Host Life-History Strategy Explains Pathogen-Induced Sterility

Matthew H. Bonds*

Institute of Ecology, University of Georgia, Athens, Georgia 30602

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abstract: Virulence is often equated with pathogen-induced mortality, even though loss of fecundity is also common. But while the former may be understood as a simple consequence of lost host resources for the purposes of pathogen transmission, pathogen-induced sterility is often not associated with changes in host mortality. As a result, a separate literature has emerged to explain fecundity effects of parasitism that has not been integrated into general theories of the evolution of virulence. Here, I present a model of pathogen-induced sterility that is based on the assumption that hosts and pathogens vie for the same host resources for both reproduction and maintenance. Loss of host fecundity can then be explained by the host compensating for its future loss of resources, before infection. Such preinfection "fecundity compensation" may often cause preinfection investment in maintenance to be as low as postinfection levels, despite a loss of total host resources after infection. Thus, sterility is simply explained as a host life-history strategy in a system where the pathogen necessarily steals host resources for its own transmission. In certain circumstances, the pathogen may even be able to manipulate the host to redirect resources away from reproduction and toward maintenance through castration, causing gigantism.

Keywords: evolution of virulence, life-history strategy, sterility, gigantism, evolutionarily stable strategy (ESS), coevolutionarily stable strategy (CoESS).

Host fitness can be decomposed into two essential components: reproduction and longevity. Theory on the effect of pathogens on the latter has received much attention in the past several decades and indeed has largely come to define virulence (Bremmermann and Pickering 1983; Frank 1996; Day 2001; Bonds et al. 2005), but the ability for pathogens to decrease host reproduction has received only minimal theoretical treatment (Obrebski 1975; Forbes 1993; Jaenike 1996; Perrin and Christe 1996; O'Keefe and Antonovics 2002). In reality, virulence can and often does manifest itself in the reduction of host fecundity without significantly altering host mortality.

Pathogen-induced fecundity reduction has been found in a wide range of taxa (Kuris 1974; Baudoin 1975; Hurd 2001) and is perhaps especially common in invertebrate systems such as crustaceans (Ebert et al. 2004) and mollusks (Sorenson and Minchella 2001). Though some have considered such fecundity effects to be simply an incidental consequence of infection (Sousa 1983; Polak 1996), general explanations tend to focus on whether fecundity reduction is an explicit evolutionary strategy of the host (McClelland and Bourns 1969; Moret and Schmid-Hempel 2000; Hurd 2001) or of the pathogen (Rothschild and Clay 1952; Baudoin 1975; Ebert et al. 2004). In the case of the former, the host is thought to mount a defense against the disease, which involves the redirection of host resources away from reproduction and toward survival (van Baalen 1998; Day and Burns 2003).

Alternatively, lost host fecundity has been thought to result from the general loss of host resources to the pathogen for its own transmission (Salt 1927; Reinhard 1956) or from the outcome of the pathogen selectively targeting host reproductive resources in order to minimize the negative effect of infection on host survival and thus pathogen survival (Summerfelt and Warner 1970; Cheng et al. 1973). This latter scenario has been formalized by Jaenike (1996) and O'Keefe and Antonovics (2002), who assume a negative relationship between host and pathogen reproduction and therefore find that the optimal pathogen strategy would be complete sterilization, which is relatively rare in nature. In contrast, Gandon et al. (2002) considered the possibility that investments in both reproduction and survival evolve in response to parasitism; they found that if virulence is in the form of greater host mortality, pathogens should induce the host to increase reproductive effort upon infection. How can these results be reconciled?

At first glance, the dearth of theory on pathogen-induced fecundity reduction would seem to be easily remedied and integrated into the general evolution of virulence literature. After all, the principles on which this literature currently relies—that disease transmission depends on host resources, often causing death—would seem to also explain loss of fecundity. That is, because host reproduc-

* E-mail: mbonds@uga.edu.

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tion also requires resources, we should naturally conclude that it would be compromised by infection. Indeed, this common need for scarce resources is the basis of the long-standing principle of life-history theory that organisms face a trade-off between reproduction and longevity (Stearns 1992). However, in reality, the effect of parasites on host reproductivity can be even more complex and interesting. For example, sterilized hosts have been known to become larger or live longer after infection (Baudoin 1975; Moore 2002; Ebert et al. 2004), betraying the simple loss of host resources as a general explanation. Clearly, parasitism sometimes influences the allocation of those resources. But how?

I present a general model of the evolution of pathogen-induced changes in host fecundity that integrates into the evolution of virulence literature by assuming that virulence is the result of the pathogen's need for host resources for its own transmission. Importantly, I do not assume that the pathogen explicitly targets either host reproductive resources or maintenance resources. Rather, I assume that the host can direct its resources to either objective, and thus its resources are used for both host reproduction and survival. Sterility is then treated as the result of two driving forces: the loss of total host resources that are directed to the pathogen for its own transmission and the loss of resources for host reproduction due to their reallocation toward maintenance after infection.

I find that, assuming plasticity in the allocation of host resources, a pathogen that necessarily steals some of those resources for its own transmission will always induce the host to invest a greater proportion of its total resources toward reproduction before infection compared to after infection. This is because the benefits of investing in reproduction of an uninfected host are enjoyed solely by that host, whereas the investments in longevity are partly stolen by the pathogen. Moreover, such preinfection "fecundity compensation" may be sufficiently high that it reduces preinfection investment in survival to its post-infection levels, despite the loss of total available resources after infection. In other words, the relative effect of a pathogen on host reproduction and survival may be determined by the host life-history strategy.

However, the special case of pathogen-induced gigantism can be explained in this context only by the direct interference of the host reproductive system—that is, castration—inducing the infected host to decrease its reproductive effort in order to increase its investment in maintenance. Thus, the pathogen manipulates the host's self-interest for its own survival.

Model

To analyze the evolution of pathogen-induced changes in host fecundity, I determine evolutionarily stable (ES) allocations of host resources toward reproduction and maintenance before and after infection. The evolutionarily stable strategies (ESSs) are derived from a classic susceptible-infected (S-I) population framework. This model framework does not allow for host recovery, and therefore it would not apply to acute disease systems where the pathogens are cleared rapidly, but it would apply to many parasite systems, such as that of *Daphnia magna* infected with the sterilizing bacterium *Pasteuria ramosa* (Ebert et al. 2004). The expected effects of host recovery on the ES resource allocations are considered in "Discussion."

Consider the following S-I equations (for definitions of variables, see table 1):

$$\frac{d\ddot{S}}{dt} = (b_S\ddot{S} + b_I\ddot{I})\left(\frac{K - \ddot{N}}{K}\right) - d_S\ddot{S} - \lambda\ddot{S}, \tag{1}$$

$$\frac{d\ddot{I}}{dt} = \lambda\ddot{S} - d_I\ddot{I}. \tag{2}$$

A scale-free model can be derived by dividing equations (1) and (2) by the carrying capacity, K, and setting $S = \ddot{S}/K$, $I = \ddot{I}/K$, and $N = \ddot{N}/K$, which results in

$$\frac{dS}{dt} = (b_S S + b_I I)(1 - N) - d_S S - \lambda S, \tag{3}$$

$$\frac{dI}{dt} = \lambda S - d_I I. \tag{4}$$

The parameters b and d represent birth and death rates, respectively. Notice that they are allowed to change after infection, with the "S" and "I" subscripts indicating the rates for susceptible and infected individuals, respectively. The variable N represents the total population, which is the number of susceptibles, S, plus the number of infecteds, I, scaled by the carrying capacity. The parameter λ is the force of infection.

The specific model used above is very similar to that used by O'Keefe and Antonovics (2002) and Gandon et al. (2002). The important difference between their models is that the former assumes that, for the purposes of transmission, the pathogen must directly reduce host reproduction, and the latter assumes that the pathogen must reduce host survival. These assumptions are very important because they are what drive O'Keefe and Antonovics (2002) to conclude that complete sterilization is the optimal pathogen strategy, whereas Gandon et al. (2002) determine that host reproduction should rise after infection. I do not make any assumptions about which host life-history properties are compromised by pathogen virulence, but instead I assume that reproduction and survival both rely on a fundamental resource, r, that is limited per

Table 1: Definitions of variables

Variable	Definition
$\ddot{S}$	Number of susceptible individuals
$\ddot{I}$	Number of infected individuals
$\ddot{N} = \ddot{S} + \ddot{I}$	Total population
K	Carrying capacity: maximum sustainable population in the absence of the disease
$S = \ddot{S}/K$	Number of susceptible individuals adjusted by the carrying capacity
$I = \ddot{I}/K$	Number of infected individuals adjusted by the carrying capacity
$N = \ddot{N}/K$	Total population adjusted by the carrying capacity
$b_S = ar_{b,S}^{\alpha}$	Birth rate of susceptibles
$b_I = \rho a r_{b,I}^{\epsilon\alpha}$	Birth rate of infecteds
$d_S = g r_{m,S}^{-\gamma}$	Death rate of susceptibles
$d_I = g r_{m,I}^{-\gamma}$	Death rate of infecteds
$r_{b,S}$	Reproductive effort of susceptibles
$r_{b,I}$	Reproductive effort of infecteds
$r_{m,S}$	Investment in maintenance of susceptibles
$r_{m,I}$	Investment in maintenance of infecteds
$r_v = \bar{r}_S - \bar{r}_I$	Amount of host resources lost to the pathogen
$\bar{r}_S = r_{b,S} + r_{m,S}$	Total resources available for reproduction and survival for susceptibles
$\bar{r}_I = r_{b,I} + r_{m,I}$	Total resources available for reproduction and survival for infecteds
$\rho \in [0,1]$	Pathogen sterility parameter
$\epsilon \in [0,1]$	Pathogen sterility parameter
λ	Force of infection: rate at which susceptibles become infected

time period and that the pathogen also marshals for its own transmission.

Host fecundity can be decomposed into two basic phenomena: reproductive effort, which I define as the investment of resources into reproduction, and reproductive efficiency, defined as the number of offspring produced per unit of reproductive effort. Reduction of host reproductive effort on infection has been further reduced to two mechanisms: loss of host resources to the pathogen for its own transmission and reallocation of host resources away from reproduction and toward survival. Such a tradeoff between reproduction and survival is accounted for in this model by the assumption that the fundamental resource, r, has a fixed value per time period of $\bar{r}$. The general functions for the birth and death rates for the susceptible individuals are $b_S = ar_{b,S}^{\alpha}$ and $d_S = g r_{m,S}^{-\gamma}$, respectively, with $r_{b,S}$ and $r_{m,S}$ representing the respective investments in reproduction and maintenance for susceptible individuals. The parameters a, α, g, and γ determine the efficiency by which the host converts its resources to reproduction and survival. The allocations of host resources toward reproduction and survival are therefore in direct competition with each other as well as with the pathogen, so that $\bar{r}_S = r_{b,S} + r_{m,S}$ and $\bar{r}_I = r_{b,I} + r_{m,I} = \bar{r}_S - r_v$, where $r_{b,I}$ and $r_{m,I}$ are the amount of the infected-host resources invested in reproduction and maintenance, respectively, and r_v is the amount of host resources stolen by the pathogen. For an illustration of the relationship between $\bar{r}_I$, $\bar{r}_S$, and r_v, see figure 1.

To allow for the loss of host reproductive efficiency, such as would result from pathogen-induced castration, the birth function for infected individuals is $b_I = \rho a r_{b,I}^{\epsilon\alpha}$, with $\rho \in [0,1]$ and $\epsilon \in [0,1]$ representing sterility parameters that are controlled by the pathogen. The difference between the effects of ϵ and ρ on host reproductive efficiency is discussed in "Pathogen Manipulates Host Life-History Strategy, Causing Gigantism." The death function for infected individuals is $d_I = g r_{m,I}^{-\gamma}$. Thus, the pathogen has two avenues by which it can reduce host fecundity: indirectly, through stealing resources from the host, represented by an increase in r_v, or directly, by "castrating" the host, which corresponds to a decrease in ρ or ϵ.

Pathogen-Induced Sterility as Host Life-History Strategy

Because the allocation of resources into reproduction and maintenance has fitness consequences for the host, natural selection should favor such allocations that maximize the host's lifetime reproductive success when the population is in equilibrium. The question addressed in this section is, how would we expect parasitism to influence the change in the optimal allocation of host resources? What are $r_{b,S}^* - r_{b,I}^*$ and $r_{m,S}^* - r_{m,I}^*$? To answer this, we must first determine the host's fitness, ω, measured as its lifetime reproductive success:

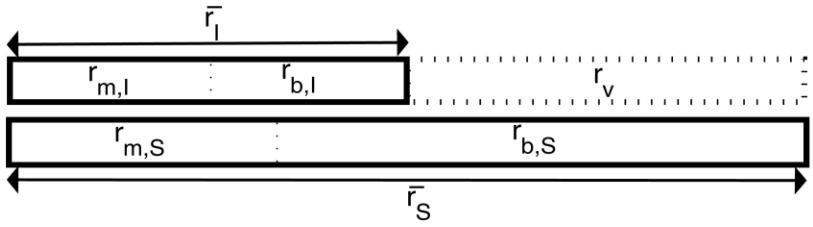

Figure 1: Resource budget of the infected host, $\bar{r}_I$, is equal to the preinfection resource budget, $\bar{r}_S$, minus the resources stolen by the pathogen, r_v.

$$\omega = \frac{b_S(1-N)}{d_S+\lambda} + \frac{\lambda}{d_S+\lambda}\frac{b_I(1-N)}{d_I} \tag{5}$$

$$= \frac{ar_{b,S}^{\alpha}(1-N)}{gr_{m,S}^{-\gamma}+\lambda} + \frac{\lambda}{gr_{m,S}^{-\gamma}+\lambda}\frac{\rho a r_{b,I}^{\epsilon\alpha}(1-N)}{gr_{m,I}^{-\gamma}}. \tag{6}$$

The first term, $b_S(1-N)/(d_S+\lambda)$, represents the number of offspring the individual has while uninfected. The term $\lambda/(d_S+\lambda)$ represents the probability of infection as opposed to death. The final term, $b_I(1-N)/d_I$, refers to the number of offspring an individual has while infected. For a more detailed treatment of the evolutionary stability of this general fitness function, see studies by van Baalen (1998) and Gandon et al. (2002).

There are two sets of ES allocations of host resources: before infection, $r_{b,S}^*$ and $r_{m,S}^*$, and after infection, $r_{b,I}^*$ and $r_{m,I}^*$. While the ES allocation before infection depends on the behavior after infection, the optimal behavior after infection is independent of the preinfection allocation. Thus, we can find the postinfection strategy by reducing equation (6) to an "infected-fitness" function, equal to the number of offspring while the host is infected,

$$\omega_I = \frac{\rho r_{b,I}^{\epsilon\alpha}}{gr_{m,I}^{-\gamma}} \propto r_{b,I}^{\epsilon\alpha} r_{m,I}^{\gamma}, \tag{7}$$

and maximizing it with respect to $r_{b,I}$ and $r_{m,I}$, subject to the budget constraint $\bar{r}_I = r_{b,I} + r_{m,I}$. Figure 2 is a graphic representation of how the ES allocation of host resources is determined given the budget constraint.

The optimal postinfection allocations are

$$r_{b,I}^* = \frac{\bar{r}_I}{1+\gamma/\epsilon\alpha}, \tag{8}$$

$$r_{m,I}^* = \frac{\bar{r}_I}{1+\epsilon\alpha/\gamma}. \tag{9}$$

For simplicity, I begin this analysis with a parsimonious assumption that the pathogen has no direct effect on host reproductive efficiency but does deplete host resources (i.e., $\epsilon = 1$ and $r_v > 0$). In this case, we see from equations (8) and (9) that the postinfection investments in reproduction and maintenance are determined entirely by the resource budget $\bar{r}_I$ and the efficiency parameters α and γ, which determine the curvature of the "returns" (in terms of reproduction and maintenance) to those investments. If, for example, we assume that host reproduction and life expectancy are directly proportional to the investments in each (i.e., $\alpha = \gamma = 1$), then the host simply splits those investments evenly between the two objectives (fig. 2).

Now, to determine the change in the use of host resources, we must compare $r_{b,I}^*$ and $r_{m,I}^*$ with the allocations

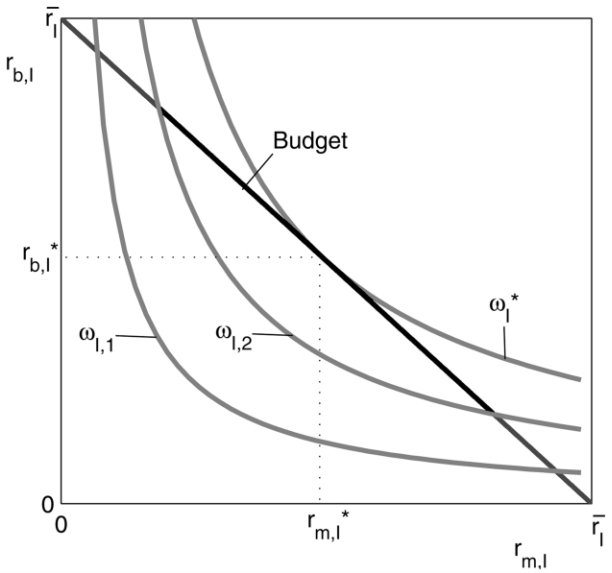

Figure 2: Fitness curves $\omega_{I,1} < \omega_{I,2} < \omega_I^*$ represent all combinations of resources required to maintain a given level of fitness while infected. The budget line represents the amount of resources that are available to the host; any allocation of resources under the budget line is therefore feasible. The evolutionarily stable allocation of host resources $r_{b,I}^*$ and $r_{m,I}^*$ is therefore the allocation associated with the highest fitness curve within the budget constraint, which is where the budget line and the fitness curve ω_I^* are tangent; $\epsilon = 1$, $\alpha = 1$, $\gamma = 1$, $g = 10$, $a = 1$, $\bar{r}_S = 100$, $r_v = 50$, $\omega_1 = 0.25\omega_I^*$, $\omega_2 = 0.6\omega_I^*$.

before infection, which are found by inserting equations (8) and (9) into the fitness function (6) and maximizing with respect to $r_{b,S}$ and $r_{m,S}$, subject to the resource constraint $\bar{r}_S = r_{b,S} + r_{m,S}$. Figure 3 illustrates the effect of parasitism on investments in fecundity and maintenance. The change in investments of host resources can be attributed to two separate mechanisms. The budget effect (BE) refers to the changes in investments in reproduction and survival that result from the loss of resources to the pathogen. The reallocation effect (RE) refers to the change of investments that results from the strategic reallocation of resources in response to parasitism:

$$\text{change in reproductive effort} = \text{BE}_b + \text{RE}_b, \quad (10)$$

$$r^*_{b,S} - r^*_{b,I} = (r^*_{b,H} - r^*_{b,I}) + (r^*_{b,S} - r^*_{b,H}), \quad (11)$$

where $r^*_{b,H}$ refers to the optimal reproductive effort if the host is never parasitized, and

$$\text{change in investment in maintenance} = \text{BE}_m + \text{RE}_m, \quad (12)$$

$$r^*_{m,S} - r^*_{m,I} = (r^*_{m,H} - r^*_{m,I}) + (r^*_{m,S} - r^*_{m,H}), \quad (13)$$

where $r^*_{m,H}$ refers to the optimal investment in maintenance if the host is never parasitized.

To illustrate the impact of a resource-depleting pathogen on host reproductivity, figure 4 presents the optimal pre- and postinfection allocations of host resources, $\hat{r}_{b,S}$, $\hat{r}_{m,S}$, $\hat{r}_{b,I}$, and $\hat{r}_{m,I}$. Note that, for heuristic purposes, these values were not calculated at the demographic equilibrium and are therefore "optimal" but not necessarily "evolutionarily stable" (the ES allocations are presented in fig. 5). They are treated as if pathogen virulence and the force of infection were independent exogenous forces. Figure 4 shows that the loss of host fecundity can be explained by the rate at which a host is infected, λ, and the rate at which the host loses resources upon infection, r_v. When the pathogen depletes no resources from the host (i.e., it is avirulent), there is no change in host fecundity after infection (fig. 4*a*). But as both virulence and the force of infection rise, so does the difference between pre- and postinfection reproductive effort. This is because the urgency of reproduction increases relative to survival as a host loses its future resources. After all, when the host invests in survival, a portion of that investment is stolen by the pathogen, but when it invests in reproduction, it is not. After infection, however, the pathogen depletes resources from both causes. The host therefore compensates for its future loss of resources by investing more in reproduction before infection. Indeed, such preinfection fecundity compensation eventually becomes sufficiently high (fig. 4*a*) that

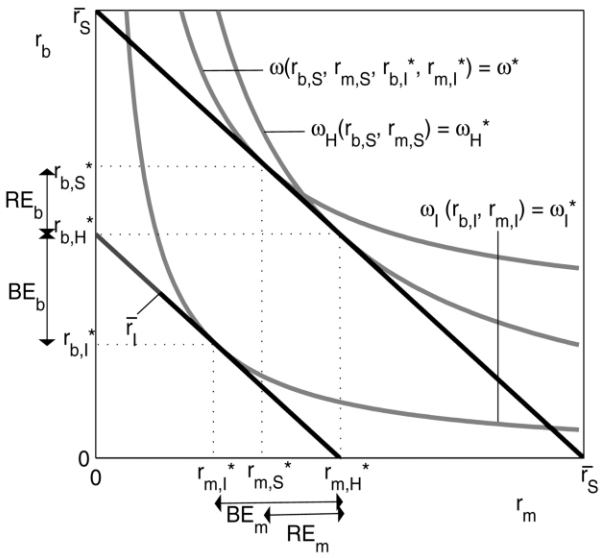

Figure 3: Curve $\omega(r_{b,S}, r_{m,S}, r^*_{m,S}, r^*_{m,I})$ represents all combinations of resource allocations when uninfected that result in a level of fitness that is equal to the maximum attainable fitness given the resource constraints and the postinfection strategy $\omega^*(r^*_{b,S}, r^*_{m,S}, r^*_{b,I}, r^*_{m,I})$. The curve $\omega_I(r_{b,I}, r_{m,I})$ represents all combinations of resource allocations of an infected individual that result in an "infected fitness" equal to the maximum number of offspring an infected individual can have given its resource constraint, $\omega^*_I(r^*_{b,I}, r^*_{m,I})$. The curve ω_H represents all combinations of resource allocations that result in a level of fitness that is equal to the maximum attainable fitness if the host is never infected, $\omega_H = \omega^*_H$. The change in fecundity and survival can be explained as a combination of two factors: a budget effect (BE) and a reallocation effect (RE). The BE refers to the change in fecundity that results purely from the loss of host resources upon infection: $\text{BE}_b = r^*_{b,H} - r^*_{b,I}$, $\text{BE}_m = r^*_{m,H} - r^*_{m,I}$. The RE is the additional change that results from reallocating resources toward maintenance after infection: $\text{RE}_b = r^*_{b,S} - r^*_{b,H}$, $\text{RE}_m = r^*_{m,S} - r^*_{m,H}$; $\epsilon = 1$, $\alpha = 1$, $\gamma = 1$, $g = 10$, $a = 1$, $\bar{r}_S = 100$, $\bar{r}_I = \bar{r}_S - \bar{r}_v$, $r_v = 50$.

preinfection investment in maintenance is reduced to its postinfection levels, despite the loss of total host resources after infection (fig. 4*b*). In other words, for systems in which there is a high probability of infection (due to high disease prevalence or high transmission rate) or a significant loss of resources upon infection (due to high virulence), pathogens may often be effectively sterilizing while appearing to have minimal impact on host mortality. This is true for all positive values of α and γ and is entirely based on the host life-history strategy.

The results in figure 4 represent optimal host behavior over a range of values of pathogen virulence and force of infection, which are treated independently. However, if transmission were modeled as being either frequency or density dependent ($\lambda = \beta I/N$ or $\lambda = \beta I$, where β is the rate of transmission), pathogen virulence would feed back on the force of infection because higher virulence would

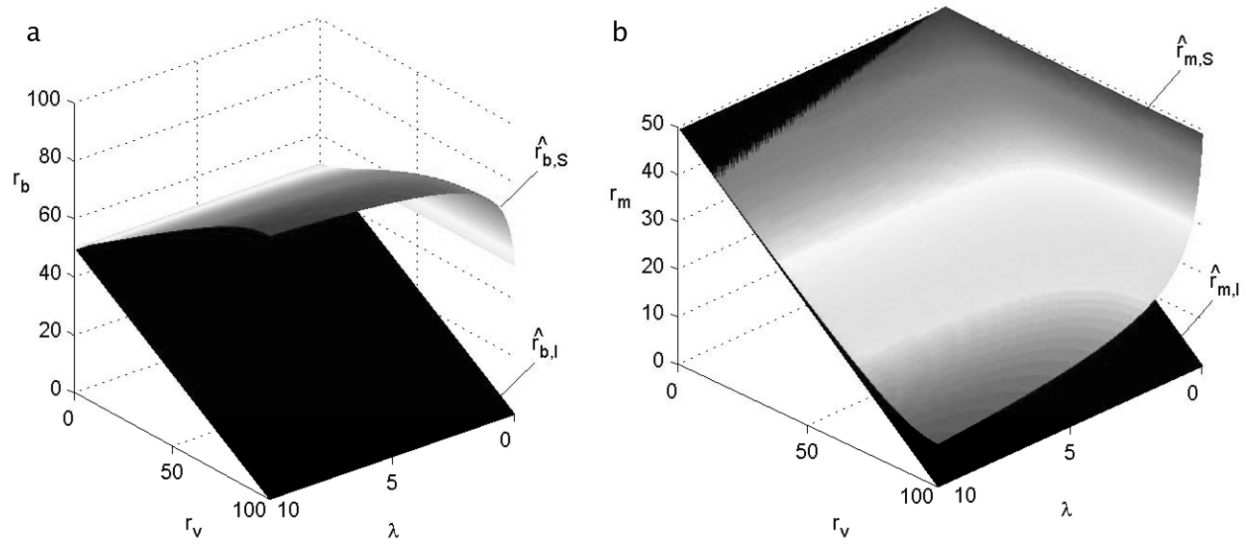

Figure 4: *a*, As the force of infection, λ, and pathogen virulence, r_v, rise, so does the difference between the optimal pre- and postinfection fecundity, $\hat{r}_{b,S}$ and $\hat{r}_{b,I}$. *b*, As preinfection reproductive effort rises from greater force of infection, the preinfection investment in maintenance, $\hat{r}_{m,S}$, approaches the postinfection investment, $\hat{r}_{m,I}$, lowering the apparent mortality effect of the pathogen; $a = 5$, $g = 10$, $\alpha = 1$, $\gamma = 1$, $h = 1$, $\bar{r}_S = 100$.

result in greater host death rate, which lowers the equilibrium disease prevalence, but would also increase the rate of disease transmission, which raises the equilibrium disease prevalence. As a result, one might expect the relationship between the ES preinfection reproductive effort and pathogen virulence to be nonmonotonic. This is illustrated in figure 5, where the effect of the pathogen on the preinfection reproductive effort becomes zero when virulence is very high because the high mortality rates reduce the equilibrium disease prevalence, and therefore the force of infection, to zero. However, note that the change in reproductive effort after infection is always negative.

Coevolution of Pathogen Virulence

From figure 4 we know that the burden of the pathogen in terms of the force of infection and virulence is what determines the difference between pre- and postinfection reproductive effort. However, from figure 5 we can see that pathogen virulence feeds back on the force of infection, $\lambda = \beta I$, suggesting that in nature we would expect to find a nonmonotonic relationship between disease virulence, disease prevalence, and pathogen-induced fecundity reduction. But the analysis above ignores pathogen evolution, which we would expect to have predictable consequences on this feedback between disease prevalence and virulence, given that the pathogen would be expected to evolve to maximize its basic reproductive ratio, which would maximize the equilibrium disease prevalence.

Consider the pathogen's basic reproductive ratio, R_0:

$$R_0 = \frac{\beta}{d_I} \propto r_v^{\delta} r_{m,I}^{*\gamma} = \left(\frac{\gamma}{\epsilon\alpha + \gamma}\right)^{\gamma} r_v^{\delta}(\bar{r} - r_v)^{\gamma}. \qquad (14)$$

Notice that the pathogen's fitness function incorporates the ES behavior of the host, r_m^*, because that behavior constitutes the regime in which the pathogen evolves. Thus, the pathogen's ESS is also coevolutionarily stable (CoES).

Because this section is concerned with only pathogen virulence, not direct castration, on host reproductive behavior, I continue to assume here that ϵ is fixed at 1, which reduces the fitness function (14) of the pathogen to

$$R_0 \propto r_v^{\delta}(\bar{r}_S - r_v)^{\gamma}. \qquad (15)$$

From equation (15), we can see that the CoES virulence should be influenced by only two parameters in this system: δ, which affects the rate of conversion of host resources to pathogen transmission, and γ, which affects the rate of conversion of host resources to pathogen (and host) survival. Both of these parameters also influence the equilibrium prevalence of the disease. For a clearer illustration of how δ and γ influence pathogen transmission and survival, see figure 6.

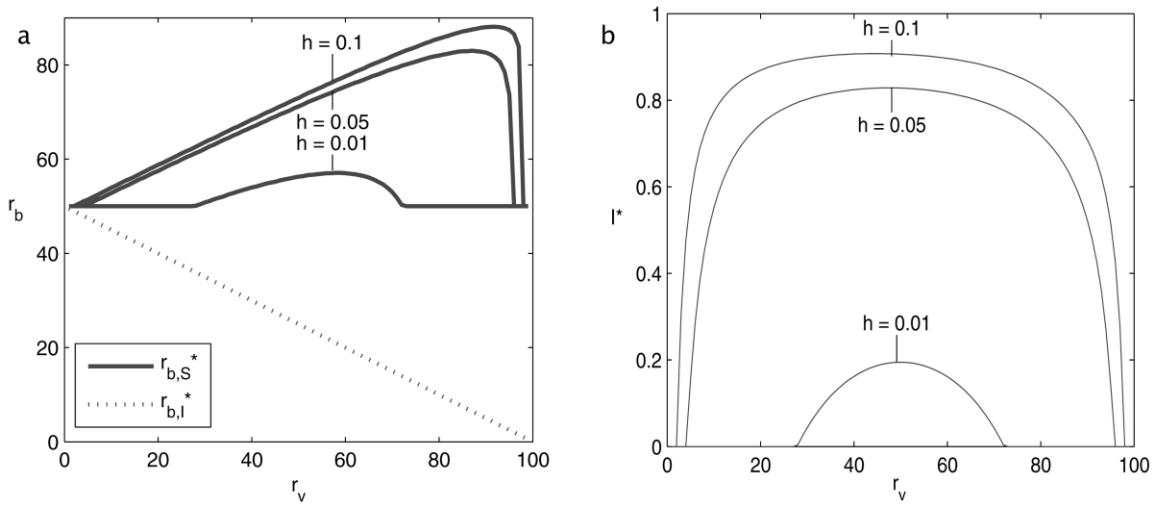

Figure 5: *a*, Assuming frequency-dependent transmission ($\lambda = \beta I$), the evolutionarily stable preinfection reproductive effort, $r^*_{b,S}$, responds nonmonotonically to pathogen virulence, r_v. This is because the "optimal" preinfection reproductive effort responds monotonically to independent increases in virulence and the force of infection (fig. 4*a*). *b*, However, the relationship between virulence and the force of infection is nonmonotonic because of the effect of virulence on the equilibrium disease prevalence; $g = 10$, $\alpha = 1$, $\gamma = 1$, $\bar{r} = 100$, $\lambda = \beta I$, $\beta = hr_v^{\delta}$, $\delta = 1$.

Figure 7 presents the effect of changes in δ and γ on the CoES levels of pathogen-induced changes in host reproductive effort. In all cases, the relationship between the CoES loss of fecundity and the corresponding risk factors, virulence and force of infection, is monotonic.

Figure 7*a* and 7*b* depicts the effect of δ on the relationship between the equilibrium force of infection, $\lambda^* = \beta(r_v^*)I^*$, and the CoES change in fecundity, $r^*_{b,S} - r^*_{b,I}$, and between the CoES virulence, r_v^*, and the CoES change in fecundity. Low δ implies a relatively low transmission efficiency per unit of resources taken from the host, and if $\delta > 1$, this efficiency diminishes with increasing investments (see fig. 6). As δ rises, transmission efficiency rises, and the pathogen, which maximizes the number of infected individuals in its lifetime, evolves toward higher virulence, which necessarily corresponds to both a higher transmission rate and higher equilibrium force of infection. Thus, over δ space, the relationships between the equilibrium force of infection and the CoES loss of fecundity and between the CoES virulence and the CoES loss of host fecundity are both positive and monotonic.

Figure 7*c* and 7*d* depicts the effect of γ on the relationship between the equilibrium force of infection and the CoES change in fecundity and between the CoES virulence and the CoES change in fecundity. Low γ implies that each additional unit of host resources invested in maintenance results in relatively low increases in life expectancy and that these increases actually diminish with each additional unit of investment if $\gamma > 1$. As γ rises, maintenance efficiency rises, increasing the benefits of preserving the host relative to transmission and decreasing the CoES level of virulence. The greatest reduction in host fecundity occurs when γ is low, which cor-

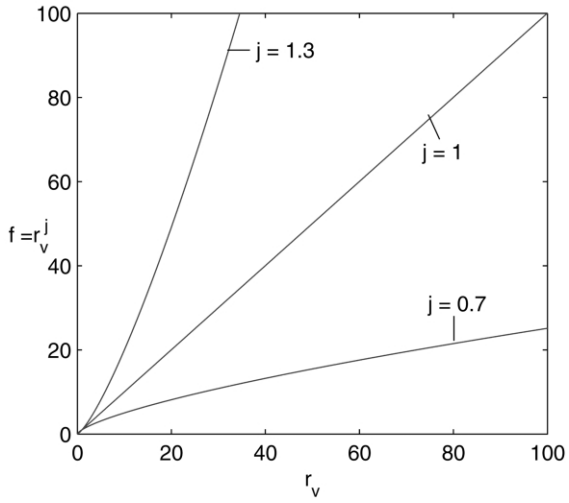

Figure 6: Pathogen transmission term $\beta = hr_v^{\delta}$ and host life expectancy $r_{m,I}^{\gamma}/g$ have the general functional form $f \propto r_v^j$. The parameter j (i.e., δ and γ) determines the rate at which additional investments of host resources influence transmission and survival. If $j > 1$, then the benefits to the pathogen of investing in transmission or survival rise with each additional unit of investment. If $j = 1$, then each additional unit of investment confers the same marginal benefits. And if $j < 1$, then the benefits of investing in transmission or survival fall with each additional unit of investment.

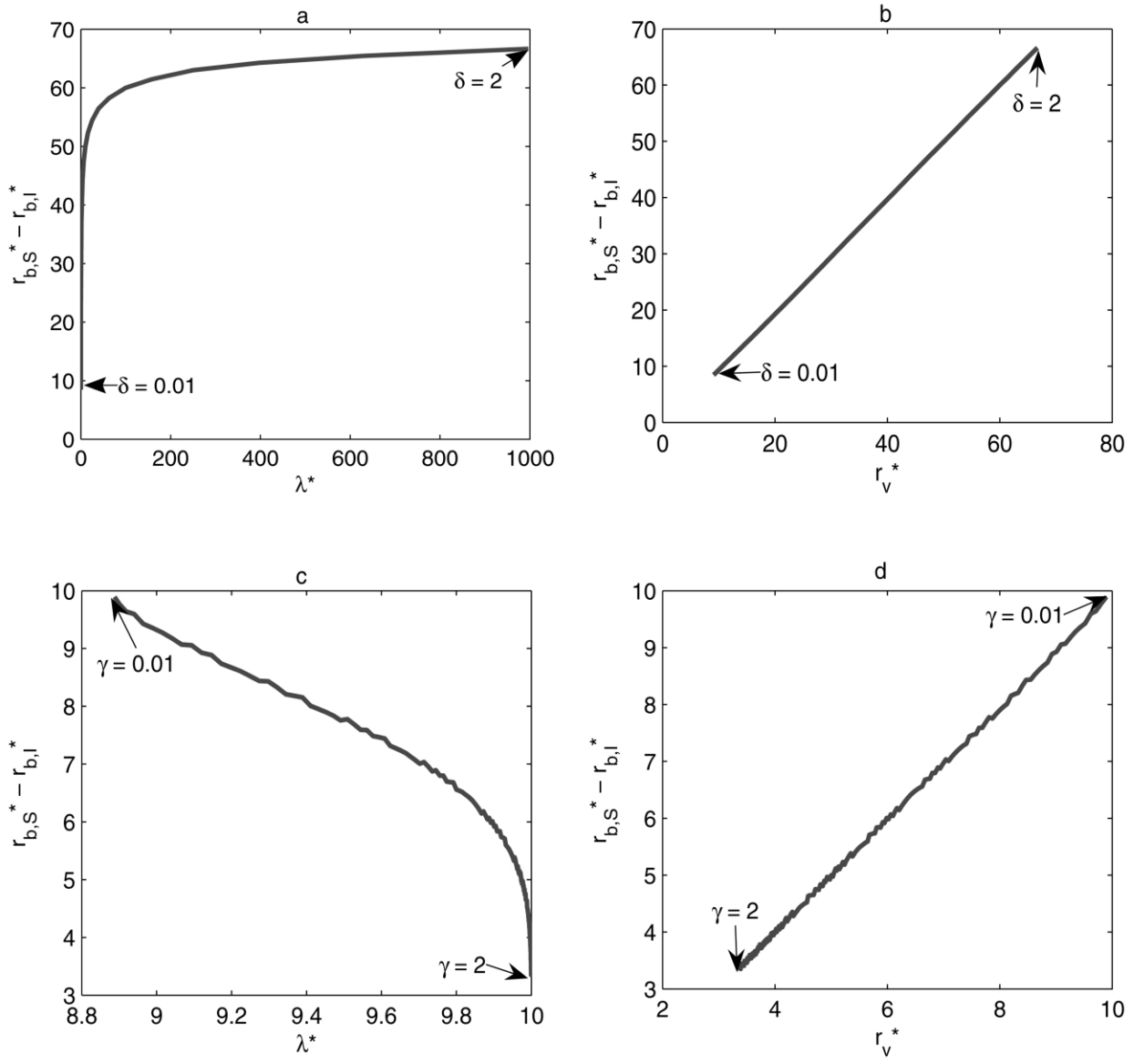

Figure 7: Coevolutionarily stable (CoES) change in fecundity, $r^*_{b,S} - r^*_{b,I}$, with its corresponding CoES virulence, r^*_v, and the equilibrium force of infection, $\lambda^* = \beta(r^*_v)I^*$, over a range of δ and γ values; $\rho = 1$, $a = 1$, $\epsilon = 1$, $\alpha = 1$, $g = 1$, $\bar{r}_S = 100$, $h = 0.1$, $\gamma = 1$ (*a*, *b*), $\delta = 1$ (*c*, *d*).

responds to a high virulence but a low force of infection. Thus, over γ space, the CoES virulence and force of infection are negatively correlated, allowing for a monotonically decreasing relationship between the force of infection and CoES pathogen-induced fecundity reduction.

From the analysis so far, there are two important conclusions. First, all combinations of the force of infection and pathogen virulence result in reduced host fecundity after infection (fig. 4). Second, the direct effect of the force of infection and virulence on host fecundity reduction is always positive. Because pathogen virulence interacts nonmonotonically with the force of infection, the indirect effects of pathogen virulence make it impossible to make an a priori prediction of how the force of infection will correlate with pathogen-induced fecundity reduction in the natural world. However, in all cases, I find a positive and monotonic relationship between the CoES level of virulence and pathogen-induced fecundity reduction. The simple role of pathogen virulence, however, never reduces preinfection maintenance to below the postinfection levels, and therefore it cannot explain gigantism.

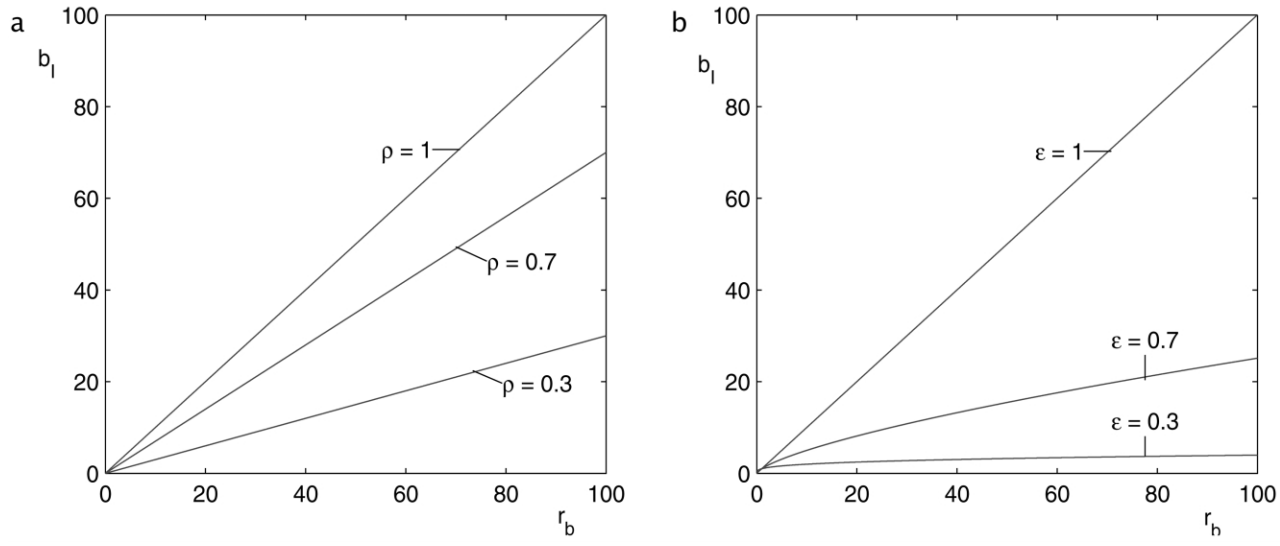

Figure 8: Infected-host birth function $b_I = \rho a r_{b,I}^{\epsilon\alpha}$ allows the pathogen to interfere with host reproductive efficiency through the sterility parameters ρ and ϵ. *a*, A decrease in ρ results in a proportional decrease in reproductive efficiency but does not alter the curvature of the birth function; $a = 1$, $\alpha = 1$, $\epsilon = 1$. *b*, The parameter ϵ influences the curvature of the birth function. If ϵ falls below 1, the per-unit reproductive efficiency of the host diminishes as the reproductive effort rises; $a = 1$, $\alpha = 1$, $\rho = 1$.

Pathogen Manipulates Host Life-History Strategy, Causing Gigantism

The section above shows that a simple host life-history strategy can explain pathogen-induced fecundity reduction but cannot explain gigantism. That analysis assumes that the pathogen harms the host through the loss of host resources, an assumption that holds true for a wide variety of host-pathogen relationships, such as that of the fruit fly *Drosophila nigrospiracula* and its parasitic mite *Macrocheles subbadius* (Polak 1996) or that of the mosquito *Aedes aegypti* and the filarial nematode *Brugia pahangi* (Javadian and Macdonald 1974). However, the explicit destruction of host reproductive tissue, known as parasitic castration, has also been shown in large-range host-pathogen systems and is often associated with host gigantism (Arnott et al. 2000; Krist 2001; Ebert et al. 2004).

No formal theory has been developed to explain the evolution of parasite-induced gigantism, but the conceptual arguments emphasize the benefits to the pathogen. Indeed, the prospect of a host strategically evolving toward complete castration has been considered by some to be untenable. After all, completely sterile individuals do not reproduce, eliminating a mechanism for the heritability of such a strategy; "consequently, adaptation can only be on the side of the parasite" (Rothschild and Clay 1952, p. 35). The proposed benefit for the pathogen is that the inability for host reproduction results in more resources available for pathogen survival and transmission. But it is important to emphasize here that this reasoning implicitly assumes that decreased reproductive efficiency somehow translates to decreased reproductive effort. What drives this relationship? In search of such a mechanism, this section con-

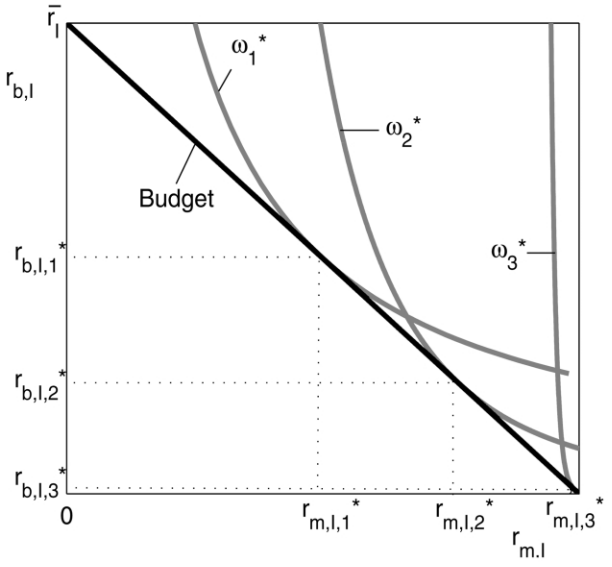

Figure 9: As the pathogen castrates the host by reducing ϵ, the host invests more in survival; ω_1^*, ω_2^*, and ω_3^* correspond to the maximum host fitness when $\epsilon = 1$, 0.3, and 0.01, respectively; $h = 1$, $g = 100$, $\bar{r}_S = 100$, $\alpha = 1$, $\gamma = 1$.

siders the optimal host response to a parasite's direct interference of the host's reproductive system.

Remember from the birth function $b_I = \rho a r_{b,I}^{\epsilon\alpha}$ that host castration is represented by the fecundity parameters ρ and ϵ taking on values >1. However, notice from equations (8) and (9) that ρ has no influence on the optimal allocation of host resources, and therefore its manipulation would confer no strategic benefit to the pathogen. Intuitively, this may be surprising, as we might expect a decrease in the marginal benefits of investing in reproduction to result in a decrease in reproductive effort. But from the infected-fitness function $\omega_I \propto \rho a r_{b,I}^{\epsilon\alpha} r_{m,I}^{\gamma}/g$, we can see that decreasing the marginal benefits of reproduction by, for example, halving ρ and decreasing the marginal benefits of survival by doubling g are evolutionarily equivalent. Though the mechanism is different, the effect on host fitness remains the same; both parameters are simply scalars of the fitness function, and therefore, while influencing the fitness of the host, they do not alter the trade-off between investments in survival and reproduction. This is an especially important point because a simple proportional decrease in reproductive efficiency (i.e., a decrease in ρ) would be the most intuitive kind of interference of the host reproductive system. To gain a better understanding of the difference between the sterility parameters ρ and ϵ, see figure 8.

On the other hand, the value of the parameter that influences the curvature of the returns to reproductive effort, ϵ, does influence the optimal allocation of host resources. If the pathogen castrates the host by lowering ϵ, it will result in a strategic decrease in host reproductive effort and a corresponding increase in the investment toward maintenance (fig. 9).

From equation (15), we can see that the evolutionarily stable ϵ for the pathogen is

$$\epsilon^* = 0, \tag{16}$$

implying that complete castration, if done properly (i.e., not through reduction of ρ), is an optimal pathogen strategy. To understand the meaning of ϵ, consider a case where preinfection reproductivity is proportional to reproductive effort (i.e., $\alpha = 1$). An ϵ of >1 implies that as postinfection reproductive effort rises, the output per unit of effort will fall. These diminishing returns to reproductive effort—or increasing costs of reproduction—induce the host to reallocate resources toward maintenance (fig. 9). What is especially interesting is that this act of manipulation is passive, as opposed to direct, in that it relies on the host's optimal response, which is not even heritable at the limit but is heritable up until the limit. Moreover, such direct castration can increase host investment in maintenance beyond the preinfection levels despite the loss of total resources after infection. Thus, direct castration in the form of lowering ϵ could cause host gigantism (fig. 10) via the manipulation of the host's self-interest. A biological mechanism for this specific form of castration is presented in "Discussion."

Discussion

There is a great deal of evidence that pathogens often cause host fecundity to fall, with proposed explanations spanning the full range of evolutionary possibilities. Loss of fecundity could be a host strategy (Hurd 2001), a pathogen strategy (Baudoin 1975; Ebert et al. 2004), a coevolutionary outcome, or none of the above—it could be an incidental outcome of depleted host nutrients (Polak 1996).

The explanations for the evolution of pathogen-induced fecundity reduction rely on a common principle: the trade-off between host longevity and reproduction. The simplest theories merely assume that pathogen transmission is a negative function of host reproduction and that therefore the pathogen evolves to become completely sterilizing (Jaenike 1996; O'Keefe and Antonovics 2002). These theories treat sterilization as if it were a separate kind of virulence

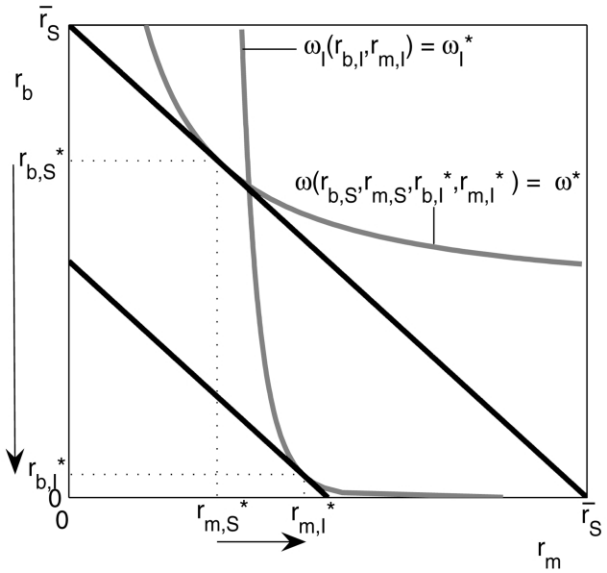

Figure 10: Curve $\omega(r_{b,S}, r_{m,S}, r_{m,S}^*, r_{m,I}^*)$ represents all combinations of resource allocations when uninfected that result in a level of fitness that is equal to the maximum attainable fitness given the resource constraints and the postinfection strategy $\omega^*(r_{b,S}^*, r_{m,S}^*, r_{b,I}^*, r_{m,I}^*)$. The curve $\omega_I(r_{b,I}, r_{m,I})$ represents all combinations of resource allocations of an infected individual that result in an "infected fitness" equal to the maximum number of offspring an infected individual can have given its resource constraint, $\omega_I^*(r_{b,I}^*, r_{m,I}^*)$. Despite a loss of total resources to the pathogen after infection, the optimal host investment in maintenance may actually rise in response to castration; $h = 1$, $g = 100$, $\bar{r}_S = 100$, $\alpha = 1$, $\gamma = 1$, $\epsilon = 0.1$.

from that of pathogen-induced mortality, requiring new assumptions and new models that are not integrated into the general evolution of virulence framework. Alternatively, assuming the host can recover, lost fecundity has been considered a possible indirect consequence of the host mounting costly defenses against pathogens that directly target host survival (van Baalen 1998; Day and Burns 2003).

Here, I show that explaining lost host fecundity does not require that the pathogen target host reproductive resources, nor must it be a consequence of host defense. Rather, it is an implication of general theories of virulence, where the pathogen is assumed to require host resources for its own transmission. Such resources, in this model, are used for both host survival and reproduction but are constrained by a total resource budget.

There is a simple but powerful implication of this tradeoff in the context of a resource-depleting pathogen: if the host can freely transfer its resources between reproduction and survival, then it should always be expected to reduce its fecundity after infection, not merely because of a loss of total resources for the host but also because the threat of infection causes the host to allocate preinfection resources to greater reproduction, with preinfection maintenance being correspondingly lower. This is because such pathogens always steal host investments in survival but cannot steal preinfection investments in reproduction. After infection, on the other hand, the pathogen steals resources from both causes. As illustrated in figure 4, the strongest sterilizing effect is expected when the threat of the disease is very high, such as at high pathogen prevalence or virulence. Consistent with this theory, Krist (2001) found a positive correlation between average size-adjusted reproductivity of eight populations of uninfected freshwater snails *Elimia livescens* and the prevalence of sterilizing trematodes. My result is in contrast to the findings of Gandon et al. (2002) that the host should increase reproduction after infection. The key difference between my model and that of Gandon et al. (2002) is that they assume that pathogen virulence directly affects host mortality, while I assume that the pathogen takes host resources, whose relative allocation between reproduction and survival is determined by the host.

There is a wrinkle to this theory that can explain another commonly observed phenomenon in the field: early-infection fecundity compensation (Thornhill et al. 1986; Polak and Starmer 1998). In cases where there is both sufficient plasticity in the use of host resources and enough time between the initial infection and the maximum parasite burden, the host does not necessarily need to completely anticipate the infection but can wait until it is infected before redirecting resources into reproduction. In this case, reproductivity is expected to quickly rise before dropping off when the parasite burden is high. This was found, for example, in *Daphnia magna* that invested in early reproduction when exposed to the parasitic microsporidian *Glugoides intestinalis* (Chadwick and Little 2005).

The analysis presented here suggests host strategic behavior as a parsimonious explanation for pathogen-induced sterility. Whether the host compensates before infection or immediately after infection is determined by the time after initial infection that it takes the pathogen to become a burden on host resources relative to the time (and cost) required to redirect host resources to reproduction. However, such a simple model does not explain gigantism.

It is often postulated that castration "frees" host resources that would have been otherwise relegated to reproduction, which explains gigantism as either an incidental consequence of a parasite targeting host reproductive resources (Sousa 1983) or a strategy of the pathogen (Baudoin 1975; Ebert et al. 2004). What has not previously been demonstrated is a specific mechanism for converting lost host reproductive efficiency to lower reproductive effort and therefore greater maintenance. After all, a completely sterilized host benefits from neither. Indeed, by facilitating the prosperity of the costly parasite, castrated hosts are harmed by self-preservation in that their kin are necessarily worse off, if only marginally, while they are not better off. A more specific mechanism for the redirection of host resources is therefore warranted. I present a model that relies on a few simple assumptions: host and pathogen vie for limited host resources, such resources can be used for either host reproduction or maintenance, and the host does not recover. In a laboratory system of *D. magna* infected with the bacterium *Pasteuria ramosa*, Ebert et al. (2004) present the most careful study to date of parasitic castration and confirm that these assumptions hold true for their system.

An interesting and obvious extension of this model would be to allow for host recovery, which is often found in host-macroparasite systems, where the host outlives the parasite. While the results presented here cannot be directly applied to such systems, which are inherently more complex, the principles on which these results rely are applicable. Specifically, even with recovery, parasite-induced loss of host resources puts inherent selective pressure on reproduction before the host loses such resources (i.e., before infection). Presumably, the prospect of recovery would put additional pressure on surviving until the pathogen was cleared, after which the host would again invest disproportionately in reproduction before its future loss of resources was stolen again by another infection.

Despite previous, and highly intuitive, suggestions that parasitic castration cannot be a host strategy because such

a strategy is not heritable, the analysis presented here suggests that it is heritable—indeed, evolutionarily stable—up until (but not at) the limit, where reproductive effort is zero. This is true only for a specific castrating effect: the pathogen must force the reproductive efficiency of the host to fall as reproductive effort rises. Such a mechanism would be possible where pathogen abundance was based on the consumption of host reproductive resources, such as is common of trematode infections of mollusks (Wilson and Denison 1980; Hurd 2001), and if one of two forces were working for the pathogen: an Allee effect or a Type II functional response. In either case, as pathogen abundance rose in response to increased host investment in reproduction, pathogen consumption of those resources would rise at an increasing rate because of either increased consumption efficiency (Type II functional response) or increased aggregate growth efficiency (Allee effect). Both mechanisms would clearly reduce the incentive of the host to invest in reproduction. Whether such a mechanism is truly at work is unknown because it has not been previously searched for. Such a test would constitute valuable future experimental work. This coevolutionary dynamic could potentially result in complete castration. Thus, castration and gigantism would in fact be the product of host-pathogen coevolution, where the pathogen manipulates the host's self-interest.

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