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Coevolution of recovery ability and virulence

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Most models for coevolution of hosts and parasites are based on the assumption that resistance of hosts to parasites is an all-or-nothing effect. In many cases, for example where parasites require an appropriate receptor on host cells, this is a reasonable assumption. However, in many other cases, for example where hosts mount an immune response, this picture may be too simple. An immune system is expensive to maintain, which poses a question as to how much of its resources a host should allocate to resist parasites: if the risk of infection is low, natural selection may favour hosts with less effective immune systems. As optimal allocation to defence will depend on the force of infection, and the force of infection, in turn, depends on the level of defence in the rest of the host population, a game-theoretic approach is necessary. Here I analyse a simple model for the evolution of the ability to recover from infection. If parasites are not allowed to coevolve, the outcome is a single evolutionarily stable strategy (ESS). If the parasites coevolve, multiple evolutionary outcomes are possible, one in which the parasites are relatively avirulent and common and the hosts invest little in recovery ability, and another (the escalated arms race) where parasites are rare but virulent and the hosts invest heavily in defence.

Keywords: host–parasite systems; coevolution; virulence; defence; immune systems

1. INTRODUCTION

There are many ways in which a host can defend itself against infectious disease. Next to various first lines of defence preventing infection in the first place (e.g. thick skin), a host can maintain a second line of defence to fight an infection whenever a parasite has managed to overcome the first line of defence, i.e. it can maintain an immune system. On the other side of the struggle, parasites may have various quantitatively and quantitatively different strategies to counter their hosts' defence strategies. This is the classical setting for coevolution, as evolution in the host population depends on the strategies present in the parasite population and vice versa.

Most model studies for host–parasite coevolution are based on a population genetics framework, which assumes a set of parasite strains differing in their mode of attack and a set of genes coding for various ways of defence (May & Anderson 1983; Beck 1984; Levin *et al*. 1990; Hamilton *et al*. 1990; Hamilton 1993; Frank 1991; 1993*a*,*b*). This may be a reasonable simplification for first-line types of defence (types of defence that prevent infection in the first place). For example, the interaction between plants and their fungal parasites and between bacteria and their viruses is often an all-or-nothing effect (Thompson & Burdon 1992; Frank 1993*b*). For second-line types of defence (fighting parasites that have broken through the first line of defence) the situation is different, as the efficacy of a host's immune system depends on how much of its resources it has allocated to it. This poses the question of how optimal allocation strategies depend on parasite abundance and virulence. And on the longer time-scale, as host recovery affects optimal virulence (Frank 1996), what will happen if hosts and parasites coevolve?

Here, I analyse an ESS model in combination with a population dynamics model. This approach is based on the assumption that there are continuous cost–benefit relations for virulence and defence. For the hosts, a negative relationship is assumed between the efficacy of its immune system and its rate of reproduction; for the parasites, there is a positive relationship between transmission efficiency and disease-induced mortality.

One of the advantages of the ESS approach is that it draws attention to the game theoretical nature of parasite–host interactions, not only between the trophic levels but also within trophic levels. For example, optimal defence strategies will depend on the risk of infection, and this will depend on the defence strategy adopted by the resident host population. If the resident hosts are heavily defended, parasite incidence in the population is likely to be low (note that to study this effect, the evolutionary model should be combined with a population dynamical model!), a situation in which those mutant hosts that economize on defence and allocate more to reproduction are favoured. Conversely, if all hosts economize on defence, the incidence of the parasite is likely to rise, making it advantageous for mutant hosts to invest more in defence.

The situation becomes more complex when parasites also evolve. It will pay parasites to reduce virulence if it sufficiently prolongs the infectious period (Eshel 1977; May & Anderson 1983). Therefore, the evolution of defence may have an adverse evolutionary effect (from a host's point of view): a more efficient immune system will reduce the opportunities for the parasites to prolong exploitation of their host, and it pays to increase the

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Received 15 September 1997 *Accepted* 15 October 1997

probability of immediate transmission. The evolution of improved host defence may therefore favour increased parasite virulence (Mitchell 1991; Bonhoeffer & Nowak 1994; Frank 1996). What will happen if recovery rate and virulence coevolve is as yet unclear, and to explore the consequences is the main aim of this article.

To disentangle the life history aspects from the population dynamical effects and the coevolutionary aspects, this paper is structured in three sections. In the first section, I will investigate optimal allocation to recovery ability under given, fixed, conditions by treating it as a life history problem. That is, I will analyse the optimal allocation of resources to defence and reproduction in a given setting, characterized by a certain risk of becoming infected (i.e. for a fixed force of infection). In the second section the life history model is embedded into a population dynamical setting, to work out how the individual optimum depends on the resident strategy (through the force of infection, which is now allowed to vary) and analyse ESS recovery rates. Finally, the parasite population is allowed to coevolve, and coevolutionarily stable strategies (CoESSs) for defence and virulence are analysed.

A note on terminology: since I focus on what happens *after* infection, 'virulence' refers to the epidemiological concept (the effect on host's fitness; in this article specifically, disease-induced host mortality) rather than the plant-pathologist's definition (the ability to infect). Likewise, 'defence' refers to the host's ability to expel the parasite (clearance) rather than its susceptibility to infection. In this article recovery rate (assumed to be the same as clearance rate) will be assumed to be the host's defence strategy; this is the only component of host defence that is allowed to evolve.

2. OPTIMAL RECOVERY RATES

The first step is to determine how optimal allocation to recovery ability depends on the force of infection and the parasites' characteristics. In other words, how do individual hosts maximize their lifetime reproductive output, in a given setting. The second step is then to work out how the force of infection depends on the allocation strategy of the resident host population. By combining the results, ESS conditions can then be found.

I will use a simple susceptible–infected–susceptible (*SIS*) model. On the individual level the model is as follows. The force of infection, h, is the probability per unit time that a susceptible host becomes infected. Note that this depends on the host's susceptibility; if susceptibility varies, individual hosts may experience different forces of infection. Here I will assume that all hosts are equally susceptible. Once infected, the host may either die (with a probability per unit time $\mu+\alpha$) or its immune system clears the infection (with probability per unit time γ) after which the host becomes fully susceptible again.

Clearly, if there were no costs involved, it would pay a host to increase its recovery rate γ to infinity. However, this strategy is likely to be costly: resources have to be allocated to maintain a population of immune cells, etc. This cost can manifest itself in many ways, but one of the simplest cases is that increasing recovery rate will reduce the host's rate of reproduction b. (Being infected or not is assumed not to affect the rate of reproduction, only the rate of mortality.)

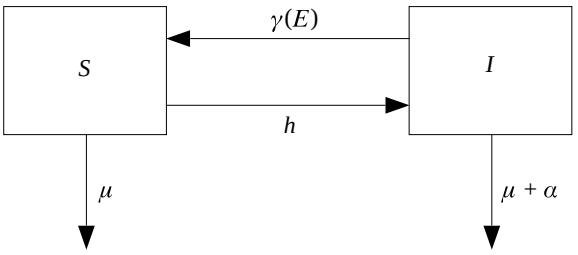

Figure 1. A simple *SIS* model for infection, in which a host can either be healthy and susceptible, or infected. The force of infection is h, recovery rate is $\gamma(E)$, background mortality rare is μ, disease-induced mortality rate is α.

Let the strategy E stand for the host's investment in its immune system, i.e. in its ability to eliminate parasites that have overcome its first line of defence. The assumption is the higher the investment, the greater the rate of recovery $\gamma=\gamma(E)$. Increasing the recovery rate is assumed to be associated with a decrease in the host's rate of reproduction $b=b(E)$. Hence $\gamma(E)$ and $b(E)$ describe the trade-off between defence and reproduction.

A host possessing the ability to recover will alternate between the susceptible and the infected states (see figure 1); from the susceptible to the infected state with rate h and back again with rate $\gamma(E)$. The hosts have a constant probability per unit time μ to die of causes unrelated to disease, and, when infected, to die with increased mortality rate $\mu+\alpha$. The force of infection depends on the resident strategy, $h=h(E^*)$, but I will begin by assuming it is a given constant. The host's expected longevity then is the sum of the expected cumulative time spent in both states.

Let $p_S(a)$ denote the probability of finding the host of age a alive and susceptible, and $p_I(a)$ denote its probability of being alive but infected. Then we can write

$$\frac{\mathrm{d}p_S}{\mathrm{d}a} = -(\mu+h)p_S + \gamma p_I$$

$$\frac{\mathrm{d}p_I}{\mathrm{d}a} = hp_S - (\mu+\alpha+\gamma)p_I \qquad (1)$$

(if there is no vertical transmission, $p_S(0)=1$ and $p_I(0)=0$). Solution of this set of equations (see Appendix 1) allows the host's expected longevity, L_h, as a function of its defence strategy E, given the force of infection h, to be calculated:

$$L_h(E) = \frac{\mu+\alpha+\gamma(E)+h}{(\mu+\alpha+\gamma(E))\mu + h(\mu+\alpha)}. \qquad (2)$$

Expected longevity is minimal (approximately $1/(\mu+\alpha)$ when h is large) for $\gamma(E)=0$, and increases to $1/\mu$ (life expectancy in a disease-free world) as $\gamma(E)$ increases.

Assuming that the rate of reproduction $b(E)$ is independent of whether a host is healthy or not (the model can easily be modified to include such a dependence, see Appendix 1), the host's expected lifetime reproductive success is

$$W_h(E) = b(E)L_h(E), \qquad (3)$$

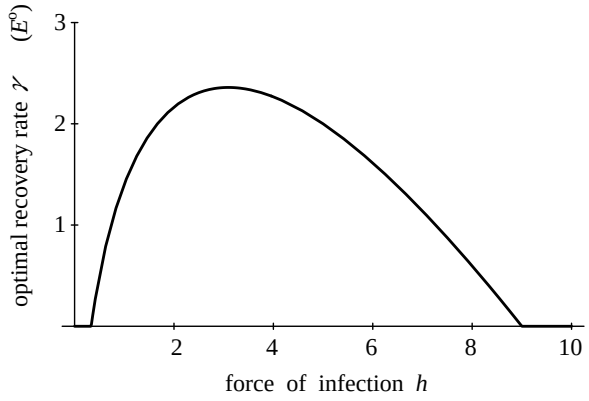

Figure 2. Optimal investment in recovery ability $\gamma(E)$, as a function of the force of infection h. (Parameter values: $\mu=1$, $\alpha=2$, $c=0.05$.)

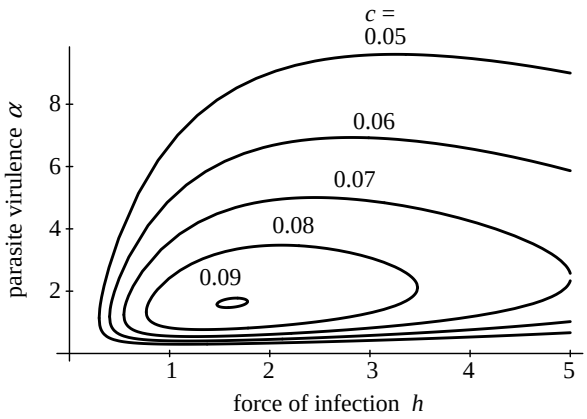

Figure 3. Conditions for the evolution of recovery ability, for various levels of c, the cost of maintaining an immune system. Outside the enclosed region, it does not pay to allocate resources to recovery ability. (Other parameters: $\mu=1$.)

and thus an optimal defence strategy E (if it is not a boundary optimum, with $\gamma(E)=0$) should satisfy

$$W'_{\mathrm{h}}(E^{\mathrm{o}}) = b'(E^{\mathrm{o}})L_{\mathrm{h}}(E^{\mathrm{o}}) + b(E^{\mathrm{o}})L'_{\mathrm{h}}(E^{\mathrm{o}}) = 0, \tag{4}$$

the prime denoting the derivative with respect to E. (If a solution with $\gamma(E)>0$ exists, it is most likely to be a maximum, because $b(E)$ is assumed to be a decreasing function and $L_{\mathrm{h}}(E)$ is an increasing but satiating function. This does not preclude multiple local optima, but in what follows I will assume that optima are always unique. Assuming $\gamma(E)$ increases monotonically, the function $b(E)$ therefore should not 'wobble' too much.) Some algebra leads to the condition

$$\frac{b'(E^{\mathrm{o}})}{b(E^{\mathrm{o}})}$$

$$= -\frac{\alpha h}{(\mu+\alpha+\gamma(E^{\mathrm{o}}))\mu + h(\mu+\alpha)} \frac{\gamma'(E^{\mathrm{o}})}{\mu+\alpha+\gamma(E^{\mathrm{o}})+h} \tag{5}$$

for an optimum $\gamma'(E^{\mathrm{o}})>0$.

Unfortunately, here the simple expressions end, and there seems to be no easy graphical solution either. Choosing the rather arbitrary strategy set $\gamma(E)=E$ and $b(E)=b_{\mathrm{m}}e^{\mathrm{o}}-cE$; (which is a convenient choice because $b'(E)/b(E)=-c$, and here c expresses the cost of increasing recovery rate so that a unit increase in recovery rate decreases the logarithm of the rate of reproduction by c units) one ends up with a quadratic expression in E^{o}, a typical solution of which is shown in figure 2. If the force of infection is less than a critical value, it does not pay to invest in any recovery ability at all. When the force of infection increases beyond this threshold, it pays to allocate more and more into recovery ability, until a point is reached where the optimal recovery ability starts to decrease, eventually reaching zero again. This is because when the force of infection is high, there is no point in trying to recover as a new infection will occur too quickly. Making the best of a bad job then means allocating all resources to reproduction. This pattern is not very sensitive to the details of the constraints (a similar give-up-hope effect is discussed by Abrams (1990), for optimal anti-predator traits in prey.)

Would there be lifelong immunity (SIR; susceptible–infected–recovered), then the optimal allocation to the immune system strongly depends on variation among the parasites. If there is only a single strain of parasites, optimal allocation *always* increases with the force of infection. However, this increase slows down when the number of parasite strains increases (assuming no cross-immunity among strains), and eventually, if the number of strains becomes very large (so that a particular host is unlikely to be infected with the same strain twice) the results converge to those described here, where optimal allocation drops. The relation between immunity and parasite variability will be discussed elsewhere in more detail (M. van Baalen, unpublished data).

Figure 3 shows that it only pays to invest in an immune system for intermediate values of parasite virulence (α) and force of infection (h). It also shows that the more expensive the immune system is (c is large) the smaller is the region where it is profitable. As can be inferred from figure 3, the effect of increasing virulence, α, is qualitatively similar to that of increasing the force of infection. This counterintuitive result is explained as follows: if the parasites are too virulent, it is simply too costly for a host to maintain an immune system that can eliminate the parasite before it is killed itself. This result is a consequence of the assumption that the immune system does not affect virulence (disease-induced mortality!). It is likely that this the conclusion will be different if one assumes a relationship between the immune system and parasite virulence (i.e. when the host does not try to eliminate the parasite, but merely to lessen its effects).

3. ESS RECOVERY RATES

The force of infection is not an arbitrary constant, but varies with the number of infected hosts. This causes a feedback in the evolution of resistance, because the number of infected hosts will depend on the defence strategies adopted by all hosts in the population. Consider the following simple model for the dynamics of the resident

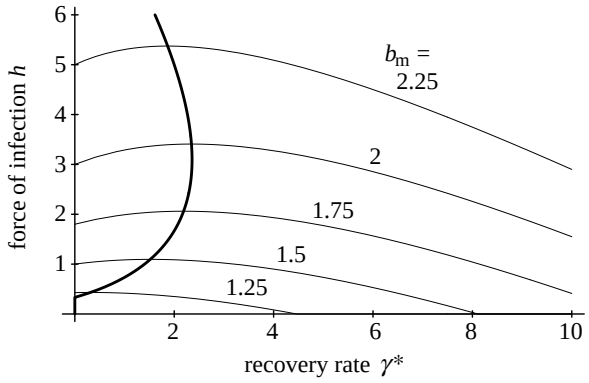

Figure 4. The equilibrium force of infection $\bar{h}$ as a function of the resident host's defence strategy γ^* for five values of maximum rate of reproduction b_m (thin lines). Superposed is the curve (thick line) that relates the equilibrium force of infection to the optimum defence strategy for a rare mutant (this is, in effect, figure 2*a* with the axes interchanged). The ESS level of host defence (for a given value of b_m) is given by the intersection of the two curves. (Other parameters: $\mu=1$, $c=0.05$, $\alpha=2$.)

host (that has adopted the strategy E^*, so that $b^*=b(E^*)$ and $\gamma^*=\gamma(E^*)$) and the parasite:

$$\frac{dx}{dt} = b^*(x+y) - \mu x - \beta xy + \gamma^* y$$

$$\frac{dy}{dt} = \beta xy - (\mu+\alpha)y - \gamma^* y. \qquad (6)$$

Here, x denotes the density of susceptible hosts and y the density of infected hosts. To arrive at this model, two additional assumptions are necessary. First, no other density-dependent processes affect host reproduction, so that the host population is regulated entirely by the disease. Secondly, the rate of infection is determined by mass-action, so that the force of infection experienced by each susceptible host is directly proportional to the density of infected hosts, i.e.

$$h = \beta y.$$

A positive equilibrium, if it exists (if $\mu+\alpha>b^*>\mu$) is always ecologically stable, which allows the equilibrium force of infection to be expressed in terms of the resident defence strategy E^*, calculated from the ecological equilibrium:

$$\bar{h} = \frac{(b^*-\mu)(\mu+\alpha+\gamma^*)}{\mu+\alpha-b^*} \qquad (7)$$

Evaluating this expression shows that the resident population of hosts can reduce the incidence of infection to arbitrarily low numbers (or even cause extinction of the parasites), if only they invest enough in parasite resistance (see figure 4).

The question now is whether such a high level of defence is evolutionarily stable and, if not, which lower level is then the ESS. To answer this question, we have to work out the invasion dynamics of a rare mutant that is introduced into the resident system. It can be shown that if such a mutant has a positive invasion exponent, its lifetime reproductive success (as defined by equation (3)) is greater than one. Therefore, the results from the previous section can be direcly combined with the dynamical model. (For a more in-depth discussion of how to relate invasion exponents to lifetime reproductive success, see Mylius & Diekmann (1995).)

Thus, since an ESS E^* is the optimal strategy in a system dominated by itself, it is given by the intersection of the curves of the optimal investment and the resident force of infection (figure 4). From this intersection, it becomes clear that the ESS is to allocate only a limited amount of resources to defence.

Figure 4 shows that the evolution of defence strategies will lead to a *maximal* force of infection. This may seem a counterintuitive result, but it is in fact an instance of the 'pessimization principle' (Mylius & Diekmann 1995): only those individuals that can maintain themselves in the worst possible world will remain. The defence ESS is that which forces its competitors out by maximizing the force of infection while just maintaining itself.

4. PARASITE COEVOLUTION

Things become even more interesting if the parasites coevolve with the hosts. Then, virulence α and transmission efficiency β will become evolutionary variables as well, and changes in these will affect the optimum defence strategy as well as the population dynamics.

The following model for the evolution of parasite virulence is an adaptation from the model of Van Baalen & Sabelis (1995). Assume that the trade-off between transmissibility (β) and virulence (α) is given by

$$\beta(\alpha) = \frac{\beta_m \alpha}{\alpha+\delta}, \qquad (8)$$

which implies that parasites can always increase transmissibility, but at an accelerating cost in terms of disease-induced mortality rate. Assuming that multiple infections do not occur, the fitness of a mutant parasite is given by

$$R_0(\alpha,\alpha^*,\gamma^*) = \frac{\beta(\alpha)\bar{x}}{\mu+\alpha+\gamma^*}, \qquad (9)$$

where the equilibrium density of susceptible hosts $\bar{x}$ depends on the traits of the resident populations of hosts and parasites, but not on those of the mutant parasites. The equation expressing the mutant's R_0 can thus be written as the product of the density of susceptible hosts $\bar{x}$ and the per-host transmission factor $B(\alpha, \gamma^*)$, where

$$B(\alpha,\gamma^*) = \frac{\beta(\alpha)}{\mu+\alpha+\gamma^*}, \qquad (10)$$

which itself is the product of the transmission rate and the expected duration of the infectious period (this is a function of the mutant parasite's virulence, the resident defence strategy, but not the resident parasite's virulence as multiple infections are not allowed).

A mutant parasite's fitness is maximal if its virulence is

$$\alpha_{opt}(\gamma^*) = \sqrt{(\mu+\gamma^*)\delta}. \qquad (11)$$

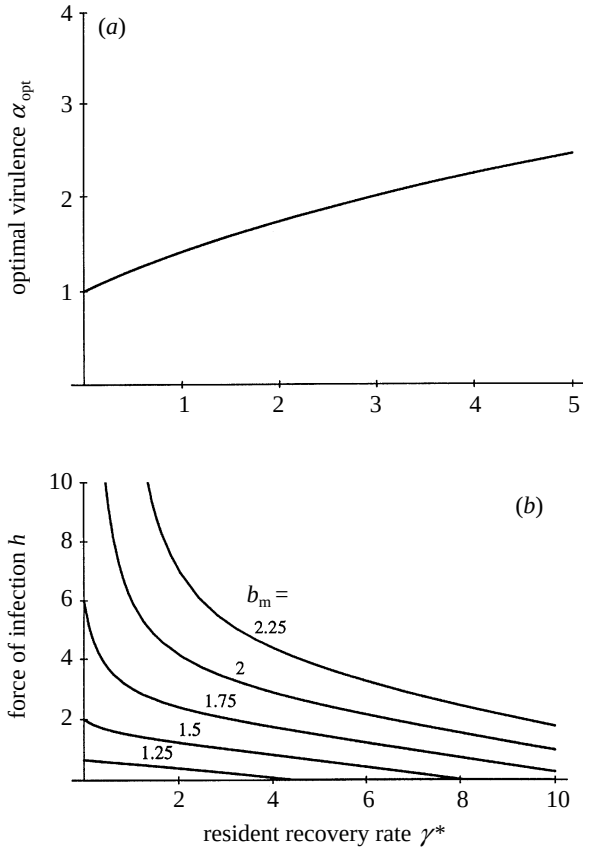

Figure 5. The relationship between the resident defence strategy γ^* and optimal virulence α_{opt} (*a*), and the resulting equilibrium force of infection $\bar{h}$ for a number of values of the host's maximum rate of reproduction b_m (*b*). Note that if the hosts reduce investment in recovery ability, the parasites may reduce their virulence to such an extent that they actually fail to control the host population, and the force of equilibrium goes to infinity with the host population.

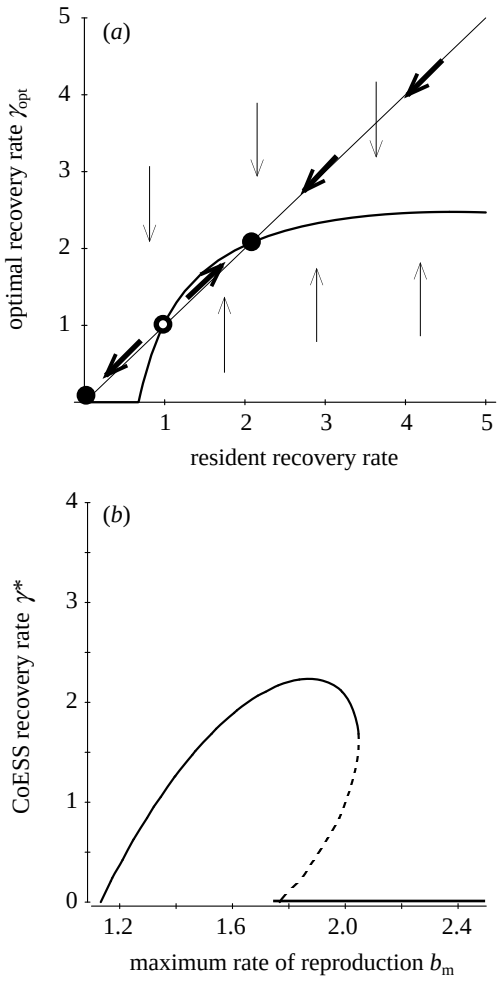

Figure 6. Optimal defence strategies γ as a function of resident defence strategy γ^*, given that the parasites coevolve. (*a*) Selection phase plot showing multiple CoESSs (parameters $b_m=2$, $\mu=1$, $c=0.05$, $\delta=1$, $\beta_m=10$). The thin arrows indicate when mutant fitness increases, the change in resident strategy that results when mutants invade is indicated by the thick arrows. ESSs are indicated by filled symbols, the unstable evolutionary equilibrium by an open symbol. (*b*) CoESS recovery rates as a function of the maximum rate of reproduction b_m. The drawn curves correspond to CoESSs (the filled symbols in figure 6*a*), the dashed curve corresponds to the unstable evolutionary equilibrium (the open symbol in figure 6*a*). (The other parameters are the same as those in figure 6*a*.)

(For a derivation, see Appendix 2.) According to this expression, the faster hosts are able to expel the parasite and recover, and the greater virulence is favoured. This makes intuitive sense, because recovery robs the parasite of the benefit associated with reduced virulence, namely prolonged infectiousness. A more efficient immune system therefore compels the parasite to switch to increased transmissibility, and this amounts to increased virulence (figure 5*a*).

When the parasite coevolves with the host, both the shape of the relationships between the force of infection and optimal investment in recovery ability, and between resident recovery ability and the force of infection change. Figure 5*b* shows the equilibrium force of infection for a range of parameter values.

The most pronounced feature is that the force of infection may rise sharply when recovery ability decreases. Then, the parasites' evolutionary response is to decrease their virulence, and if virulence decreases, so does the parasites' ability to control the host population. Since there are no other density-dependent factors, the host population then grows to infinity, and with the host population, the parasite population too. This is indicated by the force of infection growing to infinity in figure 5*b*. Later, I consider a model that includes density-dependent growth, so that there is a maximum host density, but first I will characterize the ESS for the simple model.

Now we know how a resident defence strategy γ^* leads to a level of virulence α^* and how these together determine the equilibrium force of infection, $\bar{h}$, we can work out the optimal defence strategy for a rare mutant host.

A marked consequence of parasite coevolution is that the curve of optimal recovery rate γ may intersect the $\gamma=\gamma^*$ line (characterizing evolutionary equilibria) at more than one point (see figure 6). One of these coevolutionary equilibria is unstable: there may be evolutionary bistability. One of the coevolutionarily stable strategy pairs (CoESSs) is characterized by heavily defended hosts and virulent parasites, the other by undefended hosts and relatively (but not completely!) avirulent parasites. In the latter case, the model becomes unrealistic as the parasites

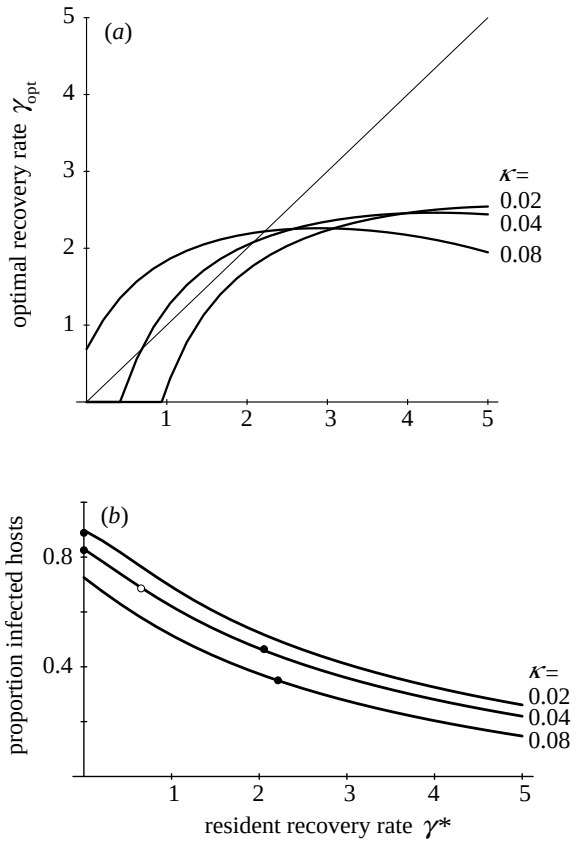

Figure 7. The effect of additional density dependence. The intensity of intraspecific competition among the hosts is measured by κ. (*a*) Optimal recovery rate versus resident recovery rate. (*b*) Effect on proportion of infected hosts. The position of the CoESSs (filled symbols) and an unstable coevolutionary equilibrium (open symbol), derived from figure 7, is indicated. Maximum rate of reproduction $b_m=2.5$, other parameters are the same as those in figure 6.

may no longer regulate the host population, which then grows exponentially. (If the curves do not intersect, only the undefended–avirulent combination is evolutionarily stable.)

However, even if this example is unrealistic, it serves as a warning: control of the host population by parasites may not be the inevitable outcome in a given setting. However, a sufficiently large disturbance may escalate an arms race, which eventually settles at the other CoESS combination where the host population is regulated by the parasite.

(a) *Additional factors regulating the host population*

In the simple model, the ESS combination of low defence and low virulence is characterized by exponential growth of the host population, a situation that cannot persist indefinitely. To assess whether this ESS combination can still exist when the hosts are regulated by other density-dependent factors, consider the following model. On the individual level all is the same, except that the hosts' rate of reproduction is uniformly reduced (as a consequence of competition for resources or space) by a density-dependent factor $1-\kappa(x+y)$, where the intensity of competition is measured by κ. This gives the following resident host–parasite system:

$$\frac{dx}{dt} = b^*(x+y)(1-\kappa(x+y)) - \mu x - \beta^* xy + \gamma^* y$$

$$\frac{dy}{dt} + \beta^* xy - (\mu+\alpha^*)y - \gamma^* y \qquad (12)$$

Since this density-dependent factor applies uniformly to all hosts in the population, its evolutionary effect is equivalent to a decrease in b_m. As b_m does not figure in the selection differential, the only change of introducing this form of density dependence is through its effect on dynamics. In contrast, if density dependence was to increase the mortality rate, the selection differential would change, as the optimum depends critically on μ.

Now there are two non-trivial population dynamical equilibria. First, there is the disease-free equilibrium $\bar{x}=K^*, \bar{y}=0$ with K^* given by

$$K^* = \frac{1}{\kappa}\left(1-\frac{\mu}{b^*}\right) \qquad (13)$$

(Note that because K^* depends on b^*, K^* depends on the resident hosts' defence strategy; well-defended hosts reproduce less quickly and will therefore settle at a lower equilibrium density in the absence of disease.) This equilibrium cannot be upset by any parasite if $R_0(\alpha, \alpha^*, \gamma^*)<1$, that is, if

$$\frac{\beta(\alpha)K^*}{\mu+\alpha+\gamma^*} < 1 \qquad (14)$$

for all values of α.

If parasites of type (α^*,β^*) can invade, there will be an endemic equilibrium, satisfying

$$\bar{x}+\bar{y} = \frac{1}{\kappa}\left(1-\frac{\mu+\alpha^*\dfrac{\bar{y}}{\bar{x}+\bar{y}}}{b^*}\right) \qquad (15)$$

which shows that $\bar{x}+\bar{y}<K^*$, i.e. the parasites depress the host population below their carrying capacity. The equilibrium density of susceptible hosts is the same as in the previous model as this follows from $dy/dt=0$, which is not affected by the introduction of density-dependent host reproduction.

One effect of such a density-dependent reduction in the rate of reproduction is that the host population can, in principle, force the parasites into extinction without going extinct itself (see also Hochberg 1991). Without density dependence, the parasites will be absent (that is, the force of infection is zero) only if $b^*=\mu$, which implies that the hosts themselves are at their invasion boundary.

The other effect is that if the host population escapes parasite regulation, it does not grow to infinity, but will settle at a high density close to its carrying capacity. The equilibrium force of infection, and the resulting optimum recovery rate, as a function of resident recovery rate (while parasites are at their ESS) is shown in figure 7*a*. Figure 7*b* suggests that such an escalated arms race only occurs when the parasites have a potentially less important role in host population regulation (i.e. when intraspecific competition is intense, κ is high)! This is further illustrated in figure 8, in which the CoESS defence strategy is shown

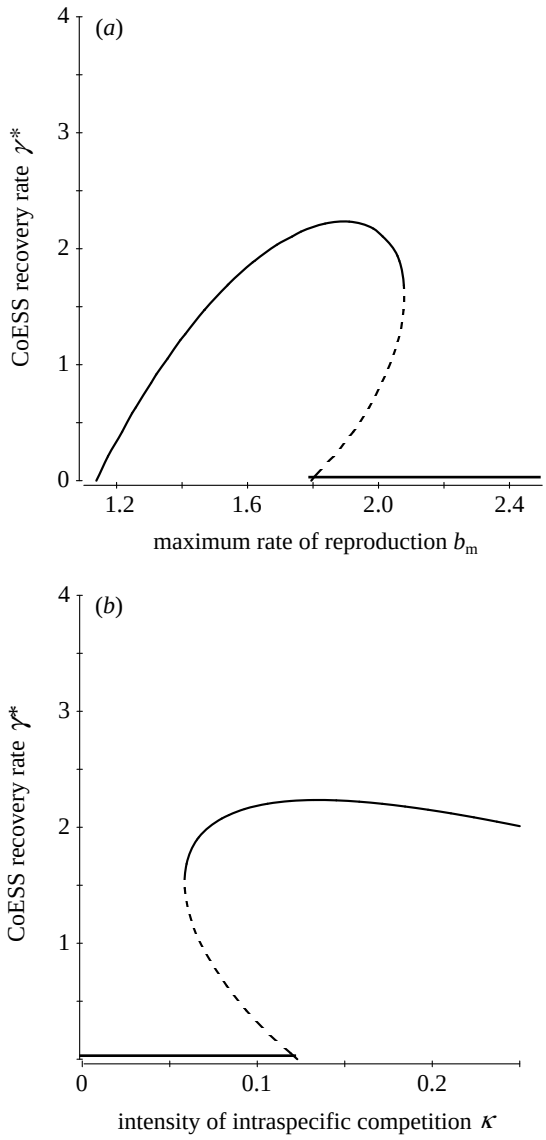

Figure 8. CoESS recovery rate as a function of population dynamical parameters; (*a*) host maximum rate of reproduction (other parameters: $\mu=1$, $c=0.1$, $\beta_m=10$, $\delta=1$, $\kappa=0.01$) and (*b*) intensity of intraspecific competition in the host population. (Other parameters: $\mu=1$, $c=0.1$, $\beta_m=10$, $\delta=1$, $b_m=2.25$). The drawn lines indicate stable CoESS, the dotted lines indicate unstable evolutionary equilibria.

for a range of values of maximum birth rate b_m and a range of values of the intensity of intraspecific competition κ.

5. DISCUSSION

One of the most striking conclusions of this analysis is that, depending on the parameters and initial conditions, coevolution of hosts and parasites may have contingent outcomes: either the hosts invest little in defence and the parasites are common, but avirulent, or the hosts are heavily defended against rare, but virulent parasites. This bistability arises when even a weak immune system is so costly that the hosts are better off without one as long as the parasites are not too virulent. Of course, if the parasites are very virulent, the hosts have no choice but to defend themselves.

A consequence of such evolutionary bistability is that it is possible that a disturbance may trigger an escalating arms race (van Valen 1973; Dawkins & Krebs 1979). The model studied here leads to the somewhat counterintuitive conclusion that such bistability may only occur under (relatively) unfavourable conditions for host population growth (see figure 8). However, it is only under these conditions that the parasites are able to regulate the host population, and therefore significantly affect host fitness. If conditions are favourable enough, competition among the hosts is not mediated through parasites but through competition for resources, which essentially decouples the mutual selective pressures of hosts and parasites.

(a) *Evolution and the force of infection*

If multiple infection occurs, it should favour increased virulence, because an avirulent parasite loses the benefit of prolonged infectiousness when, later on, the host is also infected by more virulent parasites (Eshel 1977; Bremermann & Pickering 1983). As with the evolution of defence strategies, population dynamics mediates a feedback: when virulence decreases, the force of infection is likely to rise and, with it, the frequency of multiple infection (van Baalen & Sabelis 1995). The multiple-infection model thus predicts a positive correlation between the force of infection and virulence. Interestingly, this pattern is just opposite to the one predicted in this paper. Such a negative correlation seems to be the case for at least the example of *Neisseria meningitidis*, discussed below.

Firm conclusions can obviously be based only on models for host–parasite coevolution that include multiple infection. Such models are likely to be rather complex to analyse, even if they simplify within-host dynamics and the action of the immune system. However, given that under conditions of a high force of infection more virulent parasites are favoured, incorporating multiple infection will lead to a less pronounced relationship between resident host recovery rate and virulence (i.e. the curve in figure 5*a* will be less steep), and therefore the intensity of the feedback in the evolution of recovery ability is reduced. Whether or not this is sufficient to exclude the possibility of multiple coevolutionary equilibria is a case that remains to be investigated.

(b) *Possible example:* Neisseria meningitidis

Many parasites that are normally avirulent have virulent strains, for example, the species/strains of the bacterium *N. meningitidis* (Maiden 1993). Serotypes *B* and *C* are very common. Molecular genetics studies of these serotypes have shown a high frequency of genetic exchange (indicated by the mosaic structure of their genome). This would imply that multiple infection is frequent, and therefore the force of infection should be relatively high. In contrast, serotype *A* of *N. meningitidis* is rare and has a clonal population structure (characterized by very little crossing-over). If virulence were wholly determined by within-host competition, we would expect serotypes *B* and *C* to be the virulent types (multiple infection favours virulence) and serotype *A* to be the avirulent one (single infection allows prudent host exploitation) (Frank 1992; Nowak & May 1994; van Baalen & Sabelis 1995). In fact, the situation is the reverse: serotype *A* is the virulent type, whereas serotypes *B* and *C* are usually

asymptomatic. This situation is more in line with the predictions from host–parasite coevolution as studied in the present paper: strains that are not fought by the immune system are common, whereas strains that are fought are rare and virulent.

Frank (1996) explains the pattern of bacterial meningitis as a consequence of the occasional occurrence of 'short-sighted' mutants. However, it may also be that the different serotypes represent different endpoints of the coevolutionary process. To what extent different strains can be at the different endpoints *simultaneously* was not studied in the present paper. To investigate this problem more detailed models of parasite–immune system interactions must be studied. It also may prove important to consider time-scales more carefully. In the present paper, changes in defence strategies can only occur over evolutionary time-scales. Immune system processes occur at the physiological time-scale, and analysis of idiotype network models has shown that the immune system itself may be bistable, having both passive and active states (Takumi & de Boer 1996). Whether a sufficient proportion of hosts having their immune system in the 'active' state can also trigger an arms race seems to be an open question.

(c) *Wild speculation*

A simple model, like the one that has been studied here, has certain disadvantages: there will be no example from reality that exactly satisfies its assumptions. However, its very simplicity allows interpretations and generalizations outside the realm for which it was originally intended. For example, within the framework of this paper, there is no structural difference between a physiological immune system and an artificial one, consisting of medical doctors, antibiotics (recovery) and health insurance (cost). The most simple model to study the evolutionary consequences of a public health system would be the very model that was analysed in this article.

This analogy serves a warning: it is at least conceivable that public health systems may trigger arms races between the parasites and (in this case) the public health system. The model is too simple to decide whether this is actually the case, but it leaves one wondering whether public health systems may cause such bistability. If so, it poses some awkward questions relating to public health policies: striving to help the individual (being cured from an infectious disease) may have detrimental consequences for the community.

D. Ebert, W. J. Edmunds, M. E. Hochberg, C. J. Nagelkerke and M. W. Sabelis are thanked for their valuable comments on previous drafts of this paper. This research was supported by the Applied Nonlinear Mathematics Initiative of the UK Engineering and Physical Science Research Council (EPSRC) and by the UK Natural Environment Research Council (NERC).

APPENDIX 1. LIFETIME FITNESS

If the probabilities of being in the various states are ordered in a vector $\boldsymbol{p}(a)$, we can write

$$\frac{\mathrm{d}\boldsymbol{p}}{\mathrm{d}a} = \mathbf{A}\boldsymbol{p}. \tag{A1}$$

In the two-state *SIS* model,

$$\boldsymbol{p} = \begin{pmatrix} p_\mathrm{S} \\ p_\mathrm{I} \end{pmatrix}. \tag{A2}$$

and

$$\mathbf{A} = \begin{pmatrix} -\mu - h & \gamma \\ h & -\mu - \alpha - \gamma \end{pmatrix} \tag{A3}$$

but the method works for any number of states n. The differential equation being linear, there will be an explicit solution $\boldsymbol{p}(a)$, giving the expected probability that a host is any of states p_i at time a after birth ($a=0$). If the host's rate of reproduction depends on the state it is in (i.e. $b = b_\mathrm{i}$), its expected lifetime reproductive success is then

$$W = \int_0^\infty p_1(a) b_1 da + \ \ldots \ + \int_0^\infty p_\mathrm{n}(a) b_\mathrm{n} da \tag{A4}$$

or

$$W = \int_0^\infty \boldsymbol{p}(a) da . \boldsymbol{r} \tag{A5}$$

It is an elementary result in Markov chain theory that

$$\int_0^\infty \boldsymbol{p}(a) da = -\mathbf{A}^{-1}\boldsymbol{p}(0)$$

which gives the expected time spent in each of the states. (They therefore sum to the expected longevity of the host.)

For the *SIS* model, $\boldsymbol{p}(0) = (1, 0)$, as I assume that the host is born uninfected (no vertical transmission). This leads to

$$\int_0^\infty \boldsymbol{p}(a) da$$

$$= \frac{-1}{(\mu + h)(\mu + \alpha + \gamma) - h\gamma} \begin{pmatrix} -\mu - \alpha - \gamma & -\gamma \\ -h & -\mu - h \end{pmatrix} \begin{pmatrix} 1 \\ 0 \end{pmatrix}$$

$$= \frac{1}{(\mu + h)(\mu + \alpha + \gamma) - h\gamma} \begin{pmatrix} \mu + \alpha + \gamma \\ h \end{pmatrix} \tag{A6}$$

and hence

$$W = \frac{(\mu + \alpha + \gamma) b_\mathrm{S} + h b_\mathrm{I}}{(\mu + h)(\mu + \alpha + \gamma) - h\gamma} \tag{A7}$$

If the rates of reproduction of susceptible and infected individuals are the same, equation (3) is obtained.

APPENDIX 2. OPTIMAL VIRULENCE

Given the recovery rate γ^* of the resident host population, and given that multiple infections do not occur, parasite fitness is maximal if the per host transmission factor

$$B(\alpha, \gamma^*) = \frac{\beta(\alpha)}{\mu + \alpha + \gamma^*} \tag{B1}$$

is maximized. Optimal virulence α_opt should thus satisfy

$$\frac{\mathrm{d}B(\alpha, \gamma^*)}{\mathrm{d}\alpha} = 0 \tag{B2}$$

or

$$\frac{\mathrm{d}(\alpha)}{\mathrm{d}\alpha}(\mu+\alpha+\gamma^*)=\beta(\alpha) \tag{B3}$$

for $\alpha=\alpha_{\mathrm{opt}}$. Given the constraint

$$\beta(\alpha)=\frac{\beta_{\mathrm{m}}\alpha}{\alpha+\delta} \tag{B4}$$

this results in

$$\frac{\beta_{\mathrm{m}}\delta}{(\alpha+\delta)^2}(\mu+\alpha+\gamma^*)=\frac{\beta_{\mathrm{m}}\alpha}{\alpha+\delta} \tag{B5}$$

which yields, after some algebra,

$$\alpha^2=(\mu+\gamma^*)\delta, \tag{B6}$$

the positive solution of which is the expression for optimal α employed in the text.

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As this paper exceeds the maximum length normally permitted, the author has agreed to contribute towards production costs.