4

Adaptive Dynamics of Pathogen–Host Interactions

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4.1 Introduction

Over the past few decades, the expectations of scientists regarding stable patterns of pathogen–host interaction have undergone major transformations. During an initial phase it was widely agreed that pathogens and their hosts evolve in ways that would render benign the consequences of infection (May 1983). These predictions, fostered by the idea that evolution tends to act "for the benefit of the species", are challenged by the conspicuous existence of highly virulent, yet apparently rather stable, human and animal diseases. Within the paradigm of species-level selection, such examples could only be interpreted as transitory cases in which a pathogen has jumped to a new host species so recently that the predicted evolutionary loss of virulence has not yet progressed far enough.

To explain stable intermediate levels of pathogen virulence therefore required a paradigm shift in evolutionary theory: the seemingly conclusive (and, from today's perspective, almost too enthusiastic) demolition of scientific credibility for selection above the level of individuals (Williams 1966). This change in perspective was accompanied by the insight that, although a benign form of infection might benefit a pathogen population as a whole, individuals of a more aggressive pathogen strain might nevertheless invade to reap their harvest. The decisive criterion for the success or failure of such pathogens is their rate of spread through a given host population: if the new pathogen spreads faster than its predecessor does, it may invade and replace that predecessor. It is easily shown that this transmissibility of a pathogen can be highest at intermediate levels of virulence (Anderson and May 1982, 1991). If virulence is too low, symptoms may be absent or harmless and the pathogen may therefore have little opportunity to multiply massively and/or to leave its host. By contrast, if virulence is too high, the resultant symptoms are so severe that the host is likely to perish before it has spread much of the harbored pathogen population. It therefore appeared that evolution would tend to maximize the transmissibility of pathogens, rather than minimize their virulence.

This idea can be made precise. The so-called basic reproduction ratio of a pathogen, denoted by R_0, is defined as the expected number of infections produced by a single infected host individual *in an otherwise uninfected host population* (see Box 2.2). Analyses of relatively simple epidemiological models led to the conclusion that it is the value of R_0 that is raised by the successfully invading pathogens and that is therefore maximized by the evolutionarily stable strain. Since R_0 is a

measure of effective transmissibility, maximizing a pathogen's R_0 is equivalent to maximizing its transmissibility.

This chapter explores how far the technique of R_0 maximization can take us when studying evolution in more complex epidemiological models. Section 4.2 reviews the conceptual limitations of the conventional R_0-based approach, and Section 4.3 introduces adaptive dynamics theory to overcome these limitations. Sections 4.4 and 4.5 focus on two different settings – pathogen evolution in a constant host population and pathogen–host coevolution – and illustrate how the results obtained by application of the new toolbox differ in interesting ways from those of traditional analyses.

4.2 Limitations of R_0 Maximization

The notion of R_0 maximization is plausible in general, applies rigorously to many well-studied models, and undoubtedly helps us to understand some major features of observed pathogen–host interactions. Yet it is not the full story – four crucial problems are not addressed by this approach.

First is the realization that it is not always R_0 that is maximized by evolution. Consider pathogen strains *A* and *B*, for which the R_0 of *A* exceeds that of *B*. The argument above leads us to expect that, among these strains, *A* will win the evolutionary race. This expectation is based on the infection's rate of spread in an uninfected host population, as specified in the definition of R_0. What we really should ask, however, is what happens once pathogen *A* has spread and substantial parts of the host population have thus become infected? In this situation the success or failure of a new strain is no longer determined by its performance in the initial environment, which comprised uninfected hosts only. Instead, we have to consider the strain's rate of spread in the current environment of hosts already infested by strain *A*. It may well be that in this case pathogen *B* is better adapted than *A* to the actual challenge of spreading in a partially infected host population. Under such circumstances, strain *B*, and not *A*, will be evolutionarily stable. In general, whenever the resident strains change the actual epidemiological environment in such a way that the performance of different strains in the uninfected environment is no longer indicative of their invasion success in the actual environment, R_0 maximization does not apply. This option raises the possibility of alternative optimization principles. It turns out that in some models it is indeed possible to find quantities other than R_0 that are maximized by evolution. In particular, it can be shown that the type of density regulation that operates in the system critically influences which quantity is maximized (Mylius and Diekmann 1995; Metz *et al.* 1996b).

Unfortunately, it is by no means clear that for a given system such an optimization principle exists at all. This is a second reason why the assumption of R_0 maximization often misleads. The well-known rock–scissors–paper game (rock beats scissors by crushing, scissors beats paper by cutting, paper beats rock by wrapping) is a very simple example of a situation in which no single quantity can be construed as being maximized by evolution. Likewise, it can happen that pathogen

strain *B* outcompetes strain *A* in the environment that results from the prevalence of *A*, while strain *C* wins against *B* in the environment set by *B*, and *A* beats *C* in the *C* environment. The salient feature of such a scenario is frequency-dependent selection: selective pressures and the resultant invasion success depend on the composition of the established, or resident, pathogen population against which a variant strain is competing. Since frequency-dependent selection is ubiquitous in nature and also naturally arises in epidemiological models (unless the modeler explicitly tries to avoid it), the absence of an optimization principle is the rule, rather than the exception, in realistic pathogen–host interactions. It is important to stress that this does not imply our understanding cannot be furthered through modeling efforts. It merely shows that – instead of always having available the convenient shortcut of maximizing a certain quantity – we often have to evaluate which sequences of invasions are possible and to which evolutionary outcome they lead.

So far we have restricted attention to the evolution of a pathogen in a nonevolving population of hosts. Since pathogens often have much shorter generation times than their hosts, they may be expected to evolve faster than the hosts and therefore to experience essentially a nonevolving host population in the course of their adaptation. This situation appears to apply to acquired immunodeficiency syndrome (AIDS), in which evolutionary change on the part of the human immunodeficiency virus is so unusually rapid that it not only overwhelms the evolutionary potential of the host population, but it even tends to beat the immune system of individual hosts. However, even for the AIDS pandemic, which (in evolutionary terms) is still very recent, some genes that confer host resistance have been reported. Other examples show that evolutionary change in pathogens and their hosts can occur on similar time scales. A case in point is the swift coevolutionary race between the European rabbit and the myxoma virus in Australia, which commenced with the virus's introduction to the Fifth Continent in 1950 (see Figure 4.2a). As in this case, sexual recombination often allows hosts to match effectively the evolutionary pace of their asexual pathogens. It must therefore be concluded that pathogen and host evolutions do not always have different time scales. To conceive the adaptation of pathogen–host interactions in terms of coevolutionary dynamics makes it plain that no general optimization principle can predict adequately the evolutionary outcome of all possible arms races. Instead, we have to consider the potential for the invasion of a variant pathogen or host type into the environment jointly brought about by the prevalent pathogen and host types. This highlights the importance of the environmental feedback loop (Metz *et al.* 1996b; Heino *et al.* 1997) that operates in evolving pathogen–host systems: the current environment determines current selection pressures and, in turn, these selection pressures determine the future environments that result from the invasion of selectively favored types. In such a context, the rates at which new types are generated by mutation or recombination may be critical (Dieckmann and Law 1996) and dynamic descriptions therefore become essential – static optimization principles simply cannot account for such complexity.

Box 4.1 Pairwise invasibility plots

The invasion fitness of an evolving species (see Section 4.3) defines pairwise invasibility plots for resident and mutant phenotypes (Van Tienderen and de Jong 1986; Metz *et al.* 1992, 1996a; Kisdi and Meszéna 1993; Geritz *et al.* 1997; see also Taylor 1989). In the simplest case, these phenotypes are described by a single metric character or quantitative trait. Plotting the sign of the invasion fitness f for each of the possible combinations of mutant phenotypes x' and resident phenotypes x reveals the shapes of the zero contour lines at which $f(x', x) = 0$. As shown in the left panel below, these lines separate regions of potential invasion success ($f > 0$) from those of invasion failure ($f < 0$). The resident population precisely renews itself when it is at equilibrium, so the resident trait value is neutral in its own environment and the set of zero contour lines therefore always includes the main diagonal.
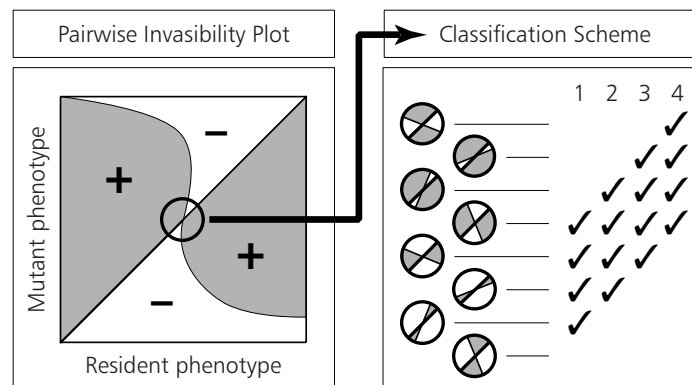
The shape of the other zero contour lines carries important information about the evolutionary process. In particular, possible evolutionary endpoints are located at the resident phenotypes for which a zero contour line intersects with the main diagonal. In characterizing these so-called evolutionarily singular points, adaptive dynamics theory uses an extended classification scheme in which four different questions are tackled simultaneously:

1. *Evolutionary stability*. Is a singular phenotype immune to invasions by neighboring phenotypes? This criterion amounts to a local version of the classic evolutionarily stable strategy (ESS) condition that lies at the heart of evolutionary game theory (Maynard Smith 1982).
2. *Convergence stability*. When starting from neighboring phenotypes, do successful invaders lie closer to the singular phenotype? Here the attainability of a singular point is addressed, an issue that is separate from its invasibility (Eshel and Motro 1981; Eshel 1983).
3. *Invasion potential*. Is the singular phenotype capable of invading populations of its neighboring types (Kisdi and Meszéna 1993)?
4. *Mutual invasibility*. If a pair of neighboring phenotypes lies either side of a singular phenotype, can they invade each other? Assessment of this possibility is essential to predict coexisting phenotypes and the emergence of polymorphisms (Van Tienderen and de Jong 1986; Metz *et al.* 1992, 1996a).

Box 4.1 *continued*

All four questions are important to understand the nature of potential evolutionary endpoints. It is therefore remarkable how the four answers are obtained simply by examining the pairwise invasibility plot and reading off the slope of the zero contour line at the singular phenotype (Metz *et al.* 1996a; Geritz *et al.* 1997), as illustrated in the right panel above.

Three particularly interesting types of evolutionarily singular points are illustrated below. In each case, the staircase-shaped curve depicts a possible trait substitution sequence during which populations of resident phenotypes are repeatedly replaced by advantageous mutant phenotypes that invade successfully.
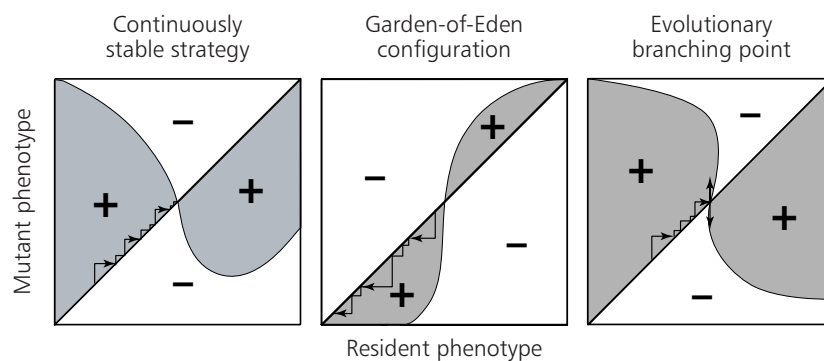
The left panel shows a singular point that is both evolutionarily stable and convergence stable. Such an outcome is called a continuously stable strategy (CSS; Eshel 1983). In the middle panel, the singular point is evolutionarily stable but not convergence stable. This means that, although the singular phenotype is protected against invasion from all nearby phenotypes, it cannot be attained by small mutational steps – a situation aptly referred to as a Garden-of-Eden configuration by Nowak and Sigmund (1989). The right panel shows an evolutionary branching point: here the singular point is convergence stable but evolutionarily unstable. This implies convergence to disruptive selection and thus permits the phenotypic divergence of two subpopulations that straddle the branching point (Metz *et al.* 1992, 1996a).

There is a fourth reason that necessitates a departure from classic concepts of evolutionary epidemiology. The principle of R_0 maximization is based on the notion that we should expect to see as evolutionary outcomes those types of pathogen or host that are unbeatable or evolutionarily stable against all possible other types that can, in principle, arise in their species. However, hopeful monsters are not frequently encountered in the biological world and substantial changes in morphology or physiology tend to be lethal. For this reason, adaptation can usually explore only the small range of variation that is accessible by gradual change. It is therefore not always meaningful to seek out those types of pathogens or hosts that cannot be beaten by any potential variant, including those that require major evolutionary reconstruction. In the presence of frequency dependence, this simple

observation has substantial consequences. First, some evolutionary outcomes predicted by the analysis of evolutionary stability alone cannot actually be reached by a sequence of small adaptive steps, and, second, some outcomes actually attained in the course of evolution turn out not to be evolutionarily stable at all (for an illustration of these points, see Box 4.1). Consequently, evolutionary stability and attainability must always be considered in conjunction; it is only in the simple case of evolutionary processes governed by an optimization principle that the two notions coincide of necessity (Meszéna *et al.* 2000).

The conventional approach to maximize R_0 for a pathogen therefore has some fundamental limitations as a tool to describe the complex processes that arise from the evolution of general pathogen–host interactions. To overcome this obstacle, an extended framework is required to encompass the successful classic approach as a special case. In the following section the theory of adaptive dynamics is introduced as a candidate to meet this challenge.

4.3   Adaptive Dynamics Theory

The starting point of adaptive dynamics theory is to understand that the fitness of a type can only be evaluated relative to the environment that type experiences. This implies that we have to know the current ecological and epidemiological status of a host population before we can assess whether a given pathogen can spread within that population or not. A characterization of this status includes, *inter alia*, information about the types and abundances of other pathogen strains that are present in the host population. Likewise, we have to specify the resident host type, as well as the endemic strain or strains of the pathogen, to predict which variant host types excel at the evolutionary play staged in the given ecological theater.

These considerations naturally lead to the concept of invasion fitness (Metz *et al.* 1992). The invasion fitness of a type x is the expected long-term per capita growth rate f of that type in a given environment E, $f = f(x, E)$. If the invasion fitness of a type is positive it may invade in that environment, otherwise not.

As discussed above, those types $x_1, x_2, \ldots$ that are present in a given system in general affect the environment, $E = E(x_1, x_2, \ldots)$. One possible complication here is that the environment may not yet have fully settled to reflect the present set of types. This can happen, for instance, in the wake of an ecological perturbation or shortly after new types, very different from their predecessors, have started to invade the system. Often, however, evolution is slow enough for ecological processes to respond swiftly in comparison, in particular since gradual evolutionary change usually does not even require much ecological response for a population to stay at its ecological equilibrium or, more generally, its ecological attractor. To simplify matters, it is therefore convenient to assume that the state of the environment has come close to the attractor determined by the resident types. Under such conditions, the dependence of the invasion fitness f of a type x on the current environment E can be replaced by a dependence on the resident types $x_1, x_2, \ldots$, $f = f(x, x_1, x_2, \ldots)$. These types can belong to the same species as type x does,

or involve other coevolving species. For simplicity, it is often sufficient to characterize a population by its prevalent or average type (Abrams *et al.* 1993). Although strictly monomorphic populations are rarely found in nature, it turns out that the dynamics of polymorphic populations (which harbor, at the same time, many similar types per species) can often be well described and understood in terms of the simpler monomorphic cases.

For pathogen–host systems that allow the coevolution of virulence x and resistance y, we thus arrive at the notation $f(x', x, y)$ for the invasion fitness of a variant pathogen of virulence x' in a host population of resistance y that is infected by resident pathogens of virulence x. Analogously, in this infected host population $f_h(y', x, y)$ is the invasion fitness of a variant host of type y'. Notice that the variant types can arise from mutation, as well as from recombination and immigration. In the absence of host evolution, pathogen fitness is simply denoted by $f(x', x)$. (Throughout this chapter a prime denotes variant types, whereas no prime refers to resident types; this keeps the notation shorter than using the more explicit notation x_{mut} and x_{res}.) Based on these fitness functions so-called pairwise invasibility plots can be constructed to explore which variant pathogens can successfully invade which resident pathogens, and the same analysis can be carried out for evolution in the host (Box 4.1). Moreover, one of the explicitly dynamic models of adaptive dynamics theory can be used to investigate the time course of evolutionary or coevolutionary change in such systems (Box 4.2).

4.4   Pathogen Evolution

To illustrate how the theory of adaptive dynamics can elucidate the evolution of virulence, consider a generalized susceptible-and-infected (SI) model (see Box 2.1),

$$\frac{dS}{dt} = + b_S(x, S, I)S + b_I(x, S, I)I - d_S(x, S, I)S$$
$$- \beta(x, S, I)SI + \theta(x, S, I)I , \tag{4.1a}$$

$$\frac{dI}{dt} = -d_I(x, S, I)I + \beta(x, S, I)SI - \theta(x, S, I)I , \tag{4.1b}$$

which describes the dynamics of the density S of susceptible hosts and of the density I of hosts infected by a single pathogen strain with virulence x. The per capita birth and death rates, b and d, as well as the transmission rate β and the recovery rate θ, can all depend on the virulence of the resident strain x and on the current composition of the host population, in terms of densities S and I. The birth rates of susceptible and infected hosts, b_S and b_I, can differ, as can their death rates d_S and d_I; in particular, the pathogen-induced death rate is $\alpha = d_I - d_S$. Hosts are born uninfected and the host population is assumed to be spatially homogeneous.

Evolutionary invasion analysis

A variant strain of the pathogen is now introduced into the resident population described by Equations (4.1). The variant strain has virulence x' and the density

Box 4.2 Models of adaptive dynamics

Adaptive dynamics theory derives from considering ecological interactions and phenotypic variation at the level of individuals. Extending classic birth and death processes, as well as ecological descriptions of structured populations, adaptive dynamics models allow offspring phenotypes to differ from those of their parents, and thus enable studies of the interplay between population dynamics (changes in the abundance of individuals) and adaptive dynamics (changes in their heritable traits). Four types of dynamic model are used to investigate the resultant eco-evolutionary processes at different levels of resolution and generality:
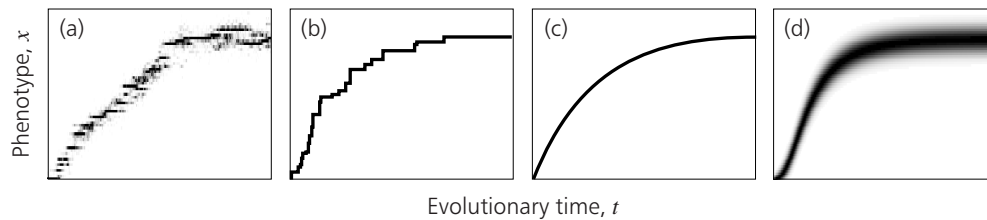
- With an individual corresponding to a single point in a population's trait space, situated at the individual's combination of trait values, populations can be envisaged as clouds of such points. These stochastically drift and diffuse through trait space as a result of selection and mutation (Dieckmann 1994; Metz *et al.* 1996a); see panel (a) above.
- If populations are large and mutation rates are sufficiently low, evolutionary change in clonal populations proceeds through sequences of trait substitutions (Metz *et al.* 1992; Dieckmann 1994; Dieckmann and Law 1996). During each such step, an advantageous mutant quickly invades a resident population, ousting the former resident. These steps are analyzed through the pairwise invasibility plots introduced in Box 4.1 and used in Figure 4.1. Concatenation of such substitutions results in a description of evolutionary change as a directed random walk in trait space; see panel (b) above.
- If, in addition, the mutation steps are sufficiently small, the staircase-like dynamics of trait substitutions are well approximated by smooth deterministic trajectories; see panel (c) above. It can be shown that these trajectories follow the canonical equation of adaptive dynamics (Dieckmann 1994; Dieckmann and Law 1996),

$$\frac{d}{dt}x_{jk} = \frac{1}{2}\mu_j n_j^*(x) \sum_l \sigma_{j,kl}^2 \frac{\partial}{\partial x_{jl}'} f_j(x_j', x)\bigg|_{x_j'=x_j} , \tag{a}$$

where x_{jk} is the value of trait k in species j, x_j is the resultant trait vector in species j, and x collects these trait vectors for all species in the considered ecological community. For species j, μ_j is the probability for mutant offspring, $n_j^*(x)$ is the equilibrium population size, σ_j^2 is the variance–covariance matrix of mutational steps, and f_j is the invasion fitness. The partial derivatives of f_j in Equation (a) are the components of the selection gradient g_j. Evolution in x_j comes to a halt where g_j vanishes, and the curves on which this happens are therefore known as evolutionary isoclines.

continued

Box 4.2 *continued*

■ If, by contrast, mutation rates are high while populations are large, stochastic elements in the dynamics of phenotypic distributions become negligible; this enables mathematical descriptions of the reaction–diffusion type; see panel (d) above. However, the infinitely extended tails that phenotypic distributions acquire in this framework easily give rise to artifactual dynamics that have no correspondence to processes in any finite population.

At the expense of ignoring genetic complexity, models of adaptive dynamics are geared to analyze the evolutionary implications of ecological settings. This allows the study of all types of density- and frequency-dependent selection mechanisms within a single framework, into which coevolutionary dynamics driven by interspecific interactions are also readily incorporated.

of hosts thus infected is denoted by I'. Assuming that the resident population is at its demographic equilibrium $[S^*(x), I^*(x)]$, the mutant is rare, and super- or coinfections are negligible, we obtain

$$\frac{dI'}{dt} = f(x', x)I' , \tag{4.1c}$$

where $f(x', x)$ denotes the mutant's invasion fitness,

$$\begin{aligned} f(x', x) = &- d_I(x', S^*(x), I^*(x)) + \beta(x', S^*(x), I^*(x))S^*(x) \\ &- \theta(x', S^*(x), I^*(x)) . \end{aligned} \tag{4.2a}$$

The lifetime reproductive success of the mutant in the resident population at equilibrium can also be determined,

$$R(x', x) = \frac{\beta(x', S^*(x), I^*(x))S^*(x)}{d_I(x', S^*(x), I^*(x)) + \theta(x', S^*(x), I^*(x)} . \tag{4.2b}$$

Analogously, the lifetime reproductive success of the mutant in an infection-free resident population that comprises S_0 susceptible hosts can be obtained,

$$R_0(x') = \frac{\beta(x', S_0, 0)S_0}{d_I(x', S_0, 0) + \theta(x', S_0, 0)} , \tag{4.2c}$$

and is known as the mutant's basic reproduction ratio R_0 (see Box 2.2).

From Equations (4.2a) and (4.2b) it can immediately be seen that the invasion fitness of the mutant is positive – which indicates that the mutant can invade the resident population – if and only if its lifetime reproductive success exceeds one: $f(x', x) > 0 \Leftrightarrow R(x', x) > 1$. This is expected biologically and can be regarded as a trivial correspondence.

What is much less straightforward, however, is to formally link f and R to the widely used basic reproduction ratio R_0. For this link to become more transparent, we can exploit the relation $R(x, x) = 1$, which implies that, by definition, the

density of infected hosts accurately replenishes itself once the disease has reached its endemic equilibrium. Applying this consistency condition to Equation (4.2b), an expression for $S^*(x)$ is obtained. This, in turn, yields

$$R(x', x) = \frac{\beta(x', S^*(x), I^*(x))/[d_I(x', S^*(x), I^*(x)) + \theta(x', S^*(x), I^*(x))]}{\beta(x, S^*(x), I^*(x))/[d_I(x, S^*(x), I^*(x)) + \theta(x, S^*(x), I^*(x))]}.$$
(4.2d)

This equation can be rewritten as $R(x', x) = R_0(x')/R_0(x)$ if the epidemiological rates β, d_I, and θ are density independent, that is, if the corresponding functions do not depend on their second and third arguments. It is therefore only under this condition that the convenient equivalence $R(x', x) > 1 \Leftrightarrow R_0(x') > R_0(x)$ can be taken for granted. Whether this equivalence also holds for some restricted types of density-dependent rates remains an open research question; to date no results on this have been obtained.

Next, these general considerations are illustrated with a suite of specific examples.

Virulence evolution toward benignity

Example I. Let us start by investigating the most simplistic version of Equations (4.1). The rates for birth, transmission, recovery, and natural mortality are assumed to be constant: $b_S(x, S, I) = b_I(x, S, I) = b$, $\beta(x, S, I) = \beta$, $\theta(x, S, I) = \theta$, and $d_S(x, S, I) = d$, while the death rate of infected hosts increases with the virulence of the infecting strain, $d_I(x, S, I) = d + x$. The last relation sets the scale of virulence x in terms of disease-induced host mortality α.

With $S^*(x) = (x + b + \theta)/\beta$ the invasion fitness $f(x', x) = x - x'$ is obtained. A corresponding pairwise invasibility plot (Box 4.1) and evolutionary trajectory (Box 4.2) are shown in Figure 4.1a. Mutant strains x', with lower virulence than the resident strain x, can always invade and, therefore, the system will evolve toward the most benign strain. The same conclusion can be obtained by maximizing $R_0(x') = \beta S_0/(x' + d + \theta)$ with regard to x' – pathogen strains that harm their host as little as possible are always favored by natural selection.

Virulence evolution under transmission trade-offs

Under the simplistic assumptions made above, pathogens do not benefit from harming their hosts. However, many pathogens are more readily transmitted during individual contacts if they have a higher virulence: this introduces a trade-off for the pathogen between transmission probability and host longevity.

Example II. It can be assumed, for instance, that transmission rates increase proportionally with virulence, $\beta = cx$. This results in $f(x', x) = (x' - x)(d + \theta)/x$, and $R_0(x') = cx'S_0/(x' + d + \theta)$. Thus an ever-increasing virulence (Figure 4.1b) would be expected, which is clearly unrealistic.

Example III. Following the seminal work by Anderson and May (1982, 1991) a diminishing return for increased virulence is often considered by choosing, for

instance, $\beta = x/(x + c)$; see also Equation (2.1). While maintaining a trade-off between transmission efficiency and host longevity, more emphasis is thus put on the latter. The resultant invasion fitness $f(x', x) = (x - x')[xx' - c(d + \theta)]/[x(x' + c)]$ has a vanishing selection gradient $g(x) = \left.\frac{\partial}{\partial x'} f(x', x)\right|_{x'=x}$ (Box 4.2) at the intermediate virulence $x^* = \sqrt{c(d + \theta)}$, where also the basic reproduction ratio $R_0(x') = x' S_0/[(x' + d + \theta)(x' + c)]$ is maximized. A corresponding pairwise invasibility plot is shown in Figure 4.1c.

The ubiquity of density-dependent rates

Now consider situations in which the rates in the SI model depend on the densities of susceptible and/or infected hosts. Such density dependence can apply to the basic demographic rates d_S and b_S, as well as to the epidemiological rates. The latter include the disease-induced mortality $d_I - d_S = \alpha$, the disease-induced loss in fecundity $b_S - b_I$, the transmission rate β, and the recovery rate θ.

It is actually very implausible that all of these rates are density independent. Density dependence of demographic rates is already assumed in all simple non-epidemiological population models and is needed to prevent the density of susceptible hosts from diverging without bounds in the absence of the disease. The only justification for neglecting such dependence in simple versions of Equations (4.1) is to assume that the disease itself is fully responsible for regulating the host population density. However, even for the severest of diseases this must remain an approximation, whereas for most other infections the assumption is plainly wrong. A second way to avoid considering density-dependent demographic rates is to assume that the total host population size, $N = S + I$, stays strictly constant – independent of the virulence of the resident strain. Obviously, this is also an approximation at best and is likely to apply to very benign diseases only. As usual, reality lies between these mathematical extremes and density regulation in an infected population occurs partially through disease-independent factors and partially through the disease itself (May 1983).

The case for density-dependent rates becomes even stronger when the epidemiological rates, which are directly affected by the disease, are considered. An almost endless variety of mechanisms can cause such dependence; hence the following list is certainly not exhaustive:

- The number of patients an average doctor must treat may rise with the density of infected hosts. This can affect disease-induced mortality and loss of fertility, as well as recovery rates.
- The nutritional status of hosts, and thus their resistance against disease symptoms, may deteriorate with increases in total population density or in the population's morbidity level.
- The quality of medical services in terms of diagnostic and therapeutic options may improve with the wealth of a population. Such wealth may either increase or decrease with total population density and is likely to deteriorate with an increase in the density of infected hosts.
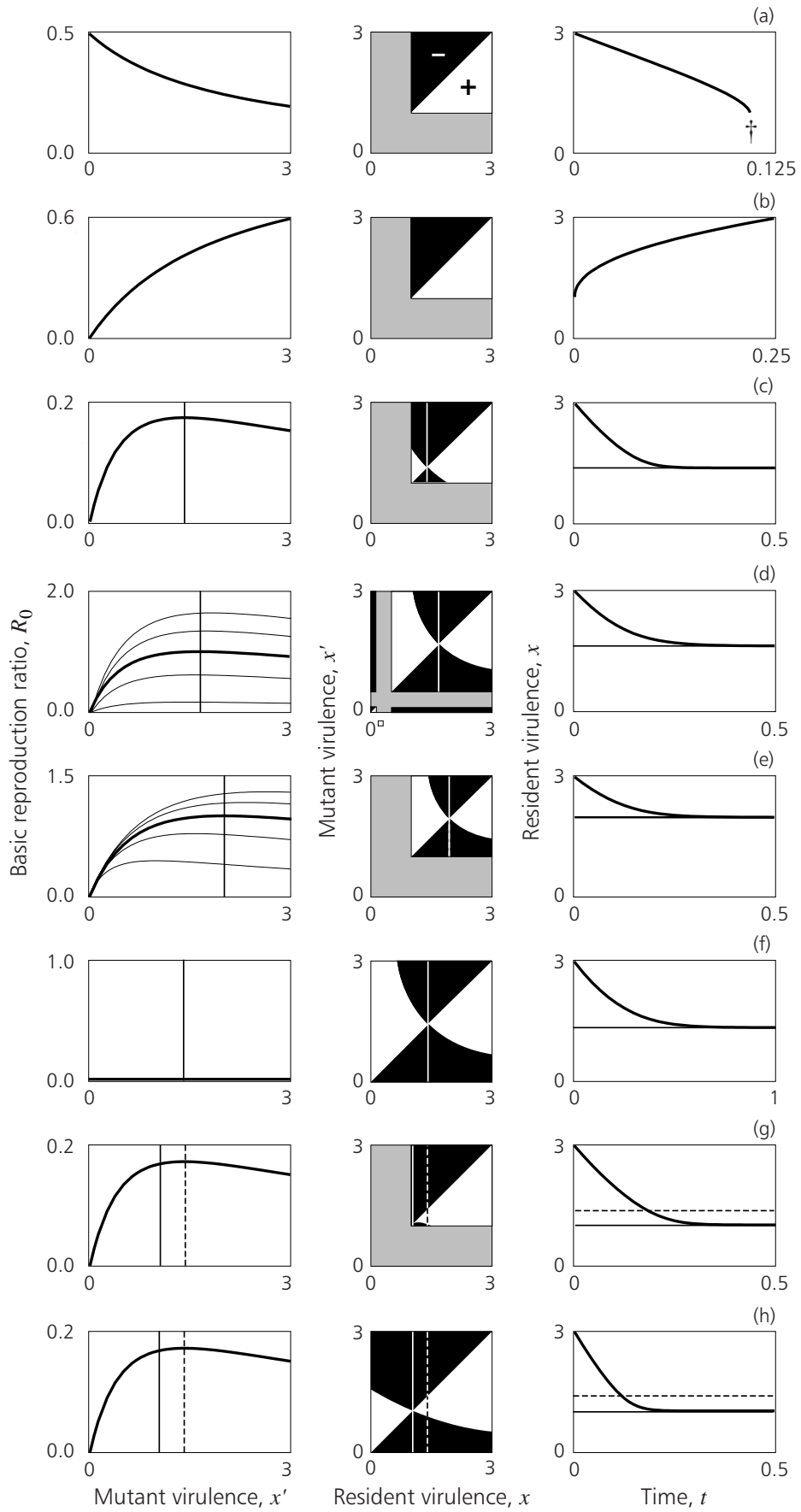
Basic reproduction ratio, R_0 (left column, x-axis: Mutant virulence, x'); Mutant virulence, x' (middle column, x-axis: Resident virulence, x); Resident virulence, x (right column, x-axis: Time, t). Panels (a)–(h).

Figure 4.1 Evolution of pathogen virulence as described by R_0 maximization (left column), pairwise invasibility plots (middle column), and evolutionary trajectories (right column, based on the canonical equation of adaptive dynamics). Rows (a) to (h) correspond to Examples I to VIII in the text. In the middle column, outcomes of virulence evolution are indicated by continuous lines and false predictions that result from R_0 maximization by discontinuous lines. Virulence ranges that do not allow the pathogen to remain endemic are depicted as gray areas. Whereas evolution in cases (a) and (b) leads to ever-increasing or -decreasing virulence, respectively, case (c) shows how a trade-off between transmission probability and host longevity induces evolution toward intermediate virulence. For these first three cases the outcome of virulence evolution can be predicted by R_0 maximization. Evolution in cases (d) and (e) also leads to intermediate virulence, but does not allow R_0 maximization, since the optimal virulence depends on which density of susceptible hosts is assumed. For these examples the left column shows several curves, corresponding to different assumptions about this density; the thick curves describe the self-consistent solutions. Rows (f) to (h) show cases for which R_0 maximization results in seriously misleading conclusions. Parameters: $b = 2$ (a–h), $d = 1$ (a–h), $\theta = 1$ (a–f, h), $\theta_0 = 1$ (g), $\beta = 1$ (a–b), $c = 1$ (c–d, f–h), $c = 0.5$ (e), $K = 10$ (d–h), $\mu\sigma^2 = 1$ (a–h, this scales the evolutionary time t).

- Awareness about potential transmission routes is expected to grow under conditions of high incidence. Transmission rates are then predicted to decrease when the density of infected hosts increases.
- The density of infected hosts changes the ambient density of infectious propagules to which susceptible hosts are exposed. Through the operation of the host's immune system, this propagule density may not translate linearly into the rate at which susceptible hosts acquire infections, and transmission rates then become dependent on the density of infected hosts.
- Changes in total population density are known to reshape social contact networks and thereby to affect the chances of disease transmission.

The last three mechanisms imply that the population-level rate of disease transmission is not proportional to the densities of susceptible and infected hosts and therefore cannot be described by the simplifying assumption of mass action (see Box 2.1). All six mechanisms together illustrate how far-fetched the assumption of fully density-independent rates really is. This conclusion, however, only has major consequences for virulence evolution if evolutionary outcomes in models with density-dependent rates can differ significantly from those in their simpler, density-independent counterparts. We therefore examine below how robust the method of R_0 maximization and the specific predictions thus obtained are for epidemiological models with density-dependent rates. To address this question, five further examples are studied.

Virulence evolution with rates dependent on susceptible host density

Example IV. This example originates from a slight modification of Example III by considering a density-dependent natural mortality of logistic type, $d_S =$

$d + S/K$, with carrying capacity K. The disease-induced mortality and the transmission rate remain density independent, $\alpha = d_I - d_S = x$ and $\beta = x/(x + c)$. This means that, in this example, density dependence extends only to the basic demographic rates, but not to the epidemiological rates. Examining the resultant invasion fitness $f(x', x)$ reveals that under the given conditions evolution converges toward the intermediate virulence $x^* = [c + \sqrt{c^2K + cK(K-1)(d+\theta)}]/(K-1)$ (Figure 4.1d).

This conclusion cannot be reached directly by maximizing the basic reproduction ratio $R_0(x') = x'S_0/[(x' + d + \theta + S_0/K)(x' + c)]$, since the resultant optimal virulence depends on the density of susceptible hosts in the absence of the disease, S_0. It is therefore clear that simple R_0 maximization ceases to work for examples like this. The reason is obvious: the optimal level of virulence depends on the density of susceptible hosts available for infection by a new strain, and this density in turn is affected by the resident strain. In other words, the existence of such an environmental feedback renders selection frequency dependent and usually precludes predicting the outcome of evolution through R_0 maximization.

It is therefore quite remarkable that this example nevertheless allows an optimization principle other than R_0 maximization. It can be shown that the optimal virulence x^* in this example can also be predicted by maximization of the function $\Phi(x') = [x'(K-1) - c]/[K(x' + d + \theta)(x' + c)]$ (J.A.J. Metz, personal communication). In agreement with the findings of Mylius and Diekmann (1995) and Metz *et al.* (1996b), the form of such alternative optimization functions is very sensitive to the way in which density dependence affects the rates of the epidemiological model, which implies that the generality of this particular choice of Φ is very limited. Notice that an analogous conclusion holds for R_0 itself: it primarily applies as an optimization principle for models with density-independent rates. Yet, such models have prevailed in the literature so far, which might have fostered a rather different impression.

Example V. As a second example for density-dependent rates, we return to density-independent mortalities, but now let the density of susceptible hosts affect the transmission rate, $d_S = d$, $\alpha = d_I - d_S = x$, and $\beta = x/(x + c/S)$. This means that the gain in transmission that results from a rise in virulence increases with the density of susceptible hosts. Analysis of the invasion fitness $f(x', x)$ shows that evolution again converges toward an intermediate virulence, this time given by $x^* = \sqrt{d + \theta}[\sqrt{d + \theta + 4\sqrt{c}} - \sqrt{d + \theta}]/2$ (Figure 4.1e). Also, this example allows an alternative optimization principle, $\Phi(x') = x'/[z + \sqrt{z(z + 4c)}]$ with $z = x'(x' + d + \theta)$. Since the form of density dependence has changed relative to that in Example IV, the two corresponding optimization principles also look very different.

While, for the previous two examples, the approach of R_0 maximization may be inconclusive, at least it does not turn out to be misleading. This is because, in these examples, the existence of the environmental feedback loop is unmistakably signaled by the dependence of R_0 on S_0. Subsequent to conventional R_0

maximization, the feedback loop can therefore be respected by choosing S_0 self-consistently. This is achieved by solving for a pair (x^*, S_0) such that, first, x^* maximizes R_0 given S_0 and that, second, S_0 is the equilibrium density of susceptible hosts for a resident virulence x^*. By adhering to such an extended R_0-based framework, it is thus sometimes possible to bypass the explicit analysis of invasion fitness. While evolutionary invasion analysis is applicable much more widely, the described alternative (but of course fully equivalent) route might appeal to those already familiar with conventional R_0 maximization.

Virulence evolution with rates dependent on infected host density

Example VI. Bypassing evolutionary invasion analysis is no longer an option when demographic or epidemiological rates that depend on the density of infected hosts are considered. Such a situation arises, for example, when the infection rate of susceptible hosts is assumed to change nonlinearly with the density of infected hosts. The relation $\beta = xI/(x+c)$ describes a setting in which the host's immune system is more likely to succumb to the onslaught of a disease if the ambient density of pathogens is high. Keeping the other rates as simple as in Example V, exactly the same expression is obtained for invasion fitness as when $\beta = x/(x+c)$, which predicts convergence toward the intermediate virulence $x^* = \sqrt{c(d+\theta)}$ (Figure 4.1f). Notice, however, that in this example R_0 for pathogens with any level of virulence x' vanishes, $R_0(x') = 0$ – erroneously suggesting that virulence is an evolutionarily neutral trait. The same conclusion pertains to any SI model in which the standard mass action term βSI is replaced by βSI^q with $q > 1$. For all these examples, an alternative optimization principle applies, $\Phi(x') = x'/[(x' + d + \theta)(x' + c)]$, and application of R_0 maximization is seriously misleading.

Example VII. Unfortunately, the error incurred by adhering to R_0 maximization can be even less conspicuous. Now consider an example in which the rate of recovery from the disease decreases with the number of infected hosts, $\theta = \theta_0/(1 + I/K)$. As mentioned above, such a situation could arise, for instance, when the care extended to individual infected hosts declines with their overall density. Here θ_0 is the recovery rate at very low disease incidence and K is the density of infected hosts at which that rate is halved. All other rates are assumed to be density independent, as in the previous examples; for the transmission rate we again revert to the classic trade-off relation $\beta = x/(x + c)$. As in Example III, R_0 for this setting is given by $R_0(x') = x'S_0/[(x' + d + \theta_0)(x' + c)]$ and it is immediately obvious that the density dependence of the recovery rate leaves this expression unchanged. This means that the parameter K cannot influence the optimal virulence $\tilde{x}^* = \sqrt{c(d+\theta_0)}$, predicted from maximizing R_0. Also, the birth rate b does not show in this result. For a particular choice of parameters ($b = 2$, $d = 1$, $c = 1$, $\theta_0 = 1$, and $K = 10$) R_0 maximization thus leads us to believe that, independent of b and K, evolution converges toward the intermediate virulence $\tilde{x}^* = \sqrt{2} \approx 1.414$. By contrast, a proper analysis of invasion fitness reveals that the selection gradient for this example actually vanishes at a significantly lower virulence, $x^* = 1.061$ (Figure 4.1g). Moreover, this evolutionarily stable outcome

changes to $x^* = 1.253$ for $b = 1.75$ and to $x^* = 1.367$ for $K = 100$, qualitative effects that are altogether missed by the erroneous application of R_0 maximization.

Example VIII.   The same conclusion applies when the density of infected hosts influences the disease-induced mortality. Here, consider an example described by $d_S = d$ and $d_I = d + x(1 + I/K)$. When disease incidence is low, disease-induced mortality $\alpha = d_I - d_s$ is given by x, just as in the preceding examples. Now, however, α increases with the density of infected hosts. As already mentioned, this could result, for instance, from the diminished care available to each infected host. For the other rates the same choices are made as in Example VII, except for the recovery rate θ, which is again simply kept density independent. Maximization of $R_0(x') = x'S_0/[(x' + d + \theta)(x' + c)]$ yields the by now familiar expression $\tilde{x}^* = \sqrt{c(d + \theta)}$, which (for $b = 10$, $d = 1$, $c = 1$, $\theta_0 = 1$, and $K = 10$) gives $\tilde{x}^* = 1.414$. This prediction for the outcome of virulence evolution dramatically differs from $x^* = 0.194$, the accurate value derived from evolutionary invasion analysis. As in the previous example, R_0 maximization also fails to capture the dependence of x^* on b and K: $b = 2$ gives $x^* = 1.043$ (Figure 4.1h), and $K = 100$ gives $x^* = 0.219$.

Notice that the pairwise invasibility plots in all but the last two examples are skew-symmetric, that is, invariant under reflection along the main diagonal and simultaneous sign inversion (Figures 4.1a to 4.1f). The symmetry applies to the invasion fitness itself, $\mathrm{sgn}\,f(x', x) = -\mathrm{sgn}\,f(x, x')$, and hence is independent of the particular parameters chosen for the figures. According to the theory laid out by Metz *et al.* (1996b), this implies that the feedback loop in these examples acts through a one-dimensional environmental characteristic. If, in addition, the dependence of f on this characteristic is monotone, an optimization principle Φ can always be found – although the correct one often differs from R_0. By contrast, pairwise invasibility plots in Figures 4.1g and 4.1h are not skew-symmetric. As Metz *et al.* (1996b) have demonstrated, this means that the dimension of the environmental feedback loop exceeds one and no optimization principle can exist.

4.5   Pathogen–Host Coevolution

Evolution of pathogen virulence does not occur in isolation from other adaptive processes and is often accompanied by hosts changing their resistance toward infection. At first sight, the short life cycles of most pathogens suggest that pathogen adaptation greatly outpaces evolutionary responses on the part of the host. However, sexual reproduction in hosts often compensates for the pronounced asymmetries in demographic rates, and thus helps host populations to survive arms races with their pathogens.

This section briefly illustrates how models of adaptive dynamics are used to describe pathogen–host coevolution. Keeping in mind that R_0 maximization can be safely employed to predict virulence evolution only when demographic and epidemiological rates are density independent, the focus here is on the correspondence (or lack thereof) between processes of pathogen–host coevolution under
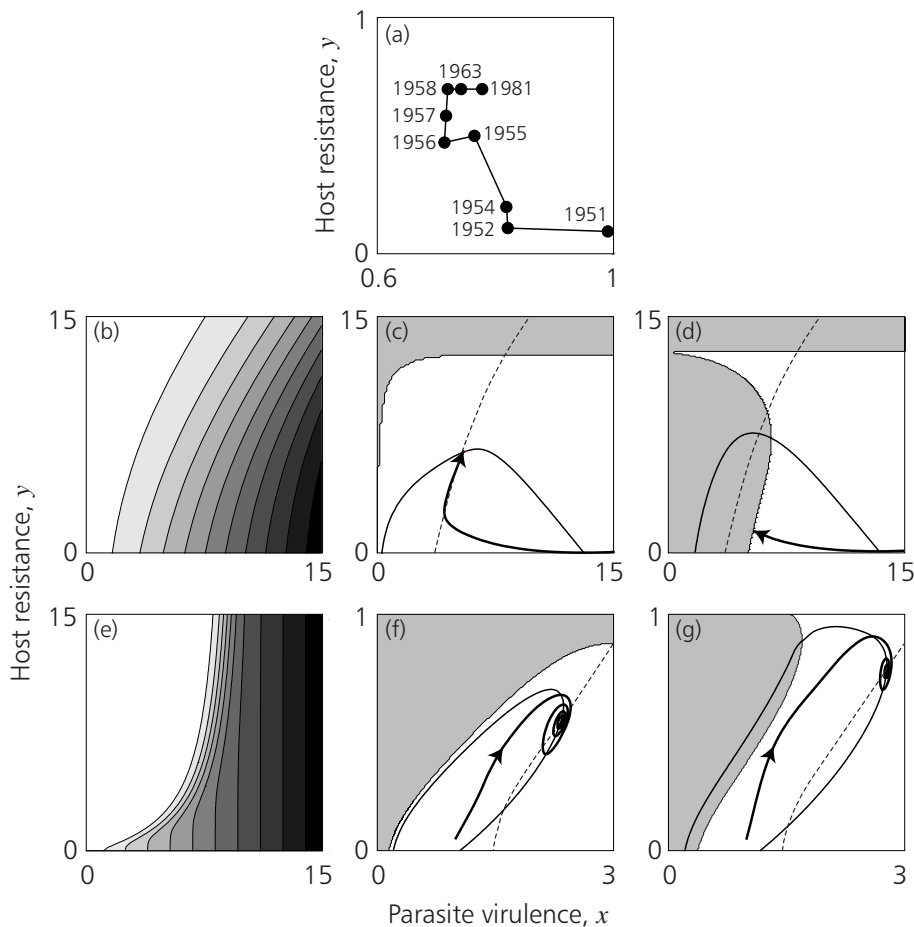
Figure 4.2 Coevolution of pathogen virulence and host resistance. (a) Coevolutionary trajectory observed after the introduction of the myxoma virus into the Australian rabbit population in 1950. Based on the trajectory's shape, a slight "viral backlash" can be conjectured, potentially resulting from the evolution of host resistance. *Data source*: Fenner and Ross (1994). (b) to (g) Coevolutionary trajectories that result from Examples IX to XII. Left column: dependences of disease-induced mortality on virulence and resistance (white: zero mortality, black: maximal mortality). Middle column: phase portraits of density-dependent models. Right column: phase portraits of corresponding density-independent models. Ranges of virulence and resistance that do not allow the pathogen to remain endemic are depicted as gray areas. Thin curves show the evolutionary isoclines of host (continuous) and parasite (discontinuous). Parameters: $b = 5$, $d = 1$, $\theta = 1$, $c = 2$, $K = 100$, $c_x = 4$, $y_0 = 10$, $c_y = 2$ (b–d); $b = 1.5$, $d = 1$, $\theta = 1$, $c = 1$, $K = 100$, $c_x = 0.4$, $y_0 = 1.75$, $c_y = 1$, $y_{max} = 10$, $c_{max} = 2$ (e–g); $(\mu\sigma^2)/(\mu_h\sigma_h^2) = 1$ (b–g).

density-dependent and density-independent conditions. To this end, host resistance y is introduced as a second trait in addition to pathogen virulence x, by slightly extending the SI model of Equations (4.1): all rates may now depend on (x, y, S, I), instead of on (x, S, I) as assumed in Section 4.4.

As a rough motivation for the examples considered below, Figure 4.2a shows the well-documented coevolutionary trajectory that resulted from the "escape" of the myxoma virus into the Australian wild rabbit population in 1950 (Fenner and

Ratcliffe 1965; Fenner and Ross 1994; Fenner and Fantini 1999). The data seem to indicate a slight gradual increase in pathogen virulence after about 1958, potentially in response to the substantial increase in host resistance between 1950 and 1958.

Below four models are considered to illustrate the evolutionary implications of density regulation. It must be emphasized that these simple models are by no means intended to capture the biological and dynamic complexity of myxoma–rabbit coevolution (for work in this direction see, e.g., Dwyer *et al.* 1990). For more details on the myxomatosis epidemic see Chapter 3, Section 3.6; the actual complexity of the involved evolution is neatly highlighted by the discussion of alternative selection pressures in Chapter 27, Section 27.2.

Example IX.   The first example assumes that disease-induced host mortality decreases with increased resistance, $\alpha = x/[1 + e^{-(x-y)/c_x}]$ (Figure 4.2b). This function implies that, in the absence of resistance, disease-induced mortality is essentially proportional to virulence. If, however, resistance exceeds virulence, this mortality is greatly reduced (with the sharpness of the reduction determined by c_x). Also accounted for is that resistance is costly for the host, $b_S = b/[1 + e^{(y-y_0)/c_y}]$: while low levels of resistance are relatively cheap, resistance that approaches y_0 greatly reduces fertility (the sharpness of the cost increase is determined by c_y). Host mortality is assumed to be density dependent, $d_S = d + (S + I)/K$. Such density dependence is required to prevent the host population from diverging when the pathogen is not endemic. The other rates are given by $b_I = b_S$, $d_I = d_S + \alpha$, $\beta = \alpha/(\alpha + c)$, and θ. Evolutionary isoclines are those curves on which the selection pressure on virulence or resistance vanishes, $dx/dt = 0$ or $dy/dt = 0$. These isoclines are shown in Figure 4.2c, together with a coevolutionary trajectory that has a shape vaguely reminiscent of the empirical one in Figure 4.2a.

Example X.   Example IX is now simplified by removing the density-dependent component of host mortality, $d_S = d$. A corresponding coevolutionary trajectory is shown in Figure 4.2d. Compared with Figure 4.2c, it is immediately obvious that the range of combinations of virulence and resistance for which the disease is endemic is greatly reduced. In particular, the coevolutionary attractor is now situated such that the coevolutionary process results in pathogen extinction. This is an example of evolutionary suicide, a process during which adaptation in a species is responsible for the extinction of that species (Matsuda and Abrams 1994; Ferrière 2000; Parvinen *et al.* 2000). Notice that, relative to Figure 4.2c, the shapes of the evolutionary isoclines, and therefore the position of the coevolutionary attractor, also change. The conclusion is therefore that to remove the density dependence of host mortality has serious implications for the expected coevolutionary outcome.

Example XI.   Returning to density-regulated host mortality, $d_S = d + (S + I)/K$, now consider a slightly different dependence of that mortality on virulence and resistance, $\alpha = x/[1 + e^{-(x-\tilde{y})/c_x}]$ with $\tilde{y} = y_{\max} y/(y + c_{\max})$ (Figure 4.2e). This function describes a "resistance-is-futile" scenario. With investment in resistance exhibiting a diminishing return, effective resistance $\tilde{y}$ cannot increase beyond a

maximum y_{max}, which is approached for large values of y (with the sharpness of the approach determined by c_{max}). This means that, in contrast to the two previous examples, it is now impossible for the host to fend off arbitrarily high virulence levels by increasing its resistance. Evolutionary isoclines and a coevolutionary trajectory that result from this scenario are given in Figure 4.2f, and show that the model gives rise to damped oscillations in virulence and resistance levels.

Example XII. The density-independent model that directly corresponds to Example XI can be considered by setting $d_S = d$. Comparing the results in Figure 4.2f with those in Figure 4.2g demonstrates that, for this case also, the shape of the evolutionary isoclines, the position of the coevolutionary attractor, and the domain over which the disease is endemic alter significantly. Coevolution now results in higher levels of virulence as well as resistance, and the coevolutionary oscillations become less pronounced. Notice in particular that the boundary of disease viability and the evolutionary isocline of the host essentially exchange their relative position. Thus, evolutionary suicide can again occur in the density-independent model, whereas such evolution-driven extinction of the disease is excluded in the density-dependent counterpart.

4.6 Discussion

This chapter evaluates the extent to which the traditional technique of R_0 maximization can be relied upon when studying the evolution of virulence traits. It is shown that R_0 maximization must be applied with great care to avoid erroneous conclusions. When demographic and epidemiological rates are density independent, R_0 maximization works well – unfortunately, however, such cases are quite simplistic. Once density regulation in these rates is accounted for, R_0 maximization may fail. Such failures may be conspicuous, as when the necessity to close the environmental feedback loop is signaled explicitly in the prediction derived from R_0 maximization, or they may go unnoticed and lead to serious mistakes. With such dangers lurking, the benefits of evolutionary invasion analysis are evident.

This conclusion is accentuated by comparison of models that describe the coevolutionary dynamics of parasite virulence and host resistance as resulting from density-dependent and density-independent rates. Although there are some rough similarities between the corresponding evolutionary scenarios, the shapes of the coevolutionary trajectories, as well as the positions of the evolutionary isoclines and attractors, turn out to be greatly affected by density regulation. A particularly intriguing finding in this context is that the conditions under which the evolution of virulence and resistance is expected to result in the extinction of the disease can differ greatly between these contrasting scenarios.

As pointed out in Section 4.4, density-dependent demographic and epidemiological rates appear to be virtually ubiquitous, so it is difficult to justify their omission from disease models. It may be argued that in industrialized nations human population densities are regulated by factors other than diseases; while the impact of population density on pathogen evolution must then still be considered,

the feedback from disease evolution on population density may be negligible. This situation, however, is clearly different for the developing world, in which the prevalence of human diseases is highest and their evolution takes place. The same is true for many animal and plant populations, the demographies of which are greatly affected by endemic viral strains.

Although providing a convenient starting point, it is clear that the class of SI models studied in this chapter cannot capture the great variety of ecological stages on which processes of virulence evolution unfold in nature. Incorporating density regulation and the resultant mechanisms of frequency-dependent selection into more complex epidemiological models is therefore an exciting challenge. Such theoretical extensions have to address, in particular, the evolutionary implications of coinfection and metapopulation structure (Chapters 9, 10, and 11), spatially heterogeneous host populations (Chapters 7 and 8), and tritrophic interactions (Chapters 21 and 22).

As far as measures of virulence management are concerned, accurate predictions of the qualitative and quantitative effects of managerial interference on virulence evolution are indispensable. The theoretical consideration laid out in this chapter may foster this goal in several regards:

■ First, it is not only asymptotic evolutionary outcomes that count in assessing strategies of virulence management: evolutionary transients toward such states may last long and must hence receive equal, if not primary, attention. Describing evolutionary transients requires dynamic models of adaptation and cannot be accomplished through consideration of optimization principles. Oscillatory transients, like that illustrated in Example XI, might actually be relatively widespread. A manager must be aware of such intrinsic instabilities, lest turning points in the dynamics are misinterpreted as indicators of faltering containment strategies.

■ Second, R_0 maximization and adherence to models with density-independent rates can lead to grossly false predictions when mechanisms of density regulation are not negligible. As illustrated by Examples VI–VII and IX–XII, the resultant errors vary between quantitative inaccuracies and qualitative blunders. If simple models predict that interference with a demographic or epidemiological rate reduces the virulence of pathogens, while in actual fact such interference, properly analyzed, is expected to be inconsequential or even to result in more aggressive strains, efforts of virulence management can be seriously jeopardized.

■ Third, the strength of density dependence may determine whether processes of evolutionary suicide can be utilized for the purposes of virulence management. Moving an evolutionary attractor out of the viability domain of the target pathogen by influencing the density dependence of demographic or epidemiological rates may sometimes result in runaway processes toward viral self-extinction, as illustrated by Examples IX–X and XI–XII. Such convenient opportunities may not arise too frequently, but, if an evolutionary attractor is

situated in the vicinity of a viability boundary, limited managerial interference may well suffice to push it over the brink.

We must thus conclude that, as much as we would prefer evolutionary models of greater simplicity, continuing to overlook the adaptational repercussions of density-dependent demographic and epidemiological rates carries a high risk.

References

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