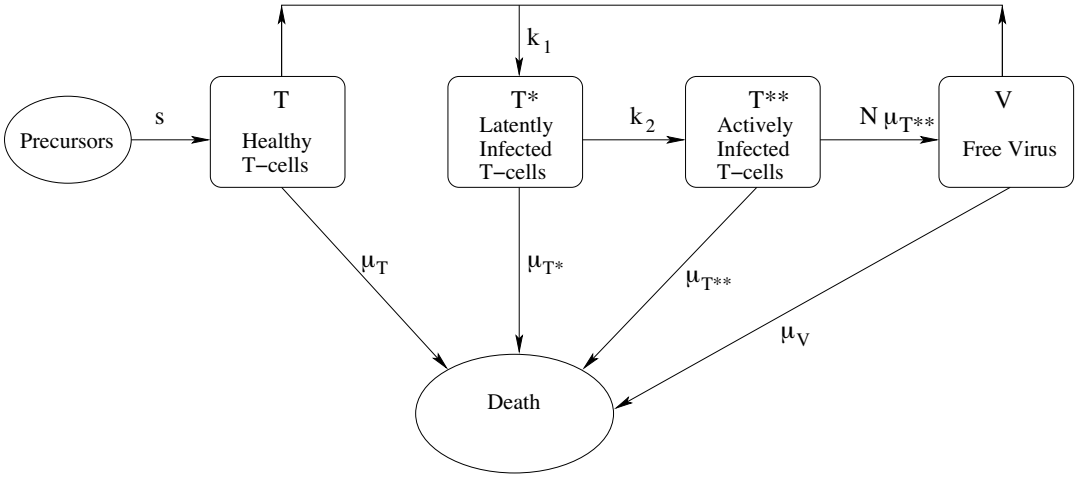

Figure 2. Rates of increase/decrease in concentrations described by Perelson's immunological model **(21)–(24)**.

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 ($-\mu_V V$).