

Virulence and age at reproduction: new insights into host–parasite coevolution

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Abstract

We consider an explicit mutation–selection process to investigate the dynamics underlying the coevolution of parasite's virulence and host's prereproductive life span in a system with discrete generations. Conforming with earlier models, our model predicts that virulence generally increases with natural mortality of the host, and that a moderate increase in virulence selects for lower ages at reproduction. However, the epidemiological feedback in our model also gives rise to unusual and unexpected patterns. In particular, if virulence is sufficiently high the model can lead to a bifurcation pattern, where two strategies coexist in the host population. The first is to develop rapidly to reproduce before being infected. Individuals following this strategy suffer, however, from reduced fecundity. The second strategy is to develop much more slowly. Because of the high virulence, the effective period of transmission is short, so that a few slowly developing individuals escape infection. These individuals, although choosing a risky strategy, benefit from high fecundity.

Introduction

The ubiquity of parasites means that their hosts are under considerable selection pressure to reduce negative impacts on reproductive success. Given the importance of life history traits for individual fitness, it is not surprising that a host should use these traits to increase its tolerance or resistance. Indeed, host–parasite associations should be particularly subject to the evolution of a central life history parameter – host reproductive effort – because parasites (and their negative effects) are expected to accumulate over an individual host's life-time (Hochberg *et al.*, 1992).

One of the earliest demonstrations of the importance of life history strategies in defence against a parasite involves the marine snail *Biomphalaria glabrata*, which lays its eggs earlier when exposed to a trematode parasite (Minchella & LoVerde, 1981). A growing number of

empirical results have since reported similar adaptations in diverse species of hosts (reviews by Minchella, 1985; Michalakis & Hochberg, 1994; Koella *et al.*, 1998). Theoretical models, in contrast, have only recently started to make specific predictions about the evolution of life history traits as a response to parasitism. Hochberg *et al.* (1992) showed that the introduction of a virulent parasite into a population of hosts would favour more rapid development and earlier reproduction. This prediction has found support by an experimental study on the yellow fever mosquito *Aedes aegypti* infected by the microsporidian parasite *Vavraia culicis* (Agnew *et al.*, 1999). A similar approach formalized the evolution of a host's reproductive effort when submitted to different sorts of parasites (Forbes, 1993, 1996; Perrin & Christe, 1996).

These theoretical approaches are similar in that they consider the selection pressure due to a parasite within a single cohort of hosts, that is, they neglect the population dynamics of the host. The dynamic process, however, has recently been shown to produce a demographic feedback that can lead to qualitatively different predictions concerning the evolution of host life histories.

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Kirchner & Roy (1999), for example, considered the evolution of the host's life span by tracking the frequencies of two host genotypes – a longer- vs. a shorter-lived one – that compete with each other for resources and are both infected by a single strain of parasite. The short-term prediction (not including the dynamic feedback) is that the shorter-lived host should come to dominate the system, as it is less strongly affected by the parasite than the longer-lived one. However, because of its demographic advantage, it is the longer-lived host that eventually eliminates its competitor. Demographic feedback has also shown to be important in determining the evolutionarily stable age at reproduction in response to parasitism (Koella & Restif, 2001). The feedback, resulting from incorporation of explicit epidemiological and evolutionary processes, induces a nonmonotonic response of the host to an increase in virulence. Thus, increasing virulence often decreases the optimal age at reproduction, as predicted by the static model (Hochberg *et al.*, 1992). When virulence is sufficiently high, however, many hosts die before they transmit the parasite. Transmission then becomes ineffective and the selection pressure on the host's life history diminishes. Therefore, as virulence increases further, age at reproduction is selected to increase towards the parasite-free optimal value. Gandon (2000) has shown how epidemiological and demographic feedbacks lead to similar nonlinearities in a model describing the effect of parasites on host reproductive effort.

Whereas these results demonstrate the importance of demographic feedback in dynamic evolutionary systems, the generality of the conclusions has not been assessed. In particular, these studies find coevolutionarily stable strategies based on defined fitness functions, and thus neglect the genetic constraints in the system. In addition they do not consider the possibility of polymorphic strategies. This is an important omission because such polymorphic strategies and associated bifurcations are often observed in complex adaptive systems (Doebeli & Ruxton, 1997; Doebeli & Dieckmann, 2000), including those describing host–parasite interactions (Koella & Doebeli, 1999).

We address the question of coevolution of a host's life history and its parasite's virulence with a model based on explicit mutation–selection processes. It keeps track of the population and evolutionary dynamics of the system. We aim at assessing the generality of previous studies (such as the nonmonotonic response of hosts to increasing virulence) and investigating any emergent phenomena, using more realistic coevolutionary models.

The model

Verbal description

We consider an asexual host species in a seasonal environment with discrete generations. Modelling this

accurately requires that we explicitly consider the hosts' life cycle, epidemiological processes and evolutionary forces.

The semelparous hosts' life cycle comprises two successive stages: egg and growth (Fig. 1a). The population is divided into strains i according to the duration of the growth stage (i.e. age at reproduction) T_i , which is genetically determined. Eggs hatch as a new season begins, but we assume that the total density of newborns cannot exceed the carrying capacity K of the environment. During the growth stage, a given fraction of hosts die at every time step. As a result, the total mortality of a strain increases with the duration T_i of this stage. At age T_i , all hosts of strain i reproduce and die. Fecundity (number of eggs laid per individual) increases with T_i (see eqns 4). The eggs then 'overwinter' before hatching at the beginning of the next growth season. In the following, we will refer to all the hosts who hatched at the beginning of a given season, whatever their genotype, as a cohort.

Parasites can infect hosts during the growth stage. We assume that (1) infected hosts suffer from additional mortality, or virulence, which depends on the parasite strain; (2) only uninfected hosts are susceptible to infection (eggs are physically protected, whereas infected individuals are 'immunized' against reinfection); (3) hosts cannot recover, so they remain infected until they die. Within this framework, we have modelled two alternative scenarios for transmission: by contact or via spores.

In the first scenario (Fig. 1b), parasites are transmitted horizontally by contact between infected and uninfected hosts. We assume that the 'density' of such contacts is given by the product of densities of both categories (Anderson & May, 1979). When hosts reproduce, parasites are transmitted vertically from infected parents to eggs. During the egg stage, parasites stop developing: neither can they contaminate other hosts (no transmission) nor do they harm their hosts (no virulence). Then a new epidemic starts next season when eggs hatch.

In the second scenario (Fig. 1c), we explicitly take into account densities of free infectious spores. Spores are continuously released in the environment by infected hosts during their growth stage. Uninfected hosts can be contaminated by contact with spores, whereby the rate of infection is proportional to the density of spores of every parasite strain. Spores disappear at a constant rate. When infected hosts reproduce, they cannot contaminate their eggs and parasites die with their hosts. Then at the beginning of the next season, all hosts are born uninfected and a new epidemic starts with the remaining spores.

Comparing these two scenarios will allow us to assess the effects of epidemiological assumptions, especially those concerning vertical transmission.

In our model, (co)evolution emerges from population dynamics. Strains of hosts and parasites, each defined by

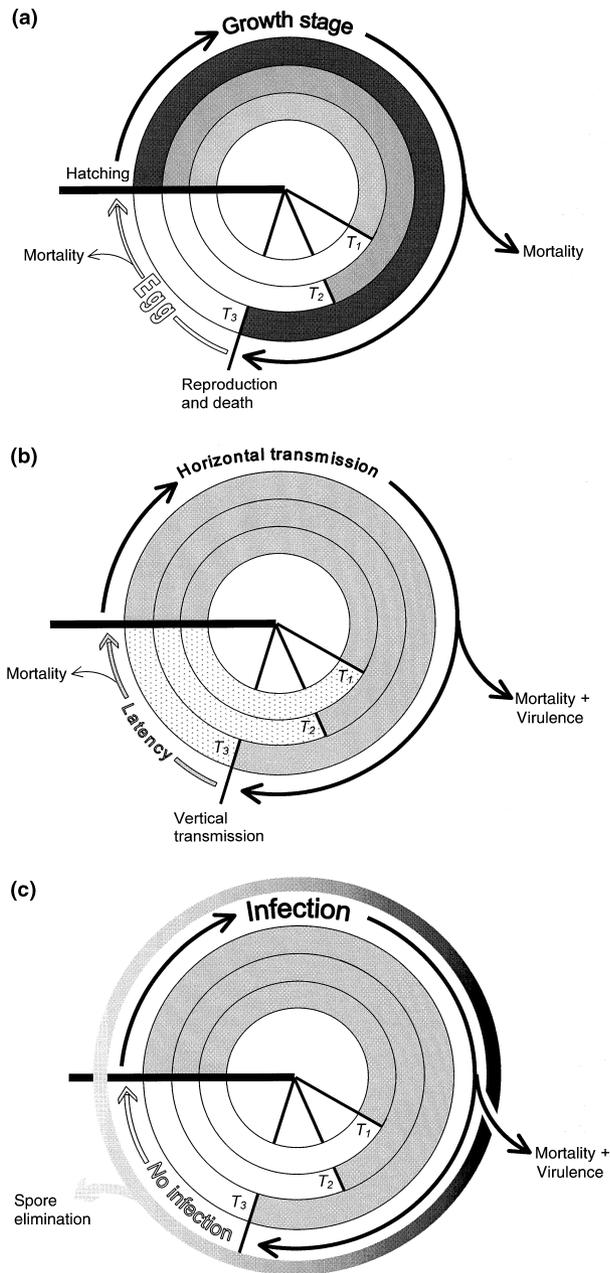


Fig. 1 Life cycle and epidemiology. The duration of a cycle is one season, starting from the left-hand bar and going round clockwise. On every diagram the three concentric circles represent three host strains with genotypes T_1 , T_2 and T_3 . Outward arrows show continuous processes of elimination of hosts (a), parasites (b and c) and spores (c). (a) Life cycle of hosts; arrows show the duration of growth and egg stages for the third strain. (b) First epidemiological scenario, showing horizontal (grey arcs) and vertical transmission and the latent phase (spotted arcs) within host eggs (infected but not infectious). (c) Second epidemiological scenario, with spore density drawn on the outside ring: darker grey represents higher density. No infections occur during egg stage (blank inner arcs).

its genotype, compete for reproduction. We track their densities over time. Genotypes are reduced to one single trait: age at reproduction for hosts, virulence for parasites. As stated before, age at reproduction is positively related to host's fecundity and negatively related to survival. Similarly, apart from its direct effect, which is to kill the host with its parasites, virulence increases rates of parasite transmission or spore production. This amounts to considering virulence as a byproduct of parasite growth within its host. The positive relation between virulence and the rate of horizontal transmission has been widely discussed (Ebert, 1994; van Baalen & Sabelis, 1995; Lipsitch *et al.*, 1996; Hochberg, 1998; Mackinnon & Read, 1999; Davies *et al.*, 2001). We extended this relation to vertical transmission and to spore release, assuming that the three possible routes of infection all rely on the replication of a parasite within its host.

Therefore the evolution of both traits is driven by opposing selective pressures: hosts and parasites face a trade-off between survival and reproduction. To ensure that a dominant strain defines an evolutionary stable strategy (ESS), mutations occur every generation to challenge its selective value.

Mathematical description

More formally, we define n strains of hosts, whose ages at reproduction are denoted T_i ($1 \leq i \leq n$), and p strains of parasites, whose virulences are denoted α_j ($1 \leq j \leq p$). The host population is divided into groups indexed by (i, j) ($1 \leq i \leq n$, $0 \leq j \leq p$). Each group contains the hosts of a given strain i infected by parasite strain j ; groups $(i, 0)$ contain uninfected hosts. Θ is the duration of a season, so eggs of strain i wait for $(\Theta - T_i)$ time steps before hatching. In order to conduct discrete-time simulations, we take the ages at reproduction T_i and the duration of a generation Θ to be integers. For a given cohort, $N_{i,j}(t)$ represents the expected density of group (i, j) at age t . Given the seasonal life cycle of hosts described earlier, t also represents time since the beginning of the current season, from 0 to Θ . Thus, in the second epidemiological scenario, spore density of strain j will be denoted $S_j(t)$ at 'seasonal' time t .

Given the densities at birth $N_{i,j}(0)$, the *intra cohort* dynamics of hosts (for $t = T_i$) are given by the following difference equations (obtained through linear approximation of classical population dynamics differential equations):

$$\begin{aligned} \text{Uninfected: } N_{i,0}(t+1) &= N_{i,0}(t) \left(1 - m - \sum_{j \geq 1} \lambda_j \right) \\ \text{Infected } (1 \leq j \leq p): N_{i,j}(t+1) &= N_{i,j}(t) (1 - m - \alpha_j) \\ &\quad + \lambda_j N_{i,0}(t) \end{aligned} \quad (1)$$

where m is the prereproductive death rate and λ_j is the force of infection of parasite strain j , that is, the rate of infection among the susceptible population.

In the first epidemiological scenario, we follow classical assumptions about horizontal transmission (Anderson & May, 1979) by defining λ_j at every time step as:

$$\lambda_j = \beta_j \sum_{i \geq 1} J_i(t) N_{i,j}(t) \tag{2a}$$

where $J_i(t)$ is the step function that equals 1 if host group i is still in growth stage ($t \leq T_i$) and 0 otherwise, and β_j is the efficiency of horizontal transmission of strain j . As noted above, the rate of horizontal transmission is positively correlated with virulence according to the following equation (Nowak & May, 1994; van Baalen & Sabelis, 1995): $\beta_j = \beta_{\max} \alpha_j / (\alpha_j + \delta_h)$, where β_{\max} is the maximal asymptotic value of transmission rate and δ_h gives the virulence when transmission rate equals $\beta_{\max} / 2$.

In the second scenario, we define p additional dynamic variables $S_j(t)$ to track the densities of free spores in every parasite strain j . During growth stage, their dynamics are coupled to host densities $N_{i,j}(t)$ as follows:

$$\begin{aligned} \lambda_j &= \beta' S_j(t) & (2b) \\ S_j(t+1) &= S_j(t)(1 - \varepsilon) + \varphi_j \sum_{i \geq 1} J_i(t) N_{i,j}(t) & (3) \end{aligned}$$

where β' is the rate of infection by spores, ε is the elimination rate of spores (both independent of strain) and φ_j is the rate at which spores are released in the environment by infected hosts. We assume that the latter is an increasing function of virulence, following the same relation as β_j : $\varphi_j = \varphi_{\max} \alpha_j / (\alpha_j + \delta_s)$, where φ_{\max} and δ_s are defined analogously to β_{\max} and δ_h .

Thus, forces of infection λ_j are updated every time step to account for variations in densities of infectious hosts or spores. This generates the epidemiological feedback described earlier. One may note that, provided the dynamics of spores be much slower than that of hosts (condition 1), the second scenario can be reduced to the first. If condition 1 holds, we assume that $S_j(t+1) = S_j(t)$ in eqn 3, which can be rewritten as:

$$S_j(t) = \frac{\varphi_j}{\varepsilon} \sum_{i \geq 1} J_i(t) N_{i,j}(t) \tag{3'}$$

Replacing $S_j(t)$ by this expression in eqn (2b) leads to:

$$\lambda_j = \frac{\beta' \varphi_j}{\varepsilon} \sum_{i \geq 1} J_i(t) N_{i,j}(t) \tag{2b'}$$

which is the same expression as (2a), provided $(\beta' \varphi_j / \varepsilon) = \beta_j$ (condition 2). Thus, if conditions 1 and 2 hold, similar behaviours in the two scenarios are expected during growth stage.

Inter-cohort dynamics are divided in four successive steps:

Step 1: At the end of a generation (age $t = T_i$), every group (i, j) lays eggs with density $\tilde{N}_{i,j}$. Fecundity of host

strain i is proportional to size at maturity, which follows Bertalanffy's (1957) growth model so that fecundity is given by $[b_{\max}(1 - e^{-kT_i})]$.

In the first epidemiological scenario, hosts infected by parasite strain j contaminate a proportion γ_j of their eggs by vertical transmission. Thus, $(1 - \gamma_j)$ is a measure of recovery from parasitism from one generation to the next. The rate of vertical transmission γ_j is assumed to have a similar association with virulence as horizontal transmission: $\gamma_j = \gamma_{\max} \alpha_j / (\alpha_j + \delta_v)$ where γ_{\max} and δ_v are defined similarly to β_{\max} and δ_h . The densities of uninfected and infected newborns are:

$$\begin{aligned} \text{Uninfected:} \quad \tilde{N}_{i,0} &= [b_{\max}(1 - e^{-kT_i})] \\ & [N_{i,0}(T_i) + \sum_{j \geq 1} (1 - \gamma_j) N_{i,j}(T_i)] \\ \text{Infected:} \quad \tilde{N}_{i,j} &= [b_{\max}(1 - e^{-kT_i})] \gamma_j N_{i,j}(T_i); \quad j \geq 1 \end{aligned} \tag{4a}$$

In the second epidemiological scenario, there is no vertical transmission, so densities of eggs are given by eqns (4a) assuming all $\gamma_j = 0$:

$$\begin{aligned} \text{Uninfected:} \tilde{N}_{i,0} &= [b_{\max}(1 - e^{-kT_i})] \sum_{j \geq 0} N_{i,j}(T_i) \\ \text{Infected:} \tilde{N}_{i,j} &= 0 \quad \text{if } j \geq 1 \end{aligned} \tag{4b}$$

Step 2: Mutations occur among hosts and parasites at rates u and v , respectively. Thus a fraction u of eggs of group (i, j) mutate to group (h, j) , and a fraction v mutate to group (i, l) , where h and l are chosen at random among all possible strains. This mutation process maintains genetic diversity in the system and ensures the evolutionary stability of a host or parasite strain that dominates the system over thousands of generations.

Step 3: Until they hatch, eggs suffer a constant death rate M , so by the end of the season, egg densities $\tilde{N}_{i,j}$ are multiplied by $(1 - M)^T$. We assume that egg mortality M is much lower than prereproductive mortality m , because of physical protection.

Step 4: At the beginning of the next season, let $\hat{N}_{i,j}$ be the remaining densities of eggs after mutations and mortality. As eggs hatch, the densities $N_{i,j}(0)$ of newborns are given by:

$$N_{i,j}(0) = \min \left\{ \hat{N}_{i,j}; \hat{N}_{i,j} \frac{K}{\sum_{h,l} \hat{N}_{h,l}} \right\} \tag{5}$$

that is, if the total density of eggs exceeds carrying capacity K , all densities are evenly reduced to match environmental constraints. The ecological assumptions underlying this equation are simplistic. Our aim is to limit the density of births by means of carrying capacity, without altering competition between strains from one cohort to the next.

These four steps give the initial densities $N_{i,j}(0)$ for the new cohort of hosts, whose internal dynamics will follow eqns (1)–(3).

The model is conceptually simple but mathematically complex enough to preclude exhaustive exploration of parameter space. After exploratory analyses, we held some parameters constant in most simulations. Unless stated otherwise, the following values were used: $n = p = 40$; $\Theta = 200$; $K = 100$; $M = 10^{-4}$; $u = v = 10^{-5}$.

Other parameters such as m , k , β_{\max} , γ_{\max} , φ_{\max} , β' , $\delta_{h,i}$, $\delta_{v,i}$, δ_s and α_j were varied within the limits given by mathematical requirements. Equations (1)–(3) were obtained through integration and linear approximation of classical continuous-time equations, which requires that parameters m , α_j , λ_j , β_j , β' , ε and φ_j be much lower than one. This condition also ensures that host and spore densities remain non-negative.

In the absence of parasites, we found an analytical solution for the optimal age at reproduction. When parasites are present, the non-linearities of the system prevent an analytical solution. Therefore, we wrote an algorithm in the programming language C to simulate the evolution of the system. Following eqns (1)–(5), simulations were deterministic, except for the random mutations. However, very low mutation rates and long-term simulations (100 000 generations on average) prevented any noticeable stochastic effect: repeated simulations using the same sets of parameters but different initial conditions always led to the same quantitative results. This allows us to draw consistent conclusions.

Results

We investigate the effects of parameters on the evolution of either host or parasite and on their coevolution. Our main results are summarized in Table 1.

Evolution of hosts

In the absence of parasites, we can express the density of newborns $N'_i(0)$ at the beginning of a season given the density of newborns $N_i(0)$ at previous season:

$$N'_i(0) = N_i(0)(1 - m)^{T_i}(1 - M)^{\Theta - T_i} b_{\max}(1 - e^{-kT_i}) \quad (6)$$

The strain of hosts with the greatest ratio $N'_i(0)/N_i(0)$ will dominate the system, given that density-dependent reduction of fecundity maintains the relative proportions of genotypes within the population (see eqn 5). Obviously, if this ratio is < 1 for all strains, the system will go extinct. We set b_{\max} to a high enough value to prevent such extinctions. Provided that prereproductive mortality is greater than egg mortality ($m > M$), maximizing eqn 6 shows that the optimal genotype (i.e. the one that will dominate the system) in the absence of parasites is:

$$T_{\text{opt}}(k, m, M) = \min \left\{ \Theta; \frac{1}{k} \ln \left[1 - \frac{k}{\ln(1 - m) - \ln(1 - M)} \right] \right\} \quad (7)$$

The optimal age at reproduction thus decreases when growth rate k or prereproductive mortality m increases, in agreement with classical life history theory (Stearns, 1992). Numerical simulations confirmed that the strain whose age at reproduction (which must be an integer) is closest to T_{opt} always invades the system and eventually eliminates its competitors.

In the presence of a parasite with a fixed virulence, we were not able to obtain analytical results. Numerical simulations showed that the system always converges towards an epidemiological and evolutionary equilibrium. If virulence is sufficiently low or if transmission is

Table 1 Summary of the main results. The novel results are in bold type.

Parameter (1)	Evolving trait (2)	Evolutionary response of trait (2) to an increase in parameter (1)
Virulence (α)	Age at reproduction	Decreases if $\alpha < \alpha^*$; increases if $\alpha > \alpha^*$; mixed ESS with vertical transmission if $\alpha > \alpha^*$ (first scenario)
Age at reproduction (T)	Virulence	Decreases
Host's growth rate (k)	Age at reproduction	Decreases
	Virulence	Decreases until carrying capacity is reached, then remains constant
	Both (coevolution)	<ul style="list-style-type: none"> • Age at reproduction decreases if $\alpha < \alpha^*$; increases if $\alpha > \alpha^*$; mixed ESS with vertical transmission if $\alpha > \alpha^*$ (first scenario) • Virulence increases until parasites disappear
Host's death rate (m)	Age at reproduction	Decreases until extinction of host and parasite
	Virulence	Increases until parasites disappear
	Both (coevolution)	Nonmonotonic responses of both traits
First scenario	Age at reproduction	Decreases until extinction
–Horizontal transmission (β_{\max})	Virulence	Decreases
–Vertical transmission (γ_{\max})	Both (coevolution)	Nonmonotonic responses of both traits
Second scenario		
–Spore release (φ_{\max})		
–Infection rate (β')		
Spore elimination rate (scenario 2) (ε)	Age at reproduction	Increases until parasites disappear
	Virulence	Increases until parasites disappear
	Both (coevolution)	Nonmonotonic responses of both traits

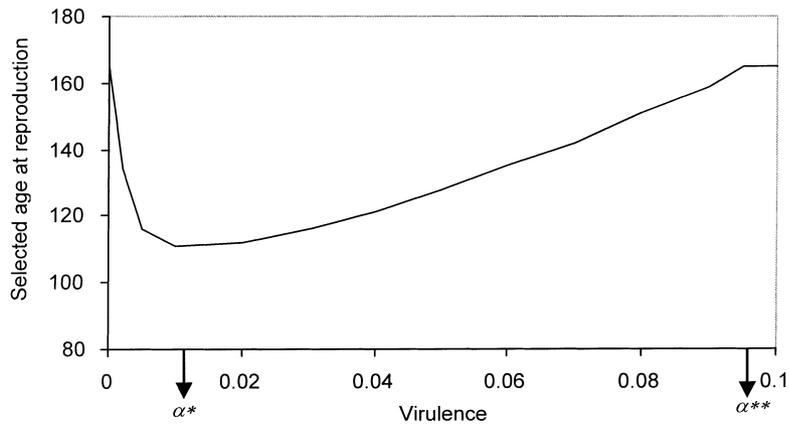


Fig. 2 Evolution of the age at reproduction against various values of virulence with the second epidemiological scenario. Parameters used: $b_{\max} = 10$, $m = 0.004$, $k = 0.005$, $\beta' = 0.01$, $\varphi_{\max} = 0.01$, $\delta_s = 2 \times 10^{-3}$, $\varepsilon = 0.05$, $u = 10^{-5}$. For these parameters, age starts increasing when virulence exceeds threshold $\alpha^* = 0.01$, and parasites disappear beyond $\alpha^{**} = 0.095$.

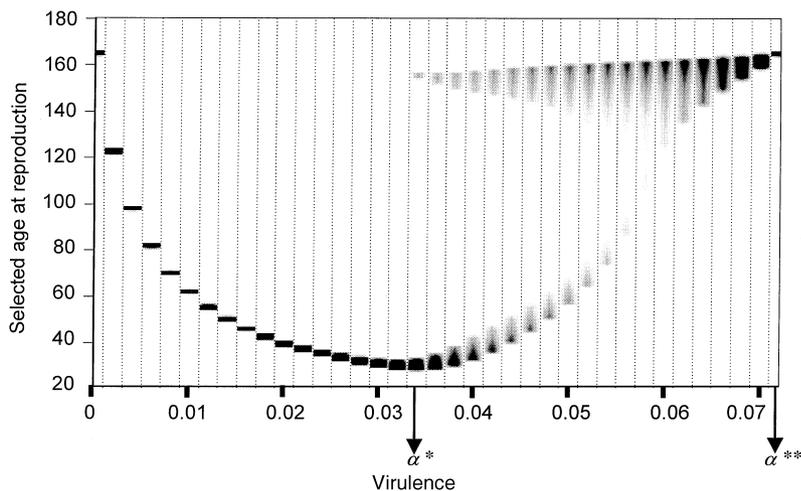


Fig. 3 Evolution of the age at reproduction against various values of virulence with the first epidemiological scenario. The graph represents the distribution of hosts at equilibrium (darker patches represent higher density) for given values of virulence. Other parameters used: $b_{\max} = 30$, $m = 0.004$, $k = 0.005$, $\beta_{\max} = 0.001$, $\gamma_{\max} = 1.0$, $\delta_H = 10^{-5}$, $\delta_V = 0.01$, $u = 10^{-5}$. For these parameters, bifurcation occurs at virulence $\alpha^* = 0.034$, and parasites disappear beyond $\alpha^{**} = 0.072$.

inefficient enough, the parasite rapidly disappears. The conditions for parasite extinction are increasingly easily satisfied as hosts develop in poorer environmental conditions (high mortality, low fecundity), although under extreme conditions the parasites cause the extinction of both themselves and their hosts. Note that the elimination of either parasites or hosts is not a random event but rather follows deterministic processes described by eqns (1)–(4). Below, we focus on results pertaining to the persistence of both species.

Conforming with earlier results (Hochberg *et al.*, 1992), a parasite with fixed virulence selects for an age at reproduction at values below T_{opt} (eqn 7). Similarly, we find a decrease in the optimal age at reproduction when prereproductive death rate m or growth rate k increases, regardless of infection and of scenario. However, the evolutionary response of the host to an increase in virulence is not monotonic. Figure 2 shows the pattern of evolution with the second scenario. As virulence increases from low values, the hosts' evolutionarily stable age at reproduction decreases: higher virulence improves transmission and thus increases the risk

of infection, making hosts more likely to die before reproduction. Above a threshold level of virulence α^* , however, age at reproduction starts increasing until it reaches T_{opt} when parasites disappear. This pattern is in accordance with recent results (Gandon, 2000; Koella & Restif, 2001). For high values of virulence, transmission ability (parameter β_j or φ_j) reaches a ceiling as virulence increases further. Thus infected hosts die rapidly and have little time to infect other hosts (in the first scenario) or to release infectious spores (in the second scenario). Consequently the risk of infection decreases, which allows hosts to grow longer and improve their fecundity.

Using ranges of parameters that allowed maintenance of the system with higher values of virulence, the first epidemiological scenario (with vertical transmission) raised a more complex and unexpected pattern of evolution. As we increase virulence beyond threshold α^* , the evolutionary process leads to a bifurcation and the equilibrium is a bimodal distribution of two strategies (Fig. 3). The first is similar to that described before: a short but increasing growth stage, for hosts to escape infection from horizontal transmission, at the expense of

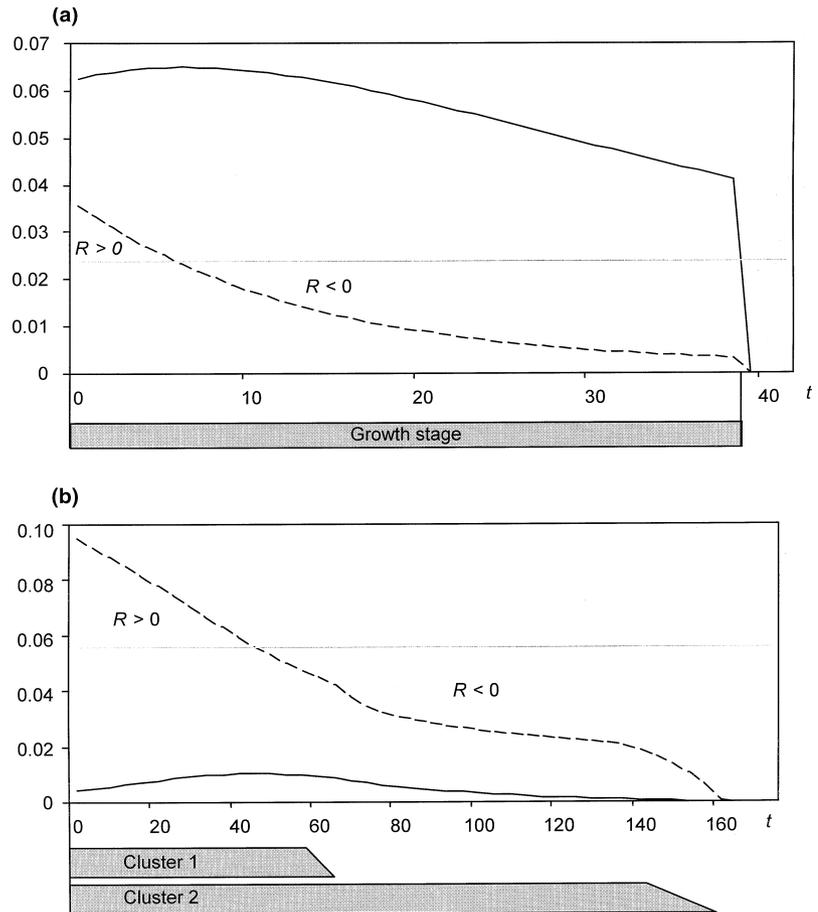


Fig. 4 Dynamics of epidemiology during a cohort at evolutionary equilibrium, using the first epidemiological scenario. Solid curves represent the force of infection λ . Dashed curves represent the rate of horizontal transmission $\beta X(t)$ and dotted lines represent the elimination rate of infected hosts $m + \alpha$. R is the difference between the dashed curve and the dotted line. The durations of growth stages of the hosts present in the system are indicated below the graphs as horizontal grey bars. (a) Virulence $\alpha = 0.02$, only one strain of host is present ($T = 39$) and (b) $\alpha = 0.05$, two clusters of hosts are present ($T \approx 60$ and $T \approx 150$). Other parameters used: same as Fig. 3. Vertical scale is the same for all curves.

a low fecundity. On the contrary, hosts following the second strategy have an age at reproduction close to T_{opt} , the value in the system without parasites. The strategy essentially consists of outliving the parasites. If virulence is high, the parasite will kill its host before it can infect other individuals. The epidemic within a cohort of hosts will therefore die out rapidly. If a host with long growth stage has survived this epidemic without being infected (although the probability that this occurs may be low), it will benefit from both a high fecundity and a low prevalence of parasites among its offspring. Thus the two strategies maximize their expected reproductive success by emphasizing survival (strategy 1) or fecundity (strategy 2). We found that the two phenomena (increase in age at reproduction and coexistence of a second strategy) appear beyond the same threshold α^* . This means that α^* is the maximal value of virulence that allows parasites to transmit more rapidly than they kill their hosts.

To obtain a more accurate description of the bifurcation, we tracked the epidemiological dynamics of a single parasite strain during one cohort at the evolutionary equilibrium, using the first scenario. To do so, let us rewrite eqn (1) in a simplified way, defining

$X(t) = \sum_i J_i(t) N_{i,0}(t)$ as the density of susceptible hosts, $Y(t) = \sum_i J_i(t) N_{i,1}(t)$ as that of infectious hosts, and $\lambda = \beta Y(t)$ as the force of infection. We introduce the basic reproductive number of the parasite $R = \beta X(t) - (m + \alpha)$, namely the rate of increase of the infectious population. Note that R is the discrete-time equivalent of the classical rate $R_0 = \beta X(t) / (m + \alpha)$ defined in continuous-time models (Anderson & May, 1982). We get the following system:

$$\begin{aligned} X(t+1) - X(t) &= -X(t)(m + \lambda) \\ Y(t+1) - Y(t) &= R Y(t) \end{aligned} \quad (8)$$

We divide the selected strains of hosts in two clusters, one with low ages at reproduction, the other with higher ages at reproduction (according to distributions shown on Fig. 3). At the start of the cohort, R is at its highest level, and decreases as mortality and infection reduce the number of susceptible hosts (Fig. 4). As R is the growth rate of density $Y(t)$ (eqn 8), and as the force of infection λ is equal to $\beta Y(t)$, R is also the growth rate of λ . Therefore, when R reaches 0, that is, the value below which the parasite cannot maintain itself in the cohort ($R_0 < 1$ in

continuous-time systems; see Anderson & May, 1982), the force of infection is maximal. When virulence is above the threshold value α^* for the bifurcation process (Fig. 4b), the force of infection λ remains low throughout the epidemic and decreases even further when the cluster of hosts with short growth stage reproduce and die. For any individual that has survived this epidemic, the added risk of infection is very low. Thus there is little selection pressure to shorten growth stage and these individuals benefit from longer development and higher fecundity. The situation is different when virulence is below the threshold value α^* (Fig. 4a). Although the basic reproductive number R also rapidly becomes negative, the force of infection remains at a high level throughout the growth period of the host, leading to a high risk of infection for those individuals that delay reproduction. The risk of being killed by the parasite therefore outweighs the benefit of high fecundity.

As virulence increases above threshold α^* , the shorter age at reproduction increases and, at high enough virulence, actually converges to the longer one. This is because higher virulence is associated with less efficient transmission, because infected hosts tend to die before they transmit their parasite. Less efficient transmission means lower prevalence of infection and reduced selection pressure by the parasite, resulting in the host adopting the same life history strategy as in the parasite-free system. At even higher levels of virulence, above a second threshold α^{**} , parasites disappear, following standard epidemiological constructs (May & Anderson, 1983).

Evolution of virulence

We now let parasites evolve freely in a monomorphic population of hosts, as in most models for the evolution of virulence (Levin & Pimentel, 1981; Lenski & May, 1994; May & Nowak, 1994; Lipsitch *et al.*, 1995; van Baalen & Sabelis, 1995). In a first series of simulations, we let the parasite evolve against a set value of the host's age at reproduction; in a second series, age at reproduction is determined by the evolutionary process in the unparasitized system (age at reproduction equals T_{opt} , as given by eqn 7), and the parasite thus evolves against a set value of the host's growth rate and mortality (in other words, against the environmental conditions that determine host's genotype). Both series were run twice, using the two alternative epidemiological scenarios. All the simulations in which hosts and parasites persist result in a single strain of parasite dominating the system at equilibrium.

The first series of simulations shows that virulence decreases as the duration of growth stage increases (because the parasites can transmit among hosts for longer periods of time) and as prereproductive death rate m decreases. Thus, when susceptible hosts have a longer expected life span and therefore parasites have a longer period of infection, weaker horizontal transmission is

outweighed by a longer transmission process, which selects for lower virulence. Moreover, when the hosts' population density is regulated by the parasite (i.e. it is lower than K), virulence is also negatively correlated with fecundity parameters k and b_{max} . As long as an increase in k or b_{max} increases the density of offspring (below the carrying capacity K), it ensures a higher density of hosts during all the growth stage (because death rate remains constant). For the parasite, higher densities of susceptible hosts amount to an increase in transmission or infection rate (β_j or β' , see eqns 2a and 2b): it gives a selective advantage to strains that trade off survival against transmission, namely strains with low virulence.

In the second series of simulations, we assume that the hosts have reached an evolutionary equilibrium in an environment that determines growth rate k and prereproductive mortality m . Thus all hosts have the genotype $T_{opt}(k, m, M)$. As before, an increase in prereproductive mortality results in higher evolved virulence. An increase in growth rate, however, selects for increased rather than decreased virulence, as any increase in k (or m) results in a decrease in T_{opt} , which then selects for higher virulence. In other words, if the hosts' age at reproduction is determined by growth and death rates, its effects on the evolution of virulence will swamp other effects.

Coevolution

Finally, we let very small proportions of host and parasite populations mutate at the start of each cohort, so that age at reproduction and virulence can coevolve. As before, all simulations were observed to converge towards stable demographic and evolutionary equilibria. Thus for the ranges of parameters allowing host and parasite coexistence, evolutionarily stable genotypes are selected.

Some results are straightforward combinations of those described above. For instance, a higher prereproductive death rate m or growth rate k usually (see an exception below) selects for a shorter age at reproduction and higher virulence (right-hand sides of Fig. 5a,b): once again, the evolution of virulence is driven by the duration of the hosts' growth stage.

Other results are more complex. Increases in transmission rates (β_{max} , γ_{max} or $\beta' \varphi_{max}$) results in nonmonotonic responses in hosts and parasites (Fig. 6). For example, Fig. 6(b) shows that increasing φ_{max} from 0.005 to 0.01 selects for higher virulence and for earlier reproduction. However, when $\varphi_{max} = 0.01$, further increases select for lower virulences and, if $\varphi_{max} = 0.02$, for higher ages at reproduction. In the latter case, we observed that more than 90% of hosts are infected by the time they reproduce. This means that, if hosts cannot avoid infection, they opt to shift their investment to fecundity, whereas parasites are so infectious that they shift their investment to survival, thus reducing their virulence.

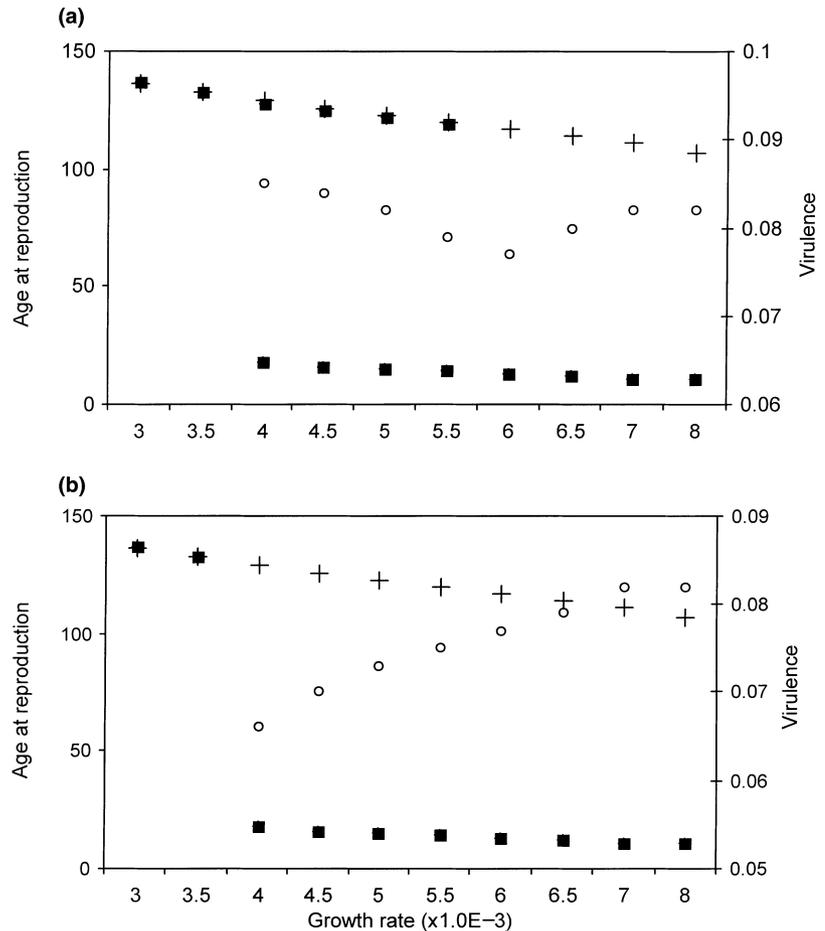


Fig. 5 Coevolution for various values of hosts growth rate k . Only the modal values of distributions at equilibrium are plotted. Solid squares: hosts' ages at reproduction, crosses: optimal age at reproduction T_{opt} without parasites (both left-hand axis); open circles: parasites' virulences (right-hand axis). (a) Simulations using random mutations with large effects. (b) Simulations using nonrandom simulations with small effects. All simulations (a and b) were initiated with single strains $T = 50$ and $\alpha = 0.03$. Other parameters: $b_{max} = 30$, $m = 0.006$, $\beta_{max} = 0.008$, $\gamma_{max} = 1.0$, $\delta_H = \delta_V = 0.08$, $u = v = 10^{-5}$.

This pattern is found with both scenarios, although it is less pronounced with the first (Fig. 6a).

For certain conditions, a slight change in one parameter can drive virulence beyond threshold α^* , and thus give rise to two coexisting host strategies. As before, bifurcation appears only with the first scenario. For example, a slight change in the hosts' growth rate k can lead to qualitatively different levels of virulence and development time (Fig. 5a). For the parameters shown in this figure, a decrease in k from 0.006 to 0.005 (which could result for instance from an environmental impoverishment) will turn the monomorphic, rapidly developing, population of hosts into a dimorphic population, made up of both rapidly and slowly developing individuals. This consequently changes the selection pressure on virulence, so that, instead of reduced virulence being favoured by slower growth, virulence increases as growth rate decreases. Because of the dimorphic development times, the parasites do not transmit rapidly enough to infect hosts before the epidemic dies out. Therefore they are selected to increase their transmission by increasing their virulence, which in turn increases

selection for the slower strategy of the host. The decrease in growth rate thus initiates an arms race: parasites increase virulence to infect hosts more rapidly, whereas hosts develop more slowly to outlive parasites and balance high mortality by a better fecundity. At too slow a growth rate ($k < 4 \times 10^{-3}$ in Fig. 5), hosts with the longer growth stages win the race so that parasites are eliminated.

The results presented so far have been obtained using random mutations generated every season for hosts and parasites. They are independent of initial conditions or values of mutation rates.

Alternative models of mutation

We studied two alternative mutation processes. First, to allow for the possibility that microparasites evolve faster than their hosts, we reduced the hosts' mutation rate so that hosts mutate only every S seasons ($S \gg 1$), whereas parasites still do so every season. This allows parasites to adapt to the dominant host genotype(s). Although the host is constrained to evolve very slowly,

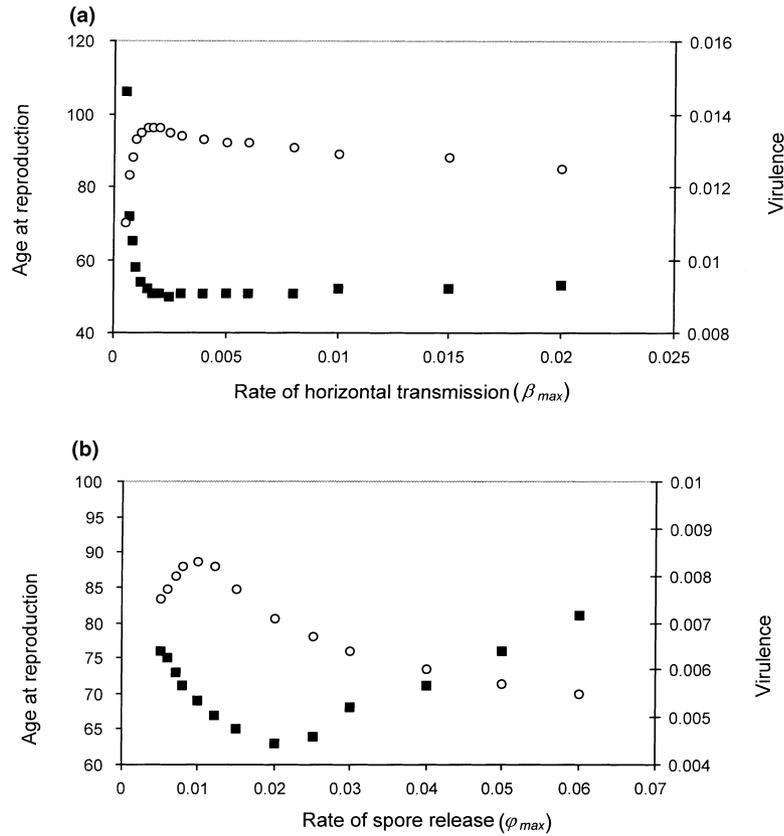


Fig. 6 Coevolution for various values of (a) horizontal transmission rate β_{max} using the first scenario; (b) spore release rate φ_{max} using the second scenario. Same symbols as Fig. 5. Other parameters: $b_{max} = 20$, $m = 0.004$, $k = 0.005$, $u = v = 10^{-5}$, (a) $\gamma_{max} = 1.0$, $\delta_H = \delta_V = 0.01$, (b) $\beta' = 0.01$, $\delta_S = 0.002$, $\varepsilon = 0.05$.

the system, for a given set of ecological parameters (k , m , M , b_{max} ; β_{max} , γ_{max} , δ_H , δ_V or β' , φ_{max} , δ_S) always reached the same equilibrium as presented in the above analyses.

In a second alternative model, we assumed that mutations with only small effects could occur. We therefore performed simulations with deterministic 'mutations', where every strain i of hosts gives birth to a fraction u of mutants, half of which have genotype $i - 1$ and the other half genotype $i + 1$ (strains 1 and n lose a fraction $u/2$ of their offspring). Similarly parasites of strain j mutate to strains $j - 1$ and $j + 1$ with equal rates $v/2$ at the beginning of every host generation. This process leads to the same equilibria as the random mutation assumption employed in our main model, except when the latter leads to a bimodal distribution of hosts (with the first epidemiological scenario). Here, only particular initial distributions of hosts and parasites (at least two strains of hosts including one with a long duration of growth stage, together with a highly virulent strain of parasite) allow the system to converge to the same polymorphic equilibria as the process with random mutations. Starting with other distributions leads to a single host–parasite pair at equilibrium (see Fig. 5b). Note that in this case, virulence continues to decrease

with decreasing growth rate, in contrast to the arms race because of the bifurcation. As with previous mutation models, the distribution of strains at equilibrium does not depend on mutation rates.

Discussion

We describe a model that includes explicit epidemiological and evolutionary dynamics in order to investigate (co)evolutionary processes in a host–parasite system. In particular, it combines recent empirical and theoretical ideas on the evolution of a host's life history as a response to parasitism (Agnew *et al.*, 1999; Kirchner & Roy, 1999; Gandon, 2000) with a more intensively explored field of research, namely the evolution of virulence. In a previous description of this coevolutionary process, we developed a numerical model in which epidemiological and evolutionary processes occurred over different time scales (Koella & Restif, 2001). This enabled us to point out an epidemiological feedback in the evolution of host, and thus to extend Hochberg *et al.*'s (1992) static approach. In the present study we go one important step further, incorporating (co)evolution based on a continuous mutation–selection process.

Evolution of the host and ecological feedbacks

In many ways, our model yields classical predictions. For example, increasing prereproductive mortality favours earlier reproduction (Berrigan & Koella, 1994) and increasing the expected duration of infection (either by increasing the age at reproduction or decreasing prereproductive mortality) selects a lower level of virulence (May & Anderson, 1983). Although this confirms robustness of these classical findings, our study yields additional novel results.

We were particularly interested in the evolutionary response of hosts to an increase in virulence. We identified three ranges of virulence that lead to qualitatively different responses. Below a first threshold level of virulence α^* , increasing virulence selects more rapid development. This is in agreement with previous results (Hochberg *et al.*, 1992; Kirchner & Roy, 1999). Beyond this threshold, the optimal age at reproduction increases, confirming recent results (Gandon, 2000; Koella & Restif, 2001), but in some conditions (which we discuss below) a bifurcation occurs, allowing the contemporaneous existence of a second strategy with longer prereproductive development. Finally, beyond a second threshold α^{**} , high virulence kills hosts and their parasites before spreading infection and parasites disappear.

Let us now focus on the bifurcation and the mixed ESS that emerges among hosts. The strategy for short development allows the hosts to escape infection, albeit at the cost of low fecundity. In this strategy, as virulence increases above α^* , infected hosts are more likely to die before infecting other hosts. The intensity of transmission thus decreases, which in turn weakens the selective pressure on the hosts. With increasing virulence, hosts therefore approach the optimal strategy of unparasitized hosts. The second strategy for hosts to manage highly virulent parasites is to develop slowly. Hosts with a long growth stage will suffer strong mortality during the epidemic within the cohort. However, because an epidemic of highly virulent parasites dies out rapidly, the period of transmission is short and the hosts following this second strategy can outlive the parasite to reach an age where mortality is low. Should this age be reached, the risk of early mortality is more than balanced by the high fecundity. Finally, as virulence increases to very high levels, the parasite cannot persist in the population, as predicted by classical models of epidemiology (May & Anderson, 1983), and the host is simply selected to develop at the rate predicted for an unparasitized system.

Comparing both epidemiological scenarios helps to understand the conditions for the bifurcation. In the first scenario, death of the shorter-lived hosts, caused by early reproduction, prevents their parasites from being transmitted any longer, hence reducing the force of

infection (Fig. 4). In the second scenario, death of the shorter-lived does not reduce the force of infection so rapidly, because spores remain infectious: longer-lived hosts suffer strong infection and die before reproduction. So the defence strategies can strongly differ whether the infectious form of the parasite remains in the host and dies with it, or is free and survives for some time.

In addition, the bifurcation predicted by our model may be a result of seasonal reproduction. We would not expect this phenomenon to appear if reproduction were continuous or iteroparous and within-cohort epidemics were not discrete. Note also that the bifurcation was not observed in a previous model of the coevolution age at reproduction and virulence (Koella & Restif, 2001), because the force of infection remained constant for every generation. Therefore, hosts with slow development could not benefit by escaping to an age with low risk of infection and thus mortality.

In an approach similar to that taken by Koella & Restif (2001), Gandon (2000) describes the coevolution of virulence and a different life history trait of the host: its reproductive effort. As in the present study, the evolutionarily stable reproductive effort against a wide range of virulences shows a nonmonotonic pattern. As virulence increases, reproductive effort (and thus fecundity) first increases up to a threshold of virulence and then decreases. This pattern, at least with respect to the fecundity, is the opposite to what we find here, where selected age at reproduction (and thus fecundity) first decreases. The difference lies in the life cycles of hosts. Although we consider a semelparous species that does not reproduce until it reaches a given age, Gandon (2000) assumes that hosts reproduce continuously as soon as they are born. In Gandon's model, the direct effect of a higher natural mortality or virulence is to reduce the duration of reproduction, and hosts must compensate for the shorter reproductive period with higher reproductive effort. In our model, a similar increase in mortality or virulence reduces the probability to reach reproduction, therefore hosts will evolve a shorter growth stage. A further difference between the predictions of the two models is the lack of bifurcation in Gandon (2000). Again, this lies in the lack of age structure, the continuous reproduction and the associated lack of parasite dynamics within discrete host cohorts in Gandon's model.

Evolution of the parasite

Patterns of evolution for parasites are more simple and intuitive. Interestingly, we found no qualitative differences between the two scenarios. We showed that intra cohort dynamics are equivalent, if variations in spore densities are much slower than variations in host densities, and if $(\beta' \varphi_j / \varepsilon) = \beta_j$. Conversely, dynamics among cohorts are quite different: in the first scenario,

parasites contaminate eggs by vertical transmission, thus some hosts are born infected, whereas in the second scenario, all newborns are uninfected, so parasites must start a new epidemic every generation. Thus, even if the two conditions hold, one cannot compare quantitatively the evolutionary outcomes of the two scenarios. In particular, given common values of β_j and $\beta'\varphi_j/\varepsilon$, selected age at maturity also depends on the rate of vertical transmission in the first scenario, and on the exact value of each parameter β' , φ_j and ε in the second scenario.

In our model, vertical transmission does not modify the evolution of virulence. In contrast, previous studies (Bull *et al.*, 1991; Agnew & Koella, 1997) showed that vertical transmission should favour low virulence. However, vertical and horizontal transmission do not compete in our model; they are complementary. More precisely, the three routes of transmission, although positively related with virulence, benefit from low host mortality: the longer the host survives, the more parasites it will transmit.

Coevolution

Although the results discussed above assume that either virulence or age at reproduction is constant (within any given simulation), similar results are found when the parasite can evolve along with the host. Variation in environmental parameters (such as the hosts' natural mortality m or rate of increase k) can modify virulence which, in turn, leads to a bifurcation of the hosts' strategies.

We found that parasites never evolve a polymorphic strategy, although it has recently been shown (Regoes *et al.*, 2000) that a heterogeneous host population can lead to bimodal parasite distributions. The requirement for this polymorphism is that every strain of parasites trades off its virulence on one type of host against the other, that is, generalists are less efficient than parasites that specialize on one type of host. If, in addition, this trade-off function is convex, the system can be dominated by the specialists, thus raising as many modes in the parasites distribution as host types. Thus, the reason for the lack of polymorphic parasite strategies in our coevolutionary model is that no such trade-off exists: a given strain of parasite is associated with the same virulence for all hosts.

Using an ESS approach, van Baalen (1998) showed that bistability was a likely outcome of the coevolution of recovery ability and virulence. Given sets of parameters raise two stable equilibria: either low virulence associated with no recovery, or both high and costly investments in virulence and recovery. This result is closer to the classical vision of an arms race between host and parasite, except for the stability of the benign strategy. But contrary to our findings, in van Baalen's model coevolution does not lead hosts to develop two alternative

strategies as a response to a single value of virulence. The reason for this is that his optimization process allows an epidemiological feedback (variable force of infection) but no demographic feedback. Our main result, the mixed ESS, depends on this feedback.

We can conclude from the different examples described above that the details of the mutation process (e.g. the phenotypic effect of the mutation) can be crucial in determining not only the dynamics of the system, but also its equilibrium. Thus, bifurcations are only likely to appear if all possible genotypes can easily be produced by random mutations.

Conclusions

Apart from the novel insights on the complexity of the coevolutionary process, the most important conclusions of our model are quite general. First, it emphasizes, as did in previous models (Gandon, 2000; Koella & Restif, 2001), the importance of combining the long-term demographic and evolutionary processes. Only this combination leads to the nonmonotonic responses of the hosts' age at reproduction or the parasite's virulence. Secondly, it shows that adding age structure into models of host-parasite evolution can lead to novel predictions (compare with Gandon, 2000). Thirdly, it demonstrates the importance of considering explicit dynamics at all time scales. Only by including the dynamics of the parasite within and among cohorts of hosts would the bifurcation pattern be observed. A similar conclusion was drawn in a model describing the evolution of a parasite in hosts with discrete generations, where explicit consideration of the epidemiology within and among cohorts could lead to dynamic bifurcations in the parasite's virulence (Koella & Doebeli, 1999). It can only be hoped that the near future will put such results into critical contact with laboratory systems dealing with experimental coevolution.

This work expands the theoretical knowledge on coevolution in host-parasite systems as it sheds light on the complex interactions between ecological (including demographical, epidemiological and environmental) and evolutionary dynamics. Naturally, its predictions are only as good as its assumptions, and relaxing assumptions may well lead to different conclusions. Thus, as discussed above, polymorphic strategies are most likely to occur if the host has discrete cohorts. Furthermore we have neglected any spatial variation in transmission (either in a metapopulation approach or using viscous models) and we have simplified epidemiology by assuming that no super-infection can occur. Although it is clear that such assumptions can lead to qualitatively different results (spatial variation: Lipsitch *et al.*, 1995; Thrall & Burdon, 1997; Gandon *et al.*, 2001; superinfection: Nowak & May, 1994; van Baalen & Sabelis, 1995), we leave their elucidation for future work.

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