EVOLUTION OF VIRULENCE

11

EVOLUTIONARY CONSIDERATIONS of host–parasite interactions provide a fascinating topic for experimental and theoretical biologists. I use the term "parasite" to denote anything that lives and multiplies inside another organism and usually causes some harm. Phages are parasites of bacteria. Many viruses and bacteria are parasites of humans. There are many single and multicellular eukaryotic parasites that cause infectious diseases in humans and other animals. Our genome contains "parasitic" DNA that simply wants to increase its own abundance without much concern for other genes.

Parasites are as old as life itself. As soon as there were self-replicating machines, there were parasites to exploit them. Much of the design of individual cells and higher organisms can be explained as an adaptation to defend against parasites and limit the damage that is associated with infection. Bacteria have enzymes to cut viral genomes into pieces. Plants produce a vast library of chemicals in self-defense. The vertebrate immune system is a highly complicated, costly organ with the task of protecting against infectious agents. Even sexual reproduction has been explained as an adaptation to maintain genetic

diversity and to help evolve away from parasites. In return, sexually transmitted parasites use this mode of reproduction of their hosts to their own advantage.

The conventional wisdom of many medical textbooks has been that well-adapted parasites are harmless to their hosts. This notion is based on the argument that killing its host does not help a parasite that relies on its host for reproduction. Some well-known observations seem to support this view. A much-cited example is the evolution toward reduced virulence of the myxoma virus in Australian rabbit populations. A more recent example, which we encountered in the previous chapter, is the observation that long-standing primate lentivirus associations seem to be apathogenic. Simian immunodeficiency viruses (SIV) apparently do not cause disease in their natural hosts. These viruses and their hosts have been coevolving for millions of years. In contrast, the human immunodeficiency virus (HIV) entered the human population only a few decades ago and causes a fatal disease.

There are also many counterexamples, however, where long-standing host–parasite systems have not evolved to become harmless. A major example is human malaria, which is estimated to have caused more human death than any other infectious disease. Another well-known example is provided by nematodes in fig wasps. These nematodes have a strong detrimental effect on their host, despite the observation that fig wasps preserved in twenty-million-year-old amber have already been infected by nematodes.

Mathematical epidemiology is one of the oldest disciplines of theoretical biology. In 1760 Daniel Bernoulli, hoping to influence public health policy, developed a mathematical model to evaluate the effectiveness of variolation against smallpox. In 1840 William Farr performed a statistical analysis of deaths from smallpox in England and Wales. In 1908 Ronald Ross, who had discovered that malaria was transmitted by mosquitoes, formulated a simple mathematical model to explore the relationship between the prevalence of mosquitoes and the incidence of malaria. William Ogilvy Kermack and Anderson Gray McKendrick, in 1927, established the important "threshold theory": introducing a few infected individuals into a population will cause an epidemic only if the density of susceptibles is above a certain threshold. In 1979 Roy Anderson and Robert May formulated many new approaches for theoretical epidemiology and laid the foundation for much subsequent work.

They developed simple mathematical models in order to explain laboratory experiments or epidemiological data. They also studied ecological questions by analyzing how infectious agents regulate the population size of their hosts. They emphasized the importance of the "basic reproductive ratio" and its consequences for vaccination programs.

May and Anderson also point out that parasite evolution does not necessarily lead to avirulence, but instead selection works to increase the parasite's basic reproductive ratio, R_0. If the rate of transmission is linked to virulence, then selection can favor increasing virulence. They reanalyzed the classical myxoma virus infection of Australian rabbits and argued that evolution had led to intermediate levels of virulence. The data actually suggest an equilibrium distribution of viruses with different levels of virulence; after many years, both the most virulent and the least virulent virus strains are still present in the virus population. Most infections are caused by virus strains with intermediate levels of virulence.

In this chapter we will study the evolutionary dynamics of parasites, but will assume that the host does not evolve on the time scale that is under consideration. This is a good assumption because, in general, parasites evolve much faster than their hosts. We begin by investigating the basic model of epidemiology, where parasite evolution maximizes the basic reproductive ratio. This result is based on the assumption that an already infected host cannot be superinfected by another parasite strain. We will subsequently remove this constraint and explore the evolutionary dynamics of superinfection. Superinfection means that an already infected host can be infected and taken over by another parasite strain.

In the classification of Anderson and May, this whole chapter deals with "microparasites," which typically include viruses, bacteria, and protozoans. They have small sizes, short generation times (compared with those of their hosts), and high rates of direct reproduction within their hosts. In contrast "macroparasites," which comprise parasitic helminths and arthropods, have longer generation times than microparasites and reproduce only very slowly within a host individual. Mathematical models for microparasites are typically formulated in terms of infected and uninfected (and immune/recovered) hosts. Models for macroparasites, in contrast, must keep track of the number of parasites in individual hosts.

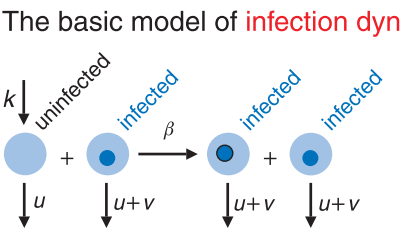


Figure 11.1 The basic model of infection dynamics describes the spread of an infectious agent (a parasite) in a population of hosts. An infected host meets an uninfected host and passes on the infection. It is often useful to think of biological dynamics as chemical kinetics: here an infected host "reacts" with an uninfected host to produce two new infected hosts. The rate constant of this reaction, β, denotes the infectivity of the parasite. The normal mortality of hosts is described by the death rate u. The disease-induced mortality (virulence) is given by v. Uninfected hosts enter the population at a constant rate, k.

11.1 THE BASIC MODEL OF INFECTION BIOLOGY

The basic epidemiological dynamics of a host–parasite interaction (Figure 11.1) can be described by the following system of ordinary differential equations

$$\begin{aligned} \dot{x} &= k - ux - \beta xy \\ \dot{y} &= y(\beta x - u - v) \end{aligned} \tag{11.1}$$

Uninfected and infected hosts are denoted by x and y, respectively. In the absence of the parasite, the host population is regulated by a simple immigration-death process, with k specifying the constant immigration rate of uninfected hosts and u their natural death rate. This represents a simple, if somewhat artificial, way of attaining a stable host population in the absence of infection. Infected hosts transmit the parasite to uninfected hosts at the rate βxy, where β is the rate constant characterizing the parasite's infectivity. Infected hosts die at the increased rate $u + v$. The parameter v defines the virulence of the infection; it is the excess mortality associated with infection. More generally, virulence can be defined as the parasite's effect on reducing the fitness of infected hosts.

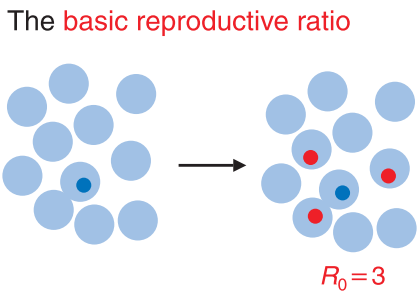


Figure 11.2 The basic reproductive ratio, R_0, of an infectious agent is given by the number of secondary infections that are caused by one infection that is introduced into an uninfected population of hosts. R_0 is a crucial quantity that determines whether or not a parasite can spread in a host population. If $R_0 < 1$, then the parasite will die out after a few rounds of infection. If $R_0 > 1$, then an explosive increase in the number of infections (an epidemic) will occur.

The basic reproductive rate of the parasite is defined as the number of new infections caused by a single infected host if introduced in a population of uninfected hosts (Figure 11.2). For system (11.1), the basic reproductive ratio is given by

$$R_0 = \frac{\beta}{u+v}\frac{k}{u}. \tag{11.2}$$

This can be understood as follows. The average lifetime of an infected host is $1/(u+v)$. The rate at which one infected host produces new infections is βx. The product of these two quantities is the average number of new infections caused by a single infected host in its lifetime if there are x uninfected hosts. The equilibrium abundance of uninfected hosts prior to the arrival of the infection is given by $x = k/u$. Hence equation (11.2) represents the basic reproductive ratio, R_0, which is a crucial concept of epidemiology.

If R_0 is less than one, then the parasite cannot spread. The "chain reaction" is sub-critical: a single case might cause a few additional cases, but then the transmission chain will die out again. An epidemic cannot take place.

If R_0 is greater than one, then the chain reaction is super-critical. There will be an exponential increase in the number of infected hosts. An epidemic will occur. After some time, the number of infected individuals will peak and then start to decline. Damped oscillations lead to a stable equilibrium given by

$$x^* = \frac{u+v}{\beta} \qquad y^* = \frac{\beta k - u(u+v)}{\beta(u+v)} \tag{11.3}$$

A successful vaccination program must reduce the population size of susceptible hosts such that the basic reproductive ratio is below one. If $R_0 = 5$, then more than 80% of the population must be vaccinated to prevent an epidemic. If $R_0 = 50$, then more than 98% of the population must be vaccinated. In general, successful vaccines are those that are directed against infectious agents with low reproductive ratios.

I call system (11.1) the "basic model of infection biology," because it describes not only the dynamics of an infectious agent in a population of hosts but also the dynamics of a virus within a single infected host. In the latter case, x and y denote, respectively, uninfected and infected cells. The application of this model to HIV infection is described in my book *Virus Dynamics*, coauthored with Robert May.

11.2 SELECTION MAXIMIZES THE BASIC REPRODUCTIVE RATIO

To understand parasite evolution, we have to study the epidemiological dynamics of at least two parasite strains competing for the same host. Extending equation (11.1), we obtain

$$\begin{aligned} \dot{x} &= k - ux - x(\beta_1 y_1 + \beta_2 y_2) \\ \dot{y}_1 &= y_1(\beta_1 x - u - v_1) \\ \dot{y}_2 &= y_2(\beta_2 x - u - v_2) \end{aligned} \tag{11.4}$$

The two parasite strains differ in their infectivity, β_1 and β_2, and in their degree of virulence, v_1 and v_2. The basic reproductive ratios of strains 1 and 2 are, respectively, given by

$$R_1 = \frac{\beta_1}{u + v_1} \frac{k}{u} \tag{11.5}$$

and

$$R_2 = \frac{\beta_2}{u + v_2} \frac{k}{u}. \tag{11.6}$$

Coexistence between the two parasite strains is only possible if $R_1 = R_2$, which is ungeneric. At equilibrium, the time derivatives, $\dot{x}$, $\dot{y}_1$, and $\dot{y}_2$, must be zero.

Furthermore, stable coexistence between strain 1 and strain 2 requires that both y_1 and y_2 are positive at equilibrium. From $\dot{y}_1 = 0$ and $y_1 > 0$, we obtain $x = (u + v_1)/\beta_1$. But from $\dot{y}_2 = 0$ and $y_2 > 0$, we obtain $x = (u + v_2)/\beta_2$. Both conditions can only hold simultaneously if $R_1 = R_2$. Generically, however, we expect that $R_1 \neq R_2$, in which case coexistence is not possible.

If both basic reproductive ratios are less than one, $R_1 < 1$ and $R_2 < 1$, then the only stable equilibrium is the uninfected population,

$$E_0: \qquad x = \frac{k}{u} \qquad y_1 = 0 \qquad y_2 = 0 \tag{11.7}$$

If $R_1 > 1 > R_2$, then strain 2 becomes extinct and the only stable equilibrium is

$$E_1: \qquad x^* = \frac{u + v_1}{\beta_1} \qquad y_1^* = \frac{\beta_1 - u(u + v_1)}{\beta_1(u + v_1)} \qquad y_2^* = 0 \tag{11.8}$$

If $R_1 < 1 < R_2$, then strain 1 becomes extinct and the only stable equilibrium is

$$E_2: \qquad x^* = \frac{u + v_2}{\beta_2} \qquad y_1^* = 0 \qquad y_2^* = \frac{\beta_2 - u(u + v_2)}{\beta_2(u + v_2)} \tag{11.9}$$

If both basic reproductive ratios exceed one, $R_1 > 1$ and $R_2 > 1$, then the strain with the higher basic reproductive ratio will outcompete the strain with the lower basic reproductive ratio. If $R_2 > R_1$, then all infected individuals will eventually carry strain 2, while strain 1 becomes extinct. The system will converge to equilibrium E_2.

Note that $R_2 > R_1$ is precisely the condition that strain 2 can invade equilibrium E_1. This means that the derivative $\partial \dot{y}_2/\partial y_2$, evaluated at equilibrium E_1, is positive. $R_2 > R_1$ is also the condition that strain 1 cannot invade equilibrium E_2. This means that the derivative $\partial \dot{y}_1/\partial y_1$, evaluated at equilibrium E_2, is negative. These derivatives characterize the growth rate of an infinitesimal amount of the invading strain at a particular equilibrium point. We conclude that E_1 is unstable, while E_2 is stable. Coexistence between the two strains is not possible. Therefore strain 2 outcompetes strain 1.

Therefore evolution will tend to maximize the basic reproductive ratio (Figure 11.3). If there is no constraint between infectivity and virulence, then the

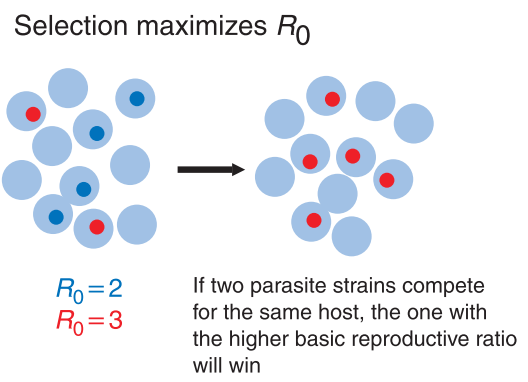


Figure 11.3 In simple models of infection dynamics, selection acts to maximize the parasite's basic reproductive ratio. If two parasites compete for the same host, then the parasite with higher R_0 will outcompete the other parasite. Therefore well-adapted parasites have a high R_0, but not necessarily low virulence.

evolutionary dynamics will increase β and reduce v. This represents the conventional wisdom that infectious diseases will evolve to become less virulent.

In general, however, we expect an association between virulence v and infectivity β; usually the harm done to hosts (v) is associated with the production of transmission stages (β). For certain functional relations between v and β there is an evolutionarily stable degree of virulence, corresponding to the maximum value of R_0. Other situations allow evolution toward the extreme values of very high or low virulences. The detailed dynamics depend on the shape of β as a function of v. It is interesting to note that along some trajectories where virulence increases, parasite evolution can lead to lower and lower parasite population sizes (in terms of total number of infected hosts).

If the infectivity is proportional to virulence, $\beta = av$, where a is some constant, then the basic reproductive ratio, R_0, is an increasing function of virulence, v. In this case selection will always favor more virulent (and therefore more infectious) strains.

If the infectivity is a saturating function of virulence, $\beta = av/(c + v)$, then the basic reproductive ratio, R_0, is a one-humped function of virulence. The maximum R_0 is achieved at an intermediate optimum level of virulence given by $v_{\text{opt}} = \sqrt{cu}$. If the virulence of a parasite population is greater than v_{opt}, then selection will reduce virulence. If it is less than v_{opt}, then selection will increase virulence.

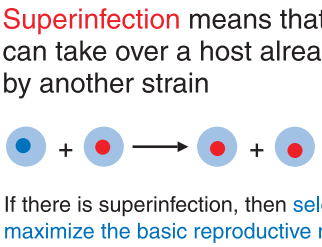


Figure 11.4 Superinfection means that an already-infected host can be infected by another parasite strain. There is competition between the two parasite strains in the superinfected individual; one parasite strain may win this competition and outcompete the other. A consequence of superinfection is that natural selection no longer maximizes the basic reproductive ratio. Instead there can be coexistence of different parasite strains with different levels of virulence. In general, superinfection leads to increased virulence beyond what would be optimum for the parasite. Superinfection introduces competition on two levels: within an infected host and in the population of hosts.

11.3 SUPERINFECTION

The analysis of the previous section did not include the possibility of superinfection. An infected host is not susceptible to another infection. We will now remove this limitation and allow for an infected host to be superinfected by another parasite strain (Figure 11.4).

We will consider a heterogeneous parasite population with a range of different virulences, and assume that more virulent strains outcompete less virulent strains within an infected individual. Thus increased virulence provides a competitive advantage over other parasites in the same host.

For simplicity, we assume that the infection of a single host is always dominated by one parasite strain. Therefore superinfection means that a more virulent strain takes over a host infected by a less virulent strain. This can be described by the following system of ordinary differential equations:

$$\begin{aligned} \dot{x} &= k - ux - x\sum_{i=1}^{n}\beta_i y_i \\ \dot{y}_i &= y_i(\beta_i x - u - v_i + s\beta_i\sum_{j=1}^{i-1} y_j - s\sum_{j=i+1}^{n}\beta_j y_j) \qquad i = 1,\ldots,n \end{aligned} \tag{11.10}$$

Here v_i denotes the virulence of strain i. We order the strains such that $v_1 < v_2 < \ldots < v_n$. A more virulent strain can superinfect a host already infected with a less virulent strain. The parameter s describes the rate at which superinfection occurs relative to infection of uninfected hosts. If either the host or the parasite has evolved mechanisms to make superinfection more difficult, then s is smaller than one. If already-infected hosts are more susceptible to acquiring a second infection, then s is greater than one, which means superinfection occurs at increased rates.

For the numerical simulations shown in Figure 11.5, we assume a functional relation between virulence and infectivity given by

$$\beta_i = \frac{a v_i}{c + v_i}. \tag{11.11}$$

For low virulence, infectivity increases linearly with virulence. For high virulence, there is a saturation of infectivity at a maximum level. The basic reproductive ratio is given by

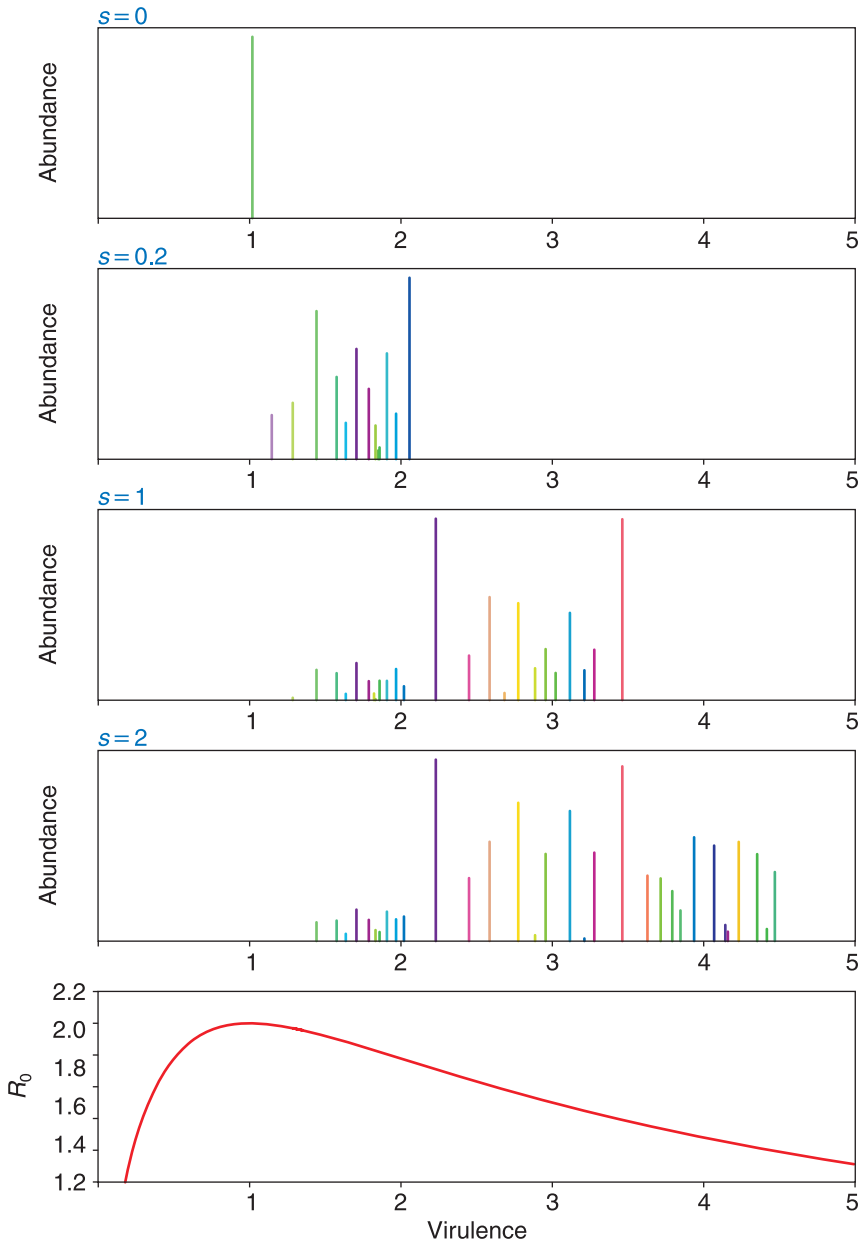
$$R_{0,i} = \frac{a k v_i}{u(c + v_i)(u + v_i)}. \tag{11.12}$$

The optimal virulence, which maximizes R_0, is given by

$$v_{opt} = \sqrt{cu}. \tag{11.13}$$

Figure 11.5 shows the equilibrium population structure of the parasite for various values of s between 0 and 2. We have assumed $k = 1$, $u = 1$, and $\beta_i =$

Figure 11.5 The equilibrium distribution of parasite strains with different levels of virulence. The simulation is performed according to equation (11.10) with $k = 1$, $u = 1$, $n = 50$, $\beta_i = 8v_i/(1 + v_i)$, and $s = 0, 0.2, 1, 2$ as indicated. The individual v_i are randomly distributed between 0 and 5. In the absence of superinfection, $s = 0$, the strain with the maximum basic reproductive rate, R_0, is selected. With superinfection, $s > 0$, we find the coexistence of many different strains with different virulences, v_i, within a range $v_{\min}$ and $v_{\max}$, but the strain with the largest R_0 is not selected. Superinfection does not optimize parasite reproduction. For increasing s, the values of $v_{\min}$ and $v_{\max}$ increase, as well. The x-axis denotes virulence, the y-axes indicate equilibrium frequencies (always scaled to the same largest value).



$8v_i/(1+v_i)$. We simulated $n = 100$ strains of parasites with virulences randomly distributed between 0 and 5. For this choice of parameters, the strain with a virulence closest to 1 has the largest R_0. Indeed we find that this strain is selected in the absence of superinfection, $s = 0$. If superinfection is possible ($s > 0$), then there is selection of an ensemble of strains with a range of virulences between two boundaries, $v_{\min}$ and $v_{\max}$, with $v_{\min} > v_{\text{opt}}$. Thus superinfection has two important effects: (i) it shifts parasite virulence to higher levels, beyond the level that would maximize the parasite's reproductive rate; and (ii) it leads to a coexistence between a number of different parasite strains with a range of virulences. There are amusing ups and downs in the equilibrium densities of strains. A strain has a high equilibrium frequency if the strain with a slightly larger virulence has low frequency, and vice versa. Only a subset of strains survive at equilibrium. What determines this complicated and unexpected equilibrium structure?

11.4 AN ANALYTICAL MODEL OF SUPERINFECTION

Let us now derive an analytical understanding of the complexities introduced by superinfection. Instead of using a constant immigration rate k for uninfected hosts, we choose a variable immigration rate that balances exactly the death of uninfected and infected hosts. This can be done by setting

$$k = ux + uy + \sum v_i y_i \tag{11.14}$$

in equation (11.10). The total number of infected hosts is given by $y = \sum_{i=1}^{n} y_i$. The sum $x + y$ remains constant and without loss of generality we choose $x + y = 1$. We obtain the following system of n equations

$$\dot{y}_i = y_i \left[\beta_i(1-y) - u - v_i + s\left(\beta_i \sum_{j=1}^{i-1} y_j - \sum_{j=i+1}^{n} \beta_j y_j \right) \right] \qquad i = 1, \ldots, n \tag{11.15}$$

Note that y remains in the closed interval $[0, 1]$.

System (11.15) is a Lotka-Volterra equation. It can be written in the form

$$\dot{y}_i = y_i(R_i + \sum_{j=1}^{n} A_{ij} y_j) \qquad i = 1, \ldots, n \tag{11.16}$$

Here $R_i = \beta_i - v_i - u$. The matrix is given by

$$A = -\begin{pmatrix} \beta_1 & \beta_1 + s\beta_2 & \beta_1 + s\beta_3 & \ldots & \beta_1 + s\beta_n \\ \beta_2(1-s) & \beta_2 & \beta_2 + s\beta_3 & \ldots & \beta_2 + s\beta_n \\ \beta_3(1-s) & \beta_3(1-s) & \beta_3 & \ldots & \beta_3 + s\beta_n \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \beta_n(1-s) & \beta_n(1-s) & \beta_n(1-s) & \ldots & \beta_n \end{pmatrix} \tag{11.17}$$

For an analytic understanding, we take the limit $c \to 0$ in our expression for $\beta_i = a v_i/(c + v_i)$. Now all parasite strains have the same infectivity, β, and differ only in their degree of virulence, v_i. We obtain

$$\dot{y}_i = y_i \beta [1 - y - \frac{v_i + u}{\beta} + s(\sum_{j=1}^{i-1} y_j - \sum_{j=i+1}^{n} y_j)] \qquad i = 1, \ldots, n \tag{11.18}$$

This is a Lotka-Volterra equation with $R_i = \beta - v_i - u$ and

$$A = -\beta \begin{pmatrix} 1 & 1+s & 1+s & \ldots & 1+s \\ 1-s & 1 & 1+s & \ldots & 1+s \\ 1-s & 1-s & 1 & \ldots & 1+s \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1-s & 1-s & 1-s & \ldots & 1 \end{pmatrix} \tag{11.19}$$

This system belongs to a class of Lotka-Volterra equations for which Josef Hofbauer and Karl Sigmund have shown the existence of a unique globally stable equilibrium. This equilibrium attracts all orbits from the interior of the positive orthant. If this equilibrium lies on a face of the positive orthant, then it also attracts all orbits from the interior of this face.

Equation (11.18) can be rewritten as

$$\dot{y}_i = y_i \beta [f_i - s y_i]. \tag{11.20}$$

Here

$$f_i = 1 - \frac{v_i + u}{\beta} - (1 - s)y + 2s \sum_{j=i+1}^{n} y_j. \tag{11.21}$$

All equilibrium points of equation (11.20) are given by the following relations:

$$\begin{aligned} y_1 &= 0 \quad \text{or} \quad y_1 = f_1/s \\ y_2 &= 0 \quad \text{or} \quad y_2 = f_2/s \\ &\vdots \\ y_n &= 0 \quad \text{or} \quad y_n = f_n/s \end{aligned} \tag{11.22}$$

Note that each f_i only depends on the total sum y and all y_j with $j > i$. Suppose we know y; then we can construct a specific equilibrium point in a recursive "top-down" way:

$$\begin{aligned} y_n &= \max\{0,\ f_n/s\} \\ y_{n-1} &= \max\{0,\ f_{n-1}/s\} \\ y_{n-2} &= \max\{0,\ f_{n-2}/s)\} \\ &\vdots \\ y_1 &= \max\{0,\ f_1/s\} \end{aligned} \tag{11.23}$$

The notation max{., .} simply denotes the larger of the two numbers. This equilibrium point has to be stable, because either $f_i < 0$ and hence $y_i \to 0$, or $f_i > 0$ and $y_i \to f_i/s$.

11.4.1 The Case $s = 1$

The case $s = 1$ offers a quick solution, because y drops out of equation (11.23). Hence the unique stable equilibrium distribution is given recursively in the following way:

$$
\begin{aligned}
y_n &= \max\{0,\, 1 - \frac{v_n + u}{\beta}\} \\
y_{n-1} &= \max\{0,\, 1 - \frac{v_{n-1} + u}{\beta} - 2y_n\} \\
y_{n-2} &= \max\{0,\, 1 - \frac{v_{n-2} + u}{\beta} - 2(y_n + y_{n-1})\} \\
&\vdots \\
y_1 &= \max\{0,\, 1 - \frac{v_1 + u}{\beta} - 2(y_n + y_{n-1} + \cdots + y_2)\}
\end{aligned}
\tag{11.24}
$$

This is the only stable equilibrium. For each parasite strain i with equilibrium frequency $y_i = 0$, we have $\partial \dot{y}_i / \partial y_i < 0$ for a generic choice of parameters. Moreover, equation (11.24) corresponds to a simple and elegant geometric method for constructing the equilibrium configuration of the population (Figure 11.6).

11.4.2 The General Case $s > 0$

Let us consider an equilibrium distribution with $y_i > 0$ for $i = 1, \ldots, n$, which means we count only those strains that are present at equilibrium. From equation (11.15) we can write $\sum_{j=1}^{i-1} y_j = y - y_i - \sum_{j=i+1}^{n} y_j$, to get

$$
y_i = B_i - 2 \sum_{j=i+1}^{n} y_j \tag{11.25}
$$

with $B_i = [1 - \frac{v_i + u}{\beta} - (1 - s)y]/s$. We obtain

$$
\begin{aligned}
y_n &= B_n \\
y_{n-1} &= -2B_n + B_{n-1} \\
y_{n-2} &= 2B_n - 2B_{n-1} + B_{n-2}
\end{aligned}
\tag{11.26}
$$

For even n we obtain $y = B_1 - B_2 + B_3 - \cdots - B_n = (v_n - v_{n-1} + \cdots - v_1)/\beta s$. For odd n we obtain $y = B_1 - B_2 + B_3 - \cdots + B_n$ and hence $y = (\beta - u - v_n + v_{n-1} - \cdots - v_1)/\beta$. At first sight the expressions for odd and

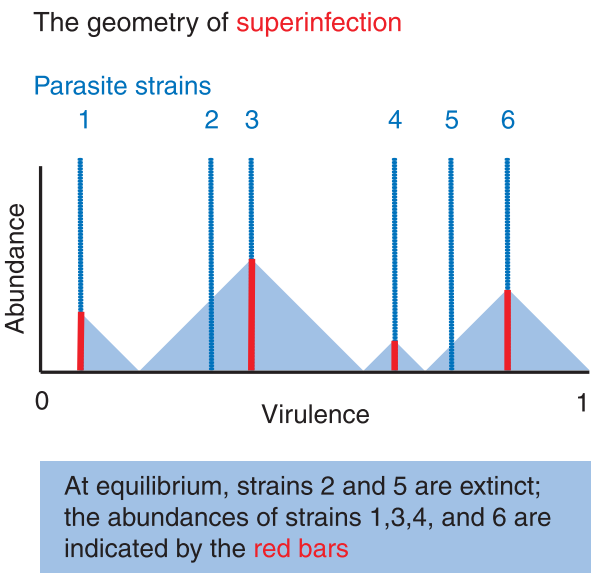


Figure 11.6 For $s = 1$, there is an elegant geometric method to construct the equilibrium distribution of the parasite population. Suppose there are n strains with virulences v_1 to v_n, all between 0 and 1. Start by drawing vertical lines at v_1 to v_n (shown in blue). Draw a 45-degree line running up to the left from $v = 1$; the intersection with the vertical line at v_n determines the abundance y_n. This corresponds to $y_n = 1 - v_n$. Now mirror the construction triangle (shaded in blue) at the axis given by the vertical line at v_n. The intersection with the downward-pointing 45-degree line with the baseline determines the point $v = 1 - 2y_n$. Now there are two possibilities: (i) either $v_{n-1} < v$, in which case draw a new 45-degree line up to the left from v; the intersection with the vertical line at v_{n-1} gives y_{n-1}; this corresponds to $y_{n-1} = v_n - v_{n-1} - (1 - v_n)$; or (ii) $v_{n-1} > v$, in which case the strain $n - 1$ will not be present at equilibrium and the construction method proceeds directly with strain v_{n-2}, and so on. The figure is self-explanatory. We choose $n = 6$ strains. Four of those strains are present at equilibrium; their abundances are indicated by red bars. Two strains are extinct.

even n look quite different. We want to calculate $v_{\max}$, the maximum level of virulence present in an equilibrium distribution for a given s. Assuming equal spacing (on average), that is, $v_k = kv_1$, leads to $y = v_n/2\beta s$ for n even and to $y = 1 - u/\beta - v_n/2\beta$ for n odd. (For n odd we have used the approximation $n - 1 \approx n$.) From $y_n \geq 0$ we derive in both cases

$$v_{\max} = \frac{2s(\beta - u)}{1 + s}. \tag{11.27}$$

This is the maximum level of virulence that can be maintained in an equilibrium distribution. For $s = 0$, this is simply $v_{\max} = 0$, that is, the strain with the lowest virulence, which for our choice of parameters is also the strain with the highest basic reproductive ratio. For $s > 1$, strains can be maintained with virulences above $\beta - u$. These are strains that are by themselves unable to invade an uninfected host population, because their basic reproductive ratio is smaller than one.

Finally resolving the even- and oddities, we insert $v_{\max}$ for v_n into the two different expressions for y and find in both cases

$$y = \frac{\beta - u}{\beta(1 + s)}. \tag{11.28}$$

This is the equilibrium frequency of infected hosts. The more superinfection, the fewer infected hosts.

11.5 DYNAMICAL COMPLEXITIES

Let us now return to the model with different strains having different infectivities, β_i, as given by equation (11.15). Here the solutions need not converge to a stable equilibrium. Equation (11.15) can lead to very complex dynamics.

For two strains of parasite ($n = 2$) we may find coexistence (that is, a stable equilibrium between the two strains) or a bistable situation, where either one or the other strain wins, depending on the initial conditions. An interesting situation can occur if $s > 1$ and strain 1 has a virulence too high to sustain itself in a population of uninfected hosts ($R_0 < 1$), whereas strain 2 has a lower virulence but an $R_0 > 1$. Since $s > 1$, infected hosts are more susceptible to superinfection, and thus the presence of strain 2 can effectively shift the reproductive rate of strain 1 above one. Superinfection can stabilize parasite strains with extremely high levels of virulence.

For three or more strains of parasite, we may observe oscillations with increasing amplitude and period, tending toward a heteroclinic cycle. Imagine

three parasite strains, each of which by itself is capable of establishing an equilibrium between uninfected and infected hosts (that is, all have $R_0 > 1$). The system in which these three strains occur simultaneously has three boundary equilibria, where two strains always have frequency 0 and the population consists of uninfected hosts and hosts infected by the third strain only. There is also one unstable interior equilibrium with all three strains present. The system converges toward the boundary equilibria and cycles from the first one to the second to the third and back to the first. The period of such cycles gets larger and larger. There will be long times where the infection is just dominated by one parasite strain (and hence only one level of virulence), and then suddenly another strain takes over. Such a dynamic can, for example, explain sudden upheavals of pathogens with dramatically altered levels of virulence. If we wait long enough, one of the parasite strains may become extinct by some fluctuation when its frequency is low. Then one of the two remaining strains will outcompete the other.

For small values of s all elements of matrix (11.17) will be negative. Such a Lotka-Volterra system is called "competitive," and all trajectories will converge to an $n - 1$-dimensional subspace, which reduces the dynamical complexities. This implies that for $n = 2$ there are no damped oscillations, and for $n = 3$ one can exclude chaos.

SUMMARY

- The basic reproductive ratio of an infectious agent (parasite) is the number of secondary infections caused by one infected individual that has been introduced into a population of uninfected individuals.
- Parasite evolution tends to maximize the basic reproductive ratio.
- If there is a functional relationship between infectivity and virulence, then well-adapted parasites need not be harmless. Parasite evolution can lead to intermediate levels of virulence.
- Superinfection means that an already infected host can be infected by another parasite strain.

- Superinfection triggers intrahost competition for increased levels of virulence and reduced transmission rates.
- Superinfection increases the average level of virulence above what would be optimum for the parasite population.
- Superinfection does not maximize the basic reproductive ratio. Even the strain with the highest R_0 can become extinct.
- Superinfection leads to a coexistence of parasite strains with many different levels of virulence within a well-defined range.
- Superinfection can maintain strains with very high levels of virulence, including strains that are so virulent that they themselves could not persist alone in an otherwise uninfected host population.
- Superinfection can lead to very complicated dynamics, such as heteroclinic cycles, with sudden and dramatic changes in the average level of virulence.
- The higher the rate of superinfection, the smaller the number of infected hosts. Hence superinfection is not advantageous for the parasite population as a whole.