The Evolutionary Economics of Immunity

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ABSTRACT: How much of its resources should an individual invest in a costly immune system? In this article, we apply an evolutionarily stable strategy analysis to an epidemic model to answer this question. On the one hand, an investment in immune function confers protection to infectious agents by reducing host susceptibility, pathogen virulence, or the length of the infectious period. On the other hand, an immune system is costly since it absorbs resources that otherwise might be invested in increasing the host's fertility or longevity. In addition, an active immune system may be able to clear pathogens efficiently but at the same time may result in immunopathology. By means of a reproductive value approach, we show how to compare the costs and benefits of an immune system systematically and how to derive the evolutionarily stable level of immune function. We then apply these methods to various plausible scenarios. The analysis reveals that the relationship between the life span of an organism and the optimal level of investment in immune function is less straightforward than one might expect. First, the prevalence of infection is reduced to the lowest possible level only under special circumstances. Second, members of a long-lived species do not necessarily have to invest more in immune function than those of a short-lived species. In fact, the opposite may be true. Third, the outcome of evolution can be contingent on the initial conditions. Depending on its initial investment strategy, a population may evolve to a state where very much or almost nothing is invested in a costly immune system.

Keywords: epidemic model, density dependence, stable class distribution, reproductive value, evolutionary stability, trade-off.

How much of its resources should an individual allocate to a costly immune system? Is it true that individuals of a long-lived species should invest more in immune function than do those of a short-lived species? Does it matter whether the cost of resistance is paid by infected individuals only or by all individuals irrespective of immune status? It is known that the ability to resist invasion and colonization by pathogens or to clear pathogens after colonization varies widely between individuals. Variation in the susceptibility or resistance to infectious disease often has a genetic basis (Mims et al. 1995; Hill and Motulsky 1999). Hence, on an evolutionary timescale, there are ample opportunities for selection to mold the level of immune function (for recent reviews, see Schmid-Hempel and Ebert 2002; Zuk and Stoehr 2002; Schmid-Hempel 2003).

The answers to the questions mentioned above are not obvious. Consider, for instance, a highly virulent pathogen that can rapidly kill the host. It seems plausible that the host should invest substantially in immune function when faced with such a pathogen. However, the very fact that infected individuals die quickly could imply that the prevalence of infection and hence the infection pressure are rather low. But if the infection pressure is low, it may not pay to invest much in an immune apparatus (for similar arguments, see van Baalen and Sabelis 1995).

As a second example, consider a short-lived species. One could argue that for an individual of such a species, it does not pay to invest much in an immune system since it will die quickly anyway (e.g., Medzhitov and Janeway 1997; Rinkevich 1999; Zuk and Stoehr 2002). However, the fact that individuals of the species are short-lived implies that the rate of demographic turnover is high. If newborn individuals enter the population being susceptible to infection, a high rate of demographic turnover implies that the rate at which susceptible individuals enter the population is also high. Since susceptible individuals are the fuel that keep transmission of the pathogen going, one might just as well argue that especially short-lived species should invest heavily in immune function.

In this article, we investigate how the optimal level of immunity depends on the life-history characteristics of the host and on the trade-off between life-history characteristics and immune function. To this end, we apply an evolutionarily stable strategy (ESS) analysis to a susceptible-infected-recovered (SIR) epidemic model. Throughout, an investment in immune function is assumed to

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reduce the susceptibility of the host to infection, to increase the ability of the host to clear the pathogen, or to reduce the amount of infection-induced mortality (i.e., virulence). However, an investment in immune function is costly in that it reduces the reproductive output of the host. Hence, there is a trade-off between immune function and fertility. Using a reproductive value approach (e.g., Taylor and Frank 1996), we show how the fitness costs and benefits of immunity can be compared systematically and how this evolutionary cost-benefit analysis allows us to derive the evolutionarily stable investment in immunity. We illustrate this general method by considering various plausible cost-benefit scenarios. Taking life span of the host as the life-history parameter of interest, we ask how, in evolutionary equilibrium, host longevity affects the characteristics of its immune system and the resulting prevalence of infection.

The article is structured as follows. First, we introduce an epidemic model describing the dynamics of a genetically homogeneous population with a fixed investment x in immunity. Assuming that population size is kept constant because of density-dependent factors, we derive basic epidemic parameters of this resident population, such as the reproduction ratio of the pathogen and the prevalence of infection (i.e., the relative frequency of infected individuals). Then, we introduce genetic variation in the model, thus allowing us to study the invasion prospects of a rare mutant with a slightly different investment strategy y. We are mainly interested in evolutionarily stable strategies x^*, that is, in a resident population that cannot be invaded by any rare mutant strategy y. We show how to derive such ESSs by means of a cost-benefit analysis.

Next, we consider three scenarios for the potential benefits of immune function: reduced susceptibility, virulence, and infectious period. Similarly, we consider three different cost scenarios corresponding to a constitutive immune function that is costly irrespective of immune status, a memory-based immune function that is costly only after the pathogen has been encountered, and an acute immune function that is costly only if the individual is infected. After having derived an ESS criterion for each scenario, we finally consider three examples in more detail. The analysis will reveal that the properties of an evolutionarily stable investment in immune function are less obvious than one might expect intuitively.

Epidemic Model

Model Structure

A discrete time susceptible-infected-recovered model in which individuals are either susceptible (S), infected and infectious (I), or recovered and immune (R) forms the basis of our analysis (see app. B for a corresponding continuous time model). The dynamics of the model is determined by the recurrence equations $\boldsymbol{n}' = \mathbf{A}\boldsymbol{n}$, where the population state vector $\boldsymbol{n} = (n_S, n_I, n_R)^{\mathrm{T}}$ gives the numbers of susceptible, infected, and recovered individuals, while the elements a_{ij} of the state transition matrix $\mathbf{A}$ represent the per capita contribution of individuals in class j to class i in the next time step ($i, j \in \{S, I, R\}$). Throughout, we consider a transition matrix of the form

$$\mathbf{A} = \begin{bmatrix} P(1-\eta) + \xi F_S & \xi F_I & \xi F_R \\ P\eta & P\sigma(1-\rho) & 0 \\ 0 & P\sigma\rho & P \end{bmatrix}, \qquad (1)$$

corresponding to the following assumptions: P denotes the probability that an individual survives in the absence of infection-induced mortality ($0 < P < 1$). Accordingly, the expected life span of the host in the absence of infection is given by $1/(1 - P)$. The probability of infection or infection pressure is given by η ($0 \le \eta \le 1$), while the probability of recovery is given by ρ ($0 < \rho < 1$). Hence, the expected length of the infectious period in the absence of deaths is $1/\rho$. The probability that an infected individual does not die from the infection in a single time step is represented by σ ($0 < \sigma \le 1$). Hence, $1 - \sigma$ corresponds to virulence as it is usually defined in theoretical studies. Notice that this particular definition of virulence differs from the definition routinely employed in empirical studies, which tends to focus on the probability of death over the whole infectious period (Day 2002). The terms ξF_j represent the per capita production of surviving offspring of individuals in class j. All newborn individuals enter the population in the susceptible class. As explicated in more detail below, net fecundity is affected by two processes: offspring production F_j (which is dependent on the investment in immune function) and offspring survival ξ (which is dependent on external factors, such as population density).

To close the model formulation, we now introduce two feedback loops that will later play a crucial role: first, a demographic feedback loop ensuring that the population is, in the long run, regulated to a constant size, and second, an infection feedback loop reflecting the fact that the infection pressure on susceptible individuals is closely related to the frequency of infectious individuals.

Population Regulation

In the long run, the population will grow by a factor λ per time step, where λ is the dominant eigenvalue of the state transition matrix $\mathbf{A}$ (e.g., Caswell 2000). Indefinite population growth is, of course, unrealistic. In reality, density-dependent factors will regulate population size, implying $\lambda = 1$ in a longer-term perspective. As derived

in appendix A, the condition $\lambda = 1$ corresponds to the requirement

$$1 - P(1 - \eta) = \xi\left[F_S + \frac{P\eta}{1 - P\sigma(1 - \rho)}\left(F_I + \frac{P\sigma\rho}{1 - P}F_R\right)\right], \tag{2}$$

meaning that the rate at which the susceptible class is left because of death or infection (the left-hand side of eq. [2]) is exactly balanced by the rate of offspring production (the right-hand side of eq. [2]). Here we assume that density dependence acts through decreased juvenile survival ξ. Fortunately, for our purposes, it is not necessary to model the details of this process. Instead, we view equation (2) as a consistency requirement, and we assume that, in demographic equilibrium, juvenile survival ξ adapts to the other model parameters in such a way that equation (2) is satisfied.

Of course, it depends on the population or species under consideration whether the form of density dependence considered here is realistic. If, for example, density were regulated through adult survival, then the parameter P should be split into an "internal" and an "external" component. We refer to Mylius and Diekmann (1995) for a discussion of the consequences of the precise mechanism of density dependence for evolutionary predictions (for a concrete example, see Pen and Weissing 2000). Epidemic models that explicitly take into account density dependence are analyzed in Diekmann and Kretzschmar (1991).

Infection Feedback Loop

In a realistic model, the infection pressure η cannot be considered constant but should reflect the prevalence of infection $u_I = n_I/n$ (where $n = n_S + n_I + n_R$ denotes total population size; see Begon et al. 2002). Here we assume that each individual encounters c individuals per time step ($c > 0$) and that the probability of transmission of infection in an encounter between a susceptible and infected individual is given by the product of the infectiousness f of the infected individual and the susceptibility g of the susceptible individual ($0 \le f, g \le 1$). These assumptions are reflected by the following expression for the infection probability η:

$$1 - \eta = (1 - fgu_I)^c. \tag{3}$$

If the product fg is small, it is reasonable to approximate equation (3) by

$$\eta = cfgu_I. \tag{4}$$

In the examples considered below, we have chosen $c = 1$, in which case equation (4) applies exactly. Notice that the contact number c, infectiousness f, and susceptibility g enter equation (4) only through the product

$$\beta = cfg, \tag{5}$$

which we shall call the infection potential.

Stable Class Distribution

Under the above assumptions, the relative frequency distribution of the individuals over the three classes converges to a vector $\boldsymbol{u} = (u_S, u_I, u_R)$ that can be determined from the equation $\boldsymbol{u} = \mathbf{A}\boldsymbol{u}$ (see app. A). A simple calculation shows that the prevalence of infection u_I can be expressed in terms of the relative frequency of susceptibles u_S as follows:

$$u_I = \frac{P\eta}{1 - P\sigma(1 - \rho)}u_S \tag{6}$$

(where, for the moment, we have suppressed the dependence of η on $\boldsymbol{u}$). In words, equation (6) states that the frequency of infected individuals is proportional to the inflow of freshly infected individuals, $P\eta u_S$, and to the expected duration of infection, $1/[1 - P\sigma(1 - \rho)]$. In the same manner, u_R can be expressed in terms of u_I:

$$u_R = \frac{P\sigma\rho}{1 - P}u_I, \tag{7}$$

implying that u_R is proportional to the inflow of individuals into the recovered compartment, $P\sigma\rho u_I$, and to the life expectancy of recovered individuals, $1/(1 - P)$. An explicit expression for the prevalence of infection in terms of the model parameters is given in appendix A (eq. [A4]).

Persistence and the Prevalence of Infection

We are now in the position to investigate whether or not the pathogen can persist stably and to explore how the prevalence of infection depends on the life span of the host, in a nonevolving host population. In a population consisting of susceptible individuals only, the pathogen will successfully invade if the reproduction ratio of the pathogen, R_0, exceeds 1. The reproduction ratio is given by the number of surviving new infections caused by a single infected individual in one time step in a population of susceptible individuals, βP, times the length of the infectious period, $1/[1 - P\sigma(1 - \rho)]$:

$$R_0 = \frac{\beta P}{1 - P\sigma(1 - \rho)}. \tag{8}$$

Notice that persistence of the pathogen is guaranteed whenever $\beta P > 1$, that is, whenever one infectious individual already infects more than one surviving susceptible individual in a single time step in a population consisting entirely of susceptible individuals.

Figure 1 shows the reproduction ratio R_0 (*top*) and the endemic prevalence of infection u_I (*bottom*) as a function of life span of the host. The figure shows that the reproduction ratio increases monotonically with increasing life span of the host, while the prevalence of infection is maximal for an intermediate life expectancy. This can be understood as follows. If the life span of the host is long, the rate of demographic turnover is small. Since a constant supply of susceptible individuals is needed to keep the infection chain going, the endemic level of prevalence decreases as the rate of demographic turnover becomes smaller. However, a very short life span implies that the rate of demographic turnover is high and, as a consequence, that infected individuals are quickly removed from the population. If the rate of demographic turnover is very high, the pathogen cannot even persist.

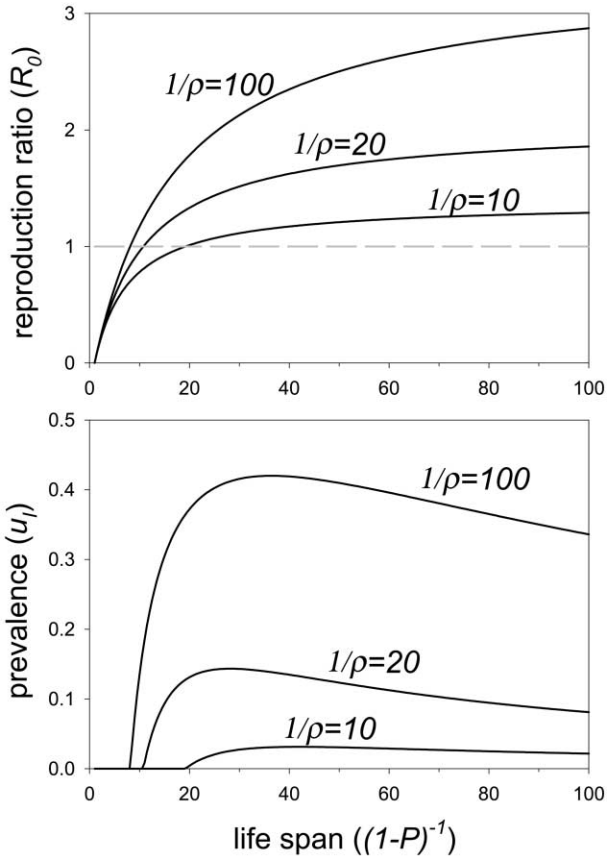

Figure 1: Reproduction ratio R_0 (*top*; eq. [8]) and prevalence of infection u_I (*bottom*; eq. [A4]) as a function of the life span of the host ($1/[1 - P]$) in a nonevolving population. The infectious period ($1/\rho$) is varied from 10 to 100 time steps. Other parameters are $\beta = 0.2$ and $1 - \sigma = 0.05$. Notice that the prevalence of infection is maximal at an intermediate life span.

Evolutionary Stability

Up to here, we considered a nonevolving population with fixed epidemic and life-history parameters. Now we change perspective by assuming that some of these parameters reflect the population-specific investment x in immune function. More specifically, we assume that a higher investment in immunity reduces the susceptibility to infection g, and/or increases the probability to survive infection σ, and/or enhances the recovery rate ρ. In other words, $g = g(x)$ is viewed as a nonincreasing function of x, while $\sigma = \sigma(x)$ and $\rho = \rho(x)$ are nondecreasing functions of x.

However, immunity does not come for free. There is a trade-off since resources spent on immune function cannot be invested in growth and reproduction. Moreover, a highly active immune system may be able to clear pathogens efficiently but, in comparison with a less active immune system, is also more likely to result in immunopathology. Here we assume that one or several of the fecundity parameters are negatively affected by a higher investment in immunity. In other words, $F_S = F_S(x)$, $F_I = F_I(x)$, and $F_R = F_R(x)$ are viewed as nonincreasing functions of x.

For simplicity, the model parameters P, c, and f are viewed as independent of x. In contrast, the parameter ξ reflecting density-dependent juvenile survival is related to the other model parameters by equation (2) and, hence, is indirectly dependent on x: $\xi = \xi(x)$. Similarly, the prevalence of infection is determined by the investment in immune function: $u_I = u_I(x)$. Finally, the infection potential and the infection pressure are also closely related to x: $\beta(x) = cfg(x)$ and $\eta(x) = \beta(x)u_I(x)$.

Mutant and Resident Dynamics

To perform an ESS analysis, we consider a genetically homogeneous resident population with investment strategy x and a rare mutant strategy $y \neq x$. The question is whether the frequency of the y strategists will increase when rare. The mutant is confronted with an environment set by the resident, that is, with a juvenile survival rate $\xi = \xi(x)$ and a prevalence of infection $u_I = u_I(x)$. As a consequence, the mutant's infection pressure depends not only on its own investment y but also on the immune investment x of the resident: $\eta(y, x) = \beta(y)u_I(x)$. Putting it all together, we find that the dynamics of the mutant subpopulation is determined by the transition matrix

$$\mathbf{A}(y, x) = \begin{bmatrix} P[1 - \eta(y, x)] + \xi(x)F_S(y) & \xi(x)F_I(y) & \xi(x)F_R(y) \\ P\eta(y, x) & P\sigma(y)[1 - \rho(y)] & 0 \\ 0 & P\sigma(y)\rho(y) & P \end{bmatrix}. \tag{9}$$

It is well known (e.g., Caswell 2000) that, in the long run, the growth rate of the mutant population is given by the dominant eigenvalue $\lambda(y, x)$ of the transition matrix $\mathbf{A}(y, x)$. The mutant strategy y will spread in the population if its asymptotic growth rate exceeds that of the resident (which is 1 because of density dependence), that is, if $\lambda(y, x) > \lambda(x, x) = 1$. If, however, $\lambda(y, x) < 1$, the mutant strategy is ousted from the population.

Fitness and Reproductive Values

The above considerations imply that the asymptotic growth rate $\lambda(y, x)$ is a fitness measure (called invasion fitness; see Metz et al. 1992) allowing one to derive evolutionary predictions. In fact, the resident strategy $x = x^*$ is evolutionarily stable if no alternative strategy y can spread when rare, that is, if $\lambda(y, x^*) < \lambda(x^*, x^*)$ for all $y \neq x^*$. In other words, for x^* to be an ESS, the function $\lambda(y, x^*)$ has to attain a maximum in y at $y = x^*$.

In principle, the method outlined above allows one to characterize all evolutionarily stable strategies. In practical applications, however, this method is of limited importance for two reasons. First, eigenvalues are difficult to calculate. Second, the analytical expressions for these eigenvalues are typically so complicated that they inspire little insight (for a worked example, see Pen and Weissing 2002).

Fortunately, an intuitively more appealing method is available, which is based on the concept of reproductive value (Fisher 1930; Williams 1966; Goodman 1982; Frank 1998; Gandon et al. 2000). In the resident population, the reproductive values $v_S = v_S(x)$, $v_I = v_I(x)$, and $v_R = v_R(x)$ quantify the relative contribution of a susceptible, an infected, and a recovered individual to the gene pool of future generations. In a sense, reproductive values allow one to compare individuals in the various classes as to their evolutionary importance. Such a comparison makes it possible to frame evolutionary considerations in terms of a systematic cost-benefit analysis.

Reproductive values are readily calculated. In fact, the reproductive value of an infected individual, v_I, can be expressed in terms of the reproductive values v_S and v_R (see app. A):

$$v_I = \frac{\xi F_I v_S + P\sigma\rho v_R}{1 - P\sigma(1 - \rho)}, \tag{10}$$

where $\xi = \xi(x)$, $\sigma = \sigma(x)$, and so on. The interpretation is as follows. The reproductive value of an infected individual is proportional to the time spent in the infected class, $1/[1 - P\sigma(1 - \rho)]$, and to the contribution to the population per time step. Contributions are made by births (ξF_I) and by recovery events ($P\sigma\rho$) and are weighted by the reproductive values of the individuals produced (v_S and v_R). Likewise, the reproductive value of recovered individuals can be expressed as

$$v_R = \frac{\xi F_R v_S}{1 - P}. \tag{11}$$

Hence, the reproductive value of a recovered individual is proportional to its life expectancy, $1/(1 - P)$, and to the offspring produced weighted by the reproductive value of the offspring, $\xi F_R v_S$.

Cost-Benefit Analysis

As shown in appendix A, an ESS x^* can be calculated on the basis of the criterion

$$\sum_{i,j} v_i^* u_j^* \frac{\partial a_{ij}(y, x^*)}{\partial y}\bigg|_{y=x^*} = 0, \tag{12}$$

where $v_i^* = v_i(x^*)$ and $u_i^* = u_i(x^*)$ are the reproductive values and the relative frequencies of the three classes in the resident population, while the differential describes how the stage transitions are affected by an increased investment in immunity. In practice, equation (12) boils down to a balance equation for the positive and negative consequences of a slight increase in the strategic parameter y.

Inserting the elements of the transition matrix (9) into equation (12), we arrive at the following condition for an evolutionarily stable investment in immune function:

$$P\left[(v_I^* - v_R^*)u_S^* \frac{\partial \eta}{\partial y}\bigg|_{x^*} + v_I^* u_I^* \frac{\partial \sigma}{\partial y}\bigg|_{x^*} + (v_R^* - v_I^*)u_I^* \frac{\partial \sigma\rho}{\partial y}\bigg|_{x^*}\right] = -\xi^* v_S^* \left[u_S^* \frac{dF_S}{dy}\bigg|_{x^*} + u_I^* \frac{dF_I}{dy}\bigg|_{x^*} + u_R^* \frac{dF_R}{dy}\bigg|_{x^*}\right], \tag{13}$$

where the notation indicates that all components are evaluated at the ESS x^*. The left-hand side of equation (13) summarizes the evolutionary benefits of an increased investment in immunity due to a reduced susceptibility (i.e., a smaller infection pressure η), a higher probability σ to

survive an infection, and a higher recovery rate ρ. The right-hand side summarizes the evolutionary costs of an increased investment in terms of a reduced fecundity.

Scenarios

We will now show how the balance equation (13) can be used to derive the evolutionarily stable level of immune function. To simplify the analysis, we fasten attention on a number of specific scenarios. First, we only consider situations where an investment in immunity affects susceptibility, the recovery rate, or the probability to survive the infection but not several of these aspects simultaneously. As a consequence, the left-hand side of the balance equation (13) boils down to a single term. Second, we focus on three cost scenarios, thereby simplifying the right-hand side of equation (13). To this end, let us assume that F is maximal fecundity (in the absence of immune investment) and that investment in immune function y is parameterized in such a way that y corresponds to the fraction of fecundity lost because of this investment.

Our first cost scenario considers a constitutive immune system that is active and costly irrespective of the infection status:

$$F_S(y) = F_I(y) = F_R(y) = (1 - y)F. \tag{14}$$

In this scenario, one might, for example, think of genetically determined differences in the number of circulating lymphocytes, which are costly to produce. In our second cost scenario, we consider a memory-based immune system that only starts to become active (and costly) once an infection has been encountered:

$$\begin{aligned} F_S(y) &= F, \\ F_I(y) = F_R(y) &= (1 - y)F. \end{aligned} \tag{15}$$

Here one might, for instance, think of the maintenance of costly immune memory. Finally, we consider an acute immune system that is only active (and costly) during the infection:

$$\begin{aligned} F_S(y) = F_R(y) &= F, \\ F_I(y) &= (1 - y)F. \end{aligned} \tag{16}$$

This may apply to immune responses that are set in action on recognition of the pathogen and that are active during infection only (e.g., inducible immune responses in vertebrates).

Below we consider a specific example in more detail where an investment in immunity affects the recovery rate (but not susceptibility and the probability to survive an infection), while the costs of immunity are paid only when infected (scenario [16]). In this case, the balance equation (13) boils down to

$$\left.\frac{d\rho}{dy}\right|_{x^*} = \frac{\xi^* F v_S^*}{P\sigma(v_R^* - v_I^*)}. \tag{17}$$

Notice that this example is analogous to the studies of van Baalen (1998) and Day and Burns (2003), where the hosts also evolved by adjustment of the recovery rate. If we insert ξ^* (obtained from eq. [2]) and the reproductive values into equation (17), we get an equation in terms of the basic parameters:

$$\left.\frac{d\rho}{dy}\right|_{x^*} = \frac{(1 - P)[1 - P\sigma(1 - \rho^*)]}{P\sigma[P(1 - \sigma) + x^*(1 - P)]}. \tag{18}$$

For each specific function ρ, the evolutionarily stable investment x^* is readily calculated with the help of equation (18). Notice that equation (18) does not depend on F, the base number of offspring produced. It is straightforward to derive similar ESS criteria for all other cost-benefit scenarios (see tables 1, 2).

Examples

With the above analysis at hand, we are in the position to investigate how the evolutionarily stable investment in immune function depends on life-history characteristics of the host. We focus on three examples. First, we consider the case where an investment in immune function reduces the infectious period and is costly for infected individuals only (acute cost scenario). Second, we analyze an example where an investment in immunity reduces virulence. In this scenario, an investment in immune function is costly irrespective of infection status (constitutive cost scenario). Finally, in our third example, an investment in immune function reduces the susceptibility of the host to infection, while the cost of immune function is paid only during infection (acute cost scenario).

Example 1: Investment for Enhanced Recovery

Consider the situation where the recovery rate is positively affected by an investment in immune function, while the costs of immunity are restricted to the infectious period (scenario [16]). To arrive at numerical results, we assume that the recovery rate is related to the investment in immune function through the three-parameter equation

$$\rho(x) = \rho_0 + (\rho_1 - \rho_0)x^q, \tag{19}$$

Table 1: Evolutionarily stable strategy (ESS) criteria in terms of the stable class distribution and reproductive values

	Constitutive	Memory based	Acute
$\left.\frac{d\rho}{dx}\right\|_{x^*} =$	$\frac{v_S^* F}{(v_R^* - v_I^*)P\sigma u_I}$	$\frac{v_S^* F(u_I^* + u_R^*)}{(v_R^* - v_I^*)P\sigma u_I^*}$	$\frac{v_S^* F}{(v_R^* - v_I^*)P\sigma}$
$\left.\frac{d\sigma}{dx}\right\|_{x^*} =$	$\frac{v_S^* F}{[v_I^*(1-\rho) + v_R^*\rho]Pu_I^*}$	$\frac{v_S^* F(u_I^* + u_R^*)}{[v_I^*(1-\rho) + v_R^*\rho]Pu_I^*}$	$\frac{v_S^* F}{[v_I^*(1-\rho) + v_R^*\rho]P}$
$\left.\frac{d\eta}{dx}\right\|_{x^*} =$	$-\frac{v_S^* F}{(v_S^* - v_I^*)Pu_S^*}$	$-\frac{v_S^* F(u_I^* + u_R^*)}{(v_S^* - v_I^*)Pu_S^*}$	$-\frac{v_S^* F u_I^*}{(v_S^* - v_I^*)Pu_S^*}$

Note: The three cost scenarios (constitutive, memory based, and acute) are described in the main text (eqq. [14]–[16]).

where ρ_0 and ρ_1 are the recovery rates in case of zero and maximal investment in immune function, respectively ($\rho_0 < \rho_1$), and $q > 0$ determines the shape of the function ρ.

Taking the derivative of equation (19) and equating it with the right-hand side of equation (18) allow one to determine the ESS x^*. Figure 2 shows the results for a scenario where returns on investment decrease with x (i.e., $0 < q < 1$). The figure gives the stable class distribution (*top*), reproductive values (*middle*), and the derivative of equation (19) together with the right-hand side of equation (18) (*bottom*) as a function of the investment in immune function. The life span of the host is set at 50 time steps ($P = .98$).

If the investment in immune function is minimal ($x = 0$), the infection pressure and the prevalence of infection are relatively high ($u_I > 0.4$). In this particular example, a slight increase in the investment in immune function is accompanied by a considerable increase in the recovery probability. As a consequence, the infection pressure and prevalence of infection rapidly decrease as the investment in immune function increases. If the investment in immune function is increased further, the returns on an increase in x become smaller. As a consequence, the prevalence of infection decreases more slowly if the investment in immune function x is high.

Furthermore, a slight increase in x strongly increases the reproductive value of susceptible and infected individuals relative to the reproductive value of recovered individuals (fig. 2, *middle*). Again, the reason is that an increase in x strongly increases ρ, so the infection pressure is considerably decreased. As a consequence, a susceptible individual is less likely to become infected, and if it is infected, it pays the price of being infected (virulence) for a much shorter time. As the investment in immune function increases, the reproductive value of susceptible individuals gradually approaches the reproductive value of recovered individuals. This is due to the fact that the probability that a susceptible individual will ever be infected becomes increasingly small and that the cost of an investment in immune function is paid by infected individuals only.

The bottom panel of figure 2 shows the marginal effect of investment in recovery (the derivative of eq. [19] and the right-hand side of the ESS criterion [18]), where a balance between costs and benefits is achieved. The point of intersection of the two curves gives the evolutionarily stable (ES) investment in immune function x^*. Notice that x^* does not reduce the prevalence of infection u_I^* to the lowest possible level.

Figure 3 shows the results of a systematic investigation of the relation between host longevity and the ES investment in immunity. The top panel gives the evolutionarily stable investment in immune function x^* and corresponding infectious period $1/\rho^*$ as a function of the life span of the host. The panel shows that the ES investment in immune function increases steadily as the life span of the host increases. This is due to the fact that a long life span of the host implies that the rate of demographic turnover is small. As a consequence, individuals of a long-lived species should value their own lives higher in comparison with their offspring than those of a short-lived species (see "Discussion").

The bottom panel of figure 3 gives the prevalence of infection corresponding to the ES investment in immune function. The panel should be compared with figure 1, where the host population did not evolve. If the life span of the host is short, the ES investment in immune function is small, and the corresponding infectious period is long. Nevertheless, the prevalence of infection is relatively low because of the high rate of demographic turnover. As the life span of the host increases, the ES investment in immune function increases, and the associated infectious period decreases. However, the rate of demographic turnover decreases as the life span of the host increases. The balance between these factors makes the ES prevalence of infection

Table 2: Evolutionarily stable strategy (ESS) criteria in terms of the parameters of the model

	Constitutive	Memory based	Acute
$\left.\frac{d\rho}{dx}\right\|_{x^*} =$	$\frac{\beta[1-P\sigma(1-\rho^*)][1-P(1-\sigma\rho^*)]}{P\sigma(1-\sigma)\{P[\beta+\sigma(1-\rho^*)]-1\}(1-x^*)}$	$\frac{[1-P\sigma(1-\rho^*)][1-P(1-\sigma\rho^*)]}{P^2\sigma(1-\sigma)(1-x^*)}$	$\frac{(1-P)[1-P\sigma(1-\rho^*)]}{P\sigma[x^*(1-P)+P(1-\sigma)]}$
$\left.\frac{d\sigma}{dx}\right\|_{x^*} =$	$\frac{\beta[1-P\sigma^*(1-\rho)][1-P(1-\sigma^*\rho)]}{[1-P(1-\rho)]\{P[\beta+\sigma^*(1-\rho)]-1\}(1-x^*)}$	$\frac{[1-P\sigma^*(1-\rho)][1-P(1-\sigma^*\rho)]}{P[1-P(1-\rho)](1-x^*)}$	$\frac{(1-P)[1-P\sigma^*(1-\rho)]}{P[1-P(1-\rho)(1-x^*)+x^*(1-\rho)]}$
$\left.\frac{dg}{dx}\right\|_{x^*} =$	$-\frac{cf(g^*)^2P(cfg^*+\sigma-1)}{(1-\sigma)\{P[cfg^*+\sigma(1-\rho)]-1\}(1-x^*)}$	$-\frac{g^*P(cfg^*+\sigma-1)}{P(1-\sigma)+x^*[1-P(1-\sigma\rho)]}$	$-\frac{g^*P(1-P)(cfg^*+\sigma-1)}{[1-P(1-\sigma\rho)][x^*(1-P)+P(1-\sigma)]}$

Note: An investment in immune function decreases the infectious period ($1/\rho$), virulence ($1-\sigma$), or the host's susceptibility to infection (g). Further, for the acute and memory-based cost scenario, the ESS criteria do not depend on the infection potential β if an investment in immune function affects virulence or the infectious period.

depend on the life-history characteristics of the host in a fairly complicated manner. In this particular example, the ES prevalence of infection is highest if the life span of the host is 17 time steps, while the investment in immune function is maximal ($x^* = 1$) if the life span of the host is 58 time steps or more.

Example 2: Investment for Reduced Virulence

We now consider an example where an investment in immune function decreases virulence instead of the infectious period. Furthermore, we assume that an investment in immune function is costly irrespective of immune status (constitutive cost scenario; eq. [14]). This example serves to illustrate that the ES investment in immune function may depend crucially on the initial investment strategy.

The analysis runs along the same lines as in example 1. The balance equation (13) simplifies to

$$\left.\frac{d\sigma}{dx}\right|_{x^*} = \frac{\beta[1-P\sigma^*(1-\rho)][1-P(1-\sigma^*\rho)]}{[1-P(1-\rho)]\{P[\beta+\sigma^*(1-\rho)]-1\}(1-x^*)} \tag{20}$$

(see table 2). In analogy with example 1, we assume that there is a trade-off between the investment in immune function x and the probability to survive the infection σ given by the equation

$$\sigma(x) = \sigma_0 + (\sigma_1 - \sigma_0)x^q \tag{21}$$

($\sigma_1 > \sigma_0$, $q > 0$). Together, equations (20) and (21) determine the location of the ESSs.

Figure 4 shows the results for a scenario with diminishing returns on investment ($0 < q < 1$). The top panel shows the candidate ES investment in immune function as a function of the life span of the host, while the bottom panel shows the corresponding prevalences of infection. The bold lines refer to fitness maxima and correspond to ESSs, while the thin line represents a fitness minimum.

The top panel shows that if the life span of the host is short (here <186), it does not pay to invest in immune function at all. At the ESS, the investment in immunity is minimal ($x^* = 0$), while virulence is maximal ($1 - \sigma(0) = 1$). As a consequence of its very high virulence, the pathogen has difficulty in persisting. In fact, the population evolves to a state where the reproduction ratio of the pathogen is smaller than 1 ($R_0(x, P) < 1$), and the pathogen succumbs to its high virulence.

If life span of the host is higher than 186 time steps, bistability occurs, and there is an ESS with positive investment in immune function in addition to the ESS with zero investment in immunity. In this case, the population evolves to a state where either a minimal or a large amount of resources is directed to immune function, depending on the initial population strategy. This finding is corroborated by simulations based on equations (9) and (21).

The intuitive explanation for this phenomenon is as follows. If the initial investment in immune function is initially not too low, the host population evolves to a state where an intermediate amount of resources is invested in immune function, corresponding to the bold upper branches of the lines in figure 4. Moreover, the evolutionarily stable investment in immune function of this branch increases with increasing life span (for similar reasons as in example 1). In this state where hosts invest considerably in immune function, virulence is low enough to allow persistence of the pathogen. In fact, the pathogen may reach a considerable prevalence in the population.

If, however, the population investment in immunity is initially low, the prevalence of infection will also be low (infected individuals die quickly). As a consequence, the probability of infection is so low that it pays to reduce the investment in immune function further. Ultimately, the population evolves to a state where nothing is invested in immune function but where the pathogen cannot persist because it kills the host almost instantly.

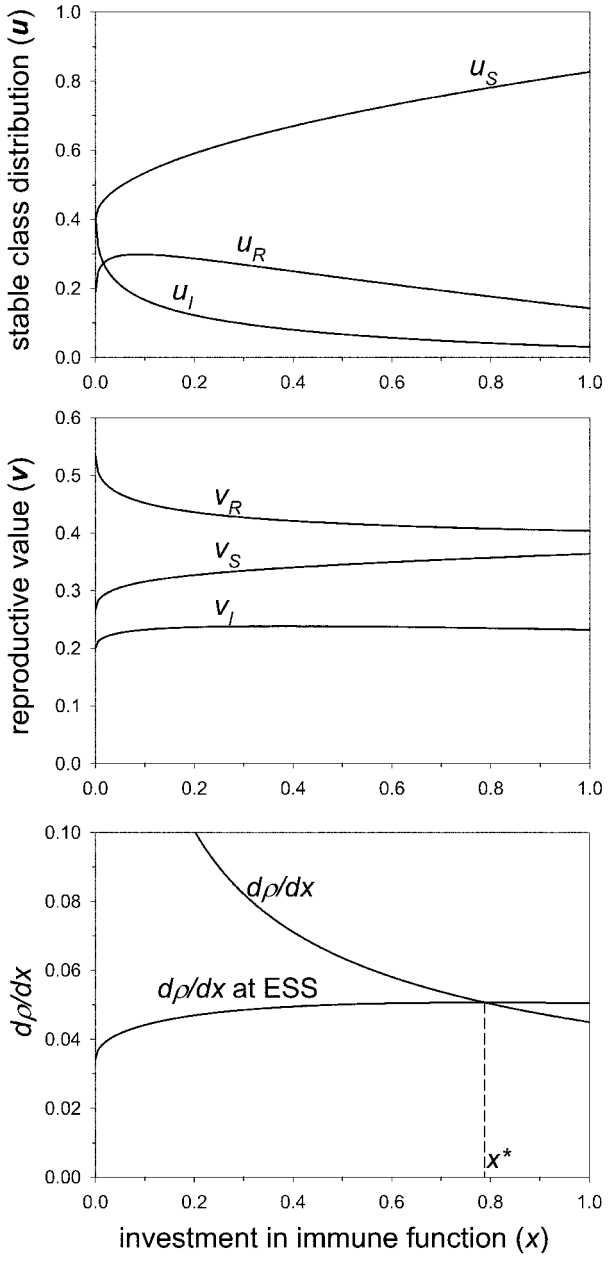

Figure 2: Stable class distribution (*top*), reproductive values (*middle*), and equations (18) and (19) (*bottom*) as a function of the investment in immune function. The evolutionarily stable level of immunity is at the intersection of the two curves (*bottom*). Parameter values are $P = .98$, $\beta = 0.2$, $1 - \sigma = 0.05$, $\rho_0 = 0.01$, $\rho_1 = 0.1$, and $q = 0.5$.

Although this state where the host invests nothing in immune function is, from the point of view of the host population, the most desirable outcome, it is not at all certain that the dynamics of selection will favor this ESS. In fact, only if the initial investment strategy is already very low will the population evolve to a state where ultimately nothing is invested in immunity. The far more likely outcome is that the population evolves to the state where hosts defend themselves heavily but nevertheless suffer considerably.

Example 3: Investment for Reduced Susceptibility

Our final example considers the case where an investment in immune function decreases the susceptibility of the host to infection (g), while the costs are paid only by infected individuals (acute cost scenario; eq. [16]). This example will exemplify that the ES investment in immune function does not necessarily increase as the life span of the host increases.

The ESS equation corresponding to this scenario reads

$$\left.\frac{dg}{dx}\right|_{x^*} = -\frac{g^*P(1-P)(cfg^* + \sigma - 1)}{[1 - P(1-\sigma\rho)][x^*(1-P) + P(1-\sigma)]} \qquad (22)$$

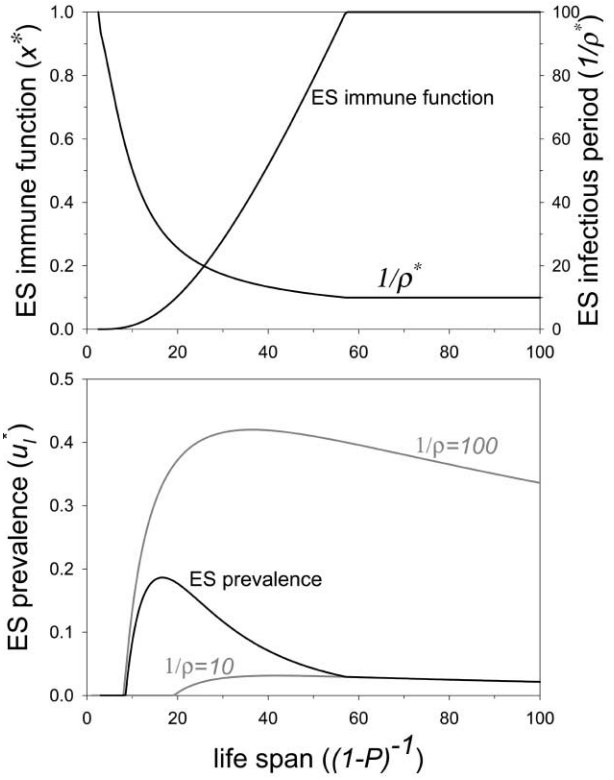

Figure 3: Evolutionarily stable (ES) investment in immune function and corresponding infectious period (*top*), and the ES prevalence of infection (*bottom*) as a function of the life span of the host. Parameter values are as in figure 2.

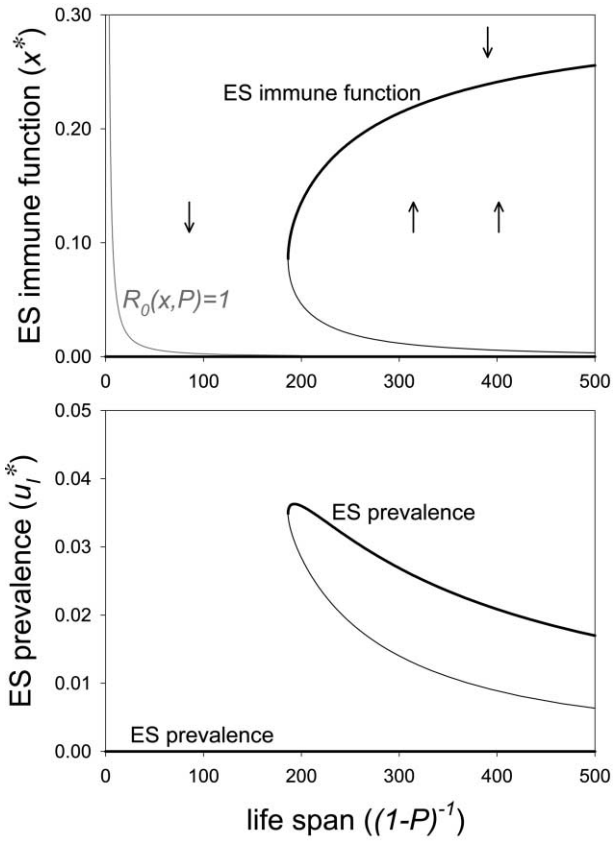

Figure 4: Evolutionarily stable investment in immune function (*top*) and the corresponding prevalence of infection (*bottom*) as a function of the life span of the host. In contrast to figure 3, an investment in immune function is costly irrespective of infection status (constitutive cost scenario), and it reduces virulence instead of the infectious period. The pathogen is driven to extinction below the line $R_0(x, P) = 1$. Parameter values are $\beta = 1$, $\rho = 0.1$, $1 - \sigma_0 = 1$, $1 - \sigma_1 = 0$, and $q = 0.75$.

(see table 2). To arrive at numerical results, we assume that the trade-off function takes the by now familiar form

$$g(x) = g_0 + (g_1 - g_0)x^q \tag{23}$$

($g_0 > g_1$, $q > 0$). Figure 5 summarizes the results for a scenario with constant returns on investment (i.e., $q = 1$). If the life span of the host is very short, the pathogen has difficulty in persisting because of the high rate of demographic turnover. In fact, in a nonevolving population with maximal susceptibility ($g = 1$), the pathogen cannot persist if host life span is shorter than 2.3 time steps, while it reaches a maximal prevalence of $u_I = 0.42$ if life span is 6.2 time steps. If the susceptibility of the host is halved to $g = 0.5$, the pathogen cannot persist if life span is shorter than 4.3 time steps, and it reaches a maximal prevalence of $u_I = 0.22$ if life span is 11.0 time steps.

If the host population is allowed to evolve between these two extremes ($g_0 = 1$ and $g_1 = 0.5$), we find that, as the life span of the host increases, the investment in immune function first increases to a maximal value of $x^* = 1$ if life expectancy is 7.7 time steps or more. If the life span of the host exceeds 17.6 time steps, the ES investment in immunity starts to decrease monotonically with increasing life span. If the life span of the host is 189.8 time steps or more, the host should invest nothing in immunity.

Intuitively, the observation that the investment in immune function may decrease as life span increases can be understood as follows. In a long-lived host population, the rate of demographic turnover is small, and, as a consequence, the supply of susceptibles into the population will be low. This implies that the infection pressure in the population is mainly determined by the demographic process of the host population and much less by the characteristics of the host-pathogen interaction (infectiousness, susceptibility, infectious period, and, to a lesser extent,

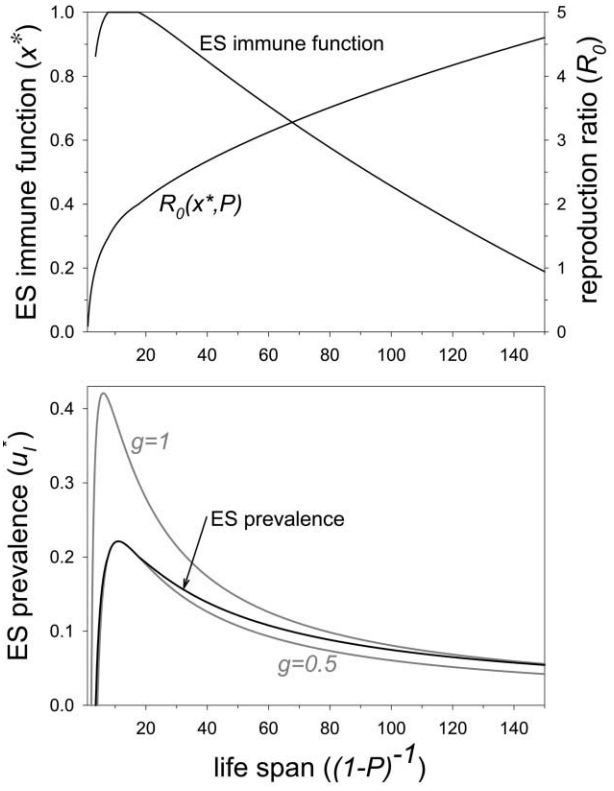

Figure 5: Evolutionarily stable (ES) investment in immune function and corresponding reproduction ratio (*top*), and the ES prevalence of infection (*bottom*) as a function of the life span of the host. An investment in immune function reduces susceptibility of the host to infection and is costly during infection only (acute cost scenario). Parameter values are $c = 1$, $f = 1$, $\rho = 0.1$, $1 - \sigma = 0.1$, $g_0 = 1$, $g_1 = 0.5$, and $q = 1$.

virulence). Figure 5 illustrates this point. If life expectancy of the host is short, such as 10 time steps, halving susceptibility of the host also halves the infection pressure and the prevalence of infection. If, however, life expectancy is high, such as 150 time steps, halving the susceptibility of the host (from $g = 1$ to $g = 0.5$) has only a marginal impact on the infection pressure and the prevalence of infection. As a result, for members of a long-lived species, it does not pay to invest much in immune function since the benefits in terms of a lowered probability of infection are small. Accordingly, the benefits of investment are much smaller in long-lived species than in short-lived species, and it is therefore not too surprising that the evolutionarily stable investment decreases with life expectancy.

Discussion

Life History and Immune Function

The study of adaptive variation in immune responses between populations or species resulting from differences in life-history characteristics and environmental conditions is, for good reasons, currently a topic receiving considerable attention (see the reviews by Williams and Nesse 1991; Schmid-Hempel and Ebert 2002; Zuk and Stoehr 2002; Schmid-Hempel 2003). Usually, in these studies a verbal argument is given of how population density, mate numbers, feeding conditions, stress factors, longevity of the host, or other factors will affect the evolutionarily optimal level of immune investment. However, verbal arguments can be highly misleading in the context of host-pathogen interactions, because life-history characteristics of host and pathogen, population dynamics, and immunology are closely intertwined. In fact, the life-history characteristics of host and pathogens determine the population dynamics of pathogens and host, which in turn determines the optimal investment in defense against pathogens and so affects the life history of the host and pathogens (Frank 1996, 2002; van Baalen 1998; Day and Burns 2003).

In this article, we have focused on the question of how the evolutionarily optimal investment in immune function is molded by longevity of the host. An increase in the longevity of the host decreases the level of demographic turnover. As a result, individuals of a long-lived species should value their own lives higher in comparison with their offspring than those of a short-lived species (newborn individuals of a long-lived species are less likely to make it to the adult stage than those of a short-lived species). Hence, one could expect that the investment in immune function would increase with increasing life span of the host. However, a decrease in the rate of demographic turnover reduces the number of susceptibles that enter the population (assuming that immunity is lifelong) and so may decrease the prevalence of infection. Hence, one could just as well argue that an increase in longevity would result in a decrease in immune function as the risk of infection decreases.

Our results show that both scenarios may occur. If immune function is costly for infected individuals only and decreases the infectious period, the intuitive expectation that the evolutionarily stable investment in immune function should increase as life span increases still holds (example 1; fig. 3). However, for other scenarios, the optimal investment in immunity may just as well decrease as the life span of the host increases (example 3; fig. 5), and it is even possible that the outcome of selection is contingent on the initial investment in immune function (example 2; fig. 4).

A perhaps irritating message of our study is that no broad patterns valid over a wide range of scenarios have emerged. In fact, we have shown that the optimal investment in immune function can be highly dependent on (1) the parameters that are affected by an investment in immune function (susceptibility, infectious period, or virulence), (2) the type of individuals that pay the cost of an investment in immune function (e.g., infected individuals only or all individuals irrespective of immune status), and (3) the relation between the investment in immune function and the ability to cope with pathogens. In addition, we will argue that the optimal investment in immune function may also depend on (4) whether the infection induces permanent immunity in the host or not and (5) the mechanism of density dependence in the host population.

The Reproductive Value Approach

In addition to analyzing specific scenarios, our article serves a more general purpose to demonstrate how the complexity of an epidemic model can be overcome to allow an evolutionary analysis of the optimal level of host defense to infectious diseases. In particular, we have shown how two essential feedback loops (population regulation of the host population and the transmission feedback loop) can be incorporated in an epidemic model while still allowing a formal analysis.

The most direct way to study the evolution of host resistance in a theoretical framework would be to write down equations for the dynamics of a rare mutant host type and then determine the initial growth rate (the dominant eigenvalue) of all conceivable mutants in a population where a resident type is present. Those resident strategies that cannot be invaded by any mutant strategy are then considered evolutionarily stable.

Although this method is, in principle, straightforward, it has severe limitations in practical applications. In fact,

calculation of dominant eigenvalues as a function of one or several strategic variables is feasible only in very simple systems. It is therefore not surprising that, until now, a combined epidemiological and evolutionary analysis has only been applied to very simple epidemic models (e.g., the essentially one-dimensional models of van Baalen [1998] and Day and Burns [2003]).

Here we have shown that the inherent complexity of realistic epidemiological interactions can, to a certain extent, be overcome by using the potent reproductive value approach (Fisher 1930; Williams 1966; Goodman 1982; Taylor and Frank 1996; Frank 1998). This approach is appealing to intuition, since it is based on a systematic analysis of the evolutionary costs and benefits of a strategic decision. In fact, the use of reproductive values enabled us to express the various costs and benefits of an investment in immune function in terms of a single common currency.

From a mathematical point of view, the reproductive value approach has the advantage that it circumvents the determination of the dominant eigenvalue for all conceivable mutant strategies (which is difficult). All that is required for deriving a candidate ESS are the characteristics of the resident population (dominant eigenvalue, stable stage distribution, and reproductive values), which are much easier to determine. As shown in appendix A, second-order conditions (determining, for example, whether a candidate ESS does indeed correspond to a fitness maximum) can also be checked on the basis of the properties of the resident population.

Throughout, we have illustrated the reproductive value approach by means of an SIR-type epidemic model. However, we hope that it is clear to the reader that the methods are generally applicable and can easily be applied to other or more complex epidemic models (e.g., SI, SIS, SIRS, SEIRS models, extension to models with more infectious classes) or to more complex life histories of the host (e.g., aging in the host population, models with separate sexes for sexually transmitted diseases).

Model Assumptions

Although the reproductive value method employed in this article is generally applicable, it is good to realize that the specific results of the relation between longevity and immune function depend on a number of key assumptions. For instance, whether or not the ES level of immune investment increases with increasing life span may well depend on whether or not the pathogen induces long-lived immunity in the host. In our model, individuals that have cleared the infection cannot be infected anymore. As a consequence, the supply of susceptible individuals into the population depends crucially on demographic turnover. This is not so anymore if immunity after infection is temporary. Such scenarios have been considered by van Baalen (1998) and Day and Burns (2003). In fact, these authors considered SIS-type epidemic models where, on recovery, individuals are immediately susceptible again.

Van Baalen (1998) focused in detail on the evolution of the host recovery rate if immune function is costly regardless of immune status cost (constitutive costs). The main conclusion of van Baalen was that the host population will evolve to a state where the recovery rate is such that it maximizes the force of infection (the rate at which susceptible individuals are infected). This result was interpreted as an instance of a "pessimization principle" where only the host type that is able to persist under the worst conditions will ultimately prevail. In our model, we did not find such a simple pessimization principle. In fact, in none of our examples was the infection pressure maximized at the ESS. This difference between our model and the model of van Baalen is probably due to the fact that there is a very simple relation between the force of infection and the number of susceptibles at equilibrium in the one-dimensional model of van Baalen (the number of susceptibles decreases monotonically with increasing force of infection), while in our two-dimensional model, this relation is more intricate. We refer to Mylius and Metz (2004) for an insightful discussion of the relation between the (dimensions of the) environmental feedback loop and the existence of optimization principles.

Day and Burns (2003) also focused on the evolution of the host recovery rate in an SIS model. In contrast to the study of van Baalen, the costs of immune function were paid only by infected individuals in this study (acute cost scenario), corresponding to our first example (fig. 3). These authors showed that the ES recovery rate decreases with increasing host life span. This also contrasts with our study where the recovery rate could increase or decrease with increasing background mortality. Most likely, the difference is due to the fact that demographic turnover plays a central role in our model, while it is almost irrelevant in the model of Day and Burns.

Both studies mentioned above used a continuous time rather than a discrete time epidemic model. To show that the differences in the results of our study and the studies mentioned above are unlikely to be due to this fact, we demonstrate in appendix B that, with a few simplifying assumptions, our discrete time epidemic model is easily translated in a conventional continuous time model. We further show in appendix B that the reproductive value approach applies essentially unchanged in the context of continuous time models.

Throughout this article, we have assumed that there is a trade-off between immune function and fertility arising from the argument that the host has a limited amount of

resources that it can only invest once. There are, however, other types of cost of immune function and other plausible trade-offs between immune function and life-history characteristics (Schmid-Hempel and Ebert 2002; Zuk and Stoehr 2002; Schmid-Hempel 2003). For instance, a highly active immune system may be able to clear pathogens efficiently but at the same time result in considerable tissue damage (immunopathology). In fact, our third example was inspired by this idea: the advantage of an immune system is through a general upregulation of immune function that, on the one hand, makes it less likely that susceptible hosts are infected but, on the other hand, makes it more likely that the unborn offspring of infected hosts die before delivery (e.g., Mellor and Munn 2000). However, in a more realistic model incorporating immunopathology, probably not only fecundity F but also host survival P should be made explicitly dependent on investment in immune function.

The mechanism of density dependence in the host population can also have important consequences for evolutionary predictions (Mylius and Diekmann 1995; Mylius and Metz 2004). In our model, the size of the host population is kept constant through density-dependent juvenile survival. From an evolutionary point of view, this implies that the value of one's own life relative to offspring depends on the juvenile survival probability ξ. Since we assume a stationary population, a longer life expectancy of the host is automatically reflected in a lower fraction of juveniles surviving to adulthood. As a result, the value of one's own life relative to offspring increases with increasing life span. As a consequence, in our model, members of a long-lived species are inherently more likely to invest more in immune function than those of a short-lived species. Still, this general effect may be dominated by the infection feedback loop, which makes it possible that the returns on an investment in immune function decrease quite strongly with increasing life span (example 3). How our results would be affected if the host population were regulated by other factors (e.g., density-dependent survival, solely by pathogen-induced mortality) remains an open question. On the basis of the above arguments, however, one would expect that scenarios where the investment in immune function decreases with increasing life span are most difficult to find if density dependence operates through variable survival of offspring.

Finally, in this article, we have focused in detail on the question of how a host population will evolve when faced with a harmful pathogen with fixed characteristics. It is, however, plausible that the characteristics of the pathogen are molded by adaptation to the life history of the host. Consequently, it is conceivable that the relation between the host's life-history characteristics and its evolutionarily stable investment in immune function can change considerably if the coevolution of host and pathogen is taken into account. For simple epidemic models, the joint study of the coevolution of host resistance and pathogen virulence has been undertaken in a number of recent studies (van Baalen 1998; Gandon et al. 2002; Day and Burns 2003). In principle, it would not be difficult to extend our model along similar lines. In view of the results derived in this article, we consider it unlikely that simple and general patterns will emerge when the adaptations of pathogens to an evolving host population are taken into account. Instead, it is far more likely that the outcome of coevolution depends crucially on the details of the interaction between host and pathogen.

Acknowledgments

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APPENDIX A

Evolutionary Stability

Resident Dynamics

Two feedback processes hamper the analysis of the resident population: population regulation through density-dependent juvenile survival and the infection feedback loop through the infection pressure. Here we show how these feedback loops can be incorporated while still allowing a formal analysis.

In the absence of the feedback loops, the analysis would be straightforward, since the dynamics would be given by the set of linear recurrence equations $\boldsymbol{n}' = \mathbf{A}\boldsymbol{n}$, with a nonnegative transition matrix $\mathbf{A}$. In such a situation, the process converges to a fixed distribution $\boldsymbol{u} = (u_S, u_I, u_R)$ of the individuals over the three infectious classes. Once the stable class distribution is reached, each class and the population as a whole will grow with a constant factor λ per time step: $\boldsymbol{u}' = \mathbf{A}\boldsymbol{u} = \lambda\boldsymbol{u}$. Formally, $\boldsymbol{u}$ is a right eigenvector with respect to the dominant eigenvalue λ.

In our model, the condition $\mathbf{A}\boldsymbol{u} = \lambda\boldsymbol{u}$ corresponds to the system of equations

$$\begin{aligned} \lambda u_S &= P(1-\eta)u_S + \xi(F_S u_S + F_I u_I + F_R u_R), \\ \lambda u_I &= P\eta u_S + P\sigma(1-\rho)u_I, \\ \lambda u_R &= P\sigma u_I + P u_R, \end{aligned} \tag{A1}$$

which is readily solved for λ and $\boldsymbol{u}$. The last two equations imply that the stable class distribution, which is determined up to a constant factor, is of the form

$$u_S : u_I : u_R = \frac{\lambda - P\sigma(1-\rho)}{P\eta} : 1 : \frac{P\eta\rho}{\lambda - P}. \qquad \text{(A2)}$$

However, the situation is complicated by the fact that the transition matrix $\mathbf{A}$ is not constant but depends on the population state $\boldsymbol{n}$. First, juvenile survival is assumed to be density dependent: $\xi = \xi(\boldsymbol{n})$. Second, the infection pressure is assumed to be a function of the prevalence of infection: $\eta = \eta(n_I/n)$. Hence, the resident dynamics is characterized by a set of nonlinear recurrence equations $\boldsymbol{n}' = \mathbf{A}_{\boldsymbol{n}}\boldsymbol{n}$, where the notation indicates the dependence of the transition matrix on the population state. Throughout, we make the assumption that the resident dynamics converges to a stable rest point $\boldsymbol{u}$. This is given by $\boldsymbol{u}' = \mathbf{A}_{\boldsymbol{u}}\boldsymbol{u} = \boldsymbol{u}$ and, hence, corresponds to a right eigenvector of the matrix $\mathbf{A}_{\boldsymbol{u}}$ with respect to the eigenvalue $\lambda = 1$. As a consequence, equations (A1) and (A2) still apply, with the reservation that $\xi = \xi(\boldsymbol{u})$, $\eta = \eta(\boldsymbol{u})$, and $\lambda = 1$. Inserting equation (A2) into the first equation of (A1) immediately yields requirement (2) on juvenile survival at demographic equilibrium.

It is useful to normalize the stable class distribution (that is given by eq. [A2]) such that $u_S + u_I + u_R = 1$, since with this normalization, u_I directly corresponds to the prevalence of infection at demographic equilibrium. A straightforward calculation shows that, with this normalization, u_I is given by

$$u_I = \frac{P\eta}{1 - P\sigma(1-\rho) + P\eta[1 + P\sigma\rho/(1-P)]}, \qquad \text{(A3)}$$

where $\eta = \eta(u_I)$. Inserting $\eta = \beta u_I$ and solving equation (A3) for u_I yields an explicit expression for the equilibrium prevalence of infection:

$$u_I = \frac{(1-P)\{P[\beta + \sigma(1-\rho)] - 1\}}{\beta P[1 - P(1 - \sigma\rho)]}. \qquad \text{(A4)}$$

Mutant Dynamics

Let us now consider a mutant with strategy y in a resident population with strategy x^* and stable class distribution $\boldsymbol{u}^*$. The mutant dynamics is characterized by the set of recurrence equations $\boldsymbol{m}' = \mathbf{A}(y, x^*)\boldsymbol{m}$, where the transition matrix is given by equation (9). Notice that the transition matrix depends on y, x, and $\boldsymbol{u}^*$ but not on the mutant class distribution $\boldsymbol{m}$. As a consequence, the mutant dynamics is linear, which simplifies the analysis considerably. In particular, the asymptotic growth rate of the mutant population is given by $\lambda(y, x^*)$, the dominant eigenvalue of the transition matrix $\mathbf{A}(y, x^*)$. The mutant will spread in the resident population if $\lambda(y, x^*) > 1$, and it will be ousted from the population if $\lambda(y, x^*) < 1$.

The resident strategy x^* is evolutionarily stable if no mutant strategy can spread, that is, if $\lambda(y, x^*) < \lambda(x^*, x^*) = 1$ for all mutant strategies y in a neighborhood of x^*. In other words, $\lambda(y, x^*)$ should attain a local maximum at $y = x^*$. At such a maximum, the selection gradient is equal to 0:

$$\left.\frac{\partial\lambda(y, x^*)}{\partial y}\right|_{y=x^*} = 0, \qquad \text{(A5)}$$

which is a standard criterion for locating a candidate ESS x^*. With the help of the second-order condition

$$\left.\frac{\partial^2\lambda(y, x^*)}{\partial y^2}\right|_{y=x^*} < 0, \qquad \text{(A6)}$$

it can be checked whether x^* does indeed correspond to a fitness maximum (rather than a fitness minimum) and, hence, whether x^* is indeed evolutionarily stable. The second-order condition

$$\left.\frac{\partial^2\lambda(y, x^*)}{\partial y^2}\right|_{y=x^*} + \left.\frac{\partial^2\lambda(y, x)}{\partial x\partial y}\right|_{x=y=x^*} < 0 \qquad \text{(A7)}$$

is also relevant, since it allows one to judge whether a candidate ESS is "convergence stable," that is, whether it can be reached by a series of strategy substitution events (Eshel 1983; Taylor 1996).

Reproductive Values

It is well known from linear algebra (e.g., Caswell 2000) that an eigenvalue $\lambda = \lambda(y, x^*)$ of a matrix $\mathbf{A} = \mathbf{A}(y, x^*)$, as well as its derivative with respect to y, can be expressed in terms of right and left eigenvectors $\boldsymbol{u} = \boldsymbol{u}(y, x^*)$ and $\boldsymbol{v} = \boldsymbol{v}(y, x^*)$:

$$\lambda = \frac{\boldsymbol{v}\mathbf{A}\boldsymbol{u}}{\boldsymbol{v}\boldsymbol{u}},$$
$$\frac{\partial\lambda}{\partial y} = \frac{\boldsymbol{v}(\partial\mathbf{A}/\partial y)\boldsymbol{u}}{\boldsymbol{v}\boldsymbol{u}}. \qquad \text{(A8)}$$

As a consequence, condition (A5) for a candidate ESS corresponds to

$$\boldsymbol{v}^* \frac{\partial \mathbf{A}(y, x^*)}{\partial y}\bigg|_{x^*} \boldsymbol{u}^* = 0, \tag{A9}$$

where $\boldsymbol{v}^*$ and $\boldsymbol{u}^*$ are dominant left and right eigenvectors, respectively, of the transition matrix $\mathbf{A}^* = \mathbf{A}(x^*, x^*)$. Equation (A9) is identical to the ESS criterion (12) given in the main text.

The right eigenvector $\boldsymbol{u}^*$, which is given by $\boldsymbol{u}^* = \mathbf{A}\boldsymbol{u}^*$, corresponds to the stable class distribution of the resident population that has been calculated above. The left eigenvector $\boldsymbol{v}^*$ corresponds to the vector of reproductive values of the three infectious classes in the resident population. It is given by the equation $\boldsymbol{v}^* = \boldsymbol{v}^*\mathbf{A}$, which determines the reproductive values up to a constant factor. For our model, a straightforward calculation yields

$$v_S^* : v_I^* : v_R^* = 1 : \frac{1 - P(1 - \eta) - \xi F_S}{P\eta} : \frac{\xi F_R}{1 - P}. \tag{A10}$$

Second-Order Conditions

From a technical point of view, the ESS criterion (A9) has the advantage that it does not require the calculation of the invasion fitness $\lambda(y, x^*)$ for all conceivable mutant strategies y. All that is required is the calculation of the dominant left and right eigenvectors of the transition matrix characterizing the resident population. Fortunately, the second-order conditions (A6) and (A7) can also be checked on the basis of the characteristics of $\mathbf{A}^*$. For simplicity, let us assume that all left and right eigenvectors are normalized such that $\boldsymbol{v}\boldsymbol{u} = 1$. Then, equation (A8) implies that

$$\frac{\partial^2 \lambda}{\partial y^2}\bigg|_{x^*} = \boldsymbol{v}^* \frac{\partial^2 \mathbf{A}}{\partial y^2}\bigg|_{x^*} \boldsymbol{u}^* + \frac{\partial \boldsymbol{v}}{\partial y}\bigg|_{x^*} \frac{\partial \mathbf{A}}{\partial y}\bigg|_{x^*} \boldsymbol{u}^* + \boldsymbol{v}^* \frac{\partial \mathbf{A}}{\partial y}\bigg|_{x^*} \frac{\partial \boldsymbol{u}}{\partial y}\bigg|_{x^*}, \tag{A11}$$

$$\frac{\partial^2 \lambda}{\partial x \partial y}\bigg|_{x^*} = \boldsymbol{v}^* \frac{\partial^2 \mathbf{A}}{\partial x \partial y}\bigg|_{x^*} \boldsymbol{u}^* + \frac{\partial \boldsymbol{v}}{\partial x}\bigg|_{x^*} \frac{\partial \mathbf{A}}{\partial y}\bigg|_{x^*} \boldsymbol{u}^* + \boldsymbol{v}^* \frac{\partial \mathbf{A}}{\partial y}\bigg|_{x^*} \frac{\partial \boldsymbol{u}}{\partial x}\bigg|_{x^*}, \tag{A12}$$

where the notation indicates that all derivatives are evaluated at $x = y = x^*$. The first terms on the right-hand side of equations (A11) and (A12) can easily be evaluated, but the other terms seem to require the calculation of the dominant eigenvectors $\boldsymbol{v}(y, x)$ and $\boldsymbol{u}(y, x)$ as a function of y and/or x.

However, this calculation can be avoided. As shown in Caswell (2000, chap. 9.4), the derivatives of $\boldsymbol{v}$ and $\boldsymbol{u}$ can be expressed in terms of the eigenvalues of the resident matrix $\mathbf{A}^*$:

$$\frac{\partial \boldsymbol{v}}{\partial y}\bigg|_{x^*} = \sum_j \frac{\boldsymbol{v}^* (\partial \mathbf{A}/\partial y)|_{x^*} \boldsymbol{u}_j^*}{1 - \lambda_j^*} \boldsymbol{v}_j^*,$$

$$\frac{\partial \boldsymbol{u}}{\partial y}\bigg|_{x^*} = \sum_j \frac{\boldsymbol{v}_j^* (\partial \mathbf{A}/\partial y)|_{x^*} \boldsymbol{u}^*}{1 - \lambda_j^*} \boldsymbol{u}_j^*, \tag{A13}$$

and

$$\frac{\partial \boldsymbol{v}}{\partial x}\bigg|_{x^*} = \sum_j \frac{\boldsymbol{v}^* (\partial \mathbf{A}/\partial x)|_{x^*} \boldsymbol{u}_j^*}{1 - \lambda_j^*} \boldsymbol{v}_j^*,$$

$$\frac{\partial \boldsymbol{u}}{\partial x}\bigg|_{x^*} = \sum_j \frac{\boldsymbol{v}_j^* (\partial \mathbf{A}/\partial x)|_{x^*} \boldsymbol{u}^*}{1 - \lambda_j^*} \boldsymbol{u}_j^*, \tag{A14}$$

where λ_j^* ($j = 2, \ldots, n$) denote the $n - 1$ subdominant eigenvalues of $\mathbf{A}^*$, and $\boldsymbol{u}_j^*$ and $\boldsymbol{v}_j^*$ denote the corresponding left and right eigenvectors (normalized such that $\boldsymbol{v}_j\boldsymbol{u}_j = 1$). Hence, knowledge of all eigenvalues and eigenvectors of the resident matrix $\mathbf{A}^*$ suffices to evaluate the second-order conditions (A6) and (A7) by inserting equations (A13) and (A14) into equations (A11) and (A12), respectively.

Proceeding this way, we could check, for example, which of the candidate ESSs in figure 4 is actually evolutionarily stable and which is not. In all cases, the analysis based on reproductive values was corroborated by simulations based on equations (9) and (21). We would like to add that, in practical applications, only few elements of $\partial \mathbf{A}/\partial y$ are unequal to 0 and that, as a consequence, only a few components of the vectors in equations (A13) and (A14) have to be calculated explicitly.

APPENDIX B

Continuous versus Discrete Time Models

In this article, we employed a discrete time epidemic model rather than a more conventional continuous time model. In practical applications, the time structure of the host-pathogen interaction will determine which modeling approach is more adequate. In the case of general theory development, the choice of model formalism is largely a matter of taste. As exemplified below, continuous time models are typically derived from discrete time models, thereby implicitly making a number of additional assumptions on time limits and interdependency of events. Accordingly, discrete time models are conceptually more transparent. This is a significant advantage when jointly modeling epidemiological, population dynamical, and evolutionary processes. However, continuous time models tend to be simpler than discrete time models, mainly because higher-order terms can be neglected. Moreover, the

analysis of a continuous time model usually is less involved technically than that of a comparable discrete time model. As a service to the reader, we will show here how our discrete time model can be translated into a continuous time model and how continuous time models can be analyzed by means of the reproductive value approach (see also Gandon et al. 2000).

A Continuous Time SIR Model

On the basis of the model in the body of the text, we first derive recurrence equations for the dynamics of residents and mutants for a small time interval Δt. For a mutant y, this is of the form

$$\boldsymbol{n}(t + \Delta t) = \mathbf{A}_{\Delta t}(y, x^*)\boldsymbol{n}(t), \tag{B1}$$

where $\mathbf{A}_{\Delta t}$ is the transition matrix for a small discrete time step Δt. To obtain $\mathbf{A}_{\Delta t}$ from equation (9), we focus on the basic events in the model (birth, death, infection, recovery), assuming that all these events occur at a rate proportional to Δt. To streamline the equations, we will in the following use the shorthand notation $\mu = 1 - P$, $\nu = 1 - \sigma$, and $b_i = \xi F_i$ ($i \in \{S, I, R\}$). Now the probability of death by causes unrelated to infection is $\mu\Delta t$, the probability of death due to the pathogen is $\nu\Delta t$, the probability of infection is $\eta\Delta t$, the probability of recovery is $\rho\Delta t$, and the number of offspring produced by an individual of type i is $b_i\Delta t$. Replacing P, σ, η, ρ, and ξF_i in equation (9) by these new terms and neglecting all second-order and higher-order terms in Δt, we arrive at the transition matrix

$$\mathbf{A}_{\Delta t} = \begin{bmatrix} 1 - (\mu + \eta)\Delta t + b_S\Delta t & b_I\Delta t & b_R\Delta t \\ \eta\Delta t & 1 - (\mu + \nu + \rho)\Delta t & 0 \\ 0 & \rho\Delta t & 1 - \mu\Delta t \end{bmatrix}. \tag{B2}$$

It is now standard to translate equation (B1) into a continuous time process (e.g., May 1974):

$$\frac{d\boldsymbol{n}}{dt} = \mathbf{B}(y, x^*)\boldsymbol{n}, \tag{B3}$$

where $\mathbf{B}(y, x^*)$ is obtained from $\mathbf{A}_{\Delta t}(y, x^*)$ by subtracting 1 from the main diagonal, dividing the result by Δt, and letting Δt shrink to 0, that is, by

$$\mathbf{B}(y, x^*) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \cdot [\mathbf{A}_{\Delta t}(y, x^*) - \mathbf{Id}], \tag{B4}$$

where $\mathbf{Id}$ denotes the identity matrix. In our case, the matrix $\mathbf{B}(y, x^*)$ characterizing the continuous time process (B3) is of the form

$$\mathbf{B} = \begin{bmatrix} -\mu - \eta + b_S & b_I & b_R \\ \eta & -\mu - \nu - \rho & 0 \\ 0 & \rho & -\mu \end{bmatrix}. \tag{B5}$$

Evolutionary Stability

The dynamics (B3) of a mutant population is governed by the eigenvalue of $\mathbf{B}(y, x^*)$ with the largest real part. Consider the dominant eigenvalue $\lambda_{\Delta t}(y, x^*)$ of $\mathbf{A}_{\Delta t}(y, x^*)$, that is, the eigenvalue that is largest in absolute value. This eigenvalue is nonnegative, since the matrix $\mathbf{A}_{\Delta t}(y, x^*)$ is nonnegative (e.g., Caswell 2000). In view of equation (B4), this fact implies that

$$\kappa(y, x^*) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \cdot [\lambda_{\Delta t}(y, x^*) - 1] \tag{B6}$$

is the eigenvalue of $\kappa(y, x^*)$ with the largest real part. Notice that $\kappa(y, x^*)$ is a real number. Moreover, the same left and right eigenvectors are associated with $\kappa(y, x^*)$ with respect to $\mathbf{B}(y, x^*)$ as there are with $\lambda_{\Delta t}(y, x^*)$ with respect to $\mathbf{A}_{\Delta t}(y, x^*)$.

In view of our assumption of population regulation, the resident population is stationary, implying $\kappa^* = \kappa(x^*, x^*) = 0$. A mutant y will spread in the resident population if $\kappa(y, x^*) > 0$, and it will be ousted if $\kappa(y, x^*) < 0$. The resident strategy x^* is evolutionarily stable if no mutant strategy can spread, that is, if $\kappa(y, x^*) < \kappa(x^*, x^*) = 0$ for all $y \neq x$. Hence, analogously to the discrete time model, x^* is an ESS if $\kappa(y, x^*)$ attains a local maximum in y at $y = x^*$.

Reproductive Values

In view of equation (B6), maximization of κ corresponds to maximization of $\lambda_{\Delta t}$ (for sufficiently small Δt). In appendix A, we have seen how maximization of the dominant eigenvalue of the discrete time process (B1) can be translated into the reproductive value criterion (A9) involving the dominant eigenvectors $\boldsymbol{v}^*$ and $\boldsymbol{u}^*$ of $\mathbf{A}^*_{\Delta t} = \mathbf{A}_{\Delta t}(x^*, x^*)$. As indicated above, $\boldsymbol{v}^*$ and $\boldsymbol{u}^*$ are also eigenvectors of $\mathbf{B}^* = \mathbf{B}(x^*, x^*)$, corresponding to the eigenvalue $\kappa^* = 0$. As a consequence, all considerations on reproductive values in discrete time are directly applicable to the continuous time model (B3). In particular, an ESS x^* of equation (B3) has to satisfy the condition

$$\boldsymbol{v}^* \frac{\partial \mathbf{B}(y, x^*)}{\partial y}\bigg|_{x^*} \boldsymbol{u}^* = 0, \tag{B7}$$

where $\boldsymbol{v}^*$ and $\boldsymbol{u}^*$ are a left and a right eigenvector of the

matrix $\mathbf{B}^*$ with respect to the eigenvalue $\kappa^* = 0$. Again, $\boldsymbol{v}^*$ and $\boldsymbol{u}^*$ correspond to the vector of reproductive values and the stable state distribution, respectively.

As a consequence, by replacing the matrix **A** in equation (9) by the matrix **B** in equation (B5), the analysis in the body of the article directly extends to the continuous time model (B3). Doing this slightly simplifies the analysis (since eq. [B5] is simpler than eq. [1]) but does not lead to qualitatively different results. In fact, ESS criteria of the continuous model (B5) corresponding to the ESS criteria in table 2 of the discrete model are readily calculated, and the patterns found in our three examples can also be found in continuous time (results not shown).

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