10

Super- and Coinfection: Filling the Range

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10.1   Introduction

How many different strains of a disease can coexist in a single population of hosts?
What effect do different mechanisms of coexistence have on the properties of dis-
eases? The principle of competitive exclusion (Armstrong and McGehee 1980;
Levin 1970) states that no more species can coexist in a system than the number
of resources or limiting factors allow, which can be thought of, somewhat impre-
cisely, as stating that a single trade-off can support only a single species – the one
that deals best with that trade-off. Disease models describe a simple ecological
interaction, with hosts acting as resources, to test the limits of competitive exclu-
sion. Trade-offs for the disease often involve virulence, a trait of abiding interest
to hosts.

In the absence of a trade-off between host mortality and transmission efficiency,
the disease strain with the lowest virulence would always win out in competi-
tion, and diseases would be favored to evolve ever-reduced virulence. When such
a trade-off between host mortality and transmission efficiency exists, the single
strain that maximizes the basic reproduction ratio R_0 will persist (see Boxes 2.2,
5.1, and 9.1; Bremermann and Thieme 1989). Ecological factors that affect this
trade-off, such as host density, might favor higher or lower virulence (Ewald
1994a). However, in the absence of spatial or temporal variation in these fac-
tors, only one strain persists [but see Andreasen and Pugliese (1995) for a case in
which coexistence is due to density-dependence in the host].

As many authors have shown, including an additional trade-off between viru-
lence and competitive ability (ability to take over from or share hosts with less
virulent strains) may not only favor higher levels of virulence, but may also sup-
port coexistence of multiple strains (Hastings 1980; Levin and Pimentel 1981).
In fact, this single additional trade-off has the potential to support an entire con-
tinuum of strains (May and Nowak 1994, 1995; Nowak and May 1994; Tilman
1994; see also Chapter 9). In addition, the pattern of coexistence has been shown
to differ depending on the mode of interaction between strains, whether it is coin-
fection (two strains sharing the same host) or superinfection (one strain having the
capability to quickly take over a host from another).

This chapter investigates two issues related to this coexistence based on some
earlier work (Mosquera and Adler 1998; Adler and Mosquera 2000). Mosquera
and Adler (1998) explicitly derive the superinfection model as a limit of the coin-
fection model, based on the argument that hosts are removed rapidly from the

doubly infected class through either recovery or death. This sort of derivation points out an often neglected subtlety of the super- and coinfection processes: the existence of a discontinuous function relating virulence to the ability to coinfect or superinfect (Pugliese 2000).

Let the coinfection function $\phi(\alpha, \eta)$ describe the rate at which a strain with virulence α can coinfect a host infected with strain with virulence η, relative to its ability to infect an uninfected host (Mosquera and Adler 1998, Pugliese 2000). This function will be increasing in α and decreasing in η. Competition is asymmetric because more virulent strains have an advantage within hosts. Other models have used a step function for the coinfection function (see Figure 10.2a), such as

$$\phi(\alpha, \eta) = \begin{cases} \sigma & \text{if} \quad \alpha > \eta \\ 0 & \text{if} \quad \alpha \leq \eta \end{cases} \tag{10.1}$$

(Tilman 1994; May and Nowak 1994). Biologically, a slightly more virulent strain has the same advantage as a much more virulent strain, which is probably quite unrealistic. Mathematically, $\phi(\alpha, \eta)$ is discontinuous at $\alpha = \eta$.

Mosquera and Adler (1998) derived pairwise invasibility plots for smooth forms of the coinfection function, showing that the picture changes qualitatively when $\phi(\alpha, \eta)$ is continuous or differentiable at $\alpha = \eta$ (Figures 10.2b to 10.2d). Furthermore, the possibilities for coexistence in superinfection models differ depending on how the superinfection limit is approached (the mechanism by which doubly infected hosts are rapidly removed). Pairwise invasibility plots, however, address only two strains at a time. They show that every strain is invasible when the coinfection function is discontinuous, but cannot reveal the actual diversity of creatures that can coexist in the model.

In related work, Adler and Mosquera (2000) investigated diversity in a superinfection model, simplified by ignoring the trade-off between virulence and transmission efficiency. Smoothing the superinfection function (so that it has a continuous second derivative) eliminates the infinite number of strains that can coexist. Smooth superinfection functions can, when sufficiently steep at $\alpha = \eta$, support a large number of strains, but the number depends sensitively on the slope.

This chapter outlines an approach to diversity and virulence with two trade-offs: the trade-off between virulence and transmission efficiency, and that between virulence and coinfection ability. We present the coinfection model, and take the superinfection limit. The shape of the resultant superinfection function depends both on the underlying assumptions about the coinfection process and on how the superinfection limit is approached. We then examine the number and virulence of coexisting strains. Management of virulence through public health measures requires an understanding of the sensitivity of the results to the details of intrahost competition.

10.2   Coinfection and the Superinfection Limit

Complete models of coinfection can be crushed by the weight of their own notation. Authors have avoided this collapse by assuming that the interaction between

strains is simple (May and Nowak 1995; see also Chapter 9), weak (Adler and Brunet 1991), or that hosts can harbor no more than two strains at one time (Van Baalen and Sabelis 1995a).

To illustrate some of the complexity and to introduce the notation, we present a model of a population of hosts beset by many strains of a disease. For simplicity, we assume that the population size is constant and that a single host can be infected by no more than two strains simultaneously. The variables α and η both represent the virulence level and index the disease strains. Let $i(\alpha)$ denote the fraction of hosts infected only by strain α, and $i(\alpha, \eta)$ denote doubly infected hosts who were first infected with strain α and later with η (Figure 10.1). If $\beta(\alpha)$ gives the rate of infection of susceptible hosts by strain α, the differential equations describing this system are

$$\frac{di(\alpha)}{dt} = \beta(\alpha)(1 - i_{++})i_+(\alpha) - \alpha i(\alpha)$$

$$+ \int \left[\theta_1(\eta, \alpha)i(\eta, \alpha) + \theta_2(\eta, \alpha)i(\alpha, \eta) \right] d\eta$$

$$- \int \beta(\eta)\phi(\eta, \alpha)i_+(\eta)i(\alpha)\, d\eta\, , \tag{10.2a}$$

$$\frac{di(\alpha, \eta)}{dt} = \beta(\eta)\phi(\eta, \alpha)i_+(\eta)i(\alpha)$$

$$- \left[(\theta_1(\alpha, \eta) + \theta_2(\eta, \alpha) + \delta(\alpha, \eta) \right]i(\alpha, \eta)\, . \tag{10.2b}$$

The shorthand i_{++} represents the total infected fraction, or

$$i_{++} = \int i(\alpha)d\alpha + \iint i(\alpha, \eta)\, d\eta\, d\alpha\, , \tag{10.2c}$$

while $i_+(\alpha)$ represents the total infectivity of strain α or

$$i_+(\alpha) = i(\alpha) + \int \left[i(\alpha, \eta) + i(\eta, \alpha) \right] d\eta\, . \tag{10.2d}$$

$\theta_1(\alpha, \eta)$ gives the rate of recovery from strain α if infected first by α, $\theta_2(\alpha, \eta)$ gives the rate of recovery from strain α if infected second by α, and $\delta(\alpha, \eta)$ gives the death rate when infected first by α and then by η. The notation is summarized in Figure 10.1.

There are four ways that the virulence of a strain affects its success. First, it has a direct effect on mortality. Second, the infectiousness $\beta(\alpha)$ generally is an increasing function of α. More virulent strains have an advantage in transmission. In the absence of coinfection or superinfection, the strain that maximizes the ratio of transmission efficiency $\beta(\alpha)$ to virulence α excludes all others in competition (Bremermann and Thieme 1989). Third, the coinfection function $\phi(\alpha, \eta)$ describes how virulence determines the ability of strain α to coinfect strain η.

Finally, the virulence might affect the rate of recovery from each strain and the host mortality in doubly infected hosts. If hosts infected with two strains tend
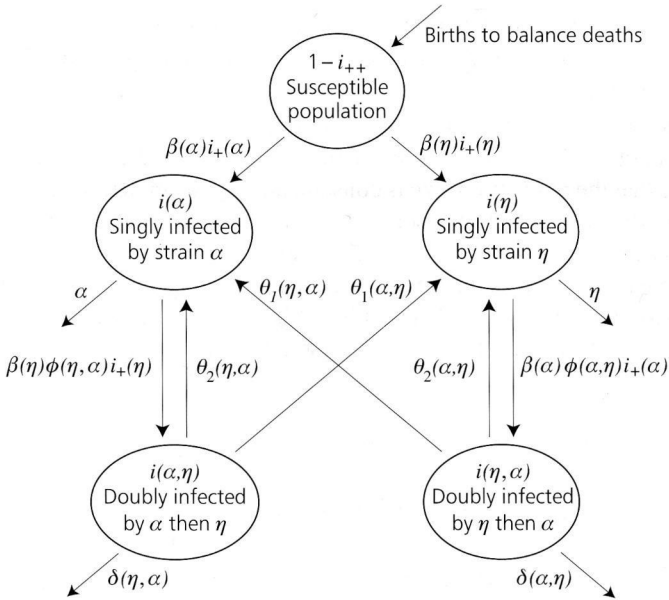
Figure 10.1 Transitions in the general coinfection model. Hosts can be infected with at most two strains. The arrows give the per capita rate at which hosts move from one category to another; arrows pointing into empty space represent deaths.

to recover from the less virulent strain, then the more virulent strain has another advantage in intra-host competition. If hosts tend to recover from the more virulent strain, then the less virulent strain acts as a vaccine, and might be using the host immune system to gain an advantage in intra-host competition. If doubly infected hosts die quickly, the model reduces to the single-infection case (Mosquera and Adler 1998).

Suppose that Equation (10.2b) has reached equilibrium. We can solve for $i(\alpha, \eta)$ and obtain

$$i(\alpha, \eta) = \frac{\beta(\eta)\phi(\eta, \alpha)i_+(\eta)i(\alpha)}{\theta_1(\alpha, \eta) + \theta_2(\eta, \alpha) + \delta(\alpha, \eta)} . \tag{10.3}$$

If the dynamics within hosts are fast relative to the infection dynamics, we can substitute Equation (10.3) into the differential Equation (10.2a) for $i(\alpha)$ to find

$$\frac{di(\alpha)}{dt} = \beta(\alpha)(1 - i_{++})i_+(\alpha) - \alpha i(\alpha)$$

$$+ \int \frac{\theta_1(\eta, \alpha)}{\theta_1(\eta, \alpha) + \theta_2(\alpha, \eta) + \delta(\eta, \alpha)} \beta(\alpha)\phi(\alpha, \eta)i_+(\alpha)i(\eta)\, d\eta$$

$$- \int \frac{\theta_1(\alpha, \eta) + \delta(\alpha, \eta)}{\theta_1(\alpha, \eta) + \theta_2(\eta, \alpha) + \delta(\alpha, \eta)} \beta(\eta)\phi(\eta, \alpha)i_+(\eta)i(\alpha)\, d\eta . \tag{10.4}$$
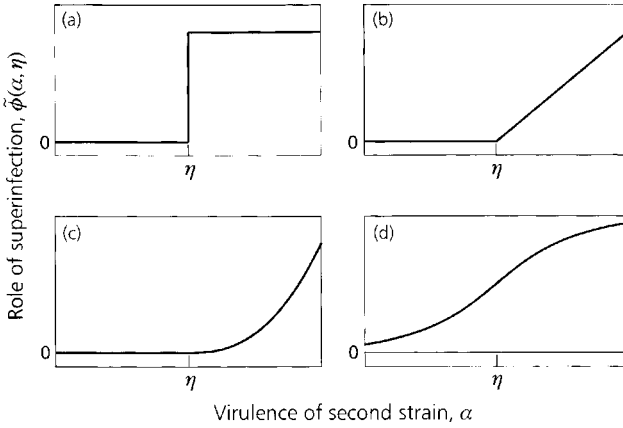
Figure 10.2 Four possible shapes of the superinfection function. Each shows the rate at which strain α takes over individuals already infected with strain η. In the first three panels, a less virulent strain cannot superinfect. (a) The discontinuous case, in which a slightly more virulent strain has a high ability to superinfect. (b) The piecewise differentiable case, in which the ability to superinfect begins increasing immediately. (c) The differentiable case, in which the ability to superinfect shows no sharp change at $\alpha = \eta$. (d) The differentiable case, in which less virulent strains superinfect more virulent strains at a low rate.

Although this might appear to be a one-dimensional superinfection model because doubly infected hosts are not tracked explicitly, they appear implicitly in $i_+(\alpha)$ and $i_+(\eta)$, the total infectivity of strains α and η. To write a closed system solely in terms of $i(\alpha)$ and $i(\eta)$, we generalize the approach of Mosquera and Adler (1998) by considering the limiting case in which hosts are removed rapidly from the doubly infected class. In this case, $i_+(\alpha) = i(\alpha)$ and Equation (10.4) becomes

$$\frac{di(\alpha)}{dt} = \left\{ \beta(\alpha)(1 - i_{++}) - \alpha \right. $$
$$\left. + \int \left[\beta(\alpha)\tilde{\phi}(\alpha, \eta) - \beta(\eta)\tilde{\phi}(\eta, \alpha) \right] i(\eta)\, d\eta \right\} i(\alpha) $$
$$+ \beta(\eta)\tilde{\delta}(\alpha, \eta) \,, \tag{10.5a}$$

where

$$\tilde{\phi}(\alpha, \eta) = \frac{\theta_1(\eta, \alpha)}{\theta_1(\eta, \alpha) + \theta_2(\alpha, \eta) + \delta(\eta, \alpha)} \phi(\alpha, \eta) \,, \tag{10.5b}$$

and

$$\tilde{\delta}(\alpha, \eta) = \frac{\delta(\alpha, \eta)}{\theta_1(\alpha, \eta) + \theta_2(\eta, \alpha) + \delta(\alpha, \eta)} \,. \tag{10.5c}$$

The form of the superinfection function $\tilde{\phi}(\alpha, \eta)$ depends on the coinfection function $\phi(\alpha, \eta)$ and the mechanism that leads to quick removal of hosts from the

doubly infected class. Most simply, hosts could be removed quickly if one of the three terms of the denominator of $\tilde{\phi}(\alpha, \eta)$ is large:

■ Rapid mortality when doubly infected [large value of $\delta(\alpha, \eta)$]. In this case, $\tilde{\phi}(\alpha, \eta) = 0$ and the coinfection process is irrelevant (this rapid mortality does matter when host population size can change). We do not consider this case explicitly and henceforth assume that $\tilde{\delta}(\alpha, \eta) = 0$.

■ Rapid recovery from the less virulent strain [large values of $\theta_1(\alpha, \eta)$ and $\theta_2(\alpha, \eta)$ if $\alpha < \eta$]. In this case, $\tilde{\phi}(\alpha, \eta) = 0$ when $\alpha < \eta$ because a less virulent strain cannot superinfect (Figures 10.2a to 10.2c).

■ Rapid recovery from the more virulent strain [large values of $\theta_1(\alpha, \eta)$ and $\theta_2(\alpha, \eta)$ if $\alpha > \eta$]. In this case, $\tilde{\phi}(\alpha, \eta) = 0$ when $\alpha > \eta$. A less virulent strain acts as a vaccine, favoring evolution of a lower level of virulence (results not shown).

In addition, it is possible that individuals recover rapidly from strains as a function of absolute rather than relative virulence. For example, suppose that $\theta_1(\alpha, \eta) = \theta_2(\alpha, \eta) = \theta_0 \alpha$ for some large value of θ_0, meaning that recovery is proportional to virulence. The superinfection function is

$$\tilde{\phi}(\alpha, \eta) = \frac{\eta}{\eta + \alpha} \phi(\alpha, \eta) \,. \tag{10.6}$$

This particular choice for the recovery rate reduces the advantage of more virulent strains in a superinfection model.

If the coinfection function is nonvanishing for $\alpha < \eta$, the superinfection function retains this property (Figure 10.2d). A less virulent strain can take over hosts from a more virulent strain, although probably at a low rate.

10.3 Coexistence and the Superinfection Function

The shape of the superinfection function affects several aspects of the evolutionary outcome in the system:

■ the value and existence of an evolutionarily stable strategy (ESS);
■ the number of strains in an evolutionarily stable coalition when there is no ESS;
■ the abundances of strains in the evolutionarily stable coalition.

We illustrate results with pairwise invasibility plots to show the structural differences among the cases, and with numerical simulations of multiple strains in competition.

As a baseline, we compute the ESS in the single-infection case. A single strain α in isolation follows the equation

$$\frac{di(\alpha)}{dt} = \left[\beta(\alpha)(1 - i_{++}) - \alpha \right] i(\alpha) \,, \tag{10.7a}$$

with stable equilibrium at

$$i^*(\alpha) = i^*_{++} = 1 - \frac{\alpha}{\beta(\alpha)} \ . \tag{10.7b}$$

In the absence of superinfection, the ESS occurs where i^*_{++} is maximized. With the function

$$\beta(\alpha) = 5\frac{\alpha^2}{4 + \alpha^2} \ , \tag{10.8}$$

the ESS virulence level in the single-infection case is equal to 2.

With superinfection, the per capita growth rate of a strain α invading a population at equilibrium for strain η is

$$f(\alpha, \eta) = \beta(\alpha)(1 - i^*_{++}) - \alpha + \Big[\beta(\alpha)\tilde{\phi}(\alpha, \eta) - \beta(\alpha)\tilde{\phi}(\eta, \alpha)\Big]i^*_{++} \ , \tag{10.9}$$

where $i^*_{++} = i^*(\eta)$ obeys the equilibrium for strain η [Equation (10.7b)]. A critical point or evolutionary singularity (Geritz *et al.* 1998) occurs where

$$\frac{\partial f(\alpha, \eta)}{\partial \alpha}\bigg|_{\alpha=\eta} = 0 \ . \tag{10.10}$$

The second derivative of $f(\alpha, \eta)$ with respect to α is negative if $\beta''(\alpha) < 0$, meaning that this critical point is a local maximum when transmission shows diminishing returns. When the critical point becomes invasible, therefore, the invading strain has virulence rather different from that of the former ESS. From Equation (10.9), the critical point occurs where

$$\begin{aligned}
\frac{\partial f(\alpha, \eta)}{\partial \alpha}\bigg|_{\alpha=\eta} = \ & \beta'(\alpha)(1 - i^*_{++}) - 1 \\
& + \Big[\beta'(\alpha)\tilde{\phi}(\alpha, \alpha) + \beta(\alpha)\frac{\partial \tilde{\phi}(\alpha, \eta)}{\partial \alpha}\bigg|_{\alpha=\eta} \\
& - \beta(\alpha)\frac{\partial \tilde{\phi}(\eta, \alpha)}{\partial \alpha}\bigg|_{\alpha=\eta}\Big]i^*_{++} = 0 \ .
\end{aligned} \tag{10.11}$$

The critical point depends on both the value and the derivative of the superinfection function at the point $\alpha = \eta$. Positive values of $\tilde{\phi}(\alpha, \alpha)$ or of the derivative of $\tilde{\phi}(\alpha, \eta)$ increase the virulence at the critical point above that in the single-infection case.

With a discontinuous superinfection function (Figure 10.2a), every strain can be invaded by a slightly more virulent strain (Figure 10.3a). There is thus no critical point or candidate ESS, although highly virulent strains can be invaded only by slightly more virulent strains. The resultant coalition (not shown) does not consist of one of the many pairs of mutually invasible strains that appear in black in the pairwise invasibility plot, but of a continuum of strains (Tilman 1994; May and Nowak 1994). Although any single strain could be invaded by a more virulent
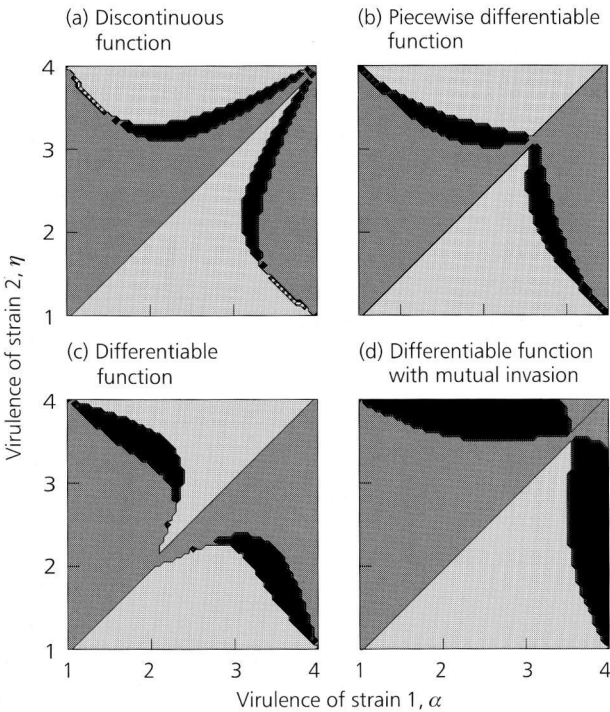
Virulence of strain 2, η

Virulence of strain 1, α

(a) Discontinuous function
(b) Piecewise differentiable function
(c) Differentiable function
(d) Differentiable function with mutual invasion

Figure 10.3 Pairwise invasibility plots. The virulence of strain 1 is plotted on the horizontal axis, and the virulence of strain 2 is plotted on the vertical axis. In the lightly shaded regions, strain 1 can invade strain 2, in the darker regions strain 2 can invade strain 1, and in the black regions both can invade each other. In each case, the transmission function is $\beta(\alpha) = 5\alpha^2/(4+\alpha^2)$, chosen to set the uninvasible virulence at $\alpha = 2$ in the absence of coinfection [Equation (10.8)]. (a) Discontinuous superinfection function (Figure 10.2a). (b) Piecewise differentiable superinfection function (Figure 10.2b). With $x = \alpha - \eta$, the functional form is $\tilde{\phi}(\alpha, \eta) = \sigma x/1 + \sigma x$ if $\alpha > \eta$ and $\tilde{\phi}(\alpha, \eta) = 0$ if $\alpha < \eta$. The parameter σ represents the slope at $x = 0$, and is set to $\sigma = 1$. (c) Differentiable superinfection function (Figure 10.2c). With $x = \alpha - \eta$, the functional form is $\tilde{\phi}(\alpha, \eta) = \sigma x^2/1 + \sigma x^2$ if $\alpha > \eta$ and $\tilde{\phi}(\alpha, \eta) = 0$ if $\alpha < \eta$. The parameter σ is set to $\sigma = 1$. (d) Differentiable superinfection function with nonvanishing invasion rate by a less virulent strain (Figure 10.2d). The functional form, with $x = \pi/2(\alpha - \eta)$, is $\tilde{\phi}(\alpha, \eta) = 2/\pi \tan^{-1}(\sigma x) + c$, where σ is the slope at $x = 0$. The slope at $x = 0$ is set to 1.

strain, the mix of more and less virulent strains in the coalition places an upper bound on the persisting virulence.

A piecewise differentiable superinfection function (Figure 10.2b) does include a critical point (Figure 10.3b). As the slope of the positive part of the curve increases, the virulence at the critical point increases and then undergoes evolutionary branching (Figure 10.4). With the parameter values in Figure 10.3b, the critical value is unstable, and thus can be invaded by a less virulent strain. With a yet steeper slope, the coalition includes several less virulent strains. Unlike the
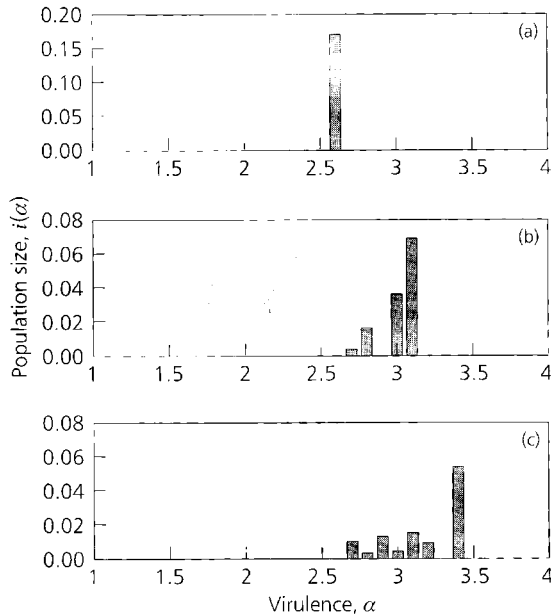
Figure 10.4 Evolutionary outcomes for the piecewise differentiable superinfection function (Figure 10.2b). Slopes σ at $\alpha = \eta$ are 0.5, 1.0, and 2.0 in panels (a), (b), and (c), respectively. The simulations are based on forty evenly spaced strains started from uniform initial conditions and were run until convergence occurred.

discontinuous case, the number of strains increases one by one as the slope of the superinfection function is increased.

A differentiable superinfection function with no invasion by less virulent strains (Figure 10.2c) maintains the critical point at $\alpha = 2$, even as the positive part of the curve increases more quickly (Figure 10.3c). This occurs because the slope at $\alpha = \eta$ is always 0 (Mosquera and Adler 1998). As the curve increases more quickly, the ESS value remains at 2 until it bifurcates, when the more common strain both begins to increase in virulence and is invaded by a less common strain of even higher virulence (Figure 10.5). With a more rapid increase in the curve, more strains join the coalition one by one. This case differs from the piecewise differentiable case in that virulence levels only increase after the critical point destabilizes, and in that the most common strain is the least rather than the most virulent.

A differentiable superinfection function that allows some invasion by less virulent strains (Figure 10.2d) produces results most similar to the piecewise differentiable case because the slope at $\alpha = \eta$ is neither infinite (as in the discontinuous case) nor 0 (as in the differentiable case). In both cases, the critical virulence increases as the slope increases, and the coalitions that arise are dominated by the most virulent strain (Figure 10.6).
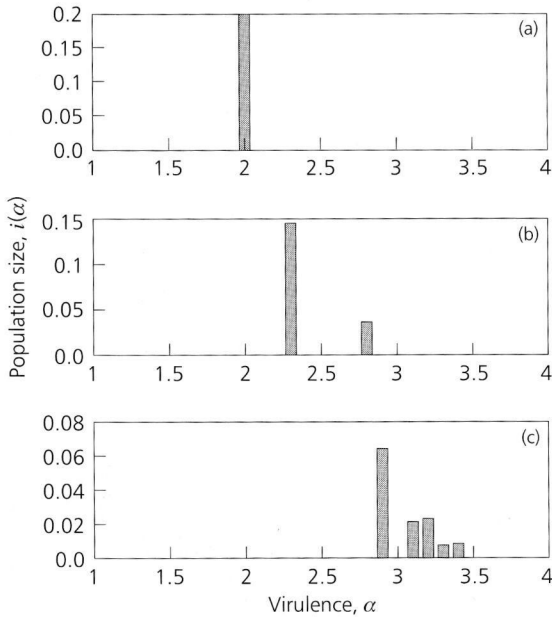
Figure 10.5 Evolutionary outcomes for the differentiable superinfection function (Figure 10.2c). The parameter σ takes on values 0.5, 1.0, and 2.0 in panels (a), (b), and (c), respectively.

However, the virulence levels supported in this case tend to be higher because of the additional mixing among strains. As a simple example, consider the invasion criterion in Equation (10.11) in the simplified case in which any strain can take over from any other at the same rate, or $\hat{\phi}(\alpha, \eta) = \overline{\phi}$ for any α and η. Substituting into Equation (10.11) gives

$$\frac{\partial f(\alpha, \eta)}{\partial \alpha}\Big|_{\alpha=\eta} = \beta'(\alpha)(1 - i_{++} + \phi i_{++}) - 1 = 0 . \tag{10.12}$$

Substituting for i_{++} [Equation (10.7b)] and solving for $\beta'(\alpha)$ gives the condition

$$\beta'(\alpha) = \frac{\beta(\alpha)/\alpha}{1 - \phi + \phi\beta(\alpha)/\alpha} . \tag{10.13}$$

When $\phi = 0$, this reduces to the usual condition (Mosquera and Adler 1998). If we treat the critical value of α as a function of ϕ and differentiate both sides, it is not difficult to show that α is an increasing function of ϕ at $\phi = 0$. Superinfection, even in the absence of any competitive advantage for the more virulent strains, favors strains with higher virulence.

10.4 Discussion

The virulence and coexistence results obtained from models of coinfection depend on the assumptions underlying the coinfection process:
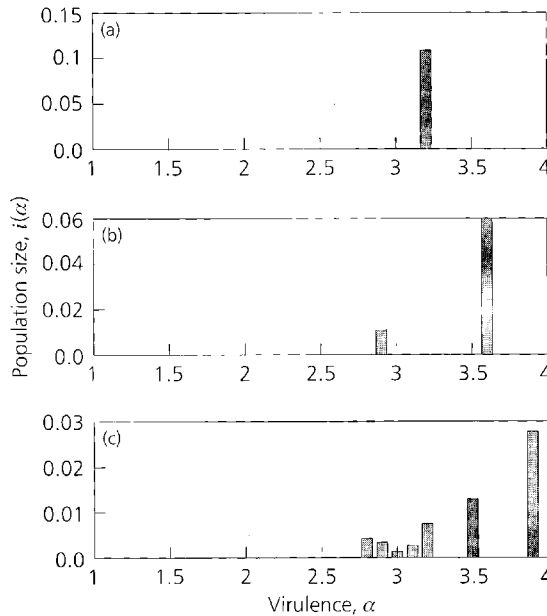
Figure 10.6 Evolutionary outcomes for the differentiable superinfection function with non-vanishing invasion rate by the less virulent strain (Figure 10.2d). The slope σ at $\alpha = \eta$ is 0.5, 1.0, and 2.0 in panels (a), (b), and (c), respectively.

- Which strains can coinfect;
- How coinfection depends on the virulence of the two strains;
- The fate of doubly infected hosts.

When the time scale of double infection is short, these assumptions manifest themselves in the shape of the superinfection function in the resultant model.

The evolutionarily stable coalition that results depends on the shape of the superinfection function for similar strains. If there is a discontinuity, so that slightly more virulent strains can superinfect at a high rate, a continuum of strains can coexist. This result vanishes with a continuous function. In general, as the slope becomes larger, the community adds strains one by one, with a concomitant increase in average virulence. Furthermore, a nonvanishing rate of superinfection by identical strains increases the virulence in any coalition. The virulence of the most abundant strain in the coalition also depends on the shape of the superinfection function. Only for the differentiable superinfection function (see Figure 10.5) is the least virulent strain the most common.

Different shapes of the superinfection function thus produce different patterns of coexistence, with more detailed differences including whether the most abundant strain is the most or least virulent. Ideally, these predictions could be compared with estimates of real superinfection functions to test whether the real systems exist in the region of parameter space where large numbers of strains can

coexist, or whether this particular trade-off tends to support only a few strains with a characteristic pattern of abundance.

Is manipulation of the superinfection function a viable strategy for virulence management? In general, reducing the extent of superinfection reduces virulence. More specifically, our models show that decreasing the competitive advantage of more virulent strains reduces not only the mean virulence, but also the variance in virulence that provides the potential for further evolution. Any control measures that selectively harm more virulent strains could help control virulence in both the short and long term.