Chapter 15

Diseases

We live in dangerous, deadly times. More than 25% of all deaths world-wide are caused by infectious diseases (Morens et al. 2004): HIV/AIDS, SARS, HPS (Hanta), Lyme, Ebola, BSE/vCJD (Mad Cow), STDs, West Nile, Plague, to mention only a few to which humans are susceptible. The list lengthens dramatically if we include diseases attacking cherished and economically important plants and animals. It would seem that humans are not the ultimate predator, even though we can be extremely efficient when we set our minds to decimating populations. As the human population increases with the associated increase in crowding and dispersal rates, the dynamics of diseases is well-worth careful study. These dynamics are made all the more complicated by the rapid evolution of many of the causative agents.

This chapter illustrates concepts from Part I, such as mass action, age structured population models, validation, parameter sensitivity, conservation equations, and nullclines.

15.1 Simple Models

A large number of simple models of epidemics have been studied, many yielding valuable analytical results. Here, we survey a few of these.

Constant Infection

Perhaps the simplest model is one that assumes the number of diseased persons (D) increases with a constant rate of infection (a), and that each diseased person has a constant probability of being cured (b):

$$\frac{dD}{dt} = a - bD.$$

As a result, the absolute rate of cure increases as the number of cases increases. This simple model has an analytic solution:

$$D(t) = \frac{1}{b}\left(a - e^{-bC}e^{-bt}\right) \tag{15.1}$$

where the constant of integration is $C = -\ln(a - bD(0))/b$. Using either graphical or analytical methods, it is clear that this model has a single (non-trivial) stable equilibrium at $D^* = a/b$. In other words, the disease is never lost from the population.

15.1.1 SIR and Derivatives

The disease modeled by Eq. 15.1 is unrealistic since it attributes no biological properties to the disease; infection is independent of the number of cases. It is a better descriptor of a physical or chemical agent such as radiation or toxic chemicals than of a biological disease or epidemic. The next level of realism comes by relating the rate of infection to the number of cases, i.e., an infectious disease. A much-studied family of such models is the SIR models of three compartments in a diseased population: Susceptible, Infected, and Removed individuals. This model was originally derived from a probabilistic argument by Kermack and McKendrick (1927), but the derivation is clearly and concisely restated in Hoppensteadt and Peskin (1992, Chap. 3). The Kermack-McKendrick model is:

$$\frac{dS}{dt} = -\alpha S I \tag{15.2}$$

$$\frac{dI}{dt} = \alpha S I - \beta I \tag{15.3}$$

$$\frac{dR}{dt} = \beta I, \tag{15.4}$$

where S, I, and R are the numbers of susceptible, infected, and removed individuals in a population of fixed size $N = S + I + R$. Removed individuals are those that have acquired the disease, but are not able to infect susceptibles. This situation may arise because the removed individuals have died, been quarantined, or have survived and acquired immunity. α is the infection rate for a mass action process between susceptibles and infectious subpopulations. β is the "cure" rate by which infected individuals become resistant to further infection by future contact with infected individuals. Since we are assuming that the time scale of the epidemic dynamics is very small compared to the birth and death rates of individuals, we assume a constant population size. From the conservation equation above, we can define $R = N - (S + I)$ and can therefore eliminate Eq. 15.4.

The nullclines of the model are $I = 0$, $S = 0$, and $I = \beta/\alpha$. Thus, there is only one equilibrium: $(0, 0, N)$; i.e., all individuals are "removed" (dead or cured, depending on the disease). However, the fact that $dI/dt = 0$ has a nullcline at β/α implies that for $S > \beta/\alpha$, $dI/dt > 0$, and $dI/dt < 0$ when $S < \beta/\alpha$. This means there is a threshold in S above which the disease will increase (become an epidemic). This is reflected in the phase-space dynamics for various initial conditions. Figure 15.1 shows trajectories (time increases from right to left) of three starting values, the $dI/dt = 0$ nullcline, and constraints on the initial conditions for $N = 800$.

MBS-CD contains `SimSIR-theory` for Fig. 15.1.

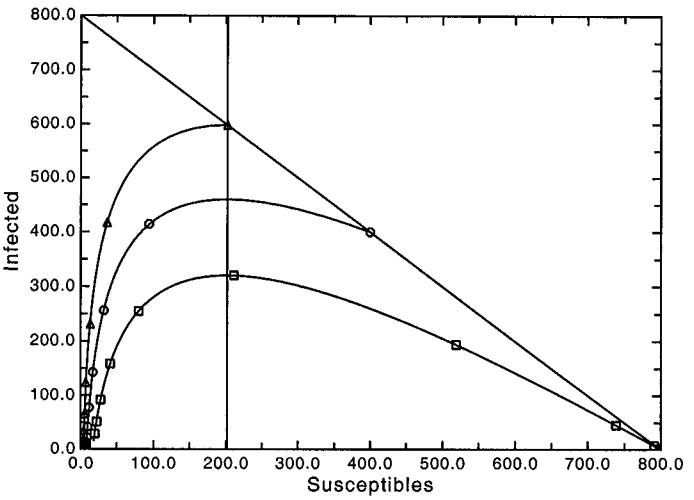

Figure 15.1: Phase space portrait of the SIR model. Marked lines are three initial conditions, vertical line is the $dI/dt = 0$ nullcline, and the diagonal line $N = I + S = 800$ line.

This model works well for several epidemics. Murray (1989), using data for a flu outbreak in an English boys boarding school in 1978 that lasted 14 days, fit the parameters of Eqs. 15.2–15.4. The model is remarkably accurate for this short-term, controlled set of observations (Fig. 15.2). In this case, boys showing symptoms were quarantined, so, effectively, I represents the number of new cases arising from a diminishing pool of susceptibles.

MBS-CD contains `SimSIR-valid` that produced Fig. 15.2.

15.2 AIDS

Almost exactly twenty years before 9/11/01, another terrorist struck the United States. Although it does not act in isolated, spectacular events, the death and welfare toll

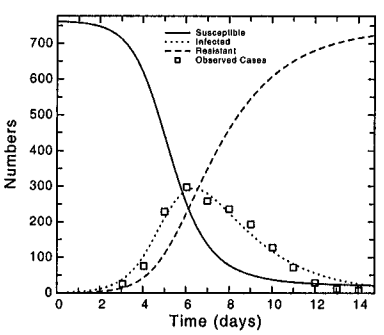

Figure 15.2: Model and data for a 1978 flu epidemic in an English boarding school for boys. Parameters are: $S(0) = 762$, $I(0) = 1$, $\alpha = 0.00218$, $\beta = 0.4404$, $N = 763$.

from this agent of destruction far exceeds the devastation of the New York World Trade Center. In June 1981, a report in the Center for Disease Control's publication *Morbidity and Mortality Weekly Report* (Gottlieb et al. 1981; Fannin et al. 1982) first announced this new threat. As with human terrorists, the *human immunodeficiency virus* (HIV) respects no political borders, uses stealth to achieve its ends, and seeks to conquer by destroying the system's infrastructure. Because of the huge impact on human misery and economic development, many mathematical models of HIV/AIDS have been developed. In this section, we explore some of these models and the biology on which they are based.

15.2.1 Biology of HIV/AIDS

HIV is the causative agent of AIDS (*acquired immune deficiency syndrome*). AIDS, itself, is clinically defined to be the condition of a patient having fewer than 200 CD4+ white blood cells per milliliter of blood and testing positive for HIV antibodies. HIV has some unique properties that explain not only the devastating affect it has on individuals, but also the virus' ability to become pandemic. See Table 15.1 for basic definitions.

In addition to mechanical barriers such as skin and mucous, an organism relies on its immune system to identify and destroy foreign material (*antigens*). Much of this action is accomplished by a system of white blood cells, particularly *leukocytes*. A class of these (*lymphocytes*), has the ability to adapt to and interact with specific antigens. Lymphocytes are white blood cells that secrete *antibodies* to specific antigens. *B cells* are a subclass that defeat antigens circulating in the blood stream, while *T cells* form antibodies for antigens inside or associated with normal cells. There are many kinds of T cells. Some of them (T_C, *cytotoxic cells*) bind to infected cells and secrete enzymes that lyse the foreign or infected cell. Another class (T_S, *suppressor T cells*) has the important role to suppress the specific response of the immune system after the population of antigens has been reduced to tolerable levels. But for the HIV/AIDS story, the most important class of T cells is the *helper T cells* (T_H). These T cells play the pivotal role of enhancing and stimulating the destructive lymphocytes (T_C and B cells). T_H cells interact with macrophages adapted to recognize specific antigens and when all three are present, T_H cells proliferate and secrete *cytokines*, a class of signaling molecules that target the corresponding B or T_C cells.

Viruses can attack many different kinds of cells, including T cells. If a virus attacks and decimates a particular destructive lymphocyte only the ability to attack a specific antigen is lost. However, to lose T_H cells means that the entire immune system is imperiled. HIV attacks the T_H cells, which is why it is so debilitating. The particular T_H cells targeted by HIV are those which have on their surface binding molecules called *CD4+*. Thus, the levels of CD4+ T_H cells in the blood are an indicator of the health of the immune system. While this attack strategy makes HIV particularly deadly, it is, none the less, just another antigen, so you might expect that other T_H cells would evolve to stop HIV. Unfortunately, another aspect of the life cycle of HIV makes this difficult.

In order for HIV to be a successful virus it must reproduce. But as with all parasitic-like organisms that rely on a host, too much reproduction and too rapidly

Table 15.1: Definitions for HIV/AIDS.

Term	Definition
AIDS	Acquired Immune Deficiency Syndrome
antibody	agents that act in antagonism to harmful foreign bodies
antigen	a harmful foreign body that stimulates the production of antibodies
B cell	leukocytes attacking antigens circulating in the blood; originate in the bone marrow
CD4+ cell	T cell with CD4+ receptor that recognizes antigens on the surface of a virus-infected cell and secretes lymphokines that stimulate B cells and killer T cells
cytokines	chemicals from T_H cells signaling the presence of antigens and stimulating B and T_C cells
Cytotoxic T cell	killer cells specific to particular antigens
Helper T cell	cells specific to antigens and secreting stimulating cytokines; targeted by the HIV
HIV	Human Immunodeficiency Virus
Killer T cell	cytotoxic T cell
leukocyte	white blood cells that engulf and digest bacteria and fungi
lymphocyte	leukocytes reacting to specific antigens
macrophage	a white blood cell that engulfs foreign bodies and displays antigens on their cell surface
retrovirus	a virus having only RNA
reverse transcriptase	an enzyme that converts RNA to DNA
Suppressor T cell	A T cell that reduces or suppresses the immune response of B and T cells to an antigen.
T cell	a leukocyte attacking antigens inside or attached to specific cells; originates in the thymus
T_C cell	cytotoxic T cell
T_H cell	helper T cell
T_S cell	suppressor T cell

killing the host will prevent the virus from spreading. Too little viral reproduction will also reduce the spread of the virus, so an intermediate level must evolve. HIV's life cycle mechanism is unusual in that it both prevents rapid destruction of the host and prevents the host from establishing an immunity.

HIV enters the host in fluids that get past the non-specific mechanical barriers (skin, mucous). These pathways are well known: sexual transmission, blood transfusions, shared intervenous needles. (Fortunately, HIV is not airborne and is not viable after dehydration.) Once inside, HIV enters the blood stream and from there attacks T_H cells. HIV is a *retrovirus*, which means it contains only RNA, no DNA. Recall that in normal eukaryotic cells, segments of DNA transcribe themselves into single stranded forms called messenger RNA, which leaves the nucleus and interacts with ribosomes

to form proteins. During mitosis, double stranded DNA makes two copies of itself by the process of *transcription*. So, in this mode, DNA (not RNA) is required for cellular reproduction. HIV, having only RNA, requires the host cell to provide the DNA machinery for its replication. HIV accomplishes this by binding to the cell, injecting its RNA into the cytoplasm, and subsequently using a viral enzyme called *reverse transcriptase* to form double stranded DNA. This viral DNA is ultimately incorporated into the host cell DNA and is replicated along with host DNA during normal mitosis. This process does not, itself, produce new HIV cells, only more copies of the DNA required for new virus cells. Over time (many months to years), poorly understood events in the infected host cells cause the viral DNA to produce viruses that bud out through the membranes of the infected host cells and enter the blood stream where it can infect new cells. This can happen repeatedly for each infected cell.

This basic life history provides a mechanism for two important properties of HIV. The processes of reverse transcribing viral RNA and subsequent incorporation into host DNA is error-prone. Viral DNA/RNA is mutated during the process; therefore, HIV is very variable within a given host organism. This makes it difficult for the host immune system to adapt to the antigen (invader). Second, HIV does not immediately kill the host. By residing inside cells, the viral DNA is preserved (and replicated at low rates) without running out of control and killing the host. As a result, the dynamics of HIV and its effect on the immune system is as follows. After the initial infection, blood HIV increases rapidly and the population of CD4+ T cells decreases. The host immune system, if healthy, responds to this invasion, forms HIV antibodies, and the blood HIV concentration is greatly reduced while CD4+ T_H cells increase almost to previous levels. However, the viral RNA/DNA is not eradicated but hides in the CD4+ T_H cell DNA and is therefore not further attacked by the immune system. Over time, the viral DNA gradually produces buds and new HIV cells that reinfect new host cells. This continues over 1–10 years, resulting in the gradual diminution of the CD4+ T_H cell population from a healthy level of about 1200 cells per milliliter of blood to the stage of clinical AIDS: 200 CD4+ T_H cells per ml of blood. Once the immune system has been degraded to this level, the host organism is susceptible to attacks from other antigens and usually dies from these extraneous attacks.

15.2.2 Epidemiology of HIV/AIDS

The epidemiological history of HIV/AIDS since its first clinical report in 1981 is grim indeed. Twenty-five years later, a total of 37.8 million humans are estimated to be infected. Of these 2.1 million are children below the age of 15 (UNAIDS 2004). In 2003, there were 4.8 million new cases of HIV. Almost 3 million died from AIDS in 2003, and nearly one-half million of these were children (UNAIDS 2004).

Spatially, the epidemic is not randomly distributed. Ninety percent of infections occur in developing countries (Way and Gibbs 2002). Sub-Sahara Africa is the most severely affected: seventy percent of current infections occur there. Over all of Sub-Sahara Africa nine percent of all adults are infected, but this average hides high infection rates in the most heavily impacted countries. Seven countries in southern Africa have infection rates above 20%, including Botswana, Namibia, South Africa, and Zimbabwe. Another high infection zone occurs in a belt across central Africa from

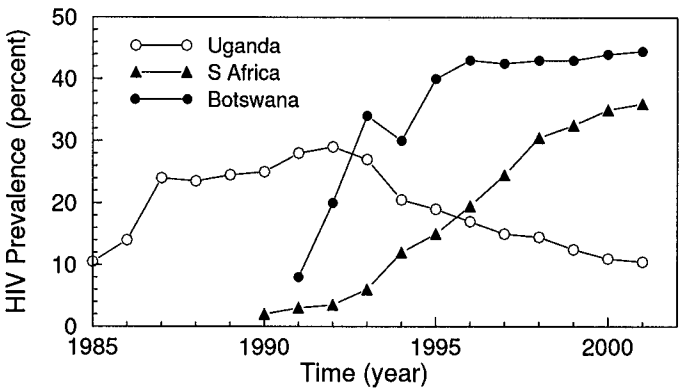

Figure 15.3: Prevalence of HIV as percent in three cities of southern Africa countries: Kampala, Uganda; Francistown, Botswana; and Kwazulu/Natal, South Africa. Source: U.S. Census Bureau, International Programs Center, HIV/AIDS Surveillance Data Base (2002 Release).

Cameroon to Kenya.

Developing countries on other continents have not yet seen these high prevalence values. In southeast Asia, the highest prevalence is in Cambodia with about 5% infections among pregnant females. But in recent years, these values are declining, as they are in Thailand that has much lower prevalence. Values for Latin America pregnant females, while not as high as the highest in Africa, are 10% in Haiti, and 5% in Honduras and Guyana (Way and Gibbs 2002).

The disease progression in many countries follows the classic dynamics of epidemics (Fig. 15.3). Uganda is now a model of HIV/AIDS control as that country was able to reduce its HIV incidence from a high of 30% to the current 10-11%. Senegal, also has undertaken control measures to keep its epidemic below 2%. Other countries, however, are not so fortunate. Botswana values are apparently leveling at 45% for the total population, and South Africa appears to be approaching the same point.

Women have higher occurrences of HIV than men, which is expected from the primary sexual transmission mode of virus infection. In Sub-Saharan Africa, this phenomenon is dramatic for ages 15–40: as many as 20% of women are infected compared to about 15% of men.

HIV/AIDS has a direct effect on population demography. Extrapolated population growth rates in the presence and absence of AIDS shows significant reduction in population growth due to AIDS. Botswana, for example, currently has a negative growth rate, but is estimated to have, were AIDS not present, a positive growth rate of 2.3%/year (Way and Gibbs 2002). Many other countries show a growth reduction of 30–50% due to increased mortality rates caused by AIDS. Projecting these growth rates to 2010 predicts even greater negative effects. These dry statistics become more real when couched in terms of life expectancy. The average Botswanan, without AIDS, would be expected to live to 72, but currently, with AIDS, the average time of death is 39 years (Way and Gibbs 2002).

15.2.3 Modeling Approaches

There are 3 main approaches to modeling and forecasting AIDS. First, a single, time-dependent equation is statistically fit to extrapolate a historical dataset into the future. This approach may simply use the historical data and find any best-fitting equation (Kramer 1992), and, thus, requires a long time series for accurate fitting. Alternatively, a suitably flexible function (e.g., a gamma distribution) that fits a large number of historical data sets is used (Chinn and Lwanga 1991). This method requires less data than the previous method, but is restricted to the properties of the gamma distribution. Both of these approaches suffer from the fact that the extrapolations are usually valid for a short time horizon and, by ignoring mechanisms, can not be used to analyze possible disease prevention strategies.

A second general model structure is individual-based (Sec. 13.1.4). As mentioned there, this class of model when applied to human demographic problems is called by its practitioners *micro-simulation*. Examples of this approach is `SimulAIDS` (Auvert et al. 1990; Robinson et al. 1995), and `STDSIM` (Van der Ploeg et al. 1998). This approach, as do most IBMs, allows detailed, mechanistic description of the relevant processes. STDSIM incorporates individual behavior on disease propagation mechanisms (e.g., demography, sexual behavior, and transmission methods) as well as intervention strategies (e.g., condoms, clean needles, and health care facilities). As with many IBMs, this model, being stochastic, requires detailed data to estimate probability distributions and relies exclusively on computer simulation for analysis.

The third class of models are compartment models, generally based on the SIR models. Applied to HIV/AIDS, these models are made significantly more complex than the simple SIR model to incorporate the effects of age, gender, sexual behavior, and disease stage (Hethcote and Van Ark 1992). A complex example of this approach is the `iwgAIDS` model: the Interagency Working Group AIDS model (Seitz 2002). This model was produced as a broadly applicable tool for computer simulation by the World Health Organization, CDC, and the World Bank. This model has produced good fits to historical data, but has a complex description that is difficult to encapsulate for expository purposes.

A similar model, that is easier to describe is that produced by a group at the Imperial College (London) (Garnett and Anderson 1993; Garnett et al. 2002). We will approach the description of this model (the "IC" model) in two steps: a preliminary simplified version, and then a fuller version that includes greater demographic structure and human sexual behavior complexity.

15.3 Simple IC Model (sIC)

Most models of sexually transmitted diseases, including the IC model of HIV/AIDS, have parameters that are age-specific. Since compartment models of epidemics are basically population models, the basic structure of age-based models as presented in Chapter 13 is applicable.

To simplify the IC model, assume we have 2 sexes (male, female), and these are similar in their sexual behavior and drug usage. We will also assume that there is a only a single stage to the development of AIDS from HIV. Figure 15.4 shows the basic

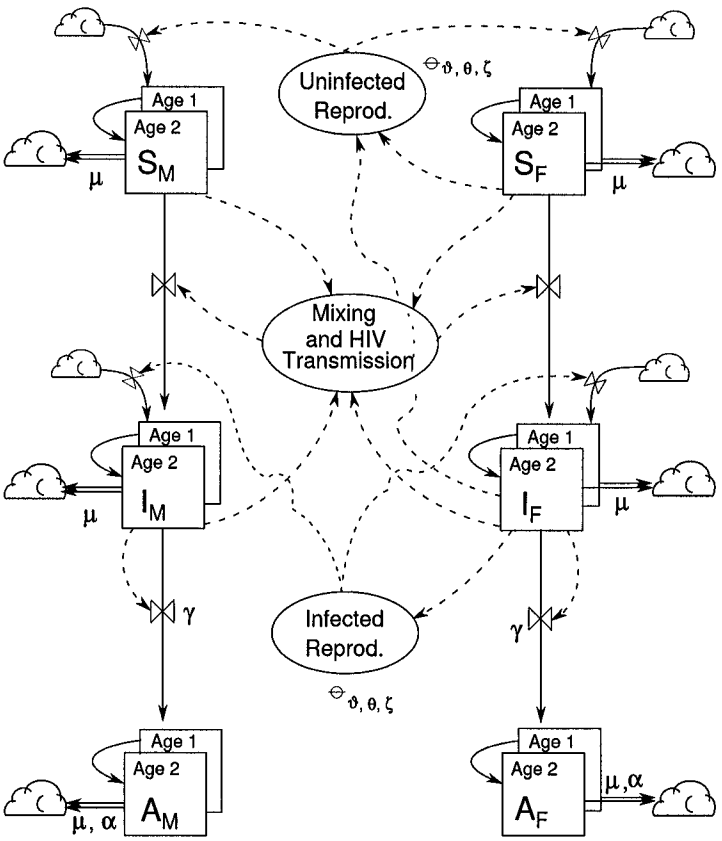

Figure 15.4: Forrester diagram for the simplified IC AIDS model. For clarity, Forrester diagram parameter symbols are not shown.

structure of the model with two age classes and two sexes (M and F). Age 1 comprises newborns to age 15. Age 2 comprises ages 16 → death. New born susceptibles are created from susceptible females (S_F) having a birth rate per female of θ and probability ζ of being sexually active as well as infected females (I_F), but which have a probability $1 - \vartheta$ of not transmitting HIV to their fetuses. Note that there is no information flow from males to reproduction; we assume the number of males do not limit female reproduction: there are always enough males to impregnate females. Members of the youngest age class considered (*Age 1*) progress to *Age 2* (the next age class) according to the basic time step of the model, the intervals of the age groupings, and mortality rate. I.e., if the interval is 5 years, the time step is 1 year, and mortality is 0.4, then the proportion of individuals aging in 1 time step is (0.2)(1-0.4)=0.12 per year. Production of infected new borns follows the same pattern, except susceptible (uninfected) females can not infect their offspring.

New cases of HIV are produced by the interaction of infected and susceptible individuals. The *per capita force of infection* is the rate of spread of HIV for an average susceptible individual engaging in sex or other activities that transmit HIV (e.g., shared

needle use by injecting drug users). Conceptually, it is the product of the rate of having sex (or sharing needles) with different types of individuals and the proportion of the population that has HIV but not AIDS. We assume persons with AIDS (as opposed to those without the clinical symptoms) do not engage in sex or transmit HIV. We also assume in this simple version that homosexual activity and shared needle use are not important. A central problem in calculating the rate of having sex is the rates and rules by which individuals choose new partners. If there is very little mixing between susceptible and infected individuals, then the force of infection should be small. Large mixing will increase the spread of HIV. Finally, infected individuals acquire AIDS at rate γ and accrue added mortality (α) in addition to natural mortality μ.

sIC Equations

Based on the above, we need 12 differential equations to describe the flow individuals among the compartments. The female equations are as follows. The definitions and values of the parameters are given in Table 15.2.

$$\frac{dS_{f,1}}{dt} = \underbrace{\eta\theta\zeta}_{\text{fertility}} \underbrace{\left(S_{f,2} + (1-\vartheta)I_{f,2}\right)}_{\text{non-infecting females}} - \underbrace{\mu S_{f,1}}_{\text{mortality}} - \underbrace{\xi S_{f,1}}_{\text{ageing}} \tag{15.5a}$$

$$\frac{dS_{f,2}}{dt} = \underbrace{\xi S_{f,1}}_{\text{ageing}} - \underbrace{(\lambda_{S_{f,2}} + \mu)}_{\text{infection/death}} S_{f,2} \tag{15.5b}$$

$$\frac{dI_{f,1}}{dt} = \underbrace{\eta\theta\zeta\vartheta I_{f,2}}_{\text{infected birth}} - \underbrace{(\mu+\xi)I_{f,1}}_{\text{death \& ageing}} - \underbrace{\gamma I_{f,1}}_{\text{to AIDS}} \tag{15.5c}$$

$$\frac{dI_{f,2}}{dt} = \underbrace{\lambda_{S_{f,2}} S_{f,2}}_{\text{infection}} - \underbrace{(\mu+\gamma)I_{f,2}}_{\text{death \& AIDS}} + \underbrace{\xi I_{f,1}}_{\text{ageing}} \tag{15.5d}$$

$$\frac{dA_{f,1}}{dt} = \underbrace{\gamma I_{f,1}}_{\text{to AIDS}} - \underbrace{(\mu+\xi+\alpha)A_{f,1}}_{\text{death \& ageing}} \tag{15.5e}$$

$$\frac{dA_{f,2}}{dt} = \gamma I_{f,2} + \xi I_{f,1} - (\mu+\alpha)A_{f,2}. \tag{15.5f}$$

The force of infection for susceptible females ($\lambda_{S_{f,2}}$) is a function based on current infected levels:

$$\lambda_{S_{f,2}} = c_{S_{f,2}}(t)\rho_{S_{f,2}} \frac{\beta_{m,f} I_{m,2}}{S_{m,2} + I_{m,2}}, \tag{15.6}$$

where $c_{S_{f,2}}(t)$ is the current rate of choosing a new male partner by a sexually active, susceptible female. $\rho_{S_{f,2}}$ is the probability that the new male partner will come from a particular age and sexual activity class. ρ is a measure of the degree that females choose different types of partners; it is a social mixing function. Since in the current,

simplified model that has only 1 age class and 1 activity class, $\rho = 1.0$. $\beta_{m,f}$ is the probability of an infected male transmitting the disease to a female. The expression $I/(S + I)$ in Eq. 15.6 represents the probability of encountering an infected individual from the population of possible partners.

The six equations for males are similar.

$$\frac{dS_{m,1}}{dt} = (1-\eta)\theta\zeta\left(S_{f,2} + (1-\vartheta)I_{f,2}\right) - (\mu+\xi)S_{m,1} \tag{15.7a}$$

$$\frac{dS_{m,2}}{dt} = \xi S_{m,1} - (\lambda_{S_{m,2}} + \mu)S_{m,2} \tag{15.7b}$$

$$\frac{dI_{m,1}}{dt} = (1-\eta)\theta\zeta\vartheta I_{f,2} - (\mu+\xi)I_{m,1} - \gamma I_{m,1} \tag{15.7c}$$

$$\frac{dI_{m,2}}{dt} = \lambda_{S_{m,2}} S_{m,2} - (\mu+\gamma)I_{m,2} + \xi I_{m,1} \tag{15.7d}$$

$$\frac{dA_{m,1}}{dt} = \gamma I_{m,1} - (\mu+\xi+\alpha)A_{m,1} \tag{15.7e}$$

$$\frac{dA_{m,2}}{dt} = \gamma I_{m,2} + \xi I_{m,1} - (\mu+\alpha)A_{m,2}, \tag{15.7f}$$

where

$$\lambda_{S_{m,2}} = c_{S_{m,2}}(t)\rho_{S_{m,2}}\frac{\beta_{f,m}I_{f,2}}{S_{f,2}+I_{f,2}}. \tag{15.8}$$

sIC Results

The basic behavior of the sIC model is shown in Fig. 15.5a. Since these parameter values were chosen to represent a developing country where birth rates are high, the population as a whole is increasing. An auxiliary variable (*sensu* Forrester Diagram) of particular interest is the proportion of the population that has the virus. Results from sIC show that, unlike a disease that terminates in resistance (e.g., the flu Fig. 15.2), HIV/AIDS does not go away.

In the recent past, efforts to halt the epidemic have focused on education and reducing the avenues for transmission. The use of condoms is one method, since sexual contact is one of the most important mechanisms by which HIV is spread. sIC can be used to determine the effects of condom use by altering the parameters $\beta_{f,m}$ and $\beta_{m,f}$ from 0.1 and 0.2, respectively, to 0.05 and 0.1. Figure 15.5b illustrates that condoms can have a significant effect on HIV prevalence. The equilibrium prevalence for females and males reduced from 0.9 and 0.75 to 0.7 and 0.45, respectively (note axis scale differences). In addition, the time lag for the disease to exceed 10% of the population increases from about 20 years to 50 years. By slowing the disease spread to this extent, the society might be able to save many lives by being provided time to develop cures and put in place social infrastructures to provide even greater reductions in prevalence.

Another important variable controlling HIV dynamics is the rate of acquiring new sexual partners and the degree of mixing among sexual activity groups (Garnett and

Table 15.2: Parameters for the Simple IC AIDS Model. Values based on Garnett and Anderson (1993). Values for variables are initial conditions used in simulations.

Symbol	Meaning	Value
Variables		
$S_{f,1}$	Susceptible females, age class 1	3000 Numbers
$S_{f,2}$	Susceptible females, age class 2	1000 Numbers
$S_{m,1}$	Susceptible males, age class 1	3000 Numbers
$S_{m,2}$	Susceptible males, age class 2	1000 Numbers
$I_{f,1}$	Infected females, age class 1	0 Numbers
$I_{f,2}$	Infected females, age class 2	0 Numbers
$I_{m,1}$	Infected males, age class 1	0 Numbers
$I_{m,2}$	Infected males, age class 2	0 Numbers
$A_{f,1}$	Aids females, age class 1	0 Numbers
$A_{f,2}$	Aids females, age class 2	0 Numbers
$A_{m,1}$	Aids males, age class 1	0 Numbers
$A_{m,2}$	Aids males, age class 2	5 Numbers
Parameters		
α	AIDS death rate	1.0/year
$\beta_{f,m}$	female to male transmission probability	0.075
$\beta_{m,f}$	male to female transmission probability	0.2
$c_{S_{m,2}}$	rate of new partners at $t = 0$	2.35/year
η	proportion females of newborns	0.5 unitless
γ	transition rate from infected to AIDS	1.16/year
μ	natural death rate	$0.0227/\text{year}^1$
ρ	social mixing probabilities	1.0
θ	female fecundity	0.2088/year
ϑ	probability perinatal transmission	0.35 unitless
ξ	proportion moving to age class 2	0.0667
ζ	proportion individuals in sexual activity class	1.0

Anderson 1993). Figure 15.6 illustrates the rapid rise of HIV as infected individuals increase the number of new sexual partners with which they interact. This confirms the common sense view that monogamy reduces the spread of sexually transmitted diseases. It also illustrates that adding just one partner per year ($c = 1.0 \rightarrow 2.0$) dramatically increases the spread of HIV.

15.4 Full IC Model

As complicated as the above sIC model is, the complete IC model (Garnett and Anderson 1993) is considerably more complex. The full IC model has effectively 18 distinct age classes, three stages of HIV infection, and four classes of sexual activity. As a result, single parameters in the sIC model for the important processes have multiple values in the full model that vary over the 133 classes. For example, persons with HIV are not all equally infectious depending on the time since they contracted the disease. As a result, the constant γ in the sIC model is decomposed into three levels according

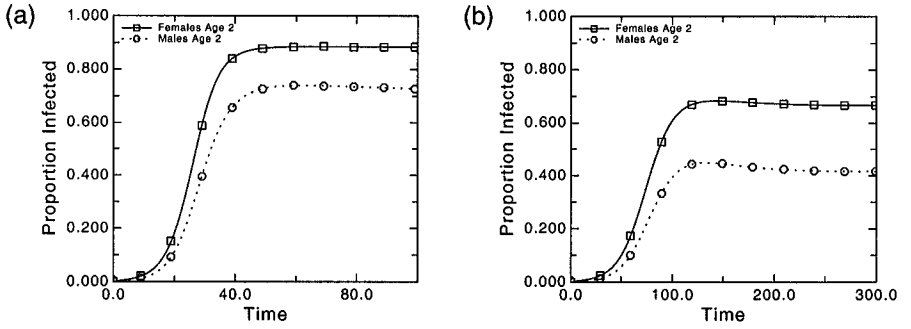

Figure 15.5: Results for sIC using nominal parameter values in Table 15.2 [panel (a)] and when improved condom use is simulated by halving parameters $\beta_{f,m} = 0.0375$ and $\beta_{m,f} = 0.1$ [panel (b)]. Note the differences in the x-axis scale.

to disease stage. Infectiousness is initially high, drops significantly in stage 2, and rises to a moderate level for the transition from HIV to AIDS. Further, some individuals are more sexually active than others of the same age. This property is reflected in the rate at which new partners are acquired. Typical values used in the IC model are 1-4 new partners per year, depending on sexual activity class.

However, the largest complication, by far, in the IC model is implementation of partner mixing. This is the phenomenon that when a person switches partners he or she does not necessarily interact only with members of the same age and activity group. The sIC model conveniently side-steps this issue by assuming a single sexually mature age and a single activity group. Garnett and Anderson (1993) implement mixing based on three types of social interchange: among ages, among sexual activity groups, and the propensity for old males to switch to younger females. The result of the Garnett and Anderson (1993) algorithm is a *mixing matrix* that defines the probability that a male or female individual of a given age (or activity group) will mate with an individual of the opposite gender and some other age (or activity group). The amount of mixing may vary from perfectly *assortative* (stay within your group) to perfectly *dissortative* (always mate outside your group). Real mixing is a continuum with

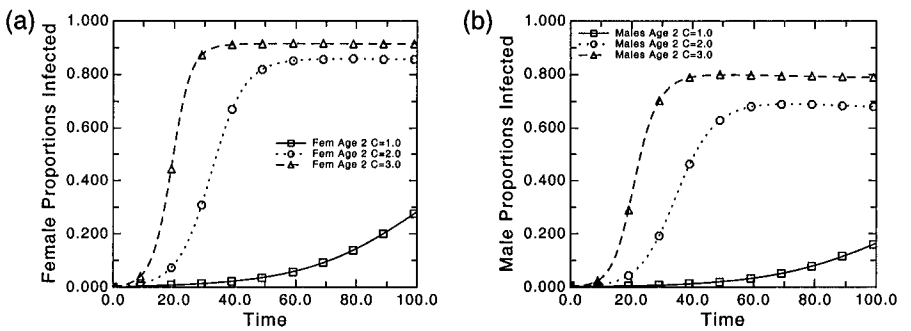

Figure 15.6: Effects of increasing numbers of new partners per year ($c = 1.0, 2.0, 3.0$). (a) Proportion of infected females. (b) Proportion of infected males.

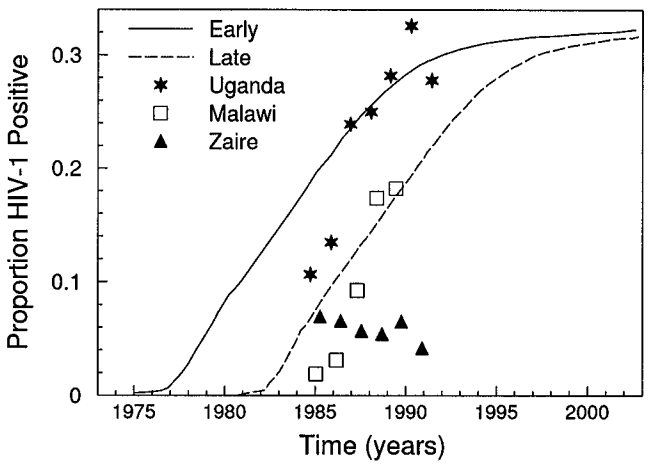

Figure 15.7: Comparison of the full AIDS model with observed infection prevalence for females of reproductive age in three African populations. ✶ = Uganda; □ = Malawi; ▲ = Zaire. Continuous lines are IC model predictions for early (1975) and late (1980) initiations of the HIV epidemic. (Redrawn from Garnett and Anderson 1993, Fig. 13 ©1993 The Royal Society. Reprinted with permission of the publisher.)

these two as extremes; intermediate to these is *proportionate* mixing in which individuals choose mates randomly, or equivalently, in proportion to each group's presence in the population. Without elaborating the details (the interested reader should consult Garnett and Anderson 1993, and the references cited there), ρ for the target group (age class or activity group) is computed based on three free parameters (ε_i) which define the degree of assortivity for the three types of mixing. Once the ρ are known, the rate of sexual partner change is computed. This latter quantity is subject to two constraints. First, the number of pairings in males and females must be equal. That is, if p males of age i and activity group l pair with q females of age j and activity group m, then the females of age j and activity group m must pair with p males of age i and group l. Second, the mixing matrix is a matrix of probabilities, so the rows must sum to 1.0.

A final adjustment to c, the rate of partner change for a given age and activity group, is required because that class of persons might wish to acquire more partners from another class than there are individuals in the second class. That is, the number of males of age i and activity group l wishing to pair with females of age j and activity group m must not exceed the number of females in j and m. I.e., demand for partners must not exceed the supply of partners. Of several possible approaches, Garnett and Anderson (1993) choose to modify the demands (the c) of one class of persons for another class of persons so that the ratio of demand to supply equals the original ratio of the two classes at $t = 0$. This approach is not perfect (and may be false), but it has the merit of being a simple assumption that individuals within a class will not change their behavior from that which they did at the beginning of the simulation.

15.4.1 Full Model Results

The dynamics of HIV prevalence is shown in Fig. 15.7 where we see that the simple

version of the theory (sIC) produces results similar to the full model. Although validating these models are difficult due to inadequate reporting and surveys in developing countries, the basic pattern of the infection is captured by the IC model. Figure 15.7 shows data for pregnant females in three African countries plotted with model predictions using parameters similar to those in Table 15.2 and hypothesized early and late epidemic starting times. Given the large number of parameters in the model and the great uncertainty in their values, further parameter tuning would produce a better fit to the data.

The age-distribution of HIV is also of great concern, and the IC model, being age-structured, allows us to examine this question. Data reported in Garnett and Anderson (1993) indicate 18 distinct age classes, but the model formulation considers age to be a continuous variable. This is formulated using partial differential equations in a manner analogous to the advection of a substance in flowing water as described in Chapter 5. For aging, "advection" of individuals (s) over age (a) is represented as $\partial s/\partial a$ which represents the net flow of individuals into and out of a small segment (age class) of a continuous variable age. In addition to this flow, the number of individuals within an age class can increase or decrease depending on biological processes such as reproduction and death. To conserve the number of individuals, analogous to conservation of mass in physical transport, all the possible dispositions of individuals must be accounted for. That is, the rate of change in time of s is the sum of fluxes occurring within an age class plus the flux of individuals into and out of the age class due to ageing:

$$\frac{\partial Z_{kl}(a,t)}{\partial t} = f(\text{infection, death, disease progression, etc.}) - \frac{\partial Z_{kl}(a,t)}{\partial a}$$

where Z represents the number of individuals that are either susceptible, infected, or AIDS cases. The subscripts k and l represent gender and sexual activity group. Thus, this simple notation hides a great deal of complexity. But once all the equations are written explicitly (somewhat like sIC Eqs. 15.5 and 15.7), the solution produces predicted HIV prevalence as a function of time since epidemic initiation and age of individual.

Figure 15.8 shows one scenario using the nominal parameters for females. Epidemic (simulated) time increases toward the back of the graph; individual age increases from left to right. Note the high fraction of very young children with HIV (25%) due to transmission in the womb. Once females reach sexual maturity (age 15), HIV prevalence increases dramatically after the initial outbreak. After 100 years, the age distribution of HIV infection is constant with about 80% of females between the ages of 25 and 50 having the virus. The proportion of infected females drops steeply after age 50 due to the progression of HIV infection to clinical AIDS and due to high mortality once this occurs. Male HIV infection proportion shows a similar pattern.

15.5 AIDS Modeling Prognosis

Many models and modeling approaches exist for infectious diseases in general and HIV/AIDS in particular. Current work focuses on new applications in HIV hotspots

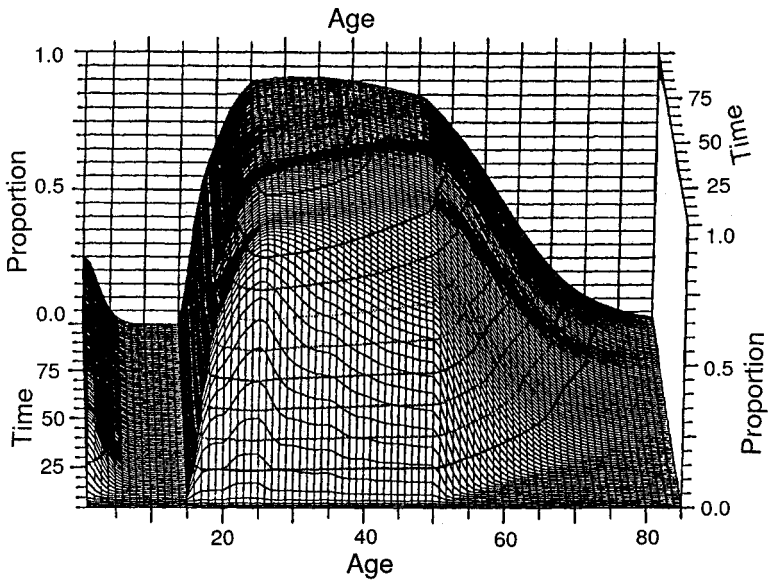

Figure 15.8: Prevalence of HIV positive females as proportion of population by age in the full IC model. (From Garnett and Anderson 1993, Fig. 14b ©1993 The Royal Society. Reprinted with permission of the publisher.)

(Asia, Brown and Peerapatanapokin (2004), and South America). There is also a growing concern that forecasts of HIV prevalence are strongly model-dependent. This concern has been addressed by recent comparisons of models (Bernstein et al. 1998; Stover et al. 2002). These have found broad agreement, but also significant differences in quantitative predictions, particularly on the effects of the demographic effects of immunization programs (e.g., Stover et al. 2002). A third development is addressing various intervention strategies (condoms, clean needle programs, vaccinations). Overall, there is great progress in HIV/AIDS treatment to reduce mortality and prolong life expectancy in developed countries (Jaffe 2004). But exporting these successes to developing countries is a political and logistic challenge. Not all possible strategies are acceptable or economically feasible. Mathematical models can help identify ineffective policies.

15.6 Exercises

1. For Eq. 15.1:
   a) Derive the equation and the expression for the initial condition.
   b) Use local stability analysis (Sec. 9.3.2) to explore the stability of the equilibrium.
2. Draw a Forrester diagram for the SIR model.
3. Show algebraically for the SIR model that $dI/dt < 0$ if $S < \beta/\alpha$, and that $dI/dt > 0$ if $S > \beta/\alpha$.

4. Below are the data for the English flu epidemic. Use validation techniques (Chapter 8) to access the value of the model. (Note: these data were used to estimate the parameters, so this is not a valid validation test, but rather an assessment of the calibration quality.)

Day	No. Infected	Day	No. Infected
3	25	9	192
4	75	10	126
5	227	11	71
6	296	12	28
7	258	13	11
8	236	14	7

5. Examine the effects of a HIV vaccination on the sIC AIDS model (loosely based on Garnett et al. (2002)). Assume that the vaccine is applied to $S_{f,2}$ and $S_{m,2}$ at rate $\upsilon = 0.65/year$ per individual. Vaccinated individuals become protected (i.e, move into variables $P_{f,2}$ and $P_{m,2}$). Further assume that a fraction of vaccinated individuals lose protection at rate $l = 0.1/year$.
Address the following questions. Will vaccination cause the epidemic to peak and, if so, when will the decline occur? How much will it cost (assume one vaccination costs $10)? Which intervention strategy is better: vaccination or safe-sex education and the use of condoms?

MBS-CD contains `sIC_AIDS` to model Eqs. 15.5 and 15.7 that will help with this exercise.

6. The original data fit by Kermack and McKendrick (1927) was the 1905 Bombay plague data for number of deaths per week.

MBS-CD contains the Bombay plague data and `SimSIR-Bombay`

   a) Use the parameter hints contained in `SimSIR-Bombay.ctrl` as a starting point to closely approximate the data with the model.
   b) Modify `SimValidate-Template.c` to determine the accuracy of this curve fitting.

7. One proposal for reducing HIV that has significant political and social implications is *abstinence*. Although the sIC model has only coarsely defined age-structure (just two age classes), it is possible to examine the effect of abstinence on the development of the HIV epidemic with this model. Propose changes to one or more parameters in sIC that will approximate the effects of abstinence and then alter the parameter(s) to determine if promoting what is for many populations a radical behavioral modification.

MBS-CD has `sIC_AIDS` to help with this problem.